Part 1: Developing new vaccines for pandemics

If an effective vaccine against the SARS-CoV-2 virus is developed and approved, it must be produced at sufficient quantity and at the lowest cost possible to have maximum impact at a global scale. Over two briefings we will look at how vaccines are discovered and manufactured, and some of the challenges that will be faced in delivering a COVID-19 vaccine to a global population of 7.8 billion. This series is produced by the Future Vaccine Manufacturing Research Hub (Vax-Hub), whose mission is to secure supply of essential vaccines to LMICs.

In the ten months following reports of a cluster of pneumonia cases in Hubei Province in China,[1] COVID-19 (the disease caused by the SARS-CoV-2 virus) has become a global pandemic, affecting over 40 million people worldwide and killing over 1.1 million.[2] A range of policies have been implemented by governments around the world to mitigate the humanitarian and economic impacts of the COVID-19 pandemic, but it is acknowledged that securing an effective vaccine is essential to global recovery and to decreasing society's vulnerability to recurrent waves of the virus.[3]

According to the World Health Organisation (WHO), there are currently 198 COVID-19 candidate vaccines in development, 44 of which are undergoing clinical trials in humans and 154 of which are in pre-clinical evaluation.[4] If any of these candidates proves successful in clinical trials, new manufacturing and supply challenges must be overcome to produce and distribute vaccines to a global population of 7.8 billion people, and ensure equitable access to these vaccines for all.

How do vaccines work?

Vaccines train the immune system to recognise and kill disease-causing microorganisms and viruses, known as pathogens, before they can lead to a potentially serious illness. When the body encounters a new pathogen, proteins or sugars on the surface of the pathogen (known as the "antigenic" parts of the pathogen) trigger an immune response in which antibodies are created that destroy the pathogen. Those antibodies are deployed when the pathogen is encountered again, protecting from future infections.

COVID-19 vaccines in numbers

10-15 years

The average time it takes to bring a vaccine to market

12-18 months

The estimated time from identification of SARS-CoV-2 to the first COVID-19 vaccine being available

198

Vaccine candidates currently under investigation, according to the World Health Organisation (WHO)[4]

Box 1: Vaccine Discovery

The first known vaccine was developed in 1796 by Edward Jenner against smallpox, although the practice of variolation (deliberate infection to trigger a mild form of the disease) had been undertaken in China for centuries. Prior to development of a vaccine, smallpox had a mortality rate of around 30% and left those who survived with extensive scarring and sometimes blindness. Jenner's vaccine against smallpox involved exposure of the patient to cowpox, a harmless related disease, which created immunity to smallpox. Jenner's discovery eventually led to the eradication of smallpox with the last naturally occurring case diagnosed in October 1977, and the World Health Organization (WHO) certifying the global eradication of the disease in 1980.

Vaccines have since transformed our ability to manage a huge range of diseases and are bringing us closer to a future where deadly communicable diseases can be eradicated.

Types of vaccine

Early vaccination strategies involved exposing individuals to closely related pathogens which cause a milder form of disease than the target pathogen. The goal was to create immunity to the more serious pathogen without needing to expose the individual to it, see Box 1. Scientists have since developed a huge toolkit of different vaccination strategies that don't rely on the need to identify a related, yet less harmful pathogen. The vaccination strategy chosen can be tailored according to the pathogen, its mode of infection and how the immune system responds to it. The main types of vaccine in use today are displayed in Table 1.

How do we prove that vaccines are safe and effective?

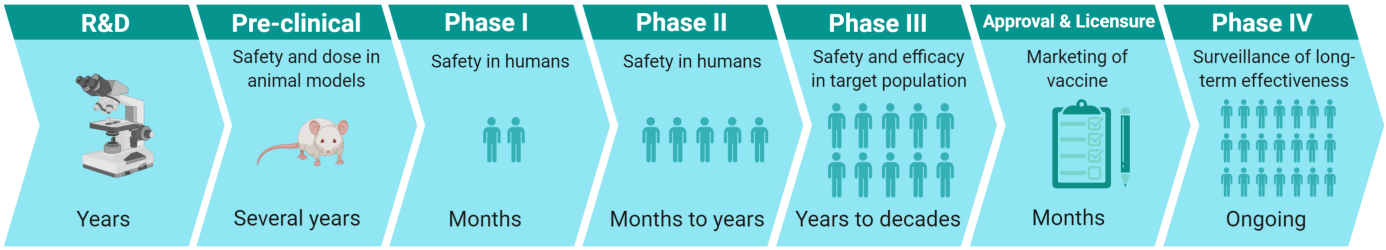
Once scientists have completed the many years of research that it takes to identify a new vaccine candidate, they must prove that the vaccine is safe and effective before it can be routinely administered. This is achieved by entering the vaccine into clinical trials, which are separated into four phases. Phases are conducted on an increasingly large number of participants and are designed to capture information on the safety, efficacy and dosage required of the vaccine, see Figure 1. Vaccines are some of the most stringently regulated medicinal products because they are given to people who are otherwise healthy (in most cases children) to protect against contracting a disease in the future.

Once the vaccine has successfully completed first three phases of a clinical trial, it can be licenced and placed on the market. There are a number of different licences required depending on where the manufacturer wants to market the vaccine. Licencing is necessary as it provides procurement bodies with assurance that the vaccine is safe and effective. In the UK, licencing and marketing authorisation is provided by the Medicines and Healthcare products Regulatory Agency (MHRA).[6] The Joint Committee on Vaccines and Immunisation (JCVI) provide advice to the NHS on the cost-effectiveness of new vaccines to assist with procurement and reimbursement decisions.

International procurement agencies who make bulk purchases of vaccines for distribution in resource-poor settings, such as UNICEF, require that the vaccine receives WHO pre-qualification to assure its safety and effectiveness. The WHO maintains a list of prequalified medicinal products that meet the specified requirements, and for which the sites that manufacture that product are compliant with WHO standards.

Once a vaccine is on the market and in general use, phase IV of the clinical trial commences. This is a long-term period of "surveillance" to check the vaccine's performance in real world scenarios, determine the magnitude of any long-term benefits and identify any rare side effects not observed during the previous phases of the clinical trial.

Figure 1: Vaccine development timeline. Created with BioRender.com



How can we speed up vaccine development during disease outbreaks? Oxford Jenner Institute vaccine as an exemplar

For vaccines to form part of a viable epidemic or pandemic recovery strategy, they must be available quickly and be manufacturable at scale. Vaccine development is typically hugely time intensive; the average time to bring a candidate vaccine to market is in excess of ten years.[7] This timeline must be urgently accelerated to halt transmission of COVID-19, the rate of which continues to increase globally despite current restrictions in place. In the week to 11 October 2020 the WHO reported over 2.2 million new cases and 39,000 deaths of COVID-19 around the world. This is the highest number of reported cases so far in a single week.[8] There are several ways that we can speed up the availability of a vaccine, in both the discovery and clinical trial phase.

1. Rapid discovery

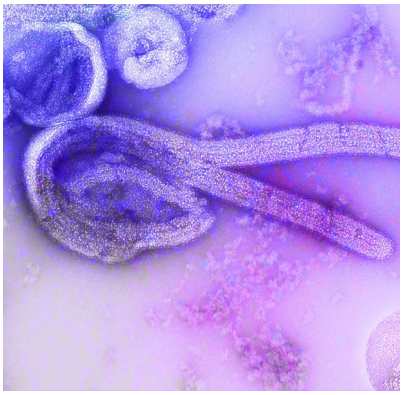
When a new disease is identified, scientists must first undertake a period of research to find a vaccine promising enough to enter into clinical trials which can take many years. One way to significantly shorten this discovery timeline is through the use of 'vaccine platforms'. Vaccine platforms use a 'plug-and-play' approach where generic components of vaccines are developed and tested in advance of disease outbreaks. When an outbreak does occur, the DNA of the pathogen is sequenced and an appropriate antigen is identified for inclusion in the ready-made vaccine delivery system, allowing a rapid-response to the new disease.

Viral vector vaccine platforms have emerged as very useful candidates to combat emerging diseases in outbreak scenarios and are one of the three platforms under investigation in the Vax-Hub. Viral vector vaccines take viruses that are harmless to humans and genetically modify them to deliver instructions to cells in the body on how to produce small, harmless, parts of disease-causing viruses. The body's immune system learns to detect and destroy these "encoded" proteins so that if the actual virus is encountered, the immune system will be primed to destroy it before the disease can take hold. It was a viral vector vaccine that was the first to be approved by the European Medicines Agency to protect against the Ebola virus. The Ervebo® vaccine was deployed with the most accelerated timeline for a vaccine to date, taking 18-months between the first reports of the devastating 2014/15 outbreak of Ebola in West Africa and vaccination of 800 individuals in Guinea in 2016.

In the context of the COVID-19 pandemic, one of the leading vaccines against the SARS-CoV-2 virus uses a platform developed by Vax-Hub co-director Professor Sarah Gilbert and her colleagues at the University of Oxford Jenner Institute. The research team had been developing their viral vector platform, ChAdOx1, for many years and had used it as a plug-and-play delivery system for antigens of several diseases, including Rift Valley Fever, and the closely related Middle Eastern Respiratory Syndrome (MERS) coronavirus. Importantly, the platform had shown significant promise in animal and early-stage human testing for MERS, so the research team had the confidence to immediately start work on a COVID-19 vaccine once the gene sequence was available. Using the ChAdOx1 platform, the team have been able to shorten a research process that can take many years into the space of 4 months.

85% of infants worldwide received 3 doses of DTP3 vaccine in 2019. Photo by CDC on Pexels

In 2020 Africa was declared free of wild polio thanks to extensive vaccination campaigns



The Ervebo Ebola vaccine was quickly deployed during the outbreak in 2016. Photo by CDC on Unsplash

Platform approaches mean COVID-19 vaccines may be available in record time

Table 1. Main types of viral vaccines in use today

Vaccine Type	How does it work?	Pros	Cons	COVID-19 candidates?[4] (in clinical trial)
Live-attenuated vaccine (LAV)	Contains a weakened (or attenuated) form of the pathogen	Mimics natural infection providing a strong, long-lasting immune response	Unsuitable for immune compromised individuals. Must be kept cool. In extremely rare cases, natural mutations can cause LAVs to revert to a form of the virus that can cause disease, e.g. the oral polio vaccine Requires whole pathogen cultivation	3(0)
Inactivated	Contains a killed version of the pathogen	Better safety and stability profile than LAVs	Weaker immune response than LAVs so may require adjuvants (ingredients added to enhance the immune system response) and booster doses for long term protection. Requires mass culture of dangerous infectious virus or microbes	19(7)
Protein subunit	Contains only antigenic proteins of the pathogen responsible for triggering the immune response	No live components so very safe Good stability profile	Antigenic properties of pathogen subunits must first be examined to determine the combinations to produce an effective immune response with the correct pathway. Tend to produce a weaker immune response (low "immunogenicity"), which means adjuvants and booster doses are required for long term protection.	67(13)
Virus-like particle (VLP)	Proteins from outer shell of a virus are assembled into a particle which closely resembles the virus but does not contain the viral genome	VLP resembles the virus and so creates a strong immune response. Non-replicating with no viral DNA so safer than LAVs	Assembly of proteins can be challenging.	16(2)
Viral Vector	Non-pathenogenic live viruses are used to carry DNA into cells containing instructions on how to produce a disease-specific antigen. The cell then makes those antigens and an immune response is triggered. The viral vector can be replicating (infects multiple cells) or non-replicating (infects only one cell)	Produces cell mediated immunity so potential for strong and long lasting immunity. Use of adjuvants generally not required.	Pre-existing immunity and antibodies against the viral vector used to carry DNA into cells can compromise the vaccine efficacy. Live virus so vaccine must be kept cool.	48(12)

DNA	A small circular piece of DNA called a plasmid carries genes to cells and uses the cell machinery to make a viral or bacterial antigenic protein which the immune system recognises as being foreign to the body.	Produces cell mediated immunity so potential for strong and long lasting immunity. Good stability profile. No need to culture bacteria or virus so can be made in a short time at low-cost using well established techniques.	Relatively low levels of immunogenicity observed for this type of vaccine thus far.	18(4)
RNA	Cells use DNA as a template to make messenger RNA (mRNA) molecules, which are then translated to build proteins. An RNA vaccine consists of an mRNA strand that codes for a disease-specific antigen. The mRNA strand is delivered to the body's cells which use the genetic information to produce the	No pathogen particles or inactivated pathogen, so non-infectious. Quick and easy to produce	Delivering the vaccine effectively to cells is challenging since free RNA in the body is quickly broken down. As such, the mRNA strand must be contained in a capsule that breaks down on delivery. RNA vaccines do not have good thermal stability and require special handling	25(6)
Toxoid	Based on a toxin produced by the target bacteria when it infects cells in the body. An inactivated version of the toxin is used as the antigen in the vaccine to elicit immunity.	Excellent safety and stability profile	Targets the toxin not the pathogen itself Requires adjuvants and frequent booster doses	0 (technology not applicable to viruses)
Polysaccharide	Trains the body to launch an immune response against polysaccharides (sugars) found on the surface of bacteria.	Easily to identify polysaccharide	Weakly immunogenic and requires adjuvants. Booster doses needed. Limited immunogenicity in infants.	0 (technology not applicable to viruses)
Polysaccharide conjugate	Similar to polysaccharide vaccines, an immune response is created to a bacteria's sugar capsule. In conjugate vaccines the polysaccharide is also bound (conjugated) to an antigenic protein to strengthen the immune response.	Stronger immune response than polysaccharide vaccines and longer term immunogenicity. Can be used in infants.	Booster doses may be required for long-term protection.	0 (technology not applicable to viruses)

"This will not be the last pandemic. History teaches us that out-breaks and pandemics are a fact of life. But when the next pandem-ic comes, the world must be ready – more ready than it was this time."

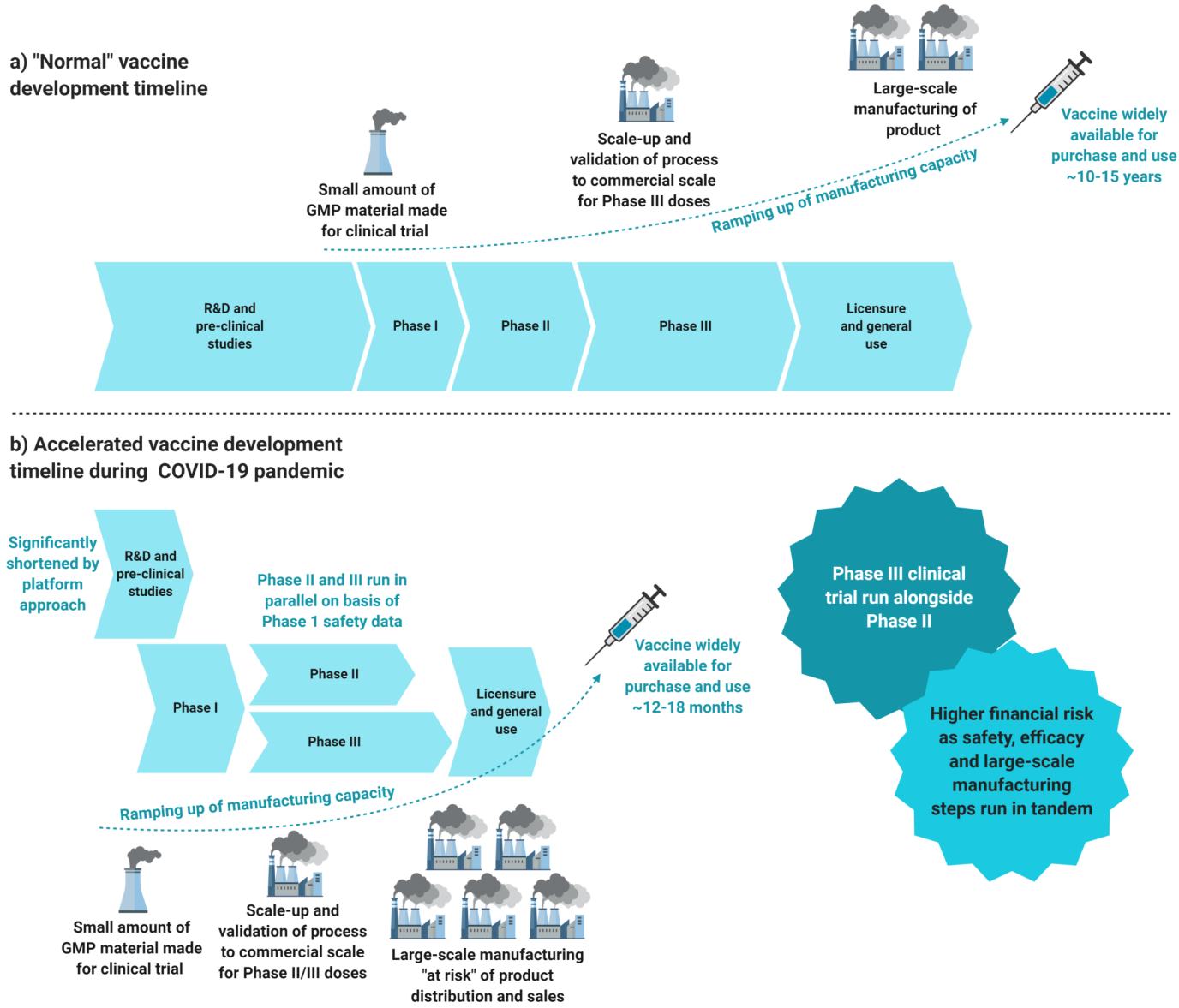
- Tedros Adhanom Ghebreye-sus, Director-General, World Health Organization (WHO)

2. Expedited clinical trials

The longest step in vaccine development is the end-to-end clinical trial process, which usually takes many years to complete. In light of COVID -19, regulators around the world are adapting and using flexible and novel approaches to enable a COVID-19 vaccine to be delivered more rapidly, whilst ensuring that safety criteria are still met. For the Oxford vaccine, phases 2 and 3 clinical trials have run in parallel on the basis of phase 1 safety data. This will save months, if not years of waiting be-fore finding out whether a vaccine is effective. This strategy does mar-ginally increase the risk to the volunteers in the phase 3 trial compared to traditional linear trials where full phase 2 data would be available be-fore phase 3 commences, however this risk is small and volunteers are required to fully understand and consent to this risk.

Phase 3 of a clinical trial is usually the lengthiest since it requires statis-tically significant data to show that participants are protected from the disease which the vaccine is targeting. This requires volunteers to be

Figure 2: expedited vaccine development timeline during the COVID-19 outbreak. Created with BioRender.com



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exposed to the disease which can take some time if case rates are low, such as in the UK. In order to get this data more quickly, clinical trials are being conducted using the Oxford vaccine in areas where there are high incidence rates of the disease, such as in Brazil. In light of the huge impact to global health caused by COVID-19, there have been calls to consider the use of human challenge trials as a means to expedite results and identify an effective vaccine as quickly as possible. In human challenge trials, immunised participants are deliberately infected with the virus and their immune response is monitored. Although they can expedite vaccine development, human challenge trial pose huge ethical questions, especially in the case of COVID-19 for which there is currently no effective treatment widely available.

Manufacturing of a vaccine usually commences once phase 3 trials are complete, and providing that the trials show the vaccine is effective in protecting from the target disease. Due to the humanitarian and economic fallout resulting from COVID-19, manufacturing of vaccine doses has commenced at-risk, meaning that companies do not know whether they will be able to get a return on the investment required to scale up manufacturing capabilities and capacity. As such, many governments have put in place funding schemes to rapidly advance COVID-19 vaccine development. The rights to manufacture the Oxford vaccine have been acquired by AstraZeneca who have named the vaccine AZD1222, and who have begun manufacturing the vaccine at risk, with the first available doses expected by the end of 2020.

Conclusions

Vaccine discovery and development is traditionally a lengthy and expensive undertaking, with timelines hugely out of step with those demanded by emergency scenarios such as the current COVID-19 pandemic. Scientists, regulators, manufacturers and governments have developed strategies to speed the delivery of safe and effective vaccines, including vaccine platform approaches and flexible clinical trial design. Once an effective vaccine has been found, a new and unprecedented challenge will be faced by manufacturers to make and deliver the vaccine rapidly to the global population of 7.8 billion people and stem the COVID-19 pandemic. The next briefing in this series will take a closer look at the ways in which vaccines are manufactured and some of the challenges that might be faced for COVID-19 vaccines. The manufacturing strategies used within the Vax-Hub to make the world more resilient to future pandemics will also be explored.

Our research

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To find out more, please visit: https://www.ucl.ac.uk/biochemical-engineering/research/research-and-training-centres/vax-hub

Contributors

Department of Biochemical Engineering, UCL: Professor Martina Micheletti (m.micheletti@ucl.ac.uk) who specialises in engineering of bioprocess operations. Dr Steve Morris (stephen.morris@ucl.ac.uk), is a research fellow in vaccine process analytics.

STEaPP, UCL: Dr Penny Carmichael (p.carmichael@ucl.ac.uk), is a policy engagement specialist in the PIU.

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