Archana Chatterjee *Editor*

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Archana Chatterjee, M.D., Ph.D.
School of Medicine
Creighton University
Omaha, NE, USA

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This book is dedicated to the memory of
my parents and Stephen A. Chartrand, M.D.

Foreword

"If you can bear to hear the truth you've spoken
Twisted by knaves to make a trap for fools,
Or watch the things you gave your life to, broken,
And stoop and build 'em up with worn-out tools…"

Rudyard Kipling
"If," 1895

As long as there has been scientific advancement, there has existed the possibility that reports of its origins, safety, efficacy, and implementation would be twisted and misunderstood—either intentionally or unintentionally—to further agendas that reach far beyond the pure science of discovery itself.

The science of vaccination is one research area that has come to the forefront in recent years. Vaccines are one of the most beneficial public health measures available. Smallpox, once a scourge of humanity that killed millions over the 12,000 years of its recorded existence, has been eradicated through the use of vaccination. There are now a total of 17 vaccines that prevent infectious diseases across the childhood/adolescent and adult immunization schedules. Two of these—the hepatitis B vaccine and human papillomavirus (HPV) vaccine—go even beyond the microbes from which they are derived to prevent cancer caused by the diseases.

Despite these successes, real and perceived concerns about vaccines and the immunization process have resulted in a subpopulation of "vaccine-hesitant" people—those who delay or deny immunization for either themselves or their minor children. Since concerns over vaccine hesitancy are multifactorial, approaches to these concerns are equally complex. And the complexity is only heightened with the advent of more vaccines and nuances in vaccine recommendations.

Lack of acceptance of vaccines may, in actuality, have less to do with minor and uncommon adverse effects attributed to the shots and more to do with a lack of knowledge and appreciation of the rigorous pre- and post-licensure testing of vaccines, the serious nature of the diseases they prevent, and a lack of scientific basis upon which decisions should be made.

Vaccinophobia and Vaccine Controversies of the Twenty-First Century addresses in an accessible manner the complicated facets of the vaccine hesitancy phenomenon—one that is by no means new despite the uptick in recent mass media coverage. Important considerations that fall under its aegis include issues with hesitancy and fear of vaccines that date back to Jesty and Jenner. The successes of progressively more refined inoculation in disease reduction have reduced drastically the potential for parents in developed countries to experience the morbidity and mortality associated with vaccine-preventable illnesses that still persist in many other parts of the world.

Vaccine development, approval, recommendation, and regulation processes are detailed, including the safety testing mandates put in place both prior to and after a vaccine is licensed by the United States Food and Drug Administration. While continued refinements of these processes have made new vaccines much safer than older ones, safety does come at a price. Newer vaccines are costly, and some are less immunogenic than their predecessors (i.e., acellular pertussis and conjugated meningococcal vaccines), resulting in the need for additional doses in order to maintain protection.

This book emphasizes the need for everyone from parents to pediatricians to government officials to make decisions based on science rather than emotion or unsupported information that has proliferated throughout print and broadcast media as well as on the Internet. Separate chapters examine misconceptions with which parents will be confronted regarding the recommended vaccine schedules; thimerosal and other additives; and even the notion that vaccines lie at the root of serious medical and behavioral complications. Even propagation and penetration of these notions across various forms of media and socioeconomic groups are discussed in depth.

Each of the 11,000 infant births every day in the USA begins the cycle of immunization over again. In each place in which that cycle is broken, there lies the possibility of intrusion by pathogens many practicing physicians and nurses have not even seen manifest—due to the success of vaccines.

Rather than try to warn, debunk, or condemn, the overarching focus of *Vaccinophobia and Vaccine Controversies of the Twenty-First Century* is on communication—between physicians, health care organizations, government agencies, the media, and parents. At the top echelons, among the policymakers, the burden of communication lies in providing and disseminating consistent, correct, and accessible information free of hype and hyperbole. This book also emphasizes the concomitant responsibility of those on the ground—the physicians, nurses, pharmacists, parents, and more—to educate themselves using these verified sources. These pages do not so much contain a solution to the problems of vaccinophobia and vaccine hesitancy but provide a foundation for its development.

Larry K. Pickering, M.D., F.A.A.P.
L. Reed Walton, M.A.
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Atlanta, GA, USA

Preface

A baby born today in most developed countries can look forward to an average life span of nearly 80 years, almost 25 years longer than a baby born in 1900. While improvements in nutrition, water quality, and sanitation as well as the introduction and widespread use of antibiotics have all contributed to this increase in life expectancy, vaccines have played a major role also in reducing the morbidity and mortality associated with a number of infectious diseases, especially among children. In fact, vaccines have been counted among the greatest achievements in modern medicine, leading to the eradication of smallpox and significant decline in many vaccine-preventable diseases such as polio and measles. As these diseases have become less common, particularly in developed countries, the morbidity and mortality associated with them has faded from the public's memory and anxiety over vaccine-related adverse events has been increasing. Even among healthcare workers, especially those who have grown up in the vaccine era, knowledge of these deadly diseases is limited and concern over vaccine-related adverse events is rising.

It is important to note that opposition to vaccination is not new. It has existed from the time of Edward Jenner who was both lauded and also widely ridiculed for his work on the smallpox vaccine in the late 1700s. Many of his critics, especially the clergy, claimed that it was repulsive and ungodly to inoculate someone with material from a diseased animal. A famous satirical cartoon of 1802 showed people who had been vaccinated sprouting cow's heads, illustrating popular eighteenth-century fears about vaccination. The Anti-Vaccination Society of America was founded in 1879, based on the belief that no one should ever be "complied to submit to any surgical operation" including vaccination, and that vaccines caused "corruption of the blood," and spread diseases rather than preventing them.

It has been said that vaccines have become a victim of their own success. With some parents and other caregivers refusing or delaying vaccines for their children/wards, some vaccine-preventable diseases that were well-controlled have staged a comeback. Outbreaks of these diseases have been reported from countries where they were virtually unknown for many years. This situation is continuing to worsen, despite efforts by public health agencies and others to curb the spread of

misinformation about the risks associated with these diseases and vaccine-related adverse events.

While there are many articles and a few book chapters published in the medical literature, to date, there is no authoritative textbook on the subject of modern-day vaccine controversies. As such, this book is intended to fill a much-needed gap in information, providing a comprehensive resource for information related to current vaccine controversies. I am deeply grateful to the authors who have contributed their expertise in the preparation of this book. It is my hope that this book will provide in-depth coverage of a topic that has only superficially been addressed so far. I would also like to take this opportunity to acknowledge my mentors, colleagues, and family members for their encouragement as I worked on editing this book.

Omaha, NE, USA Archana Chatterjee, M.D., Ph.D.

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Contributors

Narendra K. Arora The International Clinical Epidemiology Network (INCLEN) Trust International, Child Health and Nutrition Research Initiative (CHNRI), New Delhi, India

Roman Aydiko Ayele Wisconsin Department of Health Services, University of Wisconsin School of Medicine & Public Health, Madison, WI, USA

Nandini Bakshi The Permanente Medical Group, Oakland, CA, USA

David M. Berman Division of Pediatric Infectious Diseases, All Children's Hospital, Johns Hopkins Medicine, St Petersburg, FL, USA

Archana Chatterjee Creighton University School of Medicine, Omaha, NE, USA

James H. Conway Division of Pediatric Infectious Diseases, University of Wisconsin School of Medicine & Public Health, Madison, WI, USA

Rajib Dasgupta Center of Social Medicine and Community Health, Jawaharlal Nehru University, New Delhi, India

Paola Dees Division of Hospital Medicine, All Children's Hospital, Johns Hopkins Medicine, St Petersburg, FL, USA

Harold C. Delasalas Division of Allergy and Immunology, Department of Pediatrics, Creighton University Medical Center, Omaha, NE, USA

Creighton University School of Medicine, Omaha, NE, USA

Melissa Durham Titus Family Department of Clinical Pharmacy and Pharmaceutical Economics and Policy, University of Southern California School of Pharmacy, Los Angeles, CA, USA

Jeffery Goad Titus Family Department of Clinical Pharmacy and Pharmaceutical Economics and Policy, University of Southern California School of Pharmacy, Los Angeles, CA, USA

C. J. Harrison Section of Infectious Diseases, Department of Pediatrics, Children's Mercy Hospitals and Clinics, Kansas City, MO, USA

Department of Pediatrics, University of Missouri at Kansas City, Kansas City, MO, USA

Russell J. Hopp Division of Allergy and Immunology, Department of Pediatrics, Creighton University School of Medicine, Omaha, NE, USA

John Iskander Office of the Associate Director for Science, Centers for Disease Control and Prevention, Atlanta, GA, USA

Laura A. Jana Practical Parenting Consulting, Omaha, NE, USA

Anna M. Johnson Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Allison Kennedy Immunization Services Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

Kate LaVail Office of Health Communication, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

Yvonne A. Maldonado Division of Pediatric Infectious Diseases, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA

Clancy McNally Department of Pediatrics, Creighton University School of Medicine, Bellevue, NE, USA

Donald B. Middleton Department of Medical Education, UPMC St. Margaret, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Kody Moffatt Department of Pediatrics, Creighton University School of Medicine, Bellevue, NE, USA

Kari Neemann Pediatric Infectious Diseases, Creighton University School of Medicine, University of Nebraska Medical Center, Omaha, NE, USA

Glen J. Nowak National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

Advertising and Public Relations, College of Journalism and Mass Communication, University of Georgia, Athens, GA, USA

Ann-Christine Nyquist Sections of Infectious Diseases and Epidemiology, Department of Pediatrics, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA

Catherine O'Keefe Creighton University School of Nursing, Omaha, NE, USA

Linda K. Ohri Department of Pharmacy Practice, School of Pharmacy and Health Professions, Creighton University, Omaha, NE, USA

Leonard Ortmann Office of Scientific Integrity, Centers for Disease Control and Prevention, Atlanta, GA, USA

June E. Osborn Josiah Macy Jr Foundation, New York, NY, USA

University of Michigan, Ann Arbor, MI, USA

B.A. Pahud Section of Infectious Diseases, Department of Pediatrics, Children's Mercy Hospitals and Clinics, Kansas City, MO, USA

Department of Pediatrics, University of Missouri at Kansas City, Kansas City, MO, USA

Sharon Plummer Council Bluffs, IA, USA

Alice Pong Division of Pediatric Infectious Diseases, University of California San Diego, Rady Children's Hospital San Diego, San Diego, CA, USA

Meghan Potthoff Creighton University School of Nursing, Omaha, NE, USA

Clea Sarnquist Division of Pediatric Infectious Diseases, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA

Mark Sawyer Division of Pediatric Infectious Diseases, University of California San Diego, Rady Children's Hospital San Diego, San Diego, CA, USA

James J. Sejvar Centers for Disease Control and Prevention, Atlanta, GA, USA

Avinash K. Shetty Department of Pediatrics, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC, USA

Kristine Sheedy Communication Science, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

Michael J. Smith Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Louisville School of Medicine, Louisville, KY, USA

Robert M. Wolfe NorthShore University Health System, Evanston, IL, USA

Pritzker School of Medicine, University of Chicago, Chicago, IL, USA

Chapter 1
The History of Vaccine Challenges: Conquering Diseases, Plagued by Controversy

Laura A. Jana and June E. Osborn

Introduction

For anyone familiar with the fact that vaccines have been deemed one of the ten greatest public health achievements of the past century [1], it would be understandably tempting (and accurate) to start a book about vaccines by simply stating that vaccines are the most effective weapons ever developed for the prevention of serious infectious diseases. Yet to simply leave it at that and move on to a study of the science and successes of vaccines would be a serious oversight. Any informed discussion of vaccines needs to acknowledge and address the fact that vaccines have the very real potential to excite controversy, not only among potential beneficiaries but even within the medical community itself. This phenomenon is certainly not new. In fact, over the years, virtually every new vaccine has been met with a certain degree of suspicion, if not outright hostility. The later half of the twentieth century in particular—marked by a remarkable plethora of new, highly effective vaccines—has also borne witness to a rising volume of public protests against their routine use. Some of the forces, fears, and figureheads fueling these protests persist yet today—in some instances to such a coalescing extent as to invoke the word "vaccinophobia." While true vaccine phobia of the sort that would qualify for a DSM-IV diagnosis is technically quite rare, common vaccine fears and anxiety have persistently plagued public health efforts throughout history to such an extent that they are very deserving of the careful consideration they will be given throughout the many chapters of this book.

L.A. Jana, M.D., F.A.A.P. (✉)
Practical Parenting Consulting, Omaha, NE 68116, USA
e-mail: laurajanamd@yahoo.com

J.E. Osborn, M.D.
Josiah Macy Jr Foundation, New York, NY, USA

University of Michigan, Ann Arbor, MI, USA

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Jenner's Luck and the Era of Daring Vaccine Trials

To better understand fear of and opposition to vaccines, it helps to take a closer look at the context in which they were first introduced. Modern medicine and evidence-based science as we now know it did not exist until the twentieth century. That said, progress within the medical world of vaccines did come quite a bit earlier, albeit for some distinctly unscientific reasons. Pertinent scientific insight was almost nonexistent as the first steps toward smallpox vaccination initially unfolded in the 1770s. When Edward Jenner seized the opportunity soon thereafter to publicly advocate on a grand scale the use of crude cowpox scar material to proactively prevent smallpox, the relative success of his risky inoculation experiment was primitive to say the least (and a technique that it is safe to say would *never* pass any modern-day IRB review). Epidemiology was not yet born as a discipline, and even the recognition of specific microbes and the demonstration of submicroscopic viruses as biologic entities (much less an understanding of the body's reaction to these infectious agents) lay far in the future. While Jenner's observations that milkmaids who sustained mild cowpox infections seemed impervious to smallpox were purely anecdotal and he acted on them after testing only one human subject—a young boy at that—Jenner (and the world) was lucky. The boy survived the challenge without evident damage, Jenner's later work was credited with having saved more lives than the work of any other man, and a template of daring vaccine trials was created [2].

Interest in variolation against smallpox was also being augmented in the fledgling United States by General George Washington, who in 1777 decided to apply the crude practice to all American troops fighting under his command in the revolutionary war [3]. British troops of the day were more likely to have had and survived smallpox than were their American opponents, and their resultant immunity to smallpox had been serving to their notable advantage as smallpox swept through crowded American military camps. While the American rebels were a somewhat unruly bunch, the fear of smallpox facilitated acceptance of the mandate to be vaccinated, and subsequent protection against the debilitating and sometimes deadly disease worked well, except of course for the small percentage of troops who died from it. There is little surviving record of the controversy that must have surrounded this hotly contested (and sometimes lethal) immunization practice, but in the end, the war against the British was won. The war against the ravages of smallpox, however, was not. Ongoing smallpox epidemics in subsequent decades continued to fuel the desire to improve strategies for the prevention of smallpox and, by extrapolation, other vaccine-preventable diseases.

The practice of using vaccinia virus (virologically similar to but distinct from cowpox) to vaccinate against smallpox was made available to the public on an even wider scale at the end of the nineteenth century. This resulted in dramatic decreases in the occurrence of one of humanity's worst killer diseases. Unfortunately, it also led to vigorous, often political controversies. The story of what became a grand march to total smallpox eradication has been well recounted in a careful history by Donald Hopkins (1979) [4] and, notably, in a recent book by William H. Foege

(2011) [3] who played a key role in the eradication program. As one of the earliest in the history of vaccines and vaccine challenges, this grand march serves to exemplify critical factors with which one must grapple in order to understand the frequent controversies surrounding vaccines—controversies that persist to this very day. Public fear of disease is often replaced by fear of preventive intervention as soon as the disease itself begins to fade from collective memory. Additionally, the use of healthy human subjects continues to be both a necessary and mandatory component of vaccine validation. Yet these core aspects of vaccine science predictably and repeatedly raise troubling ethical issues—especially when threats from vaccine-preventable diseases themselves wane.

While the smallpox vaccine was unquestionably saving lives and challenging scientists to reach higher levels of scientific understanding, it was also causing considerable discomfort at the site of inoculation, initiating rare but serious complications, and invoking controversy. As a result, public resistance, especially in developed countries where smallpox had already disappeared, threatened the scientific progress so crucial to the creation and improvement of other newly developing vaccine programs. This was certainly true in the United States, where the decision was made in 1964 to abandon routine smallpox immunization entirely; a decision followed thereafter by the World Health Organization's official proclamation in 1980 that smallpox as a human disease had been successfully eradicated.

While the world celebrated the dramatic (and unique) elimination of smallpox as a human disease, there arose an understandable but troubling tendency toward scientific neglect—in this case of poxvirus studies. It is important to remember that until the 1940s when tissue culture was introduced as a medium for viral propagation [5], the cultivation of viruses for study and attenuation was entirely dependent on animals or embryonated eggs. Even after the advent of tissue culture, the techniques used to make vaccines remained relatively crude. In the case of smallpox, subsequent iterations of smallpox vaccines were duly purified using modern virologic techniques; yet lymph taken directly from vaccinia-infected calves was still used as the source of inoculum for smallpox immunization well into the 1970s. In other words, while there remained great room for scientific improvement, it was not until early in the twenty-first century that a renewed fear of smallpox and new threats of bioterrorism reactivated belated interest in smallpox virology, immunology, and critically important efforts to create a less reactogenic vaccine for mass use [6].

At the Crux of Controversy

With smallpox as a prime example, the first and most striking feature of all vaccine programs is that they involve doing something, most often by injection, to healthy people. It is a curious and challenging fact that in many human societies, medical treatment of ailments is often considered inadequate if *not* accompanied by injection. Yet in the context of prevention, such intrusion on well-being, typically

delivered by needle and syringe, often evokes fear that extends well beyond just a fear of needles. This fear of vaccines is more likely to be evoked if the illness being vaccinated against is not visible in the community, when its effects are no longer vivid in the memory of recipients (such as long-vanished smallpox or paralytic poliomyelitis), or—in some modern instances—is only occasionally overt (such as hepatitis B). It is especially true when children are the intended recipients.

Vaccines as Their Own "Worst Enemy"

In what is justifiably considered a paradox of public health and prevention, there is no better example of this tendency for "out of sight" to transition to "out of mind" than vaccine science. Simply put, when vaccines are successful, they become their own worst enemy. No abstract tale of vanquished disease can conjure up the deep dread of sickness and tragedy that once surrounded infectious illnesses, motivated people to eagerly vaccinate themselves and their children, or served as the impetus for vaccine creation in the first place. The history of public reaction to (and acceptance of) particular vaccines illustrates this point clearly.

Consider poliomyelitis, for instance. Polio was known to civilizations as far back as ancient times. It was an epidemic disease of the twentieth century (especially in developed countries), and escalated in its fearsomeness by the end of the Second World War. Commensurate with an escalating public fear of the dreaded paralytic disease, there was an initial joyous and widespread celebratory response to the availability of an inactivated (or "killed") poliovirus vaccine in the mid-1950s. Accompanying Jonas Salk's creation of this first polio vaccine were clamorous calls for immediate and widespread access to it. In fact, so great was the fear of polio and so urgent was the demand for the newly licensed vaccine that in one or two tragic instances (such as the Cutter incident in 1955 [5]), inactivation of the vaccine virus was incomplete. As a result, live virus persisted in early and hastily manufactured batches of vaccine, resulting in the exposure of several thousand children to live polio virus [5]. Despite being what would in this day and age be considered a pharmaceutical disaster, dismay over the tragedy and public scrutiny of vaccine safety was muted as mass immunization continued to be generally welcomed by a public still deathly afraid of the disease of polio.

How long this relatively exuberant public acceptance of the Salk vaccine (with its tragic potential to be ineffectively inactivated) might have lasted was made moot by the rapid, subsequent introduction of Albert Sabin's orally administered vaccine only a few years later. This new, live attenuated polio vaccine had been tested widely in Eastern Europe. The American public, while tolerant of being injected by the Salk vaccine, was attracted by the lack of a need for injection with the new oral vaccine and thus readily accepted the safety assurances from these overseas studies. Public fear of the use of live attenuated viruses had not yet developed to the extent that it exists today, while the ease of orally administering a vaccine on sugar cubes made it

possible (not to mention more palatable) to deliver a large number of doses to children and others who flocked en masse to "Sabin-on-Sunday" clinics to receive it.

Outside of the experimental deployment of smallpox vaccine (as well as a few others) within the military, and a few specific smallpox outbreaks (the last of which had occurred in 1947), these public polio vaccination clinics were possibly the first instance of efforts to reach entire populations through mass immunizations, and they were enthusiastically embraced. It was not until the natural occurrence of paralytic disease succumbed to the effectiveness of these mass immunization efforts that it gradually became evident that the Sabin vaccine could itself, on rare but serious occasions, also cause paralysis in vaccine recipients or their contacts (on the order of one in every ten million doses). The polio vaccine story might well be said to mark the beginning of a new era of vaccine controversies.

Outsmarting the Microbes, Engaging the Profession

Whether summarizing the introduction of a smallpox vaccine, the concerted efforts to combat poliomyelitis, or addressing any of a whole host of other tales of triumph over vaccine-preventable diseases, there have clearly been several dynamics at play at each step along the way to the present abundance of highly effective preventive vaccines. Public fear of disease often drives an initially eager uptake of newly created vaccines, as was strikingly the case with polio. Conversely, when the disease is not perceived by the public to be serious (as was the case when both the rubella and the chicken pox vaccines were introduced), protests against vaccine use arise more quickly.

However, in order to accurately assess vaccine controversies of the past few decades, it is also instructive to consider the medical and scientific advances that took place in the years leading up to the modern era of vaccines. From an ages-old starting point of fearful and helpless acceptance, active preventive immunization against infectious diseases that carried off young children with special fury had a long way to go to achieve widespread use and acceptance as an integral feature of public health.

Yet public acceptance was not (and is not) the only challenge facing vaccines. Doctors themselves often challenged the emerging pathogenic theory of medicine and contributed to vaccine resistance as well. Even as the contagiousness of infectious illness was becoming plain to see, the very notion that there were specific pathogens that each caused distinctive disease was quite novel. When the germ theory of disease was first put forward and validated toward the end of the nineteenth century, acceptance of what is now a fundamental premise of modern medicine continued to proceed erratically as the sciences of bacteriology, virology, epidemiology, and immunology evolved. In the absence of firm medical understanding of disease causality, paternalism was a prime component of physicians' power in designing care and treatment for their patients and newly evolving scientific approaches were not routinely taught in medical schools until later in the twentieth

century. Vaccines were therefore perceived by some practicing physicians not only with suspicion and doubt but also as outright challenges to their authority. The fact that lesser trained health professionals were often deployed to deliver vaccines only added to their sense of threat. Each step along the professional path to accurate diagnosis, treatment, and prevention was made additionally tortuous by public disbelief, fear of modern change, rebellion against mandated programs of immunization, and/or controversies revolving around the propriety of interference with the "natural order of things."

The Beginning of the Dissent as We Know It

It is interesting to note that rumblings of unease about vaccines in the United States began to increase in volume in the l960s, just as many of the current and effective vaccines came on line. Measles, rubella, and mumps were all yielding to virologic efforts at attenuation through the use of improving tissue culture technology, and highly effective live virus vaccines for these previously fear-inducing and epidemic diseases of childhood were being introduced during that decade. This was also the period in which schools in some states began to require immunization records for entry.

Around the same time, the need to pay closer attention to influenza epidemics was underscored by new pandemic strains of influenza viruses that appeared in 1957 and 1968. In the former episode, no vaccine was available. In the latter, it was too late to stem the ensuing epidemic tide. That is because influenza vaccines were little changed from the early 1940s and still required virus isolates to be grown in embryonated hens' eggs for many months before being inactivated ("killed") and made available for use. Influenza viruses also posed a unique vaccine challenge, as strains changed from year to year. This established characteristic of influenza viruses resulted in the need to update the influenza vaccine each year—a process that necessitated informed guess work each winter as to which circulating influenza strain(s) halfway around the world would predominate in the United States during the following fall's "flu season." As one might imagine, the fact that the development of influenza vaccine continues to rely so heavily on informed guess work is not one that is always well received by a public that has come to expect much more definitive solutions to medical ailments.

Regulation and Resistance

In the period of time leading up to the attention-grabbing influenza epidemics, regulation of the growing number of immunologic products, including influenza vaccine and all its annual complexities, was the assigned task of the Division of Biologic Standards at the National Institutes of Health. In the late 1960s, however,

management troubles arose within the ranks of this division, in the wake of which regulatory control of all vaccines and related biologic products was transferred to the aegis of the US Food and Drug Administration (FDA)'s newly created Bureau of Biologics. Such changes rarely occur quietly, and they received much public attention [7], including high-visibility Senate hearings chaired by Senator Estes Kefauver. These Kefauver hearings resulted in two significant changes that expanded the scope of vaccine regulation considerably: first by solidifying the 1971 transfer of vaccine oversight to the FDA, and by also mandating for the first time a fresh comprehensive review of all licensed biologics for not only safety and proper labeling but also proof of efficacy. New leaders at the FDA assumed their evaluation and oversight responsibilities, and in short order established a process [8] by which a number of older products were either discontinued or brought into line with modern technology. The FDA leaders were not, however, successful in their attempts to placate the disaffected scientists involved in the inciting troubles at the NIH. On the surface, this might all appear to have been bureaucratic restructuring of little to no significance to the overall history of vaccine challenges, were it not for the fact that the cry of "whistle blower" was newly in vogue, and strident claims of improper or incompetent vaccine activities were made from within the health profession that extended well into the public eye. After extensive review, the complaints were found to be without merit and the chief instigator was dismissed. However, the battlefield moved again to the Congress where five senators were persuaded to demand further vaccine-related investigations (all subjects of which had already undergone recent review). Only a subsequent uprising in support of the new FDA management prevented what would have been a tragic attrition of excellent scientists from the vaccine arena [9].

The Swine Flu "Fiasco"

Were that the end of the story it would be instructive although a bit sad in that valuable scientific time was lost in reiterative review. However, it was a big step forward for anti-vaccine mobilization. Ongoing clamor about influenza vaccine coincided with the worrisome advent of yet another new strain in 1976—the so-called swine flu—that was indistinguishable from the influenza virus that had killed 50,000,000 people at the end of World War I. The too-little/too-late experiences of 1957 and 1968 had demonstrated that several months of lead time would be necessary to prepare enough influenza vaccine to immunize the whole population. As the many advisory panels moved toward recommending massive efforts at production, most advisors supported "warehousing" the vaccine until an actual epidemic began. Just the task of producing sufficient amounts of effective vaccine alone would have been daunting, even in the absence of any additional hurdles or controversies.

Then major political intervention occurred that would serve to put the public's fears about vaccines on heightened alert. In 1976, President Gerald Ford gathered a new group of scientific advisors and, along with the help of Salk and Sabin (who had not

been involved in "swine flu" efforts until then), declared a mass immunization campaign of unprecedented scale against "swine flu" that was to reach "every man, woman, and child." As these efforts got under way in the fall of 1976, three elderly vaccine recipients in Pittsburgh suffered heart attacks shortly after getting their influenza vaccine. Later analysis concluded that these events were almost surely coincidental, but this epidemiologically based reassurance was also to prove too little, too late. The public's collective anxiety level had already been raised. Adding to the problems, an untoward increase in the number of the relatively rare neurologic disease called Guillain–Barré syndrome (GBS) noted in the 2 weeks after immunization only served to intensify the anxiety about "swine flu" vaccine even further and, some might say, pose a challenge to vaccination practices in general. Both public and professional alarm at the possible association between "swine flu" vaccination and GBS caused government officials to stop the program entirely. In the end, the "swine flu" virus of 1976 never caused the feared pandemic. As a result, the public was understandably left with a greater fear of the vaccine than of the virus itself, and the massive "swine flu" immunization effort of the 1970s became known as "the swine flu fiasco" [10–12].

Public Dissatisfaction with DPT

Even as influenza controversies raged within the medical profession and in the public eye, anti-vaccine groups began focusing their collective attention on the bacterial vaccine, DPT. DPT was an old vaccine that contained a number of *Bordetella pertussis* antigens against whooping cough, combined with toxoids from both diphtheria and tetanus bacilli. Since pertussis was (and still is) most deadly in early infancy and maternal immunity was known to carry over less well to the fetus than for other infectious agents, DPT vaccine was given routinely at 2, 4, and 6 months with subsequent booster doses later in childhood. It was well known at the time that DPT was more reactogenic than most other vaccines, but the local discomfort and mild fevers that occurred on occasion were considered a reasonable price to pay for what was demonstrable efficacy: all three diseases had been brought under remarkable control. As attention focused on DPT, however, observers noted that some children had prolonged episodes of crying after immunization and, rarely, some developed neurologic disease such as infantile spasms. At this point it is important to note that many rare but distressing neurologic disorders of childhood express themselves early in infancy, and that many of them to date have continued to defy understanding of causality. In any event, a group calling itself Dissatisfied Parents Together chose pertussis vaccine as its target and took up a hue and cry against the DPT vaccine, asserting regulatory malfeasance or indifference.

A similar effort in the United Kingdom had, in the late 1970s, so thoroughly and effectively alarmed the public that pertussis immunization rates plummeted. While the reoccurrence of whooping cough disease did eventually restore higher levels of immunity and subsequent protection against pertussis in the UK, it was not before the outbreak resulted in significant disease and preventable deaths. In the United

States, we did not learn our lesson from the effects of decreased vaccination in Britain. Opposition to pertussis vaccine did vary in intensity, but in regions where immunization rates fell markedly, the return of whooping cough was observed in the United States as well. The role of media during this time period was quite notable, as an enterprising news reporter who lacked scientific background took up the cause of the Dissatisfied Parents. The results of the ensuing media attention were impressive and widespread, with a marked increase in public distrust and the implication that public health advocates were in some way self-serving.

Controversies Over Cause and Effect

While virtually all newly introduced vaccines encountered resistance to some extent, the timing and nature of public response varied greatly. Certainly the degree of "reactogenicity" (side effects such as fever or swelling after immunization) played a role, and inconvenience contributed as well: a multi-injection regimen was less readily accepted by the public than a single inoculation. However, the greatest public outcry resulted from the occurrence of serious disease in close temporal proximity to active immunization.

Such events in 1969 and 1971 complicated the story of polio prevention.[1] The live attenuated (Sabin) vaccine was in widespread use by then, and in two instances (out of millions) children who had received it subsequently developed paralytic disease that was ascribed to the vaccine. In both cases parents sued and courts decided in favor of the plaintiffs. While it was later shown that one case represented Coxsackie virus infection and the other was caused by wild poliovirus rather than the vaccine, the effect of the lawsuit outcomes took a great toll on the future development of vaccines. With the settlements being over a million dollars in each case (not so surprising these days but novel and alarming then), they served to quickly and effectively chill the enthusiasm of vaccine manufacturers. An alarming attrition of companies from the field of biologics production ensued—one that affected not only poliovirus vaccine production but virtually every other generic vaccine. For many vaccine manufacturers, lack of profitability coupled with justifiable concern about corporate risk made the decision to abandon their vaccine enterprise easy.

Two results in particular exemplify the chilling effect that such legal controversies had on the world of vaccines: when the FDA undertook the congressionally mandated review of all vaccines in 1973, there were five licensed manufacturers of measles vaccine in the United States. By 1977, when the review was completed and the effects of the aforementioned lawsuits had settled in, only one licensed US vaccine manufacturer remained (see footnote 1). Similarly, the manufacture of poliovirus vaccine was sufficiently fraught with concern that, for a brief but worrisome while, there was *no* licensed US manufacturer [13].

[1] FDA Panel proceedings, see [8].

Safeguarding Against Side Effects and Controversy

Congress moved relatively quickly to stabilize this dire situation, and by 1986 the National Childhood Vaccine Injury Act (NCVIA) was passed that in essence "immunized" vaccine manufacturers against such extreme litigious harm when accepted production practices had been followed [14]. Furthermore, the FDA established ongoing review groups to advise it on new and improved vaccines, and the Centers for Disease Control and Prevention (CDC) monitored vaccine programs and established vaccine adverse event reporting systems. The Department of Health and Human Services created a National Vaccine Advisory Committee and a parallel Advisory Committee on Childhood Vaccines—both of which were regularly consulted and included nonscience members. However, the long-lasting effect was in some ways pernicious. The very existence of Congress's Childhood Vaccine Compensation law and its protection aroused public suspicions. Simply put, the mounting mistrust of government undercut the impact of the advisory structure, and a growing tendency for the public to blame and to sue in matters of vaccines was augmented. It was in this environment that anti-vaccine groups such as Dissatisfied Parents Together thrived.

It is not an exaggeration to say that the agitation about pertussis and DPT created by Dissatisfied Parents Together cast a pall over the entire immunization scene. Efforts were intensified to find a variation of the pertussis vaccine that would be less reactogenic, and the so-called acellular pertussis vaccine (DTaP) was substituted for the earlier ("whole cell") DPT vaccine. Rather than settling their concerns, however, such responsiveness turned the attention of anti-vaccine groups to other facets of vaccinology. New and markedly effective vaccines were quickly coming on line: hepatitis B, *Haemophilus influenzae* type b, chickenpox, and multivalent pneumococcal vaccines, all of which could be given in childhood, carried great promise of further preventing disease. That meant that the number of injections recommended in infancy increased, and efforts were made to combine several antigens in single injections. While such combinations were always studied to be sure that potency was not lost and/or new side effects did not arise, the anti-vaccine groups nevertheless proceeded to raise loud and sometimes contradictory complaints.

Over the past two decades, vaccine controversy has coalesced around a central issue: autism. Like most neurologic illness in childhood, the emergence of autistic signs in seemingly normal infants or toddlers is understandably distressing. Given that the age group in which the first signs of autism were typically recognized was also the time during which many vaccines were given, the worry was raised that vaccines might play a causal role in the development of autism. In particular, strident groups focused on the measles/mumps/rubella (MMR) combination vaccine. Later, the mercury-containing preservative thimerosal that was used in miniscule amounts in some vaccines was subsequently added to their list of things to fear about vaccines, despite the fact that the mercury in thimerosal was in a different form from that associated with neurologic toxicity. Since its use was no longer deemed essential for vaccine stabilization, thimerosal was dropped from all vaccine

formulations except influenza as of 2002, but the imputation of its association with autism persisted in organized protests and public perception.

As a final addition to a harmful brew of autism-related concerns, in 1998 British physician, Andrew Wakefield, reported a study in which he claimed to document a causative role for the MMR vaccine in children who developed autism under his care. He was rapidly embraced by protesters and rode a wave of high visibility as he persevered with his assertions. Even though the journal that had published his initial paper subsequently called his claims into question and eventually retracted the article altogether [15], and even though he was ultimately reprimanded for his false assertions and stripped of his medical license [15], his loyal following remains yet today. The net negative impact on immunization programs, both in the United Kingdom and the United States, was massive. Even though immunization was required for school entry in the United States for example, parents began pleading conscientious (usually religious) objection with increasing frequency, and such vanished diseases as measles have since reappeared in isolated outbreaks and in newspaper headlines across the country—serving as important reminders to the public of what happens when vaccination rates drop. [16]

Spreading the Word

During the time since vaccines were first introduced, the emergence of mass media has certainly provided support for combating unfounded controversies and enhancing efforts at prevention. But mass media has also played an increasingly efficient part in raising public alarm about untoward side effects and the spread of misinformation—both factors that serve to fuel unfounded fears. As a result, public interest, but also public concern surrounding vaccines, is being intensified like never before. Before the 1950s, when newspaper and radio reporting prevailed, coverage of medical advances such as vaccines was necessarily limited. As television coverage of health and medicine came to the fore increasingly in the 1960s, the few reporters then available to deal with scientific issues often struggled to accurately present new and increasingly complex medical information. They were joined only gradually by specifically trained medical journalists. Even then, a carefully crafted presentation of new biomedical information could be readily undercut by the off-handed remarks of local and/or untrained news reporters.

The entry of the Internet into such discussions has made it ostensibly easier to educate the public on these matters. After all, the World Wide Web has made it possible for ideas to spread as virally as viruses themselves. However, while authoritative and clear communication is now technically widely available, the task to inform both the public and health professionals has actually been made more challenging. The elevation and easy accessibility of disinformation can easily confuse and often obscure admittedly complicated evidence-based messages. With the advent of today's ever-expanding options for mass communication, information can "go viral" at alarming speed, even in the absence of scientific clarity.

This has been particularly troublesome since the rise of anti-vaccine movements (see Chaps. 6 and 10).

Finally, the "doctor knows best" paternalism of medical professionals that once served to reinforce preventive messages has become almost counterproductive in the Internet age, where information is ready at hand for a general public no longer in need of medical knowledge dispensed at the sole discretion of the doctor. Indeed, distrust of professionals has sometimes leant credibility to more questionable or opinionated sources; and the lack of a filter for putative knowledge combined with a dearth of public scientific background has in fact helped to render inflammatory anti-vaccine messages easily accessible and truly dangerous.

Looking Forward and Lessons Learned

In case it seems that we are asserting that these issues contribute uniquely to matters of vaccine controversy, it is important to point out that the same confluence of factors has characterized most biomedical advances in the past few decades, including everything from antibiotic usage, cardiovascular medical and surgical interventions to even such remarkable and bold developments as organ transplantation and in vitro fertilization. All have carried the double-edge of success vs. controversy as their initial novelty recedes. One could argue, in fact, that these components of controversy affect most of the advances in the non-biomedical modern world as well.

What makes the vaccine context and controversy so distinctive gets back to the two simple but perplexing challenges we discussed at the outset. First, that vaccination at its core involves doing intrusive things to healthy people—usually children. Second, the clear irony that in achieving vaccine success, the diseases which once served as compelling forces for ongoing preventive action become less and less persuasive over time. And finally, in the face of such inherent challenges, the best way to approach and arm oneself against both legitimate and irrational fears about vaccines is to keep top of mind the many lessons learned while at the same time committing to an even deeper understanding of modern-day fears. Doing so will be crucial for the future success and acceptance of vaccines [17] as we look toward a future that includes newly emerging infections, the challenge of sexually transmitted diseases, and even vaccines against cancer.

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Chapter 2
Vaccine Development and Safety

Avinash K. Shetty and Yvonne A. Maldonado

Introduction

Development of vaccines to prevent infectious diseases has been one of the most significant public health advances in the twentieth century [1]. Since the eradication of naturally occurring smallpox in 1980 [2] and the near eradication of wild-type poliomyelitis globally [3], significant advances have occurred in the development of newer vaccines resulting in a dramatic reduction in many other infectious diseases especially in many resource-rich countries [4]. In the USA the incidence of most childhood VPDs is at historic lows while the number of diseases prevented by vaccines has increased steadily in the past few years [4].

In recent years, there has been a steady increase in vaccine refusal among the US population resulting in several outbreaks of VPDs [5–7]. The problem of vaccine refusal has been attributed to a number of factors including the relative rarity of many VPDs coupled with the public perception that disease severity and susceptibility is very low, and concerns related to vaccine safety [8]. Fear of vaccines has been triggered by incorrect or biased information, not supported by scientific evidence, provided over the Internet, television programs, newspapers, and magazines [9]. Strong opposition to vaccines by celebrities further complicates the issue [9]. In a recent report, the Institute of Medicine (IOM) Committee strongly emphasized the safety of commonly used vaccines [e.g., influenza (except 2009 H1N1), hepatitis B, measles–mumps–rubella (MMR), varicella zoster, hepatitis A, human papillomavirus vaccine, meningococcal vaccine, and vaccines that contained tetanus toxoid] [10].

A.K. Shetty, M.D. (✉)
Department of Pediatrics, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA
e-mail: ashetty@wakehealth.edu

Y.A. Maldonado, M.D.
Division of Pediatric Infectious Diseases, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, USA

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Health care providers play a critical role in communicating vaccine safety to parents and patients by providing a strong, evidence-based recommendation [11].

Development and introduction of new vaccines is a multistep process requiring collaborations between the federal government, academia, and industry, and can take several years from concept to licensure [12–14]. Vaccine development has evolved significantly over the last several decades. In the past, immunogenicity and efficacy of vaccine was the primary focus in vaccine development targeted for infectious diseases with high morbidity and mortality. In the current era, vaccine safety is a major focus for patients and parents, health care providers, federal regulatory agencies and the pharmaceutical industry [14–19]. Safety issues are examined at every stage of vaccine development and monitoring for adverse events continues during the post-licensure period via surveillance through a broad range of organizations, including government-funded and government-conducted programs [14–19]. Public perceptions of the adverse events associated with disease and vaccination, health economics and cost-effectiveness of immunization programs also play an important role in the introduction of new vaccines and are likely to increase in the future [15, 18, 19]. Scientific, social, political and economic factors also influence the development and implementation of new vaccines [20, 21].

In the past decade, the capacity for global vaccine production, distribution and access has significantly improved in low and middle income countries (LMICs) due to increasing investment in research and development, advocacy and policy, and creative financing schemes [22–24]. Nongovernmental agencies such as the Global Alliance on Vaccines and Immunizations (GAVI) have played a vital role in global access to vaccines [25–27]. However, the global vaccination system face unique challenges related to vaccine development including improved surveillance of health outcomes and adverse events, sustained financing for universal access to all vaccines, need to strengthen delivery systems, and the need for operations research to determine the full economic benefits and optimize the vaccine schedule and delivery [22].

In this chapter, we review the stages of vaccine discovery, development, and evaluation in the USA, discuss the vaccine safety system with a focus on regulation and testing of vaccines, draw attention to the current challenges for vaccine development, and discuss novel approaches for new vaccine development and safety.

Development of Vaccines

Discovery, development, evaluation, and successful implementation of a vaccine is complex, multifaceted, expensive and warrants a meaningful public–private collaboration [28–30]. Figure 2.1 depicts the multiple steps that are involved in the development of a new vaccine that benefits public health and safety is addressed at every stage of the vaccine-development pathway [14, 30].

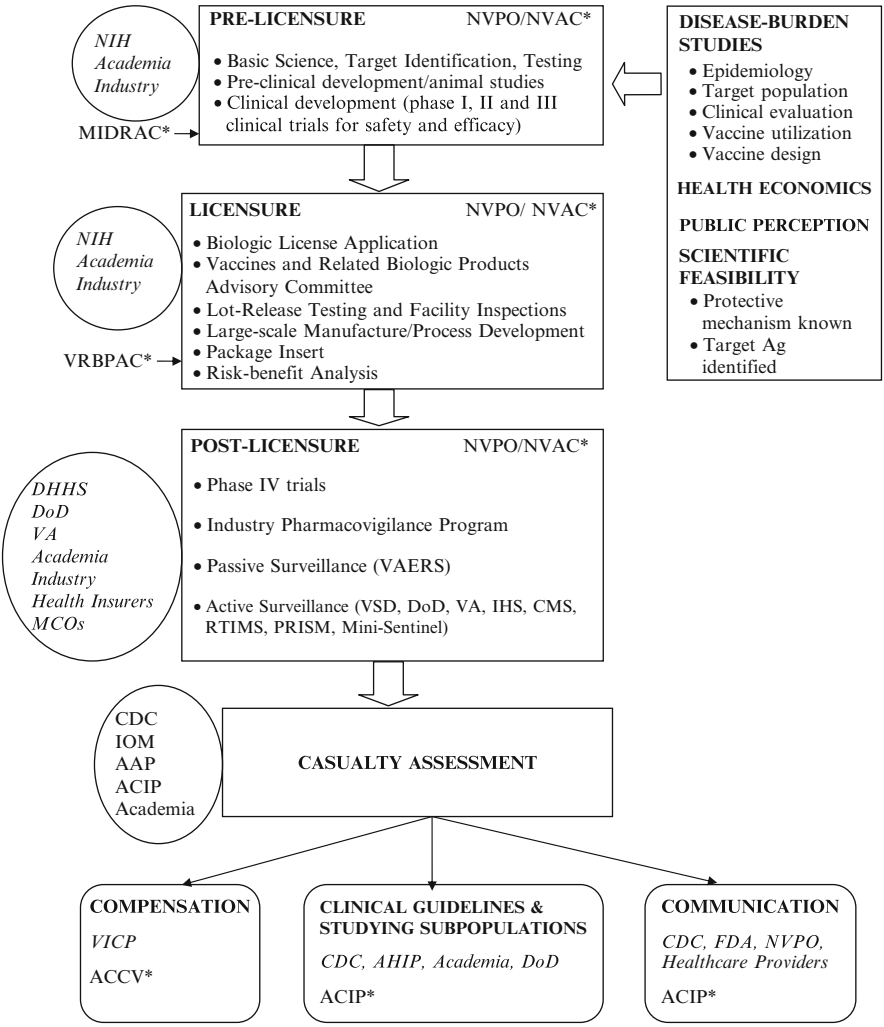

Fig. 2.1 Vaccine development and safety monitoring in the USA. *ACCV* Advisory Committee on Compensation for Vaccine Injury, *ACIP* Advisory Committee on Immunization Practices, *CDC* Centers for Disease Control and Prevention, *AHIP* America's Health Insurance Plans, *CISA* clinical immunization safety assessment network, *DHHS,* Department of Health and Human Services (DHHS), *DoD* Department of Defense, *FDA* Food and Drug Administration, *HRSA* Human Resources Service Administration, *IHS* Indian health service, *IOM* Institute of Medicine, *MCOs* managed care organizations, *MIDRAC* Microbiology and Infectious Diseases Review Advisory Committee, *NVAC* national vaccine advisory committee, *NVPO* national vaccine program office, *PRISM* post-licensure rapid immunization safety monitoring, *RTIMS* real-time immunization monitoring system, *VA* veterans administration, *VAERS* vaccine adverse event reporting system, *VICP* vaccine injury compensation program, *VRBPAC* Vaccines and Related Biological Products Advisory Committee, *VSD* vaccine safety Datalink; *Asterisk*: Advisory Committee

Estimation of Disease Burden

The first step in the complex, multifactorial vaccine development process is assessing the infectious disease burden [20, 31, 32]. Estimation of disease burden is usually accomplished by conducting surveillance studies that quantifies disease burden, provides data on important serogroups or serotypes, monitors overall impact after widespread implementation, and recognizes unusual adverse events after routine use [20]. Disease burden determination, especially longitudinal population-based studies provide crucial epidemiology data (e.g., incidence rates, geographic distribution, age groups, seasonality, and risk factors). Other factors considered in the introduction of new vaccines include the impact on quality of life (QOL), health care resource use, implementation policy and cost-effectiveness, often assessed as cost per quality-adjusted life years (QALYs) gained [33]. In practice, determination of cost-effectiveness is often limited due to lack of sufficient data regarding the efficacy of the vaccine and other related factors, such as induction of herd immunity [21, 34].

Determination of disease burden must also take into consideration the pathophysiology of the disease, pathogenicity of the etiologic agent and the potential for spread of infection in the community [12]. The role of the laboratory to identify the etiology of infectious diseases is vital in vaccine targeting. Health burden determination is the primary responsibility of the federal agencies including the CDC and the National Institutes of Health (NIH) [14]. Globally, special surveillance sites have been established resulting in invaluable epidemiological data in well-defined populations on various bacterial and viral pathogens in LMICs especially in sub-Saharan Africa and Asia.

Basic Science Research

The vaccine development pathway begins with basic science research consisting of studies that evaluate the pathogen biology and pathogenesis, host–pathogen interactions, antigen development and evaluation of the host immune response [12, 14]. Advances in new sciences and technology such as genomics, structural biology, computational studies, and quantitative sciences can provide a more detailed understanding of microbes and characterize their significant and critical elements of survival in the host [35].

Basic research related to the discovery of a new vaccine candidate is sponsored primarily by the NIH and may take place in academic settings, be industry-supported, occur at foundations or governmental research institutions, or through collaborations between these groups [14, 36]. The National Institute of Allergy and Infectious Diseases (NIAID) is the lead agency at the NIH for basic science discoveries and development of safe and effective vaccine candidates against emerging and reemerging infectious diseases. Investigators at NIAID have pioneered the discovery of

many life-saving vaccines to prevent invasive diseases caused by *Haemophilus influenzae* type b, pneumococcus, varicella, pertussis, influenza, and hepatitis A and B. Several networks have been established at NIAID including the Vaccine and Treatment Evaluation Units (VTEUs), HIV Vaccine Trials Network (HVTN) and the Vaccine Research Center (VRC) to support vaccine research studies based primarily at academic medical centers, public health departments and community clinics across the nation [14].

Antigen Selection and the Host Immune Response

After pathogen identification, antigen selection is guided by understanding the host immune response. In addition to the role of innate immunity, the protective role of serum antibody and cell-mediated immune responses need to be elucidated. Every vaccine exhibits unique characteristics depending on the pathogen biology, the nature of the disease and the target population for immunization. In recent years, advances in antigen discovery have resulted in more attention to the vital role played by antigen-presenting cells and immunologic interplay between the innate and adaptive immune systems. Antigen discovery is dependent on several factors such as highly conserved antigens that are crucial for pathogen virulence and inclusion of naturally immunodominant B/T epitopes depending on pathogen biology [37].

The immune correlates and mechanisms of protection induced by vaccine candidates is an important step during the process of vaccine development [38, 39]. Besides antigen discovery, other key considerations relevant for the design and development of a vaccine include the differentiation of relevant T helper (Th) subset populations (Th1 vs. Th2 vs. Th17) that induce protective immunity, need for CD8+ T cells that enhance activity against intracellular pathogens, need for specific memory T-cell subsets required for long-term immune protection, and avoidance of excessive regulatory T (Treg) cells (since Treg inhibits effector T-cell responses but may be needed for inducing long-term memory) [37, 40–45]. Advances in immunology, cellular, and molecular technologies are currently playing a vital role in the development of safe and effective vaccines [37, 46–48].

Old Vaccine Development Approaches

Historically, vaccines (e.g., rabies, smallpox, poliomyelitis, diphtheria, tetanus, pertussis, BCG, influenza) have been developed using empirical approaches through isolation, attenuation, or inactivation of the etiologic agent, and use of crude preparations that were associated with safety issues [21]. Traditional vaccines have comprised live-attenuated microorganisms, killed microorganisms, purified microbial components, polysaccharide-carrier protein conjugates, or recombinant proteins (Table 2.1). Application of recombinant DNA technology

Table 2.1 Vaccine development technologies

Technology	Developed vaccines
Animal pathogen	Smallpox, BCG
Whole inactivated organisms	IPV, hepatitis A, whole cell pertussis
Toxoids	Diphtheria, tetanus
Live attenuated organisms	OPV, MMR, varicella, RV1, YF
Polysaccharide	MPSV4, PPS23
Polysaccharide conjugated to protein	Hib, PCV7, MCV4
Purified protein	Acellular pertussis vaccine
Purified protein vaccines through recombination	Hepatitis B, HPV
Reassortment	RV5, LAIV

BCG Bacillus Calmette-Guérin, *IPV* inactivated polio vaccine, *HPV* human papillomavirus vaccine, *LAIV* live attenuated influenza vaccine, *MCV4* meningococcal conjugate vaccine, *MMR* measles mumps rubella, *MPSV4* meningococcal polysaccharide vaccine, *OPV* oral polio vaccine, *PPS23* pneumococcal polysaccharide 23-valent, *RV1* monovalent rotavirus vaccine, *RV5* pentavalent rotavirus vaccine, *YF* yellow fever

resulted in the development of hepatitis B vaccine (1982) and covalent binding (glycoconjugation) of polysaccharides to protein carriers resulted in the development of effective vaccines against diseases caused by *H. influenzae* type b (1997), *Streptococcus pneumoniae* (2000) and *Neisseria meningitidis* (2001) [49–52]. Compared to the unconjugated polysaccharide vaccines, polysaccharide-conjugate vaccines offer significant beneficial effects such as providing immune protection in children younger than 2 years of age, ability to induce immune memory, longer duration of immunity, and herd protection especially noted after the introduction of *H. influenzae* type b vaccines into routine practice [51]. Likewise, herd immunity has been reported for pneumococcal conjugate vaccine and meningococcal C conjugate vaccine resulting in significant public health benefits [52–54].

New Technologies for Vaccine Development (Table 2.2)

Genetic Engineering

In the present era, vaccinology is moving towards the development of subunit (purified protein or polysaccharide), genetically engineered and vectored antigens [55]. Developed through a genetic engineering approach, two recently licensed, recombinant vaccines against human papillomavirus (HPV) are currently approved for clinical use in the USA to prevent cervical cancer [56]. HPV virus-like particles (VLPs) are prepared from recombinant HPV L1 major capsid protein and expressed in yeast or in cultured insect cells. The expressed HPV L1 proteins self-assemble during the purification process into icosahedral structures that are identical to the naturally occurring virus particle but without viral DNA, RNA, or proteins that can propagate infection and disease [56].

Table 2.2 New approaches to advance vaccine Development

Approach	Comments	Current vaccine targets
Adjuvants	*Innate immune activation*	
MF-59	Oil-in-water emulsion	Influenza/pandemic influenza
AS03	Oil-in-water emulsion	Influenza/pandemic influenza
AS02	Oil-in-water emulsion	Malaria vaccine containing MPL and Q-21
ASO4	TLR4 agonist, combination of aluminum salts and MPL	HPV, HSV
CPG oligonucleotides	TLR9 agonist	HBV, malaria, cancer
Vectors		
Viral vectors	rMVA	HIV, TB, HPV, Cancer
	Canarypox virus	HIV
	Adenovirus	HIV, HCV, Malaria, TB
	Yellow fever virus	Dengue
Bacterial vector	*Salmonella typhi*	Typhoid, HBV, HIV, ETEC
	Vibrio cholerae	Cholera
	Listeria monocytogenes	HPV
Dendritic cell vaccines	Antigen-loaded monocytes, therapeutic vaccine development	Therapeutic prostate cancer vaccine
DNA vaccines	Potential application in therapeutic vaccines	Melanoma, AML, Alzheimer's disease, HIV, HBV, HCV
RNA vaccines	Use mRNA for antigen expression, mRNA vaccines encoding TAA	Cancer immunotherapy
Reverse genomics	Epitope-based vaccines	Meningococcal serogroup B, group A *Streptococcus*, group, B *Streptococcus*, *S. aureus, Clostridium difficile*
Systems biology	Use high-throughput technologies (e.g., microarrays) and computational modeling to identify specific molecular signatures of individual vaccines	Predict vaccine efficacy and safety

AML acute myelocytic leukemia, *ETEC*, enterotoxigenic *Escherichia coli, HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *HPV* human papilloma virus, *MPL* monophosphoryl lipid A, *MVA* modified vaccinia virus Ankara, *TAA* tumor-associated antigens, *TB* tuberculosis, *TLR* toll-like receptor

Novel Adjuvants

Modern elements of vaccine development are diverse including advances in antigen design, novel modes of antigen delivery and use of new adjuvants (e.g., lipids and immune enhancers targeting the innate immune system) in order to enhance the adaptive immunity with minimal toxicity [55, 57]. Historically, alum (aluminum

salt-based adjuvant) was the most frequently used adjuvant in vaccines to boost the immune response but the response has been suboptimal for many diseases [58]. In recent years, newly licensed adjuvants (such as MF59, a squalene-based oil-in-water emulsion and AS04, a combination adjuvant composed of monophosphoryl lipid A [toll-like receptor (TLR) 4 agonist] adsorbed to alum) with unique immunological characteristics have been introduced in modern vaccines in order to induce a stronger and broader immune response and local proinflammatory effects with minimal safety concerns [59–62].

The impact of new adjuvant technology on vaccine efficacy has already been demonstrated in influenza vaccines [63]. Other novel adjuvants in development include TLR agonists (e.g., TLR9 agonist for the hepatitis B virus (HBV) vaccine target) and oil-in-water emulsions (e.g., AS03 for the influenza vaccine target) that enhance T cells [21, 57]. Given the current trend in the development of purified protein and peptide antigens, the role of innovative adjuvants is very important to stimulate innate immunity that in turn augments B and T cell expansion and adaptive immunity. Development of safe and effective mucosal adjuvants is a high priority given the potential to induce effective immune responses at the mucosal portals of pathogen entry and needle-free mode of delivery of the candidate vaccine to mucosal inductive sites [64]. Development of mucosal vaccines against poverty-related diseases is a significant advance in global health [65].

Reverse Vaccinology

In recent years, vaccine development has evolved from microbiological to sequence-based approaches [66]. Considerable progress has been made in the improvement of vaccine efficacy by use of reverse vaccinology, a genome-mining approach with the use of computer-based algorithms to define more effective vaccine antigens that cannot be identified with classic techniques [67, 68]. Reverse vaccinology technology is currently being applied to develop new vaccines for several pathogens such as Meningococcus serogroup B, group A Streptococcus, group B Streptococcus, *Staphylococcus aureus*, *Escherichia coli*, *Clostridium difficile* [21, 67–69].

The application of pharmacogenomics and pharmacogenetics to vaccine design, recently labeled “vaccinomics” is an emerging area of vaccine research [70]. In conjunction with bioinformatics, innovative approaches are being explored for developing novel peptide-based vaccines against hypervariable viruses such as the human immunodeficiency virus (HIV), hepatitis C and emerging avian and swine influenza [70]. One example of reverse vaccinology is the development of epitope-based vaccines which use T-cell epitope mapping and prediction algorithms to identify potential peptide epitopes as vaccine immunogens. Given the extreme polymorphism of the MHC molecules which represents a major hurdle to vaccine development, poly-epitope technology can be applied to generate a synthetic protein carrying antigenic epitopes from multiple strains or pathogens [56]. Other next generation technologies include the use of structural vaccinology, viral vectors, DNA vaccines, RNA vaccines, and systems biology [21, 71–75].

Structural Vaccinology

Structural vaccinology is a promising strategy for the rational design of specific target epitopes for use as vaccine candidates [21, 69, 76]. This approach enables atomic resolution of antigen structure and is based on the evidence that epitopes inducing protective immune responses are restricted to specific domains within an immunogenic protein [21, 76]. After identification, the domains can be expressed in a recombinant form and used as potent immunogens. Structural vaccinology studies have led to a better understanding of the various mechanisms by which paramyxoviruses use their attachment glycoproteins to hijack specific protein and glycan cell-surface receptors to facilitate viral entry [77]. This approach could result in the development of new vaccines for measles [21].

Vectors, DNA Vaccines, RNA Vaccines and Dendritic Vaccines

Candidate viral vector vaccines are being developed using a non-replicating virus such as poxvirus and adenovirus (which can serve as DNA delivery systems) to deliver pathogen-specific antigens that elicit robust and durable B- and T-cell responses that mimic natural pathogen invasion strategies [71]. Viral vector vaccines can be easily engineered, may be applied to the mucosal surface facilitating oral delivery, and offer promise for the development of preventive and therapeutic vaccines. Examples include therapeutic cancer vaccines such as fowl-pox-virus vaccine that encodes a prostate-specific antigen [78]. Viral vectors are also being studied in the development of malaria vaccine [79]. Live vector approach can also utilize live attenuated bacteria as carriers of macromolecules [80, 81].

DNA-based vaccines stimulate synthesis of antigens only in cells and elicit predominantly cell-mediated immunity [71, 73]. However, studies have been disappointing given the challenges of establishing proof-of-principle and immunologic potency [71, 82]. Application of heterologous prime-boost approaches that combine DNA-based and viral-based vaccines with recombinant protein vaccines to induce both T-cell responses and antibody responses has shown promise in a recently concluded HIV vaccine efficacy trial (RV144) [83]. Studies are ongoing to evaluate combining other vaccine platforms with DNA, enhanced methods of delivery, and inclusion of molecular adjuvants. Clinical trials of second generation DNA vaccines are currently underway for noninfectious disorders such as Alzheimer's disease, cancer, and infectious diseases caused by viral pathogens such as HIV, Ebola virus, and West Nile virus [84–89]. RNA vaccines directly utilize messenger RNA for antigen expression; mRNA vaccines encoding tumor-associated antigens (TAAs) have shown promise, especially in the field of oncology [90]. mRNA transfected dendritic cells (DCs) are potent antigen-presenting cells to T cells and can generate a specific immune response [90]. DC vaccines offer an individualized approach to therapeutic vaccine development by using monocytes harvested from the vaccine recipient's own blood; the autologous DCs can generate potent T-cell immune responses [55]. Although expensive, DC vaccines offer promise for the treatment of cancer, HIV and other chronic infections [55].

Systems Biology

Systems biology offers a new, robust, integrated approach to vaccine design by improving our understanding of the complex immune system and investigates how changes in the expression of specific genes correlate with protective immune response [74, 77]. Immunological networks or biomarkers can identify molecular signatures associated with optimal immune response [37, 46–48]. Systems biology approaches use high-throughput technologies (e.g., microarrays, RNA-seq, mass spectrometry-based proteomics and metabolomics) and computational modeling to identify specific molecular signatures of individual vaccines that predict vaccine efficacy and safety [78].

Other New Approaches

Potential new strategies for development of attenuated vaccines include reverse genetics, temperature-sensitive mutations and reassortment, control of replication fidelity, microRNA insertion, and gene delivery by invasive bacteria [55, 91]. Other key areas of antigen discovery include screening of pathogen peptide libraries, high-throughput screening of peptides using T-cell stimulation to identify T-cell antigens and methods to increase antigen purity, cross-protection and thermostability [55].

Other new vaccine pursuits include expansion of the immunization targets to other special populations (e.g., pregnant women, healthy adults, elderly individuals) besides infants and children, and exploratory vaccines against non-communicable diseases such as autoimmune disorders, chronic diseases of ageing and cancer [21].

Advances in Preclinical Vaccine Safety Evaluation

Advances in the analysis of host innate and adaptive immune responses may help create safer vaccines by the ability to study whole genome-wide expression patterns in cells, isolation of individual, antigen-specific B and T cells using special reagents, use of bioinformatics tools and systems biology [14, 37, 48]. These immunological memory networks provide support to better understand the host immune response to vaccines by detailed human immune phenotyping, and contribute to creation of effective vaccines and identification of correlates of protection [14, 38, 39, 48].

Other approaches include the evaluation of cross-reactive antibodies or T cells after vaccination in relevant animal models. Preclinical animal models can help detect early immune gene activation profiles after the use of vaccine adjuvants using microarray technologies and through analysis of cellular phenotypes at vaccine injection sites and draining lymph nodes [61, 62, 92]. The immune systems of mice

and humans differ in many key aspects such as TLR expression on DC subsets, leading to delay in rapid vaccine development [93]. In 2010, the NIAID founded a consortium consisting of several institutions across the USA with the goal of characterizing the diverse human immune system in its steady state and in response to immunizations and infections, or adjuvants that target a known innate immune system receptor by using high-throughput approaches [14, 94]. Using a systems biology approach, the technology of human immune phenotyping has been successfully applied to the development of yellow fever vaccine [95].

Studies related to genetic variability in host immune responses to microbes and vaccines is currently an important area of vaccine safety research [14]. Other new approaches for preclinical safety assessments include the utilization of bioinformatics technology to map promising pathogen vaccine targets and relevant epitopes and compare them with human proteins to avoid homologies and potential risk of autoimmunity [21]. Such approaches may be useful in evaluating polysaccharide antigens that are known to mimic human cell-surface proteins (e.g., neural adhesion molecules) [49].

Preclinical (Animal) Studies

Before testing investigational vaccines in clinical trials, the lead candidate vaccine is identified through relevant in vitro studies and in vivo animal models to evaluate its safety, immunogenicity, pharmacokinetics, and efficacy [12, 14]. Animal studies help in evaluating dosing and schedules and assure no major adverse effects occur. Candidate vaccines are subjected to three types of toxicity studies including acute toxicity, in vivo pyrogenicity, and tolerability studies, typically in rabbits and/or guinea pigs [16]. Toxicity studies must be performed in accordance with good laboratory practices (GLPs). Before human use, safety studies are completed in rats and primates in certain cases. These tests include studies of organ histology to screen for potential safety concerns. If the candidate vaccine has unacceptable reactogenicity in animal models or exhibits lack of immunogenicity, further development is not pursued. Other specific preclinical studies include reproductive toxicology evaluation in pregnant animals and in vivo testing of recombinant vaccines [16].

The Center for Biologics Evaluation and Research (CBER) of the FDA provides regulatory guidance to sponsors throughout the multifactorial vaccine development process. During the preclinical evaluation, dialogue between the sponsors and the FDA is useful in clarifying the study design, the nature and extent of preclinical studies needed and the requirements for preclinical toxicity data depending on the risk–benefit of the vaccine candidate, the target population, available clinical studies from the use of related products, product characteristics, and the availability of animal models. The FDA has published guidance for industry on the assessment of reproductive toxicity studies of preventive vaccines for infectious diseases that are indicated for women of childbearing age and pregnant females [96].

Clinical Development and Pre-licensure Testing in Humans

The clinical development of a new vaccine candidate begins with the submission of an investigational new drug (IND) application to the FDA by the sponsor. The IND submission must detail the proper identity of the vaccine, manufacture, strength or potency, quality and purity of the vaccine, control testing for release of the vaccine, scientific rationale, available preclinical animal safety data, and a clinical study protocol. The quality and safety of phase 1 material are controlled by establishing appropriate quality assurance (QA) and quality control (QC) procedures and follow current good manufacturing practices (cGMPs) and GLPs. This clinical testing must minimally demonstrate acceptable safety and suitable protection in the population that will ultimately be targeted for the vaccine in public health practice. Good Clinical Practice (GCP) guidelines govern conduct of clinical trials. After receipt of the IND application, the FDA has 30 days to determine if the clinical trial may begin or be placed on clinical hold [17]. Clinical hold is reserved for safety concerns with the vaccine candidate, unqualified investigators, inadequate information to evaluate risk, deficiency in the investigator's brochure or study design [17].

Some trials are conducted by the Division of Microbiology and Infectious Diseases of the NIH through VTEUs located primarily at major academic centers. Other clinical studies are conducted by pharmaceutical companies (or clinical research organizations contracted by pharmaceutical companies) at academic medical centers or private offices led by local principal investigators [97]. All studies need approval by Institutional Review Boards or Human Studies Committees and must follow strict federal guidelines related to human subject protection and potential conflicts of interest.

Clinical testing in humans begins after approval of the preclinical data package by the US FDA. Pre-licensure clinical (human) studies are divided into three phases and represent a crucial, very expensive and time-consuming component of vaccine development [98]. The FDA monitors the clinical trials program with close scrutiny [17]. Phase I trials are often conducted during the stage of vaccine discovery and provide preliminary safety and immunogenicity data in small numbers of subjects ranging from 20 to 80 vaccinees [99]. In the beginning, the study population often consists of adults and then special target populations are studied such as young children. If the vaccine candidate demonstrates promising data in preclinical and phase I studies, vaccine development proceeds further and continues until such a candidate vaccine gets licensure for routine use by the appropriate regulatory agency [100].

Phase II trials evaluate the safety, immunogenicity proof-of-concept (and in some instances, efficacy) and dose-range of a vaccine candidate in larger groups, often involving several hundred vaccinees. Phase II (dose-ranging) studies are divided into two types. Phase IIa studies and larger Phase IIb studies. Phase IIa studies are undertaken once the preliminary safety and immunogenicity are shown in phase I trials. During this phase, the vaccine product is defined, the manufacturing process well determined, and the most appropriate immunologic assays for clinical

specimens are agreed upon. Larger Phase IIb trials can provide more information on dose selection and intervals, and inform the design of phase III studies [31].

At the completion of the phase II studies, sponsors are encouraged to meet with the CBER of the FDA to review the study design of the proposed phase III trial. Before phase III studies can begin, technology transfer must occur from a research facility making small lots of vaccine doses to the final vaccine manufacturing site making several large consistency lots (each containing 10,000–20,000 doses or more) in a facility in compliance with strict cGMPs [31]. The cGMP comprises guidelines ranging from raw materials QA to record keeping, cleanliness standards, personnel qualifications, in-house testing, process validation, warehousing, and distribution [97]. In addition, information related to storage and handling must be provided.

Phase III pivotal studies are large, randomized, double-blind, placebo-controlled trials, which may recruit thousands to tens of thousands of subjects depending on the study design and the incidence of the disease to be prevented. Phase III trials evaluate the efficacy of a vaccine candidate by measuring the decrease in the incidence of clinical disease among vaccine recipients compared to placebo recipients. Phase III trials may also include substudies evaluating immunogenicity of potential vaccine candidates such as serum antibody titers that correlates with disease protection. Given the large number of study participants, phase III trials also allow a rigorous investigation of vaccine safety for common adverse events, by comparing vaccine and placebo recipients. In recent years, pre-licensure phase III vaccine trials have recruited a large number of subjects to ensure vaccine safety; the two recently licensed rotavirus vaccines manufactured by different pharmaceutical companies had a sample size of over 70,000 children each to demonstrate that the vaccines were safe and did not cause bowel intussusception [101, 102]. Participants are often closely followed for adverse events following vaccination for up to 42 days. During the course of phase III trials, independent Safety Monitoring Committees (SMCs) and Data Safety-Monitoring Boards (DSMBs) are established to monitor and review vaccine safety data. Based on the review of the safety data, the SMC or DSMB may recommend that clinical trials be continued, modified, or stopped [14].

Vaccine Licensure

The vaccine licensing stage is initiated once the IND stage (clinical development) is completed. The vaccine-licensing process in the USA is regulated by the CBER to ensure safety, purity, and potency of licensed vaccines as defined in Title 21 Code of Federal Regulation (CFR) 600 [17, 103, 104]. The FDA periodically publishes guidance documents to clarify sections of the CFR and provide recommendations to improve vaccine candidate development. The guidance documents pertain to manufacturing methods, product testing, compliance with cGMP requirements, clinical studies, and toxicity assessments of vaccines [17, 105–109]. Other federal Acts and regulations related to vaccine development include the Public Health Service Act;

Food, Drug, and Cosmetic Act; Prescription Drug User Fee Act (PDUFA) of 1992, 2002, and 2007; Food and Drug Agency Modernization Act (FDAMA) of 1997; and the Food and Drug Agency Amendments Act (FDAAA) [105–109]. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a collaborative organization of regulators from the USA, Europe, and Japan. The ICH is charged with providing recommendations related to harmonization and application of global regulatory requirements and has published several documents pertinent to vaccine development [110]. For global vaccine approval, the World Health Organization (WHO) publishes documents and formulates guidelines for vaccine products used internationally [111].

Biologic License Application

After completion of phase I, II, and III pivotal clinical trials, the vaccine manufacturer submits the Biologic License Application (BLA) to the Director of the CBER Office of Vaccines Research and Review of the FDA [17]. The BLA is a request for permission to introduce or deliver a biologic product into interstate commerce and includes a dossier from the sponsor that contains all the clinical, safety and technical details that demonstrate that a vaccine meets accepted standards for safety, purity, and potency. In the BLA, the sponsor must provide details regarding manufacturing methods, compliance with cGMP requirements, data depicting product stability, samples representative of the product for introduction to interstate commerce, details pertaining to equipment and facility, and the process for large-scale manufacturing [17]. In addition, the FDA requires documentation of raw materials used in the creation of the master and working seeds, details of cell substrates used in vaccine production, description of the production of the seeds and cell banks, testing and characterization of viral vaccine seeds and cell substrates to ensure safety and purity of the product without any extraneous infectious pathogens such as bacteria, mycobacteria, fungi, or viruses [17].

The typical review of the BLA by a multidisciplinary CBER review team is completed in 10 months, although there is a fast-track mechanism for approval of products intended to treat serious illnesses that fill an unmet medical need [17]. Priority reviews are completed in ~6 months and may be undertaken if the product has the potential for prevention or treatment of a serious or life-threatening illness when no adequate therapy exists. At the end of the formal review period, the FDA issues an action letter granting approval if all of the information contained in the BLA is satisfactory; if approval is not granted, the sponsor must respond to CBER formally and the application undergoes subsequent reviews every 4–6 months until all issues related to vaccine manufacturing, testing, stability, safety and efficacy are addressed.

In addition to the BLA submission, other regulatory review activities are involved in vaccine licensure to ensure vaccine product safety and quality. After approval, samples of each lot of vaccine must be submitted to the FDA and tested for safety, potency and purity before it can be released for use. The review process includes

a detailed inspection of the manufacturing facilities and processes, and the sponsor's compliance with cGMPs. In addition, bioresearch monitoring entails inspection of the clinical research sites for compliance with GCPs in conjunction with a review of the proposed vaccine product label [17].

Vaccines and Related Biologic Products Advisory Committee

Prior to approving most BLAs, the CBER of the FDA may recommend that the sponsor present their product data to the Vaccines and Related Biologic Products Advisory Committee (VRBPAC), especially if there is a concern regarding safety or efficacy [17, 97]. VRBPAC consists of 12 core voting members appointed by the FDA commissioner and comprises of clinicians and experts in vaccine science, consumer representatives, and a nonvoting representative from the pharmaceutical company. The committee reviews the data related to safety and efficacy of the vaccine product in the target population and makes recommendations to the FDA commissioner regarding vaccine licensure, indications and if any additional studies need to be performed before licensure. In general, the FDA commissioner follows the VRBPAC recommendations and licensure is often granted within a few months of the application. The FDA also approves a product label/package insert.

Product Label/Package Insert (PI)

Vaccine manufacturing companies provide product-specific information with each licensed vaccine. The product label/package insert must be compliant with the FDA regulations detailing indications and usage, dosages, routes of administration, clinical pharmacology, contraindications, and adverse events. The PI lists the vaccine contents including preservatives, stabilizers, antimicrobial agents, adjuvants, and suspending fluids. The PI is available in the Physicians' Desk Reference published annually and on the FDA Web site. New information related to licensed vaccines and change in labeling is often posted on the Manufacturers' Web sites. Physicians should be familiar with product labels of the vaccines they administer in clinical practice.

Lot-Release Testing and Facility Inspections

After vaccine licensure, vaccine production activities are continually monitored through lot-release testing, facility inspections, and postmarketing surveillance programs [17]. Lot-release tests include screening for bacterial and fungal contaminants, general safety, purity, identity, potency, and sterility of constituent materials (e.g., diluents and preservatives). In general, vaccine manufacturing facilities are inspected every 2 years; facilities that manufacture influenza vaccines are inspected annually. Licenses may be suspended or revoked if the inspections reveal failure to meet product standards or noncompliance with regulations or cGMP requirements [17].

Development of Immunization Policy

Once the vaccine is licensed in the USA by the FDA, the Advisory Committee on Immunization Practices (ACIP) of the CDC develops the US immunization policy [112]. The primary responsibility of the ACIP is to review the scientific evidence surrounding new vaccines and offer evidence-based recommendations for use of licensed vaccines in infants, children, adolescents, and adults. The ACIP recommendations are often embraced by other professional organizations such as the American Academy of Pediatrics with the goal of harmonization of the vaccine schedules [113, 114]. The Social Security Act (section 1928) established the Vaccines for Children Program in 1994, which enable uninsured children and children from poor socioeconomic strata to receive free vaccines as part of routine primary care [113].

Vaccine Safety

No vaccine is universally safe and some adverse events are expected, although serious adverse events are unusual [115]. As the number of cases of VPDs is at an all-time low [4], vaccine safety concerns have emerged on the forefront [116, 117]. Regulatory issues are critical in the development of new vaccines with a special focus on safety issues since vaccines are often administered to healthy individuals, primarily infants and children. In the USA, vaccine safety is a shared responsibility involving several federal agencies such as the US FDA, the CDC, and other federal agencies working in close partnerships with vaccine resources in the public and private sectors [17, 31, 118–124].

Historical Perspective and Important Milestones

True safety issues surrounding the use of vaccines have been recognized and emphasize the importance of the vaccine safety net in early detection and quick remedial action [116, 117, 125]. In 1955, 260 cases of polio were attributed to one manufacturer's inadequately inactivated polio vaccine formulations ("Cutter incident") [126]. Serious adverse events were associated with the use of the killed measles vaccine in the 1960s [127]. In the late 1960s, studies of major adverse events following smallpox vaccination led to end of routine smallpox vaccine use in the USA in 1972 [128]. In 1976–1977, the swine influenza vaccine was associated with an increased risk of Guillain–Barré Syndrome (GBS), especially within 6 weeks after vaccination [129]. In the 1990s, the current US vaccine safety infrastructure (Vaccine Adverse Event Reporting System [VAERS], Vaccine Safety Datalink [VSD]) was formally established. In 1999, the unexpected occurrence of intussusception following routine use of a rhesus-human reassortant rotavirus vaccine tetravalent was detected by VAERS leading to withdrawal of this vaccine from the market [130].

Post-licensure Federal Vaccine Safety Enterprise

Although vaccine safety is rigorously examined during clinical development, inadequate sample size may not detect unusual adverse events, long-term adverse events are not evaluated, and the study populations are not heterogenous [121]. The current US vaccine safety monitoring system consists of several systems that vary primarily by data collection method (active or passive), access to patient medical records, and the underlying population size and characteristics [31].

The FDA/CBER monitor postmarketing vaccine adverse event surveillance using a three-component toolbox approach including signal detection (hypothesis generation), signal strengthening and verification, and signal confirmation (hypothesis testing) [17]. General approaches for safety monitoring of new vaccines including review of pre-licensure safety data, identified or uncertain risks from phase III trials, post-licensure studies, passive surveillance via a VAERS monitoring plan, active surveillance via Rapid Cycle Analysis through the VSD plan, availability of standardized case definitions for vaccine adverse events, identification of candidate Clinical Immunization Safety Assessment (CISA) Network protocols and identification of the need to conduct special studies [120–124].

Phase IV Post-licensure Studies

Population-based post-licensure studies of new vaccines are important to measure the impact and safety under real-life conditions; rare adverse events temporally associated with vaccination may be detected during phase IV post-licensure studies that were not previously detected during prelicensure clinical trials [131]. In addition, postmarketing surveillance may detect an increase in known adverse events associated with a particular vaccine. These studies may inform modifications in formulations, immunization schedules, and require sponsors to make safety labeling changes [17].

Industry Pharmacovigilance Program

After vaccine licensure, many pharmaceutical companies continue to monitor the safety profile of vaccines by conducing large-scale clinical trials, enhanced passive reporting, and active surveillance systems, which evaluate specific adverse events and general safety.

The FDA has the authority to require postmarketing studies from the sponsor to monitor vaccine safety issues [17]. Pharmacovigilance plans submitted by the sponsor as part of the BLA is carefully reviewed by the CBER using a diverse group of individuals with expertise in epidemiology, clinical protocols, compliance and vaccine safety issues. Requirements for vaccine pharmacovigilance studies include an understanding of background/baseline data of rare events, ongoing risk–benefit assessment, and the collection and reporting of adverse events to the FDA in a timely fashion [12]. Industry-sponsored post-licensure pharmacovigilance programs complement those of the CDC and the FDA such as the VAERS and the VSD [16].

Signal-Detection Methods Using Passive Surveillance Tools: VAERS

Established in 1990 in response to the National Childhood Vaccine Injury Act of 1986, VAERS is a voluntary, nationwide, passive, ongoing surveillance system to detect rare, serious, and previously unrecognized adverse events after licensure of vaccines [132–134]. The CDC and FDA co-manage VAERs and review daily reports and alerts of all serious adverse events (SAEs) from health care providers, vaccine companies, and consumers. VAERS is a signal detection (hypothesis-generating) program and allows near real-time, nationwide, lot-specific surveillance and can detect rare or unexpected events using statistical data-mining techniques [134]. VAERS has detected signals including syncope, febrile seizures, GBS, and intussusception following vaccination [135–138]. However, VAERS has many limitations including reporting bias, underreporting, variable data quality, lack of true denominator data and unvaccinated control group, all of which make VAERS data not suitable for causality assessments except in very limited instances [132]. In 2002, Internet-based reports (IBRs) were added to VAERS to allow timely and complete vaccine adverse event reporting [120]. Information about VAERS is available via a 24-h telephone contact (800-822-7967) or accessing the Web site (http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/VaccineAdverseEvents/default.htm).

Signal-Strengthening, Verification and Assessment of Associations Using Active Surveillance Tools: VSD

Developed by the CDC in collaboration with large linked databases of eight managed care organizations (MCOs), VSD is a real-time population-based active surveillance system for vaccine safety [121]. Established in 1990, VSD remains the most established and high quality federal vaccine active surveillance system in the USA [122].

Over the last two decades, the VSD has enrolled 9.2 million individuals (3 % of the US population), including all age groups, and an annual birth cohort of ~95,000 [121].

The eight collaborating MCOs in the VSD are Group Health Cooperative (Washington State), Harvard Vanguard Medical Associated and Harvard Pilgrim Health Care (Massachusetts), HealthPartners (Minnesota), Kaiser Permanente of Colorado, Kaiser Permanente of Northern California, Kaiser Permanente of Southern California, Marshfield Clinic (Wisconsin), and Northwest Kaiser Permanente (Oregon and Washington). Demographic and vaccination data linked to outpatient and inpatient diagnosis are updated each week.

Through a secure distributed data model followed by creation of data-dynamic files, VSD can conduct near real-time post-licensure surveillance. Using rapid cycle (real-time) analyses (RCA), the VSD can evaluate pre-specified outcomes and associations. The VSD can be used to implement epidemiologic studies to determine if the incidence rate of a given adverse event is higher among vaccine recipients compared to non-vaccinees [31]. Besides research on vaccine safety and

disease incidence, the VSD can conduct other studies related to vaccine coverage, methodology, cost-effectiveness, and medical informatics [139–156].

There are several advantages of VSD for vaccine safety research including rapid access to large and well-defined populations of large MCOs, with computerized linked full electronic medical records to evaluate outcomes. However, VSD does not capture all immunizations received outside the MCOs, and for rare adverse events, the VSD's population size may limit the speed at which safety problems may be detected [157, 158]. In addition, quality assessment studies have noted that there is variability in the accuracy of the computerized medical records to determine outcomes [159]. Therefore, other methods such as medical chart review are undertaken to validate data [121].

Postmarketing surveillance by VSD in collaboration with VAERS have examined possible associations of adverse events with newly licensed vaccines by comparing the number of VAERS reports versus the background rates for these events from the VSD. Postmarketing monitoring of intussusception after RotaTeq® vaccination and GBS after Menactra® vaccination are examples of this collaborative effort [136, 160]. In recent years, VSD has invited outside experts to offer their opinion related to design and implementation of high-priority vaccine safety studies and also allowed external researchers to conduct analysis of existing VSD data sets or create novel analytic data analysis through data-sharing and oversight [161].

In recent years, the FDA has collaborated with other federal agencies including the Centers for Medicaid and Medicare Services (CMS), Indian Health Service, Department of Veteran Affairs (VA), and the Department of Defense (DoD) in developing vaccine safety surveillance in defined populations [162, 163]. The DoD uses the Defense Medical Surveillance System (DMSS) to conduct medical surveillance for the US armed forces comprising ~1 million personnel. The DMSS captures the DoD's mandatory vaccination program and clinical data from the electronic health records to investigate outcomes after vaccination. The Department of Defense Serum Repository (DoDSR) serves as a central repository of sera drawn from service personnel for medical surveillance purposes. The DMSS and DoDSR provide population-based surveillance of the US armed forces and play an important role in the vaccine-safety monitoring process unique to military personnel [164–166]. Since 2008, the FDA has collaborated with the VA to assess the safety of vaccines including the 2009 H1N1 monovalent influenza vaccine [167]. In 2006, the FDA and the CMS began a prospective pilot project to evaluate unusual vaccine adverse events in the Medicare population (comprising ~45 million individuals aged ≥65 years and younger individuals with disabilities or end-stage renal disease) [167]. This collaboration has near real-time surveillance capability, like that used in the VSD and recently applied to monitor H1N1 vaccine safety.

Clinical Immunization Safety Assessment Network

Launched in 2001, the CISA Network is an active collaboration between the CDC Immunization Safety Office (ISO) and six academic centers, each with experts in

vaccine safety to investigate the biologic mechanisms and risks of adverse events following immunization (AEFI) and to provide evidence-based vaccine safety assessments [123]. The goals of the CISA network are to study the pathophysiology of AEFIs by using hypothesis-driven protocols, to identify host genetic and other risk factors associated with developing an AEFI, to develop immunization algorithms and clinical protocols for vaccinating individuals at high risk of AEFI and serve as an expert resource to clinicians and policy makers for vaccine-safety issues [123].

Given the unique expertise in clinical, pathophysiologic and epidemiologic aspects, the CISA network reviews cases of AEFI (though the Clinical Consult Case Review (CCCR) working group), provides clinical guidance to health care providers for treatment of patients with AEFI, conducts special studies to evaluate the pathogenesis of adverse events, investigates causal relationships between vaccines and adverse events, and maintains a central archive for biological specimens and adverse event clinical registry [123, 168]. Examples of important studies conducted under the leadership of the CISA network include the following: active telephone surveillance to evaluate adverse events among civilian smallpox vaccine recipients, adverse events following receipt of trivalent inactivated influenza vaccine in children aged 6–23 months of age, association of transverse myelitis and vaccination, and the role of genetics in the immune response to varicella vaccine [169–172]. Besides educational and outreach programs, a Vaccine Safety fellowship program has been established by the CISA Network to train future generations of vaccine safety experts [123].

Brighton Collaboration

Established in 2000, the Brighton Collaboration is a global collaboration of professionals and organizations focused on immunization safety standards [173]. The collaboration includes a diverse representation of health professionals and volunteers in the fields of patient care, public health, industry, academia, and regulatory agencies with the oversight of an elected steering committee, and with staff at the CDC and the University Children's Hospital, Basel, Switzerland [173, 174]. The aims of the Brighton Collaboration include development of the standardized case definitions for AEFI, formulation of guidelines for collection, analysis and presentation of safety data, implementation and evaluation of these newly developed standardized case definitions and guidelines [175]. The AEFI case definitions are intended for use in the setting of clinical trials and surveillance programs to facilitate comparability of data and interpretation. In collaboration with CISA Network investigators, the Brighton Collaboration has developed case definitions for encephalopathy, injection-site nodules, generalized convulsive seizures, and smallpox vaccine-related adverse events [175–184]. Several regulatory and professional organizations such as the FDA, the American Academy of Pediatrics (AAP), the European Medicines Agency, and the WHO have endorsed or recommended the case definitions of the Brighton Collaboration [175].

Vaccine Injury Compensation Program

Established in 1986, the Vaccine Injury Compensation Program (VICP) is a federal no-fault alternative system for individuals claiming vaccine injuries [185]. The VICP is composed of three federal organizations including the US Department of Health and Human Services (DHHS), the US Department of Justice, and the US Court of Federal Claims (CFC). The public health goal of the VICP is to ensure adequate vaccine supply, stabilize vaccine costs, and to provide compensation to clients who can show that a serious injury occurred with the use of a CDC-recommended vaccine. The legislation mandates reporting of adverse events following vaccination; availability of vaccine-information materials that discuss vaccine benefits and safety; recommends studies led by the IOM investigating possible vaccine-related adverse events; and the development of new and safe vaccines [186]. Since its inception, the VICP is a resource for vaccine manufacturers and consumers to seek liability protection and compensation. All vaccines recommended by the CDC for routine use in infants and children are covered, whether administered individually or as combination vaccines. There are no age restrictions for filing claims. Information about VICP is available via a 24-h telephone contact (800-388-2382) or accessing the Web site (http://www.hrsa.gov/vaccinecompensation) [185].

Ad-Hoc Groups, Taskforce and Committees

Taskforce on Safer Childhood Vaccines

The National Childhood Vaccine Injury Act of 1986 led to the establishment of the Taskforce on Safer Childhood Vaccines (TFSCV) by the Secretary of DHHS at the direction of the US Congress. The TFSVC includes the Director of the NIH, Commissioner of the FDA, Director of the CDC, and several other representatives of the Public Health Service. The charge of the Task Force Interagency Group is to make recommendations regarding promotion of safe development of childhood vaccines and ensuring improvements in licensing, labeling, manufacturing, processing, testing, storage, administration, adverse event monitoring, and research. Periodic reports are published; the 1998 report emphasized the need to assess and address public concerns about the safety of vaccines, conduct research on the biological basis of vaccine adverse events, foster partnerships between various stakeholders, enhance the ability to detect adverse events and improve coordination between agencies [97].

Institute of Medicine: Immunization Safety Review Committee

The National Childhood Vaccine Injury Act of 1986 also led to the establishment of the Immunization Safety Review Committee (ISRC) at the IOM. The ISRC is an ad hoc

committee charged with the task of reviewing a list of adverse events associated with 8 of the 12 vaccines covered by the VICP and to evaluate the scientific evidence about the adverse event–vaccine relationship. Several important studies have been published by the IOM providing insights on the adverse events associated with childhood vaccines [10, 187, 188].

National Vaccine Advisory Committee Vaccine Safety Risk Assessment Working Group

During the recent 2009 H1N1 pandemic, The NVAC Vaccine Safety Risk Assessment Working Group (VSRAWG) was created by the National Vaccine Program Office (NVPO) to establish a mechanism for independent assessment of the H1N1 vaccine safety data from all NIAID-sponsored clinical trials as it became available [189]. Reports were made available to the public and posted on the National Vaccine Advisory Committee (NVAC) Web site to ensure transparency [190].

Global Advisory Committee on Vaccine Safety

The Global Advisory Committee on Vaccine Safety (GACVS), established by the WHO is an expert scientific and clinical advisory group charged to provide independent, rigorous evaluation of vaccine safety concerns of potential global importance [191, 192]. The GACVS reviews vaccine safety studies ranging from basic science to epidemiology in close collaboration with experts from industry, academia, and governmental agencies, from various disciplines, and makes a determination of causal relationships between vaccines and adverse events. Additionally, through the creation of ad hoc specialist teams, the GACVS monitors and investigates any safety concerns related to vaccines and suggests future research [192].

New Approaches to Post-licensure Vaccine Safety

Enhanced Active Surveillance Programs

There are a number of limitations to the currently used methods for monitoring post-licensure vaccine safety evaluation. Existing surveillance methods are based on expert reviews of reported cases and statistical data mining algorithms (DMAs). The current DMAs use a methodological approach focused on reporting associations disproportionally, which may not recognize all known associations in VAERS [193]. Therefore, organizing multidimensional data to facilitate pattern recognition by clinical experts remains a challenge [194]. Given recent advances in technology

and research methodology, the FDA leadership has developed newer statistical, epidemiologic and risk assessment approaches to evaluating vaccine safety throughout the life cycle [119]. The use of computerized clinical data systems and sophisticated disease-surveillance represent a significant advance in vaccine safety surveillance. Examples include the active surveillance program for GBS through the CDC Emerging Infections Program (EIP) and the use of network analysis (NA) to visualize multidimensional patterns among vaccines and adverse events (AEs), providing a structural framework for evaluating AE data in VAERS and other safety databases [194].

Post-licensure Rapid Immunization Safety Monitoring Program

In 2009, the DHHS established the new post-licensure rapid immunization safety monitoring (PRISM) program, an innovative active surveillance program to monitor the safety of the H1N1 influenza vaccine [124]. PRISM has access to data from approximately 42 million individuals enrolled in three large national health insurance plans and eight state and local immunization registries. In 2010, the FDA integrated the PRISM program into the Mini-Sentinel pilot program to evaluate medical product safety [124]. The PRISM program strengthens the federal vaccine safety system by developing an operational framework by selection of health outcomes of interest after vaccination for evaluation which is complementary to other existing vaccine safety systems [195]. Recently licensed vaccines including HPV vaccine (Gardasil®), and two rotavirus vaccines (RotaTeq® and Rotarix®) are currently being evaluated by the PRISM surveillance program [124].

Vaccine Safety Education and Communication

Health care providers play a vital role in identifying and effectively communicating vaccine-safety issues to parents [11]. Parents need to be educated regarding known, trustworthy Web sites for finding reliable health information about vaccines and VPDs [8, 196]. Examples include the AAP, CDC, NIH, WHO, The Tufts University Child and Family WebGuide, The National Network for Immunization Information (NNii), and The Immunization Action Coalition Web sites [197]. An excellent book has previously been published related to vaccine safety [198]. In the current era of complex media environments, effective public communication and engagement regarding vaccine safety concerns is crucial. Therefore, the NVPO is using media analysis and Influencer Network Analysis to better understand how to most effectively communicate about vaccination and vaccine safety issues [199]. Besides education, physicians should ensure proper storage and administration of vaccines by following ACIP recommendations, identify contraindications, report and treat adverse reactions, and refer and follow up as appropriate.

Table 2.3 Challenges to modern vaccine development

Development of vaccines against persistent, highly variable, and complex pathogens
Antigenic drift and shift in pathogens and changing pathogen characteristics
Emergence of novel pathogens
New antigens, innovative approaches to antigen presentation, need for novel adjuvants and vaccine delivery platforms, prime-boost regimens to improve efficacy, application of newer vaccine technologies
Development of rational trial design
Improve preclinical vaccine safety through translational medicine and systems biology approaches
Stringent regulatory and manufacturing requirements
Need for multidisciplinary collaboration
Vaccine financing, funding, and market incentive issues
Vaccines targeting populations with special needs (e.g., elderly, pregnant women, neonates, immunocompromised individuals)
Vaccination of adolescents
Development of nontraditional vaccines (to prevent or treat cancer, Alzheimer's disease, and autoimmune disorders)
Development of vaccines to target diseases specific to LMIC (such as tuberculosis, typhoid fever, malaria, and other neglected tropical diseases)
Global clinical trial capacity and surveillance
Effective public communication regarding vaccines and vaccine-preventable diseases

LMIC low and middle income countries; data taken from [21]

Challenges to Vaccine Development and Safety

There are many unique scientific and policy challenges to new vaccine development as shown in Table 2.3 [22, 24, 200]. Despite the significant advances in the understanding of immune responses to infection, development of vaccines has been difficult for infectious diseases characterized by persistent or latent infections, complex host–pathogen interactions, or pathogenesis (such as HIV), given the lack of immune correlates of protection and limitations of immunological tools to measure protective immunity (e.g., innate and adaptive) [12, 201]. Differences in immune responses to vaccines in different populations pose a significant challenge and a better understanding of the possible genetic mechanisms of immune responses and adverse events may lead to insights for vaccine development. In the absence of definite immune correlates of protection, vaccine efficacy is best assessed through conduct of large, randomized, clinical trials that must include innovative trial design and well-defined clinical end-points [12].

Other challenges to vaccine designers pertain to drift and shift in pathogens subject to selective pressures, special populations (e.g., the elderly, pregnant women, neonates, immunocompromised hosts), and the emergence of novel pathogens [55]. Therefore, discovery of suitable antigens, new and improved adjuvants and delivery systems must be encouraged to ensure progress in the field. Application of new technologies to develop vaccines for diseases with substantial health burden (such as HIV,

malaria, tuberculosis, respiratory syncytial virus, and meningococcal B disease) and emerging new infections (such as Dengue) is a priority. Development of nontraditional preventive and therapeutic vaccines against disorders such as cancer, Alzheimer's disease, and autoimmune disorders are being pursued. The current era of global travel poses a serious threat of new, emerging infections warranting the development of new epidemiologic, manufacturing, and regulatory frameworks [21].

To achieve the scientific objectives, sustained political support, more research funding, incentives for scientific innovation, and effective collaboration from different disciplines, such as systems biology, nanotechnology, genomics, proteomics, and structural biology, will be crucial. Education and training of new investigators in translational research is needed to accelerate vaccine development from concept, antigen discovery, and early vaccine development in the laboratory to product development in the market place.

Besides the scientific discovery barriers to vaccine development, regulatory, technical, and manufacturing challenges are formidable and require tremendous leadership, skill, determination, and patience. Process development must occur simultaneously with development of advanced analytic methods for characterization and determination of the potency of newer vaccines [202]. Other major issues for the future of vaccine production include safety, vaccine financing, and adequacy of supply. Additional stresses in the current immunization system include vaccine safety, and delivery of vaccines to adolescents and adults [31].

There are unique scientific and real-world challenges to global vaccine development and making new vaccines available to LMICs, especially in sub-Saharan Africa and Southeast Asia [24, 30]. Antigenic diversity, naturally occurring mutations and microbial selection under immunological pressure influence the global epidemiology of microbial pathogens targeted by novel vaccination strategies. The principal obstacle to new vaccines introduction in LMIC has been their expense. The GAVI alliance reported a $3.7 billion funding gap recently indicating the dire need for sustained financial support for global vaccine access [203]. New financing and market incentive mechanisms are needed to support the delivery of new and existing vaccines to LMIC. The introduction of new conjugate vaccines could drastically reduce mortality caused by *H. influenzae* type b, *S. pneumoniae* and *N. meningitidis* in sub-Saharan Africa and Asia. Accordingly, innovative global health partnerships have been recently developed to accelerate new pneumococcal and meningococcal vaccines at affordable prices to LMICs such as the Meningitis Vaccine Project and the Advanced Market Commitment [30]. Vaccines targeted to protect against diseases specific to LMICs such as tuberculosis, malaria, other neglected tropical diseases, or diarrheal illness due to enteric bacteria, such as *Salmonella typhi*, *Shigella* species, *E. coli*, and *Vibrio cholerae* should be developed [20, 204]. Expansion of global infrastructure and developing surveillance programs to monitor safety and efficacy of such vaccines will be challenging [21].

Public health systems and services must be strengthened in LMICs by addressing missed prevention opportunities, improving coverage, educating health care workers and parents regarding the overwhelming benefits of vaccines and integrating immunization services within comprehensive primary care services [24].

Critical gaps in policy and advocacy must also be addressed by the WHO, UNICEF, the Bill & Melinda Gates Foundation, the Hilleman Institute, and other partners to improve access to new and established vaccines in LMICs [24].

Improvement in global public health in LMIC is among the UN Millennium Development Goals. High-resourced countries must contribute to implement new vaccines against poverty-related diseases by greater mobilization of public and private funds for research projects, including vaccine development. A global multidisciplinary collaborative approach is required between the various stakeholders from industry, academia, and governmental agencies from both resource-rich countries and LMICs. Global health should be made a national priority in the developed countries, while development of new vaccines should be supported according to their public health values.

Conclusions

Vaccines are considered one of the most effective public health achievements of the twentieth century. Development of vaccines is a complex, multistep process requiring the collaboration of multiple partners from basic science research through vaccine delivery and outcome monitoring. Vaccine safety remains an integral component of any immunization program. A trusting relationship between patients, parents and primary care providers is critical to effectively communicate vaccine risk–benefit issues [205].

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Chapter 3
Known Vaccine-Associated Adverse Events

B.A. Pahud and C.J. Harrison

Adverse Event Following Immunization: Perspective

The benefits of vaccines rank them among the most successful interventions in the twentieth century having saved hundreds of thousands of lives worldwide, with dramatic documented effects in the USA alone [1]. However, vaccine-induced protective immunity to the specific targeted pathogen can be accompanied by unwanted adverse event following immunization (AEFIs). According to the US Food and Drug Administration (FDA), a vaccine adverse reaction is defined as an undesirable side effect that occurs after a vaccination [2]. AEFIs can be categorized for discussion by frequency, seriousness, time of onset, duration, and/or sequelae. AEFIs can be caused by vaccines or coincidentally occur after vaccination by chance alone (Table 3.1). Most vaccine-caused AEFIs are mild and transient such as fever or local reactions to injectable vaccines. On very rare occasions, vaccines can cause more severe AEFIs, such as Guillain–Barré Syndrome (GBS) or anaphylaxis.

History shows, however, that vaccine benefits far outweigh the risks in terms of overall public health and in most instances, the individual vaccine recipient. Vaccines have been so successful in developed countries, that much of the public has forgotten the morbidity/mortality from vaccine-preventable diseases when they were endemic. The result is that segments of the public are more afraid of AEFIs, caused by vaccines or rumored to be caused by vaccines, than of the diseases they are designed to prevent. It is thus important to understand AEFIs and the subset that are causally related, and put them in perspective, thereby helping parents, public policy makers, and health care providers understand the risk versus benefit of vaccination. It is critical to remember that by definition AEFI is an all inclusive term.

B.A. Pahud, M.D., M.P.H. (✉) • C.J. Harrison, M.D.
Section of Infectious Diseases, Department of Pediatrics, Children's Mercy Hospitals and Clinics, 2401 Gillham Road, Kansas City, MO 64108, USA

Department of Pediatrics, University of Missouri at Kansas City, Kansas City, MO, USA
e-mail: bapahud@cmh.edu

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Table 3.1 Categories of adverse effects, classified by severity or causality, as utilized in this chapter

Adverse event following immunization(s) (AEFI)	An unwanted or unfavorable event or medical occurrence (sign, symptom or disease) following one or multiple immunizations (single or multiple antigens). Such an event, including serious events, may be coincidental (temporally related—see below) while others are truly vaccine related (causally related—see below)
Serious AEFI[a]	An AEFI that results in any of the following outcomes: Death Life-threatening Inpatient hospitalization or prolongation of existing hospitalization A persistent or significant disability/incapacity A congenital anomaly/birth defect
Temporally related	An inclusive term which includes all AEFIs that occur soon after vaccination. Temporally related AEFIs may be either causally related (i.e., anaphylaxis), *or* simply related to vaccination by chance (i.e., it would have occurred regardless of vaccination)
Causally related	A subset of AEFIs. This subset has been confirmed to be caused by vaccine (e.g., oral polio vaccine-associated paralytic polio [VAPP]). Causally related AEFI may be temporally related (i.e., anaphylaxis), or not (e.g., Herpes Zoster following varicella vaccine) (see section "Causality")

[a]21CFR312.32 & 314.80

The term AEFI includes *all* reported adverse effects occurring anytime after vaccines. By definition AEFI includes those that are (1) causally associated, but not necessarily temporally related, and (2) temporally related, but not necessarily causally related (Table 3.1). For example, if a person dies in a tornado during the week after vaccination, by definition this death is an AEFI. It is obvious that the death-by-tornado is not caused by the prior vaccine, but it could legitimately be listed in certain datasets, e.g., in the VAERS, as a vaccine-associated death. VAERS is the spontaneous reporting surveillance system in the USA designed to detect any signal indicating a potential vaccine safety concern, but confirmation of causality is not required for an AEFI to be listed. In addition, anyone can submit a report of an AEFI to VAERS, e.g., medical provider, lawyer, a parent. The presence of these AEFIs that are not caused by vaccines in certain official reports or on Web sites can produce confusion for those who attempt to interpret or quote AEFI data, unless they have a clear understanding of causality.

Common Adverse Events Following Immunization

While the ideal vaccine would generate complete immune protection in all recipients with no AEFIs, such a vaccine is impossible. So what are the most common AEFIs and what is their severity? For discussion purposes, common AEFIs may be categorized as local or systemic. Some are due to the local physical effects of the

needle penetrating skin, subcutaneous tissue, muscle, nerves or vascular structures. Examples of this would be a local hematoma or tissue injury due to the needle passing through a vein, or a superficial laceration-like injury if the child moves suddenly as the needle is being inserted.

However, other AEFIs can result from the vaccinee's immune system reacting to either the vaccine or a component. These host reactions can be allergic or hypersensitivity reactions or an aspect of the desired but evolving protective immunity [3].

By definition, effective vaccines must be immunogenic. To be immunogenic, the host–vaccine interaction generates some local or systemic inflammation as part of the initial innate and subsequent adaptive immune responses. This means that vaccines are bound to generate local (at site of vaccine injections or mucosal application) and/or systemic signs or symptoms in some vaccinees. Despite the expectation of some local or systemic reaction from practically any vaccine, nearly all AEFIs are transient and lack long-term injury or sequelae.

Nevertheless, before administering any vaccine, providers should inform the patient or caregiver about potential AEFIs and why they occur. The required Vaccine Information Statement (VIS) for each vaccine can be a starting point. Pre-vaccine counseling helps eliminate the element of surprise. If a patient or caregiver is aware of the likelihood of a reaction and why that reaction may occur (i.e., the vaccine is doing its job by getting the immune system to recognize the pathogen and produce protective responses), a parent may feel more reassured and less concerned that something unexpected or terribly wrong is happening post-vaccine. What follows is a brief description for the most common AEFIs and aspects of their pathogenesis.

Fever

Fever is a normal part of the immune response to invading organisms and sometimes foreign materials. It is partly due to direct pathogen effects, e.g., bacterial toxins; and is partly due to cytokine/chemokine release from host cells, e.g., interferons. Because vaccines must contain modified pathogens or their components in order to induce a protective response, fever is to be expected as an AEFI from many vaccines. In fact, other than local injection-site reaction, fever is the most common vaccine-caused AEFI. The proportion of recipients developing fever varies by vaccine and sometimes by age. Most vaccine-induced fevers begin within 24 h of dosing and are of short duration, i.e., <36 h. Exceptions are the live attenuated measles, mumps, rubella (MMR) and varicella (V) vaccines, which can cause fevers in a timeframe similar to the incubation period of the targeted diseases, i.e., 5–14 days post vaccine. Vaccine-caused fevers are troublesome to families but are rarely if ever, dangerous. Fever should produce no long term sequelae, but can be associated with seizures (see "Febrile Seizure" under sections "Common Adverse Events Following Immunization" and "MMR-Containing Vaccines"). Fever alone is not a contraindication to continuing the recommended vaccine schedule. Hyperpyrexia ($T \geq 105$ °F) is a precaution after pertussis-containing vaccines.

Traditionally, routine use of antipyretics, even preemptively, was advocated for vaccinees; however, this has been tempered by reports of somewhat lower antibody titers (still in protective range however) in children who have received antipyretics [4]. At present, routine, preemptive antipyretics are not advised, but can be considered for moderate to severe fever or discomfort post-vaccine after a discussion of the pros and cons with the family.

Rash

Rashes after vaccines are often nonspecific and truncal in distribution, reminiscent of "nonspecific viral rashes" with which clinicians are familiar. They generally occur within 72 h of immunization but require no special therapy. Urticaria can occur and suggests an allergic or hypersensitivity reaction (see section "Hypersensitivity"). Antihistamines are commonly prescribed to alleviate symptoms such as pruritus. Immersing in hot bathwater or even modest exercise can cause urticaria (and sometimes other rashes) to become transiently more prominent. Urticaria also can accompany anaphylaxis (see section "Anaphylaxis").

MMR vaccine produces a different rash and at a different post-vaccine timeframe. The most recognized pattern is the maculopapular truncal rash that usually starts 7–10 days after vaccine, lasting only a few days and requiring no specific treatment. Less frequently, ecchymoses and/or petechiae can accompany thrombocytopenia, for which there is a slightly increased risk after MMR vaccine (see section "Idiopathic Thrombocytopenic Purpura"). Varicella vaccine can also cause specific rashes. One form is a maculopapular to mildly vesicular rash within a limited area (usually <12 lesions) near the injection site. The second is the appearance of similar lesions but distant from the injection site. On rare occasions, full-blown varicella can result, usually in inadvertently vaccinated immunocompromised hosts, e.g., T-cell or NK-cell deficient [5, 6]. There are also several reports of actinic rash up to 32 days post vaccine, limited to the area of the sunburn [7, 8].

Crying

Some crying is expected with any child receiving an injection but also may transiently accompany post-immunization fever or myalgia. Analgesics such as acetaminophen or ibuprofen can help alleviate some of these symptoms, but as noted above, reports suggest that preemptive or even post-dose antipyretics may somewhat reduce the antibody response in infants [4].

There is another form of crying that is classified as "inconsolable." Infants with this AEFI are irritable and cry incessantly for periods of time ranging from less than 1 h up to 18 h. The specific cause of this condition is not known. These episodes classically occurred after whole-cell pertussis vaccine (DTwP) and thus have

decreased dramatically since introduction of the acellular pertussis (aP) vaccines. There are no specific effective preventive measures or therapy for these episodes. There appear to be no sequelae from these episodes and they are not a contraindication to future vaccination with the same vaccine.

Febrile Seizure

A febrile seizure is defined as a brief seizure associated with fever, lasting less than 15 min, seen in a previously neurologically normal infant or young child without central nervous system infection [9, 10]. Febrile seizures result from a combination of environmental triggers and genetic factors. While some are triggered by immunization, more often they accompany a nondescript febrile viral illness. Between 2 and 5 % of children will have a febrile seizure before 5 years of age [11].

A prominent genetic predisposition exists for febrile seizures. Epidemiologic studies demonstrate that up to 25 % of children with febrile seizures have a family history of febrile seizures, with heritability estimated at 75 % [12]. Febrile seizures are overwhelmingly benign in that there are no expected sequelae after the initial post-ictal period. Nonetheless, they are frightening to the family and are thus less well tolerated as AEFIs. Despite this, benign febrile seizures can be acceptable for both the family and public health when compared to the potential disease and its sequelae. Uncomplicated febrile seizures following vaccination are not a contraindication to future immunizations.

In some instances, however, there are satisfactory alternatives that decrease risk of febrile seizures while still conferring protection. For example, when the combination MMR plus varicella vaccine (MMRV) was initially licensed, the ACIP recommended it preferentially over separate injections of MMR and V vaccines. This harmonized with their 2006 general preference for combination vaccines [13]. However, an increased risk of febrile seizures (one additional febrile seizure per 2,300–2,600 children) was noted postlicensure among children 12–23 months of age during the 5–12 days after their first dose of MMRV [14]. For this reason, in 2009 the ACIP listed personal or family history of seizures as a precaution for MMRV. They recommended separate administration of MMR and V over combined MMRV for the first dose in the at-risk age group unless parents preferred the single injection MMRV [15]. Because no increased seizure risk occurs with the second dose of MMRV at 4–6 years of age, the ACIP still preferentially recommends MMRV over separate MMR and V injections at this age.

Syncope

Syncope is a loss of consciousness from decreased blood flow to the brain. Its pathogenesis varies with the precipitating event. Syncope following vaccination is

usually due to a vasovagal reflex [16]. Although the pathophysiology is not fully understood, it is believed to result from autonomically altered blood flow. Pain from the injection stimulates the sympathetic nervous system, increasing the pulse and arterial pressure [17]. A secondary signal from aortic arch baroreceptors via the vagus stimulates a parasympathetic response. This causes a rebound decrease in pulse and blood pressure reducing blood flow to the brain. Syncope results [18]. Thus, syncope is a reflex reaction to the *injection procedure* rather than to the specific vaccine components.

Syncope following immunizations is frightening to patients and family members. It is more common in older children/adolescents and thus more frequently reported with adolescent vaccines, i.e., Tdap, meningococcal vaccines. Although syncope is usually benign, serious injury has been reported from head injuries, e.g., skull fractures or cerebral hemorrhages. The majority (63 %) of syncopal episodes occur within 5 min of vaccination and 89 % of them occur within 15 min [13]. Thus, "prevention by anticipation" is paramount. Patients should be observed for 15 min post-immunization. In addition, falls can be prevented by ensuring that patients are sitting or lying down during both vaccination and the observation period. The 2011 Institute of Medicine (IOM) report on AEFI found convincing evidence of a causal relationship between the physical act of injecting a vaccine and syncope [10]. Adding this AEFI to the vaccine injury table has been proposed, with a risk window of 1 h from vaccination.

Uncommon or Serious Adverse Events Following Immunization

Individual practitioners have limited experience with uncommon and or serious AEFIs. Serious AEFIs are defined as such based on criteria found in the Code of Federal Regulations (21CFR§314.80). This definition states that an serious adverse event (SAE) is one for which the report contains information that the AEFI resulted in death, life-threatening illness, hospitalization, prolongation of hospitalization, persistent or significant disability, or a congenital anomaly/birth defect (Table 3.1) [19].

It is most important to assess as correctly as possible whether a serious AEFI is causally related to the vaccine (see section "Causality"). However, most serious AEFIs are rare so that investigation does not always distinguish whether the event was caused by the vaccine or would have occurred even in the absence of the vaccination. Because serious AEFIs may produce permanent disability or be life threatening, they generate a great deal of concern and interest among medical practitioners, the lay public and the media. This interest causes Internet activity with postings that range from reliable to totally unscientific in regard to interpreting the event and its true cause. It is also important to remember that serious AEFIs, even in reliable databases such as VAERS, can include *any* event after immunization.

These datasets do not differentiate events that are causally related from events that are only temporally related to immunization. These AEFIs are sometimes referred to as "vaccine-associated," but note that "vaccine-associated" also does not mean vaccine-caused. The take home message is that vaccine-associated or temporally related is not synonymous with causally related (Table 3.1) (see section"Causality").

So the fact that a rare AEFI, whether serious or not, temporally follows vaccination does not prove vaccination was the cause. For this reason we discuss rare AEFIs in more detail than might seem warranted based on their frequency to hopefully help clinicians have a better idea of the causes and presentations.

Pyogenic and Sterile Abscesses

An abscess is a fluctuant or draining fluid-filled lesion occurring at the site of injection, which may present with or without fever. Pyogenic abscess formation (infected) after injectable immunization is often due to *Staphylococcus aureus*, and is usually a complication of the residual puncture, allowing skin pathogens entry through the normally protective skin barrier. It may also be caused by contaminated material in the vaccine or the injecting equipment, e.g., the needle [20, 21]. Single unit-dosing and adhering to sterile technique when withdrawing vaccine from multidose vials can reduce contamination. Swabbing the vaccine vial and diluent stopper (when present) with an effective antiseptic also decreases the risk of pyogenic abscesses.

Sterile abscesses (not infected) are less frequent than pyogenic abscesses. They likely result from a nonspecific inflammatory response to the vaccine antigen/s or another vaccine component. Sterile abscesses are more frequently reported following inactivated vaccines containing diphtheria–tetanus toxoid–pertussis and aluminum (alum) adjuvants [22, 23]. They are believed to be a hypersensitivity reaction to the alum, so choosing formulations with less or no alum may be beneficial. Whether other adjuvants such as MF-59 or ASO4 will have similar issues remains to be seen.

Extremity Swelling

Mild local swelling is not uncommonly seen with conjugate polysaccharide vaccines, e.g., PCV7 or PCV13, and after diphtheria/tetanus/pertussis containing vaccines. It is less common, but still reported, during the primary series with diphtheria, tetanus, and acellular pertussis vaccine (DTaP) compared to DTwP.

Since introduction of aP vaccines, however, the surprise has been an increase in local reactions after the fourth and fifth doses, some (2–6 %) involving the entire upper arm or thigh [24]. These reactions are thought to be due to high vaccine-antigen-specific antibody titers at the time of the fourth or fifth dose induced by multiple prior vaccine doses. Interestingly, such extensive swelling is also more

common during the primary series of aP than DTwP. A small study evaluating safety of revaccinating following extensive limb reactions suggests that while reactions are more common if a child previously had such a reaction, they are usually well tolerated and resolve within 4–5 days without sequelae [25]. These reactions even when involving a relatively large area of the extremity are thus not contraindications to subsequent vaccination with the same product.

Arthus-type exaggerated reactions (see section "Delayed Type Reactions") have also been reported in adults, usually hours after administration of booster doses of diphtheria–tetanus containing vaccine or pneumococcal polysaccharide vaccine. These "whole arm swellings" from shoulder to elbow, are generally quite painful. History of Arthus-type hypersensitivity reactions after a previous dose of tetanus toxoid-containing vaccine is a precaution to further vaccination. Deferral of vaccination until at least 10 years have elapsed since the last tetanus toxoid-containing vaccine is recommended.

Deltoid Bursitis

Deltoid bursitis is an inflammatory process of the deltoid bursa causing shoulder pain, stiffness and/or restricted range of motion. It may be idiopathic or secondary to injury (e.g., local needle injection of a medication or vaccine) [10]. As with syncope, it is an *injection procedure*-related AEFI, not an immune reaction to the vaccine antigen/s such as seen with whole arm reactions from direct physical injury discussed above. It is most frequently reported in adults following influenza or a tetanus-containing vaccine, likely because these have been the vaccines given most often in the deltoid area. They have been reported when vaccine administration occurs "too high" in the deltoid area. The plausible mechanism of injury is the unintentional needle penetration and deposition of foreign material in the synovial tissues associated with the subdeltoid bursa. This causes a local foreign body reaction, and subacromial bursitis (contiguous to the subdeltoid bursa), bicipital tendonitis, and inflammation of the shoulder capsule [26, 27]. Patients with deltoid bursitis as an AEFI generally have not had a history of prior shoulder dysfunction, and commonly report rapid onset of pain and limited range of motion.

Unfortunately, symptoms in most of these patients persist in the form of pain, limited range of motion, and pain on active or passive motion for months to years following the injury. Use of correct injection technique and site when administering intramuscular vaccinations should reduce the risk of shoulder injury. The US Department of Health and Human Services HRSA (Health Resources and Services Administration) has defined this AEFI as "Shoulder Injury Related to Vaccine Administration" or SIRVA. The 2010 IOM review ruled that convincing evidence supports a causal relationship between vaccination and SIRVA, and thus, adding this AEFI to the vaccine injury table has been proposed, with a risk window of 48 h [10].

Of course, to meet criteria for SIRVA, pain and reduced range of motion should be limited to the shoulder in which the vaccine was administered, and other potential causes for the pain should be ruled out. Thus, no other condition or abnormality can be present that would explain the patient's symptoms (e.g., radiculopathy, brachial neuritis, mononeuropathies, or any other neuropathy).

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) may seem similar to SIRVA but differs in that not only is there pain, swelling, and decreased range of motion, but there is also autonomic dysfunction affecting one or more extremities. CRPS also differs by pathogenesis, i.e., being the result of nerve trauma, not synovial trauma, following an injection. However, it is another *injection procedure*-related AEFI, and is not related to the particular vaccine or antigen in the vaccine. Other accompanying features of CRPS include skin discoloration, local edema, fluctuation in skin temperature in the affected extremity(s), allodynia (pain from stimuli that would not ordinarily be painful), and abnormal local sweating [28]. Although not well understood, proposed causes for the unusual clinical findings in CRPS include the following: (a) altered skin innervation of sweat glands and hair follicles; (b) increase in the expression of adrenergic receptors on pain fibers, thus dysregulating sympathetic signals that then cause skin discoloration, temperature changes, increased sensitivity to pain; (c) increased proinflammatory cytokines that produce local third spacing (localized edema); and (d) potential psychological factors which could impact all other factors [28].

Neurologic Adverse Events

Most of the reported neurologic AEFIs are so rare that even if a true association exists, it is difficult to distinguish from background rates of the disease. Neurology and/or ophthalmology consultation is usual when considering these diagnoses.

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is an acute inflammatory demyelinating disease of the central nervous system with variable symptoms postulated to result from allergic or autoimmune response following an infectious disease or vaccination. ADEM has been reported following several vaccines, including influenza, meningococcal, human papillomavirus (HPV), rabies, and DT, TT, or aP containing vaccines. The latest IOM review confirmed that there is inadequate evidence to conclude that hepatitis A, hepatitis B, HPV, influenza, meningococcal, varicella, MMR,

or DT, TT, or aP containing vaccines cause ADEM [10]. Neurology consultation is important to decisions on therapy, including glucocorticoids.

Transverse Myelitis

Transverse myelitis (TM) is a rare spinal cord disease affecting both children and adults. It presents with sudden onset of back pain followed by progressive weakness in the lower extremities. It is postulated to be an autoimmune process with various triggers, such as an infection or vaccination. As in the case of ADEM, sporadic TM cases have been reported following many childhood vaccines, as well as rabies, typhoid, oral polio, and most recently 2009 pandemic H1N1 vaccine. Despite these anecdotes, the 2010 IOM review concluded there is inadequate evidence to conclude that TM is caused by any of the following vaccines: hepatitis A, hepatitis B, HPV, influenza, meningococcal, varicella, MMR, or DT, TT, or aP containing vaccines [10]. Further studies are ongoing to better define any associations.

Optic Neuritis

Optic neuritis (ON) is a demyelination of the optic nerve(s) with unknown pathogenesis. There is rapid vision deterioration over hours or days. One or both eyes may be affected. Some patients regain their vision, but others are left with permanent vision loss. Some datasets list ON following various vaccinations, but the latest IOM review concluded there is inadequate evidence that ON is caused by any of the following vaccines: hepatitis B, influenza, MMR, or DT, TT, or aP containing vaccines [10].

Bell's Palsy (Seventh Nerve Neuropathy)

This is an acute and usually idiopathic paralysis of the face due to injury/inflammation/compression of the seventh cranial nerve, producing distortion on one side of the face. Anecdotal cases have been reported following trivalent inactivated influenza (TIV) and hepatitis B virus (HBV) vaccines. Results of a recent study evaluating varied time-risk windows and different vaccines suggest no association between immunization and Bell's palsy in children [29]. In addition, the latest IOM review concluded there is inadequate evidence that Hepatitis A, DT, TT, or aP containing vaccines cause Bell's palsy [10].

Guillain–Barré Syndrome

GBS is a rare neurological disease characterized by loss of reflexes and usually temporary, ascending, symmetric paralysis [10]. A recent overall review of all

published peer-reviewed data from 1950 to 2008 did not find evidence to support a causal association between GBS and vaccines, with the exception of the 1976 influenza vaccine [30].

However, the reported increase in GBS case reports following immunization with the 1976 swine influenza vaccine [31] raised concern about the H1N1 vaccine for the 2009 pandemic. An increased risk of GBS has been suggested in some but not all 2009 H1N1 studies of influenza vaccines [32–36].

Thus, only the 1976 pandemic swine influenza vaccine and older rabies vaccine formulations (cultured in brain tissue) have been found to increase the risk of GBS. The newer formulations of rabies and influenza vaccine do not appear to be associated with GBS, i.e., the rate is no greater after vaccine than is expected per the background rate in those not receiving vaccine. The latest IOM review also concluded there is inadequate evidence to conclude that current hepatitis A, hepatitis B, HPV, influenza, meningococcal, varicella, MMR, or DT, TT, or aP containing vaccines cause GBS [10].

Hypersensitivity

Allergic reactions to vaccines range from mild local swelling to severe life-threatening shock. An allergic or hypersensitivity reaction is an immune-mediated reaction to a substance (allergen) to which most people in the population do not react [10]. Allergic reactions can be classified as immediate or delayed in relation to the exposure, or symptomatically as local or systemic. The World Health Organization (WHO) recommends categorizing by timing in order to increase recognition of immediate Type 1 reactions because reexposure to the allergen can cause potentially life-threatening anaphylaxis.

Although the true incidence of allergic reactions to vaccines is not known, estimates range from 1 per 500,000 to 1 per million doses for most vaccines [3]. Potential allergens in vaccines include components of the infectious agent itself (antigens, toxoids, attenuated pathogens), but more likely the additives or excipients (antibiotics, preservatives or stabilizers) or residuals from the manufacturing process (vaccine components/excipients are listed at http://www.vaccinesafety.edu/components.htm). These include culture media ingredients (serum, egg, monkey kidney cells, etc.) or traces of biochemicals (casein, peptone). Some vaccines have latex stoppers in the storage vial or dispensing instrument that may potentially cause allergic reactions. Vaccines that have more allergens, such as egg proteins or gelatin, are more likely to have higher rates of hypersensitivity reactions. Even though allergic reactions following vaccinations are rare, clinicians should be familiar with them, given their potential severity. An algorithm to treat patients with suspected hypersensitivity reactions has been developed by the Clinical Immunization Safety Assessment (CISA) Network and is available online [37].

Immediate Reactions

Immediate reactions usually occur within 15–30 min. They tend to be Type I reactions mediated by immunoglobulin E (IgE), i.e., IgE-mediated hypersensitivity reactions. Common skin findings include urticaria, flushing, or angioedema. Among gastrointestinal (GI) signs/symptoms are nausea, vomiting, abdominal pain, and/or diarrhea. Respiratory signs include rhinoconjunctivitis, cough, stridor, bronchospasm (wheezing), or shortness of breath. Cardiovascular signs include tachycardia, weak pulse, vertigo, syncope, hypotension or, in extreme cases, shock. When severe, such reactions may be classified as anaphylaxis.

Anaphylaxis

Anaphylaxis is a rare (0.65 cases/million vaccine doses) [38], but frightening, rapidly developing and potentially fatal systemic allergic reaction [39]. It is the most severe Type I IgE-mediated hypersensitivity reaction and among the most serious causally associated AEFIs, but there is no one specific confirmatory diagnostic test.

Because early recognition and initiation of treatment is needed for optimal outcome, clinicians need awareness of its rapid onset and characteristic multi-system involvement. Allergen-specific IgE antibodies induced by a previous allergen exposure bind to high affinity receptors (CD23) on mast cells and basophils during allergen reexposure. This rapidly activates cell-signaling and release of inflammatory mediators, e.g., histamine, tryptase, leukotriene B4, prostaglandin D2. Thus, patients present within minutes or at most hours post vaccination (sporadic reports indicate rare delays up to 12–72 h) with various signs and symptoms, primarily involving four systems (skin, cardiovascular, GI and respiratory) [40]. However, not all four are involved in every case, even in some severe presentations (incomplete presentations). Skin findings (generalized urticaria, erythema, localized or generalized angioedema, and /or pruritus) are not dangerous unless swelling occurs in/near the airway. Cardiovascular manifestations include hypotension and/or shock (indicated by tachycardia, decreased capillary refill, reduced central pulse volume and decreased level of consciousness). Shock defines the most severe anaphylaxis. GI findings are nonspecific, i.e., nausea, emesis, cramping, or diarrhea. Respiratory manifestations include bronchospasm (wheezing), stridor, upper airway swelling (lip, tongue, throat, uvula, larynx), and respiratory distress (i.e., tachypnea, cyanosis, grunting).

According to the two latest IOM reviews, evidence convincingly supports a causal relation of anaphylaxis to MMR, hepatitis B vaccine (in yeast-sensitive individuals), diphtheria or tetanus toxoids, as well as varicella, influenza, and meningococcal vaccines. The evidence also favors causality between HPV and anaphylaxis [10, 41]. Vaccination-caused anaphylaxis is a contraindication to further doses of that vaccine. Estimates of the incidence of anaphylaxis following common vaccines can be found in Table 3.2.

Table 3.2 Estimates for the incidence of anaphylaxis [3, 42–44]

Vaccine	Anaphylactic reactions per 100,000 doses
Measles	0.68
Rubella	0.73
Mumps	0.44
Varicella	1.33
Hepatitis B Vaccine	<1
HPV	2.60
Meningococcal polysaccharide vaccine	0.1

Delayed Type Reactions

Delayed type hypersensitivity (DTH) reactions classically present at 3–8 h post exposure, but intervals of 12–72 h or even weeks after initial exposure to the vaccine have occurred. DTH can manifest as local reactions (arthralgias), various rashes (urticaria, erythema multiforme), or fever [37]. Unlike immediate type reactions, DTH less commonly involves multiple systems and is not always immune mediated [3]. However, confusion can arise because DTH reactions may also present with urticaria and/or angioedema, but are not IgE-mediated events. Most delayed type reactions are actually Type III. They often result from IgG- or IgM-related immune complexes and involve consumption of complement (C3a, C4a, C5a). The most recognized forms of Type III reaction are serum sickness and Arthus reactions.

Allergic Reactions to Egg-Related Antigens or Products

Egg allergy issues have been most problematic in relation to influenza vaccine because influenza vaccine virus is grown in chicken eggs. However, recent data caused a shift in official recommendations regarding egg allergy and influenza vaccines in 2011 [45], so that now egg allergic patients are candidates for influenza vaccine when given by certain providers. These include an allergist or clinician experienced in dealing with severe allergic reactions [46]. Some egg protein is also found in yellow fever, MMR, and some rabies vaccines, although the amounts are thought to be clinically significant only in yellow fever vaccine.

Special Concerns by Vaccine Type

In the following section we will review concerns associated with specific vaccine types.

Diphtheria, Tetanus, or Pertussis Containing Vaccines

It should not be a surprise that public concerns regarding vaccine AEFIs arose in the 1970s. By then DTwP vaccines had substantially reduced the burden of these diseases, shifting public focus to vaccine AEFIs because fear of the diseases had diminished. The DTwP vaccines were in the forefront because they were moderately reactogenic. This created increasing negative publicity that peaked in the 1990s. Because of this, immunization rates were beginning to dwindle, so less reactogenic acellular pertussis vaccines were developed and replaced the DTwP in the USA in the late 1990s. Even though DTwP vaccines are no longer used in the USA, their use continues in other countries.

Despite being less reactogenic, acellular DTaP vaccines have also been purported to cause a number of sequelae. Current aP vaccines, however, do not cause asthma, autism, brain injury, sudden infant death syndrome (SIDS), or type 1 diabetes as recently confirmed by the 2011 IOM review [10]. What follows is a brief review of reactions causally related to DTaP vaccines.

Approximately 50 % of DTaP vaccinees will have mild reactions, e.g., local injection site pain, fever, irritability, reduced appetite, fatigue, or emesis. Temporary (1–3 days) swelling of the whole or nearly entire arm or leg, into which the DTaP was injected, occurs rarely. Discussion of extremity swelling reaction can be found earlier (see section "Extremity Swelling"). Approximately 1 % of DTaP recipients can have one of the following: prolonged crying (inconsolable episodes), fever ≥105 °F (hyperpyrexia), febrile seizures (see "Febrile Seizure" under section "Common Adverse Events Following Immunization"), or HHE (see section "HHE"). These reactions after DTaP produce no long-lasting sequelae. However, they are precautions to further vaccination.

HHE

HHE is a rare AEFI most often seen prior to 1996 in the DTwP era. It has also been reported, albeit less commonly, in postlicensure trials of PCV 13 and of DTaP containing vaccines. HHE has been defined as an acute decrease in sensory awareness or apparent loss of consciousness together with pallor and/or cyanosis and muscle hypotonicity in patients ≤10 years old. It sometimes has been described as a "shock-like" state with or without collapse.

HHE usually has its onset within 12–24 h after immunization. Median time interval between immunization and HHE presentation was significantly different in children less than 2 years old (5 min) compared to those older than 2 years (215 min) [47]. Most patients are initially febrile and irritable, but then develop shallow breathing, pallor, limpness and become less responsive. The episodes last from several minutes to 36 h. A good review is available for those seeking more details [47]. The reported risk of HHEs after whole-cell pertussis vaccine has been estimated at 1/1,000–6,000 doses [48]. VAERS data in the USA show a decrease in HHE reports

after introduction of acellular pertussis vaccines [49]. Other large reports from Europe and Canada had similar findings [50, 51]. There are no apparent long-term sequelae following HHE, and most children return to their prevaccination state within a few hours. The pathophysiology of HHE is possibly in the severe end of the spectrum of syncope (see section "Syncope") although the exact cause is still unknown. As mentioned, HHE can occurred following non-pertussis-containing vaccines, in which cases the age of presentation tends to be higher with the median age being 9.3 months versus 3.9 months of age with DTwP or 4 months of age with acellular pertussis vaccine [49]. HHE within 48 h of a DTaP containing vaccine is a precaution to further vaccination. However, data show that patients that have been reimmunized have not reported further AEFIs [52, 53].

Acute Encephalopathy

Concerns that DTaP containing vaccines may cause encephalitis or encephalopathy continue among the public and anti-vaccine groups based on a 30-year-old report from 1981 by The National Childhood Encephalopathy Study group in Great Britain. This report showed an apparently increased risk of encephalopathy with permanent residua in DTwP immunized children. These cases were *temporally* associated by virtue of symptom onset within 7 days of receiving DTwP [54]. Follow-up investigations in that cohort and others, however, found no evidence of a real increased incidence of encephalitis following DTwP [55, 56]. In addition, the most recent IOM report concludes that the evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and encephalitis or encephalopathy [10].

Recently, a severe seizure disorder (Dravet Syndrome) due to mutations of the sodium channel gene, SCN1A, has been shown to be responsible for some encephalopathy cases previously thought to be caused by pertussis-containing vaccines [57, 58]. In these cases, it is possible that pertussis vaccine may have simply been a nonspecific trigger that uncovered an underlying congenital abnormality that had not yet been diagnosed. In these children, any inflammatory condition is capable of being such a trigger, including common viral infections. Despite these findings, encephalopathy not attributable to another identifiable cause within 7 days of administration of previous dose of DTwP or DTaP remains a contraindication to pertussis-containing vaccination.

GBS

Although there is no evidence to support an increased risk of GBS following immunizations with tetanus toxoid-containing vaccines [59, 60], GBS within 6 weeks after a previous dose of tetanus toxoid-containing vaccine is a precaution to further vaccination.

Table 3.3 Selected vaccine-caused adverse effects attributable to MMR vaccine

MMR	Rate	Timing	Duration	Other notable facts
Fever	5–15 %	7–12 days post vaccine	Lasts 1–2 days	103 °F or higher; related to the measles component
Rash	5 %	7–10 days post vaccine	Transient	Usually truncal and maculopapular
Transient arthralgias	25 % women, less often in girls, and even less often in males than in girls	Age dependent, see text	Up to 3 weeks, rarely can last for months to years	Related to the rubella component
Thrombocytopenia	<1/30,000–40,000 doses	Within 2 months, highest rates noted 2–3 weeks post-vaccine	Transient, often diagnosed as ITP (see section "Idiopathic Thrombocytopenic Purpura")	The risk during natural infection is much greater than the risk after vaccination

MMR-Containing Vaccines

Only ~20 % of pediatric MMR recipients have AEFIs to the vaccine. Adult women have a higher rate of joint AEFIs which are due to the rubella component. Most AEFIs associated with MMR are due to the effects of the replication of one or more of the three live, but attenuated viruses, coupled with the host immune response that occurs usually at 5–12 days post vaccination (the usual incubation period for measles and mumps) [2]. Common vaccine-caused AEFIs after MMR are listed in Table 3.3.

Idiopathic Thrombocytopenic Purpura

Infrequently, idiopathic thrombocytopenic purpura (ITP) may occur within 6 weeks after MMR immunization, with a reported incidence ranging from 0.087 to 4 (median 2.6) cases per 100,000 vaccine doses [61]. The thrombocytopenia is self-limited, severe bleeding manifestations are uncommon, and revaccination of patients with prior ITP (associated with MMR or not) has not been associated with

recurrence of thrombocytopenia [62–67]. Still, history of thrombocytopenia or ITP is a precaution to further vaccination. A recent study showed no increased risk of ITP after any vaccines in young children other than MMR and concluded ITP is unlikely after childhood vaccines other than MMR [68].

Arthralgia/Arthritis

MMR is associated with transient joint symptoms with a higher incidence in adult women (12–26 %) than in children (0–3 %). The duration and intensity of symptoms increase with increasing age, being the shortest and least notable in infants/toddlers but most notable and longest in adult women. Joint complaints usually persist 1–4 weeks, although symptom duration of several months or even years has been reported. In the latest IOM review, the evidence favored a causal relationship between MMR vaccine (rubella component) and transient, *but not chronic*, arthralgia in women and children. So a short duration arthralgia seems caused by the rubella component of MMR, but any prolonged arthralgia may not be. No changes to the vaccine injury table have been proposed. Nonetheless, when joint AEFIs occur, they usually are reasonably well tolerated and respond at least somewhat to NSAIDs. The affected girls or women can almost always go about their usual activities even while symptomatic.

Meningitis

Meningitis secondary to MMR vaccination is thought to be related to the mumps component. The Merck MMR vaccine currently used in the USA contains the Jeryl-Lynn strain that has not been associated with aseptic meningitis. The highest risk of association with aseptic meningitis has been observed after doses containing the Urabe-mumps strain of a vaccine used mostly in Europe. With this MMR vaccine, aseptic meningitis occurs within the third week after immunization [risk ratio (RR) 14.28; 95 % confidence interval (CI) 7.93–25.71] [69]. The risk of aseptic meningitis is also increased after use of the MMR vaccine that contains the Leningrad-Zagreb (LZ) strain. This LZ containing vaccine has been used in South America, e.g., Brazil [70]. With this LZ vaccine, aseptic meningitis is also most frequent in the third week, [RR 22.5 (95 % CI 11.8–42.9)] but has added risk in the fifth week, [RR 15.6 (95 % CI 10.3–24.2)], post vaccine [69].

Febrile Seizure

The 2011 IOM committee concluded that the evidence convincingly supports the fact that MMR vaccine can cause febrile seizures. This association has been known and reported for years. The risk of febrile seizure has been reported to be increased versus controls among MMR vaccinees with an RR of 1.10 (95 % CI

1.05–1.15), being highest within 2 weeks of immunization (RR 2.75; 95 % CI 2.55–2.97) [71]. Febrile seizures after MMR vaccine, however, have no reported long-term sequelae nor have they been associated with subsequent neurodevelopmental disability or epilepsy risk. The rate of febrile seizures caused by MMR vaccine is higher in younger than in older children, with overall number of febrile seizures attributable to MMR estimated to be 6–9 per 100,000 children [72]. MMRV vaccine increases this rate by one additional febrile seizure per 2,300–2,600 children receiving a first dose of MMRV vaccine, when compared MMR plus V injected at different body sites simultaneously. The increased seizure activity occurs 5–12 days after the first MMRV dose but has not been seen after the second dose (4–6 year olds) (see "Febrile Seizure" under section "Common Adverse Events Following Immunization").

Encephalitis

Since the formation of The National Vaccine Injury Compensation Program (NVICP) in 1988, measles virus-containing vaccines are listed as presumed causes of encephalitis, eligible for compensation if no other cause is identified [73]. In order to be compensation eligible, encephalitis must occur in the biologically plausible risk window of 5–15 days following measles virus-containing vaccines. These criteria are meant to be as inclusive as possible and their use necessarily means that some qualifying cases will not be causally related but only temporally related to immunization, i.e., due to chance alone. Thus, before discussing encephalitis as an adverse event following measles containing vaccines, one must understand the varying forms of measles encephalitis after natural wild-type measles infection.

Acute post-infectious measles encephalitis (APME) occurs at a rate of 1 case per 1,000–2,000 following natural measles infections. Acute but delayed encephalitis (a.k.a. subacute measles encephalitis or immunosuppressive measles encephalitis) occurs after wild-type measles infection, and is designated as measles inclusion body encephalitis (MIBE) due to histological findings. A third but lethal form, subacute sclerosing panencephalitis (SSPE) occurs at a rate of 1 SSPE case per 100,000 measles infections. APME usually presents during the convalescent period in the second to fourth week following infection. MIBE presents within months after acute measles infection whereas SSPE presents years after initial infection.

Another factor in understanding the risk of potential encephalitis after measles vaccine is that there is a background rate of acute encephalitis without a known cause (one case per one million). So encephalitis cases following measles virus-containing vaccines must be compared to the background rate of nonspecific encephalitis that would occur even without vaccine. And the rate needs to be balanced against the rate of three forms of encephalitis due to wild-type natural measles infections.

Despite reports of temporal clustering of some encephalitis cases between days 5 and 15 [74] following MMR vaccine (temporally related), acute encephalitis post-MMR is so rare that it has been impossible to distinguish from the background encephalitis rate of 1 in one million in immune competent hosts [75]. An IOM scientific review in 1994 concluded there was insufficient evidence that measles or mumps cause encephalopathy or encephalitis but did acknowledge biologic plausibility of such cause and effect [41]. A more recent 2011 IOM report confirmed that the evidence is inadequate to accept or reject a causal relationship between MMR vaccine and encephalitis or encephalopathy in immune competent hosts [10].

Measles Inclusion Body Encephalitis

MIBE is very rare even with wild-type infection, and reported only in immune compromised hosts. The classic clinical presentation is that of difficult-to-control seizures plus altered consciousness progressing to coma and death. The CSF is usually normal, but there may be mild pleocytosis and an elevated protein. Unlike SSPE, measles antibody titers in the CSF are rarely elevated [76]. Diagnosis is most definitive when supported by brain biopsy histopathology. This can reveal intranuclear and intracytoplasmic paramyxovirus particles by electron microscopy (the source of the disease's name). Immunohistochemical staining of tissue may also reveal measles hemagglutinin and matrix proteins, or measles virus RNA may be detected by RT-PCR. MIBE has mortality as high as 75 %. There is a high incidence of neurological sequelae among survivors. There is no proven effective treatment for MIBE [76].

Cases of MIBE have also been reported in immunocompromised patients following MMR vaccine [77–79], some of whom had clinically disseminated measles [80, 81]. Evidence of measles virus has been found in CSF [81], and in one well documented post-vaccine case, measles-specific monoclonal antibody staining revealed measles nucleoprotein and matrix proteins within neuronal cytoplasm [77]. Measles virus was also detected by RT-PCR in brain tissue of immunocompromised patients with MIBE [76, 77]. Based on four unique reference sequences differentiating Moraten and Schwarz vaccine strains from wild-type measles [82], vaccine strain was detected in tissues of an immune compromised child with a preexisting profoundly depressed CD4 cell count and post-vaccine MIBE [77]. This is fairly convincing evidence for vaccine-induced encephalitis. Recently, the IOM concluded that evidence convincingly supports MMR (measles component) vaccine as a cause of MIBE in immunodeficient hosts [10]. Current Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) and American Academy of Pediatrics (AAP) recommendations for MMR exclude most immune compromised hosts from vaccination, although HIV infected children can be candidates if their immune status is adequate, i.e., if CD4+ T-lymphocyte count is >15 % [2].

Varicella

Pain and redness at the injection site occurs in approximately 20 % of children and in ~30 % of adolescent varicella vaccinees. When combined in the same injection with MMR (MMRV), AEFIs are similar but not identical to MMR and V injected at different sites. However, MMRV recipients have somewhat higher rates of fever (22 % vs. 15 %), rash at the injection site, and benign febrile seizures (~1: 1,000 more than children receiving MMR and V vaccine at different sites on the same day) (see "Febrile Seizure" under sections "Common Adverse Events Following Immunization" and "MMR-Containing Vaccines").

Dermal Dissemination

Varicella-like lesions occur at the injection site in ~20 % of recipients. Such rashes in the first weeks following varicella vaccination could be due to wild type virus or vaccine strain, with differentiation between strains possible by PCR of material from a lesion [83–85]. One to three weeks after vaccination, approximately 5 % of patients develop a less focal rash usually with less than ten lesions, described as maculopapular more than vesicular. Despite this, rashes within 2 weeks of vaccination and/or containing more than 20–30 lesions are more likely to be due to wild type disease. Rashes due to vaccine virus are associated with rare transmission of vaccine virus [86]. The IOM 2011 report supports a causal relationship between varicella vaccine and dermally disseminated Oka VZV rash [10].

Organ Dissemination

Varicella vaccine Oka virus has very rarely disseminated to organs beyond the skin following vaccination in immune compromised patients, causing pneumonia, meningitis and/or hepatitis [6, 83, 85–88]. All of these are also sites of dissemination in wild type infection. The 2011 IOM report concluded that mechanistic evidence convincingly supports varicella vaccine as a potential cause of organ dissemination resulting in meningitis, pneumonia or hepatitis in immunodeficient patients [10]. Thus, varicella vaccine should not be given to immune deficient patients.

Dermal Reactivation (a.k.a. Herpes Zoster)

Although the varicella Oka vaccine strain can reactivate in rare instances to cause Herpes Zoster (HZ) both in immunocompromised and immunocompetent patients, the exact incidence is not known. Surveillance data are not conclusive as to whether HZ is more common in the post vaccine era due to vaccine virus or wild type virus

reactivation [83–86, 89]. But HZ was reported less commonly in leukemics who received varicella vaccine than those who suffered wild-type disease [90]. The IOM report found enough clinical evidence to conclude a causal association between varicella vaccine and HZ reactivation [10]. The Oka vaccine strain is susceptible to acyclovir if treatment is needed.

CNS Reactivation

Only a few cases of vaccine-associated CNS disease have been described in the literature, most of them presenting with meningitis and a few with encephalitis, both in immunocompromised and immunocompetent hosts [91, 92]. It is interesting to note that all vaccine-caused meningitis cases had HZ for a median of 5 days prior to CNS symptoms. The reactivation time also varied widely, ranging from 3 months post-vaccination in an immunocompromised host to 11 years in an immunocompetent patient. Based on these few cases, clinical presentation of vaccine strain CNS disease does not appear to differ from wild type VZV CNS disease. This makes diagnosing vaccine strain reactivation difficult based on clinical presentation alone, and highlights the importance of genotyping and strain surveillance in distinguishing wild type from vaccine strain infections. According to the 2011 IOM report, the evidence convincingly supports a causal relationship between varicella vaccine and vaccine strain reactivation with subsequent VZV meningitis or encephalitis.

Polio

Oral Polio Vaccine

Vaccine Associated Paralytic Polio

Inactivated injectable polio vaccine (IPV) was introduced in the 1950s and dramatically reduced paralytic cases. However, it was after the switch from IPV to OPV that endemic polio was eliminated from the USA. The problem was that, while vaccine associated paralytic polio (VAPP) occurs rarely (4–6 VAPP cases annually or 1 case per 2.4 million doses); it occurs only after oral polio vaccine (OPV) and is as clinically severe as paralytic disease due to wild type polio virus [93]. By the 1990s, VAPP were the only non-imported paralytic polio cases in the USA. Thus, the ACIP recommended switching back to exclusive IPV in 2000 in the USA, to eliminate VAPP but maintain herd immunity against all three poliovirus serotypes. Since then VAPP in the USA has been diagnosed only in returning travelers from countries still using OPV [94].

Inactivated Polio Vaccine

For the most part only local reactions and fever are seen with any frequency, although allergic or hypersensitivity reactions may rarely occur after inactivated polio vaccine (IPV) (see section "Hypersensitivity"). No serious or unusual AEFIs have been noted due to IPV since the increased use of IPV in mixed regimens starting in1996 and the exclusive IPV use since 2000 [95, 96].

Influenza

The most common AEFI is local reaction to injectable TIV, which is expected in 15–20 % of recipients. Injection procedure-related reaction in the arm and shoulder may rarely occur (see sections "Pyogenic and Sterile Abscesses," "Extremity Swelling," "Deltoid Bursitis," and "Complex Regional Pain Syndrome"). Less common reactions are noted below.

GBS

The incidence of GBS has not been detected in influenza vaccine recipients at above expected background rates for the past 30 years. One vaccine nominally associated with an increased risk was the 1976–1977 vaccine that was commonly called the "swine flu vaccine." Vaccines with swine influenza-derived strains since that time have not had this issue, including the 2009 pandemic influenza vaccine (see section "Guillain–Barré Syndrome").

Mercury/Thimerosal

Thimerosal (also known as merthiolate) is a preservative in use since the 1950s to prevent growth of inadvertently introduced bacteria/fungi into multi-dose vials of injectable medications or vaccines, with influenza vaccine in multi-dose vials now being the only routine vaccine containing thimerosal in the USA. Because thimerosal contains a compound with mercury as one element, there has been confusion that it could contribute to mercury poisoning or toxicity. One source for the confusion is that the form of mercury in thimerosal has been mistakenly misinterpreted as having the same toxicity profile as that of *methyl* mercury or even *elemental* mercury, but this is not true. Thimerosal is not retained for long in the body post-immunization and is an organic *ethyl* mercury product that is quickly metabolized and its breakdown products rapidly excreted [97]. As a parallel example, this difference in toxicity is similar to that between ethyl alcohol and methyl alcohol, where

the human toxicity profile is very high for the methyl form but low for the ethyl form of the alcohol.

Nevertheless, since the year 2000, no routine pediatric vaccines contain thimerosal as a preservative. Some vaccines have trace levels of thimerosal left over from the manufacturing process (less than 0.3 μg thimerosal per 0.5 mL dose of vaccine), which is considered insignificant. The only pediatric vaccine with this trace is Tripedia®. The timeline for FDA rulings and findings concerning thimerosal and vaccines can be found on the CDC and FDA Web sites.

One misunderstanding about thimerosal in vaccines was the false theory of mercury poisoning from amounts in the routine vaccines back in the 1990s. Another false theory was that thimerosal increased the risk of autism. Neither is a true sequela of vaccines [98, 99].

A true thimerosal-caused AEFI, although uncommon, is thimerosal allergy, at times from topical exposure perhaps in the form of cosmetics. But not all such allergic skin-sensitized persons react when thimerosal is injected under the skin [100, 101]. Hypersensitivity to thimerosal has been postulated to be due to the thiosalicylic acid part of the molecule and occurs in approximately 0.1–1.3 % of multiply-exposed subjects [102]. Another true reaction to thimerosal is a delayed hypersensitivity reaction (see section "Delayed Type Reactions"). These are usually minor reactions, e.g., redness and swelling at the injection site. However, large >5 cm reactions can rarely occur.

Intranasal Live Attenuated Influenza Vaccine

In the week post vaccine, adult live attenuated influenza vaccine (LAIV) recipients have nearly twice the rate of rhinorrhea as placebo recipients (44.3 % vs. 26.6 %) with the duration averaging 2 days (range 1–7 days). Sore throat was more frequent in LAIV than placebo recipients (26.6 % vs. 16.3 %) [103]. In pediatric LAIV recipients ($N=4{,}179$), rhinorrhea occurred in 32 % compared to 21 % for TIV recipients ($N=4173$). The duration ranged from 1 to 10 days. Because LAIV is more protective than TIV, these mild AEFIs should not discourage providers from using this vaccine.

There was no overall increase in medically significant wheezing in the 42 days after LAIV compared to TIV. However, more wheezing was observed in children receiving their first LAIV dose at less than 12 months of age versus first dose of TIV prior to 12 months of age (3.8 % vs. 2.1 %, $P=0.08$) [104]. The investigators in this study pointed out that wheezing occurred mostly in week 2–4 post-vaccine when immune responses would be expected. Thus, it would not likely be the replicating vaccine virus triggering the wheezing, but the vaccinee's own immune system. The apparent excess wheezing in the youngest vaccinees is the rationale for LAIV not being indicated at less than 2 years of age and in those 2–4 years of age with a history of asthma.

Oculorespiratory Syndrome

Oculorespiratory syndrome (ORS) was first described as an AEFI in 2001 in Canada [105]. Clinical presentation includes bilateral red eyes plus respiratory symptoms (cough, sore throat) or facial edema between 2 and 24 h post immunization but resolving within 48 h [106]. Clinical manifestations of ORS vary with age, with a more rapid onset of symptoms in younger individuals but longer duration for older ones [107]. In one study, the risk of ORS in Canada was 6.3 % after influenza vaccine and 3.4 % after placebo injection, which yielded a significant vaccine-attributable risk of 2.9 % (95 % confidence interval, 0.6–5.2) [108]. According to the latest 2011 IOM report, there is a causal relationship between influenza vaccine and ORS, but only for the two particular vaccines used in three particular years in Canada [10].

Narcolepsy

Narcolepsy, an uncommon sleep disorder characterized by excessive daytime sleepiness (EDS) and cataplexy, is thought to be caused by the loss of hypocretin/orexin neurons in the hypothalamus, presumed to be secondary to an autoimmune process. Increased cases were reported following the H1N1 pandemic, raising the question whether cases were secondary to H1N1 infection or vaccination [109, 110]. Recently in Finland, narcolepsy has been associated with ASO3-adjuvanted H1N1 vaccine (Pandemrix®) with various intervals from vaccination to onset of narcolepsy [111]. In this report, the incidence of narcolepsy was 9.0 in vaccinated versus 0.7/100,000 person years in unvaccinated recipients, translating into a rate ratio of 12.7 (95 % confidence interval 6.1–30.8). This vaccine was not used in the USA. Investigations are ongoing, and include search for a narcolepsy-susceptible gene. In another Finnish report, 34 of the 54 narcoleptic children had the narcolepsy-risk allele DQB1*0602/DRB1*15 [112].

Rotavirus Vaccine

Prolonged Shedding

Shedding of vaccine virus from the pentavalent bovine-based oral vaccine (RV5, Rotateq®) occurs in 20–25 % of recipients of the first dose as early as post-vaccination day 3 and as late as day 9, with the peak on post-vaccination days 6 through 8 [113]. Shedding is more frequent (53 %) in premature infants born at 26–34 weeks gestation and immunized with the first dose at 6–14 weeks of age [114].

In different preclinical studies, vaccine virus shedding from dose one of the monovalent attenuated human-rotavirus based vaccine (RV1, Rotarix®) ranged from 50

to 80 % on day 7, 20 to 65 % on day 15, 0–24 % on day 30, and 0 to 3 % on day 60 post-dose. For dose 2, shedding ranged from 4 to 18 % on day, 7 to 16 % on day 15, and 0 to 1 % on day 30 [115].

In addition, reports of children with severe combined immunodeficiency who developed vaccine-associated rotavirus infection caused a 2011 revision in the package insert cautioning use in children with a severely immune compromised patient in the household [116]. The concern is that there could be transmission from vaccine virus in the stools of vaccinated infants [117, 118].

Intussusception

A temporal and likely causative relationship was determined for the rhesus-rotavirus-based oral vaccine (Rotashield®) released in the late 1990s in regards to the risk of intussusception. The vaccine was withdrawn later that same year. The rate was estimated at 1 case per 5,000–10,000 vaccinated infants, with most cases in the 3–14 days post dose, and most cases after the first dose of the series. Because of this, very large clinical trials with >60,000 subjects per arm were required to license the currently available bovine-based RV5 and the attenuated human RV1. Neither vaccine has been associated with increased risk of intussusception either in preclinical or postlicensure studies [119–121]. A recent suspicious signal for increased intussusception in Mexican children receiving RV1 has not been confirmed upon review of data from the USA, Canada, or Europe.

Quadrivalent (A, C, Y, W135) Meningococcal Conjugate Vaccine (MCV4)

The most common vaccine-caused AEFI are mild local reactions lasting 1–2 days in up to 50 % of recipients.

GBS

GBS received much attention in the lay press in 2005–2007 because of VAERS data that appeared to have a signal of a potential relationship. The two dozen or so GBS cases noted in the 6 weeks after MCV4 have not been causally related and appear to represent the background rate of GBS (see section “Guillain–Barré Syndrome”) a usually transient but serious nervous system disorder. There is insufficient evidence to determine whether any of these cases were actually caused by the vaccine. As of 2012, there were approximately 25–30 million immunized 11–19 year olds. Given that GBS has an estimated background rate of 1 case per 100,000 in 11–19 year olds, it is feasible that most if not all reported post MCV4 cases could be by chance.

However, the CDC and ACIP recommend continued watchfulness since data are not sufficient to completely rule out a very small increased risk. The CDC and AAP continue to recommend this vaccine because the risk of invasive meningococcal disease is 0.3–1.5 cases /100,000 in the overall population and the highest mortality (up to 50 %) occurs in teens and young adults.

HPV

Approximately 40 million doses of HPV vaccine had been administered as of March 2012. Most AEFIs following HPV vaccine have been minor, e.g., pain (80 %) and swelling at the injection site (25 %), fever, headache (30 %), dizziness, and nausea. Syncope has also been reported (see section "Syncope"). Anecdotally, girls have complained that the pain from HPV vaccine is more intense than with other vaccines, e.g., concomitant Tdap. This may contribute to post-vaccine syncope. Fever, usually low grade of up to 100 °F, occurs in ~10 %, but moderate fever, up to 102 °F, can occur in 1–2 %. Reports in VAERS of GBS or deaths after HPV vaccination, as of the first quarter of 2012, have not been found to be due to the vaccine.

Lymphadenopathy

There have been a few case reports of regional adenopathy after HPV vaccine [122]. No specific treatment is needed.

Vaccines for Special Populations

Rabies

The most common AEFIs after the human diploid rabies vaccine have been residual pain, erythema, swelling, or pruritus at the injection site (30–74 %); headache (20 %), nausea, abdominal pain, myalgia, or dizziness (5–40 %). A serum sickness like illness (urticaria, arthralgia, fever) also can occur and is more frequent (6 %) with booster doses than the primary series. GBS has been reported after rabies vaccine, but is so rare that current data do not allow differentiation as to whether this is by chance or from the vaccine [123].

The old duck embryo derived rabies vaccine that is no longer in use and was given subcutaneously in the abdomen was far more systemically and locally reactogenic and required more than twice the number of injections as the current vaccines [124, 125].

PPV23

Adults receiving a repeat dose of PPV23 had more arthralgia, fatigue, headache, arm swelling, and limitation in arm movement than those receiving first doses [126]. The rate of these AEFIs in children is unclear but there were few systemic AEFIs in one small study of revaccinated asplenic children [127, 128]. However, local reactions are more frequent (~50 %) and there are anecdotal reports of large local reactions in children with revaccination (~1 %) [129].

Causality

In assessing AEFIs, several questions need to be considered when trying to establish a causal link [130–132]. First, does the AEFI occur within a reasonable time after the vaccine? Second, is there scientific plausibility that the event could be due to the vaccine? And finally, is there an alternative confirmed cause of the event?

AEFIs that are *caused* by vaccines usually occur in close temporal relationship with vaccination, e.g., fever after DTaP, but may rarely occur years after inoculation, e.g., herpes zoster after VZV vaccine. When the event is not closely related in time to vaccination, linking the vaccine to the event is more difficult. Exceptions include isolating Oka virus vaccine strain from a clinical specimen even if the zoster AEFI occurred years after vaccine. In the zoster example, isolation or PCR detection of Oka vaccine strain virus, and not wild type virus, from zoster lesions confirms that vaccine caused the clinical zoster regardless of time since vaccination.

On the other hand, events that occur in close temporal relationship to vaccination are not necessarily vaccine related, because temporality is not proof of causation. These events may have occurred even without vaccination and therefore are merely part of the background rate of the event that occurs at all times in non-immunized populations. Fever is a good example of this. Because fever is such a common childhood event, it is practically impossible to be absolutely confident in any individual case that a fever in the first few days post vaccine is caused by the vaccine. It is also uncommon to have proof that the fever is due to another cause, e.g., a concurrent viral illness. Thus, temporal proximity does not prove or disprove causation in the evaluation of AEFIs. One could postulate that a child was incubating a viral illness when the vaccine is administered so that the fever would, in this situation, have occurred regardless of vaccine receipt. But to be sure would require laboratory confirmation, a test that is not routinely indicated clinically when a child presents with an uncomplicated viral illness.

Febrile seizures following vaccines are another AEFI for which there is a known background rate in children (immunized or not), for whom a febrile viral illnesses is the trigger. So how do we establish that a febrile seizure was caused by a given vaccine? Epidemiological data and background rates of febrile seizures have been useful tools when a vaccine is suspected of causing febrile seizures. This same

approach can be used for other AEFIs, e.g., the disproven theory that MMR vaccine caused autism, to bring clarity to whether the rate after vaccine is greater than the background expected rate in a similar cohort that has not received the vaccine. This in fact is one aspect of how AEFIs nominally linked to vaccines are evaluated [133]. However, these data are not easily used in assessing causality at the individual case level. Meticulous algorithms may be of use in such cases [130, 131]. In addition, novel-case-centered or self-controlled methodologies have been recently used in the assessment of vaccine AEFIs [14, 134, 135].

Biological or scientific plausibility also needs to be considered along with epidemiologic evidence. For example, even if the number of deaths due to automobile accidents is higher than background in a cohort of subjects who received an infant vaccine, there is no scientifically plausible explanation for an infant vaccine causing more automobile accident deaths.

In assessing causality, other recognized causes of the clinical event need to be evaluated. For example, fainting spells in HPV vaccine recipients was determined to be due to vasomotor events that can occur after any needle puncture in a cohort of the same age. Thus, the syncope is not due to the HPV vaccine, but the *injection procedure* itself [136]. However, in causality evaluation, a clinical investigation surrounding an event may not always take place. It depends on if further diagnostic tests are thought necessary by the provider for clinical care, if they would change patient management, or if they are even attainable. In short, it can be difficult in any individual case to determine causal association without considering a large number of additional factors. Thus, a true association requires that the AEFI be scientifically plausible and it occurs at a higher rate in vaccine recipients than the general population in a cohort matched for age, underlying conditions, etc.

Genetic Predisposition to Adverse Event

It is a well established fact that some children more likely have AEFIs post-vaccination (temporally related) than adults. This occurs for several reasons.

Children receive routine immunizations at ages when they are too young to have shown signs or symptoms yet of a congenital immune deficiency. Those with immune deficiencies are more likely to have complications with live virus vaccines (which is why in some immune-deficient hosts live vaccines are contraindicated, or the risk–benefit needs to be considered prior to administration).

There are also metabolic or genetic issues that may predispose a child to AEFIs and these are often not diagnosed until ages beyond those when routine vaccines are given. For example, a severe seizure disorder (Dravet Syndrome) associated with mutations of the sodium channel gene SCN1A has been shown to be responsible for a number of encephalopathy cases previously thought to be caused by pertussis-containing vaccines [57, 58]. In these cases, the pertussis vaccine appears to have uncovered this congenital underlying abnormality that had not yet been diagnosed.

These children will inevitably develop the same symptoms even without immunization due to other stresses, perhaps even a common viral illness. The genetic predisposition makes them particularly vulnerable to external insults, such as metabolic imbalance, infections or vaccinations.

For selected other conditions, such as inborn errors of metabolism, recent studies have actually demonstrated that recommended immunizations are not associated with increased risk for serious AEFIs [137, 138]. As in these examples, many other genetic or metabolic defects are being discovered as science links disease to gene variations. Vigilance is needed to evaluate these individually as they are discovered to determine whether or not the genetic abnormality predisposes those with the abnormality to a worsening of or simply uncovering their condition.

Conclusion

There will not likely ever be a vaccine that is both effective and free of risk from any AEFI. The clinician's role is to understand this concept and constructively advise families on the risks–benefits prior to administration. Further, when events occur after vaccine administration, it is important to understand if any specific or just supportive care is needed. The provider, as best as possible, also needs to decide whether the event is caused by the vaccine/s or coincidental with recent vaccine administration. Clinicians and public health or policy makers must be clear in statements about AEFIs so that the public is not misinformed as to which AEFIs are truly caused by vaccines. The information in this chapter adds a concentrated source of information about expected and rare AEFIs and the ones that are known to be caused by vaccines. This should hopefully reduce the difficulty of the task of advising families about AEFIs, help with the decisions on whether the remaining vaccine schedule needs to be modified, and assist in policy decisions about vaccines.

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Chapter 4
Communicating Vaccine Risks and Benefits

Clea Sarnquist and Yvonne A. Maldonado

Background

Parents of pediatric patients as well as adult patients themselves have many concerns and sometimes, misperceptions, about vaccination. These concerns lead to under-immunization in both pediatric and adult populations. Among children, a 2010 study showed that approximately 22 % of parents intentionally delay vaccinations [1]. Among adults, only about 62 and 37 % of healthcare workers received, respectively, a seasonal influenza vaccination and an H1N1 vaccine in 2009–2010 despite the national attention to the H1N1 pandemic [2]. Insufficient vaccine coverage leads to preventable cases of infectious diseases [3–5]. In addition, children and adults who cannot be immunized, as they are too young (children) or have other contraindications (either population), or those who have been vaccinated but had an insufficient immune response, are put at risk [6, 7]. Timely and complete immunization coverage is thus of significant public health importance, and healthcare providers are on the front line of ensuring such coverage.

Although many of the fears that both parents and adult patients have are unfounded, some are realistic. In order to ensure that both evidence-based risks and benefits are understood, it is essential that providers are prepared to communicate effectively about vaccination. Many studies have shown that possibly the most important component in the decision to immunize is the individual's relationship with their healthcare provider. In particular, trust in the provider, the provider's recommendation for vaccination, and the provider's responses to questions and concerns about immunization, are essential [1, 5, 8–12].

This chapter aims to briefly review barriers to vaccination (which are discussed more in-depth in other chapters), to review communication practices to overcome

C. Sarnquist, Dr. P.H., M.P.H. • Y.A. Maldonado, M.D. (✉)
Division of Pediatric Infectious Diseases, Department of Pediatrics,
Stanford University School of Medicine, Stanford, CA, USA
e-mail: bonniem@stanford.edu.

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these barriers, and to provide a set of practical best practices and resources, some of which are updated regularly, that providers and educators can access to improve vaccine risk–benefit communication.

Parent and Patient Barriers to Vaccination

Objections to vaccination by both parents and adult patients have been extensively documented and are discussed in other chapters of this book. In brief, they include the following: (1) beliefs that vaccines are unsafe (for example MMR causing autism or the influenza vaccine causing flu) and/or ineffective [13, 14]; (2) fear of real or perceived side effects, including mild side effects like pain and fever [8]; (3) beliefs that too many vaccines are given in one visit or the early years of life, causing immune system overload [12]; (4) beliefs that the diseases vaccines are given to prevent are mild (for example varicella) and/or uncommon [8, 15]; (5) mistrust of healthcare providers, government and officially endorsed vaccine research [16]; (6) trust in nonofficial information sources (for example the Dr. Sears alternative vaccine schedule [17]); (7) resentment of the perceived pressure to risk their own or their child's safety for public health benefit [18, 19]; and (8) concerns that vaccines are too new or insufficiently tested, for example the H1N1 and Human Papilloma Virus (HPV) vaccines.

Effective Risk–Benefit Communication

Many of the aforementioned barriers can be overcome or mitigated by timely and effective communication between the provider and patient or parent. As previously discussed, most studies find that the leading source of trusted information on vaccination are healthcare providers.

There is considerably more literature available on risk–benefit communication in medicine in general than specifically related to vaccines. Regardless of the field, risk communication is a challenging topic since a person's belief system, values, and personal experiences all shape their perception of risk, often regardless of the available evidence [20, 21]. Furthermore, in medical risk communication, the beliefs and experiences of the provider shape the discussion [22]. It is also rare that an individual seeks information from only one source, as family members, friends, and the media provide many perspectives. Therefore, risk communication becomes a complex process where the provider must understand the patient's background and values, as well as his/her own biases, and shape appropriate messages.

Several barriers to effective communication about vaccine risks and benefits in both adult and pediatric populations have been documented, including (1) the amount of time that sensitive and effective communication takes [23], (2) other

health issues that take precedence, (3) the belief that a conversation is unlikely to change the parent or patient's mind about vaccination or that the parent/patient would not understand risk and benefit information, and (4) lack of sufficient knowledge about vaccine safety or how to communicate risk [23–26]. A variety of techniques have proven to be effective in helping overcome many of the aforementioned barriers for children and adults. Specifically, effective communication about risks and benefits regarding vaccines includes some or all of the following:

1. Listening carefully to concerns, soliciting questions, and acknowledging risks associated with vaccination [10, 27].
2. Providing a tailored mix of scientific information and anecdotes, both verbally and via printed materials, to convey risks and benefits depending on individual patient needs and literacy levels. This may also include providing the same information in different formats or at different levels when providers are uncertain which format will resonate with or be understandable to the patient or parent [20, 28, 29].
3. Preparing to respond to at least the most common concerns about vaccination, such as MMR or thimerosal causing autism, there being too many vaccines in one visit or early in life, vaccines being "too new" or insufficiently tested, or the probability of serious adverse effects [27].
4. Encouraging dialogue and conversation to build trust around vaccination over time [10, 19].
5. Clarifying risks associated with vaccine-preventable diseases in adults and children, and managing those risks where possible [16, 19].
6. Providing information about the benefits of vaccination [23].

In addition, if providers give strong personal support to vaccination, for example saying "I vaccinated (or intend to vaccinate) my children according to schedule and believe strongly that this is important for your child," or "I get my flu vaccine every year and really believe it is important," evidence suggests that patients and parents are more likely to vaccinate [5, 11, 23]. Finally, the ideal communication strategy includes providing information in small pieces over time, often starting at the first well baby visit, rather than all at once at the same time parents have to make vaccination decisions [30]. Resources to help providers achieve all of the above, in a limited time, during vaccine conversations are covered in the section below entitled "Resources and Promising Practices."

While the above principles are generally relevant in conversations with adult and adolescent patients, as well as with parents of pediatric patients, there are of course some important differences. Pediatric and adolescent vaccine risk communication is both subject to legal requirements and, with older children, frequently involves both a minor adolescent and one or more parents. Federal law, the National Childhood Vaccine Injury Act (NCVIA) of 1986, requires that providers present, at the minimum, a vaccine information statement (VIS) when administering each dose of certain childhood vaccines [31]. These statements may be a valuable jumping-off point for vaccine-related conversations. Research suggests, however, that up to 31 % of pediatricians and 28 % of family medicine specialists do not even provide that, despite the federal mandate to do so [32, 33].

Vaccination rates among adolescents are much lower than among children, yet adolescents are at increased risks of some serious diseases, such as meningococcal meningitis and HPV. Therefore, they may require additional attention at clinic visits in order to convey the importance of vaccination to them and/or their parents. This is especially important since it can be difficult to maintain adherence to recommended clinic visits during the adolescent years.

Resources and Promising Practices

Despite the barriers to communication, there are many resources and educational materials available to providers to facilitate and learn more about vaccine risks–benefits communication.

Resources for Provider Education and Patient Materials

Several recent resources are available for providers to learn about how to educate and interact with both adult patients and parents of pediatric patients. Most notably, the Centers for Disease Control and Prevention (CDC), American Academy of Family Physicians (AAFP), and the American Academy of Pediatrics (AAP) recently collaborated to create a Web site (http://www.cdc.gov/vaccines/spec-grps/hcp/conversations.htm) with materials both for provider reference and for providers to give parents. This Web site includes written materials, videos, and reference materials such as immunization schedules, and covers topics from suggestions for preparing for conversations with parents to facts on vaccine safety to ways to respond to vaccine refusers [34]. Providers can also opt-in to receive e-mails when materials are updated. CDC also maintains a "Healthcare Provider Portal" with up-to-date immunization information and patient education materials at: http://www.cdc.gov/vaccines/hcp.htm.

There are also many online resources for providers and teachers of medical students and residents to find self-education opportunities as well as teaching tools. Ideally, training in risk–benefit communication related to vaccination would be strengthened in medical school and residency programs [35], as a recent study found that 85 % of primary care residents felt that such communication skills would be "very" or "somewhat" important in their careers [36]. Continuing education opportunities for practicing physicians across their careers are also important [37].

Examples of learning and/or teaching materials include:

1. A CDC clearinghouse for self-education and teaching materials at http://www.cdc.gov/vaccines/ed/courses.htm. This resource includes webcasts and self-paced modules covering adult, adolescent, and pediatric immunizations [38].

2. The World Health Organization's E-learning course on Vaccine Safety Basics at http://www.who.int/vaccine_safety/initiative/tech_support/ebasic/en/index.html. These resources cover risk communication as well as the origin and nature of adverse events and the importance of pharmacovigilance. Resources are available in online format or as a downloadable PDF and CD-ROM.
3. The "Teaching Immunization Delivery and Evaluation (TIDE)" Project: This resource, at http://www2.edserv.musc.edu/tide/menu.lasso has self-paced modules on pediatric and adolescent immunization, as well as more general vaccine-related topics, and provides continuing medical education credits (CMEs) [39].
4. A resource for medical residents in pediatrics, family medicine, and internal medicine, and those who teach residents, has recently (2011) been released by AAP-California (http://vaccinecommunicationresource.wikispaces.com). It is specifically aimed at teaching residents in pediatrics, family medicine, and internal medicine about how to communicate vaccine risks and benefits. It includes a set of online cases that residents can review at their own pace, a set of written cases for use by preceptors or in small group discussions, and a set of slides that can be tailored or mixed and matched to create presentations on vaccine risk communication [40]. Preliminary evaluation data suggest that residents found this curriculum to be a good use of time, likely to be useful in their future practice, as well as increasing skills such as answering vaccine-related questions and being more comfortable discussing vaccines [41].
5. Another resource for teaching medical residents and medical students about vaccination was created and tested by the "Teaching Immunization for Medical Education (TIME)" Project. TIME consists of case-based modules for small group and contextual learning. Pre-post testing showed that TIME significantly increased immunization knowledge [42, 43].

Promising Practices

There are many models available in the literature that focus on improving communication in order to increase uptake of vaccines, although virtually none of them quantify vaccine uptake as an outcome. Nonetheless, these models show promise in improving communication, and may be able to be adapted and used by providers in their own offices or by researchers or public health officials looking to improve vaccination rates in a community. Most of these are focused on simplifying the process in order to communicate effectively in a limited amount of time. They are broken into two categories:

Educating Healthcare Providers on Communication

A 2002 study involving a brief intervention with practicing pediatricians found that a combination of a practice-based in-service and practice materials such as an

examination room poster significantly increased VIS distribution, physicians and nurse dialogue with parents, and parents asking questions [33]. Importantly, physicians reported spending only an extra 20 s with patients in order to realize these gains.

A similar model from 2006 focused on public health nurses, also providing in-service training and educational materials to nurses in public health clinics. This intervention resulted in significantly more discussion of some, but not all, aspects of vaccination (specifically severe adverse effects), and significantly increased both parent questions about vaccines and parent satisfaction with vaccine risk-communication [44]. Average vaccine communication time increased by 6 s, from 16 to 22 s.

Improving Delivery of Information to Parents and Patients

Traditionally, vaccine risk and benefit communication with patients and parents by providers has taken place entirely in the office setting. It is rare, however, that parents are only looking for such information in the visit setting, and some parents who report feeling rushed or that they were given insufficient information are less likely to immunize. In addition, written materials such as the VIS may not be the ideal method for communicating with parents who have low literacy levels and/or are more accustomed to digesting information through other forms of media. The ideal may be enhancing the information in the VIS with other sources. For example at least one study has shown that videos can enhance parental understanding about vaccines [45]. One such video can be found at the previously mentioned CDC resource, http://www.cdc.gov/vaccines/spec-grps/hcp/conversations.htm.

Furthermore, modern communication options, such as e-mail, texting (SMS), and directing parents to reliable Web-based sources of information may provide new avenues for fast, efficient communication around vaccine risks and benefits beyond just the VIS. As electronic medical records and appointment reminders become more common, opportunities to use technology to enhance the information transfer process will increase. For example, a 2008 study found that sending targeted text messages describing the consequences of reduced vaccine coverage, but not other vaccine-related topics, to mothers who previously reported vaccine safety concerns resulted in these mothers reporting more positive opinions about vaccination compared to a control group [21].

As previously discussed, ideal vaccine-related communication is an ongoing process and not something that only happens minutes before vaccines are given. For example, a combination of proven materials can be offered [46], including a vaccine information packet to be given at a visit before immunizations are given so that parents have the opportunity to read and digest the information before making decisions. Examples of materials a packet may include are (1) appropriate VIS, (2) an “open communication” letter stating the physicians commitment to vaccines as well as encouraging communication on the topic [47], (3) a list of discussion questions to help parents think through the immunization discussion and start dialogue with the provider, such as “Do you have any fears about vaccine safety that you’d like to

discuss?" [48], and (4) a list of vaccine information sources that can be trusted, such as the Web sites of the CDC (www.cdc.gov), the AAP (www.aap.org), and the Immunization Action Coalition (http://www.immunize.org/) [49]. Sometimes communication about vaccination begins even earlier than the well-baby visit, with obstetricians or prenatal care group classes at hospitals providing early information [50].

Conclusions

Effective healthcare provider communication and positive recommendations are essential in encouraging patients and parents to follow recommended vaccination schedules for themselves and their children. As vaccination is one of the most cost-effective, simple ways to keep people and communities healthy, ensuring that providers have adequate resources to support their knowledge about vaccination risk–benefit communication is essential. Therefore, this chapter focused on providing information on resources for learning about vaccine-related communication as well as examples of successful vaccine communication interventions and strategies.

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Chapter 5
Vaccine Refusal: Perspectives from Pediatrics

Kody Moffatt and Clancy McNally

Introduction

Most histories of immunization cite the leadership of Lady Mary Montague, who in 1717, 2 years after her brother died and she herself was scarred by smallpox, observed the practice of variolation (inoculation of infectious fluid from a lesion from a mild case of smallpox to induce immunity) in Constantinople, Turkey [1]. Just 79 years later, in 1796, the work of Benjamin Jesty and Edward Jenner culminated in the vaccination of Jamie Phipps, and the rest is history. The scourge of small pox was declared eradicated in 1980 [1, 2].

More than 70 bacteria, viruses, parasites, and fungi are serious human pathogens [3, 4]. Vaccines are available against some of these agents and are being developed against almost all the other bacteria and viruses and about half of the parasites [4]. Over the last four decades, routine childhood immunization in the USA has led to the eradication or control of several vaccine-preventable diseases, including smallpox, polio, diphtheria, *Haemophilus influenzae* type b (Hib), measles, mumps, and rubella [5–8]. Vaccines have been described as the single most life-saving accomplishment of the twentieth century [9, 10]. Parents and many health care providers of the twenty-first century, particularly in more developed areas of the world such as the USA and WE, have limited or no experience with the devastating effects of these diseases. In the US public health officials now recommend 28–31 vaccine doses before the age of 18 years, many of which are administered together to provide protection early in life, for the convenience of families and health care providers, and to decrease distress to the infant [9]. Public health experts recommend that 95 % of the population be vaccinated to provide herd immunity and minimize the possibility of resurgence of these deadly infections. However, parents in developed countries who

K. Moffatt, M.D., M.S. (✉) • C. McNally, M.D.
Department of Pediatrics, Creighton University School of Medicine,
4802 Shannon Dr., Bellevue, NE 68133, USA
e-mail: kmoffatt@childrensomaha.org

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have not seen these diseases or their disastrous consequences sometimes feel that they are being pressured into immunizing their children involuntarily for public good rather than personal benefit [9, 11]. Some parents even perceive a greater risk to their children from vaccination than from the diseases themselves, not recognizing that the threat from these diseases is reduced simply because we do have effective vaccines to prevent them. Vaccination has thus regrettably become a polarizing issue with some parents stressing their own child's well-being at the one extreme and health experts advocating for public health outcomes on the other [9].

Vaccine Refusal History and Parental Concerns

Historically, the first modern systematic review of the reasons for parents refusing to vaccinate was published in response to parental actions during the polio epidemic when researchers endeavored to learn why parents failed to vaccinate their children with the Salk polio vaccine [12, 13]. Rosenstock et al. showed that there were four psychosocial domains that influenced parents' decisions to vaccinate their children: (1) susceptibility—parents' assessment of their child's risk of contracting polio; (2) seriousness—their assessment of whether polio was a sufficient health concern to warrant vaccination; (3) efficacy and safety—their assessment of whether vaccinating their child can reduce the chance of their child's contracting polio, and whether the vaccine is safe; and (4) social pressures and convenience—the concerns and influences that facilitated or discouraged their decision to get their child vaccinated. These factors soon became the basis for the Health Belief Model which has been used throughout public health to explain why people adopt behaviors that lead to healthy lives [12].

Today, little has changed. A 1999 national telephone survey indicated that almost one fourth of parents felt uncertain about the increasing number of childhood vaccines, and parents with alternative medical orientations had more concerns and were more likely to have misconceptions about vaccines than parents with a conventional medical orientation [14, 15]. Fredrickson et al. provide a thorough contemporary review of the subject [14]. Their analysis showed several reasons for parent refusal of child vaccinations, including erroneous beliefs about contraindications, not wanting to expose children to perceived dangers of vaccines, and not wanting to deliberately expose healthy children to diseases. In addition, studies focusing on vaccine decision-making have found that parents may prefer to make errors of omission (bad outcomes due to lack of action; here, not vaccinating a child) rather than errors of commission (bad outcomes due to action; here, vaccinating a child) and that they may find it easier to accept "natural" risks rather than "man-made risks" [14]. Parents' cognitive processes—specifically their perceived ability to control their child's susceptibility to the disease and the outcome of the disease, as well as doubts about the reliability of vaccine information—have also been noted as reasons some parents forgo some childhood vaccines [14]. Some parents disagree with the practices of conventional medicine, and of this group, some believe in "natural healing"

and think it is better for children to be exposed to the diseases and get over them naturally. Others refuse based on religious convictions, while others view compulsory vaccination as an unnecessary infringement on individual rights [14].

School immunization requirements have been one of the most useful tools in increasing immunization rates in children. Laws requiring that children be immunized before they begin school have contributed to a 98–100 % reduction in the incidence of most vaccine preventable diseases [16, 17]. All states permit exemptions for individuals who have medical contraindications to vaccination. Nonmedical exemptions are generally categorized as religious or philosophical. Forty-eight states permit religious exemptions (all but Mississippi and West Virginia), and 19 permit philosophical or personal exemptions [17]. Some religious leaders from faiths such as Islam, Christian Science, Mennonite, and Amish counsel against some or all immunizations [18, 19]. Vaccines may be perceived as invasive, unnatural, immoral, or directly prohibited by God or another supreme authority [18]. Some parents have expressed moral concerns regarding certain vaccines due to the acquisition of the initial cell lines in which vaccine viruses are grown, from voluntarily aborted fetuses. The specific vaccines are:

1. Single-antigen vaccines against rubella
2. Multiantigen vaccines against MMR
3. Single-antigen vaccine against chickenpox
4. Vaccines against hepatitis A [20, 21]

In response to these concerns, the US Conference of Catholic Bishops has issued statements relieving parents of the obligation to refuse these vaccines based on the Catholic Church's opposition to voluntary abortion. The Catholic Bishops have noted that the source of the cell line for the vaccines was not the choice of the parents and the only viable option to protect their child and the community from serious illness is to take the vaccine [20, 22].

Those who are "philosophically opposed" to vaccines often argue that parents' civil rights, including the right to determine the liberty of their children, are being violated, and that the government (which they view as including both public health workers and other governmental officials) is misleading the public about the safety of vaccines. These individuals oppose universal childhood immunization on the grounds that vaccines are not safe. They question the leadership of the government and public health agencies who they believe push for unquestioning acceptance of childhood vaccines and argue that the government is being influenced by highly profitable pharmaceutical companies [23].

Early in US history, compulsory vaccination was linked to school attendance. Parents were required to have their children vaccinated in order for them to be allowed in school. In protest, many parents refused to send their children to public school. In a 1905 US Supreme Court case, Jacobson v. Massachusetts, the Court upheld the right of the state to use penalties (such as exclusion from school) to pressure people to be vaccinated [23].

There is considerable documentation of the relationship between exemptions and increased risk of vaccine-preventable diseases. Feikin et al. showed exempt children

in Colorado were 22 times more likely to contract measles and about 6 times more likely to contract pertussis than vaccinated children [24]. Their study showed schools that had pertussis outbreaks had a higher percentage of exempted children than schools without outbreaks (4.7 % versus 1.3 %; $p<0.001$) [24]. At least 11 % of children who developed measles after having received one dose of vaccine were infected through contact with an exempted child [24]. Salmon et al. showed in a national study, exempt children were 35 times more likely to contract measles than vaccinated children [25]. Salmon was later quoted as saying choosing not to vaccinate has consequences because most vaccine preventable diseases "are still around and reemerge when children are not vaccinated" [26]. Glanz et al. later found that while unvaccinated children made up about 0.5 % of the examined population, they accounted for about 12 % of the pertussis cases [5]. Children who cannot be immunized for medical reasons, children who are too young to be vaccinated, and the few who do not respond to vaccines are at risk of contracting vaccine preventable diseases from unimmunized or underimmunized children with exemptions.

Rooted in the social context of the individual, lay knowledge arises from numerous sources of data, which may be viewed as illegitimate by the expert, but are nonetheless considered valid by the lay person. Expert knowledge, in contrast, is grounded in scientific evidence, in theories supported and disproved, in trends, and objectivity [27]. Lay perceptions are based on personal experience and personal (i.e., nonscientific) information gathering [28]. As Johnston notes, specific to anti-vaccination groups, "A theme that runs through all the criticisms of specific vaccines is an insistence that individual experience, even if highly emotional, has just as compelling a claim on public attention as the cool, rational claims of science" [29].

One widely circulated report that is often cited by members of the anti-vaccination movement links the economic interests of the pharmaceutical industry and members of the Advisory Committee on Immunization Practices (ACIP) [30]. By insinuating financial connections and that the ACIP board members are profiting from their recommendations, this report and others like it attack the credibility of ACIP's recommendations. Other anti-vaccination Web sites explore connections between funding for vaccine research and research findings, calling into question the validity of research that was funded by pharmaceutical companies, findings that shape both the policy and the practice of individual physicians [23].

The child, maternal and household characteristics associated with vaccine delay and refusal have been studied as well [12]. Generally, parental delay/refusal has been associated with factors related to higher socioeconomic status. For example, children whose parents delayed and refused vaccines were significantly more likely to live in a household with an annual income >400 % of the federal poverty level; to have a mother who was married, ≥30 years of age, English-speaking, or a college graduate; to be covered by private health insurance; and to live in a household with ≥4 children who were 18 years of age or younger [12, 31]. Also, children whose parents delayed and refused vaccines were more likely to be of non-Hispanic white race/ethnicity than those who neither delayed nor refused [12]. These parents were more likely to agree that if they vaccinate their child, he/she may have serious side effects, and that

too many vaccines can overwhelm a child's immune system. They were more likely to say that the reason for delaying and refusing was because "there were too many shots". Also parents who refused vaccines were significantly more likely to report that the reasons for their decisions were due to concerns about autism, vaccine effectiveness, and vaccine side effects, or because they had heard or read negative things about vaccines in the media [12].

Gullion et al. suggest members of today's anti-vaccination movement are educated and belong to the middle class. The individuals in their study were highly educated (all had some college education and 44 % had some level of graduate school education). They subscribed to a natural-living philosophy with 88 % describing aspects of their lifestyle that could be categorized as "alternate living," such as veganism/vegetarianism; organic gardening; use of natural healing remedies, including herbal and homeopathic agents; and seeking chiropractic care for primary health maintenance. Mention of use of midwives and natural child birth as well as breastfeeding were also frequent [23]. Evidence of sophisticated data collection and information processing was a repeated theme in their subjects (vaccine refusers). This finding may reflect the overall high education level of the participants. Data were gathered from a number of sources and then processed by the participants, who then arrived at the conclusion that vaccines were harmful. Recurrent phrases included "medical journals," "peer-reviewed," "extensive research," "reading case studies," "research on the internet," "books and educational materials," and "alternative magazines and books." One participant noted,

> I put faith in, you know, obviously, peer-reviewed medical journals are obviously probably my most favorite source, but then also I take independent doctors that have written articles outside of peer-reviewed journals as a good source of information as well. And then also, you know, books that have been written by pediatricians or people that are involved in children's health in general.

While peer-reviewed journals were seen as a source of reliable information, there seemed to be little understanding of how individual studies fit into the broader body of knowledge. For example, while the participants were generally aware of the Wakefield et al. [32] paper that proposed a link between the MMR vaccine and autism, they were not familiar with the studies that followed which refuted that finding. In this case, Wakefield and his colleagues are viewed as the reliable experts while researchers with dissenting opinions are viewed as biased. Part of what defines expert knowledge is the understanding of the history and development of ideas, as well as the ability to make connections between works, which is lacking in the lay review of the literature [23].

A second theme prevalent in Gullion et al.'s work revolved around perceived bias in the data on vaccines. While participants placed a high value on scientific knowledge, they also expressed high levels of distrust of the medical community. Who qualified as a trustworthy source of information varied. Several mentioned that they valued the opinion of their midwife over that of their pediatrician. Physicians who had written books about the dangers of vaccines were also viewed positively. There was a perception that these doctors were courageous for speaking out against their

peers, possibly to the detriment of their careers. Many felt that physicians were biased in their attempt to get parents to vaccinate, that they had specific agendas, including profit from the sale of vaccines [23].

Fredrickson et al. analyzed the cognitive process of parents in two focus groups of vaccine refusers. They found these parents believed that breast-feeding their babies into childhood and keeping them out of day care would protect their children from most vaccine-preventable diseases [14].

In a well-designed study in Wisconsin, Salmon et al. investigated the differences in vaccine attitudes, beliefs, and information sources among parents of exempt and vaccinated children. In their study, the most common reason reported for parents claiming nonmedical exemptions for their child was the vaccine might cause harm (57 %). Additional reasons reported by 20 % or more of the parental respondents include the following: it was better to get natural disease than a vaccine, the child was not at risk for the disease(s), risk of autism, safety concerns regarding thimerosal, vaccines might overload the immune system, and the disease(s) were not dangerous [19]. Parents of vaccinated children were more likely than parents of exempt children to report individual benefit from vaccination (93 % versus 61 %) and community benefit from vaccination (88 % versus 57 %). Parents of vaccinated children were less likely than parents of exempt children to report a benefit for vaccine companies when a child is fully vaccinated (74 % versus 82 %). The trust in health care professional construct showed high internal consistency with parents of vaccinated children being more likely to report high trust in health care professionals than parents of exempt children (87 % versus 68 %). Parents of vaccinated children were more likely to have high trust in government compared to parents of exempt children (35 % versus 24 %). However nearly 25 % of parents of vaccinated children reported that children get more immunizations than are good for them, and 34 % expressed concern that children's immune systems could be weakened by too many immunizations. The majority of parents of vaccinated (92 %) and exempt (84 %) children reported their child's primary care professional to be a doctor or physician. Among parents of exempt children, 5 % relied on chiropractors and 5 % on naturopathic doctors as their primary health care professionals; no vaccinated children relied on these types of professionals as their primary health care professional [19].

In a four-state study, approximately 30 % of parents of vaccinated children had vaccine safety concerns that are not supported by available data. This study also found that 30 % of parents of exempt children reported that their children were fully vaccinated despite the school having an exemption on file and investigated why this may have occurred. Less than half of these parents believed their children were immune, and the reasons provided for waivers remaining on file were diverse [19, 33]. This finding is important for at least two reasons. First, state level estimates of exemptions may overestimate the number of children who are actually susceptible to vaccine preventable diseases. Second, studies that have examined the relative risk of measles and pertussis for exempt compared to vaccinated children (exempt incidence divided by vaccinated incidence) included all children with exemptions in school records in the denominator for exempt incidence [19, 24, 25].

Kata studied anti-vaccination misinformation on the Internet in the USA and Canada and found safety themes were present on all anti-vaccination Web sites analyzed. Every site claimed vaccines are poisonous and cause idiopathic illness. Sites stressed that vaccines contain substances poisonous to humans, including antifreeze, ether, formaldehyde, mercury, and nanobacteria. Pertinent information was not elaborated upon—for instance, that the amount of potentially harmful substances in vaccines is not enough to produce toxic effects in humans, or that ether does not refer to the anesthetic but to a chemical compound. Studies showing no link between vaccines and illnesses such as autism were ignored [34].

Examples of unsubstantiated claims made about some vaccines include the following [35]:

Measles	Autism and related developmental disorders
Diphtheria–pertussis–tetanus	Sudden infant death syndrome; epilepsy
Haemophilus influenzae type b	Diabetes mellitus
Inactivated polio	Paralytic poliomyelitis; simian virus 40 infection
Anthrax	Fatigue; Gulf War syndrome
Lyme disease	Chronic inflammatory arthritis
"Hot Lots" (some batches of any vaccine)	Multiple systemic problems
Multiple vaccinations	Undefined harmful immunologic interaction effects

Overall, there is no firm scientific or clinical evidence that the administration of any vaccine causes a specific allergy, asthma, autism, multiple sclerosis, or the sudden infant death syndrome [4].

Addressing Parental Concerns

Vaccine safety concerns were identified as the primary reason for vaccine refusal during investigation of a recent measles outbreak in Indiana, the largest such outbreak in the USA in a decade [36]. There are solid data available to address at least some of these parental concerns. Dr. Paul Offit is notably one of the world's experts in vaccine medicine. In 2002 he and his colleagues sought to address the question of the potential for multiple vaccines to overwhelm or weaken the infant's immune system [37]. Their well-written review remains one of the foremost publications on the subject.

Offit et al. noted that the young infant is fully capable of generating protective humoral and cellular immune responses to multiple vaccines simultaneously. Approximately 90 % of infants develop active protective immune responses to the primary series of diphtheria–tetanus–acellular-pertussis, hepatitis B, pneumococcus, Hib, and inactivated polio vaccines given between 2 and 6 months of age [37, 38]. Conjugate vaccines induce protective immune responses in infants that are often greater than those found after natural infection [37, 39].

In specifically addressing the question of whether or not vaccines "overwhelm" the immune system, current data suggest that the theoretical capacity determined by the diversity of antibody variable gene regions would allow for as many as 10^9 to 10^{11} different antibody specificities [40]. But this prediction is limited by the number of circulating B cells and the likely redundancy of antibodies generated by an individual. A more practical way to determine the diversity of the immune response would be to estimate the number of vaccines to which a child could respond at one time. If we assume that (1) approximately 10 ng/mL of antibody is likely to be an effective concentration of antibody per epitope, (2) generation of 10 ng/mL requires approximately 10^3 B-cells per mL, (3) a single B-cell clone takes about 1 week to reach the 10^3 progeny B-cells required to secrete 10 ng/mL of antibody (therefore, vaccine-epitope-specific immune responses found about 1 week after immunization can be generated initially from a single B-cell clone per mL), (4) each vaccine contains approximately 100 antigens and ten epitopes per antigen (i.e., 10^3 epitopes), and (5) approximately 10^7 B-cells are present per mL of circulating blood, then each infant would have the theoretical capacity to respond to about 10,000 vaccines at any one time (obtained by dividing 10^7 B-cells per mL by 10^3 epitopes per vaccine) [37, 41].

Most vaccines contain far fewer than 100 antigens (for example, the hepatitis B, diphtheria, and tetanus vaccines each contain 1 antigen), so the estimated number of vaccines to which a child could respond is conservative. But using this estimate, Offit et al. predict that if 11 vaccines were given to infants at one time, then about 0.1 % of the immune system would be "used up". However, because naive B- and T-cells are constantly replenished, a vaccine never really "uses up" a fraction of the immune system [37].

Chatterjee and O'Keefe expand on this subject noting that infants have an amazing capacity to respond to a vast array of antigens, including vaccines. However, the infant's immune system is not capable of responding with adult efficiency. Maturation of the immune response occurs in an orderly fashion from approximately 16 weeks gestation and slowly gains momentum in the first year of life. This, along with the presence of maternal antibodies provided passively, may account for the need for multiple injections to complete the primary series of several vaccines [20, 42, 43].

Medical advances in vaccinology have contributed to the decline in the number of antigens in modern vaccines. For example, the whole-cell pertussis vaccine contained approximately 3,000 proteins compared with the two to five proteins found in the current acellular pertussis vaccines [20, 37]. Today's vaccines contain far fewer antigens than the immune system is designed to respond to. Based on these data, vaccines will not overwhelm or weaken the infant immune system [20].

These conclusions are supported by the observation that children respond to multiple vaccines given at the same time in a manner similar to individual vaccines. If vaccines overwhelmed or weakened the immune system, then one would expect lesser immune responses when vaccines are given at the same time as compared with when they are given at different times [37, 44, 45]. However, when multiple vaccines are given at the same time, similar humoral immune responses are induced compared to when they are separated by time [37].

Also of note, vaccinated children are not at greater risk of subsequent infections with other pathogens than unvaccinated children. On the contrary, in Germany, a study of 496 vaccinated and unvaccinated children found that children who received immunizations against diphtheria, pertussis, tetanus, Hib, and polio within the first 3 months of life had fewer infections with vaccine-related and -unrelated pathogens than the nonvaccinated group [37, 46]. Bacterial and viral infections, on the other hand, often predispose children and adults to severe, invasive infections with other pathogens. For example, patients with pneumococcal pneumonia are more likely to have had a recent influenza infection than matched controls [37, 47]. Similarly, varicella infection increases susceptibility to group A β-hemolytic streptococcal infections such as necrotizing fasciitis, toxic shock syndrome, and bacteremia [37, 48].

Many parents have addressed their concerns regarding vaccine safety by adopting alternative vaccination schedules which differ from the childhood vaccination schedule recommended by the Centers for Disease Control and Prevention (CDC) for their children. Chatterjee and Moffatt have previously written on this subject [9] noting, in 2007, Dr. Robert Sears, a pediatrician from Southern California published *The Vaccine Book*: *Making the Right Decision for Your Child* [49]. In it he offers two alternative schedules (that are not approved or endorsed by any public health authority or professional physician group) to parents who are concerned about vaccines so that they may delay, withhold, separate, or space out vaccines for their children. Dr. Sears has publicly stated that he is not against vaccinations [50]. Instead, his book suggests an untraditional "alternative" schedule that delays vaccines or spaces them further apart. If parents are unwilling to vaccinate at all, he offers a separate "selective" schedule to encourage them to give their child(ren) at least the "bare minimum" of vaccinations. Healthcare providers are facing many parents who are questioning the need for immunization and insisting that their children receive vaccines according to Dr. Sears' schedule, rather than that recommended by the CDC, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians. The problem with Dr. Sears' schedules is the fact that it can take up to 5–6 years for children to complete their immunizations, during which some children will be at risk for contracting vaccine-preventable diseases due to lack of adequate immunity. Dr. Sears' book has been described as dangerous by some, because it validates the pervasive myths that are currently scaring parents into making ill-informed decisions for their children [51].

Compromises such as those proposed by Dr. Sears prioritize vaccines deemed more important while spacing out the full vaccination schedule over a longer period of time, theoretically reducing both the risk of harmful interactions between simultaneously administered vaccines and the burden on the patient's immune system. These theoretical concerns have been extensively studied, and there is no evidence that the timing and spacing of the current recommended vaccination schedule presents risks for healthy patients [51, 52]. The risks of delaying vaccines, however, are far more clearly understood. These risks include the increased likelihood that a multidose vaccination series will not be completed, as a result of the additional office visits required by alternative schedules, and the longer period of time that children lack full protection [51, 53, 54].

Dr. Sears' schedules are probably the most well known, but as found by Dempsey et al. who studied the subject, among alternatively vaccinating parents, only 8 % reported using his alternative [55]. It was more common for alternative vaccinators to indicate that they themselves (41 %) or a friend (15 %) developed the schedule. Several parents indicated they had "worked with their child's physician" to develop the alternative schedule [55]. They found influenza vaccine was most commonly refused altogether (76 %). The vaccines most commonly delayed to an age older than that recommended were the measles–mumps–rubella (MMR) (26 %) and varicella (46 %) vaccines. The vaccines most commonly provided over an extended dosing period were the MMR (45 %) and diphtheria–tetanus–acellular pertussis (43 %) vaccines. Among alternative vaccinators, 8 % indicated that they had to change providers because their child's doctor refused to go along with their vaccination preferences, 30 % indicated that their child's doctor "seemed hesitant to go along" with their vaccination preferences but still agreed to do so, 40 % indicated that their child's doctor "seemed supportive" of their vaccination preferences, and 22 % indicated that their child's doctor had been the one to suggest using an alternative vaccination schedule [55]. They also found 30 % of alternatively vaccinating parents had initially followed the recommended vaccination schedule but subsequently changed to an alternative schedule. In contrast, only 11 % of alternatively vaccinating parents reported changing from an alternative schedule to the schedule recommended by the CDC. Among the parents who changed schedule type, the majority (61 %) did so because it "seemed safer." Less commonly, parents reported changing schedule type because they thought it would create less distress for their child (20 %) or would be more effective (12 %) [55].

Attitudes of alternative vaccinators were also analyzed. These parents were less likely than parents following the recommended schedule to think that alternative schedules increased the risk of contracting and spreading disease. Interestingly, a large proportion of parents following the recommended schedule held beliefs that seemed counter to this practice. Nearly one of four parents (22 %) following the recommended schedule disagreed or strongly disagreed that the schedule "recommended by vaccination experts" was the best one to follow. Similarly, one of five parents who followed the recommended vaccination schedule thought that delaying vaccine doses was safer than providing them according to the recommended schedule. A history of alternative schedule use was consistently associated with nonmainstream beliefs about vaccination. Such beliefs also tended to be more common among parents whose children did not have a regular health care provider and those with higher incomes, although this was not consistent across all attitude questions [55]. This new finding is not surprising, because a strong physician recommendation for vaccination has been shown to be a consistent predictor of vaccine utilization. What is not clear, however, is which phenomenon occurs first. Do parents who follow an alternative schedule have a difficult time finding a physician for their child who supports their vaccination beliefs, or are parents who tend not to engage in regular health care for their children those who also tend to follow an alternative vaccination schedule? [55].

Dempsey et al. found that most parents who wish to follow an alternative vaccination schedule are able to access physicians who will support their beliefs; only 8 % of the alternatively vaccinating parents reported having to change providers to maintain the vaccination schedule they wanted. Fortunately, many parents who are "on the fence" about vaccination have views that might be modifiable through targeted educational approaches [55]. The vast majority of parents of vaccinated and exempt children reported receiving vaccine information from their health care professionals and that these professionals were good or excellent sources of vaccine information [19]. Interestingly, a large proportion of alternative vaccinators agreed that undervaccination of children increases the risk of infection and spread of disease [55]. This perceived risk of infection has been shown to be a significant predictor of vaccination across a wide range of studies [55, 56].

When it comes to changing behavior, Smith et al. found that at least 40 % of all parents did not report that their decision to vaccinate was influenced by a doctor or nurse. They did however report observing an increasing vaccine hesitancy which was associated with an increasing percentage of parents who seek advice and information from a practitioner of complementary or alternative medicine who may not fully accept childhood vaccines [57]. Of greater importance was their finding that children are at risk of having lower vaccination coverage if their parents have a poor working relationship with their child's vaccination provider or mistrust the medical profession in general [12].

Along this line, Rosenstock et al. [13] noted some parents' decisions to seek vaccination may be determined by social pressures applied by a person who is important to them. They also found that parents who are more vaccine-hesitant are likely to be influenced only through personal, face-to-face contact, especially with their physician [13]. A trusting relationship between parents and health-care providers is key to vaccine-hesitant parents accepting recommended immunizations. Smith et al.'s work suggests that a strong provider–parent relationship and trust of medical professionals are significant predictors of vaccination coverage [12].

Assuming additional information will influence vaccination decisions reduces the issue to one in which two sides are separated only by a gap in information [34, 58]. Attempts to provide the "correct" information have not been effective, demonstrated by both research and anti-vaccination advocates suing challengers for libel [34, 59, 60]. Historical evidence also illustrates that education has been unsuccessful. Vaccination protests emerged alongside modern vaccinology and have changed little over time [34, 61]. Historical protest methods included emotional appeals emphasizing parental devotion, denouncing germ theory, accusing medical professions of duplicity, and alternative analyses of data to portray vaccination as ineffective. Common themes included worries over safety, encroachments on individual rights, distrust of scientific authority, advocating "natural healing", promoting sanitary reform, disbelief in theories of contagion, and alleging monetary motivation as the driving force behind immunization [34].

Kata further notes, many "hardcore activists" are not persuadable, no matter the amount in information provided [34, 62]. Combating vaccine misinformation with

education is necessary, but not sufficient [34, 63]. Accusations of conspiracies were present on every anti-vaccination Web site analyzed. Given this lack of trust, providing more "education" will be ineffective [34].

Physician Response to Vaccine Refusal

The body of published literature is fairly unified in advice to primary care physicians (pediatricians in particular) regarding dealing with parents who refuse to immunize their children. Diekema and the AAP Committee on Bioethics published the following guidance for pediatricians on the subject in 2005 (renewed in 2010) [64]. When faced with a parent who refuses immunization for his or her child the AAP recommends the pediatrician should listen carefully and respectfully to the parent's concerns, recognizing that some parents may not use the same decision criteria as the physician and may weigh evidence very differently than the physician does. Pediatricians should also assist parents in understanding that the risks of any vaccine should not be considered in isolation but in comparison to the risks of remaining unimmunized. Many parents have concerns related to one or two specific vaccines. A useful strategy in working with families who refuse immunization is to discuss each vaccine separately. The benefits and risks of vaccines differ, and a parent who is reluctant to accept the administration of one vaccine may be willing to allow others. Parents also may have concerns about administering multiple vaccines to a child in a single visit. In some cases, taking steps to reduce the pain of injection may be sufficient. In other cases, a parent may be willing to permit a schedule of immunization that does not require multiple injections at a single visit. Physicians should also explore the possibility that cost is a reason for refusing immunization. For all cases in which parents refuse vaccine administration, pediatricians should take advantage of their ongoing relationship with the family and revisit the immunization discussion on each subsequent visit. As respect, communication, and information build over time in a professional relationship, parents may be willing to reconsider previous vaccine refusals [64].

The AAP further recommends that continued refusal after adequate discussion should be respected unless the child is put at significant risk of serious harm. Physician concerns about liability should be addressed by good documentation of the discussion of the benefits of immunization and the risks associated with remaining unimmunized. In this report the AAP further states:

> In general, pediatricians should avoid discharging patients from their practices solely because a parent refuses to immunize his or her child. However, when a substantial level of distrust develops, significant differences in the philosophy of care emerge, or poor quality of communication persists, the pediatrician may encourage the family to find another physician or practice. [64]

Such decisions should be unusual and generally made only after attempts have been made to work with the family. Families with doubts about immunization

should still have access to good medical care, and maintaining the relationship in the face of disagreement conveys respect and at the same time allows the child access to medical care. Furthermore, a continuing relationship allows additional opportunity to discuss the issue of immunization over time [64].

Keyserling, a member of the AAP Committee on Infectious Diseases aided the discussion on this document by stating, "The resolution of fear most likely will come from discussions between parents and their children's pediatrician, and some pediatricians become so frustrated with reluctant parents that they want to drop these children as patients. That would be wrong. Many physicians are uncomfortable taking care of parental refusers, but there is always the opportunity for the parents to change their minds. So at each visit, the issue needs to be brought up again" [26].

Fredrickson et al.'s research supports this approach. Their interviews with parental focus groups demonstrated consensus findings indicating that most parents with concerns ended up immunizing after having discussions with their physician about why the vaccine was important for their child. Furthermore, parents in these groups reported that the trustworthiness of the media, the Internet, and word of mouth was small in comparison to a trusted provider. It is important to note that parents greatly preferred to see the same provider, someone who would "know" their child [14].

The work of Gust et al. echoed these findings. Their analysis of parental behavior showed that parents who changed their minds after considering delaying or refusing a vaccine for their child gave the credit to the child's health care provider. This underscores the fact that health care providers are key to the immunization program and can affect the decisions of parents who have doubts about vaccines [65]. Other research also found that health care providers who are able to communicate effectively and with respect can positively affect patient satisfaction and adherence. Conversely, the parental attitude that the child's provider is not easy to talk to is associated with the belief that the parents do not have access to enough immunization information [65, 66].

Lyren and Leonard address this ethical issue as well [18]. They note that the physician also may view refusal of vaccination as symbolic of threatened trust that is seminal to a positive, productive doctor/patient relationship. The doctor may even want to dismiss the family from the practice. Although all of these feelings are legitimate, many of them are not constructive for physicians whose mission is the care and advancement of children. Some physicians view vaccine refusal as catastrophic to the doctor/patient relationship and excuse such families from the practice or, alternatively, prevent them from entering the practice. Some physicians who feel very strongly about immunization may even ponder contacting the county child protection service, arguing that refusing to immunize a child is consistent with medical neglect [18]. Diekema and the AAP's Committee on Bioethics address this issue by taking the position that continued refusal after adequate discussion should be respected unless the child is put at significant risk of serious harm (as, for example, might be the case during an epidemic). Only then should state agencies be involved to override parental discretion on the basis of medical neglect [64].

Lyren and Leonard further argue that for the most part, parents have the right and responsibility to act as surrogate decision-makers for their children who do not yet have adequate decision-making capacity. In general, parental autonomy supersedes societal paternalism despite the fact that parents do not always make the best decisions for their children's health. Some parents smoke cigarettes in the presence of their children, drive them unrestrained in cars, and sit them on the couch to watch violent television in reach of nonnutritious food. Physicians who dismiss from their practices families who refuse vaccines must carefully examine the effects of their actions. Of course, the lengthy deliberations with the refusing parents are eliminated, but so are the opportunities for meaningful and important dialog as well as the chance to convince the parents to vaccinate their children in the future through persistence, respect and education. Although physicians who dismiss patients from their practice should refer them to another provider, shunned families may not seek alternative medical care thereby jeopardizing other critical pediatric health issues. Instead of fostering a mutually respectful decision-making partnership with the family, the physician risks being labeled as overly paternalistic or too easily thwarted [18].

If parents continue to refuse immunization after repeated counseling, physicians are left with two principal alternatives: either to document refusal and continue the doctor–patient relationship or to discharge the patient and direct them to seek care elsewhere. Schwartz and Caplan have written extensively on the topic and the following summarizes their work [52]:

Documenting refusal ensures that the patient or their parent clearly understands the seriousness of that decision. As with alternative schedules, medical organizations provide sample documents that clearly explain the significant, potentially fatal consequences that may result from vaccine refusal [52, 67].

Physicians should also advise those opting against vaccination of the additional consequences related to state vaccination requirements. Unvaccinated individuals must obtain either a religious exemption (available in all states except for West Virginia and Mississippi) or a philosophical exemption, available in 21 states to attend school or day-care facilities [52, 68]. Individuals with exemptions can be excluded from these facilities during outbreaks.

Some physicians believe that continuing care when vaccination is refused may be interpreted as implicitly condoning poor choices. A growing number of physicians endorse ending the doctor–patient relationship as the appropriate response for these patients. In one survey, 39 % of pediatricians said they would dismiss a family refusing all vaccinations, and 28 % would dismiss a family that refused select vaccines [52, 69]. Dismissing these patients is thought to reflect the gravity of the decision to refuse vaccination. It also has the practical benefit of reducing the number of unvaccinated children in doctors' offices, settings harboring a concentration of patients which increases susceptibility to infection [52, 70].

The prospect of terminating care for patients who refuse vaccines is part of a larger legal and ethical discourse on the duty to treat and patient abandonment. In general, a physician is legally and ethically obliged to continue to provide care to a patient with whom a relationship has been established unless "that relationship

is terminated by the mutual consent of the physician and patient, the patient's dismissal of the physician, the services of the physician are no longer needed, or the physician properly withdraws from the physician/patient relationship" [52, 71]. Specific requirements for terminating a doctor–patient relationship vary among states, but they typically require reasonable notice provided by the physician in writing, and adequate time for the patient to identify another physician. Failure to terminate care properly may constitute patient abandonment and breach of physician duty if injury results subjecting the provider to disciplinary action and potential civil liability [52, 71].

Legal and ethical guidelines govern the termination of care, but physicians are under no obligation to establish a doctor–patient relationship with a specific individual in ordinary circumstances. Providers could make their policy regarding vaccines clear to prospective patients at the time an initial appointment is scheduled. Those patients hesitant or opposed to vaccines would understand this policy and would be free to seek care elsewhere if so desired. Although this method reflects the importance of vaccination and the corresponding commitment of physicians using it, it is a missed opportunity for communication with patients or parents that might correct inaccurate perceptions and change attitudes in favor of vaccination. If patients hesitant about vaccines seek care only from so-called vaccine-friendly physicians who are open to any approach to vaccination, the debates and confusion surrounding vaccination are more likely to persist [52].

The CDC takes a similar position against terminating treatment due to vaccine refusal. It recommends that instead of excluding patients who refuse vaccines, "an effective public health strategy is to identify common ground and discuss measures that need to be followed if the decision is to defer vaccination" [52, 72].

Schwartz and Caplan further state, beyond the legal and ethical complexities associated with terminating care, doing so as a general practice does nothing to advance the case for vaccination, forestalling the opportunity to subsequently change minds through continued education and dialog. It also may reinforce the divisions and distrust that explain the persistence of controversies over vaccine safety despite considerable evidence to the contrary [52].

Individuals with reservations about vaccines already believe that their voices are marginalized or ignored by the medical establishment. Rather than actions that would effectively establish parallel networks of care for parents and patients based on their views about vaccines, a far better solution is to continue open, honest, and factual communication about the risks and benefits of vaccines. These activities require ongoing dissemination of accurate information about vaccine safety and effectiveness, as well as support for continued research and surveillance to ensure that the considerable existing public trust in vaccination remains warranted [52, 73].

Health care providers should view individuals hesitant about or opposed to vaccines not as frustrations or threats to public health, but as opportunities to educate and inform. Excluding patients who question or oppose vaccines may appear to be an attractive method to demonstrate the importance of vaccination, but it leaves vulnerable infants and children without advocacy, and only adds to the climate of antagonism that often poisons contemporary discussions of vaccination in the USA.

Through ongoing dialog, mutual respect for opposing views, and the demonstration of the importance of vaccination through one's own behavior, public support for vaccines can be preserved and broadened [52].

Flanagan-Klygis et al. conducted a survey of 452 pediatricians nationwide regarding their attitudes and practices surrounding dismissal of families who refuse vaccination. In their experience, when a parent refuses one, some, or all vaccines, the relationship between that pediatrician and parent weakens [69]. In their study 85 % of sampled pediatricians reported encountering partial vaccine refusal during the preceding 12 months. Fifty-four percent of pediatricians reported encountering a parent who refused all vaccines. Pediatricians' perceptions of the reason parents refuse vaccines were similar in the two cases. For refusal of specific vaccines, a substantial majority perceived parents refused based on safety concerns (73 %), multiple vaccines at once (22 %), philosophical objections to vaccination (13 %), and religious beliefs about immunization (7 %). For complete vaccine refusal, the reasons cited were similar: safety concerns (79 %), philosophical objections (41 %), and religious beliefs (17 %) [69]. In the case of parents refusing specific vaccines 28 % of pediatricians said that they would ask the family to seek care elsewhere; for refusal of all vaccines, 39 % of pediatricians said that they would refer the family [69].

Factors important to pediatricians in the decision to dismiss families who refuse some versus all vaccines were similar. Seventy-eight percent (facing refusal of some vaccines) versus 82 % (facing refusal of all vaccines) regarded lack of shared goals as "extremely important." Seventy-three percent versus 70 % regarded lack of trust as "extremely important." Fear of litigation was regarded as "extremely important" by only 15 % for partial refusal and 12 % for total refusal. Concern about decreased reimbursement was regarded as "irrelevant" by pediatricians facing partial (94 %) and total (12 %) vaccine refusal [69].

Finally, for pediatricians who would dismiss a family for refusing some vaccines, only 27 % felt that the type of vaccine refused was an "extremely important" factor [69]. Their data also underscore previous findings that undervaccinated children tend to be black and living below the poverty line, while unvaccinated children tend to be white and living above the poverty line. Further they confirmed other studies that have shown the existence of unvaccinated populations in geographic clusters, thereby creating the potential for concentrated points of disease transmission [69, 74].

Termination of a physician–patient relationship represents a last resort when all other attempts at patient compliance have failed or difficult patient behavior makes it impossible to maintain a relationship [69, 75]. Stokes et al. have published several interview-based studies in which they examined the practice of patient dismissal among general practitioners in the UK. They found dismissal to be an "overwhelmingly negative and distressing experience for patients" [69, 76] based on patient interviews in the weeks following dismissal. However, their interviews with physicians revealed dismissal to be a right that physicians very much value when faced with patients who are noncompliant or difficult long-term [69, 77].

Flanagan-Klygis et al. provide a counter argument to this practice by stating, "However justified family dismissal may or may not be, dismissing a family from a practice ends further opportunities to provide meaningful patient/family education on vaccines and other aspects of high quality pediatric care…Does the practice of family dismissal, in fact, promote or undermine immunization for particular children or children as a group? Might family dismissal generally damage relationships between pediatricians and families such that parents become less likely to seek or successfully obtain other needed primary preventive services or care for acute or chronic illness?" [69].

In Connecticut, Leib et al. surveyed 133 pediatricians concerning their views on vaccine refusal, and more than 30 % of responding physicians reported families who had been asked to leave the practice due to the families' decision not to vaccinate their children [78]. Nearly 40 % of respondents who dismissed families noted that it was their practice's policy to dismiss families who refused all vaccines. More than 40 % of physicians agreed with dismissing families who refused all vaccines. Suburban physicians were more likely to agree with dismissing families who refused all vaccines when compared with urban respondents (48 % versus 26 %, $p<0.05$). Similarly pediatricians who reported working with higher socioeconomic status families (as estimated by physicians) were more likely to dismiss families for refusing vaccines than physicians who reported working with poor, working-class, or middle-class families (42 %, versus 9 %, 24 %, and 35 %, respectively, $p<0.05$). Forty-five percent of pediatricians responded that they found the issue of parental vaccine refusal "mildly annoying—it is part of being a pediatrician," while 28 % said it had a "negative impact" or "decreased their overall satisfaction with pediatrics." Negative personal impact was associated with practicing in suburban/rural areas when compared with practicing in an urban setting (25 % versus 3 %, $p<0.01$). Comments by some respondents are as follows [78]:

> Most times it does not matter, parents have made up their minds. It is frustrating!
>
> Another wrote that he/she was only "somewhat comfortable" discussing vaccine refusal with parents "because I get so mad!"
>
> For most families inclined to refuse vaccines, none of these [resources] works and I am becoming more inclined to dismiss these families.
>
> I often spend too much time on this and it takes time away from others.

Negative feelings on the part of physicians may interfere with their ability to communicate and form trusting relationships with families who refuse vaccines. Poor communication and dismissal of families limit open discussion with parents and may make it harder to convince hesitant parents to immunize their children [66, 78, 79]. Children whose parents refuse immunizations still deserve quality pediatric care. Dismissed families may seek care from practitioners who further encourage or are more tolerant of their decision not to vaccinate [33, 78, 80–82].

Halperin et al. document the Canadian experience on the subject and present the following compelling ethical argument: Making a decision that the doctor is not in agreement with, from an ethical view, should not preclude the patient or family from

receiving other ongoing care [82]. Patients and families dismissed for vaccine refusal and unable to find a new physician may become marginalized from health care and thus vulnerable. If all opportunities to discuss vaccination have been exhausted and the parent still refuses to have his or her child vaccinated, the primary care physician may need to effect transfer to another provider who is more compatible with the family's goals [82].

However, dismissing a patient because of vaccine refusal effectively prevents any ongoing attempts to keep the lines of communication open and eliminates any possibility that a solution may be negotiated. When vaccine preferences are negatively polarized, physicians must work to suspend judgment and promote collaboration and an exchange of ideas in an atmosphere of mutual trust and respect [82]. They are in a privileged position to communicate the far-reaching implications of vaccine refusal for the individual, the family and the population; to explain the public health ethical principles of solidarity and protection of the vulnerable; as well as being able to respond effectively to vaccine concerns and questions [83].

Halperin et al. further conclude, the family that refuses vaccination should receive the same supportive and compassionate management as other patients who show hesitancy toward specific medical advice [82]. Dismissing the family will neither get the child vaccinated nor provide for preventive counseling in the event of exposure to a vaccine-preventable disease. To sever these lines of communication by dismissing the patient from care eliminates any possibility for subsequent discussion, and may lead to mistrust of the "medical system" and to the patient dropping out of formal health care. Thus, dismissal serves neither the best interest of the patient nor that of the public and is therefore an unacceptable strategy from a public health perspective [82].

Grossman et al. examined primary care pediatricians' perceptions of vaccine refusal in Europe [84]. They found a majority of responding pediatricians preferred a shared decision-making approach when facing refusing parents. Only 9 % endorsed the option of discontinuing care. However, 27 % would favor this approach toward parents who refuse all vaccines [84].

These data along with those of Flanagan-Klygis et al. as well as Leib et al. who independently found approximately 40 % of practicing pediatricians support dismissing families who refuse all childhood immunizations, demonstrate the considerable disconnect between the published ethical arguments and the actual practice patterns of almost half of pediatricians surveyed [69, 78]. It would appear that a significant number of rank and file practicing primary care pediatricians do not share the same opinions as the authors of the published ethical discussions on the subject.

We support the position of the AAP insofar as pediatricians should listen carefully and respectfully to the parent's concerns and educate these parents in understanding the risks and benefits of immunization versus remaining unimmunized with the hope that over time respect, trust, and information might allow reluctant parents to reconsider previous vaccine refusals [64]. However, over time, as we recognize, there will be a subset of parents who will simply never consent to immunization. This is a parental choice, and like the parent who chooses to allow their

child to ride unrestrained in a car, they must recognize that their choices have consequences. Pediatricians may try to be flexible with parents and adopt their alternative vaccination schedules, but in the end, studies have shown that many of these children never become fully immunized [12]. The physician–patient relationship is like a two-way street and if parents make a choice not to participate with a physician's plan when strong feelings are present and if in the physician's view, the necessary trust and working relationship deteriorate, the physician must retain the right to terminate the relationship (following accepted practices for this process). We agree and encourage repeated consultation and education of parents which should take place first, but when all else fails and if in the physician's judgment the relationship is sufficiently damaged, the physician–patient relationship can be justifiably terminated.

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Chapter 6
The Anti-vaccine Movement: A Pharmacist's View

Jeffery Goad and Melissa Durham

The Role of the Pharmacist in Immunizations

As early as the 1800s, pharmacists supported smallpox vaccine distribution and then again in the 1950s and 1960s for the polio vaccine campaign [1]. Following a 1993 letter from Donna Shalala, then the US Department of Health and Human Services Secretary, asking the American Pharmaceutical (now Pharmacists) Association (APhA) to help define the role of pharmacists in immunizations, the first immunization training program for pharmacists was established in 1994 [2]. Starting in 1994 with Washington State and concluding with Maine in 2009, all 50 states in the USA now allow pharmacists to vaccinate [3]. However, all 50 states also define differently which vaccines, ages and by what mechanism (i.e., protocol, prescription, or a combination of the two) a pharmacist may administer a vaccine. Figure 6.1 details the minimum age limits for pharmacist administered vaccines by state. There are no federal laws that explicitly allow the pharmacist to vaccinate, but Medicare Parts B and D do recognize pharmacists as providers of vaccination for compensation purposes.

Even before pharmacists had the legal right to vaccinate, APhA adopted a policy in 1996 that defined the role of the pharmacist in vaccine advocacy as an educator (motivating people to be immunized), as a facilitator (hosting others who immunize), and as an immunizer (protecting vulnerable people, consistent with state law) [4]. At the same time, a comprehensive training program was developed by APhA and a senior Centers for Disease Control and Prevention (CDC) immunization epidemiologist. The program is still known as the APhA Pharmacy-Based Immunization Delivery certificate training program. This program is constantly updated and has

J. Goad, Pharm.D., M.P.H. (✉) • M. Durham, Pharm.D.
Titus Family Department of Clinical Pharmacy and Pharmaceutical Economics and Policy, University of Southern California School of Pharmacy, 1985 Zonal Ave, Los Angeles, CA 90033, USA
e-mail: goad@usc.edu

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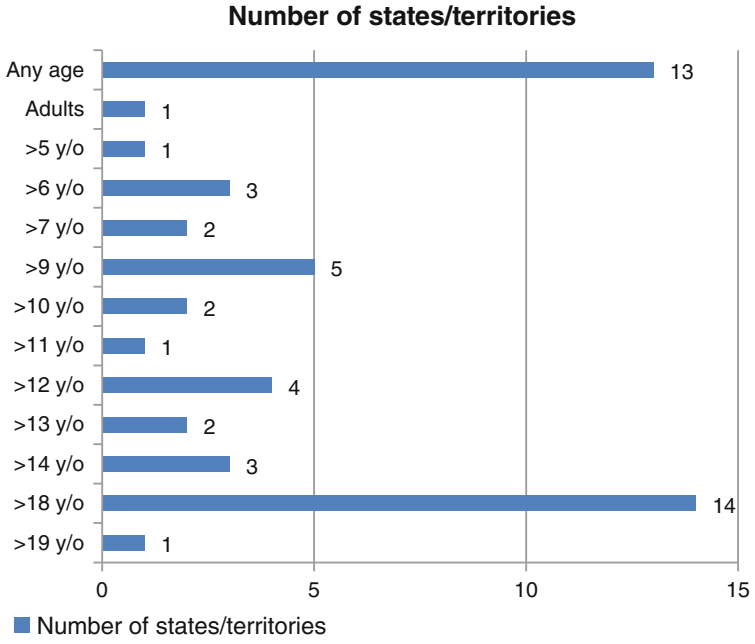

Fig. 6.1 Minimum age restrictions among states/territories in the USA, 2012. Based upon APhA/NASPA Survey of State Immunization Laws/Rules June 2012

trained over 175,000 post-graduate pharmacists as well as student pharmacists still in training (www.pharmacist.com). There are specific sections that deal with common myths of vaccination and where to find credible information for patients as well as health belief model descriptions for motivational interviewing. The Bureau of Labor Statistics estimates there are over 270,000 pharmacists in the USA and the Federal Pharmacy Manpower Project indicates the majority practice in a community or outpatient environment [5]. The combination of community access and standardized national training make the pharmacist an incredible ally for vaccine education and administration.

In 1950, the University of Southern California started the first doctor of pharmacy (Pharm.D.) program in the USA and by 2000, all schools of pharmacy were required to graduate the Pharm.D [6]. The Pharm.D. degree emphasizes a clinical approach to patient care through various means including "hands-on," such as immunizations, and patient education. It is this patient education, also known as patient counseling, piece that allows the pharmacist to dialogue with patients not only about medical information, but also the myths or misconceptions they have developed about a given disease or drug/vaccine. Since human vaccines are licensed by the US Food and Drug Administration (FDA) and considered prescription products in the USA, just like medications, pharmacists have a unique opportunity to expand the provider base and public trust in them as drug experts to vaccine experts as well. Gallup polls have consistently ranked the pharmacist in the top three for

honesty and ethics among all categories of professions for more than a decade (www.gallup.com). Finally, the CDC as well as other physician groups, such as the American College of Physicians, endorse the use of pharmacists in the provision of immunization education and administration [7, 8].

The Impact of Communication with the Pharmacist on Patient Behavior and Vaccine Acceptance

Communication with the pharmacist can have a significant impact on patient or caregiver behavior. It is well-documented that pharmacist interventions such as counseling, patient care or patient coaching programs can improve medication adherence [9–14], clinical outcomes, and economic outcomes [15–17]. Much of the data on pharmacists' ability to improve these outcomes comes from management of chronic disease states such as diabetes, dyslipidemia, asthma, and HIV. Data from the "Asheville Project" [15–17] demonstrated that frequent visits with the pharmacist in a coaching program for diabetes, hypertension, and dyslipidemia improved clinical outcomes such as hemoglobin A1c, and also showed that this type of intervention can contribute to significant health care cost savings. This is due not only to an increase in medication adherence, but also an increase in compliance with other routine health care measures such as laboratory testing, doctor visits, and recommended immunizations.

Although the majority of data regarding the impact of pharmacist interventions on patient behavior are in the management of chronic diseases, it can be inferred that these outcomes also apply to recommendations for preventative measures. Over the last 15 years, pharmacists have established themselves as advocates for vaccines and preventative health [1]. Community pharmacists have made interventions targeting patient groups who are candidates to receive specific vaccines. One study in particular demonstrated a significant increase in the rate of pneumococcal vaccinations for at-risk patients when pharmacists made targeted interventions [18]. In addition, community pharmacists play an important role in increasing the rates of influenza vaccination. The scope of practice of pharmacists is subject to state regulations [19], hence the ability of pharmacists to give different vaccines will vary from state to state. It has been shown that rates of influenza vaccination are higher in states where pharmacists are allowed to immunize [20].

Pharmacists employ a variety of techniques in order to promote and enhance medication adherence. Again, most of the literature describing these techniques is in the management of chronic diseases. However, many of the techniques used by pharmacists in motivating patients to take their medications also apply to encouraging compliance with routine, required, and recommended immunizations [21].

There are a variety of reasons why patients do not adhere to their medication regimens, and many of these issues also apply to compliance with immunizations. Most commonly, patients will not take medications due to the occurrence of adverse effects. For vaccines, patients may not comply with recommendations due to fear of

adverse effects, or misconceptions about adverse effects. Classic examples include concerns regarding contribution of vaccines to the development of autism, or patients believing that "the flu shot causes the flu." Also, patients are more likely to be nonadherent to their medications when the condition does not have obvious symptoms, such as dyslipidemia. Similarly, since vaccines do not have an obvious immediate effect, people may be less likely to finish vaccination series or start vaccines in general. Some people perceive themselves as very healthy, and therefore feel they do not need preventive medicine. Complicated medication regimens involving multiple daily dosing is another significant reason why patients may be nonadherent to medications. This idea may apply to patients not complying with immunization schedules that require multiple doses, such as Hepatitis B or HPV vaccines. These vaccines have different minimum spacing recommendations that requires compliance to maximize safety and efficacy of the vaccine. And lastly, low health literacy, health beliefs and cultural issues may also contribute to both nonadherence to medications and noncompliance with vaccine recommendations [21].

The intervention strategies used by pharmacists to promote both medication adherence and vaccine compliance need to be individualized to address the underlying cause. Pharmacists address these issues and help to dispel vaccine myths and misconceptions by engaging in open two-way communication with patients. Principles of risk communication are exercised by providing education regarding the risks and benefits of vaccines. And since most pharmacists who provide immunizations have undergone a standardized training program through the APhA as well as a rigorous Pharm.D. program, they are well-equipped to determine indications, contraindications and educate patients on all routinely recommended vaccines.

Regular interaction with a health care provider helps to establish a trusting relationship so patients are more likely to follow recommendations. Pharmacists are in the perfect position for these interactions as they are often the health care provider who is seen most frequently by patients. Pharmacists can monitor medication adherence either through patient self-reporting or through the use of pharmacy refill databases [21]. Patients are asked "Are you taking your medications?" or "Did you receive your flu shot this year?" which gives the pharmacist the opportunity to make recommendations and address any reasons for nonadherence or noncompliance. Automated pharmacy refill databases are another option to track whether a patient receives their medications or vaccines. In most community pharmacies, vaccines are entered into the pharmacy information system as any drug would be entered, allowing safety alerts and refill reminders to occur.

The Effect of the Pharmacy Environment on Patient Behavior and Vaccine Acceptance

Patient expectations of the role of pharmacists in immunizations, and acceptance of vaccine recommendations may vary depending on the practice setting of the pharmacist. In the community pharmacy setting, expectations of the pharmacist will

vary greatly depending on the type of pharmacy practice (i.e., whether they offer immunizations or not) and the patient's relationship with the pharmacist and pharmacy staff. Patients often picture pharmacists in the traditional dispensing role, and do not perceive provision of immunizations or vaccine recommendations as the role of the pharmacist, since these are traditionally roles of the physician or nurse. But in recent decades, acceptance of the pharmacist as a provider of vaccines has grown greatly, especially due to the convenience for patients and widespread advertising campaigns from chain pharmacies. As a result, the community pharmacy setting has great potential for reaching a wide variety of populations, including the underserved [22, 23]. However, the role of the pharmacist as a provider of immunizations in the community setting is largely limited to adult and adolescent immunizations [24, 25]. Pharmacists have demonstrated the ability to increase influenza vaccination rates among chronic medication users less than 65 years old and those that had not previously received influenza vaccination [26].

Although most literature exists on the role of the pharmacist in the community setting, pharmacists also play an integral role in immunizations in the hospital setting. In this setting, patients do not often interface with the pharmacist, and vaccine administration is primarily the role of the nursing staff. The pharmacist will interact with other members of the health care team to make vaccine recommendations. Also, pharmacists have played an important role in the development of institutional protocols that ensure at-risk patients are identified and applicable immunizations are administered prior to discharge [1]. Protocols and standing orders for influenza and pneumococcal vaccination, in particular, are extremely common in the hospital setting [27].

Pharmacists also routinely conduct medication therapy management services in the ambulatory care/clinic setting under collaborative practice agreements with physicians. In this model, which also will vary from state to state according to the pharmacists' allowed scope of practice, pharmacists will make recommendations or will initiate or adjust medication therapy according to protocol. These recommendations or interventions can include immunizations. In this setting, the environment and the interaction with the patient are very similar to a typical outpatient physician office visit, and therefore, patients may discern less of a difference between this and the community pharmacy.

As stated in previous chapters, it is becoming more common for physicians to not accept patients who refuse vaccines. This has not yet become a common practice among pharmacists for a variety of reasons. First, the profession of pharmacy has a unique history where pharmacists have dichotomous roles as health care providers who are also retailers. Community pharmacies are considered public places of business as opposed to the typical health care setting of a clinic office or hospital. The public therefore has an expectation of the ability to come and go freely in community pharmacies, and it is not a common expectation of the public for pharmacists to refuse service or access to the retail side of a community pharmacy.

Second, although pharmacists have the right to refuse to fulfill medication orders, the public may not be very accepting of pharmacists exercising this right. It is commonly the expectation of the public that pharmacists are supposed to carry out the legal orders of the physician or other prescriber. Laws vary from state to state, but

in general pharmacists may refuse to fill prescriptions/complete medication orders when (1) the pharmacist believes that the medication will cause the patient harm, (2) the pharmacist has reason to believe that the prescription or medication order is in error, is fraudulent, or is not valid, or (3) the pharmacist has a moral or ethical opposition to fulfilling a particular prescription or medication order. The latter has been a source of significant controversy and public outcry, when there were a few highly publicized incidents of pharmacists refusing to fill oral contraceptives or emergency contraception due to personal moral conflicts. In some of these cases the pharmacists lost their jobs, while in others they were sued [28]. While individual pharmacists may refuse to provide oral contraception, there is no evidence we are aware of that would indicate pharmacists may not provide certain immunizations on moral or ethical grounds.

The official position of the American Pharmacists Association recognizes the pharmacist's right to refuse based on moral/ethical conflict, as long as there is a contingency plan in place ahead of time to ensure a patient's access to the legally prescribed therapy [28]. Keeping these incidents and the history of the practice setting of community pharmacies in mind, it stands to reason that if a pharmacist were to deny service to a patient as a result of the patient refusing vaccination, it would be met with significant public opposition and protest. On the other hand, pharmacists who practice in a hospital setting or in a clinic/ambulatory care setting would likely be allotted the same expectations and freedom to refuse as physicians and other prescribers.

Community pharmacies, primarily some large chain pharmacies, now require their pharmacists to be trained to administer immunizations. It is unclear if they are required to actually administer vaccines or just be trained. At a minimum, pharmacists would be expected to know how to identify indications and contraindications and provide sound immunization information.

Barriers to Patients Receiving Immunizations from Pharmacists

There are a number of barriers to pharmacists offering immunizations in the community pharmacy setting. Some barriers include the setup and workflow of the pharmacy itself, time available to the pharmacist, and adequate space to administer the vaccines [29]. The business model of a particular pharmacy may be highly prescription volume driven, which restricts the time available to the pharmacist to administer vaccines. In addition, there may not be adequate staff or support on the corporate/administrative level for pharmacists to deliver such services. Different models of pharmacy workflow may either hinder or support pharmacists administering vaccines. Pharmacists often end up carrying out duties that can be completed by a pharmacy technician or clerk, such as reimbursement resolution or medication dispensing functions. The pharmacy workflow models that designate these tasks to ancillary staff are typically most successful in facilitating pharmacist delivery of

immunizations. To date, there are no states that allow pharmacists to delegate the administration of vaccines to technicians or clerks—they must be administered by the pharmacist.

Access to information is also a significant barrier for pharmacists in the community pharmacy setting. Community pharmacists typically only have access to the patient's medication profile, which only includes the medication that they have received at that particular pharmacy. There has been significant growth in the development of immunization registries used throughout the country. These registries are state or local government-maintained and when updated consistently by vaccine providers, allow patients and other vaccine providers to view a complete immunization history [30]. While some states require all vaccine providers, including pharmacists, to update the immunization registry, other states make it optional, thus creating gaps in immunization records. Pharmacists who consistently use this resource may be more likely to not duplicate vaccinations and may find many opportunities to refer pediatric patients who have fallen behind schedule to their pediatrician and to vaccinate adolescents and adults.

In contrast to other health care professionals, the current structure for compensation of pharmacists in the USA is generally for product and not for service. In the community pharmacy setting claims are adjudicated online to third party payers, and pharmacies are typically reimbursed a negotiated rate for the cost of the medication plus a dispensing fee. This may be due to the history of the profession as "retailers," which has resulted in pharmacists not being recognized as health care providers by the Social Security Act and the Centers for Medicare and Medicaid Services (CMS) [31]. The Social Security Act recognizes physician assistants, nurse practitioners, certified nurse midwives, clinical social workers, clinical psychologists, and registered dieticians/nutrition professionals as health care providers, but not pharmacists [31]. As a result, health insurers rarely compensate pharmacists for cognitive services, and there is a lack of mechanism/infrastructure in place for pharmacists to bill medical plans [19]. In hospital and ambulatory care/clinic settings, this is also a major issue as clinical pharmacists conducting medication therapy management typically cannot bill a medical plan directly for their interventions. Pharmacists are burdened with having to justify their positions with either improvements in clinical outcomes or cost savings rather than generating revenue to support their salaries [32]. While pharmacists pride themselves on being the most accessible health care professional, spending time with a patient explaining the risks and benefits of vaccination is currently an uncompensated encounter.

Vaccines, for the most part, are covered by medical benefits and not pharmacy benefits, with some exceptions. For Medicare eligible patients, influenza, pneumococcal, and Hepatitis B vaccines are covered by Medicare Part B. Varicella Zoster vaccine is typically covered by Medicare Part D [33]. Other than the Medicare population, patients who wish to receive vaccines in a community pharmacy setting typically have to pay out-of-pocket for the cost and administration of the vaccine and are responsible for submitting to their medical plan for reimbursement [19]. This is a significant barrier to patients receiving vaccinations from pharmacists, as the patient may go to their physician and only have to pay a co-pay, if anything.

From a pharmacist's perspective, it is clear that changes are warranted in the current structure for compensation and reimbursement of pharmacists for cognitive services and vaccinations [19]. Compensation systems must become more equitable among providers of vaccines and the processes for submitting claims other than Medicare Part D vaccines must become less cumbersome for pharmacists to fully participate in national immunization efforts [32]. When pharmacists are adequately compensated for immunization services, they may also be more likely to engage in discussions of risk, benefits and myths about vaccines.

Underlying these issues of compensation, reimbursement, and billing infrastructure are potential turf issues between pharmacists and other health care providers. Pharmacists have been carefully balancing their roles as vaccine advocates and providers while attempting to not encroach upon what other health care providers view as their territory [1]. Hopefully in the future, patients, regulators, and other health care professionals will recognize pharmacists not just as complementary vaccine providers, but as qualified traditional providers of immunizations and will support their role as integral members of the patient care team [19]. A recent report to the Surgeon General from the Office of the Chief Pharmacist in the US Public Health Service strongly called for recognition of pharmacists as providers by CMS. As stated in this report, "One of the most logical, evidence-based decisions that can be made to improve care is to maximize the expertise and scope of pharmacists, and minimize expansion barriers of an already existing and successful health care delivery model" [31].

Depending upon practice setting, pharmacists may be more or less likely to receive vaccinations and thus recommend them for their patients. A recent national survey of pharmacists in various practice settings reported a 78 % influenza vaccination rate compared with the CDC reported 42 % coverage among other health care providers [34]. This same study also highlighted that community pharmacists may have more misconceptions about vaccinations. A study of health professional students indicated that high knowledge of the risks and benefits of influenza vaccination did not necessarily translate into a higher immunization rate [35]. Thus, it would appear that student pharmacists get influenza vaccination for reasons beyond basic knowledge of the risks and benefits of vaccination. Previously cited work in this chapter indicates, however, that pharmacists are effective at encouraging patients to get vaccinated.

Conclusion

Pharmacists have established themselves as vaccine advocates as well as qualified and highly trained providers of immunizations. Because of their accessibility to patients and caregivers, pharmacists are uniquely positioned to provide patient education and dispel vaccine myths. Overcoming some of the barriers faced by pharmacists such as lack of infrastructure for compensation/reimbursement and access to information can greatly increase the role of the pharmacist as a vaccine provider, and as a result, increase public access to immunizations and credible vaccine information.

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Chapter 7
Antivaccinationism: Parental Viewpoint

Anna M. Johnson

Most doctors and epidemiologists consider vaccines to be one of the most effective tools available to prevent disease today [1]. They are commonly considered to be the single most important health intervention after clean water and sewage disposal [2]. In the USA, European nations, and other developed countries, the historically high vaccination rates for routinely recommended vaccine-preventable childhood diseases have brought about a dramatic reduction in the incidence of these diseases [3]. Although immunization rates remain high—over 90 % for vaccines such as polio, measles, hepatitis B, and varicella (chickenpox)—parental vaccine refusal rates have been steadily rising over the last decade, increasing by 4 percentage points in 2009 alone [4]. Likely due to the very success of the vaccination program, parents' concern has shifted from disease prevention to vaccine safety, and vaccination is increasingly met with confusion, anxiety, suspicion, and mistrust among some parents, even among those who follow the recommended immunization schedule [3]. Concerns range from the necessity and effectiveness of immunizations to vaccine safety and personal liberties. The rapid growth of the Internet and social media has made it easier to propagate such concerns as well as a great deal of misinformation and a number of important misperceptions [3]. With an increasing number of parents refusing or delaying immunizations for their children, some previously well-controlled vaccine-preventable diseases have returned, with outbreaks reported in regions where they were previously eradicated. In order to address this critical issue, public health agencies and the medical community must understand the nature, source, and context of parents' concerns in order to most effectively develop a strategy for helping parents understand the true risks associated with vaccination, the risks associated with refusal, and the relevance of vaccination today.

A.M. Johnson, M.S.P.H., Ph.D. (✉)
Department of Epidemiology, Gillings School of Global Public Health,
University of North Carolina at Chapel Hill, 137 E Franklin St, Bank of America Center,
Suite 306, Chapel Hill, NC 27514, USA
e-mail: anna.johnson@unc.edu

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As discussed in greater detail in Chap. 1, the public's concerns about vaccinations has a long and active history. Protests about the vaccination movement being an invasion on personal autonomy, privacy and concerns over adverse events have been present in the USA and Europe since the 1800s. In the USA, the first compulsory immunization law was passed in Massachusetts in 1809. However, it was not until the 1830s, after smallpox vaccination had begun and the incidence of smallpox declined significantly, and again at the end of the nineteenth century when states began enforcing existing vaccination laws and passing new laws in order to contain a smallpox outbreak, that the anti-vaccination movement in the USA became particularly vigorous [5]. Compulsory vaccination laws for school entrance were not enacted in all 50 states until 1980, when the Centers for Disease Control and Prevention (CDC) notified states that federal vaccine funding would be tied to states' laws and enforcement policies requiring immunization before school entry [6]. Resistance to compulsory school vaccination laws is largely based on arguments that have continued since the vaccination debate began, with the primary concerns over autonomy, privacy, and safety [7].

As the vaccination program has continued to successfully maintain low vaccine-preventable disease rates, the anti-vaccination sentiments and concerns have persisted to the present day. The profile of parents who choose not to give their children all or some vaccines is not uniform, however. While under-vaccinated children tend to be black, have a younger, unmarried mother without a college degree, and live in a household near the poverty level and in a central city, *un*vaccinated children tend to be white, have a married mother with a college degree, and live in a middle to upper-middle income household and in Western and Midwestern states [8, 9]. Families with similar attitudes and beliefs regarding vaccinations tend to cluster in particular communities [9]. Parents in such families are more likely to report that physicians have little or no influence on their vaccination decisions and are unlikely to change their decision not to vaccinate, so that children who are not vaccinated during younger years are likely to remain unvaccinated into the school-age years. Although parents of unvaccinated children are far from homogenous group, the majority are making decisions because of their concerns and want to do what is best for their children [10]. Following is a discussion of these concerns and the main reasons that parents refuse or delay vaccinations for their children.

Ease of Opting Out

Although vaccinations are compulsory for public-school aged children across the USA, exemption rules vary by state. All states allow parents to exempt their child for medical reasons (e.g., immunocompromised, previous allergic reactions to vaccines or constituents, moderate to severe illness, or other medical contraindications to vaccination) and require that parents provide documentation from a physician. In addition, all but two states (Mississippi and West Virginia) also permit exemption where vaccination contradicts parents' "sincere religious beliefs." Further, 20 states

allow exemptions based on "personal beliefs," also known as philosophical exemptions. The philosophical exemption option provides parents with a means for opting out that is not restricted to purely religious or spiritual beliefs and may be provided based on "moral, philosophical or other personal beliefs" as in the state of Maine or based simply on more nebulous "individual beliefs," as in the state of California [11]. The primary philosophical conflict that parents have with vaccination tends to focus on the belief that required immunization is an invasion of privacy and autonomy. Some parents who opt out of vaccination for philosophical reasons view the requirement that children be vaccinated in order to participate in the public school system as an invasion by government into their private decisions about their bodies and their personal health.

The philosophical exemption option is increasingly used by parents to opt out of vaccinations for other reasons, however. The difficulty of obtaining philosophical exemptions varies widely among states; in some states, opting out of vaccination for school-age children requires simply signing a card stating as much. Although the majority of parents who opt out of immunization based on personal beliefs have sincere philosophical conflicts with childhood vaccinations, in some states the process of opting out is so simple that some parents simply see it as easier to check a box to opt out rather than go through the time, trouble, expense, and discomfort of vaccination. Some worry that by making it too easy to opt out of vaccinations, it may be sending the message that vaccinations are not important. Vaccination rates are significantly lower in states that allow philosophical exemptions—particularly in states with the least onerous processes—and, reciprocally, rates of infection with vaccine-preventable diseases are significantly higher [9]. While overall exemption rates are still low, nonmedical and philosophical exemption rates are increasing [12].

States vary not only on the types of exemptions offered but also on the way those nonmedical exemptions are implemented. Of the 34 states where religious but not philosophical exemptions are permitted, 13 have never denied a request for exemption. In these states, then, the religious exemption functions as a *de facto* means for philosophical exemption [13]. Although many vaccination advocates view nonmedical exemptions as entirely disruptive to the vaccination program, others believe that they represent an effort on the part of the government to accommodate the views of a small minority who, for whatever reasons, do not believe in immunizations, and may actually serve to bolster the integrity and sustainability of childhood immunization laws by mitigating concerns that they represent government coercion [14]. Indeed, cognitive psychology studies have found that individuals are willing to accept a higher level of risk if the decision is perceived as voluntary [15].

Misperceptions and Misinformation

A parent's decision to vaccinate is based on an analysis of the risks and benefits of vaccination, as well as the risks and benefits of abstaining. This analysis is not the same for all parents, and it is not necessarily the same for all vaccines, as some

parents have concerns about some vaccines but not others. Discussed in greater detail in other chapters, the negatives associated with vaccination include cost, discomfort, inconvenience, and potential side effects ranging from minor to very serious, while the predominant benefit is a reduction in the likelihood of contracting an illness. In a recent qualitative study of mothers' perceptions of the relative risks and benefits of immunization, researchers found that mothers who immunize their children completely and according to the recommended schedule believe that the risk of vaccination is lower than the risk of contracting the vaccine-preventable disease, even though the probability of contracting many of the diseases is low [16]. In contrast, mothers who incompletely immunize their children tend to perceive vaccines as not very effective in preventing disease and were often confused about which diseases were prevented by vaccines. Finally, those who abstained from immunizations altogether perceived a relatively high risk of unknown, long-term side-effects of vaccinations compared to the risk of contracting the diseases they are designed to prevent.

The low perceived risk of vaccine-preventable diseases among non-vaccinators persists mainly due to the very success of the vaccination program. Few parents have seen anyone with measles, mumps or rubella, leading some to wonder if they are putting their children at unnecessary risk to protect them against diseases that are no longer a threat. Just over a century ago, but well outside the memory of the current generation of parents, the US infant mortality rate and the under-five childhood mortality rate were 20 % [17]. Now that vaccination rates are so high however, certain vaccine-preventable diseases crop up so rarely in developed countries that parents can wonder if vaccines are even necessary anymore.

Although other vaccine-preventable diseases such as influenza, rotavirus, and varicella are more widespread today, the perception of the harm caused by the "flu," "stomach virus," or chicken pox is minimal. Parents may recall having had these diseases themselves as children and not have come into contact with children who have had suffered long-term consequences. In reality, however, influenza infections are associated with thousands of deaths each year in the USA, and, before the varicella vaccine became available in 1995, chicken pox was responsible for 11,000 hospitalizations and 50–100 deaths each year [18]. Since 1995, there has been a 96 % reduction in mortality from chickenpox in persons under the age of 50 [19].

While the perceived benefits of vaccination may be low for many parents, the perceived risks may be unacceptably high, particularly given that vaccines are given to healthy children rather than to treat an existing illness. Further complicating the assessment of risk, as the anti-vaccination movement grows, new, alternative, postmodern hypotheses rapidly replace those supported by research findings [12]. One of the primary contemporary misperceptions about vaccinations is that there is sound scientific evidence demonstrating that vaccines cause developmental disorders, primarily autism. Autism is currently a poorly understood yet tragic disease, and in the past few years, US Department of Education statistics suggest that autism incidence has dramatically increased, leading some to conclude that they have reached epidemic levels. According to widely publicized estimates, 1 in 166 US children now suffer from autism, a more than sixfold increase over the past 10 years

from the 1 in 2,500 estimate that had previously been accepted for decades [20]. Despite concerns over the increase in the number of reported cases, numerous studies have unambiguously demonstrated that the so-called "autism epidemic" is due to a 1994 change in the American Psychiatric Association's diagnostic manual definition of autism, as well as to an attendant increase in the awareness of its signs and symptoms and improved diagnostic tools, rather than a true increase in incidence. However, media focus over the past decade about this debilitating disorder has increased attention and parental concern on the possible causes of autism [20]. As parents seek explanations for the cause of autism, and as genetic influences alone cannot explain its origins, many parents and researchers look to environmental exposure for potential explanations. Because autism has an average age of onset (18–19 months) that coincides with the recommended age for the administration of the measles–mumps–rubella (MMR) vaccine (before the age of 2), a main focus of the search for environmental explanations has been placed on childhood vaccines.

Interest in a possible vaccine–autism link was initially sparked by the 1993 research led by Dr. Wakefield in London, who suggested an association between the MMR vaccine and inflammatory bowel disease (IBD) based on a small series of case studies of children with Crohn's disease [21]. He followed these reports with a 1998 *Lancet* study of 12 children, which suggested a link between the MMR vaccine and a type of IBD associated with developmental disorders such as autism [22]. After this study's publication, MMR immunization rates declined, and measles outbreaks increased, particularly in the UK where the study was conducted. Despite the fact that the paper was partially retracted in 2004 and fully retracted in 2010 due to considerable methodological and ethical problems, and despite the fact that subsequent large-scale epidemiologic studies have found no association between the MMR vaccine and autism, concern over the MMR vaccine–autism link persists [23]. The extensive media coverage of the Wakefield reports—as well as the media giving equal attention to both sides of the argument—is thought to have led many parents to erroneously conclude that there is truth in the theory that MMR causes autism and that the scientific community was undivided on the matter [24]. Indeed, Dr. Wakefield has frequently been presented in the media as a whistleblower, championing the best interests of families, in contrast to "uncaring" scientists, physicians, and public health officials, who may have their own vested interests [25, 26].

Similar concerns that the vaccine preservative thimerosal, discussed in greater detail in Chap. 11, is the source of the increased the risk of autism in children have been propagated, despite results from numerous toxicologic and epidemiologic studies which have found no association [27]. Concerns over the vaccine–autism link also stem from one of the most commonly held vaccine-related concerns among parents [3], which is that too many vaccines are given at once or within the first 2 years of life. A recent nationally representative telephone interview of 1,600 US parents of children under the age of 6 found that a quarter of respondents believe that too many vaccines given at once can overwhelm or weaken a child's immature immune system [28], and that this overload can cause adverse effects such as autism [29, 30], in spite of a lack of credible evidence to support these conclusions and even evidence to the contrary [29, 31]. Similar misperceptions have been

propagated that vaccines cause other learning disabilities or diseases such as cancer, autoimmune disease, allergies, or asthma [32]. Despite a preponderance of large-scale studies finding no such associations [23], such diseases and disorders are very real to parents—far more real than measles or polio—and can be lasting in parents' minds.

Another common misperception is that vaccines today contain full-fledged, live viruses, and that children can contract the vaccine-preventable disease from the immunization itself. In reality, however, vaccines contain only a dead or weakened germ (or parts of it) that causes a particular disease. Only those immunizations derived from weakened live viruses (e.g., varicella or MMR vaccine) have the potential to lead to a very mild form of the disease. Confusion likely stems from the more real concern that for children with weakened immune systems, such as those being treated for cancer, these vaccines may cause problems.

Further complicating the risk–benefit decision-making process for parents, herd immunity, while a fundamental theory behind population vaccination programs, may not be properly or fully understood by parents. Indeed, in a recent study, 81 % of parents who refused or delayed vaccinations reported that they believed that their vaccination decision did not put their child or the population at risk for disease [33]. Such parents clearly do not understand that vaccination not only provides a high probability of direct protection to the vaccinated child, but it also dramatically reduces the probability that that individual will be a source of infectious transmission to others. In this way, herd immunity provides indirect protection to unvaccinated individuals by surrounding them with vaccinated individuals. While often accused of "freeloading" off herd immunity designed to protect only those who need it the most [2], parents who delay or refuse vaccinations for eligible children may not understand that by withholding or delaying immunizations, they are putting not only their child, but also a vulnerable population, at risk. Herd immunity is critical for the protection of individuals who must remain unvaccinated due to age (e.g., children under the age of 12 months for the MMR and varicella vaccines) or medical contraindications (e.g., cancer, autoimmune disease, past allergic reaction to a vaccine), as well as the small segment who remain susceptible to disease despite vaccination. When vaccination rates drop too low, herd immunity is compromised and the population is put at risk. Indeed, studies have found that vaccine-preventable diseases such as measles and pertussis (i.e., whooping cough) have recently reemerged in some communities with higher exemption/opt-out rates, primarily among unvaccinated children [34].

Anti-vaccine literature also frequently calls into question the necessity of vaccines at all, providing alternative explanations for the decrease in vaccine-preventable diseases that include improved socioeconomic conditions, better nutrition, the development of antibiotics and other treatments, less crowded household living conditions and lower birth rates that decrease the number of contacts. However, looking at the incidence of disease over time demonstrates the significant and direct impact that vaccines have had. For example, as shown in Fig. 7.1 below, although the incidence of measles in the USA has fluctuated over time, the significant decline coincided directly with the 1963 licensure and widespread use

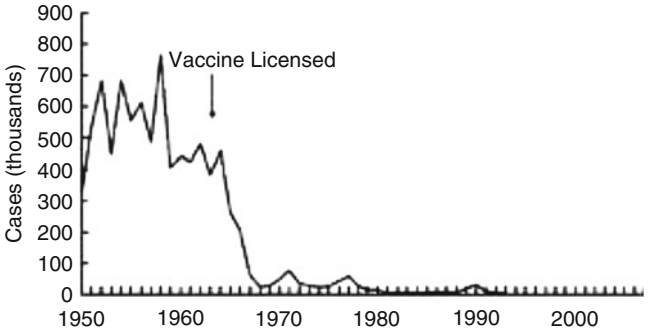

Fig. 7.1 Measles—The USA, 1950–2009. *Source*: http://www.cdc.gov/vaccines/pubs/pinkbook/meas.html

of the measles vaccine. Graphs for most other vaccine-preventable diseases (e.g., varicella, *Haemophilus influenzae* type b [Hib], etc.) show a similar pattern [35].

Reciprocally, when vaccination rates decrease, sharp increases in disease incidence can follow. For example, Great Britain and Japan, where pertussis immunization levels sharply declined in 1974 because of concerns over the safety of the vaccine, pertussis epidemics followed in 1978, including 36 pertussis deaths in Great Britain and 41 deaths in Japan [35]. Similarly, in the former Soviet Union, low childhood vaccination and adult booster vaccination rates for diphtheria were directly followed by a major epidemic between 1989 and 1994, over which period the number of new cases increased from 839 to 50,000, and which resulted in 1,700 diphtheria deaths in 1994 alone [35].

Anti-vaccination groups also frequently call into question the effectiveness of vaccines, as, like most medical interventions, vaccines are not effective 100 % of the time; rather, they successfully confer immunity in 85–99 % of individuals who receive them, for most routine childhood diseases [35]. While vaccinated individuals can still contract the disease for which they have been immunized, when outbreaks occur, vaccinated individuals have a significantly lower probability of contracting the disease than unvaccinated individuals. For example, unvaccinated individuals are 35 times more likely to contract measles than those who have been vaccinated [36]. However, the complicating—and often misunderstood—factor is that because vaccination rates in the USA are so high, when outbreaks occur, the *absolute number* of vaccinated individuals who contract the disease often is higher than the number of unvaccinated individuals. Anti-vaccination groups frequently use the higher proportion of infected vaccinated individuals to continue a faulty line of reasoning and conclude that outbreaks of vaccine-preventable diseases are frequently *caused* by ineffective vaccines, and that many of the recent disease outbreaks have been initiated by recently vaccinated children [37], even though studies have shown that few outbreaks can be attributed to vaccine failure and generally begin in clusters of unvaccinated individuals [38].

Due to the widespread use of the Internet, where the quality and validity of published material is not monitored, anti-vaccination messages are widely available and accessible. Further, unlike the vast majority of science-based medical and research articles, anti-vaccine Web sites are highly interlinked and are optimized in such a way that they appear as high as possible on results for vaccine-related Internet searches. Cognitive psychology studies have demonstrated that risk perception may be affected by media availability, with more information giving a stronger effect, thus artificially magnifying the acceptability, validity, and value of their messages [39]. Patients today increasingly look to the Internet for answers to health and medicine-related questions and are also increasingly wary of experts, either in the medical profession or governmental health agencies. Feeding off parents' desire to become more informed healthcare consumers as well as many parents' postmodern skepticism toward what may be seen as coercive government sources or authoritative medical professionals, many sites reject scientific evidence in favor of alternative interpretations [40], engaging in a rhetoric that is persuasive, despite a lack of scientific support for their claims [41]. Their messages are often presented in a manner that is far more accessible—in language as well as emotionally—to readers than what is available in the medical literature or on the sites of government agencies or medical groups [42]. Further, the anti-vaccination movement has successfully identified and made use of articulate and outspoken spokespersons to propagate its messages as well as testimonials, which are personal and appeal to the emotions of parents as they relate to their children. While some sites do reference articles published in the medical literature, many parents are unaware of important differences in the quality of both journals and the articles they publish and are unlikely to be able to identify potentially important and influential flaws and biases in design and possibly inappropriate or overstated conclusions that the authors may have drawn.

Mistrust

Some parents' concerns over the safety of vaccines stem from a more general mistrust in the government, the pharmaceutical companies supplying the vaccines to the government and physicians and the government's connection and impartiality with these companies [43]. Some anti-vaccination Web sites highlight concerns that high-level employees in agencies such as the US Food and Drug Administration (FDA) and CDC are able to, and often do, move between positions in government and the pharmaceutical industry. They also inaccurately claim that physicians who are involved in the FDA approval process are not barred from receiving or required to disclose consulting fees from pharmaceutical companies seeking approval for their products. These sites discuss concerns shared by many parents that government agencies often feel—and respond to—pressure from drug companies for contracts and for speedy approval, which can lead to concerns that vaccines enter the market before they are truly safe for widespread use by children of all ages [44]. Another common concern is that the high-tech lobbying, business savvy, marketing,

and promotion of products by the drug industry have led to overblown messages of the dangers of vaccine-preventable childhood diseases so that doctors and drug companies increase profits.

The growing number of different vaccine products and manufacturers has also led to concerns among some parents about the ability of the government to oversee the safety of each, even though most of the new products are variations or combinations of products that have been used for years [45]. Mistrust in the government's ability to ensure uniform quality among so many different products has recently focused on concerns that there are "hot lots" of vaccines that are associated with a higher probability of adverse events than other lots. The concept of hot lots is based on the misconception that the more reports that a particular vaccine lot has in the CDC/FDA's Vaccine Adverse Event Reporting System (VAERS) database, the more dangerous that lot is [35]. However, this conclusion is flawed, as vaccine lots vary widely in size—from several hundred thousand doses to several million—and some are in distribution for far longer periods than others; thus, lots that are larger and/or in distribution longer are more likely to have a higher number of VAERS reports filed. Further, identification of a problem with a vaccine lot based on reports to the voluntary, self-reported VAERS surveillance database alone, without additional scientific analysis, is not possible. Reports are not confirmed, so that only some of the reported events are truly side effects from vaccines, and it often cannot be determined whether events occurred by chance alone among persons who have been recently vaccinated. For serious reported events (e.g., hospitalization, permanent disability, or death) follow-up with parents and/or healthcare providers is attempted in order to collect additional information such as laboratory results; however, this is not successful in all cases. Given that background mortality and neurological disorder diagnosis rates for children are highest during the first year of life, and due to the multiple limitations of a passive reporting system such as VAERS, determination of causality based on these data is not feasible. Still, the FDA reviews the VAERS database weekly to identify potential "hot lots" and has the legal authority to recall a lot immediately.

Parents may further lack a trust in the government to have an interest in the health of their individual child. The government assesses risk at the level of the population, which may not necessarily result in the same decision-making processes or endpoints as a parent's individual-level assessment of risk. Because vaccines are not completely risk-free, the government must accept a certain (very low) level of risk for the population. Parents, however, may not be willing to accept *any* risk for the benefit of the population if it occurs at the possible expense of their child. Further, because the decision at hand is about the health of their children, parents may perceive the government's accepted risk level—however low—in a different, more complex, and emotional manner that is not based on facts and statistics alone. Also, not all parents weigh individual and population risks in the same way. As discussed in greater detail in Chap. 17, individuals have different ways of valuing personal and social responsibility; while some feel it is part of their responsibility, as a member of a community, to vaccinate their children, others do not.

Parents' mistrust may stem not only from a concern that the government does not have their child's best interest in mind, but they may also worry that government agencies are not always perfectly organized and do not always move swiftly if a problem is identified. For example, a recent study of a sample of healthcare employees in King County, Washington reported that 61 % of respondents were unclear on the definition of a reportable vaccine-related adverse event, 17 % would not know how to report such an event, and 18 % were unsure whose responsibility it is to report an adverse event [46]. These results are from a state with one of the nation's highest parental opt-out rates, and the study had a low response rate on the mail-based surveys (36 %), allowing for the potential for significant selection bias. However, parents reading the abstract of this published study on an anti-vaccination Web site may not understand the importance of such potentially influential details and may conclude that the government is not adequately reporting the true incidence of vaccine-related adverse events. Indeed, a 2002 study of the main concerns expressed by anti-vaccination Web sites reported that 95 % of included sites claimed that vaccine reactions (or vaccine failure) are underreported [47]. The most common reasons listed on these anti-vaccination Web sites for underreporting were: physician failure to recognize delayed reactions; physician failure to report; government and pharmaceutical industry pressure to purposefully obscure the truth. Such perceptions likely stem from the fact that the VAERS reporting system is a passive, voluntary system and is therefore subject to multiple limitations, including underreporting, self-reported and unconfirmed diagnoses, and lack of denominator data and unbiased comparison groups, hampering the development of causal associations between vaccines and adverse events based on VAERS. Parents may not realize that the government acknowledges that VAERS is an imperfect and incomplete reporting system, and that the government depends also on additional epidemiologic and laboratory data for the detection and reporting of adverse events [48]. The primary source of surveillance data used by the National Center for Health Statistics is the Vaccine Safety Datalink Project (VSD), established in 1990 as a collaborative effort between the CDC and managed care organizations to study the adverse side effects of vaccines among children from birth through age 6 years [49]. This database is less well recognized by the general public but allows for the study of vaccine safety in a manner that is not affected by imperfect reporting.

Mistrust in the safety of the vaccines produced by the pharmaceutical industry and lack of confidence in the oversight of the government over the safety of these products has led some parents to look to alternative methods of protection against vaccine-preventable diseases. Parents may believe that if they provide alternative homeopathic or naturopathic alternatives, vaccinations are not necessary. In addition to home remedies such as dietary changes (reduction in intake of saturated fats and sugar) and homeopathic "prophylaxis" such as taking human or bovine colostrum or supplements such as vitamin A, vitamin C, and Echinacea [50], some parents opt out of vaccination in favor of immunity acquired through direct exposure to infected individuals, citing that the pharmaceutical industry has taught parents to fear "natural immunity" [51]. Some parents believe that the immunity gained from exposure to a full-strength, live virus is stronger than what they get from

immunizations, discounting the far greater risk that they are introducing to their child—and other people their child interacts with—by such exposure. For example, some parents leery of the varicella vaccine participate in "chicken pox parties," where otherwise healthy children are exposed to a child with varicella in order to reduce their risk of serious infection as adults. The rapid and widespread communication provided by the Internet has promoted such gatherings on sites such as the Facebook page "Find A Pox Party Near You." A Facebook user even advertised lollipops contaminated with the varicella virus targeting parents who wanted to expose their children to the virus naturally [52]. Similarly, and of potentially greater concern, there is a report of an individual seeking items tainted with measles—a highly infectious disease with a high rate of mortality and complications—to avoid a school-required vaccination. Although health agencies intervened in many of these more dangerous activities [53], the persistence of attempts to find alternative "natural" methods to confer immunity underscores parents' continued mistrust of vaccines and the government agencies, pharmaceutical companies, and medical professionals that provide and encourage them.

Foreign-born parents, particularly those who are in the country illegally, may have additional reasons for having feelings of mistrust for the government and for thus abstaining from vaccinations. Foreign-born parents are more likely to have language or access to care barriers [54] and are more likely to report discrimination and negative experiences in the medical care system [55, 56]. However, multiple studies have revealed that their children have DPT, polio, and MMR vaccination rates that differed little from US-born children, despite more frequent moves [54, 57]. Foreign-born children in these studies did have lower vaccination rates for Hib and hepatitis B, however, even after controlling for factors including socioeconomic and health insurance status and access to care, possibly reflecting the fact that these vaccine-preventable diseases were not included in the World Health Organization's recommended vaccination schedule for many source countries at the time that these studies were conducted. As more immunizations are added to the recommended schedule in the USA, immigrant children may fall further behind in vaccination coverage unless access is improved and other barriers are removed to reduce disparities in vaccine coverage. According to many legal and public health advocates, lower vaccination rates for particular antigens among children of parents who are in the country illegally are likely due to a general mistrust or fear of the governmental system, as well as inadequate access and insufficient knowledge of safe and unthreatening ways to have their children vaccinated that will not compromise their presence in the country [58].

Where Parents Seek Information

When making the decision of whether or not to vaccinate at all or according to the recommended schedule, parents cite healthcare professionals as their primary source of information [3, 59]. Indeed, the majority of parents who changed their

minds about delaying or declining vaccinations for their children cited "information or assurances from healthcare provider" as the primary reason [59]. As discussed in greater detail in Chap. 5, many pediatricians, particularly in Western and Midwestern states with higher opt-out rates, are increasingly weary of discussing the issue with skeptical parents and have begun refusing to treat or "firing" parents that refuse to vaccinate their children at all or on time [60]. While some parents have made up their minds not to vaccinate their children before entering the physician's office or health department, others seek information and reassurance from healthcare professionals about the safety of vaccination. Although many pediatricians may be growing weary of the issue, many concerned parents are not aware that they are uninformed or misinformed about vaccination risks and benefits but do seek a trusting relationship with their provider and seek additional information and guidance in the vaccination decision [61]. The CDC and other medical and public health experts encourage pediatricians to continue the vaccine discussion with wary parents, as failure to do so may result in parents uncritically accepting flawed information [25]. To gain and maintain trust, physicians are encouraged to take time to listen, solicit and welcome questions, acknowledge both the benefits and the risks and respect parents' authority [62]. Public health experts stress the importance of establishing a nonconfrontational dialogue with skeptical parents at an early stage and providing both accurate and comprehensible answers to parents' questions. They also suggest sharing personal stories of children they have known who have been adversely affected by vaccine-preventable diseases and reports of outbreaks, to make the decision meaningful to them [63]. Equally important are honesty and accuracy, as vaccines are not entirely without risk, and although acknowledging these risks may increase a parent's concern in the short term, providing improbable or inaccurate reassurances can erode trust in the long term [25, 26]. How the vaccine is administered also matters to parents; a recent study reported that those who experience negative immunization experiences are twice as likely to have under-immunized children [56]. Negative experiences included not allowing parents to comfort scared or uncomfortable children while the vaccine was administered, providing slow or unskilled delivery, not helping the parent to comfort the child after the administration, and being dismissive when children experience an adverse reaction to vaccination. From a parent's perspective, the doctor–patient relationship is an important one, and it is critical that healthcare professionals respectfully, accurately, and compassionately communicate with parents about immunization decisions as well as during and after administration of vaccines.

Public health agencies such as the CDC continue to play an important role in how parents view vaccinations and their importance, despite a recent finding that only 23 % of parents reported placing "a lot" of trust in government vaccine experts and officials [64]. As previously discussed, parents cite quite a few reasons for having feelings of mistrust for the government's role in vaccine decisions. Further, to quote an expert group report published in the aftermath of the Wakefield debate, "it is much easier to create doubt and damage a vaccine's reputation than it is to restore it" [65]. Although it is not reasonable to expect that 100 % trust can be restored, the government can improve the way that it communicates with and responds to

skeptical parents. One of the main areas where parents continue to feel mistrust in the government is in the level of coercion that parents feel to get their children immunized. For example, mistrust increased in the UK when general practitioners were reimbursed by the National Health Service (NHS) for having high vaccination rates in their practices [25]. Parents also want to feel that they are being listened to and that their concerns are being met with respect. When the NHS refused to support the use of alternative schedules and single rather than combined vaccines, although this decision certainly made the most sense scientifically and financially, it eroded skeptical parents' trust that the public health agency was taking its concerns seriously and led some to feel that their autonomy in decision-making for their children's health was at risk. Reciprocally, in the aftermath of the Wakefield MMR–autism debate when MMR vaccination rates decreased dramatically, the NHS removed the compulsory status of the MMR vaccine—though continued its strong support—likely contributing to parents' feelings of autonomy and respect [25]. A similar demonstration of the government's commitment to vaccine safety and recognition of parents' concerns is that the US Congress passed the National Childhood Vaccine Injury Act in 1986 [66]. Spearheaded by parents, this law represented a collaborative effort between parents and the federal government that acknowledged that vaccine injuries and deaths, however rare, do occur, that families should be financially compensated when adverse events occur, and provided a commitment to ensure strong safety protections in the vaccination program. How health agencies respond when outbreaks do occur is also important in establishing a trusting relationship with the public. For example, when the bovine spongiform encephalopathy (BSE; mad cow disease) outbreak occurred in the UK, health agencies reassured the public that the beef was safe, an assertion that was later disproved [25]. Similarly, confidence in the US public health system waned during the H1N1 "swine flu" outbreak, when inadequate and apparently disorganized supply of vaccine was available to many counties across the USA, and when a number of vaccines were approved for use within only 3 months since the pandemic was declared [67]. While this short approval time was a huge success from the perspective of the government—representing an unprecedented collaboration among health authorities, manufacturers and scientists—to some in the general public it appeared too rapid for proper testing to occur and that what was seen as successful collaboration by the public health community was, in fact, seen as collusion by some in the general public [68]. These examples highlight the importance of individual autonomy in vaccination laws as well as transparency, honesty, and accuracy in risk communication. They also underscore the importance of having an organized, dependable public health system and vaccine supply to ensure public confidence.

As previously discussed, the Internet is also an important source of information for parents making vaccine decisions. A parent's level of trust in the medical community or public health entities as well as accessibility of information presented may thus affect whether parents form opinions based on results from population-based data, large-scale clinical studies and other information presented on government Web sites or on more nontraditional sources that include anecdotal information and personal accounts from other parents who believe their child has been harmed

by a vaccine [64]. The mistrust and suspicion of ulterior motives that some parents feel toward the medical or public health community may not be present when reading accounts of parents who believe their children have been injured after receiving a vaccine. Indeed, in a recent study, nearly three quarters of parents reported placing at least some trust in other parents who believe their child was harmed by a vaccine [64]. In addition to trust, one of the primary reasons that parents vaccinate their children is simply not wanting to diverge from the cultural norm, or "bandwagonning" [69]. The preponderance of anti-vaccination Web sites may make the vaccine refusal option appear more common than it is and more acceptable.

Conclusion

In the absence of firsthand experience with most vaccine-preventable diseases, sustaining high confidence in recommended vaccinations and schedules will likely always be a challenge, as the perceived threat level remains low for many parents [3]. In addition, with a wealth of misinformation circulating on the Internet and in other media outlets and anti-vaccination communities, parents may require assistance in distinguishing factual information from inaccurate reports and claims. Parents try to make the best vaccination decisions that they can based on the information available to them; however, the general public—including many anti-vaccination Web site content authors as well as many parents—is generally not equipped to critically appraise the medical literature [70], and public education efforts should aim to synthesize the current literature in a timely and accessible way. Efforts to educate parents are needed both at the level of the pediatrician as well as at the federal, state, and local levels. Additional information alone is inadequate to shift perceptions away from alternative, emotionally charged interpretations [40, 71]. Decision makers must understand and take into account not only the scientific evidence and economic forces driving parents' decisions about vaccination, but also the psychosocial, cultural, and political factors affecting these decisions [45]. When communicating with parents, medical professionals, government agencies and other health care organizations must remember the importance of individual risk for these parents, recognize the important role of the parent as the child's primary advocate, respect parents' autonomy in medical decision-making, retain their credibility by being honest that risks are not zero, and take the time to educate parents about the true risks and benefits of vaccination in order to make decisions for their children that are based upon accurate information. Disdain and alienation from the medical providers toward parents who do not vaccinate their children or refusal to address the emotional or nonscientific reasons for not vaccinating may serve to further entrench opponents to vaccination and further fuel the anti-vaccination movement [72], particularly as one of the primary reasons for abstaining from vaccinations is mistrust [40]. Similarly, for the government's part, trust is equally important and requires improved transparency, honesty, and accuracy in risk communication. As skepticism and refusal of the vaccination program is unlikely to disappear entirely or any time soon, healthcare

providers and public health officials must continue to appreciate the nature, context and sources of parents' concerns about vaccination and be committed to educating parents in an honest, accurate, and respectful way about the truth of vaccine efficacy, safety, and public health importance.

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Chapter 8
The Vaccine Misinformation Landscape in Family Medicine

Donald B. Middleton and Robert M. Wolfe

Introduction

This chapter covers the problems of under-vaccination and vaccine resistance in family medicine. Vaccination rates in family medicine are somewhat lower than rates in pediatrics and somewhat higher than rates in internal medicine. Overall, adult vaccination rates remain below objectives [1]. The authors hope to provide some insight into why many family practitioners (FPs) are not in full compliance with vaccination recommendations and offer some advice as to how to overcome this deficiency. In some respects the problems posed are unique to family medicine because FPs have to deal with every aspect of the vaccine program and every aspect of the family unit which often extends beyond the traditional nucleus to include grandparents, aunts, uncles, and cousins. In addition, considered integral to family medicine practice, many allied health have experiences with vaccine practices that often must be addressed. Unfortunately anti-vaccination sentiments are mounting in both FPs and patients. The forces leading to these sentiments are obviously multifactorial.

D.B. Middleton, M.D. (✉)
Department of Medical Education, UPMC St. Margaret, University of Pittsburgh School of Medicine, 815 Freeport Rd., Pittsburgh, PA 15215, USA
e-mail: middletondb@upmc.edu

R.M. Wolfe, M.D., F.A.A.F.P.
NorthShore University Health System, Evanston, IL, USA

Pritzker School of Medicine, University of Chicago, Chicago, IL, USA

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Postmodernism and Anti-vaccination

"Postmodernism is characterized by relativism, namely that there are no such things as objective facts and that reality has a plurality of meanings and is contingent" [2]. Part of the dynamic of postmodern thinking is that science and "experts" are open to questioning. Scientists are scrutinized as having served politicians and business rather than the people and are accused of bias and arrogance. Postmodern thinking puts greater emphasis on intuition and social relationships and tends to distrust the scientific method as the best path to healing our ills. Anti-vaccination attitudes are an expression of postmodern thinking in that anti-vaccinationists tend to be suspicious of authority and insist on alternative methods of healing rather than traditional medicine. One of the attractions of alternative healers is the sense of looking at the whole person, rather than trying to reduce the person to a biological or molecular problem [3]. The FP not only has to look at the whole person but also at the whole family unit, and may deal with many, often conflicting opinions.

In reaction to the postmodern point of view, many in the medical community have attacked the anti-vaccination point of view as ignorant. Poland has decried the dangers of slipping into a relativistic point of view. "… increasingly…many within the healing professions…have abandoned the careful metrics and wisdom of the scientific method, for empiricism and an embracement of 'individual voice and opinion.' This is in essence a type of post-modern, post-intellectualism. … Sophiology, vaccinology, and professional ethics demand that we not abandon reason and the scientific method to the unorthodox, nor acquiesce to the demands of the scientifically illiterate, nor to those ignorant and afraid—rather we must insist as healing professionals that what we recommend and do for our patients be evidence-based and carefully teach our students and peers the necessity of scientific truth and wisdom in relation to vaccines" [4]. In another article, Poland and Jacobson wrote: "…antivaccinationists have done significant harm to the public health. Ultimately, society must recognize that science is not a democracy in which the side with the most votes or the loudest voices gets to decide what is right" [5]. The struggle between these voices and others in the medical community who feel that persons opposing vaccination must be met and understood on their own terms will continue. What is certain is that FPs and patients will demand more information and more of a share in decision-making about what vaccines they give and receive [2].

Physician Issues

The authors have found mistrust of authority to be growing especially in light of immunization schedule changes such as the removal of RotaShield® from the market and the change from oral to IM polio virus vaccine. Comments from FPs such as "Vaccines are not safe.", "The drug companies [whose products are saving their patients' lives!] are just out for profit.", or "I don't trust the government." are not rare.

Vaccines are among the safest and most highly tested of all products physicians employ. Drug companies do make profits but the financial return on vaccines hardly matches the return on medications prescribed daily. Low margins coupled with legal risks have caused many manufacturers to leave the vaccine market [6]. The authors do not believe that the government is actually out to control a patient's life but that it has a societal responsibility, or else it would not be existent. Vaccine requirements are protective for the individual and reduce societal costs in both suffering and expenditures but these benefits seem to be lost to many patients and practitioners [7, 8].

Increasing the number of recommended immunizations strangely often acts as a negative force. Rather than viewing new vaccines or broader coverage recommendations as boons, many FPs and their patients see only increasing costs and complexity to control illnesses they rarely face. The recommendation to repeat MCV4 in adolescents serves as an example: high cost with little disease prevention. Staying abreast of the at least annual changes in vaccine schedules over the entire life span remains a challenge [9]. That last year's advice (e.g., influenza vaccine for everyone over age 18 years [at least compliance took only one dose of any product per person!]) doesn't match this year's recommendation (e.g., influenza vaccine for everyone over age 6 months [with multiple doses, dosages, and products]) may lead to misinformed office vaccine administration policies. Until new vaccine recommendations are widely disseminated, even electronic record reminders which are often programmed by some central technology department may be at least temporarily out of date.

Knowledge deficiency accounts for some difficulties in compliance with the vaccine schedules [10]. Efforts to educate medical students and FP residents about immunizations account for only a few hours over 4 years or 3 years of education respectively [11, 12]. Zimmerman's et al. team developed the TIME project which uses multistation clinical teaching scenarios to address immunization education deficits for medical students and residents [13]. The Association of Family Medicine Residency Directors offers an immunization training program at http://www.afmrd.org/i4a/pages/index.cfm?pageid=3470. Although continuing medical education (CME) hours devoted to immunization education are limited, most FPs strive to keep current through consulting some of a multitude of available educational resources [9].

Vaccines that are commonly used in pediatrics may be infrequently needed in family medicine so many FPs are not as expert with some products. As FPs see fewer infants, staff may experience confusion in the timing or administration of vaccines, e.g., the two rotavirus vaccines that have different dosage schedules [14]. As an example of an administration dilemma, FPs may not know how to manage a regurgitated dose of RotaTeq™ versus Rotarix®. Additionally, the contents of even frequently used vaccines are often a mystery in daily practice. An informal 2012 questioning of 44 FP residents showed that they were uniformly unable to voice the difference in the contents of DTaP versus Tdap vaccine [personal information]. Some FPs are unaware that Pediarix® is not indicated for age 12–18 months or wonder whether a dose of Pentacel® can be given at that age if the primary series was with Pediarix®. Infrequently utilized vaccines can lead to troubling administration

Table 8.1 Areas of difficulty with the CDC unified vaccine schedule in family medicine

I. Thoughtful debate
A. Benefit of vaccination
B. Timing of vaccination
C. Risk–benefit ratio
D. Cost–benefit ratio
E. Ethical issues
1. Vaccine manufacturing process
2. Universality of recommendations
II. Knowledge deficiency
A. Challenge to stay current
B. Recognition of the nature and true risk of vaccine preventable diseases
C. Management of vaccine side effects
III. Financial issues
A. Failure to benefit from compliance with vaccination recommendations
B. Capital investment to stock vaccine products, many of which are used infrequently
C. Supply management and shortages
D. Storage difficulties; power outages

errors, e.g., failure to mix the Pentacel® DTaP-IPV component into the ActHIB® component before injection. Of course, similar questions can arise over issues with adult vaccines. FP-generated varicella vaccine or zoster vaccine questions arise continually. "If a 60-year-old patient reports never having had chickenpox, must I first vaccinate that person with Varivax® before giving Zostavax®?" "After a 63-year-old husband develops shingles, his 65-year-old wife asks whether she needs Zostavax® so she won't get the shingles from him." "After a patient develops shingles, should he/she get a shingles vaccine? If so, when?" "If I never had chickenpox, but get exposed to a case of shingles, do I need Zostavax® even though I am only 54 years old?" Many if these questions are already addressed in the *Ask the Experts* feature of the Immunization Action Coalition (IAC) Web site at www.immunize.org. In the lower left hand corner of this Web site is the information needed to contact IAC for anyone with a vaccination related-question.

Although FPs want the best for their patients, an individual FP's mindset and independence can lead to debate with the unified vaccine schedules. Table 8.1 lists some of these difficulties. Comments that a particular FP's patients won't contract hepatitis B or HPV are not unusual. Unlike pediatric well-visits, adult well-visits most often focus on other problems such as heart disease or cancer prevention. Outside agencies may give little weight to vaccination records. For example, most insurance physicals do not require immunization information or updates. So FPs may have to switch from thinking about the goals of common disease prevention or treatment to the need for vaccination for uncommon illnesses and may wrongly conclude that vaccines can be skipped.

A partial list of roadblocks to full compliance with vaccine schedules follows. Time-pressured visits interfere with vaccine-oriented cogitation: busy practitioners may simply forget to give appropriate vaccines. Minor illnesses that have no effect on vaccine response may mistakenly be considered contraindications to immunization. Many FPs do not know whether they are financially benefiting from in-office vaccine administration. Infrequently utilized vaccines such as rotavirus or varicella vaccine may prove to be too costly for some FPs to stock. The difficulties of ordering vaccines, storage, and vagaries of administration lead some to simply refer patients to the local health department for immunizations or not worry about vaccination at all. FPs recognize that free meals and other gifts from vaccine manufacturers' representatives are best avoided, but many feel the loss of information that these representatives used to provide. Because keeping up with the constant adjustments to and nuances of the vaccine schedules is difficult, a reliable source of vaccine information is critically important for accuracy. Signing up for the free periodic email updates from the Centers for Disease Control and Prevention (CDC) at www.cdc.gov/vaccines, reviewing the Advisory Committee on Immunization Practices (ACIP) meetings, or downloading an iPhone application such as the CDC-supported *Shots by STFM* really helps to meet this challenge [9, 15].

The CDC recaps strategies to alleviate these dilemmas, aimed at both physicians and patients [16]. Tools that take the decision out of the doctor's hands such as standing orders, or those that require physician or office staff action, e.g., electronic record reminders, are the most effective. In published studies, standing orders to vaccinate markedly increased vaccination rates from 0–29 % to 78–81 % [16]. The IAC has standing orders sets for virtually every vaccine at www.immunize.org. In other studies, computerized record reminders improved rates from 29 to 86 % [16]. Chart reminders are also effective but somewhat less so. State immunization registries may also improve vaccination rates, but these registries are often aimed at children, excluding adults, failing to check the forces that reduce adult vaccination rates. Even the CDC site on vaccine registries at http://www.cdc.gov/vaccines/programs/iis/default.htm mostly discusses childhood records.

Many FPs, especially those without electronic records, lack the resources to utilize these tools. Hainer reviews methods to increase office vaccination rates [17]. Chief among his suggestions is the appointment of an office vaccine champion: an MD, nurse, or any office employee will do. The office vaccine champion should also freely consult useful vaccine Web sites such as www.cdc.gov/vaccines, www.immunize.org, and www.immunizationed.org [9]. One author's personal approach is to provide this individual with a copy of the latest edition of the American Academy of Pediatrics (AAP) Red Book (currently 2012 29th edition) [18] and of Marshall's The Vaccine Handbook (The Purple Book) (currently 2012 4th edition) [19]. The Red Book is an unmatched reference on vaccine schedules and special circumstances. The Purple Book covers every aspect of vaccination including safety nets, side effects, and vaccine history. Marshall provides evidence-based, thoughtful responses to virtually every individual or societal dilemma to dispel common misinformation. The fourth edition provides information about vaccine standards, principles, and regulations and addresses specific vaccine concerns. In Chap. 7 Table 7.2

lists 26 Web sites with anti-vaccine postures, including sites with names such as http://vaccineinfo.net that falsely suggest pro-vaccine stances. Unfortunately The Purple Book is not widely known among FPs but is an extraordinary reference currently available for $25 from Professional Communication, Inc. books.

Office tools to improve vaccination rates aimed at patients include mailed or telephoned vaccination reminders, personal health records including allowing patients access to the immunization history portion of the electronic record, and patient education [16]. Wallet cards for adults to record administered vaccinations are available from IAC. Although their effectiveness is unproven for adults, for years similar vaccine records were the major record-keeping tool for children and proved to be effective.

In published studies, performance feedback increased vaccination rates in private practice from 34 to 66 % [16]. Obviously, most physicians are motivated to do well on feedback evaluations especially if these data are shared with colleagues. In some financial systems, immunization rates are directly linked to payments to FPs. Many health systems or group practices incentivize employed FPs based partly on vaccinations rates or concordance with Healthcare Effectiveness Data and Information Set (HEDIS) criteria, which emphasize vaccination.

Concerns About the Benefits and Risks of Vaccination

The disappearance of vaccine-preventable diseases from daily life and from practice has left both the public and physicians wondering whether some vaccines are really necessary. Most practicing FPs have never seen once common vaccine preventable diseases (VPDs) and have almost no experience with VPD consequences. Most FPs do not consider that measles still kills tens of thousands worldwide every year or causes severe consequences such as subacute sclerosing panencephalitis (SSPE) [20]. Likewise, the public considers VPDs conquered or so uncommon that many do not vaccinate themselves or their children and have lost the cooperative spirit required to keep communicable disease in check [6, 21]. Some avoid vaccination for themselves and their families but rely on others to be vaccinated in the hopes that herd immunity or effect will provide protection [6]. The point at which the percentage of persons vaccinated falls below the threshold required for herd immunity for a particular VPD puts the public at risk of recurrence of that VPD. For some VPDs such as measles, about 95 % of the public must be vaccinated or immune to achieve herd immunity. Mergler and Omer concluded that younger doctors have an altered perception of the risk–benefit of immunization and that concern over vaccine side effects may be the most significant factor contributing to vaccination barriers [22].

Patients feel the same. Freed et al. pointed out that although parents tend to follow the doctor's advice, 54 % are concerned about vaccine side effects, 31 % feel they have the "right" to refuse any vaccine, 25 % believe vaccines cause autism, and 11 % believe that vaccines are unnecessary for rare diseases [23]. Dempsey et al. reported that among 748 polled parents 13 % preferred an alternative vaccine

schedule, 53 % refused some vaccines, 55 % delayed some vaccines, and 2 % refused all vaccines [24].

Real or imagined side effects from vaccination serve as fodder for vaccination denial. MMR can cause many worrisome side effects such as febrile seizures or thrombocytopenia, so when faced with the choice of the immediate small risk of seizures versus the extremely low future risk of contracting measles, some turn down vaccination. In Gardner's study, nearly half of all Americans still thought that MMR causes the imagined side effect of autism [25]. Although some health care workers (HCWs) including FPs remain skeptical about the benefits of influenza vaccine especially in elderly patients, annual influenza vaccination programs do the most to remind both patients and FPs that vaccines are a critical part of wellness. But some fear vaccine side effects more than influenza itself! The vaccination rate among HCWs remains below targeted levels. Many in the population including HCWs and FPs suffer from trypanophobia (fear of medical procedures involving injections or hypodermic needles) or have irrational worries about vaccine safety.

VPD outbreaks serve to remind the public and FPs of the continued risk [26, 27]. However, awareness of these problems remains suboptimal. The news media often fails to stress VPD outbreaks, unless a tragedy such as death is a consequence [27]. Contrary to that choice, the news media often report unproven vaccines side effects that stir up controversy [6]. The best source for VPD outbreak news remains *Morbidity and Mortality Weekly Report*, available free online from the CDC.

Medical advances have colored the FP response to patients' refusals to be vaccinated with specific immunizations. Medications for the treatment of influenza, pertussis, and varicella zoster allow the patient and the FP to think that the disease can still be controlled if a vaccine refuser becomes ill. The fallacy in this logic is that these illnesses are not always amenable to treatment and that others can be exposed to the illness before treatment is begun or has a chance to be effective.

Particularly uncommon illnesses such as hepatitis A or B are often targets for non-vaccination. Some FPs feel that both hepatitis A and hepatitis B vaccines are given too early in life or are not necessary at all. In rebuttal, 2011 data from Alaska concerning hepatitis B once again demonstrates the wisdom of routine universal infant vaccination [28]. Disease due to hepatitis B including hepatocellular carcinoma in person's age 20 years and below has virtually disappeared [28].

Disappointment over vaccine effectiveness often stems from a misunderstanding of the vaccine's benefits. Many FPs do not understand that pneumococcal polysaccharide vaccine (PPSV23) may not prevent pneumonia but does prevent invasive pneumococcal disease. Thus when a PPSV23-vaccinated patient develops pneumonia, the primary FP may conclude that the vaccine does not work, failing to take into consideration the patient's avoidance of an otherwise potentially fatal accompanying bacteremia.

The cost–benefit of some vaccines leaves their use open to challenge. A prime example is the quadrivalent meningococcal vaccine (MCV4) which must now be repeated to boost protective antibody levels in high-risk young adults [29]. The quality adjusted year of life (QALY) is high for a single dose of MCV4; the repeat dose QALY is even more disturbing [30]. Smith et al.'s economic evaluation of

Table 8.2 Disproven vaccine to illness links commonly voiced in family medicine

Pertussis	Encephalitis
MMR	Autism
Thimerosal preservative	Autism
Meningococcal	Landry–Guillain–Barré syndrome
Hepatitis B	Multiple sclerosis/autoimmune disorders
DTaP	Sudden infant death syndrome
Influenza	Flu illness

pneumococcal vaccines states that a QALY of less than $20,000 is ideal, $20,000 to $100,000 generally acceptable, and greater than $100,000 unacceptable [31]. The QALY for the current schedule of MCV4 is $157,000 [30]. In rebuttal placing a true value on preventing the death of even one child is impossible.

Wide spread VPDs such as influenza, pertussis, and HPV are not age-limited. Some are infectious across the entire family. Pertussis in infants comes from infected parents, siblings, grandparents or HCWs [32]. The importance of vaccinating anyone with any exposure to infants under age 12 months is obvious. Conjugated pneumococcal vaccination of infants reduces pneumonia in adults through herd effect [33, 34]. Influenza infects persons of every age, sometimes afflicting the young adult such as 2009 pandemic H1N1 did with increased vehemence. So FPs need to counsel the families they care for to have everyone keep up to date with vaccinations, but few if any electronic records or office reminders list the vaccine status of the entire family in a particular family member's chart. On top of that, failure of patients or HCWs to be vaccinated can put anyone in the office at risk through intra-office transmission of illnesses such as measles or pertussis.

When faced with troubling personal experiences, individual FPs may dismiss scientific information. A fainting teenager who cracks off her top incisors in a fall after an HPV immunization may curtail the FP's use of HPV vaccine. The onset of an autoimmune disorder shortly after adolescent hepatitis B vaccination, which flares up after the second dose, may forever lead an FP to hepatitis B vaccine avoidance. The sudden death of an infant recently vaccinated with DTaP may forever lead to DTaP avoidance. Of course many of these experiences are not causally linked to the vaccine at all, but they certainly reflect the sorts of experiences that keep some FPs from vaccinating. The Institute of Medicine reports dispelling these vaccine-bad event linkages are available at http://www.immunizationinfo.org/issues/iom-reports. Some common, disproven, but still voiced linkages are listed in Table 8.2. A further difficulty is that poor outcomes may also engender lawsuits, some of which target the FP and/or the manufacturer. The entire vaccine industry has changed due to successful lawsuits that in hindsight have no merit [6].

Some FPs are intensely concerned about vaccine ethics. Three vaccines serve as examples: HPV, rotavirus, and the combination vaccine Pentacel®, containing DTaP, IPV, and Hib (OMP-PRP). The issue about HPV is whether it should be required, given that the virus is behaviorally acquired [35]. Zimet et al. reviewed the reasons for non-HPV vaccination among 19–26 year old women [36]. Fifty-five percent cited a monogamous relationship as the chief reason, suggesting that many young

women do not consider that they will ever be at risk. These folks miss the chance to be vaccinated at ages at which HPV vaccination is highly effective and seem not to understand that high-risk HPV types infect about 35 % of women at some point in their lives. Both FPs and patients may be unaware of the prevalence of HPV in non-cervical sites such as the oral cavity or that HPV in sum accounts for at least 15,000 cancers in US women and 7,000 cancers in US men annually [37, 38].

Misinformation about the impact of some vaccine contents such as thimerosal makes many FPs reluctant to use specific products. For example, the "cow" virus component or "pig" virus remnant in the rotavirus vaccines lead some to choose not to use these products. These components or trace substances have absolutely no bearing on vaccine safety or effectiveness [14].

The issue over Pentacel® is how it is made. FPs may object to the manufacturing process for some vaccines such as Pentacel®. The polio vaccine portion is produced in aborted fetal cells, MRC 5, which came from a 14-week old fetus aborted due to maternal psychiatric difficulties from a 27-year old otherwise healthy woman, who allegedly did not give her consent to use the cells. The National Network for Immunization Information details the use of human fetal cells including WI-38 and MRC 5 to produce vaccines [39]. Suffice it to say, the vaccines produced in these cells have saved countless lives and greatly reduced the burden of suffering.

The Internet

A Pew Internet & American Life Project study from a survey done in August and September 2010 found that 74 % of American adults use the Internet, and 80 % of Internet users look online for health information [40]. A similar study by The Harris Poll, based on a phone survey between August 9 and 15, 2011, found that 74 % of all adults have gone online at some time to look for health information, and that 60 % have done so in the previous month. Of persons searching for online health information, 69 % use search engines and 62 % use medical Web sites [41].

Unfortunately the Internet is particularly prone to be a source of misinformation. The Internet lacks a "frame" or setting by which the validity of information can be assessed. For example, for a medical journal, the library in which it sits is a "frame" lending credence to the contents; a magazine on a rack in a grocery store has a different frame and level of credibility. The Internet lacks such a frame: anyone can make a Web site appealing and well-designed, and an average Web user may have difficulty distinguishing true information from false. Anti-vaccination sites are highly visible. In several American studies, searching the first ten Web results on the search engine Google for the word "vaccination" produced more anti-vaccination sites than pro-vaccination sites [42–46]. This finding is particularly important in light of a German study that showed that 97.2 % of health information seekers on the Internet only look at the first ten search engine results [47].

A number of themes have been found on anti-vaccination Web sites, based on the work of Leask and Chapman and later by Bean [46, 48]. These can be divided into

"content" attributes and "design" attributes. Overall, anti-vaccination sites are characterized by three main content themes: concerns about vaccine safety and effectiveness, concerns about governmental abuses, and a preference for alternative health practices [44]. Most anti-vaccination Web sites argue that vaccines are ineffective or dangerous. Some of them indict Pasteur as a phony and his germ theory as being false. Often such sites promote alternative health practices, such as homeopathy. The argument is frequently used that VPDs have declined and vaccines are not needed. A companion argument is that a larger number of vaccinated children develop VPDs than unvaccinated children, ignoring the fact that studies of measles outbreaks showed that vaccine exemptors were between 22 and 35 times more likely to contract measles than were vaccinated persons [49, 50].

Most anti-vaccination Web sites emphasize civil liberties as a major issue and the right of a parent to choose the type of health care given to his/her child. A related theme is that physicians, vaccine manufacturers, and the government conspire to force children to be vaccinated so that the manufacturers can make money. Drug companies and the medical establishment are often accused of covering up the truth about numerous harmful medical conditions caused by vaccines, including "AIDS, asthma, autism, cancers, diabetes, fibromyalgia, leukemia, lupus, Sudden Infant Death Syndrome, and many more" [6]. A more recent accusation is that health authorities exaggerate a threat to promote vaccination, such as the accusation that the 2009 H1N1 outbreak was a "manufactured threat" [46]. Alternative medicine is promoted by many anti-vaccination sites, which endorse a variety of alternative medical practices, including chiropractic, naturopathy, and herbal medicine.

Since the publication in the Lancet of an article by gastroenterologist Andrew Wakefield and 12 colleagues describing a self-selected sample of 12 children referred to the Royal Free Hospital in London, attributing autism to vaccines, especially to the MMR vaccine or to thimerosal, has been prominent on the Internet [6, 51]. Wakefield created a storm of controversy leading to widespread media coverage and a significant drop in parental acceptance of MMR vaccine for their children in the UK with disastrous results [52]. Although the original article by Wakefield et al. was subsequently denounced by several of its authors and Wakefield himself was accused of fraud, many anti-vaccination groups and support groups of parents with autistic children still consider Wakefield to be a hero and martyr. Support for Wakefield's theory can be found on celebrity Web sites such as that of popular actress Jenny McCarthy, who believes her son became autistic from MMR vaccine [53]. Although autism is a tragedy, it is NOT caused by MMR vaccine.

Design attributes of anti-vaccination sites include emotional testimonies about children harmed by vaccines, stories of negative experiences with healthcare providers, and pictures of scary needles. Most anti-vaccination sites are heavily linked to other anti-vaccination sites. This strong linkage is in part what causes them to appear near the top of searches using the word "vaccination", whereas using the words "immunization" or "immunisation" produces mostly pro-vaccination search results. Google uses both word content of sites and the number of strong links to a site to rank that site. Anti-vaccinationists do not believe vaccines produce immunity. They tend to prefer words with the Latin root "vacca", meaning "cow", since Jenner

made the first smallpox vaccine from cowpox material, and eschew the Latin root "immunis", meaning "exempt from service" ("im" meaning "not" plus "munia", "duties"). Since Google also takes into account the use of words on linked sites, it is unlikely that pro-vaccination sites will ever be able to displace anti-vaccinationists' control of the word "vaccination" on Internet searches [45].

External Forces Limiting Vaccine Compliance

Poland et al. have attempted to categorize the underlying pathophysiology of vaccine refusal [54]. Denial about disease risk or fear over vaccine safety motivates the majority. Joining the bandwagon against immunization or accepting the misinformed advice of others, especially non-scientifically presented media sources such as sensationalistic television presentations, may lead to staunch vaccine refusal. Even advice from a neighbor may outweigh the FP's. To skirt school entrance immunization requirements for their children, some parents have turned to home schooling. FPs whose childhood charges are being home schooled should encourage completion of all vaccinations for everyone in the family regardless of the home schooling plans.

Literature documenting the issue of vaccine refusal for children is prolific, but similar studies in adults are less abundant [55–58]. Older studies from the CDC may not apply now [59]. However, Johnson et al. found little change from an old CDC study: lack of physician recommendation, mistaken indications, side effects, fear of needles, and lack of insurance (still a plague for young adults) served as the major impediments to vaccination [60]. High has pointed out the financial barriers to zoster vaccine which is highly effective but not covered under part B of Medicare [61]. When suggesting vaccination, the FP often faces a double barrier: reluctant parents need to be convinced to vaccinate their children *and* to vaccinate themselves. Many parents wisely chose to vaccinate their children, to keep them safe, but unwisely turn down vaccination for themselves. Adults often fail to understand that *they were vaccinated* when they were young and have grown up just fine. FPs may find themselves embroiled in debate or an educational session in the middle of a busy office session and may choose to delay vaccination or simply give up.

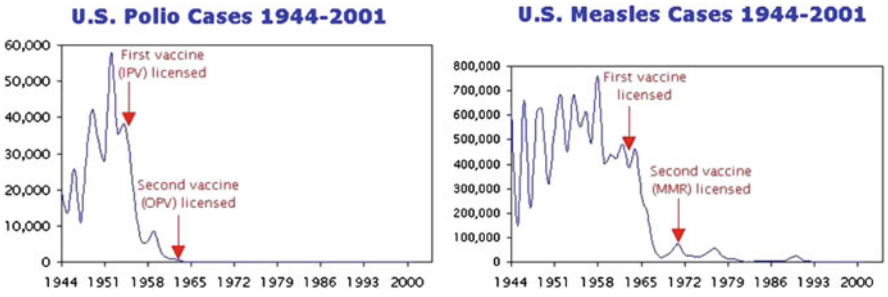
Literature offers much advice as to how to convince parents to vaccinate their children, including the threat of dismissal from the practice [62–64]. However, most FPs do not dismiss vaccine-reluctant adults from their practices, often because of other significant medical issues that really form the basis of the doctor–patient relationship. Much of the adult-oriented literature reviews low vaccination rates in specific groups such as HCWs or residents of long term care facilities but few studies cover well adults [65]. Even the office staff may be vaccine-reluctant, and FPs hardly ever fire personnel over this single issue. Some health systems may make vaccination requirements key to employment as with chickenpox, hepatitis B, and in some settings, pertussis. Despite the great number of informational pamphlets and pro-vaccine Web sites, government/employment-mandated or public vaccination education is minimal.

Specific groups are anti-vaccination. Hard line naturopaths, professionals such as some groups of chiropractors, and some religious sects dismiss all or some vaccines or make a distinction between vaccination and immunization [66]. Examples of misinformation these groups promulgate include the chiropractic pamphlets: "Vaccination: 18 Reasons to Just Say No" and "Do You Know What's in a Flu Shot?" [67]. The anti-vaccine Web site, www.VacTruth.com, lists 108 anti-vaccination books. However, a Canadian survey found that the majority of chiropractors were not anti-vaccination [68]. Russell et al. reported that 300 of 500 surveyed chiropractors expressed interest in participating in immunization activities [69]. Rather than dismiss chiropractic advice altogether, collegial discussion about vaccines may prove fruitful.

Countering Myths

Common myths about vaccines, largely promoted by anti-vaccination Web sites, have significant effect: a German study found that viewing Web sites critical of vaccination for only 5–10 min increased the perception of the risks of being vaccinated and decreased the perception of the risks of omitting vaccinations as well as the intention to vaccinate [70]. The CDC has a Web page containing common myths and their refutations, a helpful resource to "immunize" the patient against falsehoods [71]. FPs should be aware of some of the more common myths so that they can confidently answer questions about vaccine safety.

Myth #1: VPDs had already begun to disappear before vaccines were introduced, because of better hygiene and sanitation. This idea began to appear in anti-vaccination literature during the nineteenth century [6]. Although improved sanitation and health care have contributed to lower death rates from VPDs, the direct impact of vaccines is beyond doubt. Two graphs give examples:



Images from http://www.drwile.com/lnkpages/render.asp?vac_effective#r5. Original from CDC. MMWR Summary of Notifiable Diseases, United States, 1993. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00035381.htm. Accessed March 19, 2012.

Myth #2: "Hot lots" of vaccine have been associated with more adverse events and deaths. The CDC attributes this concept to misreading of data from the Vaccine Adverse Event Reporting System (VAERS): a high number of reports to VAERS about a vaccine lot means that lot is more dangerous [71]. Kata found that 38 % of anti-vaccination Web sites suggested "hot lots" of vaccines were associated with more injuries, and one anti-vaccination site was selling a list of suspicious lot numbers [42]. In truth, the FDA monitors reports more closely than any watch dog and will recall any vaccine lot suspected of causing an undue reaction rate.

Myth #3: Giving a child multiple vaccinations for different diseases at the same time increases the risk of harmful side effects and can overload the immune system. This myth is found commonly on anti-vaccination Web sites but is not scientifically credible. Offit estimated that each infant has the theoretical capacity to respond to about 10,000 antigens at any one time [72]. The infant immune system has the ability to replenish about two billion CD4+ T lymphocytes each day. Vaccinated infants are not more prone to other infections than unvaccinated infants.

Risk Communication in Family Practice

> When someone is honestly 55 % right, that's very good and there's no use wrangling. And if someone is 60 % right, it's wonderful, it's great luck, and let him thank God. But what's to be said about 75 % right? Wise people say this is suspicious. Well, and what about 100 % right? Whoever says he's 100 % right is a fanatic, a thug, and the worst kind of rascal. (An old Jew of Galicia, quoted in Milosz C. The Captive Mind. Vintage; 1990).

Much has been written about communicating with the public regarding vaccine safety and heuristics (cognitive shortcuts used to simplify complex decisions and judgments) [73]. What seems certain is that the public continues to be concerned about vaccine safety in spite of the efforts of public health authorities to reassure them. Risk communication expert Sandman has stated that public health institutions can no longer expect the same level of trust they used to hold [74]. The best risk communication efforts of the vaccine community will require acceptance that we live in a new world in which trust no longer comes automatically to physicians or public health officials. Three themes are prevalent:

1. The parental decision to vaccinate their child(ren) and themselves is based on a desire to protect loved ones from illness and a solid relationship of trust with their physician.
2. Persons who are vaccine-refusers or vaccine-hesitant often express concerns that physicians or public health officials do not really listen to them or take their concerns seriously or spend enough time explaining vaccine issues.
3. Reasons for vaccine refusal/hesitancy vary and are often aimed at specific vaccines and not all vaccines [75, 76].

A distinction can be made between vaccine refusal and vaccine hesitancy [21]. Whereas vaccine-refusers usually have deeply held religious or philosophical beliefs opposing vaccination or unreasoning fear about vaccine side effects, the vaccine-hesitant have a variety of less firmly held concerns and are more open to persuasion on vaccine-related issues [75]. To spur the vaccine-hesitant into action the FP should:

1. Listen to the person's concern using compassion and understanding, not just more science, to dispel fear
2. Assess what hazards the person perceives and plan for the reaction
3. Not over-reassure and offer assistance for any post-vaccination problems
4. Be involved in the debate as withdrawing gives the wrong message because critics and mavericks are most credible when they have the only voices
5. Acknowledge uncertainties and that these uncertainties are distressing (admitting uncertainty enhances trust; insisting one is 100 % correct creates suspicion [see Milosz quote above])
6. Provide a narrative or human face to support your case, e.g., parents supporting vaccination and your own choices for yourself and family
7. Be malleable so that when a response is ineffective develop an adaptive response
8. Draw attention to the overwhelming medical, scientific, community, and government support for vaccination
9. Be clear about your key message and always return to it, e.g., vaccination protects people from disease
10. Refer patients to trusted sources of vaccine information [9]

FPs need to approach all who question their advice to vaccinate with honesty and respect, while continuing to work with experts in communication to ensure that the message is presented in a manner that best reaches the hearts and minds of the listeners.

Summary

The vast majority of FPs consider themselves to be expert in preventive health services. As such they fully embrace the vaccine schedules and do their utmost to fully vaccinate their charges, their staffs, and themselves. Standing in opposition are sources of misinformation on the Web and in the media, rumor, misplaced fear, and dismissal of scientific and historical fact [5, 42]. Standing in support are the histories of VPDs, vaccine manufacturers, public health agencies, scientific investigation, and personal testament. Further information to assist those who need to develop skills to combat anti-vaccinationists is available through the CDC [77].

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Chapter 9
Vaccines: Boon or Bane—A Nurse's Outlook

Catherine O'Keefe and Meghan Potthoff

Introduction

The development and widespread uptake of vaccines has been one of the most successful public health accomplishments of modern health care. Consequently, vaccines have been considered the medical *boon* of the twentieth Century. However, with this success has come a concerning sense of complacency toward vaccinations. Parents and nurses of the twenty-first Century have not seen the devastating effects of diseases such as polio, pertussis, and measles because of the significant reduction in these vaccine-preventable diseases. In addition, the reporting of sometimes faulty information and media sensationalism of rare vaccine adverse events has alarmed the general public. These events have in many instances created an atmosphere of public distrust of vaccines and increasing parental refusal of vaccines [1]. The general public and nurses have benefited greatly from the twentieth Century *boon* of vaccines but must now deal with the very real twenty-first Century *bane* of vaccine complacency, refusals, and mistrust.

Nursing Roles

There are many roles for nurses in the health care setting. Nursing practice occurs whenever a nursing professional interacts with a patient, family, or community group to provide health promotion, health maintenance, or health restoration. This translates into many varied opportunities to advance vaccine efforts- from education to administration.

C. O'Keefe, D.N.P., A.P.R.N. (✉) • M. Potthoff, M.S.N., A.P.R.N.
Creighton University School of Nursing, 2500 California Plaza, Omaha, NE 68178, USA
e-mail: kokeefe@creighton.edu

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Registered Nurse

Staff nurses, whether in a primary care clinic, nursing home, community setting, or medical/surgical floor, have an important role in advocating for vaccines. The American Nurses Association (ANA) scope and standards of practice for professional nurses includes standards of assessment, outcome identification, planning, coordination of care, and health teaching and promotion [2]. These standards provide a framework and context for the professional nurse's role in vaccinations. Nurses must first and foremost be aware of the Centers for Diseases Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) most current vaccine recommendations in order to effectively plan and coordinate preventive care for their patients and families. Regardless of the setting, nurses must capitalize on every opportunity to teach patients, families, and groups about vaccine safety and efficacy.

Advance Practice Nurse

Within the advance practice nurse (APN) arena there are four roles: nurse practitioners (NP), clinical nurse specialists (CNS), certified nurse midwives (CNM), and certified registered nurse anesthetists (CRNA). APNs practice within a broader context of health care and thus have increased opportunities to positively influence patients, families and communities in the vaccine arena. APNs are prepared for and expected to provide expert nursing care and participate in health care policy activities at the local, state and national levels to increase access to vaccines for all citizens.

Nurse practitioners provide health care services across the lifespan and in all health care settings. The National Organization of Nurse Practitioner Faculty (NONPF) has published core competencies for nurse practitioners [3]. These core competencies include health promotion, disease prevention, health protection, and anticipatory guidance and education activities. Within these domains, nurse practitioners provide education regarding the importance and safety of vaccinations as well as prescribing and administering appropriate vaccinations depending on the setting and population with whom they work.

The core competencies published by the National Association of Clinical Nurse Specialists (NACNS) in 2008, describe the CNS as an expert in patient care, a change agent in nursing practice, and a leader in systems improvement [4]. The CNS takes into account the unique educational needs of the staff nurses, patients, and families as they translate current research and evidence-based practice to direct patient care. In order to achieve this, the CNS must remain current on CDC/ACIP recommendations and changes in vaccine research, development, and administration. In addition, the CNS should be a leader in vaccine policy development, education, and administration in their institutions and agencies.

Nursing Administrators/Executives

Nursing executives are responsible for personnel as well as patient care provided in their health care organizations. They are guided by the core competencies developed by the American Organization of Nurse Executives (AONE). The core competencies include patient safety, risk management, health care policy, and advocacy [5]. Within the context of these core competencies, the nurse executive is responsible for promoting a culture of safety. This can be accomplished by developing and implementing policies consistent with CDC/ACIP recommendations for vaccination of health care personnel [6] as well as screening patients for their vaccination status on admission and discharge. Nurse executives are at the forefront of policy development at the national, state, and institutional levels. They serve on intra-agency committees that establish organizational quality and safety benchmarks. Nurse executives also serve on community boards and have an opportunity to participate in a health care agenda that could increase vaccination rates.

The nursing and advanced practice nursing professions have long been recognized for their roles in patient advocacy and education. The scope and standards of practice for the various roles in nursing have been reviewed. This discussion further demonstrates the importance of the registered nurse, advanced practice nurse, and nurse executive in addressing the vaccine *bane* of the twenty-first century.

Nursing Settings

Registered nurses and advanced practice nurses work in a variety of settings: acute-care hospitals, long-term care facilities such as nursing homes and skilled nursing facilities, primary care and outpatient offices/clinics, rehabilitations centers, home health, community health including schools, and emergency services (inpatient, outpatient, and transport). Regardless of the setting, nurses have the potential to promote patient safety, education and compliance with recommended immunizations.

Primary Care Setting

The staff nurse in a primary care office is positioned well to provide the initial information about vaccines and generate reminders for subsequent vaccines. The primary care setting is typically a health care home for patients and families. Thus, it is an ideal environment for the nurse in any role to provide education and advocacy for vaccinations.

In today's world the consumer is bombarded with "mis"-information from a variety of sources. Patients and families rely upon their primary care providers to answer their health care questions. There is evidence that patients place the most trust in their health care providers when it comes to decisions about vaccines [7]. The primary care nurse can serve as an authoritative source for answers to some of the concerns and fears expressed by vaccine-hesitant patients and families. Nurses function as good listeners and can provide nonjudgmental feedback when a patient/parent expresses fears regarding vaccines.

The primary care nurse is often responsible for the ordering, storage, handling, and administration of the vaccines in a primary care setting. Intermittent vaccine shortages have created a situation in which an individual may not receive their vaccinations on time. This situation creates a need for efficient tracking of those individuals who did not receive their vaccine(s) due to the shortage. With this in mind the nurse should be familiar with available tracking systems to be used to recall patients who need to receive their vaccines when the shortage is relieved.

The nurse practitioner (NP) serves as a provider in the primary care setting and as such is responsible for regular evaluation of a patient's vaccination status and ordering appropriate vaccines. The NP works within the context of the primary care team and serves to support the front line effort to increase and maintain immunization uptake.

The nurse executive in the primary care setting may serve as a clinic operations director, human resource manager, and/or nurse manager. In this capacity, the nurse executive should maintain a regular stock of vaccines and appropriate pricing and billing information. In addition, the nurse executive needs to provide opportunities for the staff to maintain their knowledge of safe handling, storage, and administration of vaccines as well as patient education. The nurse executive as a member of the administrative team should create and support a culture of safety in all aspects of patient care. This can in part be accomplished by developing and implementing policies for immunizing health care personnel and evaluating each patient's vaccination status.

Acute Care Setting

The acute care setting is often thought of as the place to provide health restoration during an illness or after an injury. Nurses working in this setting are often focused on the treatment and management of specific disease states. However, it is equally important to utilize this setting as an opportunity to assess the patient's vaccination status and provide access to vaccines. For example, admission to the acute care setting can provide an opportunity for patients to receive seasonal vaccinations like influenza or other routine vaccinations like Tdap. Nurses have a responsibility to advocate for their patients as well as the general community. An important part of this advocacy role is taking advantage of opportunities whenever individuals come

in contact with the health care setting to advance health promotion and prevention strategies. A large part of health promotion and prevention is remaining up to date with current vaccine needs. It is imperative that nurses in the acute care setting stay up to date with CDC/ACIP vaccination recommendations for the population they are serving so that they can effectively educate and advocate.

Long Term Care

Residents of long-term care facilities are considered medically fragile and at high risk for contracting life-threatening infections. These residents can include young and older individuals with weakened immune systems and chronic illnesses. Nurses in all roles must function as the first line of protection for these high-risk patients. This is accomplished by providing all long-term care residents with recommended vaccinations, most notably seasonal influenza and pneumococcal vaccines. In addition, family members/visitors should be encouraged to be current with all their vaccinations, particularly during the influenza season.

Public/Community Health Setting

The public health nurse has historically been a key player in the national and international vaccine movement. In some countries such as Norway and Finland, the community and public health nurses are on the front line for vaccine education and administration [8]. In the USA and many other countries, public health services serve to augment the acute and primary care activities to ensure comprehensive access to vaccines for all populations. Community health nursing programs across the country have developed immunization programs for rural and urban areas that have increased access to vaccines. These community health programs have brought the vaccines to the people and thus served to eliminate vaccination barriers such as transportation and limited resources.

The impact that community health nursing has on vaccination rates has been seen for centuries as vaccines have been developed to prevent or eliminate devastating diseases such as small pox and polio. Most recently, this impact has been seen with the H1N1pandemic in 2009. This outbreak called for large numbers of vaccine doses to be distributed quickly and in an organized fashion to ensure that high-risk populations received the vaccine first and then the larger public. Community and public health nurses again were at the forefront. They organized vaccination programs to be set up in local community centers and churches that allowed successful vaccination of large volumes of people.

Another important aspect of community health nursing relates to school settings. Significant debate at the state and national levels has occurred over the past few

years about the role of the school health nurse because of the lack of resources and funding for public education systems. Most research supports that the school health nurse assumes many responsibilities including health education, assessment, and treatment for students, families, teachers, and administrators in the school system [9]. School health nurses have long served as "vaccine champions", responsible for maintaining vaccination records for students and staff as well as enforcing compliance with state vaccination regulations for school entry. Because school nurses have direct access to school aged children, adolescents and their parents, they have many opportunities to educate staff, families, and students on the importance and safety of vaccinations. Depending on the local policy, some school health nurses also have the approval to administer vaccines in the school setting with appropriate consent from parents. Despite the debate and the lack of current resources, the school health nurse plays a vital role in vaccine education, advocacy, and safety.

Barriers like transportation, inflexible work hours, and lack of insurance have been identified as reasons that patients and families often are not current with vaccinations [10]. The Expert Panel of the Infectious Disease Society of America identified in their guidelines a priority to increase vaccine rates by improving access to immunizations [11]. The development of school-based health centers (SBHCs) is one way that advanced practice nurses have attempted to improve access to immunizations as part of a comprehensive pediatric health care program. SBHC's immunization programs managed by APNs have increased vaccination rates in school aged children and adolescents [10].

The American Academy of Pediatrics' (AAP) Council on School Health has issued a policy statement entitled "School-Based Health Centers and Pediatric Practice" [12]. In this statement, the AAP acknowledges the success of SBHCs in increasing vaccination rates among school-aged children and their families. Furthermore, the AAP supports the SBHCs efforts to provide pediatric health care in collaboration with the pediatric medical home.

Summary

It is apparent that nurses in all roles and settings have a responsibility to provide education and advocacy for as well as safe administration of vaccines. The nurse, regardless of the setting, must provide good role modeling of health promoting behaviors. This would include complying with all CDC/ACIP recommendations for immunizations of health care personnel. In all settings, the general public looks to the nurse to set a standard for good health care practices as well as ethical behavior. Protecting patients and families by receiving their own vaccines is one way in which nurses can demonstrate these behaviors. Nurses are also educated in interpersonal communication skills that are necessary when encountering the vaccine-hesitant patient/parent. Open and honest dialogue with the patient/parent creates an environment of trust which in turn may serve to convince the fearful patient/parent to proceed with the recommended vaccines [1].

Population-Focused Care

In the past, vaccine education and advocacy were predominantly limited to the pediatric population. Now, nurses caring for individuals and families across the lifespan need to be well schooled in vaccine indications and schedules. Consequently, the nurse must adapt their vaccine education and advocacy efforts to each developmental life stage.

Prenatal, Infancy and Early Childhood

Vaccine awareness ideally should start preconceptually. However, the prenatal period offers an additional opportunity to evaluate a woman's immunization status. Mothers are routinely tested for their rubella and hepatitis B status during pregnancy in order to determine the risks for the developing fetus. Pregnant women may also be tested for varicella immunity if they have a negative history of varicella disease or vaccination. If a mother is found to be rubella and/or varicella nonimmune then she is recommended vaccination against these diseases during the postpartum period. Special protocols are implemented to protect the infant of a mother who is hepatitis B surface antigen positive during her pregnancy.

The pregnant woman should also be evaluated for protection against other vaccine-preventable diseases such as influenza and pertussis. Influenza vaccination during pregnancy decreases maternal and infant morbidity and mortality. Since 2004, the ACIP and the American College of Obstetricians and Gynecologists (ACOG) have recommended influenza vaccination for pregnant women [13]. Recent reports have indicated that until 2009, influenza vaccination rates during pregnancy were low (~15 %) [14]. The CDC and ACOG stepped up their efforts to vaccinate pregnant women against influenza during the 2009 H1N1 pandemic and vaccination rates reached an all-time high of nearly 50 % [13]. This impressive vaccination rate persisted into the 2010–2011 influenza season with a reported 49 % vaccination rate. Notably, the majority of the pregnant women who received the influenza vaccination in the 2010–2011 influenza season (61 %) reported receiving the vaccine at their OB/GYN's or CNM's office [13].

With the rising incidence of pertussis in the USA, the CDC/ACIP recommended the use of Tdap during pregnancy [15]. ACOG followed with a published opinion supporting the CDC/ACIP recommendation and encouraging women's health providers to facilitate Tdap updates [16]. The most recent CDC/ACIP Tdap recommendation includes assessing the Tdap vaccine status of both parents and future close contacts of the infant, such as siblings, grandparents, and day care providers.

The nurse and/or the CNM have an opportunity to influence the decision the mother makes regarding her own vaccinations as well intentions to vaccinate her infant. During the prenatal period, parents with the most concerns about vaccinating their child will be seeking vaccine information and trying to make informed

decisions [17]. Expectant parents need to receive information about all childhood vaccines but especially the Hepatitis B vaccine and the recommended dose at birth.

The birth of a healthy baby heralds a time of joy for the parents but also brings with it a bevy of concerns. The period of infancy and early childhood is a time when parents are bombarded with parenting decisions not the least of which are decisions regarding a myriad of vaccines. Today's parents do not have experience with many of the vaccine-preventable diseases and thus may not perceive the value of immunizing their infant or young child. The nurse needs to be knowledgeable of the many vaccines offered to infants and children in order to be responsive to parent's concerns. This includes, but is not limited to, the recommended age and interval between immunizations, expected side effects and how to manage them, rare adverse events, and the anticipated ages of future vaccines. Vaccine information statements (VIS) are written and provided by the CDC. The VIS for each vaccine needs to be reviewed with the parents and all questions answered before the vaccine is administered. The nurse should not be surprised to find that parents have been researching vaccines on the Internet and may have concerns and questions about the manufacturing process for the vaccine(s) and the various adjuvants in the vaccine. In order to respond to these concerns and questions, the nurse must first be familiar with the Internet sites most frequently visited by young parents. This will allow the nurse to do some research and be prepared with appropriate factual information.

Adolescents

The AAP continues to recommend annual health maintenance and preventive care through adolescence. Despite these recommendations, few adolescents actually receive annual well-child visits. A large study done from 2001 to 2004 showed that only 38 % of children age 10–17 received a preventative care visit in the 12 month time frame [18]. The CDC immunization recommendations include multiple vaccines that should be administered during these preteen and teen years. These include a Tdap booster, meningococcal (MCV4) vaccine, Human Papillomavirus (HPV) vaccine, and continued annual influenza immunizations. Research supports several reasons for low immunization rates in this population including missed opportunities, low awareness of immunization recommendations, misperceptions of vaccine safety, and lack of knowledge about the importance of continued vaccinations [19]. Nurses should assume some of the responsibility to help overcome these barriers and help to improve vaccination compliance in the adolescent population.

The development of the HPV vaccine and its addition to the CDC recommended immunization schedule was a significant public health achievement but with this achievement comes much controversy and debate. The CDC currently recommends that all 11–12-year-old children should receive a three dose series of the HPV vaccines [20]. The main controversy for this vaccine has revolved around recommending an immunization against a sexually transmitted disease for young adolescents. The discussion in the lay media has focused on how administration of this vaccine

to young adolescents has the potential to send mixed messages about the importance of abstinence. Individuals opposing the recommendation of the HPV vaccine also felt it was not necessary as it provided protection against a virus that often was asymptomatic in individuals and not commonly seen in the USA [21]. Research has supported HPV as the virus responsible for nearly all cervical cancers. Administration of the HPV vaccine has been shown to reduce the incidence of precancerous lesions of the cervix [22]. The health care community has repeatedly supported and educated the public that the HPV vaccine is more than a vaccine against a sexually transmitted disease, it is imperative that it be viewed as a medical breakthrough that can help to significantly reduce cervical cancer [21, 23]. It is crucial that nurses be aware of the controversy surrounding this vaccine. Nurses must remain current on both the lay and medical literature so that they can most effectively educate their patients and others on the importance and significance of immunizations such as the HPV vaccine.

With the knowledge that adolescents are significantly less likely to come in for annual preventive visits, nurses should take a proactive role in identifying strategies to reach this population for vaccines. Without preventative services being sought, it is highly unlikely that the adolescent will receive the CDC/ACIP recommended vaccines for 11–12 year olds. Nurses can take the initiative to develop campaigns to increase awareness for preventative health care visits through the adolescent years.

Adults

In the past adult immunizations were limited to seasonal influenza vaccines and tetanus/diphtheria boosters. Today, this is not the case. In addition to influenza and tetanus, ACIP recommends that adults be vaccinated against pertussis (along with tetanus/diphtheria) and varicella zoster. Meningococcal (MCV4) and pneumococcal (PPSV) vaccines should also be offered to special populations of children and adults with risk factors. Criteria for PPSV include: age >65 years of age and those younger with immune deficiencies and chronic illnesses such as cardiorespiratory diseases, liver disease, and diabetes. MCV4 is indicated for immune-deficient individuals down to 2 years of age as well as college freshmen living in dormitories [20].

Quality and Safety

Today's nurses in all roles and settings have the opportunity to boost consumer confidence in vaccines by their ability to provide appropriate responses to a myriad of Internet-savvy consumer's concerns regarding vaccines. The range of questions may include "When was this vaccine licensed?" "Who decides what is safe for children to receive?" "What happens if I or my child experiences an adverse reaction to

a vaccine?" "How is this vaccine manufactured?" "What, if any, preservatives are added to this vaccine?" These are not routine topics covered in the basic education of a registered nurse. However, fundamental to all nursing education is a keen awareness of quality and safety issues as well as an appreciation for life-long learning; thus, the nurse should be self-directed in seeking the answers to these questions. The CDC's Web site is an excellent place to start (www.cdc.gov). Nurses need to understand the process of vaccine research, development, and manufacturing as well as FDA licensure and regulation. Lastly, a familiarity with the expert, evidence-based CDC/ACIP review and recommendation process can add to the nurse's general knowledge of the stringent oversight of vaccine safety.

The nurse must also recognize and acknowledge his/her own misgivings as well as any knowledge deficits in the areas of vaccine research, development, and safety. Nurses then need to arm themselves with the most current scientific evidence that addresses their own questions and discomfort and then those expressed by patients, families and other health care providers.

Health care providers in general, regardless of setting, should be familiar with the Vaccine Adverse Event Reporting System (VAERS). This system provides a mechanism for health care providers, manufacturers, as well as consumers to report an event that occurs any time after vaccination. Nurses should understand their mandatory reporting role as there are adverse events that are required by law to be reported [24].

Nurses, by their own health care behaviors, can influence the patients in their care. Yet, nurses have reportedly had dismally low immunization rates. A study done in 2009 evaluated nurse's attitudes and practices towards influenza vaccination. This study found that about 60 % of the nurses were very aware of the CDC recommendations that all health care workers receive an annual influenza vaccine. Of those nurses, only 40 % identified that the main reason for this requirement was protection of patients [25]. It has been suggested that annual influenza vaccination of health care workers is within the ethical mandate of "*Primum non nocere*: Above all do no harm" [26]. Health care-associated infections cause significant morbidity and mortality. By the very nature of their job, nurses have the potential for exposure to and subsequent transmission of vaccine-preventable diseases. Therefore, it is imperative that all nurses stay current with the CDC/ACIP recommendations for immunization of health-care personnel. The nurses' adherence to the ACIP recommendations for vaccines is a matter of good clinical practice, first-line protection for their patients and community as well as ethical nursing behavior.

Nursing Perspective on Vaccine Refusal

Vaccines are one of the best protections available to prevent infectious diseases. Scientific research continues to support the safety and efficacy of immunizations in the reduction or eradication of many life-threatening diseases. Despite the reported science, the lay media continues to focus on dangers and risks associated with vaccines that may or may not be supported in the scientific literature. Health care

providers need to acknowledge the reality of lay media as the first and sometimes only source of information that patients receive about vaccines. Studies have reported that up to one third of parents want more information on vaccines when they visit their health care provider and that the greatest influence in the final decision on vaccine safety is the conversation they have with their health care provider [1, 27, 28]. The communication that occurs between patients/parents and the nurse or APN is critical to increase vaccination rates and combat the vaccine myths reported in the lay media.

Nurses often have the most frequent contact with patients both in the office and on the phone, so they are a key component of the vaccine education process. It is essential that nurses establish rapport with families and patients. In order to best establish this relationship, nurses must put any judgments and biases aside and seek to have an open, honest dialogue with the patient and/or family. These initial conversations with families who have concerns can be time-consuming which is difficult for busy clinics, but literature has supported that taking the time to listen to patients talk about vaccine concerns in an open dialogue is an effective way to identify what the true concerns are regarding vaccine safety [1, 29]. This information is invaluable because health care providers can then directly target the specific concerns of that patient instead of overloading them with information that they are not concerned about.

Another key component in the education of vaccine-leery patients is a review of the vaccine risk-benefit analysis. Patients and families need to know that there is a rigorous process for testing and validating vaccine safety, but they also need to know that no vaccine comes without some risks and that vaccines are not 100 % effective for all individuals. Health care providers should not be complacent about vaccine safety when talking with patients; it is their responsibility to educate on the benefits as well as the types and frequency of adverse events that have been reported.

Patients/parents are more likely to be open to hearing new information when their concerns and their rights regarding this difficult decision are acknowledged. The reasons for vaccine refusal are complex and the patient/parent needs a trusted source of information. Establishing the goal of shared decision-making is the first step in establishing a trusting relationship between families and the nurse [30].

Most patients are open to education and discussion regarding vaccines; however, it is essential that nurses acknowledge that some families are unlikely to change their position regarding vaccine safety regardless of the amount of time and education that is provided. This is important to recognize so that nursing staff do not get discouraged or frustrated with the education process. Regardless of a patient's final decision, the majority of patients and families appreciate all respectful discussions that occur in regards to vaccine practices [1].

What remains is the course of action to be taken when a patient/parent, in spite of the nurse's efforts, persists in their refusal to vaccinate themselves or their child. Nurses, including the APNs, need to keep in mind the best interest of the patient and continue to provide safe and effective primary and preventative health care. Ongoing education with credible and respectful communication has more potential to create a trusting relationship in which the patient/parent may subsequently make the decision to immunize [30].

Conclusion

Nurses in all roles have an integral part in providing education, safe administration, and advocacy for vaccinations. Several national nursing organizations have developed position statements about immunization practices and the significance of the nursing role. A list of nursing organizations with published position statements regarding nursing practice and vaccinations have been reviewed (see Table 9.1). All of the position statements developed by professional nursing organizations support the tenet that professional nurses in all settings have a responsibility to advocate for and educate patients and families on vaccines. Educating patients includes direct one-on-one education, but also referring individuals to outside resources. Families and patients are often unsure of what information on the Internet can be viewed as credible and it is the responsibility of nurses to guide families as they seek additional information. Table 9.2 provides a list of trustworthy sources that can be utilized by nurses for patient/family education.

Table 9.1 Professional Nursing organizations with immunization position statements

Nursing organization	Web site
National Association of School Nurses (NASN)	http://www.nasn.org/PolicyAdvocacy/PositionPapersandReports/NASNPositionStatementsFullView/tabid/462/ArticleId/8/Immunizations-Revised-2010
National Association of Pediatric Nurse Practitioners	http://www.napnap.org/Files/NAPNAP_PS_Immunizations_Final2010.pdf
Society of Pediatric Nurses	http://www.pedsnurses.org/pdfs/downloads/gid,64/index.pdf
National Association of Nurse Practitioner Faculty	http://www.nonpf.com/associations/10789/files/AdolescentImmunizations06.pdf

Table 9.2 Reliable sources of vaccine information

Internet resources
American Academy of Pediatrics: http://www2.aap.org/immunization/pediatricians/pediatricians.html
Centers for Disease Control and Prevention: http://www.cdc.gov/vaccines/
CDC: For Parents, Adolescents, and Teens: http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm#parents
Childhood Immunization Support Program: http://www.who.int/immunization_safety/safety_quality/_cisp/en/index.html
Every Child By Two: Vaccinate Your Baby: www.vaccinateyourbaby.org
Immunization Action Coalition: www.immunize.org
Institute of Medicine: http://www.iom.edu/Global/Topics/Children-Families.aspx
Meningitis Angels: www.meningitis-angels.org
National Alliance for Hispanic Health: www.hispanichealth.org

(continued)

Table 9.2 (continued)

National Foundation for Infectious Disease: www.nfid.org
National Institute of Allergy and Infectious Diseases: http://www.niaid.nih.gov/Pages/default.aspx
National Institute of Health: http://health.nih.gov/topic/ChildhoodImmunization/ChildTeenHealth
National Library of Medicine: http://www.nlm.nih.gov/medlineplus/childhoodimmunization.html
National Meningitis Association: www.nmaus.org
National Network for Immunization Information: www.immunizationinfo.org
Parents of Kids with Infectious Disease: www.pkids.org
Red Book® Online: http://aapredbook.aappublications.org/
Texas Children Hospital: Center for Vaccine Awareness and Research: www.vaccine.texaschildrens.org
Tufts University Child and Family Web Guide: www.childandfamily.info
Vaccine Education Center at Children's Hospital of Philadelphia: www.chop.edu/service/vaccine-education-center/home.html

Resources on vaccine refusal

http://www.aap.org/immunization/pediatricians/pdf/refusaltovaccinate.pdf
http://www.immunize.org/catg.d/p4059.pdf
http://www.immunize.org/catg.d/p2069.pdf
Clear answers about your baby's vaccines: http://www.immunize.org/catg.d/p2068.pdf

Book resources

Offit PA, Bell LM. *Vaccines*: *What Every Parent Should Know*. New York, NY: IDG Books; 1999
Humiston SG, Good C. *Vaccinating Your Child*: *Questions and Answers for the Concerned Parent*. Atlanta, GA: Peachtree Publishers; 2000
Fisher MC. *Immunizations and Infectious Diseases*: *An Informed Parent's Guide*. Elk Grove Village, IL: American Academy of Pediatrics; 2005
Myers, MG and Pineda D. *Do Vaccines Cause That*? *A Guide for Evaluating Vaccine Safety Concerns*. Immunizations for Public Health. 2008

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Chapter 10
The Controversy That Will Not Go Away: Vaccines and Autism

Archana Chatterjee

Introduction

Swiss psychiatrist Eugen Bleuler is credited with the first use of the term autism in 1911 [1]. The term "autism" stems from the Greek word "autos," meaning self. Bleuler originally described autism as a basic disturbance in schizophrenia, an extreme withdrawal of oneself from the fabric of social life [1]. Leo Kanner in his seminal paper published in 1943, first described autism as a condition that manifests in infancy and is characterized by impairments in three domains—repetitive or stereotypic behaviors, interests and activities, accompanied by significant impairments in a child's ability to socialize and communicate [2]. Restricted and repetitive behaviors include unusual preoccupations with narrow interests, inflexibility to routines, stereotyped and repetitive mannerisms, and preoccupations with parts of objects. Social impairments are marked by poor use of nonverbal communication, difficulty in establishing peer relationships, lack of social-emotional reciprocity, and a lack of shared enjoyment. Communication deficits include partial or complete failure to develop intelligible speech, use of stereotyped or delayed echolalia, and difficulties maintaining conversations. Social and communication impairments may also result in a lack of symbolic or imaginative play.

Definition and Early Theories About the Etiology of Autism

In 1952, autism defined by Kanner's narrow description was diagnosed as "early-onset schizophrenia"; it was renamed "infantile autism" in 1980 and then "autism disorder" in 1987 [3]. Recognizing that clinical patterns and severity of impairment vary among

A. Chatterjee, M.D., Ph.D. (✉)
Creighton University School of Medicine, Omaha, NE, USA
e-mail: achatter@creighton.edu

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these dimensions, the term "autism spectrum disorders (ASDs)" began to be used in the 1990s to describe this group of conditions. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-TR) categorizes ASDs under "pervasive developmental disorders (PDDs)" [4]. These disorders include autistic disorder (classic autism which is also referred to as early infantile autism, childhood autism or Kanner's autism); Asperger disorder/syndrome; pervasive developmental disorder-not otherwise specified (PDD-NOS), including atypical autism; childhood disintegrative disorder; and Rett disorder. The American Psychiatric Association (APA) has proposed new diagnostic criteria for autism for the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) to be published in May 2013 [5]. The proposal by the DSM-5 Neurodevelopmental Work Group recommends a new category called "autism spectrum disorder" which would incorporate several previously separate diagnoses, including autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified. The proposed diagnostic criteria for autism spectrum disorder specify a range of severity as well as describe the individual's overall developmental status in social communication and other relevant cognitive and motor behaviors.

In the first few decades after autism was described, it was thought to be a consequence of bad parenting, particularly by the mother. The "refrigerator mother" label was based on the assumption that autistic behaviors stem from the emotional frigidity and detached behavior of the children's mothers [6]. Although it is hard to find the specific instance when the "refrigerator mother" hypothesis of autism was first used, it should be noted that as early as his 1943 paper, Leo Kanner was calling attention to what he saw as a lack of parental warmth and attachment to their autistic children [2]. In his 1949 paper, he attributed autism to a "genuine lack of maternal warmth" and the "refrigerator mother" theory of autism was born [7]. A number of articles and books published during the 1950s and 1960s [8] continued to blame autism on a maternal lack of affection, while there was a growing sense in the medical community that this did not explain autism as it was seen in the population [9]. In 1964, a landmark book was published that argued that autism had biochemical roots and upended the then conventional wisdom that it was a child's response to "refrigerator mothers" who didn't show adequate affection [10]. By the late 1960s however, it was shown that there was no difference in the parenting styles of parents of autistic and non-autistic children, and a neurobiological basis of autism was suggested [11, 12]. Despite decades of research since then, a specific scientific cause or definitive treatment for ASDs remains elusive. This lack of evidence has in recent years fueled the development of numerous hypotheses and possible associations based on case reports/series and small cohort studies.

Epidemiology of Autism

Another reason for concern is that the prevalence of ASDs has increased over the past several decades (Fig. 10.1). Estimated to occur in 4.5 per 10,000 children in 1966 [13], the most recent report from the Centers for Disease Control and

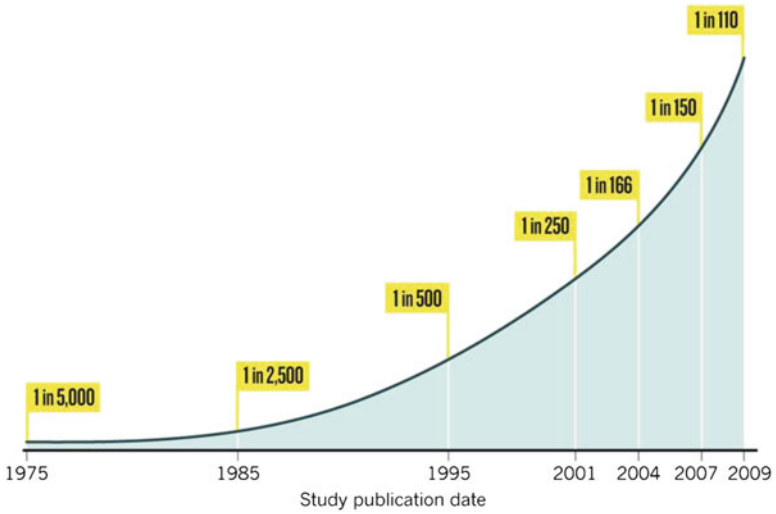

Fig. 10.1 Diagnosis of autism has been rising in the USA

Prevention (CDC) shows that between 1 in 80 and 1 in 240 children have ASDs [14]. Therefore, on average, 1 in 110 children are diagnosed with ASDs in the USA at an estimated prevalence of about 1 %. These results reflect data collected in multiple communities throughout the USA from 2006 [14]. In a recent study from the UK, the weighted prevalence of ASD in adults was estimated to be 9.8 per 1,000 (95 % confidence interval, 3.0–16.5), close to the prevalence reported among children in the USA [15]. Similar data have been reported from other countries, strengthening public fears that there is an "epidemic" of ASDs. While it is generally accepted that the number of new autism diagnoses is increasing, it is unclear whether this is due to a true increase in cases, increasing awareness of ASDs, or differences in the methods used to diagnose these conditions and assess their prevalence. The controversy about what is causing the rise in diagnoses of ASDs boils down to two basic hypotheses: (1) That the true incidence of autism is rising due to an environmental cause, (2) That the rise in incidence is mostly or completely an artifact of increased surveillance and broadening of the definition of autism [16]. This confusion about the epidemiology of autism is not unique in scientific medicine. Changing definitions and practices over time distort comparisons to historical data, but as the understanding of biology and diseases progresses, such changes are unavoidable, as is the confusion around the interpretation of the data.

Diagnostic Substitution and Improved Ascertainment

Recent epidemiological surveys of autistic disorder and other PDDs have heightened awareness of and concern about the prevalence of these disorders among families and the medical community; however, differences in survey methodology,

particularly changes in case definition and case identification over time, have made comparisons between surveys difficult to perform and interpret [17]. In a comprehensive review of the topic, Rutter emphasizes the flaws in early studies on the prevalence of autism—they were mostly conducted on children attending some type of clinical facility, special school or residential unit, excluding those who were mainstreamed; few clinicians in the 1960s and 1970s were experienced in the recognition and diagnosis of ASDs; the diagnostic criteria used were different [18]. The broadening of the diagnosis to include conditions such as Asperger's Syndrome has been described as "diagnostic substitution" [19]. In a landmark study of the prevalence of disabilities among children in US special education from 1984 to 2003, it was found that in locations where the prevalence of autism had increased, there was a corresponding decrease in the prevalence of other disabilities [19]. In another study previously diagnosed language disorders were diagnosed instead as autism, with a corresponding decrease in nonspecific language disorders [20].

Along with the inclusion of additional diagnoses under the autism umbrella, the social and medical network supporting ASDs has also increased. Surveillance efforts have been enhanced to try and discover cases of autism that may have gone undiagnosed before. Parents and other caregivers have become much better educated about and more accepting of the diagnosis, partly due to the fact that in some cases the diagnosis is associated with access to special services [16, 18]. As clinicians have become more knowledgeable about ASDs their ability to make the diagnosis, even in subtle cases, has improved. This improved recognition, with changes in diagnostic practice associated with more trained diagnosticians; broadening of diagnostic criteria to include a spectrum of disorder; a greater willingness by parents and educationalists to accept the diagnosis (in part because of entitlement to services); and better recording systems, have all been identified as reasons for the increase in the rates of ASDs [21].

Impact of Autism on Families and Society

A diagnosis of ASD presents significant familial and societal challenges. Families with children diagnosed with an ASD experience grief as parents and siblings mourn the hopes that they may have had for their family [22]. Caring for the autistic child, expensive evaluations and therapies can place significant financial burdens on families and society as a whole [23–25]. Lack of support from friends and family, difficulty in finding childcare, the stress of managing the autistic child and feelings of guilt, blame and shame have all been reported by family members of children diagnosed with ASDs [24, 26]. Siblings may experience jealousy due to the extra attention given to the autistic child, anger at their destructive behavior or embarrassment because of their bizarre behavior [24, 27, 28]. Most autistic children will require a lifetime of support, with up to 75 % becoming institutionalized or unable to live independently [29]. The lifetime per capita societal cost of ASD has been estimated to be $ 3.2 million in the USA, while in the UK, for someone with ASD

and intellectual disability it is estimated at approximately £1.23 million, and for someone with ASD without intellectual disability it is approximately £0.80 million [30, 31]. These costs result from both childhood and adult care and lost productivity of both individuals with autism and their parents. The costs of supporting children with ASDs were estimated to be £2.7 billion each year. For adults, these costs amounted to £25 billion each year [31]. Thus the burden of ASDs for families and communities is considerable both monetarily and emotionally.

What Causes Autism?

This simple question has plagued families of patients with ASDs and the medical and scientific communities alike for nearly 70 years. Undoubtedly there has been a dramatic increase in the prevalence of ASDs since they were first described, with their attendant costs to families and society. There has therefore been keen interest in elucidating both genetic influences and environmental exposures that may have led to this increase over the past several decades. Although the etiology of ASDs is not known, they clearly have a strong genetic component that is revealed by up to 60 % concordance between monozygotic twins and almost 90 % heritability [32]. Sibling risk of developing an ASD is 2–7 %, compared to the general population risk of 0.01–0.08 % [33]. While a small proportion of ASDs are associated with known congenital conditions, in only 10–15 % of cases can a specific genetic aberration be identified [34]. A recent review identifies at least three phenotypic presentations of ASDs with distinct genetic underpinnings: autism plus phenotype characterized by syndromic ASD caused by rare, single-gene disorders; broad autism phenotype caused by genetic variations in single or multiple genes, each of these variations being common and distributed continually in the general population, but resulting in varying clinical phenotypes when it reaches a certain threshold through complex gene-gene and gene-environment interactions; and severe and specific phenotype caused by "de novo" mutations in the patient or transmitted through asymptomatic carriers of such mutation [35]. Some of the purported environmental "triggers" for ASDs include intrauterine exposure to toxins or medications, lack of breastfeeding, supplemental feeding with infant formulas that do not contain docosahexaenoic acid and arachidonic acid supplementation, childhood vaccinations, the use of acetaminophen and other analgesics, certain viral infections, and various other environmental exposures [36–39]. Of these, vaccinations have garnered the most interest and attention of both the public as well as the medical and scientific communities. This is understandable, given that young children are recommended to receive more vaccines than ever, with multiple/combination vaccines given at each visit, to provide early protection against several infectious diseases. ASDs are usually diagnosed in children with onset of symptoms under the age of 3 years [4], at the peak time for vaccine delivery. This coincidence in time has led many parents and a few members of the medical and scientific community to attribute the rise in rates of ASDs to the increase in childhood vaccinations, despite a lack of rigorous scientific evidence to support their contention. The question

of whether ASDs and vaccines are related continues to cause conflict between healthcare personnel, public health authorities and scientists on one hand and worried parent groups supported by a minority of physicians and scientists on the other. In this chapter details of the arguments on both sides will be reviewed, and an analysis of the scientific evidence that supports the view that ASDs and vaccines are not likely to be linked will be provided.

The Incredible Success of Vaccines

Vaccination is arguably among the greatest achievements of modern medicine. Naturally occurring smallpox has been eradicated and a host of other infectious diseases such as polio have all but disappeared from many countries, primarily due to successful vaccination efforts [40]. In fact, early vaccines against smallpox and rabies were proven to be effective long before the identification of these viruses as infectious agents [41]. Vaccination has a relatively short history in medicine and public health when compared to the pre-vaccine era during which humans had few defenses against infectious diseases. Although vaccines have been available for a few centuries, vaccination of large populations is primarily a twentieth century phenomenon [42]. Despite this, vaccination has been instrumental in the worldwide eradication/control of 12 major infectious diseases, including smallpox, diphtheria, tetanus, yellow fever, pertussis, *Haemophilus influenzae* type b disease, poliomyelitis, measles, mumps, rubella, typhoid, and rabies [42]. Vaccination has contributed to the significant decline in morbidity from nine vaccine-preventable diseases and their complications between 1900 and 1999 in the USA (Table 10.1) [43], and vaccines have been described as the single most life-saving accomplishment of the twentieth century [44].

As a result of their phenomenal success, parents and many health care professionals in the current era, particularly in more developed areas of the world, have limited or no experience with the devastating effects of these communicable diseases. In the USA, public health officials now recommend 28–31 vaccine doses before the age of 18 years, many of which are administered together or in combination, to provide protection early in life, for the convenience of families and health care providers, and to decrease distress to the infant. In order to provide herd immunity and minimize the possibility of resurgence of these deadly infections, most public health experts recommend that 95 % of the population be vaccinated. However, parents in developed countries who have no personal experience with these diseases or their disastrous sequelae, may feel that they are being pressured into immunizing their children involuntarily for public good rather than personal benefit [45]. Some parents even perceive a greater risk to their children from vaccination than from the diseases themselves, not recognizing that the threat from these diseases is reduced because we have effective vaccines to prevent them [46]. In recent years, vaccination has unfortunately become a very polarized issue with some parents stressing their own child's well-being while health experts are advocating not only for their patients, but the health of the public as a whole.

Table 10.1 Comparison of annual morbidity from vaccine-preventable diseases during the twentieth century and 2010

Disease	Twentieth century[a]	2010[b]	% Reduction
Diphtheria	21,053	0	100
Hepatitis A	117,333	8,493[c]	93
Hepatitis B, acute	66,232	9,419[c]	86
Haemophilus influenzae type b in children aged <5 year	20,000	240[d]	99
Measles	530,217	63	>99
Mumps	162,344	2,612	98
Pertussis	200,752	27,538	86
Pneumococcus, invasive			
All ages	63,607	44,000[e]	30
<5 years	16,069	4,700[e]	72
Poliomyelitis, paralytic	16,316	0	100
Rotavirus, hospitalizations	62,500[f]	28,125[c]	55
Rubella	47,745	5	>99
Congenital rubella syndrome	152	0	100
Smallpox	29,005	0	100
Tetanus	580	26	96
Varicella	4,085,120	408,572[c]	90

[a]Estimated annual average number of cases in the pre-vaccine era for each disease. *Source*: JAMA 2007;298:2155–63
[b]*Source*: MMWR 2011;60(32):1088–1101
[c]2009 Estimate
[d]23 type b and 223 unknown serotype (among children <5 years of age)
[e]*Source*: http://www.cdc.gov/abcs/reports-findings/survreports/spneu09.html
[f]*Source*: MMWR 2009;58(No. RR-2)

The Beginning of the Controversy

One of the earliest claims that vaccines might be related to autism was made by Harris Coulter and Barbara Loe Fisher in a book entitled "A Shot in the Dark," in which the authors wrote, "With the increasing number of vaccinations American babies have been required to use has come increasing numbers of reports of chronic immune and neurologic disorders … including … autism [47]." Although this assertion received little attention at the time, it garnered far greater support when a British physician and researcher Dr. Andrew Wakefield and his colleagues published a now infamous article describing abnormal gastrointestinal features and developmental disorder among 12 pediatric patients [48]. Nine of the children had been diagnosed with autism, and in six of them, either a parent or a physician had linked the onset of developmental regression with the receipt of the MMR vaccine. Wakefield et al. proposed the following: that measles virus from the live-attenuated MMR vaccine caused intestinal inflammation, the inflamed intestines became "leaky," allowing undefined harmful proteins to enter the bloodstream, travel to the brain and cause

autism [48]. In a follow-up article, Wakefield and his associates reported that measles virus RNA fragments were found in the white blood cells of 3 out of the 9 children, but none were noted in 22 controls, thus supporting their "leaky-gut" theory of "autistic enterocolitis" [49].

Other theories of the alleged association between vaccines and ASDs include the following:

1. The mercury-containing preservative thimerosal (which was used in childhood vaccines for many years) produces toxic effects on the developing central nervous system in children
2. A combination of MMR and thimerosal-containing vaccines leads to additive or synergistic toxic insults on children's brains
3. The simultaneous administration of multiple vaccines may "overwhelm" or "weaken" the relatively immature immune system in young children

The Response from the Scientific Community

The scientific limitations of the paper published by Wakefield et al. [48] were highlighted shortly after it first appeared [50]. It was observed that the authors reported on a small series of cases with no controls, linked three common clinical conditions, and relied on the recall and beliefs of parents [51]. Subsequently, a number of large population- and ecologic-based studies were performed that consistently found no evidence of a connection between the MMR vaccine and autism and failed to provide supportive evidence for Wakefield's hypothesis [52–55]. This lack of an association between MMR vaccination and autism in children is further supported by 19 additional scientific studies conducted by independent groups of investigators using different research methodologies involving diverse groups of patients over more than a decade [56–74]. Several review articles have discussed these studies in detail [75–78]. In summary, despite substantial efforts by multiple groups of scientists, the findings of Wakefield et al. [48] could neither be replicated nor confirmed. On the contrary, in a case–control study conducted in Poland, where the MMR vaccine was introduced later than in most other European countries, the risk of autism was found to be lower in children who received the MMR vaccine than in those who did not [74]. The authors correctly report that the decreased risk of autism among vaccinated children may have been due to other confounding factors in their health status besides vaccination such as, healthcare workers or parents noticing signs of developmental delay or disease before the actual autism diagnosis and for this reason avoiding vaccination [74]. Unfortunately, in studies that support the contention that the MMR vaccine is associated with ASDs this type of scientific rigor and unbiased analysis is absent [79–81].

Forced to acknowledge that "no causal link was established between MMR vaccine and autism as the data were insufficient" in their original article, 10 of the 12 coauthors on Wakefield's paper asked to "formally retract the interpretation" of their report [82]. Using a larger sample size than Wakefield and his colleagues'

original study [49], D'Souza et al. reported the absence of measles virus RNA in the peripheral blood of children with ASDs [83]. Further studies also could not find measles virus genome sequence in the blood of autistic children who had received MMR vaccination [84, 85]. Finally, in a case–control study of 25 children in the USA with autism and gastrointestinal (GI) disturbances and 13 children with GI disturbances alone (controls) undergoing clinically indicated ileocolonoscopy, ileal and cecal tissues from all subjects were examined by real-time reverse transcription (RT)-PCR for presence of measles virus RNA in three separate laboratories blinded to diagnosis, one of which had reported the original findings suggesting a link between measles virus and ASDs [86]. No differences were found between case and control groups in the presence of measles viral RNA in the ileum and cecum [86].

Although it is difficult to scientifically prove a negative, the Institute of Medicine (IOM) has conclusively stated that there is no causal relationship between the administration of the MMR vaccine and the onset of ASDs [87]. In their eighth and final report of the Immunization Safety Review Committee, the hypothesis that vaccines, specifically the MMR vaccine is causally associated with autism was critically evaluated. Committee members reviewed all published and unpublished epidemiological studies regarding causality as well as studies of potential biologic mechanisms by which immunizations might cause autism, and arrived at the conclusion that the body of epidemiological evidence favored *rejection* of a causal relationship between the MMR vaccine and autism [87]. They further found that potential biological mechanisms for vaccine-induced autism that have been generated to date are theoretical only [87].

Thus, the best available scientific literature indicates that the MMR vaccine is safe and efficacious. It therefore continues to be recommended by public health authorities around the world, and is supported by most medical professionals. Regrettably, despite the large body of scientific evidence to the contrary, some vaccine opponents continue to support the initial theory that vaccines cause autism [36, 47, 88].

Consequences of the Fears About MMR Causing Autism

An unfortunate result of the publications by Wakefield and his colleagues [48, 49] was that many parents began to refuse the MMR vaccine for their children due to concerns about the risk of autism. MMR vaccination compliance dropped significantly in the UK from 92 % in 1996 (before the controversy began) to 80 % in 2003 [89]. In South-East London, it was as low as 62 %, far below the rate needed to avoid an epidemic of measles [89]. Coverage for MMR for children at 24 months of age in the UK was 85 % in 2006, significantly lower than the 94 % coverage rate for other vaccines [90], indicating specific refusal of this vaccine by parents and caregivers of children. The "fallout" from decreased vaccination rates for MMR vaccine was inevitable—an increase in the incidence in the UK of measles and mumps [91]. There were 56 confirmed cases of measles in the UK in 1998, compared to 449

cases by the first five months of 2006, with the first death due to measles reported since 1992. Predictably, these cases all occurred in incompletely vaccinated or unvaccinated children [92].

After many years, cases of mumps also began rising in 1999, and by 2005, a mumps epidemic had erupted in the UK with nearly 5,000 reports in January 2005 alone [93]. That year, there were 56,390 cases of mumps reported in England and Wales [94]. Most patients who contracted mumps were between 15 and 24 years of age, too old to have received the routine MMR vaccine around the time the paper by Wakefield et al. was published, and too young to have contracted natural mumps as a child. Due to high vaccination rates of MMR in the UK prior to 1998, mumps had declined significantly, and these individuals had not been exposed to the disease, and thus had no immunity, either natural or vaccine-induced. Once the disease reemerged after immunization rates fell following the controversy, they were susceptible to infection [94].

Measles and mumps cases continued to be reported in 2006, at incidence rates 13 and 37 times greater than their respective 1998 levels [95]. Sadly, two children were severely and permanently injured by measles encephalitis [96]. Measles outbreaks also resulted in casualties. There were three deaths and 1,500 cases of measles reported in an outbreak in Ireland [96]. In another study, 111 patients with measles were reported to be hospitalized with complications such as pneumonia, tracheitis, and dehydration, 13 of them needing admission to the ICU and 7 of the children requiring mechanical ventilation [97]. For the first time after 14 years, measles was declared to be endemic again in the UK in 2008, caused by the preceding decade's low MMR vaccination rates, creating a population of susceptible children able to spread the disease [95]. MMR vaccination rates for English children remained at too low a level to prevent measles outbreaks in 2007–2008 [98]. A British 17-year-old with a congenital immunodeficiency died of measles in 2008, the first such fatality in the UK since 2006 [95]. Large outbreaks of measles were also reported from Italy, Austria and Switzerland [95].

Selective nonreceipt of the MMR vaccine increased to 2.1 % of children according to the 2000 National Immunization Survey (NIS), compared to 0.77 % in 1995 [99]. Children who were included in the 2000 NIS were born at around the time that the association between the MMR vaccine and autism surfaced. Although the disease was declared eliminated in 2000, sporadic importations of measles into the USA had continued to occur without widespread outbreaks. During 2001–2008, a median of 56 (range: 37–140) measles cases were reported to CDC annually [100]. However, since 2008, even though endemic or sustained transmission has not occurred, several measles outbreaks have been reported in the USA, mostly affecting unvaccinated or partially vaccinated individuals [101–107]. During the first 19 weeks of 2011, 118 cases of measles were reported in the USA, the highest number reported for this period since 1996, with 89 % associated with importation from other countries including the European and South-East Asia regions [108]. Of the 118, 105 (89 %) patients were unvaccinated, 47 (40 %) of the patients were hospitalized and nine had pneumonia [108]. In another study, 94 % of the patients were US residents, 93 % were unvaccinated and 86 %

of the cases were imported (69 % from Europe) [101]. The increased number of measles importations into the USA and outbreaks related to these in recent years, underscores the importance of vaccination to prevent measles and its complications.

MMR and Autism: Was the Original Hypothesis an Honest Error or an Elaborate Fraud?

This question has been directly addressed by the editors at the BMJ who claim that it has taken the diligent skepticism of Brian Deer, an investigative journalist from outside the realms of medicine and science, to show that the initial paper by Wakefield et al. [48] was in fact an elaborate fraud [109]. In a series of articles published in 2011, Deer reported on how Wakefield altered numerous facts about his patients' medical histories in order to support his claim to have identified a new syndrome [110]; how his institution, the Royal Free Hospital and Medical School in London, supported him as he sought to exploit the ensuing MMR scare for financial gain [111]; and how key players failed to investigate thoroughly in the public interest when Deer first raised his concerns [112].

The charge that Wakefield's original paper was fraudulent is based on the definition of fraud by the Office of Research Integrity in the USA as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results [113]. Each term in the definition is further explained as follows:

(a) *Fabrication* is making up data or results and recording or reporting them.
(b) *Falsification* is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
(c) *Plagiarism* is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.
(d) Research misconduct does not include honest error or differences of opinion.

Brian Deer's initial investigation into Wakefield's paper was published in 2004 [114], uncovering the possibility of research fraud, unethical treatment of children, and Wakefield's conflict of interest through his involvement with a lawsuit against manufacturers of the MMR vaccine [109]. Building on these findings, the General Medical Council (GMC) of the UK launched proceedings that focused on whether the research conducted by Wakefield et al. [48] was ethical.

Through the disciplinary panel's public examination of the children's medical records, Brian Deer was able to compare them with what was published in the *Lancet* article. He focused on whether the article in the *Lancet* was factually accurate. Over several years, he conducted interviews, reviewed documents and data made public at the GMC hearings and discovered clear evidence of falsification in Wakefield et al.'s [48] paper. He found that in every one of the 12 cases reported by Wakefield et al. [48], there was misrepresentation or undisclosed alteration, and that

in no single case could the children's medical records be fully reconciled with the descriptions, diagnoses, or histories published in the article. The blame for the falsified data has been unequivocally placed upon Andrew Wakefield [109]. The editors of the BMJ question whether it is possible that he was wrong, but not dishonest: that he was so incompetent that he was unable to fairly describe the project, or to report even one of the 12 children's cases accurately, and conclude that the article resulted not from honest errors, but a deliberate attempt to defraud [109]. Their conclusion is based on the argument that a great deal of thought and effort must have gone into drafting the paper to achieve the results he wanted, since the discrepancies all led in one direction and the misreporting was gross [109].

Aftermath of the "MMR Causes Autism" Fraud

The journal *Lancet* fully retracted the article by Wakefield et al., based on several elements of the paper being proven to be false, almost 12 years after its original publication [115]. Having completed its longest-ever "fitness to practice" hearing, the GMC withdrew Dr. Wakefield's license to practice medicine [116]. Andrew Wakefield was denounced as being "dishonest," "unethical," and "callous" [117]. His associate Professor John Walker-Smith, the senior clinician in the project, was found to have presided over "high risk" research without clinical indication or ethical approval, and also struck off the medical register [118]. Further details about this controversy and autism research have been published in several recent books [119–121].

The Wakefield case and its repercussions have resulted in a reevaluation of the regulation of biomedical research. In the UK, there have been calls for a national Health Research Agency to be established to oversee the regulation and governance of health research by some [122], while others have advocated for public access to raw data, arguing that the apparent discrepancies between the patient records and the data in the article by Wakefield et al. [48] might have come to light sooner, perhaps even before publication, had the raw data been available for public scrutiny [123]. Yet others have proposed that in order to improve research integrity, traditional hierarchies and authority gradients may need to be bypassed enabling everyone involved in the research enterprise—particularly those on the front lines, such as research assistants, data analysts, and project managers—to raise questions and be able to report suspected misconduct without fear of retaliation [124]. They suggest that to protect the safety of research subjects, the mechanism of investigating research incidents needs to be strengthened using the best tools and techniques available [124]. They also propose that traditional customs and culture surrounding biomedical research need rethinking and reform. They point out that Wakefield's flawed study has had a significant negative impact on vaccine coverage, leading to the reemergence of vaccine-preventable diseases and erosion of the public's trust in science, and advocate rapid action to remedy the current system of ensuring research integrity [124].

After reviewing the relevant, peer-reviewed literature on the subject, most rational individuals would admit that Wakefield et al.'s paper was fatally flawed

both scientifically and ethically, if not outright fraudulent. Unfortunately, an allegation may be remembered and believed to be true long after it has been disproved or discredited. The authors of a systematic review on the subject published in 2010, noted that vaccine-declining parents believe that vaccines are unsafe and ineffective and that the diseases they are given to prevent are mild and uncommon; they mistrust their health professionals, Government and officially endorsed vaccine research but trust media and nonofficial information sources and resent perceived pressure to risk their own child's safety for public health benefit [125]. In a survey of parent's decisions, attitudes, and use of information about MMR immunization in the UK, although both MMR-accepting and refusing parents were supportive of immunization in general, they had a high level of concern about the vaccine's safety [126]. A survey of parents conducted in 2009 in the USA showed that while most parents agreed that vaccines protect their child(ren) from diseases, more than half of the respondents also expressed concerns regarding serious adverse effects of vaccines [127]. Overall, 11.5 % of the parents had refused at least 1 vaccine that their doctor had recommended for their child(ren), with 17.7 % refusing the MMR vaccine [127]. A quarter of the survey responders either strongly agreed or agreed with the statement "Some vaccines cause autism in healthy children" [127]. So while there appears to be a shrinking group of parents now rejecting MMR vaccine, comprising mainly those with more extreme and complex anti-immunization views, it is disheartening to note that some parents are still opting for single vaccines using second-hand information about the controversy [128]. Wakefield's impact on the controversy about the MMR vaccine and autism promises to live on.

Genesis of the Thimerosal and Autism Hypothesis

Another controversy that has been hotly debated is the relationship between the onset of ASDs and exposure to thimerosal, which has been used as a preservative in vaccines since the 1930s [129]. Multidose vaccine vials have thimerosal added to them to preserve the sterility of their contents. Thimerosal contains 49.6 % mercury by weight and metabolizes into *ethylmercury* and thiosalicylate. Towards the end of the twentieth century, the US government became aware of and concerned about mercury exposure in the general population [130] and the US Environmental Protection Agency (EPA) published standards of safe limits of oral *methylmercury* exposure particularly from fish and shellfish [131, 132]. These statements from the EPA clearly indicate that people in the USA are mainly exposed to organic *methylmercury*, by consuming fish and shellfish that contain it. The EPA identifies the following factors that determine how severe the health effects from mercury exposure may be:

- The chemical form of mercury.
- The dose.
- The age of the person exposed (the fetus is the most susceptible).

- The duration of exposure.
- The route of exposure—inhalation, ingestion, dermal contact, etc.
- The health of the person exposed.

Various agencies and organizations including the EPA [133, 134], US Agency for Toxic Substances and Disease Registry (ATSDR) [135], the US Food and Drug Administration (FDA) [136], and the World Health Organization (WHO) [137] have developed guidelines for "safe" exposure to *methylmercury*. These exposure levels varied ranging from 0.1 μg/kg body weight/day (EPA) to 0.47 μg/kg body weight/day (WHO), but were within the same order of magnitude. It is important to note that the different mercury guidelines were based on epidemiological and laboratory studies of *methylmercury*, whereas thimerosal as mentioned before, is a derivative of *ethylmercury*. As they are distinct chemical entities, i.e., *ethyl* versus *methylmercury*, different toxicological profiles are to be expected for the two compounds. It is not commonly known or understood that there was uncertainty in applying the *methylmercury*-based guidelines to thimerosal. For example, the FDA has noted that these guidelines may be used as screening tools in risk assessment to evaluate the "safety" of mercury exposures, but are not meant to be bright lines above which toxicity *will* occur [138].

A law known as the FDA Modernization Act of 1997 was passed, giving the FDA 2 years to "compile a list of drugs and foods that contain intentionally introduced mercury compounds and provide a quantitative and qualitative analysis of the mercury compounds in the list" [139]. It received little public or press attention at the time, but in accordance with the law, the FDA did conduct a comprehensive review of the use of thimerosal in childhood vaccines in 1999, finding *no evidence of harm* from the use of thimerosal as a vaccine preservative, other than local hypersensitivity reactions [140]. Based on the recommended childhood immunization schedule in the USA at that time, the maximum cumulative exposure to mercury from vaccines was found to be within the acceptable limits for the *methylmercury* exposure guidelines set by FDA, ATSDR, and WHO. However, depending on the weight of the infant and on the choice of vaccine formulations, some infants could have been exposed to cumulative levels of mercury during the first 6 months of life that exceeded EPA recommended guidelines for safe intake of *methylmercury*.

With additional thimerosal-containing vaccines being added to the recommended infant and child immunization schedule in the USA, theoretical concerns based on the cumulative amounts of thimerosal that a child was receiving in the first 2 years of life were raised. Based on these purely theoretical concerns, the US Public Health Service (USPHS) (which includes the FDA, National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC) and the Health Resources and Services Administration (HRSA)) and the American Academy of Pediatrics issued two Joint Statements, urging vaccine manufacturers to reduce or eliminate thimerosal in vaccines as soon as possible, as a precautionary measure [141, 142]. This action was taken through an "abundance of caution," even though there was no scientific evidence linking thimerosal-containing vaccines to toxic mercury levels in children, and it was known that *ethylmercury* does not have the neurotoxic effects of

methylmercury. Unfortunately, statements issued by the USPHS and AAP had significant and unintended impacts on the public's concerns about vaccine safety in young children. Advocacy groups were founded by many parents based on the belief that thimerosal had caused their children's autism [143]. Bernard Rimland, who had been instrumental in debunking the "refrigerator mother" theory of the etiology of autism [10], and a staunch advocate of families affected by autism since the 1960s, became one of the chief supporters of the new hypothesis that the thimerosal in childhood vaccines was linked to autism [144].

Is There Credible Scientific Evidence Linking Thimerosal with Autism?

The clinical manifestations of autism are quite different from those of mercury poisoning. Children with the latter have characteristic motor, speech, sensory, psychiatric, visual, and head circumference changes that are fundamentally different from those of or absent in children with autism. Therefore, a biologic basis for concerns about mercury as a cause of autism appeared unlikely [145]. Despite this, reports began to be published of adverse neurological effects including autism due to *ethylmercury* exposure from the use of thimerosal in vaccines [146–154]. Interestingly, a majority of the studies that found an association of thimerosal with neurodevelopmental disorders including autism were performed by the same group of researchers [149–154], using the CDC's Vaccine Adverse Events Reporting System (VAERS) as their data source. The VAERS is a passive reporting system to which anyone can report adverse events alleged to be associated with vaccines. A report by Goodman and Nordin showed that in recent years, most reports to the VAERS system regarding thimerosal were influenced by litigation, and therefore unsuitable for scientific study [155]. Stated in another way, most adverse reports entered into VAERS regarding thimerosal and autism were related to pending lawsuits for vaccine injury, resulting in a biased dataset that should not have been used to assign causality.

In the meantime, a number of scientific studies performed by diverse groups of researchers did not find evidence to support an association between thimerosal and ASDs [71, 156–163]. Three ecological studies were performed in three different countries comparing the incidence of autism with thimerosal exposure from vaccines [71, 157, 158]. In each country, thimerosal had been removed from childhood vaccines, so that comparisons between vaccination with thimerosal-containing and thimerosal-free products could be made. A large study from Denmark showed no difference in the incidence of autism among children who had received vaccines containing different amounts of thimerosal [157]. Despite the removal of thimerosal from vaccines in 1992 in Sweden and Denmark, the incidence of autism continued to increase steadily from 1990 to 2000 [158]. Thimerosal exposure and pervasive developmental disorder diagnosis were found to be independent variables in a study from Canada [71]. In this study, the highest rates of pervasive developmental disorder were actually found in children who had received thimerosal-free vaccines [71].

Several large epidemiologic studies also failed to show any association between thimerosol exposure from childhood vaccines and ASDs. Researchers from Denmark reported that there was no difference in the risk of autism between children vaccinated with thimerosal-containing vaccines and those vaccinated with thimerosal-free vaccines or between children who received larger or smaller amounts of thimerosal [156]. They also noted that the rates of autism continued to increase after the removal of thimerosal from all vaccines. In the USA, researchers at the CDC used the Vaccine Safety Data Link to examine the health records of 140,887 children born during 1991–1999, including over 200 children diagnosed with autism [159]. Again, no relationship between receipt of thimerosal-containing vaccines and autism was found. In a similar study conducted in the UK, researchers evaluated the vaccination records of 100,572 children born during 1988–1997, 104 of whom were affected with autism [160]. Once again, a relationship between thimerosal exposure and developmental disorders could not be established. In a separate study from the UK, researchers prospectively followed 12,810 children born during 1991–1992, for whom they had complete vaccination records, and again found no relationship between early thimerosal exposure and subsequent adverse neurological or psychological outcomes [161].

A long-term follow-up study conducted by the CDC showed that early thimerosal exposure from vaccines did not cause adverse neuropsychological outcomes after 7–10 years [164]. In another long-term follow-up study performed in Italy, two groups of children with exposure to different doses of thimerosol were examined [165]. In this study, 24 neuropsychological outcomes were evaluated, and only two were found to be significantly associated with thimerosal exposure. The authors noted that due to the large number of statistical comparisons performed, the few associations found between thimerosal exposure and neuropsychological development might be attributable to chance [165]. The associations that were found, although statistically significant, were based on small differences in mean test scores, and their clinical relevance could not be determined [165]. A case–control study was conducted in three managed care organizations (MCOs) in the USA that included 256 children with ASDs and 752 matched controls [166]. The authors report that in their study, prenatal and early-life exposure to *ethylmercury* from thimerosal-containing vaccines and immunoglobulin preparations was not related to increased risk of ASDs [166]. Multiple scientific and public policy review committees having carefully evaluated the existing data have concluded that there was insufficient evidence of a link between autism and thimerosal in vaccines [87, 138, 167]. In fact, the Institute of Medicine's 2004 evaluation included a strong statement that rejected the idea that thimerosal-containing vaccines cause autism, concluding that "…epidemiological evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism" [167].

In animal models, comparisons of *methylmercury* and *ethylmercury* tissue distribution following exposure in young mice [168] and monkeys [169] both reported significantly less mercury deposited in the brain following *ethylmercury* or thimerosal exposure, as compared to *methylmercury* exposure. The authors of these studies concluded that the clearance and tissue distribution of the two compounds differ significantly in these animal models [168, 169]. The route of exposure (injection

versus ingestion) to *methylmercury* also resulted in differences in the amount of mercury deposited in the brain in mice, with exposure via intramuscular injection resulting in *less* mercury deposition than via ingestion [168]. Pichichero, et al. measured mercury levels in blood and other samples from infants who had received routine immunizations with thimerosal-containing vaccines [170]. Blood levels of mercury did not exceed safety guidelines for *methylmercury* for all infants in this study [170]. The researchers found that mercury was cleared from the blood in infants exposed to thimerosal faster than would be predicted for *methylmercury* [170]. Infants in the study did excrete significant amounts of mercury in stool after thimerosal exposure, thus removing mercury from their bodies [170]. These results indicate that there are differences in the way that thimerosal and *methylmercury* are distributed, metabolized, and excreted in young infants. Thimerosal appears to be removed from the blood and body much more rapidly than *methylmercury*. Due to the differences in the biological behavior of these two compounds, the flaws in extrapolating the risk assessment of thimerosal by direct comparison with *methylmercury* are well described in a review by Aschner and Ceccatelli [171]. Authors of another review article summarizing the studies investigating thimerosal exposure and the development of ASDs, note that only two studies conducted by the same group of researchers report an association, while eight other studies performed by different groups of investigators failed to find such a link [172].

Thimerosal has been removed from all childhood vaccines in the USA, with only some preparations of influenza vaccine still containing thimerosal (see Table 10.2). Despite this, many parents remain reluctant to have their children receive this vaccine based on concerns about the adverse effects of thimerosal. What the lay public and even many health care providers often fail to recognize is that influenza viruses cause significant morbidity with hundreds of thousands of hospitalizations, and although rare, even deaths among children every year [173]. In an attempt to protect their children from a perceived risk, these parents inadvertently place them at the real risk of being hospitalized or killed by influenza. The birth dose of hepatitis B vaccine which in 1999 contained thimerosal was subsequently withheld from many children and the hepatitis B vaccination campaign in the USA experienced a serious setback [174]. Although thimerosal-free hepatitis B vaccines became available shortly thereafter, the effort to vaccinate infants at birth remains challenging in some areas. The public may also not understand that the removal of thimerosal from childhood vaccines has increased production costs which are ultimately passed on to the consumer.

Do Multiple Vaccines "Overload" or "Weaken" the Immune System?

As it became evident that the claims about the MMR vaccine causing ASDs were based on poorly designed studies and perhaps scientific misconduct, and a number of reports showed no link between thimerosal-containing vaccines and autism, new theories about the role of vaccines in causing ASDs have been proposed [36]. Among these, the most popular assertion is that the simultaneous administration of multiple vaccines

Table 10.2 Thimerosal content in some US licensed vaccines

Vaccine	Brand name		Manufacturer	Thimerosal concentration[a]	Mercury mcg/0.5 ml
Anthrax	BioThrax		BioPort Corp	0	0
DTaP	Daptacel		sanofi pasteur	0	0
	Infanrix		GlaxoSmithKline	0	0
	Tripedia		sanofi pasteur	*	*
DTaP+HepB+IPV	Pediarix		GlaxoSmithKline	0	0
DTaP+Hib	TriHIBit (ActHIB+Tripedia)		sanofi pasteur	*	*
DTaP+IPV	Kinrix		GlaxoSmithKline	0	0
DTaP+IPV+Hib	Pentacel		sanofi pasteur	0	0
DT	Diphtheria & Tetanus Toxoids Adsorbed USP		sanofi pasteur	*	*
Td	Decavac		sanofi pasteur	*	*
	Tetanus and Diphtheria Toxoids Adsorbed		Mass Biolocial Labs	*	*
Tdap	Adacel		sanofi pasteur	0	0
	Boostrix		GlaxoSmithKline	0	0
Tetanus Toxoid	Generic		sanofi pasteur	0.01 %	25
Hib	ActHIB		sanofi pasteur	*	*
	Hiberix		GlaxoSmithKline	0	0
	PedvaxHIB		Merck	0	0
Hib+HepB	Comvax		Merck	0	0
Hepatitis A	Havrix		GlaxoSmithKline	0	0
	Vaqta		Merck	0	0
Hepatitis B	Engerix-B		GlaxoSmithKline	0	0
	Recombivax HB		Merck	0	0
Hep A+B	Twinrix		GlaxoSmithKline	0	0
HPV	Cervarix		GlaxoSmithKline	0	0
	Gardasil		Merck	0	0
Influenza 2011/12 Formula	Afluria	Single dose	CSL Limited	0	0
		Multi-dose		0.01 %	24.5
	Agriflu		Novartis	0	0
	Fluarix		GlaxoSmithKline	0	0
	FluLaval		GlaxoSmithKline	0.01 %	25
	FluMist		MedImmune	0	0
	Fluvirin	Prefilled syringe	Novartis		≤1
		Multi-dose		0.01 %	25
	Fluzone	All single dose	sanofi pasteur	0	0
		Multi-dose		0.01 %	25
Japanese Encephalitis	Ixiaro commercial | military		Intercell Bio	0	0
	JE-Vax		sanofi pasteur	0.007 %	
Meningococcal	Menactra		sanofi pasteur	0	0
	Menomune--A/C/Y/W-135	Single dose	sanofi pasteur	0	0
		Multi-dose		0.01 %	25
	Menveo		Novartis	0	0

(continued)

Table 10.2 (continued)

Vaccine	Brand name	Manufacturer	Thimerosal concentration[a]	Mercury mcg/0.5 ml
MMR	M-M-R II	Merck	0	0
MMR+Varicella	ProQuad	Merck	0	0
Polio	IPOL	sanofi pasteur	0	0
Pneumococcal	Pneumovax 23	Merck	0	0
	Prevnar	Wyeth-Ayerst	0	0
	Prevnar 13	Wyeth-Ayerst	0	0
Rabies	Imovax	sanofi pasteur	0	0
	RabAvert	Chiron	0	0
Rotavirus	Rotarix	GlaxoSmithKline	0	0
	RotaTeq	Merck	0	0
Typhoid Fever	Typhim Vi	sanofi pasteur	0	0
	Vivotif	Berna Biotch	0	0
Varicella Zoster	Varivax	Merck	0	0
	Zostavax	Merck	0	0
Yellow Fever	YF-VAX	sanofi pasteur	0	0

Available at http://www.vaccinesafety.edu/thi-table.htm. Accessed 2/18/12

*This product should be considered equivalent to thimerosal-free products. This vaccine may contain trace amounts (<0.3 mcg) of mercury left after post-production thimerosal removal; these amounts have no biological effect. JAMA 1999;282(18) and JAMA 2000;283(16)

[a]A concentration of 1:10,000 is equivalent to a 0.01 % concentration and contains 25 mcg of Hg per 0.5 mL. Thimerosal is approximately 50 % Hg by weight

"overwhelms" or "weakens" the immature immune system in young children and through some interaction with the nervous system "triggers" autism in a susceptible host. Intense media attention to this hypothesis has led to some parents and caregivers believing it to be true. This theory became popularized after a 9-year-old girl with a mitochondrial enzyme deficiency whose encephalopathy, which included features of ASD, was judged to have worsened following the receipt of multiple vaccines at age 19 months [175]. Her family received compensation through the US Vaccine Injury Compensation Program (VICP) which was developed in the 1980s to fairly compensate individuals who feel they have been harmed by a vaccine. Following numerous media reports about this case, despite reassurances by the CDC that the VICP's action should not be interpreted as scientific evidence that vaccines cause autism, the theory that multiple vaccines given simultaneously can trigger autism has gained credence not only among the lay press and public, but even some scientists [36].

The theory that multiple vaccines given to young children might either overwhelm an immature immune system or generate a pathologic, autism-inducing autoimmune response is flawed for a number of reasons. Although the infant immune system is relatively naive, it is capable of generating a vast array of protective responses, starting at birth [176]. Kennedy and Lawrence note that a newborn encounters a vast array of antigens during and immediately after birth, and the amount of vaccine antigens is infinitesimal compared to those encountered in the environment by young children [176]. For example, the average child is infected with 4–6 viruses per year [177], exposing its immune system to numbers of antigens

that far exceed those present in simultaneously administered childhood vaccines. Proponents of the theory point out that an increasing number of vaccines are being administered to young children [36]. However, what most people fail to recognize is that although the *number* of recommended childhood vaccines has increased during the past 30 years, with the improved technologies that are used to manufacture modern vaccines, the antigenic load has actually *decreased*. The childhood vaccines given today contain <200 bacterial and viral antigens, compared with >3,000 of these immunological components in the vaccines administered to children in 1980 [178]. In fact, combinations of vaccines are actually known to induce immune responses that are comparable to those given individually [179].

It is interesting to note that susceptibility to non-vaccine-preventable infections does not differ in vaccinated and unvaccinated children [180–182]. In other words, vaccination does not suppress the immune system in young children in a clinically relevant manner. On the contrary, infections with some vaccine-preventable diseases are known to predispose children to severe, invasive infections with other pathogens [183, 184]. Therefore, the available scientific data do not support the contention that vaccines "weaken" the immune system in any way. It is also well-recognized that while immune system dysregulation has been reported in patients with autism, there is considerable controversy regarding an immunologic basis for the pathophysiology of ASDs [185]. There is no evidence of immune activation or inflammatory lesions in the brains of autistic people [167]. Instead, new research suggests that genetic variation in neuronal circuitry that affects synaptic development in the brain might in part account for the symptoms of autism [186]. The wide phenotypic variability of the ASDs likely reflects the interaction of multiple genes within an individual's genome and the existence of distinct genes and gene combinations among those affected [187]. Recent technical advances, such as microarray-based whole-genome analysis has enabled the identification of common as well as rare genetic alterations associated with ASDs. The most commonly noted genetic variations that have been identified in individuals with ASDs include single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) [188]. A study published in 2011 that compared post-mortem brain tissue samples from autism cases and normal controls provides strong evidence for converging molecular abnormalities in ASDs, and implicates transcriptional and splicing dysregulation as underlying mechanisms of neuronal dysfunction in these disorders [189]. Thus, the theory that an exaggerated or inappropriate immune response to vaccination results in autism is increasingly at variance with the most recent scientific studies that address the pathogenesis of autism.

Why the Controversy Over Vaccines and Autism Persists

There are three broad categories of reasons that this controversy continues even though it lacks scientific merit. As may be expected in a highly litiginous milieu, the question of whether childhood vaccines cause autism has moved from the scientific into the legal realm [190–192]. Alleging that their child's autism was caused by

vaccines, parents of children with autism have submitted thousands of claims seeking damages to the federal VICP. While some have been successful in being compensated through this process [175], the US Court of Federal Claims which was established to review these claims as a group under the Omnibus Autism Proceeding, found that the MMR and thimerosal-containing vaccines, independently or together, were not causal factors in the development of autism or ASD [77, 78, 193]. Even the Supreme Court of the USA has held that the National Childhood Vaccine Injury Act "preempts all design-defect claims against vaccine manufacturers brought by plaintiffs who seek compensation for injury or death caused by vaccine side effects" [194]. These recent legal developments may decrease the fervor of those seeking compensation for claims about vaccines causing autism, but the lure of financial gain through successful litigation of this issue remains.

One of the reasons many parents are hesitant about vaccinating their children is the media attention paid to this issue over many years [99, 195]. In spite of overwhelming scientific evidence to the contrary, the debate over vaccines and ASDs rages on, due at least in part, to media reports fueling the general public's fear. The disconnect between the scientific literature and the popular media is clear in a study published by researchers at the Stanford University School of Medicine [196]. They found that while 41 % of research funding and published scientific papers on autism dealt with brain and behavior research, only 11 % of newspaper stories in the USA, the UK, and Canada dealt with those issues. Instead, 48 % of the media coverage dealt with environmental causes of autism, particularly the childhood MMR vaccine [196].

A famous cartoon was published in 1802 depicting individuals growing cow-like appendages following vaccination against smallpox with the material obtained from cowpox lesions [176]. It reflected the irrational beliefs that were sometimes held by the public and propagated through the media regarding adverse effects of vaccination from its early years. Poland and Jacobson note that there has been opposition to vaccination published in newspapers since the introduction of the first vaccine for smallpox over 200 years ago [197]. According to them, little has changed since that time, although now the antivaccinationists' media of choice are typically television and the Internet, including its social media outlets, which are used to sway public opinion and distract attention from scientific evidence [197]. The authors propose various methods to correct the misinformation about vaccines that may be presented in the media. Among these, they emphasize the importance of enhanced public education and public persuasion, with increasing scientific literacy at all levels of education. In addition, they recommend that public-private partnerships of scientists and physicians be developed to make accurate vaccine information accessible to the public in multiple languages, at a range of reading levels, and through various media outlets. Without such efforts, vaccine hesitancy is likely to continue, fueled by a lack of trust in those who make vaccine recommendations, a suspicion of the profit motive of pharmaceutical companies, misinformation on the Internet, and constant stories in the media claiming that vaccines cause a variety of illnesses, ranging from allergies to autism [198].

A third reason that the controversy about vaccines and autism is kept alive is the involvement of advocacy groups such as the Autism Research Institute, Defeat Autism Now!, Cure Autism Now, Autism Speaks, SafeMinds, the National Vaccine

Information Center, Generation Rescue, etc. [199, 200]. Basing many of their claims on publications that do not go through an unbiased peer review process, these groups continue to cling to the hypotheses that have largely been rejected by mainstream scientists. Some of these organizations were even formed with the express purpose of raising money to support Andrew Wakefield [200]. A number of celebrities and media personalities are supporters of these organizations and their beliefs about vaccines and autism [201]. The tide may however be beginning to turn. A growing number of individuals that had originally supported the alleged association between vaccines and autism are moving away from this viewpoint. In January 2009, Alison Singer who was the top communications executive at Autism Speaks resigned from her position, convinced by the evidence that vaccines do not cause autism [202]. Five months later, Dr. Eric London, a cofounder of the National Alliance for Autism Research and member of the Scientific Advisory Committee of Autism Speaks dissociated himself from the latter organization and resigned from his position on the committee citing concerns about the stance that Autism Speaks was taking concerning vaccinations [203]. In his letter of resignation he warned the organization that their position on vaccines being responsible for causing autism was adversely impacting the advancement of autism research, that reports of outbreaks of measles and other vaccine-preventable diseases were on the rise, and that if their misguided stance continued, there would be deaths and potentially the loss of herd immunity which would result in serious outbreaks of otherwise preventable diseases [203].

Conclusions

Thanks to the vaccines developed during the twentieth century and the success of worldwide immunization programs, many infectious diseases such as smallpox, polio, and measles have either been eradicated or become rare. The public as well as many health care providers of the twenty-first century have limited or no experience with the devastating effects of these diseases. While the consequences of these infections have faded from the public conscience over the last few decades, there has been an alarming increase in the number of children diagnosed with ASDs [3, 204]. Although some explanations for the increase have been offered by the medical and scientific community [16, 205, 206], in most cases, the causes of ASDs remain shrouded in mystery. Given the grim statistics of ASDs—one out of ten autistics cannot speak, nine out of ten have no regular job, and four out of five autistic adults are still dependent on their parents, it is no wonder that families affected by these disorders are desperate for answers [207].

ASDs are often diagnosed in young children at about the same chronologic age at which most vaccines are given. This coincidence in time of two disparate but significant child health issues, has led to the unfortunate situation where fear of disease has shifted to concerns about vaccine safety, particularly ASDs among some members of the public. Although scientific evidence has countered many of the misconceptions regarding vaccines and ASDs, this information has not been

disseminated adequately among the lay public, resulting in an erosion of public confidence in vaccines. This in turn has led to the reemergence of some vaccine-preventable diseases such as measles and polio in parts of the world where they had previously been nearly eliminated. At the same time, in recent years, physicians, scientists, government policy advisors, and child advocates who publicly state that vaccines do not cause neurologic problems or autism have been harassed, threatened, and vilified, receiving hate mail and occasionally even death threats [143]. In order to reestablish the public's trust in vaccination, all stakeholders including parents, healthcare providers, the scientific community and public health authorities need to ensure that rigorously researched scientific information on the issue of vaccines and autism is accurately collected and appropriately disseminated.

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Chapter 11
Thimerosal and Other Vaccine Additives

James H. Conway and Roman Aydiko Ayele

Introduction

While vaccine products that contain only the antigens necessary to induce immunity would be ideal, the reality of vaccine production requires the addition of other materials, sometimes called "excipients." These include a variety of preservatives and substances to maintain vaccine stability, as well as adjuvants considered necessary to induce protective immunity. In addition, there are other materials sometimes introduced into the final products either as a result of the manufacturing process or packaging.

Vaccine additives have been a topic of interest since early in the development of vaccines for immunization. In 1925, Ramon noted that horses receiving diphtheria toxoid vaccines that developed abscesses at the injection sites appeared to achieve higher diphtheria antitoxin levels when compared to animals that had not developed infectious complications [1, 2]. He subsequently experimented with an array of other substances and found that noninfectious substances, including tapioca, were also capable of augmenting immune response when co-administered with other antigens [1, 2].

This information proved to be extremely valuable as further investigators pursued vaccine development. While whole and viable organisms could sometimes be more immunogenic than isolated components, there was also more risk of developing infectious complications. Understanding the need to prevent vaccine

J.H. Conway, M.D., F.A.A.P. (✉)
Division of Pediatric Infectious Diseases, University of Wisconsin School of Medicine & Public Health, 600 Highland Ave., H4/450 CSC, Madison, WI 53792, USA
e-mail: jhconway@pediatrics.wisc.edu

R.A. Ayele, M.P.H.
Wisconsin Department of Health Services, University of Wisconsin School of Medicine & Public Health, 1 West Wilson Street, Madison, WI 53702, USA
e-mail: Roman.Ayele@Wisconsin.gov

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contamination and yet utilizing materials that could augment the immune response represented a challenge in the development of most subsequent vaccines.

The additional materials found in vaccines have been a significant source of misunderstanding, and misinformation. Much of the controversy related to vaccine safety is a result of spurious associations between these vaccine additives and exaggerations of real, or perceived, side effects from immunization. While a few of these chemicals can be toxic in large quantities, most are only present in trace amounts in most vaccines. An exhaustive listing of all vaccine additives is beyond the limits of this book, and substances such as sodium chloride, phosphate dehydrates, calcium carbonate, sucrose, lactose, and amino acids are not discussed. This chapter reviews some of the more common or controversial vaccine excipients, and related information regarding safety concerns.

Preservatives

Preservatives are substances added to vaccines during formulation to prevent unintentional bacterial or fungal growth and thus contamination [3]. Such contamination is considered undesirable due to the risk of either exotoxin or endotoxin production in containers and subsequent introduction into hosts, and soft tissue abscess formation or even sepsis after injection. Besides the use of standard licensed antibiotics, the US Food & Drug Administration (FDA) has licensed four other preservatives for use in vaccines distributed in the USA. These include thimerosal, 2-phenoxyethanol, phenol, and benzethonium chloride (Phemerol).

Thimerosal

Thimerosal is an organic, ethyl mercury-containing compound with broad antimicrobial activity that has been used since the 1930s as a vaccine preservative [3, 4]. While thimerosal-containing vaccines included only a minute amount of ethyl mercury, in the late 1990s concerns were raised that multiple vaccine injections may exceed Environmental Protection Agency (EPA) guidelines on acceptable mercury exposure for small children relative to their weights. However, these estimated health risks were based on methyl mercury toxicity studies, despite the fact that ethyl mercury differs markedly from methyl mercury, a known and well-studied neurotoxin [5]. Nonetheless, the FDA Modernization Act of 1997 required an FDA review of risk for all mercury containing foods and drugs.

US federal agencies (EPA, FDA, and the Agency for Toxic Substances Disease Registry (ATSDR)) responsible for developing guidelines regarding environmental exposures to potential toxins established differing standards for mercury and infants. Much of the discrepancy seems to be related to either a lack of data or interpretations of available data. The most stringent standards came from the EPA, which permitted a range for infants <6 months of only 65–106 μg, depending on the child's weight.

The least stringent guidelines were from the FDA, where a range from 259 to 425 μg was allowed depending on infant body weight [3]. While no individual vaccine came close to these amounts, calculations suggested that in the late 1990s an infant could have received a cumulative mercury dose of 187.5 μg by age 6 months [6].

It is important to acknowledge that the acceptable levels of mercury for infants and children were actually derived from extrapolations of data on the effects of mercury on fetuses of pregnant women exposed to large quantities of methyl mercury. While this included information from the Faroe and Seychelles islands [7] most of the data were from an incident in Iraq. In October 1971, a large quantity of grain was imported into Iraq that was contaminated by massive amounts of methyl mercury. This grain was subsequently used to make bread, and consumption resulted in over 6,000 hospitalizations and 450 deaths. The frequency of neurologic abnormalities in the children born to these women and the amount of mercury found in the mother's hair was used to create an estimate of acceptable environmental mercury exposure for children [6, 8, 9].

After review, the FDA recommended that thimerosal be removed as a precautionary measure [6]. Two years after the FDA's decision, the American Academy of Pediatrics (AAP), the US Public Health Service (USPHS) and other stakeholders released statements supporting the decision to remove thimerosal from pediatric vaccines [9]. Although no attributable risk to humans from thimerosal had been identified, most manufacturers agreed to voluntarily reduce or eliminate thimerosal in most vaccines marketed in the USA (and many other countries) as a precautionary measure. This change was largely achieved by switching from multidose vial presentations that had some risk of contamination due to repeated accessing, to single-dose vials and prefilled syringes [2, 9].

Unfortunately this switch was widely perceived by the media and some members of the public as a concession by industry, regulators and the medical community that thimerosal could represent a neurotoxin. In conjunction with the controversies generated by Andrew Wakefield's claims that MMR vaccine caused "autistic enterocolitis," [10] concerns about thimerosal fueled public doubts about vaccine safety.

Difference Between Ethyl Mercury and Methyl Mercury

Besides the usual safety studies done for FDA-licensure that are required to monitor for short- and long-term issues from immunizations, many studies have been performed to specifically understand ethyl mercury and thimerosal-containing vaccines, and examine characteristics of distribution and excretion, as well as potential toxic effects on various organs. When investigators compared blood mercury levels of full-term infants who received thimerosal-containing vaccines, they found that there was no mercury measured that sustained above levels considered unusual or dangerous compared to infants not vaccinated with thimerosal-containing vaccines [11, 12]. Interestingly, Pichichero et al. were also able to demonstrate that vaccine-associated mercury is effectively cleared and excreted in both normal and preterm infants through stool and urine.

Studies comparing blood and brain mercury levels in infant monkeys exposed to methyl mercury, or vaccines containing thimerosal, suggest that methyl mercury is not a suitable reference for risk assessment from exposure to thimerosal-derived mercury. Although the initial distribution volume of total mercury is similar for the two groups, thimerosal is cleared from the infant monkeys much more quickly than methyl mercury [13]. Even if access to the brain cells were the same for ethyl and methyl mercury, ethyl mercury decomposes faster than methyl mercury, suggesting less potential neurotoxicity than for ethyl mercury [5]. Experiments in rats and mice exposed to high levels of mercury indicate that brain levels of total mercury in the animals were significantly lower with ethyl mercury while inorganic mercury levels in kidneys were higher [5, 14]. Methyl mercury is transported across the blood–brain barrier via an active transport system, whereas ethyl mercury is not. Thus methyl mercury is far more likely to cause nervous system toxicity [14–16].

While these findings and others have demonstrated a substantial difference between ethyl mercury and methyl mercury, fear of their similarities and a perceived link to neurodevelopmental issues has been a source of confusion leading to vaccine hesitancy.

Fear of Autism Due to Ethyl Mercury in Thimerosal

It has been well documented that whole-cell DPT vaccines could induce seizures, and occasional encephalopathy. Most vaccines can cause fevers, and in occasional children therefore trigger febrile seizures. Combined with the increasing recognition of autism-spectrum disorders in the early 1990s, some proposed a link between vaccines and neurodevelopmental disorders. With the knowledge that exposure to high-doses of *methyl* mercury could cause neurologic symptoms, even in adults, the presence of a mercury-containing compound in vaccines seemed concerning to some.

A purported "proof" was initially published in a non-refereed publication [17] and mistakenly thought to represent a scientific publication by the media and public. However, others in the scientific community had also hypothesized a relationship between autism among children and thimerosal-containing vaccines [18, 19]. While these same groups attempted to identify an epidemiologic link, there appear to be no valid studies showing that children exposed to vaccines containing mercury have higher rates of autism than children with less or no exposure [20]. In fact, using a variety of study designs (cohort, case–control, and ecologic), investigators have concluded that there is no association between thimerosal-containing vaccine use and autism.

A thorough review and meta-analysis of articles published between 1966 and 2004 that addressed an association of thimerosal and autism-spectrum disorders identified 12 papers, with 10 being epidemiologic assessments. Here Parker et al. enumerate the substantial methodological issues and design flaws in studies that claimed to identify a link [21]. In this review, it is clear that there is neither a biologic plausibility for an association, nor any evidence of a link between thimerosal and autism spectrum disorders.

Evidence of no Association Between Thimerosal-Containing Vaccines and Autism

A population-based cohort study of 467,450 children in Denmark compared those vaccinated with thimerosal-containing vaccine to children vaccinated with thimerosal-free vaccines. This study found no causal relationship between childhood vaccination with thimerosal-containing vaccines and autism spectrum-disorders [22]. More conclusively, Ip et al. compared mercury levels between autistic children and controls using a cross-sectional cohort design. The authors found no significant differences between hair and blood mercury levels obtained from the two groups [23]. Investigators in Quebec, Canada assessed for associations between immunizations and pervasive developmental disorders (PDD) among 22,749 children. They concluded that thimerosal exposure was unrelated to PDD, including autism [24]. They suggested that factors such as broadening diagnostic criteria, improved awareness about the disorders, and improved access to services are the primary source of increased prevalence of PDDs. Such factors were confirmed when US school utilization data were analyzed, and in addition, issues related to diagnostic substitution were identified as significant contributors to rising rates of autism and other PDD [25].

No Decrease in Autism Prevalence After Thimerosal Removal from Vaccines

Finally, if there was a true association between thimerosal-containing vaccines and autism spectrum disorder, both the incidence and prevalence rates of autism should have shown evidence of decline in immunized populations after thimerosal removal from vaccines, as well as in unimmunized populations. However, autism remains prevalent and in many areas continues to be increasingly recognized. Another study in Denmark showed negative ecological evidence from a population-based data. Even among children born after thimerosal removal in vaccines, autism incidence continued to increase [26]. Another study done in California's developmental services system showed, despite the exclusion of thimerosal from vaccines in any amounts other than trace levels, a continuing increase in autism prevalence [27].

Thimerosal Content of Currently Available Vaccines

Vaccines currently marketed in the USA now have markedly reduced amounts of mercury, as shown below in Table 11.1. Most of the remaining thimerosal represents trace amounts introduced during the manufacturing process.

Table 11.1 Thimerosal content in currently manufactured US vaccines (FDA list of vaccines and their thimerosal content currently manufactured in the USA) [Adapted from FDA's Web site] [28]

Vaccines	Trade name	Manufacturer	Thimerosal concentration	Mercury
Influenza	Alfuria®[a]	CSL Limited	0 (single dose) 0.01 % (multidose)	0/0.5 mL (single dose) 24.5 μg/0.5 mL (multidose)
	Fluzone®[a]	Sanofi Pasteur	0.01 %	25 μg/0.5 mL dose
	Fluvirin®[a]	Novartis	0.01 %	25 μg/0.5 mL dose
	Fluvirin®[a] (Preservative Free)	Novartis	<0.0004 %	<1 μg/0.5 mL dose
	FluLaval®	D Biomedical Corporation of Quebec	0.01 %	25 μg/0.5 mL dose
Japanese Encephalitis	JE-VAX®	Biken/Sanofi Pasteur	0.007 %	35 μg/1.0 mL dose 17.5 μg/0.5 mL dose
Meningococcal	Menomune® A, C, AC and A/C/Y/W-135	Sanofi Pasteur	0.01 % (multidose) 0 (single dose)	25 μg/0.5 mL dose 0
TT	No trade name	Sanofi Pasteur	0.01 %	25 μg/0.5 mL dose
DT	No trade name	Sanofi Pasteur	<0.00012 % (single dose)	<0.3 μg/0.5 mL dose
		Sanofi Pasteur	0.01 %	25 μg/0.5 mL dose
Td	No trade name	Mass Biologics	≤0.00012 %	≤0.3 μg mercury/0.5 mL dose
	Decavac®	Sanofi Pasteur	≤0.00012 %	≤0.3 μg mercury/0.5 mL dose
DTap	Tripedia®[a]	Sanofi Pasteur, Inc	≤0.00012 %	≤0.3 μg/0.5 mL dose
HepA/HepB	Twinrix®	GlaxoSmithKline Biologicals	<0.0002 %	<1 μg/1 mL dose

[a]Routinely recommended vaccines for children aged 6 and under in the USA. All other vaccines routinely recommended for this age group are free of thimerosal

2-Phenoxyethanol (2-PE)

2-Phenoxyethanol is a preservative used to stabilize vaccines and currently found in US licensed vaccine formulations of IPV, some Hepatitis A formulations, diphtheria and tetanus toxoids and acellular pertussis vaccines [29]. Study has shown that it would be a reasonable preservative for Prevnar13® in a multidose formulation to reduce contamination [30]. Numerous toxicology studies have been done with 2-PE, and no animal-based studies demonstrated any neurotoxic properties, even at high levels of exposure. Besides allergies, toxic effects are rare in humans and thus the preservative is used in various cosmetics and pharmaceutical products [31]. Patch testing can be done to detect if someone is allergic to 2-PE [32]. There has

been a generalized contact eczema described in a single case after receiving DTP vaccine [33]. Other than this one reported case of contact eczema, 2-PE is widely used without any adverse events.

Phenol

Phenol is an antibacterial vaccine preservative used in the manufacturing of a variety of vaccines, including pneumococcal polysaccharide, typhoid inactivated, influenza, and vaccinia vaccines. Phenol red (phenolsulfonphthalein) is also used as a pH indicator and dye in rabies and rotavirus vaccines.

Phenols are naturally occurring substances, most commonly produced by plants and plant decomposition, but also in chemical reactions occurring in the environment. They are used or produced in a wide array of industrial settings, including pesticides, oil, glue and steel manufacturing, paper processing, and as a disinfectant for medical equipment. They have been documented to accumulate in water tables leading to pollution issues near many of these same industrial plants [34]. While they are used as antiseptics and disinfectants, they are also found in mouthwash and throat lozenges. In the typical quantities seen in most environments, they quickly degrade either in air or water [35].

Most human exposure occurs through occupational settings and from cigarette smoke, but also occurs by simply breathing air or drinking water. Phenols can irritate the skin at high concentrations, and in large exposures can cause organ damage. Toxicity is largely dependent on the organic compound form, with increasing hydrophobicity leading to increased cellular penetration and more damage. Extremely large-scale phenol exposures were documented to have caused neurotoxicity, and even death at doses between 30 and 60 g, with a minimum lethal dose at about 70 mg/kg [34]. Some forms are considered carcinogenic, and employees exposed to high doses for long periods in pesticide and vinyl plants have been found to have increased risk for liver and lung cancers, and some lymphomas [36].

Given this history, some vaccine-hesitant groups have recommended avoidance of immunization due to concerns about the presence of these chemicals. However, as with most of the other contents of FDA-approved vaccines, the extremely small concentrations present do not even approach the scale of exposure to consider these toxigenic.

Phenol preservative forms in vaccines are found in concentrations of less than 0.25 %, or a total amount of less than 250 μg [7]. While these are approximately the same amounts or concentrations seen in the natural environment around some industrial areas, the formulations used in vaccines are the less toxic, naturally occurring, less hydrophobic forms, similar to those used in medicinal preparations. In addition, the total quantity delivered in all the vaccines containing any constitutes no more than a sip of water. Animal models suggest that neurotoxicity would require repetitive doses with at least 1.8 mg/kg/day, and even greater doses for clinically evident hematological or other organ effects [35]. It seems that the small amounts contained in vaccines are innocuous [34].

Benzethonium Chloride (Phemerol)

Benzethonium chloride is categorized as a cationic detergent, and is a synthetic derivative of ammonium chloride. It is used as a wound disinfectant and cleaning agent, and is found in spermatocides and mouthwash. Large ingestions of 1–3 g cause gastrointestinal symptoms and can cause necrosis superficially when concentrated exposure occurs. Benzethonium chloride does not appear to be absorbed or to cause any systemic symptoms at lower concentrations, but is still bactericidal at concentrations of 1:1,000. It can occasionally cause contact hypersensitivity [37].

Antibiotics

Antibiotics are often used to prevent bacterial contamination during vaccine manufacturing and packaging [38]. The selection of antimicrobial preservative is based on antimicrobial activity, effects on the active antigenic ingredient, and the preservative dose needed to ensure sterility [39]. The most commonly used antibiotics are *neomycin, polymyxin B, streptomycin, chlortetracycline,* and *amphotericin B* [3]. Neomycin is the only antibiotic that is found in detectable amounts in the final vaccine products while others are present at levels that are essentially trace or non-detectable.

Neomycin is currently found in MMR, rabies, smallpox, hepatitis A, and varicella-containing vaccines, as well as in most combination vaccines (e.g., DTaP-IPV-Hib, DTaP-HepB-Hib, DTaP-IPV). Amounts range from trace detectable to 0.025 mg [7].

There are two main issues raised regarding antibiotic use in vaccines. One is the fear of possible allergic reactions and the other is concern about possible antimicrobial resistance through antibiotic "pressure" on normal colonizing bacterial flora.

Fear of Allergic Reactions

Antibiotics administered enterally or parenterally can certainly cause systemic hypersensitivity reactions. However, antibiotics delivered intradermally, subcutaneously, and intramuscularly can cause contact dermatitis and/or immediate-type hypersensitivity reactions. Due to the small amount of antibiotics contained in vaccines, these injections are generally unlikely to cause systemic hypersensitivity reactions, and such reactions are monitored during vaccine testing. While reports of significant hypersensitivity reactions are rare, patients with anaphylactic reactions to topical or systemic neomycin should not be vaccinated with vaccines that contain neomycin [40]. Topical neomycin is known to cause contact dermatitis, but the amount of neomycin found in vaccines has not been shown to cause delayed-type

hypersensitivity reactions. Therefore vaccines may be given to persons with delayed type sensitization to neomycin [41, 42]. The antibiotics most likely to cause hypersensitivity reactions are β-lactams and sulfa-based. No vaccines currently licensed in the USA contain penicillin or its derivatives, nor any sulfa-based antibiotics [43].

Fear of Antimicrobial Resistance

While antibiotics are used in vaccine production and are present in the final vaccine, these represent either very small amounts or are undetectable. These quantities do not represent sufficient amounts to obtain serum or tissue levels that would have any activity against any bacterial flora regardless of colonizing location—gastrointestinal, cutaneous, or pharyngeal. Without such antibiotic "pressure," at least approaching the minimum inhibitory concentration (MIC) for an organism, the risk of resistance being produced is negligible.

Adjuvants

Vaccine adjuvants are substances that are added to vaccine formulations to increase the immunogenicity of vaccine antigens. While a wide variety of substances have been studied and found to boost immunologic responses to vaccines, aluminum-containing adjuvants are the only ones FDA-approved for use in the USA. Current licensed adjuvants used in US manufactured vaccines include primarily aluminum salts, but a recent addition has been Adjuvant System 04 (AS04) [43]. While such adjuvants were initially thought to slow the elimination of antigens from tissue, it appears more likely that they act by enhancing the uptake of antigen by cells involved in immunologic processing, and enhance the immune responses. While aluminum adjuvanted vaccines are more immunogenic, they are also known to cause more local reactions at the injection site. These may include erythema, swelling, granulomas, and even hypersensitivity [3].

Aluminum Salts

Aluminum adjuvants have been used for over 80 years in vaccines, with hundreds of millions having received doses. The variations of aluminum products used include aluminum hydroxide, aluminum phosphate, and aluminum potassium sulfate (or alum) [44]. Aluminum-based adjuvants are potent immune system stimulators [45–47].) The Food and Drug Administration (FDA) has determined that aluminum used as food additives and medicinals such as antacids are generally safe [48].

Table 11.2 Quantity of Aluminum in US licensed vaccines [3, 7]

Vaccine	Dose
Pneumococcal conjugate	0.125 mg/dose
Diphtheria-tetanus-acellular pertussis (DTaP and Tdap)	<0.17 to <0.625 mg/dose
Haemophilus influenzae type b (Hib)	0.225 mg/dose
Hib/Hep B vaccine	0.225 mg/dose
Hepatitis A vaccine (Hep A)	0.225–0.25 mg/dose (pediatrics) 0.45–0.5 mg/dose (adults)
Hepatitis B vaccine (Hep B)	0.225–0.5 mg/dose
Hep A/Hep B vaccine	0.45 mg/dose
DTaP/IPV/Hep B vaccine	<0.85 mg/dose
DTaP/IPV/Hib vaccine	0.33 mg/dose
Human Papillomavirus (HPV) vaccine	0.225 mg/dose
Ixiaro®	250mcg
DTaP-IPV	≤0.6 mg

The adjuvant aluminum is present in US childhood vaccines that prevent hepatitis A, hepatitis B, diphtheria-tetanus-pertussis (DTaP, Tdap) *Haemophilus influenzae* type b (Hib), human papillomavirus (HPV), and pneumococcal infection.

The quantity of aluminum contained in these vaccines is shown in Table 11.2.

Childhood vaccines used in the USA that do not contain adjuvants include live attenuated viral vaccines against measles mumps rubella, chickenpox, and rotavirus, and inactivated vaccines against polio (IPV) and seasonal influenza. However, some combination vaccines that include IPV do include aluminum adjuvants.

Fear of Aluminum-Containing Vaccines

Large amounts of aluminum have been shown to cause serious neurologic disorders in humans [49]. There is some evidence suggesting an association between aluminum exposure through food and drinking water (at levels markedly exceeding exposure levels from vaccines) and the development of Alzheimer's disease [50, 51]. Another recent study showed that tissue biopsies in patients with Macrophagic Myofasciitis (MMF) have aluminum residua within tissue, but there is no evidence that this resulted from aluminum-containing vaccines [52]. Based on this, and other evidence, the ATSDR has established guidelines quantifying acceptable exposure to aluminum.

It is also well established that aluminum-containing vaccines do cause more local reactions at the injection site. The most frequent reactions aluminum-containing vaccines produce in vaccine recipients are painful and itchy nodules at the injection site [53, 54]. Other than these minor side effects and rare, localized or systemic dermatitis due to hypersensitivity reactions to aluminum, there are no reported significant adverse systemic events after using aluminum-containing vaccines in humans.

However, concerns were raised when mouse animal model experiments did seem to demonstrate systemic reactions to adjuvants. These included immunologic phenomena, such as fever, arthritis, and uveitis [55]. Subsequent studies have suggested

that these animal models do not properly approximate humans, and no similar findings have been substantiated in human trials. But it is clear that adjuvanted vaccines do have more local side effects than non-adjuvanted vaccines. A meta-analysis comparing DTP vaccines with and without alum showed that children <18 months had nearly double the risk of local reactions, particularly erythema and swelling, at or near the injection site if immunized with an aluminum adjuvant product. Older children reported more pain at the site of injection but no significant induration or erythema. Most importantly, however, neither group demonstrated increased systemic reactions [56].

This combination of information has led to concerns about the safety of aluminum adjuvants though. Some families specifically request "aluminum free" vaccines, based on suggestions they find on the internet or in the lay press. During the Influenza A H1N1 outbreak of 2009–2010, there were concerns about vaccine supply and availability. When some manufacturers suggested that available antigen could be extended through the use of available adjuvants, there was significant resistance in many regions.

Evidence Showing No Harm

Aluminum is a ubiquitous element, to which infants are exposed continuously. The ATSDR's guidelines suggest that the safe amount of aluminum for oral ingestion by infants is 1 mg/kg/day [48]. A study that compared aluminum exposure from vaccinations among infants fed with breast milk and formula found that the quantity of aluminum ingested exceeds that contained in vaccines. In addition, the amount of aluminum intake through vaccines is far less than the levels considered safe in the ATSDR acceptable exposure guidelines [49]. Another study that evaluated aluminum levels in immunized infants demonstrated that the aluminum level in infants for either median or low-birth weight babies is far below the minimal risk level [52]. This study took into consideration the following parameters: current pediatric baseline vaccination schedule, baseline aluminum levels at birth, human aluminum retention function that incorporates glomerular filtration rates in infants, most recent minimum risk level (MRL) for aluminum, kinetics of aluminum efflux at the injection site, and current infant body weight data for children 0–60 months [52].

There are several studies that have demonstrated the safety of aluminum adjuvants in vaccines. As mentioned previously, a systematic review with meta-analysis done in 2004 concluded that, other than seeing more local reactions at the injection sites among both young and older children who received aluminum containing vaccines, there is no evidence that aluminum salts in vaccines cause any serious or long-lasting adverse events [56].

More importantly, it is evident that aluminum is chelated and excreted after being introduced into tissues. Studies in rabbits showed that, similar to what has been shown for mercury excretion, radiolabelled aluminum adjuvants given intramuscularly are gradually absorbed into blood over 28 days and do not remain either in the muscle or interstitium [57]. Subsequently, the material is then excreted.

According to the Global Advisory Committee on Vaccine Safety, at present there is no evidence of a health risk from aluminum-containing vaccines or any justification for changing current vaccination practices. However, they do suggest that more research is required to determine if there are links between macrophagic myofasciitis (MMF) and aluminum-containing vaccines [58].

Adjuvant Systems 04 (AS04)

The novel vaccine adjuvant AS04 is composed of aluminum hydroxide (Al (OH) 3) and 3-*O*-desacyl-4′-monophosphoryl lipid A (MPL). The MPL within AS04 enhances the initiation of the immune response through the activation of innate immunity, leading to an improved cellular and humoral adaptive immune response [59, 60].

AS04 is currently licensed for use in human papillomavirus (HPV) HPV-16 /18 (HPV2) vaccine in the USA. However, AS04 is used as an adjuvant for hepatitis B virus (HBV) and herpes simplex virus (HSV) vaccines in other countries, which are currently in development for introduction more broadly [61]. The only AS04-containing vaccine currently licensed for use in the USA is Cervarix® (HPV2).

As with all newly introduced products, there are concerns about the safety of AS04. However, several epidemiologic and case–control studies show that the adjuvant is safe and effective for use in protecting against HPV. A recent case–control study included an integrated analysis to evaluate the safety of AS04 adjuvanted vaccines with regard to adverse events of potential autoimmune etiology, and concluded that there was no association between AS04 adjuvanted vaccines and development of autoimmune disorders [61]. Another study assessing the clinical and nonclinical profile of AS04 concluded that other than injection site inflammatory reactions, there were no pertinent adverse reactions to AS04. Immune-mediated disorders were rare, and similar to the incidence rates noted for aluminum salt-adjuvanted vaccines [62]. Other studies investigating adverse reactions among patients who received AS04-adjuvanted vaccines found that other than local redness and soreness at the injection sites, there were no adverse reactions in patients [63–65]. Some of these studies included longitudinal follow-up in patients up to 21 months after receiving AS04-adjuvanted vaccines, and demonstrated no late development of complications.

Other Additives

Additives in vaccines are used to stabilize vaccine contents, especially the critical antigens, from adverse conditions. These can include freezing and heating, as well as the presence of other noxious substances. Several types of additives are used in vaccines. These include: sugars, amino acids, and proteins. Sugars and amino acids are used in stabilizing vaccines, primarily involving those with live active agents. Most controversy around vaccines additives are due to concerns about the presence of various proteinaceous materials.

Proteins

There are several issues raised when using protein additives in vaccine manufacturing: immediate type hypersensitivity reactions, theoretical concern that human serum albumin might contain infectious agents and that bovine-derived products could contain agents associated with "mad cow" disease (Bovine Spongiform Encephalopathy). The primary forms of proteins used in vaccine formulation include egg proteins and human serum albumin; however bovine derived materials include gelatin, enzymes, serum and amino acids [3].

Egg Proteins

Egg proteins are used as stabilizers in manufacturing vaccine, but can also be introduced during the culturing process for both influenza and yellow fever viruses. In terms of allergic reactions to vaccines, hen's egg allergy is one of the most discussed topics among vaccine hesitant individuals. Much of the concern appears to arise from an over-estimation of the frequency of egg allergy. Ovalbumin, the main protein in egg whites, has been thought to be primarily responsible for allergic reactions among those with egg-allergies. Egg allergies occur in approximately 5 % of atopic children and 0.5 % of the population [3].

Vaccines that currently contain egg proteins include MMR, influenza, tick-borne encephalitis, herpes simplex, yellow fever, and rabies vaccines. Influenza and yellow fever vaccines are propagated in allantoic sacs of chick embryos, where egg proteins are present in the final product in highest amounts [3, 66]. MMR vaccines however, are propagated in chick embryo fibroblasts, making the residual egg protein content significantly less than that in influenza vaccines; the quantity of egg protein in MMR vaccines is about 500 fold less than the amount found in influenza vaccines [3]. In fact, the majority of life threatening allergies among children who received MMR vaccines are suspected to be due to gelatin or neomycin contained in the vaccines, rather than egg allergy [66]. Skin testing for egg allergy is not predictive of possible MMR vaccine reactions.

Updated recommendations and methods for safely administering egg-protein containing vaccines for children with egg-allergies have been recently modified, as there is increasing evidence that egg-allergies are over-estimated. In addition, safety data suggest that children with mild-to-moderate allergies can safely receive influenza vaccine due to the low amounts of ovalbumin contained in current versions of the vaccines [67, 68]. Children with mild or moderate egg-allergies are now recommended to receive trivalent-inactivated influenza vaccine routinely. Children with severe allergies still require careful monitoring and should be managed by a specialist, but it is clear that such children are quite rare [15].

Table 11.3 Gelatin content of vaccines licensed in the USA, 2008 [3, 7]

Vaccine	Trade name	Quantity (per dose)
DTaP	Tripedia®	0.0015 mg
Influenza	Fluzone®	≤0.025 mg
	Flumist®	2 mg
Measles, Mumps, Rubella	MMR II®	14.5 mg
Varicella	Varivax®	12.5 mg
Shingles	Zostavax®	15.58 mg
Japanese Encephalitis	JE-Vax®	500 mcg
Rabies	RabAvert®	<12 mg
MMRV	ProQuad®	11 mg
Yellow Fever	YF-Vax®	Contaminant level[a]
TriHIBit®	TriHIBit®	Contaminant level[a]

[a]Contaminant level per dose means below detectable amount

Gelatin

Gelatin is an animal protein, which can be derived from swine or cattle tissue, and is used primarily as a stabilizer in attenuated viral vaccines. Amounts of gelatin used vary from vaccine to vaccine. Table 11.3 lists various vaccines licensed in the USA with their gelatin quantity.

Fear of Allergic Reactions to Gelatin

Hypersensitivity to gelatin is the most common form of immediate-type hypersensitivity reactions caused by gelatin-containing vaccines, and the most common cause of concern [15, 69]. However, the incidence of anaphylaxis to gelatin is very low, approximately one case per two million doses [3]. If children have had previous allergic reactions to gelatin-containing foods or vaccines, precautions and evaluations must be performed to avoid systemic reaction. Discussion with an allergist or immunologist is generally recommended before gelatin-containing vaccine administration.

Concerns About Theoretical Risk of Mad Cow Disease from Bovine-Derived Agents

Some vaccines contain gelatin that is derived from cows, or have bovine serum albumin in some of the manufacturing processes. By 2000, both humans and cows were being identified as having a progressive deterioration of the central nervous system, found to be caused by a transmissible prion. Because of concerns regarding the identification of variant Creutzfeldt-Jakob disease (vCJD), or mad cow disease, in humans, and recent increase in vCJD, in 1993 the FDA prohibited the use of bovine-derived materials obtained from countries with known mad cow disease

infected cattle. Because some of the gelatin used in vaccines is bovine-derived, there was fear of the theoretical risk of being exposed to mad cow disease [70].

There has not been any proven link between vCJD and vaccination [3, 71]. It would seem that there is little reason to suspect any risk from vaccines that involve bovine products in manufacturing, though. It is likely that humans who develop vCJD have ingested bovine neural tissue, in substantial quantities, which is not included in any of the materials used in vaccine manufacture [7].

Yeast

Saccharomyces cerevisiae, commonly known as brewer's or baker's yeast, is used in preparation of recombinant hepatitis B vaccines as well as HPV vaccines [72]. The yeast protein in the final vaccine product can cause allergic reactions to yeast-sensitive patients. The occurrence of anaphylactic reaction following hepatitis B vaccination is rare, 1.1 per million doses; however precaution should be taken with those that have experienced any allergic symptoms previously [73]. Generally, the benefits of receiving hepatitis B or HPV vaccine far outweigh the rare occurrence of allergic reactions to yeast-containing vaccines.

Human Serum Albumin

Concerns about the use of human serum in the production of vaccines is related to the possibility of transmitting infectious agents, such as HIV, Hepatitis B, Hepatitis C, or other pathogens. Human serum is only required in a limited number of vaccines, primarily those involving measles, mumps, and rubella products, but also in some rabies and smallpox vaccines [7]. Most manufacturers have moved to using a recombinant version of human albumin to avoid such issues.

For those vaccines still utilizing donated human blood as the source, the FDA requires that human serum albumin only be used from screened donors and processed in a manner similar to intravenous immunoglobulin, to eliminate any risk of viral pathogen transmission. There are no reported cases of viral transmission related to human albumin products, and certainly none related to immunization [3].

Other

Formalin

Formaldehyde, also known as formalin, is used to inactivate live organisms for inclusion in vaccine products. As with other excipients, there is a minimal amount of formalin present in the final products. Formaldehyde inactivation is primarily

utilized in the production of viral vaccines, especially influenza, polio, and hepatitis A. However, there are also trace amounts detectable in some *Haemophilus influenzae* type b, diphtheria, and tetanus toxoid vaccines [3, 7].

Some investigators have suggested that formalin inactivation may not represent the ideal technique for this process, as it can alter the composition of antigens. For example, pertussis toxin treated with formaldehyde did not seem to affect antibody levels, but did seem to affect the neutralizing activity of those antibodies [74].

Formaldehyde occurs naturally in the environment, and is also released after combustion of organic materials such as burning wood or smoking tobacco, as well as from motor vehicle emissions. Formaldehyde is actually a normal metabolite found in all mammalian cells, and does not appear to be stored in tissues. It is important in the synthesis of normal nucleotides [3]. There is probably more than 2,000 μg/ml circulating in the blood of an average person at any given time [75]. Formalin is rapidly metabolized to formate, which is either metabolized to carbon dioxide or excreted through urine as formic acid [76].

The primary source of exposure concern is from occupational activities, especially in the processing of lumber and adhesives. Toxicity generally occurs from either dermal exposure or inhalation, and it can be irritating to both skin and the respiratory tract [76, 77].

However, most safety concerns regarding the use of formaldehyde have focused on documentation of potential DNA damage from high concentrations, and the risk of induced malignant cellular division [78]. In situations where the local detoxification process could be overwhelmed, carbonyl groups from the formalin molecule can react with nucleophilic sites on DNA [79].

Fortunately this does not appear to be a pertinent concern related to immunizations, due to the small quantities of formalin in currently licensed vaccines. These vaccines contain up to 100 μg of residual formaldehyde, which for a 10 kg child would represent only 10 μg/kg of exposure in *one day*. Guidelines currently suggest that daily ingestion of up to 200 μg/kg/day of formaldehyde does not represent any risk of deleterious effects *during a person's lifetime* [7, 79].

Latex

Natural latex rubber is used to produce materials such as medical gloves, catheters, syringe plungers, and vial stoppers. The most common known form of latex allergy occurs when a person experiences prolonged contact with latex-containing gloves or items. However, latex stoppers are found in some vaccine presentations, mostly related to multidose vials. While the amount of latex exposure is extremely small, a patient with latex allergy could mount a hypersensitivity response to a vaccine involving such a stopper. In fact, there have been rare allergic reactions in individuals who received hepatitis B vaccine [80] and latex allergies associated with injection procedures have been described among patients with diabetes mellitus [80–84].

However, contact allergy to latex is neither a contraindication nor a precaution to the use of quadrivalent meningococcal conjugate vaccine (MCV4) in the absence of an anaphylactic allergy [85]. For latex allergies other than anaphylactic allergies (e.g., a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain dry, natural rubber or natural rubber latex may be administered [85].

Conclusion

The development and manufacture of vaccines is a complicated process. To achieve the best possible immunogenic response, with the safest product possible, requires intensive investigation. To achieve this, a variety of excipients are required, to maintain sterility and augment immunologic responses.

It is important to recognize that FDA-approval of all new vaccines involves not only assessment of the antigens and final contents, but the entire process of synthesis. Each and every component introduced and used in the manufacture is scrutinized. While there are a wide array of excipients required to either manufacture, package or deliver effective immunity, each of these is part of this approval process.

While most of these excipients exist naturally in nature, some of these materials can also be toxic to humans with high-level exposure. It is understandable why people may be concerned after reading the ingredients contained in vaccines administered to infants and children. However, the critical part of understanding whether there is true risk is to recognize that for all materials, there is a toxic dose and an acceptable level of exposure below which there is little risk. The problem for most people is trying to understand the quantity and scale of the exposures.

Fortunately, vaccines contain minimal amounts of most of these excipient materials. In addition, the majority of these additives present little risk even were they to be present in more significant quantities. It should be reassuring to both parents and practitioners that academic researchers and industry investigators continue studying these excipients, so as to continue to improve the final products.

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Chapter 12
Perceived Risks from Live Viral Vaccines

Alice Pong and Mark Sawyer

Introduction

The challenge in the development of live virus vaccines, is achieving a balance between inducing a strong enough immune response to protect against wild type infection and minimizing vaccine-related adverse effects. In the case of live virus vaccines, insufficient attenuation of vaccine strains can lead to symptomatic disease and in some cases, the virus can even revert back to its more virulent parent strain. Rigorous prelicensure testing of vaccines makes the risk of developing significant disease extremely low and symptoms are significantly less severe than those associated with natural infection. However, the idea that the vaccine itself may cause any illness discourages many individuals from being vaccinated. This is especially true in developed countries for diseases such as measles and mumps, that are uncommonly seen and disease sequelae are not fully appreciated by the general population.

Because live virus vaccines contain the viruses responsible for disease, albeit attenuated strains, it is expected that there will be effects from the vaccine similar to those caused by the parent virus. Prelicensure studies are performed to assure these adverse effects are recognized and weighed against the benefit derived from preventing wild type illness. Rare adverse effects may not be detected during prelicensure studies and post marketing surveillance is performed to detect these conditions. If an increase in a specific event is noted, further studies are done and may lead to changes in vaccine recommendations. An example of this is an increased rate of intussusception noted during post marketing surveillance of the first rotavirus vaccine licensed in 1999. Further evaluation led to withdrawal of the vaccine within 1 year of licensing.

A. Pong, M.D. (✉) • M. Sawyer, M.D.
Division of Pediatric Infectious Diseases, University of California San Diego,
Rady Children's Hospital San Diego, San Diego, CA, USA
e-mail: apong@rchsd.org

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Some of the perceived risks associated with vaccination are related to temporal associations and have not been shown to be due to the vaccine. Concerns of the measles vaccine causing autism is an example.

Finally as with many vaccines, poor acceptance of the vaccine may have less to do with side effects from the vaccination, and more to do with perceived lack of appreciation of the harm the vaccine preventable disease can cause. This is certainly the case with varicella, rotavirus, and influenza where many people who have had the disease and "lived through it" do not see a need to for a vaccine to prevent these illnesses in their children. This chapter discusses real and perceived issues associated with the more widely used live viral vaccines.

Live Attenuated Influenza Virus Vaccine

Influenza causes an acute respiratory illness characterized by fever, cough, and myalgia. Influenza can be complicated by central nervous system involvement, myocarditis, and primary viral and secondary bacterial pneumonia. Central nervous system complications, particularly in children have been reported by a number of centers [1–3]. One hundred forty-eight patients with encephalitis were reported from Japan during the 1998–1999 influenza season [2]. Approximately 82 % were in children less than 5 years old and a third of patients presented with seizure or coma with the onset of fever. Death was reported in 31.8 % and neurologic sequelae in 27.7 % of patients.

Two main types of influenza viruses cause human disease, influenza A and influenza B. These RNA viruses mutate frequently leading to changes in the strains that circulate every winter. The strains are characterized by differences in the hemagglutinin (H) and neuraminidase (N) proteins. Minor changes to the H and N proteins are referred to as antigenic drift. When there are major changes to the H or N proteins, this is referred to as antigenic shift. The severity and extent of any given influenza season is related to the circulating strains of virus and the immunity of the population to circulating strains. During pandemic years (associated with antigenic shift), there can be little or no immunity in the population to the strains of virus circulating. Influenza viruses cause significant morbidity and mortality every winter. Thompson et al. [4], estimated an annual average of 23,607 (3,349–48,614) influenza-associated deaths in the USA between 1976 and 2007 with 89.4 % reported in adults ≥65 years of age. Risk factors for severe influenza include underlying chronic disease including asthma and diabetes, immunocompromised state, age <5 years, and age ≥65 years. The highest morbidity and mortality with seasonal influenza is seen in adults ≥65 years; however, this can change depending on the immunity of the population to a given strain. During the 2009 H1N1 pandemic, higher percentages of severe disease were seen in young patients with lower percentages seen in persons ≥65 years [5]. Pediatric deaths associated with influenza have been reportable in the USA since 2004. CDC data report 47–88 deaths annually for all years except for the 2009 H1N1 pandemic year when there were 300 [6].

Influenza vaccine is a trivalent vaccine that includes two influenza A strains (usually an H1N1 and H3N2) and an influenza B strain. The specific strains are determined based on virus strains recently circulating in the global community. Influenza vaccination with inactivated virus vaccine has been available since 1945. The inactivated vaccine (TIV) has varying degrees of efficacy depending on what is measured and how well vaccine strains match circulating virus. The live attenuated intranasal vaccine (LAIV) was approved for children and adults age 5–50 years in 2003. This age cutoff was dropped to 2 years in 2007 [7]. One of the main benefits of the live attenuated vaccine over the inactivated vaccine is needleless administration. The vaccine is administered via nasal spray. LAIV is immunogenic for influenza A H3N2, H1N1 and influenza B virus strains as well as efficacious. In one pediatric trial during the 1996–1997 influenza season, 14 of 1,070 vaccinated children developed influenza following vaccination compared to 95 of 532 in the placebo group and symptoms were milder in vaccinated patients [8]. The vaccine was further studied in 7,852 patients 6–59 months of age and compared to inactivated vaccine during the 2004–2005 influenza season. In this study 153/3,916 cases of influenza were seen in the LAIV group compared to 338/3,936 cases of patients receiving TIV. There were lower numbers of influenza cases in LAIV recipients caused by the three virus types covered by the vaccine [9]. The vaccine was also shown to have improved cross-reactivity to drifted vaccine strains, thus potentially providing improved cross-protection to related virus strains [910]. Vaccination with LAIV has also been associated with decreases in influenza-related otitis media [10]. Interestingly the vaccine has not been noted to be more efficacious than TIV in adult populations [11, 12] and one study showed superior efficacy of TIV [12]. As with the inactivated (TIV) vaccine, previously unimmunized children <9 years of age are recommended to receive two doses of LAIV at least 4 weeks apart. Unlike children >9 years and adults, younger children who have not been vaccinated before have an inadequate response to a single dose of vaccine but almost all respond to two doses [6]. LAIV is not recommended for patients with asthma, chronic underlying disease, or immunosuppression [6] although there are data that LAIV may be safe for older children with asthma [13].

Side effects associated with LAIV include fever (1–5 %), sore throat, runny nose, and other upper respiratory symptoms [8–11]. Wheezing was noted in children 18–35 months of age in 1 study [14] and in a later study there was a higher rate of wheezing post vaccination in LAIV recipients compared to TIV recipients primarily in children less than 24 months [9]. Another study in Europe which also found superior efficacy of LAIV over TIV did not find a difference in the incidence of wheezing post vaccination [15]. The reason for the possible increase in post vaccination wheezing is unclear and currently the vaccine is not recommended in the USA for children under 2 years of age.

Transmission of vaccine virus from vaccinated patients to contacts is low. One study evaluated 197 children in a day care setting. Although 80 % of LAN vaccinated children shed virus for 2 weeks after vaccination, there was only 1 confirmed vaccine strain isolated from an asymptomatic contact [16]. The Advisory Committee on Immunization Practices (ACIP) and Hospital Infection Control Practices

Advisory Committee (HICPAC) recommend contacts to severely immunocompromised patients such as bone marrow transplant patients, to either receive TIV vaccine or avoid contact with such patients for 1 week following LAIV vaccination. Contacts to patients with lesser degrees of immunosuppression including HIV patients and neonates, can receive LAIV [6].

Measles–Mumps–Rubella Vaccine

Measles

Measles (Rubeola) is a disease responsible for significant mortality worldwide with 164,000 deaths reported in 2008 [17]. Prior to vaccine use, estimates were much higher at 5–8 million per year [18]. Complications of measles infection include encephalitis with subsequent brain damage, and pneumonia. Measles can also cause a rare subacute sclerosing panencephalitis that becomes symptomatic years after the initial measles infection and causes unremitting gradual neurodegeneration [19].

In the USA, prior to routine vaccination, the average annual number of reported measles cases was 530,217 cases with 440 deaths per year [20]. The majority of patients developed disease in early childhood. Measles is caused by the rubeola virus which is highly contagious and spread through small droplets. Rates of measles dropped significantly after licensing of the measles vaccine in 1963 [20].

The first measles vaccine licensed was an inactivated Edmonston strain vaccine in 1963. Unfortunately, this vaccine was associated with short-lived immunity and when exposed to wild type virus, vaccine recipients were at risk for developing an atypical form of measles which was more severe than typical measles. This vaccine was withdrawn in 1967 [18]. In 1963 a live attenuated vaccine was licensed and early versions of the vaccine were associated with a significant risk of vaccine-associated fever and rash that decreased when given in conjunction with immunoglobulin [18]. These side effects decreased significantly with further virus attenuation [18]. The currently used measles vaccine in the USA contains the further attenuated Enders-Edmonston vaccine strain [21]. Rash and fever are still observed following this vaccine however at a much lower rate [21, 22].

Measles rates decreased in the USA by greater than 99 % after routine use of the vaccine and by 1983, only 1,497 cases per year were reported [21]. Measles outbreaks continued to occur and during the large 1989–1991 measles outbreak in the USA it was noted that cases were being seen in older school-aged children including those who had received immunization [23]. Most of the patients with breakthrough measles despite immunization are felt to be primary vaccine failures that did not respond to the first dose rather than secondary vaccine failures that did respond to the vaccine yet still developed measles [24, 25]. In 1989 the recommendation was made for two doses of vaccine to be given after the first birthday, in addition to lowering the initial dose of vaccine to 12 months of age [23]. Measles

rates decreased significantly and measles was declared eliminated in 2000 from the USA with no endemic transmission [26]. Similar decreases in the incidence of measles were seen in Canada and Mexico following adoption of a two dose program [26]. Small outbreaks of measles continue to be reported in the USA mainly related to unvaccinated foreign travelers from countries with endemic measles [27].

In 1998, measles vaccination was challenged when Dr. Andrew Wakefield and colleagues published a paper suggesting an association of MMR vaccination with neurodevelopmental disease including autism and gastrointestinal abnormalities suggestive of inflammatory bowel disease [28]. Other studies by the same investigator reported identification of measles virus in patients with inflammatory bowel disease [29, 30]. This paper raised concerns in the public of the dangers of measles vaccination. Numerous other investigators have sought to replicate Dr. Wakefield's findings. However, there have been no studies to date to support his conclusions [31–34]. A conference was convened in 2000 including a multidisciplinary panel to review available data. The conclusion of the review was that the "available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders or IBD" [35]. Moreover, the collaborators and the journal that published the original paper retracted the publication in 2010 [36]. Unfortunately, unfounded concerns with the safety of this vaccine remain and result in parental refusal of vaccination [37, 38].

Immune suppression specifically related to lymphopenia and altered T cell function has been associated with measles virus infection [39, 40]. This immune suppression can lead to secondary bacterial infection and inability to mount sufficient T cell responses to other infections. Both measles disease and measles vaccine can affect T cell responses to delayed hypersensitivity testing, e.g., PPD skin test and tuberculin skin testing is recommended to be done either at the same time as vaccination or waiting 4 weeks after vaccination [41–43]. There is also a reported decrease in response to varicella vaccination if given within 28 days of MMR vaccine [44]. The potential immune suppression of one live virus interfering with the response of a second live virus vaccine is the basis for the recommendation to give live virus vaccines either simultaneously or spaced at least 4 weeks apart [43].

Mumps

Mumps virus causes both clinical and subclinical infections. The most commonly associated symptoms are fever and parotitis which affects approximately 40 % of infected patients [21]. More severe complications associated with mumps infection include orchitis and oophoritis which occur more commonly in post pubertal adolescents and adults [21, 45], encephalitis, and pancreatitis [21, 46]. Although sterility after mumps is considered rare [21], decreased levels of testosterone and other hormone levels have been reported in patients with mumps orchitis [45]. Mumps was also a significant cause of sensorineural hearing loss prior to vaccination [21]. The mumps vaccine was initially licensed in the USA in 1967 and was

recommended for routine use in 1977. Although the incidence of mumps has decreased significantly since then, cases continue to occur sporadically. An epidemic of mumps in the UK in 2004–2005 and in the USA in 2006 [47, 48] identified a high number of young adult cases, many of whom had not received two doses of MMR vaccination. Although one type of mumps vaccine (Urabe strain) was associated with vaccine-associated meningitis, the vaccine currently used in the USA and most other countries includes the Jeryl Lynn strain of mumps virus and is associated with few side effects [33].

Rubella

Rubella virus causes a self-limited febrile, exanthematous illness often associated with adenopathy in older children and adults. Arthritis and arthralgias can be seen especially in adult patients. Encephalitis and thrombocytopenic purpura can also rarely occur as complications of the disease. The most significant associated morbidity with rubella infection is congenital rubella syndrome which affects the fetus of women infected during pregnancy. In addition to miscarriage and stillbirth, congenital rubella syndrome leads to a variety of birth defects including mental retardation, cataracts/blindness, heart disease(most commonly PDA, pulmonic stenosis), and hearing loss [21, 49]. Congenital rubella syndrome is more likely to occur in susceptible women who contract the infection early in pregnancy; an estimated 20–25 % of women infected in the first 20 weeks of pregnancy [21]. The rubella vaccine was licensed in the USA in 1969 and reported cases of congenital rubella syndrome decreased by 69 % from 1970 to 1976 [21]. In 1977, the current rubella vaccine using the 27/3 strain became the recommended vaccine based on superior immunogenicity and fewer side effects than other vaccines [33, 50]. Rubella was declared eliminated in the USA in 2005 [51]. Only five cases of congenital rubella syndrome were reported in the USA from 2001 to 2004 [52]. However, rubella continues to be present in other countries, despite significant progress to increase vaccination abroad [53]. Imported cases still occur and maintenance of immunity through ongoing immunization continues to be important [52, 54].

Mumps and rubella vaccines are combined with measles vaccine in the MMR vaccine and all three vaccines are combined with varicella vaccine in the measles–mumps–rubella–varicella (MMRV) formulation. MMR is the most widely used vaccine for these infections in the USA. MMR is recommended at 12 months of age with a second dose given, usually at age 4–5 years. This second dose can be given any time after the first birthday and at least 28 days from the first dose [21]. Most of the vaccine-associated adverse effects are attributed to the measles component. As discussed above, fever and rash are associated with the measles vaccine; however, rubella vaccine can also lead to a rash approximately 2 weeks following the dose. An increased risk of febrile seizures occurring 7–17 days after vaccination is associated with the MMR vaccine [33, 55, 56]. Vestergaard reported a 10 % higher risk of febrile seizures in children receiving MMR vs. those not vaccinated; however, no

long-term risk of seizures has been seen [56]. Barlow reported a relative risk for febrile seizures of 2.83 in MMR vaccine recipients 8–14 days after vaccination compared to patients who had not received the vaccine [55]. Transient thrombocytopenia and more infrequently immune thrombocytopenic purpura have been associated with MMR vaccine [34, 57–60]; both occurring at significantly lower rates than that seen with natural disease.

Transient arthralgias are associated with MMR vaccination, presumably associated with the rubella component [34, 61, 62]. The risk of congenital rubella syndrome following vaccination of pregnant women is theoretical. Although positive rubella IgM antibodies have been seen in infants born to mothers inadvertently vaccinated during pregnancy, no cases of congenital rubella syndrome due to vaccine have been reported [63].

Immunoglobulin can interfere with the immunologic response to measles and rubella vaccination [64] and it is recommended to wait several months subsequent to receiving immunoglobulin, to give the MMR vaccine.

Oral Polio Vaccine

Polioviruses were the primary cause of acute flaccid paralysis until the mid-1950s when the first polio vaccines were approved. Three serotypes (1, 2, and 3) are responsible for disease and all three are included in both inactivated and live polio vaccines. Although over 90 % of patients infected with polio have minimal to no symptoms. In 1–2 % of patients the central nervous system can be affected. Aseptic meningitis and/or acute paralysis may develop. Patients with paralytic polio can develop respiratory failure due to paralysis of the diaphragm and other muscles involved in respiration and those that survive often are left with neurologic sequelae [65]. There was an estimated annual average of 16,316 cases of paralytic polio in the USA from 1951 to 1954 with an annual average of 1,879 associated deaths [20]. Although disease rates dropped after licensure of the inactivated Salk vaccine, it was not until widespread use of oral polio vaccine licensed in 1963, that eradication of polio was considered possible on a global level. Live oral polio vaccine had the advantage of being less costly, more easily administered and the associated excretion of virus to patient contacts and resultant herd immunity was able to more effectively block transmission of wild type poliovirus in the community [66]. Use of oral polio vaccine led to the elimination of polio in the Western hemisphere in 1994 [67]. Globally, polio has been eliminated in the majority of countries. In 2006, only four countries (Afghanistan, India, Nigeria, and Pakistan) reported endemic wild polio infections. However, since that time outbreaks have been reported in several other countries related to imported cases [68]. These outbreaks exemplify the importance of maintaining immunity through vaccination in all populations even when endemic disease no longer exists. Ongoing transmission of virus is dependent on having a susceptible patient population.

It is unlikely that without oral polio vaccine, the idea of global eradication of this disease would be possible. Despite the benefits of live oral polio vaccine, one of the drawbacks is that the vaccine strains can cause paralytic polio disease. This "vaccine associated paralytic polio (VAPP)" occurs rarely with a risk of 1 case per 2.4 million doses [69]. However, with no cases of wild-type polio in many parts of the world, even this very low risk becomes significant. As a result the USA and other developed countries have switched to exclusive use of inactivated polio vaccine [69]. Another concern associated with live oral polio vaccine is disease associated with vaccine derived polioviruses (VDPVs) [66]. These strains arise from excretion of vaccine virus strains from live virus recipients that revert to more virulent forms and can lead to disease outbreaks similar to those caused by wild-type virus. Examples of this include the outbreak of polio in Hispaniola in 2000–2001 and that in Egypt in the 1980s [66]. These strains are propagated when overall vaccination rates are low and there are susceptible individuals in the community. These outbreaks are controlled by increased vaccination of the susceptible population.

Global eradication of polio continues to be a reachable goal and currently the Global Polio Eradication Initiative plan is to end transmission of wild-type polio virus in all countries by the end of 2012 [68].

Rotavirus Vaccine

Rotavirus is the most common cause of diarrheal illness in the world. Parashar et al. estimated median annual 440,000 deaths worldwide in children <5 years are due to this virus [70]. In the USA, prior to vaccination, it was estimated that rotavirus caused 37 deaths and 59,600 hospitalizations annually in children under 5 years of age [71].

In 1998 a live attenuated oral rotavirus vaccine was licensed in the USA. The vaccine was a tetravalent rhesus based vaccine that was extensively studied in multiple trials involving over 17,000 patients. The vaccine was reported to be efficacious with 49–68 % efficacy against rotavirus diarrhea [72]. Although cases of intussusception had been noted in early trials, the rate was not significantly greater than that seen in controls [73]. Within a year of licensure, 15 infants were reported to the Vaccine Adverse Event Reporting System (VAERS) with intussusception following rotavirus vaccination. Further studies demonstrated that the rate of intussusception in patients receiving vaccine exceeded the expected rate for the population and a recommendation was made to hold further administration of the vaccine [73]. A case control study performed by the CDC found a significant increased risk of intussusception with rotavirus vaccination, with the highest number occurring 3–14 days after the first and second doses [74]. The vaccine was subsequently withdrawn from use.

Two different rotavirus vaccines have been licensed since then. Both are live attenuated orally administered vaccines. The first is a pentavalent human bovine reassortant vaccine (WC3), licensed in 2006, and given as a three dose series 4–6

weeks apart starting at 2 months of age. This vaccine was studied in a double blind, placebo controlled trial involving 70,301 subjects. There was a 94.5 % decrease in hospitalization/ED visits for rotavirus gastroenteritis in vaccinated patients vs. controls and an 86 % decrease in office/clinic visits for rotavirus gastroenteritis. The efficacy of the vaccine against any rotavirus gastroenteritis was 74 % and 98 % for severe gastroenteritis. Of note there was no increase in the number of subjects with intussusception in the vaccine group (12 of 34,644) compared to the placebo group (15 of 34,630) during the 1 year study period. There were six cases in vaccine recipients and 5 in placebo recipients that occurred within 42 days of any vaccine dose. None of the vaccine recipients and 1 placebo recipient experienced intussusception within 42 days of the first vaccine dose [75].

The second vaccine is an attenuated human rotavirus vaccine (HRV) licensed in 2008 given as a two dose series. This vaccine was also studied in a large cohort of subjects to assess the risk of intussusception following vaccination. Vaccine efficacy against severe gastroenteritis was 84.7 and 85 % for hospitalization for severe rotavirus gastroenteritis. Intussusception was seen in 9 (of 31,973) vaccine recipients and 16 (of 31,552) placebo recipients during the 100 day study period. Six vaccine recipients and seven placebo recipients, experienced intussusception within 31 days of either dose and one vaccine recipient and two placebo recipients experienced intussusception within 31 days of dose 1 [76].

Both vaccines are orally administered, infect the mucosal surface and induce both IgG and IgA. The vaccines are generally well tolerated and studies showed similar rates of fever, vomiting, and diarrhea in vaccinated and placebo groups [75, 77]. Viral shedding is reported in 12.7 % of patients following WC3 [75] and 35–44 % of patients with HRV [77] in the first week following the first dose.

Since widespread use of the rotavirus vaccine, total positive tests for rotavirus have decreased and the duration of rotavirus seasons has decreased significantly in the USA [78]. Data suggest the decrease in disease is seen not only in vaccinated patients but in non-vaccinated patients as well [79]. Hospitalizations in the USA due to diarrhea decreased 16 % in 2007 and 45 % in 2008 [80]. Outpatient visits due to gastroenteritis have also decreased [78].

Smallpox Vaccine

Smallpox was a severe disease that killed an estimated 30 % of those infected and left significant scarring in many of those that survived [81]. The first attempts at vaccination for smallpox (variola virus) involved inoculation with material containing live virus from other diseased patients. This is was the earliest live virus vaccine. While this practice decreased disease in outbreak situations, the vaccination was not completely protective and some patients developed disease from the inoculation itself. Others who were vaccinated were not quarantined and subsequently passed infection on to other susceptible persons [82]. Jenner's now famous use of cowpox virus, as vaccination against the more virulent variola virus utilized the principle of

using a less virulent agent to protect against a more virulent one, similar to the use of attenuated forms of viruses in modern day vaccines. Despite the imperfections of these early vaccines, they made a significant difference in the incidence of smallpox disease. In 1958 global smallpox eradication became a goal of the World Health Organization and with much work, the disease was declared eradicated in 1979 [82].

The vaccine had been further refined since Jenner's initial trials, including substitution of vaccinia virus for cowpox virus [83]. However, significant adverse reactions are still associated with smallpox vaccination, including local skin reactions, rashes including erythema multiforme, and inadvertent inoculation from the vaccination site to eyes, and other body sites. Transmission from the vaccinated persons to other household contacts also occurs. Generalized vaccinia and eczema vaccinatum are also seen infrequently [84].

Smallpox vaccination became an issue in the early part of the twenty-first century due to concerns for potential use of smallpox as an agent for bioterrorism [81]. Concerns resurfaced regarding the side effects related to smallpox vaccination especially with a population that was in large part naïve to prior infection or vaccination. The most commonly reported adverse reactions occurring in a military population of 450,293 individuals, included local reactions and malaise. More severe reactions included 36 cases of generalized vaccinia, 48 self-inoculations, 21 contact transfers, 1 case of encephalitis, and 37 cases of myopericariditis [85]. Although myocarditis had been a reported associated risk from vaccinia, of some concern were two cases of dilated cardiomyopathy reported in civilian vaccinees [86]. This had not been an associated condition with vaccinia in the past. Review of cardiac deaths after smallpox vaccination in 1947 was performed and did not show an increase in cardiac deaths at that time [87]. To date there has not been an established link between ischemic heart disease and smallpox vaccination. Fortunately the risk of reintroduction of smallpox has decreased and smallpox vaccination has been halted, at least for now.

Varicella Vaccine

Varicella virus is a herpes virus that causes a febrile illness associated with a vesiculopustular rash. Like measles, varicella is spread through small droplets and is highly contagious. In most children, the course of varicella illness consists of a few days of fever associated with a pruritic rash with characteristic vesiculopustular lesions that appear in crops. Typical patients have between 200 and 500 lesions. In adults, the course of illness is often more severe and complications are more likely. Meyer et al. reported a case fatality rate for adults >20 years of age that was 25 times higher than that of children 1–4 years of age [88]. Complications of varicella include primary viral and secondary bacterial pneumonia (27.6 % of deaths due to varicella from 1970 to 1994) [88], as well as secondary bacterial skin and soft tissue infections. Group A streptococcal necrotizing fasciitis has been associated with

varicella infection [89, 90]. Central nervous system complications of varicella include aseptic meningitis and encephalitis. Twenty-one percent of varicella-associated deaths from 1970 to 1994 were related to encephalitis [88]. Cerebellar involvement leads to cerebellar ataxia [89, 91]. In immunocompromised patients, varicella can become disseminated and cause severe disease and death [91]. In both healthy and immunocompromised patients, varicella may result in a persistent infection, with later reactivation in the form of herpes zoster. Patients with zoster often experience severe and recurrent episodes of pain and neuralgia.

The varicella vaccine is a live attenuated vaccine originally developed in Japan using the OKA strain in 1974 [91]. The vaccine was licensed in the USA in 1995 with an initial recommendation for a single dose at 12–18 months of age and catch up vaccination up to age 12 years. Two doses of vaccine showed significantly better protection [92]. Adolescents showed a lower seroconversion rate than children with a single vaccine dose and for persons ≥13 years old, two doses of vaccine are recommended 4–8 weeks apart [93].

Following licensure, there has been increased use of vaccine to 89 % in 2006 [94]. Decreases in mortality rates due to varicella have been dramatic: 92 % for children 1–4 years, 89 % in children 5–9 years, 78 % in children <1 year, 75 % for children 10–19 years and 74 % for those 20–49 years of age [95]. Post licensure studies showed the vaccine to be 80–85 % effective at preventing varicella disease and 97–100 % effective at preventing severe disease [96]. More recent data show that even infants too young to be vaccinated show a decrease in varicella disease of 89.7 % [97]. The vaccine was also shown to be 90 % effective at preventing or modifying disease in susceptible individuals immunized after an exposure [96]. Outbreaks of varicella continued to occur despite decreases in overall disease. Two doses of vaccine have shown improved efficacy over a single dose in preventing infection [92] and in 2006, a recommendation was made to give a second dose of varicella vaccine for all ages [93].

Overall adverse effects related to the varicella vaccine are low. The most common events are pain and/or redness at the injection site and rash. In children, injection site pain, swelling, rash at injection site, and/or redness was reported in 27 % of vaccinees, compared to 19 % of controls. A varicella-like rash was reported in 4 % of vaccines compared to 2 % of controls [98]. In adolescents and adults, injection site complaints were reported in 24.4 % after the first dose. Rash was reported in 3 % (injection site) and 5.5 % (non-localized) of patients after the first dose of vaccine [93]. Disseminated varicella rash has been reported in 4–6 % of patients receiving the vaccine, with an average of five lesions [91]. Postmarketing surveillance from Merck, reports rashes where the vaccine strain was isolated, a median of 21 days from vaccination [99]. Seven cases of disseminated varicella occurred with six patients having primary immunodeficiencies and one with Down syndrome [99]. Secondary transmission of vaccine virus to contacts is reported but very rare and all cases have been mild [93].

Although herpes zoster has been reported in patients receiving varicella vaccine, the rates are lower than those seen with natural infection [93], possibly because of fewer if any skin lesions that lead to infection of sensory nerves where the virus

becomes latent [100]. Hardy et al. studied the incidence of zoster in leukemic patients vaccinated with varicella vaccine. They found the incidence of zoster in vaccinated patients to be significantly lower in vaccinated patients vs. controls (0.8 vs. 2.46 cases per 100 person years) [101].

Recently a varicella zoster vaccine has been licensed in the USA for adults with a higher antigenic load of virus than the standard varicella vaccine [91, 102]. This vaccine is designed to prevent zoster in older individuals. Oxman et al. reported a decrease in overall disease burden of 61 %, decrease in post herpetic neuralgia of 67 %, and decrease in zoster of 51 % in vaccinated individuals [103]. Adverse effects from the vaccine were primarily related to injection site reactions [103–105]. A subsequent retrospective study performed through a managed care organization, showed a similar 55 % reduction in the incidence of zoster [106]. Although specific data do not exist showing interference of immune globulin to varicella and zoster vaccine response, using measles and rubella as examples, this effect is presumed and vaccination should wait several months after immune globulin is given [93].

A combined measles-mumps-rubella-varicella (MMRV) vaccine was licensed in 2005. This combined vaccine contains slightly more varicella antigen (3.99 log10 PFU vs. 3.13 log10 PFU) than varicella vaccine [93]. Immunogenicity and safety were compared to MMR and varicella vaccines given separately and it showed similar efficacy. There was a slightly higher rate of fever (21.5 % vs. 14.9 %), measles like rash (3 % vs. 2.1 %), and local injection site rash (2.3 % vs. 1.5 %) in patients receiving MMRV than with separate vaccinations [107]. Subsequent studies have revealed an increase in febrile seizures in children given MMRV vs. MMR and varicella vaccines separately in children 12–23 months of age for their first dose [108, 109]. This increase in febrile seizures was not observed in older children (4–6 years) given MMRV for their second dose of measles, mumps, rubella, varicella vaccination [110]. Current recommendations are to give MMR and varicella vaccines separately as a first dose at 12–15 months of age unless families request the combined vaccine. The second dose at 4–6 years can be given as combined MMRV or MMR + varicella with a preference for MMRV [111].

Yellow Fever Vaccine

Yellow fever is an acute febrile illness caused by the Yellow Fever virus. This flavivirus is transmitted through infected mosquitoes (notably *Aeges aegypti*) and is endemic in tropical regions of South America and Africa [112]. The disease is characterized by fever, headache, photophobia, jaundice, back and extremity pain, and vomiting. Hepatitis, coagulopathy, liver and renal failure are complications. Case fatality rates for yellow fever can be high not only to persons living in endemic areas but to travelers. Between 1970 and 2002, nine cases of yellow fever were reported from the USA and Europe with an 89 % mortality rate [113]. Yellow Fever vaccine was licensed in 1937. Vaccines currently in use are the 17D-204 and 17DD formulations, both derived from the 17D yellow fever virus strain. Yellow Fever vaccine is

only indicated for patients traveling to areas of Central and South America and Africa where Yellow Fever is endemic. This vaccine is immunogenic [114] and overall adverse events are low [113]. The most common reported adverse effects are headache, malaise, and pain at the injection site [114]. Two serious adverse events that are rarely reported but likely associated with yellow fever vaccination are Yellow Fever Vaccine-Associated Neurotropic Disease (post-vaccinal encephalitis) and Yellow Fever Vaccine-associated Viscerotropic Disease [112, 115]. Yellow Fever Vaccine-Associated Neurotropic Disease presents as encephalitis with reported symptoms of fever, headache and focal neurologic signs following Yellow Fever vaccination. The majority of reported cases were in infants less than 9 months of age [113]. Yellow Fever Vaccine-associated Viscerotropic Disease has been described more recently (1996–2001) as a syndrome of fever, jaundice, hepatitis, and multiorgan failure. Seven cases were reported in the USA from 1996 to 2001 and additional cases have been reported from other countries [112]. The rate of these two severe processes are extremely low [116] however due to the higher rate of Yellow Fever Vaccine-Associated Neurotropic Disease, in young infants, the vaccine is recommended only for individuals 9 months and older, who reside in or visit high-risk areas. Severe allergic reactions (anaphylaxis) are reported rarely (1 in 58,000–131,000) [113].

Immunocompromised Patients and Live Virus Vaccines

Vaccine associated disease is a risk in immunocompromised patients, especially those with humoral and cellular immune deficiencies. In general live virus vaccines are contraindicated in patients with primary immunodeficiencies such as severe combined immunodeficiency (SCID) and agammaglobulinemia; however, these vaccines can be given to patients with primary neutrophil defects, complement deficiency, and asplenia [43]. Live virus vaccines are also more likely to cause adverse effects and be less immunogenic in individuals being treated with immunosuppressive drugs such as cancer chemotherapy, bone marrow or solid organ transplant recipients, and HIV infected patients. Patients with SCID and agammaglobulinemia are at increased risk for VAPP [69]. Disseminated varicella and measles have been reported in immunocompromised patients secondary to vaccination [99, 117] but are rare. Exceptions to the general rule of withholding live virus vaccines to immune compromised patients exist in certain populations and situations where the vaccine has been specifically studied and the risk of disease outweighs risk associated with vaccination. For example, measles can be life- threatening in HIV patients [118]. MMR vaccine has been studied in HIV patients without severe immunodeficiency (CD4 % >15 %), and was not associated with significant adverse effects [21]. MMR vaccine is recommended for asymptomatic HIV infected patients and those without severe immunosuppression [21]. Similarly, varicella vaccine has also been studied in HIV infected patients without severe immunodeficiency [119–121] and felt to be safe. Rotavirus, live attenuated influenza virus vaccine, and Yellow Fever

vaccine are not currently recommended for HIV infected patients, although in certain situations, risk of contracting the primary infection may outweigh the risks of vaccination.

Live virus vaccines are in general not recommended for pregnant women due to possible risk to the fetus [43]. However, MMR, varicella, LAIV, and rotavirus vaccines can be given to household contacts since the risk of transmission to household contacts is low. Smallpox vaccination should not be given to household contacts of pregnant women. MMR and varicella vaccines can be given to breastfeeding women; however, smallpox and yellow fever vaccines should not [43].

Live Virus Vaccines and Egg Allergy

Concern for adverse reactions to live virus vaccines in persons with egg allergies has been significant. Measles and mumps vaccines are prepared in cultures of chick embryo fibroblasts with very small amounts of egg protein likely in the vaccine. Studies [21, 122] have shown patients with a history of egg allergy, including severe egg allergy can receive these vaccines. Gelatin and other proteins in the MMR vaccine are postulated to be more likely the cause of anaphylactic reactions to the MMR vaccine.

Influenza and smallpox vaccines are prepared in embryonated chicken eggs and therefore also carry a risk of allergic reactions to eggs. Studies have shown influenza vaccines are safe in most patients with egg allergies [123, 124]. Current recommendations are that only persons with severe anaphylactic reactions to eggs not receive influenza vaccine [43] and yellow fever vaccine not be given to patients with egg hypersensitivity [113].

Conclusion

In the last 60 years, the use of live virus vaccines has significantly decreased the incidence of major infections in industrialized countries where vaccinations are available. This decrease in disease includes eradication of smallpox and near eradication of polio worldwide. Surveillance for adverse effects associated with vaccination is ongoing and recommendations for use of live virus vaccines evolve both as the epidemiology of infectious diseases change and as advancement in vaccine technology provides safer, more efficacious products. Physicians and other health care personnel should be mindful of the real and perceived effects of these vaccines to be able to provide the general public with an accurate idea of risks associated with vaccination (Table 12.1).

Table 12.1 Adverse effects associated with live viral vaccines [8, 23, 70, 76, 77, 82, 85, 94, 112]

Vaccine	Adverse effects	Rate in vaccinees
Live attenuated influenza vaccine	Fever, URI symptoms	1–5 %
Measles-mumps-rubella vaccine	Fever, rash 7–12 days after vaccination	5 %
	Febrile seizures	1/3,000 doses
	Thrombocytopenia	Rare (1/1 million doses)
	Arthralgia, arthritis	Rare in children, more common in adults
	Parotitis	Rare
Oral polio vaccine	Vaccine-associated paralytic polio	1/2.4 million doses
Rotavirus vaccine	Intussusception	Not seen with currently licensed vaccines
Smallpox vaccine	Fever, malaise, headache	Almost 100 %
	Vaccine site tenderness, lymphadenopathy	86 % site tenderness 54 % adenopathy
	Secondary autoinoculation	Common
	Eczema vaccinatum, generalized vaccinia	Rare
Varicella vaccine	Injection site tenderness/rash	27 %
	Disseminated varicella	4–6 % (generally few lesions)
Yellow fever vaccine	Fever, headache, myalgia	≤25 %
	Yellow Fever vaccine-associated neurotropic disease, Yellow Fever vaccine-associated viscerotropic disease	Rare

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Chapter 13
Can Vaccines Cause Cancer?

Ann-Christine Nyquist

What Is Cancer and What Causes Cancer?

Cancer is a complex group of diseases where abnormal cells grow out of control and invade other tissues. Multiple causes and factors may promote cancer including genetic factors; lifestyle factors such as tobacco use, diet, and physical activity; certain types of infections; and environmental exposures to different types of chemicals and radiation.

Infections That Cause Cancer

Current estimates indicate that more than 20 % of the global cancer burden is related to chronic infections with viruses, bacteria, and parasites. The predominant infections associated with cancer are viruses, but rarely bacteria (*Helicobacter pylori)*, and in an endemic fashion parasitic infection with flatworms (*Opisthorchis viverrini*, *Clonorchis sinensis*, and *Schistosoma hematobium)* can also promote the development of cancer. For example, *H. pylori* is the major cause of stomach inflammation that results in peptic ulcer disease (10–20 %), distal gastric adenocarcinoma (1–2 %), and gastric mucosal-associated lymphoid tissue (MALT) lymphoma (<1 %) [1]. Epidemiological studies have shown a significant correlation between endemic helminth infections and certain types of cancer. Squamous cell carcinoma of the bladder is associated with *Shistosoma haematobium* in endemic geographic areas of Africa and the Middle East and cholangiocarcinoma with *Opishorchis viverrini* in Thailand and *Clonorchis sinensis* in Korea [2–4].

A.-C. Nyquist, M.D., M.S.P.H. (✉)
Sections of Infectious Diseases and Epidemiology, Department of Pediatrics,
Children's Hospital Colorado, University of Colorado School of Medicine,
13123 East 16th Avenue B-276, Aurora, CO 80045, USA
e-mail: Ann-Christine.Nyquist@ucdenver.edu; Chris.Nyquist@childrenscolorado.org

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Epidemiologic Causation Criteria

Viral infections are common among humans and some of these infections are caused by cancer-associated or oncogenic viruses. Despite the prevalence worldwide of these oncogenic viral infections, not all infections lead to cancer. Infections may be transient or lifelong and the onset of cancer typically occurs years to decades after the initial infection. The worldwide prevalence of cancer-associated viruses is far greater than the incidence of corresponding neoplastic disorders, so cancer is a rare secondary consequence rather than an inevitable outcome of the viral infection. Other factors are critical in the neoplastic transformation process and although infection is necessary it is not sufficient to cause cancer. The majority of human cancer viruses appear to function as factors that initiate or promote the oncogenic process as opposed to absolute oncogenes. Because cancer is caused by accumulated genetic and epigenetic changes, viruses can cause cancer either by inducing or allowing the accumulation of genetic mutations, or by expressing oncoproteins that modify cell survival and proliferation control.

Given the difference in prevalence of viral infections versus cancer incidence, mere detection of a virus or its genetic sequence in a particular tumor is not sufficient to clearly prove the virus as a causal factor in the genesis of the disease. Since human cancer viruses are often ubiquitous and only rarely produce tumors in infected individuals, accumulating enough evidence to establish causal association between any given virus and cancer is a challenge.

The Bradford Hill broader epidemiologic criteria for causality provide a framework to confirm the association of certain infections with the development of cancer [5]. Key criteria include the strength and consistency of the association between and agent and the disease with consistent findings across studies; the specificity of the association such that the infection is associated with selected cancers; the temporal relationship such that the infection precedes disease onset; the biological plausibility such that the association between the infection and cancer is reasonable given current knowledge and there is coherence with known factors; and experimental verification is possible.

Currently, six human viruses have been classified by the International Agency for Research on Cancer (IARC) as “carcinogenic to humans” (group 1) based on sufficient evidence supporting their etiologic association with human cancer: Epstein–Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV) of several types, human T-cell lymphotropic virus type 1 (HTLV-1), and Kaposi’s sarcoma-associated herpes virus (KSHV), also known as human herpesvirus 8 (HHV-8) [6, 7].

EBV

Genetic (e.g., translocation of *myc* gene) and environmental factors (e.g., malaria, malnutrition, alteration in the immune system) in some people allow EBV infection to

progress towards malignancy. Currently, EBV is associated with Burkitt's lymphoma, nasopharyngeal carcinoma (NPC), Hodgkin's lymphoma, immune-suppression-related non-Hodgkin's lymphoma, and extranodal NK/T-cell lymphomas [1].

HBV and HCV

Worldwide, primary liver cancer, hepatocellular carcinoma (HCC) is the third leading cause of cancer-associated death. More than 80 % of primary liver cancers are related to HBV and HCV infections. Persistent HBV infection combined with chronic inflammation sometimes results in chronic liver disease, progression to cirrhosis, and eventual development of HCC. Patients with chronic HBV infection are 100-fold more likely to develop HCC than uninfected individuals. Newborns and young children are at the highest risk as the majority of children with HBV infection develop chronic infection which confers a high risk of progression to HCC. The leading hypothesis for HCV-induced hepatocarcinogenesis is that HCC develops in the context of chronic liver injury followed by regeneration and cirrhosis [8].

HPV

Cervical cancer is the second most common cause of cancer mortality in women worldwide. HPV infection is the human cancer virus responsible for causing virtually all cases of cervical cancer in women [9]. Walboomers et al. found an HPV prevalence of 99.7 % in 932 cervical cancers studied [10]. There are over 100 HPV genotypes which have been identified and these are classified into two major groups: cutaneous and mucosal HPV types. High-risk HPVs 16, 18, 31, and 45 account for up to ~80 % of cervical cancer. HPV types 33, 35, 39, 51, 52, 56, 58, and 59 are also associated with cervical cancer and several other types have been classified as "probably carcinogenic to humans" or "possibly carcinogenic."

HPV infection is the primary cause of cervical cancer and plays a central role in cervical carcinogenesis. Prospective studies have shown that women persistently infected with high-risk HPV types are at a significantly greater risk of developing cervical intraepithelial neoplasia (CIN) compared with women who are only transiently infected. Epidemiological and biological studies have shown that HPV-16, and -18 are the two most frequently detected oncogenic types within the high-risk group accounting for 50 and 20 %, respectively, of cervical cancers. High-risk HPVs have been linked to anogenital cancer and to a subset of head and neck cancers. Cofactors such as tobacco use, exogenous estrogen, or UV exposure work in concert with persistent HPV infection with high-risk types to promote progression to cancer [11].

HPV infects squamous epithelial cells and infects both mucosal and cutaneous sites. Oncogenic HPV types target infection in the basal cells of the squamocolumnar junction at the transformation zone of the cervix (that variable part of the ectocervix where the epithelium undergoes transformation from columnar to squamous during a woman's lifetime), and it is here that neoplasia usually originates. Cervical carcinogenesis is caused by the expression of two oncogenes of high-risk HPVs, E6 and E7. DNA damage normally induces cell cycle arrest, DNA repair, or apoptosis (programmed cell death), but these mechanisms get disrupted by HPV oncogene interactions and lead to bypassing of cell arrest and apoptosis. These oncoproteins (E6 and E7) impair the ability of a cell to repair DNA damage, lead to genetic instability and accumulation of cellular mutations by specific interactions with other factors that lead to abnormal cellular proliferation. Longitudinal studies demonstrate that HPV infection precedes the development of virtually all high-grade dysplasias and that the distribution of HPV types in these dysplasias is similar to that of cancers. HPV infection is now considered a necessary intermediate step in the genesis of cervical cancer [12].

HTLV-1

HTLV-1 was the first human retrovirus to be identified and the first to be associated with human malignancy, adult T cell leukemia (ATL). HTLV-1 proviral DNA is detectable in virtually every ATL patient tested. Unlike many tumorigenic animal retroviruses, HTLV-1 does not encode a classical oncogene that causes cellular transformation. Instead HTLV encodes an essential protein Tax that activates pathways (NF-kB, AP-1, CRE pathways) with subsequent HTLV-1-related tumors developing decades after the primary infection [1].

HHV-8

HHV-8 or Kaposi's sarcoma-associated herpes virus (KSHV) was discovered in the 1990s in patients with uncontrolled HIV infection and significant immune suppression with AIDS defining illness [13]. Better management and control of HIV infection has coincided with a decrease in the incidence of Kaposi's sarcoma as well as other AIDS-related opportunistic infections.

Nucleic acid screens and other molecular technology have accelerated the identification of new viruses that infect human beings. Some of these yet unidentified viruses could be human cancer-associated viruses and some newly known viruses could be found within cancer cells. The human BK and JC polyomaviruses are

ubiquitous in the human population and widely distributed geographically. In vitro and animal model studies support that these viruses could be associated with different types of human cancers and there are reports that BK and JC are present in certain tumors. Yet their role in human cancer still remains under debate [14].

Vaccines Developed to Prevent Cancer

HBV Vaccine

HBV vaccine was the first prophylactic vaccine developed for an oncovirus and was generated by recombinant DNA technology in 1986. The HBV vaccine is based on noninfectious virus-like particles (VLPs) containing the structural viral protein L1, similar to the newly developed HPV vaccine. A global vaccination program in addition to continued improvement of the HBV vaccine has led to a significant decrease in the rate of new annual cases of HBV infections and will likely result in a remarkable reduction of HBV-related HCC in future decades. Antiviral vaccines also represent one of the best opportunities for reducing cancers in low resource settings such as developing countries where the incidence of virus-associated cancer is up to three times higher. The WHO recommends that all infants should be vaccinated with HBV vaccine [1].

HPV Vaccine

HPV is the second oncovirus for which prophylactic vaccines have been developed to prevent HPV infections in both women and men, thus reducing the burden of HPV-associated diseases. Two vaccines have been developed: HPV4 (VLPs 16, 18, 6, 11) and HPV2 (VLPs 16, 18) vaccines. Both vaccines are composed of HPV L1 proteins that assemble into VLPs. DNA-free VLPs synthesized by self-assembly of fusion proteins of the major capsid antigen L1 (or of both L1 and L2) induce a strong humoral response with neutralizing antibodies [15]. Each HPV vaccine (HPV2 and HPV4) is produced using different cell lines and each contains different aluminum adjuvants. Both are administered by intramuscular injection in three doses (at 0, 1 or 2, and 6 months). Very high prophylactic efficacies were found in blinded, randomized, and placebo-controlled trials of over 50,000 individuals in different countries. Prophylactic efficacy was measured considering HPV infection and disease endpoints consisting of neoplasia. Both vaccines were highly immunogenic in clinical trials with essentially 100 % seroconversion [16].

Vaccines to Treat Cancer

Using vaccines as therapies to treat cancer rely upon the properties that vaccines have to stimulate the immune system. Recently an experimental therapeutic HPV vaccine to treat HPV disease has been developed, which induces regression of precancerous lesions or remission of advanced cervical cancer [17].

BCG Vaccine

BCG is an attenuated strain of *Mycobacterium bovis*, where the virulence has been brought under control. BCG is used throughout the world to vaccinate young children to prevent *Mycobacterium tuberculosis* meningitis and miliary tuberculosis [18]. Zbar and Rapp determined the conditions necessary to obtain an antitumor effect with BCG: the ability to develop an immune response to mycobacterial antigens; an adequate number of living bacilli; close contact between BCG and tumor cells, and a small tumor burden [19]. Subsequently, Morales made the link to the intravesical treatment of non-muscle-invasive bladder cancer with BCG [20, 21].

For over 35 years, Bacillus Calmette-Guérin (BCG) vaccine has been used in the intravesical treatment of non-muscle-invasive bladder cancer although its use is still a subject of controversy and its exact mechanism of action is not fully understood. Urothelial carcinoma of the bladder is the second most common urologic neoplasm after prostate carcinoma in the USA, with an estimated 70,530 new cases and 14,680 deaths in 2010 [22]. Non-muscle-invasive bladder cancer (NMIBC) includes tumors confined to the epithelial mucosa, tumors invading the lamina propria and carcinoma in situ. Transurethral resection of bladder tumor (TURBT) is the primary treatment with intravesical BCG therapy as adjuvant treatment to prevent recurrence and progression of disease and is the treatment of choice for carcinoma in situ [23].

A functional host immune system is a necessary prerequisite for successful BCG immunotherapy. The effects of intravesical BCG depend on the induction of a complex inflammatory cascade event in the bladder mucosa reflecting activation of multiple types of immune cells and bladder tissue cells. This starts with the initial adherence of mycobacteria to the urothelial lining and proceeds through the secretion of cytokines from urothelial cells, a process that attracts a large array of inflammatory cells (neutrophils, monocytes) [24]. The development of a predominant Th1 cytokine profile (e.g., IFN-γ, IL-2, and IL-12) is associated with the therapeutic effects of BCG, whereas the presence of a high level of Th2 cytokines (e.g., IL-10) is associated with BCG failure. Activation of the innate immune system is a prerequisite for the BCG-induced inflammatory responses and the subsequent eradication of bladder cancer by intravesical BCG [23].

The classic BCG therapy course is initiated 2–3 weeks following TURBT consisting of six weekly intravesical instillations. Lyophilized powder BCG (81 mg corresponding to $1–5 \times 10^8$ colony-forming units of viable mycobacteria) is

reconstituted in 50 mL of saline and administered via urethral catheter into an empty bladder with a dwell time of 2 h. Maintenance BCG is more effective in decreasing recurrence as compared to induction therapy alone. Maintenance instillations over a minimum of 12 months maintain cellular immune response which decreases over time while still providing a beneficial treatment effect [23].

The most frequent local side effects of BCG intravesical instillations include BCG-induced cystitis, irritative voiding symptoms, and hematuria in 75 % of all patients. These symptoms usually subside within 48 h and do not require discontinuation of BCG instillations. More rare, serious local adverse events as a result of BCG infection (symptomatic granulomatous prostatitis and epididymo-orchitis) require permanent discontinuation of BCG treatment [24]. The most common systemic side effects consist of a few days of influenza-like symptoms, such as malaise and low-grade fever. Rare, major systemic BCG reactions may occur due to active BCG infection and the accompanying immune response, which typically consists of systemic granulomatous illness generally associated with high-grade fever and may progress to multiple organ failure. BCG sepsis is due to the systemic absorption of BCG and its onset may occur several months or even years after the last instillation. Although BCG therapy is generally considered safe, it has potential local and systemic adverse effects that may either lead to treatment cessation in up to 30 % of patients or lead to a delay or reduction in the number of instillations in 55–83 % of patients.

Potential contraindications to intravesical BCG include transurethral resection within the previous 2 weeks, traumatic catheterization, hematuria, urethral stenosis, active tuberculosis, prior BCG sepsis, and immunosuppression. Immunocompromised patients are at increased risk of systemic infection; thus intravesical BCG is not recommended in these patients because of the theoretical risk of severe morbidity and sepsis.

There is clear evidence that BCG reduces or at least delays the risk of progression of urothelial carcinoma to muscle-invasive disease, but only when BCG maintenance is given. BCG has been established as the intravesical treatment of choice in high-risk patients where the primary goal is to preserve the bladder by preventing progression to muscle-invasive disease. No single prognostic factor is capable of predicting an outcome on BCG. Patients failing BCG have a very poor prognosis with a high risk of progression to muscle-invasive disease and death as a result of bladder cancer. The 3-year bladder cancer-specific survival is 67 % in patients initially presenting with muscle-invasive disease, but only 37 % in patients who progress after intravesical treatment [21].

Myths? Controversies?

Greater than 50 % of the Internet-using population utilizes the Internet to access medical information including information about vaccines and vaccination [25]. Information on Web sites may be excerpted from scientific publications out of

context, provide misinformation, or may be modified to perpetuate an anti-vaccination perspective to sway the reader [26]. The shift in Internet usage toward more interactive Web sites, for example social media and online discussion boards, where interaction among users is promoted and opinion is espoused versus science debated will continue to challenge dissemination of the scientific evidence.

The success of vaccines and the decrease in vaccine-preventable diseases in the USA have set the stage for allegations that the risk of a vaccine is greater than the risk of the disease. Two specific theories perpetuate the myth that vaccines cause cancer. Some viruses used in the manufacturing of vaccines are grown in immortalized cell lines. Critics have raised concerns that these cell lines are contaminated with other viruses or products that may cause cancer. Additionally, there are specific substances contained within some vaccines, such as formaldehyde, that are the by-product of the manufacturing process or a necessary component of the vaccine to ensure a safe, sterile product that have been targeted in the "vaccines cause cancer" mythology [27–29].

Vaccine Components

Vaccines primarily contain immunogens, inactivated bacterial toxins or bacterial polysaccharides in addition to live or killed viruses or their purified viral proteins, that promote the immune response in addition to other substances that are secondary to the vaccine manufacturing process. Vaccines may contain preservatives to prevent bacterial or fungal contamination, adjuvants to enhance antigen-specific immune responses or residual quantities of substances used during the manufacturing process such as formaldehyde, antibiotics, egg proteins, and yeast proteins.

Inactivating agents within vaccines are used to remove the capacity of infectious particles to replicate or to eliminate the harmful effects of bacterial toxins. Formaldehyde is an agent used to inactivate influenza virus, poliovirus, and diphtheria and tetanus toxins within their associated vaccines. High concentrations of formaldehyde can damage DNA and cause cancerous changes in vitro [30, 31], and post-manufacturing residual quantities of formaldehyde may be found in several current vaccines with no vaccine containing more than 0.1 mg per dose [32].

All humans have some detectable formaldehyde in their circulation because formaldehyde is an essential intermediate in human metabolism and is required for the synthesis of thymidine, purines, and amino acids. Assuming approximately 2.5 μg of formaldehyde/mL of blood, the amount of naturally occurring formaldehyde in a 2-month-old 5 kg infant with 85 mL/kg of blood would be 1.1 mg of formaldehyde, which is ten times the amount contained in any vaccine currently administered to children.

Formaldehyde does not seem to be a cause of cancer in humans [33] and animal models with exposure to large quantities of formaldehyde (single dose of 25 mg/kg or chronic exposure at doses of 80–100 mg/kg/day) do not develop malignancies [34].

Vaccine Contamination

The first live polio vaccine was grown in mice and subsequently tested on humans in 1950. Smallpox, yellow fever, and rabies viruses were cultured in the brains of mice for vaccine production and several live, attenuated vaccines are produced in mammalian cell lines from mice, pigs, chickens, and cats [35].

From 1955 to 1963 as many as 100 million Americans may have been exposed to simian virus 40 (SV40) that contaminated the inactivated polio vaccine when it was first introduced [36]. The first oral polio vaccine was also contaminated with SV40 but was only given to people in the original clinical trials. SV40 also contaminated some of the adenovirus vaccines used in that period among military recruits. The SV40 virus came from monkey kidney cell cultures used to produce the vaccines and was not discovered until 1960. Once contamination was recognized, steps were taken to eliminate it from future vaccines. No vaccines licensed for use in the USA currently are contaminated with SV40.

In 1961, SV40 was found to cause tumors in rodents [37]. SV40 can transform human cell cultures into malignant-like cells and has been extensively studied in the laboratory and in epidemiologic studies. Additionally, studies have detected SV40 in some rare human tumors (mesotheliomas, ependymomoas, and osteosarcomas); however, it has not been determined that SV40 causes these cancers [38, 39].

In 1998, the National Cancer Institute undertook a large study, using cancer case information from the Institutes SEER database. The published findings from the study revealed that there was no increased incidence of cancer in persons who may have received vaccine containing SV40 [40]. Another large study in Sweden examined cancer rates of 700,000 individuals who had received potentially contaminated polio vaccine as late as 1957; the study again revealed no increased cancer incidence between persons who received polio vaccines containing SV40 and those who did not [41]. Newborn babies who received SV40 in polio vaccine were followed for 35 years and had no excess risk of cancer [42]. HIV-infected people are at increased risk of development of non-Hodgkin's lymphoma and had no increased risk if they received SV40-contaminated polio vaccine compared to those who had not received it [43]. A case–control study of cancers among Army veterans showed no risk of brain tumor, mesothelioma, or non-Hodgkin's lymphoma associated with receipt of adenovirus vaccine that contained large amounts of SV40 [44].

A 2002 Institute of Medicine Immunization Safety Review Committee was assembled to assess the effects on the people who received the SV40-contaminated vaccine and found the available data "sufficiently flawed" so they were unable to conclude whether or not the contaminated polio vaccine may have caused cancer [45].

The question of whether SV40 causes cancer in humans remains controversial, however, and the development of improved assays for detection of SV40 in human tissues will be needed to resolve the controversy. Early studies showed that many people had antibodies against SV40 but it is unclear if the antibodies used at that time measured antibodies to human viruses similar to SV40 as new testing methods for SV40 antibodies have demonstrated a lack of antibody response in humans in

contrast to animals [46]. Increased detection with more sensitive molecular tools may have detected SV40 laboratory contamination versus presence of SV40 in actual cancerous tissues [47].

In 2010 a controversial report suggested an association between xenotropic murine leukemia virus (MLV)-related virus (XMRV) with prostate cancer and chronic fatigue syndrome [48]. MLV can cause leukemia, lymphoma, and neurological disorders in mice and XMRV shares 96 % nucleotide identity with MLV but only replicates in non-mouse cells. Large epidemiologic studies have shown an absence of XMRV or MLV in humans reflecting no endemicity in human populations. Furthermore, human serum has the ability to inactivate MLV casting further doubt on the links between XMRV or MLV to prostate cancer and chronic fatigue syndrome. XMRV was found to originate as a laboratory artifact during passaging of a prostate tumor xenograft (22Rv1 line) in inbred mice around 1996 by Paprotka and colleagues [49].

In later studies, reagents, human cell lines, and specimens were found to be contaminated with MLV sequences and concern was raised that there may be contamination of human vaccines. Switzer et al. tested eight live attenuated human vaccines using PCR and metagenomics and found no evidence of XMRV in live attenuated human vaccines [50]. Japanese encephalitis virus (JEV) (SA-14-14-2), varicella (Varivax®), measles, mumps, and rubella (MMR-II®), measles (Attenuvax®), rubella (Meruvax-II®), rotavirus (Rotateq® and Rotarix®), and yellow fever vaccine were all negative for XMRV and highly related MLV. The researchers did find novel hamster genomic and retrovirus sequences in the JEV vaccine, most likely originating from vaccine production in Syrian hamster cells.

Conclusion

Cancer is caused by a host of factors. Vaccines have a role in preventing and potentially treating some types of cancer. Components of vaccines and their associated cell lines that viruses are grown in are safe and have not been shown to induce cancer in the vaccinated host.

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Chapter 14
Autoimmunity, Allergies, and Asthma: A Relationship to Vaccines?

Harold C. Delasalas and Russell J. Hopp

Introduction

Perhaps one notable irony related to the practice of medicine today is the evolution of parental attitudes and beliefs related to childhood vaccinations. Despite the undisputable impact that vaccinations have had in improving morbidity and mortality related to serious childhood infections such as bacterial meningitis, smallpox, and polio, we live in an era wherein we take for granted the rarity and potential complete eradication of these illnesses. The other trends that have contributed to the movement of "vaccine refusal" include the widespread dissemination of information, both factual and erroneous; the transition towards patient autonomy; and greater health care literacy within the patient population. The proportion of children exempted from school immunization requirements for nonmedical reasons is the primary measure of vaccine refusal in the United States. Between 1991 and 2004, the mean rate of nonmedical immunization exemption at kindergarten entry increased from 0.98 to 1.48 % at the state level [1]. In a 2009 national survey of parents/guardians of children ≤6 years of age, 93 % indicated that their youngest child had or would receive all recommended vaccines, but only 80 % believed that immunizations were very important to their children's health [2]. In the 2003–2004 National Immunization Survey, 6 % of parents reported having refused at least one vaccine [3], while in another survey 11.5 % of parents refused a vaccine in 2009 [4]. As reflected by these statistics, despite a relatively low

H.C. Delasalas, M.D., Pharm.D. (✉)
Division of Allergy and Immunology, Department of Pediatrics, Creighton University Medical Center, 601 North 30th Street, 3M-100, Omaha, NE 68131, USA

Creighton University School of Medicine, Omaha, NE, USA
e-mail: harolddelasalas@creighton.edu

R.J. Hopp, D.O., F.A.A.A.P., F.A.A.A.I.
Division of Allergy and Immunology, Department of Pediatrics, Creighton University School of Medicine, Omaha, NE, USA

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percentage of children who are under-vaccinated, there is a trend of increasing prevalence of this practice, possibly motivated by potential misconceptions of safety or efficacy. Besides this concerning trend, one also needs to recognize that despite a relatively high vaccination rate *nationally*, there is great *regional* variability. In reality, there are several areas, such as Washington State's San Juan County, wherein 72 % of kindergartners and 89 % of sixth graders are either noncompliant or exempt from vaccination requirements for school entry [5]. Outbreaks of pertussis, measles, and *Haemophilus influenzae* type b (Hib) serve as reminders that the US vaccination levels are inadequate. As health care providers committed to the health and welfare of our patients, it is imperative for us to play a proactive role in countering these alarming trends [6].

An important consideration which drives this debate is the prevalence of media and Internet discussions that often give equal or greater weight to unsubstantiated opinion and anecdotal claims regarding vaccines as compared to the rigorous scientific studies that are required to prove their safety and efficacy. In the media, it is often a divergent opinion that receives greater publicity which may inadvertently place unsubstantiated ideas in the minds of well-intended parents. The Internet is another potential source of biased and unsubstantiated opinion that may lend fodder to further misconceptions. It is easy to fixate and read one viewpoint of an argument without hearing and evaluating rebuttals or opposing evidence. Not only laypersons but even some medical professionals have contributed to the argument against vaccination, thus making it even more difficult for conscientious parents to know whom to trust. There are numerous Web sites that patients and their parents may find online that provide unsubstantiated information regarding the safety of vaccines including www.vactruth.com, www.vaccinetruth.org, and often others of similar voice.

In the 2001 National Immunization Survey, under-vaccinated children were more likely to be black, living in poverty, and having an unmarried younger mother without a college education. In contrast, unvaccinated children were more likely to be white, have a married mother with a college degree, and have an annual family income >$75,000 [7]. Other studies also demonstrate that parents who refuse vaccines or seek parental exemptions are older (36–40 years) and have higher levels of education and household incomes. While awareness efforts have previously been directed towards the first group of parents [8], in order to provide more opportunities for their children to receive necessary vaccinations, an alternative approach will need to be directed towards the latter group of individuals who present their children to our offices for routine pediatric care, but do not accept standard vaccines or the recommended vaccine schedule.

One valid concern posed by patients and parents to primary care providers is drug safety. While we may be accustomed to encountering these inquiries when offering therapy that may not be commonly utilized or the proposal of a novel therapy, it is surprising to encounter similar concerns when it comes to vaccines that have been widely used since the early nineteenth century. Similar to the criticism and skepticism garnered when it was first introduced, several question whether it is truly efficacious, the risk of contracting illness from the attenuated/killed microbe, adverse drug reactions, or alleged development of conditions such as autism and

sudden infant death syndrome (SIDS), among others. Many of these concerns and ideas are unfortunately driven by tenuous evidence or dogmatic propaganda. Some even further question the efficacy of vaccination, denouncing the practice as "money-making schemes of drug companies and doctors." It is imperative as providers to many of these vulnerable children, whose parents' "well intentions" are placing them at risk, to address these concerns tactfully and convincingly. One of the alleged adverse events associated with vaccinations is its potential to promote/exacerbate atopic or autoimmune disorders due to its underlying immunomodulatory properties.

In an editorial published in the New England Journal of Medicine, the author suggests several options that health care providers, individually and as a group, may pursue in order to effectively counter the "anti-vaccination" movement [6]. While there are parents vehemently opposed to vaccinations from a personal beliefs standpoint, there are a significant number of parents that are amenable to vaccinating their children, but encounter barriers or are hesitant due to concerns regarding their safety. To remove barriers to access, efforts need to be made to minimize if not eliminate disincentives to the public, such as copayments or administration fees. Second, school entry requirements for vaccinations should be strengthened and enforced. While complete elimination of options for exemption may inevitably lead to strong opposition, efforts should be made to address the ease of obtaining exceptions and strengthening policies enforcing school entry requirements. Third, both public health officials and professional organizations should address efficiently and effectively misinformation regarding vaccines that is being publicly disseminated through the media. Lastly, we should recognize our audience. While some resistant parents may be effectively convinced by hard statistics and evidence, others are more amenable to facts delivered through a compelling story or an experience they can relate to. Primary care providers represent the best opportunity to influence the vaccine hesitant since they often have a long-standing relationship with the child as their patient. Parents are likely to be more receptive if they recognize that the providers' intentions and actions are motivated by their child's welfare rather than acting as just a messenger for an abstract public health goal [6].

Part I: Vaccinations and Atopic Disease

A phenomenon that has puzzled many scientists and clinicians alike has been the increased prevalence of atopic diseases, such as asthma, allergic rhinitis, and eczema over the past few decades [9]. Since the onset of these conditions is often in early childhood, there is speculation regarding their relationship to vaccinations that are given over the same time period. Moreover, with the significant morbidity associated with atopic conditions, there is an inherent motivation to identify whether there is a contributory or attenuating impact of vaccine exposure upon genetically susceptible individuals.

The hygiene hypothesis is a popular theory which suggests an underlying association between atopic disease and vaccinations [10]. It is based on the observation that decreased or altered exposure to environmental microbes, including vaccine-preventable diseases, improved sanitation, smaller family sizes, shorter duration of breastfeeding, and a lack of serious childhood illness, results in altering the intrinsic immunoregulation which suppresses atopy [11]. There is evidence to support the role of the "hygiene hypothesis" in "promoting atopy" since living in a large family, attending day care in early life, and growing up in a rural area, or ascribing to what is considered an "anthroposophic lifestyle," have been shown to reduce the risk of asthma and allergic diseases [12, 13].

At the molecular level, studies have considered the "yin and yang" of lymphocyte populations (the Th1 and Th2 lymphocyte subsets) as the immunologic basis to of the "hygiene hypothesis." The T-lymphocytes may be divided into two distinct subsets primarily based on their cytokine profile and different immune responses. Th1 type produces IL-2, tumor necrosis factor-beta (lymphotoxin), and interferon gamma and is involved in delayed-type hypersensitivity responses and promoting the effector response of the cellular immune system. On the other hand, Th2 cells secrete IL-4, IL-5, IL-9, IL-10, and IL-13 and promote antibody responses and allergic inflammation. In utero and in newborns, the Th2 profile plays a predominant role. Early in life, it is believed to follow the pattern of the prominent Th2 subset seen in pregnancy. This is believed to play a protective role due to the toxic effects of Th1 cytokines in fetal life. While non-atopic individuals are able to suppress the Th2 profile and promote a more Th1-deviated immune response, atopic children can be programmed to consolidate Th2 responses to allergens within the first 6 months of life [14]. Since early exposure to certain viral respiratory infections and gastrointestinal pathogens promote the development of the Th1 response, some believe that infant vaccines limit and attenuate the maturity of the Th1 response leading to the development of atopy in predisposed individuals. Infants with a positive family history of atopy appear to have an attenuated Th1 response capacity [13, 15] and vaccination of these genetically predisposed children could theoretically increase the Th2:Th1 ratio.

Although this paradigm helps facilitate understanding regarding general principles of allergic diseases, it is likely too simplistic to explain the immunologic mechanisms underlying the hygiene hypothesis. Some have proposed arguments against the concept of the aforementioned relationship between atopy and a skewed Th2 response. One example is that despite the ability of parasitic infections to induce a strong Th2 response [16], parasitic infection exposure actually appears to be inversely associated with the development of atopy and atopic disease [17].

Others have offered alternative explanations to describe the relationship between early infectious exposures and development of atopy. One major theory is based on the ability of regulatory T-cells to control pathogenic immune responses by the secretion of IL-10 and TGF-β, regulatory cytokines that inhibit both Th1 and Th2 responses in experimental models. Studies have demonstrated that infectious exposure in childhood may be crucial in the production and development of T-regulatory (Tr) cell response and its ability to regulate autoimmune and allergic processes [18].

Other components of the innate immune system such as dendritic cells and toll-like receptors also appear to play a protective role against the development of allergic disease. Dendritic cells (DC), the professional antigen-presenting cells, are stimulated to produce cytokines that may down-regulate allergic responses depending on host factors. The induction of the Th1 response in adults appears to be dependent on optimal activation of the individual's dendritic cells during infancy. The activation of DC and their maturation are typically triggered by stimulation of toll-like receptors (TLR) identified on their surface. Microbial antigens have the intrinsic capacity to activate dendritic cells and T-regulator cells efficiently. The absence of substantial microbial antigen exposure in early life may also attenuate the interaction between dendritic cells which help mediate differentiation and effector function of T-cells as well as stimulation of Tr cells. Since modern subunit vaccines often lack various microbial components such as lipopolysaccharides, heat-shock protein, and cPG motifs of bacterial DNA, this may result in suboptimal activation of dendritic cells compared to a natural infection [19]. The relationship proposed between early infectious exposure and regulatory role of the aforementioned immune effector cells (i.e., dendritic and Tr cells) affords a novel advancement to the hygiene hypothesis [13].

Studies do reveal differing Th1/Th2 profiles in children who were vaccinated against pertussis (with both the acellular and whole-cell formulations), tetanus, measles, and Bacillus Calmette–Guerin (BCG) compared to those who were unvaccinated. However, a consistent promotion of the Th2 profile was not always seen. In infants who received acellular *Bordetella pertussis* vaccine (aP), a mixed Th1–Th2 response was observed. Infants receiving BCG at birth, however, developed a preferential Th1 response more rapidly, compared to the natural decay of Th2 seen in unvaccinated infants. In general, T-cell responses following vaccination of human infants are characterized by an attenuated Th1 response, and it is uncommon for preferential Th2 polarization to occur in human infants [13, 20]. The lack of Th2 polarization is believed to be due to the remaining susceptibility and exposure of children to natural infections to facilitate the aforementioned role of immune regulatory cells in ensuring a balanced Th1/Th2 response.

Associations of Selected Vaccinations with Atopic Disease

Pertussis/Diphtheria/Tetanus

Whole-cell pertussis was the first vaccine that was proposed to have an association with atopic risk. A cross-sectional survey showed that the relative risk of asthma after vaccination with whole-cell pertussis vaccine was over five times that of controls not vaccinated against pertussis. Inherent in this observation is the inability to establish causation, but merely association [21]. One strong piece of evidence in support of a possible association between pertussis vaccination and asthma comes from a prospective cohort of children in Christchurch, New Zealand. In the subset

of patients who received neither pertussis nor oral polio vaccine, there were no reported episodes or consultation for asthma or other allergies at the 5- and 10-year follow-up. Between age 11 and 16 years, some asthma/allergy events were recorded but the risks were still relatively low. On the other hand, asthma developed in >20 % of the 1,184 children who were vaccinated [22]. Some have theorized that the tendency for atopy lies in the propensity for increased IgE production that occurs after natural pertussis infections, and possibly after pertussis vaccination.

However, subsequent prospective studies did not support these earlier outcomes. A Swedish trial randomized 669 children into four groups to receive components of acellular pertussis (aP) versus whole-cell pertussis (wP) and compared this to a control group who received only DT vaccine. Incidence rate after adjustment for family history of atopic disease at the age of 2.5 years demonstrated similar incidence rates for atopic disease [13, 23].

A large cohort study involving 167,240 children enrolled in four HMO organizations, between 1991 and 1997, with follow-up from birth until at least 18 months to a maximum of 6 years has been conducted. Vaccinations for diphtheria, tetanus, and whole-cell pertusiss vaccine, among others, were evaluated for association of asthma risk. While adjustment for gender, date of birth, racial, ethnic, and socioeconomic characteristics of residence were made, no information on family history of asthma or other risk factors was ascertained. Diagnosis of asthma was based on identification by physician of asthma diagnosis and prescription of asthma medications. The relative risk for diphtheria/pertussis/tetanus (DTP) was found to be 0.92 (0.83–1.02) and hence no significant association was ascertained [24].

In a population-based project evaluating data from the International Study of Asthma and Allergies in Childhood (ISAAC) to determine if an epidemiologic link between infant immunizations and prevalence of atopic disease in childhood exists on a population level, a negative correlation between rates of local DTP immunizations and wheezing, hay fever, and eczema was found in 13–14-year-old children. No association between atopic disease and local immunization rates was found in the 6- to 7-year-old age group. No association with national immunization rates and atopy was found in either age group. Since there was consideration that factors influencing immunization rates and atopic disease may be influenced by economic aspects of each participating country, analysis was adjusted for per capita GNP. This resulted in only marginal reduction in magnitude of effect estimates, but the negative and absent associations remained constant [13, 25].

One study evaluated the propensity of the acellular pertussis vaccine to mediate atopy in an adult population. One hundred adult hospital employees were randomized to receive either a two-component acellular pertussis or a meningococcal vaccine as a control. Serum-specific IgE levels to two indoor allergens, cat and dust mite, and two outdoor allergens, Alternaria and ragweed, were measured by radioimmunoassay on blood collected before and 1 month post vaccination. No significant change in the serum-specific IgE levels was found after vaccination [26]. Some limitations of the Assa'ad study would be timing of exposure to various allergens, which may impact the increase in serum-specific IgE levels, and a 1-month

reassessment after vaccination may be insufficient. Additionally, the study evaluated sensitization without characterizing patient symptomatology.

Influenza

Influenza vaccine is unique in that it is reformulated annually to cover the predominant strains of the anticipated flu season. There have not been significant studies to date that have supported or denied the relationship of influenza vaccination with the development of asthma. There has been recent scrutiny concerning the use of live attenuated influenza vaccine compared to the trivalent inactivated vaccine in a 2007 study. The large multinational clinical trial compared the safety and efficacy of the intranasal trivalent attenuated vaccine with the intramuscular inactivated vaccine in children 6–59 months of age prior to the 2004–2005 influenza season. It found that wheezing within 42 days after administration of dose 1 was more common with the live attenuated vaccine than that seen with the inactivated vaccine, primarily in children 6–11 months of age (3.8 % versus 2.1 %, $p=0.076$) [27]. A follow-up study was done in the subset of children who had contributed to these results through atopy surveys and DNA collection. One significant finding was that a family history of asthma ($p=0.001$) was associated with wheezing after vaccination. There was initial concern that live attenuated cold-adapted influenza vaccine-trivalent (CAIV-T) was associated with more wheezing exacerbations than the inactivated form. Fleming et al. found that children and adolescents tolerated this well without any significant increase in adverse pulmonary sequelae [28]. Still, given these data and other studies that appear to demonstrate an increase in adverse outcomes related to wheezing in children, some guidelines have limited the use of the intranasal vaccination in children less than 2 years of age, in children 2–4 years of age with a history of recurrent wheezing, or even in older children with a diagnosis of asthma [29].

Influenza is a viral infection that has long been implicated as a mediator of acute asthma exacerbations which may result in hospitalizations. A population-based retrospective cohort study with medical and vaccination records in four large health maintenance organizations in the United States during three influenza seasons revealed that controlling for asthma severity, influenza vaccination protects against acute asthma exacerbation in children 1–6 years of age [30]. Despite this, there continues to be an ongoing conversation regarding the efficacy in preventing influenza-related exacerbations. One randomized double-blind placebo-controlled trial in the Netherlands evaluated children 6–18 years of age comparing inactivated influenza vaccine versus placebo in over 600 children, throughout one flu season. Results failed to demonstrate a difference between interventions between the groups related to the number or the severity of influenza-related asthma exacerbations. Despite data from questionnaires that supported improved health-related quality of life and respiratory symptoms, spirometry results during all seasons were similar. Only 1.8 % of all asthma exacerbation was found to be influenza related. Again, consideration needs to be made related to geographical region, the prevalence of

influenza during a particular season, and the role of herd immunity in reducing exposure when evaluating data that fails to demonstrate benefit of intervention [31].

Pneumococcus

There have not been any studies that have suggested or explored the potential for pneumococcal vaccination promoting atopic disorders. *Streptococcus pneumoniae* is known to cause a variety of diseases in both children and adults, including meningitis, sepsis, and pneumonia. Patients with asthma may be colonized with pneumococcus and when it is present it appears to increase the risk for asthma exacerbation and invasive pneumococcal disease [32]. In children, colonization of the upper airways with pneumococcus is found to be associated with increased risk of wheezing and asthma [33]. The adult pneumococcal vaccine is a 23-valent polysaccharide preparation approved for prevention of invasive disease [34]. The 13-valent pneumococcal conjugate vaccine (Prevnar-13®) has replaced the 7-valent conjugate vaccine and is approved for children aged 6 weeks through 71 months for the prevention of invasive pneumococcal disease and otitis media [35].

Measles/Mumps/Rubella

In 1994, skin prick tests for atopy of a group of 262 adolescents showed that the prevalence of atopy in the group that survived the 1,979 measles epidemic in Guinea Bissau was half that of the group not naturally infected, but vaccinated against measles. Criticism of this study cited potential for confounding bias, given that atopy is associated with decreased cellular immunity, and children who were naturally infected with measles would have been more likely to die in the epidemic and hence be underrepresented in this arm of the study [36]. In a large prospective study of a British birth cohort who were evaluated for the development of atopic disease from birth to the age of 5, the 7,440 children vaccinated against measles had a risk of atopy that was similar to those not vaccinated against measles [37]. More recent studies including a British and an American cohort demonstrated no increased risk of atopic disease associated with measles/mumps/rubella (MMR) vaccination [24, 38]. In a large prospective study [39], measles and mumps vaccination was found to significantly reduce the prevalence of atopic dermatitis and hay fever, with a tendency towards reduction of asthma and allergic sensitization. Based on the large epidemiologic study utilizing data from ISAAC, a protective role for measles vaccination was found with regard to hay fever and eczema [25].

Smallpox

In a national birth cohort study from 1997 to 2001, detailed information from nearly 2,000 women including smallpox vaccination from school health records, atopic

status assessed serologically, and telephone interviews evaluating atopic symptoms was analyzed and reviewed. No association between vaccination status in childhood and risk of atopy or allergic rhinitis was found. Adjusting for birth cohort, sibship size, age of woman's mother at birth, and social class in childhood did not alter these results [40].

Bacillus Calmette–Guerin

Though not administered routinely in the United States, the BCG vaccine is given in other countries primarily to prevent tuberculosis (TB). Notably, its efficacy is best established in preventing tuberculous meningitis or disseminated tuberculosis (military TB), in the pediatric age group. Its effect on pulmonary TB is more variable and depends on geographic susceptibility patterns [41]. Distinct from the aforementioned vaccines, early evidence appeared to support a protective versus contributory role of BCG in the development of atopic disease. It is found to have Th1 stimulatory effect along with a Th2 inhibitory effect and hence has drawn attention for potentially affording a protective effect against the development of atopic diseases. An early retrospective study reviewed the correlation of atopic symptoms, serum IgE, and Th1/Th2 cytokine profiles in patients who had been vaccinated with BCG and developed a positive tuberculin response at the age of 12. It was found that of 867 patients, 36 % manifested atopic symptoms at some time. A strong inverse association was found between positive tuberculin responses and atopic symptoms, IgE, and Th2 cytokine profiles at both 6 and 12 years of age. Also, asthmatic symptoms were notably 1/2–1/3 as likely in positive tuberculin responders as compared to negative responders [42]. Despite these earlier observations, subsequent and more recent studies have confirmed a long-term neutral association between BCG vaccination and atopic disease. One German birth cohort study evaluated more than 900 children from birth to 5 years of age, regularly examining them for the development of atopic disease along with measuring serum IgE concentrations. Despite a transient suppressive effect on atopy at 24 months, no statistically significant difference existed between the BCG-vaccinated and non-BCG-vaccinated infants in either atopic manifestations or total IgE concentrations in long term [39]. Additionally, a large epidemiologic study, utilizing data from ISAAC, supported these findings that no correlation was identified with vaccination rates against tuberculosis and the prevalence of symptoms related to atopic disease [25].

An international study of 1,704 infants in Thailand, Argentina, and Turkey sought to evaluate whether exposure to the standard BCG vaccine, given at birth, would modulate the development of asthma or allergic symptoms. At 2 years of age, vaccinated children were evaluated based on atopic symptoms evaluated by the ISAAC questionnaire as well as allergic sensitization. Data were evaluated to determine if an association existed between BCG response (based on PPD induration) and the presence of atopy (positive wheal response on skin prick test) or a positive response to the ISAAC core questions for wheezing, asthma, rhinitis, and eczema. A negative versus a positive PPD response was found to correlate to the risk of

having allergic history by 2 years of age in infants in Turkey (RR 2.11, $p=0.005$) and Thailand (RR 2.16, $p=0.02$) but not Argentina (RR 1.09, $p=0.70$). On the other hand, atopic sensitization was not found to be significantly correlated with PPD response [43].

A recent meta-analysis [44] has reviewed the literature encompassing 17 major studies, only one of which was a randomized controlled trial. It found no protective effect of BCG vaccination against the risk of sensitization as judged by specific IgE tests, OR 1.31, 95 % CI 1.07–1.60, or skin prick testing, OR 0.87, 95 % CI 0.67–1.13; risk of atopic eczema/dermatitis, OR 0.84, 95 % CI 0.67–1.09; and risk of allergic rhinoconjunctivitis, OR 1.07, 95 % CI 0.89–1.28. There was an associated protective effect identified against the risk of asthma OR 0.73, 95 % CI (0.56–0.95). Among the strengths of this work are the inclusion of several relevant atopic outcomes, consideration of heterogeneity of studies, as well as publication bias. Given the limitations of epidemiologic studies and relatively modest benefit seen in preventing the development of asthma, it would be unlikely that BCG would be considered for incorporation into vaccination programs in the United States, for the purposes of "atopic prophylaxis." Since the risk of allergen sensitization was not found to be influenced by vaccination with BCG, the nature of the suppressive role of BCG vaccination on the development of atopic symptoms is unclear. In a study by Choi et al., BCG vaccination in adult patients with moderate to severe asthma was found to have improved lung function and reduced medication use [45]. Ideally, randomized controlled trials in countries where BCG vaccination are routinely performed should be undertaken to definitively evaluate its potential association with atopy.

Role of Adjuvants

Pure recombinant or synthetic antigens used in modern-day vaccines are generally less immunogenic than older live or killed whole-organism vaccines. Alum remains the sole adjuvant approved for human use in the majority of countries worldwide. Many conventional vaccines have been designed to induce antibodies using classical adjuvants such as oil-based emulsions and aluminum salts to prolong the release of antigen. The increased humoral response induced by aluminum salts appears to be associated with a predominant Th2 profile. Evidence of this was found in a series of children who received booster vaccinations with aluminum-adsorbed DT which demonstrated an increased IgE response to tetanus toxoid compared to non-adsorbed DT. However, this was not found to translate into increased atopic symptoms in the Al-adsorbed DT group at the age of 12 [46]. Despite the absence of evidence to support its contributory role in the development of atopic conditions, the trend in current vaccine design has been to utilize adjuvants that may induce a broader immune response, encompassing both humoral and cellular pathways, theoretically producing a balanced response [47]. Some chemical adjuvants such as MF59, ISCOMS, IFA, SBAS2, SBAS4, Montanide ISA51, and others have been tested in humans,

finding antigen-specific T-cell responses, but only a few published reports of MHC-1 restriction and insufficient Th1 response. Some limitations related to the development of new adjuvants include the following:

1. Unacceptable side effects and toxicity, especially in the pediatric population.
2. Since adjuvants can only be approved as part of a vaccine combination, many good candidates may not reach the registration phase because the vaccine combination was found to be ineffective or had an unacceptable toxicity profile.
3. With considerable funds invested in the development of new vaccine antigens, few companies are prepared to risk the investment by conducting clinical trial programs of candidate antigens with new and unproven adjuvants.
4. Most vaccine companies keep proprietary adjuvant data secret until they wish to register a product based on their adjuvant and there is a limited amount of information shared with other companies which could facilitate novel adjuvant development [48].

Thimerosal

Thimerosal, a preservative which is mostly historic in its application, received a significant amount of attention due to a concern for its purported association with the development of autism. Thimerosal contains ethyl mercury and has been used in various vaccine formulations since the 1930s. In 1997, the US Food and Drug Administration (FDA) noted that due to the increasing number of vaccines being recommended in early infancy, the exposure to ethyl mercury may exceed the level set by the US Environmental Protection Agency (EPA) guidelines [49]. There is no convincing evidence of harm caused by low doses of thimerosal except for minor local reactions like redness and swelling. In July 1999, the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC) issued a joint statement asking vaccine manufacturers to remove thimerosal from childhood vaccines as expeditiously as possible. This statement, intended to reassure the public regarding the safety of vaccines, paradoxically raised concerns among those who believed vaccinations fueled the ‘autism epidemic’. No studies evaluating the association between thimerosal and atopy have yielded any positive evidence of a causal relationship. Additionally, despite its removal, there was no significant change or reduction in the incidence of autism in the United States. Similarly, there is no evidence to associate it with the development of atopy, exacerbation of underlying autoimmune conditions, or promotion of autoimmune processes [50]. Since 2001, vaccines licensed by the FDA for use in children have been thimerosal-free or contain only trace amounts, with the exception of multi-dose formulations of influenza vaccine. Multi-dose vials are formulated with thimerosal to safeguard against contamination once the vial is opened. All single-dose units, including the live attenuated version of the vaccine, do not contain thimerosal. To date, three US health agencies (the CDC, FDA, and NIH) alongside three independent

organizations (National Academy of Sciences' Institute of Medicine, Advisory Committee on Immunization Practices, and the American Academy of Pediatrics) have reviewed the published research and deem thimerosal a safe product for use in vaccines [49].

Vaccination series as a whole

While each individual vaccine has been discussed with respect to its potential for promoting atopy, some recent studies have evaluated the standard vaccination series as a whole for a potential association to atopic disorders. One such international, multicenter study by Gruber et al. evaluated greater than 2,000 infants, with established atopic dermatitis and family history of atopy, between the ages of 11 and 25 months. In this population, the mean age at first vaccination was 1 month, 63 % received some vaccination at birth, and by 3 months, 90 % had received some form of immunization. Exposure to vaccines against DTP, polio, Hib, hepatitis B, varicella, meningococci, pneumococci, MMR, and BCG vaccines were reviewed from immunization cards. Patients had IgE levels drawn to various environmental allergens and eczema severity (measured by SCORAD) included in the analysis. Results found that immunization against any target was not associated with an increased risk of allergic sensitization to food or inhalant allergens. Incidentally, varicella immunization (although only 0.7 % participants were immunized) demonstrated an inverse association with total IgE and eczema severity. Cumulative received vaccine doses were found to be inversely associated with eczema severity ($p = 0.0107$) [39].

Another well-controlled study was performed using computerized records from four large HMOs from 1991 to 1997 to evaluate 18,407 children (11 % developed asthma). No significant increase in the relative risk of asthma in vaccinated versus non-vaccinated children was found [RR 0.92 for DTP, 1.09 for polio, 0.97 for MMR, 1.07 for Hib, and 1.09 for hepatitis B vaccine] [24]. In a German atopy risk-enhanced birth cohort of 1,314 neonates in five German cities, Grueber et al. evaluated atopic symptoms and diagnoses derived from structured interviews, total IgE, and specific IgE via CAP FEIA. Children were subsequently grouped in dose percentiles according to cumulative dose of any vaccine given up to 5 years. Analysis of the data demonstrated that cumulative vaccine dose was inversely related to atopic dermatitis and asthma at 6 months, 2 years, and 5 years of age. Allergic sensitization rates were inversely related to cumulative dose at age 2 [39].

Childhood Immunizations and Atopic Disease

Matheson et al. were interested in evaluating the impact of immunizations on the development of symptoms of atopic disease into middle age. Result from their study, looking at over 500 individuals who participated in the Tasmanian

Longitudinal study, was that there was no association between immunization and specific allergens including animals, pollen, and dust mites. No association was found between any routine childhood immunization and risk of atopic symptoms in this study. Risk of asthma identified at age 7 in an earlier analysis of this study was not found to continue into adulthood for these patients [51].

Conclusion

While the benefits of the standard vaccination series have been substantiated in children and adults, speculation and hesitation have arisen over the past few decades related to potential vaccine-related adverse events. The morbidity associated with atopic conditions and their increasing prevalence have motivated many epidemiologists and clinicians to reconsider environmental factors that are either causing or contributing to this phenomenon. Given the evidence available in the literature today, there are no substantial data to support the need to modify our current vaccination practices in order to prevent the promotion of atopic conditions. It is imperative that clinicians provide patients and parents of patients a consistent message in order to safeguard not only their health but also those in the community they live in.

Part II: Vaccination and Autoimmunity

While vaccine administration is regarded as an effective tool in preventing infectious diseases, theoretical concerns have arisen in utilizing an agent with immune-stimulating properties in a patient with an underlying autoimmune disease. Despite this, it is important to recognize that individuals with autoimmune disorders are often at higher risk for developing infectious complications secondary to an underlying dysregulated immune system or through immunosuppressant therapy [52]. It is imperative that these concerns be systematically addressed by evaluating the literature to determine the extent in which vaccines pose the aforementioned risks to this patient population. This review is intended to improve awareness, identify authentic concerns, and dispel myths regarding the relationship between vaccines and autoimmunity. With better understanding of the risks and benefits of vaccination in patients with underlying autoimmunity, future guidelines may provide recommendations to guide both primary care providers and specialists caring for this vulnerable patient population.

Purported mechanisms by which vaccines may induce autoimmune disease are primarily extrapolated from the capacity of the natural course of infection to promote autoimmunity. Two of the proposed mechanisms are through molecular mimicry (an antigen-specific pathway), and bystander activation, which is nonspecific. Molecular mimicry is based on the structural similarity between the epitopes found on host antigens and those of microbial agents. A classic example is found in

rheumatic fever wherein there is cross-reaction between antibodies directed against the group A beta-hemolytic Streptococcus and host heart tissue antigens. Another example is seen with HSV-1 infections wherein the T helper clones elicited by HSV-1 cross recognize HSV-1 peptides as well as self-antigens such as corneal protein and immunoglobulin G2a. It is important to recognize that besides shared epitopes, it is necessary for these peptides to be presented to autoreactive T-cell clones. Additionally for an autoimmune disease to develop, the presence of an infection or a strong adjuvant, such as complete Freund's adjuvant (CFA), should be present. In a historical vaccine against Lyme disease (LYMErix®) [discontinued in the United States in 2002] molecular mimicry was noted between the outer protein A (OspA) and human alpha myosin heavy chain, HLFA1, in neural tissue. This has been implicated as the potential pathogenic mechanism for chronic arthritis that may develop in certain susceptible patients exposed to the LYMErix vaccine. Another example is with BCG-induced arthritis, wherein animal models have demonstrated that *Mycobacterium tuberculosis*-specific T-cell clones are able to recognize antigens belonging to human joint proteins [53].

The theory of bystander activation is based on the release of sequestered self-antigens from infected host tissue leading to activation of antigen-presenting cells and subsequently dormant auto-reactive T-cell clones [54]. Bystander activation may occur when vaccines that contain many pro-inflammatory nonspecific antigens, including the lipid A fraction of LPS (which function as adjuvants), are injected. Other adjuvants such as alum (aluminum phosphate or aluminum hydroxide) may invoke the process of bystander activation by releasing pro-inflammatory cytokines that activate intracellular innate immune responses and dendritic cells. Notably, the development of specific autoantibodies, without outward clinical symptomatology has been described, such as rheumatoid factor after vaccinations with tetanus toxoid (TT), typhoid–paratyphoid A and B (TAB), diphtheria, polio, smallpox, and mumps [55]. Recently Toplak et al. observed an increase (15 %) or an appearance (13 %) of autoantibodies, 6 months after flu vaccination, in 92 apparently healthy medical workers. Since this population apparently had a high baseline (pre-vaccination) rate of autoantibody positivity, one should be cautious regarding extrapolation or generalization of these data [56].

Besides molecular mimicry and bystander activation, there have been other reported autoimmune reactions where vaccines have been implicated. One example is immune thrombocytopenic purpura (ITP) occurring after MMR vaccine administration wherein the process of autoimmunity has been ascribed to the same one invoked through the course of the natural disease, such as an immune response to infected megakaryocytes or their precursors. Other autoimmune associations (Table 14.1) have also been reported and are discussed in greater detail below.

The National Academy of Sciences' Institute of Medicine has validated associations related to Td, polio, and measles vaccines with Guillain–Barré Syndrome (GBS), MMR vaccine with ITP, and rubella with chronic arthritis. The vaccine found to be most commonly associated with autoimmunity is hepatitis B with systemic lupus, rheumatoid arthritis, and other nonspecific autoimmune manifestations. The prevalence of autoimmune reactions that have been linked to vaccinations

Table 14.1 Vaccines and autoimmune reactions in which molecular mimicry or bystander activation mechanisms have not been suggested or demonstrated

Autoimmune disease	Vaccine	Rate or number of reported cases
ITP	Measles/mumps/rubella	1:30,000
GBS	Menactra®	0.2:100,000 person-months
Myopericarditis	Smallpox	8:100,000
Transverse myelitis	Different vaccines	37 cases in the period 1971–2007
Encephalomyelitis–polyneuritis	Semple rabies vaccine	0.1–0.2:100,000
Encephalitis–ADEM–GBS	Yellow fever	0.4–0.58:100,000
Vasculitides	Influenza–hepatitis B–other vaccines	48 cases since 1974
Inflammatory myopathies	Different vaccines	13 cases
SLE	Hepatitis B and other vaccines	25 cases
RA	Hepatitis B–tetanus–anthrax diphtheria/tetanus/polio	16 cases

Modified from Salemi S, D'Amelio R. Could autoimmunity be induced by vaccination? Int Rev Immunol. 2010;29:247–69

ITP immune thrombocytopenic purpura, *GBS* Guillain–Barré syndrome, *ADEM* acute disseminated encephalomyelitis, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis

is fairly small, much less than 1:10,000 with respect to the millions of vaccinations given annually worldwide. In comparison to infection- versus vaccine-implicated autoimmune reactions, the latter typically have a milder, self-limiting course and a lower incidence rate. Clinical autoimmune syndromes most often associated with post-vaccinations are those with prominent neurologic features (multiple sclerosis, acute demyelinating encephalomyopathy, and transverse myelitis) [53].

Association of Selected Autoimmune Diseases with Vaccinations

Multiple Sclerosis

There are two large case–control studies, at the time of this publication, evaluating the association between hepatitis B vaccination and development of multiple sclerosis. The nurses' study evaluated greater than 100,000 nurses, of whom 192 women had received a diagnosis of multiple sclerosis (MS) and compared them to 645 matched controls. The main analysis demonstrated that the age-adjusted relative risk of MS for vaccinated versus unvaccinated healthy women was 0.9 (95 % CI (0.5–2.9)), while the corresponding relative risk for women vaccinated within 2 years before their MS diagnosis was 0.7 compared to healthy unvaccinated controls [57]. Another study evaluated the potential role of hepatitis B, tetanus, or influenza vaccines to exacerbate MS symptoms. Six hundred and forty-three patients with MS

relapse symptoms were identified by a European database and confirmed by neurology visits. Vaccination status was determined by telephone and confirmed by medical records. The vaccines evaluated did not appear to exacerbate MS with RR of relapse with any vaccine at 0.71 (RR for individual vaccines: 0.67 for Hep B, 0.75 for Td, and 1.08 for influenza) [58]. The US Committee for Immunization Safety Review recognizes the conflicting evidence in the literature and upholds their position that there is no definitive evidence to confirm the association between MS onset or relapse with hepatitis B vaccination [59].

Systemic Lupus Erythematosus

The potential for systemic lupus erythematosus (SLE) onset post vaccination has been rarely reported. In a large case control study on 265 SLE patients and 355 healthy controls, hepatitis B vaccination was not identified as a risk factor for SLE onset [60]. In contrast, hepatitis B vaccination compared to TT was reported to represent a risk factor for different autoimmune conditions including SLE and rheumatoid arthritis (RA) [61]. Vaccination of patients with known SLE with a variety of vaccines has been proven safe and vaccine-induced flares are found to be infrequent and mild [62]. In 2010, Wiesik-Szewcyk examined influenza vaccine safety and immunogenicity in 62 SLE patients. Despite anecdotal episodes of disease worsening with inactivated influenza vaccine, the evidence supports its safety in these patients as long as patients were in a quiescent state when immunized [63]. In a review of nearly 940 SLE patients, by Salemi et al., substantial safety and immunogenicity of vaccines such as influenza, pneumococcal polysaccharide, hepatitis B, tetanus toxoid, and Hib were reported, despite findings that the mean antibody titers were generally lower, dependent on the degree of immunosuppression in these patients [64].

Guillain–Barré Syndrome

GBS has been associated with infections such as Campylobacter and Haemophilus through molecular mimicry mechanisms between pathogen antigens and peripheral nerve gangliosides. GBS has reportedly been associated with different vaccines including BCG, small pox, rubella, and diphtheria, but the strongest association was with swine influenza in 1976–1977. GBS was found to have developed in 1:100,000 vaccinees (approximately 5–10 times the background rate) in a population of over 40 million persons vaccinated. Notably, no association was noted with the swine influenza pandemic in 2009 and GBS. A slight but statistically significant association has been found between tetravalent diphtheria toxoid-conjugated meningococcal vaccine and GBS (1.25 risk of GBS per million doses distributed to patients aged 11–19) [64].

Several natural infections have been associated with the onset of insulin-dependent diabetes mellitus (IDDM) postulated through mechanisms of molecular mimicry, bystander activation, or direct viral B cell infection. The role of vaccinations as possible IDDM inducers has been debated. In a study published by Hiltunen

et al., IDDM development was reported on average 2.5 years after MMR vaccine administration in 364 healthy children [65]. The pathogenesis was believed to be secondary to a defective post-vaccine mumps-specific antibody response which may mediate pancreatic beta cell damage. In contrast, a Swedish study in children found that measles vaccine was likely to play a protective role in recent onset diabetes. In 2001, DeStefano and colleagues conducted a large study that found no supporting evidence for an increased risk of IDDM related to various childhood vaccines or the timing of their administration [24]. This observation was recapitulated in a study done in 2004 [66].

In 2009, Zuccotti et al. found that in 105 IDDM patients, protective antibody response was comparable at one month between virosomal influenza and standard subunit influenza vaccine [67]. In comparing evidence gathered in nearly 307 IDDM children and adults, hepatitis B appears to be safe albeit less immunogenic than in healthy controls [68]. Notably, immune-stimulating agents such as thymopentin (TP5) or supplementary vaccine doses have been found to improve this response. In a small group of patients studied by Kostinov et al. who were vaccinated against pneumococcus, a lower immunogenic response was noted in patients with IDDM versus their healthy counterparts [69]. Safety of vaccination in IDDM pts was established with 23-valent pneumococcal vaccine [69].

Rheumatoid Arthritis

In 2009, Salemi et al. evaluated safety and immunogenicity of 28 patients treated with TNF-alpha blockers and immunized with influenza vaccine. Results confirmed safety and demonstrated protective antibody titers that remained at protective levels 6 months afterwards. After 1 year, comparable degree of protection against influenza was found between patients treated with TNF anatagonists versus healthy controls [70]. In 2010, Van Assen et al. noted that while a reduced specific antibody response was seen in those vaccinated 4–8 weeks after receiving treatment with Rituximab (RTX), a slightly restored response may be achieved by delayed administration (6–10 months) after RTX dosing [71].

For data compiled with pneumococcal polysaccharide vaccines, which is T-cell independent, in 710 RA patients (328 treated with TNF-α blockers, 68 under RTX), safety is established but immunogenicity is heavily reduced by RTX and appears to be compromised by methotrexate more than by TNF-α blockers. In 2010, Bingham et al. reported that response to tetanus toxoid demonstrated a comparable response in both RTX- versus MTX-only-treated patients [72].

Immune Thrombocytopenic Purpura

Cases of ITP post MMR are considered causally linked (1:30,000) less than that seen with natural cases of measles and rubella infection. A recent study demonstrates that ITP that develops within 1 month post MMR vaccination may

demonstrate resolution within 1 month in 75 % of patients and in a small minority may take 6 months to resolve [64].

Transverse Myelitis

Agmon-Levin et al. conducted a review of cases of transverse myelitis arising post vaccination from 1970 to 2009 and identified 37 cases that developed after different vaccines, including DTP, rabies, OPV, and pertussis. The most frequently implicated vaccine was hepatitis B (associated with 13 cases), followed by MMR (6 cases). Given that several vaccinations are implicated, one hypothesis is that a common factor, such as a common adjuvant, may be implicated [73].

Vasculitides

Since 1974, 48 cases of vasculitides have been reported in the literature with a temporal association after vaccinations. Most often implicated has been the influenza vaccine (30/48 cases) [64]. The underlying mechanism is unclear but is postulated to be that these individuals have an underlying indolent autoimmune condition with symptomatology that is "triggered" by vaccination. In 2008, Stassen et al. evaluated the safety and efficacy of influenza vaccine through a retrospective study of 230 patients with vasculitides, a majority of which were Wegener's. Outcomes demonstrated safety with relapse rate actually being found to be lower in the vaccinated versus unvaccinated group. Seroconversion rate was fairly comparable for the various influenza strains tested at that time [74].

Myasthenia Gravis

In patients with a definitive diagnosis of myasthenia gravis, a retrospective study of those vaccinated against influenza established its safety without any increase in hospitalizations [75].

Chronic Arthritis

Arthritis has been reported to be associated with immunizations, most often with the hepatitis B vaccine. These findings however are primarily derived from case reports and small case series. In children with chronic arthritis, safety and immunogenicity were comparable to those observed in normal controls for influenza, hepatitis B, conjugated meningococcal, or MMR vaccines [64]. Notably, despite the previously

mentioned description linking the outer surface protein in *Borrelia burgdorferi* with various human antigens, the arthritis that arises in some recipients of the vaccine against Lyme disease does not appear to be related to the mechanism of molecular mimicry [76].

Encephalomyelitis–Acute Disseminated Encephalomyelitis–GBS

Yellow fever vaccine has been reported to be related to neurological complications including encephalitis, acute disseminated encephalomyelitis (ADEM), and GBS. However, the incidence of this is extremely rare. During a vaccination campaign in Kenya, the incidence of post-vaccine encephalitis was quoted as 5.8 per million immunized. Neurologic complications such as GBS, ADEM, or encephalitis were found to occur in 4 per million distributed doses in 2005 [77, 78].

Quadrivalent Human Papilloma Virus Vaccine and Autoimmunity

The quadrivalent human papilloma virus (HPV4) vaccine (Gardasil®) has demonstrated efficacy in reducing the risk of cervical dysplasia and genital warts caused by HPV types 6, 11, 16, and 18. Since gaining FDA approval in 2006, it has become widely available and is recommended for use in females between the ages of 11 and 12 years to prevent cervical and anal intraepithelial neoplasia and cervical and anal cancer. It may be administered as young as 9 years of age with catch-up vaccination for females aged 13–26 years. There is a bivalent vaccine also available (Cervarix®) which was approved in 2009 and has provided similar albeit slightly less efficacy in preventing CIN2 and severe cervical disease in women compared to studies evaluating its quadrivalent counterpart (30 % versus 20 % efficacy in preventing CIN2 or more severe disease due to all HPV types). No head-to-head efficacy trials have directly compared these two vaccines, and guidelines have not supported the use of one over the other in the general patient population. In 2009, the FDA approved the use of the quadrivalent vaccine in males aged 9 through 26 to reduce the likelihood of acquiring genital warts. The indication was further expanded in 2010 to include the prevention of anal intraepithelial neoplasia and anal cancer. There has been some speculation, especially among vaccine skeptics, that an increasing use of HPV4 may promote a higher incidence of autoimmune disorders in a population (young women) already considered to be at high risk for developing these conditions [79].

The vaccine contains virus-like particles composed of the L1 major capsid protein of the four principal HPV types implicated in CIN and related diseases (6, 11, 16, and 18). It also contains an aluminum adjuvant, but does not contain whole

HPV virus, thimerosal, or antibiotics. In a recent study, Chao and colleagues prospectively evaluated the development of autoimmune conditions in over 180,000 young (aged 9–26) female subjects. Participants from two managed care organizations received 1–3 doses and were followed for 180 days, between August 2006 and March 2008. Investigators looked for 16 autoimmune conditions, which included SLE, RA, type 1 IDDM, Hashimoto's thyroiditis, Grave's disease, and MS, among others. New-onset cases were identified by a review of electronic medical records comprising ICD-9 codes, abnormal laboratory values, and pharmacy prescriptions. Any cases identified prior to January 2004 and date of first dose of HPV-4 vaccine were excluded and considered preexisting. In-depth case review was conducted for potential new-onset cases who had been health plan members for ≥12 months prior to receiving the first dose of HPV4. De-identified medical records were reviewed by three clinician expert panels from Kaiser Permanente specialized in the diagnosis and treatment of cases they were evaluating. The panel rated the level of diagnostic certainty as either strong or weak. Members were also masked to the dates of HPV4 vaccination. Incidence rates in the vaccinated population were compared to "background" incidence rates of autoimmune conditions in similar age-matched controls who were also enrolled participants in these HMO groups [80].

Of the 149,306 women who had met the 12-month membership criteria and were eligible for case review, 719 potential new-onset cases were identified and 347 were sampled for case review. Of those autoimmune cases that underwent review, there were 48 cases of endocrinopathies, 21 cases of neurologic/ophthalmic, and 19 rheumatologic that were regarded by the committee to have a "strong level of diagnostic certainty." The incidence rate ratio was calculated from comparison to the aforementioned unvaccinated age-matched women. There was no significantly elevated risk in the vaccinated group except for Hashimoto's disease (RR 1.29; 95 % CI 1.08–1.56) but due to lack of temporal clustering and biological plausibility of the relationship, the investigators concluded that there was no consistent evidence to support an association between HPV4 and autoimmune thyroid conditions. HPV4 was found to be associated with a significantly lower RR for type 1 IDDM (RR 0.57) and juvenile rheumatoid arthritis (RR 0.48). Despite this, the investigators recognize that no conclusions related to HPV4 and autoimmunity may be drawn, based on the outcomes of this study alone. Notable strengths of the study include the 180-day observation period (lag time) used to evaluate symptom onset after each dose of vaccine, broad and highly sensitive case identification criteria, and use of expert panels to confirm diagnoses and dates of disease onset. Limitations are inherent in identifying exact timing of symptom onset since this may implicate cases classified as new-onset that may have actually preexisted. Despite the duration of the follow-up period in the study, some are skeptical whether this would be sufficient time to identify the development of these autoimmune processes. The authors argue otherwise—that while 6 months is relatively arbitrary, there is a greater likelihood that vaccination-induced autoimmunity would develop by this time and further temporal spacing would likely encompass more coincidental events [80].

Conclusion

When evaluating the safety and immunogenicity of vaccinations in various autoimmune conditions, it is important to consider limitations related to comparing data with variable types and modalities of monitoring, differing methods in evaluating immunogenicity, safety often being reported as "clinical worsening" without providing immune correlates (autoantibody titers), and variable follow-up periods. Studies presented in the detailed and comprehensive systematic review performed by Salemi et al. demonstrate that in patients with low disease activity, vaccine safety should not be a significant concern [70]. However, there are certain cases wherein the current evidence suggests a higher disease activity rate in vaccinated versus unvaccinated individuals, such as with influenza vaccine in RA patients or hepatitis B vaccination in SLE patients. The theoretical possibility of inducing disease reactivation is counterbalanced by an expected higher immune response, which is the intended benefit from vaccines. While there is increasing awareness about the issues related to the use of vaccine in this patient population, studies have been performed on relatively few (~5,000) patients with autoimmune disease. It is imperative that future research strives to further elucidate the efficacy and safety of vaccinations in patients with autoimmune conditions or undergoing immunosuppressive or immunomodulatory therapy. Through evidence-based medicine, appropriate practices and interventions to optimize the health of this vulnerable patient population may be implemented.

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Chapter 15
The Role of Public Health Ethics in Vaccine Decision Making: Insights from the Centers for Disease Control and Prevention

Leonard Ortmann and John Iskander

Introduction

The ethics of vaccination involves a broad range of issues, in part because vaccination overlaps the fields of public health with its focus on populations and clinical medicine with its focus on individuals. This overlap means, for example, that individual vaccine decisions, through their impact on herd immunity, become votes on community solidarity [1]. This obligation to protect community health often places public health at odds with the high value democratic societies place on individual autonomy. Thus, policies which have implications for individual autonomy generate lively debate, such as vaccine mandates, exemptions, or allocations [2, 3]. Research ethics issues involving clinical trials have drawn attention as well, in particular those involving children in developing countries [4, 5]. But vaccination raises a host of ethical issues, primarily because from the beginning safety concerns about vaccines have generated controversy. The resultant ethical tensions have grown as the scope of vaccination has grown. This chapter touches on these issues but focuses on the growing yet underappreciated role ethics plays in the decision making that sets vaccine policies. Getting buy-in for policies typically requires incorporating stakeholder concerns into policy decisions. In crafting vaccine policy, the overarching ethical challenge is to balance the competing values of diverse stakeholders: public health scientists and practitioners, care providers and

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

L. Ortmann, Ph.D. (✉)
Office of Scientific Integrity, Centers for Disease Control and Prevention,
1600 Clifton Rd. NE, Mailstop D-74, Atlanta, GA 30333, USA
e-mail: hsq3@cdc.gov

J. Iskander, M.D., M.P.H.
Office of the Associate Director for Science, Centers for Disease Control and Prevention,
1600 Clifton Rd. NE, Mailstop D-50, Atlanta, GA 30333, USA

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organizations, and the public. To get buy-in from a public with safety concerns increasingly requires transparency on the part of policy makers. The magnitude of the problem that lack of transparency causes is difficult to gauge. It is clear, however, that controversy strains, while transparency fosters, the trust that programs involving public cooperation require. The ethical challenge of transparency is the unifying theme of this chapter, linking safety concerns to building a social consensus on vaccine policy. In particular, the chapter considers how, in the light of two recent proposals to increase transparency in the process of evaluating evidence, the Advisory Committee on Immunization Practices (ACIP) employs expert judgment informed by stakeholder values to translate evidence into vaccine policy [6–8]. In addressing these topics, we adopt a public health ethics perspective.

Public health ethics prioritizes protecting the public from harm, preventing diseases at the population level, and promoting the health of the entire community. This population or community orientation distinguishes public health ethics from the individual orientation of clinical ethics [9]. The field of public health ethics has established a set of ethical principles and values that apply specifically to public health practice rather than research [10, 11]. These specific principles and values differ from the four well-known principles of beneficence, non-maleficence, autonomy, and justice central to bioethics, clinical ethics, and research ethics. A fair statement of these public health ethics principles can be found in the Public Health Leadership Society's 2002 Principles of the Ethical Practice of Public Health [12]. A lynchpin of these principles is the recognition of the interdependence of people, which creates obligations toward others and sets limits on individual liberty. So, while public health needs to respect individual values and social norms in formulating evidence-based vaccine policy, the public needs to appreciate the trade-offs between individual rights and public obligations involved in crafting that policy. Only in this way can individual vaccine decisions be properly informed and a social consensus on vaccines reached.

The Lancet's 2010 retraction of Andrew Wakefield's 1998 article linking vaccines and autism may signal the end of a specific episode in the history of vaccination, yet attitudes antithetical to vaccination persist [13]. The status quo to which we have returned displays increasing levels of both vaccine refusal and disease outbreaks linked to them [14]. Some current attitudes mirror the long history of vaccine hesitancy, distrust of vaccine safety assurances, and divergence between scientific risk management and the public's approach to risks. Other attitudes represent perceptions linked to social trends that work counter to vaccine acceptance. First, science and government policy based on scientific evidence increasingly are being challenged [15, 16]. Second, there is concern that the pharmaceutical industry unduly influences government policy and the agenda of government-sponsored scientific research [17]. Third, a series of notorious abuses of vulnerable human research subjects has sowed a general mistrust of biomedical research and government health programs [18]. An undercurrent of this mistrust of research remains, that diffuses over to vaccination, despite all the efforts of bioethicists to address these abuses [19]. A central outcome of their efforts in individual health care, heightened respect for individual autonomy, resonates with a fourth social trend, libertarianism [20]. Libertarian opposition to collective decisions that limit

individual autonomy has been viewed as antithetical to the very idea of public health intervention [21, 22]. To the extent that vaccination programs are promoted, let alone mandated, by government, or perceived as experimental or unduly influenced by industry, vaccine hesitancy can be reinforced. Given these trends and the vaccine status quo, vaccine promotion faces a daunting communications and community engagement challenge.

Additionally, the loss of confidence in vaccines in some communities may reflect inherent features of the life cycle of a vaccine program [23–25]. Initially, high disease burden creates public support for implementing a vaccine program. Over time, if herd immunity is achieved, the number of vaccine adverse events can approximate the number of cases of the targeted vaccine-preventable disease. As memory of the disease fades, the public becomes more acutely aware of adverse events. In this mature phase, support wanes for the vaccine program, and vaccine refusal in the context of herd immunity, so-called free riding, becomes more attractive from an individual risk perspective. The current vaccine challenge for national immunization programs of industrial nations may reflect this "paradox of success," compounded by social attitudes and exacerbated by incidents like the Wakefield controversy.

Even if periodic losses of confidence are inevitable, building a social consensus on vaccination could reduce their incidence and duration. Moreover, such a consensus might also be the best long-term solution to addressing persistent social attitudes at odds with vaccine policy. Because building such a consensus requires educating and engaging the public, a return to an earlier era where scientific expertise in isolation set vaccine policy would be out of place. Fortunately, the approach to setting vaccine policy has progressed to an outlook that is both more flexible and more comprehensive. Better communication and greater transparency are complementing enhancements to vaccinology and vaccine safety. Focusing on the ethical values and assumptions that inform policy decisions, this chapter makes the case for greater transparency and a more comprehensive vaccine policy as steps toward achieving a social consensus on vaccine policy.

A Glance at Science and Risk Communication

Effectively implementing vaccine policies requires public cooperation, making communication critical for their success. Developments in risk communication, while not our focus, are important for building a social consensus on vaccine policy. To make informed decisions and give consent to policies, communities need information from public health officials. Accuracy of information is critical, but to insure the effectiveness of communication, public health also needs to build and maintain public trust. Gaining this trust often requires engaging with the community in ways that take community values into account. Such flexible approaches are both requirements for better communication and professional obligations of public health [12].

Besides taking community values and beliefs into account, a more flexible approach would appreciate the role emotion and values play in the acceptance of messages.

Such thinking aligns with both classical rhetoric and modern research. Aristotle favored rational, scientific discourse, but acknowledged that appealing to emotions and values more effectively persuades the public [26]. Messages that appeal to community values or ones delivered by respected community leaders can help practitioners reach individuals for whom alignment with beliefs and values is paramount to receiving a message. A growing body of literature suggests that outreach and education efforts can be improved if promoted through religious and faith-based venues [27]. The World Health Organization's Global Polio Eradication Initiative, for example, recognizes the importance of directly involving religious leaders in Pakistan and Nigeria in order to secure community engagement [28]. Similar lessons apply at the clinical level. Vaccine information from a trusted provider improves confidence in the immunization process. Such trust, however, develops best from a long-standing relationship where not only communication content but also communication styles play key roles. The lesson is that providers need to provide information adapted to the way parents want to receive it [29].

Communicating risk effectively becomes all the more important in the mature phase of an immunization program when herd immunity has been achieved for a number of diseases, because providers cannot depend on the presence of disease to motivate parents. Many of the outbreaks occurring today are the result of failures of communication and confidence. Regarding risk perception, modern psychological research has shown that people solve complex problems by relying on heuristics [30]. These evolutionarily evolved rules of thumb generally help us assess complex situations, but sometimes create problematic cognitive biases. For example, people perceive familiar risks like childhood measles as less dangerous than unfamiliar risks like an adverse vaccine reaction. Strategies informed by heuristics may be better received than messages that scientifically compare disease risk to risk of adverse reactions and use academic jargon [31]. As one expert on vaccine controversies puts it, "scientific evidence, no matter how clear it seems to be to the people who produce it and vouch for it, does not have magical power to change minds" [32]. Public health needs to find compelling ways of complementing the scientific message, which is a legitimate approach as long as it neither falsifies facts nor diverts attention away from critical issues [26]. Outbreaks, unfortunately, are the most compelling persuaders, but a more flexible approach can help ensure that they are not the result of communication failures.

Two Proposals for a Just and Transparent Vaccine Policy

The two proposals alluded to earlier call for crafting vaccine policies in a manner that transparently incorporates ethical values. Achieving the proposed degree of transparency would entail a broader notion of communication to work in tandem with policy decision making regarding immunizations.

Poland and Marcuse (PM) propose a "holistic policy-making paradigm" based on "the essential tenets of 'just' immunization policy" [7]. These tenets include familiar principles of public health practice such as reasonable, timely policies

based on disease morbidity/mortality and vaccine risks/benefits. To evaluate benefits and distribute them equitably, they call for both individual and public perspectives as well as for shared governance between individuals and government. Key elements of their just policy include transparency regarding the evidence base used in decisions, a standardized framework for decision making that involves a spectrum of subject matter expertise, and broad dissemination of policy decisions. These tenets are operationalized by means of a just policy template composed of ethical and evidential elements, including evidence of cost–benefit analyses. The template distills the information, the data set, and the explicit assumptions and values on which the policy discussion rested. Because the template indicates how trade-offs between different elements were made in designing and implementing policy, it can serve later to explain policy decisions or to educate and engage the public.

The PM paradigm is holistic in three key aspects. First, the template formalizes procedures and yields a comprehensive policy record or master document. Second, it incorporates ethics into evidence-based decision making (EBDM). Third, its notion of social dissemination goes beyond transparently communicating information and sharing policy decisions. It also involves creating and sustaining a social consensus regarding just policy. Arguably, their ambitious proposal is proportioned to the dimensions of the current vaccine challenge.

Partly in response to PM, Field and Caplan (FC) offer an approach for resolving "clashes" between the demands of just policy and EBDM applied to vaccination [8]. These clashes begin with efforts to quantify ethical values, for example, in estimating quality-adjusted life years (QALYs). Although setting a monetary value on life strikes some as inherently problematic, FC acknowledge the usefulness of such quantifications for comparative purposes. But because ranges for such values vary widely depending on different stakeholder assumptions, these assumptions need to be made explicit. Second, because EBDM is geared to assessing long-term population outcomes, it may obscure immediate impacts on vulnerable populations and individual values. Third, because achieving herd immunity means many vaccine recommendations apply to everyone, clashes with social norms are likely. Clashes with individual values and social norms, we might add, typify a kind of ethical tension that public health routinely faces. To the extent that EBDM favors population perspectives and the population-wide interventions associated with them, policy makers and practitioners should expect ethical tensions to arise.

To anticipate such tensions and harmonize EBDM with just policy consideration, FC broaden the range of ethical values to be taken into account and extend the ways in which various elements are quantified for comparative purposes. Their version of a just policy template operationalizes a wider range of ethical considerations: notably, impact on vulnerable populations, individual values, and social norms. They also anticipate a need to compare not only different vaccine options for a disease but also vaccine options with other prevention options and even with treatment options. For each option, template elements would be quantified with respect to not only effectiveness, safety, and cost but also ethical considerations. FC harmonize EBDM with just policy, then, by extending the notion of trade-offs between evidentiary and economic elements to include a wider range of ethical values and intervention options.

Public Health Ethics and Vaccine Policymaking at CDC

Examining the current vaccine challenge has provided a context for considering proposals about the role ethics should play in crafting vaccine policy. Here, in order to situate the role ethics plays in ACIP deliberations at the Centers for Disease Control and Prevention (CDC) and the resources the agency has for its deliberations, we examine the broader context of public health ethics at CDC [33]. A core CDC value is integrity, especially as it relates to basing policy on the best available scientific evidence [34]. The creation of CDC ethics committees reflected recognition that scientific evidence can be unavailable or fall short of what is necessary to make timely decisions [35]. Their creation equally reflected a desire to show that proposed science-based policies not only were government mandates but also took moral considerations into account. Finally, their creation reflected appreciation of both the need and the obligation to achieve greater transparency in order to build and maintain public trust.

CDC's Ethics Committees

Controlling infectious diseases has long been a cornerstone of CDC's public health activities. It is therefore appropriate that a national influenza vaccination campaign provided an impetus for a formal structure of public health ethics at CDC. In October, 2004, in response to an influenza vaccine shortage, CDC established a panel of outside ethicists. The creation of the panel was widely reported on in the news. The shortage had raised issues of fairness and prioritization of target groups. In CDC's public statements explaining the creation of the 2004 ethics panel, the issue of equity figured prominently [36]. In 2004, outside ethics consultation was not new at CDC. But the public notice of a standing ethics panel did signal a response to public skepticism regarding the decision-making process behind the rationing plan. With input from this panel and other ethical perspectives, the ACIP and the National Vaccine Advisory Committee (NVAC) jointly attempted the first effort at seasonal flu vaccine prioritization in 2005.

Also in 2005, CDC conducted three public engagement and stakeholder meetings in different US cities on pandemic vaccination [37]. A premise of those meetings was that formulating vaccine policies that entail consideration of values as well as science requires an understanding of the public's values. Going into the meetings, greater susceptibility to disease had led experts to prioritize the vaccine for persons over 65 years old. All three meeting groups prioritized protection for target groups as follows: critical care providers and people working to fight the pandemic, providers of community essential services, vulnerable populations, and children. A surprise was that persons over 65 years old—a quarter of meeting participants—placed a higher value on protecting children than on persons in the over-65 age group, even though it was explained that older persons are more vulnerable to severe disease and death. This unanticipated result regarding the values of the

over-65 age group underscored the importance of giving communities and the public a hearing, especially when no single best scientific answer is available. More recently, in efforts related to vaccine safety research, the Immunization Safety Office at CDC has sought broad public input that included public engagement meetings in three US cities to identify public concerns and priorities related to vaccine safety research [38]. In both the earlier and later public engagement efforts, a crucial assumption was that to build and maintain trust with the public, government must be responsive to citizens' needs, concerns, and input.

Three members of the ACIP ethics panel became members of an ethics work group convened at CDC in February 2005. By June 2005, the work group had become a subcommittee of the Advisory Committee to the Director of CDC. The Ethics Subcommittee (ES) is composed of academic and professional ethicists from outside CDC who serve up to 4 years [39]. The ES's initial charge was broader than the ethics panel: to counsel CDC on a wide range of public health ethics issues and to support CDC efforts to develop internal capacity to address ethical issues. The ES has produced ethical guidance documents on pandemic influenza response, stockpiling antivirals for pandemic influenza, ventilator usage during an influenza pandemic, and general emergency preparedness and response [40].

Early on, the ES recommended that CDC create a standing internal Public Health Ethics Committee (PHEC). PHEC's mission is to provide leadership in public health ethics and to work with CDC staff to integrate the tools of ethical analysis into day-to-day decisions and activities across CDC. PHEC consists of representatives from CDC's national centers and other organizational components within CDC, whose activities are coordinated by a Public Health Ethics Unit within the Office of the Associate Director for Science. PHEC offers public health ethics training and an ethics consult service, often in conjunction with CDC subject matter experts and current or former ES members. PHEC members also staff an ethics desk during activation of CDC's Emergency Operations Center (EOC). During its activation for the H1N1 pandemic, PHEC members provided input into deliberations about vaccine implementation strategies. An ACIP workgroup requested an ethics consult from PHEC to obtain input on ethical issues that new data raised that indicated use of the combined measles, mumps, rubella, and varicella (MMRV) vaccine increased the risk of febrile seizures compared to use of the separate MMR and varicella vaccines [41]. The consult group weighed both population and individual risks and benefits in using the combined and separate vaccines. Then-available evidence revealed no advantage for either vaccine either in regard to program implementation or in regard to efficacy, effectiveness, immunogenicity, or burden of disease prevented with the first dose. However, in children aged 12–23 months, use of the combined vaccine doubled the risk for fever and febrile seizures during the 5–12 days after the first dose compared to the separate vaccines. Although the prognosis for young children who have had febrile seizures is generally excellent, these frightening medical events can negatively affect family members and caregivers, often resulting in a visit to the emergency department. Conversely, the combined vaccine requires one less injection than the separate MMR vaccines, protects against MMRV with one injection, and may result in some children getting varicella protection at an

earlier age. The eventual ACIP recommendation acknowledged these safety concerns but placed them in ethical equilibrium with the value of individual choice, thus leaving the final decision in the hands of providers and parents.

The ACIP

The ACIP, which has existed since 1964, has been described in detail elsewhere [42, 43]. The focus here is on transparency, a core public health value, and the relation of ethical values to evidentiary considerations, including evidence regarding cost–benefit analyses. The ACIP is a Federal Advisory Committee that complies with statutes of the Federal Advisory Committee Act (FACA) designed to ensure openness. Establishment of the ACIP grew out of recognition of the need for an expert group outside the Federal Government to develop objective national immunization policy recommendations. The 15 voting members include a consumer representative, along with experts across vaccine-relevant fields. Meetings are announced in the Federal Register and open to the public. The extensive advance preparations that policy recommendations require are the charge of ACIP Working Groups (WGs). WGs do not deliberate or vote on specific policy recommendations. They focus on fact finding and data review, which they organize for presentation in public ACIP meetings. Public comments are solicited at these open meetings and taken into account in decision making. Meeting minutes are available to the public on the ACIP Web site and final recommendations are published in the Morbidity and Mortality Weekly Report (MMWR).

Both evidentiary and ethical considerations have played a role in ACIP deliberations, though recommendations rely primarily on the evidence base concerning the disease burden, vaccine effectiveness, and vaccine safety. Health economic analyses are increasingly being factored into ACIP decision making, but no threshold value has been set for cost-effectiveness of a vaccine as this could discount other determinations of value [42, 44]. Health economic standards have been adopted by the ACIP which make value assumptions explicit [45]. Making the assumptions explicit at least can mitigate the problem that FC note in the quantifications of health economic measures, such as QALYs, namely, that the value assumptions underlying quantifications can vary widely depending on the stakeholder. Although these standards call for making the societal perspective the default, if specific population subgroups exhibit markedly higher or lower baseline risks, separate recommendations can be made for these subgroups. This option indirectly addresses equity issues by making room for considering the needs of special or vulnerable populations. Public uptake of recommendations has also been a topic of discussion relevant to ethics and social norms and attitudes. For a pressing ethical issue such as vaccine allocation, input can be provided through public engagement, an outside ethics panel, or a PHEC consult.

The ACIP has weighed ethical issues and values in relation to other evidentiary and economic factors as occasion demanded but has not developed a standardized ethics checklist. Nor did it have standardized procedures for rating the quality of the

evidence base. That changed in October 2010, when the ACIP unanimously adopted a new framework based on an internationally used EBDM model, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach [44]. To date, GRADE reports have been published on HPV vaccine for males, hepatitis B vaccine for adults with diabetes, and two pneumococcal vaccines (PCV13 and PPSV23) for adults with immunocompromising conditions [46–48]. The intent behind the new ACIP framework is to achieve greater consistency while allowing for continuous improvement. Although meeting the demands of a just policy as proposed by PM and FC is not the intent, the goal of consistency results in standardizations that support transparency, while the flexibility implied by continuous improvement leaves open the possibility of incorporating just policy elements.

The Ethical Dimension of the ACIP's New Framework

In discussing the new framework, features that pertain to ethical issues will be highlighted. The entire approach of the framework is to maximize net health benefits for populations and is thus utilitarian in outlook. Besides rating the strength of the evidence base, other factors explicitly recognized in developing recommendations include the balance of harms and benefits, values and preferences, and economic costs. The range of factors and values involved in crafting policy recommendations require that methodological elements be stated explicitly and with sufficient transparency to merit the confidence of stakeholders. That requirement extends to values and pointedly includes values of individual stakeholders such as parents and clinicians. In establishing that requirement, the ACIP Evidence Based Recommendation Work Group (EBRWG) explicitly refers to the MMRV Report for which PHEC conducted an ethics consult [44]. Along with the provisions for specific population subgroups, this last requirement can mitigate concerns that EBDM's long-range population emphasis overlooks individual values and effects on vulnerable populations.

Within ACIP's adoption of the GRADE framework, values are defined as the relative importance of outcomes related to benefits, harms, and costs. But it is acknowledged that judgments involved in weighing the strength of evidence and prioritizing values cannot guarantee reproducible results [44]. This is an implicit acknowledgement that evidence informs action and defines parameters for it, but ethics and values determine how we use evidence. Because ethical values are most subject to different weightings by individuals or stakeholder groups, being transparent and explicit about ethical values is all the more important. Judgments depend on those who make the evaluation and reflect their value perspectives. To resolve disagreements—or simply understand them—judgments and the assumptions behind them as well as the decision-making process need to be made transparent. Because values can offset each other, some combination of high economic costs and ethical controversy theoretically could offset effectiveness and safety values sufficiently to lower a vaccine's recommendation level. In public discourse, major ethical value conflicts often preclude reaching consensus on substantive ethical issues. When

substantive agreement is unattainable, parties must rest content with a fair and open deliberative, democratic process. In ACIP vaccine deliberations, sufficiently high variability or uncertainty in values or preferences provides a basis for lowering a vaccine's recommendation level.

GRADE operationalizes procedures for determining the recommendation of a vaccine based on four key factors: net balance of benefits and harms, quality of evidence, values and preferences, and health economic analyses. It applies specific criteria to its evidence base in order to rate it. Evidence can be downgraded because of risk of bias, inconsistency, indirectness, imprecision, and publication bias. The evidence base is categorized into four types that represent a general hierarchy reflecting the confidence in the estimated effect of vaccinations on health outcomes. The procedure methodically condenses a wealth of complex information into clear, direct rating terms that are transparent to those who will make the recommendation. The end result is a summary comparison in tabular form of the relevant factors: a statement of whether benefits outweigh harms, a rating of the quality of evidence, a description of any values that figured prominently in the recommendation, and a statement of general cost-effectiveness qualified if necessary for subgroups. GRADE reports are posted online, while detailed information about GRADE is available on CDC's Web site [49]. In the GRADE reports published in MMWR, disease prevention, a key public health value, has been listed as an important value in determining the recommendation [50, 51]. GRADE goes a long way toward achieving transparency regarding the ACIP's process of vaccine recommendations.

Discussion

The ACIP's use of GRADE should be viewed along the trajectory of vaccine policy deliberations that have been advancing from the world of expert opinion toward greater transparency and use of EBDM in a forum open to the public [7]. Along with health economic factors, ethical values, too, are being explicitly incorporated into vaccine decision making. Given the degree of vaccine hesitancy, some, like PM and FC, have called for a more robust incorporation of ethical considerations. Social norms and individual values do need to be taken into consideration in crafting vaccine policy, but a public health ethics perspective also needs to inform that policy. Interdependence creates shared obligations that force us to consider how far individual liberty should extend, when the public's health is at risk or when disease can be prevented. Public health ethics is better situated to articulate the trade-offs between individual values and shared obligations. Transparency helps to inform, but consent in the public health arena will also depend on building trust and creating a social consensus through proper communication and engagement.

GRADE's more transparent incorporation of values into deliberations represents a development in the spirit of a just policy document. As a possible next step, quantifying elements on a template or a checklist of ethical values and social norms would not pose a major hurdle. To develop such a checklist, CDC could draw on

ethics expertise from its standing ethics committees. CDC also has considerable experience working with tools such as a modified Delphi process that allow a decision-making body to quantify values important in choosing amongst alternatives [52]. Determining what should be on such a checklist, who should create it, and who should do the ratings pose additional but not insurmountable challenges. Nor would it pose insuperable difficulties to use GRADE to compare a vaccine to other vaccines or intervention options, along the lines that FC propose.

A more crucial consideration is whether a just policy template's added value would justify its development and implementation costs. ACIP procedures and the new framework already go a long way toward realizing the objectives behind a template. Meetings are open, minutes published, comments of the public considered, and ethics panels, consults, or public engagement utilized as occasion demands. The new ACIP framework improves transparency, acknowledges the importance of individual values, and considers a recommendation's effect on specific populations to ensure equity. GRADE explicitly includes values important to decision makers and affords an appreciation of the trade-offs between the various factors underlying recommendations.

Given the crucial role of values, the ethical sensibilities of the ACIP's voting members will play a critical role in their judgments. These judgments can be informed by values and preference estimates from population-based studies, public comments, media reports about vaccine issues, and ethics resources available at CDC. GRADE's current procedure explicitly incorporates value considerations into decision making and could be expanded to routinely factor in a spectrum of ethical values and social norms. Whether that becomes necessary will depend on a host of factors internal and external to vaccine policy deliberations. These factors include improvements in vaccine safety, GRADE's impact, trends in measured vaccine refusal and hesitancy, outbreaks of vaccine-preventable diseases, and strength of the social consensus on vaccine policy.

The interplay between some of these external factors and the overall process of vaccine policymaking constitutes an implicit dialogue between vaccine policy makers and the public that needs to become explicit [6]. The notion of consumer choice resonates with the public, but having safer choices regarding vaccines provides too narrow a basis for moving the public dialogue about national immunization policy forward. Consumer demand for safer vaccines has a psychological dimension that technical improvements do not fully address. The psychological dimension of vaccine controversy can also index the degree to which public health has to engage the public to earn trust, build consensus, and work toward shared governance regarding vaccine policies. Regarding shared governance, emerging threats of new pandemics or bioterrorism also underscore the need for society to think in a proactive, coordinated way about national immunization policy [53]. Herd immunity against vaccine-preventable childhood diseases not only is a public good but also a national asset [54]. As such, herd immunity can be framed as an issue of community resilience for public health preparedness and response (PHPR). A resilient community not only bounces back from disturbances but also withstands them without losing integrity or continuity of function [55]. If community resilience entails herd immunity and

PHPR requires community engagement, then the public must become a partner in implementing immunization programs [56, 57]. A public dialogue built around a notion of shared health governance that puts equal weight on choice and civic responsibility to protect oneself and others may provide a bridge between individual and communal values [58].

Conclusion

The current challenges of vaccine hesitancy may not represent a deepening trend so much as a phase in the cycle of a mature vaccine program. That does not imply that the periods during which segments of the public lose confidence in a vaccine cannot be shortened or decreased. Just as a fracture becomes the occasion for the body to make a bone stronger than before, so does a vaccine-preventable disease outbreak provide an occasion to strengthen prevention. In this regard, the ACIP has significantly raised awareness of the importance of childhood immunization and has redoubled efforts to raise it for adults. These "unofficial" efforts of ACIP might seem at odds with the charge of objectively weighing evidence, but they do indicate recognition of the need to proactively create a climate of vaccine acceptance. Clear, consistent scientific messaging must form the basis on which to raise awareness, but raising awareness is not tantamount to gaining acceptance. The prevention strategy best suited to countering any vaccine refusal inherent in the mature phase of the vaccine cycle may well lie in building a durable social consensus on vaccination. But doing so will require a comprehensive effort that involves not only evidence and economics but also ethics and engagement. Engagement embraces a more flexible communication approach that creatively harnesses the power of emotion and appeals to community values. The tools of public health ethics can help to articulate the rationale behind such a comprehensive effort that creates a social consensus. Framing vaccination as a shared obligation of public health and the public can help ensure the effectiveness of vaccine programs whose success ultimately depends on public acceptance.

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Chapter 16
Alternative Schedules: Why Not?

Michael J. Smith

Introduction

Immunizations are one of the most successful public health interventions of all time. Smallpox has been eliminated from the world. Diseases that afflicted generations of Americans such as measles and polio are no longer endemic in the United States and have faded from public memory. Over the past decade, the number of vaccines included in the childhood immunization schedule has continued to increase. Diseases that affected today's parents and physicians are now vaccine preventable. While this represents a triumph against the threat of infectious diseases, an increasing number of parents have become worried that children receive more vaccines than are good for them.

This is not a new concern. A nationally representative survey performed in the late 1990s demonstrated that 23 % of parents agreed with the statement: "Children get more immunizations than are good for them" [1]. A similar proportion reported "I am concerned that my child's immune system could be weakened by too many immunizations." This survey was conducted at a time when the immunization schedule was fairly simple; infants received vaccines against diphtheria, tetanus, and pertussis (DTaP), hepatitis B, *Haemophilus influenzae* type b (Hib), and polio; 1-year-olds were vaccinated against measles, mumps, rubella (MMR) and varicella; 4–6-year-olds received a second dose of MMR and boosters against DTaP and polio. Centers for Disease Control and Prevention (CDC) [2]. The adolescent schedule consisted of only one routine vaccine—a single dose of Td. All of these recommendations fit on a single page.

In the past decade vaccines against rotavirus, pneumococcal disease, and hepatitis A have been added to the routine childhood schedule. Indications for existing vaccines have been expanded to include a second dose of varicella vaccine, and a

M.J. Smith, M.D., M.S.C.E. (✉)
Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Louisville School of Medicine, 571 S. Floyd Street, Suite 321, Louisville, KY 40202, USA
e-mail: mjsmit22@louisville.edu

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universal recommendation for influenza vaccine in all children older than 6 months. An entirely new adolescent vaccination platform has also emerged. The single dose of Td is now given with a pertussis booster as Tdap, and two-dose meningococcal and three-dose human papillomavirus primary series are recommended for all adolescents. The current immunization schedule spreads out over three pages—one for children, one for adolescents, and a third for "catch-up" immunizations—and is confusing for parents and healthcare providers alike.

As the schedule has become more complex, many parents are questioning the safety and necessity of all of these vaccines. A small percentage of parents has always delayed or refused certain vaccines, or refused vaccines completely. Over the past 5 years "Too many too soon" has become the rallying cry of the anti-vaccine movement and an increasing number of parents began to request the use of specific alternative vaccine schedules. These schedules pose several challenges to any healthcare provider who cares for children. In this chapter we review the science and politics behind the creation of the immunization schedule and review parental concerns about the schedule. We also provide evidence-based talking points and strategies for discussions with families who request alternative vaccine schedules.

The Immunization Schedule

Before discussing alternative schedules it is important to understand how the official immunization schedule is created. As outlined in Chap. 2, the ACIP is tasked in the United States with recommending which vaccines are included in the schedule, and at what age. One of the factors involved in the recommended age at vaccination relates to the epidemiology of the disease in question. For example, pertussis is associated with significant morbidity and mortality in young infants, and vaccination is included at the earliest age possible. By vaccinating at 2, 4, and 6 months children complete the primary series by the time transferred maternal immunity wanes. However, before recommendations can be made, a given vaccine must also be shown to be safe and effective in that age group. For example, pneumococcal disease is also associated with significant morbidity and mortality during the first year of life. Although a pneumococcal polysaccharide vaccine has been available since the 1980s, children younger than two do not respond to polysaccharide vaccines. Until a pneumococcal conjugate vaccine (PCV) was created in the late 1990s, pneumococcal vaccine was not included in the routine childhood immunization schedule.

Before a vaccine is included in the schedule it undergoes rigorous testing as outlined in Chap. 2. This process requires that new vaccines be studied within the context of the existing immunization schedule. This assures that the new vaccine is not only safe and effective by itself but also that the safety and immunogenicity of other childhood vaccines are not impacted by the new vaccine. Such "concomitant use" studies are required by the US Food and Drug Administration (FDA) and considered

by the ACIP prior to new recommendations [3]. For example, a quadrivalent meningococcal conjugate vaccine (MenACWY-D) was licensed for use in children 9–23 months of age in April 2011. Because studies of concomitant MenACWY-D and PCV use demonstrated poorer PCV immunogenicity in children who received MenACWY-D as compared to those who received PCV alone, the ACIP recommended that children who are at increased risk of meningococcal AND pneumococcal disease receive MenACWY-D at 2 years, after completion of the primary PCV series Centers for Disease Control and Prevention (CDC) [4]. In contrast, children with no risk factors for invasive pneumococcal disease may be immunized at 9 months. Similar studies are reviewed each time a new vaccine is added to the schedule. Prior to the universal recommendation for hepatitis A vaccine, studies demonstrated that simultaneous administration of hepatitis A vaccine with DTaP, Hib, hepatitis B, MMR, or inactivated poliovirus vaccines did not affect the immunogenicity or reactogenicity of these other vaccines [5].

Since 1995, the immunization schedule has been updated each year by an ACIP working group specifically assigned this task. Each year this group reviews the latest studies to ensure that the immunization schedule is safe and effective. While some skeptics claim that the safety of the current immunization schedule is untested, this could not be further from the truth. The same cannot be said for alternative schedules.

Alternative Schedules

Webster's Dictionary defines "alternative" as "different from the usual or conventional" [6]. Using this strict definition, any immunization pattern that deviates from the ACIP-endorsed schedule is an "alternative schedule." However, this term reached national prominence in 2007, with the publication of *The Vaccine Book: Making the Right Decision for Your Child*, by Dr. Robert Sears [7].

In his book, Dr. Sears offers parents two different immunization schedules. "Dr. Bob's Alternative Vaccine Schedule" is designed for parents who would like their children to be completely vaccinated, but are concerned that children receive too many vaccines in a single visit. No more than two vaccines are given at any visit on this schedule which requires monthly visits from 2 to 7 months. In contrast, "Dr. Bob's Selective Vaccine Schedule" avoids certain vaccines, such as polio and influenza vaccines, completely. Another popular alternative schedule is the "User-Friendly Vaccine Schedule," created by Dr. Donald Miller [8]. This schedule has three basic tenets: no immunization until children are at least 2 years old, no thimerosal-containing vaccines, and no live virus vaccines (unless smallpox recurs). This schedule only recommends vaccinating against polio as well as pertussis, diphtheria, and tetanus—not as DTaP but given as separate vaccines, which is not technically possible (because the separate vaccines are not manufactured and therefore, not available).

A visit to the Web site "toomanytoosoon.org" offers providers a brief glimpse of other alternative schedules available to parents with an Internet connection [9]. It

includes the Sears and Miller schedules as well as four other options. The easiest of these to understand is "Nature's Vaccine Schedule" which offers nothing more than a picture of happy children running through a field under a banner proclaiming "No vaccines at all." Also provided is a link to the 1974 immunization schedule, which only included DTP, OPV, and separate measles, mumps, and rubella vaccines—implying that the last three decades of vaccinology are completely irrelevant. Finally, there are two additional schedules recommended by physicians. Though they have slight differences, each recommends no vaccines until 4 months of age, separating measles, mumps, and rubella vaccines and delaying pneumococcal vaccine until 2 years of age.

Because parents may have specific questions about these published schedules it is a good idea for providers to have a basic familiarity with them. But how commonly are they used? A recent nationally representative survey found that 13 % of parents reported using an alternative vaccination schedule [10]. Of note, only 8 % of these parents followed one of the published vaccine schedules; 6 % used the Sears schedule and 2 % the Miller schedule. Instead, more than half of alternative vaccinators used a schedule that they (41 %) or a friend (15 %) developed. These authors strictly defined alternative vaccinators: ANY deviation from the standard schedule qualified as an alternative vaccination schedule. Nearly one-half of the alternative vaccinators (53 %) stated that their children did not receive certain vaccines, while 17 % reported that their children received no vaccines. The most commonly *refused* vaccines were related to influenza; 86 % refused H1N1 vaccine and 76 % refused seasonal vaccine. Fifty-five percent reported that they delayed some vaccines until their children were older than the recommended age; the most commonly *delayed* vaccines were MMR (54 %) and varicella (44 %). More than 80 % of the alternative vaccinators had made more than one change to the standard schedule.

While the specific vaccines delayed or refused differed across the study population, all parents that deviated from the standard immunization schedule shared similar attitudes and beliefs about vaccine-preventable diseases, vaccine safety, and parental decision making. More than 75 % of alternative vaccinators agreed or strongly agreed with each of the following statements:

> Allowing parents to delay vaccine doses or skip some vaccines lets parents be more in charge of their children's healthcare
>
> Delaying vaccine doses is safer for children than providing them according to the CDC-recommended vaccination schedule
>
> Delaying vaccine doses is associated with fewer vaccination side effects than providing them according to the CDC-recommended vaccination schedule
>
> Allowing parents to delay vaccine doses or skip certain vaccines lets parents avoid those vaccines that aren't really necessary

These attitudes and beliefs need to be considered when speaking to parents who are interested in pursuing alternative vaccination schedules, and are addressed in the following section.

What Impact Does Intentional Delay Have on the Immunization Schedule?

While the above study provides the most recent description of beliefs and attitudes of alternative vaccinators, it relies on parental report of immunization receipt. Studies using the National Immunization Survey (NIS) have the ability to correlate parental attitudes and beliefs about vaccines to actual provider-verified receipt of childhood immunizations. Smith and colleagues used data from the 2003 NIS to do just this [11]. Among parents of children 19–35 months of age, 21.8 % intentionally delayed at least one vaccine for their child. 44.8 % did so because of concerns about vaccine safety or efficacy. Other reasons for delay included child illness (36 %), missed appointments (7.7 %), or cost of vaccination (5.6 %). These data demonstrate that 10 % of parents, even as far back as 2003, intentionally delayed vaccines due to vaccine safety concerns.

This sentiment was precisely the rationale behind Dr. Sears's book; because parents are already refusing some vaccines anyway, why not offer information that may be used to help them prioritize vaccines? This is not an unreasonable idea—receiving some vaccines is surely better than receiving none. In fact, the American Academy of Pediatrics (AAP) Committees on Bioethics [12] and Infectious Diseases [13] both recommend a "schedule of immunization that does not require multiple injections at a single visit" for "parents who have concerns about administering multiple vaccines to a child in a single visit." But there is a key difference between the recommendations of the AAP and Dr. Sears. The 2009 Red Book continues, "Any alternative schedule should adhere to age ranges of vaccine administration provided for many vaccines in the Recommended Childhood and Adolescent Immunization schedules." In contrast, the published and widely disseminated alternative schedules imply that some vaccines are less important than others and may not even be necessary at all. In the next section we discuss some of the other specific problems with alternative immunization schedules.

Problems with Alternative Schedules

The simplest reason that parents should be discouraged from delaying immunizations relates to the timing of the immunization schedule. As described above, the schedule is designed to protect children against diseases when they are most susceptible. Delaying vaccination increases the amount of time children are at risk of acquiring these infections. If we could predict precisely when our patients would be exposed to vaccine-preventable diseases, then perhaps it would be reasonable to delay vaccines. However, this is not possible. Recent outbreaks of measles at airports [14] and the Super Bowl [15] demonstrate that these diseases may strike anywhere at any time. As more and more children go unvaccinated, the risks of coming

into contact with a vaccine-preventable disease during the routines of daily life—at daycare, school, or the supermarket—only increase further.

No studies to date have quantified the increased risk of infectious diseases associated with the use of a particular alternative schedule. However, a handful of studies have evaluated the incidence of specific infectious diseases in children whose parents have requested exemptions for individual vaccines. One study published a decade ago demonstrated that children with nonmedical exemptions for MMR were 22 times more likely to contract measles [16]. Those with nonmedical exemptions for pertussis were 5.9 times more likely to develop pertussis as compared to vaccinated controls. In three more recent case–control studies that used administrative data from Kaiser Permanente of Colorado, Glanz and colleagues demonstrated that children whose parents had refused one or more immunizations for nonmedical reasons had much higher rates of vaccine-preventable diseases. Children who did not receive pertussis vaccine had a 23-fold increased risk of developing pertussis [17]. The increased risk of disease due to intentional nonreceipt of varicella (8.6) and pneumococcal (6.5) vaccines was smaller but still significant [18, 19]. In these three studies, vaccine refusal was determined by blinded review of the primary medical record for explicit documentation of parental vaccine refusal. Taken together, these data clearly show that measles, pertussis, and varicella are still prevalent in the United States, and that unvaccinated children remain at increased risk. These data also shed a worrisome light on current parental use of alternative schedules. After influenza vaccines, varicella was the most commonly refused (46 %) vaccine. MMR and varicella were the most commonly delayed vaccines. MMR (45 %), DTaP (43 %), and PCV (33 %) were the top three vaccines administered over a prolonged dosing interval [10].

Closely related to the notion of prolonged susceptibility to infection is the issue of prioritization. Suppose that the family of a 2-month-old infant is only willing to receive two or three vaccines at an office visit, and asks you to choose which vaccines to give and which to delay. How would you answer? If asked to choose, most pediatricians will prioritize the diseases that are most prevalent and most severe Centers for Disease Control and Prevention (CDC) [20]. The problem is that these perceptions of disease are not objective but are clearly affected by personal experience. Recent pediatric graduates might be strong advocates for rotavirus vaccination because rotavirus gastroenteritis was such a significant part of their residency training. Their mentors might defer rotavirus and choose the Hib vaccine, remembering on-call nights with countless children admitted with bacterial meningitis. Those who trained outside of the United States might argue for making polio vaccine a priority. Which one of these responses would be right? Because children have the right to be protected against as many infectious diseases as possible this is a near-impossible decision for individual healthcare providers. Yet Dr. Sears believes that parents can and should make these decisions on their own.

Another reason to discourage alternative vaccine schedules is that delay of vaccines may lead to series non-completion. Strine and colleagues showed that children with late receipt of the third DTaP were less likely to complete the series [21]. Those who did receive a fourth dose received it late. A more recent study used data from the

2009 NIS [22]. Parents were asked if they had ever delayed or refused a vaccine for their child. Sixty percent of parents neither delayed nor refused a vaccine, 26 % delayed a vaccine only, 8 % refused a vaccine only, and 6 % both delayed and refused. For most vaccines, there was an ordinal trend in up-to-date status for immunizations at 19 and 24 months. As expected, children whose parents neither delayed nor refused vaccines had the highest coverage levels, followed by those who only delayed, those who only refused, and those who both delayed and refused. Although some parents with intentional vaccine delay did bring their children in for catch-up vaccines, coverage in these children remained significantly ($p < 0.05$) lower for each vaccine assessed, offering further evidence that delay does lead to vaccine nonreceipt. In addition to prolonging the period of susceptibility to vaccine-preventable diseases, parental vaccine delay may result in some children *never* being protected.

So far, we have only addressed one specific parental belief—that alternative vaccination schedules allow children to skip those vaccines that are not necessary. The reality is that it is impossible for healthcare providers, much less parents, to figure out which vaccines those might be. However, establishing the consequences of not following the recommended schedule is only part of effective vaccine risk communication. Parents also want to be assured that the existing schedule is safe. Are alternative vaccination schedules safer? What about the concern that the increasing number of vaccines in the schedule somehow overwhelms the developing immune system?

The immunologic challenges that vaccines provide to the developing immune system are minuscule as compared to the challenges of everyday life [3]. From the moment infants are born they are bombarded by microbes—including those colonizing the maternal genitourinary tract and the environment. The respiratory and gastrointestinal tracts of infants become colonized with bacteria within hours of birth. In most cases, this colonization does not result in infection because the infant immune system is capable of mounting an appropriate immunologic response to these threats. The antigenic burden from vaccines pales in comparison. Furthermore, while the number of vaccine-preventable childhood diseases has increased from 1 (smallpox) in 1900 to 16 in 2012, the total number of antigens to which children are exposed through vaccines is significantly less today than it had been for most of the twentieth century [3, 23]. This is due to the discontinuation of the whole-cell pertussis vaccine, which contained 3,000 proteins, and the smallpox vaccine, which contained 200 proteins. In contrast, the combined antigenic burden of all current childhood vaccines is less than 200 proteins or polysaccharides. Finally, although immunizations now protect children against many more diseases than in the past, the majority of childhood infections are still not vaccine preventable. For instance, viral upper respiratory infections (URIs) are one of the most common infections in children. While yearly influenza vaccination may prevent some of these, children are still susceptible to rhinovirus, adenovirus, and respiratory-syncytial virus, which account for more than 2/3 of URIs in children [24]. Therefore, vaccines represent only a small proportion of the antigenic burden to the developing immune system.

A related concern among some parents is that receipt of immunizations may actually weaken the immune system. This does not appear to be the case. As

discussed above, studies of concomitant vaccine use demonstrate that vaccine immunogenicity is not altered by giving multiple vaccines at the same time. Additionally, children who are vaccinated may actually be protected against infections that are not included in the childhood immunization schedule, such as secondary *Staphylococcus aureus* pneumonia after influenza or Group A streptococcal infections after varicella infection [3].

In summary, there is no biologically plausible argument to support spacing out childhood immunizations. This is a critical point when discussing alternative vaccine schedules with parents. Since 1995, the official ACIP-recommended immunization schedule has been revised each year, after thorough review of high-quality epidemiologic studies. In contrast, alternative schedules are not based on scientific data [25]. For instance, the author of one popular alternative schedule writes: "My schedule doesn't have any research behind it. No one has ever studied a big group of kids using my schedule to determine if it's safe or if it has any benefits" [7]. Is such a study even feasible?

Epidemiology and Vaccine Safety

As outlined in Chap. 2, randomized, controlled clinical trials offer the highest level of epidemiologic support and are required by the FDA before any pharmaceutical can enter the marketplace. If a vaccine for the disease of interest exists, the new vaccine is compared to the old one. If there is no vaccine, then a placebo group is used. Many anti-vaccine advocates have argued that a randomized, controlled clinical trial be used to demonstrate the long-term safety of the current immunization schedule as compared to alternative vaccination schedules. However, such a study is not possible on ethical grounds. First, because vaccines are part of routine medical care, children randomized to an alternative schedule would miss out on the opportunity to be protected against deadly vaccine-preventable diseases. However, even if potential study participants and their parents understood this and gave informed consent, such a study would not be ethical because the community at large would remain at increased risk due to the loss of herd immunity. For these reasons, a randomized, controlled clinical trial of long-term outcomes associated with alternative vaccine schedules is unlikely to happen.

So, how can these safety concerns be addressed? The National Vaccine Advisory Committee Vaccine Safety Working Group has suggested that retrospective observational studies of populations with natural variation in vaccination schedules may have value [26]. As outlined in Chap. 2, the Vaccine Safety Datalink (VSD) project is one of the most rigorous systems in place to assess vaccine safety in the United States, and may be the best resource for assessing the safety of alternative vaccine schedules [27].

While many VSD studies focus on acute adverse events associated with vaccine receipt, a few studies have included long-term outcomes. For instance, one recent VSD study found no evidence to support a causal association between thimerosal

exposure during the first 7 months of life and neuropsychological outcomes at 7–10 years of age [28]. Researchers from the University of Louisville used publicly available data from this study to evaluate whether children who received all recommended vaccines on time in the first year of life had different neuropsychological outcomes as compared to children with delayed or nonreceipt of these vaccines [29]. This study included 1,047 children from the VSD who underwent neuropsychological testing using 42 different outcomes. Although the original study focused on the amount of thimerosal receipt, publicly available data included age in days at vaccination for all vaccines received during the first year of life. These data were used to generate a timeliness variable. Children who received all vaccines within 30 days of the recommended age were considered to have timely receipt; the rest were considered untimely. Using this basic definition, 491 of 1,047 (47 %) children met the study definition for timely receipt. An additional 235 (23 %) received all recommended vaccines during the study period, but not on time. The remaining 311 (20 %) did not receive all recommended vaccines during the study period.

When neuropsychological outcomes were compared between children with and without timely vaccinations, children with timely vaccine receipt performed better on 12 of the 42 outcomes. There were no statistically significant differences for the other 30 tests, and the children vaccinated on time never performed worse. After controlling for potential confounding using logistic regression, the majority of this advantage disappeared. However, timeliness remained associated with better performance on 2 of the 42 outcomes and was not associated with poorer performance for any outcome.

The authors used a strict dichotomous definition to provide a clear public health message; children who received all vaccines on time had no apparent neuropsychologic deficiencies. However, this strict definition may have blunted potential differences between "mild delayers" and "significant delayers." To better address this issue, a second set of analyses was performed to more precisely measure the association between age at vaccine receipt and neuropsychological outcomes.

In these analyses, children were divided into three groups based on the number of vaccines they had received during the study period. The most timely vaccinated group received a minimum of ten vaccines in the first 7 months of life. The least vaccinated group was defined as those in the cohort who received ≤6 vaccine doses of any type during the first 7 months of life (defined as ≤209 days). No benefit to delayed vaccination was detected when the least and most timely groups were compared.

The biggest limitation to this study is that it was not randomized. While many potential confounders were included and adjusted for in the main analyses, there may have been other unmeasured variables that were not considered. Another limitation that children in this study were born in the late 1990s and did not receive the current immunization schedule is actually a strength; these children were assessed at 7–10 years of life, so any study of long-term outcomes associated with the current immunization schedule could not be performed until the next decade. Despite these limitations, this is the only study to date that has assessed the long-term outcomes of children receiving the recommended schedule as compared to those who did not.

Working with Families Who Request Alternative Schedules

In the preceding sections we have discussed the underlying beliefs and concerns behind parental requests for alternative schedules. Which strategies work well with parents who have concerns about the immunization schedule? This depends largely on the underlying reasons for parental concern. For some parents, the sheer number of injections is a limiting factor. In a study including 32 pediatric offices, Meyerhoff and colleagues demonstrated that 34 % of vaccination visits between 2 and 8 months were associated with deferral of some vaccinations [30]. They found a statistically significant trend between number of vaccine doses due and likelihood of deferral. When three or fewer vaccines were due, deferral was only 26 %. This increased to 34 % when four vaccines were due and 48 % when five were due.

Parents who are concerned about the number of injections may be reassured by the use of combination vaccines which significantly reduce the number of injections required. At the 2-month visit, for example, children receive vaccines against seven diseases: diphtheria, tetanus, pertussis, polio, pneumococcus, Hib, and rotavirus. One of these is an oral vaccine, and there is a combination vaccine that includes all of the other components except PCV. Some parents may find it helpful to frame this immunization encounter as two injections and an oral vaccine rather than "immunization against 7 diseases." A hexavalent vaccine is in clinical trials currently—this will decrease the number of injections required in the first year of life even further [31]. In our local community, the use of newer combination vaccines that combine multiple antigens has anecdotally been associated with fewer concerns about the immunization schedule.

Other parents may be concerned about the pain associated with multiple injections and may believe that by reducing the number of injections at a single visit this pain may be reduced. It turns out that this may not be true. Granted, a single injection clearly causes more pain than no injections. However, studies of salivary cortisol response in infants who receive one or two injections show no difference in objective stress responses [32]. By extension, receiving five vaccines at once allows for one painful stimulus that does not need to be repeated until the next routinely recommended visit. Spacing out the same injections over two or three visits may actually lead to more infant stress and eventual needle phobia in addition to more time spent in the doctor's office. There may also be an advantage to giving vaccines simultaneously rather than sequentially [33]. A recently published randomized, controlled trial involving 4-month-olds compared administration of three vaccines given sequentially to the same vaccines administered two at the same time followed by a third [33]. Children randomized to the simultaneous group had fewer pain behavior responses [33]. Finally, providers should be familiar with strategies that have been shown to reduce immunization pain [34].

Despite these reassurances some parents may remain concerned about the challenge posed by vaccines to the infant immune system. We hope that our brief review will help primary care physicians assuage these fears. There is hope—several studies have shown that physicians remain the most trusted source of immunization information, even for parents who are considering exemptions [35, 36]. Nevertheless, there will still be some parents who are not convinced that the immunization schedule is safe.

There are two options for such families—agree to work with them OR dismiss them from the practice. This is a controversial and highly personal choice; indeed there are pros and cons to both possibilities. As mentioned above, the AAP encourages that providers engage in ongoing dialogues with families who are concerned about vaccine safety [12]. Dismissing such patients may result in families seeking care from providers (who may or may not have formal medical training) who do not support routine immunization. Furthermore, it is unethical to dismiss patients actively under one's care without a solid transition plan.

A recent survey of 209 primary care pediatricians from Washington State suggests that many physicians are comfortable with alternative schedules, at least for some vaccines [37]. Seventy-seven percent of respondents noted that parents frequently or sometimes requested alternative schedules. Physician willingness to accept alternative schedules varied by the specific vaccine in question. Eighty-seven percent of respondents were willing to consider an alternative schedule for hepatitis B. Alternative varicella (76 %) and IPV (74 %) vaccine schedules also tended to be accepted. In contrast, fewer physicians were willing to accept alterations to the schedule for DTaP, Hib, and PCV.

If a family refuses one or more vaccines at a given office visit, it is a good idea to personally schedule a follow-up visit in a short period of time to administer any deficient vaccines. Providers who find themselves in this position should make sure to be up to date on the local epidemiology of vaccine-preventable diseases, if prioritization is a necessity. For instance, strong consideration should be made for protecting patients against pertussis and measles, which have reached historical peaks in the past 2 years. Unfortunately, even "playing the odds" is not risk free—and it is important to explain this to parents. In 2008, there was an outbreak of Hib in Minnesota, which included five cases of invasive disease, the most since 1992 in that state, and one death Centers for Disease Control and Prevention (CDC) [38]. Three of these cases, including the child who died, occurred in patients who had received no doses of Hib vaccine. At the time, there had been only one case of invasive Hib disease during the past 3 years.

On the other hand, allowing a child who is not up to date on vaccines to sit in a waiting room does place other patients, especially those with contraindications to vaccination, in harm's way. For example, during a 2008 measles outbreak in San Diego, four children were exposed to measles in their pediatrician's office when an intentionally unvaccinated 7-year-old presented with fever, sore throat, and rash after a trip to Switzerland Centers for Disease Control and Prevention (CDC) [39]. These included three infants younger than a year, one of whom was admitted to the hospital.

If you are determined to follow the recommended schedule in your practice the best way to avoid this ethical dilemma may be to make your vaccine policies clear up front. Many practices have written policies that are given to potential new patients and their families before they join the practice. This may include a statement to the effect of "Our practice follows the immunization schedule recommended by the ACIP and endorsed by the AAP. If you are not comfortable with this, we suggest you seek care at another practice." Such a policy protects patients who are unable to be immunized while avoiding the ethical dilemma of firing a family.

Conclusions

At first glance, alternative vaccine schedules seem to provide the ideal solution for parents who are concerned about vaccine safety. In theory, they encourage parents who might have refused some or all childhood vaccines to have their children partially immunized. But such schedules create more problems than solutions. They force prioritization of vaccines and may increase healthcare utilization, as Dr. Sears himself admits: "If some of the theoretical problems with vaccines are real, this schedule circumvents most of them. If the problems aren't real, then the only drawback is the extra time, effort, and cost for the additional doctor's office visits" [7]. Unfortunately, proponents of alternative schedules have missed the most important point. The biggest drawback is more than the inconveniences noted above. Alternative schedules leave children at increased risk of vaccine-preventable diseases when they are most susceptible. The odds are that children will be protected by the herd, but it is not a sure bet. These odds get even smaller as more and more parents seek alternative schedules or refuse vaccines outright. If there were an advantage to such schedules, they might be defensible. However, there is absolutely no evidence that delaying childhood vaccines has any benefit whatsoever. For this reason allowing patients and their families to do so only puts all children in harm's way.

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Chapter 17
Influenza Vaccines and Guillain Barré Syndrome

Nandini Bakshi and James J. Sejvar

Introduction

Guillain Barré syndrome

Guillain Barré syndrome (GBS) is an acute immune-mediated polyradiculopathy affecting children and adults, which usually presents with acute flaccid paralysis. Although GBS-like illness was first described by Octave Landry in 1859, the disease has been named after the French neurologists George Guillain, Jean-Alexandre Barré, and André Strohl who described two soldiers with acute areflexic paralysis and reported the characteristic finding of albuminocytologic dissociation (i.e., elevation of CSF protein with normal CSF cell count) [1, 2]. The condition is typically characterized by distal weakness, ascending numbness, and autonomic dysfunction due to involvement of peripheral nerves and nerve roots [2].

Subtypes

Guillain-Barré syndrome encompasses a spectrum of clinical pathological subtypes. Acute inflammatory demyelinating polyneuropathy (AIDP) is the most common type of GBS in North America and Europe and is characterized by focal demyelination

N. Bakshi, M.D. (✉)
The Permanente Medical Group, Oakland, CA, USA
e-mail: nandini.bakshi@kp.org

J.J. Sejvar, M.D.
Centers for Disease Control and Prevention, Atlanta, GA, USA

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of motor and sensory nerves and nerve roots [2]. The axonal variant of GBS, termed acute motor axonal neuropathy (AMAN) is more common in certain areas of the world such as China, and is characterized by axonal damage to motor nerves [3]. Other variants of GBS include Fisher syndrome (a triad of ophthalmoplegia, ataxia and areflexia), and Sensory GBS [2].

Incidence

The annual incidence of GBS is estimated at between 0.4 and 4.0 cases per 100,000 population per year depending on the study methodology [2]. In developed countries, most well-designed prospective studies have suggested an incidence of one 1–2 per 100,000 population per year [4, 5]. While most cases are sporadic, seasonal patterns have been observed in some countries (e.g., China, Pakistan, Sri Lanka) [3].

Pathophysiology

GBS is an immune-mediated disorder resulting from autoimmune antibodies and/or reactive T cells that cross react with epitopes on peripheral nerves and nerve roots, resulting in nerve damage [6, 7]. The most common subtype (AIDP) resembles experimental autoimmune neuritis which is predominantly caused by T cells directed against proteins in the myelin sheath of peripheral nerves [2, 6]. Approximately two thirds of patients have a history of either an antecedent respiratory tract or gastrointestinal infection; the strength of evidence for an etiologic role in GBS for specific infectious agents varies. The enteric bacterium *Campylobacter jejuni* is the most commonly identified infectious agent associated with GBS and *Campylobacter* infections commonly occur in places where sanitation and hygiene are poor. *Campylobacter*-associated GBS often results in the AMAN or Fisher syndrome variants of the illness [2, 3]. The most common viruses associated with GBS include influenza, Epstein–Barr, cytomegalovirus, enteroviruses, hepatitis A and B, and varicella viruses [8].

GBS and Vaccination

GBS has been temporally associated with a number of vaccines, including rabies, combined diphtheria, pertussis and tetanus (DPT), rubella, tetanus toxoid, hepatitis B, hepatitis A, polio, influenza, and meningococcal conjugate vaccines [9–13]. Of these, the association between influenza vaccination and GBS has been the most studied [13–21].

GBS and Influenza Vaccination During the 1976 Influenza Epidemic

In 1976, the US government sponsored the National Influenza Immunization Program (NIIP). This program was developed with the intent to vaccinate the entire US population, including children and adults that were thought to be at risk of serious influenza illness from a newly identified H1N1 influenza virus of swine origin (A/New Jersey swine influenza virus). Concern about this virus was based in part, on its antigenic similarity to the influenza virus that resulted in the catastrophic 1918 "swine flu" pandemic. The nation-wide vaccination program began on October 1, 1976, and resulted in over 35 million doses of vaccine given by December 2 of the same year [13]. Two of the manufacturers produced whole virus antigen, whereas the other two produced split virus antigens; all manufacturers produced inactivated vaccine. The feared influenza outbreak did not materialize, and the vaccination program was discontinued 2 weeks after two clusters of GBS among vaccine recipients were reported from different US states. These reports led the Centers for Disease Control and Prevention (CDC), in cooperation with state health departments, to initiate an epidemiologic investigation as to a possible causal relationship between GBS and the A/New Jersey swine influenza vaccine. By December 15, 1976, preliminary data from four US states (Alabama, Colorado, Minnesota, and New Jersey) suggested a sevenfold increase in GBS cases among recently vaccinated individuals than among the nonvaccinated population. These preliminary data suggesting a possible causal association, and weakening evidence that a swine flu pandemic was imminent, led to the suspension of the NIIP on December 16, 1976.

At the time of the suspension, the CDC and state health departments expanded the ongoing GBS surveillance study nationally. A total of 1,098 patients with GBS were reported from October 1, 1976, to January 31, 1977, from all 50 states, the District of Columbia, and Puerto Rico. Of these, 532 had received the A/New Jersey vaccine; results of this epidemiologic surveillance program showed that when compared to the unvaccinated population, the vaccinated population had a significantly elevated attack rate of GBS in at least the 6 weeks following vaccination in every adult age group studied. The estimated attributable risk of vaccine-related GBS in the adult population was just under one case per 100,000 vaccinations. The distribution of cases by week after vaccination clustered in the first 5 weeks, particularly week 2 and 3 following vaccination. The relative risk of GBS during weeks 2 and 3 after vaccination exceeded 12. There was no significant difference in GBS rates between the 4 manufacturers or between whole and split virus vaccines [13]. This strong epidemiological data linking the 1976 swine influenza vaccines to GBS suggested a true causal relationship. However, the precise biological mechanism for this relationship has yet to be understood.

GBS and Influenza Vaccination 1978–2009

Due to the association of the 1976 influenza vaccine with GBS, there was concern that subsequent seasonal influenza vaccines would have a similar association. Subsequent prospective surveillance studies and retrospective epidemiologic studies on seasonal influenza vaccines and GBS from 1978 through 2009 showed either no or very low risk of GBS [14–21].

Two studies have suggested a small but statistically significant increase in risk of GBS following administration of influenza vaccine. Lasky et al. [18], reviewed hospital discharge data and patient follow-up in four US states. When adjusted for age, sex, and season, a small but statistically significant increased risk of GBS following influenza vaccination was found during the 1992–1993 and 1993–1994 influenza seasons combined (RR 1.7; 95 % CI 1.0–2.4). There was no statistically significant increased risk when each season was evaluated separately. The best estimates of the overall attributable risk in the 6-week period after vaccination for both seasons combined ranged from 0.6 per million vaccinations to an adjusted risk of 1.6 per million vaccinations. In this study, however, the authors were unable to validate the vaccine status of all included cases.

Juurlink et al. [19], found a small but statistically significant increased risk of GBS in the 6 weeks following vaccination (presumed to be influenza vaccine) based upon administration in October of each year over the period of 1993–2004 in Ontario, Canada (RR 1.45, 95 % CI 1.05–1.99). There was no change found in the incidence of hospital admissions for GBS following influenza vaccination before and after the implementation of a universal vaccination campaign in Ontario in 2000. In this study, however, the actual nature of the vaccine was not known and was only presumed to be influenza vaccine, and other possible antecedent events such as infections were not ascertained.

Six studies [14–17, 20, 21] with varying methodologies and sample sizes, have suggested a lack of association between GBS and influenza vaccine. One study described findings within the vaccine adverse events surveillance database consistent with a possible association between GBS and influenza vaccine, but did not have a study design that would permit a quantitative assessment of risk [22].

GBS and Pandemic (H1N1) 2009 Influenza Vaccine (2009–2011)

In 2009, an influenza A (H1N1) 2009 virus was identified and quickly spread worldwide. In response to this influenza virus, new monovalent adjuvanted and nonadjuvanted influenza A (H1N1) vaccines were developed [23–25]. In the USA, the Food and Drug Administration (FDA) licensed the first influenza A (H1N1) 2009 monovalent vaccines ("H1N1 vaccines") on September 15, 2009. The pandemic influenza A (H1N1) 2009 vaccines were available as a live, attenuated monovalent

vaccine for intranasal administration and as monovalent, inactivated, split-virus, or subunit vaccines for injection. The licensure and manufacturing processes for the monovalent H1N1 vaccines were the same as those used for seasonal trivalent inactivated or trivalent live, attenuated influenza vaccine; none of these vaccines contains an adjuvant. Because of partial similarities between the influenza A (H1N1) 2009 virus and the 1976 influenza A/NJ virus, surveillance for vaccine-related adverse events was established in many countries following the introduction of the influenza A (H1N1) 2009 vaccines. This was based upon widespread concern that similar to the 1976 influenza vaccine, these vaccines might be associated with an increased risk of GBS.

In Europe, the Vaccine Adverse Event Surveillance and Communication (VAESCO) consortium, a network of public health institutes, regulatory agencies, and academic research centers, participated in vaccine surveillance. A multinational case–control study involving five European countries (Denmark, France, the Netherlands, Sweden, and the UK) matched 104 patients with GBS and Fisher syndrome to one or more controls [24]. The study period ran from November 1, 2009, through March 30, 2010. Influenza A (H1N1) 2009 vaccines from two manufacturers were most commonly used in Europe, both were monovalent inactivated split-virion adjuvanted vaccines for intramuscular use. In the source population of approximately 50 million people, the study concluded that the pandemic influenza A (H1N1) 2009 vaccines were not associated with an increased risk of GBS after adjusting for influenza-like illness and seasonal influenza vaccinations. The authors noted that it was unlikely that there would be more than one excess case of GBS per 340,000 vaccinated people given a risk window of 6 weeks and a background incidence of 1.5 per 100,000 person years [24]. In this analysis, several controversial adjustments of data were made, including adjusting for receipt of seasonal influenza vaccine, and experiencing influenza-like illness. Both of these adjustments had an effect on the risk estimates associated with pandemic influenza vaccine, causing a significant reduction in the pooled estimates. There were other limitations of the study, including underreporting and incomplete data available from some countries. The study noted that the absolute risk based upon the upper confidence limit of 2.7 would be less than 3 excess cases of GBS per 1 million vaccinations, and not of the magnitude of that observed in association with the A/NJ/76(H1N1) vaccine in the USA in 1976.

In the USA, several federally sponsored surveillance systems were put into place to monitor the effects of the influenza A (H1N1) 2009 vaccine [25, 26]. Early in the vaccine program, due to concerns about potential vaccine safety, more than 20 % of parents reported that they would not vaccinate their children [25]. To address these concerns, in October 2009, the CDC's Emerging Infections Program began active surveillance to assess the risk for GBS after influenza A (H1N1) 2009 vaccination [26]. Results from an analysis comparing GBS cases in children and adults hospitalized from October 1, 2009, through March 31, 2010, who did and did not receive influenza A (H1N1) 2009 vaccination showed an estimated age-adjusted rate ratio of 1.77 (GBS incidence of 1.92 per 100,000 person-years among vaccinated persons and 1.21 per 100,000 person-years among unvaccinated persons). This corresponded

to 0.8 excess cases of GBS per 1 million vaccinations, similar to that found with seasonal influenza vaccines [26].

The Vaccine Adverse Event Reporting System (VAERS) is a US national spontaneous reporting system for adverse effects following vaccination. Because it is a passive surveillance system, it is subject to limitations, including differential reporting, misclassification of illness, and over- or underreporting [27]. From October 2009 through January 2010, an estimated 82.4 million doses of influenza A (H1N1) 2009 vaccine were administered. During this period, VAERS received reports of adverse events relating to the seasonal influenza vaccine and the H1N1 vaccine. The percentage of serious reports following influenza A (H1N1) 2009 vaccination (with or without concomitant seasonal vaccine) was lower as compared to the 2009–2010 seasonal influenza vaccines given without the H1N1 vaccine [27]. The VAERS analysis of GBS reports from October 1, 2009, to January 31, 2010, showed no difference in any age group in proportional reporting following 2009 H1N1 vaccination compared with the 2009–2010 seasonal influenza vaccine. The overall reports of GBS after vaccination were found to be less than 2 cases per million doses of vaccine administered (0.42 for ages under 25 and 1.75 per million vaccinations for ages 25 and older) [27].

These various assessments of the influenza A (H1N1) 2009 vaccine suggested that the safety profile was similar to that for seasonal influenza vaccines and were not associated with a risk of GBS of a similar magnitude of that observed with the 1976 influenza vaccine.

Biologic Evidence

While epidemiologic studies, particularly those pertaining to the 1976 swine influenza vaccines have shown an increased risk of GBS with influenza vaccination, the precise biologic mechanisms behind this relationship are not fully understood.

There have been several theories postulated regarding the cause of vaccine-related adverse events on the peripheral nervous system but a biological mechanism has yet to be conclusively proven [28, 29].

Brostoff et al. [30], hypothesized that the 1976 influenza vaccines could have been contaminated with peripheral nerve myelin protein (P2). P2 protein is able to induce experimental autoimmune neuritis (EAN) in animal models. EAN is an animal model for GBS. In order to test this hypothesis, nine 1976 A New Jersey H1N1 influenza vaccines from different manufacturers were tested for P2 protein; however, no P2 protein was detected in any of the vaccines tested.

Ziegler et al. [31], tested the possibility of influenza vaccines inducing EAN in rabbits. This study included monovalent whole virion A/New Jersey H1N1 influenza vaccines (including a subvirion formulation) and a trivalent formulation of influenza vaccine used in the 1980–1981 season. The study found that EAN was induced by all three formulations but only with high doses of vaccine and only when

Freund's complete adjuvant and neuritogenic ganglioside epitopes were used. The actual role vaccines may have played in the development of EAN was unclear.

Gangliosides are glycosphingolipids that are present in all tissues but are especially abundant on nerve sheaths. Anti-ganglioside antibodies play a role in the pathophysiology of some variants of GBS particularly AMAN, which is often preceded by infection with certain serotypes of *C. jejuni*. It has been postulated that there is molecular mimicry between the between bacterial surface lipooligosaccharides that express ganglioside-like epitopes resulting in cross-reactive proteins that target peripheral nerves [2].

Haber et al. [22], proposed that because *C. jejuni* is frequently present in poultry and influenza vaccine is made using chicken eggs, contamination of vaccines by *C. jejuni* could result in GBS. Since the inception of VAERS, there has been variability in the reporting rates of GBS, however there had been a marked decline in the reporting of GBS in the years following 1996–1997 and this was not the case with the reporting trends of other vaccine-related adverse events. Due to enhanced food safety during 1996–2003, there was a 28 % reduction in the rates of *Campylobacter* infection in humans and this led the authors to postulate a possible link between the reduced reporting of GBS following vaccination with the reduced rates of *Campylobacter* infections in humans.

Nachamkin et al. [32], obtained archived lots of monovalent and bivalent 1976 A/New Jersey H1N1 influenza vaccines as well as several contemporary influenza vaccines not associated with GBS. These vaccine lots were tested for hemagglutinin (HA) activity (an important surface protein of influenza viruses), the presence of *Campylobacter* DNA, and the ability to induce anti-*Campylobacter* and anti-GM1 antibodies after inoculation into C3H/HeN mice. Anti GM-1 antibodies are a type of anti-ganglioside antibody, often associated with *Campylobacter*-related GBS [3, 7]. The immunized mice were found to have no antibodies to *C. jejuni* suggesting that *Campylobacter* antigens were not present in vaccine formulations. All immunized mice developed anti-GM1 antibodies and it was suggested that incomplete removal of the HA protein during vaccine preparation elicited these antibodies. The significance of this finding is uncertain, since all tested vaccine formulations including those not associated with GBS were able to induce anti-GM1 antibodies. Anti-GM1 antibodies are not specific to GBS; elevated levels of these antibodies are also found in other neurologic conditions. Sivadon-Tardy et al. noted that GBS temporally related to influenza virus infection is not associated with an anti-ganglioside antibody response [8].

Influenza Vaccination in Persons with a History of GBS- to Vaccinate or Not

The Advisory Committee on Immunization Practice (ACIP) currently recommends avoiding influenza vaccination in persons who are not at high risk for severe

influenza illness complications and who have a history of GBS developing within 6 weeks after a previous influenza vaccination [33, 34]. Data on the true risk of recurrence of GBS in the setting of vaccination, however, are limited. A large population-based study examined the incidence of recurrent GBS following vaccination using hospital data. Baxter et al. [35], identified 550 cases of GBS over 33 million person-years from 1995 through 2006 and followed the confirmed GBS cases through 2008 for vaccinations and recurrent GBS. Following their GBS diagnoses, 989 vaccines were given to 279 of these individuals, including 405 inactivated influenza vaccinations administered to 107 individuals with a prior diagnosis of GBS. Eighteen of the 550 cases of GBS were found to have an onset within 6 weeks of influenza vaccination; of these, two were revaccinated for influenza without a recurrence of GBS. The study found only six cases of recurrent GBS; none of these cases occurred after influenza vaccination and none occurred within a 6-week risk interval for adverse events following any vaccination. In this study, vaccination did not appear to increase the risk of recurrent GBS. Despite the large size of the study, and because recurrent GBS is very rare, the sample size of GBS cases identified within the 6-week interval following influenza vaccination provided insufficient power to evaluate a definite assessment of risk Even identification of zero cases of GBS within this sample population, for example, would not be statistically inconsistent with the risk observed following the A/NJ/76(H1N1) vaccine.

Conclusion

GBS is a rare neurologic condition, one in which the pathophysiology is not fully understood. The 1976 A/New Jersey swine influenza vaccine was associated with a substantial increased risk of GBS at least 6 weeks following vaccination. Epidemiologic studies since 1979 have shown a small but significant risk of GBS following influenza vaccination, but that risk remains in the order of less than 1 case per 1,000,000 vaccinations. Put in perspective, this risk is much less than the risk of influenza-related illness in the nonvaccinated population. Influenza vaccines greatly reduce the morbidity and mortality associated with influenza outbreaks. Patients and clinicians need to balance the very small increased risk of a vaccine-related adverse event such as GBS with the potential risk of serious influenza-related illness. With increased surveillance efforts and further research into the mechanisms behind vaccine-related neurologic events, the true risk of GBS and other vaccine-related neurologic events could be better understood.

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Chapter 18
Can Vaccines Cause Chronic Diseases?

Ann-Christine Nyquist

A chronic disease is a long-lasting condition that can be controlled but not cured. Chronic illness affects the population worldwide and is a leading cause of death and disability in the USA. Chronic illness and disease can be caused by some vaccine-preventable infections yet the vaccines that prevent these infections have been alleged to also cause chronic illness.

Adverse events following immunization may be caused by the active antigen in the vaccine or other constituents, such as adjuvants, or may be merely coincidental. When any suspected adverse reactions are reported with vaccines, the following criteria are used to assess a causal relationship: strength of association, consistency, specificity, temporal association, dose–response effect, biological plausibility, coherence, experimental evidence, and analogy to other biologic systems [1]. The Institute of Medicine (IOM) recently published the book, "Adverse Effects of Vaccines: Evidence and Causality." This 2012 document utilizes strict criteria to provide conclusions that favor, reject, or state there is a paucity of data or evidence to confirm a causal relationship between a vaccine and an adverse effect [2]. The committee did conclude that the evidence favors acceptance of four specific vaccine–adverse event relationships. These include HPV vaccine and anaphylaxis, MMR vaccine and transient arthralgia in female adults, MMR vaccine and transient arthralgia in children, and certain trivalent influenza vaccines used in Canada and a mild and temporary oculorespiratory syndrome. The committee concluded the evidence favors rejection of five vaccine–adverse event relationships. These include MMR vaccine and Type 1 diabetes; diphtheria, tetanus, and pertussis (DTaP) vaccine and Type 1 diabetes; MMR vaccine and autism; inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes; and inactivated influenza vaccine and Bell's palsy.

A.-C. Nyquist, M.D., M.S.P.H. (✉)
Sections of Infectious Diseases and Epidemiology, Department of Pediatrics, Children's Hospital Colorado, University of Colorado School of Medicine, 13123 East 16th Avenue B-276, Aurora, CO 80045, USA
e-mail: Ann-Christine.Nyquist@ucdenver.edu; Chris.Nyquist@childrenscolorado.org

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This chapter will ask whether there is an association between a vaccine and a chronic illness, describe some of the infectious causes of chronic illnesses and the vaccines that prevent them and discuss the chronic disease myths associated with these vaccines.

Does Oral Poliovaccine Cause Vaccine-Associated Paralytic Polio (VAPP)?

Poliomyelitis is an acute infectious disease caused by an enterovirus consisting of three serological types of poliovirus that can cause paralytic disease. The trivalent oral poliovirus vaccine (OPV) consists of three live attenuated viruses that multiply in the gastrointestinal tract, mimicking a natural process of exposure to virus which results in serologic and mucosal immunity to the disease.

OPV has been the most important tool in the worldwide campaign attempting to eradicate poliomyelitis. The rapid reduction of cases of polio worldwide has largely resulted from using OPV because it is easy to use in mass campaigns, provides long-term immunity, and rapidly reduces the spread of the polioviruses when many in the community are immunized. Most people vaccinated against polio have no adverse reactions. Vaccinees can excrete live attenuated virus for several weeks, and OPV recipients or contacts may become infected with the virus. Immunocompromised people are at increased risk for VAPP and may shed neurovirulent viruses for years. Between 250 and 500 cases of VAPP occur each year worldwide. In the past when OPV was used in the USA, 1 out of 2.4 million doses of OPV distributed in the USA caused vaccine-associated paralytic polio (VAPP) [3].

OPV continues to be used in countries where polio infections still occur. Due to the known risk of VAPP many countries without endemic polio have switched to an inactivated injectable polio vaccine (IPV). Although IPV is used exclusively in the USA, if there were to be an outbreak of polio in the USA, OPV would be the preferred vaccine to contain an outbreak.

Does Measles, Mumps, Rubella (MMR) Vaccine Cause Thrombocytopenia?

Serious complications of wild-type measles include pneumonia, postinfectious encephalitis, subacute sclerosing panencephalitis (SSPE), and death [4–6]. Other complications of measles include acute otitis media, appendicitis, hepatitis, myocarditis, and thrombocytopenia [7]. Idiopathic thrombocytopenic purpura (ITP) is known to occur after many types of infections, including numerous vaccine-preventable diseases such as measles, rubella, mumps, varicella, and other viruses. MMR vaccine can also cause thrombocytopenia although thrombocytopenia occurs

more commonly after wild-type measles or rubella infections than after the vaccine [8]. MMR-associated thrombocytopenia occurs in about 1 in 40,000 children aged 12–23 months. The course is usually short and mild and occurs more commonly in boys than girls [9]. The risk for complications is greater with a history of prior ITP, although in one study none of 31 children who had thrombocytopenia after the first dose of MMR vaccine developed thrombocytopenia after a second subsequent MMR immunization.

In a recent large retrospective cohort study of 1.8 million children in five managed care health care systems, there was no increased risk of ITP for any of the commonly given childhood vaccines other than MMR in younger children [10]. In older children, O'Leary et al. found a potential increased risk of ITP with Hepatitis A vaccine, Tdap vaccine, and varicella vaccine. Vaccine-associated ITP cases were acute and mild with no vaccine-exposed cases developing serious permanent complications. Further study will be needed to explore the possible associations of ITP with these other vaccines in older children.

Do Vaccines Cause Encephalopathy or Encephalitis?

The Vaccine Adverse Event Reporting System (VAERS) was established in 1990 to monitor the number and type of adverse events following vaccination, and is operated collaboratively by the US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). VAERS receives over 10,000 adverse event reports annually. The goals of VAERS include identifying signals of previously unrecognized adverse events, increasing reporting of known events, and identifying risk factors for adverse events [11]. Ball et al. have developed some reproducible case definitions for acute encephalopathy, encephalitis, and multiple sclerosis for the VAERS system, enhancing the utility of the reporting system but it is still a passive reporting system and does not have the ability to determine causality [12].

Pertussis Vaccine and Encephalopathy

Pertussis (whooping cough) is an upper respiratory infection caused by *Bordetella pertussis*, a gram-negative, pleomorphic bacillus that attaches to cells lining the respiratory tract. *B. pertussis* infections range from asymptomatic to severe with symptomatic disease characterized by three phases: catarrhal, paroxysmal, and convalescent. Apnea and respiratory arrest are the most common complications of pertussis followed by pneumonia and gastroesophageal reflux. Encephalopathy, including evidence of *B. pertussis* antibodies in the cerebrospinal fluid, is a well-known but rare complication of pertussis occurring most often in young infants [13, 14]. Other complications include seizures, ataxia, aphasia, blindness, deafness, subconjunctival hemorrhages, syncope, and rib fractures [13].

The first pertussis vaccines, licensed in the USA in 1941, were suspensions of killed pertussis bacteria and combined with diphtheria and tetanus toxoids to produce whole-cell DTP vaccine. As soon as DTP was first broadly used for vaccination, the first reports of seizures, encephalopathy, and other signs of neurological pathology after vaccination were noted. In January 1974, a case-series report was published describing 36 children admitted to a hospital in London over an 11-year period with "neurological complications" such as mental retardation and epilepsy after receiving the DTP vaccine [15]. The media interpreted the report as evidence that whole-cell DTP immunization caused brain damage despite a caution by the authors that these were merely observations. Later reevaluation of the cases found that in only 12 of the original 36 cases the manifestations of brain damage occurred close to the time of vaccination and that 2 of the children included in the report had never actually received the DTP vaccine [16, 17].

The National Childhood Encephalopathy Study (NCES), conducted in the UK from 1976 to 1979, suggested the possibility of a relationship between the DTP vaccine and encephalopathy in a small number of children at a rate of 1 in every 310,000 doses [17]. Methodological problems with this study were quickly highlighted, the results were questioned, and other studies in the UK, Denmark, and Tennessee were published refuting the initial findings of the NCES [18–22]. In a large case–control study conducted in Washington and Oregon involving 218,000 children, 424 cases with neurological illness were matched with 2 controls and no association was seen with whole cell DTP administration, even when the analysis was restricted to encephalopathy or complicated seizures and adjusted for factors that might have affected vaccine administration [23].

In 1991, the IOM independently analyzed the NCES data and concluded at that time that there was a rare but causal relationship with encephalopathy in the immediate 7-day post-vaccination period, even though there was no evidence that permanent brain damage occurred [24]. It was unclear whether the number of cases of encephalopathy was increased by the vaccine or that it was a result of a preexisting brain or metabolic disorder [25].

Multiple conflicting reports continued to generate concern that whole cell DTP vaccination caused brain damage and the anti-vaccine movements thrived. Media coverage of the NCES report caused a decrease in pertussis immunization rates in British children from 81 to 31 %; the decrease in vaccine use resulted in 100,000 cases and over 600 deaths from pertussis [26]. A 1998 study examined the impact of the whole-cell pertussis anti-vaccine movements on the number of pertussis cases in different countries. The incidence of pertussis was 10–100 times higher in countries where immunization programs were compromised by anti-whole-cell pertussis vaccine movements (Sweden, Japan, UK, Ireland, Italy, Australia, former West Germany, Russian Federation) than in countries where high vaccine coverage was maintained (Hungary, former East Germany, Poland, and the USA) [27].

Due to the high reactogenicity of DTP, acellular vaccines composed of purified filamentous hemagglutinin (FHA) and leukocytosis-promoting factor hemagglutin were developed to replace whole cell DTP [28]. Acellular pertussis-containing vaccines have many fewer reactions of all types than the whole-cell DTP although

adverse events are still reported. Japan reported a rate of 0.5 per 10 million children for any encephalopathy or encephalitis within 7 days of DTaP vaccination [29]. In Canada, between 1993 and 2002, seven cases of encephalopathy were detected within 7 days of DTaP vaccination, but all had other explanations for their encephalopathy [30]. Currently, the acellular pertussis vaccine is the only available vaccine in the USA to prevent pertussis in combination with diphtheria and tetanus.

In a case–control study published in 2006, the records of four large US health maintenance organizations were used to readdress the issue of a causal relationship between whole-cell pertussis vaccine and the onset of encephalopathy [31]. A total of 452 children with encephalopathy diagnosed between 1981 and 1995, when DTP was commonly used, were compared with matched controls without encephalopathy. Exposure to pertussis vaccine in any post-vaccination time period was no more common among cases than controls. The maximum possible all-cause incidence of encephalopathy after pertussis immunization was 1 in 370,000 which was no different from the background rate of encephalopathy in young children. The risk of encephalopathy was no greater in vaccinated children compared to unvaccinated control patients, thus again refuting an association between DTP and encephalopathy [31].

Encephalopathy occurring after acellular pertussis-containing vaccines is rare and usually there are alternative explanations for the brain injury. Children with certain genetic diseases may begin showing symptoms of their underlying conditions after fever, stress, or coincidentally, immunizations. In a landmark 2006 study, de novo mutations in the gene encoding a neuronal sodium channel protein were found in 11 of 14 patients who allegedly had suffered vaccine encephalopathy related to pertussis vaccination [32]. Since then, additional cases have been reported of this common genetic cause of a number of epileptic encephalopathies [33, 34].

Encephalitis and Measles-Containing Vaccines

Encephalitis occurs in about 1 in 1,000 children with wild-type measles; many die and many others have severe brain damage. In 2012, the IOM concluded that the evidence convincingly supports a causal relationship in individuals with demonstrated immunodeficiencies between the measles component of the MMR vaccine and measles inclusion body encephalitis.

One study could find no cases of encephalitis within 30 days after the receipt of MMR—or any other vaccine—in about 300,000 children 12–23 months old [35]. Another large study found no excess encephalitis among 561,000 children who received MMR [36]. Two case–control studies also found no difference between those who received MMR vaccine and controls [31, 37]. In 1994 and (reaffirmed) in 2012, the IOM felt that the data were insufficient to decide whether encephalitis or encephalopathy occurs after measles vaccination in children with normal immune systems [2, 38].

Subacute Sclerosing Panencephalitis and Measles Vaccine

Subacute sclerosing panencephalitis (SSPE) is a persistent measles virus infection of the brain that leads to severe physical and mental impairment. SSPE occurs in about 1 in 100,000 children with wild-type measles and is ultimately fatal. Symptoms of SSPE usually develop years after the initial measles infections. After measles vaccination was introduced in the USA the number of cases of SSPE declined from 40–50 cases per year to 1 or 2 per year. A resurgence of more than 55,000 cases of measles between 1989 and 1991 resulted in a corresponding increase in cases of SSPE. Analysis of measles viruses from the brains of patients with SSPE were the same type associated with the measles outbreak and have never demonstrated vaccine virus [39].

Meningoencephalitis and Mumps Vaccine

Mumps is an acute viral infection causing classic parotitis in only 30–40 % of infections. Asymptomatic infection is more common in adults, while parotitis occurs most often in children age 2–9 years [40]. Complications of mumps infection can occur without the presence of parotitis. Wild-type mumps causes a mild aseptic meningitis in 4–6 % of children. Neurological complications (aseptic meningitis, encephalitis, cerebellar ataxia, transverse myelitis, poliomyelitis-like disease, and cranial nerve palsies) are more common in adults, occur three times more often in men than in women, and are responsible for more than 50 % of mumps-related fatalities [40–46]. Some mumps vaccine strains used in vaccines throughout the world have caused aseptic meningitis in a few children but the Jeryl Lynn mumps vaccine strain used in the US vaccine has not been associated with an increased risk of aseptic meningitis [35, 36].

Do Vaccines Cause Guillain–Barré Syndrome?

Guillain–Barré Syndrome (GBS) is an acute, immune-mediated, demyelinating peripheral neuropathy characterized by progressive symmetric weakness and is the leading cause of acute flaccid paralysis in developed countries. GBS is believed to be an immune-mediated disorder resulting from the generation of autoimmune antibodies that cross react with epitopes on peripheral nerves, leading to nerve damage. Autoantibodies may form in response to a variety of antigenic stimuli, such as bacterial or viral infections. About two-thirds of GBS cases occur several days or weeks after an apparent infectious illness, commonly a diarrheal illness or upper respiratory infection (URI). Infections temporally associated with GBS include *Campylobacter jejuni*, influenza viruses, *Mycoplasma pneumoniae*, HIV, EBV,

CMV, and the vaccinia virus used in smallpox vaccination [47]. Most patients recover completely, although about 10 % of patients die and as many as 20 % will have some permanent disabilities.

GBS is reported to have an annual incidence of between 0.4 and 4.0 cases per 100,000 population per year, with most studies reporting 1–2 cases per 100,000 population per year. Several population-based studies indicated that the annual incidence of GBS in children is 0.1 cases per 100,000 population between the ages of 5 and 14 years, and 0.62 cases per 100,000 population between the ages of 10 and 19 years [48].

Due to a temporal association between vaccines and GBS, a number of vaccines have been suggested as causes of GBS but there is little evidence to support a causal association with most vaccines. Causal association of any particular vaccine or other antecedent event with subsequent GBS is difficult to demonstrate. In general, the association of prior infection or vaccination with the development of GBS is based upon a close temporal relationship and additional supportive epidemiological evidence. Biological mechanisms of causation have failed to be demonstrated. Although aluminum has been associated with post-vaccination macrophagic myofasciitis and heavy metal ingestion has been associated with a single case of GBS, the role of aluminum in the genesis of GBS is not clear [49–51].

GBS and Influenza Vaccines

Concerns about the risk of developing GBS after vaccination have been present since the mass vaccination with the A/New Jersey/H1N1 vaccine in the USA in 1976–1977 during the "swine flu" campaign. Nearly the entire adult population of the USA was vaccinated with more than 35 million doses of vaccine. A significantly increased risk of GBS became evident within 6–8 weeks after vaccination, with the largest percentage of cases occurring 2–3 weeks after vaccination especially in those over the age of 25 years. The vaccine probably caused approximately 1 extra case of GBS per 100,000 immunized persons above the estimated background rate of 0.87 cases per million persons in a 6-week time period [52, 53]. The risk of GBS from other influenza vaccines has been followed closely in several studies and has been shown to be much lower, approximately one extra case per million people vaccinated [54].

GBS and Tetanus Toxoid-Containing Vaccines

Active surveillance of GBS has found no increased risk within 6 weeks of immunizations with tetanus toxoid-containing vaccines among children less than 2 years of age, children 2–5 years of age, or adults [55]. There is one case report of

one man who had three episodes of GBS following receipt of repeated doses of tetanus toxoid causing the IOM to conclude that "the evidence favored acceptance of a causal relation between…tetanus toxoid-containing vaccines" and GBS [38].

GBS and Meningococcal Conjugate Vaccine

In January 2005, MCV4 (Menactra®) was licensed for use among persons aged 11–55 years. The ACIP recommended routine MCV4 vaccination for 11–12 year old children and before high school entry for individuals who had not been vaccinated previously [56]. By October 2005, after about 2.5 million doses were distributed, five cases of GBS following MCV4 vaccination had been reported to VAERS and the US FDA issued a warning of possible association between the receipt of MCV4 vaccine and GBS [57]. A year later, there were 15 cases reported in 11–19 year olds within 6 weeks of MCV4 vaccination [58]. The rate of GBS among immunized teenagers, calculated based on doses distributed, was estimated to be about 0.20 cases per 100,000 person-months. This rate was similar to the background rate of GBS calculated from the Vaccine Safety Datalink (VSD) database, but it was slightly higher than that seen in the Healthcare Cost and Utilization Project, a multistate hospital discharge database. Combined data from these two very large studies showed no incident cases of GBS within 6 weeks of 2.3 million vaccinations, for an estimated upper 95 % confidence limit of the attributable risk of one case per million doses, which is not above background rates. A subsequent Vaccine Safety Datalink case control study found no association between MCV4 vaccination and GBS and also no association between MCV4 and facial paralysis or seizures [59, 60]. In June 2010, the ACIP removed history of GBS as a precaution for receipt of MCV4, which had been in place since the initial VAERS data came to light in 2005.

Rabies Vaccine and GBS

GBS has been associated with two rabies vaccines—the Semple rabies vaccine, which was produced by inoculation of rabies virus into mature sheep or goat brain and inactivated with phenol, and the SMB rabies vaccine. Approximately 7 % of individuals hospitalized with adverse events from the Semple strain developed a neuroparalytic adverse event characteristic of GBS. This neuroparalytic event was thought to be due to presence of brain protein in the formulated vaccine with the possible generation of autoantibodies strongly cross-reactive with neural tissues [61, 62]. These significant adverse events led to the discontinuation of these vaccines in 1980 in the USA and other countries. Newer formulations of rabies vaccine, derived from chick embryo cells, do not appear to be causally associated with subsequent GBS.

OPV and GBS

Two controlled observational studies conducted in Finland assessed the potential association between OPV and GBS. The first study in southern Finland found an increase in the incidence of GBS during surveillance from 1981 to 1986 following a nationwide immunization campaign for children and adults against polio [63, 64]. At that time, Finland transitioned from using inactivated polio vaccine (IPV) due to an outbreak of ten cases of poliomyelitis between August 1984 and January 1985. Ninety-four percent of the Finnish population was vaccinated with OPV during a 5-week period between February 10 and March 15, 1985. The US IOM panel in 1994 concluded that evidence favored a causal association between OPV and GBS [38]. In 1998, the original Finnish authors, Kinnunen et al., published extended results from their earlier study that was inclusive of all of Finland versus merely the southern portion showing that the increase in GBS actually occurred before the vaccination campaign started and may have been related to an influenza epidemic during that winter and circulation of wild-type poliovirus or of influenza virus in addition to OPV [65]. Epidemiologic studies in California and more recent subsequent studies in South America and Finland have found no temporal association or increased incidence of GBS during poliovirus mass vaccination campaigns [66, 67].

Do Vaccines Cause Multiple Sclerosis?

Multiple sclerosis (MS) is an autoimmune disorder of the CNS in which the myelin sheath that surrounds the nerve cells in the brain is destroyed. About 400,000 people in the USA are affected; women more commonly than men. Most new cases are diagnosed between the ages of 20 and 40 years. Clinical presentation varies; optic neuritis may occur as part of MS or individually; severity varies from person to person, and most experience relapsing courses. Causes are unknown but most likely involve genetic and environmental factors.

The Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines published a meta-analysis to address concerns about the safety of immunization in patients with MS, particularly the concern for risk of relapse after vaccination [68]. They found that there is strong evidence for an increased risk of MS exacerbations during weeks around an infectious episode and that strategies to minimize the risk of acquiring infectious diseases should include the use of vaccines for prevention. There was strong evidence against an increased risk of MS exacerbation after influenza immunization and there was no evidence that hepatitis B, varicella, tetanus, or Bacille Calmette-Guerin vaccines increased the risk of MS exacerbations. Due to the evidence that MS exacerbations occur around infectious episodes and that these exacerbations could potentially be prevented by vaccination it is recommended that patients with multiple sclerosis should follow the CDC recommendations for immunizations.

MS and Hepatitis B Vaccine

Hepatitis B virus causes both acute infection and long-lasting chronic infection; more than half of people infected show no signs or symptoms at the time of infection, although they may become chronically infected, developing liver disease and ultimately hepatocellular carcinoma.

The hypothesis that vaccines might cause MS was fueled by anecdotal reports of MS following a mass Hepatitis B vaccine (HBV) immunization campaign in France in 1996. Because of concerns that the vaccine was causing MS, hepatitis B immunization in French schools was discontinued in 1998.

Two subsequent large case–control studies evaluated whether hepatitis B causes MS or whether HBV, tetanus, or influenza vaccines exacerbate symptoms of MS. The first study in a cohort of nurses identified 192 women with MS and 45 matched controls and found no association between MS and any exposure to hepatitis B, exposure within the 2 years before diagnosis, or the number of doses of HBV received [69]. The second study included 643 patients in Europe with MS relapse occurring between 1993 and 1997 and found no association between relapse and exposure to any vaccine, or specifically HBV, tetanus, or influenza vaccines, in the 2-month period before relapse, compared with the four previous 2-month periods [70].

In 2002, the IOM found that the plausibility of HBV causing MS was weak. Published studies consistently showed no link between the HBV of adults and MS. They concluded that the evidence favored rejection of a cause-and-effect relationship between HBV and new cases of MS or MS relapse [71]. Subsequent studies found no increased risk of MS or optic neuritis in adults following HBV, anthrax, smallpox, influenza, tetanus, measles, or rubella immunizations [72, 73].

There is even less evidence for a link between HBV and MS in children. A French case–control study compared 143 children less than 16 years of age with MS with 1,122 children who were matched for age, sex, and area of residence. Immunization with HBV within 6 months or at any time since birth or the number of doses of vaccine did not elevate the risk of a first MS episode [74]. Additionally, HBV or tetanus immunization after a first episode of illness did not increase the risk of a second episode [75].

MS and Influenza Vaccine

Well-controlled studies have found that influenza vaccine does not exacerbate symptoms of MS. In a retrospective study of 180 patients with relapsing MS, infection with influenza virus was more likely than immunization with influenza vaccine to cause an exacerbation of symptoms, suggesting that influenza vaccine may actually prevent exacerbations of MS [76]. In a multicenter, prospective, randomized, double-blind trial of influenza vaccine among 104 patients with MS, immunization was not associated with exacerbation of symptoms or change in disease course [77].

In 2004, the IOM concluded that the data consistently demonstrated that influenza immunization did not cause MS relapse, but that there were insufficient data regarding the hypothesis that influenza immunization might trigger new cases of MS. According to the IOM's report, they agreed that there was "no reason to suspect that a causal relationship might exist between influenza vaccines and onset of MS" [52].

Do Vaccines Cause Diabetes?

Type 1 diabetes is an autoimmune disease in which the beta cells in the pancreas are attacked as nonself. Environmental factors are thought to trigger the autoimmune attack on beta cells in genetically susceptible individuals although genetic susceptibility appears to be a necessary but not a sufficient factor for developing Type 1 diabetes. Many possible environmental triggers have been suggested, but except for congenital rubella infection where 20 % of children will ultimately develop Type 1 diabetes, none have been shown to trigger the onset of Type 1 diabetes [78].

Theoretically, if infections can trigger an autoimmune disease then vaccines might also do it. A matched case control study in Sweden between 1985 and 1986 compared 339 children with Type 1 diabetes to 528 children without diabetes. Measles and MMR vaccine appeared to have a protective effect against Type 1 diabetes and BCG, smallpox, tetanus, pertussis, mumps, or rubella vaccines conferred no other significant risks [79]. In Sweden, due to the discontinuation of pertussis vaccine because of vaccine safety concerns in September 1979, Heijbel et al. were able to compare the likelihood of developing diabetes between high exposure to whole-cell DTP vaccine and low exposure to the vaccine. They found no difference between the two groups risk of developing diabetes [80].

In 1997, a small study suggested that if children received the Hib vaccine at certain times during their infancy, they were more likely to develop Type 1 diabetes than children who received the vaccine at different ages [81]. A much larger national study examined three groups of children born in Finland who differentially received Hib vaccine at different times and showed no difference between the cumulative risk for Type 1 diabetes among the groups of children [82].

Children with a sibling or parent with Type 1 diabetes were evaluated as to whether vaccines or the ages when vaccines were given contributed to the development of autoantibodies (prediabetes cases) or not (controls). There were no differences in the proportion developing prediabetes among groups of children receiving HBV, Hib, polio, or DTP vaccines nor with the age when immunizations where given [83].

A European population-based registry was used to identify 1,028 children who developed Type 1 diabetes before 15 years of age and compare them with a matched control group. There was no link between BCG, polio, DTP, MMR, or Hib vaccination and the development of Type 1 diabetes [84]. In Denmark, no associations were found between the vaccines, the dose or time since vaccination, or the total number of vaccinations with Type 1 diabetes for the almost 740,000 children born between January 1, 1990, and January 1, 2000 [85].

A VSD study conducted in four HMOs compared children born in 1988 through 1997 who developed Type 1 diabetes with 768 non-diabetic children matched for same HMO, sex, birth within 7 days, length of time at HMO. No link was found between any of the vaccines (HBV, Hib, whole-cell or acellular pertussis, MMR, or varicella) or timing of HBV vaccine and an increased risk of Type 1 diabetes [86].

In 2002, the IOM immunization Safety Review Committee concluded that the "epidemiologic and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of Type 1 diabetes" [78]. Subsequent studies confirm this lack of linkage between vaccines and the development of Type 1 diabetes.

Do Vaccines Cause Arthritis?

Rubella illness in a child or adult is usually benign although arthritis and arthralgia has been observed in association with viral replication in the synovial cavity of the joints [87]. Joint pain and arthritis occur during wild-type rubella infection more commonly in women than in children and men, and chronic joint complaints can persist. Other complications of rubella include encephalitis, GBS, progressive rubella panencephalitis, and thrombocytopenia [87, 88].

Arthritis and Rubella Vaccine

Joint pain and arthritis occur less frequently after vaccination than after wild-type rubella. Joint pain and arthritis in adult women occurs 11 % of the time at 7–21 days after immunization and in only 8 out of 1,000 young children. Joint symptoms usually resolve quickly and appear to be caused by virus infection of the joint. A number of studies suggest that natural rubella virus might persist and/or cause autoimmunity leading to chronic arthritis. Some of the early rubella vaccines were associated with higher rates of acute and chronic joint complaints but this has decreased with newer vaccines [89].

In a large study, women 15–59 years of age who were immunized, unimmunized but immune, and unimmunized susceptible, matched for age and testing date, were followed for chronic joint complaints post immunization. There was no evidence of increased risk of new onset chronic joint complaints over 12 months after immunization [90]. Another study done between 1989 and 1992 of 546 rubella-susceptible women 18–41 year of age randomized to receive rubella vaccine or placebo showed that acute joint reactions occurred more frequently in the women who were vaccinated than in those who received placebo but there was no difference in the frequency of persistent joint complaints after a year [91].

Arthritis and Aluminum Containing Vaccines

Aluminum salts (aluminum hydroxide, aluminum phosphate, and alum) have been the main adjuvants used in vaccines for almost 80 years and are the only adjuvants currently licensed for use in humans in the USA. The most important mechanism of alum is probably mediated through activation of antigen-presenting cells. Aluminum adjuvants strongly influence the type of immune response and are important for stimulation of antibody production but probably do not induce cell-mediated immunity. Serious adverse effects attributable to aluminum adjuvants are rare. Localized reactions such as redness, swelling, and/or tenderness at the injection site occur commonly following injection of vaccines containing an aluminum adjuvant. More severe local reactions such as a large area of swelling, sterile abscesses, subcutaneous nodules, and allergic responses also can occur but are much less common.

US vaccines containing aluminum include: DTP; DTaP; some Hib; pneumococcal conjugate vaccine; hepatitis B vaccines; all combination DTaP, Tdap, Hib, or hepatitis B vaccines; hepatitis A vaccines; HPV vaccines; anthrax vaccine; and rabies vaccine. IPV, MMR, Varicella, MCV4, and influenza vaccines do not contain aluminum salts. A systematic review of studies of aluminum-containing vaccines against DTP found that aluminum-containing vaccines caused more localized reactions—such as pain, redness, and swelling at the injection site—but there was no evidence that aluminum salts caused any serious or long-lasting adverse events [92]. Large studies with thousands of adults who were given whole-cell pertussis-containing vaccines, acellular pertussis-containing vaccines, and hepatitis B vaccines have shown no evidence of long-term effects in adults [73, 93].

Do Vaccines Cause Macrophagic Myofasciitis?

During the last 15 years, a syndrome called macrophagic myofasciitis has been reported to be associated with aluminum-adjuvanted vaccines. Most cases have been reported in France and most of the patients have been adults but there are also descriptions of cases in other countries and in children [50, 94]. The patients have presented with a variety of clinical symptoms, but usually they have myalgias, arthralgia, and fatigue. Some cases are reported to have more serious neurological diseases such as multiple sclerosis. Muscle biopsies from the deltoid region show macrophages surrounding the muscle fibers forming a characteristic histological lesion. Electron microscopy has shown the presence of aluminum hydroxide inclusions in the lesions. Most scientists believe the tissue findings show a normal immune response to the aluminum adjuvant in some vaccines [95, 96]. Relationship between these lesions and the clinical symptoms is still considered an unproven hypothesis.

Do Measles Vaccines Cause Inflammatory Bowel Disease?

The initial report in 1995 from Dr. Wakefield in Great Britain set into play concerns about MMR vaccine and autism but interestingly, his initial paper actually tried to describe a link with inflammatory bowel disease (IBD) and then subsequently autism or pervasive developmental delay [97]. A Cochrane review of subsequent studies has not found any link between MMR or other measles vaccines with the development of IBD [98]. In addition, a case–control study in the USA of 155 children with IBD, an ecologic study over a 20-year period in England of hospitalized cases with IBD, and a case–control study in adults found no association between MMR or measles vaccine and the development of IBD [99–101].

Do Vaccines Cause Gulf War Illnesses?

Military personnel returning from the 1990 to 1991 Persian Gulf War reported numerous health problems that some believed were related to their service. In 1998, the IOM evaluated possible associations between illness and a variety of potential exposures including anthrax, botulism and other vaccines, and found "no cluster of symptoms that constitute a syndrome unique to Gulf War veterans and insufficient evidence to establish an association with most exposures including vaccines" [102].

Do Vaccines Cause HIV/AIDS?

Acquired Immunodeficiency Disease Syndrome (AIDS) was first described in the early 1980s followed quickly by the identification of its viral cause, Human Immunodeficiency Virus (HIV). The search for the origin of HIV brought forth many theories that have ultimately been disproven. In 1999, British journalist Edward Hooper theorized in a widely publicized book, "The River: A Journal to the Source of HIV and AIDS," that the origin of the AIDS pandemic was from field trials of an early OPV used in the Belgian Congo between 1957 and 1960. He speculated that monkey cells used in the production of the experimental polio vaccine lots were contaminated with chimpanzee cells that were infected with chimpanzee immunodeficiency virus which ultimately evolved into HIV-1 after ingestion of the "contaminated" OPV. Although this experimental vaccine was tested in Central Africa, close to the region where AIDS cases were initially recognized, the same lot was also tested throughout Europe with over 7.2 million people vaccinated in Poland. Testing of old vials of vaccine showed only evidence of monkey cells and only polio virus. There was no evidence of chimpanzee cells or any HIV-like virus. In addition, HIV evolutionary studies have shown that HIV was first acquired by humans 30 years before the experimental polio virus vaccine studies of the late 1950s [103, 104].

Do Vaccines Cause Prion Disease?

Transmissible spongiform encephalopathies (TSE) are a group of illnesses caused by the abnormal folding of a normal brain protein, prion, that ultimately accumulates in brain cells causing rapidly progressive dementia leading to death. Five to ten percent of all Creutzfeldt-Jakob disease (CJD) cases, 1–2 cases per million people, occur sporadically in man as an inherited mutation of the gene that codes for the prion. The defective protein can also be transmitted by contaminated harvested human brain products, intravenous gammaglobulin (IVIG), corneal grafts, or dural grafts. First identified in 1996, variant CJD (vCJD) is presumed to be transmitted from cattle to humans by the consumption of meat that is contaminated with cattle nervous tissues.

Because bovine-derived materials such as serum, albumin, and gelatin have been used in vaccine manufacture, there was a theoretical concern that prions could be transmitted through vaccination. Prions are found in neuronal tissues of infected cows but these tissues are not used in vaccine manufacture. Fetal bovine serum, used to support cell growth in culture and ultimately removed from the final product, and gelatin, used as a stabilizer in vaccine preparations and derived from connective tissues of cows and pigs, are not known to contain prions or transmit vCJD. In 2000, as a precaution, the FDA recommended that vaccines use bovine materials originating from countries without endogenous bovine spongiform encephalopathy (BSE) [105]. In July 2000, FDA's Center for Biologics Evaluation and Research conducted a comprehensive review of vaccines containing bovine components and the origin of bovine products. They determined that the theoretical risk of any bacterial or viral vaccine contamination by BSE prions was remote, ranging from 1 in 2 billion to 1 in 200 billion doses [106, 107]. Vaccine safety in relation to potential contamination with BSE is high and there have been no cases of variant CJD related to vaccines [108].

Conclusions

Wild-type infections that are vaccine preventable have the ability to cause chronic illness and disease. Vaccines have known adverse events that are most often mild and short-lived but rarely have a causal association with chronic diseases. Myths connecting vaccines to chronic illness often occur when illnesses are not well explained and the associated vaccines may reflect a temporal but not necessarily causal relationship to the disease. Continued utilization of the VAERS reporting system, VSD, and scientific studies is necessary to ensure that vaccines are continually and carefully assessed for potential adverse events and potential causal associations with chronic diseases.

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Chapter 19
Kawasaki Disease and Sudden Infant Death Syndrome: Any Connection to Vaccination?

Kari Neemann

Kawasaki Disease

Epidemiology

Kawasaki disease (KD), first described in 1967 by Tomisaku Kawasaki, is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and young children [1]. It is seen worldwide in all populations, with the highest incidence occurring in children of Asian background. It is an illness of early childhood, as the median age of illness is 2–3 years and 80 % of affected children are <5 years old. KD may occur in adolescents and is more prevalent in boys than girls, at a rate of 1.5–1.7:1 [2]. In the continental United States, population-based and hospitalization studies have estimated an incidence of KD ranging from 9 to 19 per 100,000 children younger than 5 years of age [3]. Race-specific incidence rates derived from administrative data indicate that Kawasaki disease is most common among Americans of Asian and Pacific Island descent (32.5/100,000 children <5 years old), intermediate in non-Hispanic African Americans (16.9/100,000 children <5 years old) and Hispanics (11.1/100,000 children <5 years old), and lowest in whites

K. Neemann (✉)
Pediatric Infectious Diseases, Creighton University School of Medicine, Omaha, NE, USA

Pediatric Infectious Diseases, University of Nebraska Medical Center, Omaha, NE 68198, USA
e-mail: kneemann@unmc.edu

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(9.1/100,000 children <5 years old) [2]. In 2009, the estimated number of hospitalizations with KD was 5,547, of which 4,040 were in children <5 years of age [4].

Etiology

While the etiology of KD is unknown it has been speculated to be of infectious origin given the clinical presentation and seasonality which favors winter–spring. The rarity of KD in infants <3 months old is well matched with protection from passive maternal antibody. The lack of KD in adults suggests widespread immunity. Yet, while different infectious etiologies have been proposed nothing has been found to be consistently associated with this illness. Multiple hypotheses have been proposed: from bacterial superantigen toxins (polyclonal) that incite the cascade to KD [5], which is somewhat controversial, to a recently more favored explanation where an immune response that is antigen driven (oligoclonal) with immunoglobulin A plasma cells [6] playing a more central role. More recent data indicate that cytoplasmic inclusion bodies are present in acute KD ciliated bronchial epithelium [7]. A single monoclonal antibody is bound to these inclusions in acutely affected KD patients, and these structures resemble protein/nucleic acid aggregate inclusion bodies formed by viruses, suggesting that KD results from a single, previously unidentified, respiratory virus [7]. Environmental investigations have linked the syndrome to exposure to freshly cleaned carpets, humidifier use, and residence near a body of water, but these findings have not been consistently replicated in other studies [8–14].

Clinical Presentation

KD is a syndrome that is characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Coronary artery aneurysms or ectasia develop in 15–25 % of untreated children with this disease and may lead to myocardial infarction, sudden death, or ischemic heart disease [2]. Infants are at higher risk of developing coronary artery abnormalities than older children [15]. KD has now surpassed acute rheumatic fever as the leading cause of acquired heart disease in children in the United States [3]. As there is no diagnostic test for KD, clinical criteria have been established to confirm the diagnosis of KD (Table 19.1). The concept of "incomplete" (atypical) KD should be used for patients with fever for at least 5 days, and at least two of the clinical criteria for KD with no other reasonable explanation for the illness, and laboratory findings consistent with severe systemic inflammation [16]. Incomplete KD is more common in infants than older children.

The fever which is typically high-spiking with peak temperatures frequently >39 °C (102 °F) and not uncommonly to > 40 °C (104 °F) is usually remittent.

Table 19.1 Diagnostic criteria (principal clinical findings[a])

Fever of at least 5 days' duration[b]
Presence of four of the following principal features:
Changes in extremities
Polymorphous exanthem
Bilateral conjunctival injection
Changes in the lips and oral cavity
Cervical lymphadenopathy
Exclusion of other diseases with similar findings

[a]Patients with fever and fewer than four principal clinical features can be diagnosed as having Kawasaki disease when coronary artery disease is detected by two-dimensional echocardiography or coronary angiography

[b]Many experts believe that, in the presence of classic features, the diagnosis of Kawasaki disease can be made by experienced practitioners before the fifth day of fever

From Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. Circulation. 1993;87:1776–80

Without treatment the fevers may persist for a mean of 11 days, but may continue for 3–4 weeks. Generally, with appropriate treatment, the fever abates in 1–2 days [17]. The rash in KD can be maculopapular, scarlatiniform, or erythema multiforme-like; vesicles and bullae do not occur. Perineal accentuation of the rash occurs in two-thirds of patients [18, 20]. The subacute phase, which lasts from about day 10 to 25, is associated with resolution of the fever, lymphadenopathy, and rash. Frequently the development of periungual desquamation of the fingers and toes, arthritis, and thrombocytosis will be observed. Children tend to remain fairly irritable throughout the acute and subacute phases. Finally, the convalescent phase begins when all clinical signs abate and ends when the ESR is normalized, generally in 6–8 weeks [19, 21].

Treatment

Aspirin has been an important part of the treatment for KD for the past 30 years. Once the diagnosis is established, high-dose aspirin should be administered at 80–100 mg/kg in four divided doses daily till 14 days after the onset of illness. When high-dose aspirin is discontinued, the patient should be transitioned to low-dose aspirin (3–5 mg/kg per day) and maintained on it until the patient shows no evidence of coronary changes by 6–8 weeks after the onset of illness [17]. IVIG is the second mainstay of therapy; though its exact mechanism of action is unknown, multiple studies have shown it to be beneficial in reducing the incidence of developing coronary artery abnormalities [20–22].

Patients should be treated within the first 10 days of illness, and ideally within 7 days of illness with IVIG at 2 g/kg in a single infusion. Treatment of KD prior to the

fifth day of illness appears no more likely to prevent cardiac abnormalities than treatment from days 5 to 7 [17]. IVIG also should be administered to children presenting after the tenth day of illness if they have either persistent fever without other explanation or cardiac aneurysms and ongoing systemic inflammation [23, 25]. Several multicenter studies have demonstrated that when IVIG is given within the first 10 days of illness it hastens resolution of fever, decreases levels of acute-phase reactants, and reduces the prevalence of coronary artery abnormalities from about 20 % in aspirin-treated patients to about 5 % in those treated with IVIG and aspirin [24, 26]. If the patient remains febrile 48 h after infusion of IVIG a second infusion of 2 g/kg is often initiated.

Kawasaki Disease and RotaTeq™ Vaccination

In February 2006 a new human-bovine reassortant rotavirus vaccine, RotaTeq™ (Merck and Co.), was licensed by the US Food and Drug Administration (FDA) for the purpose of preventing rotavirus-associated gastroenteritis, the leading cause of severe gastroenteritis worldwide [25, 27]. In pre-licensure trials of the RotaTeq™ vaccine there was an observation of a non-statistically significant excess of KD in the RotaTeq™ arm (5 cases in vaccinees versus 1 case in controls) which prompted the FDA in June 2007 to amend the product information to note the occurrence of such cases, but stated that the causality had not been established [26, 27]. The Vaccine Adverse Event Reporting System (VAERS) is a national postmarketing spontaneous reporting system for vaccine adverse events, jointly operated by the FDA and Centers for Disease Control and Prevention (CDC). Hua et al. reviewed the VAERS database from 1990 to 2007 (before and after the label change) looking for an association between RotaTeq™ and KD [28]. They found that the reporting rate was 0.65 per 100,000 person-years before the label revision and 2.78 per 100,000 person-years after the label revision. This remained below the background rate of KD of 9–19/100,000 person-years for children <5 years [28, 30]. Additionally, the pattern of reporting had not shown a consistent effect in terms of time of symptom occurrence following vaccination (onset varied between 0 and 54 days) [29, 31]. Further studies have confirmed this conclusion and the CDC maintains that there is no known cause-and-effect relationship between receiving RotaTeq™ and the occurrence of KD [30, 32].

Kawasaki Disease and Pneumococcal Conjugate Vaccine

Prevnar™ (7-valent pneumococcal conjugate vaccine [PCV7], Wyeth Pharmaceuticals Inc.) was approved by the FDA in February 2000 and the updated Prevnar13™ (13-valent pneumococcal conjugate vaccine [PCV13], Wyeth Pharmaceuticals Inc.) was approved in February 2010 for the prevention of invasive pneumococcal

diseases due to *Streptococcus pneumoniae* serotypes in the vaccine. A post-licensure observational safety surveillance study ($N = 162{,}305$) conducted at Northern California Kaiser Permanente following the introduction of PCV7 found that the rate of KD hospitalization increased post-vaccine introduction compared to historical controls. Yet, after adjusting for potential confounding variables, this difference was found not to be significant ($P = 0.083$) and the authors concluded that there was no association between KD and PCV7 [31, 33]. Secondly, a 2-year post-licensure study that reviewed the VAERS reports following the receipt of PCV7 did not mention KD occurring in this period [32, 34].

Kawasaki Disease and Hepatitis B Vaccine

Routine hepatitis B vaccination initially was recommended for some US adults and children beginning in 1982, and became part of the routine childhood schedule in 1991. Hepatitis B infection has been known to be associated with vasculitis that occurs rarely in adults, specifically polyarteritis nodosa (PAN). Hepatitis B virus-related PAN is an acute disease, occurring shortly after infection and sharing the characteristics of classic PAN and has only been described in adults [33, 35]. There have been rare cases of vasculitis following vaccination with hepatitis B vaccine in adults. These include small, medium, and large vessel vasculitis, and cryoglobulinemia [34–38]. There is one case-report of KD following hepatitis B vaccination in an infant [39]. KD occurred in a 35-day-old infant 1 day after hepatitis B vaccine was given and resulted in the development of coronary artery dilatation that was treated successfully with IVIG [39, 41]. This case-report meets all clinical criteria for KD; yet it is impossible to determine a causative relationship between hepatitis B vaccination and development of KD. The relationship may represent a coincidence. Overall, KD in infancy is rare, with less than 2 % of disease occurring in infants less than 90 days of age, and 0.01 % occurring in those less than 1 month old [40, 42].

Kawasaki Disease and Yellow Fever

Yellow fever is a disease mainly seen in the United States in returning travelers from African and Latin American countries. Yellow fever is a mosquito-borne illness that in the majority of infected individuals causes an asymptomatic or mild viral illness, but that in up to 15 % can develop moderate to severe disease with jaundice. Among those who develop severe disease, mortality approaches 20–50 % [41, 43]. The yellow fever vaccine (YFV) is a live-attenuated vaccine that has been commercially available since the 1950s. YFV is recommended for persons aged ≥9 months who are traveling to or living in areas at risk for YFV transmission. In a recent systematic review, four randomized control trials identified no serious adverse events in children and infants associated with the administration of YFV [42]. There have been five reports of infant transmission after maternal vaccination with YFV [42, 44].

There is one case-report in the literature of KD occurring 20 days after YFV in a 12-year-old white male. The patient met clinical criteria and developed cardiac artery dilatation [43, 45]. Once again, it is impossible to state that there is a cause-and-effect association.

Incomplete Kawasaki Disease and BCG Vaccination

BCG, or bacille Calmette–Guerin, is a vaccine against tuberculosis (TB). Many foreign-born persons who come from countries where there is a high prevalence of TB have been given the BCG in childhood. Multiple randomized controlled trials and case–control studies have shown consistently high efficacy of BCG vaccination against severe forms of childhood tuberculosis, principally miliary disease and meningitis, but variable efficacy against pulmonary tuberculosis in adults [44]. BCG is not generally recommended for use in the United States because of the low risk of infection and potential interference with tuberculin skin test reactivity.

Redness or crust formation at the BCG inoculation site has been described as occurring in KD in multiple case-reports and case series [45–48]. A Japanese nationwide epidemiologic survey conducted in 2007 on KD found that among children aged 3–20 months in countries with a BCG vaccination program, the development of redness or crust at the BCG site was a useful diagnostic sign [49, 51]. The American Heart Association scientific statement on KD lists "erythema, induration at BCG inoculation site" as another clinical symptom to aid in the diagnosis [17]. For patients who present with incomplete KD and have a history of BCG it would be beneficial to look for this finding. It has been proposed that cross-reactivity between specific epitopes of mycobacterial and human heat-shock proteins (HSP) may play a role in the development of the tissue damage characteristically seen at the BCG site [50, 52].

Kawasaki Disease and Mercury (Thimerosal)

Acrodynia was a systemic disorder characterized by high fever lasting greater than 5 days, a varying rash (erythematous plaques, or measles- or scarlet fever-like), swollen lymph nodes, irritated eyes, and bright red mouth, lips, and throat that would often be accompanied by cardiovascular and neurological symptoms. At its epidemic height (1880–1950), it affected about 1 in 500 children in industrialized countries [51, 53]. In 1953, as a result of work by Warkany and Hubbard it was discovered that mercury-containing baby powders, teething powders, and calomel-(85 % mercurous chloride) treated diapers were the cause of acrodynia [52, 54]. Following a federal ban of these mercury-containing products in 1954, acrodynia disappeared.

In the 1980s there were several case-reports of KD, which is clinically similar to acrodynia, associated with mercury exposure. A 13-year-old female was diagnosed with KD and concomitant mercury poisoning after having an extended 2½ month exposure to mercury [53, 55]. A second series of six patients with KD were noted to have high urinary levels of mercury, although urinary mercury levels have not necessarily been predictive of severity of disease [54–57]. The similarities between the two illnesses and the increase in reporting of KD, especially following the amendment to the product safety information for RotaTeq™, led to concern that thimerosal (a mercury-based preservative in multi-vial vaccines) may be contributing to the increased reporting. There are two main types of organic mercury compounds. The first, methylmercury, is found in the environment and at high levels may be toxic [56, 58] Thimerosal contains ethylmercury, which is broken down and excreted much more rapidly than methylmercury and therefore is less likely to accumulate in the body [56, 58]. In 1999 the American Academy of Pediatrics (AAP) and the US Public Health Service reviewed the use of thimerosal in childhood vaccines and while they found no causal evidence of harm, they recommended removing thimerosal from routine vaccines [56, 58]. Since then the FDA and vaccine manufacturers have eliminated thimerosal from routine childhood vaccines [56, 58].

SIDS

Epidemiology

The sudden death of an infant while sleeping has been described for well over 2,000 years. In the book of First Kings within the Bible there is mention of "overlaying," where an infant is presumed to have died from accidental suffocation secondary to an adult rolling on the infant while asleep. Greek physician Soranus of Ephesus in his medical text *The Gynecology*, also addressed this by instructing mothers and wet-nurses to not sleep with infants to prevent suffocation. It wasn't until 1969 that the National Institutes of Health held the first consensus conference to address this phenomenon and defined sudden infant death syndrome (SIDS).

SIDS currently is defined as "the sudden death of an infant under 1 year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" [57]. Sudden unexpected infant death (SUID) is a term used to describe any sudden and unexpected death, whether explained or unexplained (including SIDS), that occurs during infancy. Currently SIDS is the third leading cause of infant mortality in the United States, following congenital anomalies and preterm and low-birth-weight infants, accounting for 8 % of all infant deaths [58, 60]. SIDS deaths have been observed to peak at 2–4 months of age, with most deaths having occurred by 6 months [59, 61]. SIDS mortality rates are higher for male infants than for females and occur among all socioeconomic, racial, and ethnic

groups, but the rates vary widely [60, 62]. The most significant advancement in the understanding of SIDS was the determination that prone sleep position more than tripled the risk of SIDS [61–63]. In response to these findings, in 1992 the AAP recommended that infants sleep nonprone as a way to reduce the risk of SIDS [64, 66]. With the initiation of the "Back to Sleep" campaign in 1994 the rates of SIDS progressively declined and then leveled off in 2001, with rates reported in 2006 of 0.55/1,000 live births (2,323/year), where prior to 1992 the rates had been stable at 1.3–1.4/1,000 live births (about 7,000 infants/year) [65, 67]. Two meta-analyses have revealed that pacifier use is associated with decreased risk of SIDS by 50–60 % [66, 67]. The AAP now recommends offering a pacifier at nap time and bedtime, with delayed introduction for nursing infants until after breast-feeding has been well established [68, 70].

Risk Factors

Multiple studies have identified the following as independent risk factors for SIDS: prone sleep position, sleeping on a soft surface, maternal smoking during pregnancy, overheating, young maternal age, late or no prenatal care, preterm birth and/or low birth weight, and male gender [60, 69, 70]. Additionally, rates of SIDS are 2–3 times the national average in black and American Indian/Alaska Native children [71, 72]. In an attempt to explain both the intrinsic and extrinsic factors associated with the pathogenesis of SIDS, in 1994 Filliano and Kinney proposed a "Triple-Risk" hypothesis. They hypothesized that SIDS resulted from the intersection of three overlapping factors: (1) a vulnerable infant, (2) a critical developmental period in homeostatic control, and (3) an exogenous stressor(s). The authors inferred that an infant will die of SIDS only if he/she possesses all three factors; that the infant's vulnerability lies latent until he/she enters the critical period and is subject to an exogenous stressor [73, 75]. Since the incidence of SIDS peaks at a time when infants are receiving numerous immunizations (2–4 months) there has been some concern about a causal relationship. In 2003, the Institute of Medicine of the National Academy of Sciences reviewed all available data and concluded that "the evidence favors rejection of a causal relationship between exposure to multiple vaccinations and SIDS" [74, 76].

Etiology

There has been extensive research in an attempt to identify the etiology of SIDS; yet by definition SIDS is an unexplained death. One avenue has been to look for viral infections in this age group, but there has been no consistent evidence that viral infections are more prevalent in this group. In case–control studies, there have been no specific signs of illness that are more prevalent in infants who had died of SIDS

when compared to controls. [75, 77]. It has been hypothesized that viral infections, alone or in conjunction with bacteria and their toxins, might induce an uncontrolled cytokine cascade leading to a toxic shock-like picture and ultimately SIDS [76, 78]. Viral infections have been demonstrated to enhance bacterial binding to epithelial cells in vitro [77, 79]. *Staphylococcus aureus* is the most common isolate from the nose and throat of infants during the first three months of life (39–57 %) [78, 79]. It has been suggested that pyrogenic toxins of *S. aureus*, such as toxic shock syndrome toxin 1, staphylococcal enterotoxins A, B, and C1, are involved in events leading to some cases of SIDS. In one series, more than 50 % of SIDS patients had the toxins identified at autopsy. The authors concluded that in a proportion of infants colonized with *S. aureus*, when exposed to certain conditions which would raise the temperature in the nasopharynx to between 37 and 40 °C, pyrogenic toxin production could be induced. Conditions which could increase that temperature would include upper respiratory tract infections and the prone sleeping position [80, 82].

Another possible etiology that has been proposed is the association between sudden unexpected deaths among infants during periods of epidemic pertussis, which is not surprising as apnea is a common complication of pertussis among young infants [81, 83]. Heinenger et al. reported in a prospective, matched-control study that unrecognized *Bordetella pertussis* infections were identified in 5.1 % of 254 enrolled sudden infant deaths (5.3 % of controls) when polymerase chain assays were used on nasopharyngeal specimens [82, 84]. Data from Sweden and Norway indicate a direct correlation between the incidence of pertussis and the occurrence of SIDS. In Sweden, where the national use of diphtheria–pertussis–tetanus (DTP) vaccine ceased in 1979, the SID mortality rate followed the monthly prevalence of *B. pertussis*. This was compared to Norway where the DTP was used nationally during the same time period and SID mortality rate increased only at times of epidemic *B. pertussis* [83, 85]. Lastly, while DTP immunization might prevent some unexplained infant deaths due to asymptomatic whooping cough, there are also data that indicate that immunization with DTP induces antibodies that are cross-reactive with pyrogenic staphylococcal toxins, as previously described another possible etiology of SIDS [84, 86].

SIDS and DTP

In 1942 Pearl Kendrick and Grace Eldering developed the first modern whole-cell pertussis vaccine, combining whole-cell pertussis with toxoided diphtheria and tetanus to form DTP [85, 87]. In the decades that followed its introduction there were several case-reports that suggested that DTP increased the incidence of seizures and other neurological sequelae, which now has been completely refuted [86, 88]. Then in the late 1970s there were several case-reports suggesting a causal relationship between vaccination with DTP and SIDS [87, 88]. Several case–control studies were performed to evaluate this temporal association and found no relationship between DTP and subsequent SIDS [89, 90]. The concerns about side effects led

Yuji Sato to introduce an acellular version of the pertussis vaccine (DTaP), which contains inactivated pertussis toxin, for Japan in 1981 [91, 93]. As fever was frequently seen following DTP vaccination, the goal with DTaP was to decrease the incidence of fever with the hope of decreasing the parental association of fever with vaccines. In 2004, Kuno-Sakai and Kimura reported Japan's 23-year experience with DTaP and found the vaccine to be both safe and effective [91, 93]. The acellular pertussis vaccine was approved in the United States in 1992 for use in the combination DTaP vaccine. Wilson et al. have hypothesized that one possible explanation for the SIDS deaths reported in the late 1970s was the lack of ability to diagnose inborn errors of metabolism, and that the inflammatory response that some children experienced after vaccination with DTP (i.e., fever, anorexia, irritability) may have resulted in metabolic decompensation that ultimately could have led to hypoglycemia and encephalopathy/seizures and/or death [92, 94].

SIDS and Hexavalent Vaccines

Polyvalent vaccines have been developed to increase the acceptance of vaccinations by decreasing the overall number of injections. Several safety studies have been completed that showed good tolerability without new adverse events [93, 94]. There have been two instances in the literature (one case-report, one letter) suggesting an association between hexavalent vaccines and SIDS [95, 96]. A total of seven post-mortem cases are described, though poorly reported, where the infants may have had elevated levels of mast cell tryptase [95, 96]. Buckley et al. had previously reported that in a proportion of SIDS victims there may be increased levels of β-tryptase, a marker for anaphylaxis [97, 99]. A separate case-report of death in a 3-month-old following hexavalent vaccination was found on autopsy to be secondary to arcuate nucleus hypoplasia in the brainstem and resorptive degeneration in the cardiac conduction system, stressing the importance of a detailed autopsy [98, 100]. Lastly, a retrospective analysis based on epidemiology data in Germany found that there was no causal relationship between vaccination and SIDS [99]. An unexpected occurrence of deaths in temporal association with booster vaccination in the 2nd year of life was found for one of the hexavalent vaccines evaluated (3 cases in 700,000 children vaccinated) but thought to be secondary to limited data and not to represent a true association [99, 101]. A follow-up Italian study could not confirm this finding [100, 102].

SIDS and Haemophilus influenzae Type B

In October, 1990 the conjugate *Haemophilus influenzae* Type B (Hib) vaccine was licensed for infants in the United States, where prior to that it was only available to infants greater than 15 months [101, 103]. SIDS and invasive Hib have similar epidemiologic patterns with SIDS most prevalent at 2–4 months and invasive Hib most

prevalent at 6–11 months in the pre-vaccine era [102, 104]. There have been several studies suggesting decreased SIDS rates following the routine introduction of the conjugate Hib vaccination in infancy. Sepkowitz noted that in Los Angeles, CA, following the introduction of the conjugate Hib vaccine not only did the incidence of invasive Hib decreased (in ages 0–5 months, the incidence went from 90 cases per 100,000 in 1990 to 50 cases per 100,000 in 1991, and 10 cases per 100,000 in 1992) but that incidence of SIDS also decreased by 13 % following the introduction of the vaccine [103, 105]. While several studies were being published at that time regarding the benefit of nonprone sleeping, the ACIP had not yet adopted this guideline. In Hungary, the 2-month Hib immunization was not introduced until 1999. Following this there was not only a drop in the rates of invasive Hib, but the proportion of SIDS infants 2 months of age or older also decreased from 48 % in 1990–1998 to 39 % in the period 1999–2002 [104, 106]. Despite nearly a decade of evidence of the benefits of prone sleeping, the rates of SIDS in Hungary did not decrease until the introduction of the Hib vaccination suggesting that the Hib vaccine had a protective affect against SIDS.

Immunization as Cause of Decreased SIDS

SIDS deaths occur during the age range when many vaccinations are given and thus you would expect vaccinations to precede SIDS simply by chance. In an effort to cease the speculation that immunizations have any role in the development of SIDS there have been many national case–control studies performed to assess for any temporal association between the two. In the United Kingdom a large case–control study was done following the introduction of an accelerated immunization schedule in 1990, with immunization against diphtheria, tetanus, pertussis, and oral poliomyelitis given at ages 2 months, 3 months, and 4 months, respectively, instead of at ages 3 months, 5 months, and 9 months. The authors concluded that moving up the immunization schedule did not lead to increased sudden unexpected deaths, and that immunization tended toward protection rather than risk [105]. In France, a prospective case–control, multicenter study found that there was no association between SIDS in infants less than 3 months and immunization with DTP, oral poliomyelitis, and Hib vaccines [106]. The New Zealand Cot Study, a nationwide 3-year case–control study, found that immunizations do not increase the risk of SIDS, and may even decrease it [107]. Vennemann et al. performed a large case–control study with immunization data on 307 SIDS cases and 971 controls in Germany. They found that SIDS cases were immunized less frequently and later than controls and that there was no increased risk of SIDS in the 14 days following immunization [108]. Finally, the same authors performed a meta-analysis reviewing nine case–control studies evaluating for an association between SIDS and immunizations and found that immunizations are associated with halving the risk of SIDS [109]. Overall, it appears that immunizations should play an active role in SIDS prevention campaigns.

Conclusion

Kawasaki disease and SIDS are two entities that are trying to both clinicians and parents. The etiology of both is not well defined despite decades of research. With the mortality the greatest in the time period when infants and children are receiving the majority of their immunizations it is not unexpected that people may try to associate them. Fortunately though, the data suggest that there is no relationship between the two, and that for SIDS, immunizations may have a positive benefit.

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Chapter 20
Political and Legal Issues in Vaccination

Linda K. Ohri

Introduction

According to public health historian James Colgrove, "one of the most fundamental and enduring tensions in the enterprise of public health is the balance between the rights of the individual and the claims of the collective." [1] In his 2006 book, *State of immunity: The politics of vaccination in twentieth-century America*, Colgrove discusses the political and legal challenges to US health policies mandating immunization for certain groups. The author suggests that political dissension impacting vaccine acceptance arises particularly from the following factors: (1) The procedure is performed on healthy people; (2) Skepticism about vaccine efficacy and safety; (3) Religious or philosophical objections; (4) Objections to state coercion; and often (5) Combinations of these factors [1]. According to Colgrove, it has been a collection of diverse and loosely organized groups that have opposed vaccination. He notes that "pragmatism and political acuity, rather than doctrinaire adherence to epidemiological theory or ethical principles," has generally guided the public health response when mandated vaccination has been challenged by individuals or groups [1]. He cautioned against too rigid or punitive mandates that could create a backlash and inadvertently strengthen anti-vaccine movements.

University of Michigan researcher Anna Kirkland wrote in 2012 about the "trajectory of the vaccine-critical movement's legitimacy," as consensus has evolved disputing their autism hypothesis of vaccine harm. [2] She based this assessment on her qualitative studies examining the rhetoric, priorities and strategies of recent anti-vaccine political movement leadership. Kirkland presents a "typology of vaccine critics," in order of their importance within what she calls the "vaccine-critical movement." First and foremost, she identifies "Activist Parents" as the lead

L.K. Ohri, Pharm.D, M.P.H. (✉)
Department of Pharmacy Practice, School of Pharmacy and Health Professions,
Creighton University, Omaha, NE 68178, USA
e-mail: lohri@creighton.edu

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initiators of the most prominent vaccine-critical groups of the last three decades. She describes them as typically mobilized by a family story of a child with a disability that they consider to have been a result of vaccine exposure. She describes the typical profile of these leaders as white, middle-upper income, and with a college education. The second most important group of vaccine critics according to Kirkland are "Allied Professionals with Long-Standing Antivaccine Views." She further identifies two subgroups of this category: (1) Alternative health care providers such as homeopaths and chiropractors; and (2) Traditionally trained medical doctors who oppose mandatory vaccination as part of a libertarian political ethic. This group may provide critical funding and publicity to the vaccine-critical movement, as well as offering an alternative source of credibility supporting parental decisions to forgo vaccination for their children. Kirkland notes that it was a 1993 donation from a group of chiropractors that saved what is considered by many to be the strongest vaccine-critical group, the National Vaccine Information Center, led by Barbara Loe Fisher. Ron Paul (libertarian Presidential Candidate, 2008 and 2012), is identified on vaccine-critical Web sites relative to his opposition to mandated vaccinations, [3–5] and is quoted as stating the following in a YouTube interview transcript posted on a fan Web site: "I never want to belittle the principle of inoculations. I think people get way, way to [*sic*] many and we break down our immune system, but the whole idea, if it's a shot that's good or bad, why is it that it has to be the government? Why can't the parents make these decisions?" [6] Kirkland identifies four other key categories of vaccine critics politically active in the USA: (3) Donors, who come from across the political spectrum, representing conservative to liberal ideologies; (4) Researchers, primarily funded from within the vaccine-critical movement, and including generally discredited figures such as Andrew Wakefield as well as Mark and David Geier, (Diane Harper, a controversial but more mainstream vaccine researcher has also been quoted extensively by anti-vaccine sources) [7, 8]; (5) Journalists, Bloggers, and Other Media Producers, including names such as David Kirby, [9, 10] Robert F. Kennedy Jr, [11, 12] and Arianna Huffington; and lastly (6) Celebrities, such as Jenny McCarthy [2]. Kirkland describes the vaccine-critical movement as "blending holistic self-care with the elevation of the individual and the private family over collective goods." While those movement supporters from conservative ideology tend to be libertarian and anti-regulatory mandates of any kind, on the liberal end of the movement there tends to be a focus on "self-healing" and concern about environmental and medical pollutants. The reader is referred to Kirkland's cited report for further description of these vaccine-critical activist groups and ideologies [2].

Political Controversy at the Federal Level on Vaccine Safety

On April 6, 2000, Congressman Dan Burton, Chair of the Government Reform Committee in the US House of Representatives, convened the first of what his current Web site [13] indicates was "no fewer than 20 hearings" on the issue: "Autism:

Present Challenges, Future Needs—Why the Increased Rates?" He continued these hearings from 2003 to 2005 as Chairman of the Congressional Subcommittee on Human Rights & Wellness. Chairman Burton spoke in his opening statement at the first Congressional Hearing about his grandson who he claimed acquired autism as the result of exposure to thimerosal from vaccines. During the last decade, Congressman Burton has championed efforts by parents of children with autism to receive compensation for their alleged thimerosal-associated injuries from the Vaccine Injury Compensation Program (VICP); writing and speaking on their behalf prior to and during the time of the 2007 Omnibus Autism Hearings, [14, 15]. As of May, 2012, Representative Burton's congressional Web site continues to provide materials purporting a link between thimerosal and autism, despite an accumulation of extensive evidence counter to this claim and rejection of autism claims at the Omnibus Autism Hearings [13]. House bills H.R. 2832, 110th/3069, 111th Congresses: Comprehensive Comparative Study of Vaccinated and Unvaccinated Populations Act of 2007–2009 were co-sponsored by nine House Republicans, including Representative Burton, and 13 House Democrats [16]. These bills sought to require continued federal government funded research on the risks for autism associated with vaccination. The first bill was introduced but not enacted in the 2007 Congressional session. It was reintroduced in 2009; but was referred back to its originating House Committee on Energy and Commerce. There has been no further action documented on this federal legislation.

State Legislative Efforts to Restrict Use of Vaccines Containing Thimerosal

A substantial level of advocacy and legislative action has taken place over the past decade at the state level regarding the thimerosal/mercury issue, even though thimerosal has not been present at clinically significant levels in pediatric vaccines manufactured since 2001 [17]. Some influenza vaccines labeled for adults and children are still marketed in multi-dose vials; such vials legally require use of a preservative, generally thimerosal, to protect from bacterial contamination. Reasons for this continued practice include primarily the need for rapid production of influenza vaccine, but also the relatively lower cost of multi-dose versus unit-dose products. However, most influenza vaccines labeled for either adult or pediatric use, and all US vaccines specifically labeled for pediatric administration are now manufactured in unit dose syringes, thereby eliminating the legal requirement for use of preservative in the final product container. Nevertheless, in 2006 alone, based on a report compiled for the Council of State Governments, 23 states debated 43 bills on the issue of thimerosal/mercury containing vaccines [18]. Since 2008, seven states (California, Delaware, Illinois, Iowa, Missouri, New York, and Washington) have enacted laws banning or limiting allowable levels of thimerosal in vaccines labeled for use in children or pregnant woman (all except Iowa), with a ban in Illinois for all age patients [17].

In the author's state of Nebraska, attempts were made 4 years in a row (2004–2007; LB1158, LB569, LB790, LB49, respectively) to pass legislation restricting use of thimerosal containing vaccines, [19–22]. All of these bills mandated eventual ban of vaccines containing even trace amounts of thimerosal preservative; one bill (LB569) was limited to pediatric vaccines for children less than 8 years of age, while LB1158 applied to all vaccine products (human and veterinary) sold in Nebraska, and the last two bills applied to all human vaccines. The last two bills required vaccine providers to "educate" parents about the risks of thimerosal (with misdemeanor penalties for failure to do so) pending full ban of such vaccines. This included a requirement to teach that "exposure to even low levels of mercury may result in irreversible systemic damage to the brain, nervous system, and other organs and systems in humans and animals" and "mercury ingestion may cause adverse behavioral and other changes" [21, 22]. These bills also required the state to test a random sample of vaccines used in the state for presence of thimerosal. The first bill offered (LB1158) was amended and limited to a duty to warn; the amended bill was moved to general file. This amended bill was replaced by Legislative Resolution, LR357, directing the Health and Human Services Committee of the Legislature to conduct an interim study to: (1) Examine the relationship between autism and thimerosal; (2) Examine treatment options available for those with autism; (3) Examine current autism education programs offered by postsecondary institutions in Nebraska; and (4) Examine state funding for the treatment of autism [23]. Over the next 3 years, many immunization partners were involved in advocacy efforts to educate the legislature on the scientific evidence pertinent to the issue, and on the potential negative impacts of these legislative bills. In 2006, print files of educational materials were distributed to every member of the legislature by the largest immunization coalition in the state, to provide background and inform on the potential unintended consequences of such legislation. The 2005 (LB569) and 2006 (LB790) bills did not make it out of committee, while the 2007 (LB49) bill was referred directly to general file through a procedures rule, but was indefinitely postponed with automatic dismissal at the end of the session. No further bills have been submitted on this issue in Nebraska. No updated information was found regarding any additional states that have enacted thimerosal-related legislation since 2008. With evidence for continuing autism rate increases even after thimerosal was removed from pediatric vaccines, and with growing evidence to refute a thimerosal/mercury link with autism, legislative efforts to ban use of thimerosal have diminished [24]. However, a quick scan of the Internet demonstrates that there are groups who still profess such a link as one basis for their promotion of the individual right to refuse some or all mandated vaccinations.

Immunization Mandates

See Table 22.1 for sources where listings of state and organizational immunization mandates may be located on the Internet.

In the USA, a primary focus of immunization mandates has been on assuring that children are vaccinated against vaccine preventable communicable diseases prior to attending school [25]. This was largely limited to Measles/Mumps/Rubella, Tetanus/Diphtheria/Pertussis, and Polio vaccinations required prior to entry into kindergarten until the mid-1990s. Most states currently also have state mandated vaccinations for entry into daycare, with monitoring and enforcement conducted at varying levels of intensity and typically only for licensed daycares [26]. Presence of daycare and school mandates have been shown to be associated with increased immunization and decreased infection rates [25, 27].

States have been relatively slow to adopt school mandates for Hepatitis B and Varicella vaccination. The earliest daycare Hepatitis B vaccination mandate was enacted in 1993 in Massachusetts, 7 years after the first recombinant vaccine was licensed in 1986, [28, 29]. Thirty states had some level of school mandate by 1997, but as of November 2005 a Centers for Disease Control and Prevention (CDC) report indicated that only 34 states required Hepatitis B vaccination for middle-school entry [30]. As of 2011, 11 states still did not have a middle school mandate, and three states (AL, MT, and SD) had neither daycare nor any school mandate [26]. Many states initiated the mandate on a progressive basis (starting with a school entry requirement and adding one grade at a time), slowing full coverage for all age cohorts up to 18 years of age. The CDC reported that by 2003 the full Hepatitis B series was documented for 50–60 % of adolescents 13–15 years of age [30]. Uptake of Varicella vaccine school mandates for elementary school entry was achieved for most states by 2005 (10 years after FDA approval in 1995), with nine states enacting legislation in or after 2005 [31]. However, 17 states did not have a middle school mandate as of 2011. Montana currently has no Varicella vaccination school mandate, but as of 2006 does require vaccination for daycare entry. A 2002 medical report examined associations between physician agreement with Varicella immunization guidelines and their likelihood of recommending this vaccine for their pediatric patients [32].

There have been a substantial number of challenges made on moral, parental rights and safety grounds against mandating both Hepatitis B vaccine and Human Papillomavirus (HPV) vaccine, since its licensure in 2006, [33, 34]. A New York Times article discussed controversy that arose at a September 12, 2011 Republican primary debate over presidential candidate Rick Perry's 2007 executive order, while Texas Governor, to mandate HPV vaccination for adolescent girls entering sixth-grade [34]. The article noted controversy over issues such as "overreach of government in health care decisions, suspicion that sex education leads to promiscuity and even the belief … that childhood vaccinations may be linked to mental disorders" [34]. The first issue continues the long standing controversy which has already been discussed over parental rights to make immunization decisions for their children versus the interest of society in reducing risk for transmission of communicable diseases. The second expressed concern that HPV vaccination encourages promiscuous sexual behavior also continues a message that a 2006 Times article suggested would not be a serious argument among social conservatives [35]. That report suggested that conservative's "major point of contention surrounds whether to make the

vaccine mandatory." Regardless of the chief issue of concern, there has been some recent reassurance offered from a 2012 study report that found no association between HPV vaccination of young women and risky sexual behavior [36].

Statements made by presidential candidate Michele Bachman after the September 12, 2011 Republican Primary debate regarding a claim that HPV vaccine caused mental retardation were subsequently challenged by two bioethicists, who offered substantial rewards for evidence to back up this claim, [37, 38]. An accompanying map with the New York Times article identified that since 2006 legislation has been introduced in 22 states to mandate HPV vaccine use prior to middle-school entry for young girls. In most cases the bills were later withdrawn or died in committee. In New Mexico a mandate bill was passed in 2007, but was vetoed by the governor. In Texas, in 2007, legislation was quickly passed by large margins in both houses of state government to rescind Perry's executive order; the governor did not veto this legislation. HPV school mandates were passed in 2007 in both the District of Columbia and in Virginia. In Virginia, according to a Washington Post article, there was a 2011 attempt in the Virginia House of Representatives to overturn the 4-year-old mandate, but companion legislation was killed in the Senate committee leaving the mandate standing [39]. The same Washington Post article describing this controversy noted that the mandates in both Virginia and the District of Columbia had liberal exemption procedures, allowing parents to simply sign a waiver. This article indicated that completion of the full vaccination series has been lagging in both jurisdictions. In Virginia 17 % of those eligible at sixth grade had received the first of the three dose HPV vaccine series [39]. Furthermore, a second article noted that only 23 % of D.C. sixth-graders in the first cohort immunized (eighth graders by 2011) had received all three doses in the series [40]. The report indicated that parents of over 40 % of eligible girls had opted out of the HPV immunization completely.

Mandated vaccinations for college entry are a more recent phenomenon, primarily over the last decade, with state legislation generally addressing MMR, Hepatitis B and Meningococcal vaccinations [26]. MMR requirements are set at the state for 31 states, with some postsecondary institutions having vaccination requirements in the other states [41]. Twenty-two states have legislation requiring education and 15 require vaccination with Hepatitis B vaccine for at least some student groups prior to college entry [42]. Education on Meningococcal disease is required in 39 states, with 16 mandating this vaccination for specified student groups. Providing signed waiver documentation is generally an option for those students (or parents if under age) who wish to refuse these vaccines [43]. Health sciences students may have more negative ramifications for refusing Hepatitis B vaccination, such as loss of access to experiential rotation sites.

Long-term care facilities are required to offer influenza vaccination and pneumococcal vaccine to residents in approximately half of US states; however, existing documentation is somewhat out-of-date [44]. The CDC maintains an interactive search resource providing access to immunization mandate information on a variety of facilities (hospitals, ambulatory care facilities, individual providers' practices, correctional facilities, and facilities for the developmentally disabled), but not for long-term care facilities [45]. The data notes accompanying this CDC resource indicate that it is updated at least every 6 months.

Minorities of states require that specified categories of health care workers in acute care hospitals, and also ambulatory care facilities in some states, are offered or have vaccination required for one or more of the following vaccines: Hepatitis B, Influenza, MMR, Varicella, and/or Pneumococcal [45]. Despite the high risk of severe illness in aged populations from influenza, no listing was found of state legal mandates for influenza vaccination of health care providers in long-term care facilities. While it has also been suggested to the author by other stakeholders on this issue that long-term care facilities routinely offer free influenza vaccination to their employees, no evidence was found to document such availability. The Immunization Action Coalition Web site (http://www.immunize.org) provides a listing of a wide range of healthcare organizations, arranged by state, that have established institutional mandates for influenza immunization of their personnel [46]. Many articles have addressed the reasons behind health care worker acceptance/nonacceptance of influenza vaccination, [47–49]. Such reports leave no doubt that even among health care workers there is controversy over mandated immunization. Commentaries have been written, particularly since the H1N1 influenza pandemic, about the legal basis for and ethical implications of requiring health care workers to be vaccinated against diseases such as influenza that they might otherwise pass on to their patients [50]. While New York State was certainly dealing with vaccine shortage issues when withdrawing a mandate for H1N1 influenza vaccination for health care workers, a New York Times article noted that there was also a legal challenge brought against the prevention measure [51].

Immunization Mandate Exemptions

See Table 22.1 for sources where listings of state immunization mandate exemptions may be located on the Internet.

There have been political and legal challenges to vaccine mandates at least since the time of smallpox mandates instituted through the Vaccination Act of 1853 in England and Wales [52]. This law was opposed both by anti-vaccination groups and by those who saw it as an intrusion on personal autonomy. By 1889, opposition led to a Royal Commission on Vaccination study investigating the usefulness of vaccination in control of smallpox. This Commission ultimately recommended a conscientious exemption to vaccination "for people who were 'honestly opposed' to vaccination" [52]. The Commission sought to avoid applying this designation to those who were deemed "too lazy or indifferent to have their children vaccinated." In 1905, the US Supreme Court rejected constitutional arguments against a compulsory vaccination law in Jacobson versus Massachusetts, allowing the mandate to continue. Again, in 1922, the Court upheld the constitutionality of school vaccination laws. However, today in the USA, opposition to such mandates continues and has progressed. This is evidenced by the number of states enacting legislation that allows parents to sign "philosophical" exemptions to immunization, [53, 54]. The Association of State and Territorial Health Officials (ASTHO) provides listings of

recent state legislation related to immunization that show much recent flux in mandate laws [55]. Legislators in some states have successfully added philosophical or personal belief statutes, while in other states exemption mandates are being tightened up to require that parents document having received educational counseling from a health care practitioner as part of obtaining a waiver to vaccination. One concern expressed by vaccine advocates is that in some states it has become more convenient for parents to sign an exemption waiver than it would be to have their child immunized. This raises the risk for children to be unvaccinated even in the absence of strongly held religious or philosophical beliefs against immunization, and also without assuring that parents fully understand the potential health risks for their child. A draft legislative model for immunization exemption has been prepared by representatives of the Institute for Vaccine Safety [56]. This draft legislation would require that parents wishing to obtain a personal belief or philosophical exemption to vaccination for their child must provide (1) A signed documentation that they had received "individual counseling concerning the risks and benefits of vaccination to the child and to the public health" and also (2) A "signed, personal statement explaining the reasons for requesting the certificate of exemption, setting forth the strength and duration of his or her belief that a vaccination or immunization is inappropriate for the child." Washington state enacted legislation based on this model which took effect in July, 2011 [57]. A review of the most recent 5 years listed (2007–2011), in a database (created by Debold and Yang) of state legislation related to immunization requirements and/or exemptions showed that annually 7–17 states enacted new legislation over this period (2007: 7 states, 35 bills; 2008: 11, 21; 2009: 7, 13; 2010: 9, 17; and 2011: 17, 81) [58]. During this time period 25 states proposed new or updated legislation addressing vaccine mandates. Legislation on Varicella second dose, Meningococcal vaccination for secondary or postsecondary students, and Pneumococcal vaccination for children in daycare was brought forward. Proposed bills also addressed mandate parameters for groups such as military families, home schooled and private school students, as well as children in special education, foster care and the homeless. Legislation proposed in 24 states during the 5 year period typically initiated or reiterated medical, religious, and/or personal belief or philosophical exemptions to school mandates without a requirement for documented pre-waiver education.

Controversy Over the Affordable Care Act, and Potential Impacts on Vaccine Access

The Affordable Care Act (ACA) was signed into US law on March 23, 2010. According to a US Department of Health & Human Services Web site explaining this law, children and adults in a new health insurance policy beginning on or after September 23, 2010 have access to ACIP (Advisory Committee on Immunization Practices) recommended immunizations, without cost-sharing requirements [59]. Improved funding for prevention services, including immunizations will also be

phased in for seniors and Medicaid recipients during 2011 and 2012. In 2010 a $15 billion Prevention and Public Health Fund was also first funded that among other prevention measures provides $112 million to expand immunization services and activities. An interactive Web site last updated on February 14, 2012 allows individuals to track additional immunization and other prevention activities at the state level that are being supported by this Fund [60].

As most Americans are aware, the Affordable Care Act has been challenged mostly unsuccessfully before the US Supreme Court (by 26 state attorneys general and others) in perhaps the ultimate demonstration of political and legal controversy in this country [61]. On another front, there has been much recent controversy in the US Congress over the issue of whether the Public Health Prevention Fund should be defunded as a means to offset costs of extending current interest rates for student loans [62]. Given the funding for vaccines as well as immunization-related infrastructure and services that is an inherent part of both the ACA and the Public Health Prevention Fund, it is clear that the outcomes of these political and legal controversies will have significant impacts on immunization access. Any change in these programs must take into account how optimal immunization rates will be supported over the foreseeable future.

In summary, immunization has been surrounded by political and legal controversy since the earliest days of smallpox vaccination. Modern controversies directly related to immunization tend to focus on questions regarding vaccine benefits and safety, as well as on issues of individual or parental choice versus collective societal protection. Optimal immunization for all members of society is also continually affected by external political and legal forces that impact access and affordability.

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Chapter 21
The Media's Role in Vaccine Misinformation

Paola Dees and David M. Berman

Introduction

Where Parents Turn for Vaccine Information

Research has shown that there are three major resources parents utilize when seeking information on immunizations: their health care providers, the media, and the Internet[1] [1]. While some investigators have cited pediatricians as the primary resource for providing information on vaccines [2], several studies have suggested that the news media is, in fact, the leading source for parental education [3, 4]. Unfortunately, a great degree of disparity exists when examining the suitability of these resources to stand as reliable sources of information. The pediatrician has often seen the devastation of vaccine preventable diseases first-hand, has been formally trained to interpret scientific reports, and is systematically exposed to reliable evidence-based medicine from credible resources such as the American Academy of Pediatrics (AAP) and the Centers for Disease Control (CDC). To the contrary, the media holds no formal requirement to understand the science behind vaccines or the data that support their safety, nor do they carry a professional obligation to protect the health status of their audience. Inherently, this creates a problematic situation where one of the leading resources families uses to gather information on the safety and utility of immunizations is flawed in its usefulness to serve as a reliable source of information.

[1] The role of the internet will be discussed separately in Chap. 22.

P. Dees, M.D. (✉)
Division of Hospital Medicine, All Children's Hospital, Johns Hopkins Medicine,
Outpatient Care Center 5th Floor, 601 5th Street South, St Petersburg, FL 33701, USA
e-mail: paola.dees@allkids.org.

D.M. Berman, D.O., F.A.A.P.
Division of Pediatric Infectious Diseases, All Children's Hospital, Johns Hopkins Medicine,
Outpatient Care Center 5th Floor, 601 5th Street South, St Petersburg, FL 33701, USA

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Media's Insertion into Vaccine Controversies

Controversies surrounding the use of vaccines and vaccine safety have been around as long as immunizations themselves. However, prior to the modern era, matters of vaccine development and potential adverse effects were housed largely in technical journals. Expert dialogue was kept between physicians and scientists. However, in the 1970s there was a marked increase in publicized reports of families claiming vaccine-related injuries, data on litigation awards, and class action advertisements that pushed the issue of vaccine safety into the forefront of popular media [5]. Although a detailed historical perspective on modern day vaccine controversies is covered in Chap. 1, it is important to understand the timing of the media's insertion into the debate in order to contextualize how media misrepresentations have perpetuated and intensified the public's misperceptions.

Media Defined and Redefined

The relationship between the media and vaccine misinformation is complicated. Merriam-Webster defines media as a medium of communication that is designed to reach the mass of the people. Specifically, it offers newspapers, radio, and television as representative platforms to disseminate such information. However, the reality is that the modern day concept of media extends far beyond this superficial definition.

With the advent and popularization of the Internet in the late twentieth century, the concept and construct of media as we know it has been forever changed. There are no longer distinct lines between each vehicle within the broader umbrella of mass communication. Newspapers have Web sites, TV programs are available as podcasts thru your cellular phone, and scientific journals once available only to subscribing academics are now searchable by the average consumer. Nowadays, a topic that first appeared in a print journal can be recounted later on a news show and eventually be the subject of an Internet blog. Much like the Swiss Cheese Model used to describe the evolution of sentinel events in aviation and health care [6], the media's interlaced yet disconnected parts create the perfect recipe for propagation of inaccurate information.

Previously, mass communication was a two-way street: the organization responsible for selecting newsworthy topics would create an agenda, gather data, then report it to a passive audience. Today, the public interacts with information. They demand it, comment on it, modify it, and propagate it. Anyone can start a blog, edit a TV clip on YouTube®, or call into a radio show claiming to be an expert. By its very nature, the real-time ebb and flow of our modern media has created a barrier for compulsory editing, fact-checking, and censorship of inaccurate information. The evolution of the modern media to its current form has facilitated the progression of vaccinophobia.

The Media and the Public

Journalistic Principles

The purpose of the media is to disseminate information to the masses. Autonomy and objectivity are two driving principles in journalism that apply to vaccine related-reporting [7]. Autonomy mandates that the press report unbiased information, free from external influence or partiality. Objectivity challenges the media to report accurate information by researching facts, utilizing experts, and presenting all sides of a story with balanced reporting.

Confounding Interests

Unfortunately, the current climate of commercialism and sensationalism has created conflicting interests that the media must attempt to balance. While autonomy and objectivity remain guiding principles, the reality is that today "scandals, scares, and exposes" are incentivized [8]. Print and media journalists are encouraged to mine stories and pique audience interest in order to sell their product. At times, news stories selectively emphasize or shade elements of an issue to create controversy and therefore drive sales. This has been seen even as it relates to health-care related stories. For example, one retrospective review of newsprint coverage found significant misrepresentation of the prevalence of health risk factors and causes of death. The authors proposed that competition for viewership and commercial interests were the motivating factors spurring the trend in inaccurate reporting [9]. This complex relationship has been perpetuated in the literature by describing the media as a virtual "gatekeeper" of public awareness [4]. In effect, the subject matter for newsworthy stories is driven by the press' perception of public interest and, in turn, the goal of increased exposure and revenue.

Agenda Setting

While the influence of the public's perceived need clearly drives what the press deems as newsworthy, the converse is also true. Mass media has the potential to not only reach every household, but has the capacity to influence public opinion and heighten collective concerns [1, 10]. The press plays a pivotal role in setting the agenda for various topics, including matters of public health. Rather than balancing opposing views, stories are frequently slanted in support of one perspective over another [11]. Thus, journalists have the opportunity to play a pivotal role in making sense of information and determining whose voice is heard [12].

Framing

Beyond setting specific agendas, the media also frames stories to make their content more accessible to the public. When reviewing various facets of a story, journalists themselves determine which data are relevant to focus upon and utilize their reporting skills to make those points more relevant to the public [7]. This selective inclusion and exclusion of salient data creates a slanted perspective that can be misleading in relation to the scientific data they intent to report [11]. By painting an incomplete and often erroneous picture, viewers who rely on the information can be harmed [13]. Perhaps even more dangerous, is when people fixate on certain dominant themes reported by the media and use them to make unfounded assumptions and generalizations [14].

The Influence of Health Reporting

Exposure to health media is associated with change in public knowledge [15]. The media plays a central role in assembling the public's understanding of science [12], and journalists hold significant power when reporting on health-related controversies [14]. The public can unreasonably adopt certain prejudices and distrust of doctors when encouraged to do so by media health stories [16].

The influence of the media also extends to vaccine reporting. The press plays a central role in guiding public perception and acceptance of vaccines [11]. When inaccurate or incomplete data on vaccines are offered to the public, families can be misinformed [15]. Even in the face of organized public health communication, mass media has the power to overshadow reliable dissemination of information with negative reporting [11]. This skewed representation also has the power to perpetuate further misinformation, purvey controversy, validate sources of inaccurate information, and increase public doubt [1]. The MMR controversy was a perfect example of the media's power to not only influence the public but create unfounded panic.

Media Misinformation and Vaccinophobia

Sensationalism

One constant in the evolution of twenty-first century media, is the notion that "if it bleeds, it leads." Sensationalism and the propensity to prey on the public's fears, remains alive and well in modern media. The press has been accused of exaggerating health risks to appeal to a larger audience [4].

One of the most glaring examples of the media challenging the public's perception of vaccine safety was the rapid and widespread coverage of Wakefield et al.'s [17]

report in 1998 claiming a link between the MMR vaccine, autism, and bowel disease. The press in the UK and the US quickly reported, headlined, and sensationalized the report and its claims for years [18], despite numerous contradictory studies. Selective elements of the story were repeated over and over, and only certain themes were highlighted. Headlines associated the immunization with fear, doubt, and uncertainty [14].

A powerful caption or moving image can prove more powerful than a thousand words [19]. Research has shown that people remember themes, not details. The public has a tendency to internalize overarching ideas and frames, rather than specific facts. At the end of the day, principal and relevant pieces of data are lost [10] and catchy headlines and images leave a lasting impression. Numerous media stories featured parents claiming their child was developmentally on target prior to receiving the MMR vaccine. The aggregate effect of these and similar stories increased parental uncertainty and fear of the MMR vaccine and immunizations in general [4].

Over-Representation

Another way the media has misinformed the public is by over-representing public vaccine opposition. When examining the MMR controversy specifically, many glaring examples emerged. Although studies consistently showed that the majority of families still chose to vaccinate their children, the press painted a very different picture. When reviewing multiple media stories on the vaccine controversy, parents who were against the MMR vaccine were featured in 67 % of stories, where only 13 % of families in favor of the vaccine were quoted [14]. The disparity was even more egregious on the radio, where not one pro-MMR parent was quoted in the studied sample [14]. Another article reported that parents referenced in news stories were five times more likely to speak against the vaccine than in support of it [10]. These and similar misrepresentations only fed the public's fear that the vaccine was rapidly falling out of favor, and therefore perpetuated the notion that the vaccine was unsafe [10].

Communicating Risk

"There is a fine line between public perception and misperception of risk" [5]. The press has a history of misinforming the public regarding causes of morbidity, mortality, and their associated risk factors. This misrepresentation can negatively influence the public's understanding of health threats [9]. The way in which health information and potential adverse effects are communicated impacts how the public perceives risk [19].

Observations of the modern MMR vaccine controversy bolster the notion that a potential threat is deemed more newsworthy than the lack of threat [14]. In Lewis' study reviewing various newspapers, tabloids, TV, and radio programs, 11 % of stories mentioning MMR also mentioned that the vaccine was considered safe in 90 countries, while 69 % of the reports highlighted the purported link to autism and/or bowel disease [10]. As one author succinctly described, what we have experienced is the "domination of the visible over the invisible" [20]. Specifically, the countless patients who have been spared from contracting potentially life-threatening vaccine preventable diseases were overshadowed by random, unproven anecdotes of vaccine-injured children.

Personal Anecdotes

We have seen time and time again that personal anecdotes are a compelling story teller, regardless of how accurate or reliable the story may be. Despite the fact that it is at times sensational and inaccurate, the fact remains that anecdotes sell. No matter how many times they are repeated or replicated, and irrespective of their relation to truth, they remain powerful sellers [20].

Unlike most matters of public interest, the media uniquely utilized the lay public during the MMR controversy to provide personal testimony to back the claims that there was a link between the vaccine and autism [14]. Second only to scientists, one study found that parents were the next most likely group to be quoted in media reports [10]. Anecdotes are persuasive and can overwhelm evidence to the contrary [18].

Unbalanced Reporting

As previously discussed, media sources determine news content by looking for topics of public interest. In reporting the issues, the goal is typically to present each side of the issues in a balanced way. However, the danger in doing so is that the very nature of this method of reporting is polarizing. Without explicit instruction on the respective weight of the evidence, the public will assume that these opposing views are more than likely equal in merit [8].

One of the most impactful roles the media has played in propagating vaccinophobia was accomplished by creating the illusion of controversy on vaccine safety when reporting on the MMR story. Speers and Lewis [14] reviewed popular print, television, and radio programs in Britain during the height of the controversy and found that most outlets presented their stories to suggest conflicting evidence on the issue. They pointed out that most of the stories, even the ones that presented both sides of the argument, failed to point out that the majority of existing scientific evidence was firmly in support of the vaccine's safety with no proven causal link between the MMR immunization and autism or bowel disease.

Multiple retrospective studies on the MMR controversy have shown that the press has failed to supply balanced reports on vaccine risks [3]. One author proposed that the media likely created and maintained the illusion of controversy by presenting two equivalent arguments in the debate to sell their stories [20]. Unfortunately, the message that the public extracts from news stories, even ones that provide a weighted review of the evidence, is that there is a debate with conflicting authorities on the issue [14]. An official from the Harvard School of Public Health has gone as far to say that when reporting on vaccines, it is "outright deceptive to pretend that all sides are equal in authority" [18].

During the peak of the MMR controversy, less than one in four respondents to a survey correctly identified that the weight of existing scientific evidence supported no link between the MMR vaccine and autism. Over 50 % indicated that there was equal evidence on both sides of the debate [10]. While balanced reporting is typically heralded as a central principle in journalism, in this instance it inappropriately gave weight to unsupported reports of a link between MMR with autism and detracted from the substantial body of evidence against it [10].

Non-Journalist Influence and the Media

There are countless examples of non-journalists influencing the media, and therefore impacting the public's perception of vaccine safety. The interplay between the antivaccine lobby and the press will be reviewed. In addition, an abbreviated review of politicians and celebrities that have played a critical role in perpetuating the notion that immunizations are somehow unnecessary, unsafe, and even dangerous are offered. Some players have taken an active role in seeking out the media to push their agendas, while others have been drawn into the controversy.

Antivaccine Lobby

The term "antivaccine lobby" is used to represent individuals, parent groups, and organizations who vocalize their opinions against the safety of vaccines. They primarily operate through blogs and Internet sites, but also interact with the mainstream media in an effort to disseminate their message. The antivaccine lobby is not regulated, nor are they required to utilize scientific evidence to support their theories. They rarely provide their audience with unbiased information. Collectively, rather, they represent a voice of dissent against organized medicine and the government, which is valued by many especially in Western civilization [8].

Antivaccine groups tend to prey on public fears by creating the illusion that organizations such as the AAP and US Food and Drug Administration (FDA) are conspirators, hiding important safety information from the public in order to profit financially. Therefore, stories run in the media that illustrate such activity inflame and enrage the public [8].

Another danger presented by many antivaccine groups is that they present themselves as experts and national authorities, despite no actual endorsement by recognized establishments or governing bodies. For example, the National Vaccine Information Center (NVIC), founded by prominent antivaccine activist Barbara Loe Fisher, can easily be mistaken for a regulated and trustworthy federal agency by the lay public, given their apparently official title. In fact, this was demonstrated when the NVIC sponsored a paid video advertisement on Delta airlines flights that focused on preventing influenza by using proper hand hygiene and vitamin supplements. It went on to caution viewers to question the influenza vaccine if offered by their physician [21]. The end of the video directed families to the NVIC Web site as an authority on vaccine safety and resource for information on how to question physicians on immunizations. The NVIC has also previously paid for video advertising on a CBS sponsored JumboTron in Times Square [22]. Unfortunately, these tactics exemplify the manner in which the antivaccine lobby has influenced the media by posing as an authority figure in order to gain access to the public and perpetuate their beliefs and contradict national recommendations on childhood immunizations.

Public Officials

British Prime Minister Tony Blair

The Prime Minister was thrust into the center of the MMR debate in 2002 when he was asked by reporters if he had given his youngest son, Leo, the MMR vaccine. Initially, he declined to answer directly, and cited the issue as a private family matter. He publicly supported vaccine programs, stating the MMR immunization was "safe enough" for his son, but refused to elaborate on whether he and his wife had actually vaccinated Leo with the combined MMR injection. His refusal to comment on his son's immunization status fueled speculation about the vaccine's safety. It became a recurrent theme in many news reports. In fact, one review found that a third of stories mentioned Leo Blair [10]. When surveyed, only 3 % of British citizens selected "Don't Know" when asked about the Prime Minister's position on vaccinating his son [10].

U.S. Congresswoman Michele Bachmann

In 2011, Republican Congresswoman, and then presidential hopeful, Michele Bachmann became a source of inaccurate information relayed by the media when she presented a single anecdotal story from a stranger on national television without first verifying the validity of the claim. After voicing opposition of fellow republican candidate Governor Rick Perry's executive order mandating that the Human Papilloma Virus (HPV) immunization be given to all girls in Texas during a nationally televised

debate, she attempted to further support her position against the vaccine during a post-debate interview by claiming she had met a mother who claimed her 12-year-old daughter suffered mental retardation as a result of the HPV vaccine. Referring to the unidentified woman, Bachmann stated, "She told me her little daughter took that vaccine, that injection. And she suffered from mental retardation thereafter…This is the very real concern and people have to draw their own conclusions" [23].

Naturally, the story spread like wildfire. Not only did Bachmann relay a story from an unverified source that completely contradicted the existing body of evidence on the safety of the HPV vaccine, she led the public one additional step down the slippery slope by challenging them to "draw their own conclusions" rather than directing them to trusted and reliable sources such as the CDC or AAP.

Celebrities

Miss America

In 1994, Heather Whitestone, a young deaf woman, was crowned Miss America. In a pre-pageant interview Whitestone told The Associated Press that she lost her hearing as a toddler as a result of "strong medications" used to treat a high fever that developed after receiving the diphtheria/tetanus toxoids and pertussis (DTP) vaccine [24]. In the subsequent days, the story morphed and multiple separate reports were published claiming Ms. Whitestone's disability was the result of a near-fatal reaction to the DTP immunization [5]. This story ran until Whitestone's pediatrician came forward and clarified that, in fact, her deafness was the sequela of *Haemophilus influenzae* type B meningitis [24]. However, unlike the headlines the original version of the story garnered, the correction was published in the paper's second section [5].

Jenny McCarthy

Former MTV host and *Playboy* Playmate Jenny McCarthy has been a vocal champion for the antivaccine lobby and autism community since her son Evan was diagnosed with autism in 2005. Like many frustrated parents of autistic children searching for answers, McCarthy latched onto Wakefield's report to justify her perception that vaccines were the cause of Evan's developmental abnormalities. She, along with other members of the antivaccine lobby argued Wakefield's hypothesis as fact, and the press not only gave her a platform to voice her opinions and anecdotes, they effectively legitimized her claims by giving her airtime. One author recounted that during her many television appearances, "she decried what she claimed was a vast, profitable conspiracy to vaccinate children, which she said was responsible for the great upsurge in autism diagnoses… She glibly and with irate dismissal of the scientific evidence, accused pediatricians and doctors of poisoning children and then withholding the treatments that could save them" [25].

McCarthy's far-reaching influence on the public, especially well-educated and progressive families, was summarized by Mnookin [26] when he commented, "My wife and I first noticed our friends' preoccupation with autism and vaccines in late 2007, right around the time former TV star and *Playboy* Playmate Jenny McCarthy published the first of several bestsellers in which she claimed that the measles–mumps–rubella (MMR) vaccine had probably given her son autism. As we soon discovered, McCarthy's intuition-based approach to medicine (she referred to it as 'mommy instinct') had a number of adherents among our friends." When reflecting on how the Wakefield paper, media, and advocacy groups have damaged public health in an editorial, Drs. Poland and Spier [17] commented, "Sadly, we have moved from evidence-based, to media- and celebrity-based medicine."

Vaccine-Specific Examples of Media Influence

DTP

In 1974, Kulenkampff et al. [32] published a report claiming an association between the DTP vaccine and serious neurologic complications. Despite the fact that numerous independent studies had shown no causal link between the immunization and permanent brain damage, the media continued to cover the Kulenkampff study. Rates of immunization dropped from 81 to 31 % and more than 100,000 cases and 36 deaths from pertussis followed [27]. Despite the report being published in England, the press coverage extended internationally and vaccination rates decreased while increased mortality due to pertussis were reported in Japan, Sweden, and Wales [27]. The media once again failed to report the increased rates of morbidity and mortality, and preferred to focus on the controversy created by the Kulenkampff report.

In 1982, a teledocumentary produced by a Washington, D.C. news station, WRC-TV, called *DPT*: *Vaccine Roulette* included commentary from a former US FDA employee and neurologists who supported accounts that the DTP vaccine caused serious and permanent brain damage. Although the program was speedily debunked by medical experts, it is hailed as the catalyst for the modern vaccine controversy and ultimately garnered an Emmy award [5].

MMR

Much like the *Vaccine Roulette* film did for the DTP controversy, Wakefield's report linking the MMR immunization to autism was dramatized to the masses by the British Broadcasting Company (BBC) program Panorama in 2002. They televised a segment called *How safe is MMR*? and brought the vaccine controversy to the front of the press' news agenda and therefore into the public eye [10].

As previously discussed, the media has been criticized for inaccurately balancing claims of a causal link between the MMR vaccine and autism, despite powerful evidence to the contrary. The press was also faulted for not providing information that parents could turn to in order to address vaccine-related questions [28]. In addition, several studies found that, astonishingly, more resources and mobilizing information were actually offered to proponents of the vaccine-autism link than to the contrary [10, 28]. The fact that Wakefield's co-author's never supported his claim to use single immunizations over the triple MMR vaccine also went largely unreported [10].

Speers and Lewis [14] published that rates of MMR uptake tangibly decreased as media coverage of the vaccine controversy increased, and vice versa. They attributed this directly to the public's perception that the vaccine was unsafe following significant periods of focus in the press, and noted that once media interest fell away, immunization rates subsequently increased. These findings were replicated on a local scale when Mason and Donnelly [29] examined the impact of the South Wales Evening Post's campaign against the MMR vaccine in Wales. Before the promotional push began, immunization rates were significantly higher in the distribution area when compared to their control population. However, after the *MMR*: *Parents Fight for Facts* campaign ran, vaccination rates fell by 13.6 % in the target community, compared to only a 2.4 % drop in areas outside of the paper's circulation.

HPV

Despite the lessons from the DTP and MMR media scares, stories of more recently developed vaccines, such as the HPV immunization, continue to highlight inaccuracies. Although the HPV vaccine received a significant amount of press when it was approved by the FDA, many news stories left out critical pieces of information [15]. One of the main themes in the media's coverage of this vaccine is that recipients will increasingly engage in risky sexual behavior, which has negatively influenced parent's perceptions on the vaccine [30].

Future Considerations

Undoubtedly, the media has the power to influence the public's perception. They are enlisted to both educate and warn people on matters of public health. By reviewing the press' role in modern vaccine controversy, it is clear that we cannot devise methods of disseminating trustworthy health information to the public without considering the role of the media. Lewis [10] summarized this best by stating, "The battle for public trust, in other words, can no longer be won by straightforward appeals to authority: it needs to be based on an understanding of the nature of public concern and an awareness of media frameworks." By revisiting the press' obligations to the

public we can identify ways to proactively interact with and guide the media's coverage of vaccines in the future to avoid replicating previous public health scares.

Charge to the Media

The public relies on the media to provide reliable information. As is the guiding principle in medicine, the press should also follow the tenet *primum non nocere*, or first, do no harm [10]. Disseminating critical public health information is a serious matter and should be approached cautiously and carried out in a balanced and responsible manner.

Social Contract

Freed et al. [5] proposes that while parents, health care professionals, and the general public are responsible for maintaining and promoting the health of our children, the news media must be included in this social contract. The press has an obligation to inform their audience. Although we cannot reasonably expect that they will avoid new reports contradicting the safety of vaccines, what we can demand is that they strive to present the information in a way that accurately weighs existing evidence. We accept that the media will increase coverage of controversial topics in order to respond to public demand. But as the press owes it to the public to report on potentially contradictory information, they also have a responsibility to properly credit data endorsed by unbiased scientists and accredited resources free from external influence that conform to the accepted medical consensus [18].

Expert Guidance

The public tends to demand reliable, accurate information or none at all [10]. Interestingly, this may not fully extend to issues surrounding vaccine safety. In one survey, almost half of the respondents indicated that when there are claims that contradict or challenge accepted science, they would prefer the media avoid reporting the issue until there are confirmatory studies to back them. However, a third of the participants requested that all information be shared as it becomes available, regardless of supporting evidence [14]. This phenomenon may help us understand why the public grabbed on to reports linking the DTP vaccine to permanent brain damage and MMR to autism. However, knowing this tendency, the press should tread that much more cautiously when reporting such potentially inflammatory information.

When looking at reporting of the MMR controversy, what most journalists failed to do was challenge Wakefield's claims and determine if any existing data substantiated his findings [14]. The media must demand high-quality information and seek

expert input to help weight the strength of evidence being offered by opponents of vaccine safety. In addition, reporters should question the motives and integrity of contrarians. By offering balanced expert opinion and questioning the veracity of claims against the safety of routine immunizations, the media can fulfill its obligation to the public.

Medical Correspondents

Typically, health and science stories are reported in the media by correspondents with special training or background in the field. Yet remarkably, studies reviewing coverage of the MMR controversy revealed that only 20 % of the stories were covered by medical reporters [14]. This may have contributed to the inaccurate reporting and propagation of slanted information and anecdotal reports versus balanced reporting of evidence. Although clearly a matter of public health, coverage of immunizations moved from medical journals to the popular press and stopped commanding the attention of medical correspondents [14]. Given that specialty reporters are better equipped to interpret and relay scientific information in a more comprehensive manner, future stories regarding vaccine safety should be funneled through these medical correspondents.

Mobilizing Information

Finally, the media should mobilize information to properly guide and empower the public to seek reliable resources, educate themselves, and seek further assistance when faced with new and controversial information [28]. For example, the media should point families to their pediatricians, and trusted authorities such as the AAP and CDC in order to seek answers to questions they may have regarding vaccine safety. By providing names of local experts, contact information for local public health officials, and URL addresses for dependable Web sites, the media can help parents properly educate themselves in a responsible manner.

The Role of the Public Health Community

Proactive Role with Media

Physicians engaging the media proactively may help lessen the impact of future public health concerns [28]. In retrospect, many criticized the delayed response from leading authorities on vaccine safety in the wake of the MMR-autism controversy. By failing to respond swiftly and in a unified manner, anecdotes ran rampant and the established body of evidence on vaccine safety went largely unheard by the public. If faced with a similar controversy in the future, public health officials

should mount a coordinated and expeditious response and offer vigorous debunking of sensational media reports [17]. Data should be presented without hesitation in a condensed, yet approachable manner. Efforts should capitalize on the easy accessibility offered by the modern media, and should utilize all reasonable means to spread the message far and wide. Most critically, the voice of the accredited medical community should be genuine, truthful, and transparent in order to ensure the public's ultimate trust [17]. After all, a generalized acceptance of vaccines depends on the community having confidence that health officials will objectively and promptly investigate any potential vaccine-related dangers [3].

Physicians as Buffers

Armed with timely advisories and credible resources, pediatricians and family practitioners can serve as an important buffer against potentially negative reports from the media on vaccine controversies [2]. Studies have shown that information provided by physicians has the potential to counteract damaging misinformation offered in media scare stories [31]. Physicians should take an active role in educating their patients and families when controversies regarding vaccines begin to circulate in the media. They must listen and empathize with parental concerns but confidently relay information in an approachable manner. The AAP and CDC have handouts and Web sites that are targeted to help medical providers understand and accurately address parental concerns.

Physicians as Advocates

Finally, physicians and health care providers should take an active role in protecting the health of children, not only by caring for them in clinics and hospitals but also by interacting with the public on local, state, and national levels to promote their continued well-being. When inaccurate or damaging information is distributed in the media providers should actively seek knowledge to educate themselves, their patients, and their community. Like the media, they should refrain from being persuaded by sensational claims and moving anecdotes but rather seek evidence-based reliable information. As individuals, their voices can be heard. As a group, they can effect change and ensure vaccine preventable diseases do not unnecessarily claim the lives of their patients.

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Chapter 22
Vaccines and the Internet

David M. Berman and Paola Dees

Introduction

"Trying to get health information from the Internet is like drinking from a fire hose and you don't even know what the source of the water is": Spokesperson for the US Department of Health and Human Services [1].

The way health care information is communicated has changed dramatically over the last few decades. Vaccine information is easily disseminated over the Internet. With ease of access, virtually anyone can search for information if they have an electronic device with Internet access: computer, smart phone, or tablet. Only 1,000 computers were linked to the Internet in 1985. By 1998, that number had grown to four million Internet connections [2]. In 1997, almost half of the Internet users were seeking health information [2]. By the twenty-first century, it was estimated that 67 % of the US population had access to the Internet and upwards of 80 % used it to access health information [3, 4]. Fifty two percent of those seeking health information believed almost all or most of what they viewed on the Internet [5]. As much as the Internet has been used to promote positive messages regarding vaccine safety and efficacy, it has also allowed a voice for individuals and groups with vaccine-critical messages.

Although it would appear that modern day opposition to vaccines began with the Internet, it is a not a new phenomenon. One of the reasons for this perceived rise of vaccine "paranoia" might be the consequence of declining print journalism [6]. Vaccine opposition has been present since Edward Jenner introduced the smallpox

D.M. Berman, D.O., F.A.A.P. (✉)
Division of Pediatric Infectious Diseases, All Children's Hospital, Johns Hopkins Medicine, Outpatient Care Center 5th Floor, 601 5th Street South, St Petersburg, FL 33701, USA
e-mail: david.berman@allkids.org

P. Dees, M.D.
Division of Hospital Medicine, All Children's Hospital, Johns Hopkins Medicine, Outpatient Care Center 5th Floor, 601 5th Street South, St Petersburg, FL 33701, USA

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vaccine in England at the end of the eighteenth century. What has changed, however, is the way vaccine opposition is communicated. Prior to the "Internet Age," vaccine opposition was commonly spread through newspapers, pamphlets, books and public forums with demonstrations. Twenty thousand people gathered in Leicester, England against smallpox vaccine mandates and Edward Jenner was hung in effigy [7]. Today, these "public forums" in opposition to vaccines are carried out on the Internet with social networks (Twitter, MySpace and Facebook) [8–10].

It was only two decades ago, when health information was sought through print with travel to a bookstore, public or college library. Under most circumstances, to seek any health information, was more time consuming. But the library is arranged in an orderly fashion; books and journals are well organized. If needed, a librarian would assist you to find information. To the contrary, finding information on the Internet is very different. The same standards are not used for Web sites that have been used for print. Print publishing rules of engagement have been worked out over the last five centuries [11]. Comparing information from the Internet to the library as one author described: "is one of chaos; all the books have been donated by patrons and placed randomly on the shelves. On the Internet, there are no call numbers or other types of classification, books can be moved around from shelf to shelf with a rapidly expanding library with thousands signing up every week to roam through the stacks" [12].

The Internet has continued to expand over the past two decades from a "non-interactive" to an "interactive Web"; described as the transition of Web 1.0 to Web 2.0 [13]. Web 1.0 content was under the control of the provider, but Web 2.0 allows any user to create information and upload it to the Internet. This has permitted the dissemination of social media (bulletin boards, blogs, video, and photographs), sharing of medical treatments (including treatment failures and side effects of vaccines), as well as the development of vaccine-critical Web sites. There has been a shift of vaccine information coming from authoritative sources such as peer-reviewed books and journals, physicians, scientists and government authorities to anyone that has access to an Internet connection and wants to share their "beliefs" about vaccines. Stories and messages conveyed use "emotional appeal" and "theoretical risks" to persuade Internet users to avoid vaccines.

However, not all Web sites are vaccine-critical. Accurate and scientifically based Web sites are widespread and exist for vaccine education. Other uses of the Internet include electronic immunization registries (e.g., Florida Shots) and research (e.g., tracking the onset of vaccine preventable epidemics such as influenza) [14]. Additionally, the Internet has provided the opportunity for anyone to report suspected vaccine adverse events more readily via the Vaccine Adverse Event Reporting System (VAERS) (http://vaers.hhs.gov/index) using an electronic reporting form. This has allowed VAERS to detect a signal of possible new or rare vaccine adverse events more rapidly [4, 15]. This information can then be analyzed scientifically to determine the relationship between the reported event and the vaccine.

Motives for Seeking Vaccine Information on the Internet

At first glance, science and snake oil may not always look all that different on the Net [11].

Part of understanding vaccine opposition on the Internet is to recognize motives for Internet use. Some reasons include social interaction, inclusion, entertainment, and escape [16]. It may also facilitate solidarity for parents that feel abandoned by the medical community [17]. Others seek information to find individuals with common beliefs about vaccines. Sometimes a parent will believe "perceived harm" occurred from a vaccine, which leads them to seek information on the Internet. As more access is gained to health and vaccine advice, whether it is accurate or not, some parents may feel empowered to make their own decisions about vaccines. Lack of trust may play a role in information-seeking on the Internet as well. Data based on the US National Immunization Survey found 71 % of parents stated that their physician did not influence their decision to vaccinate their children [18]. There is also a perceived lack of trust of those in government that make vaccine recommendations, and a concern that pharmaceutical companies are solely driven by profit motives [19].

Because the Internet has become an integral part of our media environment, dependency on the Internet has occurred among younger people [20]. Today, children and college students use the computer for many educational purposes. One survey found that today's college students began using computers by the age of 5 and 8. By the time they reach college, most are using computers [21]. College students use the Internet for more than 3 h a day [16]. Kortum described 34 high school science magnet students using the Google search engine with terms "vaccine safety" and "vaccine danger." They were asked to describe what they learned from the Web sites and answer questions regarding statements about vaccination. The majority of the students thought the Web sites discovered had accurate vaccine information. However, more than half of the sites had inaccurate information about efficacy and safety of vaccines. After viewing the Web sites, a vaccine video with accurate information was shown to the students. Following the video, most participants reported accurate vaccine information [22]. This study suggests that individuals using the Internet may learn inaccurate vaccine information without recognizing the poor quality. Even more troubling, the content found on the Internet could potentially influence some students in a negative way and impact vaccine decision-making in the future. Betsch evaluated the impact of viewing vaccine critical Web sites for short periods. The study showed that accessing vaccine-critical Web sites for only 5–10 min increased the perception of risk of vaccinating and decreased perception of risk of omitting vaccines [23]. So whether adults or older students, the viewing of vaccine-critical Web sites may contribute to changes in perception and the willingness to get vaccinated [24].

Vaccine-Critical Web sites and Internet Search Engines

Vaccine-critical Web sites are more widespread and unrestrained than any other media form [17]. There is a lack of accountability for those individuals or organizations promoting inaccurate vaccine information. Because an abundant number of vaccine-critical sites do not follow guidelines of quality Web content, many design flaws and the lack of peer review is obvious. Of the 63.6 % of Web sites aimed at both health care providers and the general public, there was no clear separation of documents or entry routes [25]. Many sites did not state the target audience [26]. This creates confusion for users when trying to interpret the content on a vaccine Web site. Other examples of poor quality Web sites include the following: links to other vaccine critical sites, advertising law firms, pharmaceutical industry, vitamin/food/nutritional products, and other nonmedical products (e.g., cookware, skin products, tanning beds) [27–32].

The Internet should facilitate and not be a barrier to high quality information [33]. But Internet search engines are not designed to distinguish high quality from poor quality content. The search engine (e.g., Google, America Online, Yahoo) allows users to seek out vaccine information without going directly to a known reliable vaccine Web site. Google and other search engines only act as a "disorganized" library. It is up to the user to distinguish credible and non-credible vaccine information. Search engines such as Google use computer programs that scan the Internet based on words found on Web sites (text content and HTML language). Google uses an algorithm to order Web pages higher that have more incoming links. These links become important. The more incoming links a site has, the higher the site will be listed on Google [34]. The quality of content has nothing to do with ranking. Yet the "ranking" becomes an important issue when parents are searching for vaccine information. The vaccine-critical individuals and groups have used this concept to create a strategy controlling search terms. Many vaccine-critical activists use the term "vaccination" over "immunization" because they do not believe vaccination leads to immunity [34]. One very popular vaccine-critical site, the National Vaccine Information Center (NVIC) (www.nvic.org) is popular among vaccine-critical groups. Its many incoming links allow it to appear as one of the top Google "hits" immediately following the Centers for Disease Control and Prevention (CDC) when using the search term "vaccination." Therefore, the more incoming links, the more likely the popular sites will appear in the first display of search terms. Users typically choose one of the first results that appear on the first display page. Rather than moving to the second Web page, they usually "rephrase" their search terms to look for new results. Most of the time, they only view the first ten search results [35] and sites that have the "higher ranking" are more likely to be viewed. Therefore, search terminology and search engines impact the vaccine information found and potentially lead to poor quality Web sites.

A few studies have used search terms "vaccination" and "immunization" to determine the type of hits that lead to anti-vaccine Web sites. Wolfe and Sharp hypothesized that the use of specific search terms would impact information found

about vaccines. Words with the Latin root "vacca" increased the number of hits from anti-vaccine sites but using "immunization," most Web sites were pro-vaccine [34]. In an earlier study, Nasir used multiple search engines with terms "vaccination" and "immunization" and identified 51 sites that had vaccine-critical messages targeting childhood immunizations. Twenty-six were randomly chosen and reviewed. Many sites promoted alternative medical practices or products [36]. Davies also used the same terms with different search engines. When evaluating Google alone, the first ten sites encountered were all anti-vaccine with the term "vaccination." However, using Google alone, the term "immunization" displayed no anti-vaccine Web sites. Other search engines using the term "vaccination" had between 10 and 50 % anti-vaccine sites resulted in the first ten displayed [17]. Abbot investigated the search term "MMR vaccination" and found 42.5 % of the hits were anti-vaccine [37].

Once a parent has decided to pursue a vaccine site found with a search engine, they need to determine if the vaccine "content" is useful to them. This can be a difficult problem for individuals lacking a background in medicine or vaccine science. In one case–control study, parents of vaccine-exempted children were more likely to have searched the Internet for vaccine information than parents of vaccinated children. The vaccine-exempting parents rated the Web site "Dissatisfied Parents Together" (A.K.A. DPT) as a good/excellent source of information. DPT is a known vaccine-critical organization. But what is most intriguing is that parents that had vaccinated their children gave the NVIC a good/excellent rating as well. NVIC was formerly DPT, the vaccine-critical Web site [38]. This study demonstrates the difficulty parents have distinguishing quality vaccine content from poor content. Wolfe et al. examined specific Web site attributes using ten search engines. They analyzed a total of 22 anti-vaccine sites. Some of the information Wolfe found among these sites included claims of contaminated vaccine lots, idiopathic illness, erosion of immunity, vaccine-preventable disease decline is unrelated to immunization, adverse reactions are underreported deliberately by doctors, vaccines motivated by profit, violation of civil liberties, and sites claiming alleged accounts of harm (including photographs of children allegedly harmed by vaccines) [39, 40]. Every site had links to other anti-vaccine sites [40]. Nasir found other false claims including vaccines causing Crohn disease, impulsive violence, and behavior problems. One site contended that vaccines were responsible for "Gulf War Syndrome" [41]. Some sites attempted to be "unbiased" and ambiguous about vaccines, questioning safety and effectiveness [36]. Terminology like "unnatural" has been used to describe vaccines. The assumption is that "natural" is better and since vaccines are "not natural" they are bad [13]. There have also been specific campaigns over the Internet such as "Green Our Vaccines" [42] to remove "toxins" from vaccines. The "Green Our Vaccines" organization is promoted as a "pro-safe" vaccine group but in fact, is merely another anti-vaccine movement [43]. This organization claims that vaccine contents include formaldehyde, aborted fetal tissue and "antifreeze." Other anti-vaccine claims on Web sites include "mercury" poisoning. These messages can be confusing to parents that may not understand differences between ethyl and methyl mercury or even why the multi-dose vial of influenza contains thimerosal.

This position is usually not explained on vaccine-critical Web sites. Parents may not understand the concept "it is the dose that makes the poison" (Paracelsus—sixteenth century). However, with all the false claims that are made, as one hypothesis is rejected by science, there is a shift to the next perceived problem; as the mercury toxin hypothesis was rejected, some sites moved to aluminum as a vaccine toxin (Is Aluminum the new Thimerosal?) [44].

Besides perceived toxins in vaccines, the vaccine critics exploit opportunities for parents to avoid immunizations legally. There are several states in the USA that allow vaccine exemption on religious or philosophical grounds [36]. Zimmerman reviewed 15 Web sites that included information about vaccines for humans that are grown in cell strains derived from an abortion. Nine of the Web sites gave advice on how to legally avoid vaccines [45] (Table 22.1).

Anti-vaccine Content: Social Media and Video on the Internet

Video has become commonplace on the Internet for vaccine content. One popular site, YouTube (www.youtube.com), has an international viewing audience that allows millions to view videos at anytime. Keelan searched YouTube using keywords "vaccination" and "immunization." The videos were labeled as negative toward immunization if they emphasized risk, promoted distrust in science and alleged conspiracy. They analyzed 153 videos and found that 32 % of immunization videos were opposed to vaccines. They also had more views and higher ratings than videos that supported vaccination [48]. YouTube is filled with anti-vaccine content that is viewed many times. The "Girl Gets Flu Shot and Now Can Only Walk Backwards" was viewed 2,386,817 times [24]. Her condition was blamed on the influenza vaccine. It was later suspected that the featured video was possibly a hoax or that the patient had a psychogenic rather than a neurologic disorder [49]. Celebrities can be found on YouTube promoting anti-vaccine messages. Cable News Network (CNN) featured an interview with Jenny McCarthy that was posted on YouTube. She describes how she cured her son's autism. She blatantly spoke out against immunization claiming vaccines trigger autism, and are a huge business in the pharmaceutical industry (implying that companies only produce vaccines to make money), and people are dying from vaccines [50].

Social media has become a popular means of sharing beliefs. Many vaccine-critical groups can be found on Facebook, blogs and other Web discussion groups. It is estimated that 8 million Americans have blogs [51] and Facebook has 800 million active users [52]. These social networks are primarily text-based but also can incorporate photographs, video and links to other sites promoting anti-vaccine content. They allow users to read, write, provide advice and update personal comments. One of the most popular blogs is MySpace (www.myspace.com). Keelan searched MySpace for information related to Human Papilloma Virus (HPV) immunization. Analyzing MySpace blogs on HPV vaccines, 43 % of blogs had negative information and 6 % were ambivalent. The highest percentage argument was that the

Table 22.1 Alphabetical listing of 38 vaccine critical Web sites (All sites accessed 2/05/2012)

Title Web site	Web site URL
Autism, ADD, ADHD Vaccine Related	http://www.autism99.org/articles/Autism_ADD_ADHD__Vaccine_Related.htm
Age of Autism	http://www.ageofautism.com/vaccines
Dr Bob Sears—Alternative Vaccine Schedule	www.askdrsears.com/topics/vaccines/alternative-vaccine-schedule
Dr Joseph Mercola—Natural Health Web site	http://vaccines.mercola.com/
Generation Rescue	http://www.generationrescue.org/resources/vaccination/
Global Vaccine Awareness League	http://www.gval.com
Green Our Vaccines	http://www.greenourvaccines.net/
Immunisation Awareness Society	http://www.ias.org.nz/
Informed Parent	http://www.informedparent.co.uk
International Medical Council on Vaccination	http://vaccinationcouncil.org/
Justice Awareness and Basic Support (JABS)	http://www.jabs.org.uk/
Lew Rockwell—Avoid Flu Shots	http://www.lewrockwell.com/miller/miller27.html
Medicine—No Vaccinations	http://www.medicine-no.com/vaccinations.htm
Moms against Mercury	http://www.momsagainstmercury.org
National Vaccine Information Center[a]	http://www.nvic.org
NaturDoctor	http://www.naturdoctor.com/Chapters/Articles/vaccinate.html
Natural News[a]	http://www.naturalnews.com/vaccinations.html
Safe Minds	http://www.safeminds.org/
Smartvax	http://smartvax.com
Think Twice	http://www.thinktwice.com/
Truth About Gardasil	http://truthaboutgardasil.org/
Vaccination Conspiracy[a]	http://www.whale.to/vaccines.html
Vaccines—Children's Vaccines	http://healing-arts.org/children/vaccines
Vaccine Dangers	http://vaccinedangers.com
Vaccine Dangers	http://educate-yourself.org/vcd/
Vaccination—Deception and Tragedy	http://www.shirleys-wellnesscafe.com/vaccines.htm
Vaccination Files	http://home.iae.nl/users/lightnet/health/vaccination.htm
Vaccination Information Service	http://www.vaccination.inoz.com/links.html
Vaccine Information (Australia)	http://www.avn.org.au/
Vaccine Information and Choice Network	http://www.nccn.net/~wwithin/vaccine.htm
Vaccination Liberation[a]	www.vaclib.org
Vaccination Myths	www.relfe.com/vaccine.html
Vaccination News[a]	www.vaccinationnews.com
Vaccine Risk Awareness Network	http://vran.org
World Association for Vaccine Education	http://www.novaccine.com/
Vaccine Safety Web site	http://www.vaccines.net/newpage114.htm
Vegan Family	http://www.vegfamily.com/vaccines/are-vaccines-vegan.htm
Vactruth (Your Child. Your Choice)	www.vactruth.com

None of the listed Web sites meets standards of quality vaccine content [11, 26, 46, 47]
[a]Web sites that appear on the first page using Google search engine term "vaccination" (accessed February 11, 2012)

vaccine was not safe followed by alleged financial interests of pharmaceutical companies, and serious adverse events [51].

Web discussion groups are another method used for discussing vaccine topics or obtaining advice on patient management. Anyone can access an unlimited number of discussion groups that provide non-peer-reviewed advice [53]. One potential problem is that the user may not know the qualifications of the individual or group responding to their questions. Welch examined the use of Internet-based bulletin boards among physicians (pediatric nephrologists) over a 6-month period. The most frequent provider of medical information on the bulletin board had no indexed publications or citations. Additionally, board certification was not required as a qualification to post answers on the bulletin board [53]. Therefore, not knowing the qualifications of respondents can create a challenge for those needing expert advice on any health topic including vaccines.

Popular "Self-Proclaimed" Experts Promoting Vaccine-Critical Messages on the Internet

> Belief is not the beginning but the end of all knowledge—Johann Wolfgang von Goethe 1749–1832

As Paul Offit, Chief of Infectious Diseases at Children's Hospital of Philadelphia and Head of the hospital's Vaccine Education Center has described the vaccine controversy, "Every story has a hero, victim, and villain" [54]. Unfortunately, scientists, the government and physicians have been portrayed as the villain over many sites on the Internet. Many of these vaccine-critical Web sites have used the tool of emotion—the child falling "victim" to vaccines and there are the perceived heroes on these sites, those individuals claiming to be vaccine experts, but in reality, delivering the vaccine-critical messages. The self-proclaimed "expert" uses the Internet to provide information through Web sites, social networks, and video. Sometimes it will be a physician, but at other times, a celebrity, an alternative medicine practitioner, and even a parent. Some information will be accepted as "truth" by readers just because it is the held belief of a popular celebrity regardless of their credentials. The beliefs expressed by the celebrity may support their own beliefs, irrespective of whether the information provided is factual. To some extent, the general message of many of these self-proclaimed "experts" are if you trust scientists, the government, vaccine manufacturers and leading vaccine experts, you are not being independent regarding vaccine decisions for your child. In addition, the message is that the medical community is split regarding the value of vaccines; making it appear as if there is a perceived "controversy." Self-proclaimed "experts" draw conclusions from published scientific research that is inconsistent with the content conveyed by the researcher [17, 55]. Some of the claims made on the Internet include an outbreak of measles spreading from unimmunized individuals to vaccine nonresponders therefore "supporting a claim" that the measles vaccine is ineffective, Romanian children

contracting polio from the vaccine, and immunizations causing Sudden Infant Death Syndrome [55]. On occasion, they will try to praise science or skew science only when it appears to support their point of view [13]. When those from the science-based vaccine community are critical of their theories, the self-proclaimed "experts" bring up names like Semmelweiss, Galileo, Copernicus; promoting the idea that these scientists were also criticized in their time and "look what accomplishments they made" The implication is that the large "mainstream" medical community is closed-minded and critical of the views about vaccines and these persecutions will someday be accepted as truth [13]. Statements are also brought up that science has been wrong in the past and that science does not have all the answers [13]. But in general, many of these self-proclaimed "experts" will promote personal experience that appears to triumph scientific data [40]. In one study, some Complementary-Alternative Medicine (CAM) Practitioners gave advice over the Internet against immunizations [56].

Multiple examples of physicians providing misinformation exist on the Internet. Dr. Robert Sears (AKA Dr Bob), a board certified celebrity pediatrician, has sold more than 100,000 copies of his book The Vaccine Book: Making the Right Decisions for your Child, which was published in 2007 [57]. Dr. Sears has used the opportunity to sell his book through the Sears' Web site as well as on Amazon.com. He provides vaccine advice to parents. Dr Sears is promoted as a vaccine authority on the Hachette Speakers Bureau Web site.

Hachette Web site statement about Dr. Robert Sears:

> One of the most trusted names in childcare today provides clear, concise answers to the countless questions parents have about vaccines. He offers the most up-to-date information in the latest addition to the Sears Parenting Library, *The Vaccine Book* [58].

Although he is promoted as an "expert," Dr. Sears has no background in immunology, vaccine research and has no peer-reviewed publications in vaccine science. He offers very confusing messages about vaccine-preventable disease on his Web site and in his book. This engages parents to act on their own fears without abandoning vaccines but still sends an anti-vaccine message [19]. Sears has marketed his own alternative vaccine schedule that has never been studied for safety or effectiveness. He promotes this schedule not only in his book but also makes reference to it on the Sears' Web site [59]. Confusing and inaccurate information on the Sears' Alternative Schedule Web site include the following:

> Don't give the Hepatitis B vaccine to newborns in the hospital. It's better to delay this shot for the first two months of life, especially since the disease doesn't even occur in newborns. Check antibody titers for various shots before boosters, spread shots out over more time, and limit large combination shots.

> If you are starting the schedule late, such as at 4 or 6 months, don't hurry to catch-up. Just start the schedule as if your baby was 2 months old, and you'll go through the whole thing but always be 2 to 4 months behind.

Parents also look to other celebrity physicians for health advice such as the television and Internet personality Dr. Mehmet Oz, trained in cardiovascular surgery, author of the "You" books, "You: Having a Baby" coauthored by Dr. Michael

Roizen (internist and anesthesiologist). Dr. Oz has an average of 3.5 million viewers on television daily [60]. Not only does Dr. Oz use his media power on television and in the press, but he also shares an excerpt from his book about infants and vaccines on his Web site and additional free excerpts can be accessed through the Amazon book Web site [61, 62]. Like Dr. Bob Sears, the information parents will find from Dr. Oz does not take a position on vaccines one way or the other, but leaves the parent to make their own "informed" decision. Again, sending a message to parents to "do your own research" and come up with what you "feel is best" for your child.

Excerpt from the Dr. Oz Web site:

Against vaccines: "Large studies such as those in Europe that show no adverse effects from vaccines in more than 2.5 million kids are epidemiological, meaning that they show patterns in the population rather than biological cause and effect in the individual. Large studies ignore the significant number of stories by parents who have witnessed sudden declines in the health of their children after vaccination" [62].

Another physician with a large Internet following is Dr. Joseph Mercola. Mercola claims that his Web site is routinely among the top ten health sites on the Internet. According to the site, the "existing medical establishment is responsible for killing and permanently injuring millions of Americans" [63]. Mercola is a board-certified physician, but proclaims "alternative" therapies for health. He has used his Web site Mercola.com as a marketing tool. His health claims have included the use of a "safe" tanning bed to get vitamin D during cold winter months, or "simply whenever you can't get enough sunshine," even though the World Health Organization (WHO) has recommended against tanning beds [64]. With regard to immunizations, he recommends against influenza vaccination. He states that the statistics of death are exaggerated and not a direct result from influenza but due to bacterial pneumonia. He claims the vaccine contains "dangerous preservative ingredients such as mercury, aluminum and even antifreeze" [65]. He has links to vaccine-critical video on his Web site including claims that Gardasil® caused permanent disability in women [66]. He has a link to "The Greater Good Movie Trailer," a film that portrays harm caused by vaccines. At one point, Mercola had a free viewing of the film on his Web site. His site is now used to market the movie and to make DVD purchases to show your support [67]. Mercola has also partnered with other vaccine-critical Web sites such as the NVIC (www.nvic.org) and provides links to other vaccine-critical Web sites. Mercola sells items including food products, vitamins, personal care, fitness equipment, pet supplies, and household goods. Like Robert Sears, Mercola appears to come across as a "vaccine expert," but he has no experience with immunology, vaccine research or infectious disease and has no published peer-reviewed vaccine research [63].

The father and son team, Drs. David and Mark Geier have been critical of vaccines, used Lupron to treat autism and their theories have been supported by several vaccine critical Web sites [68–70]. Their theories have been unfounded [71]. Dr. Mark Geier's medical license has now been suspended in Maryland [72].

Besides physicians, other "self-proclaimed" experts have included lawyers and parents.

Robert Kennedy Jr. claimed a link between thimerosal in vaccines and neurologic disorders in his 2005 article "Deadly Immunity" that ran simultaneously on the Salon.com Web site and *Rolling Stone* Magazine [73].

Kennedy stated:

> I devoted time to study this issue because I believe that this is a moral crisis that must be addressed. If, as the evidence suggests, our public-health authorities knowingly allowed the pharmaceutical industry to poison an entire generation of American children, their actions arguably constitute one of the biggest scandals in the annals of American medicine.

The article implicated the CDC and the pharmaceutical vaccine manufacturers in a cover-up. Salon.com eventually retracted the article from the Web publication. The editor admitted a mistake in judgment [74]. The Web publication was an example of irresponsible vaccine science journalism over the Internet. Seth Mnookin, author of The Panic Virus, discussed the need for responsible science journalism and the impact on the public: "Unfortunately, there is no restart button when it comes to public consciousness, and it will take quite a while to eradicate the effects of all of the fear and misinformation that were injected into the population" [75].

Parents have also promoted information on many of these same Web sites. Claims include "done my own research" and "I'm an expert on my own child" [13]. These statements may appeal to other parents that have similar doubts about immunizing their children.

Strategies to Address Vaccine Misinformation and Reliable Vaccine Information

Criteria for Web site publication should be strict and subjected to the same standards as traditional information sources [76]. Unfortunately, there has been no standard oversight that reviews the quality of every published vaccine Web site. If this was true, it would potentially guard against poor Web site content.

Two existing organizations have tried to set standards for quality health information on the Internet.WHO has published criteria that should be used for Web site development and lists Web sites that adhere to good information practices. This Division of the WHO is known as the Vaccine Safety Net (VSN). Four categories used by the VSN are the credibility of site, type of content, accessibility and the design [25]. A few examples of US organizations that have met this criteria include the Childhood Immunization Support Program (CISP), American Academy of Pediatrics (AAP); Institute for Vaccine Safety at Johns Hopkins Bloomberg School of Public Health; National Network for Immunization Information (NNii); US Department of Health and Human Services; CDC; National Center for Immunization and Respiratory Diseases (NCIRD) and Vaccine Education Center (VEC), Children's Hospital of Philadelphia [77]. One study published to evaluate the characteristics of Web sites that belong to the VSN found important factors of quality were transparent financing, lack of links to the pharmaceutical industry, appropriate Web site

Table 22.2 Six bullet points to use in determining quality vaccine information [11, 26, 47]

Purpose of the Web site should be clear
Author(s) and contributor(s) with listed affiliations, relevant credentials, and contact information
"Ownership" fully disclosed including funding, conflicts of interest, and arrangements in which links to other sites are posted as a result of financial considerations
Information should be current, easy to understand, concise, unbiased, accurate scientific-evidence (some sites inaccurately cite legitimate publications), references/sources listed clearly, scientific experts should review the posted information (be careful of sites with the claim of "expert")
Be able to distinguish Web site content fact from opinion
Any description of a vaccine serious adverse event must use scientific evidence rather than anecdotes (be careful of patient testimonials of alleged harm)

management, proven scientific quality, and updating of contents [25]; vaccine-critical sites do not follow many characteristics.

The second organization, Health on the Net Organization (HON) (www.hon.ch/), a nongovernmental and nonprofit organization, promotes and guides the deployment of useful and reliable online health information, and its appropriate and efficient use [46]. The site provides an entry point for medical professionals and patients. It has an electronic form that assists users in determining the trustworthiness of a Web site. After basic questions have been answered about a Web site, HON determines if the site respects elementary ethical and quality standards. Users may also print the information. HON also serves as a search engine to find health information that meets quality certification by HON (HONcode). Web sites reviewed by HON will usually have a HONcode "stamp of approval" on their Web page.

Any quality vaccine site should strictly adhere to the recommendations of the VSN and HON. Any published vaccine Web site should include the following: originating organization; creator of the site (authorship); affiliations and credentials; purpose of the site; accurate and unbiased facts (not opinions); dates of content with references; updated content listed clearly (including last update and date information was posted); full disclosures (including Web site sponsorship); and any advertising and funding (disclosure of conflicts of interests) [11, 26, 47] (Table 22.2). If the Web site includes links to other sites, those sites should have the same attributes as the linking site with the same scientific information (rigorous studies) and evidence-based medicine to counteract ambiguities they may find on other anti-vaccine sites [25]. Any Internet sources of medical information that fail to meet any of these basic standards should be considered suspect [11].

In general, parents should be advised to avoid using general search engines to find vaccine information. Any parent or physician seeking vaccine content should begin with a known trustworthy site [47]. Physicians should become familiar with these Web sites and help assist parents regarding characteristics of appropriate and inappropriate vaccine sites. Parents should be cautioned when a site contains highly emotive content, claims of privileged information unknown to the general medical community, conspiratorial claims, information that is not peer reviewed but privately published (without a source of information) [17]. In general, physicians should direct families towards specific sites that have been designed for vaccine information especially sites that follow the guidelines of the VSN and HON.

Two studies reviewed Web sites for reliable vaccine content over the Internet [78, 79]. Chatterjee reviewed Web sites using published criteria for evaluating health-related sites. Search terms such as immunization, immunize, vaccine, vaccinate, and vaccination were used in various Internet search engines. The sites found were then chosen based on balanced science content, updated information, without sponsor bias and commercial promotion [78]. In another study, Pappas used general search engines with pediatric terms such as pediatric infectious disease, infection/infectious disease, children/pediatric, and vaccination/immunization [79]. Both studies found similar quality sites in common including: the Web sites of the Immunization Action Coalition, National Network for Immunization Information, AAP, CDC, Pediatric Infectious Diseases Society, National Foundation for Infectious Diseases, Every Child by Two, and the CHOP Vaccine Education Center. Many of the sites include information for physicians, parents and scientists [78, 79] (Table 22.3).

Another effective way for physicians to communicate accurate information is to "brand" their practice by creating their own Web site [80]. The practice Web site should include information about vaccine-preventable disease transmission with links to evidence-based vaccine Web sites. The information on the Web site should be easy for families to interpret. The practice may include photographs and stories of children that suffered from vaccine-preventable diseases, which is an effective tool in conveying the importance of vaccines. Another effective Web site design tool incorporates computer-assisted learning for topics that are conceptually difficult to understand using interactive animation and video [81] as well as interactive decision aids that might improve parents' attitudes towards vaccination [82]. Wallace et al. used a Web based decision aid, written for a reading age of 12 years. They provided numerical and graphical data of the risks associated with vaccine-preventable disease, alongside the potential risks associated with vaccination and provided references for these estimates. Additionally, frequently asked questions were addressed about the alleged association of autism and MMR. The interactive decision aid improved parents' attitudes toward MMR vaccination [82].

Because the Internet is used increasingly as a source of vaccine information, tools continuously need to be developed to manage and communicate appropriate information. As we move further away from the "traditional library" for our health care information to a "virtual library," the concept of a "gate keeper" to assist in finding accurate, current, science-based vaccine information will become a necessity. One solution for this problem might be the use of the health science librarian to act as a "navigator and interpreter" of information over the Internet [83]. With their background training, health care librarians have the knowledge, skills to identify, appropriately choose and disseminate information which can assist individuals in making informed health decisions [84].

The concept of health care librarianship has been around for decades. In the 1980s, at the University of California Los Angeles (UCLA), librarians mediated online searches in the Biomedical Library. By the 1990s, UCLA and University of California San Diego (USCD) health science librarians monitored new developments and trends in electronic information relevant to health sciences and promoted electronic tools and resources [83]. Clinical librarianship (librarians brought into the clinical setting) plays a role in managing clinical information in the hospital setting with clinical

Table 22.3 Alphabetical list of 33 Web sites with vaccine information

Web site and developer	URL	Key points for Web site
Allied Vaccine Group	http://www.vaccine.org/	Links to other reputable sites that provide valid vaccine science, includes a search engine
American Academy of Family Physicians	http://www.aafp.org/online/en/home/clinical/immunizationres.htm	Vaccine schedules, links to the CDC
American Academy of Pediatrics	http://www2.aap.org/immunization/	Highly visible entry points for parents and health care providers, sign up for AAP electronic Immunization newsletter
American Medical Association	http://www.ama-assn.org/ama/pub/physician-resources/public-health/vaccination-resources.page	Adult and pediatric resource, Immunization 101: How to Start and Maintain an Immunization Practice, includes PDF file slide presentations
Autism Science Foundation	http://www.autismsciencefoundation.org/autismandvaccines.html	Organization dedicated to supporting autism science research, information for parents and health care workers with research links to multiple peer reviewed vaccine-related articles
Bill and Melinda Gates Foundation	http://www.gatesfoundation.org/vaccines/Pages/default.aspx	Global health topics with press releases, photos, videos and blogs
Canadian Immunization Awareness Program	http://www.immunize.cpha.ca/en/default.aspx	Entry site for parents and health care providers, extensive education on each vaccine-preventable disease
Centers for Disease Control and Prevention	http://www.cdc.gov/vaccines/default.htm http://www.cdc.gov/vaccinesafety/Activities/vsd.html http://www.cdc.gov/vaccines/recs/acip/default.htm http://www.cdc.gov/vaccines/spec-grps/hcp/conversations.htm http://www.cdc.gov/vaccines/spec-grps/parents.htm	Specific target group topics on vaccines, including current schedules, recomme ndations, and Vaccine Safety Datalink Project (VSD) and the Advisory Committee on Immunization Practices (vaccine recommendations and meeting information)
Children's Hospital of Philadelphia, Vaccine Education Center	http://www.chop.edu/service/vaccine-education-center/home.html	Extensive amount of educational material: videos, frequently asked questions, science of vaccines, safety topics, news and ability to register for monthly electronic newsletter from Parents PACK program: Processing, Accessing and Communicating Knowledge about Vaccines

(continued)

Table 22.3 (continued)

Web site and developer	URL	Key points for Web site
Every Child by Two	http://www.ecbt.org/	Updated immunization news, site entry for parents and health care workers
Flu.gov	www.flu.gov/prevention-vaccination/vaccination/index.html	Site dedicated to influenza infection and vaccination with this year's update and video
Food and Drug Administration (Vaccines)	http://www.fda.gov/BiologicsBloodVaccines/Vaccines/default.htm	Vaccine supporting documents and information from each manufacturer
History of Vaccines (The College of Physicians of Philadelphia)	http://www.historyofvaccines.org/	Vaccine history timeline with photographs, articles and videos for families and health care workers
Healthfinder (Immunizations)	http://healthfinder.gov/scripts/SearchContext.asp?topic=2158	Good general information for families (may be used as a health search engine), tips for parents with links to other sites
Health On the Net Foundation	http://www.hon.ch/HONsearch/Pro/hunt.html	Should be used as a search engine for vaccine information (results are free of vaccine-critical Web sites), HONcode certified Web sites
Immunization Partnership	http://www.immunizeusa.org/	Advocates for evidence-based public policy supporting immunization, link for health care providers and parents for educational material, links to other reputable sites
Immunization Action Coalition	http://www.immunize.org	Very extensive site for vaccine information including, an electronic newsletter: IAC express, Needle Tips, and Vaccinate Adults (free electronic subscription)
Infectious Disease Society of America	http://www.idsociety.org/immunization.htm	Advocacy and policy efforts to increase vaccine coverage, promote research and development, background information and position statements from the Infectious Disease Society
Institute of Medicine of the National Academies	http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx	Adverse Effects of Vaccines Consensus Report 08/25/2011 (Report can be read online)
Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health	http://www.vaccinesafety.edu/	Vaccine specific disease information, updated information including schedules, links to journals, general vaccine information

(continued)

Table 22.3 (continued)

Web site and developer	URL	Key points for Web site
MedlinePlus (Immunizations)	http://www.nlm.nih.gov/medlineplus/immunization.html	Mostly links to other government-based vaccine Web sites
National Foundation for Infectious Diseases	http://www.nfid.org/about-vaccines	Link to the Pink Book (can be viewed online free of charge and contains comprehensive information on vaccine-preventable diseases), links to personal stories and frequently asked questions
National Institutes of Health	http://health.nih.gov/topic/ChildhoodImmunization	Summary of mercury studies in vaccinated infants
National Network for Immunization Information (NNii)	http://www.immunizationinfo.org/	Extensive information for families and health care workers including articles summarizing vaccines and studies, diseases prevented by vaccines, press releases and news briefs
Parents of Kids with Infectious Disease	http://www.pkids.org/immunizations.html	Great resource for families with a link for immunization information (how vaccines work, vaccine safety and mandates and what happens if we do not vaccinate)
PATH Vaccine Resource Library	http://www.path.org/vaccineresources/	Provides free or low cost access to journal articles for users in the developing world, resources in other languages
Pediatric Infectious Disease Society	http://www.pids.org/advocacy/immunization-update.html	Immunization updates, link to AAP Sound Advice on Vaccines
Sabin Vaccine Institute	http://www.sabin.org/vaccine-advocacy-and-education	Focus on global vaccine advocacy and vaccine research
Shot By Shot	http://shotbyshot.org/	Web site for families with video stories about vaccine-preventable diseases (sponsor California Immunization Coalition)
Texas Children's Hospital Center for Vaccine Awareness and Research	http://www.texaschildrens.org/carecenters/vaccine/immunization.aspx	Site entry for parents and health care workers, immunization schedules, facts and myths for families, research, other reputable links
Vaccine Adverse Event Reporting System	http://vaers.hhs.gov/index	Electronic reporting system that collects information about possible adverse events. Physicians can submit reports electronically
Vaccinate Your Baby	http://www.vaccinateyourbaby.org/	Web site for families
World Health Organization	http://www.who.int/topics/vaccines/en/	Mostly has links to other reliable vaccine sites

All listed sites meet criteria for quality content [11, 26, 47]

teams [85]. They can train health care providers in reviewing the "quality" of information found on the Internet related to patient care [85]. In a survey assessing the clinical librarianship program at Vanderbilt University Medical Center, respondents found the librarian information to be useful, with accurate interpretation of literature and the relevance of information provided was highly rated [85]. Today and in the future, the role of the health care librarian could extend beyond the hospital, to assist the public in seeking accurate vaccine information on the Internet.

In the future, it would be the hope that there will be more uses of an "approval stamp" such as the HONcode [46] used for Web sites that promote peer-reviewed science-based vaccine content. The "stamp" of approval has to be familiar to all Internet users. If the vaccine site does not display this approval, it should be deemed as having poor content. Unfortunately, there is still no direct evidence of the influence of anti-vaccine information users are exposed to on the Internet [13]. With that being said, more studies will be needed to validate the extent to which Web site information changes perceptions of vaccine safety and willingness receive vaccines [24] as well as addressing the quality of information over the Internet [76].

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Chapter 23
An International Perspective on Vaccine Safety

Rajib Dasgupta and Narendra K. Arora

Outline

I. Global initiatives on vaccine safety
II. Adverse Events Following Immunization (AEFI): Surveillance and management challenges
III. AEFI surveillance in India: A system is born
IV. Some ongoing vaccine controversies in India
V. Vaccine hesitancy and resistance: The case of polio eradication

Global Initiatives on Vaccine Safety

Global Advisory Committee on Vaccine Safety

Established in 1999, the Global Advisory Committee on Vaccine Safety (GACVS) advises the World Health Organization (WHO) on vaccine-related safety issues and enables the WHO to respond promptly, efficiently, and with scientific rigor to issues of vaccine safety with potential global importance. The committee also assesses the implications of vaccine safety for practice worldwide and for WHO policies. It recognizes that concerns over vaccines have increased as vaccines have actually become safer and their use increasingly widespread [1]. The GCAVS recognizes an increasing responsibility towards developing countries with vaccine manufacturing capabilities who export to other countries.

R. Dasgupta, M.B.B.S., M.C.H., Ph.D. (✉)
Center of Social Medicine and Community Health, Jawaharlal Nehru University, New Delhi, India
e-mail: dasgupta.jnu@gmail.com

N.K. Arora, M.B.B.S., M.D.
The International Clinical Epidemiology Network (INCLEN) Trust International,
Child Health and Nutrition Research Initiative (CHNRI), New Delhi, India

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The GACVS decided on several criteria for establishing causality of adverse post-vaccination events. These draw upon the principles adopted by the US Surgeon General [2, 3]. The following conditions need not all be fulfilled to determine causality for each event and they need not carry equal weights.

Consistency: That the association of an adverse event under investigation should be consistent; the phenomenon being replicable in different localities, by different investigators and by different methods of investigation all leading to the same conclusion(s).

Strength of the association: The association follows the standard epidemiological dose–response relationship of the vaccine with the adverse event.

Specificity: The post-immunization adverse event should be uniquely/specifically linked with the vaccine; it should not be occurring frequently, spontaneously, or commonly in association with other conditions.

Temporal relationship: The administration of the vaccine to a recipient or group of recipients should precede the earliest manifestation of the adverse event.

Biological plausibility: The association should be coherent, plausible and explicable according to the current scientific knowledge pertaining to the biology and the natural history of the condition/s.

The association between the vaccine and the adverse event is considered strong and consistent when the evidence is based on:

- Human studies that are based on a priori testing of the hypothesis
- These should be randomized controlled clinical trials, case–control investigations, or cohort studies. Case reports do not fulfill the requirement for testing hypotheses.
- Consistent associations in multiple studies by different investigators in different settings despite different study designs.
- Similarity of the adverse event to the disease the live vaccine is intended to prevent; with a nonrandom temporal relationship (between the administration of the vaccine and the occurrence of the adverse event).

Brighton Collaboration

Despite reductions in vaccine preventable diseases (VPDs) in both developed and developing countries, very few of these diseases shall be eliminated or eradicated. The Brighton Collaboration is a multi-country effort to standardize case definitions in the context of adverse effects following immunization. This is crucial in order to achieve global consensus in immunization safety through a transparent and "new global standard of understanding" [4]. It recognizes that the quality of reporting varies across countries; reports from developing countries may be impacted by available resources, designs of clinical trials, and post-marketing surveillance. Despite standardized definitions, the quality of information from a country, or specific regions/location within them, may be of variable quality. A good example is surveillance for episodes of intussusception (following rotavirus vaccinations) based only on clinical criteria without recourse to sophisticated imaging tools, surgery, or autopsy. This is as true for vaccination programs as for clinical trials

increasingly farmed out to clinical research organizations in developing countries. Information from less-developed regions may lack in passively reported events owing to weak general health services; active surveillance obviously being the appropriate strategy.

The Brighton Collaboration made a conscious departure from the usual public health approach of suspect/probable/confirmed or possible/probable/definite formats of case definitions. This was in order to avoid possibilities of confusion in some countries of:

- The causal relation between immunization and the adverse event (e.g., whether a seizure occurring after immunization was definitely, probably, or possibly caused by a given vaccine), or conversely,
- The adverse event itself (e.g., whether the event reported definitely, probably, or possibly constituted a seizure)

Given the possibilities of countries reporting adverse events with less specific information or lacking in objective scientific evidence, adverse events can be defined with a higher "level of diagnostic certainty" if based on the best scientifically proven information available. Revision of definitions every 3–5 years has been envisaged, as more data become available from developing countries setting up surveillance systems for adverse events. Levels of certainty need to take into account resource-constrained settings and were thus envisaged as (Table 23.1):

Table 23.1 Levels of evidence for a reported event meeting the case definition

Level 1 of diagnostic certainty In the presence of: Criterion 1 and/or Criterion 2 and/or Criterion n and/or In the absence of: Criterion 1 and/or Criterion 2 and/or Criterion n and/or	*Level 1* Highest level of specificity Sensitive (least) for the respective AEFI Applicable primarily in clinical trials and settings of active follow-up and settings with more resources
Level 2 of diagnostic certainty In the presence of: Criterion 1 and/or Criterion 2 and/or Criterion n and/or In the absence of: Criterion 1 and/or Criterion 2 and/or Criterion n and/or	*Level 2* Intermediate level of specificity Sensitive (lower) for the respective AEFI Applicable in clinical trials and post-marketing surveillance
Level 3 of diagnostic certainty In the presence of: Criterion 1 and/or Criterion 2 and/or Criterion n and/or In the absence of: Criterion 1 and/or Criterion 2 and/or Criterion n and/or	*Level 3* Lower level of specificity Highly sensitive for the respective AEFI Applicable primarily in settings with less resources in clinical trials and post-marketing surveillance

Source: [2]

Comparability of data across countries is critical and both definitions and levels of certainty need to be validated across countries. As adverse events reporting systems get institutionalized and operationalized across low- and middle-income countries, extending to clinical trials and for individual case reports in pre- and post-licensure settings, it can be reasonably expected that these goals will be achieved.

The Immunization Safety Priority Project

The WHO set up the Immunization Safety Priority Project (ISPP) to provide a comprehensive system for ensuring safety of immunizations in national vaccination programs by 2003. The focus areas were as follows:

- Safer and simpler delivery systems.
- Vaccine safety: development, trial, and distribution.
- More efficient systems of safe vaccine delivery and safe management of injection sharps.
- Detection of serious or potentially serious AEFIs.

Some scholars have remarked that developing countries were often prejudiced against the vaccines produced in developed countries, often leading to findings about program errors or coincidental medical conditions [5]. Nevertheless, there were acknowledged cases of safety issues, two prominent examples being the killed measles virus in 1960s and the more recent association of rotavirus vaccine with intestinal intussusception [6, 7]. The Global Alliance for Vaccines and Immunisation (GAVI) has also committed itself to vaccine safety by supporting the supply of auto-disabled (AD) syringes and safety boxes in more than 70 countries [8]. Another key area of cooperation is the technology transfer for local production of AD syringes, some of the beneficiaries being China, India, Malaysia, Russia, and Vietnam. Needle-free delivery devices and new kinds of vaccine formulations can be crucial in augmenting injection safety in countries with weaker health service systems [9]. The Global Training Network (GTN) is another initiative that works towards strengthening safety through capacity building of regulatory authorities, national reference laboratories, vaccine producers (in the matter of Good Manufacturing Practice), post-marketing surveillance, and AEFI monitoring and management [10].

The Uppsala Monitoring Center

The WHO Collaborating Centre for International Drug Monitoring, popularly known as the Uppsala Monitoring Center, with 100-plus members has the international perspective of vaccine safety (within the fold of patient safety) as an important agenda [11]. VigiBase™ provides information through its AEFI database and is increasingly accessible in different languages [12]. The Vaccine Safety Specialist coordinates with other countries in the Global Network for Postmarketing

Surveillance of Newly Pre-qualified Vaccines. China and India are two of the largest countries with which close cooperation is emerging. It has been a partner to the WHO department of Immunization, Vaccines and Biologicals (IVB) in the development of the "Blueprint" project, which aims at improving vaccine pharmacovigilance globally in a sustainable manner. It seeks to develop vaccine safety assessment and response systems at global, regional, and country levels. With a focus on low-income countries, it seeks to define the indicators of a minimal capacity for ensuring vaccine safety through a coordinated effort of the major stakeholders [13].

AEFI: Surveillance and Management Challenges

Vaccines, largely a public good, can nevertheless cause unintended harm—through unwanted, adverse events. AEFIs are mostly minor, but some can be serious in nature and even fatal. Surveillance and management of AEFI is important programmatically in order to increase acceptance. It transcends programmatic pragmatism and ought to be considered as an ethical imperative.

AEFI is *defined* as any adverse event that occurs after a vaccination, which might be related to the vaccine itself or to its handling or administration [14]. Death, life-threatening illness, requirement of hospitalization or a condition resulting in permanent disability is considered a *serious* adverse event. Not all such events are however caused by vaccines. It is critical to take note of the fact that while the event and the act of vaccination has a temporal relationship, it is not necessary causal and indeed requires rigorous investigation to establish such a relationship. Such processes are understandably complex in nature and often more so in developing country contexts.

AEFI *surveillance strategies* typically consist of:

- Monitoring trends of known adverse events.
- Detecting new, unusual or rare vaccine adverse events.
- Determining patient risk factors for particular types of adverse events.
- Identifying vaccine lots with increased numbers or types of reported adverse events.
- Monitoring adverse events after the marketing of newly introduced vaccines.

Passive surveillance systems are based on voluntary reporting by vaccinees visiting heath service institutions or by healthcare or health service providers, even if there is uncertainty about whether the event is caused by vaccination. Passive AEFI surveillance systems are thus prone to (1) variability on reporting standards, (2) reporting bias, and (3) underreporting.

Experiences of AEFI Management from Across the World

Al Awaidy et al. [15] documented the experience of a decade (1996–2005) of AEFI surveillance in *Oman*. The country has a system of notification of all adverse events

within 24 h. During the decade, 790 reports were received for about seven million doses of vaccine that were administered. The reported rate for all types of vaccines was 10.8 per 100,000 doses administered to children below 6 years of age. This compared well with the rates for the USA (11.4 per 100,000 doses) and Australia (11.8 per 100,000 doses for children below 7 years) [16, 17]. The analysis did rule out underreporting on account of a passive reporting system [18]. In general, little difference among sexes was reported and if any, a higher prevalence was noted among females. In Oman, however, higher preponderance of adverse events occurred among males; a marker of differential access of health services by gender of the child.

The polio eradication campaign began in *Uganda* in 1996. National Immunization Days (NIDs) were held during August–September 1997, which coincided with the beginning of the malaria season. A number of child deaths were claimed to be linked to the Oral Polio Vaccine (OPV). While epidemiological analysis put it to a spurious association, in popular impressions, the association was causal. Poor social mobilization, lack of involvement and micro-planning of health workers in the NID, and lack of appropriate information among parents resulted in a decline in routine immunization coverage in 1998. Parents were not proactively contacted after the coincidental deaths. This lack of information created fertile ground for the anti-vaccine opposition, leading to circulating rumors. This underscores the necessity to provide timely and adequate information to parents about both the benefits of vaccines and about AEFI [19]. Later in 1999, a radio channel started broadcasting anti-OPV messages. Program managers were able to counter the rumors and inform communities about immunization, including the possibility of adverse events. This was done through a survey of people's knowledge, attitudes and perceptions of immunization and broadcast messages through multiple channels.

Such setbacks are not the exclusive preserve of low- and middle-income countries. DPT coverage in *Sweden* declined dramatically from 90 to 12 % in a space of 5 years following the adverse observations of a key medical personality. The government reconsidered the policy in 1979 and withdrew the pertussis vaccine; this resulted in a pertussis epidemic with more than 10,000 deaths in a year [20].

Following a national school-health campaign in *Jordan* in 1998, more than 800 school children believed they had suffered from the side-effects of tetanus–diphtheria toxoid (Td) vaccine administered during the campaign. With the first reports of the adverse events coming in, the campaign was put on hold. However, the news spread across the country and resulted in a mass panic among parents. The AEFI investigations concluded that the symptoms did not result from the vaccine and attributed it to mass psychogenic illness ("hysteria"). Only ten cases were established to have been true AEFI, not outside the expected range. Following the investigation, the campaign was restored [21].

Following epidemics of meningococcal disease in *Burkina Faso* in 2003 a major vaccination campaign was undertaken. The opportunity was also used to set up an AEFI surveillance system. There was no routine surveillance system and the

process was set up during the campaign to (1) assess the occurrence of AEFI temporally associated with the trivalent vaccine and (2) to obtain safety data to help develop recommendations for expanded use of the trivalent vaccine. Fever, as a sole adverse event or in association with other events emerged as the commonest adverse event. Serious AEFI was found to be about 1.5 cases per 100,000 doses including neurological complications and a death. The district reporting the highest AEFI rate had fewer serious events; this was attributed to higher educational status in that district and consequent high reporting. Interestingly, even with a passive surveillance system, AEFI rates were comparable to those associated with use of meningococcal polysaccharide vaccines in other countries with well established adverse event monitoring systems [22].

AEFI Surveillance in India: A System Is Born

The Ministry of Health and Family Welfare has recently instituted an elaborate mechanism to address the issue of AEFI, which is being rolled out across the states. India is a diverse country and the infrastructure and responsiveness of the public health system varies a lot. The private sector is also large and its regulation generally leaves much to be desired. Though immunization rates have been consistently on the rise, weaknesses of the health service system can, in part, be responsible for adverse events; societal and cultural concerns can also be a significant issue. The implementation of the measures for coping with AEFI will thus be fairly challenging.

Classification

For the national program, AEFI has been classified as follows (Table 23.2):

Table 23.2 Classification of adverse events following immunization [23]

Type of AEFI	Definition	Example
Vaccine reaction	An event caused or precipitated by the active component or one of the other components of the vaccine, due to inherent properties of the vaccine	Anaphylaxis due to measles vaccine
Program error	An event caused by an error in vaccine preparation, handling or administration	Bacterial abscess due to unsterile injection
Coincidental	An event that occurs after immunization but is not caused by the vaccine	Pneumonia after polio vaccination
Injection reaction	Event from anxiety about, or pain from the injection itself rather than the vaccine	Fainting spell in a teenager after immunization
Unknown	The cause of the event cannot be determined	

Table 23.3 Common minor vaccine reactions [13]

Vaccine	Local reaction (pain, swelling, redness)	Fever	Irritability, malaise, and nonspecific symptoms
BCG	Common		
Hepatitis B	Adults up to 30 % Children up to 5 %	1–6 %	
Measles	Up to 10 %	Up to 5 %	Up to 5 %
OPV	None	Less than 1 %	Less than 1 %
Tetanus	Up to 10 %	Up to 10 %	Up to 25 %
DPT	Up to 50 %	Up to 50 %	Up to 60 %
Treatment	Cold cloth at the injection site Paracetamol	Extra oral fluids Cool clothing Tepid sponging/bath Paracetamol	

The frequency of common minor vaccine reactions were reported as follows (Table 23.3). It is understood that the rates may vary somewhat with the vaccine, e.g., reactions to acellular pertussis vaccines are lower than to the whole cell pertussis vaccine.

In developing nation contexts (as in India) vaccines are largely delivered through programs (both in institutions and outreach sessions) rather than the clinics of pediatricians. Program errors are thus an important issue to reckon with. The commonest program error in developing countries is infection caused by unsafe/non-sterile injections; a study in India found nearly three-fourths of all injections associated with immunization to be unsafe [24, 25]. These are manifested as: local reactions (suppuration, abscess); systemic effects (sepsis, toxic shock syndrome); and, blood-borne viral infections (Hepatitis B and C). Inadvertently used chemicals or drugs as diluents (for freeze-dried vaccines) or directly injected (erroneously as vaccines) also result in adverse events. Other not infrequent errors include ignoring contra-indications of a vaccine or injecting vaccine to an individual for whom it is not intended (for example, wrong age). *Staphylococcus aureus* contamination of vaccines is commonly manifested as local tenderness, tissue infiltration, vomiting, diarrhea, cyanosis and high grade of fever. Availability of the vaccine vial is critical for ascertaining bacteriological contamination.

Prevalence surveys, such as the National Family Health Surveys, reveal that about a third of all children (eligible for vaccination) are ill during any recall period, the commonest conditions being acute diarrheal diseases and respiratory infections [26]. Not surprisingly, any illness that follows the immunization ends up being attributed to the vaccine. With large numbers of children being immunized, such coincidental events are fairly common. Sometimes attention may even be drawn to

a congenital condition and linked to the vaccine. Cultural constructs around injections are also challenging to reckon with. Injection reactions such as fainting, lightheadedness, giddiness, dizziness, tingling around the mouth/hands and breath-holding (leading to unconsciousness) can be linked to vaccines. Overcrowding in outreach sessions is another important challenge to reckon with. This can lead to both program errors and injection reactions. The relevance of micro-planning of sessions cannot be over-emphasized.

Investigation and Management

Serious AEFIs are defined as adverse events that are life threatening and result in hospitalization (including prolonged hospitalization), disability (or with a potential for disability) or death. AEFIs caused by program errors, those occurring in clusters and serious effects within 30 days of vaccination can be parental and community concerns and have been accorded high priority within the program. A cluster of cases has been defined as two or more cases of the same or similar event, which are related in time, and have occurred within the same district or geographical unit, or associated with the same vaccine, same batch number administered or same vaccinator [27].

It is the responsibility of the frontline healthcare workers to inform parents and guardians about mild AEFIs and encourage them to report these to the local health workers or the Primary Health Center (PHC). Health workers are also required to follow up all children and mothers immunized during the previous session. This remains one of the weakest links. The Medical Officer of the PHC is responsible for investigating any concern or event in connection with vaccination and file the First Information Report (FIR) for serious events. Reportable AEFIs are to be brought to the attention of the District Immunization Officer (DIO) and the vials and syringes sent under cold chain in case of any death. There is also the provision for conducting an autopsy should it be required. A “NIL” report is also to be filed every month in case there were no AEFIs. Regional Investigation Teams (RIT) have been formed and are located in the main referral hospitals in a region. Serious AEFIs are investigated by the RIT and the DIO, and a Detailed Investigation Report (DIR) is prepared. Vials and syringes are to be sent to the Central Research Institute for laboratory investigations. Private practitioners, hospitals, and professional associations (such as the Indian Academy of Pediatrics) are also being sensitized to improve reporting (Fig. 23.1).

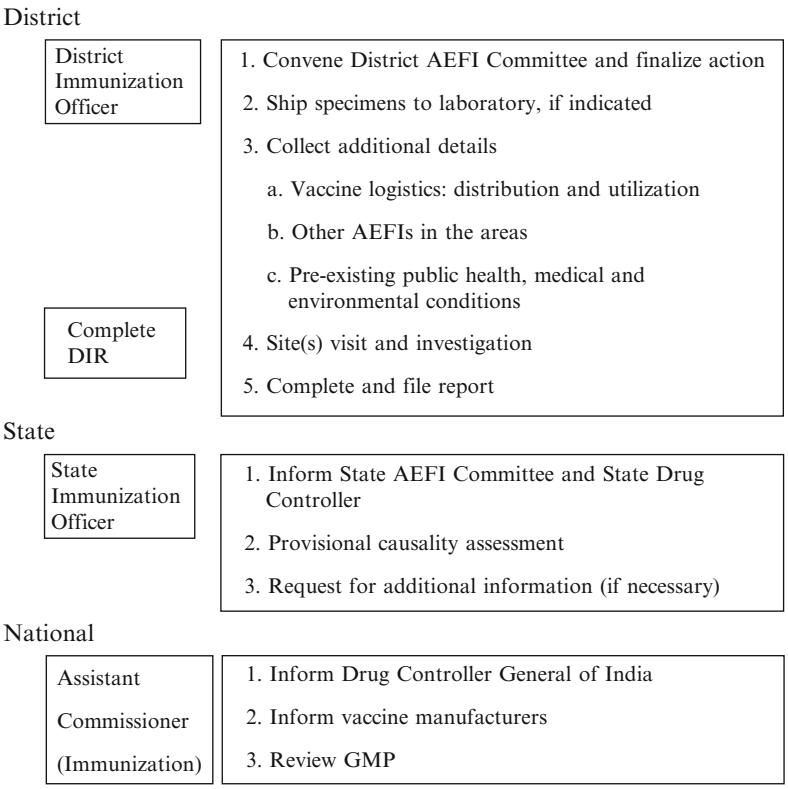

Fig. 23.1 Preliminary investigation report: Routing timeline and actions

The guidelines for sampling of clinical materials are as follows (Table 23.4):

Table 23.4 AEFI sampling guidelines

Event	Specimen from patient	Vaccine, diluent, syringe and needle sample
Severe local reaction		
Abscess	Swab, blood	Yes
Lymphadenitis	Blood	Yes
CNS adverse event		
No paralysis	CSF, blood	Yes
Paralysis	Stool	Yes
Anaphylaxis, toxic shock	Blood, blood culture	Yes
Death	Postmortem tissues	Yes

Some Ongoing Vaccine Controversies in India

Anti-leprosy Vaccine

The anti-leprosy Mw vaccine has been in consideration for some years and protective efficacy has been reported among household contacts [28]. The Mw vaccine issue is additionally complex since it is both therapeutic and prophylactic. Trials of anti-leprosy vaccine are typically long-drawn interactions (5–7 years) between the researchers and the users requiring a process of sustained motivation. The objective was to ascertain whether the Mw vaccine could change the immunological status of the most virulent type of leprosy. Four hundred and twenty-one patients were enrolled in a Phase III clinical trial to determine whether the vaccine (as an adjunct to multi drug therapy) could expedite the treatment and improve the immunological status of leprosy patients. Immunotherapeutic effects were reported with faster bacterial clearance and hastening of clinical recovery.

Tandon and Kumar analyzed the process of the trial arguing that beneficiaries ought to be located in different social contexts and not merely participants with interaction between the different sets of actors: clinicians, patients and contacts of the patients [29]. They found that notions of trial and experiment were part of the technical discourse and not understood in that context by recipients. For the patients, the clinic represented a set of doctors offering effective treatment. The trial however offered not only better medical care but also treatment for ailments other than leprosy and financial incentives to provide access to the poor. Patients accepted the vaccine from a position of trust; this has been construed as misuse of trust in the framework of bioethics. The notion of consent emerged to be relatively fluid and specific to the context. The vaccine was offered as an adjunct to Multidrug Therapy; the patients therefore responded not specifically to the trial but to the biomedical applications of a different nature than what was normally available to them.

Antifertility Vaccine

The anti-hCG vaccine, an immunological contraceptive has been researched for quite some time. Two groups—the Indian group at the National Institute of Immunology (NII) and US group at the University of Ohio have been the main contenders. The controversy over these vaccines has been analyzed in the light of women's health movements against new contraceptive technologies [30]. The WHO has closely supported the anti-hCG vaccine research at the University of Ohio. The Task Force on Immunological Contraceptives is also an important factor, among several others [31].

It was critiqued that the NII team did not conduct necessary animal trials; an additional controversy was the pregnancy of two women participants. The use of whole ß-hCG was likely to cause reactions with hLH which shares a similar ß-subunit, leading to adverse effects such as disturbances in the menstrual cycles

[32]. WHO was criticized for its conflicting positions on these two vaccines; cautioning NII on the risks of antibodies being manufactured against a self-protein while the Ohio vaccine was also based on the same principle. WHO guidelines for toxicology and animal studies for immunological contraceptives was formulated in 1978; both the vaccines had began human trials earlier in the 1970s. The NII study reportedly did not reveal complete information to the immunized women regarding the potential risks. The feminist perspective opposed the notion of treating pregnancy as a disease and therefore controlling as such [33].

HPV Vaccine

The controversies around the Human Papilloma Virus (HPV) vaccines centers round two major concerns:

1. Efficacy of the vaccine and the relevance of its induction into the routine immunization program of developing nations.
2. Concerns regarding the safety and efficacy of the HPV vaccines; the unethical promotion of the vaccines in the private and public sectors; the public health implications of their administration; the need to investigate reported deaths and adverse events post vaccination; and the consequences if the vaccines were introduced into the country's universal immunization program.

The age-standardized incidence rates of cervix cancer exceed 25 per 100,000 in developing countries (lacking screening programs) compared to 3–8 per 100,000 women in developed countries. While the HPV vaccines hold great promise, developing countries face significant operational challenges: high costs; feasibility and acceptability (pre or early adolescent girls); logistics (three doses over 6 months); and, long-term immunogenicity and efficacy (effective against certain subtypes and for a limited number of years, and the requirement of boosters) [34].

Much of the current controversy in India has been around the HPV trials under the public–private-participation model (PATH, Indian Council of Medical Research and the state governments) in two states [35]. There were seven recorded deaths during the trials, but without any conclusive evidence of causality [36]. The major issues were detailed in an exposition by Sarojini et al. [37, 38].

- Adolescent girls were selected from some of the most vulnerable communities: scheduled castes, scheduled tribes and religious minorities. Some of the girls were internally displaced populations owing to armed conflict in a neighboring state, adding to the vulnerability.
- Healthcare services on the ground are extremely poor and the girls were selected without any specific inclusion and exclusion criteria and uncertainty about long-term follow up. There were no mechanisms for reporting adverse events. Hardly any institution in the public healthcare system had Pap-smear testing facilities and gynecologists were few and far between.

- Trial subjects in many cases were residents of boarding schools for tribals. The girls were asked to obtain consent from their parents and sometimes the form was not in the local language. With the immunization card carrying the logo of the National Rural Health Mission, many parents got the impression that this was part of the routine immunization program.
- The subjects were not apprised of any adverse effects nor were they aware of the right to refuse.

Pentavalent Vaccine

The debate surrounding the introduction of the pentavalent vaccine is seemingly at two levels. First, the relevance of its inclusion in the Universal Immunization Program (UIP) and secondly, in case of its introduction, whether the vaccines are to be administered separately or together. The pentavalent vaccine will protect children from diphtheria, pertussis, hepatitis B and *Haemophilus influenzae* type b (Hib) and was introduced in the routine immunization program in the small coastal state of Goa in 2008, without any reports of adverse effects. During the next step of scaling up, the introduction in the states of Kerala and Tamil Nadu (selected on account of their strong network and performance of public health services) was noted for the criticism of the potential side effects of the vaccine and public interest litigations filed in the courts.

The vaccine was used in Sri Lanka in January 2008 but was withdrawn in April 2008 because of 25 serious adverse reactions including five deaths. The WHO expert panel investigating the adverse events concluded that the vaccine was "unlikely" to be responsible. While it did not state categorically that the adverse events were unrelated to the vaccine, conclusive evidence regarding an alternate cause was missing [39]. Critics argued that the WHO report was inappropriately cited to suggest that investigations did not establish a causal relationship between the events and the vaccine [40].

The National Technical Advisory Group on Immunization (NTAGI) was established by the Ministry of Health in 2002 to make evidence-based decisions. The NTAGI concluded that Hib disease burden was sufficiently high in India to warrant immunization and recommended the liquid pentavalent formulation to replace the DwPT vaccine on account of ease of staff training and vaccine delivery. There are established mechanisms under the National Regulatory Authority (NRA) for quality assurance and purchasing mechanisms within the Immunization Division to prevent profiteering [41, 42]. Those questioning the inclusion of the Hib component argued that mortality in under-5 children in India due to bacterial pneumonia and meningitis was negligible citing the detection of low levels of incidence in both hospital and community-based studies. Members of the NTAGI have argued that pentavalent (in rich countries with DaPT, in low income countries with DwPT) or even hexavalent (with inactivated poliovirus vaccine) vaccines are safe and currently used in over 150 countries. The conflicting positions continue till date.

Meanwhile, the pentavalent vaccine manufactured by an Indian company had its vaccines recalled after detection of white sediments by the WHO. The company is making changes to the manufacturing process and is in the process of bringing the vaccine back to the market [43]. Emerging manufacturers from developing countries have joined together to form the Developing Countries Vaccine Manufacturers' Network (DCVMN) [44]. Access to and transfer of technology is critical for this initiative to succeed and the pentavalent vaccine is one of the important target vaccines in the agenda of this collaboration.

Vaccine Hesitancy and Resistance: The Case of Polio Eradication

The polio eradication campaign in India (and several other countries) has been marked by hesitancy to repeated vaccinations and social resistance to the oral polio vaccine (OPV) [45]. There were several reasons why children (including infants) were missing the pulse polio doses. Some were missed on account of their being physically absent from their homes while accompanying parents to the agricultural fields; others kept away from the immunization rounds on account of their past experience of adverse effects. Newborn babies and sick children were kept at home during vaccination days and not administered the vaccine during home visits by health care workers [46].

The resistance spread largely through rumors. Chaturvedi et al. while deconstructing the rumors noted that although they had strong religious overtones, they also reflected the tensions of marginalized communities (Tables 23.5 and 23.6) [47].

While resistance was generally reported among Muslims, the phenomenon was not uncommon for Hindu areas as well. As far as newborns were concerned, both the communities behaved alike, not immunizing the newborns until birth-related rituals were over. Instances of previously sick children dying (coincidentally) after vaccination contributed to resistance. The problem was the most intense in peri-urban poor areas rather than in better-off urban areas or rural areas. Well-off families including doctors also refused the pulse doses as routine immunization was administered by their family physicians or practicing pediatricians. Linking acceptance of the vaccine to developmental issues was becoming increasingly common. These issues, ranged from the supply of essential goods in Public Distribution Shops (PDS) to construction of roads and bridges, and were raised by both Hindus and Muslims. There was confirmation about coercive measures being adopted by the health services and the general administration to enforce the program, as has been the experience with other eradication programs such as the smallpox eradication program [48]. It was realized that the critical path to success may lie in overcoming social resistance to available interventions and the social mobilization strategies in addition to vaccine innovations have borne positive results [49].

Table 23.5 Nature and content of rumors

Nature	Content
Negative effects of vaccine	Causing sterility/impotence
	Causes shortening of penile length even in children
	Starts showing its negative effects even after 2 doses
Undesirable constituents of the vaccine	Contains pig's fat/meat
	Is pink in color because of pig's blood
	Is prohibited (*Haraam*) for Muslims
Conspiracy/community under siege	Different vaccines are being used for Muslim populations
	Muslims are being specifically targeted through an American conspiracy
	Vaccines have been manufactured by the Jews, and the US machinery is using them to finish Muslims
Haj vaccination policy	Saudi Government requires that *adults* are vaccinated. Why then do the international authorities specifically target our *children*?
Suspicion and cynicism	Generally no one cares for us. Why are they so much interested in getting our children immunized with this vaccine?
	Sudden and intense involvement of WHO and other international agencies speaks for itself

Table 23.6 Emerging model of rumors

Phenomenon 1

A low-profile and highly local spate of rumors start gathering right before a pulse round

Phenomenon 2

The rumors are often supported by one or more of the following:

Locally circulating religious leaflets and magazines, that are often disowned by the sources
Locally restricted announcements through static and mobile public address systems
Address by a religious leader inside a religious place after a prayer ceremony
Quasi-confirmed religious edicts, that are often disowned by the sources

Phenomenon 3

The nature and content of rumors keep changing with time and locale

Phenomenon 4

When the rational constituents of the society try to reach out for the sources of rumors, they either go incommunicado or dissociate themselves from the episode. Public retraction/contradiction is never seen

Phenomenon 5

In spite of all this, most of the families in minority areas support the pulse rounds. Only a few parents among them, mostly from extremely marginalized sections, are decisively influenced by the rumors

Phenomenon 6

Through social osmosis, these rumors do reach untargeted audiences as well, and some economically and socially marginalized clusters from majority communities are affected. However, they seldom translate into a significant and lasting resistance

Table 23.7 Tensions in the polio eradication program

Short-term eradication expectations	↔	Long-term culture, community, social norms, and values change processes
Global goal	↔	Community listening
Polio	↔	All other development issues
Global strategies	↔	Local contexts
Technical wisdom	↔	Social and cultural wisdom
Global control	↔	Local control
Coherent consistent messages	↔	Responding to local dynamics

Vaccination programs by their very nature are a melting point of tensions spanning across diverse domains. Feek summarized these as follows (Table 23.7) [50]:

Conclusions

Making vaccination safe is an ongoing challenge in all situations and more so in developing countries. The constraints of weak general health services impacts upon immunization programs and health service strengthening is rightly a thrust area in the Decade of Vaccines Collaboration. Vaccine controversies in these contexts are as much about scientific debates as about differing social and cultural perceptions of technologies. As developing countries and transition economies embark upon including newer vaccines beyond the conventional universal immunization program (often dichotomized as EPI and non-EPI vaccines) questions are likely to be asked. These require honest and scientific answers with regard to both safety and epidemiological need. Vaccines are often construed as both a moral and global good. Societies that are increasingly marked by inequities and identity assertions are fertile ground for controversies around vaccines. As seen with the polio experience, eradication/elimination programs bring forth additional administrative thrusts and adverse responses in populations deprived of effective and responsive routine health services. Forthcoming campaigns such as measles elimination would do well to learn the lessons and factor in social implementation issues rather than build them post hoc. Simultaneously, the AEFI surveillance and management units need to be scaled up to be responsive systems that can cope with real and perceived concerns of vaccine safety. Building globally trusted and responsive immunization programs is thus both a matter of making vaccination safe and a public health ethics imperative.

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Chapter 24
An Infection Prevention Perspective on Immunizations

Sharon Plummer

Introduction

The Quality of Health Care in America Committee of the Institute of Medicine has (IOM) concluded that it is not acceptable for patients to be harmed by the health care system that is supposed to offer healing and comfort—a system that promises, "First, do no harm," [1] and also to ". . . devote myself to the welfare of those committed to my care." [2]. The responsibility of an Infection Preventionist in an acute care hospital is infection transmission safety for patients, their families, visitors, health care personnel (HCP), volunteers, and facility staff [3]. HCP is defined here as the Centers for Disease Control and Prevention (CDC) does in *Immunization of Health-Care Personnel*: "All paid and unpaid persons working in health-care settings who have the potential for exposure to patients and/or to infectious materials including body substances, contaminated medical supplies and equipment, contaminated environmental surfaces, or contaminated air" [4]. The Infection Prevention (IP) program should provide the best available education, information, support, and equipment needed to protect all individuals at the facility from acquiring or transmitting infectious diseases. Ludwick and Silva referred to the public's perception of and trust in nurses as patient advocates, and opened up discussion around some of the issues concerning this trust, ethics, and IP [5].

In the USA, at least one state, New York, requires Infection Control Education every 4 years for specific HCP who have to relicense including, but not limited to nurses, medical residents, medical students, and dentists. One of the goals of this state-mandated training is to "Help professionals recognize their responsibility for assuring that they, and those for whom they are responsible, apply scientifically accepted infection control principles as appropriate to their work setting and minimize the opportunity for transmission to patients and employees" [6].

S. Plummer, RN, BS, CIC (✉)
101 Pelican Drive, Council Bluffs, IA 51501, USA
e-mail: sharon.plummer@cox.net; sharon.plummer1@gmail.com

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IP should not just be a desk, an office, or a staff responsibility. It is most effectively a fostered, facility-pervasive culture of safety, supported and directed by administration: safe care of the patient being the primary concern and focus for everyone at the facility.

Infection Prevention Recommendations and Practice

IP recommendations for practice are based on the scientific principles of disease transmission, and are recommended by the CDC [7], other recognized experts in infectious disease, such as those communicated in *The Red Book®: The American Academy of Pediatrics Report on Infectious Diseases;* Society for Healthcare Epidemiology of America (SHEA); Infectious Diseases Society of America (IDSA); Association for Professionals in Infection Control and Epidemiology (APIC); and supported by the Joint Commission (JC) and American Medical Association (AMA). The roles, responsibilities, systems, techniques, and methods for Infection Preventionists' practice are discussed in detail in the *APIC Text of Infection Control and Epidemiology* [8].

Administrative support is primary to an effective IP program for funding, support, and to implement IP recommendations. The results of all surveillance outcomes in turn should be reported back to administration and those who can affect facility change for practice, performance improvement, and performance sustainability. "Surveillance is defined as the ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health" [9]. Surveillance must be maintained for Healthcare Associated Infections (HAI); and should be sustained to monitor compliance with hand hygiene; Isolation and Standard Precautions (SPs); environmental and construction IP standards; cleaning, disinfection and sterilization. Employee or Occupational Health liaison and collaboration with IP is necessary to promote facility staff policies relating to immunizations, antibiotic prophylaxis, exposures, restriction from duty for transmissible diseases [10] including tuberculosis [11], and meeting mandates from the US Occupational Safety and Health Administration (OSHA, the government agency that regulates safety for employees by federal law) for blood/body fluid exposure including sharps safety and injury prevention [12].

Written IP policies and procedures are vital to sustaining consistent practice. These should be developed with science- and evidence-based recommendations, researched with due diligence, reviewed periodically and approved by the IP Committee, Employee or Occupational Health, Administration, Human Resources, Medical Staff, and others as applicable. Policies and procedures applied equitably throughout the institution are the best legal and ethical protection for a facility when practice is questioned. Written policies and procedures set the standard for care in the facility, and can be used as a basis of practice by all HCP. In addition to being required for regulatory, statutory, or facility issues, appropriate and available written

policies and procedures assist in decision-making, provide a framework for consistency of practice, and pathways for efficacious work-flow system navigation [13]. Michele LeBourgeois states, "The purpose of a policy or health care procedure is to provide standardization in daily operational activities. Policies and procedures provide clarity when dealing with issues and activities that are critical to health and safety, legal liabilities, and regulatory requirements that have serious consequences" [14]. IP strategies include hand hygiene; respiratory and cough etiquette; Standard and Transmission-Based Isolation Precautions; cleaning, disinfection, sanitization, and sterilization; antibiotic prophylaxis and stewardship; and immunizations.

Hand Hygiene

Hand hygiene is the single most important practice to control and prevent the transmission of infectious disease and organisms [15]. In her 1859 *Notes on Nursing*, Florence Nightingale's hand hygiene guidelines were, "Every nurse ought to be careful to wash her hands very frequently during the day. If her face too, so much the better" [16]. Hand hygiene guidance and recommendations now exceed a combined 300 pages in the CDC recommendations of 2002 and the World Health Organization (WHO) recommendations of 2009. From personal experience, one of the most difficult aspects of hand hygiene, was and continues to be, implementing and sustaining the recommendation for short natural nails with no nail polish or nail enhancers such as artificial nails for HCP providing direct or indirect patient care [17]. Hand hygiene can be achieved with 15 seconds of either soap and water hand washing [18] or hand sanitization with an alcohol-based product with a minimum of 60 % alcohol [19]. In acute care: "Clean In, Clean Out" should be observed, meaning that anyone entering or leaving a patient room should practice hand hygiene regardless of glove-wearing. Even with sustained rigor in promoting hand hygiene, rates fall far below 100 %. In one 2010 study, hand hygiene rates were found to be "near or below 50 % . . ." [20]. Even with extensive return demonstration education, sustained and rigorous monitoring, feedback to the IP Committee and individual units and groups, and strong administrative support, rates at one hospital ranged from 30 to 72 % [21]. This is similar to the 25–70 % rate (depending on staffing) reported in 2002 in the MMWR [22]. Decreased hand hygiene is implicated in increased HAIs and outbreaks [22]. Facts to think about: how long can bacteria remain viable on unwashed hands? Just one example, vancomycin-resistant Enterococci (VRE), have been proven to be viable for up to 60 min [23].

Transmission-Based Precautions

Transmission-Based Isolation and SPs are not force-fields of infectious disease protection invoked by a room sign, care plan note, or Licensed Independent Practitioner

(LIP) order, but recommendations for HCP practice. Such practice includes use of personal protective equipment (PPE), engineering devices, and work practices to reduce the risk of acquiring or transmitting infectious diseases or organisms while caring for a patient who is known or suspected of being infected or colonized with an infectious agent. Engineering devices include sharps disposal per OSHA standards. Work practices include not recapping needles and using safety-shielded needles. PPE includes, but is not limited to, moisture resistant gowns, masks, goggles or shields, and gloves. PPE must be donned, used, and discarded appropriately to provide protection to the wearer. SHEA and IDSA [24], the CDC [25], OSHA [26], and the WHO [27] have published guidelines and recommendations for these practices. Transmission-Based Isolation Precautions are based on how the disease or organism is transmitted: by respiratory Droplets, Contact, or Airborne.

Transmission-Based Isolation Precautions in an acute care setting should be instituted for signs and symptoms of infection, as well as a known or suspected diagnosis or if infectious disease testing is ordered. SPs include Universal Precautions (UPs). CDC SPs promote practices that treat all body fluid, secretions, mucous membranes and non-intact skin, and excretions excluding sweat as potentially contaminated with transmissible organisms and recommend using appropriate PPE and practices. The use of SPs applies in reverse to protect patients from HCP who may be contagious. OSHA's UPs are defined as precautions to prevent potential exposure to blood, bloody body fluids, and high-risk body fluids which can transmit blood-borne pathogens. A commonly used informal definition of SPs: "If it is wet and warm and not yours, put a barrier between you and it". It can also be added: "If it is wet and cold and not yours, put a barrier between you and it." The originator of this quote is lost in time, but a debt of gratitude is owed. Efficacious Isolation and SP practice requires continuing education, skill validation and monitoring, as well as feedback.

Respiratory and Cough Etiquette Precautions [28] remind everyone to contain their own secretions with instructions to "Sneeze in Your Sleeve" [29] or disposable tissue to avoid contaminating the environment by appropriately disposing of the tissue and washing or sanitizing hands. Most facilities have some signage and hand sanitizer available outside patient rooms. The Children's Hospital and Medical Center in Omaha, NE, USA, has both free-standing and wall-mounted stations, each containing adult- and child-sized masks, disposable tissues, and alcohol-based hand sanitizers with written and illustrated instructions throughout the facility especially at entrances. The signage is the "Cover Your Cough" stick figure signs from the Minnesota Department of Health available on the Internet [30]. Adults are expected to contain their own secretions and practice good hygiene, but this is not expected of children. Thus, the burden of IP for pediatrics falls on the caregivers.

Environmental IP

Reducing the bioburden by disinfecting and sterilizing non-disposable equipment between each person is of paramount importance for shared environment, equipment, and invasive procedures. Environmental surfaces can act as fomites, a contact

bridge to transmit organisms. From an IP perspective, one-patient: one-use is the safest. It is not always the most cost-effective, and/or disposables may not be available, so policies and procedures for non-disposable, multiuse items must be in place to safely use these items without transmitting infectious organisms or diseases. The people who perform these functions are specialty trained, some go into patient rooms, and all need to be present and healthy to fulfill their functions. The CDC has published guidance and direction on environmental IP in the 42 page *Guidelines for Environmental Infection Control in Health-Care Facilities* [31]. Environmental IP is becoming increasingly important as more information is known about how long organisms survive environmentally and can cause disease if contacted. In one study, VRE and methicillin-resistant *Staphylococcus aureus* (MRSA) were found to survive days to months after drying on textiles [32]. Survival of microorganisms in the environment or on fomites is dependent on environmental conditions including temperature, humidity, and the type of surface [33].

A short, simplified list of why laundry, environmental service cleaning and disinfection are important in the prevention of disease and organism transmission:

- *S. aureus*: can remain viable, in room temperature on uncleaned, undisinfected environmental surfaces for hours to a week, and on unwashed textiles (such as lab coats, scrubs, privacy curtains, and clothes) for days to months [32].
- Influenza virus: can live on uncleaned, undisinfected environmental surfaces (such as phones, keyboards, and pagers) between 2 and 8 h, some reports indicate as long as 48 h [33].
- RSV (Respiratory Syncytial Virus): may remain viable for 6–8 h on environmental surfaces [34].
- Enterococcus: can live up to 90 days on unwashed textiles [32].
- Hepatitis B Virus: can survive outside the body at least 7 days and still be capable of causing infection [35].
- Measles: can remain viable for 2 h in the air and on uncleaned, environmental surfaces [36].

Antibiotic Stewardship

The primary goal of Antibiotic Stewardship is improved patient outcome and care. The eight rights of all medication administration are: the right medication, right patient, right dose, right time, right route, right reason, right response, and right documentation [37]. All of the eight rights with the addition of the right duration are assessed and monitored as part of an effective Antibiotic Stewardship program [38]. Eliminating unnecessary antibiotic use could reduce the antibiotic pressure to which the emergence of Multidrug-Resistant Organisms (MDROs) has been attributed [39]. Currently it is recommended to use antibiotics to prevent illness after a significant exposure to some infections, such as pertussis, *Neisseria meningitidis*, and *Haemophilus influenzae* type b (Hib). Appropriate immunization could contribute to antibiotic stewardship by decreasing the need for antibiotic prophylaxis for these

vaccine-preventable diseases. Collaboration between Employee or Occupational Health and IP for HCP infectious disease exposures is essential, the follow-up is time consuming, and the cumulative cost of prophylaxis can be expensive.

Summary of IP Practice

All of these IP practices require sustained education, skill validation, monitoring of practices, and rigor in enforcement. All are dependent on each individual practicing correctly, every time, all the time. Perhaps a better goal would be to decrease the transmissible diseases and organisms for which these actions are necessary, by immunizing against diseases for which vaccines are available.

Vaccine Preventable Diseases

Immunizations provide individual, cocoon, and herd immunity within a population which receives appropriate vaccination. Many individual stories about mortality and morbidity due to vaccine-preventable diseases are available. Texas Children's Hospital has published a booklet with photographs and moving, persuasive individual stories of those who have suffered from vaccine-preventable diseases [40]. The Immunization Action Coalition also has stories about vaccine-preventable diseases under "Unprotected People Reports" among a plethora of immunization information and assistance [41].

Immunizations are currently routinely available for 16 diseases: Diphtheria, Hib, hepatitis A, hepatitis B, human papillomavirus, influenza, measles, meningococcal disease, mumps, pertussis (whooping cough), pneumococcal disease, polio, rotavirus, rubella, tetanus, and varicella. Immunization schedule recommendations can be found on the CDC Web site. An excellent in-depth disease and vaccine description can be found in the "Pink Book" [42]. The success of immunizations in decreasing reportable vaccine-preventable diseases from 1967 through 2009 was published in 2011 [43].

Hib

A dramatic example of immunization efficacy is when the Hib vaccine became available in 1985 for children 18 months of age and older, and subsequently for those as young as 6 weeks of age in December 1987 [44]. Before the vaccine, the Children's Hospital in Omaha, NE, USA, reported, as required by law, about 40 patients hospitalized with invasive Hib disease yearly to the Health Department (personal experience). After the vaccine became available, only five cases were

reported in the first year, and 0–1 a year thereafter (personal experience). Omaha seems to be a vaccine-aware city, possibly because of the polio epidemic and subsequent immunization success in eliminating this much-feared disease; and also possibly because of the influence of two local medical schools. However, a much-publicized case of a child who survived Hib meningitis but with extensive, quality-of-life limiting sequelae, certainly helped spur public awareness and physician advocacy of this vaccine locally [45]. Before the vaccine, the only preventive strategies in an acute care setting were to practice Droplet Precautions and provide antibiotic prophylaxis to those significantly exposed. The 2011 *Pink Book* states that the incidence of invasive Hib disease "has declined by more than 99 % compared with the Prevaccine era" [46].

Pertussis

Pertussis or whooping cough is preventable, but has a high mortality and morbidity rate, especially among infants. Adults and adolescents have waning immunity from their "baby shots" which do not start until 2 months of age. A neonate born at or after 28 weeks gestational age may carry maternal antibodies against pertussis, but unless the mother is recently immunized, the newborn may be susceptible from birth to pertussis. Adults and adolescents can now get an acellular pertussis vaccine (Tdap) to boost their waning immunity.

Antibiotics can shorten the contagious period, but usually do not impact the signs and symptoms, which include a characteristic cough which can last for about 3 months even with treatment. This disease was once called the "Hundred Day Cough". In those with partial immunity, the disease may mimic a mild to moderate upper respiratory infection (URI), but is equally contagious as pertussis with the characteristic "whoop" (characteristic recordings can be found on the Internet). Pertussis is droplet spread, but exposure is preventable by masking, staying greater than 3 ft away from a person with pertussis, or by receiving the vaccine. Because infants cannot receive the vaccine until 2 months of age, it is recommended that all persons who are around the baby receive the vaccine. This is called cocooning: those able to receive the vaccine do so to protect one who cannot.

Before Tdap was available, HCP significantly exposed to a person with pertussis (within 3 ft without a mask) had to have antibiotic prophylaxis or be off work if they developed any respiratory signs and symptoms during the incubation period of 6–10 days. If antibiotic prophylaxis was prescribed, and 5 days of therapy not finished by the start of the incubation period, the HCP could not work if respiratory signs and symptoms developed. This could affect staffing especially for specialty personnel who are difficult to replace. It is also costly to the hospital.

HCP can get and transmit pertussis if they are not immune. Neither having the initial infant immunizations nor having the disease confers lifelong immunity. SP practice recommends that any HCP with respiratory signs and symptoms should wear a mask around patients and other staff members. In one instance, health care

facility coworkers at a non-work-related function were exposed to pertussis, and all had to have antibiotic prophylaxis within the guidelines described above (personal experience). In another case, a health care worker with a presumed occupational exposure to pertussis was hospitalized and required ventilator support to survive the illness (personal experience). The patient to whom the health care worker was exposed had not been in isolation despite the patient having a history of and current cough, which was diagnosed as "non-infectious" at the time, although subsequently diagnosed with pertussis. SPs would indicate masking is appropriate if within 3 ft of a person with respiratory signs and symptoms, regardless of the cause, but masking was not done when providing close personal care for this patient.

If enough of the population is immune to pertussis, it cannot be transmitted through that population. This is called herd immunity, which is an important goal for pertussis immunization. Because of the 2010 pertussis outbreak in California, during which ten infants died, the CDC's Advisory Committee on Immunization Practices (ACIP) has revised the recommendations for Tdap, to allow pregnant women who are unvaccinated to receive the vaccine after 20 weeks' gestation [47]. After the intensive public health immunization campaign, there were no reported infant deaths in California from pertussis in 2011 [48]. At Children's Hospital and Medical Center, Omaha, NE, USA, as soon as the Tdap was available in 2005, it was offered to all HCP free of charge, underlining the close liaison IP and Employee Health have to maintain to protect both HCP and patients (personal experience). Each new infant can be cocooned by those who are caring for them, whether in a household or health care setting. Unfortunately, complete herd immunity for pertussis has not been achieved.

Polio

Polio is an example of successful herd immunity in the USA. In 1994, the America's were declared free of polio by the WHO. The polio vaccine continues to be recommended and administered, as polio is still endemic in the world, although as of this writing in 2012, yet another country, India, has been removed from the WHO list of countries with polio. The polio story is as long as man's history, but became of epidemic proportions in the USA, cycling every few years after 1916. Among the public health reactions in 1916 New York was to blame stray cats and dogs, and begin exterminating them [49]. The last epidemic in the USA was in the 1940s and 1950s, causing death and disabling the survivors (mostly young children) in record numbers.

At the turn of this century, in 2000, there were still polio survivors from the 1940s and 1950s living in iron lungs. Many of these families who had a member with polio could not afford the care needed. Many Children's Hospitals were created out of the need to provide specialized care for children whose families could not afford it. As a result of President Franklin Roosevelt's polio experience, the National Infantile Paralysis Association was founded and helped fund polio care

through volunteer donations. “Paralyzed with Fear: The Story of Polio in America”, is a documentary, which can be viewed on line, and was first aired on television in 1998, provides an hour and twenty minutes of polio history [50]. In his history of what is now Children’s Hospital and Medical Center in Omaha, NE, USA, entitled *A Chance to Live*, author Hollis J. Limprecht has a chapter devoted to the Children’s Hospital—Omaha polio experience [51]. The mode of transmission of polio was initially not well understood and public health attempts to quarantine the ill to protect the well was a failure, as was the extermination of stray animals. This enteric, contact spread disease was only controlled by immunization.

Varicella

Chickenpox is the bane of the pediatric Infectious Preventionist’s life. Or at least it has been in the past. Chickenpox is caused by the varicella zoster virus (VZV), which also causes shingles. Chickenpox is contagious by the airborne route and contact with the lesion fluid. Shingles may be airborne in some hosts, but is mainly spread by contact with the lesions. If the first exposure to varicella in a susceptible person causes disease, that disease is chickenpox. Shingles is a reactivation of a person’s own virus. The incubation period for varicella in an immunocompetent susceptible person is from the tenth day after first exposure until 21 days after last exposure, each day being a new exposure day [52]. A person with chickenpox is contagious for about 2 days before the rash appears. Because of the contagious period before rash, all patients and visitors under 14 years of age at Children’s Hospital and Medical Center, Omaha, NE, USA are routinely screened for exposure to varicella among other contagious diseases. Many hospitals have adapted visitor and/or patient infectious disease screening to include varicella exposures/status. Anyone not known immune and in the incubation period of a significant exposure to chickenpox or shingles has to be in Airborne Infection Isolation (AII) Precautions. AII requires a negative air controlled room that is vented to the outside. Any HCP who are varicella antibody negative and significantly exposed cannot work for the incubation period regardless of the source of the exposure or for the time period of the disease if it develops. For example: a non-VZV-immune single parent in the pre-vaccine era had to be off work from a pediatric health care facility for close to 3 months as each of the three children in the household developed chickenpox almost at the end of each of their incubation periods. This parent did not get chickenpox, and if she had got it, the disease contagious time would have been shorter than the cumulative incubation periods. This was devastating for this person’s personal and professional life (personal experience).

Varicella vaccine cannot be given until 1 year of age, and requires two doses for an individual to be considered fully immunized. A shingles vaccine is also now available for adults [53]. IP programs periodically receive calls from families asking if the relative’s shingles could affect a baby. The answer is: “maybe—depending on host health and hygiene, and the location and condition of the shingles.” After an

experience with a trainee who developed chickenpox during orientation to the hospital, one pediatric acute care facility developed a policy that all HCP have to show documented proof of immunity: two vaccines after 12 months of age at appropriate intervals, Licensed Independent Practitioner diagnosis of varicella disease, or a positive VZV titer before working.

The people most susceptible to varicella are the unimmunized, and since immunization cannot start until age 1 year, and is not complete until the second dose at about 5 years of age, all infants and children under 5 years of age or until about 2 weeks after the second immunization are considered at risk. This means all patients in the newborn nursery and Neonatal Intensive Care Units (NICUs). A dreaded call to an Infection Preventionist may begin with a scenario such as: "My doctor just diagnosed my 3 year old with chickenpox, and she was visiting her preemie brother in your [open] NICU yesterday." The time-intensive investigation and notification of physicians whose patients had been significantly exposed would begin. One chickenpox exposure investigation took 80 work hours just to identify the susceptible exposed patients and notify their individual primary care physicians (personal experience). If criteria are met, the significantly exposed person might be able to receive immunoprophylaxis as per *Red Book* [54] guidelines; but immunoprophylaxis is expensive and time-sensitive, reported as most effective within 96 h of exposure. The varicella vaccine is definitely helping decrease the number of patients with varicella, or severe varicella, but more herd immunity is needed to cocoon those unable to receive the immunization.

Influenza

"The perfect is the enemy of the good" [55] is an adage applicable for influenza vaccine. Certainly it is not a perfect vaccine: sometimes not effective against the influenza strain that is most prevalent in the population, sometimes only partially effective, and only offering seasonal protection, requiring annual immunization. On the other hand, influenza can be a deadly disease, especially for the very young and the very old, causing about 30,000 deaths a year and burdens the health care system with about 300,000 hospitalizations annually. Although more deaths occur in the older population, infants and children are more often hospitalized [56]. This droplet spread disease is highly contagious for 24 h prior to signs and/symptoms, and contagious for about 5–10 days after signs and symptoms appear, longer in children and infants. Because those developing influenza illness are contagious before signs and symptoms start, SPs cannot protect those around a contagious, but symptom-free person.

Currently no influenza vaccine can be given to infants less than 6 months of age. This is an immunization which everyone should have who cares for infants less than 6 months of age. As soon as possible after 6 months of age, the infant should be immunized with influenza vaccine unless medically contra-indicated. Most health care facilities offer free vaccine to all HCP and some to families of NICU patients. To date, those HCP who do not receive the influenza vaccine are typically required

to mask during the influenza season. If they become ill themselves, HCP can be a source of infection to their patients and other staff, burdening the system further by their absence. Having the intranasal and intradermal influenza vaccines available will help with the immunization for those who think the current injection is too painful.

Reading Barry's *The Great Influenza, The Story of the Deadliest Pandemic in History* [57], should be enough to scare everyone into getting an annual influenza immunization. From personal experience: a family member's sister died of influenza at the age of 3 years in the 1916–1918 epidemic, and the family still remembered and recounted her death 70 years later, the experience was so frightening. The Public Broadcasting Service (PBS) even included the influenza epidemic peripherally (and in some opinions, inaccurately) in the highly popular Masterpiece series "Downton Abbey" [58]. The 1916–1918 Influenza epidemic was deadly for the young and healthy, unlike the usual pattern of highest mortality in the very young and very old [57].

Hepatitis B

The only vaccine available for a blood-borne pathogen, hepatitis B vaccine (HBV) is required by OSHA to be made available free of charge to employees who work in health care jobs in which exposure to blood, bloody body fluids, or the deep high-risk fluids which can transmit blood-borne pathogens occurs. Significant exposure is considered one of these body fluids to mucous membranes or broken skin, extended exposure on skin, or a percutaneous exposure. A high-risk significant exposure is when the donor of the exposure is known or suspected of having a blood-borne pathogen illness. This is an important vaccine for everyone, because anyone with chronic hepatitis B has a 100 times greater chance of developing hepatocellular carcinoma than someone in the general population [59].

Sepkowitz and Eisenberg [60] reported that the risk of hepatitis B has diminished by >90 % since the introduction of SPs and a recombinant vaccine. Despite vaccine availability, however, coverage is incomplete because >30 % of workers refuse to be vaccinated. As a consequence, CDC estimates that, in 2002, another 400 health care workers became infected with hepatitis B virus, a number that has been stable since 1995 [60].

Every health care facility under OSHA is now required to have an Exposure Control Plan for blood-borne pathogen exposure. This has required much collaboration among Infection Preventionists, Occupational Health, and Nursing to develop a plan that is used 24/7 as soon as an exposure occurs (personal experience). If the exposed individual has had the HBV series and is immune, the hepatitis testing does not have to be done, although the HIV and HCV follow-up needs to be done, as there are no vaccines for these two blood-borne diseases.

HBV also has implications for the NICU as birth dose HBV is now a recommended infant vaccine. Some infants have not received birth dose HBV, so neonatologists and pediatricians need to advocate for this vaccine as soon as possible. The

CDC reports, "Approximately 25 % of those who become chronically infected during childhood and 15 % of those who become chronically infected after childhood die prematurely from cirrhosis or liver cancer, and the majority remain asymptomatic until onset of cirrhosis or end-stage liver disease. In the USA, chronic hepatitis B infection results in estimated 2,000–4,000 deaths per year" [61]. Although a hepatitis B virus vaccine has been available since 1981, rates of reported hepatitis B did not start dropping in the USA until the mid-1980s. During 1990–2004, incidence of acute hepatitis B in the USA declined 75 % [62].

Measles

Measles (rubeola) is a rash and fever disease which is transmitted by the airborne route and very contagious, and therefore raises IP and public health issues when it occurs. In the USA, two doses of the combined measles, mumps, and rubella vaccine (MMR) are required for immunity. Following licensure of vaccine in 1963, the incidence of measles decreased by more than 98 % [63]. However, measles is still endemic worldwide, and with global travel, a susceptible person with a significant exposure could be in the USA within 24 h of leaving an area outside the country. There have been multiple measles exposures in the USA, one of which resulted in a physician contracting the disease as reported in the MMWR of January 20, 2012 [64].

In the Omaha, NE, USA area there have been several measles outbreaks, the largest of which in recent years was in 1989, involving a college dormitory, quarantine of several dormitory floors, and emergency vaccination clinics set up and run by the Health Department (personal experience). Recently, a visitor to Omaha who was not vaccinated has been diagnosed with measles. The visitor and susceptible household members were quarantined at the home of relatives during the illness and incubation periods. Family members had to miss time from work and make unplanned trips from their home to Omaha as a result of this, and the Health Department had to initiate a public health investigation and awareness campaign to identify secondary cases as one of the visitors had been contagious and in large public gatherings before the disease was identified [65]. Infection Preventionists at hospitals sent out special information and provided facility education. Any patient admitted with suspicion of measles during this period had to be put in AII and specific testing done as per Public Health Department recommendations. The expense and effort of follow-up and investigation, and the individual cost and inconvenience to the family certainly argue in favor of the vaccine versus disease.

Mumps

Similar to measles and varicella vaccines, the mumps vaccine is very effective, and has resulted in dramatically decreased reported cases but periodic outbreaks still

occur. The last major outbreak was in 2005–2006 involving multiple states and air travel by potentially contagious patients [66]. Mumps is contagious before signs and symptoms start. Because so few cases of mumps are seen in the USA, when the 2006 outbreak occurred, at Children's Hospital and Medical Center in Omaha, NE, USA, pictures of a child with parotitis were posted at all hand hygiene stations, and anyone with these signs and symptoms as well as URI signs and symptoms was asked to mask for this droplet transmitted disease. Mumps is not always a benign childhood disease. Complications include CNS involvement, orchitis, oophoritis, pancreatitis, deafness, myocarditis, arthralgia, arthritis, and nephritis. Prevaccine, about one death per year was reported due to mumps [67].

Meningococcal Disease

Invasive *N. meningitidis* bacteremia and meningitis are rapid, devastating diseases with about a 10 % mortality rate, even with appropriate therapy. Survivors can have quality-of-life limiting sequelae [68]. This droplet-spread disease is very easily transmitted in household or dormitory living conditions. Because of the rapid progression and severe outcome of this disease, this vaccine is especially recommended for (but not limited to) anyone working with these organisms, military personnel expected to be in open barracks living conditions, and college bound students who will be living and working in communal settings. Rates of some serogroup infections have dramatically decreased, but both sporadic disease and outbreaks continue. Identification of a patient with invasive meningococcal disease is a public health emergency. As soon as either blood or CSF has a gram stain positive for "gram negative diplococci", the local public health agency should be notified 24/7. A close working relationship to the pathology laboratory is essential for the Infection Preventionist to receive this information immediately. All close contacts to a person with a systemic *N. meningitidis* infection should have antimicrobial chemoprophylaxis as soon as possible per current recommendations. During an investigation among teenagers, it was discovered that "close contacts" includes sharing smoking materials, and lip gloss (personal experience).

Rotavirus

Rotavirus causes a diarrheal disease which can lead to dehydration and death. Although supportive care is usually readily available in the USA, deaths from rotavirus do occur. Two oral vaccine products are now available for rotavirus prevention, but very age-specific with 8 months 0 days the last date on which the vaccine can be administered. Currently (as of April 2012) the ACIP recommends that premature infants be vaccinated within the guidelines of:

1. Chronological age is at least 6 weeks
2. Clinically stable
3. Vaccine is administered at time of discharge or after discharge from a NICU or nursery [69].

Diphtheria

It is a tribute to immunization advocacy that there is very little to be said about diphtheria, as herd immunity has reduced the reportable disease to five cases since 2000 [70]. In the late 1800s before immunization, antibiotics, and antitoxin were available, the majority of families experienced deaths from diphtheria. In Nebraska, USA, there was an epidemic in 1873, recorded in genealogy documents of the time available on the Internet.

As of 2011, the overall case-fatality rate for diphtheria is 5–10 %, with higher death rates (up to 20 %) among persons younger than 5 and older than 40 years of age. The case-fatality rate for diphtheria has changed very little in the last 50 years [71]. The diphtheria experience is exemplified by "Prevention is the Best Intervention", an APIC slogan for a past Infection Prevention Week.

Cost of Vaccines Versus Cost of Investigation/Care for Vaccine Preventable Diseases

Childhood and adolescent immunizations were estimated to cost a total of about $1,170 per individual in 2008 [72]. Compare this total to the costs of some examples of vaccine-preventable disease exposure follow-ups below:

The cost of one measles exposure follow-up in Iowa, USA in 2004 was estimated at greater than $140,000. Cost of potential individual care for a person with measles was estimated from $70 to $3000, depending on severity and sequelae, in this report. Direct costs of care for the individuals who were diagnosed with measles in this case were estimated to be less than $500 per person [73].

The cost of a 2008 pertussis exposure follow-up in Omaha, NE, USA, was estimated at $52,131, the majority of which was spent during an intensive 10-day period. This is approximately $2,172 per case of pertussis found [74]. It includes not just Health Department costs, but HCP and health care facility costs as were described vividly in a pre-Tdap article [75].

During the 2006 mumps outbreak, one Chicago Hospital had seven HCP and two patients who contracted mumps, each of whom had an average of 38 people exposed to each of them when contagious. The total cost of the outbreak was $262,788 and cost per mumps case was $29,199. The authors concluded from their experience that the cost of the mumps outbreak at their facility alone during the national

outbreak was four times the cost of maintaining a routine facility MMR prevention program [76].

These are just three of the examples of vaccine-preventable disease follow-ups which can be found documented on the Internet. Exposure follow-up time, potential costs of care, and loss of staffing are health care dollars which could be otherwise spent to control and prevent infections which are not vaccine preventable. It is not only the victims of the morbidity and mortality of these diseases who pay the cost of non-vaccination, but their families, their third party payers, and the community that bears the public health cost.

Pregnancy, IP, and Vaccine-Preventable Diseases

Pregnant HCP are justifiably worried about exposing their unborn to infectious diseases, as there are many organisms and diseases which may cause either fetal and/or pregnancy issues [77, 78]. IP programs receive many calls from pregnant personnel who are concerned about either caring for a specific patient or for patients in isolation in general. Vaccine preventable diseases that pose risks during pregnancy include hepatitis B, varicella, rubella, and measles. Pregnancy also may require different antibiotics than usual for prophylaxis in the event of an exposure which requires it, as many antimicrobials cross the placental barrier. Ideally, all HCP should be adequately immunized prior to pregnancy, as there are some vaccines which should not be given during pregnancy. Influenza and Tdap vaccines can and should be given during pregnancy as per ACIP guidelines [79]. Having immunizations for vaccine preventable diseases and practicing Transmission-based Isolation Precautions and SPs appropriately and consistently will provide the best protection available to both the mother who works in health care and her unborn infant.

Hopes and Dreams for the Future of IP and Immunizations

- Immunogenic varicella vaccine for younger than 1 year of age
- More vaccines for more diseases and organisms
- More combined vaccines
- Less painful administration routes
- More user-friendly vaccine storage, mixing, and out-dates
- More immunization information and advocacy across the age span in all health care facilities
- Make vaccine administration more available to “Capture the Opportunity”
- Better-fitting, consumer-friendly PPE, especially for pediatric health care consumers
- With apologies to J.D. Robb [80] who wrote of it from a public safety viewpoint: a “sealant” for HCP hands. The sealant would act a second skin, able to withstand

the usual hand hygiene, protecting wearer's own skin and sealing in own flora, applied and removed either at intervals, or before and after shifts.
- More IP roles and hours, such as IP unit-based liaisons, champions, or educators
- More IP education in all HCP training/education programs including, but not limited to nursing, respiratory therapy, medical and dental, laboratory/pathology, central service processing, radiology, certified nursing assistants, and pharmacy
- More efficient and accurate surveillance and monitoring
- National Registry for personal immunization history, accessible by health care consumers and professionals

Conclusion

IP and Control Practices save lives and help prevent infection, but are dependent on continuing education, skills validation, surveillance, and sustained, rigorous, individual practice. Immunizations save lives and decrease, if not eliminate, disease, and can be accomplished individually for each person's benefit, and the herding and cocooning benefit of the local and global community. Immunizations exemplify the principles of IP. Readers of this chapter are encouraged to be fully immunized, advocate for immunizations across the lifespan, and exhort others to get their immunizations.

A common quote and a favorite of a nurse colleague: "Do the right thing, because it's the right thing to do" [81].

Disclaimer The views expressed herein are not necessarily those of the staff or management of Children's Hospital & Medical Center, Omaha, NE, USA.

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Chapter 25
Insights from Public Health: A Framework for Understanding and Fostering Vaccine Acceptance

Glen J. Nowak, Kate LaVail, Allison Kennedy, and Kristine Sheedy

Insights from Public Health: A Framework for Understanding and Fostering Vaccine Acceptance

Vaccines are one of the most important public health interventions ever, helping increase life expectancy and decrease mortality for a host of serious infectious diseases [32]. However, achieving maximum impact—i.e., protecting as many people as possible and preventing as much disease as possible—usually requires high immunization coverage. In the USA, for instance, very high childhood immunization rates (e.g., near or above 90 % coverage) have helped foster historically low incidence levels for most vaccine-preventable diseases and decreased childhood vaccine-preventable disease mortality by 99 % [9, 43].

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G.J. Nowak, Ph.D. (✉)
National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

Advertising and Public Relations, College of Journalism and Mass Communication, University of Georgia, 120 Hooper Street, Athens, GA 30602-3018, USA
e-mail: gnowak@uga.edu

K. LaVail, Ph.D.
Office of Health Communication, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

A. Kennedy, M.P.H.
Immunization Services Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

K. Sheedy, Ph.D.
Communication Science, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

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Achieving and maintaining high immunization rates requires high vaccine acceptance. Immunization requirements, such as those established for school or day care entry, play an important role in facilitating the highest possible vaccination rates. As Bugenske et al. [7] documented, state middle school immunization requirements fostered significantly higher coverage rates for two recommended adolescent vaccinations—tetanus/diphtheria-containing (Td) or tetanus/diphtheria/acellular pertussis (TdaP) and meningococcal conjugate (MenACWY). Vaccination coverage with one or more doses of Td/TdaP was 10 % points higher in states that had middle school immunization requirements in comparison with states with no requirement. For MenACWY, the difference was 17 % points.

As effective as requirements can be, public health officials, policy makers, and health care professionals also need to take into account public and patient willingness to accept vaccines for vaccines to achieve their full potential [33]. As such, it is vaccine acceptance—that is, a targeted population's beliefs, confidence, and voluntary intentions with respect to a recommended vaccine, coupled with their trust, beliefs, and confidence in those making the recommendation—that provides the foundation needed to achieve and sustain high immunization rates [11]. Most members of a targeted population need to believe in the value and benefits associated with an immunization recommendation, be confident in the safety of the recommendation and the recommended vaccine (including that the benefits of getting vaccinated outweigh the risks), be confident that the vaccines work, and trust the health and medical professionals who formulated the recommendation and administer the vaccination. It is such acceptance that fosters wide support for immunization recommendations, provides the social and political support for immunization requirements or mandates and achieves long-term success (e.g., the sustained high coverage rates necessary to minimize illness and achieve community immunity). It is also vaccine acceptance that provides the foundation for the success of immunization schedules, or the broader, more comprehensive set of vaccine recommendations that need to be routinely and widely implemented to prevent the transmission of a number of infectious diseases. In the USA, high levels of vaccine acceptance from health care professionals, public health and government officials, parents and the public provide the foundation for an infant and childhood immunization schedule that currently provides children with protection against at least 16 serious infectious diseases [32].

The concept of vaccine acceptance and its importance can seem obvious and simple. Some health experts or scientists, for instance, may assume that nearly all people or parents readily recognize the value and importance of vaccinations, and as such, will quickly and with few questions, accept recommended schedules or newly recommended vaccines. However, as this chapter illustrates, that scenario is but one of many that can result when it comes to vaccines and vaccination recommendations. As the historically high infant and childhood immunization rates in the USA illustrate, parent acceptance is quite strong for the vast majority of recommended vaccinations. In 2010, around 90 % of US children had received recommended

DTaP, hepatitis B, polio, MMR, and Hib vaccinations by 35 months of age [4]. However, not all recommended infant and childhood vaccinations have achieved such levels and there is also variation in immunization rates across the USA, with some states and counties having immunization rates significantly below national averages [4, 44]. There is also evidence that a significant, and possibly growing percentage of US parents, are delaying recommended infant and childhood vaccinations [12, 46, 47]. Most recently, Robison et al. [41] have reported finding the percentage of children in the Portland, Oregon, metropolitan area consistently receiving 2 or fewer vaccine injections per visit between birth and age 9 months increased threefold within a 2-year period, suggesting an increase in immunization delays. CDC data also show parental acceptance of influenza vaccination, while growing, lags that of other recommended childhood vaccines. Immunization coverage data also show that vaccine acceptance—at least as measured by vaccination uptake—is often significantly lower for most recommended adolescent and adult vaccinations. Three years after being added to the adolescent immunization schedule, only about one in three girls in the USA had received the recommended three doses of HPV vaccine [15]. Similarly, 3 years after annual influenza vaccination was recommended for all people 6 months and older in the USA, just over 40 % of adults got vaccinated in the 2011–2012 influenza season [36], and immunization rates for other recommended adult vaccines is also relatively low in the USA, including among people in at-risk populations (e.g., pneumococcal vaccination coverage was 59.7 % among people 65 years old and older and 18.5 % among high-risk adults aged 19–64 years) [53].

From the public health perspective, vaccine acceptance is a core component of achieving, maintaining and extending vaccination success [14, 17]. While not completely synonymous with high immunization rates or coverage, vaccine acceptance is a necessary foundation for achieving high rates. This chapter examines the concept and identifies some of the key aspects of vaccine acceptance. Parent and public willingness to accept vaccines and recommended vaccinations has been linked with vaccine confidence, trust in medical authorities and public health officials, beliefs regarding vaccine safety, benefit–risk perceptions, and vaccination intentions and behaviors [11, 26, 42, 46, 47]. This chapter thus starts by putting forth a framework that links cognitive factors found to be, or that have the potential to be, facilitators or inhibitors of immunization to vaccine acceptance. This framework is used to provide a context for understanding how vaccine acceptance relates to vaccine hesitancy and vaccine refusal. The cognitive factors associated with vaccine acceptance are examined more closely in the second part of the chapter. Examples of key findings and "lessons learned" regarding cognitive factors that foster or impede acceptance of vaccination recommendations are identified using published research as well as CDC public health efforts related to immunization education and promotion. The final part of this chapter then uses those assessments as the basis for putting forward four considerations for establishing, maintaining or extending vaccine acceptance.

A Framework for Understanding Vaccine Acceptance

Achieving immunization coverage rates in the 80–90 % range, as found for nearly all recommended infant and early childhood vaccinations in the USA, indicates the vast majority of parents are ultimately accepting the advice of public health agencies and professional medical societies (e.g., American Academy of Pediatrics, American Academy of Family Practitioners). That is not to say that many of those parents don't have questions or concerns related to vaccines and recommended immunizations—and in fact, it is likely the majority of them do [27]—but the presence of questions or concerns by themselves can be a poor indicator of vaccination beliefs or behavior. Nor does it mean that vaccine coverage is an adequate proxy for vaccine acceptance. While coverage is a commonly used indicator of acceptance, it must also be recognized that external barriers or factors can and do exist when it comes to getting recommended vaccinations, even when people or parents want to receive them. Vaccine availability, ease of access to vaccines, cost and affordability, having a regular health care provider and an explicit recommendation from a health care provider are leading structural or systems factors that affect vaccine coverage rates [8, 30]—and sometimes very significantly so. For example, Dempsey et al. [12] found that not having a regular health care provider for a child was the factor most strongly associated with use of an alternative or nonstandard childhood immunization schedule illustrates. Thus, to the extent health system factors are not barriers for a significant percentage of a targeted population, vaccine coverage is a useful indicator of overall vaccine acceptance.

Many government and public health efforts (e.g., the Vaccines for Children program in the USA) recognize that health system factors can impede vaccine use and vaccination uptake, and as a result, many countries take steps to address or reduce the cost, access, availability, logistical and provider education barriers to vaccine acceptance. However, as a number of published articles, media stories, and public health efforts related to immunization education illustrate vaccine and vaccination-related knowledge, perceptions and beliefs also impact intentions and behaviors (e.g., refs. [23, 42]). These cognitive factors often play an important role in determining what a person or parent does with respect to a vaccine or immunization recommendation. As Fig. 25.1 shows, there are at least six major categories of cognitive factors that individually, or in combination, influence individual or parental vaccination decisions. Extending a framework put forth by Benin et al. [2], Fig. 25.1 also shows vaccine acceptance can be conceptualized as the desired endpoint (at least from a public health perspective) on a behavioral continuum that includes deliberate vaccine refusal, non-vaccination related to lack of knowledge/awareness (i.e., "accidental" or non-intentional refusal), and vaccine hesitancy manifest in two ways—(1) vaccination delay/deferral and heightened concern but without vaccination delay and (2) actual deferral of recommended vaccinations. People and parents who get themselves or their children vaccinated as recommended represent "strong vaccine acceptance," while people and parents who purposely reject vaccines or refuse recommended vaccinations represent the opposite end of the continuum.

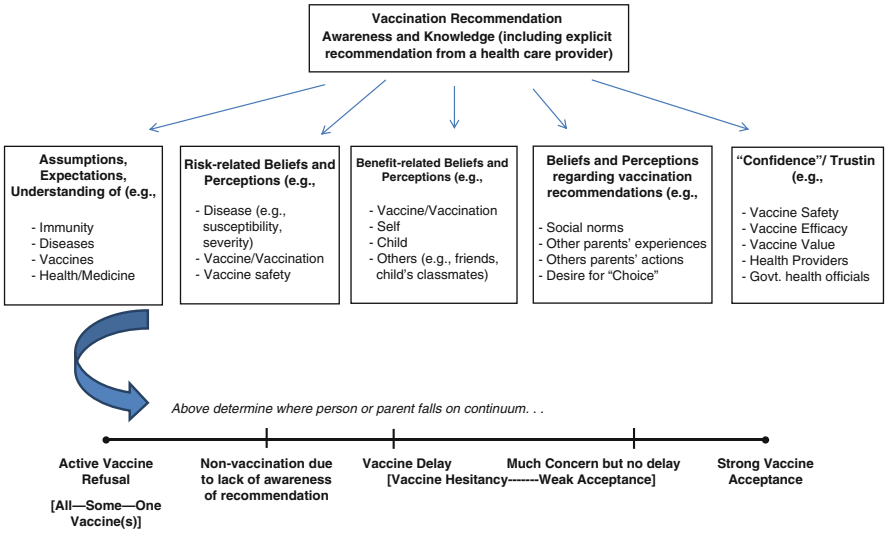

Fig. 25.1 Cognitive factors that influence vaccine acceptance

People or parents who are "vaccine hesitant" fall between these two extremes. Those who have much concern or trepidation but ultimately get a recommended vaccination for themselves or their child align most closely with vaccine acceptance. For others, their trepidation or concerns are the basis for delaying recommended vaccinations and following "alternative" or nonstandard immunization schedules. In the end, people and parents in this hesitancy group become vaccine acceptors but do so on their terms, with Dempsey et al. [12] finding the vast majority of alternatively vaccinating parents having more than one schedule alteration. This hesitancy can be problematic in that it places individual children at risk for disease/illness as well as fosters growth and parental acceptance of "alternative" immunization schedules [26, 39, 41].

In terms of context and perspective, recently published studies suggest the majority of US parents appear to be in the "strong vaccination acceptance" part of the continuum when it comes to CDC's recommended infant and early childhood immunization schedule, while as much as a third are in other parts of the continuum, with most being in the vaccine hesitant areas (vs. intentional vaccine refusal). A survey involving parents of children 6 years old and younger suggested five segments could be found when it came to immunization attitudes and beliefs, with "immunization advocate" (33 %), "go along to get along" (26 %) and "health advocates" representing vaccine acceptance, "fence sitters" (13 %) representing a more hesitant group and "worrieds" being most likely to be vaccine decliners [22]. Data from the 2003–2004 National Immunization Survey (NIS) indicated 28 % of parents overall expressed hesitancy, delay or refusal with respect to recommended vaccinations, including 9 % who accepted recommended vaccines despite their doubts and 10 % who delayed vaccinations because of doubts [23]. Data from the

2009 National Immunization Survey indicated 60 % of parents neither delayed nor refused vaccines, while 26 % only delayed one or more, 8 % only refused one or more, and 6 % of parents both delayed and refused vaccine doses [47]. These and other recent studies indicate most alternative and hesitant vaccinators tend to delay or skip only certain vaccines [12, 27, 28]. CDC's NIS studies, which include provider verification of immunizations, have consistently found less than 1 % of parents refuse all recommended immunizations [5].

Cognitive Factors that Influence Vaccine Acceptance

Published research and recent studies, along with research undertaken by the CDC to guide or assess its immunization education campaigns and materials, suggests there are at least six categories of cognitive factors associated with vaccine acceptance: disease and vaccination recommendation awareness and knowledge; assumptions, expectations, and understanding; risk-related beliefs and perceptions (including those related to the disease); benefit-related beliefs and perceptions; beliefs and perceptions regarding the disease, vaccine, and vaccination recommendations; and confidence/trust related to the vaccine, immunization recommendation and health professionals, including government health officials (Fig. 25.1). These categories, which are not mutually exclusive and in fact, are often interrelated and/or interact, represent factors that public health officials, health care providers, and immunization advocates need to be mindful of when it comes to achieving, maintaining, or extending vaccine acceptance.

Identifying where members of a targeted population are with respect to these categories, or with respect to elements within individual categories, is important for at least two reasons. One, it is often a needed first step in designing education campaigns, messages for encouraging vaccination or addressing under-immunization and vaccination-related resources (e.g., Web sites, fact sheets, flyers). Knowing which of these cognitive factor categories has the strongest association with vaccination intention or behavior helps focus or strengthen immunization education and advocacy efforts and determine which messages, materials, and media are likely to be most effective. Two, this information can help identify why some members of a targeted population accept a vaccination recommendation while others delay or forego vaccination. It may be the case, for instance, that one category of cognitive factors (e.g., vaccine confidence) matters more than another (e.g., recommendation knowledge and awareness). It may also be the case that the importance of specific cognitive factors varies depending on where people or parents lie on the vaccination continuum. For example, some cognitive factors may be more salient to parents refusing one or more recommended vaccines, while others may resonate more with parents intending to vaccinate on time or individuals (e.g., adults) who adopt an immunization recommendation.

Vaccination Recommendation Awareness and Knowledge

When trying to increase vaccine acceptance one should be careful not to assume that many or most members of a targeted population have awareness or knowledge about the vaccine, the vaccination recommendation or the disease itself. This is especially true for new or newer vaccines, new immunization recommendations, and recommendations involving older children (e.g., adolescents) and adults. A number of studies involving human papillomavirus (HPV) and HPV vaccination, for example, have shown that early adoption and acceptance requires overcoming initial low levels of knowledge and awareness. In the UK, Walsh et al. [51] found 81 % of the 420 people they interviewed in 2007 had no knowledge of HPV infection, including its links with cervical cancer. Their study also found, however, that after being provided information about the disease and vaccine, most participants supported use of the vaccine. In the USA, the 2009 National Immunization Survey found parents whose adolescents were not up to date for recommended vaccines most often cited lack of awareness of the vaccine, including via lack of an explicit health care provider recommendation [15]. More recently, a survey sponsored by a US retailer found 42 % of US adults were unaware of public health/professional medical society recommended vaccinations for their age and health condition [50]. Another 36 % believed they had knowledge of some but not all vaccine recommendations. Combined, this lack of awareness and knowledge created a significant barrier to acceptance of adult vaccines and immunizations.

Knowledge and awareness of recommended vaccines and immunizations is the critical first step in the vaccine acceptance process, but is typically a necessary but insufficient step for achieving acceptance and impacting vaccination behavior. Campaigns, materials, messages and other private and public health efforts intending to generate awareness and build knowledge typically initiate or encounter a number of other categories of cognitive factors. As Fig. 25.1 shows, the initial awareness and knowledge generated by vaccine and vaccination-related information and messages often prompts additional cognitive processing. While it is sometimes the case that becoming aware of an immunization recommendation and the benefits of vaccination can prompt acceptance, public health officials and health care providers should be prepared for a more complex scenario. In these situations, additional cognitive considerations, in the forms of assumptions and expectations, beliefs, perceptions, confidence, and trust, have greater impact on immunization intentions and behavior and ultimately determine where a person or parent falls on the vaccine acceptance continuum.

Assumptions, Expectations, and Understanding

Gaining insights into how parents or members of the population group for whom vaccination is recommended view health and medicine is often an important step in

fostering or maintaining vaccine acceptance. While health care providers, particularly pediatricians and family practitioners, are the most important and frequently identified source of immunization information for parents and the public (e.g., refs. [19, 27]), there are challenges to communication success. Studies have found, for instance, that the assumptions, expectations, and understanding that parent and public populations have regarding vaccines and immunization can be quite different from that of health and medical experts—and failure to recognize those differences can adversely impact efforts to achieve vaccine acceptance.

A common way that assumptions, expectations, and understanding can impede vaccination acceptance relates to how vaccines work. Gellin et al. [20] found 71 % of parents they surveyed understood that vaccines strengthen the immune system, but 25 % believed that their child's immune system could become weakened as a result of too many immunizations. Poland and Jacobson [40] note that scientists/clinicians can fail to effectively communicate about vaccines and immunizations if they don't recognize that vaccine safety concerns of parents or patients often stem from incorrect or incomplete knowledge of the immune system. According to Poland and Jacobson, three commonly raised vaccine safety claims—that vaccines can cause antigenic overload, that vaccines have fostered increases in autoimmune disorders, and that natural infection is better or safer than vaccine-induced immunity—are usually grounded in poor understanding and incorrect assumptions regarding the human immune system. Along this line, Brown et al. [6] found immune overload concerns and strong support for natural immunity were specific to parents opting to give no vaccines at all. More generally, Downs et al. [16] found many parents had quite limited knowledge of how vaccines work, including their timing, dosing and ability to create herd immunity. Some parents thus assumed it was unsafe for children to receive multiple vaccinations on the same day, while others were unaware of the role vaccines play in preventing disease outbreaks.

Vaccine safety-related misperceptions or beliefs are often another source of problematic assumptions, expectations, and understandings. People or parents who assume or believe that vaccines play or may play a role in fostering chronic diseases, disabilities or other types of harm are likely to be vaccine hesitant, with that hesitancy having the potential to foster vaccination delays [26]. In some cases, the result is vaccine rejection rather than acceptance. For example, even today, some vaccine hesitancy or rejection stems from believing that vaccines, either generally or specifically, are associated with autism or other learning disabilities, with Freed et al. [18] finding that as many as one in five parents believed that some vaccines could cause autism in otherwise healthy children. In the case of autism, Kirkland [31] pointed out that the needed, thorough efforts to assess whether MMR vaccine or thimerosal, a vaccine preservative, were associated with autism, produced two seemingly contradictory results—one, consistently clear and compelling scientific evidence that no associations existed, and two, the continued belief by some that the relationships did exist. According to Kirkland, differences in understanding and interpretation account for the contradiction. Where health and government officials see a rigorous scientific process and independent assessment exonerating vaccines,

vaccine doubters see research shortcomings and evidence of procedural injustice that implicate them. As a result, public health programs and health care providers need to be mindful that sound science and extensive scientific evidence while effective with most parents and people, can still be insufficient for some members of a targeted population.

Risk-Related Beliefs and Perceptions

Concern and fear are often powerful motivators, and that is often the case with respect to vaccines and vaccine acceptance. Parents or people for whom a vaccination is recommended often consider, likely very early on, the threat or risks associated with the disease and the vaccination. Recent reports suggest that pediatricians and other immunization providers are often and perhaps more frequently, encountering parents with safety concerns (e.g., refs. [13, 21, 52]), and recent studies have documented the association between safety concerns and vaccine hesitancy or delay. Gust et al. [23], for instance, found differences between the 72 % of parents who had no "vaccine doubt indicators" and the 28 % of parents who did. Compared with parents who reported no vaccine doubt indicators, the unsure, delaying and refusing parents were all more likely to report vaccine safety concerns. More recently, Freed et al. [18] reported about 1 in 8 parents (12 %) in their study refused at least one recommended vaccine, primarily as a result of safety concerns, while Smith et al. [46] found 45 % of parents of 19–35 month-old children who intentionally delayed a vaccine did so because of concerns about vaccine safety. Smith et al. [47] found parents who delayed and refused vaccines were significantly more likely to believe that if they vaccinated their child, s/he might have serious side effects (63.1 % vs. 30.9 %). Eight percent of the physicians surveyed by Kempe et al. [26] reported that in a typical month in their practice, at least 10 % of parents of children 2 years old or younger refused a vaccine and at least 20 % requested to spread out vaccines. According to the physicians, much of this stemmed from two safety-related concerns—concern about long-term complications from vaccines and/or concern about vaccination causing autism. Leib et al. [35] found 75 % of the Connecticut pediatricians they surveyed noted an increase in parental concerns and vaccine refusals compared to 10 years ago. Further, more than 60 % said they had at least one family refuse a recommended vaccine for safety concerns in the past year.

When it comes to risk-related beliefs and perceptions, research in the past decade or so also indicates people and parents: (1) perceive some vaccine-preventable diseases to be a more serious health threat than others; (2) perceive some vaccines as potentially safer than others; and (3) associate some vaccination practices with risk or potential harm. Gellin et al.'s [20] survey of 1,600 US parents of children 6 years old and under found that while most parents considered varicella (chickenpox) to be a disease highly likely to be contracted if their child was not immunized, many also perceived varicella as a less serious health threat. They also found parents indicating

the highest trust for immunizations that had been "around for a while." Freed et al. [18] found this phenomenon true in 2009 as well, with only 51 % of parents surveyed agreeing that "new vaccines are recommended only if they are as safe as older vaccines," and with three relatively new vaccines—varicella, meningococcal conjugate and HPV—associated with the highest level of safety concerns (with MMR the fourth). The survey of Connecticut pediatricians also found two relatively recent immunization recommendations—influenza vaccination for all adults and rotavirus vaccination for infants—among those most likely to be refused (with varicella and MMR also cited) [35].

With respect to immunization practices, the number of vaccinations recommended and the number administered at a given provider visit are two frequently cited parent concerns. In 2000, Gellin et al. found 25 % of parents believed that "children get more immunizations than are good for them," while in 2009, Kennedy et al. [27] found 28 % of parents were concerned that "children get too many vaccines during the first 2 years of life." In a study that looked at factors associated with delay or deferral of recommended infant and young childhood vaccinations, Dempsey et al. [12] found 1 in 10 parents using an "alternative" schedule (i.e., one that resulted in young children not receiving all recommended vaccines or not receiving all vaccinations when recommended), with about half delaying some vaccines until the child was older and about half refusing only certain vaccines completely. MMR and varicella were the most commonly delayed vaccines, with MMR and DTaP the most commonly provided over an extended dosing period. Parents who adopted a different approach were more likely than parents who followed the recommended schedule to believe "delaying vaccine doses is safer for children than providing them according to the CDC-recommended vaccination schedule" (82 % agreeing or strongly agreeing vs. 18 %) and that "delaying vaccine doses is associated with fewer vaccination side effects than providing them according to the CDC-recommended vaccination schedule" (82 % agreeing or strongly agreeing vs. 25 %). Freed et al. [18] found Hispanic parents were more likely to report that they generally do what their doctor recommends about vaccines for their children and less likely to have ever refused a recommended vaccination, but they were also most likely to believe that some vaccines cause autism in healthy children.

The number of vaccinations to be administered at a given health care provider visit can also impact vaccine acceptance. Two recently published studies using HealthStyles surveys from parents of children 6 years old and younger found similar results in 2009 and 2010. In both years, the top two vaccine-related concerns of parents were: (1) "It is painful for children to receive so many shots during one doctor's visit"; and (2) "My child is getting too many vaccines in one doctor's visit." About 4 in 10 parents expressed concern about the pain related to the number of shots, while about 1 in 3 were concerned about too many vaccines in a visit [27, 28]. When asked how many shots parents were comfortable with their child receiving in one doctor's visit, the 2009 survey found the most common response was 1–2 (42.2 %), followed by 3–4 (33.6 %), and "whatever the doctor recommends" (22.5 %). Given that many early childhood doctor visits in the USA involve four or

more vaccinations, these data align fairly well with the previously noted study findings related to vaccine delays and deferrals.

Benefit-Related Beliefs and Perceptions

While vaccine risk-related beliefs and perceptions help us understand those who refuse vaccines or accept them with hesitancy or reluctance, benefit-related beliefs and perceptions provide needed context or perspective as well as insights into vaccine acceptance. Efforts to foster, maintain or achieve vaccine acceptance need to recognize that individuals and parents are often interested in knowing what the individual benefits of doing a recommended behavior are—and need to perceive or be convinced that those are significant benefits. Parents or individuals need to know why they or their children should vaccinate in clear, meaningful terms. When it comes to immunization-related recommendations, they also need to perceive the benefits as outweighing any likely or potential risks. Often, thanks to the relative rarity of vaccine-preventable diseases, vaccine hesitancy stems from not being fully aware of the benefits of vaccines, including materials and stories that bring to life the benefits of vaccination [24].

A number of recent studies have assessed benefit-related beliefs and perceptions regarding vaccines and immunizations, with the available evidence suggesting that the majority of people—particularly parents—do see substantial benefits associated with vaccines and immunizations. Freed et al. [18], for instance, found 90 % of parents of children 17 years old and younger agreed that "getting vaccines is a good way to protect my child(ren) from disease." More recently, the 2009 and 2010 HealthStyles surveys of parents of children 6 years old and younger found around 80 % reported believing that vaccines were important to children's health and about 75 % strongly agreeing that the benefits of vaccines outweigh the risks of vaccines [27, 28]. In a similar vein, Gust et al. [23] reported that 72 % of parents of children 18–35 months of age had no indicators of vaccine doubt. Those findings, however, do indicate that there is much room and need for improvement if the goal is greater vaccine acceptance. One, Smith et al. [47] found that parents who delayed or refused vaccine doses were more likely to perceive fewer benefits associated with vaccination and were less likely to believe that vaccines do a good job in preventing the disease they are intended to prevent. Two, as recent US immunization recommendations related to influenza vaccination for all people 6 months old and older and HPV vaccination for adolescent/teenage girls illustrate, vaccine uptake can be significantly impeded if large percentages of the targeted population do not perceive significant and real benefits from vaccination. A good illustration is a study by Uscher-Pines et al. [49], which examined healthy 19–49 year old adults' beliefs regarding the expanded influenza vaccination recommendation (i.e., the expansion to a universal influenza vaccination recommendation). Compared to adults covered under previous recommendations, they found healthy 19–49 year olds much less likely to have ever received an influenza vaccination (63.6 % vs. 36.2 %) or to

indicate a willingness to be vaccinated if recommended by a health care provider (51.7 % vs. 44 %). In terms of beliefs, 19–49 year olds were less likely to agree that seasonal influenza was a serious health threat (38.6 % vs. 59.2 %) or that seasonal influenza vaccination was worth the time and expense (29.3 % vs. 52.8 %).

Beliefs Regarding Vaccination Recommendations

There are at least three sets of beliefs regarding vaccination recommendations that can be important when it comes to vaccine acceptance: (1) those related to the desire by parents or individuals to be an active decision maker when it comes to immunization recommendations and schedules, with "active" meaning having the right or ability to choose whether and/or when to get a recommended vaccine or have a child receive a recommended vaccine; (2) those related to achieving the best health and well-being outcomes; and (3) individuals or parents' perceptions regarding what similar others are doing (i.e., perceived social norms).

Given that a growing number of individuals' desire to have a greater say in their health care has emerged in recent decades, and those individuals want to see their values and beliefs be considered along with medical expertise and evidence, it is not surprising a similar phenomenon has taken place with respect to vaccines and immunization. Dempsey et al. [12] found one of the major attractions of "alternative" immunization schedules was the perception it gave parents of greater involvement and control. Eighty-five percent of parents using an alternative schedule agreed or strongly agreed with the statement "allowing parents to delay vaccine doses or skip some vaccines lets parents be more in charge of their children's health care" (vs. 49 % agreement from those following the recommended schedule), while only 25 % agreed with the statement "If vaccination experts recommend a certain schedule, then this is the best schedule to follow" (vs. 78 % agreement from those following the recommended schedule). A recent study that evaluated how parents' negative experiences at immunization visits affect child immunization status showed how this can play out in a clinical setting. Overall, one-sixth of the families studied reported having a negative immunization experience, with a third of those with a negative experience citing health care provider interactions, including failure to engage in discussions of the "pros" and "cons" of health care options and parents perceiving they had not been allowed to share decision making when it came to immunizations [48]. Those negative experiences, in turn, adversely impacted subsequent vaccination acceptance.

Studies have also identified a number of health-related beliefs among parents that can, or do, impact vaccine acceptance. Many parents, for instance, do not want or allow immunizations if their child is ill (i.e., in circumstances where the illness is not a contraindication to vaccination), and this is often a primary factor for delaying recommended vaccinations. In the 2003–2004 National Immunization Survey, the reason most often indicated by parents who had delayed a recommended

vaccination was "child was ill," with that reason often accounting for half of the reported delays [23]. The 2009 National Immunization Survey found over two thirds of all parents believing that "vaccination should be delayed if a child has a minor illness," and with that sentiment being more pervasive among parents who delayed vaccines (77 %) or delayed and refused vaccines (82 %). More broadly, the study also found parents who refused vaccines or who delayed and refused vaccines were less likely to believe that medical professionals in charge of vaccinations had their child's best interest at heart [47]. In contrast, work by Wrightman and colleagues [54] illustrates some of the ways health care provider beliefs can differ from those of parents. They found, for instance, nearly 96 % of health care providers would follow the recommended immunization schedule for their own child if they were to become a new parent, and only 8 % believed that too many immunizations were given in one visit.

Research has also shown that beliefs and perceptions regarding social norms can be an important determinant of vaccine acceptance. Benin et al. [2] found that factors that fostered vaccination included not wanting to diverge from the cultural norm (i.e., having children get recommended vaccinations) and not wanting to depart from that norm. A recent study found that parents vaccinating their child according to the recommended schedule were most likely to believe that other parents were doing the same, whereas parents who deviated from the recommended immunization schedule were more likely to believe others were doing the same [29]. It has also been found that parents who viewed HPV vaccination as normative for adolescent girls were more likely to vaccinate their own adolescent [1].

Confidence and Trust

A large part of vaccine acceptance is believed to stem from confidence and trust. Larson et al. [33] suggest (1) that vaccines are losing public trust, (2) that levels of public trust in vaccines are highly variable and context specific, and (3) that building, sustaining, or restoring confidence in vaccines requires a thorough understanding of a population or subpopulation's specific vaccine concerns, historical experiences, religious or political affiliation and socioeconomic status. They note that while traditional principles and practices of vaccine communication remain valid (e.g., provision of timely and accurate information about vaccines), new efforts and additional emphasis needs to be placed on listening to concerns and understanding public perceptions. One, this can inform risk communication efforts and result in messages and materials that better resonate with targeted populations. Two, this can foster vaccine acceptance by enabling vaccine policies and programs to better incorporate public perspectives in planning and decision making processes. Under this approach, it is dialogue and exchange that builds trust and confidence.

Trust and confidence have also been related to vaccine acceptance by evaluating who parents, the public or people for whom vaccinations are recommended turn to for information. In the USA, these research efforts have typically found doctors and

health care providers often ranking high or highest in terms of trusted or relied upon vaccine and immunization-related information sources (e.g., refs. [19, 28]). These studies have consistently found the vast majority of parents turn to their child's health care provider when it comes to seeking answers to vaccine-related questions as well as guidance on what to do. These studies also suggest that when it comes to vaccine acceptance, the amount of trust and confidence that parents have in health care providers can and does vary depending where on the vaccine continuum a parent lies. In the case of confidence and trust, (1) studies have found that parents who accept vaccines often have more confidence and trust in health professionals, including policy makers and those directly involved in providing health care; and (2) recent survey data indicate relatively high levels of trust in the safety and efficacy of recommended infant and childhood vaccines.

In the case of the former, the 2009 HealthStyles survey found 84 % of parents of children 6 years old and younger somewhat or strongly agreed that they trust the vaccine advice they get from their child's health care provider [27]. With respect to parents of 19–35 month old children, Smith et al. [47] found 95 % of parents who reported following the recommended infant/early childhood immunization schedule agreed with the statement "in general, medical professionals in charge of vaccinations have my child's best interest at heart" compared with 77 % of parents who had delayed and refused recommended vaccine doses for their children. Trust in medical professionals was even high among parents who had delayed vaccine doses (93 %) but began to decline as parents moved into the refusal category. Gust et al. [23] also found the largest proportion of parents who changed their minds about delaying or refusing a vaccination for their child listed "information or assurances from health care provider" as the main reason. More recently, a study of UK parents and MMR vaccine found perceived trustworthiness of health professionals, policy makers and researchers working in vaccination divided MMR acceptors and rejectors [6]. MMR rejectors believed that vaccine providers' clinical judgment may be "over-ridden" by financial incentives and performance targets, while MMR acceptors relied on their trust in health care providers as a way to reduce complexity and minimize anticipated regret (e.g., in the event of a negative outcome).

It is also often the case that parents who intentionally delay or refuse vaccines turn to sources other than physicians or traditional health care providers for immunization guidance. Data from the 2001–2002 National Immunization Survey found parents who believed that vaccines were not safe were significantly less likely to be influenced by a health care provider in making a decision to vaccinate their child compared with parents who believed vaccines were safe (20.7 % vs. 35.5 %) [45]. Benin et al. [2] found nonvaccinators often expressed a sense of feeling alienated by the pediatrician and/or medical establishment, and often did so because of a previous negative experience. Many parents in Benin et al.'s study turned to naturopaths or homeopaths or another person who supported not vaccinating. In addition to those groups, today it is Internet sources that are often turned to by parents or people skeptical of vaccines. Data from the 2009 National Immunization Survey found parents who intentionally delayed vaccines because of safety or efficacy concerns

were significantly more likely to seek additional information about their decision from the Internet (11.4 % vs. 1.1 %) and significantly less likely to seek information from a doctor (73.9 % vs. 93.9 %) [46]. Overall, in the HealthStyles 2010 survey, 24 % of parents cited the Internet as one of the top three most important sources of information that helped them make decisions about their youngest child's vaccinations [28].

When it comes to confidence in recommended vaccines, recent work done by researchers at the CDC has found levels of trust in the safety of recommended infant/childhood vaccines to be fairly high and relatively stable. A 2009 HealthStyles survey of parents of children 6 years old and younger found 79 % were "confident" or "very confident" in the safety of routine childhood vaccines [27]—a level similar to that found in previous years (unpublished CDC data). The 2011 HealthStyles survey found 72 % of parents were confident in the safety of vaccines, with slightly more parents expressing confidence in the effectiveness of vaccines (78 %) and the benefits of vaccines (77 %) [29]. That said, these studies also suggest that about one in five parents were not fully confident in the safety or importance of recommended vaccinations. There is also evidence that when it comes to adolescent and adult vaccines, significant percentages of targeted populations have relatively low trust or confidence in the safety and/or effectiveness of recommended immunizations (including not believing the vaccine provides significant enough benefits or protection). In the case of influenza vaccination, for example, research conducted by CDC has consistently found many adults, particularly African Americans and those 19–49 years old, are dissuaded by the relatively low efficacy of influenza vaccine or believe the vaccine may cause illness (e.g., flu or flu-like symptoms) [10, 37, 38].

Vaccine Acceptance: Conclusions and Recommendations

The framework and studies put forward here provide much helpful insight into understanding the cognitive factors associated with vaccine acceptance as well as how they can be used by public and private health care providers to foster vaccine acceptance. First, as this review and model illustrate, there appear to be discernible, meaningful cognitive differences in parents and individuals with respect to the vaccine refusal-acceptance continuum. Strong vaccine acceptance is associated with sufficient knowledge about the vaccine and recommendation, an understanding of health and disease that is in line with mainstream medicine, having little or no doubts regarding vaccine safety, believing in the efficacy of recommended vaccines and trusting or having confidence in health care providers and vaccines. Vaccine hesitancy appears to come when parents or individuals have concerns that immunization schedules are too full, start too early and/or involve too many doses before age two. It also appears to be fueled by or associated with a desire to be an active participant in health decisions, with changing or delaying recommended vaccinations seen as a viable way to do so. Perhaps not surprisingly, this also includes being unwilling to have a child get a recommended vaccination if the child is ill at the time

of the appointment. At the other end of the continuum, vaccine refusal is most consistently associated with not believing or perceiving vaccine-preventable diseases to be significant health threats, believing that not all vaccine- preventable diseases actually warrant vaccination, believing the risks associated with vaccination are greater or more likely than the risks posed by vaccine-preventable diseases, and less trust and confidence in vaccines. Many who refuse or decline recommended vaccine doses also appear to have different assumptions and understanding when it comes to health and medicine, including not accepting what mainstream medicine believes or recommends when it comes to vaccination.

The fact that a number of cognitive factors come into play to influence vaccine acceptance, and that the impact of those factors varies across the vaccine refusal-acceptance continuum, sheds light on why it can be so difficult to expand, change, or implement new immunization recommendations. Not only must public health officials and health care providers build high levels of awareness and knowledge among immunization providers, parents and people for whom vaccination is now recommended, formative research is also likely to be necessary. That is, efforts such as focus group research, in-depth interviews, message and material testing, and surveys will likely be needed to identify how people align along the vaccine refusal-acceptance continuum and why they line up where they do. The insights gained from these efforts can greatly strengthen public and private health activities to promote vaccination, and result not only in higher levels of vaccine acceptance, but also faster attainment of those levels. Parents are also more likely to feel that their information needs are being met when the educational materials and information provided to them are shaped by an understanding of their knowledge, beliefs, assumptions, and expectations.

In line with the above, the review here suggests that public health officials and health care providers should assume that much work and effort will be needed when it comes to achieving widespread adoption of new vaccines or new immunization recommendations. Individual and parents' information needs fall along a broad spectrum and many seek information from multiple sources. As longstanding (e.g., measles-mumps-rubella vaccination), new (e.g., HPV vaccination for adolescent females and males) or expanded immunization recommendations in the USA (e.g., influenza vaccination for those 6 months old and older) illustrate, "large" percentages of targeted populations may decline or defer vaccination because they are unaware of the recommendation, have little understanding of the reasons for the recommendation or the disease it helps prevent, and/or have risk–benefit perceptions that primarily or exclusively revolve around the perceived vaccine risk side of the equation. Public health officials and health care providers should also expect the challenges—and their efforts—to be greater if the new recommendation involves a brand new vaccine, multiple doses to achieve protection and/or the financial cost of vaccination is relatively high. In those cases, fostering and achieving widespread vaccine acceptance is likely to take much time and effort even when steps have been taken to minimize structural or systems barriers (e.g., reduce financial costs).

The framework provided here also serves as a reminder that efforts to build or increase vaccine acceptance will likely need to include more than just information about which vaccines are recommended and when. As many of the studies noted here show, there is much evidence that suggests most parents, including those who are strong vaccine acceptors, have relatively limited knowledge and understanding with respect to vaccines, including how they interact with or bolster the immune system. This not only highlights the need for continued public health efforts to educate parents, the public, and individuals for whom vaccinations are recommended, but also reaffirms the need for those efforts to provide, in lay terms, information on how vaccines work and the rationale for their timing. It takes time and effort to translate scientific and medical concepts into terms, examples, and information that is understandable and relevant to lay populations, but when it comes to fostering or achieving vaccine acceptance among a large population, that investment is critical. Much negative information about vaccines and immunization is widely and easily attainable (e.g., thanks to the Internet), and even though much of that information is incorrect or incomplete, it is often written and presented with readily understood words and compelling narratives and images [25]. Efforts to establish, maintain, or extend vaccine acceptance must do the same—use words, examples, narratives, and images to increase understanding of how vaccines work, the ways in which they prevent disease and protect individuals and communities (especially those who cannot be vaccinated), the reasons behind the timing, dosing, and spacing of recommended vaccines and vaccine ingredients. As Betsch et al. [3] noted, public health Web sites need to strive to be easy to find, easy to use, and attractive in presentation. Ideally, they should also be interactive and foster customized or tailored communication.

In line with the above, the CDC has developed and released a comprehensive lay language resource kit for health care providers to use in talking with parents about vaccines and immunizations (http://www.cdc.gov/vaccines/hcp/patient-ed/conversations/). This resource, developed in collaboration with the American Academy of Pediatrics and the American Academy of Family Physicians, includes fact sheets, personal stories from people whose lives were impacted by vaccine-preventable diseases, the latest vaccine safety information on each recommended vaccine and information on vaccine safety assessment and monitoring. As a result of research done with parents in developing the kit, there are two types of fact sheets. One set was created for parents who were interested in having as much information as possible, including the references or sources for the medical and scientific information. The second set was designed for parents who preferred shorter, easy to understand, vaccine information. Using this resource kit, health care providers can effectively address questions on a variety of immunization topics, including how the immune system works, how vaccine-preventable diseases happen and the challenges that can arise in treating them, how vaccines work, and how vaccine safety is assessed and monitored. While materials and information on how vaccines work and what is known about vaccine safety may not convince parents or patients who fervently or deeply adhere to a different set of assumptions regarding science or medicine, these types of materials and messages can be very effective in helping health care

providers address the concerns and questions of parents with a "naïve understanding" of vaccines as well as those whose vaccine hesitancy stems from limited knowledge or incorrect assumptions [16, 22, 34].

Finally, it should also be kept in mind that while achieving acceptance for a specific vaccine or immunization recommendation and achieving acceptance for vaccines in general are inter-related, they are also quite distinct. Thus, when it comes to building or extending vaccine acceptance, it is likely efforts will be needed on two fronts. The first front is extending and building positive connotations and associations for vaccines and immunizations. As the number of vaccines and immunization recommendations increase, it is critical that policy makers, parents, people for whom vaccinations are recommended and the public have a good understanding of the reasons vaccines exist (e.g., to prevent diseases that can cause serious, hard-to-treat illness) and associate vaccines with benefits and positive outcomes (e.g., individual and community protection). It is often assumed that the value of vaccines is readily apparent and speaks for itself (e.g., through the absence or reduction of vaccine-preventable diseases) but given the relative invisibility of most vaccine-preventable diseases, it is likely time for more proactive and visible education efforts regarding the value and role of vaccines. This is particularly true for new vaccines and new vaccination recommendations (e.g., adolescent and adult immunizations) where social norms to vaccinate do not currently exist. If social norms to vaccinate do exist, such efforts should highlight and/or reinforce the social norm of vaccination (e.g., let parents know that the vast majority of other parents are following the recommended immunization schedule). That being said, it should be expected that specific vaccines and vaccine recommendations are a distinct second front when it comes to vaccine acceptance. As some of the studies noted here indicate, parents and individuals' knowledge levels, beliefs, perceptions and trust/confidence do vary across vaccines and likely will continue to do so. Regardless of what one thinks about vaccines and immunization in general, each vaccine and vaccine recommendation is likely to be individually evaluated and assessed. Thus, public health officials and health care providers will also need to continue education and persuasion efforts for specific recommendations if the goal is to achieve high acceptance. In today's complex health, medical and information environments, it is rarely the case where things are as simple as "if you recommend it, they will be aware of it, understand it and get it." Rather, it is most likely the recommendation marks the beginning of what is likely to be a continued, concerted, and multifaceted effort.

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