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Review

# Vaccines for COVID-19: The current state of play

Archana Koirala [a,b], Ye Jin Joo [a], Ameneh Khatami [c,d], Clayton Chiu [a,c], Philip N. Britton [c,d,*]

[a] National Centre for Immunisation Research and Surveillance, Westmead, NSW, Australia
[b] Department of Infectious Diseases, Nepean Hospital, Penrith, NSW, Australia
[c] Sydney Medical School, The University of Sydney, NSW, Australia
[d] Department of Infectious Diseases and Microbiology, The Children's Hospital at Westmead, NSW, Australia

## Educational aims

The reader will be able to:

- Understand of the types of vaccine and vaccine platforms being developed for SARS-CoV-2.
- Develop knowledge regarding the concerns around coronavirus vaccine development.
- Appreciated the issues of rapid vaccine development in outbreak settings.

## ARTICLE INFO

## ABSTRACT

There is a strong consensus globally that a COVID-19 vaccine is likely the most effective approach to sustainably controlling the COVID-19 pandemic. An unprecedented research effort and global coordination has resulted in a rapid development of vaccine candidates and initiation of trials. Here, we review vaccine types, and progress with 10 vaccine candidates against SARS-CoV-2 – the virus that causes COVID-19 – currently undergoing early phase human trials. We also consider the many challenges of developing and deploying a new vaccine on a global scale, and recommend caution with respect to our expectations of the timeline that may be ahead.

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## INTRODUCTION

COVID-19 is the disease caused by a novel betacoronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). The disease was first reported in December 2019 Wuhan, China [1] and the full genome was sequenced and published by January 05, 2020 [2]. By March 11, 2020, COVID-19 had spread globally and was declared a pandemic, with, at the time of writing, June 6th 2020, there has been over 6 million people infected and 380,000 deaths [3].

The disease primarily affects the respiratory tract and disease severity can range from very mild rhinorrhoea to severe acute respiratory distress syndrome and death [4–6]. Non-respiratory symptoms such as anosmia, diarrhoea, rash, thromboembolic disorders, myocarditis and vasculitis have also been associated with COVID-19 [5–13]. The median incubation period is estimated to be 5 days with a majority developing symptoms by 11.5 days [14]. COVID-19 patients have been shown to excrete viral nucleic acid at highest levels at the onset of symptoms [15]. This, and other epidemiological data [16] suggests transmissibility within an as yet undefined pre-symptomatic period [16]. Clinical deterioration is usually delayed into the second week of illness and associated with laboratory features of an immune-mediated cytokine storm causing widespread inflammation and disseminated intravascular coagulation, usually with low level viraemia [17,18].

The case fatality rate (death amongst persons with disease) is consistently reported to be age dependent, with a higher percentage in elderly (aged > 70 years) cases dying, although other factors are also associated with intensive care admission and mortality [6,9,19] including sex (male > female), hypertension, obesity and diabetes. The reported case fatality rates [CFR] have been between 0.82% and 9.64%, with variability in CFR likely due to the testing

* Corresponding author. C/o Discipline Child and Adolescent Heath, The Children's Hospital at Westmead, Locked Bag 4001, Westmead, NSW 2145, Australia.
E-mail addresses: Archana.Koirala@health.nsw.gov.au (A. Koirala), YeJin.Joo@health.nsw.gov.au (Y.J. Joo), ameneh.khatami@health.nsw.gov.au (A. Khatami), clayton.chiu@health.nsw.gov.au (C. Chiu), philip.britton@health.nsw.gov.au (P.N. Britton).

frequency and access as well as other health system capacity factors in different locations [20]. The infection fatality rate (IFT; death amongst all people infected – asymptomatic and not tested) is a better estimate of population mortality and is modelled to be between 0.1% and 0.41% [20].

SARS-CoV-2 is one of three coronaviruses that may cause severe respiratory diseases, including fatality, in humans and have been associated with major outbreaks in the last 20 years; the other two viruses being severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Although there were some attempts at development of vaccines against SARS and MERS, including a small number of human phase 1 clinical trials, there are no licenced vaccines for any coronavirus as yet.

In addition to these novel epidemic viruses with zoonotic origins, there are four other endemic human coronaviruses in circulation, HCoV2-229E, -HKU1, -NL63 and -OC43 all predominantly causing mild symptoms of the common cold [21].

## HISTORY OF VACCINES FOR CORONAVIRUSES

Coronaviruses have a large (30 + kb) single-stranded positive sense RNA genome encased by a helical nucleocapsid (N) and an outer envelope comprised of matrix protein (M), envelope protein (E) and spike proteins (S) [22]. The S protein, which naturally occurs in a trimeric form, contains the receptor-binding domain (RBD) responsible for binding onto the angiotensin converting enzyme 2 (ACE2) and entry into the cell (Fig. 1). In SARS-CoV, of all the structural proteins, S protein was found to elicit neutralising antibody and is a major target antigen for vaccine development [23,24].

There have been difficulties in the development of coronavirus vaccines historically. Coronavirus vaccines in animal models that mimic human disease have been immunogenic but generally not shown to effectively prevent acquisition of disease [25]. Further, there is a concern that vaccination, as with natural coronaviral infection, may not induce long lived immunity and re-infection may be possible [26]. In some ways more concerning has been vaccine associated disease enhancement. Previous use of coronavirus vaccines (SARS-CoV and MERS-CoV) in some animal models raised safety concerns regarding Th2 mediated immunopathology [27]. Mice vaccinated with two inactivated whole virus vaccines, a recombinant DNA spike protein vaccine or a virus-like particle vaccine developed lung pathology including eosinophilic infiltration 2 days after being challenged with SARS-CoV which were not seen in the lungs of challenged unvaccinated mice [28]. Similar lung immunopathology was observed in several other studies, particularly in aged mice compared to younger mice [29] that were challenged following vaccination [30,31]. Mice immunised with SARS-CoV N protein vaccine developed severe pneumonia or lung eosinophilic infiltrate upon viral challenge, whereas mice immunised with viral replicon particles expressing glycoprotein did not, suggesting that the N protein antigen may be the antigen linked to this immunopathology. Similar enhanced immunopathology has been seen in mice vaccinated with inactivated MERS-CoV vaccine when challenged with live virus [32]. Vaccine associated disease enhancement may be more of a concern with certain vaccine types. Enhanced disease caused by viral challenge has been notable following administration of inactivated measles and RSV vaccines [33,34], with the possible mechanisms being a Th2 skewed response resulting from formalin inactivation as well as lack of affinity maturation of the antibodies produced [35].

## SARS-COV-2/COVID-19 VACCINES

### Context

Developing and scaling-up mass production of a vaccine rapidly in a global pandemic setting is challenging as it requires many activities to be well-coordinated and occurring in parallel, in contrast to the usual decade long, sequential process with pre-clinical testing, phased clinical trials, planned production and distribution. These challenges result in an aggregation of invested resources and elevated financial risk [36]. In outbreaks, delay in vaccine distribution can result in considerable mortality and morbidity as illustrated by the 2013/2014 West African Ebola epidemic which killed more than 11,000 people [37] and resulted in economic and social burden costing over 53 billion dollars [38]. Tragically, a vaccine had been in development and was later shown to be effective in the prevention of Ebola and may have contributed to controlling the outbreak [39,40]. Unfortunately, the SARS 2003 epidemic ended before vaccine development was complete. Disappointingly, funding agencies then reallocated funds that had been committed to vaccine development, leaving manufacturers with financial loss and setting back other vaccine development programs [36]. In 2017, the Coalition of Epidemic Preparedness Inno-
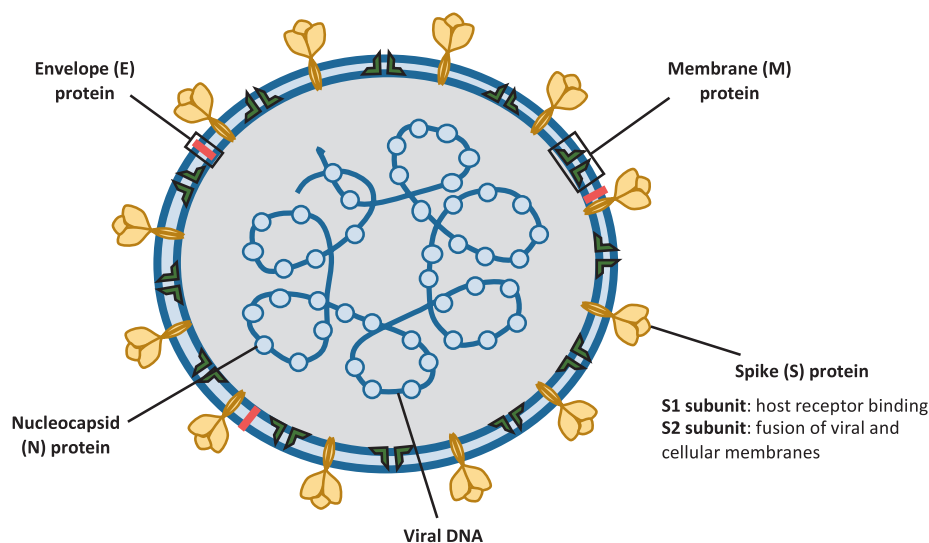


**Fig. 1.** Schematic of the structure of SARS-CoV2. *(Adapted from Lee, C-Y et al, Frontiers in Immunology, 2020)* [100].

vation (CEPI) was formed to address these past failures with a mission to develop a coordinated response to emerging infectious disease threats to ensure vaccine development and early deployment in response to epidemics [41].

*Diversity of technology platforms*

One method for overcoming road blocks has been through the use of new technology platforms to expedite vaccine development [42]. Vaccines licensed in humans have traditionally been live attenuated viruses (e.g. Measles, mumps, rubella), inactivated viruses (e.g. inactivated polio vaccine) protein or polysaccharide conjugated subunit vaccines (protein: acellular pertussis, hepatitis B; polysaccharide conjugated: pneumococcus, meningococcus), and virus-like particles. Over the last decade, a range of new technology platforms have been developed and include vaccines composed of nucleic acid (DNA and RNA) and viral vectors and recombinant proteins.

1. Recombinant vaccines/viral vectors

Viral vector technology involves the delivery of one or more genes that encode a target antigen within an unrelated, engineered virus. The viral vector can be replication competent (live attenuated) or replication deficient. For HIV, Ebola, Zika and Chikungunya, vaccines using viral vectors including adenovirus (Ad), measles virus (MV), vesicular stomatitis virus (VSV), alphaviruses, poxviruses and herpesviruses allowing for insertion of 5 kb or more of the transgene have shown ability to stimulate cellular and humoral immunity [42,43]. Concerns with this platform are with the likely slower speed of vaccine manufacturing in an outbreak setting given the need for biosafety level 2 (BSL2) laboratories, and possible pre-existing immunity in vaccine recipients to viral vectors such as Ad5 and MV decreasing the effectiveness of the vaccine. Approaches such as the selection of low human prevalence adenoviral serotypes (Ad26 or Ad35) have been used to circumvent such an issue [42,43]. The recombinant vesicular stomatitis virus-Zaire Ebola virus (rVSV-ZEBOV) Ebola vaccine is currently the only vector-vaccine that has been licensed and available for human use, and only produced and used to a limited extent [44–46].

A MERS-CoV vaccine (MVA-MERS-S_DF1) using modified vaccinia virus Ankara and expressing the spike (S) protein of MERS-CoV was evaluated in an open label, phase 1 trial on 26 individuals aged 18–55. It showed a favourable safety profile without any severe adverse effects but induced only a relatively limited humoral and T-cell response to the MERS CoV [47]. Reassuringly, the study showed that although vector specific neutralisation antibody was elicited, the vaccine still elicited antibody responses against the transgene following booster immunisation [47]. Results of the phase 1 clinical trial for an alternate vaccine, ChAdOx1 MERS vaccine that uses a replication deficient simian adenoviral vector expressing the spike (S) protein in 24 individuals aged 18–50 years showed that a single dose was able to elicit both humoral and cellular responses against MERS CoV. The majority of solicited and unsolicited adverse events (AEs) reported by participants were mild or moderate and all were self-limiting, and there were no serious AEs related to vaccine administration, which supports progression into phase 1b and 2 trials [48].

2. Nucleic acid vaccines

Nucleic acid vaccines utilize antigen-encoding plasmid DNA or RNA, messenger RNA (mRNA) or viral replicons. The nucleic acid, once taken up by a cell will initiate protein synthesis, to which a humoral and cell-mediated immune response is expected to occur,

similar to natural infection. Such vaccines have been trialled for veterinary infectious diseases and demonstrated immunogenicity, for example, for foot and mouth disease, deer powassan virus and rabies virus [49–51]. Phase I trials in humans are underway for nucleic acid vaccines against Ebola, influenza and Zika virus [42]. The benefit of a nucleic acid platform is the ease with which it allows antigen manipulation and the speed of production, as manufacturing can be synthetic and entirely cell free so circumventing the need for BSL2 laboratories. The disadvantages are that nucleic acid, especially mRNA, are fragile and require an uninterrupted cold-chain process for transport and storage [52]. Phase I clinical trials have been conducted on SARS-CoV and MERS-CoV DNA vaccine candidates. A recombinant SARS DNA vaccine candidate coding for the SARS-CoV N protein genome, developed by the National Institute of Allergy and Infectious Diseases (NIAID) was investigated in 10 adults [53]. A MERS-CoV DNA vaccine (GLS-5300), developed by GeneOne Life Science/Inovio and coding for the full length S protein genome, had a higher number of participants (*n* = 75) [54] Both showed acceptable safety profiles and induced humoral and cellular responses; the MERS-CoV DNA vaccine has advanced into a phase 2 clinical trial [55]. The only other SARS vaccine to have entered a Phase I trial is an inactivated vaccine (ISCV) produced by Sinovac Biotech [56]. There were no reports of human studies in which vaccinated subjects were challenged by the natural virus.

*Vaccine candidates*

As of 1st June 2020, there are currently 124 candidate vaccines that are under development for prevention of COVID-19 listed by the WHO Health Organization (WHO) landscape summary [57] of which 10 candidate vaccines specifically designed for prevention of COVID-19 (Table 1) have entered phase 1, combined phase 1/2 or phase 2 human clinical trials in adults. Most of these trials are enrolling healthy adults (from age 18 years) only, with the upper age limit of inclusion ranging from 50 to 60 years. Two trials are enrolling young participants, one from aged ≥ 3 years and the other ≥ 6 years with no upper age limit in both. One combined phase I/II trial includes older adults (up to age 85 years), while another early phase I trial has been extended in May 2020 to include also older adults (to age 99 years) [58,59].

## RE-PURPOSED VACCINES OF FOR COVID-19 OR OFF TARGET EFFECTS OF OTHER VACCINES

Licensed vaccines such as BCG and oral polio vaccine have been shown to have nonspecific, modulatory effects on the immune system and provide protection against other infectious diseases [60–64]. This has led to the suggestion that these vaccines may have an effect in the prevention of COVID-19 [65]. Three multi-centred randomised controlled trials on BCG vaccine administration are underway in health care workers in Australia [66], Netherlands [67] and South Africa [68]. A measles vaccine trial to prevent COVID-19 in health care workers in Egypt has been registered [58] and oral polio vaccines are being considered in the United States of America [69].

## DISCUSSION

Even if sustained immunity is attained after infection by SARS-CoV2, estimates are that 60–70% of a population would need to be immune to achieve herd immunity against SARS-CoV2 [70]. The safest and most controlled way for effective and sustainable prevention of COVID-19 in a population is to have an efficacious and safe vaccine and the majority of the population successfully vacci-

**Table 1**
Candidate COVID-19 vaccines currently in phase 1 or 2 human clinical trials.

| Platform | Description | Advantages | Disadvantages |
|---|---|---|---|
| **Recombinant Viral vector** | Unrelated virus engineered to encode the target gene of the pathogen. Viral vectors can be replicating or non-replicating | Induces high cellular and humoral immune responses | Possible pre-existing immunity against vector Risk of reversion to virulence Limitations in scaling-up production |
| *Candidate vaccines:* | **Ad5-CoV** Adenovirus Type 5 vector; antigen: Spike protein Phase I: CanSino Biologics ChiCTR2000030906 [88]/NCT04313127 [89] Phase II: Institute of Biotechnology; Academy of Military Medical Sciences ChiCTR2000031781 [90]/NCT04341389 [91] Participants: 18–60 years; Phase I *n* = 108 Phase II: *n* = 508 *Phase I: vaccine was safe and tolerable. No serious adverse effects. 63 participants (Low dose n = 18 [50%]; moderate dose n = 18 [50%]; high dose n = 27 [75%]) developed four fold rise in neutralising antibody titres by Day 28. Pre-existing immunity to Ad5 neutralising antibody titre was observed in half of the participants before vaccination. Out of these, a low proportion seroconverted* [1,76] **AZD1222 (previous known as ChAdOx1 nCoV-19)** Simian adenoviral vaccine vector; antigen: Spike protein Phase I/II: University of Oxford NCT04324606 [92] Participants: 18–55 years; *n* = 1090 | | |
| **Inactivated** | Pathogen virus inactivated by chemicals or radiation | Easy to prepare High safety | Variable efficacy |
| *Candidate vaccines:* | **PiCoVacc** Phase I/II: Sinovac Biotech Co NCT04352608 [93] Participants: 18–59 years; Phase I *n* = 144; Phase II *n* = 600 Phase I/II: Sinovac Biotech Co NCT04383574 [94] Participants: ≥60 years; Phase I *n* = 72; Phase II *n* = 350 **Inactivated novel coronavirus vaccine** Phase I/II: Beijing Institute of Biological Products/Sinopharm ChiCTR2000032459 [95] Recruitment: Age >/= 3 years; Phase I *n* = 480; Phase II *n* = 1168 **Inactivated novel coronavirus vaccine** Phase I/II: Wuhan Institute of Biological Products/Sinopharm ChiCTR2000031809 [95] Participants: Age >/= 6 years; Phase I *n* = 288; Phase II *n* = 1168 | | |
| **Live attenuated** *Candidate vaccines:* | Live virus whose genome(s) is mutated, inducing immune response but not disease Nil in clinical trials as yet | Induces long-term immunity | Expensive to produce |
| **Protein subunit** | Components of target antigen protein produced in laboratory; some vaccines may use nanoparticle technology | High safety Scalability | High cost Lower immunogenicity and may require adjuvant or repeat doses |
| *Candidate vaccines:* | **NVX-CoV2373** Phase I: Novovax NCT04368988 [96] Participants: 18–59 years; *n* = 131 | | |
| **Virus like particle** *Candidate vaccines:* | Non-infectious self- assembling viral structural proteins Nil in clinical trial as yet | Induces strong immune response | Limitations in manufacturing production |
| **mRNA** | mRNA encoding target antigen (may be complexed with lipid- or polymer-based nanoparticles) | Easier to design Induces strong immune response Rapid manufacture | Requires mRNA to be encapsulated otherwise unstable under physiological conditions |
| *Candidate vaccines:* | **BNT162** Phase I/II: BioNTech/Pfizer Four candidates, two candidates include a nucleoside modified mRNA, one a uridine containing mRNA and the fourth self- amplifying mRNA. Each combined with a lipid nanoparticle formulation. Germany 2020–001038-36 [97] Participants: 18–55 years; *n* = 196 USA NCT04368728 [96] Participants: 18–85 years; *n* = 7600 **mRNA-1273** Lipid nano-particle (LNP)-encapsulated mRNA vaccine; Coding antigen: full length S-protein Phase I/II: Moderna/National Institute of Allergy and infectious diseases NCT04283461 [59] Participants: 18–55 years, extended to 99 years *n* = 155 *Interim Phase 1 Data: 15 participants seroconverted by day 15; 8 participants: all developed neutralizing antibodies* [77] | | |

**Table 1** (continued)

| Platform | Description | Advantages | Disadvantages |
|---|---|---|---|
| **DNA** | DNA that encodes the target antigen | Easier to design<br>Rapid manufacture | May require a special approach to administer the vaccine (e.g. electroporation device)<br>May requires adjuvant Uncertainty of safety issues |
| | **INO-4800**<br>Phase I: Inovio Pharmaceuticals NCT04336410 [98]<br>Participants : 18–50 years $n = 40$ | | |
| | **Plasmid DNA oral vaccine (bacTRL-IL-Spike-1)**<br>Phase 1: Symvivo NCT04334980 [99]<br>Participants: 19 = 55 years; $n = 84$ | | |

nated. In addition, the vaccine should also be readily mass-produced inexpensively, and be easily transportable with minimal cold chain requirements to have global utility. Immunity after primary COVID-19 infection seems to protect against re-infection in primate models and is likely to occur in humans [71]; whether this can be mimicked in vaccines and for how long immunity may last is still uncertain. Following SARS-CoV infection, IgG and neutralising antibody was detectable for 1–3 years following infection which suggests that vaccine-induced protection is unlikely to be long-lasting and may require re-immunization [72–75].

The rapid progression of new vaccine candidates against SARS-CoV-2 into pre-clinical and clinical studies is encouraging. Several phase 1 trial results have recently been released. Ad5-CoV vaccine, conducted in 108 participants showed reasonable safety or tolerability profile and has now progressed to phase II. Humoral and cell mediated responses were seen in participants, albeit less in those with pre-existing Ad5 vector immunity [76]. Interim phase 1 data, released on May 18 on mRNA-1273 demonstrated seroconversion and development of neutralizing antibodies in 8 individuals [77]. It is an open question of whether these candidates will display the necessary efficacy and safety profile in humans to progress further into phase 3 trials and subsequently licensure and use to control COVID-19 transmission. In a review of 11 epidemic infectious diseases, only 1 out of 11 (21 preclinical vaccine candidates) have been shown to go through to end of phase 2a trials, at the estimated cost of USD $319–469 million (range $137 million to $1.1 billion) [78]. In the current climate, some vaccine developers are have shown willingness to start or progress later phase trial preparations even before definitive results of earlier phase trials are available [79].

There have been international collaborative efforts to expedite vaccine development and production. The prior establishment of CEPI has been an integral existing platform that has supported the rapid development of COVID-19 vaccines without having to establish new mechanisms with attendant costs. CEPI is supporting the nine COVID-19 vaccine candidates briefly presented here. Since its formation it has established measures to finance early development of vaccines, up to phase 3 clinical trials. However, it does not have a role in the manufacturing or deployment of vaccines and a consortium of public and philanthropic funders will be required for complete preparedness for vaccine manufacture and delivery.

In addition to CEPI, the WHO and the U.S. National Institutes of Health (NIH) are contributing to global collaborative efforts to accelerate vaccine development. The WHO Solidarity Trial for vaccines is a large, multi-site individually randomised controlled clinical trial to allow evaluation of the benefits and risks of each COVID-19 candidate vaccines within 3–6 months [80]. Further, Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), an international public–private partnership, has been established to co-ordinate and speed up the response to the COVID-19 pandemic. Government organisations (in the US and

one in Europe), international biopharmaceutical companies and a non-profit organisation are all involved in advancing vaccine development [81].

Vaccine efficacy in under-represented and vulnerable populations also remains an issue. A majority of vaccine trials have focused on healthy people between the ages of 18–65 years, excluding the elderly, pregnant women and children. Given the disproportionate mortality rate in people over the age of 60, the elderly need to be considered in vaccine trials to ensure safety, immunogenicity and efficacy data is collected and are prioritised to receive COVID-19 vaccines in outbreak situations. Pregnancy has not been shown to be a risk factor for disease severity and the disease burden is low in children. However, much is still unknown, especially the role of inducing an adaptive auto-inflammatory response such as Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS). There is an urgent need for a better understanding of the immunopathogenesis of COVID-19 to give guidance to the immunological assessment of vaccine responses.

There has never been a more rapid pace to vaccine development. The pandemic situation has been a challenge and a trigger to reconsidering the usual approaches to regulatory assessment and licensing processes. Vaccine companies are showing willingness to commit to scaled-up production prior to definitive phase 3 trial results [79]. The implementation of high quality, aligned surveillance for COVID-19 across multiple regions concurrently with vaccine deployment is critical both for evaluating the real-world effectiveness of a new vaccine against SARS-CoV-2, but also for monitoring its safety in so-call 'post-marketing' surveillance. The association of rotavirus vaccines with intussusception in children was only detected following licensure and deployment of these vaccines [82,83]. The experience of the Philippines with a novel dengue vaccine should also promote a degree of caution with respect to vaccine safety during their population usage even if they appear safe in phase 1, 2 and 3 studies. [84,85] There will be considerable uncertainties regarding the safety of vaccines for COVID-19 given the new vaccine platforms used without prior licensed examples, deployment to population subgroups not included in trials of that particular candidate), additional uncertainty arising from novel adjuvants in quite a number of candidates.

As we have alluded to, the development of a vaccine that shows efficacy in clinical trials is only the beginning of a process to manufacture, deploy and monitor the effectiveness of a new vaccine. The challenges ahead are numerous. As an example, in 2016 as part of the Global Poliovirus Eradication Initiative (GPEI), 155 countries were planned to synchronously shift from trivalent oral polio vaccine (tOPV) to bivalent vaccine (bOPV) [86]. This switch was to be coordinated with concurrent inclusion of at least 1 dose of inactivated polio vaccine (IPV) into routine immunization schedules in 126 OPV using countries. Significant difficulties have been encountered with vaccine manufacturing and supply chains resulting in

interruptions and delays in multiple countries [87]. This experience will certainly inform and improve a potential global COVID-19 vaccine deployment, but should influence a level of caution with respect to our expectations even were an effective vaccine developed.

Despite efforts in fast tracking vaccine development, completion dates for early clinical trials are estimated to be late 2020 to mid-2021 and it may still take longer before a vaccine is licensed for use globally, although the pandemic has triggered reconsideration of the usual approaches to regulatory assessment and licensing. This emphasises the need for proven public health strategies such as physical distancing, early detection, self-isolation and outbreak control remain as important mitigation tools.

## DIRECTIONS FOR FUTURE RESEARCH

- Ongoing progress of candidate vaccines through preclinical and clinical studies.
- Ongoing detailed characterisation of the immunopathogenesis of COVID-19.
- Implementation of large scale post marketing surveillance systems to monitor SARS-CoV2 vaccine safety.

## Acknowledgements

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