How do vaccines protect against infectious diseases?

Megan MacLeod

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*

This article is the focus of our online activity. Go to www.hoddereducation.co.uk/bioreviewextras for a worksheet with mark scheme.

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 20000 to 25000 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.

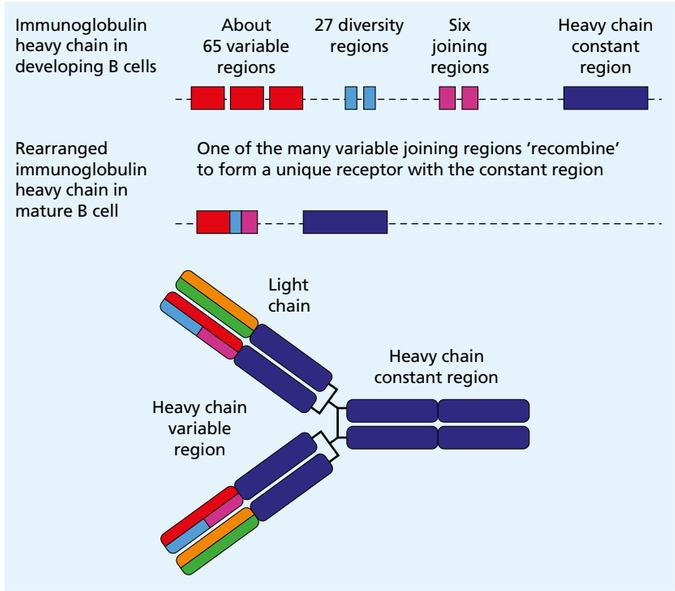


Figure 1 Unique B cell receptors (BCRs) and T cell receptors (TCRs) are generated via a process called somatic rearrangement, which involves one of many variable joining regions forming a new gene segment that codes for the BCR or TCR. The heavy chain of the BCR is depicted and similar processes occur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

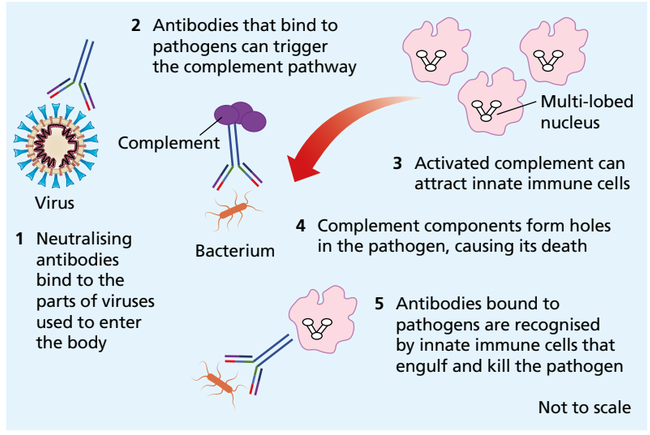
Box 1 Types of T cells

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

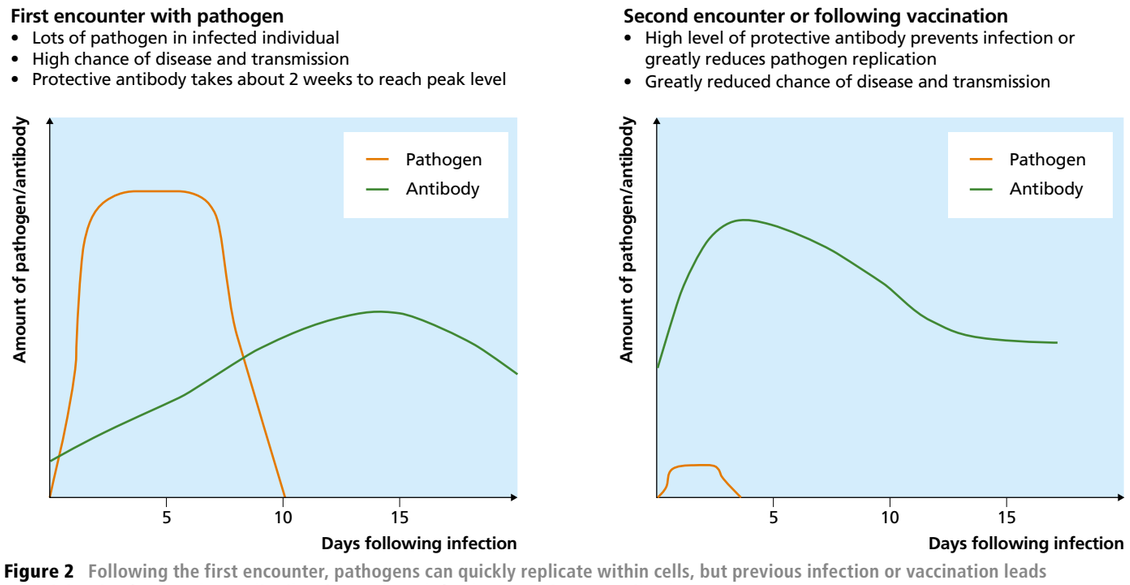


Figure 2 Following the first encounter, pathogens can quickly replicate within cells, but previous infection or vaccination leads to high levels of protective antibodies that prevent infection or pathogen replication

pathogen they protect against, the antigen. However, the form this antigen takes can be very different.

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.

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

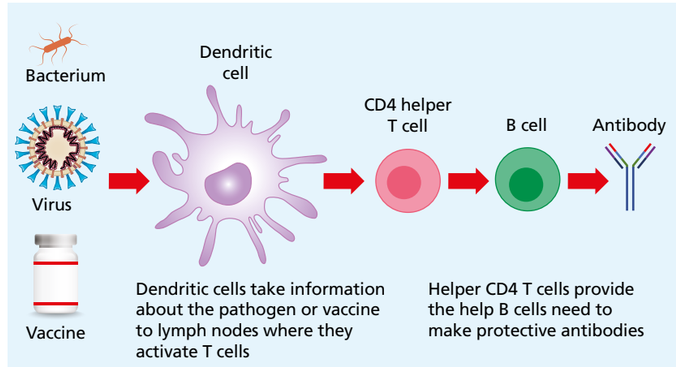


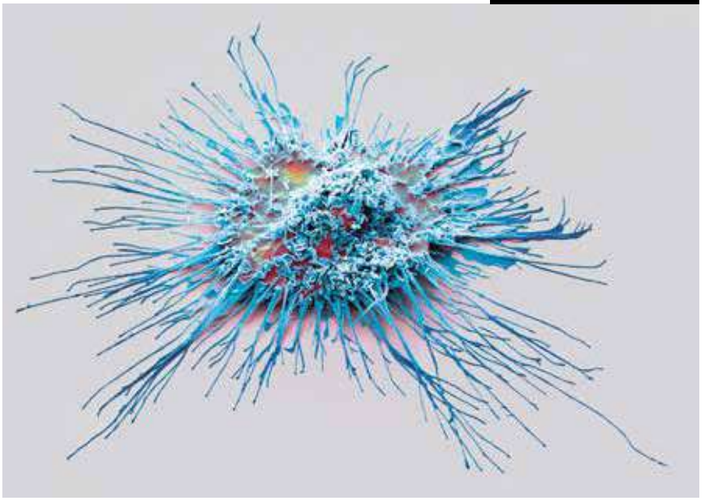
Figure 3 Pathogens and vaccines are taken up by dendritic cells that move to **lymph nodes** to activate T cells, which then help B cells produce protective antibody (not to scale)

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



been given to millions of people and are rigorously tested for safety and ability to induce protective antibody. Promoting this message and explaining how vaccines work is essential to ensure people make the right choices about protecting themselves and their families. If we have learnt anything from the COVID-19 pandemic, it is the importance of preventing infectious disease to save lives.

Things to do

- If vaccinations should be mandatory (see pp. 30–34, this issue), which diseases should it cover? Set up a debate, taking advantage of the websites given in the Resources.
- Learn more about the infectious diseases for which we do and do not have vaccines. Why don't we have vaccines against all infectious diseases?

RESOURCES

Learn more about the immune system from the British Society for Immunology: **https://tinyurl.com/y2ynz59m**

Learn more about the vaccines from the World Health Organization: **www.who.int/topics/vaccines/en**

Should vaccination be mandatory? Watch interviews from experts in the field: **https://tinyurl.com/y8oyvyou**

KEY POINTS

- Exposure to a vaccine or a pathogen leads to the formation of immune memory that, usually, protects the host from future disease.
- Vaccines contain two key elements: antigen from the pathogen, and substances that tell innate immune cells something dangerous has entered the body.
- Adaptive immune cells, T and B cells, have unique receptors that specifically recognise pathogens.

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Alternative splicing

One of the unifying principles of early molecular genetics was the one-gene-one-polypeptide hypothesis. This proposed that the nucleotide base sequence of each gene carried the genetic code for the amino acid sequence of a single polypeptide. The Human Genome Project, started in 1990 and declared complete in 2003, identified approximately 22 300 genes in the human genome. We know, however, that humans produce far more different polypeptides than this. How is this possible?

The answer lies in the way in which genes are processed. The genes of eukaryotic cells contain sequences of coding nucleotides and sequences of non-coding nucleotides. The base sequences that carry the code for amino acid sequences are called exons (**ex**pressed regi**ons**). They are interspersed among sequences of non-coding nucleotides, called introns (**intr**agenic regi**ons**). When a eukaryotic gene is transcribed, the initial RNA transcript contains sequences that are complementary to both the exons and the introns. This so-called pre-mRNA is then edited, removing the introns and recombining the exons.

So far, this is consistent with the one-gene-one-polypeptide hypothesis. Research shows, however, that this account is too simplistic. During the editing process, the RNA sequences complementary to the exons can be combined in different ways. This is called alternative splicing and results in different mRNA transcripts, called isoforms. It might involve recombining only some of the RNA complements of the exons, joining them in different arrangements, or a combination of both.

Figure 1 represents the alternative splicing of a pre-mRNA molecule transcribed from the *CALC1* gene located on chromosome 11 of humans. Of the two resulting isoforms, one encodes calcitonin (a hormone) and the other encodes calcitonin gene-related peptide (CGRP – a vasodilator).

Martin Rowland

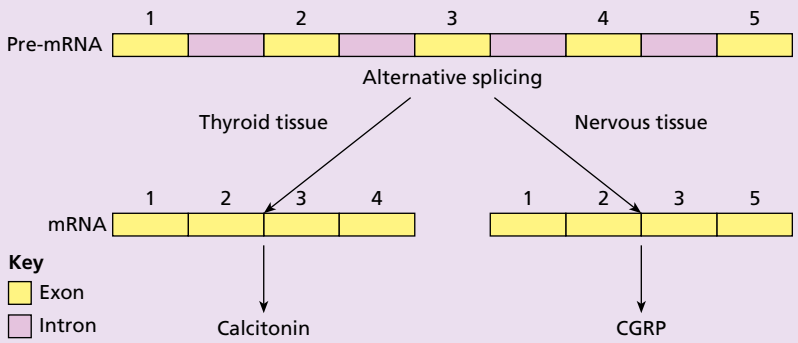

Figure 1 Alternative splicing. The RNA complements of exons can be combined in different ways. In some cases, not all are used, as shown here. In other cases, the ones that are used are combined in different arrangements