COVID-19 – Vaccines and Antivirals

By Nicola Oliver for

COVID-19 Actuaries Support Group – Learn. Educate. Inform. Influence.

What is a vaccine?

Vaccination is the administration of a vaccine to help the immune system develop protection from a disease which is achieved by essentially imitating an infection. Vaccines have historically been constructed to contain either inactivated viruses or attenuated (alive but not capable of causing disease) viruses. Following administration, the body's adaptive immune system is stimulated and primed to recognise the infectious agent if it is exposed to it subsequently. This may take several weeks to develop.

More recently, wider approaches for construction of a vaccine have been developed. This includes, for example, an mRNA vaccine which provides a synthetic mRNA of the virus, which the host body then uses to produce the viral proteins itself thus mimicking the natural infection of the virus.

Widespread immunity as a result of vaccination and herd immunity is largely responsible for the eradication of smallpox.

Vaccine production

At the start of the production process, the antigen is generated. The next challenge is how to actually manufacture the vaccine. There are many different vaccine-making platforms, each with its own set of advantages and disadvantages.

It takes between 6 to 36 months to produce, package and deliver high quality vaccines to those who need them.

Current status of vaccine development against Sars-CoV-2

Coronaviruses have caused two other recent epidemics – severe acute respiratory syndrome (SARS) in 2002-04, and Middle East respiratory syndrome (MERS), in 2012. In both cases, work began on vaccines that were later shelved when the outbreaks were contained.

These vaccines have now been repurposed for human trials, specifically by Maryland-based Novavax, and biotech company Moderna in Cambridge (USA) who are developing the vaccine in cooperation with the National Institute of Allergy and Infectious Diseases.

In addition, CanSino Biologics in China has also entered phase 1 testing of a vaccine. CanSino also markets a vaccine for Ebola virus in China.

The table below presents an overview of vaccine development.

Developer	Clinical Phase
Moderna Therapeutics (US)	Phase One
CanSino Biologics (China)	Phase One
Inovio Pharmaceuticals (US)	Phase One
University of Oxford (UK)	Phase One/Two
Sinovac R & D Ltd (China)	Phase One/Two
Biontech & Pfizer (US/Germany)	Phase One/Two
Arcturus Therapeutics (US)	Preclinical
BioNTech (Germany)	Preclinical
CureVac (Germany)	Preclinical
Eli Lilly/AbCellera (Canada)	Preclinical
GlaxoSmithKline/Clover Pharmaceuticals (China)	Preclinical
Inovio Pharmaceuticals (US)	Preclinical
Johnson & Johnson (US)	Preclinical
Regeneron Pharmaceuticals (US)	Preclinical
Sanofi (France)	Preclinical
Novavax (US)	Preclinical

The studies in phase 1 or 2 are summarised below. As can be seen, there is considerable variation in the potential study completion date.

Moderna 'mRNA-1273'

The dosing of the first participant in a phase 1 study of the so-called mRNA-1273 vaccine was announced on 16 March 2020. The early-stage, or phase 1, trial will test the vaccine on 45 males and non-pregnant females between the ages of 18 and 55. The primary and study completion date is 1 June 2021.

Moderna's primary objective is to assess the safety and reactogenicity of a two-dose vaccination schedule of its mRNA candidate. The trial's secondary objective is to study the immunogenicity to the SARS-CoV-2 S protein.

CanSino Biologics 'Ad5-nCoV'

The phase 1 trial will be conducted in 108 healthy adults 18 to 60 years of age in Wuhan, China. The study's main objective is to examine the vaccine's safety, and researchers will also evaluate efficacy measures, including levels of an antibody against the spike protein on the coronavirus cell surface which effects entry to cells through binding to ACE2 receptors, as well as neutralizing antibody against SARS-CoV-2.

The primary completion date is estimated to be 30 December 2020, and study completion date is 20 December 2022.

Inovio Pharmaceuticals 'INO-4800'

INO-4800 is a DNA vaccine candidate being developed by Inovio in conjunction with Inovio's proprietary platform hand-held smart device called Cellectra. As of 28 April 2020, this phase 1 trial is fully recruited with all 40 healthy volunteers receiving their first dose, with interim immune responses and safety results expected in late June 2020. The estimated primary and study completion date is April 2021.

University of Oxford 'ChAdOx1 nCoV-19'

University of Oxford researchers have begun testing a COVID-19 vaccine in human volunteers, the first doses were administered on 23 April 2020. This randomised controlled study will recruit a total of 1112 participants and is planning to reach primary and study completion by May 2021.

Sinovac

Sinovac has commenced a Phase I clinical trial, a randomized, double-blinded, placebo controlled study, for its vaccine candidate against COVID-19. As of 13 April 2020, enrolment of the first group of volunteers and the first dose of vaccination for these volunteers have been completed. Final study completion date is proposed for December 2020.

Biontech & Pfizer 'BNT162'

The first cohort of BioNTech's Phase 1/2 clinical trial has been dosed. Twelve study participants were dosed with vaccine candidate BNT162 in Germany since dosing began on April 23, 2020. The study will also assess the effects of repeated vaccination following a prime injection for the three vaccine candidates that contain uridine containing mRNA (uRNA) or nucleoside modified mRNA (modRNA). A fourth vaccine candidate, which contains self-amplifying mRNA (saRNA) will be evaluated after a single dose of vaccine. Subjects with a higher risk of severe COVID-19 disease will be included in the second part of the study. Primary completion is not expected until 2023.

Novavax

Novavax has produced and is currently assessing multiple recombinant nanoparticle vaccine candidates in animal models prior to advancing to clinical trials. Initiation of Phase1 clinical testing is expected in late spring of 2020.

Antivirals and other pharmaceutical approaches

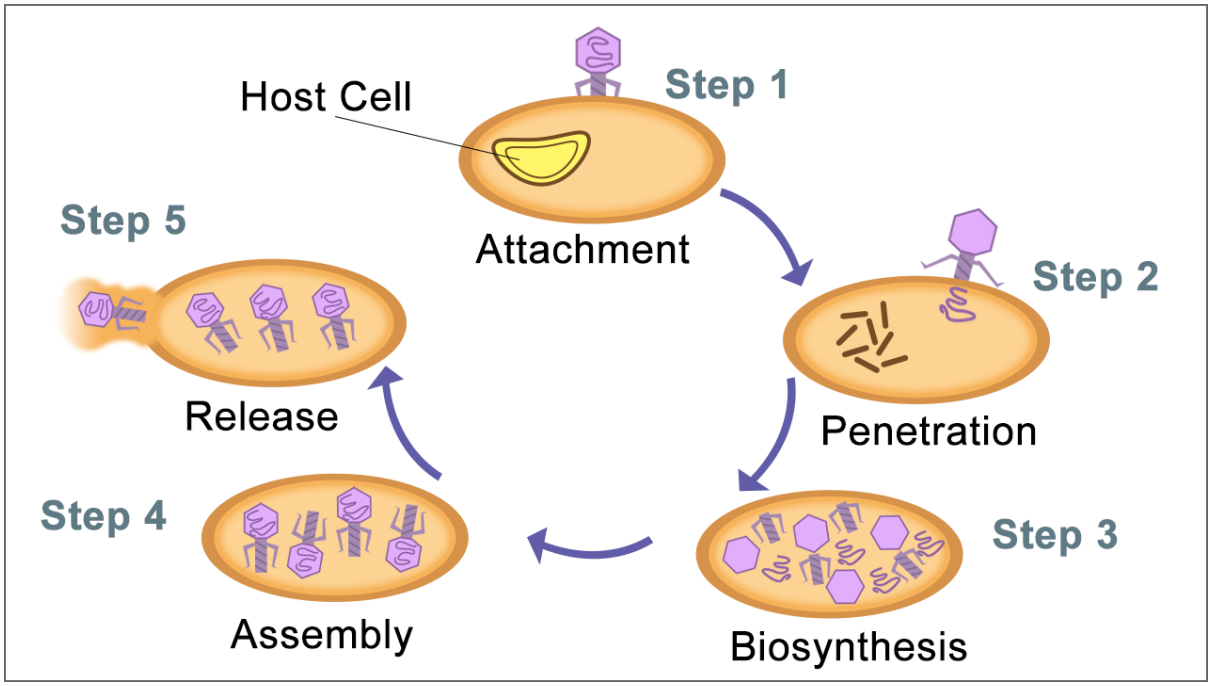
There are currently no pharmaceutical treatments that are specifically indicated to treat COVID-19 in terms of being able to eradicate the disease from the human body. Individuals that require hospitalisation are managed according to their clinical need by each body system. For instance, intensive care units have established protocols for respiratory support, cardiovascular support, and renal support.

So where are we in terms of developing a specific pharmaceutical to treat COVID-19?

Antivirals

The aim of antiviral therapy is to minimize symptoms and infectivity as well as to shorten the duration of illness. These drugs act by arresting the viral replication cycle at various stages. Antivirals are currently used to treat influenza viruses, herpes viruses, hepatitis B and C viruses, and HIV.

The image below displays the viral replication cycle; antiviral drugs work by inhibiting this cycle at a number of different stages.



There are currently 47 antiviral drug trials registered with phase 3 clinical trials for the treatment of COVID-19, 138 in total across all trial phases.

Remdesivir has been recently recognized as a promising antiviral drug against a broad spectrum of RNA virus (including MERS-CoV) infection in cultured cells. It's key mode of action is through interference of the action of viral RNA-dependent RNA polymerase causing a decrease in viral RNA production.

Remdesivir is not yet licensed or approved anywhere globally and has not yet been demonstrated to be safe or effective for the treatment of COVID-19; trial results to-date have been disappointing. There are 19 clinical trials registered at www.clinicaltrials.gov which are testing the effect of Remdesivir on patients with COVID-19; 11 of which are actively recruiting, one is terminated and one is suspended.

Favipiravir is a further drug under clinical development and has a similar mode of action to Remdesivir. There are 12 clinical trials registered at www.clinicaltrials.gov which are testing the effect of Favipiravir on patients with COVID-19; however, none are actively recruiting at this stage.

Other pharmaceuticals

In addition a number of other classes of drug are being investigated for their utility in treating COVID-19. This includes ACE inhibitors, monoclonal antibodies, (MABs), and anti-inflammatories. The drugs under investigation include existing (hence, 'repurposing') and novel compounds.

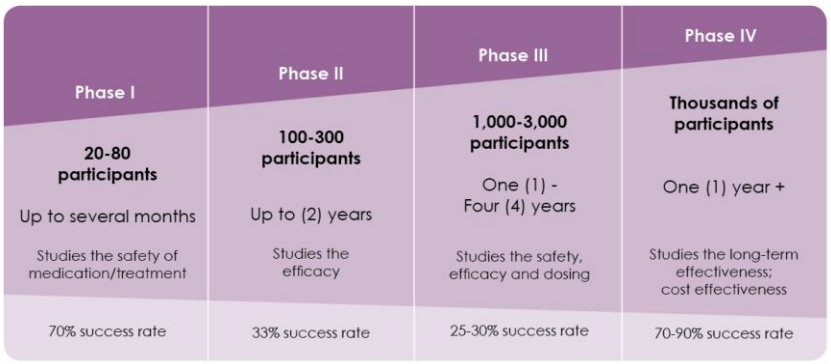
It's also worth noting the use of convalescent serum as an effective treatment. This describes administering antibodies from blood donated by people who recovered from COVID-19 and hyper-immunoglobulins. A convalescent plasma program has been instigated by physicians and investigators from across the US, and similar programs have been initiated in the UK and EU. The convalescent serum studies are focused on treating patients currently facing severe cases of COVID-19.

The following table is a summary of the drugs and classes in phase 3 of the clinical trial process registered at www.clinicaltrials.gov that are being tested against COIVD-19.

Drug class/name	Number of studies
Antibody	17
Anti-malarial	73
Convalescent plasma	6
ACE Inhibitor	4
Chinese medicine	4
Anti-inflammatory	32
BCG	4
Hyperbaric 02	2
Steroid	7
Kinase Inhibitors	3
Vitamin C	1
Vitamin D	1
Isotretinoin	1
Dalargin	1
Prebiotic	1
Dapalgin	1
Lavamisole/Isoprinosine	1
Honey/Nigella/Cumin	1
Mycobacterium	1
Melatonin	1
Sildenafil	1
Endovenous ozone	1

A note of caution

The clinical trial process is usually notoriously long and risky. The figure below displays the average timescale and success rate of each stage.



Conclusion

At the time of writing, there are around nine clinical trials in humans in progress to test a potential vaccine against SARS-CoV-2 in phases 1 and 2. The overall 'from phase 1 to approval' success rate is no more than 15%. There are, however, many antiviral drug trials at the more advanced phase 3. Cautious optimism is the key here.

Nicola Oliver
7 May 2020