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COVID-19 VACCINES – WHAT ARE KNOWN? WHAT ARE NOT YET KNOWN?

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ABSTRACT

COVID-19 is the largest pandemic in the past century since the influenza outbreak of 1918. It has resulted in countless lives lost, widespread suffering, economic ruin to many and caused major upheavals in our way of life. Vaccination is a key enabler to end this epidemic. In what was the shortest time from pathogen identification to effective vaccination in human history, numerous countries have experienced the powerful positive effect of vaccination on their population. Reports of rare but serious adverse reactions, vaccine escape variants, vaccine hesitancy and logistic hurdles have dampened our march towards herd immunity. In this article, we attempt to provide an overview of the COVID-19 vaccination landscape, review important concepts behind COVID-19 vaccinations, describe important vaccine reactions and assess their potential implications towards achieving herd immunity. As the title suggests, there are many open questions still to be answered. The certainty, urgency and importance of global herd immunity is, however, never in doubt.

Keywords: COVID-19, mRNA vaccine, spike protein, variants, breakthrough infections

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INTRODUCTION: WAVE AFTER WAVE

COVID-19 rapidly became a global pandemic of profound significance within a few months of its discovery in late December 2019. Its transmission can be slowed by drastic city or country-wide social distancing measures, economically disruptive or even destructive changes in our way of life, work or play. The case-fatality ratio is heavily dependent on access to healthcare, depth of health care resources, rigour of case reporting and contact tracing, all of which vary vastly from country to country. Disruption of viral transmission through non-pharmaceutical intervention and vaccination the two major pathways for a definitive victory over COVID-19. It is currently our only reply to this global challenge and hence in this review, we highlight key concepts and evidence already known and research gaps on this rapidly changing topic. Any complacency and misgovernance by policymakers have allowed the unforgiving SARS CoV2 to re-establish itself. At the time of writing of this article in mid-May 2021, we have seen the daily rates of infection decreasing in North America and certain countries in Europe from mid-January 2021 but resurgent waves have emerged in the Indian subcontinent, Latin America and some of our ASEAN neighbours.[1] We are of the opinion that rapid and widespread COVID-19 vaccination in the general population will be key to the control of the pandemic.

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RAY OF HOPE: VACCINE CANDIDATES

COVID-19 was partially preluded by SARS in 2003. The similarity in the Spike protein of SARS CoV and SARS Cov2 was studied not only as a critical component of its pathogenicity but also its relevance as a vaccine target. This has significantly accelerated vaccine efforts in COVID-19. A vaccine target needs to fulfil two conditions namely: 1) that an immune reaction against the vaccine target will prevent disease and 2) that the target is sufficiently immunogenic to trigger an immune response.[2]

In the inter-pandemic hiatus, research into alternative vaccine delivery platforms gained increasing importance. We learned that mRNA vaccines must have a poly-A tail, a 5' untranslated region (UTR) cap, coded efficiently to make use of more abundant cognate tRNA, high guanosine-cytosine (GC) content, purified to remove double-stranded mRNA and that it cannot be delivered naked, but should be packaged in a lipid capsule. These modifications create an mRNA similar to the molecular format that is naturally produced but artificially enhanced for maximal translation.[3] Adenoviral vectors with their removed replicative genes and vaccine protein inserted have been used to deliver successful vaccines in animal studies. The removal of the replicative genes renders the virus non-pathogenic.

At the time of writing, there are more than 270[4] vaccines in various stages of research. The mechanisms of action for these vaccines are equally diverse with various nuances within each class.

The mRNA vaccines were the first COVID-19 vaccines to be globally available. The general structure is an optimised mRNA in a lipid capsule. Delivery occurs via passive fusion of lipid capsule with the cell membrane and delivery of Spike protein mRNA into the cytosol. To be complete, mRNA vaccines are divided into self-replicating and non-self-replicating mRNA vaccine. The mRNA vaccines (Pfizer-BioNTech and Moderna) in use now are non-self-replicating. A self-replicating mRNA vaccine encodes an

RNA-dependent RNA polymerase (RdRp) that produces multiple copies of mRNA to translate into more protein of interest. Viral vectored DNA, like the Oxford, Astra-Zeneca, Russian Sputnik and Johnson and Johnson vaccines, delivers its DNA via the cell entry mechanism intrinsic to the virus, in this case, the adenovirus. However, since the pathogenic genes are removed, and the DNA of interest was inserted in their place, no further viruses may be produced by the host cell. The host cell is then employed to transcribe, then translate the DNA into the protein of interest. A protein subunit vaccine delivers the protein of interest embedded in a lipid capsule and in a form similar to that presented by SARS-CoV2. mRNA vaccine and protein subunit vaccines present a spike protein molecule in a pre-fusion configuration to the immune system. It would be immunologically less effective to present the Spike protein in the conformation it assumes after fusion with the ACE2 receptor. An inactivated virus vaccine, like Sinovac, is a proven vaccine platform. The vaccine consists of an inactivated SARS-CoV2 virus and presents an entire virion to the immune system.

VACCINE EFFICACY DATA

Multiple Phase three trials have validated the efficacy of the many COVID-19 vaccines in use today. The two mRNA vaccines[5,6] (Pfizer-BioNTech, Moderna), Oxford Astra-Zeneca[7] vaccine and the Sputnik vaccine[8] have all demonstrated to various degrees of vaccine efficacy, exceeding 90 percent in some instances for the endpoint of symptomatic disease and also their efficacy in preventing severe manifestations of the disease. Surrogate markers of immunity, as determined by titres of neutralising antibodies (humoral immunity) and robustness of Th1 response and quiescence of Th2 response (cell-mediated immunity) are available for the available vaccines, with most showing robust responses in both humoral and cell-mediated immunity to the vaccines. Furthermore, separate studies have also demonstrated that the mRNA vaccines also prevented asymptomatic transmission. Understandably, this outcome is harder to prove and requires frequent swabbing of asymptomatic individuals, both vaccinated and non-vaccinated, across a period of time. Vaccine effectiveness in preventing asymptomatic infection was 80 percent in the reports by Aaron et al[9] and 90 percent in Noa Dagan et al.[10]

FROM HOPE TO HESITANCY

Real-world data published from countries such as Israel have demonstrated a significant decrease in case numbers following the widespread deployment of the mRNA vaccine[10], so why is there still vaccine hesitancy? Most of the reasons for hesitancy stem from concerns for side effects, both short- and long-term. Of the short-term side effects, anaphylaxis needs to be addressed. The Pfizer-BioNTech vaccine and Moderna vaccine have been reported to cause anaphylaxis at a rate of 4.7 and 2.5 cases per million doses respectively.[11] By comparison, the rate of anaphylaxis in influenza vaccination is 0.1 cases per million doses.[12] Like most immediate hypersensitivity reaction, most cases of COVID-19 related anaphylaxis occur within 30 minutes of vaccination and most cases occur after the first dose. This explains the current local practice of observing for 30 minutes after vaccination.

The US CDC guidelines have stated that severe allergic reaction after a previous dose or to a component of the COVID-19 vaccines or known immediate allergic reaction to a component of the vaccine as a contraindication for COVID-19 vaccinations.[13] Local guidelines have listed many other criteria with the intention to be cautious in the administration of a novel vaccine(table). The main concern

Table 1. Summary of vaccine efficacies of five vaccines

Vaccine	Protection from symptomatic infection	Protection from asymptomatic infection	Protection from death
Pfizer-BioNTech	95 percent (95 percent CI: 90.3-97.6) *: protects against severe	0.8; 95 percent CI: 0.56-0.91; p<.0001[9]	N.A.
Moderna	94 percent (95 percent CI: 89.3-96.8 percent) *: protects against severe.		N.A.
Astra-Zeneca	90·0 percent (95 percent CI: 67·4–97) 62·1 percent (95 percent CI: 41·0–75·7)	LD/SD: 58·9 percent (1·0 to 82·9) SD/SD:3·8 percent (–72·4 to 46·3)	N.A.
Sinovac	Pending	Pending	Pending
Sputnik	91 percent (95 percent CI: 85·6–95.2) #	N.A.	N.A

is an undiagnosed allergy to polyethylene glycol, a widely used additive in pharmaceutical products. Hence patients with severe reactions to vaccines, anaphylaxis to unknown triggers and severe drug reactions (SJS, TEN, DRESS) are generally advised to avoid vaccination for now.[14] These conservative recommendations may be revised when more safety data become available.

Anaphylaxis mostly occurs after the first dose of vaccinations and mostly occurs within 30 minutes of vaccination. The latest reported rates are 4.7 and 2.5 cases per million doses for the Pfizer -BioNTech and Moderna vaccine respectively. For context, this is still considerably higher than the 0.1 cases per million doses reported for the influenza vaccine. Females and people with prior allergies are more likely to develop anaphylaxis. In view of this, 30 minutes observation period and adequate resuscitation equipment and personnel on standby are present locally at vaccination centres. Most importantly, no deaths after anaphylaxis were reported.[11]

The most serious side effect after vaccination that has received a lot of publicity has been thrombotic thrombocytopenia observed with the Astra-Zeneca ChAdOx1 nCoV-19 vaccine[15,16] and Johnson n Johnson vaccine. This is pathologically synonymous with heparin induced thrombocytopenia. Both conditions, vaccine and heparin-induced thrombocytopenia, are defined by the presence of the PF4-heparin antibody. In vaccine-induced thrombotic thrombocytopenia, central venous sinus thrombosis (CVST) is the most prominent disease manifestation, with CVST and other thrombotic events occurring in 9 out of 11 and 13 out of 23 patients in a German and English cohort respectively, all within 5-24 days of the first dose of the ChAdOx1 nCoV-19 vaccine. Treatment is strict avoidance of second dose, institution of non-heparin based anticoagulation and intravenous immunoglobulins. The mortality rate is high, 30 percent in the English cohort and 54.5 percent in the German cohort.

VACCINE BREAKTHROUGHS

MMWR recently reported that there were 5800 vaccine breakthroughs in a population of 75 million fully vaccinated persons. This gives a breakthrough rate of 0.008 percent (MMWR). As COVID vaccines do not have 100 percent protective efficacy and breakthrough infections were to be expected. Vaccine breakthrough infections were reported to be milder than infections in unvaccinated individuals. Post-vaccination serology has not been routinely recommended as proof of protection. This is mainly because serology testing and quantification has not yet been internationally standardised and serological correlates of protection, an urgently needed evaluation, has not yet been defined. Serology testing on a small subpopulation exposed to high risk of COVID-19, like healthcare workers and customs officers, for the purpose of certifying fitness for employment is currently a research question yet to be answered.

The concept of vaccine escape variants has already been invoked in many places in the world, most notably B1.1.7 in UK and B.1.351 in South Africa and B.1.617 in India. These variants are listed as variants of concern (VOC), sandwiched in the three-tiered CDC classification system between variants of interest and variants of high consequence. There are currently no variants of high consequence identified. Strictly speaking, to describe them as vaccine escape mutants would be inaccurate, as the mutations that lead to these lineages and variants could also arise when SARS2-CoV were grown and passaged in the presence of convalescent plasma. Earlier research in the use of monoclonal antibodies in COVID-19 infections have also found compensatory mutations rendering the tested monoclonal antibody ineffectual for neutralisation.[17]

There is currently no data describing the vaccine efficacy of any vaccine to individual VOC. The current understanding is that neutralising antibody titre post-vaccination is significantly lower for the VOC compared to wild-type viruses. There is some supportive evidence that a lower level of neutralising antibodies correlates with lower protection against infection but we emphasise that at this time these reports primarily focus on in vitro studies.[18] mRNA vaccines seem to confer slightly less protection against B.1.351 at 77 percent three weeks after the second dose as compared to the 92 percent exhibited against B.1.1.7 at the same time point.[18] In contrast, there is evidence that the mutations in the spike proteins that define these VOC do not result in mutation in the T cell epitopes. These VOCs are still similarly presented to T cells, meaning that vaccines may still present robust T cell immunity to VOC.[19] Hence, currently available vaccines are likely to still retain some protection against VOC. It is the exact quantification of this protection that remains to be answered.

As a final solution to waning vaccine immunity against emerging vaccine escape variants, variant-specific mRNA vaccines are now being studied[20] and hold the potential to always keep vaccine escape variants in check. This "regular booster" approach submits to an endgame of a globally pandemic but much attenuated novel respiratory virus in need of regular vaccination to keep at bay, much like influenza.[21]

One vaccination strategy that has been criticised for promoting vaccine escape variants is the strategy of the delayed second dose. This was first employed in the UK and, more recently, locally in Singapore. Clearly, this is a response to the shortage of vaccine supply and driven by the need to vaccinate as many people as possible. The argument is that partial low avidity neutralising antibodies in the population creates a selection pressure towards more vaccine resistant variants.[22] This simplistic argument is directly countered by the following few points.[23] Firstly, an acute infection like COVID-19 starts with a small founding population and undergoes relatively few generations of replications as compared to chronic infections like HIV. The acute nature of the infection is not conducive for evolutionary selection.

Secondly, single-dose vaccination confers more than half the protection of a regular two dose schedule. Thus, the decreased number of susceptible hosts greatly decreases the efficiency of transmission, further slowing the creation of dangerous variants. Lastly employing such a strategy in a low transmission setting gives an extra layer of safety as the slow evolutionary dynamics in a low transmission setting give no room for selection pressure, like a vaccine, to act.

Yet, a large part of vaccine hesitancy is not about technical facts. An article in the New England Journal of Medicine (NEJM)[24] describes the failure of correcting misinformation and using emotional appeal as a tool to decrease vaccine hesitancy. An insightful book[25] by Larson et al describes that vaccine hesitancy may have deep-seated roots in cultural, socioeconomic factors and historical context. Contextualising this to our local population, means it may not be enough to tell our patients how safe and effective the vaccine is, even less so how the vaccine is needed to reopen the country. The reasons for hesitancy may very well be different from person to person. Hence, Larson's advice is to first try to listen and understand the reasons for hesitancy before attempting to deliver a fixed formula recommendation, a concept universally relevant to the practice of medicine.

NO HERD IMMUNITY WITHOUT CHILDREN

Ever since the availability of COVID-19 vaccines, different countries have started vaccinating their population at various rates. The aim is to achieve herd immunity. In the simplest form, herd immunity is a mathematical concept and informs the proportion of the population that needs to be vaccinated. Starting with the basic reproduction number of the illness, R_0 herd immunity is reached when R_0 decreases to below one. In the case of COVID-19, an R_0 of three demands a decrease of 66.7 percent to reach less than one. 66.7 percent is then divided by the vaccine efficacy (95 percent in the case of the mRNA vaccines) to reach the proportion of the population to be vaccinated, about 70 percent. The presented figures are approximations to illustrate the calculations involved.

Then, it is clear that there are factors that would render herd immunity mathematically impossible. An increase in R_0 (by highly transmissible variants), a decrease in vaccine efficacy or a large population of people ineligible for vaccination (in the case of mRNA vaccines, children), may push the vaccinated population to exceed 100 percent. Vaccine hesitancy further slows the drive to herd immunity.

In a pandemic, sub-populations may be directly protected via vaccinations or indirectly protected through vaccination of their close contact. A modelling study by Kate et al[26] elegantly demonstrated this. In the study, years of life lost, mortality and cumulative infection rate were determined as outcomes. Two scenarios of R_0: 1.15 and R_0: 1.5 were evaluated for each of the five age-stratified vaccine prioritisation strategies, namely less than 20 years old, more than 20 years old, 20 – 49 years old, more than 60 years old and, everybody. The two scenarios simulate a mid-pandemic setting of effective infection control mitigation measures like social distancing and mask-wearing and a pre-pandemic setting without those measures and hence a higher R_0. Within other parameters of vaccine efficacy, vaccine supply, vaccine roll-out rate. the outcomes of the studies show that in both scenarios, vaccinating the mobile 20-49 years old population is more effective for preventing new cases. Greater mortality benefits are gained in vaccinating >60 years olds in R_0: 1.5 but in R_0: 1.15, greater mortality benefits are gained from vaccinating the 20-49 years old population. This study highlights the fact that the mobile population with a high daily contact rate is a very attractive vaccination target.

Initially, both mRNA vaccines and the Oxford Astra-Zeneca vaccine were not approved in children younger than 16 years and 18 years respectively. This is mainly due to these patient subgroups not being included in the initial phase three registration trials. Recently, the Pfizer-BioNTech vaccine was approved for use for children between 12 – 15 years old.[27] Both mRNA vaccines are currently undergoing clinical trials in children as young as six months.

It will be difficult to achieve the benefits of herd immunity without children being immunised against COVID-19 infection.

VACCINE PASSPORT/IMMUNITY CERTIFICATION

A vaccine passport is an attractive concept fraught with many difficulties and perhaps immune certification may be more appropriate.[28] Also, the vaccine passport or immune certification cannot be a standalone measure for reopening. The three questions to answer prior to conferring validity to a vaccine passport are as follow:

- Evidence that vaccination prevents asymptomatic infection and spread.
- Duration of immune protection in vaccinated individuals.
- The prevalence of vaccine escape mutants and rates of vaccine breakthrough infections.

The questions have been answered to varying degrees by the published literature, and some answered in this review. Also, these questions are intertwined. For example, a highly vaccinated population would be less likely to be the breeding grounds for vaccine escape mutants.[20] Viral attenuation of these mutants may render infection less significant, especially so if these mutants manifest milder disease in vaccinated individuals. Already, it is apparent that astronomical amounts of rapidly varying data are needed to grant validity to vaccine passports. Many companies have provided digital solutions to unify test results, infection status and vaccination status and present them on a

convenient platform (smart-phone), but it is likely that the complexities far exceed this. It is likely that a vaccine passport may be a fluid passport with travel permissions rapidly changing as large amounts of data supported by modelling are interpreted. Certainly, this fluidity decreases when the global vaccination population increases and hence the mantra, no one is safe until everyone is safe. The unity that this pandemic requires is truly uncompromising. Such passports and certification will not just be used for travel. Certain schools and universities require documentation of prior immunisation before the students can enter campuses. Certain "frontline" job functions also require proof of immunisation and it was reported in the lay press that several Customs officials in New Zealand were fired because they declined COVID-19 vaccination.

CONCLUSION

This short review attempts to answer the knowns and unknowns regarding COVID-19 vaccination. In any new disease, it is expected that questions often beget more questions. We do have a wealth of peer-reviewed published data that demonstrate the efficacy and overall safety of the current COVID-19 vaccines. Immunisation remains a key enabler for us to move our personal, social and economic life back to some aspects of normalcy. Its effect in controlling COVID-19 infections in the raging epidemics of certain countries is clearly evident.[29] Against the dire need to speed up vaccination globally stands vaccine hesitancy and vaccine supply shortages. Until vaccine shortages are overcome and herd immunity is achieved, drastic infection control measures should apply to curtail the rampant spread of COVID-19. An ambitious mid-pandemic review of a rapidly changing topic surely risks obsolescence. In due course, science will reveal, time will tell.

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LEARNING POINTS

- **COVID-19 vaccinations are very effective in preventing symptomatic infections, asymptomatic infections and they decrease the severity of disease.**
- **Currently, here are 4 major vaccine platforms using mRNA, viral vectored DNA, protein subunit and inactivated virus.**
- **mRNA vaccines are new in its application but established in its basic science.**
- **mRNA vaccines have demonstrated high efficacy and safety. Anaphylaxis is the main side effects and are rare.**
- **SARS CoV-2 Variants have decreased susceptibility to vaccine immunity in vitro.**
- **mRNA vaccines remain effective against most variants.**