Part 2: Manufacturing new vaccines for pandemics

The scale of the global research effort to secure a vaccine that will protect against the SARS-CoV-2 virus, and the rate of progress to this end is unprecedented. In line with the requirement for a safe and effective vaccine for global recovery from the crisis, manufacturing of candidate vaccines has already commenced at-risk. This briefing will look at some of the technological challenges to be overcome in order to manufacture a vaccine for a global population of 7.8 billion, where over 6 billion live in low and middle income countries (LMICs). Enabling technology transfer to LMICs for vaccine manufacturing will ensure longer-term resilience to future outbreaks of COVID-19 or another pathogen with pandemic potential. This briefing is part of a series is produced by the Future Vaccine Manufacturing Research Hub (Vax-Hub), whose mission is to secure supply of essential vaccines to LMICs.

Manufacturing vaccines is a risky and expensive business. A company wishing to take a vaccine from the lab to the market can expect a success rate of around 6%.[1] Combined with the high cost of vaccine development, (up to billions of dollars), it is unsurprising that about 80% of global vaccine sales come from five large multi-national corporations based in high income countries who are able to manage risk across large product portfolios.[2] This dominance of high income countries in the vaccine market has historically led to gaps in the vaccine portfolio for diseases that primarily affect LMICs, so-called Neglected Tropical Diseases (NTDs),[3] and so it is important to strengthen manufacturers in these countries, enabling them to better respond to local risks and secure supplies of essential vaccines.

In the context of the COVID-19 crisis, there are fears of vaccines being monopolised by wealthier nations, leading to the most long-term and severe effects of COVID-19 being felt in LMICs.[4] As such it is vital that vaccine manufacturers in LMICs are enabled to establish a robust COVID-19 vaccine supply with global investment and knowledge and technology transfer initiatives.[5] This will require additional process development work since the majority of current manufacturing processes are created with high income markets in mind, and are ill-suited or too costly for use in LMICs.

COVID-19 vaccines in numbers

14 billion

Between 7-14 billion doses of vaccine will be required to end the COVID-19 pandemic, depending on whether boosting is needed.

$15.8T

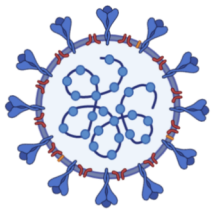
It is estimated that the COVID-19 pandemic will lead to costs between $8.1-15.8 trillion globally[6]

2 billion

Doses of COVID-19 vaccine will be delivered by the COVAX facility by the end of 2021[7]

Figure 1. Common vaccine components Created with Bio-Render.com

Active components



e.g. whole killed virus, viral vector, spike protein

Adjuvants

Added to enhance the immune system response, e.g. aluminum salts

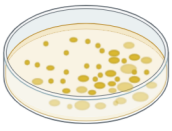
Antibiotics

Prevent bacterial contamination during manufacturing

Stabilisers

Ingredients added to extend the shelf life of the vaccine

Preservatives



Added to prvent contamination of the vaccine when being distributed

How are vaccines made and manufactured?

Vaccines contain several components including active and added ingredients, see Figure 1, and their exact formulation is determined at laboratory-scale. After the vaccine formulation is optimised, production must be scaled-up for commercial manufacturing. This step is one of the most complex and expensive aspects of vaccine development, costing up to $500 million.[8] Depending on the innovation level of the vaccine candidate, it can also take several years.

Manufacturing at commercial scale requires much larger volumes of ingredients. This affects the behaviour of the of the microorganisms used to produce active components of the vaccine, the biochemical and physiological interactions between components, and ultimately the amount of active component produced. Many validation steps must be carried out during scale-up to ensure that the final product is as safe and efficacious as that developed in the lab-scale experiments.

While there is some degree of overlap in the methods and materials to make vaccines for different platform approaches, the details of each will be governed by the nature of the vaccine. In the case of COVID-19, a large number of potential vaccines are being developed using the full range of possible manufacturing platforms. This presents a huge challenge to manufacturers who must prepare to make the 7-14 billion doses (depending on whether boosting is required) required to halt the pandemic. Additionally this must be done without knowing which vaccine will be most effective, or even work. Currently six classes of vaccine have reached the clinical trial stage and manufacturers are commencing scale-up of some of these vaccines at-risk. A brief overview of four of the most common platforms is provided below:

1. Inactivated virus

This is the most ‘traditional’ type of vaccine and relies on isolating virus strains, propagating, purifying and subsequently inactivating them. Because this approach requires large-scale expansion of pathogenic virus, extremely rigorous (and expensive) safety measures must be observed. Up to the point of inactivating the virus, the manufacturing plant must be operated to comply with a biosafety containment category level 3, which includes measures such as carefully controlled air-flow, filtered ventilation and access to equipment for decontamination.[9] Extensive safety controls must be in place at specific points during manufacture to ensure no release of active virus is possible. The inactivation procedure may be implemented at any stage during manufacturing, but for practical reasons this will often be after purification. Stringent controls ensure total inactivation before the product can be passed to the final stage where it is filled into vials for distribution.

2. Protein subunits and Virus Like Particles (VLPs)

Vaccines based on proteins that make up parts of the SARS-CoV-2 virus, e.g. its surface, are the most widely explored to-date. In this platform, an individual virus protein is expressed in a cell culture system without using any of the whole infectious virus. Many cell systems can be engineered to make the protein, including microbial (bacteria and fungi), mammalian, and plant cells. The choice of system will depend on

a combination of factors, including the nature of the protein and economic considerations. Microbial systems offer the ability to produce very large amounts of protein but are not always suitable for complex proteins. These may be better produced in mammalian cell culture, but this significantly increases production costs. Whatever the expression system, an extensive purification process is required to separate the viral protein from all other cellular proteins. Additionally, since individual proteins produce relatively weak immune responses, an adjuvant is often required. The immune response can alternatively be increased by assembling proteins into structures which resemble the virus, termed virus-like particles (VLPs). The complex nature of VLPs often reduces product yields and increases complexity of purification.

3. Non-replicating viral vectors

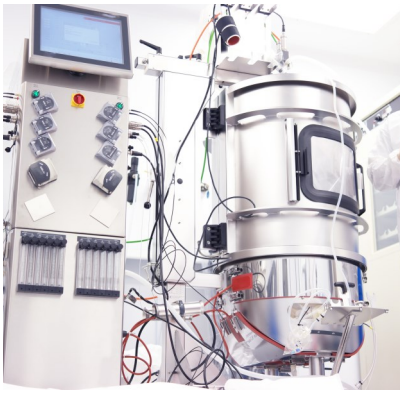
Eight vaccines currently in clinical trial use non-replicating adenoviral vectors to deliver genetic material of the COVID-19 spike protein to cells. This includes the University of Oxford/Astrazeneca AZD1222 vaccine. Non-replicating viral vectors can only infect one cell and so generally have a very good safety profile. Like inactivated viral vaccines, viral vector vaccines are cultivated using mammalian cell culture in large scale bioreactors. However, because the adenovirus itself is not a human pathogen, the degree of biosafety needed during the manufacturing process is considerably reduced. This has a number of positive effects to increase the scale at which operations can be carried out, the ease and speed of construction of new manufacturing capacity and the degree to which existing manufacturing capacity can be repurposed.

4. RNA based vaccines

There are currently six RNA vaccines in clinical trial, including one of the UK's leading candidates developed at Imperial College London. Like viral vectors, RNA vaccines function by introducing genetic coding for a small part of the virus into the body and the cells do the work of producing the viral protein. Issues of stability and the complex formulations required for uptake into the body pose considerable problems for RNA vaccines. The manufacture of RNA vaccines is unlike that of the other platforms in that they can be produced by synthetic processes, or "cell-free" systems, that do not rely on the propagation of cell cultures. This means that manufacturing times can be shortened significantly. However, it should be noted that since no RNA vaccines have yet been licenced, there is no existing large scale manufacturing capacity or experience for these vaccines. In addition, the availability of some of the critical reagents, including enzymes needed, could potentially cause a bottleneck in production at the scale required for worldwide coverage.

Vaccine manufacturing facilities for flexible manufacturing

An important aspect for vaccine manufacturers to consider when making a new product is how they will design the manufacturing facilities. There are a set of manufacturing steps that are common in nature across many vaccine platforms including: fermentation for cell growth, harvesting of product, purification, formulation, sterilisation and vial filling. How and when these operations are carried out is very specific to each different product.



Active components of vaccines are cultured in large fermentation tanks called bioreactors

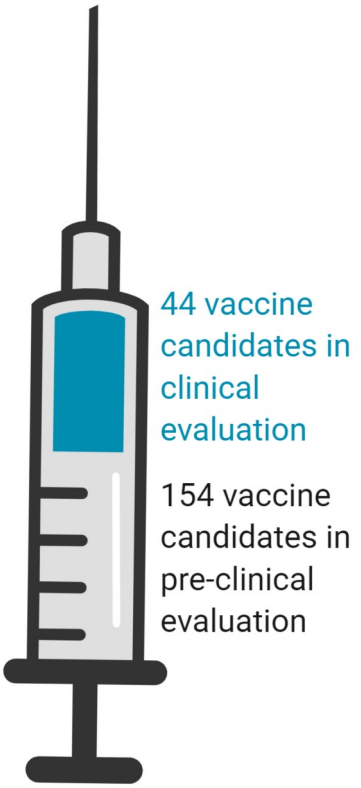
Strict biosafety controls are needed in vaccine manufacture, especially for culture of live pathogenic virus

Vaccine doses are filled into vials prior to final release checks for distribution across the globe

Release testing ensures vaccines are safe and free from contamination

"The model of countries thinking only of themselves is not going to work. Even if you're living somewhere that's somehow perfectly without any infections, your best efforts to fight the virus are going to fail unless you shut off all your borders and trade. This is a global problem that requires a global solution."

- Seth Berkley, CEO of Gavi



WHO Landscape of COVID-19 vaccines, 19 October 2020. Created with BioRender.com

Until relatively recently the most common approach to vaccine manufacturing facility design has been large centralised bespoke facilities. This has had the advantages of scale, however has often resulted in the need for lengthy chains for both supply of materials and distribution of product. The repurposing of such facilities for production of new products, either permanently or temporarily to deal with surges in demand is often difficult or impossible. As the number of licenced vaccines and technologies has increased, it has become clear that a move to more flexibility, and in some cases decentralisation, in manufacture is advantageous to reduce cost, increase supply and provide additional capacity to cope with surge situation such as pandemics, see Box 1.

We need capacity to produce billions of doses and we need it now

Securing sufficient capacity to manufacture the billions of doses required worldwide is a huge challenge and suppliers are bringing in contract development and manufacturing organisations (CDMOs) to meet demands. For example, AstraZeneca now have in place licensing agreements with a number of manufacturing organisations including the Serum Institute in India, Catalent in Italy, and Emergent BioSolutions in the US.[10] In the UK, AstraZeneca have been working with the Vaccines Manufacturing and Innovation Centre (VMIC) to manufacture doses of the AZD1222 vaccine.

VMIC, a government funded initiative to promote growth of the UK vaccine industry, was originally scheduled to open in 2022, but additional funding has brought this forward by one year.[11] Government has also provided funding for a new Cell and Gene Therapy Catapult Manufacturing Innovation Centre to accelerate production of COVID-19 vaccines in the UK, scheduled to launch December 2021. As the two government funded sites are not yet complete, interim capacity has been secured with Oxford Biomedica and Cobra Biologics to deliver an anticipated 40 million doses of the AZD1222 vaccine by the end of 2020.

Ensuring equitable access to vaccines: how can we be more resilient in the future?

Although billions of doses of COVID-19 vaccines are now in the pipeline, a challenge remains to ensure that these are distributed fairly and with equitable access for LMIC countries, which are less resilient to the impacts of COVID-19. Much of the technological transfer for COVID-19 vaccines is taking place to manufacturers in high income countries,[12] leading to fears that those doses will be delivered with priority in those high income countries.[13] The most significant commitment from a manufacturer to provide doses of a COVID-19 vaccine to those living in LMICs comes from the Serum Institute in India, a LMIC manufacturer which over the years has participated in many technological transfer programmes,[14] and is now the world's largest vaccine manufacturer by volume. The Serum Institute of India have signed an agreement with AstraZeneca to produce its AZD122 vaccine and distribute 1 billion doses in LMICs.

Whilst 1 billion does is significant, it is certainly not sufficient to vaccinate the more than 6 billion individuals currently living in LMICs and so the World Health Organisation (WHO) is taking steps to secure

Box 1: Adaptable vaccine manufacturing facility designs

Those manufacturers who are able to operate flexibly and modify facilities quickly based on the COVID -19 vaccine(s) that prove effective in clinical trials are likely to have the biggest impact on slowing the COVID-19 pandemic as they will be able to deliver doses of the COVID-19 vaccine most rapidly. Flexibility also reduces the risk to manufacturers of locking themselves into a single process early on. Two different types of flexible manufacturing layout have emerged in recent years which make use of single -use, disposable technologies for greater adaptability.

An open-plan ballroom facility. ©Sartorius AG. Image provided by courtesy of Sartorius AG.

1. Ballroom facilities

This concept relies on the similar nature of several steps across many vaccine manufacturing platforms and uses common equipment base units (skids) to which product-specific cartridges are attached. Ballroom facilities provide a large open work area with areas for storage, water, power, waste handling etc. Specific equipment skids for the vaccine being manufactured are moved in place as required. When a change of product is required, these skids are re-configured or replaced.

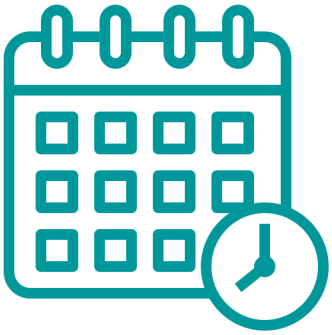
2. Modular facilities

Modular approaches are based on having a large open plan structure which contains a number of smaller self-contained manufacturing units. Each unit houses one function within the manufacturing process. While not offering quite the degree of flexibility and quick restructuring as ballroom facilities, using a modular approach can offer a number of advantages. Since units are self-contained, individual units can be operated at differing biosecurity levels unlike the open-plan ballroom where a single level is usually applied to the facility as a whole. In addition, the use of individually isolated units allows for a multi-product facility, without the risk of cross-contamination.

Modular manufacturing "pods", similar in size to a shipping container, are being designed.

$50-700M

In capital costs to establish a new vaccine manufacturing site[8]



6 years

Time it took Pfizer to establish a new vaccine manufacturing site in the USA in 2008[8]

25%

Obtaining skilled labour represents about 25% of the total manufacturing costs, although this can be significantly lower in LMICs[8]

equitable access to COVID-19 vaccines via purchasing agreements in its Access To Covid-19 Tools (ACT) Accelerator. Under this collaborative framework, Gavi the Vaccine Alliance, has launched a fund called the "COVAX Facility".[15] This market commitment makes advanced purchases of COVID-19 vaccines with an aim of accelerating their availability. Doses are distributed to participating countries (including the UK); both to those who have contributed financially, and to those who could not otherwise afford the vaccine doses. The fund has struggled to meet its $35 billion target and only obtained sufficient support to sign formal agreements with COVID-19 vaccine manufacturers in September 2020,[16] being outstripped by bilateral deals between countries and vaccine manufacturers signed over the course of the pandemic.

To bolster LMIC resilience to future pandemics and reduce the impact of vaccine nationalism, LMIC manufacturers should be enabled to produce more vaccines in-country. Technology transfer of well-established processes to LMICs can be an effective and sustainable strategy to support local production and secure supply of vaccines in LMICs. In order for these initiatives to be successful, manufacturing processes must be designed for LMICs, in particular taking account of the facilities, skills and resources are available in those contexts. To ensure the success of technology transfer initiatives, (which can be fraught with challenges including local capabilities and strength of supply chains), robust governance structures are required, including strong relationships with centres of scientific and bioprocessing excellence.[17]

The UCL-Oxford Vax-Hub: How can we design vaccine manufacturing processes with LMICs in mind?

Since many vaccine manufacturing processes are designed for developed, high income markets, they are ill-suited or too costly for use in LMICs. As such, in 2018 the Department of Health and Social Care's UK Vaccine Network funded two vaccine research Hubs under a "Future Manufacturing Research Hubs" scheme, one based between UCL and the University of Oxford and the other at Imperial College London. The aim of the Hubs is to bring together academics, manufacturers and policy makers to consider and devise novel ways to develop new vaccines for epidemic diseases in LMICs. Both Hubs are studying platform-based manufacturing approaches; with Imperial College focussed on mRNA vaccines and UCL-Oxford developing 3 different platform approaches for viral vector, virus-like particle and conjugate vaccines.

The UCL-Oxford Vax-Hub is working directly with LMIC partners including the Serum Institute in India and PT Biofarma in Indonesia to develop manufacturing processes suitable for local needs as well as providing training in key areas such as Good Manufacturing Practices. Some of the approaches being investigated in the Vax-Hub to bolster the capabilities of LMIC manufacturers are explored in the sections below.

a. Going "ultra" small can reduce vaccine translation costs

Since one of the most complex and costly steps in achieving commercial manufacture of a vaccine is translating the process from the lab, it is important for LMIC manufacturers that this is done in the most cost-effective way possible and that the best process is determined early on so that costly changes are not required after the process is scaled up.

There are many challenges to design the optimum vaccine manufacturing process, including obtaining good productivity and yield and ensuring that the product remains stable throughout the manufacturing process. One way to determine the best process conditions quickly is to adopt an ultra-scale down (USD) approach, in which the Vax-Hub has significant expertise. This process reduces materials and overheads costs, whilst enabling scientists to understand what conditions will work best for the final manufacturing process. The USD process is as follows:

- First, vaccine production is re-created in very small volumes;
- Robotics are then used to automate the vaccine production process and multiple different sets of conditions (e.g. temperature, pH, concentration etc.) are run simultaneously;
- Next, the optimised process is scaled to larger volumes amenable to commercial manufacture using methods that have been demonstrated to maintain optimised product yields.

The USD approach is very useful for application during disease outbreaks, where any time savings in optimising the manufacturing process translate to securing an effective vaccine more rapidly and delivering this to reduce the disease burden.

b. Advanced analytics: How do we know that the products we are making are the same?

In order to scale global manufacture of a vaccine, multiple sites must be set up for production. This requires not only manufacturing methodologies that are easily transferred between sites, but also robust analytics to demonstrate that the product made at the new site is the same and meets quality standards. As such, it is important to identify and define the analytical tools for product development and quality control at an early stage. In the Vax-Hub, researchers are working with instrument manufacturers and LMIC development scientists to establish transferable inexpensive analytics where these are lacking. Next generation sequencing (NGS), a type of DNA sequencing technology, is being investigated for quality-control purposes with a hope it will replace current tests that are expensive and sometimes imprecise. In the context of COVID-19, Vax-Hub scientists are investigating the potential of new fluorescence technologies for analysis of the ChAdOx vaccine during production to check for product homogeneity.

c. Single-use technologies as a speedy scaling solution?

Capital costs for establishing vaccine manufacturing sites are estimated to range between $70-500 million. Traditionally, these facilities use stainless steel bioreactors which require significant investment. To overcome this issue, the Vax-Hub is investigating use of plastic single-use technologies (SUTs), such as large plastic bags for cell culture, during disease outbreaks as they can be put in place by manufacturers both quickly and at a potentially lower cost than traditional stainless steel facilities. SUTs are well suited for outbreak scenarios and are projected to significantly reduce the costs associated with rapidly setting up manufacturing sites, which could help LMICs to increase their manufacturing capacity quickly.[8]

Vax-Hub partnerships

The Vax-Hub is funded by the Department of Health & Social Care's UK Vaccine Network and brings together academics, manufacturers and policy makers to devise novel ways to develop new vaccines for epidemic diseases in LMICs, working closely with LMIC partners.

17 partners

In the UK and internationally

9 countries

Involved in Hub research, not including the UK

13 research projects funded

In, or directly benefitting, LMIC partners

36 training places

For LMIC manufacturer's employees at vaccine related courses

Additionally, stainless steel reactors require strict and rigorous cleaning protocols to avoid contamination events, which can result in the loss of entire batches of vaccine. SUTs reduce this risk as they are disposable and don't require cleaning steps, also simplifying regulatory processes.

d. Thermostable formulations

Unlike chemical drugs, many vaccines are sensitive to heat and light and can be unstable during storage, reducing their safety and efficacy. As such, vaccines are usually transported in a 'cold chain'. A cold chain is the infrastructure required to transport and store vaccines at recommended temperatures from the point of manufacture to the point of use. Since cold chains require end-to-end refrigeration equipment, (all of which is in good order), in practice they are often fragmented and risk wastage of much needed vaccine doses. In the Vax-Hub new thermostabilisation technologies to make novel vaccines 'cold-chain free by default' are being investigated. Enabling integration of thermostabilisation from the earliest stages of vaccine manufacturing by developing methods that can be carried out in any manufacturing facility at low-cost will ensure a more resilient supply of vaccines in countries where cold chains are not well developed. Vax-Hub researchers are currently investigating methods to extend the shelf-life of the Oxford ChAdOx viral vector system by using a high-throughput formulation instrument and freeze-drying step to develop a product suitable for distribution into geographical regions lacking a cold chain.

Conclusion

The COVID-19 outbreak has focused attention on rapid vaccine development and the need for manufacturers around the world to ramp up supply in order to deliver the 7-14 billion doses of COVID-19 vaccine needed to end the pandemic. In order to meet the challenges of preparing to make huge volumes of COVID-19 vaccines without knowing yet which will be the most effective, or even work at all, manufacturers will have to adopt flexible manufacturing approaches to ensure they are ready to respond quickly to necessary changes in process, as well as making doses at risk. From a global health perspective, it will be necessary for LMIC manufacturers to be enabled to make COVID-19 vaccines to ensure secure supply at the lowest possible cost in these regions. This will be achieved by technology transfer initiatives, which can have lasting benefits of facilitating the market entry of LMIC manufacturers who will be better able to respond to emerging threats in the future.

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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

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