Current Status of COVID-19 Vaccine

Authors:
Dr Gilbert T CHUA
MBBS, PDipID, MRCPCH(UK), FHKCPaed, FHKAM(Paed)
Clinical Assistant Professor
Department of Paediatrics and Adolescent Medicine
Li Ka Shing Faculty of Medicine, The University of Hong Kong

Dr Yu Lung LAU
MBChB, MD (Hon), FRCPCH, FHKAM, FHKCPaed
Chair Professor of Paediatrics
Doris Zimmern Professor in Community Child Health
Department of Paediatrics and Adolescent Medicine
LKS Faculty of Medicine, The University of Hong Kong

INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in Wuhan, China in December 2019, rapidly spreading to 216 countries and territories and declared a pandemic by the World Health Organization (WHO) on March 11, 2020, with more than 60 million confirmed cases and 1.4 million deaths worldwide by the end of November 2020.[1] This SARS-CoV-2 is a perfect pandemic virus with higher reproduction number and case fatality rate than seasonal influenza virus, hence cannot be just treated as a "simple flu". Moreover, the incubation period is longer with infectivity begins days before symptoms onset and many cases are asymptomatic yet infectious resulting in difficulties in interrupting transmission.

There is currently no effective treatment, with only non-pharmacological strategies to control the spread of SARS-CoV-2 virus. However, measures such as social distancing, border restrictions, quarantine and isolation carry an enormous negative impact on health, economic, environmental and social changes.[2] The current hope to restore global norms is the development of an effective pandemic vaccine, compressing the usual development timeline from 10 – 15 years to 1 – 2 years by bypassing the conventional stepwise approach of vaccine development. Such compression of the timeline demands the development of multiple vaccine platforms and strategies simultaneously because there is so much uncertainty regarding vaccine efficacy and safety, demanding an approach as diverse as possible to increase the chance of success.

WHAT ARE THE CURRENT COVID-19 VACCINE CANDIDATES?

In less than 12 months since the identification of the SARS-CoV-2 virus, 44 vaccine candidates were undergoing clinical evaluation, and over 154 vaccine candidates in pre-clinical evaluation.[3] The speed of COVID-19 vaccine development is

unprecedented, as compared to no suitable vaccine developed for MERS and SARS 6 years and 17 years after their first outbreaks, respectively. It usually takes more than a decade, and over USD 500 million investment in developing a vaccine, and up to 93% vaccine candidate tested in pre-clinical animal studies would not have been not able to be registered as a final product for clinical use.[4] Multiple vaccine production platforms for these COVID-19 vaccines are being pursued, and we have chosen one each from some of these platforms which provide leading vaccine candidates being tested in phase III. Table 1 summarises the different types of production platforms that were being applied in the development of COVID-19 vaccines.

1. **Inactivated Vaccine – PiCoVacc**

   Developed by Sinovac (Beijing, China), it is an inactivated vaccine using the CN2 strain of SARS-CoV-2 virus, using β-propiolactone to inactivate and alum as adjuvant. Pre-clinical studies have demonstrated that the vaccine could induce SARS-CoV-2-specific neutralising antibodies in mice, rats and non-human primates. Challenge study showed protection in vaccinated rhesus macaques in terms of a decline in viral load and in histopathological changes in the lungs, with no infection enhancement or immuno-pathological exacerbation observed. [5] This vaccine is currently undergoing phase III study involving 8,870 subjects and is estimated to be completed in October 2021.

2. **Non-replicating Viral Vector Vaccine – University of Oxford/AstraZeneca Vaccine (Cambridge, United Kingdom)**

   It is a chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein. A phase I/II single-blind randomised controlled clinical trial conducted in the U.K. demonstrated that the vaccine induces both humoral and cellular immune responses, with homologous boosting which increased antibody responses. Local and systemic reactions were more common but were significantly reduced by prophylactic paracetamol.[6] A phase III clinical trial involving 30,000 subjects is ongoing, and is estimated to be completed in October 2022. Nevertheless, there was a six-day pause on trial for the investigation of an adverse reaction after a participant received the vaccine. Although there was no official release of information on the adverse reaction, some media outlet reported that the participant developed transverse myelitis after receiving the vaccine.[7] The trial was resumed after having been evaluated by an independent safety review committee. With regards to vaccine efficacy, 99% (208 out of 209) analysable participants had neutralising antibody responses 14 days after the booster dose, and T cell responses peaked at 14 days after a standard dose of the vaccine.[8] Latest update released by AstraZeneca on November 23, 2020 also reported that vaccine efficacy of 90% could be achieved by giving half dose first followed by a full dose and was superior to the 62% efficacy of giving two full doses at least one month

apart.[9] However, this preliminary result has been criticised, and another phase III clinical trial will be started to re-evaluate the efficacy.

3. Lipid Nano-particle Formulation with Nucleic Acid Vaccine – BNT162b1, BNT162b2 and mRNA-1273

Developed by BioNTech (Germany) and licensed to Fosun Pharma (Shanghai, China) with Pfizer (New York, USA), the two BNT vaccines are lipid nanoparticle–formulated, nucleoside-modified RNA vaccines encoding for either the trimerised SARS-CoV-2 receptor-binding domain (BNT162b1) or the membrane-anchored SARS-CoV-2 full-length spike protein (BNT162b2).[10,11] In principle, a lipid coat encases the nucleic acid segment coding for the viral antigen of interest so that it could enter the host cells The viral nucleic acid, which will not be incorporated into the human genome, will then be translated to the viral protein and expressed on the host cells, which triggers the host's immune response. In a phase I/II clinical trial involving 195 healthy adults, both vaccines reported having mainly local injection site reactions, such as pain, redness and swelling, as well as mild systemic reactions such as fever. A lower incidence of adverse reactions was observed in older adults aged between 65 and 85. No severe systemic reactions have been reported. The two vaccine candidates were able to elicit dose-dependent SARS-CoV-2–neutralising antibody titres, peaked at 7 to 14 days after the second dose. Younger adults, aged between 18 and 55, generate higher antibody titres than older adults aged between 65 and 85. Nevertheless, all subjects had similar to or higher antibody titres than those of SARS-CoV-2 convalescent serum samples.[12] BNT162b1 and BNT162b2 are currently in Phase II and III studies, respectively involving approximately 30,000 subjects and are estimated to be completed in December 2022. Recent preliminary primary efficacy analysis report for BNT162b2 released from Pfizer and BioNTech demonstrated the vaccine is 95% effective against COVID-19 28 days after the first dose given to participants without prior COVID-19 infection across age, gender and ethnicity.[13]

mRNA-1273 is another RNA vaccine developed by Moderna, which also announced in November 2020 the first interim analysis of 95 participants in the phase III trial, the COVE study, co-conducted with the National Institute of Allergy and Infectious Diseases. Ninety and five of these participants who received placebo and the vaccine respectively contracted COVID-19, therefore a vaccine efficacy of 94.5%.[14]

4. Recombinant Protein Subunit (Trimeric) Vaccine with Adjuvant – NVX-CoV2373

Developed by Novavax (Maryland, USA), the NVX-CoV2373 is a recombinant SARS-CoV-2 nanoparticle vaccine consisting of the trimeric full-length SARS-CoV-2 spike protein with a mutation at S1/S2 cleavage sites to stabilise the S2 subunit in a prefusion conformation, mixed with an adjuvant called Matrix-

M1.[15] Animal study has demonstrated that NVX-CoV2373 with Matrix-M1 protected against SARS-CoV-2 challenge with no evidence of vaccine-associated enhanced respiratory disease.[16] In a phase I/II clinical trial, NVX-CoV2373 appeared to be safe, and was able to elicit immune responses that exceeded levels in convalescent serum from symptomatic COVID-19 patients.[15] Novavax has announced that a phase III clinical trial has been initiated in late September, targeting to recruit 10,000 healthy adults.

WHAT COULD WE EXPECT FROM THE CURRENT COVID-19 VACCINE CANDIDATES

The ideal COVID-19 vaccine should interrupt transmission so that we can resume life before the COVID-19 era. However, it will require a vaccine that could generate not only high titre of neutralising antibody in blood, but also long-lasting respiratory mucosal immunological memory. Studies in COVID-19 survivors have demonstrated that although all patients developed seroconversion,[17] their antibody titres can wane significantly as early as 1 – 2 months post-symptom onset.[18] Experience from SARS survivors in 2003 showed that there was a significant reduction in patients with detectable SARS-CoV IgG three years after infection,[19] and no memory B cell responses were detectable six years after infection,[20] suggesting that antibody responses to SARS-CoV wane significantly over time. On the contrary, memory T cell responses have been reported to have a significantly better longevity.[20] Therefore, the development of the ideal COVID-19 vaccine should not only be focused on the short-term development of neutralising IgG antibodies, but also whether long term effective T and B immunological memory could be generated. All the current vaccines do not offer data on the durability of the immune response beyond the immediate post-vaccination time points; hence the need for revaccination every year or so remains uncertain.

Alternatively, the vaccine given intranasally may generate adequate mucosal immunity to reduce transmission. Studies in animal coronaviruses, SARS-CoV and MERS-CoV have demonstrated that intranasal but not subcutaneous vaccination protected mice from human coronaviruses through airway memory CD4 T cell responses.[21] MERS vaccine animal studies have also shown that intranasally administered vaccines were superior over intramuscular ones in terms of neutralising efficacy.[22,23] Nevertheless, the current COVID-19 vaccines that have entered phase III clinical trials are all to be given parenterally. Currently, one intranasally administered vaccine candidate is the COVAX co-developed by the University of Hong Kong State Key Laboratory for Emerging Infectious Diseases, Xiamen University and Wantai Biopharmaceutical Company of Mainland China. It has been approved for non-phase III human clinical trial.[24]

The currently available phase III COVID-19 vaccine candidates, including those being mentioned above, may only prevent the disease in individuals but not interrupting transmission, the latter requiring a high vaccine coverage rate of perhaps 70 – 80% of the global population. However, the next generation COVID-19 vaccines coming into phase III trials that could generate much higher neutralising antibodies titre and

memory T cells at the mucosal level to stop viral replication in the nose within 1 – 2 days of infection may be able to reduce transmission more effectively.

OTHER VACCINATION STRATEGIES – CONCEPT OF THE TRAINED INNATE IMMUNE MEMORY

Innate immune memory is a recently recognised component of immunological memory induced by several live attenuated human vaccines, including the BCG vaccine. It mediates non-specific protective responses to heterologous infections in addition to pathogen-specific adaptive immune memory. Through transcriptional, epigenetic and metabolic reprogramming of myeloid progenitors in the bone marrow, the BCG vaccinated individuals demonstrated enhanced pro-inflammatory cytokines secretions from their monocytes when stimulated in-vitro by unrelated bacterial and fungal pathogens.[25] Studies have also explored whether BCG can offer a level of protection from COVID-19, in an attempt to explain why regions with universal BCG vaccination carry lower COVID-19 mortality.[26-28] More studies will be needed to confirm the hypothesis.

WHAT ARE THE POTENTIAL COMPLICATIONS OF VACCINATION AGAINST RESPIRATORY VIRUSES?

Safety of vaccination is of utmost importance. Apart from the extremely rare neurological adverse reactions such as Guillain Barre Syndrome with inactivated influenza vaccine, vaccine-associated enhancement of respiratory disease (VAERD) was observed in children during the development of whole-inactivated measles virus and respiratory syncytial virus (RSV) vaccines in the 1960's.[29,30] VAERD is an adverse immunological phenomenon observed in vaccinated subjects that leads to enhanced respiratory diseases after subsequent exposure to the virus. The pathophysiology could be either antibody-mediated, with the generation of non-neutralising antibodies leading to the immune-complex formation and complement deposition, or T_H2-biased (aka allergic inflammation) immune response resulting in an accentuated interleukin-4 (IL-4), IL-5 and IL-13 production.[30] Although VAERD has never been seen in any human and non-human coronavirus infections, in particular, SARS and Middle East Respiratory Syndrome (MERS),[31] animal models for SARS-CoV vaccine has shown the possibility of enhanced immunopathology.[32,33] The possibility of VAERD should, however, not delay efficacy trials as long as early trials demonstrated induction of neutralising antibodies and T_H1 response in human subjects, and the protection against virus replication as well as disease severity in non-human primates.

DISTRIBUTION OF THE VACCINE – THE ART OF THE SCIENCE

The three-staged goals of COVID-19 vaccination include (i) to maintain core community activities, (ii) to reduce disease severity, and (iii) to reduce transmission, all of which begin within each country and expand globally. Otherwise, safe international travel will not be possible. Apart from the development of a safe and effective COVID-19 vaccine, ensuring the vaccine being available to all people around

the world is equally important in order to enable resumption of global travels and activities. Lower-income countries may not be able to afford these vaccines, and higher-income self-financing countries may not be able to secure adequate vaccine supplies through bilateral deals with manufacturers.

The United States Advisory Committee on Immunisation Practices (ACIP) endorsed five ethical principles targeting the development and phased implementation of recommendation for COVID-19 vaccine use. These ethical principles include maximising benefits and minimising harms, equity, justice, fairness and transparency.[34] The first phase entails the period of constrained supply, targeting to vaccinate healthcare personnel, including staff that work in the hospital, long-term-care facilities, pharmacies, etc. In the second phase, as the supply increases and a wider administration of vaccine becomes possible, coverage should include essential workers such as people working in borders, schools, law enforcement units, food industry, etc. In the third phase, as the vaccine supply further increases to meet the demand, vaccination coverage would improve to cover high-risk individuals, including the elderly aged over 65 years old or those with co-morbidities. Children were not included in the initial phase for vaccination because of much milder diseases as well as the relative lack of paediatric subjects having been included in the current vaccine trials.[5] To interrupt transmission in the community, the whole population, including children, may need to be vaccinated ultimately.

A global collaboration, known as the Access to COVID-19 Tools (ACT) Accelerator, aimed to accelerate the development and production of, as well as to ensure equitable access to, COVID-19 tests, treatments, and vaccines. The COVAX was launched in April by the WHO, the European Commission and France in response to this pandemic, and is one of three pillars of the ACT Accelerator that focuses on vaccine development with the commitment to, upon successful vaccine development, provide innovative and equitable access to COVID-19 vaccines to every place across the globe regardless of their financial capabilities. The initial aim is to have 2 billion doses available by the end of 2021, which should be adequate to protect high risk and vulnerable people, as well as frontline healthcare workers.[35] Hong Kong has adopted a two-pronged approach to securing vaccines: buying directly from manufacturers and joining the global COVAX Facility. Furthermore, logistical challenges on the implementation and distribution of the vaccines shall be considered, since some vaccines discussed above demand -70°C storage and transport condition; the need to establish such ultra-low temperature cold chain will pose barriers for low-resource countries.

CONCLUSION

Thanks to the global efforts in combating the COVID-19 pandemic, an effective and safe COVID-19 vaccine might become available in 2021. Careful analysis of phase III clinical trial data will be needed to guide the government and our expert panel in choosing safe and effective vaccines for the people of Hong Kong. In addition to healthcare and essential workers, high-risk citizens should be prioritised for vaccination when the vaccine becomes available to the market as soon as a safe and

efficacious vaccine is available. However, the uncertainty surrounding the availability and performance of these vaccines demands flexibility in the implementation of these policies.

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Table 1. Summary of different types of vaccine platforms (Excerpted from Jeyanathan M et al [26] .?)

Vaccine Platform	SARS-CoV-2 antigens	Neutralising Antibody	CD4+ T cells	CD8+ T cells	Phase III COVID-19 Vaccine Candidate
Inactivated virus	Multiple viral antigens	Strong induction	Th1 or Th2 response depending on adjuvant	Weak response	PiCoVacc
Non-replicating viral vector (ChAd)	S protein	Unimpeded as no pre-existing viral vector immunity	Th1 response	Potent response	ChAdOx1 nCoV-19
m-RNA based vaccine	S protein or RBD (mRNA encapsulated in lipid nanoparticle)	Unimpeded as no pre-existing viral vector immunity	Th1 or Th2 response depending on adjuvant	Depends on the choice of adjuvant and formulation	BNT162b1 and BNT162b2 mRNA-1273
Protein subunit vaccine	S protein or RBD	Strong induction	Th1 or Th2 response depending on adjuvant	Weak response	NVX-CoV2373
Virus-like particle	Multiple viral antigens	Strong induction	Th1 or Th2 response depending on adjuvant	Weak response	Phase I in Canada

ChAd – chimpanzee adenovirus; RBD – receptor binding domain; S – spike