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Advances in vaccine technologies

This POSTnote provides an overview of vaccine development and technologies. It also covers opportunities and challenges in vaccine discovery and manufacture, as well as policy approaches to stimulate vaccine research and development in the UK. It does not cover vaccination campaigns, access or uptake.

Overview

- Each vaccine technology has its own advantages and limitations.
- Challenges to vaccine R&D include gaps in biological and immunological knowledge (including in animals), complexity of clinical trials, manufacturing and distribution.
- Vaccine R&D can be facilitated by advances in fundamental and veterinary research, clinical trial infrastructure, and support for manufacturing capabilities.
- The Government's 2021 Life Sciences Vision focuses on, among other areas, supporting novel vaccine discovery, development, manufacture and use.

Background

Vaccines, as part of a wider array of complementary measures, are highly effective at tackling infectious diseases.[1,2] The World Health Organization estimates that vaccines prevent 4-5 million deaths every year around the world.[3] The Government's 2021 Life Sciences Vision identified supporting novel vaccine discovery, development, manufacture and use as part of its priorities.[4]

Vaccine development

Vaccines train the immune system to recognise parts of pathogens (disease-causing agents such as viruses and bacteria) or their secreted components so that it can protect the body at the next encounter.[5] Vaccines typically contain: an active component that stimulates the immune system; 'adjuvants' that enhance the immune system's response; and stabilisers, antibacterials and preservatives to extend shelf life and prevent contamination.[6–9]

Pre-clinical and clinical trials

The first step in vaccine development is creating a 'target product profile' - a strategic planning document setting out all the features of the final vaccine.[10] Pre-clinical development then occurs at a very small scale in academia or expert industrial environments. This is to identify what to use to stimulate the immune system, to create vaccine candidates, to test their safety and efficacy in animal studies and to develop manufacturing protocols. [11,12,13–15] Vaccines are then tested in clinical trials, which need prior approval of regulatory bodies such as the Medicines and Healthcare products Regulatory Agency (MHRA) and the Health Research Authority (HRA). Clinical trials involve:

- **Phase 1**: a small group of healthy adults (<100) is given the vaccine to make sure there are no clear safety concerns, to see how well it stimulates an immune response and to work out an appropriate dose.
- **Phase 2**: the vaccine is tested in a larger group (several hundred people) to see whether the vaccine works consistently, to assess the immune response and to look for rarer side effects.
- **Phase 3**: the vaccine is studied on a much larger scale in the target population (several thousand people). This aims to identify relatively rare side effects and to provide information about how well the vaccine is likely to work in the real world.
- **Phase 4:** even after a vaccine is authorised for use (see below), surveillance continues throughout roll-out to monitor adverse effects and to determine long-term effectiveness. This phase (also known as 'pharmacovigilance') may last several years.

Authorisation and manufacture

In the UK, the MHRA is responsible for granting authorisation (licence) for use, based on an assessment of: vaccine safety and efficacy using the data generated through animal studies and clinical trials; manufacturing quality and evidence that the production process is under control.[16] Vaccines are then manufactured at scale in licensed manufacturing facilities and distributed (see Vaccine Manufacturing). Prior to deployment, the manufacturing and quality control record for every batch is reviewed by the National Institute for Biological Standards and

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Control (NIBSC) and, for some products, batches are subject to independent laboratory testing at NIBSC.[17] Only those batches that meet the specifications agreed by the MHRA are approved by NIBSC. This approval is required before the manufacturer can market their vaccine.

Vaccine technologies

There are a number of approaches to developing vaccines:[18,19,20]

- **Live-attenuated vaccines**, such as the MMR (measles, mumps and rubella) vaccine, use a weakened version of the pathogen.[21]
- **Inactivated vaccines,** such as the Salk polio vaccine (a component of the 6-in-1 vaccine), use a 'killed' version of the pathogen.[22,23]
- **Toxoid vaccines,** such as the tetanus vaccine, use chemically inactivated toxins produced by the pathogen.[24] These train the immune system to tackle the harmful components of a pathogen, rather than the pathogen itself.
- **Subunit vaccines** use purified fragments of the pathogen. Some, such as the pertussis (whooping cough) vaccine, use purified proteins from the pathogen's surface.[25,26] Others, such as the pneumococcal polysaccharide vaccine (PPV), use long chains of sugar ('polysaccharides') found on the surface of some bacteria.[27] In some cases, such as for the pneumococcal conjugate vaccine (PCV), polysaccharides can be attached ('conjugated') to a protein.[27]
- **Virus-like particles (VLP) vaccines**, such as the human papillomavirus (HPV) vaccine, use structures similar to viruses, but without the virus' genetic material, that are recognised by the immune system.[28,29]
- **Bacterial outer membrane vesicle (OMV) vaccines**, such as the Bexsero Meningitis B vaccine, use 'bubble-like' structures from the bacterial surface.[30]

Vaccines developed using the technologies described above often take 10-15 years to reach the market. They often need biological systems (such as chicken eggs, cell cultures of bacteria or yeast, or plant or animal cells) for propagation of pathogens or their parts, requiring appropriate biocontainment levels to prevent their release into the wider environment.[31] New research is currently exploring the use of 'cell-free' systems or chemical synthesis to facilitate production of some of these vaccines.[32–34]

Platform-based vaccines

Platform-based technologies (often called 'plug and play technologies', see below) can be used to create vaccines that can be quickly and easily modified.[35–37] Many platform-based vaccines have been developed and tested in animals for veterinary use before being translated to humans.[38,39] The most recently approved platform-based vaccines for human use are based on the pathogen's genetic information, delivered directly to the body in different ways.[40,41] Examples are:

- **DNA vaccines:** they use part of the pathogen's DNA. Once administered in the body, this will be copied into mRNA, which will be then be 'read' by the body to produce some of the pathogen's proteins and stimulate an immune response. Research in animals has shown that DNA vaccines can provide effective immunity to influenza virus, HIV and rabies.[42] The ZyCoV-D COVID-19 vaccine is the first DNA-based vaccine to be approved for emergency use in humans in India.[43] No DNA vaccine is currently available in the UK.
- **mRNA vaccines:** use the 'ready to read' mRNA to provoke the body to produce a pathogen's protein and stimulate the immune response.[40,44] Because of their 'readable' form, mRNA vaccines tend to be more efficient than DNA vaccines, needing lower doses and fewer vaccinations per individual. Examples include the Pfizer/BioNTech and the Moderna COVID-19 vaccines (in use) and the self-amplifying RNA vaccine in development by Imperial College London.[45–47]
- **Viral vector vaccines**: use a harmless virus (the vector) modified to contain part of DNA of the target pathogen. The COVID-19 University of Oxford/AstraZeneca vaccine is an example (Box 1).

Given that these platforms can be quickly adapted by changing the genetic information they carry, they can be chosen as a way to quickly respond to new infectious diseases.[48,49] However, these technologies do not work well for all pathogens. For instance, bacterial vaccines are often polysaccharide-based (rather than protein-based), hence progress across the whole range of vaccine technologies is still needed to ensure preparedness to future threats.

Box 1: COVID-19: a case study of vaccine R&D

During the COVID-19 pandemic, the UK Government created a dedicated Vaccine Taskforce to support vaccine development, procurement and manufacturing capabilities by coordinating technologies and infrastructure investments.[50,51] These included the Oxford University/AstraZeneca vaccine, which had an accelerated development timeline in part because the viral vector was already available from previous research.[52] R&D was also supported by flexibility of existing and new research funding, robust clinical trial infrastructure and a 'rolling review' approval process from regulators.[53] Rapid manufacturing scale-up for clinical trials was supported by a group of UK biotech SMEs and the very high rate of COVID-19 cases in the population allowed clinical trials to assess vaccine efficacy quickly. Despite its rapid development, the vaccine developers highlighted challenges, including that fragmented vaccine manufacturing for clinical trials led to delays.[54]

Multiple academics and industry experts agree that the speed of COVID-19 vaccine R&D was facilitated by previous academic research on other coronaviruses. Moreover, most of these vaccines are based on the 'spike' protein, a component of the SARS-CoV-2 virus that is easy to target with platform-based technologies.

Experts agree that vaccine R&D for a pandemic triggered by a more complex pathogen (such as an unknown virus or a bacterium) will be more challenging.

Challenges and opportunities

Challenges and opportunities for vaccine R&D include progress in fundamental research, animal testing, clinical trial design and approval, and manufacturing and distribution.

The value of fundamental research

One of the biggest challenges in vaccine R&D is developing a complete understanding of pathogens, the immune system and a disease's impacts on the population (i.e., 'epidemiology').[5] For

many infectious diseases, more research is needed to understand how pathogens interact with the body and which pathogenic components ('antigens') can be targeted by vaccines. This is particularly difficult for some rapidly mutating or complex pathogens (such as those causing HIV, tuberculosis, or malaria) or for pathogens as yet unknown.[55]

Moreover, the immune system is complex, and the processes causing an immune response to a pathogen are still not fully understood.[56,57] The immune response of different individuals varies and is influenced by many factors. Some people do not develop an effective immune response following a vaccination, and the immune response may decline with age. A complete understanding of the biological signatures that predict whether a person is protected against a disease (called 'correlates of protection') is still missing for many diseases.[58] These can accelerate R&D by allowing a quicker evaluation of vaccine efficacy, thus simplifying some stages of clinical trials.

Recent innovations in fundamental research that have supported vaccine R&D include:

- **System-approaches in biology and immunology**. These rely on a series of experimental techniques, combined with computational tools, to develop an understanding of biological systems in all their parts rather than focusing on single components. For instance, reverse vaccinology uses the whole genetic information of the pathogen to identify the best antigens to trigger a strong immune response.[59] This technique was first used to develop a vaccine against Meningococcus B (MenB) and can be used to develop vaccines against complex pathogens.[59,60] Similarly, genomes and individuals' immune responses can be analysed to understand better how they respond to infections or why some show adverse effects following vaccination and others do not.[58] This would allow the development of 'personalised' vaccines, tailored to a specific individual's immune system.[61]
- **Structural biology approaches.** These seek to understand the three-dimensional structure of antigens and how they are recognised by the immune system. Combined with computational methods, they enhance effective vaccine design by facilitating selection of the best antigens.[62] This can be particularly helpful with complex pathogens. The respiratory syncytial virus (RSV) vaccine, first developed for veterinary use, is one of the first examples developed using this approach.[39,63,64]

A better understanding of how to stimulate the immune response has the potential to increase the efficacy of existing vaccines, for instance by using different adjuvants or alternative administration routes.[65,66] For example, mucosal vaccines (such as the nasal spray influenza vaccine for children) trigger an immune response at the level of the nose and the mouth, ensuring the pathogen is stopped as soon as it tries to enter the body.[67–69] Vaccines can also be used as therapeutics to treat non-communicable diseases, such as some cancers, by stimulating the immune system to attack cancer cells.[70]

Animal research and veterinary vaccines

Demonstration of vaccine safety and efficacy in animal models is required before starting clinical trials, and therefore access to high quality, laboratory capacity for animal testing is critical. Moreover, new vaccines are often developed for veterinary use before being adopted for humans.[39] Supporting veterinary research and medicine has a key role in epidemic preparedness, as 75% of emerging infectious disease threats to humans are of animal origin.[71]

Clinical trial design and approval processes

Large scale clinical trials are expensive to set up and complete, the approval process starts only after the trials are completed and it can take several months. There are a series of approaches to facilitate clinical trials and approval processes.

Flexible clinical trials and clinical trial infrastructure

Innovative clinical trial designs, such as those that allow for the trial's protocol or sample size to be adapted as data emerge, have a role in speeding up vaccine development. [72] For instance, phases can be mixed (for example, Phase 2 and 3 can be combined), allowing information about vaccine immune response levels, side effect and efficacy to be collected at the same stage. In addition, a well-established clinical trial infrastructure, such as the NIHR Clinical Research Network[73], can allow for rapid resource allocation and the recruitment of trial participants.

Human challenge trials

When a disease is not widely circulating within a population and therefore vaccines cannot be tested with conventional large-scale trials, human challenge trials can be used to demonstrate vaccine efficacy in a small population. During these trials, healthy volunteers are 'challenged' with minimal quantities of pathogen in a controlled environment to: better study correlates of protection; demonstrate that vaccines confer protection; compare different vaccines (enabling progressing of only those vaccines that appear promising).[74] Human challenge trials contributed to the development of vaccines for cholera, malaria, influenza and typhoid fever.[75–78] High safety and quality standards are key requirements for human challenge trials to be ethically acceptable.

Licensing innovation

A 'rolling-review approach', where clinical trial data are assessed as they become available without waiting for the end of the trial, has been used to streamline COVID-19 vaccine approval.[79] In March 2021, MHRA, NICE and the Scottish Medicines Consortium launched the Innovative Licensing and Access Pathway (ILAP), a programme to accelerate the time it takes for new medicines, including vaccines, to reach the market. It focuses on medicines for which there is a significant patient or public health need.[80]

Manufacturing and distribution

Scaling up manufacturing is a complex process and there are only a few hundred vaccine manufacturing facilities around the world, many of which can produce only a single type of vaccine. Vaccine supply chains often need to be temperature-controlled, from production to delivery and administration (known as the 'cold-chain' and 'ultra-cold' chain). Completely synthetic vaccines, such as those that are mRNA-based, are easier to manufacture at scale, although they require particularly low temperatures for transport and storage, which are not readily available in many settings.[81–83]

Manufacturing optimisation

Advances in small scale technologies have enabled 'ultra scale-down' approaches, which allow vaccine production to be optimised by testing different manufacturing conditions with a very small amount of material before scaling up production.[8] Designing manufacturing facilities to be adaptable and using single-use plastic technologies instead of stainless steel systems can make it easier for a facility to be quickly repurposed for the production of new vaccines.[8] Advances in vaccine formulations can improve their ability to be stable at higher temperatures, simplifying cold-chains.[84]

Global manufacturing

As demonstrated by the COVID-19 pandemic, access to vaccine manufacturing is a national security priority worldwide. Decentralising production (setting up a larger number of manufacturing facilities at different locations) could simplify distribution and improve global access, but also add challenges in quality assurance and control.[85,86] Some global health experts state that supporting manufacturing capacity in Africa, Asia and Latin America, and sharing technologies, are priorities in pandemic responses.[87]

Financial support to stimulate vaccine R&D

Approaches to stimulate vaccine R&D in the UK include financial support for research and manufacturing capabilities. The UK also supports several international vaccine development programmes (Box 2).

Supporting early stages of vaccine R&D

Support for the early stages of vaccine R&D in the UK includes:

- **The UK Vaccine Network**. A network of experts from academia, industry and funding bodies was established in 2015 with the aim of informing the Government's investment (£120m between 2016-21) in R&D of vaccines against infectious diseases with the potential to cause an epidemic.[88] The Network focused on identification and prioritisation of human and zoonotic diseases, understanding the role of vaccines in disease outbreak, and production of guidance for vaccine development and manufacturing.[89,90,91]
- **The Vaccine Research Networks.** With a total investment of £12.4m, five Vaccine Research Networks were established in 2017. They focused on complex neglected diseases, livestock and zoonotic diseases; development of human infection challenge capability; vaccines for pregnant women and newborns; and vaccines for bacterial infections, aiming to tackle antimicrobial resistance (AMR) through immunisation (PN 581)[92–96]

Accelerating manufacturing

A series of initiatives have been launched to accelerate vaccine manufacturing in the UK. These include:

- **The Cell and Gene Therapy (GCT) Catapult.** As part of the Catapult Network (a series of centres bridging the gap between research and industry), the Government set up the GCT Catapult in 2012 to accelerate the development of novel biotechnologies (including those that can be transferred to vaccine applications).[97,98]
- **The Vaccine Manufacturing and Innovation Centre (VMIC).** In 2018, the Government announced the establishment of the VMIC, the first centre in the UK with the aim to support vaccine manufacturing at scale for epidemic preparedness.[99]
- The **Animal Vaccine Manufacturing and Innovation Centre**. Modelled on the VMIC, the centre, announced in June 2021, will develop vaccines to prevent zoonotic diseases that spread from animals to humans.[100]
- **The Medicines and Diagnostics Manufacturing Transformation fund.** The scheme was launched in 2021 with the aim of increasing manufacturing capacity in medicines (including vaccines).[101]

Government support for future vaccine R&D

During the COVID-19 pandemic, the Government made more than £6 billion available to develop and procure COVID-19 vaccines with support from the Vaccine Taskforce (Box 1).[102] Funding also included support for research, training and manufacturing centres, such as the VMIC and the CGT Catapult.[103–106] The Government's 2021 innovation strategy is seeking to use lessons learned from the Taskforce, including the role of public procurement in supporting innovation.[107] In its 2021 Life Sciences Vision, the Government stated its commitment to sustain the UK's position in novel vaccine development.[4] It also made broader commitments to make the UK globally competitive in life sciences (Box 2).

Box 2: International vaccine R&D programmes

The UK supports a series of international initiatives including:

- **The WHO R&D Blueprint**, a global initiative allowing rapid activation of R&D during epidemics.[108]
- **GAVI, the vaccine alliance**, a public-private global health partnership with the objective of improving access to immunisation and vaccine equity worldwide.[109]
- **The Coalition for Epidemic Preparedness Innovations (CEPI),** a global multilateral partnership to fund vaccine platforms and R&D of vaccines against a range of priority diseases, including Ebola virus, Lassa Fever virus, MERS and SARS-CoV-2.[110] In 2020 the UK Government has pledged over £220m to CEPI.[111–113]
- **COVAX,** an initiative established by WHO, GAVI and CEPI to ensure fair access to COVID-19 vaccines, and to accelerate their production.[114]
- **CARB-X** (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator), a global non-profit public–private partnership to tackle AMR by, among others, accelerating the development of new vaccines.[115]
- **The Global Alliance for Livestock Veterinary Medicines (GALVmed),** a not-for-profit partnership to develop and deliver livestock vaccines, medicines and diagnostics accessible and affordable to developing countries.[116]

International initiatives following the G7 Summit

Vaccine R&D, pandemic preparedness and the role of vaccines in AMR were among the focuses of the 2021 G7 Summit. [117] G7 leaders endorsed the 100 Days Mission report, which outlines a strategy for better pandemic preparedness. Greater global co-operation on research and development, manufacturing, clinical trials and data-sharing were among its recommendations.[118] G7 leaders also committed to actions to improve equitable access to vaccines, such as protecting supply chains for global equitable access and strengthening international coordination in pandemic preparedness and response.[119]

POST is an office of both Houses of Parliament, charged with providing independent and balanced analysis of policy issues that have a basis in science and technology. POST is grateful to all contributors and reviewers. For further information on this subject, please contact the author, Dr Cristiana Vagnoni.

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