
# How do vaccines protect against infectious diseases?

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Vaccines protect millions of animals against infectious diseases. Immunologist Megan MacLeod describes how they stimulate our immune systems and protect us from infectious disease

**EXAM LINKS**

**AQA** Cell recognition and the immune system
**OCR A** Communicable diseases, disease prevention and the immune system
**OCR B** The immune system; Controlling communicable diseases
**Pearson Edexcel A** Immunity, infection and forensics
**Pearson Edexcel B** Response to infection
**WJEC Eduqas** Immunology and disease

The COVID-19 pandemic changed everyone's lives. One reason for this is that it is a virus that humans have never been exposed to before. This means our immune systems must start from scratch, developing the right response to eliminate the virus.

The consequences of COVID-19 would have been very different if we had already prepared a **vaccine** against the virus. Vaccines work by training immune systems to fight more effectively against pathogens. We develop what is called immune memory or specific immunity.

BiologicalSciencesReview*Extras*

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## Immune memory is the basis for vaccine success

Vaccines have formally existed since the late eighteenth century, when the physician Edward Jenner developed the smallpox vaccine. Jenner took advantage of the knowledge that exposure to a related disease, cowpox, protected people against smallpox. He used pus from the sores of people with cowpox to make a formulation that protected people from smallpox. Although the virus that causes cowpox gives rise to only mild symptoms, it stimulates the immune system to recognise and control smallpox virus. Jenner's original vaccine has been improved to make it safer, eventually leading to smallpox elimination in 1980.

All vaccines contain two key elements. The first is the **antigen**, which tells the immune system the pathogen's identity. The second are **adjuvants** – substances that alert the immune system to danger. Together these substances drive the formation of immune memory, protecting the individual from future infection.

## The adaptive immune system specifically recognises pathogens

Vaccines trigger B and T lymphocytes, which are part of our adaptive immune system. On their cell surface they have specialised receptor proteins called **B cell** or **T cell** receptors (BCRs and TCRs) respectively. Each cell makes a unique BCR or TCR and we have around $10^{13}$–$10^{14}$ different B and T cells circulating around our bodies.

For many years, this huge number of different BCRs and TCRs confused scientists, as the entire human genome contains only 20 000 to 25 000 genes. The solution to this puzzle is that receptors are formed when developing B cells and T cells undergo somatic rearrangement (see Figure 1). This process involves a family of genes that are assembled from a unique BCR or TCR gene, each with a different combination of the gene families. Each antigen receptor contains a core section that supports the variable part of the receptor that binds to the antigen.

**TERMS EXPLAINED**

**Adjuvant** Substance that increases the immune response to an antigen.
**Antibody** Molecule that binds to pathogens, preventing or reducing infection.
**Antigen** Substance that the adaptive immune cells – T and B cells – recognise.
**B cells** Adaptive immune cells that specifically recognise pathogens and go on to produce antibodies.
**Dendritic cells** Cells that sample their surroundings for pathogens and then move to lymph nodes to alert T cells.
**Isotype switching** Process of changing the part of the antibody that determines how it acts to protect the host.
**Lymph nodes** Small organs found throughout the body where B and T cells are activated.
**PAMPs** Pathogen associated molecular patterns: substances in pathogens that trigger innate immune responses.
**T cells** Adaptive immune cells that specifically recognise pathogens and either direct the immune response or kill infected cells.
**Vaccine** Substance that activates the immune system to generate immune memory against a specific pathogen.

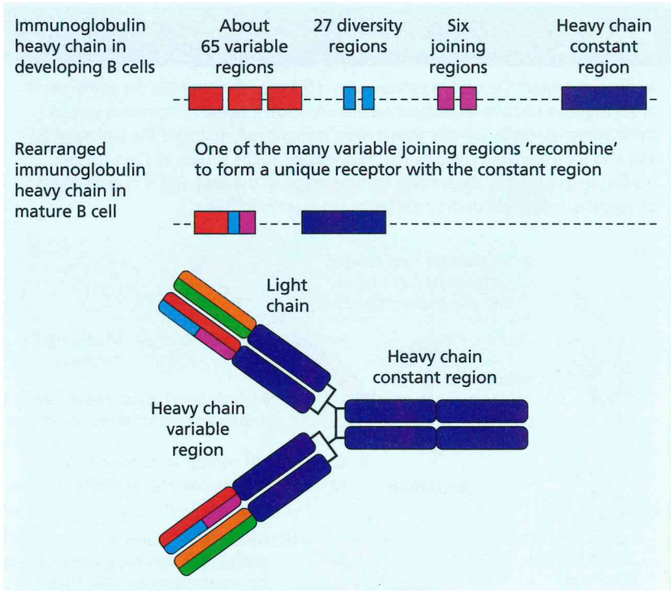



**Figure 1** Unique B cell receptors (BCRs) and T cell receptors (TCRs) are generated via a process called somatic rearrangement, which involves one of many variable joining regions forming a new gene segment that codes for the BCR or TCR. The heavy chain of the BCR is depicted and similar processes occur for the light chain of the BCR and for the two chains that make up the TCR

## Plasma cells make antibodies that prevent future infections

We need both B cells and T cells as they perform different functions. T cells come in two forms, called CD4 helper T cells and CD8 cytotoxic T cells (see Box 1). One of the most important jobs for CD4 T cells is to help B cells modify their BCR. The T cell prompts the B cell to swap nucleotides in the genes that make up the BCR to improve the ability of the

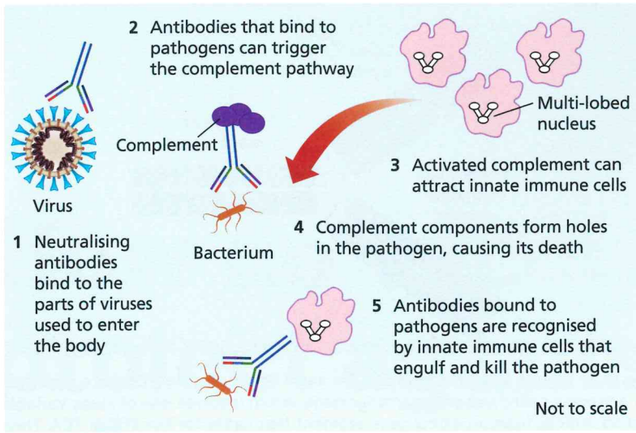
**Box 1 Types of T cells**

CD4 helper T cells are the directors of immune responses, helping other cells, including B cells, do their job effectively. Depending on the pathogen they recognise, or the danger signals in the vaccine, they make different molecules to direct the immune system. For example, the immune response they direct to expel gut worms is very different from that needed to control viruses.

CD8 cytotoxic T cells are trained to be killers, attaching to cells infected with viruses or bacteria and stimulating these cells to die. This death signal to the infected cell leads to apoptosis – a controlled form of cell death – which curbs the pathogen, limiting its ability to infect neighbouring cells.

## Box 2 Functions of B cells

Antibodies protect the host in various ways. (1) They can neutralise the pathogen, or (2) trigger a cascade of proteins collectively known as the complement system. Once triggered, these proteins recruit more immune cells to tackle the pathogen (3) and also form a protein complex that makes holes in the surface of the pathogen, leading to its death (4). Depending on the isotype of the antibody, it may also help phagocytes ingest and destroy the pathogen more readily (5).




B cell to recognise the antigen. B cells can also change the core or constant part of their BCR. In a process called **isotype switching**, the B cell removes part of the gene so it can express a new constant region. These different constant regions give the B cell different functions to fight the pathogen (see Box 2).

Activated B cells divide repeatedly. In some cases they generate cells called plasma cells that make soluble versions of their BCRs called **antibodies**. Plasma cells can live for many years, making antibodies that distribute throughout the body in blood and in mucus-lined body cavities including airways and the gut. These antibodies thus form an immediate defence against the pathogens that invade us.

Some antibodies, called neutralising antibodies, bind to the pathogen even before it enters our cells, stopping it from infecting us and causing disease. These are the most effective antibodies, providing complete protection. Even if antibodies cannot prevent an infection, by binding to the pathogen they can quickly control it (see Box 2).

In the first response against a pathogen or following vaccination, the formation of protective antibodies takes 7–14 days (see Figure 2). This gives the pathogen ample time to replicate, cause disease, and be transmitted to others. Antigen-specific immunity developed following a previous infection or vaccination reduces this time to just a few days. The replication of the pathogen is curtailed, and the chances of disease and transmission are greatly diminished.

### Vaccines alert the immune system to danger

Different vaccines protect against diseases as diverse as the paralysis caused by toxins from tetanus bacteria, respiratory diseases caused by pneumococcal bacteria and influenza viruses (flu), and the cancers caused by human papillomaviruses (HPV). All vaccines contain some part of the pathogen they protect against, the antigen. However, the form this antigen takes can be very different.

**First encounter with pathogen**
- Lots of pathogen in infected individual
- High chance of disease and transmission
- Protective antibody takes about 2 weeks to reach peak level

**Second encounter or following vaccination**
- High level of protective antibody prevents infection or greatly reduces pathogen replication
- Greatly reduced chance of disease and transmission

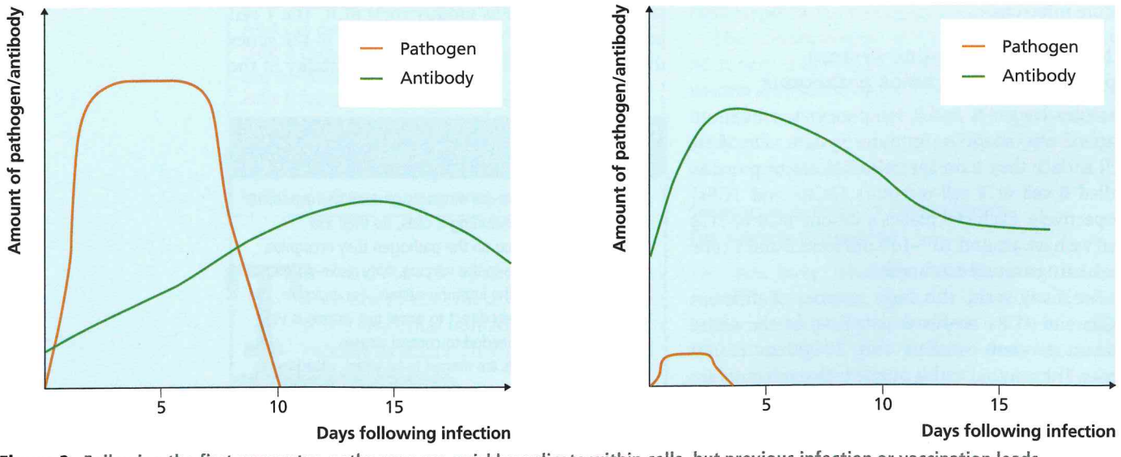



**Figure 2** Following the first encounter, pathogens can quickly replicate within cells, but previous infection or vaccination leads to high levels of protective antibodies that prevent infection or pathogen replication



Some vaccines, including the flu vaccine that is sprayed up the noses of children, contain active pathogens. These 'live' vaccines contain a modified version of the pathogen that cannot cause disease because it has been modified to grow at temperatures other than 37°C or in cells that are not human. Other vaccines, including the version of the flu vaccine injected into muscles, contain inactivated pathogen. A further form are sub-unit vaccines, which contain only a portion of the pathogen. The tetanus vaccine contains a modified, non-toxic form of the *Clostridium tetani* toxin that in its original form causes paralysis, and HPV vaccines contain the proteins that enable viruses to enter cells.

Live and inactivated vaccines contain the whole pathogen: the protein antigen that B and T cells respond to and other substances known as 'pathogen associated molecular patterns' (**PAMPs**). These PAMPs trigger our immune system to recognise that something dangerous has entered the body. The first cells to respond to these 'danger signals' are innate immune cells, including **dendritic cells**. These cells are found throughout the body where they process antigen and present it on their cell surfaces to antigen-specific T cells. This leads to activation of the T cells which can then help B cells produce protective antibodies (see Figure 3).

Unless they receive the appropriate signals, dendritic cells are unable to activate T cells. This is a problem for sub-unit vaccines that do not contain the pathogen danger substances, PAMPs. To solve this, substances called adjuvants are added. The adjuvant used in most human vaccines is a form of an aluminium salt (usually either aluminium phosphate or hydroxide) and is known as alum. While alum has been used safely since the 1930s, there is still incomplete understanding of how it stimulates the immune system. It is thought that alum leads to the release of a variety of molecules, including cytokines and metabolites, usually only found inside cells. These molecules are normally only released when pathogens cause tissue damage.

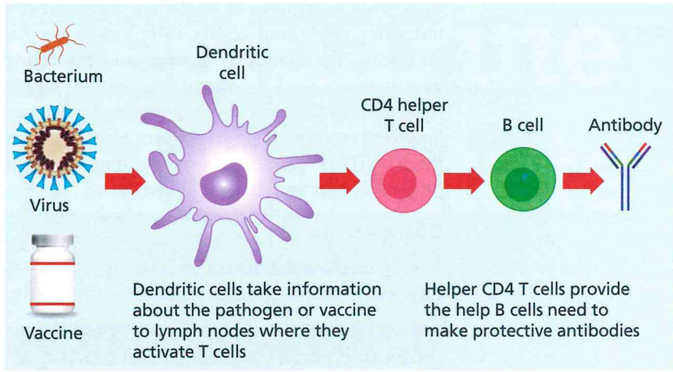



**Figure 3** Pathogens and vaccines are taken up by dendritic cells that move to **lymph nodes** to activate T cells, which then help B cells produce protective antibody (not to scale)

### We need more vaccines

We do not have effective vaccines against pathogens that are responsible for millions of deaths each year. These include the human immunodeficiency virus (HIV) that causes AIDS and the parasite *Plasmodium falciparum*, which causes malaria. A major difference between these pathogens and those for which we do have vaccines is the formation of protective immune memory following infection. The immune memory that, for example, flu vaccines generate largely mirrors that found in individuals actually infected with the flu virus. In contrast, individuals infected with HIV or who have had malaria do not form immunity against these pathogens. Instead these individuals are either chronically infected with the virus in the case of HIV, or can be infected repeatedly with *P. falciparum*. It is not known, therefore, what a successful vaccine must aim to emulate to protect us against these pathogens.

### Vaccine hesitancy

The lack of vaccines against some of the world's deadliest diseases is not the only problem we face. Even though there is a safe and effective vaccine against the measles virus, which has saved millions of lives across the globe, measles is on the rise. This is a consequence of some individuals choosing not to vaccinate their children, either because they believe vaccines are dangerous (see pp. 30–34, this issue) or because access to vaccines is difficult. Vaccines have

Coloured scanning electron micrograph of a dendritic cell