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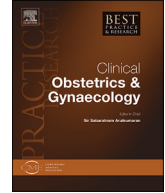
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The historical aspects of vaccination in pregnancy

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A B S T R A C T

As we live through the history-making pandemic of coronavirus disease 2019 (COVID-19), it is timely to consider the lessons that history has taught us about vaccine-preventable disease in pregnancy. Vaccinations have earned an established place in pregnancy care to prevent communicable disease in the mother, fetus and newborn. The improvements in maternal and perinatal outcome have been achieved through the evolution and application of new knowledge in many areas. These include recognition of the unique pathogenic consequences of diseases in pregnancy; improved understanding of the maternal immune system and its interplay with the fetus; optimizing safe vaccine development; ensuring pregnant women are included in appropriately designed trials of efficacy, and public health engagement to optimize uptake. As the world eagerly awaits an effective vaccine for COVID 19, these lessons of history help signpost the way, to ensure the potential of

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vaccinations to reduce morbidity for pregnant women and their newborns is fully realized.

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Introduction

Edward Jenner, a physician working in rural England, has been credited with the “discovery” of vaccines. In the late 18th century, he became aware that milkmaids who had been infected with cowpox were subsequently immune to smallpox, a disease associated with a high case-fatality rate and grossly disfiguring sequelae among survivors. He inoculated a young boy with matter from a cowpox sore on the hand of a milkmaid, and his resultant immunity to smallpox became the first scientifically documented vaccination. However, the process of violation—smearing a tear in the skin with cowpox to confer immunity to smallpox—had been practiced in China since the 17th century [1]. In the ensuing 200 or so years, systematic implementation of smallpox vaccination programs culminated in the World Health Assembly declaring the world free from smallpox in 1980 [2].

In 1885, Louis Pasteur and Emile Roux developed the rabies vaccine. They pioneered the science of attenuation by allowing infectious tissue to dry for up to 10 days before inoculating their subjects with repeated doses of increasing virulence. A similar process was applied to the development of live-attenuated cholera and anthrax vaccines. During the first half of the 20th century, further vaccines were developed, including the Bacillus Calmette–Guerin vaccine for tuberculosis and, later, the vaccines for measles, mumps, and rubella (MMR). The discovery of virus tissue culture methods led to the production of the Salk (inactivated) polio and the Sabin (live-attenuated oral) polio vaccines [3]. Mass polio vaccination programs have eradicated the disease from many regions around the world.

Population-based vaccination programs have either suppressed the transmission of vaccine-preventable disease by achieving herd immunity, or, in some instances, resulted in eradication of the disease. Childhood vaccination for the primary prevention of communicable diseases has proved one of the most effective public health interventions to reduce infant and child mortality. Throughout the world, vaccines prevent more than 2.5 million child deaths each year, with the potential to prevent a further 2 million deaths with greater access to vaccines in the developing world [4]. Delivery of vaccines prior to, or during, pregnancy confers benefit, not only to the pregnant woman, but also to her developing fetus, and newborn infant. In this chapter, we review the historical aspects of vaccine development and public health policy in pregnancy.

The benefit of any vaccine in pregnancy may be found in any, or all, of: (i) prevention of maternal morbidity and mortality (ii) reducing the risk of *in utero* infection and fetal disease or (iii) conferring passive immunity to the newborn. Accordingly, we first discuss the history that led to seasonal influenza vaccination for pregnant women to reduce their disproportionate risk of morbidity and mortality. Next, we move on to the rubella vaccine, which was developed to prevent rubella embryopathy after the discovery of the teratogenic effects of fetal infection. Finally, we present the history of pertussis and tetanus vaccination, which successfully confer passive immunity to the newborn infant.

Vaccines to prevent maternal morbidity and mortality

Pregnant women have an increased risk of severe disease from some pathogens, in part due to the pregnancy-induced shift from cell-mediated immunity (Th1 response) to humoral immunity (Th2 response). This physiological adaptation enables the semi-allogenic fetus to be protected from immunologic rejection, but these adaptive changes render pregnant women more susceptible to severe disease. The risk to pregnant women from respiratory viruses is further compounded by physiological cardio-respiratory adaptations, leading to a higher risk of morbidity and mortality among pregnant women diagnosed with pneumonia [5].

Influenza in pregnancy across history

The disproportionate impact of influenza on pregnant women is evident from the earliest recorded pandemics. The “Spanish flu” pandemic of 1918, resulted in an estimated 50–100 million deaths globally, but the mortality rate among pregnant women was disproportionately high. A survey of medical practitioners in the United States reported a case-fatality rate of 27% among 1350 pregnant women with influenza: all the reported deaths occurred among the 678 cases complicated by pneumonia [6]. A study from Chicago reported a mortality rate of 45% in pregnant women admitted with influenza complicated by pneumonia, compared with 32% among 2053 non-pregnant patients admitted with the same illness over a 7-week period [7]. While the 1957 and 1968 influenza pandemics were not accompanied by the same mortality rates, pregnant women were again disproportionately represented among the deaths. During the 1957 pandemic, influenza was a leading cause of death during pregnancy, with nearly 20% of deaths attributable to influenza [8]. Of note, approximately half of the women of reproductive age who died were pregnant.

The 2009 H1N1 influenza pandemic provided an opportunity to study the impact of influenza on pregnancy at a time when advances in obstetric and intensive care medicine had successfully reduced maternal mortality rates [9]. From its emergence in April 2009, small case series increasingly reported higher rates of maternal hospitalizations and death. This led to collaborative surveillance initiatives across the world focused on pregnant women with severe illness. Worldwide, pregnancy was identified as a significant risk factor for influenza-associated intensive care unit (ICU) admissions. In the United States, pregnant women accounted for 6.3% of influenza-associated hospitalizations, 5.9% of ICU admissions, and 5.7% of deaths [10]. Of women aged between 18 and 29 years, pregnancy accounted for up to 29% of hospitalizations and 16% of deaths [11]. Similar morbidity was reported in the United Kingdom, Australia, and New Zealand, with higher rates of intensive care unit (ICU) and hospital admissions in pregnant women, particularly in the third trimester of pregnancy [12].

Development of the influenza vaccine

Development of an influenza vaccine began in the 1930s. The first vaccine was an inactivated monovalent preparation limited to one subtype of the influenza A virus, initially used to confer immunity to the United States military from 1938 [13]. A large-scale trial conducted in the United States between 1942 and 1945 demonstrated efficacy against influenza epidemics, which led to the introduction of the first licensed vaccine for use in civilian populations [14,15]. Further discoveries of influenza subtypes led to the introduction of bivalent and trivalent vaccines. Given that influenza in pregnant women was known to result in more severe outcomes, the United States public health authorities recommended in 1960 that pregnant women should be prioritized to receive the (now widely available) inactivated influenza vaccine [16]. However, it was not until 1997 that the Centers for Disease Control in the United States endorsed their recommendation [17]. Following the H1N1 pandemic of 2009, both Australia and the United Kingdom included influenza in the recommended vaccine schedule for pregnant women [18,19].

Despite recommendations for pregnant women to receive the influenza vaccine, there was limited data on its efficacy from clinical trials involving pregnant women. Several immunogenicity studies demonstrated that pregnant women who received the vaccine developed protective antibodies against the disease [20–22], and the efficacy of inactivated influenza virus amongst non-pregnant adults was demonstrated in several randomized placebo-controlled trials [23–25]. But it was not until 2005 that a randomized clinical study in pregnant women was undertaken. The Mother’s Gift Project was carried out in Bangladesh between 2004 and 2005. Pregnant women were randomized to receive either the influenza or pneumococcal vaccine. Pregnant women receiving the influenza vaccine were 36% less likely to have respiratory illness with fever compared with those who received the pneumococcal vaccine. This study provided compelling evidence for the maternal benefits of influenza vaccine in pregnancy, but importantly, it also demonstrated a 63% lower risk of laboratory-confirmed influenza among infants <6 months of age of vaccinated mothers [26]. A similar randomized placebo-controlled trial carried out in Nepal between 2011 and 2013 confirmed that influenza immunization reduced maternal influenza-like illness, as well as reduced influenza infection in infants, and the proportion of babies born with low birthweight [27].

Given the widespread availability of influenza vaccination, its proven safety and efficacy, and that increased risks faced by pregnant and early postpartum women of influenza infection, a growing number of countries recommend that all pregnant women receive the influenza vaccine at any stage of pregnancy. Despite these recommendations to prioritize pregnant women, vaccination rates still remain lower than national targets (50% in the US and 45% in the UK) [28,29]. These low coverage rates may reflect residual safety concerns, or lack of awareness of recommendations among pregnant women. Despite the lessons of history, each influenza season is thus accompanied by potentially preventable maternal morbidity and mortality.

The story of influenza vaccination in pregnancy highlights the value of international collaborative surveillance systems for critical illness in pregnant women, the importance of including pregnant women in clinical trials to demonstrate efficacy, and the need for redoubling of effort in public health engagement and education to optimize vaccine uptake and fully realize the maternal and perinatal health benefits.

Vaccines to prevent fetal disease

Infections in pregnancy can have deleterious effects on the developing fetus, largely dependent on the timing of infection. Fetal infection in the first and second trimesters of pregnancy may interrupt embryogenesis and organogenesis. Discovery of the teratogenic potential of rubella and varicella-zoster viruses led to their inclusion in population-based vaccination programs. Ensuring a pregnant woman demonstrates serological evidence of rubella immunity is now part of routine early antenatal care.

Rubella vaccination

An important milestone in the prevention of congenital defects was the development of the rubella vaccine in the 1960s. Rubella is usually a mild disease in childhood, manifesting as a widespread rash, fever, malaise, and arthralgia. Prior to the introduction of the vaccine, rubella was endemic worldwide, with epidemics occurring every 4–7 years. In 1941, Norman McAllister Gregg, an Australian ophthalmologist, reported the association between maternal rubella infection in early pregnancy and congenital cataracts [30]. An appreciation of the spectrum of rubella embryopathy was elucidated by 1962 – the time when the rubella virus was isolated in tissue culture by two independent groups [31,32]. In the spring of 1963, a rubella epidemic occurred in Europe, subsequently reaching the United States in 1964 and 1965, afflicting 12.5 million people, and providing researchers with an opportunity to further define the characteristics of congenital rubella syndrome. The initial wave of the epidemic failed to draw serious attention across the population. Despite public health warnings to keep infected children away from pregnant women, tens of thousands of women were infected during the early stages of pregnancy resulting in approximately 10,000 abortions—both spontaneous and induced—and 30,000 births affected by congenital rubella syndrome, with 2100 neonatal deaths. Eleven thousand children were deaf, 3500 were blind, and 1800 were intellectually disabled [33].

The high rates of death and disability in the wake of the rubella epidemic of the 1960s galvanized efforts to develop a vaccine. Progress was rapid, and the live-attenuated rubella vaccine was licensed for use in the United States and Europe in 1969 and 1970, respectively. During the development of the vaccine, and in its early clinical use, concerns were raised over safety of the vaccine. Initial studies had demonstrated pharyngeal shedding of the modified rubella virus, prompting concerns about possible transmission. Reactivation and reinfection of the virus was postulated as the earlier vaccines often produced rubella-like symptoms in the recipients [34,35]. Furthermore, the presence of virus in placental specimens of women who had received the vaccine raised concern regarding teratogenic potential of the vaccine [36].

The rubella vaccination strategy adopted in the United States aimed to eradicate the reservoir of the virus in childhood, thereby reducing the risk of rubella infection and the likelihood that pregnant women would be exposed. This was achieved through vaccination programs that included all children aged from 1 year and up to puberty. The population-based vaccination program was successful in

preventing epidemics, leading to dramatic reductions in the rates of rubella infection in pregnancy, and subsequently congenital rubella syndrome, over the ensuing 25 years [37].

The United Kingdom adopted an alternative approach by vaccinating adolescent girls between the ages of 11 and 14 years, proposing that girls immunized earlier in life might have declining levels of antibodies over time, making them susceptible to rubella infection again by their childbearing years. In the UK, boys were excluded from the vaccination policy. Seronegative pregnant women received the rubella vaccine post-partum. However, the incidence of rubella infection in young children remained unchanged, and cases of congenital rubella infection persisted [38,39]. This led to a change in policy in 1988, when the MMR vaccine was recommended for all children, boys and girls, aged 1–2 years. Subsequently, repeated doses of the MMR vaccine were recommended for children at 4–5 years of age, and before entering puberty. This resulted in herd immunity and a predictable reduction in cases of rubella infection in children, and reported cases of congenital rubella syndrome [40,41].

At present, in most countries, the schedule for rubella vaccination is two doses before 24 months of age [42]. Furthermore, many developed nations routinely screen women of childbearing age for rubella antibodies to identify and vaccinate seronegative individuals. No cases of congenital rubella syndrome have been reported in women receiving the vaccine peri-conceptually or in pregnancy. Nevertheless, due to the theoretical teratogenic risk of the live-attenuated rubella vaccine, it is recommended not to vaccinate during pregnancy, and if given pre-conceptually, to delay pregnancy for 28 days following vaccination [43,44].

Worldwide, the number of reported cases of rubella has continued to decline from 670,000 in 2000 to less than 15,000 in 2018. The estimated coverage of the global population with rubella vaccine was 69% in 2018 [45]. As rubella infection and congenital rubella syndrome become rarer events in developing nations, four out of six World Health Organization (WHO) regions have shifted the goal from suppression to eradication. In 2015, the Americas declared that it had eradicated the rubella virus, with Australia following in 2018 [46]. The WHO European region missed its target in 2010 and again in 2015 owing to lower rates of vaccination in some Central and Western European countries [47].

The experience with rubella highlights the importance of identifying teratogenic links with exposure to pathogens in pregnancy, and understanding disease epidemiology so that a vaccination program can be tailored to the target population, ensuring maximal reduction in the burden of disease and thus, exposure for pregnant women.

Vaccines that confer passive immunity to the newborn

The newborn infant's immune system is not fully developed, placing them at increased risk of infection. This risk is ameliorated with the passage of maternal immunoglobulin G (IgG) antibodies through the placenta to the developing fetus from about 28-week gestation, and maternal immunoglobulin A (IgA) antibodies through breast milk to the infant. Vaccines administered to newborns have an attenuated response in antibody production secondary to the immaturity of their immune system, thereby necessitating repeated doses of the vaccine throughout infancy [48].

Vaccination in pregnancy can thus confer valuable passive protection to the newborn. As early as 1879, it was recognized that infants born to women who had received the smallpox vaccine during pregnancy were immune to the virus in early life [49]. The vaccine-induced antibody response results in transplacental passage of the immunoglobulin to the fetus, conferring passive immunity to the fetus and newborn [50]. Maternal vaccination programs for tetanus and pertussis provide protection to the newborn infant against these vaccine-preventable diseases for up to 6 months after birth, the time when the infant's own immune system becomes capable of mounting a mature immune response to vaccines.

Tetanus vaccination

Tetanus immunization and, more recently, pertussis vaccination are examples of vaccinations administered in pregnancy largely for the benefit of the newborn. Although the prevalence of tetanus has dramatically decreased around the world, neonatal tetanus remains a preventable cause of death in many developing countries. Neonatal tetanus is caused by contamination of wounds with the spores from *Clostridium tetani*. In the developing world, this is mostly through contamination of the umbilical cord stump due to unsanitary birth practices. The affected infant presents with an acute loss of the

ability to suck, generalized rigidity, and muscle spasms. In the absence of medical treatment, the case-fatality rate approaches 100%. Even with hospital care, including the availability of intensive care, between 10 and 60% of affected infants die [51].

The tetanus vaccine was first licensed for use in 1938, and widely administered during the Second World War. During the 1960s, observational studies demonstrated that use of two or more doses of tetanus toxoid during pregnancy could prevent neonatal tetanus [52]. A double-blind trial involving 1618 women was subsequently conducted in Columbia, where the neonatal tetanus mortality rate was estimated at 11.8/100. These women were followed over 5 years, and the outcomes of the subsequent 1888 deliveries (1919 livebirths) were reported. Administration of a single dose of tetanus toxoid conferred no benefit, but among women who had received two or three doses, there were no reported neonatal deaths due to tetanus, compared to 7.8 per 100 births among infants of unvaccinated mothers [53]. Subsequent studies have shown that vaccination of pregnant women, or women of childbearing age, reduces neonatal mortality from tetanus by 94% [54,55].

In the early 1980s, neonatal tetanus was estimated to be responsible for over half a million neonatal deaths globally. The World Health Assembly convened in 1988 and passed a resolution to eliminate neonatal tetanus by the year 2000. At the time, there were 6.7 deaths per 1000 live-born infants due to neonatal tetanus. The vaccination program focused on delivery of the tetanus toxoid vaccine to children, pregnant women, and women of childbearing age, and the promotion of hygiene in peri-partum care. This initiative has resulted in a 93% reduction in neonatal deaths due to tetanus, with 47 out of the 59 countries included in the program having achieved elimination status. Since 1987, deaths from neonatal tetanus have fallen from estimates of 787,000–31,000 in 2017 [56]. A similar decline in maternal deaths secondary to tetanus is likely to have occurred with the improved maternal vaccination coverage, although in some countries tetanus continues to be an important cause of maternal morbidity and mortality [57].

Pertussis vaccination

Pertussis, or “whooping cough” is a highly contagious respiratory illness caused by the bacteria *Bordetella pertussis*. The classical clinical manifestations of the illness include paroxysmal cough, inspiratory whoop, and post-tussive emesis. The first vaccine against pertussis was developed in the 1930s. Prior to the widespread introduction of whole-cell vaccine in the 1940s, pertussis was associated with a high mortality rate. During the period between 1926 and 1930, there were 36,103 deaths from pertussis in the United States, with a disproportionate number of deaths among young infants [58]. In the United States, widespread vaccination of children led to a dramatic decline in the incidence of the disease from a peak of more than 250,000 in 1943 to a nadir of 1010 in 1976 [59].

The potential for whole-cell pertussis vaccination in pregnancy to reduce the high mortality rate associated with the disease in early infancy was first explored in the 1940s. Cohen and Scadron assessed the incidence of pertussis in a group of 100 infants born to mothers who had received the vaccine compared with an equal number of infants born to unvaccinated mothers. During the first 6 months of life, infants of unvaccinated mothers had six exposures resulting in three cases of pertussis, while infants of vaccinated mothers had eight exposures but no cases [60]. Despite these encouraging findings, there was a paucity of interest in passive immunization over the ensuing years, most likely because the introduction of pertussis to the infant vaccination schedule had demonstrated significant reductions in reported cases and infant mortality [61].

The pertussis vaccine is administered in combination with the diphtheria and tetanus vaccines. The initial combined preparations of the vaccine included the whole-cell pertussis vaccine (DTwP) containing an endotoxin, but its use was associated with considerable side effects. Technological advances in molecular medicine throughout the 1970s and 1980s enabled the production of an acellular vaccine (DTaP), removing the endotoxin from the preparation and rendering it less reactogenic. The DTaP vaccine has been safely used in pregnancy with no increase in adverse perinatal outcomes reported in several large observational studies [62–64].

Antenatal vaccination revisited

A steady increase in the incidence of pertussis was reported in the 1980s and 1990s, and in 2005, there was dramatic resurgence of the disease. Reasons proposed for this increase included a waning of

immunity in cases of prior infection and vaccination, a decrease in the efficacy of the acellular vaccine, and an increased recognition of pertussis in adolescents and adults because of improved clinical awareness and better diagnostic tests. The Centre for Disease Control (CDC) subsequently recommended that adults receive the pertussis vaccine along with the diphtheria and tetanus booster [65]. A further epidemic occurred in 2010 in California where the incidence of pertussis in infants under 6 months of age reached 435 per 100,000 and 10 infants died. Nine of the deaths were in previously healthy infants, younger than 2 months of age, who had not yet been fully vaccinated against pertussis [66]. This pattern was reported in other high-income countries. A national increase in pertussis cases was reported in the United Kingdom in late 2011, initially observed in adolescents and young adults but later reported in young infants [67]. In 2012, there were 14 deaths in infants with confirmed pertussis in the UK [68].

In response to the increasing cases occurring among young infants without the protection of vaccination, the United States in 2010 recommended DTaP vaccination of pregnant women who had not previously been vaccinated to confer passive immunity to their newborns [69]. This was later updated to recommend DTaP during the third trimester of every pregnancy [70]. In the UK, following their national outbreak in 2012, DTaP was offered to pregnant women between 28 and 38 weeks of gestation. By 2016, the recommendation was amended to offer antenatal vaccination at any time between 16 and 32 weeks of gestation to improve uptake, and protection for infants born preterm. The DTaP vaccine was introduced to the Australian pregnancy schedule in 2015 [71,72]. This was a shift away from the previous “cocooning” strategy, recognizing the improved protection provided to newborns through transplacental passage of antibody.

Following the introduction of the antenatal pertussis vaccination program in the UK, there was a pleasing reduction in confirmed cases. In the first 9 months of 2013, compared with the same period in 2012, the greatest decrease in cases was seen among infants less than 3 months of age. During this period, there was a 78% reduction in confirmed cases and 68% reduction in admissions to hospitals in this age group. In 2013, there were three pertussis-related deaths, all in infants of women who did not receive vaccination in pregnancy. The 17 deaths recorded across 2012 and 2013 were all in infants too young to be protected by the infant vaccine schedule [73]. This large observational study demonstrated that administration of maternal pertussis vaccine in pregnancy—conferring passive immunity to the newborn—reduced infant pertussis infection in the first few months of life, the time of highest risk.

The reduction in infant morbidity and mortality from both tetanus and pertussis is testament to the value of antenatal immunization for the benefit of the newborn. The success of pertussis vaccination can be attributed to the collection of epidemiological data that identified young infants as being at greatest risk, and large cohort studies demonstrating vaccine safety, thus improving uptake. The prevention of neonatal tetanus has been achieved through early clinical trials that confirmed efficacy, and informed optimal dosing strategies, as well as successful global public health campaigns, such as the WHO's Maternal and Neonatal Tetanus Elimination initiative.

How can history inform the future?

What messages does history have for pregnant women, and those caring for them, in the current coronavirus disease 2019 (COVID-19) pandemic? Health crises across history have accelerated vaccine discovery and development, and the COVID-19 pandemic is no exception. At last report, there were 29 candidate vaccines to novel coronavirus (SARS-CoV-2) in clinical evaluation worldwide [74]. Many of these are entering Phase 3 trials and, if efficacy is proven, potentially be available by early 2021. As the world eagerly awaits an effective vaccine, the pandemics of history offer some valuable insights that will inform vaccine development and uptake in pregnant populations. They have highlighted the value of international collaborative surveillance systems to identify risks uniquely or disproportionately faced by pregnant women, the imperative for pregnant women to be included in clinical trials, the value of registries to document current and future adverse health outcomes of mothers and their newborns, the need for a continuing audit cycle and the critical importance of community engagement to ensure that both public health messages and effective vaccines are met with widespread uptake.

Summary

The development and uptake of vaccines has been driven by public health crises across many decades. The demonstrated improvements in maternal and perinatal outcomes in both remote and recent history mean that vaccinations prior to or during pregnancy have earned their place as public health care imperatives. The disproportionate morbidity and mortality shouldered by pregnant women during influenza pandemics has led to them being targeted for vaccination each flu season. The devastation brought by rubella epidemics spurred the development of a vaccine, which ameliorated the teratogenic impact of this viral infection. The immunity passed from mother to infant following vaccination for pertussis and tetanus ensures protection of the newborn in the early weeks of life, making enormous inroads into reducing preventable deaths globally. Vaccination prior to conception and during pregnancy is a vital public health measure to reduce preventable mortality and morbidity for the mother, fetus and infant.

Practice points

- Vaccination in pregnancy for the primary prevention of communicable diseases has proved one of the most effective public health interventions in recent decades, leading to significant reductions in maternal and perinatal morbidity and mortality
- The influenza pandemics of history have highlighted the value of international surveillance systems for critical illness in pregnant women, the importance of including pregnant women in clinical trials of vaccine efficacy and the imperative for community engagement to optimize vaccine uptake
- The rubella epidemics of the 1960s have highlighted the need for birth defect surveillance systems to identify teratogenic links with viral pathogens, and the importance of understanding disease epidemiology to optimize vaccination uptake and efficacy
- The benefits of passive immunity for tetanus and pertussis have resulted in significant reduction in infant mortality and morbidity due to optimal timing and dosing during pregnancy

Research agenda

- Ensure that pregnant women are afforded the same autonomy as other adults to participate in clinical trials of vaccines and therapies for emerging pathogens

Declaration of competing interest

None.

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