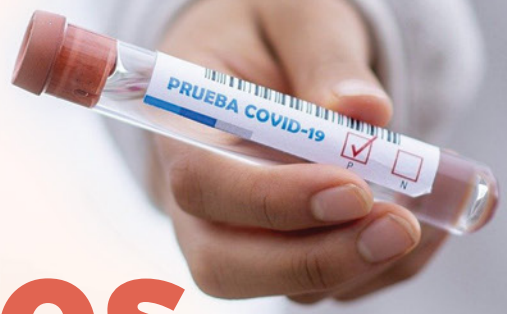
A Closer Look at COVID-19 Vaccines



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Vaccines have only been second to water in saving lives. They successfully eradicated wild-type smallpox, leaving only remnants in two secured laboratories in the world. Can a vaccine overcome the COVID-19 pandemic that has killed more than 1.7 million people? Despite the unprecedented colossal research in this new evolving disease, we expect only more questions, doubts and perhaps dismay.

In a world's first, we have two mRNA vaccines approved by the US Food and Drug Administration (FDA) for use in humans. The technology was first shown successfully in mice in 1990.[1] Since then, significant leaps in technology have enabled its effective use with good immune response. Phase I and II trials of mRNA vaccines have been done in humans for HIV, rabies and influenza, with good tolerability. At the end of 2020, mRNA vaccines were proven highly effective (>94.5%) against the new COVID-19 virus with a two-dose regimen. Emergency use approval was granted in several countries, and the UK and US have started vaccinating their citizens within the same month. Unlike popular culture, current science does not support the incorporation of the mRNA vaccine into human chromosomes. The mRNA are short-lived, cannot be transported into the nucleus and lack the reverse transcriptase to integrate into human chromosomal DNA.

Harnessing new technology: mRNA vaccines

Pfizer-BioNTech's mRNA COVID-19 vaccine (BNT162b2) requires a cold chain of -70 degrees Celsius during transport. At -20 degrees Celsius, the vaccine is stable for two weeks. In a typical clinic's refrigerator of 2 to 8 degrees Celsius, it may be stored for 120 hours (five days). Each multi-dose vial holds five doses, with possible extra doses (a sixth or seventh dose) in some vials. Vaccines must be reconstituted in sterile normal saline. Each dose is 0.3 ml administered intramuscularly, and extra doses are still valid and encouraged for use. All doses should be administered within six hours. The vaccine efficacy in preventing confirmed disease was 94.8% (95% confidence interval 90.3% to 97.6%)[2] after seven days of the second dose. There were nine cases in the vaccine arm, and 172 in the placebo arm. For severe disease, efficacy was 66.3% (95% confidence interval -125% to 96.3%). There were only one case in vaccine arm and three cases in placebo, hence the wide confidence interval.

Solicited local reactions are common with 96% of them being mild to moderate. The symptoms reported include injection site reactions (84.1%), fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%), diarrhoea (15.7%), fever (14.2%) and vomiting (2.0%). These symptoms were more than the typical vaccination at any clinic. Median onset was day two and three, with median duration of one day. Significant adverse events reported include lymphadenopathy (0.3%) and Bell's palsy (two patients out of 20,000 subjects), which occurred three and nine days after the second dose and with resolution of symptoms. Thirteen hypersensitivity reactions were reported versus six in placebo. The literature suggests that this was due to polyethylene glycol. The media has reported allergies in at least two healthcare workers (with known multiple drug allergies), and one anaphylactoid reaction in someone without prior allergies. Recommendations now are for those with multiple drug allergies to avoid vaccination, and to observe an individual for 30 minutes after the vaccination.

The Health Sciences Authority of Singapore (HSA) has approved the Pfizer-BioNTech COVID-19 vaccine under the Pandemic Special Access Route for active immunisation against COVID-19 in individuals over 16 years of age.

Moderna's investigational COVID-19 vaccine (mRNA-1273) was approved by FDA on 18 December 2020, but has not been approved by HSA at the time of writing. FDA assessed efficacy and safety data from about 30,000 participants, randomised in a 1:1 ratio of vaccine to placebo.[3] Efficacy in preventing confirmed COVID-19 cases

occurring at least 14 days after the second dose of the vaccine was 94.5% (95% confidence interval 86.5% to 97.8%) with five COVID-19 cases in the vaccine group and 90 COVID-19 cases in the placebo group. The secondary analysis suggested effectiveness in preventing severe COVID-19 (zero versus 11 cases in the vaccine and treatment group, respectively).

The vaccine tolerability was similar to BNT162b2. The most common solicited adverse reactions associated with mRNA-1273 were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%). Severe adverse reactions occurred in 0.2% to 9.7% of participants, usually after the second dose. The vaccine had other adverse events of lymphadenopathy (21.4%) and Bell's palsy (three reports in the vaccine group, and one in the placebo group).

A traditional candidate

CoronaVac, a COVID-19 vaccine by Sinovac Life Sciences, Beijing, China uses a chemically inactivated SARS-CoV-2 (CN02 strain) in pre-filled syringes. They have published Phase I/II safety immunogenicity data.[4] Two doses are required over a 21-day period. Seroconversion rates were at least 93% in the Phase I/II trials, with the media reporting similar results in Phase III trials. Final results on vaccine efficacy have not been reported but are eagerly awaited. Unlike the other vaccines, China reported that 1 million doses of vaccines (combined numbers from Sinovac Life Sciences and Sinopharm subsidiary China National Biotec Group) have been given under emergency use. United Arab Emirates and Bahrain have similarly approved the vaccine under emergency use.

Other notable vaccine candidates

Other vaccines of deserved mention include Oxford-AstraZeneca (ChAdOx1 nCoV-19) and Johnson and Johnson (Ad26.COV2.S). Both use an adenovirus, of chimpanzee origin for the former and human adenovirus 26 for the latter. The overall efficacy for ChAdOx1 nCoV-19 was 70%, ranging from 62% to 90% with different dosing regimens. Ad26.COV2.S has just completed recruitment of the Phase III trial with no reported results yet. Both vaccines had a temporary halt in their Phase III trials because of safety concerns, but were continued with their safety board approvals later.

Duke-NUS Medical School's collaboration with Arcturus Therapeutics has led to the development of the mRNA-based Lunar-COV19 vaccine. Phase III trials began in December 2020. Unlike BNT162b2 and mRNA-1273, Lunar-COV19 uses replicating mRNA technology, requiring only one dose, stored as a freeze-dried powder. We anticipate the results in early 2021.

There are at least 60 to 80 other vaccine candidates, but many of them will not survive the competition. CSL was one such company. Though the vaccine had good immunological response, it caused false positive HIV results, making it impractical.

Vaccine concerns

Despite the rapid development of the vaccines from the expected eight to ten years to under a year, Singapore's HSA adopted the same criteria for approval as with any other vaccine. These conditions were met by Pfizer-BioNTech. What was lacking was the long-term safety data. A minimum of 3,000 subjects followed up for at least six months is typically required to adequately characterise uncommon adverse events.

Singapore has the benefit of observing the effects of the vaccine on early adopting countries. At the time of writing, at least 1 million doses were administered in the US, and 600,000 in the UK. With time, any serious adverse events would be identified.

Vaccination is also a race against the mutating virus, with two reported significant mutations in 2020 alone (D614G in March 2020 and B117 in September 2020), conferring it transmission advantages. The B117 mutation has allowed it to evade some neutralising antibodies developed as treatment against COVID-19. Though there is no evidence of mutated strains against the current vaccines, one can easily imagine that the multitude of infected cases forms an easy substrate for a mutant virus to evolve against the tide of the vaccinated strain as countries start vaccination. To be successful, vaccination must continue with virus curtailment strategies like safe distancing and mask-wearing.

With the evidence before us, it is now for us to recommend the approved COVID-19 vaccines for use in our patients. May the vaccine give us the much needed boost in our fight against COVID-19. ◆

References

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Dr Leong is an infectious disease physician in private practice. He is happily married to a paediatrician with three wonderful children. He is passionate on vaccination and education. A change in the world must first begin with the broken vessel he sees in the mirror.