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## Editorial

## COVID-19 vaccine dilemmas



What a difference a year makes. We have seen the emergence of a novel zoonotic virus producing a global pandemic that has so far caused more than 92 million infections and two million deaths worldwide<sup>1</sup> with no signs of abating, despite a plethora of non-pharmacological measures deployed against it. But there is hope – the wonders of modern vaccine science have seen the rapid development of more than 68 vaccines worldwide, and around ten have received emergency authorisation and use thus far.<sup>2</sup>

This has opened a new front in the struggle to control the pandemic, offering the potential to achieve population immunity through vaccination. Vaccination is far safer than the more hazardous route of achieving population immunity through natural infection that carries a high risk of COVID-19 mortality and morbidity. Early experience with the vaccine is positive when compared directly with the effects of COVID-19 infection. For example, the roll-out of the Pfizer-BioNTech vaccine in the US observed only 21 cases of anaphylaxis after administration of nearly two million first doses of the vaccine, with no fatalities reported.<sup>3</sup> This compares favourably against the COVID-19 infection-to-fatality ratio, estimated at around 1.15% in high-income countries.<sup>4</sup> There is also a significant morbidity risk with COVID-19, including the risk of 'long COVID', that is as yet poorly understood. UK estimates are that around one in five persons infected with COVID-19 exhibit symptoms for a period of 5 weeks or longer, and one in ten respondents have symptoms for over 12 weeks.<sup>5</sup> From a population health perspective, there can be no rational reason for pursuing a population immunity strategy through natural infection now.

The advent of COVID-19 vaccines, however, has also created dilemmas. In the UK, faced with a rapidly spreading third wave of infections in December, partly driven by the emergence of a new variant (SARS-CoV-2 B.1.1.7), the Government switched from delivering the authorised two-dose schedule to prioritising first-dose coverage and delaying the second dose from 3–4 weeks to 12 weeks. This generated considerable uproar among primary care physicians involved in the delivery of vaccinations for a variety of reasons, including the turmoil and workload associated with having to consent patients and rebook hundreds of thousands of appointments.

The first dose vs two-dose prioritisation saga is also an ethical dilemma for clinicians. Clinicians typically strive to do their very best for individual patients and see it as their moral duty to do so. Giving two doses as per the vaccine authorisation and trial protocol could be seen as the 'right' thing to do. This approach has an absolutist lens as well and could be perceived as a choice between right vs wrong. Consequently, our natural tendency would be to follow the vaccine trial protocols, medical licensing and manufacturers' instructions as there is a 'certainty' to this. Failure to do so leads to an understandable concern that patients would be

receiving suboptimal protection and substandard care that is not in line with best practice.

The counter perspective is the utilitarian view of the greatest good for the greatest number. A single dose would save more lives. Where resources are limited, there will be this trade-off. Prioritising two doses for some patients means denying others the protection that the first dose affords. Indeed, further analysis of the vaccine trial data suggests that the first dose of the Pfizer-BioNTech vaccine would afford patients around 89% protection 14 days after vaccination, and the second dose would only provide a marginal gain to 95%.<sup>6</sup>

The utilitarian approach tends to align with the population health approach as the perspective is of the welfare of groups of people rather than individuals. This conflicts with the patient-centric values that most clinicians have. Done right, the population health approach saves lives. The issue with this approach is we may not always know who we have saved, and those saved are unlikely to know they have been saved. It is easier to feel guilty for letting down the patient you have seen who has to be told their second dose has been delayed than the patient you have not yet seen whose first dose has been delayed. The two-dose vaccine prioritisation approach, with the limited number of vaccines, means only half the number of people getting vaccinated for the same number of available vaccines. If viral infections are spreading slowly, there is the luxury of time, and we can adopt the two-dose schedule for the most vulnerable and let other patient groups wait. However, faced with a worsening situation in the UK with a more transmissible virus, the only expedient option was to pursue a first dose prioritisation approach in the expectation that it would save more lives.

The other concern raised by those averse to the first dose approach was that this could lead to more vaccine failure or potentially introduce a selection pressure that favours mutant variants to emerge resistant to the vaccine, i.e. vaccine escape. Reassuringly, the view from immunology experts is that delaying the second dose by 8 weeks is unlikely to have a negative effect on the overall immune response. Neither is such an approach anticipated to lead to any specific safety issues to arise for the individual.<sup>7</sup> Indeed, it can also be argued that higher numbers of infection increase the likelihood of viral mutation, and consequently, efforts to reduce infection numbers may be more important for averting the risk of vaccine escape.

Another vaccine dilemma that has emerged is the decision as to who gets immunised first. The US and UK have both focused initially on the older age groups owing to their risk of mortality. One modelling study supports this approach and found that vaccine prioritisation for the elderly saves the most lives.<sup>8</sup> However, although vaccinating the elderly may reduce the number of deaths and hospital admissions, this age group accounts for only a small

proportion of infections. Consequently, the impact on disease transmission in the community may be limited.

Indonesia, on the other hand, has adopted a different approach to mass COVID-19 vaccination, with a focus on working-age adults instead of the elderly in an attempt to revive its economy.<sup>9</sup> It is recognised that working-age adults generally mix more, and thus, this approach could decrease community transmission faster. In turn, this could provide a degree of protection to more vulnerable unvaccinated individuals. For now, it is unclear which approach will work best, and it will be interesting to compare the impacts of the different approaches on disease transmission and mortality in the coming months. It should also be remembered that a 'one-size-fits-all' approach rarely works as the social, political, economic and health system contexts will differ between countries. What is best for one country may not be best for another.

Finally, the arrival of COVID-19 vaccines has sparked a vaccine race between countries to immunise their populations in the hope it may restore some semblance of normality afterwards. This race favours high-income countries, and there are real concerns that vaccine nationalism could undermine cooperative efforts to control the pandemic globally.<sup>10</sup> This will create losers and widen global inequalities.

Mass vaccination in high-income countries does not necessarily confer security as there remains the risk of reimportation of infections from lower income countries where the virus is endemic.<sup>11</sup> There is also a moral dimension – is it right to vaccinate large numbers of predominantly lower risk individuals in high-income countries over other vulnerable individuals elsewhere? Indeed, should vaccine access not be determined by need rather than national wealth and influence? This is perhaps why the COVAX initiative is vital to ensuring equity of vaccine access.<sup>12</sup>

In an interconnected globalised world, all our fates are intertwined. Global solidarity is needed to protect our national health, wealth and human rights. In essence, we are not safe until we are all safe.

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