Elaborating on COVID-19 Vaccine Concepts

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The COVID-19 pandemic has disrupted the world in a myriad number of ways in addition to the four million deaths it has caused to date. Aside from health services, sectors such as education, global shipping and supply chains, travel and tourism are just some others that have been impacted in an unprecedented manner.

The virus has also evolved as it spread. Although coronaviruses inherently mutate slower than influenza viruses, the huge number of infections has permitted natural selection to take place at speed, resulting in newer successful variants that are more transmissible than the original virus from Wuhan, which has been outcompeted to the extent that it can only be found in laboratories now and is no longer "in the wild". The Delta variant is currently the most worrying of these, having spread to over 100 countries and outcompeting all other local variants once it has established itself. Its estimated basic reproduction number R0 is between 5 and 8, meaning that each infected person has the potential to spread the virus to between five and eight other non-immune persons on average, assuming no precautions are taken and that the population mixes randomly.

This is far more infectious than seasonal influenza (median R0 approximately 1.3) and reinforces the understanding that COVID-19 will neither disappear nor be confined to a limited, few geographical locations for the foreseeable future, unlike the earlier zoonotic epidemic coronaviruses that caused SARS and MERS.

Thus far, a few countries including Singapore have successfully kept daily COVID-19 case counts low or even zero via non-pharmaceutical interventions including mask-wearing, safe-distancing and tight border controls. However, this is costly to sustain, and we have all experienced the stress and fatigue brought on by having to live under various conditions of heightened alertness over the past year and a half.

The silver lining to this pandemic is that it triggered an unprecedented pace of research in therapeutics and vaccines against COVID-19. While the work on novel therapeutics has not delivered anything paradigm-changing, we have developed a large number of effective and safe vaccines within a short period of time, with many more in the pipeline. To have not just one, but more than seven vaccines commercially available within a period of a year and a half is nothing short of miraculous. To put things in perspective, the prior record was held by the mumps vaccine, which took four years to develop and launched between 1963 and 1967. And we can certainly expect more COVID-19 vaccines in the future, as there are over a hundred in the clinical phase of development.

These vaccines span a range of different platforms, including classical ones such as inactivated viruses and protein subunits, to next-generation platforms such as the adenovirus vector and mRNA vaccines. They offer not just the possibility of reducing disease and death from COVID-19, but also the potential to transit to a post-pandemic future with fewer safe-distancing restrictions and greater freedom of travel. However, they have also generated a host of controversies, misunderstandings, misinformation and strong emotions on an astounding scale, even among those of us in the medical profession. Two of the relatively more confusing but important concepts will be discussed below.

Vaccine efficacy and effectiveness

A significant portion of COVID-19 vaccine controversies and misunderstandings revolve around ideas about vaccine efficacy. The term refers to the percentage reduction of disease or infection in vaccinated people compared to unvaccinated people, under optimal conditions such as that of a randomised clinical trial, in order to minimise bias. Vaccine effectiveness is similar in concept, but refers to the comparison done via observational studies under "real world" conditions. In general, it is important to study how vaccines perform in the real world, because many groups of people are excluded from participating in clinical trials, including those who might be most vulnerable to a disease. Many people have this idea that once they are vaccinated, they can no longer be infected. But the important question is – what are we measuring efficacy or effectiveness against?

In clinical trials and a number of real-world observational studies, the key outcome measure is symptomatic disease. Most studies also looked at protection against severe disease (defined in various ways) and death, while a much smaller subset of studies looked at protection against asymptomatic infection as well.

A perfect vaccine will protect against not just symptomatic disease, but also prevent infection to the extent that transmission of the targeted pathogen does not occur. This latter effect is called "sterilising immunity". Sterilising immunity is not an all-or-nothing phenomenon at the population level. Measles, hepatitis A and human papilloma virus vaccines provide a very high degree of sterilising immunity, while varying degrees of sterilising immunity are seen in most other vaccines such as the influenza, pneumococcal, hepatitis B and pertussis vaccines. The current World Health Organization-approved COVID-19 vaccines do exhibit variable degrees of sterilising immunity – the evidence is particularly clear for the mRNA and Oxford-AstraZeneca vaccines which have reduced asymptomatic infection and spread of COVID-19 in observational studies.

It is important to note that vaccine efficacy and effectiveness can wane when the pathogen has mutated sufficiently. All currently approved vaccines – be it Pfizer-BioNTech, Moderna, Sinovac, AstraZeneca or Johnson & Johnson – as well as most in the development pipeline are designed based on the original Wuhan virus. The virus has evolved quite a bit since, and the Delta variant in particular is more resistant to neutralising antibodies produced post-vaccination or infection with earlier COVID-19 variants. Countries such as Thailand and Indonesia, for example, have stated that they will provide booster shots of either the AstraZeneca or Pfizer-BioNTech vaccine to healthcare workers who had previously received two doses of the Sinovac vaccine, in view of the latter's perceived poorer protection against the Delta variant. Although most of the other COVID-19 vaccines are still very effective at preventing severe disease and death from current variants of SARS-CoV-2, including the Delta variant, it is conceivable that the degree of protection may fall further against future variants of SARS-CoV-2.

The other major variable that affects vaccine effectiveness is time. Neutralising antibody levels post-vaccination inevitably fall, more rapidly in the case of Sinovac than the mRNA or AstraZeneca vaccines. Although immune memory created post-vaccination is likely to last for a long time, thus ameliorating the risk of severe disease and death, the risk of breakthrough symptomatic disease post-exposure may potentially rise over time even if the virus does not mutate significantly. This has led to discussions on the need for booster doses of vaccines or annual vaccinations just like the influenza vaccine. However, there is insufficient evidence at present to conclude whether third or annual shots are necessary. Under current circumstances where there are insufficient doses of COVID-19 vaccines for most low- and middle-income countries in the world, such discussions also come across as being inappropriate.

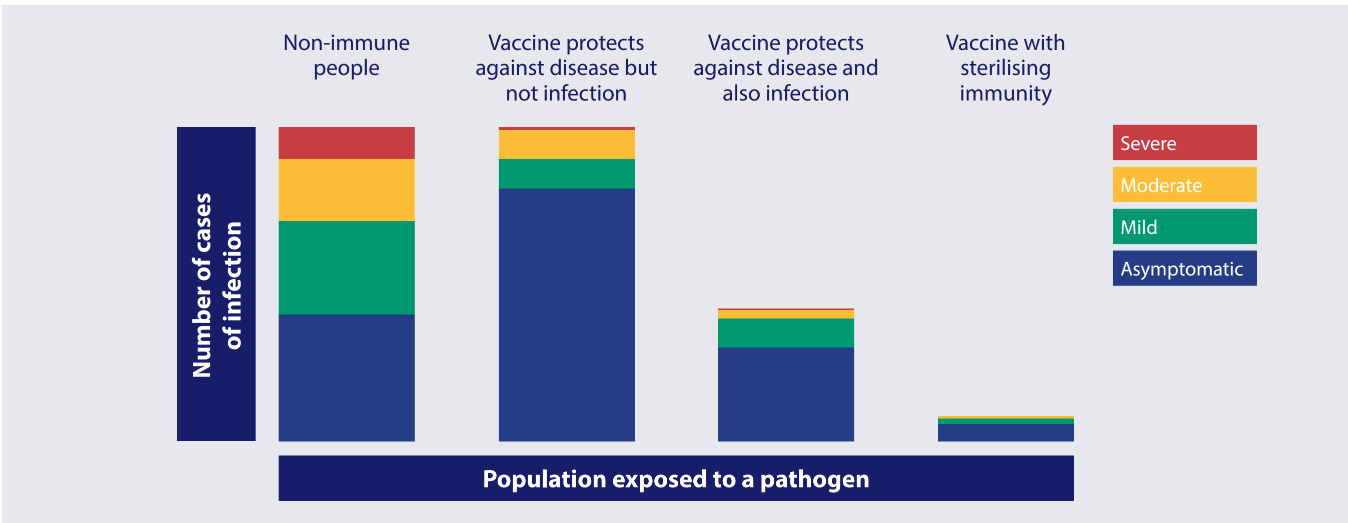

Figure 1. Illustration of vaccine effectiveness against infection and disease

Herd immunity

One formerly popular term that has seen less frequent usage recently is herd immunity. Herd immunity refers to the indirect protection provided to vulnerable members of a population by the majority that are immune – either due to vaccination or prior infection – to a particular pathogen. As the term might suggest, it was first conceived in the veterinary field, and one of the earliest records of its use was in 1894 by veterinary scientist Daniel Elmer Salmon (in whose honour the bacterium species *Salmonella* was named) from the United States Department of Agriculture, referring to resistance to disease in healthy herds of hogs.

The theoretical "herd immunity threshold" refers to the minimum proportion of a population that has to be immune, above which that pathogen will not spread successfully and will decline. The mathematical formula for calculating this theoretical herd immunity threshold would not challenge the average PSLE student, being 1 - 1/R0. Thus, this threshold is higher for a more transmissible pathogen; eg, for measles (R0 of 12-18) it would be approximately 92% to 95%, whereas for seasonal influenza (R0 approximately 1.3), a threshold of approximately 23% would suffice. For the COVID-19 Delta variant, this threshold will be between 80% and 88%.

In the real world, we humans do not move all over nor mix randomly, and the actual reproduction number R (as opposed to the basic reproduction R0) of a pathogen will vary under different circumstances. Hence, for migrant workers shut in dormitories during the circuit breaker (CB), for instance, the actual reproduction number R of SARS-CoV-2 would have been far higher than the basic reproduction number R0. The virus spread like wildfire through that population, with infection rates exceeding 50% in most dormitories, and reaching 90% in a few. However, R was <1 for the rest of us during CB, and the spread of COVID-19 was brought under control for the rest of Singapore. In the real world, therefore, the actual herd immunity threshold is very challenging to calculate, even for a small country like Singapore which will have multiple longstanding and transient communities with varying degrees of mixing.

Herd immunity conjures up images of zero COVID-19 cases or even eradication of SARS-CoV-2, but this view is fundamentally incorrect. As can be seen from the belaboured explanation above, the public health concept of the term is more nuanced: even if herd immunity is reached, there may be low levels of SARS-CoV-2 circulating in the community, as with measles in Singapore.

For many other people, herd immunity is viewed as a proxy to life returning to a near pre-pandemic normal with the relaxation of safe-distancing restrictions and greater freedom of travel. This is a fair approximation, although the outcome is neither binary nor cast in stone. The higher the vaccination rate, the more people will be protected against symptomatic and severe COVID-19. Non-pharmaceutical interventions such as mask-wearing in public and safe-distancing will also reduce the transmissibility of SARS-CoV-2. Thus, a combination of high vaccination rates and various community interventions will blunt the spread of the virus to acceptable levels that will not overwhelm our healthcare system.

Because the vaccines are imperfect, and new variants and time may reduce the effectiveness of current vaccinations, there is little certainty about what is actually required to reach herd immunity nor how long that state will last. It is probably best – which seems to be what is being practised in Singapore with regard to official communications – to drop the mention of herd immunity and develop clearer outcomes in describing the end of the transition to an endemic COVID-19 state.

Conclusion

The current aim of mass vaccination is to protect sufficient numbers of people from COVID-19, particularly those at highest risk of spreading the virus or developing complications from infection. This will prevent our healthcare system from being overwhelmed, as hospitalisations and deaths from COVID-19 remain low. In principle, if we "convert" COVID-19 into a disease that has about the same individual and population risk as influenza, then this will most likely be acceptable to most of us and will be the optimal outcome for exiting the pandemic.

We have been extraordinarily fortunate in having multiple effective and safe vaccines for COVID-19 within such a short period of time. It is now important to be clear about how we can transit out of this pandemic phase to a new normal that will be safe for as many people as possible, with relatively minimal impact to how we live our lives. Ideally, this should be done without significant fragmentation of the community, including among us doctors. ◆

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