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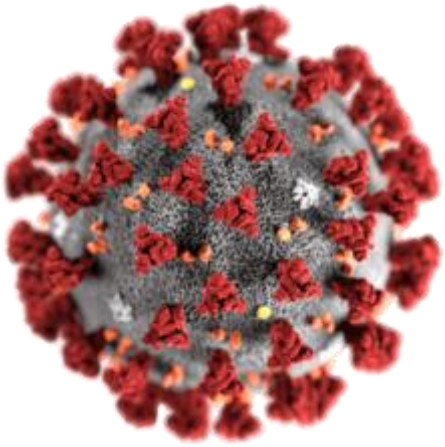

COVID-19 Science Report：Vaccines

NUS Saw Swee Hock School of Public Health

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Announcement

We started the first of our COVID-19 Science Reports in the last week of January 2020, as the very first wave of the COVID-19 pandemic reached Singapore. It was a rapid scan for the current state of development of diagnostics, therapeutics and vaccines that could be useful against the novel coronavirus, as it was called then. It was an urgent request made on a Monday night, and we managed to deliver by that week Friday afternoon.

Since then, it has been a weekly saga (some might call it a nightmare), as we continued to scan and update these reports (highlighting the updated text and paragraphs each week) and added more chapters, first on symptoms and signs, then on laboratory and imaging findings, and then on containment measures. Each addition was responding to yet another urgent request and delivered in the same three to four days, and subsequently updated each week as we continued our scans.

By the fifth week, the Science Report had grown to well over a hundred pages (not counting of course the references) and had become somewhat unwieldy. This was also the same time we were requested to make the report available for downloading on the School's website. We broke up the report into five stand-alone Science Reports and launched them online on 28 February. We were pleasantly surprised by its reception. What started off as "national service" to support our local healthcare and government sector was praised, shared, and even tweeted about.

As the pandemic progressed, we did other reports as well, of course, for the government and for other agencies, not all of which made it online for various reasons. We summarised the available data on fomite-mediated transmission, the risks and management of persons in high density accommodations, how different countries are moving into lockdowns, the use of digital technologies in containment, business continuity measures for enterprises, stay home strategies, and more.

Through it all, our small team were able to deliver on time each week, working through weekends, juggling pieces of work in progress and helped by a group of enthusiastic and hardworking medical students and Public Health interns (some of whom were volunteering their vacations to help). It's been 19 weeks since we started the Science Reports and it is a good time to review and consolidate.

There are now many repositories that cover much of the same ground as our clinical characteristics, diagnostics, therapeutics and vaccines reports. There is also a lot more known about these aspects as clinicians around the world treat their patients. Our student interns have to move on as well, some to examinations, others back to their courses. We will therefore freeze our reports on 1 June 2020, enabling us to focus on the ones that continue to be of critical importance in the global and national responses to COVID-19.

For continuing information on **therapeutics and vaccines** of COVID-19, please see:

- **UK NICE**. *Rapid review evidence summaries and guidance to support clinical practice.*
- **WHO Clinical management interim guidance V1.2**
- **CDC Interim Clinical Guidance**
- Clinical Trial Registries: **US** & **China**. *Latest clinical trials for therapeutics, treatment and vaccines.*
- **WHO Coronavirus disease (COVID-2019) R&D.** *Latest WHO information on therapeutics and vaccines.*
- **WHO draft landscape of COVID-19 candidate vaccines.** *Regularly updated table of the key vaccine candidates and their level of development.*

- **Milken Institute Treatment and Vaccine Tracker.** *Aggregation of publicly-available information from validated sources on vaccines and therapeutics in development.*

For continuing information on **other related topics** of COVID-19, please see:

- **COVIPENDIUM** *Provides information on the virus, immunity, clinical characteristics, fatalities, specific populations and many other issues.*
- **ECDC COVID-19**. *Links through to guidance and information - including non-pharmaceutical measures, discharge criteria, community engagement.*
- **John Hopkins Novel Coronavirus Research Compendium** *Curates and assesses emerging research.*
- **COVID-19 International Research Collaboration** *Aggregates research on diagnostics, vaccines, therapeutics, genomics, economic impacts, wider impacts, etc.*
- **Oxford COVID-19 Evidence Service** *Rapid evidence reviews, data analysis and briefings relating to the coronavirus pandemic and specific issues, updated regularly.*
- **Usher Network for COVID-19 Evidence Reviews** *Rapid reviews on a few key topics such as ethnicity, facemasks, schools etc.*
- **COVID-10 JBI Special Collection** *Resources with a focus on infection prevention and control measures, and mental health and well-being. The site also provides rapid reviews on topics related to treatments as well as staff and patient safety and such as preventive long-term care guidelines, antibody or antiviral treatments.*
- **WHO database** *Collates global literature and has a search function.*

Contents

Vaccines

Some references were from preprints which are preliminary and yet to be peer reviewed, the results should be interpreted with caution.

Introduction

This report highlights only the vaccines funded by CEPI and those in clinical trials, as well as key issues emerging surrounding vaccines.

There are currently no vaccines effective against COVID-19 or indeed any other coronavirus. There has been no significant change in the RNA of the virus since its emergence and potential vaccines are in development. This report provides an overview of vaccines in research and development.

Vaccines are suggested to be an efficient method of beating COVID-19 if the virus is stable and not mutable. It is known that the antibody response is short term amongst common alpha corona viruses but is persistent overtime for beta coronaviruses (SARS, MERS, COVID-19) hence the world has been looking into a viable vaccine. [1]

Many different types of vaccine are being developed as possible vaccine candidates. Inactive or live-attenuated viruses, virus-like particle (VLP), viral vectors, protein-based, DNA-based, and mRNA-based vaccines are being developed and some are now entering animal studies for assessment of toxicology. Only one is commencing phase 1 clinical trial, Moderna's mRNA vaccine. mRNA vaccines are a new technology and as yet none have been licensed for use.

Advantages and disadvantages of viral vectored vaccines, DNA vaccines and RNA vaccines.

Vaccines	Advantages	Disadvantages
Viral vectored vaccines	Stimulation of innate immune response; induction of T and B cell immune response.	induction of anti-vector immunity: cell based manufacturing
DNA vaccines	Non-infectious; stimulation of innate immune response; egg and cell free; stable, rapid and scalable production; induction of T and B cell immune response.	Potential integration into human genome; poor immunogenicity in humans.
RNA vaccines	Non-infectious, non-integrating, natural degradation, egg and cell free, rapid and scalable production; stimulation of innate immune response; induction of T and B cell immune response.	Concerns with instability and low immunogenicity.

Zhang (2019)[2]

The World Health Organization director-general estimated that it will take 18 months for the first vaccine to be available (August 2021).[3] Vaccine development for SARS-CoV-2 will benefit from previous work undertaken on closely related viruses, such as SARS and MERS, advances in vaccine technologies and international strategic collaborations. As such, the WHO has initiated the Solidarity Trial, an international collaboration intended to generate robust data on treatments for COVID-19 (including vaccines). This was also stated to prevent multiple small trials of the COVID-19 vaccine with different methodologies having insufficient evidence individually. [4] [5]

On 14 May, the European Medicines Agency said that a vaccine could be approved in about a year in an “optimistic” scenario. [6]

WHO

WHO have coordinated the development of a Global Research Roadmap for COVID-19. Vaccine development is a key priority area. The Roadmap sets out the key activities and the expected timeline.[7]

The following knowledge gaps were highlighted:

- Strength, duration of immunity, cellular immunity.
- Possibility of enhanced disease after vaccination.
- Animal models for prioritising vaccines.
- Animal models for evaluating potential for vaccine-enhanced disease.
- Assays to evaluate immune response to vaccines.
- Design of late phase vaccine clinical trials.

International Collaborations

Scientists across the world have successfully isolated and cultured the SARS-CoV-2 virus and the atomic structure of the spike protein which will aid vaccine development.[8,9]

Scientists have also identified a set of potential vaccine targets (B and T cell epitopes) that could aid vaccine design.[10]

It was reported that viral S protein subunit vaccines produced higher neutralising antibody titers and more complete protection than live-attenuated SARS-CoV, full-length S protein, and DNA-based S protein vaccines.[11] About half of the patents focused on protein vaccines for COVID-19 comprise the S protein subunit vaccine and vaccines specifically targeting the receptor binding domain (RBD) of the S1 subunit of the viral S protein.[12]

WHO Biological Reference Materials for SARS-CoV-2 are held and distributed by the UK National Institute for Biological Standards and Control (NIBSC).[13] Biological reference materials support quick and reliable diagnosis of infection, as well as the evaluation of vaccines and the effectiveness of treatments.

The Coalition for Epidemic Preparedness Innovation (CEPI) is facilitating the development of some of the vaccine candidates. CEPI is a non-profit organisation funded by some governments, the EU, the Bill & Melinda Gates Foundation, the Wellcome Trust, and the World Economic Forum.[14,15,16]

The European Medicines Agency (EMA) will offer support to vaccine developers, including accelerated assessment and conditional marketing authorisation, to expedite vaccine development.[17]

Hvivo, a company that runs a quarantine unit in a laboratory in the UK is planning to test a less harmful virus that is closely related to COVID-19. This work is being co-funded by Chinese pharmaceuticals firms. Once Hvivo has secured permission from the UK’s Medicines and Healthcare products Regulatory Agency, testing will begin. Up to 24 volunteers at a time will be kept in quarantine and infected with two common strains of coronavirus (0C43 and 229E) which cause only a mild respiratory illness.[18]

Singapore's Duke-NUS Medical School are working with CEPI and international partners to develop a trial for a vaccine for the coronavirus, with plans to begin testing around June 2020.[19]

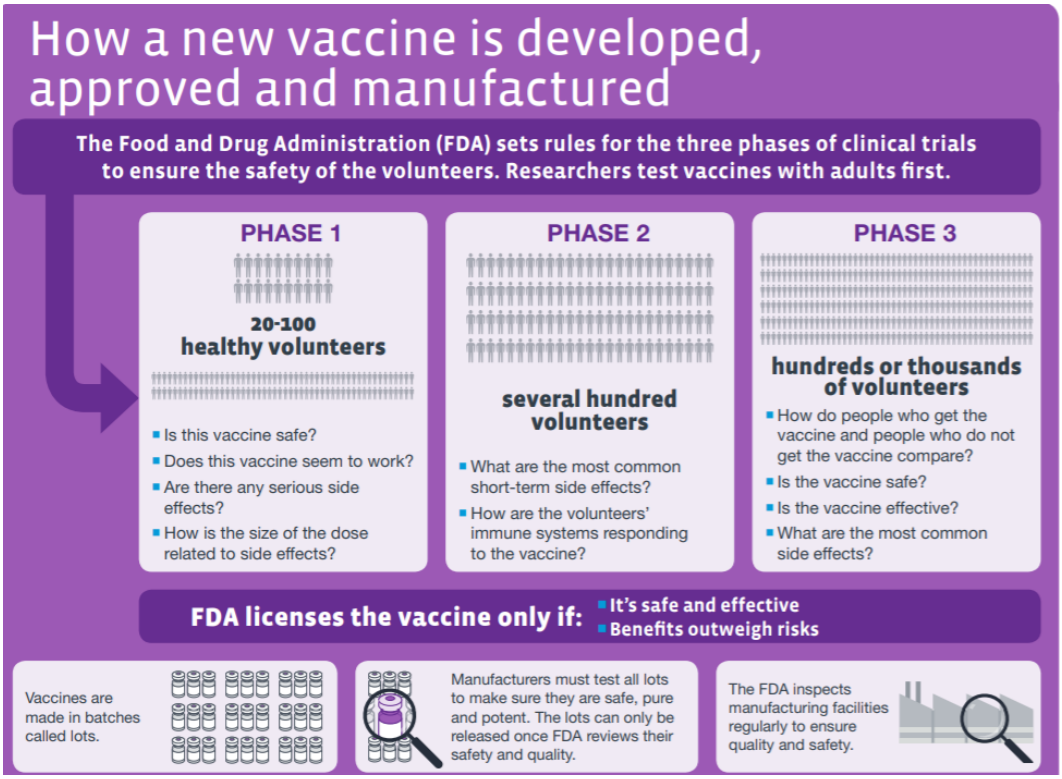
Ensuring Vaccines are Safe and Effective

Preclinical experience with vaccine candidates for SARS and the MERS raised concerns about exacerbating lung disease, either directly or as a result of antibody-dependent enhancement (outlined below).

Testing in a suitable animal model and rigorous safety monitoring in clinical trials will be critical. It is still too early to define good animal models - rhesus macaques, hamsters and ferrets are promising models.[20] Research has suggested that ferrets could be a possible animal model candidate as the virus replicates efficiently in their upper respiratory tract.[21]

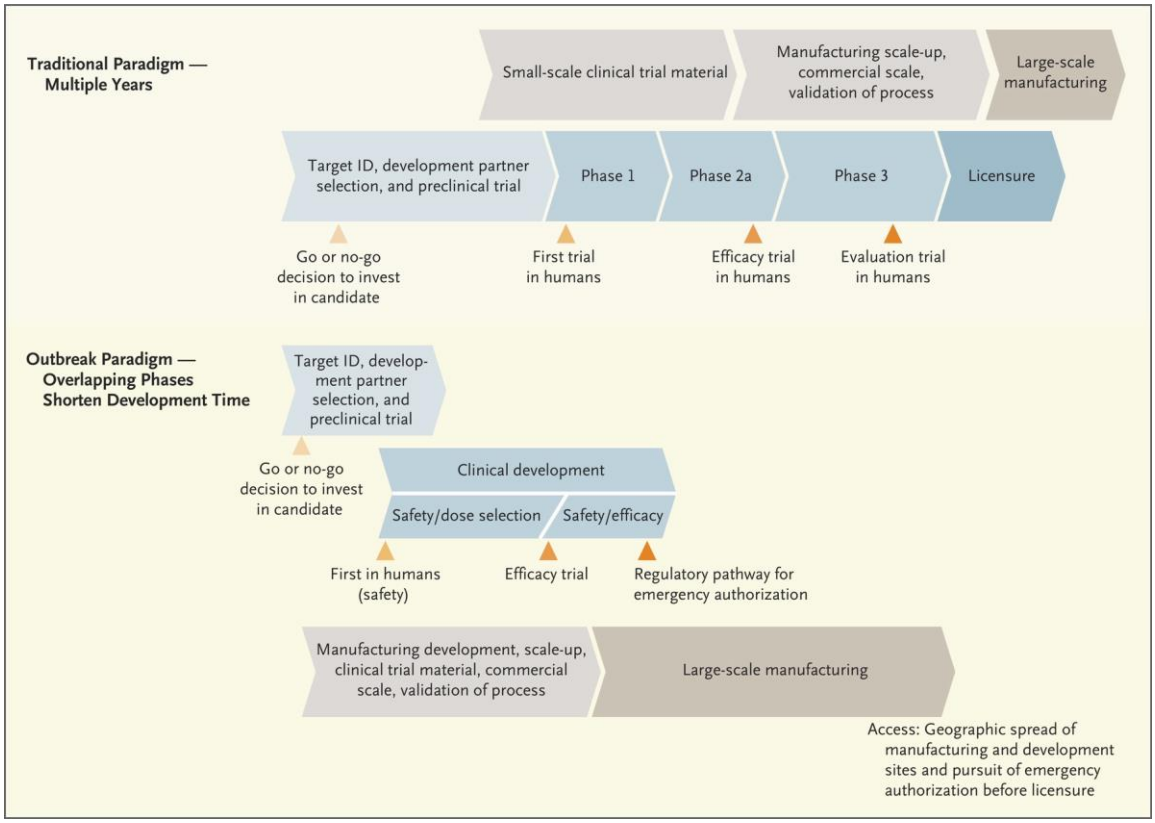
An article in 'Science' suggests that cynomolgus macaque could be an effective animal model for COVID-19 as the animal sheds the virus similarly to humans who experience asymptomatic infection. The fact that virus was shed via the respiratory tract, could explain how COVID-19 became a pandemic rapidly, similar to influenza. [22]

If a vaccine is safe in animals, and studies suggest that it will be safe in people, then the potential vaccine proceeds to clinical trials with volunteers.



CDC (2018)[23]

Vaccine development is usually a very long and expensive process, with a high failure rate, so developers take a linear approach with gateways to pass before moving to the next step. Pandemics change this linear approach to overlapping steps. Steps are taken in parallel before confirming a successful outcome of what would usually be a previous step. This can reduce time, but it rapidly increases financial risk and there can be safety concerns. The diagram outlines the two approaches.



Source: Lurie et al (2020) [24]

After vaccines are licensed, they are monitored closely as people begin using them. The purpose of monitoring is to watch for possible side effects.

If a vaccine is able to be developed, it is likely that there will be discussions on targeting implementation to higher-risk groups, due to limited availability in early phase of roll-out.[25]

Serological testing to identify efficient use of a possible vaccine is likely to be a component of a vaccine strategy.[26]

Furthermore, research highlights that a chemical adjuvant (a delta inulin-based polysaccharide) usage could mitigate the lung immunopathology observed amongst mice in challenge experiments. This was attributed to prevention of heightened Th2-polarised response, through minimising adverse effects of the vaccination, increased safety. [27]

Additional Considerations for Vaccines

A preprint status report[28] written as of 6 April 2020 outlined several additional concerns for vaccines for COVID-19.

Waning antibody response

Generally, we have assumed that developing an adaptive immune response to viruses confers immunity. However, human challenge studies have shown that reinfection of an individual with the same virus is possible after extended periods of time, where survivors for SARS-CoV or MERS-CoV have antibodies that waned after 2-3 years. Furthermore, effectiveness of the COVID vaccine needs to address the issue of reinfection, considering that if SARS-CoV-2 becomes endemic in the population, people are highly likely encounter the virus again, and might be at risk of re-infection.

Effectiveness amongst the age groups

It is widely understood that the elderly naturally undergo age-related immune senescence. This report suggests that protection of older individuals require higher neutralisation titres (based on observation of influenza) than in younger individuals.

Vaccination and safety testing

Safety testing usually performed in a manner compliant with good laboratory practice, usually takes 3-6 months to complete but parts might be skipped if there are already sufficient data for similar vaccines made in the same production process

Time delay until vaccines take effect

As most of the population is naïve to COVID-19, there will be a significant time-gap between the availability of the vaccine and the population gaining immunity to SARS-CoV-2. This is assuming the vaccine produced is effective and has an tolerable level of side effects. A 2 dose vaccination will only achieve protective immunity after 1-2 months after the first dose is administered.

Antibody Dependent Enhancement (ADE)

Vaccine safety is of prime concern as previous attempts to develop a SARS vaccine led to disease enhancement in animal experiments.[29] A 2020 review undertaken by the Saw Swee Hock School of Public Health details the previous research for SARS and MERS vaccines.[30]

A specific concern is around antibody-dependent enhancement (ADE). ADE occurs when non-neutralising antibodies help to facilitate virus entry into host cells. This leads to increased infectivity of the virus in the host. In ADE, the antibodies bind to antibody Fc receptors on the plasma membrane of the cells, and the virus binds to the antigen binding site at the other end of the antibody.[31]

ADE has been observed and studied extensively in flaviviruses (namely dengue virus), and has also been observed in coronaviruses, HIV and Ebola viruses. For these cases, antibodies cannot completely neutralise secondary viral infections, but instead guide virus particles to enter Fc receptor expressing cells. Viruses can use this mechanism to infect cells with the antibody Fc receptors (e.g. in human macrophages). In coronaviruses, the spike protein mediates viral entry into cells by first binding to a receptor on the host cell surface and then fusing viral and host membranes.[32] When ADE occurs, a normally mild viral infection can become life threatening.

The most widely known example of ADE is in the setting of dengue virus infection. The phenomenon of ADE happens when a patient who has previously been infected with one serotype of dengue virus becomes infected later with a different serotype. In the second episode of dengue infection, the clinical course of the disease is more severe, and these patients have higher viral loads compared with those whom ADE has not occurred. In dengue, ADE explains why re-infection with dengue is more likely to be associated with dengue haemorrhagic fever and/or dengue shock syndrome in both children and adults.[33]

ADE has been found and characterised in SARS-CoV. Enhancement was identified, and postulated as the reason for high mortality rate in China, with priming occurring due to infection from milder human coronaviruses (eg 229E).[34,35] In the case of SARS-CoV, anti-Spike protein antibodies were found to be responsible for infection of immune cells.[36,37] In-vitro studies and mouse models have shown that ADE hinders the host's ability to manage inflammation in the lung and elsewhere.[38] This might then lead to complications such as Acute Respiratory Distress Syndrome (ARDS) and other inflammation-based sequelae.

No ADE has been observed in MERS-CoV to date.[39] However, our understanding of MERS-CoV is relatively lesser compared to SARS-CoV.

In the current COVID-19 pandemic, there are questions regarding the nature of the SARS-CoV-2. One of the most perplexing happens to be some discrepancy of serious cases and deaths versus mild cases worldwide. An article written earlier in the outbreak postulates that COVID-19 patients suffering the most may have been primed by one or more prior coronavirus exposures, and due to antigenic epitope heterogeneity, are experiencing the effects of ADE.[40] However, this cannot be confirmed because even though the current clinical evidence suggests this is a possibility, the molecular and immunological host response to SARS-CoV-2 infection has not yet been fully elucidated to prove that ADE is actually occurring. Furthermore, there are arguments that indicate that SARS-CoV-2 primarily targets respiratory epithelial cells, which display vastly different receptors compared to macrophages, which are the main cells implicated in ADE. [41]

Although prior SARS-CoV infection might play a role in ADE, it is not likely to be the predominant priming virus.[40] This is because there is a very low level of SARS-CoV seroconversion in the population apart from workers with direct contact with animals.[42] Furthermore, several bat strains of coronavirus have higher homology with SARS-CoV-2 than SARS-CoV.[43]

In conclusion, ADE might be happening in COVID-19, but at this point it is unknown. However, if ADE is proven to be occurring in COVID-19, both treatment regimens and vaccine developments will need to take this phenomenon into account.

Immune System Trigger

BCG Vaccine

Bacillus Calmette-Guerin (BCG) live-attenuated vaccine for COVID-19. Phase 2/3 vaccine candidate.

BCG live-attenuated vaccine may have an impact on other infections outside TB by boosting the immune system to fight similar infections (eg respiratory infection, sepsis, leprosy, other nontuberculous mycobacteria).[44,45,46] A non-peer reviewed paper hypothesised that countries with BCG vaccination programs at childhood are not as affected by COVID-19 compared to those without programmes.[47] However, peer-review comment articles have outlined issues with this study. These include issues such as data validity due to testing levels varying between countries and also confounding factors, such as population age, ethnicity, rates of certain chronic diseases, time from community spread start date, major public policy decisions and income levels.[48,49,50]

Researchers are exploring whether a TB vaccine can “trigger” a response in the immune system to reduce the impact of the infection of COVID-19.

- University of Melbourne and Murdoch Children’s Research Institute (Australia): Phase 3 clinical trial currently recruiting 4,170 healthcare workers in hospitals in Australia (NCT04327206).[51]
- Radboud University Medical Center (The Netherlands): Phase 3 clinical trial currently recruiting 1,500 healthcare workers (NCT04328441).[52]
- Faustman Lab at Massachusetts General Hospita (United States): Evaluating effectiveness in protecting health workers and in type 1 diabetes.[53,54]

Hepatitis A Vaccine

A study[55] published by Baskent University in Turkey hypothesized that the immune response caused by the Hepatitis A vaccine could be protective against COVID-19 through adaptive cross reaction. However, the hypothesis still needs further in-vitro and molecular studies, which they intend to do.

Japanese Encephalitis

A paper from the Academic Emergency Medicine proposes that there might be cross-protection against COVID-19 conferred by the encephalitis vaccine. The author suggests that corona viruses access the brain though the olfactory bulbs and infect neuronal cells, and this neuro-invasive property could underlie the respiratory failure faced by patients with COVID19. This is further supported by case of meningitis that is attributed to COVID-19 in Japan. The author compares fatality rate in China who does routine JE vaccines and Italy who do not; with rates tallying as 2.3% and 7.3% respectively hence suggesting that might be cross protection by JE vaccine that can be considered in vaccine design and development. [56]

Vaccines in Development

The following section highlights only the CEPI funded vaccines and vaccines that are in clinical trials. There are many companies and partnerships embarking on the development of a vaccine. For example, Duke-NUS Medical School, Singapore and Arcturus Therapeutics have partnered to develop a vaccine. Singapore would own the rights to the vaccine in Singapore, while Arcturus will be free to market it around the world. The aim is to progress to clinical trials around September.[57]

Lists of vaccines in development:

- The WHO has a collection of the latest vaccine reports related to COVID-19, which includes a regularly updated landscape of COVID-19 vaccine candidates
- Regulatory Affairs Professional Society has a COVID-19 Vaccine Tracker

Many of the developing vaccines are based around existing vaccine platforms. A vaccine platform is an underlying, nearly identical mechanism, device, delivery vector, or cell line that can be employed to create vaccines for different viruses. This is how flu vaccines are adjusted each year.[58]

Coalition for Epidemic Preparedness Innovation funded projects

CEPI is supporting the development of a wide range of vaccine candidates and platform technologies, a full list in available on the portfolio webpage.[59]

CEPI is working with GSK to facilitate the use of its adjuvant systems to aid groups partnered with CEPI. Adjuvant systems are added to vaccines to strengthen the immune response, potentially boosting immunity conferred by treatment and allowing for more doses to be produced from a limited supply of vaccine antigen.[60]

CEPI is also funding some of Public Health England's work to evaluate vaccines in their pipeline vaccine that are destined for clinical trials as early as April 2020. PHE Porton Down researchers have collaborated with colleagues at Liverpool and Bristol universities to develop 'synthetic virus' – an exact replica of the actual virus for use in the laboratory. This will enable PHE, working with national and international academic and commercial partners, to carry out rigorous evaluation and testing of vaccines and treatments that enter the clinic.[61]

Company	Vaccine Type	Phase	Information
Moderna	mRNA vaccine	Phase I	(NCT04283461) A phase I clinical trial started on 16 March 2020 for Moderna's COVID-19 (mRNA-1273) vaccine at the Kaiser Permanente Washington Health Research Institute in Seattle. Recruiting was completed on 19 March 2020. Forty-five adults in the US, aged between 18 to 55 years of age are in the trial, split into three cohorts (receiving either 25, 100 or 250 mcg of mRNA-1273 on day 1 and 29). The primary objective is to evaluate the safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across 3 dosages in healthy adults. Participants are followed for 12 months post inoculation. The secondary objective is to evaluate the immunogenicity as measured by IgG ELISA to the 2019-nCoV S protein following a 2-dose vaccination schedule of mRNA-1273 at Day 57.[62] It has been suggested that the vaccine might be available to healthcare workers in September.[63] Moderna has gotten FDA approval to commence Phase 2 trials for its mRNA-1273 vaccine, running them in parallel with its currently ongoing Phase 1 trial. It also announced that it tentatively plans to start Phase 3 trials in the summer. [64] Moderna's COVID-19 vaccine was the first to be tested in the United States, and early data released show overall that the virus was safe and the 8 study participants all produced antibodies against SARS-CoV-2. 3 of them had "flu-like" symptoms, which were attributed to the strong immune response elicited. Moderna expects to start Phase 3 trials in July. [65]
Inovio	DNA plasmid vaccine	Phase 1	(NCT04336410) Developed using its proprietary DNA-based technology platform to design the synthetic vaccine. Inovio's collaborators include the Beijing Advaccine Biotechnology Company, Wistar Institute, GeneOne Life Science and Twist Bioscience.[66] Inovio aims to progress the vaccine through phase one clinical trials in the US and in China (via Beijing Advaccine).[67] Also obtained funding from the Bill & Melinda Gates Foundation to scale up testing and production of a portable device to deliver a DNA-based COVID-19 vaccine that the company is developing.[68]

			Phase 1 clinical trial has started at sites in Philadelphia and Kansas City. 40 participants aged 18-50. International Vaccine Institute will work with Korea National Institute of health for Phase I/II trial in South Korea that will parallel the Phase I study in the US. The trial is undergoing fast track approval in South Korea. [69] Inovio has announced that it will be collaborating with German biotechnology company Richter-Helm BioLogics GmbH & Co. KG to increase its manufacturing capabilities so as to produce its vaccine on a large scale. [70] Data regarding preliminary safety and immune responses from the Phase I clinical trial are expected in June. Phase II and III trials are planned to start in July or August and are pending regulatory approval. [71]
University of Queensland	Molecular clamp stabilized Spike protein	Preclinical	Vaccine candidate under development. They have used their 'molecular clamp' technology to engineer a vaccine candidate that could be more readily recognised by the immune system, triggering a protective immune response.[72] GSK adjuvant systems will be used to enable preclinical experiments designed to assess vaccine effectiveness.[73] Australian Government has also provided $AU17 million to fast-track the vaccine.[74]
CureVac	mRNA	Preclinical	CureVac AG aims to safely advance vaccine candidates into clinical testing as quickly as possible through a rapid-response vaccine mRNA platform for accelerated vaccine development, manufacturing and clinical tests.[75]
University of Hong Kong	Measles vector vaccine	Preclinical [76]	-
University of Oxford	ChAdOx1	Phase I / Phase II	A chimpanzee adenovirus vaccine vector called ChAdOx1. The team has previously developed a MERS vaccine.[77] PHE Porton Down are evaluating the vaccine that will potentially enter clinical trials in April.[78] Oxford's ChAdOx1 vaccine has entered Phase 1 clinical trials, it will comprise of 1112 participants aged 18-55. From this group, 10 will receive 2 doses of the vaccine 4 weeks apart, 551 will receive

			1 dose of the vaccine while the remaining 551 will receive a control vaccine (MenACWY meningococcal vaccine). [79] Expected Timeline of the trial, is that by mid-may 500 volunteers (18-55 y/o) would be vaccinated. Thereafter they would extend the maximum age of trial volunteers to 70 and then above 70. The Phase 3 trial is subsequently expected to involve 5000 volunteers and results are expected by autumn 2020. The university is thinking of initiating trials with partners in other countries to increase their ability to determine vaccine efficacy. [80] It has been reported that the University of Oxford would be collaborating with pharmaceutical company AstraZeneca to manufacture and distribute its ChAdOx1 nCOV-19 vaccine. [81] The University of Oxford has expanded the number of arms in its currently ongoing Phase 2 trial. The 2 new arms aim to investigate the effects of the ChAdOx1 Covid-19 vaccine and the MenACWY control vaccine on patients currently taking prophylactic paracetamol. [82] As of 17 May 2020, the UK government is providing an additional £84 million to accelerate the research of a COVID-19 vaccine, with hopes to make 30 million doses available as early as September 2020. [83]
Clover Bio-pharmaceuticals	S-Trimer	Preclinical	Clover is developing a recombinant subunit vaccine using its Trimer-Tag© technology. The company is developing the vaccine based on the trimeric S protein (S-Trimer) of the virus, which is responsible for binding with the host cell and causing a viral infection. Clover also identified antigen-specific antibody in the serum of fully recovered patients who were previously infected by the virus. A highly purified form of the S-Trimer vaccine is expected to be available for pre-clinical studies around the end of April 2020. GSK will provide Clover with its proprietary adjuvants.[84,85,86] CEPI has announced that it would provide funding to Clover Biopharmaceuticals for it to start Phase 1 clinical trials for its S-Trimer vaccine for COVID 19. Recruitment has started on 28 Apr in Australia. [87]
Novavax	S-protein	Preclinical	Vaccine candidate is designed to bind to the S-protein. Developed using the company's recombinant nanoparticle vaccine technology. Novavax has produced several nanoparticle vaccine candidates for testing in animal models. The company aims to carry out human trials in 2020. [88] Noravax MERS coronavirus vaccine candidate is reported to be aiming to entre phase I clinical trial in April or May 2020.[89]

			As of 11 May 2020, CEPI has invested additional funding of up to $384 million to advance the clinical development of NVX-CoV2373. [90] Novavax announced on 25 May 2020 that is has started Phase I trials of NVX-CoV2373, and have enrolled the trial's first participants. They expect preliminary immunogenicity and safety results in July. [91] Phase II is expected to be conducted in multiple countries including the United States, and would access a broader age range of participants. [92]
Institut Pasteur	Measles Vector	Preclinical	Live-attenuated measles vaccine virus with antigens from SARS-CoV-2 added to it.[93] CEPI has invested in the consortium led by Institut Pasteur. The consortium also includes Austrian biotech Themis and the University of Pittsburgh. Its candidate uses the measles vaccine virus as a vector, which allows the vaccine to deliver antigens directly into the parts of the immune system capable of memory response.[94]

Other vaccine collaborations

Company	Vaccine Type	Phase	Information
CanSino Biologics	Adenovirus Type 5 Vector	Phase I	(ChiCTR2000030906) Based at Tongji Hospital; Wuhan, China. Commencing a phase I clinical trial in humans and intends to recruit 108 healthy people (between 18-60) between 16 March and 31 December.[95] This is a recombinant vaccine (adenoviral vector). 36 people will be randomly allocated to receive low dose (5E10vp), middle dose (1E11vp), or high dose (1E11vp) vaccines. Outcomes will be monitored over 6 months.[96] According to the company announcement, preliminary safety data from the Phase 1 trial allowed Phase 2 to commence. No further details were provided.[97] The National Research Council (NRC) of Canada announced on 12 May 2020 that it was collaborating with CanSino to begin conducting Phase II human clinical trials in Canada. This would allow the NRC to advance a scale-up production process for the vaccine candidate. [98] A study of the CanSino Ad5 vectored COVID-19 Vaccine was published in the Lancet on 22 May 2020. In this study, 108 participants aged 18 to 60 years old were given either a low, moderate or high dose of the vaccine. ELISA antibodies and neutralising antibodies increased significantly at day 14 and peaked 28 days after inoculation. Specific T cell response peaked at 14 days post vaccination. The most common adverse reactions were fever, fatigue, headache and muscle pain, with the highest incidence in the high dose group. [99]
China's Academy of Military Medical Sciences vaccine	Inactivated vaccine[100]	Entered clinical trial	Randomised controlled Phase II Trial with 500 participants to test varying doses against placebo was launched on 12 April 2020. Phase I is expected complete in late December 2020, with Phase II completing in January 2021. [101]
China's National Health Commission's Science and Technology	-	-	The National Health Commission's Science and Technology Development Centre reports that they are hopeful that in April some of the vaccines being developed will enter clinical research or they would be of use in "emergency situations."[102] Unclear what emergency situation is defined as.

Development Centre			China's National Health Commission's Science and Technology Development Centre has stated that five approaches to vaccines are being developed. It is believed that applications would be made next month for some vaccines to advance to clinical trials.[103]
Shenzhen Geno-Immune Medical Institute (SGIMI)	Cellular vaccine	Phase I	SGIMI is developing a vaccine called LV-SMENP-DC. It is a cellular vaccine comprising of dendritic cells (DCs) transduced with SARS-CoV-2 spike, membrane, nucleocapsid, envelope and protease (SMENP) minigenes along with immunomodulatory genes using a lentiviral vector. The multiepitopic vaccine based on the generation of artificial antigen presenting cells through transduction expresses viral antigens and immune modulatory genes to ultimately activate T-cells. [104,105] This vaccine is currently in second phase I trial with 100 adults in Shenzhen, China expected to complete by July 31, 2020.
BioNTech	-	Phase I / Phase II	A vaccine named BNT162 developed by German biotechnology company BioNTech in collaboration with Pfizer has been approved for human clinical trials. This trial will be conducted on 200 healthy individuals ranging from 18 to 55 years old. [106] BioNTech has started Phase 1 and 2 clinical trials of its vaccine in an experimental group of 12 individuals, and is planning to eventually increase its sample to 200. [107] [108]
Migal Galilee Research Institute	-	Preclinical	MigVax, an Israeli start-up affiliated with the Migal Galilee Research institute, has obtained funds from crowdfunding platform OurCrowd to start research into a Covid 19 vaccine based on its prior research on coronaviruses. [109]
SinoVac Biotech	-	Phase I / Phase II	Sinovac has revealed that its vaccine has shown effectiveness in animal trials on rhesus macaque monkeys. However, the results are limited by a small sample and have yet to be peer reviewed. Meanwhile, the company has moved on to Phase 1 clinical trials. [110] Sinovac has commenced Phase 1 and Phase 2 clinical trials. The trials consist of 6 arms which examine three key variables: the vaccine compared to the placebo (given vaccine vs given placebo), the dosage of the vaccine (medium vs high dose), and the vaccine schedule (routine vs emergency schedule). [111] Sinovac has started talks with global stakeholders to start Phase 3 trials of its vaccine in places with widespread Covid-19 infections. [112]

Symvivo Corporation	bacTRL-Spike	Phase I	Symvivo has started Phase I trials of orally delivered bacTRL as a vaccine for COVID-19. Each oral dose contains a bacterial medium which has been engineered to deliver plasmids containing synthetic DNA that encodes the spike protein from SARS-CoV-2. [113]

Manufacturing

Once vaccine candidates are proved safe and effective, doses must be manufactured at scale. Many high-income countries will likely pay for development and manufacture of a COVID-19 vaccine to supply to their own populations. Discussions with global stakeholders about organising and financing large-scale vaccine manufacturing, procurement, and delivery are under way.[114]

Search Method

In January 2020 a systematic search was carried out in three major electronic databases (PubMed, Embase and Cochrane Library) to identify published studies examining potential vaccines for Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and the 2019 novel coronavirus (2019-nCoV). Key words included “SARS”, “coronavirus”, “MERS”, “2019 Novel coronavirus”, and “vaccine”. This systematic review was a key component of a journal article (Pang J et al 2020) on the potential rapid diagnostics, vaccine and therapeutics for SARS-CoV-2.[115]

After the initial systematic review, weekly searches were undertaken on: WHO database on global research on coronavirus disease (COVID-19), news outlets, specific journals and clinical trial sites. Key terms included “COVID”, “COVID-19”, “COVID19”, “coronavirus”. Articles were searched for vaccine references.

From April 2020, the report was shortened to focus on key issues, vaccines funded by CEPI and those in clinical trial. Therefor the search criteria shifted to a more targeted approach.

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