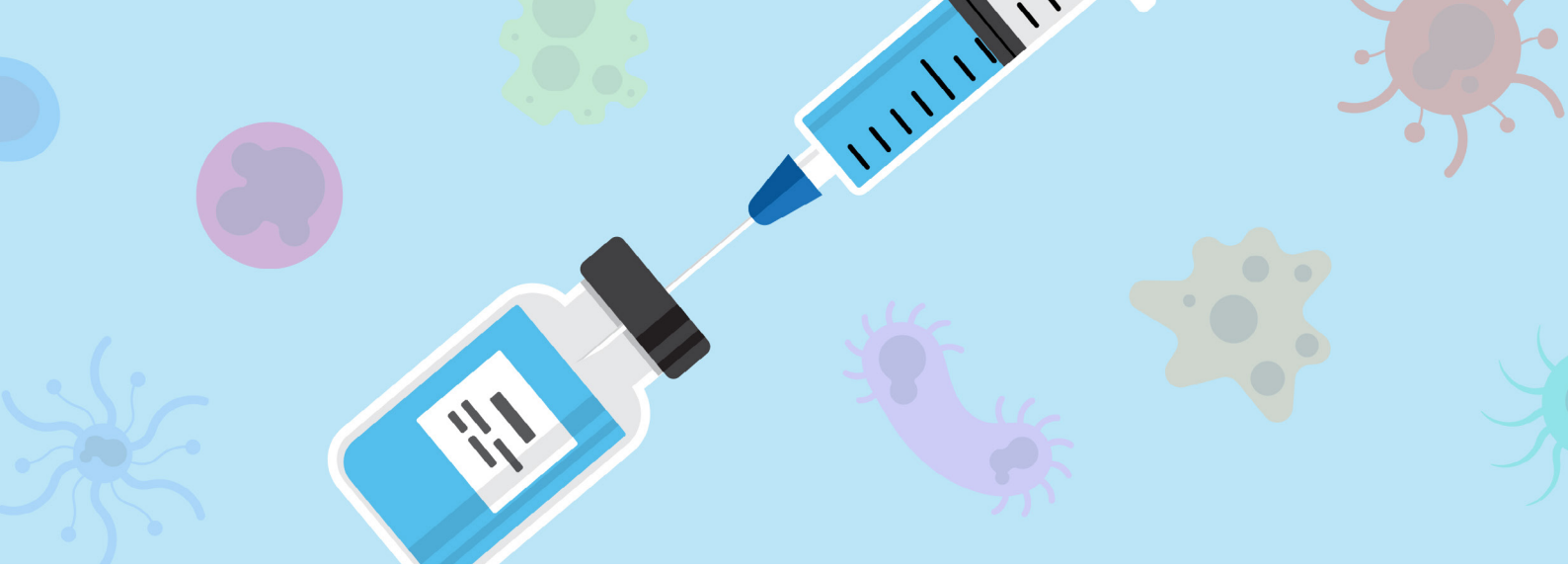

Valiant Vaccines Vanquish Viruses

Written by **Jessica Kan,**
Industrial Placement Student, GSK and University of Bath

A vaccine is a weakened or attenuated form of a pathogen that contains antigens, but is incapable of triggering disease. They stimulate an immune response to protect us from a disease. There are many types of vaccines, such as inactivated or subunit. Read on to find out what technologies are involved in producing vaccines and the future of vaccine development.

Our immune system is important for protecting us from deadly diseases. Vaccines "train" our immune system to respond to a disease causing micro-organism (a pathogen) that could make us very ill. By stimulating an immune response, without causing disease, vaccines reduce the risk of becoming seriously ill from a disease and prevent deaths. This article explores what vaccines are and why they are vital.

What are vaccines?

A vaccine can be a dead or weakened form of a pathogen, or part of a pathogen. The vaccine contains a specific antigen, which causes specialised white blood cells to generate antibodies that are complementary to the antigen. Memory cells are also generated. In other words, the vaccine stimulates a primary immune response.

Antibodies attach to the antigens on the surface of pathogens, causing the pathogens to clump together making it easier for a particular type of white blood cell, called a phagocyte, to recognise, engulf and destroy the pathogen. Some phagocytes become antigen-presenting cells and activate other types of white bloods cells called T-cells and B-cells which provide a specific and specialised response, leading to the production of antibodies and targeted destruction of the pathogen. Some T-cells and B-cells also become memory cells which help you to develop a faster immune response next time you are exposed to the pathogen, so the pathogen is destroyed before it makes you ill.

There are vaccines available for over 20 life-threatening diseases, for example, cholera, influenza, and measles[1]. Vaccinations prevent 2-3 million deaths every year, however, many people, including 20 million infants, have insufficient access to vaccines[1].

Types of vaccines

There are various types of vaccine[2] available which are made using different processes. They may include live attenuated vaccines (where the pathogen is weakened or altered so as not to cause illness); inactivated pathogens; inactivated toxins (for bacterial diseases where the toxins produced by the bacteria cause the illness), or segments of a pathogen (which includes subunit and conjugate vaccines)[3]. Researchers have also developed mRNA and viral vector vaccines. Examples are shown in the table below:

Vaccine type	Example
Live, attenuated	Measles, mumps, rubella (MMR) Varicella (chickenpox) Influenza (nasal spray) Rotavirus Yellow fever
Inactivated	Polio Hepatitis A Rabies Influenza (injection)
Toxoid (inactivated toxin)	Diptheria Tetanus
Subunit/ conjugate	Hepatitis B Influenza Pertussis (Whooping cough) Human papilloma virus (HPV)
mRNA	COVID-19 Zika virus
Viral vector	COVID-19 Ebola

A summary of the modes of action is given below:

Live attenuated vaccines contain whole bacteria or viruses that have been weakened so as not to cause disease. The pathogen can be weakened by genetic modification, heat or chemical/radiation treatments. They tend to create a strong and long-lasting immune response but are unsuitable for use in people whose immune systems are compromised – the pathogen can replicate rapidly and has the potential to cause disease in these people.

Inactivated vaccines contain whole bacteria or viruses that have been killed or altered so they cannot replicate. As such, they are safer to use in people for whom a live vaccine is not recommended but have the disadvantage that they do not provoke as strong an immune response. For this reason, booster doses are often needed.

Toxoid vaccines are made with inactivated versions of toxins (referred to as a 'toxoid') that are produced by bacteria. The immune system recognises these in the same way as the real toxin and mounts an immune response against them.

Subunit vaccines are those which contain only part of a pathogen, for example a glycoprotein or polysaccharide on the surface of a bacterial cell. These act as antigens, stimulating the immune response and resulting in immunity to the disease. In the early days of these vaccines, it was found that they worked much better when joined (conjugated) with another molecule such as a toxoid – an example would be a polysaccharide taken from the surface of the Diptheria bacterium, conjugated with a toxoid protein from the same bacterium.

mRNA vaccines are delivered into the body enclosed inside a lipid (fat) membrane. This protects the mRNA when it first enters the body and helps it to gain entry by fusing with cell membranes. Once inside a cell, the mRNA can produce antigen proteins which stimulate an immune response. The Pfizer BioNTech and Moderna COVID-19 vaccines are both mRNA vaccines.

Viral vectors are a more recent development and use harmless viruses to deliver the genetic code (DNA or RNA) of an antigen to many cells in the body. These cells will then produce the antigens which leads to an immune response, conferring immunity to the disease. Most recently, this method was used in multiple Ebola outbreaks and is useful in 'ring vaccination', where close contacts of an infected person are vaccinated to prevent further spread.

How are vaccines developed?

In vitro assays are carried out on the pathogen of interest to test and validate an idea. Next in the pre-clinical stage, in vivo studies of the pathogen are carried out in animals. If the studies pass regulations, then a phase I clinical trial is conducted where the vaccine is given to healthy humans alongside a placebo group to assess safety and adverse effects. This typically takes 1-2 years. This stage, the human trial, is important because animals are different species to humans and could react differently.

Next, in phase II the vaccine is given to patients alongside a placebo group to analyse efficacy (how well it works) and adjust dosing strategy. This lasts around 2 years. In phase III the vaccine is given to a larger group of patients over a longer period of 3-4 years. Finally, in phase VI after approval from regulatory authorities, for example FDA or MHRA, the vaccine undergoes lifecycle management where it is continually monitored by the Centre for Disease Control[4].

Rigorous testing is needed to ensure that the vaccine is safe for people, for example to prevent the use of vaccines with severe side effects. It is important to note the side effects and weigh up benefits against risks. By doing so, the developers can be assured that their vaccines are as safe as possible and work effectively whilst meeting regulatory requirements. If a vaccine fails any stage, then the trial is stopped, and the vaccine will need to be reviewed.

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How are vaccines manufactured?

Pathogens can be grown in human cells or given to a chick embryo or cultured in a bioreactor. Antigens are then harvested and purified then combined with other ingredients to create the vaccine. For example, adjuvants (compounds) are usually added to the vaccine to boost the immune response and effectiveness of the vaccine. Also, preservatives prevent contamination and stabilizers prolong storage life during transportation. Then the vaccine is stored in a vial and freeze-dried to remove water and for conservation. Next, the vaccine is packaged and undergoes the final steps of quality assurance processes that take place all the way through production, including checking by regulatory agencies. Finally, the vaccine is transported and distributed. This process takes 6-36 months with around 70% of the time spent on quality control[5].

In some circumstances, the whole process for producing a vaccine, making it available and checking it is safe is accelerated to meet human needs. For example, as part of the COVID-19 response a multitude of vaccines are being produced across the world in rapid time to cope with the major effects of the coronavirus. The downside to such rapid production of vaccines is that some side effects may become evident after the trial period. Scientists therefore must carefully consider the benefits and any potential harm of any vaccine throughout its development.

Advantages and disadvantages of vaccination

The advantages of vaccination are obvious in that they prevent people from becoming ill due to infection. Since vaccination against smallpox was first discovered by Edward Jenner in 1796, the process has transformed modern medicine and prevented serious illness and deaths across an incalculable number of the global population. With the advent of global vaccination programmes, enough people have been immunised to prevent certain pathogens from infecting whole populations – a phenomenon known as herd immunity[6]. Indeed, in a triumph of medical science, vaccination led to the eradication of the deadly smallpox virus, with the world being declared free of the disease by the WHO in 1980. It should also be noted that there is a big financial benefit to preventing disease through vaccination, rather than treating people that succumb to illness – quite apart from the cost of medical treatment, there is also the loss of working days to the economy to consider. The vaccination programme that has been rolled out in response to the COVID-19 pandemic provides a good example of how such preventative measures can once again 'unlock' restrictions and allow people to return to work and a sense of normality.

However, vaccinations are not without some risks. Thanks to the rigorous testing protocols and measures, these usually amount to mild side effects in a limited number of people, such as short lived cold-like symptoms and a slight fever – these are often signs that the immune system is responding to the pathogen or antigen and may be more evident when live vaccinations are used. In extremely rare instances (much rarer than acquiring the disease), some individuals may suffer from more severe side effects (e.g. high fever, rashes) but medical professionals are trained to deal with these if they arise. It should be remembered that vaccination is only offered if the benefits significantly outweigh potential risks, and that the system of pre-clinical and clinical trials ensures that vaccination is as safe as it can possibly be.

The future of vaccines

As manufacturing technology advances[7], we can expect to see vaccines being produced more efficiently and at reduced cost, increasing their accessibility to all members of the global population[6]. The COVID-19 pandemic has demonstrated the need to turn around vaccine development more swiftly and over a time of months rather than years. This has led to a different approach, with many development steps in pre-clinical trials, clinical trials and manufacturing being executed in parallel before confirming a successful outcome of another step[8].

Methods of delivery may also change – syringes have traditionally been used as a primary way of administering many vaccines, but there will always be a significant number of the population that are reluctant to experience injections. This is not a trivial matter, as the less people that are vaccinated, the lower the herd immunity effect becomes. New techniques that involve the use of micro-patches that can vaccinate against some diseases (e.g. hepatitis B), offers a new way which may improve uptake of vaccinations in the future.

Efficacy of vaccines may also improve. Newer and more effective adjuvants[9] (ingredients used with some vaccines that help to create a stronger immune response) will continue to be developed and help to ensure that protection is stronger and longer lasting.

The COVID-19 pandemic has demonstrated the need to turn around vaccine development more swiftly and over a time of months rather than years.

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Glossary

Adjuvant – An adjuvant is a substance that enhances the immune system's response to the presence of an antigen.

Antigen – A molecule that can stimulate an immune response. For example molecules on the surface of a pathogen. The abbreviation Ag is sometimes used, which stands for antibody generator.

Bioconjugation – a technique used to link a biological molecule and another molecule.

DNA – Deoxyribonucleic acid (DNA) is a molecule that has a double helix shape and carries genetic instructions for the development, function, growth and reproduction of all known organisms and many viruses.

FDA – The United States Food and Drug Administration is a federal agency of the Department of Health and Human Services.

In vitro – In vitro studies are performed with microorganisms, cells, or biological molecules outside their normal biological context. Colloquially called "test-tube experiments", these studies in biology and its subdisciplines are traditionally done in labware such as test tubes, flasks, Petri dishes, and microtiter plates.

In vivo – Studies that are in vivo are those in which the effects of various biological entities are tested on whole, living organisms or cells, usually animals, including humans, and plants.

MHRA – The Medicines and Healthcare products Regulatory Agency is an executive agency of the Department of Health and Social Care in the United Kingdom which is responsible for ensuring that medicines and medical devices work and are acceptably safe.

RNA - Ribonucleic acid (RNA) is a type of nucleic acid and occurs as three main types (messenger, transfer and ribosomal). It has various roles involved with synthesis of proteins and the regulation and expression of genes.

mRNA – messenger ribonucleic acid (mRNA) is a single-stranded molecule that provides the genetic code needed to produce proteins.

WHO – The World Health Organization is a specialized agency of the United Nations responsible for international public health.

Find out more

Some fun activities to learn more about vaccines: www.immunology.org/celebrate-vaccines/public-engagement/activity-packs/hands-activities

About the author

Jessica is currently studying Natural Sciences (Biochemistry with Pharmacology) at the University of Bath. She did her industrial placement at GSK (global pharmaceutical company) and gained an invaluable insight into Pharma research and development (R&D). During her time at GSK she used Flow Cytometry and MSD to investigate the phenotype and function of regulatory B-cells. Jessica also learnt about other business units within GSK such as Vaccines, Consumer Healthcare (Pfizer Joint Venture), and ViiV (HIV).