COVID-19 vaccines and herd immunity: Perspectives, challenges and prospects

Rebecca S.Y. WONG*

Faculty of Medicine, SEGi University. No. 9, Jalan Teknologi, Taman Sains Selangor, Kota Damansara, PJU 5, 47810 Petaling Jaya, Selangor, Malaysia.

Abstract

The coronavirus disease 2019 (COVID-19) is one of the biggest public health threats in the 21st century. Nearly every country in the world has been affected by COVID-19. The magnitude of the problem, with over 179 million confirmed cases and 3.8 million deaths worldwide, has driven researchers to search for vaccines to combat the disease. The discovery and development of a new vaccine, from the initial stage to the vaccine finally reaching the patients, usually take many years. However, given the urgency of the situation, many clinical trials on the COVID-19 vaccines have been conducted at extraordinary speed, whereas several vaccines against SARS-CoV-2 are being administered worldwide. This article gives an overview of the different types of COVID-19 vaccines, with a focus on those with promising results and are commonly used worldwide. It also gives an overview of herd immunity and discusses the challenges in achieving herd immunity through the global vaccination campaigns. Last but not least, some strategies that may be used to address these challenges are discussed.

Keywords: COVID-19, SARS-CoV-2, pandemic, vaccine, herd immunity

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is caused by an infectious agent known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously known as 2019-nCoV). The disease has spread uncontrollably across the world since its emergence in December 2019. As of 21st June 2021, there were more than 179 million confirmed cases of COVID-19 with more than 3.8 million people losing their lives to the disease.1 With a high number of confirmed cases and deaths every day, the world is now facing one of the most challenging health threats of the 21st century. The disease has caught the attention of scientists, healthcare professionals and government authorities globally. Identifying and treating infected individuals, as well as preventing the spread of COVID-19 have become the top priorities worldwide.

Ever since the emergence of COVID-19 in December 2019 and the declaration of COVID-19 as a pandemic by WHO in March 2020, many pharmaceutical companies have started a race against time to explore the use of various drugs to combat the disease. However, to this end, there is no definitive or curative drug for COVID-19. The current treatment of COVID-19 is mainly symptomatic. On the other hand, many pharmaceutical companies are working round the clock to develop vaccines against SARS-CoV-2 in an attempt to break the chain of transmission. Some companies such as Pfizer,2 Moderna3 and AstraZeneca4 have reported that their vaccines are highly effective against SARS-CoV-2 infection which brings great hope to the world that the pandemic may be under control in the near future.

At present, several vaccines are being investigated or have obtained authorisation for emergency use across the globe. These vaccines have been developed based on different technologies and their efficacies vary, but they all serve a common purpose, i.e. to induce active acquired immunity against SARS-CoV-2 with the aim to reduce the spread of COVID-19 or the severity of disease, in case a vaccinated...
person is infected. The first part of the article gives an overview of the different types of vaccines used in COVID-19 with regards to the current state of science related to vaccine technologies and efficacies. The second part of the review discusses herd immunity, as well as the challenges faced in achieving herd immunity against SARS-CoV-2 infection through the global vaccination campaigns.

1. Vaccine development for COVID-19

Even though pharmacotherapy may alleviate symptoms in some cases of COVID-19, one important way to bring the pandemic to a halt, so that the world will be back to normalcy, is to come up with vaccines that can slow disease spread or even break the chain of transmission. Therefore, vaccine development plays a vital role in COVID-19 research.

1.1. Stages of vaccine development

Under normal circumstances, the development of a vaccine usually takes many years. It can be divided into four main stages: 1) exploratory stage, 2) preclinical stage, 3) clinical stage and 4) post-marketing stage. Each stage has many stringent requirements by the regulatory authorities such as the FDA. Using the FDA guidelines as an example, the usual stages of vaccine development are summarised in Fig. 1.5 However, in the case of COVID-19, it will not be feasible for vaccine development to follow the usual time frame due to the urgency of the situation. To speed up the process, various phases are carried out in parallel but the usual safety and efficacy monitoring mechanisms are strictly followed.6 It is noteworthy that not all drugs and vaccines will end up in the market after many years of hard work and millions of research funds being exhausted. In general, the success rate depends on the type of research. Wong et al. estimated the probability of success for drug and vaccine clinical trials and reported an overall success rate of 13.8%. However, the probability of success for infectious disease vaccine alone was estimated to be 33.4%.7

1.2. Types of vaccine against SARS-CoV-2

Currently, there are six main types of vaccines that have reached various stages of vaccine development i.e. 1) nucleic acid (DNA or RNA) vaccines, 2) protein-based vaccines, 3) live attenuated virus vaccines, 4) inactivated virus vaccines 5) virus-like particle vaccines and 6) virus vector vaccines. For nucleic acid vaccines, either DNA or RNA is inserted into the human host cells to produce the viral protein required to stimulate an immune response in the host. For live attenuated virus vaccines, the weakened but non-infectious live virus is injected, which stimulates an immune response similar to that of a natural infection. For inactivated virus vaccines, the non-infectious inactivated virus is injected, which stimulates an immune response similar to a natural infection.

![FIG. 1: Stages of vaccine development](image)

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vaccines, the dead and harmless virus is injected while protein subunit vaccines usually contain a synthetic antigenic component of the virus (e.g. spike protein). Virus-like particle vaccines consist of empty, non-infectious virus shells and viral vector vaccines are made up of genetically engineered viral vectors (e.g. adenovirus) to produce coronavirus proteins in the body. All of them have their advantages and disadvantages and are summarised in Figure 2.

2. Candidate vaccines with reported vaccine efficacy

Several pharmaceutical companies have reported the efficacy of their vaccines either in the published literature or in their press release. Some of these vaccines have already been approved for early, emergency or conditional use in many countries. This section gives an update on vaccines with reported efficacy and/or approved use for various purposes.

### 2.1. Pfizer/BioNTech vaccine

The Pfizer/BioNTech vaccine (BNT162b2) is an mRNA vaccine. The results of the Phase III clinical trial were reported in a recent publication by Polack et al. The multinational study involved 43,548 participants aged > 16 years, who were randomly assigned to receive either placebo (n=21,728) or the RNA vaccine candidate (n=27,720). Two doses of the injection were given 21 days apart. Subsequently, 18,556 received the second dose of BNT162b2 (with 48 discontinued the trial), and 18,530 received the second dose of placebo (with 95 discontinued the trial). Among those who completed the second dose, there were 8 cases with confirmed COVID-19 in the vaccinated group, versus 162 cases in the placebo group, giving an efficacy of 95% (95% confidence interval [CI], 90.3 to 97.6). The study also reported >99.99% probability of a true vaccine efficacy, which greatly exceeded the minimum criteria for EUA (i.e. >98.6%)

![FIG. 2: Types of COVID-19 vaccines, how they work and their advantages and disadvantages.](image-url)
probability of true vaccine efficacy being greater than 30%). The efficacy was consistent across age, gender and race and the vaccine was well-tolerated with four participants reported serious adverse effects (injection-related shoulder injury, axillary lymphadenopathy, leg paresthesia and paroxysmal ventricular arrhythmia). Two deaths were reported from the vaccinated group and four from the placebo group, but were considered unrelated to the vaccine or placebo.12

2.2 Moderna vaccine
The Moderna vaccine is an mRNA vaccine. Following Pfizer’s announcement, Moderna reported key findings of its primary efficacy analysis of the Phase III COVE study on 30th November 2020 in a press release.3 Results of the study were later published in the New England Journal of Medicine by Baden et al. in February 2021. A total of 30,420 volunteers were enrolled in the trial. They were randomly assigned either vaccine or placebo in a 1:1 ratio (n=15,210 in each group). The participants received two injections of vaccine (100 µg) or placebo intramuscularly, 28 days apart. There were 185 confirmed COVID-19 cases in the placebo group, versus 11 in the vaccinated group. The study concluded that the mRNA-1273 vaccine candidate demonstrated a 94.1% efficacy against COVID-19 and was well-tolerated in general without any serious adverse effects. The efficacy was consistent across age, gender and race.13

2.3 AstraZeneca vaccine
The AstraZeneca vaccine is a viral vector vaccine. The interim primary efficacy analysis of AstraZeneca’s four randomised controlled trials (COV001, COV002, COV003 and COV005, n=11,636) on the vaccine candidate AZD1222 reported a vaccine efficacy of 62.1% (when given as a one-dose regime of two standard doses; n=2,741) and 90% (when given as a two-dose regime of a low dose followed by a standard dose one month apart; n=8,895). This gives an overall efficacy of 70%. ADZ1222 was well-tolerated for both regimes. There were 175 severe adverse events in 168 participants, of which 84 occurred in the vaccinated group and 91 in the control group. Out of these 175 adverse events, 3 were considered as possibly related (2 in the control group and 1 in the vaccinated group).14

2.4 Sputnik V vaccine
Gam-COVID-Vac (also known as Sputnik V vaccine) is a viral vector vaccine (heterologous recombinant adenovirus (rAd)-based) produced by the Gamelaya Research Institute of Epidemiology and Microbiology in Russia. Logunov et al. reported the preliminary findings from interim analysis of their Phase 3 clinical trial. Two doses of the vaccine were administered in a 21-day interval by intramuscular injection. Both doses (rAd26 and rAd5) were viral vectors that carried a full-length gene encoding a glycoprotein S of SARS-CoV-2. Of the total 21,977 adult participants, 16,501 were assigned to the vaccine group and 5,476, control group, and 19,866 were given two doses of either the vaccine or placebo. The study reported 16 (0.1%) and 62 (1.3%) confirmed COVID-19 cases in the vaccine group and control group respectively, giving a vaccine efficacy of 91.6% (95% CI 85.6–95.2). Four deaths were reported but were considered unrelated to the vaccine and the vaccine was generally well-tolerated.15

2.5 Johnson and Johnson vaccine
The Johnson and Johnson vaccine is an adenovirus-based viral vector vaccine given in a single dose. Recently, Johnson and Johnson released the findings of its Phase III ENSEMBLE study. It was reported that after 28 days of vaccination, its Janssen COVID-19 vaccine candidate, Ad26.COV2.S, had a 66% overall efficacy in preventing moderate (defined as presence of pneumonia, abnormal O₂ saturation/shortness of breath, abnormal respiratory rate, presence of deep vein thrombosis or ≥2 systemic symptoms) to severe (defined as signs of severe systemic illness, intensive care unit admission, respiratory or organ failure, shock, death etc.) COVID-19 and the efficacy in the US, Latin America and South Africa were 72%, 66% and 57% respectively, with a complete protection against hospitalisation and death related to COVID-19. When it comes to prevention of severe COVID-19 alone, the vaccine candidate demonstrated an 85% efficacy across all studied regions in those >18 years of age. Interestingly, nearly 95% of the confirmed cases in South Africa in this study involved a SARS-CoV-2 variant from the B.1.351 lineage.16

2.6 Novavax vaccine
The Novavax vaccine candidate, NVX-CoV2373, is a protein subunit vaccine. A genetic sequence of a spike protein of SARS-CoV-2 encodes for the purified protein used in NVX-CoV2373, which is produced using recombinant nanoparticle technology. On 28th
Jan 2021, Novavax reported an overall vaccine efficacy of 89.3\% (95\% CI: 75.2 – 95.4) via its press release based on 62 confirmed COVID-19 cases (n=56 for placebo group; n=6 for vaccine group) for their Phase III UK clinical trial, which enrolled >15,000 participants aged between 18 and 84 years, with 27\% > 65 years. Among these cases, there were 61 mild to moderate cases (overall) and 1 severe case (placebo group). It is noteworthy that when the efficacy was analyzed based on SARS-CoV-2 strains, a 95.6\% efficacy was reported for the original strain and an 85.6\% was reported for the UK variant strain.\cite{17}

2.7 CanSino Vaccine
AD5-nCOV (trade name Convidicea) is a single-dose candidate viral vector vaccine developed by China’s CanSino Biologics Inc. Unofficially, Pakistan reported that the vaccine has an overall efficacy of 65.7\% in preventing symptomatic COVID-19 and 90.1\% in preventing severe COVID-19. AD5-nCOV demonstrated a higher efficacy for a subset of 30,000 participants in Pakistan i.e. 74.8\% for symptomatic cases and 100\% for severe cases. However, the data has not been released officially by the Pakistan government or CanSino.\cite{18}

2.8 Other vaccines
Vaccines by Sinovac and Sinopharm are inactivated virus vaccines. China has approved the use of these two vaccines in the general public on 31st Dec 2020 and 7th Feb 2021 respectively.\cite{19} No official data on the efficacy of Sinopharm vaccine has been released but China National Biotec Group (a subsidiary of Sinopharm) claimed that the vaccine has an efficacy of 79.34\%.\cite{20} For Sinovac, the efficacy ranged from 50.65\% to 83.5\%, according to trial data from China, Brazil, Indonesia and Turkey.\cite{20, 21} Various types of vaccines used against SARS-CoV-2 infection are summarised in Table 1.

3. Overview on herd immunity
Acquired immunity to a disease can be either active or passive. Passive immunity is something a person acquires from someone else (e.g. antibodies from mother to baby) or something

<table>
<thead>
<tr>
<th>Company/ Institution</th>
<th>Vaccine type</th>
<th>Vaccine Candidate</th>
<th>Dosage/ Storage</th>
<th>Efficacy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/ BioNTech</td>
<td>mRNA</td>
<td>Comirnaty/ BNT162b2</td>
<td>2 doses/ -70°C</td>
<td>95%</td>
<td>[12]</td>
</tr>
<tr>
<td>Moderna/ NIAID</td>
<td>mRNA</td>
<td>mRNA-1237</td>
<td>2 doses/ 2 to 8°C</td>
<td>94.1%</td>
<td>[13]</td>
</tr>
<tr>
<td>AstraZeneca/ Oxford University</td>
<td>Viral vector</td>
<td>ADZ1222</td>
<td>2 doses/ 2 to 8°C</td>
<td>70%</td>
<td>[14]</td>
</tr>
<tr>
<td>Gamelaya Research Institute</td>
<td>Viral vector</td>
<td>Sputnik V</td>
<td>2 doses/ 2 to 8°C</td>
<td>91.6%</td>
<td>[15]</td>
</tr>
<tr>
<td>Janssen Vaccines (Johnson &amp; Johnson)</td>
<td>Viral vector</td>
<td>Ad26.COV2. S</td>
<td>Single dose/ 2 to 8°C</td>
<td>66%</td>
<td>[16]</td>
</tr>
<tr>
<td>Novavax Inc</td>
<td>Protein subunit</td>
<td>NVX-CoV2373</td>
<td>2 doses/ 2 to 8°C</td>
<td>89.3%</td>
<td>[17]</td>
</tr>
<tr>
<td>CanSino Biologics Inc</td>
<td>Viral vector</td>
<td>AD5-nCOV/ Convidicea</td>
<td>Single dose/ 2 to 8°C</td>
<td>66%</td>
<td>[18]</td>
</tr>
<tr>
<td>Sinopharm</td>
<td>Inactivated virus</td>
<td>BBIBP-CoV</td>
<td>2 doses/ 2 to 8°C</td>
<td>50.65-83.5%</td>
<td>[20]</td>
</tr>
<tr>
<td>Sinovac</td>
<td>Inactivated virus</td>
<td>CoronaVac</td>
<td>2 doses/ 2 to 8°C</td>
<td>79.34%</td>
<td>[20, 21]</td>
</tr>
</tbody>
</table>
else (e.g. antibodies from convalescent plasma). On the other hand, a person develops active immunity either by exposure to the infection or via vaccination (Figure 3A). Herd immunity is a type of active acquired immunity. One dictionary defines herd immunity as “protection within a population against a particular disease where a great majority of people are immune to the disease, especially because they have been vaccinated against it” (Figure 3B).22 The key here is “a great majority of people are immune” and to achieve this, vaccination is the way forward as having a great majority of people infected to achieve herd immunity will mean a high number of deaths.

3.1 Herd immunity threshold
More than a century ago, Kermack and Mckendrick carried out a mathematical investigation on the progress of an epidemic. It was concluded that a threshold exists in a homogenous population and is dependent on factors that are specific to the epidemic such as recovery rate, death rate and infectivity. If the proportion of susceptible individuals is below this threshold, then no epidemic is likely to occur. However, a small increase in the infectivity rate may result in large epidemics. In general, an epidemic can come to an end even before the exhaustion of all the susceptible individuals in the population.23

Today, we know that to achieve herd immunity, a certain percentage of the population needs to be immune to the disease. Once this level of herd immunity is reached, people who are not immunised will be protected by those who are and this is referred to as the herd immunity threshold. The herd immunity threshold is different from disease to disease as many factors contribute to the herd immunity threshold. Typically, the herd immunity threshold for contagious diseases ranges from 70-90%. For example, for measles, this threshold is about 90-95%, for polio, about 60-97% and for smallpox, about 80%. Thus far, smallpox is the only disease in the history of mankind that has been successfully eradicated since 1979 as a result of vaccination.24

3.2 Herd immunity threshold for SARS-CoV-2 infection
Even though some have estimated that the herd immunity threshold for COVID-19 ranges from 60% to 70%,25 the proportion of the population that needs to be vaccinated to achieve herd immunity remains largely unknown. It is difficult to determine the herd immunity threshold for SARS-CoV-2 simply because many factors need to be taken into consideration when calculating the herd immunity threshold. One of the factors affecting the herd immunity threshold is the reproductive number (R0) which refers to the number of uninfected people that can be infected by an infected person in a naïve population. The R0 varies from country to country and differences exist even in different parts of the same country.26

For SARS-CoV-2 infection the R0 can range from 1.64 to 6.49.27 Mathematically, it is possible to calculate the herd immunity threshold by using the formula 1-1/ R0. However, the number of susceptible people for any given population changes as the pandemic evolves. Therefore, the effective reproductive number (R) is sometimes used instead. Kwok et al. conducted a study to determine the herd immunity threshold using 1-1/ R in 32 countries and reported that a wide range from 5.66% to 85% existed. This is not surprising because R differs greatly in different countries, which may be influenced by various preventive measures implemented by each country.28 However, these calculations say very little about human behaviour and the changes that take place within the population. Even if a country does reach the calculated threshold, pockets of outbreak may still occur in areas where the vaccination rates are low.

Another factor that makes it difficult to determine the herd immunity threshold in SARS-CoV-2 infection is that the duration of the immunity after COVID-19 is unclear and contradicting findings exist in the published literature. Unlike the lifelong immunity that develops after measles or rubella infections, serial measurements of IgG antibodies against SARS-COV-2 in patients with mild COVID-19 revealed a rapid decay of antibodies within 3 months post-infection.29 Research has also shown that a greater reduction in IgG levels occurred in patients who were symptomatic compared to those who were asymptomatic. In the early convalescent phase, 40% of asymptomatic and 12.9% of symptomatic individuals were observed to be seronegative.30 Another study, on the other hand, showed that antibodies against SARS-CoV-2 lasted more than 8 months after mild infection in which high seropositivity rates ranging from 69.0% to 91.4% were reported.31

Reinfecction after recovery further complicates estimation of herd immunity threshold for SARS-CoV-2 infection. Tillett et al. reported the first
case of reinfection of SARS-CoV-2 in the United States backed by genomic evidence. Reinfection has also been reported in other countries.\textsuperscript{32} In some cases, the reinfection was more severe than the first infection, in others, it was milder.\textsuperscript{33-35} The number of re-infected cases is very likely to be under reported due to difficulties in getting the samples from the two separate infections for comparison of viral genomic differences. Reinfection tells us that depending on natural infection to achieve herd immunity may not be a practical approach.
4. COVID-19 vaccines and herd immunity
Many people have questioned the possibility of achieving herd immunity for COVID-19 through vaccination. Even though many countries have started their vaccination programs, the uncertainties in achieving herd immunity remain as there are numerous challenges ahead. This section discusses some of the challenges faced in achieving herd immunity for COVID-19 (Figure 4).

4.1 Unequal distribution of vaccines
Low- and middle-income countries (LMICs) are often slow in medical and technological advances. In comparison to the high-income countries (HICs) or upper-middle-income countries (UMICs), the LMICs may be at a disadvantage in getting adequate supplies of the COVID-19 vaccines. The LMICs need help if the world were to reach herd immunity and return to normalcy.

As of 21st June 2021, more than 2.62 billion shots of vaccine against SARS-CoV-2 have been given in 180 countries, with about 19.2 million doses being administered worldwide each day. The top countries with a high percentage of the population fully vaccinated are Seychelles (69.3%), Bahrain (60.0%), Israel (56.9%), Malta (57.9%) and Mongolia (49.7%). However, despite the exponential rate in vaccinating people globally, many countries have vaccinated less than 1% of their population, which shows a great disparity in the distribution and availability of vaccines in different countries.

In the Economic and Social Council’s Special Ministerial Meeting, vaccine inequity was viewed as a challenge during this unprecedented pandemic and the Director-General of WHO reported that 82% of the administered vaccine doses at the point of the meeting took place in HICs or UMICs, whereas the LICs only received about 0.2% of the total administered doses. HICs have 1 in 4 people vaccinated but in poorer countries the ratio was about 1 in 500. The Director General of the World Trade Organization (WTO), on the other hand, considered such disparities and inequity in vaccine distribution as “morally unconscionable”.

FIG. 4: Challenges faced in achieving herd immunity for COVID-19
4.2 Different efficacies for different vaccines

Differences in vaccine efficacy discussed in Section 4 may pose a challenge to the achievement of herd immunity. While some vaccines demonstrated >90% of efficacy, others only showed an efficacy of approximately 50%. With these differences, it is even harder to determine the percentage of the population to be immunised to reach herd immunity threshold as several vaccines may be used within the same population due to supply shortages. To overcome this problem, some researchers have suggested mixing two or more COVID-19 vaccines and believed that this could expedite the global vaccination campaign and enhance the immune response. This approach of vaccination is known as heterologous prime-boost, which can be dated back to 1992 in the early efforts of HIV vaccine development.

In one study, different types of vaccines (adenovirus vector, inactivated/recombinant subunit and mRNA vaccines) were administered into mice either alone or in a heterologous prime-boost manner. It was reported that the heterologous prime-boost approach yielded higher levels of neutralising antibodies and modulated the antibody responses. Responses of Th1-biased T cells were also observed to be enhanced. In a preprint, another study reported that the administration of one dose of ChAdOx1 nCoV-19 (AstraZeneca) prime followed by a BNT162b2 (Pfizer/BionTech) boost 8 weeks later resulted in potent immune responses. Individuals who received the heterologous prime-boost regimen demonstrated potent neutralising activity against the Alpha variant (B.1.1.7), Beta variant (B.1.351) and Delta variant (B.1.617). Interestingly, the heterologous prime-boost yielded a 3.9-fold higher neutralising activity when compared to the homologous BNT162b2 regime against the Alpha variant. In the same study, potent T cells reactivity (both CD4+ and CD8+) was also observed, whereas the heterologous prime-boost approach was not associated with serious adverse effect.

4.3 Vaccine hesitancy

In 2019, WHO identified vaccine hesitancy as one of the top ten health threats facing the world. Vaccine hesitancy refers to the refusal or reluctance in getting vaccinated even when a vaccine is available. As long as a large proportion of the population refuse to get vaccinated, herd immunity remains a distant dream. There are many reasons why people are reluctant to get vaccinated. A systematic review and meta-analysis of 28 studies revealed a decline in vaccine intention and an increase in vaccine refusal. When studies were conducted earlier (March to May 2020; n=18), the proportion of those who intended to vaccinate versus those who did not intend to vaccinate was 79% versus 12%. Later studies conducted from June to October 2020 (n=10) reported the proportion to be 60% versus 20%. Some of the factors that were associated with vaccine refusal include being female, being younger, having a lower education or income level or belonging to an ethnic minority in the population.

One study investigated three factors that influence vaccine acceptance in the United States, i.e. efficacy of vaccine, minor side effects and severe adverse effects. Vaccine efficacy was demonstrated to have the greatest effect in influencing vaccine acceptance, followed by severe adverse effects and minor side effects.

In a study involving 1144 participants, as high as 36.8% of the respondents answered “no” when asked about their intent to be vaccinated, whereas 26.4% answered “not sure”. Some of the reasons include concerns over efficacy, safety, side effects as well as the rigor of testing, which resulted in a lack of trust in the vaccines.

In April 2021, the European Union and some other countries announced to suspend or stop using AstraZeneca vaccine due to reported cases of blood clots in those who received the vaccine even though it was claimed that the incidence of blood clots is “extremely rare” previously. In an article published by the British Medical Journal, 79 people have been reported with blood clots and low platelets (of which 19 had died), among >20 million people who have been given AstraZeneca vaccine in the United Kingdom. This is equivalent to a probability of 1 out of 250,000. Most of the cases of thrombosis occurred in women who were under 60 years. Despite the claims that there was no causal relationship between the vaccine and thrombosis and that the chance of having thrombosis is small, these reported cases have led to setbacks of the AstraZeneca vaccine in European and other countries, with some countries restricting the use of the vaccine in people aged 60 or below. Such news in the main stream media might influence the confidence of the public regarding the safety of COVID-19 vaccines.

4.4 Duration of vaccine-induced immunity

The duration of vaccine-induced immunity
remains largely unknown at this point. This is something that only time can tell as the vaccine campaigns in many countries have started less than a year ago. Given the different efficacies of the various vaccines and varying immune responses by different individuals, more studies are needed to better understand the duration of COVID-19 vaccine-induced immunity. Since infection-induced immunity can offer >8 months of immunity according to existing data, some researchers infer that vaccine-induced immunity may last up to a year. In the event of waning immunity post-vaccination, revaccination may be necessary for maintaining a substantial proportion of the population to be immune to the disease.

4.5 Infection after vaccination
A small portion of the vaccinated population gets infected after COVID-19 vaccination. These individuals are referred to as vaccine breakthrough cases. According to the Centre for Disease Control and Prevention (CDC), as of 14th June 2021, >139 million people in the United States have been fully vaccinated and there were 3,729 breakthrough cases that ended up hospitalised (n=3,538, 95%) or dead (n=671, 18%). If a vaccinated person comes into close contact with an infected individual before sufficiency immunity develops, breakthrough infection can occur and he or she is still capable of transmitting the disease. In addition, the emergence of variant strains of SARS-CoV-2 may allow breakthrough infection as not all variant strains are completely covered by all vaccines. However, it is noteworthy that when infection occurs in vaccinated individuals, they may be asymptomatic or presenting with milder symptoms.

4.6 Variant strains of SARS-CoV-2
Variant strains of SARS-CoV-2 have been detected in different parts of the world. The emergence of variants will inevitably have an impact on herd immunity. The CDC has classified variant strains into three categories: 1) variant of interest (VOI), 2) variant of concern (VOC) and 3) variant of high consequence (VOHC). The variants B.1.525 (Eta), B.1.526 (Iota), B.1.526.1, B.1.617, B.1.617.1 (Kappa), B.1.617.3 and P.2 (Zeta) belong to VOI, which have a potential impact on treatment and potentially reduced neutralisation by antibodies produced during previous infection or vaccination. B.1.1.7 (Alpha, first detected in the UK), P.1 (Gamma, first detected in Japan/Brazil), B.1.351 (Beta, first detected in South Africa), B.1.617.2 (Delta, first detected in India), B.1.427 and B.1.429 (Epsilon, both first detected in the US) belong to VOC. These variant strains have demonstrated increased transmissibility and reduction in neutralisation by antibodies produced by previous infection or vaccination in varying degrees. Currently, no variant strains belong to VOHC. The discovery of VOHC must be notified to WHO, reported to CDC and requires specific treatment and prevention strategies.

Studies have shown a reduction in the immune response against various variant strains in vaccinated individuals. For example, B.1.351 (Beta variant) was shown to be 10.3–12.4-fold more resistant to neutralisation by sera of vaccinated individuals and 9.4-fold more resistant to neutralisation by convalescent plasma of individuals who have recovered from COVID-19. However, B.1.1.7 (Alpha variant) was not shown to be more resistant to neutralisation by either convalescent plasma or sera of vaccinated individuals. Another study reported that the escape of B.1.351 from natural and vaccine-induced immunity was largely related to E484K mutation, and to a lesser extent, K417N and N501Y mutations.

In one study, the efficacy of the ChAdOx1 nCoV-19 vaccine (or AZD1222) against B.1.351 was investigated. In the primary end-point analysis, the efficacy was observed to be 21.9% for mild-to-moderate COVID-19, whereas an efficacy of 10.4% in the secondary end-point analysis was observed, suggesting that two doses of the vaccine did not show protection in mild-to-moderate COVID-19 caused by B1.351. With the surge of COVID-19 cases caused by the Delta variant, another study was conducted in the UK to compare the vaccine induce immune response by BNT162b2 (Pfizer/BioNTech vaccine) against three VOCs (Delta, Beta and Alpha variants) with the original strain (Wildtype). Results showed that when compared with the Wildtype, there was a 5.8-fold, 4.9-fold and 2.6-fold reduction in neutralising antibodies for the Delta, Beta and Alpha variants respectively.

5. Can herd immunity against COVID-19 be achieved?
Some experts such as Dr Anthony Fauci referred achieving herd immunity against COVID-19 as “elusive” and “mystical” in one of his interviews, as we cannot be sure what metrics we should use to plan our way out of
the pandemic. Should it be the vaccination rates? Should the \( R_0 \), number of hospitalisations or deaths be used instead? While no one can give a definite answer, this does not mean vaccination is not important. In fact, Dr Fauci went on to say “We need to get away from waiting for this mystical elusive number and just … get as many people as we possibly can get vaccinated as quickly as possible.”

Despite the many obstacles and unanswered questions, we should still encourage people to get vaccinated because research has shown that COVID-19 vaccines do help in reducing the risk of severe disease. With billions of people getting vaccinated globally, researchers now have some real-world data on the effectiveness of vaccines, on top of earlier data obtained from the clinical trials. For example, Thompson et al reported the effectiveness of BNT162b2 (Pfizer/BioNTech vaccine) and mRNA 1273 (Moderna vaccine) in real-world conditions among frontline workers with adjusted vaccine effectiveness of 91% and 91% for individuals who were fully vaccinated and partially vaccinated, respectively. Compared to unvaccinated individuals, those who contracted SARS-CoV-2 infection after full or partial vaccination had a viral load that was 40% lower, with 2.3 fewer days in the sickbed and a 58% lower risk of febrile symptoms. Thus, findings of the study suggest that vaccination is associated with less severe disease evidenced by a reduced viral load, shorter disease duration and reduced febrile symptom risk.

In another real-world study with 86,601 vaccinated subjects matched to an equal number of unvaccinated controls, it was reported that during the follow-up period after 7 days of 2nd dose BNT162b2 vaccine, high effective rates for a wide-range of outcomes were observed. These include 92% for documented infections, 94% for symptomatic illness, 87% for hospitalisation and 92% for severe disease. Such real-world data suggests that vaccination helps in reducing the risk of infection and severe disease.

Hall et al., on the other hand, reported the findings of another real-world study that enrolled 8,203 vaccinated and 15,121 unvaccinated healthcare workers in the United Kingdom. A higher number of infections/10,000 person-days was observed in the unvaccinated group (n=977, 14 infections/10,000 person-days) when compared to the vaccinated group. In the latter, 71 infections were reported (8 infections/10,000 person-days) 21 days after first dose of BNT162b2 and 9 infections were reported (4 infections/10,000 person-days) 7 days after second dose of BNT162b2. Among the infected participants, a lower percentage of vaccinated individuals had typical COVID-19 symptoms when compared with the unvaccinated individuals (36% vs 56%), while the percentage of asymptomatic individuals was higher in the former than the latter (19% vs 14%), suggesting that vaccinated individuals were less likely to have typical symptoms and more likely to be asymptomatic in breakthrough cases.

In a nutshell, current pieces of evidence suggest that it is unlikely we will achieve full herd immunity or eradicate SARS-CoV-2. Instead of aiming for full herd immunity, a practical kind of herd immunity should be the target, in which we can live a near-normal life without having massive and prolonged lockdowns. Similar to the influenza virus, SARS-CoV-2 is likely to linger and become a seasonal infection, but with lower hospitalisation and death rates due to protection offered by the vaccines. In a Nature survey involving 119 experts (immunologists, virologists and infectious disease researchers) from 23 countries, 89% of them felt that it is highly likely or likely for SARS-CoV-2 to become endemic, while more than one-third of them felt that it is possible to eliminate the virus in some regions, with pockets of infections in others, which can be controlled quickly if enough people had been vaccinated. Therefore, people should fear the disease rather than the vaccines, as the benefits of the vaccines far outweigh the risks and vaccination plays an important role if we were to achieve this kind of “practical herd immunity”.

6. Future strategies

When experts were asked what they thought would be the biggest factors driving the circulation of SARS-CoV-2 infection if it were to become endemic, the top three factors were immune escape, waning immunity and uneven vaccine distribution. With these factors and the current challenges in focus, this section discusses some future strategies that may be beneficial as we continue our battle against COVID-19.

6.1 Intensify vaccination efforts worldwide

In a global pandemic, a world effort is needed to bring it to a halt because “no one is safe until everyone is safe”. Therefore, intensifying vaccination programs worldwide is extremely crucial. It is important that low-income and middle-income countries get sufficient vaccines...
to administer to their populations. On the other hand, high-income countries should join countries like China, Russia and the US in recognising the importance of a vaccine patent waiver, as all will eventually benefit if vaccines can be manufactured and distributed evenly worldwide.62

6.2 Genomic surveillance of variants
Since the emergence of COVID-19, numerous variant strains have been identified, whereas monitoring of variants plays a vital role in infectious disease control. Genomic surveillance of current and new SARS-CoV-2 variants gives us more information concerning how the virus evolves and the likely path it will take in the future. It will also alarm researchers and healthcare professionals if a particular variant is likely to cause surges of COVID-19 cases in certain regions. Successful surveillance networks require sequencing and sharing of adequate genomes to trace mutations.63 Moreover, the efforts in the development of good surveillance networks are helpful in navigating the development of next-generation vaccines.

6.3 Vaccine boosters
If waning vaccine immunity were to occur and full herd immunity could not be achieved, it is likely that vaccine boosters are required to prevent future surges especially during winter. In fact, experts believe that annual vaccination is likely, very much like the annual vaccination for influenza. However, it is not sure for how many years vaccine boosters need to be given to attenuate the surges of COVID-19 cases.64

6.4 Next-generation vaccines
Modifying vaccines to accommodate the changing virus is not something uncommon. For example, the composition of the flu vaccine is reviewed before each flu season. Data from genomic surveillance is updated in the World Health Organization Global Influenza Surveillance and Response System, whereas the virus strains that are likely to be circulating in the community are selected to be the targets of the seasonal flu vaccine.65 Like the quadrivalent flu vaccine which has been shown to prevent illness and reduce healthcare utilisation,66 next-generation COVID-19 vaccines can be designed to target more than one strain of SARS-CoV-2, particularly the VOCs. However, good genomic surveillance is the key for this strategy to work well, and a robust model in evaluating and predicting the variants that will be circulating during a particular season is very much needed.

6.5 Continue the quest for curative treatment
To this end, there is not a curative treatment for COVID-19. Previous clinical trials on various drugs have not produced promising results and most therapeutic options for COVID-19 are mainly symptomatic or supportive. However, this does not mean all efforts in the quest for curative treatment should stop. On the contrary, the development of drugs to treat COVID-19 should be more vigorous than ever. Learning from the experience of other infectious diseases like HIV and hepatitis C, pharmacotherapy still plays an important role even though there is no vaccine for these diseases. Hence, future research on drugs to treat COVID-19 should go on while the global vaccination campaigns continue to play their role in this pandemic.

CONCLUSION

Vaccine development for COVID-19 has progressed at extraordinary speed for the past one year, something which was not possible before the COVID-19 pandemic. Given the urgency of the current situation, several research teams have reported the efficacy of their vaccines in Phase III clinical trials in less than a year, whereas various vaccines have obtained authorisation for emergency use in many countries. While the data appear promising, much is still unknown concerning the long-term protective- and adverse effects of these vaccines.

Although determination of the herd immunity threshold for SARS-CoV-2 can be done mathematically, many factors need to be taken into consideration. The reproductive number, preventive measures implemented and human behaviours can all influence the achievement of herd immunity which makes it an elusive concept. Having said that, to achieve herd immunity by natural infection is ludicrous and vaccination is a practical way forward. The global vaccination campaigns are ongoing in many countries and vaccines have been administered at exponential speed. Nevertheless, many hurdles remain in the battle against SARS-CoV-2 infection worldwide. Among these challenges include the unequal distribution of vaccines and vaccine hesitancy. Furthermore, with the emergence of new SARS-CoV-2 variants,60 it is unsure if the currently available vaccines would be sufficient to control the pandemic.
New variant strains are of significance because they not only contribute to immune escape, reduction in vaccine efficacy and breakthrough infections, more importantly, they should be the research focus for the next-generation vaccines, where various variant strains can be targeted to prevent surges in COVID-19 cases post-vaccination. Meanwhile, monitoring of the long-term efficacy and adverse effects of existing vaccines and genomic surveillance of variants should also be emphasised. Some experts believe that SARS-CoV-2 is likely to stay for years. Nonetheless, even if full herd immunity and disease eradication are hard to achieve, a “practical herd immunity” is possible with low levels of mild infection and a near-normal life owing to sufficient vaccine-induced immunity that relieves the strains on the healthcare system.

**Author’s contribution:** The author alone is responsible for the content and writing of this article.

**Conflict of interest:** The authors declare no conflict of interest.

**REFERENCES**


27. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020; 27(2); taaa021.


46. Mahase E. AstraZeneca vaccine: Blood clots are “extremely rare” and benefits outweigh risks, regulators conclude BMJ 2021; 373: n931


60. Torjesen I. Covid-19 will become endemic but with decreased potency over time, scientists believe BMJ 2021; 372: n494.
64. Mahase E. Covid-19: Booster dose will be needed in autumn to avoid winter surge, says government adviser BMJ 2021; 372: n664