The Science of Immunisation

Questions and Answers

November 2012

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Australian Academy of Science

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President, Australian Academy of Science
May 2010 – present

Foreword

The Australian Academy of Science is strongly committed to ensuring that the public has the opportunity to understand and discuss scientific issues, and how these impact on society and on our planet. Through its Fellows and its National Committees for Science, it is able to draw on expertise from a broad sector of the Australian science community to report on important scientific issues.

This report was undertaken to enhance public understanding of how vaccination provides protection from infectious diseases and the underlying benefits and risks.

Immunisation has transformed human health by preventing the deaths of hundreds of millions of people. Based on scientific knowledge, it is one of the great advances that has changed the world as we know it. Decisions on the use of immunisation, through vaccination programs, are taken by society as a whole, taking into account not only scientific knowledge but considerations that go beyond the science, including ethics and equity, community health economics, risk management and politics. This publication is not a formulation of a policy for immunisation but it is an attempt to improve the public understanding of the science upon which immunisation policy and practices rely.

The Academy's Council established two Committees to address some of the major questions that are frequently asked about immunisation and vaccination science. First, an expert Working Group carefully formulated a set of key questions about the science of immunisation. This group consists of internationally recognised scientists who have contributed extensively to the underpinning science. Six 'big' questions were identified, which were then sub-divided into 'lower-level' questions and answers were then prepared. Second, an Oversight Committee comprehensively reviewed the answers provided to ensure that they are authoritative within the current state of knowledge. This Committee consists of eminent Fellows of the Academy and other experts with both extensive research experience in related fields and in the leadership of immunisation and vaccination-related programs and organisations.

We have all personally benefited from vaccination and most people clearly understand the value of immunisation, and the way in which it is a key tool to lower the risk of serious infectious disease in our community, particularly for children. However, we know there are a very small number within a vaccinated population who can have adverse reactions as a consequence of vaccination. No medical intervention is completely without any risk and fortunately the overall number of non-trivial reactions to vaccines is extremely small. Advances in technology are reducing even this very small risk still further each year.

As control of infectious diseases remains a prime challenge for humanity, it is important that extensive research and rigorous scientific debate continue, especially as our understanding increases to enable vaccination against a wider range of diseases. The ongoing communication of that research to the broader community, and their participation in discussions on the scientific basis of vaccination, must continue if the benefits of immunisation are to be realised. The Academy hopes that this report will provide a firm basis for understanding the science of immunisation and its implications.

The Academy is very appreciative of the pro-bono contributions made to this report by the members of the Working Group and Oversight Committee to provide authoritative answers to these important questions on the science of immunisation. The Academy also thanks the Department of Health and Ageing for providing financial support to prepare this document.

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Summary

The widespread use of vaccines globally has been highly effective in reducing the incidence of infectious diseases and their associated complications, including death. For centuries, infectious disease was the most common cause of disability and death worldwide, a situation that persists in the least developed countries of the world. Until the 19th century, it was unclear what caused these diseases and why some people became very ill with an infection while others were less seriously affected.

Based on research and observation, the medical community now knows that infectious diseases are caused by micro-organisms (pathogens). It is also now understood that the human immune system provides our defence against infectious diseases.

The immune system is made up of trillions of specialised cells (white blood cells) that detect and destroy pathogens or their toxins. Some white blood cells, which are known as lymphocytes, and the antibodies they produce, are highly specific. Each recognises only one pathogen or its toxin. A key feature of lymphocytes is that after an infection, lymphocytes specific to the pathogen will persist in the body. These specific, long-lived lymphocytes are called memory cells. If a person encounters the same pathogen again in the future, these memory cells will help the immune system mount a much quicker, larger and more sustained response that ultimately controls the infection more efficiently.

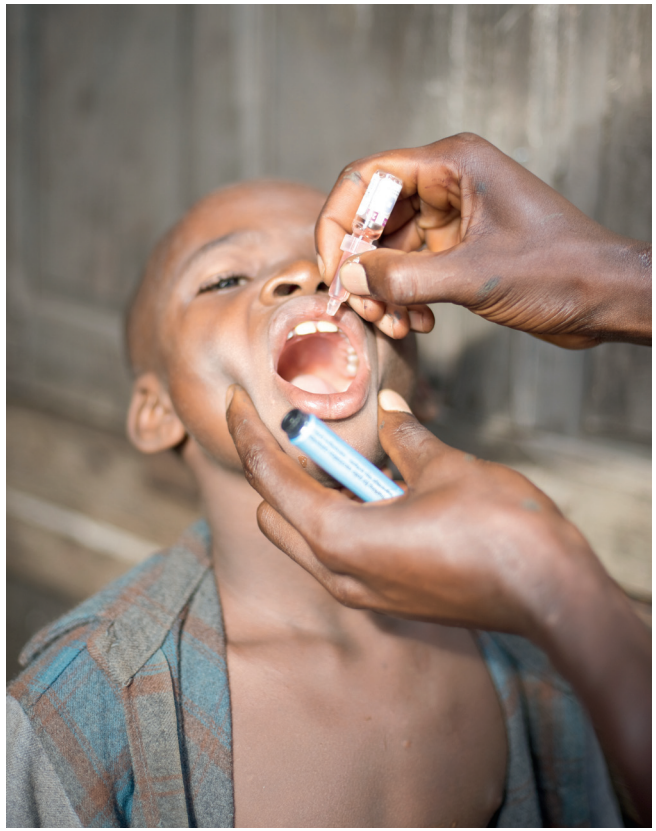
The immune system's capacity to have a memory of previous encounters with an infection is the basis for vaccination. Each vaccine contains one or more antigens from a pathogen; types of antigenic material include the killed whole pathogen or components of it, or a weakened

version of the whole pathogen. The antigens in a vaccine are recognised by lymphocytes and lead to development of memory cells. If, after successful immunisation with a vaccine, a person is exposed to the actual pathogen, the memory cells enable the immune system to mount a rapid, sustained immune response, thereby greatly reducing the complications associated with a natural infection.

Immunisation with each vaccine protects an individual from a serious infectious disease and from associated long-term complications, which may include chronic organ damage and diseases such as cancer. Decreasing the number of people in the community who are infected with a particular pathogen has a positive impact on individuals who are susceptible to the infection because they are less likely to come into contact with it. This effect is called herd immunity. As a result, several infectious diseases have been controlled or almost eliminated in Australia, which would never have occurred just due to improvements in healthcare, sanitation or nutrition.

Researchers are working to develop new vaccines for use against several infectious diseases. A critical component of this vaccine development is effectiveness and safety testing. Before release for use in the broad community, a vaccine must undergo a series of rigorous clinical trials, each of which involves a greater number of participants. New and existing vaccines also undergo stringent monitoring once they are in widespread use in the community to ensure their ongoing safety and effectiveness.

Vaccines are the most successful form of disease prevention available, and will continue to be an essential tool in controlling infections and their complications. In the future, vaccines may also be effective in treating and preventing some non-infectious diseases.



A boy in Conakry, Guinea, receives a polio vaccine.

This document aims to summarise and clarify the current understanding of the science of immunisation for non-specialist readers. The document is structured around six questions.

1 What is immunisation?

The purpose of immunisation is to prevent people from acquiring infectious diseases and to protect them against the associated short- and longer-term complications. Immunisation describes the process whereby people are protected against an infection; vaccine refers to the material used for immunisation, while vaccination refers to the act of giving a vaccine to a person. Vaccines work by stimulating the body's defence mechanisms (immune system) against an infection, helping the immune system detect and destroy the infection when it is encountered in the future without development of significant symptoms or complications.

2 What is in a vaccine?

Vaccines generally contain two main types of ingredients: antigens, which are designed to cause the immune system to produce a specific immune response; and adjuvants, which amplify the body's immune response.

3 Who benefits from vaccines?

In the short term, immunisation protects individuals from a specific infectious disease and its immediate complications. But immunisation may also have long-term protective effects – from cancer and other chronic conditions. An important feature of immunisation is that it also benefits the entire community. When a significant proportion of individuals in a community have become immune to a specific disease through immunisation, people who are still susceptible to the disease are less likely to come into contact with someone who is carrying the infectious agent.

4 Are vaccines safe?

Vaccines, like other medicines, can have side effects, but the vaccines in current use in Australia provide benefits that greatly outweigh their risks. The great majority of reactions after vaccination are minor. Some adverse events coincide with vaccination but are not caused by the vaccine. Serious side effects from vaccines are extremely rare.

5 How are vaccines shown to be safe?

Safety research and testing is an essential part of vaccine development and manufacture. Before vaccines are made available, clinical trials with increasing numbers of participants are required to study safety. After vaccines have been introduced into the community, safety monitoring continues.

6 What does the future hold for vaccination?

In recent decades, vaccine technology has greatly improved, resulting in the production of better and safer vaccines against a broad range of infectious diseases. The future of vaccination includes extending the use of existing vaccines, developing new technologies to deliver vaccines and generating new vaccines.

Definitions

Immunisation describes the process whereby people are protected against illness caused by infection with micro-organisms (formally called pathogens).
The term **vaccine** refers to the material used for immunisation, while **vaccination** refers to the act of giving a vaccine to a person.
Immunity describes the state of protection that occurs when a person has been vaccinated or has had an infection and recovered.
Vaccination, like infection, confers immunity by interaction with the immune system.
The term **micro-organism** refers to infectious agents that can only been seen under the microscope and here covers bacteria, viruses, fungi and protozoa.
Antigens are the components/fragments from pathogens or their toxins.

1 What is immunisation?

Immunisation protects against infectious disease

The purpose of immunisation is to prevent people from acquiring infections and to protect them against the short- and longer-term complications of those infections, which can include chronic illnesses, such as cancer, and death [1-6].

Vaccines work by stimulating the body's defence mechanisms against infection. These defence mechanisms are collectively referred to as the immune system. Vaccines mimic and sometimes improve on the protective response normally mounted by the immune system after an actual infection. The great advantage of immunisation over natural infections is that immunisation has a much lower risk of adverse outcomes [1, 4, 5, 7-13] (see Box 2 and Questions 3 and 4).

Immunisation harnesses the body's own defence mechanisms

To understand how immunisation protects against the diseases produced by pathogens such as viruses and bacteria, we first need to understand how the immune system works [14, 15].

The immune system consists of trillions of specialised blood cells, known as white blood cells, and their products, such as antibodies. These cells are located throughout the body, not only in the bloodstream, but also in lymph glands, the spleen, the skin, lungs and intestine.

The skin and the lining of the lungs and intestine are the first line of defence against infection. These tissues and the white blood cells located at these sites form the innate immune system (see Figure 1.1) [15, 16]. The white blood cells of the innate immune system (or guardian white blood cells) detect the presence of infection using sensors on their surfaces that recognise parts of pathogens or the toxins released by the pathogen. These fragments from pathogens or toxins are collectively known as antigens (see Question 2).

When guardian white blood cells detect the presence of pathogens, a second set of white blood cells (called lymphocytes [17]) is activated (see Figure 1.1). Lymphocytes are categorised into two types: B-cells and T-cells [18-20].

T-cells respond to infections by releasing chemicals called cytokines, which trigger protective inflammation. Furthermore, T-cells can help combat pathogens by killing cells that harbour a pathogen hidden inside them [21]. B-cells make antibodies, which are complex proteins that attach in a 'lock-and-key' fashion either to pathogens or to the toxins released by them. When antibodies attach to a pathogen, they flag it for destruction, and when they attach to a toxin, they neutralise its ability to cause damage [14, 15].

In most cases, the outcome of these immune responses is termination of the infection followed by repair of any associated damage to the body's tissues. However, some infections outstrip the immune system's capacity to respond, leading to disease and sometimes death. By giving a vaccine before exposure to the infection, such serious outcomes can be avoided through generation of protective immunity in advance.

BOX 1

How long has immunisation been around?

The knowledge that underpins immunisation has been evolving for more than 2,000 years. The ancient Greeks knew that people who had recovered from the bubonic plague were resistant to getting it again. Based on this observation, the authorities in Athens used survivors from previous epidemics to nurse sufferers when the same diseases re-emerged [27].

During the Middle Ages, the practice of inoculating people with a small amount of material from smallpox pustules (known as 'variolation') spread from India and China to Turkey and then into Europe and even as far as America. However, the procedure itself retained a significant risk of death and it was never widely adapted into clinical practice [28, 29].

In the 18th century, Edward Jenner, a British general practitioner, introduced the practice of what we now know as vaccination [30]. This was based on his observation that milkmaids who developed a mild skin infection caused by the vaccinia virus (commonly called cowpox) were resistant to smallpox, a highly dangerous disease. Because of its success in protecting against smallpox, vaccination with cowpox became widespread, finally leading to global elimination of smallpox in the late 1970s [31].

So far, this is the only time that a common fatal disease has been completely eradicated. Renowned Australian immunologist Professor Frank Fenner, chairman of the World Health Organisation's smallpox Steering Committee, was a key contributor to this remarkable achievement (see Figure 1.3).

Figure 1.3 Professor Frank Fenner announces the eradication of smallpox to the World Health Organisation Assembly.

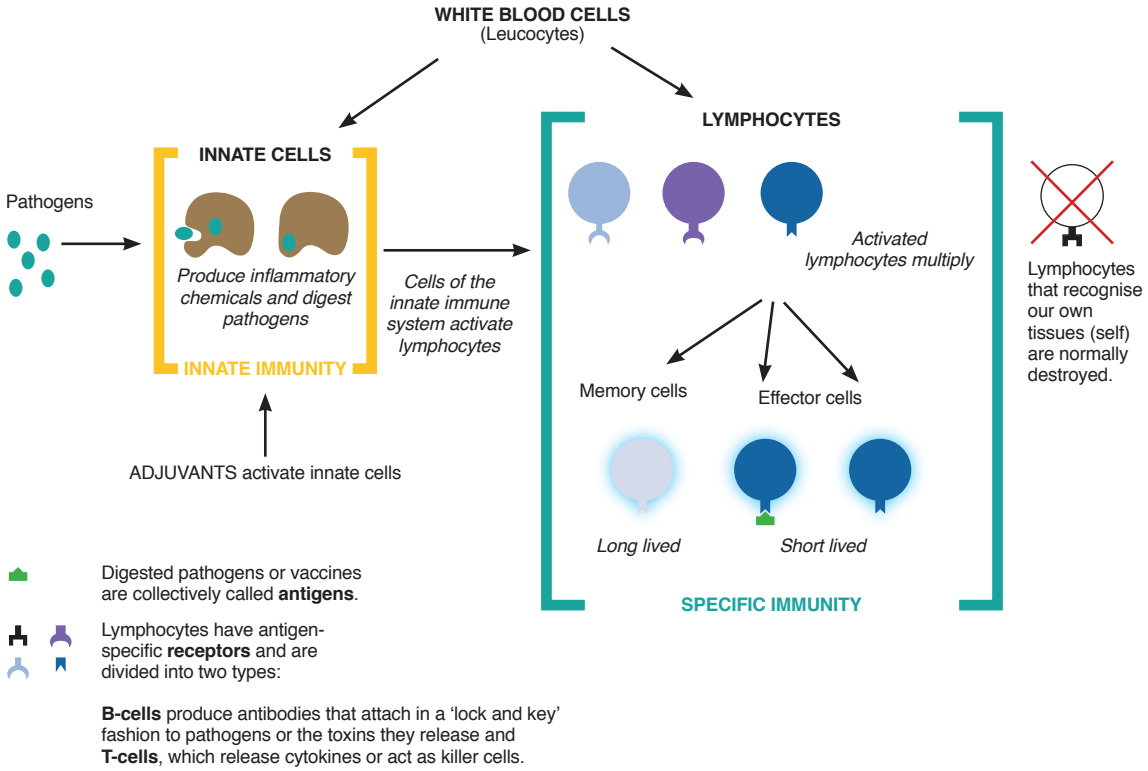


Figure 1.1 The human immune system
All blood cells originally come from the bone marrow. There are three main cell types in our blood: red blood cells, which carry oxygen to our tissues; platelets, which help the blood clot; and white blood cells (leucocytes), which are the main component of the human immune system. There are two main types of leucocytes: guardian cells responsible for innate immunity and lymphocytes responsible for specific immunity.

The guardian cells of the innate immune system form the first line of defence against infection and can digest pathogens or vaccine particles and use these to activate lymphocytes. In addition they produce chemicals capable of causing inflammation and amplifying specific immunity. These cells are the target of adjuvants in vaccines (Questions 2 and 3).

Lymphocytes have receptors for one antigen; that is, they are antigen specific. After infection or vaccination, specific lymphocytes recognise their target antigens, multiply and turn into short-lived effector cells or long-lived memory cells. Lymphocytes (T- and B-cells) have receptors on their surface for one particular antigen; that is, they are antigen specific.

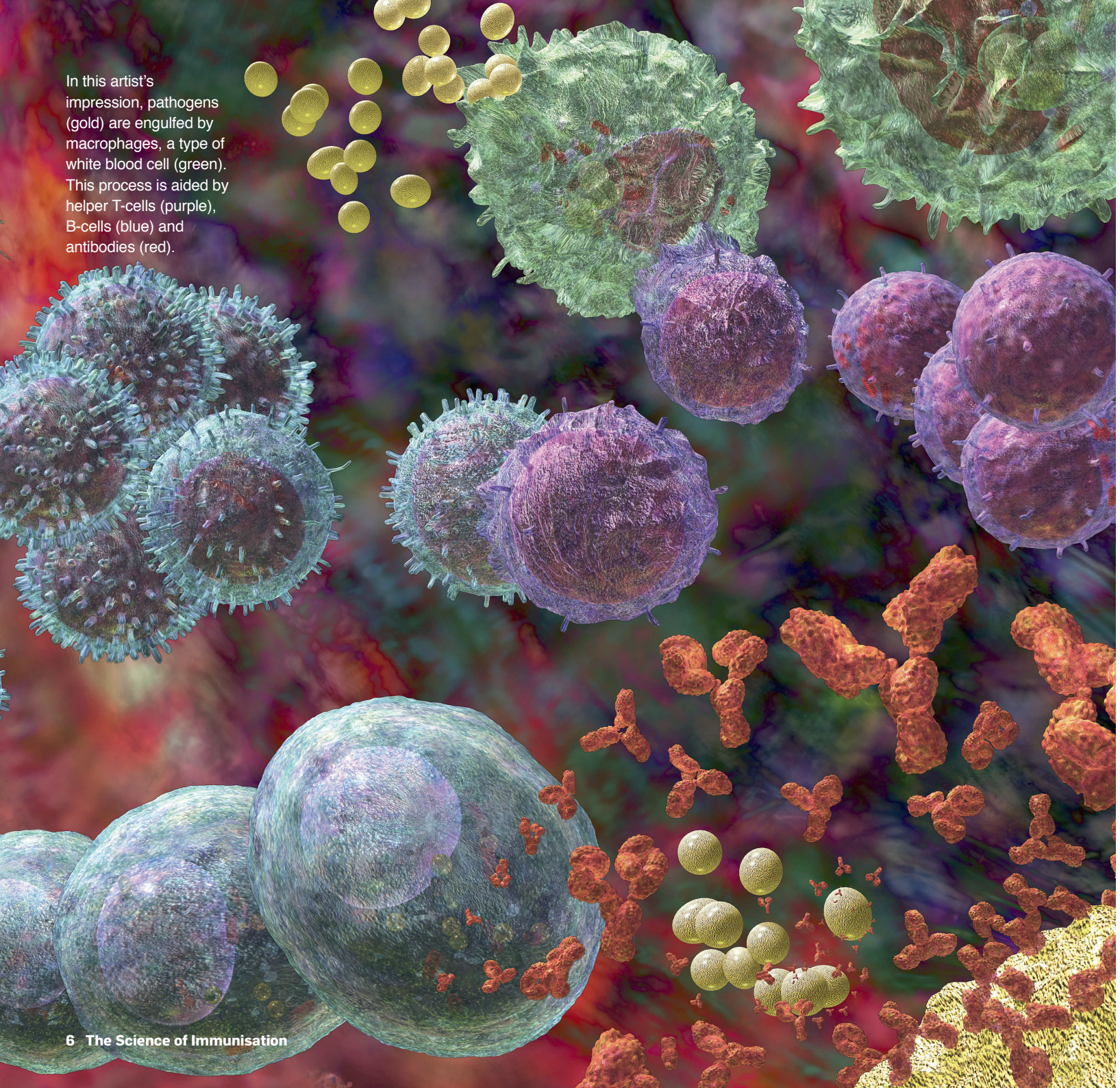
BOX 2

Is it better to get the disease than be vaccinated?

No, it is not better to get the disease than be vaccinated. The benefits of being vaccinated far outweigh those of infection with the pathogen. The rates of complications, both short- and longer-term, are much higher and generally more severe after natural infections than the rates of side effects associated with the corresponding vaccines [1, 4, 5, 7-13]. For example, one in 15 patients with diphtheria die from the disease, whereas serious side effects from the diphtheria vaccine are very rare [4]. Similarly, approximately one in four patients chronically infected with hepatitis B will die from cirrhosis of the liver (a severe, chronic inflammatory condition) or from liver cancer; this risk is reduced to almost zero after hepatitis B immunisation [32].

Vaccines have the added advantage of offering more effective protection against subsequent exposure to certain pathogens. Examples of diseases that do not always generate protective immunity include tetanus and whooping cough. In the case of tetanus, the tiny amount of toxin needed to produce life-threatening disease is too small to generate sufficient levels of protective antibodies to neutralise the toxin. To achieve protective antibody levels, it is necessary to give a much larger dose of toxin, which requires the use of inactivated toxoid (see Question 2).

Antibodies (blue) latch on to viruses (purple). Each antibody recognises a specific antigen, or component of a pathogen, such as a bacterium or virus.



In this artist's impression, pathogens (gold) are engulfed by macrophages, a type of white blood cell (green). This process is aided by helper T-cells (purple), B-cells (blue) and antibodies (red).

Immunisation is disease-specific

A healthy immune system has the capacity to generate hundreds of millions of T- and B-cells, each of which targets one particular antigen. Consequently, healthy people have the capacity to mount a protective response to essentially every infection they could possibly encounter during their lifetimes [22]. However, pathogens have evolved to overcome this defence and can sometimes overwhelm the immune response. Vaccines give the immune system a head start, providing valuable early protection against aggressive pathogens.

The specificity of these immune responses is the reason we need to have a separate vaccine for each disease. The capacity of the immune system to respond independently to each micro-organism in the environment also explains why the system cannot be 'overloaded' or damaged by giving the full range of currently available vaccines or by having multiple antigens in one vaccine preparation.

Vaccines harness the immune system's capacity for memory

When a pathogen is recognised by the immune system, individual lymphocytes not only make antibodies and cytokines against the infection, but also multiply quickly. As a result, the number of lymphocytes (T- and B-cells) specific for that infection increases greatly, enabling the body to fight the infection more efficiently. Most of the cells involved in immune responses live for only a few days as effector cells, but a small number of lymphocytes survive for months or years after the infection has been cleared and retain a 'memory' of the invading pathogen [15, 23, 24]. In the case of measles, for example, that memory has been shown to last for more than 60 years [25].

BOX 3

Can immunisation make the immune system react against the body's own tissues?

The immune system is designed to protect us against infection without causing damage to our own bodies. The capacity of the immune system to selectively target foreign pathogens for destruction is due to the fact that lymphocytes capable of recognising and attacking our own tissues are normally eliminated or prevented from doing any damage (see Figure 1.1). Occasionally, however, the immune system does target the cells and tissues of our body, resulting in what are termed autoimmune diseases, such as multiple sclerosis [33] and type 1 diabetes [34]. There is no credible scientific evidence to suggest that any vaccine in current use can cause these particular autoimmune diseases [35] (see Box 9, Question 4, for examples of other autoimmune diseases). In addition, the vast majority of people (mainly adults) who develop autoimmune diseases have no recent history of being vaccinated [13, 36-38].

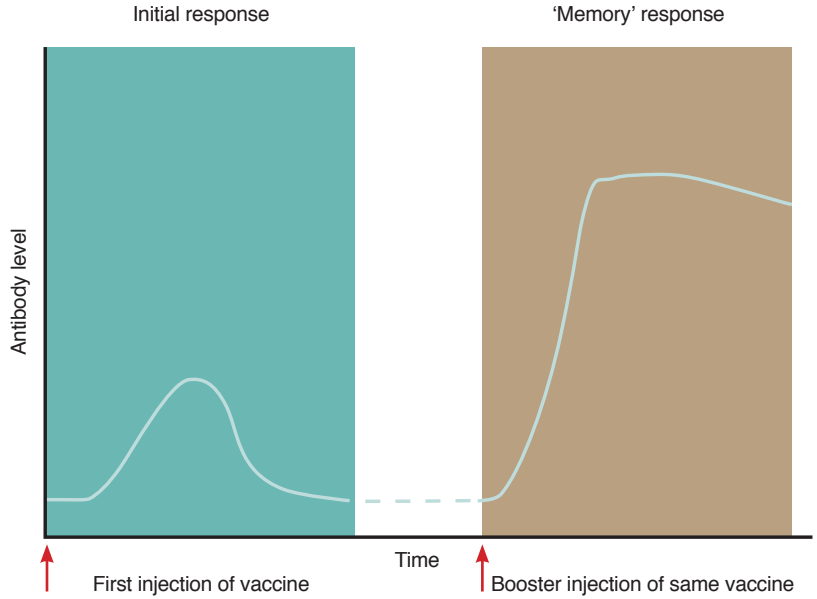


Figure 1.2 Effect of giving booster doses of vaccines
After first immunisation of a non-immune person, a small and brief response occurs. When second (booster) doses are given, memory lymphocytes created during the initial response are switched on to generate a much more rapid and longer lasting protective response. This figure shows the levels of antibodies from B-cells after first and booster vaccinations. A similar, more effective memory response is also a property of T-cells.

The immune system's memory of infections it has been exposed to previously is one of its most valuable assets. This memory means the immune system is ready to mount a much quicker, larger and more sustained response if it encounters the same pathogen again (see Figure 1.2). That response can control subsequent infection more efficiently, without leading to the unwanted and serious complications that can be associated with infection in non-immune people [15, 23, 24] (see Box 2).

A successful vaccine, like the corresponding infection, can harness the immune system's memory capability by generating a population of long-lived lymphocytes (T- and B-cells) that are specific for the targeted pathogen [15, 23, 24]. Again, the result is long-term protection against subsequent exposures to that pathogen and avoidance of the complications associated with a natural infection.

Infant vaccines work with the newborn immune system

The body's immune system begins developing before birth [26]. In the period during and soon after birth, when the functions of the immune system are still maturing, newborns are protected against many, but not all, serious infections by antibodies from their mothers (maternal antibodies). This protection usually lasts for about four months.

These maternal antibodies cross the placenta into the baby's circulation before birth and are present in the mother's breast milk. If the mother has been vaccinated recently or has recovered from infection during pregnancy, the amount of antibody transmitted to the baby can be sufficient to ensure complete protection. On the other hand, if the mother's infection (particularly with the pathogen that causes whooping cough, also known as pertussis) or immunisation occurred a long time ago, the antibody levels may be lower and protection suboptimal.

The current immunisation programs are designed to balance the capacity of the baby's immune system to respond to the vaccine, against the risk of infection.

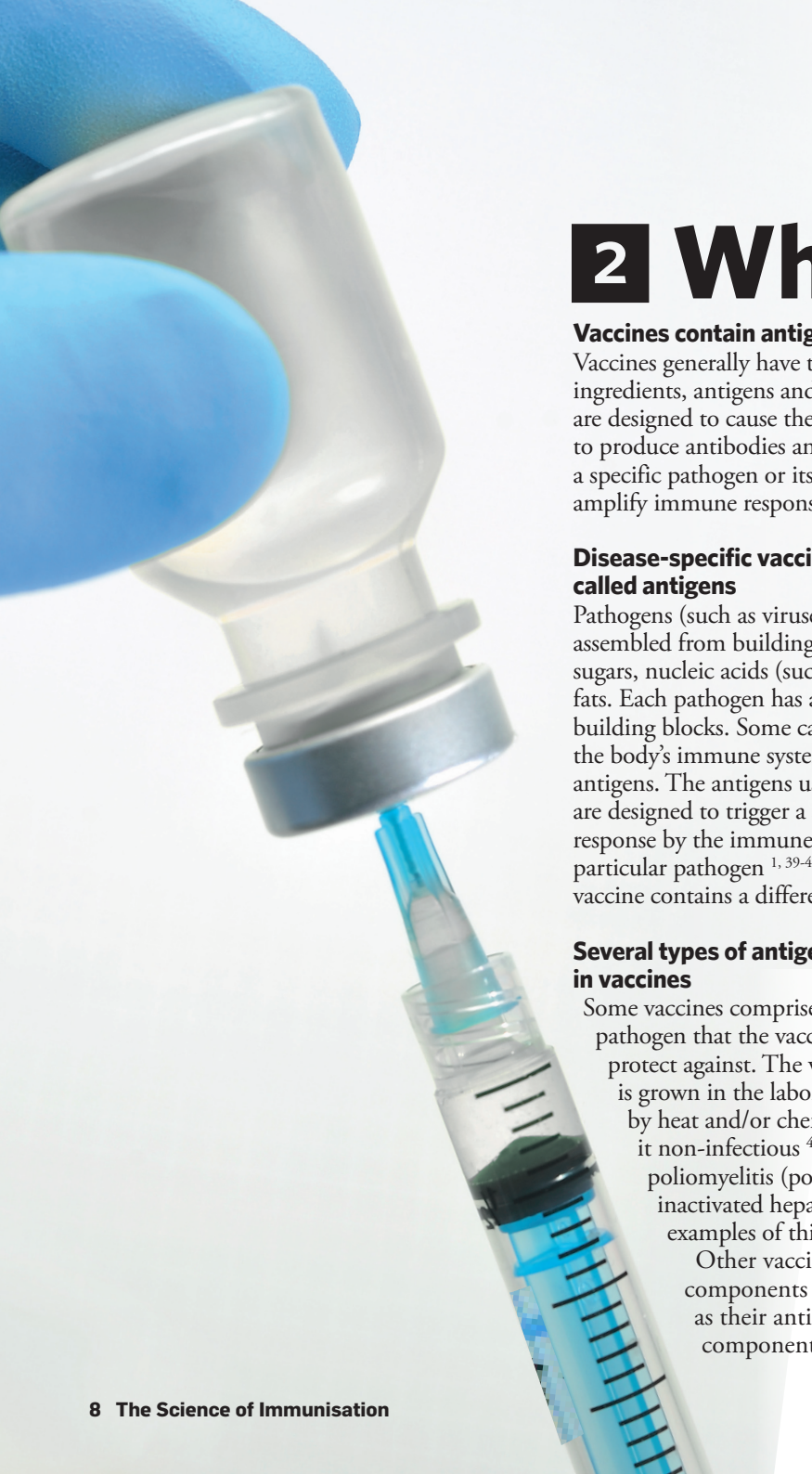
In the case of hepatitis B, for example, exposure to the virus at birth can result in the infant becoming a chronic carrier for life; hence the policy of starting vaccination within two weeks of birth.

The situation is different for other infections, which have a lower risk of infection at birth. Thus, administration of the *Haemophilus influenzae* type b (Hib) and pneumococcal vaccines is delayed until 6–8 weeks of age, when the infant's immune system can respond better. Moreover, the measles-containing MMR (measles, mumps and rubella) vaccine is not given until 12 months of age, when maternal antibodies against measles, which can interfere with vaccine responses, have essentially disappeared.

Passive immunisation provides immediate protection

Most vaccines work by actively switching on the recipient's own immune system to make the antibodies and memory cells needed to provide long-term protection against infection. Such 'active immunity' is the primary goal of all immunisation programs.

However, this kind of active immune response takes 7–21 days to develop fully. Consequently, in the case of overwhelming infections, there is sometimes a role for 'passive' immunisation, which involves giving pre-formed antibodies obtained from healthy blood donors, as these can act much more quickly [15].



2 What is in a vaccine?

Vaccines contain antigens and adjuvants

Vaccines generally have two major types of ingredients, antigens and adjuvants. Antigens are designed to cause the immune system to produce antibodies and/or T-cells against a specific pathogen or its toxin. Adjuvants amplify immune responses more generally.

Disease-specific vaccine ingredients are called antigens

Pathogens (such as viruses and bacteria) are assembled from building blocks – proteins, sugars, nucleic acids (such as DNA) and fats. Each pathogen has a unique set of these building blocks. Some can be recognised by the body's immune system and are termed antigens. The antigens used in a vaccine are designed to trigger a specific protective response by the immune system to a particular pathogen [1, 39-41]. Therefore, each vaccine contains a different set of antigens.

Several types of antigen are used in vaccines

Some vaccines comprise the killed whole pathogen that the vaccine is designed to protect against. The virus or bacterium is grown in the laboratory and killed by heat and/or chemicals to render it non-infectious [42]. The injectable poliomyelitis (polio) vaccine and inactivated hepatitis A vaccine are examples of this type of vaccine.

Other vaccines contain only components of the pathogen as their antigens. These components can be prepared by purifying them from the whole bacterium or virus, or by genetically engineering them [43-45]. Engineered vaccines include the hepatitis B virus vaccine and the human papillomavirus vaccine, which protects against cervical cancer.

In some vaccines, sugar components of the pathogen are joined with proteins to create an antigen that can generate a stronger response – this allows even 6-week-old babies to make significant amounts of antibody, which they otherwise could not do until they are older [46]. These vaccines are called conjugate vaccines, and include those against meningococcal and pneumococcal disease.

Another group of vaccines is based on the toxin produced by the pathogen that causes the disease symptoms. The toxin is chemically treated to make it into a harmless toxoid. The antibodies produced against this toxoid are still able to neutralise the toxin, and to prevent disease symptoms from developing [47]. Examples of this type include the tetanus and diphtheria vaccines.

Some vaccines contain live organisms

Some vaccines contain an infectious micro-organism. These are called live vaccines. The micro-organism may be derived from the pathogen (bacterium or virus) that the vaccine aims to protect against. This is usually achieved by growth of the pathogen in the laboratory under conditions designed to weaken or 'attenuate' it. This attenuation process permanently alters the pathogen so that it is still infectious, but is unable to cause the disease [48]. Examples include the injectable MMR vaccine, the oral polio vaccine, and the chickenpox vaccine.

Alternatively, a live vaccine may consist of a naturally occurring organism that is closely related to the pathogen, but does not cause disease in healthy humans with intact immune systems. An example is the BCG vaccine against tuberculosis and leprosy.

Vaccines containing live pathogens are not recommended for people whose immune systems are impaired due to use of immunosuppressive drugs, serious illness or genetic abnormalities of the immune system

BOX 4

Do vaccines contain preservatives?

Preservatives, such as thiomersal (also known as thimerosal) and boric acid, are chemicals designed to prevent the growth of bacteria in vaccine preparations.

In practice, preservatives are no longer needed in vaccines given in Australia, as they are now produced in single-use sealed vials. The only exception is when multi-dose vials are used during an influenza pandemic as an emergency measure or for mass vaccinations.

In the past, preservatives such as thiomersal were added to vaccines. However, the quantity was very small and the total amount received by a fully vaccinated person was minuscule [53]. These small amounts of preservatives have never been shown to be harmful [54].

BOX 5

I've heard vaccines contain DNA. Should I be concerned?

Because most vaccine antigens are prepared from whole organisms, a vaccine may contain some of that organism's genetic material in the form of DNA, or a similar type of molecule known as RNA. The amount of genetic material in a vaccine is minuscule, much less than the amount we eat in our food every day [55]. Vaccines based on living pathogens contain that organism's genetic information, which is necessary for the vaccine to work. However, the DNA (or RNA) in the pathogen does not persist or lead to long-term detrimental effects in the vaccinated person [56].

because of the risk of causing disease. Similarly, live vaccines are not recommended during pregnancy as a precautionary measure, in case the pathogens they contain cross the placenta. This is because a baby's immune system is not completely developed until after birth (see also Box 11, Question 4). Vaccines without live micro-organisms ('killed' vaccines), in contrast, are not harmful in pregnancy.

Adjuvants amplify the immune system's response

Adjuvants are substances that promote a more vigorous immune response to vaccine antigens. They can also help target the body's response. In doing so, they may cause mild local reactions (soreness, redness and swelling) at the injection site. These reactions are a healthy indicator of the strength of the underlying immune response.

Most killed vaccines incorporate adjuvants, to make the body's defences think a significant infection is present. They stimulate stronger, longer-lasting immune responses to the vaccine antigens, leading to better protection against subsequent infection. Adjuvants are not needed in vaccines based on live organisms, as these naturally produce inflammation and amplify protective immunity.

In most human vaccines that contain adjuvants, the adjuvant is an aluminium salt (known as alum), which has a track record of safety dating back to the 1950s [49]. Some newer vaccines incorporate more active adjuvants, derived from naturally occurring oil in water emulsions, fats from bacterial cell walls, or sugars. These can produce more vigorous and better targeted immune responses against the infectious agent [50].

Vaccine quality is carefully monitored

In addition to adjuvants and antigens, vaccines can contain minute quantities of materials from the manufacturing process. These can include trace amounts of detergents, nutrients from the laboratory cultures (see Box 4 and Box 6), chemicals used to kill the pathogens or small amounts of DNA (see Box 5) and parts of dead organisms.

Vaccine developers are required by regulatory authorities to test for the presence of these extra materials during the manufacturing process to ensure they do not exceed levels known to be safe [1, 51] (see Question 4).

Occasionally, individuals can be allergic to an ingredient of a vaccine, although such reactions are rare. Fewer than one in 100,000 vaccine doses delivered cause a significant allergic reaction [52] (see Box 6).

BOX 6

Why are some vaccines given with caution to people with egg allergy?

Egg allergy is a recognised clinical problem, particularly in children.

Some vaccines, such as influenza or MMR vaccines, contain antigens from viruses grown in eggs or on chick cells, and therefore may contain some egg proteins. However, newer MMR vaccines contain so little egg protein that it is now conclusively considered to be safe to give them even to someone who is already known to be very sensitive to egg protein [57]. The seasonal influenza vaccines available contain minimal amounts of egg protein and can be used in most egg sensitive children [58].

The viruses in two other less frequently used vaccines (for Q fever and yellow fever) are also grown in eggs, and specialist advice should be sought if either of these vaccines is needed for a person with severe egg allergy.

3 Who benefits from vaccines?

Individuals benefit, in the short and long term

An effective vaccine protects an individual against a specific infectious disease and its various complications. In the short term, the efficacy of a vaccine is measured by its capacity to reduce the overall frequency of new infections, and to reduce major complications, such as serious tissue damage and death [1].

All vaccines currently in use in Australia confer high levels of protection that are sufficient to prevent disease in the great majority of vaccinated individuals, and in the wider community (see section on the community at large, right). In other countries where the use of vaccination is widespread, there has been a dramatic reduction in the number of people who become ill and die from formerly common and severe infections [4] (see Box 7 and Figure 3.1). For example, the pertussis vaccine prevents disease in 85% of recipients [6], while the measles vaccine prevents disease in 95% of recipients [1, 69]. The remaining individuals may not be fully protected and remain at least partially susceptible to infection. This may be due to genetic factors, or to the presence of other medical conditions that impair the capacity of the vaccine recipient to mount a protective immune response.

Booster doses of some vaccines are required to maintain protection. Examples include the pertussis, tetanus, and polio vaccines, as well as the more recently introduced conjugate pneumococcal and meningococcal vaccines (see Question 2). In contrast, a single course of others, such as the hepatitis B vaccine, appears to be sufficient to provide lifelong protection.

Vaccines can protect against long-term complications of infections

The efficacy of vaccines is most often thought of in terms of their capacity to protect against the immediate consequences of serious diseases such as meningitis, pneumonia, hepatitis, chickenpox and measles. By preventing infection, vaccines can also prevent long-term complications associated with chronic infections, where the pathogen persists in the body after the initial infection has passed.

Certain viruses can cause dormant infections. Such persistent infections can eventually lead to chronic damage of infected organs (eg encephalitis induced by measles, called SSPE [60], or cirrhosis of the liver, caused by hepatitis B [61] or hepatitis C virus infection [62]).

Persistent viral infections can also lead to late complications, including cancer and shingles. Viruses known to cause cancer and for which vaccines are available include hepatitis B and the human papillomavirus (HPV). Hepatitis B can lead to liver cancer and liver damage, whereas HPV can cause cervical and anal cancers [63-65].

On the other hand, currently available vaccines are generally not capable of eliminating a virus infection once it has been acquired. This is why hepatitis B vaccine is administered from birth, and why HPV vaccine is delivered in late childhood or very early adolescence, before the individual is at risk of being exposed to the virus through sexual encounters [2, 66].

An exception to the rule of vaccines being unable to control established viral infections is seen with the chickenpox vaccine. This vaccine protects against the development of a long-term complication of the infection, shingles (also known as herpes zoster). Shingles is a debilitating condition characterised by the appearance of painful blisters on parts of the skin above nerves where the chickenpox virus has lain dormant since infection in childhood. Adults who had chickenpox in childhood can be given a high-dose chickenpox vaccine to boost immunity, resulting in a substantial reduction in their subsequent risk of developing shingles [67].

The community at large benefits

An important feature of immunisation is that it brings benefits not only for the individual who receives the vaccine, but also for the entire population through a phenomenon called herd immunity [1].

Herd immunity occurs when a significant proportion of individuals within a population are protected against a disease through immunisation. This situation offers indirect protection for people who are still susceptible to the disease, by making it less likely that they will come into contact with someone who is carrying the pathogen.

In addition to protecting unvaccinated individuals, herd immunity benefits the small proportion of people who fail to respond adequately to vaccination [68].

In the case of a highly infectious disease such as measles, more than 95% of the population must be vaccinated to achieve sufficient herd immunity to prevent transmission if the disease recurs [1, 69].

For other childhood infections, the proportion of the population that need to be vaccinated is lower, because the diseases are less infectious – for instance, until very recently no cases of diphtheria had occurred in Australia since the 1970s, despite immunisation coverage of much less than 95% of the population [68].

The effectiveness of herd immunity is well illustrated by reference to the introduction of a new form of the pneumococcal vaccine, which protects against disease caused by the bacterium *Streptococcus pneumoniae*. In addition to protecting susceptible infants and young children from the disease, this vaccine also reduces circulation in the community of the bacteria present in the vaccine. Consequently, older people are also protected, even though they have not been vaccinated against this organism [70] (see Figure 3.2).

Vaccines can control, eliminate and eradicate diseases

When a large proportion of a community is immunised, it can lead to a situation where there are very low levels of the disease in that population. This is referred to as control of the disease.

Even more effective and prolonged vaccination programs can result in interruption of transmission in the population for long enough to ensure that there is no residual disease – elimination of disease. However, even when high levels of community coverage with a vaccine are achieved, infection may be reintroduced, for example by unvaccinated travellers or, for some pathogens, an animal that is a carrier.

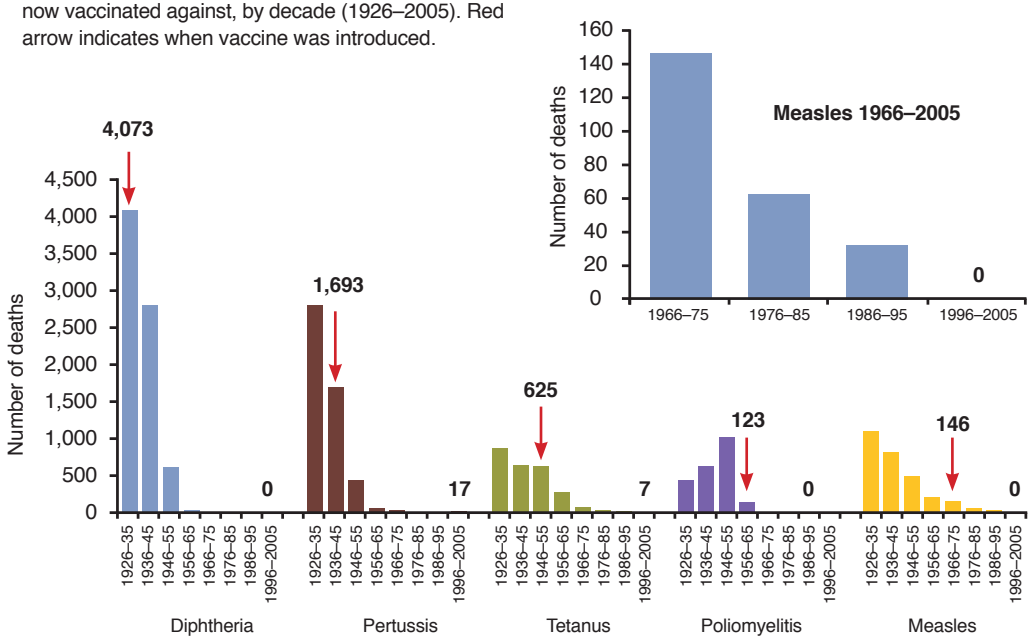
In Australia, isolated outbreaks of infectious disease such as measles have been attributed to transmission from unvaccinated carriers.

Once a high degree of control is achieved worldwide, it is theoretically possible to eradicate an organism and the associated risk of infection, provided there is no other animal that can carry the infection and transmit it back to humans. This was achieved with smallpox in the 1970s and there is hope that such a goal may also be achievable for polio and measles, for which, as for smallpox, humans are the only host. Only 650 polio cases were reported worldwide in 2011, compared with 350,000 cases in 1988 [71]. The only countries in which transmission of polio has never been interrupted are Nigeria, Pakistan and Afghanistan [71].

Vaccination brings economic benefits

Cost-effectiveness of community immunisation programs is determined by measuring the benefits – in terms of cost and quality of life – that result from preventing illness, disability and death, and comparing them with the costs of vaccine production and delivery to the population. A striking example is the benefits of polio vaccination. In the first six years after introduction of the vaccine, it was calculated that more than 150,000 cases of paralytic polio and 12,500 deaths were prevented worldwide. This represented a saving of more than US$30 billion annually in 1999 dollars [72].

Figure 3.1 Number of deaths in Australia from diseases now vaccinated against, by decade (1926–2005). Red arrow indicates when vaccine was introduced.



BOX 7

Are reductions in infections due to better health and hygiene rather than vaccination?

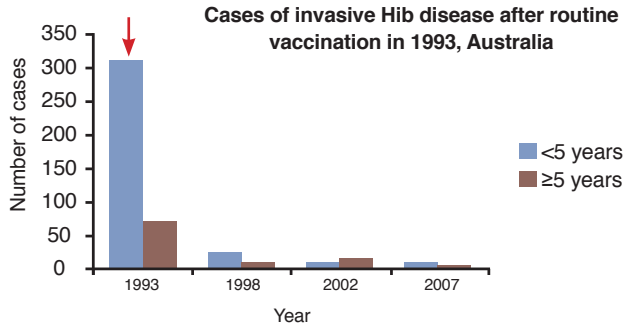
Yes and no. Improvements in healthcare, such as widespread availability of antibiotics and better overall medical support systems, have reduced deaths from all diseases. However, the additional impact of vaccines themselves on infectious diseases is dramatically illustrated by the disappearance, or near disappearance, in Australia of deaths from diphtheria, pertussis, tetanus, polio and measles (see Figure 3.1) and more recently from cases of *Haemophilus influenzae* type B (Hib) and meningococcal type C infection (see Figure 3.2).

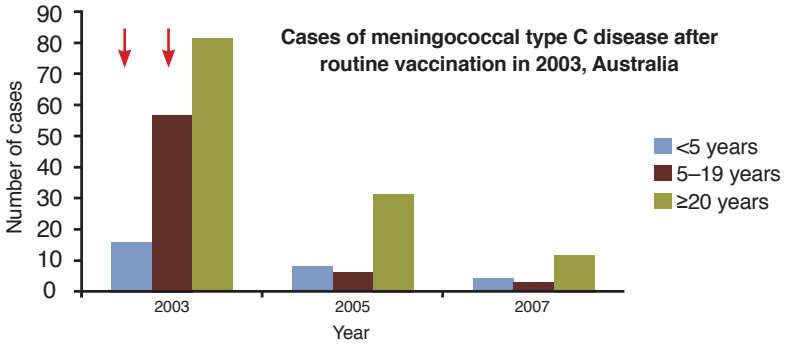
For diphtheria, the death rate fell after the toxoid vaccine became available. In the case of diseases such as pertussis, tetanus and measles, although there was some evidence of a decline in death rates before the relevant vaccines were available, the decreases in disease and death rates were much greater after introduction of the respective vaccines.

In contrast, improvement in hygiene, in the absence of vaccination, had a significant adverse impact on the incidence of polio. By lessening the chance of exposure of young people to the polio virus, the initial effect of improved hygiene was a steady increase in deaths. This is because paralysis and death were more common among older people who had not been exposed to polio during childhood. After the vaccine became available in Australia in the mid 1950s, the disease almost disappeared over the next decade.

The introduction in 1993 of the Hib vaccine and in 2004 of the meningococcal type C vaccine, led to a very rapid and obvious decline in the number of severe and sometimes fatal infections. Such a dramatic effect in recent times could not possibly be attributed to any change in living conditions or medical treatment.

Figure 3.2 Cases of *Haemophilus influenzae* (Hib) and meningococcal type C disease since the introduction of routine vaccination. Red arrows indicate when vaccine was introduced and for what age group(s). Note the reduction in both the vaccinated children and unvaccinated children.





4 Are vaccines safe?

Benefits of vaccines outweigh the risks

Vaccines, like other medicines, can have side effects. However, all vaccines in use in Australia provide benefits that greatly outweigh their risks [1, 4, 5, 7-10, 12, 13].

Most reactions from vaccination are minor

The great majority of side effects that follow vaccination are minor and short-lived. The most common side effects for all vaccine types are 'local' reactions at the injection site, such as redness or swelling, which occur within hours and are clearly caused by the vaccine. More general or 'systemic' reactions, such as fever or tiredness, can also occur after vaccination, but careful studies have shown that they are much less common than local reactions [73].

These reactions are outward signs that the vaccine is interacting with the immune system to generate a protective response. The nature of these reactions varies, depending on the type of vaccine given.

For example, if a person develops a fever due to an inactivated vaccine, they almost always do so within 24 to 48 hours – the time when the immune system is making an immediate response to the components of the vaccine [73]. In contrast, the onset of fever caused by a live attenuated vaccine, such as the MMR vaccine, is delayed for seven to 12 days because this is the time needed for the attenuated virus in the vaccine to multiply sufficiently to induce a protective response from the immune system [74, 75].

Some adverse events coincide with, but are not caused by, vaccination

Symptoms such as fever, rashes, irritability and nasal snuffles are common, especially among children. Consequently, it can be difficult to determine how many of these reactions are caused by a vaccine when the 'background rate' (how often it occurs

Does the MMR vaccine cause autism?

BOX 8

Medical conditions with unknown causes have been incorrectly linked to particular vaccines. The most prominent example is the claimed link between the MMR vaccine and autism – a disease whose first clinical signs commonly occur in the second year of life, at a time when MMR vaccine is usually given.

The original suggestion that the MMR vaccine might be linked to autism was made in 1998, when a research group proposed that the attenuated (live) measles virus in the vaccine infected the intestine. The leader of the research group claimed this led to inflammation that resulted in lower absorption of nutrients needed for normal brain development, the outcome being developmental disorders such as autism.

Many comprehensive studies subsequently ruled out this suggested link by showing conclusively that rates of autism are the same among children who have and have not been vaccinated [7]. Ultimately, the original report was shown to be fraudulent, and was retracted by the medical journal that published it.

Similarly, any link between thiomersal, which was previously used in minute quantities in vaccines, and autism has also been excluded (see Question 2) [77].

Do vaccines cause autoimmune diseases?

BOX 9

Over the past 30 years, the number of people who develop autoimmune diseases has been increasing, particularly in societies where rates of infectious disease have declined [36]. This has raised the question of whether vaccine use is contributing to the reported rise in certain autoimmune disorders. With the exception of the two rare diseases mentioned below, the answer is no (see also Box 3) [13]. This conclusion is based on the stringent monitoring procedures put in place for detecting side effects of vaccination (see Question 5).

The first exception is the small increase in risk of developing the rare condition known as idiopathic thrombocytopenic purpura (ITP), which has been reported after the MMR vaccine. In this condition there is a short-term reduction in the number of small blood cells called platelets, which can lead to an increased risk of bleeding. However, the risk of developing this disorder associated with measles infection is more than 10 times greater than associated with the vaccine [9] (see Figure 4.2). The other exception is Guillain–Barré syndrome (see Question 5) – but again, the risk of developing the disease after influenza vaccination is much lower than after the actual infection [12].

Do vaccines cause allergic diseases?

BOX 10

Like autoimmune diseases (see Box 9), allergic diseases such as asthma have become more common in the developed world over the past 30 years. However, there is no significant evidence that vaccines cause allergic diseases [78].

The question asked is whether vaccines can precipitate attacks of serious allergic reactions in susceptible children or adults. Overall, the rate of severe allergic reactions following vaccination is extremely low, between 0.02 and 4.52 per 100,000 doses [79] (see Figure 4.2). Nevertheless, precautions should always be taken by people with a past history of reaction to a specific vaccine or a strong family history of allergic disease. More information about vaccination of egg-allergic children was provided in Box 6 (Question 2).

Injectable vaccines used in Australia do not contain detectable amounts of antibiotics such as penicillin or sulphonamides to which some people may be allergic. The hepatitis B vaccine is grown in yeast. Although there have been some isolated reports of possible severe allergic reactions to this vaccine [59], supporting evidence is incomplete and the benefits of receiving the vaccine far outweigh the multiple risks associated with the infection.

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anyway) in the same age group is unknown.

In some cases, these kinds of reactions may be caused by the vaccine. But in other situations, the symptoms may be unrelated, occurring by chance at the same time as the vaccination. For this reason, scientists refer to these kinds of symptoms as adverse events following immunisation to indicate that events that follow vaccination may not be caused by the vaccine.

One unique study from Finland addressed this issue [74]. Researchers analysed common symptoms in 581 pairs of twins after one twin received the MMR vaccine and the other was given a dummy vaccine (a placebo). Between one and six days after the injection, the number of adverse events in the twin who received the MMR vaccine was almost identical to those in the twin who received placebo [74] (see Figure 4.1). Between seven and 12 days after the injection, the vaccinated group had a measurable increase in symptoms that are known to be associated with administration of the attenuated measles vaccine, such as fever, irritability and rash. On the other hand, no difference between the two groups could be detected over that period in cough- and cold-like symptoms – which occur commonly with or without vaccination. Moreover, even some of the symptoms known to occur after MMR vaccine were also seen in the group who received placebo, but at a lower rate.

In summary, this valuable study showed that many common symptoms that occur after a vaccine is given are not caused by the vaccine, but occur by chance at that time.

Serious side effects from vaccines are extremely rare

Potentially serious side effects, such as transient febrile seizures, have been reported after vaccination. However, such severe side effects occur much less often with the vaccine than they would if a person caught the disease itself [1, 8, 10].

This is well illustrated in young children by comparing the frequency of adverse events from the MMR vaccine with the frequency of adverse events with measles itself (see Figure 4.2).

About three in every 10,000 children who receive the MMR vaccine develop a fever high enough to cause short-lived seizures. In contrast, the risk of such a fever is more than 30 times greater among children who develop the disease – affecting about 100 in 10,000 children [8, 10]. Importantly, worldwide measles vaccination was estimated to prevent 9.6 million deaths from the infection during 2000 [5]. Similarly, around one in 10 young children develop a fever after receiving influenza vaccine [3], whereas around nine in 10 children develop a fever after a proven influenza infection [76].

The frequency of side effects associated with some earlier vaccine preparations (no longer in use in developed countries such as Australia) was higher than with the current generation of vaccines. Lastly, some alleged links between administration of certain vaccines and onset of diseases, particularly when the causes are unknown, have proven to be unfounded (see Boxes 8, 9 and 10).

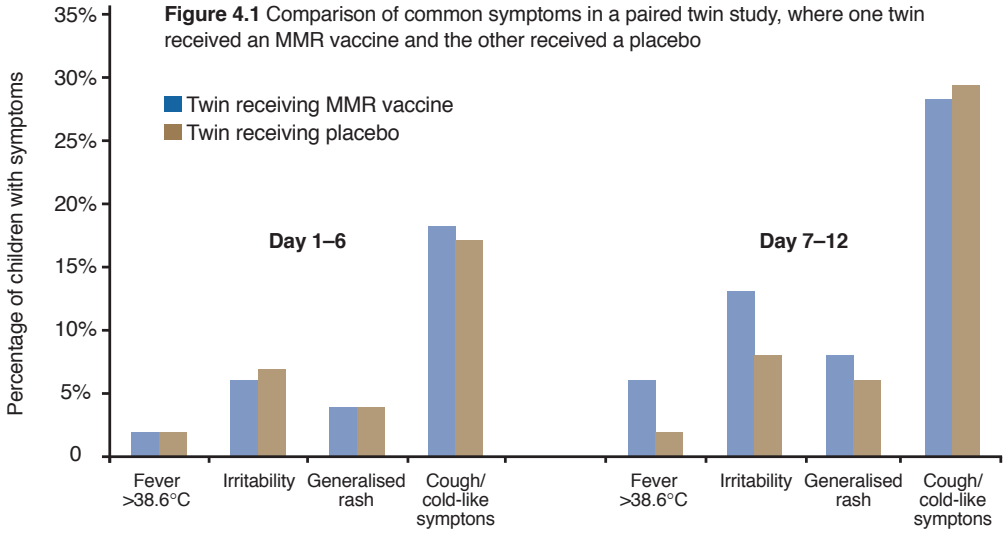


Figure 4.1 Comparison of common symptoms in a paired twin study, where one twin received an MMR vaccine and the other received a placebo

Figure 4.2 Severe complications due to MMR vaccine and measles among 1 million children aged under 5 years

MMR vaccine	Measles
Uncommon complications	
300 children have seizures	10,000 children have seizures or convulsions induced by fever
Rare complications	
26 children have a temporary tendency to bruise or bleed more easily (thrombocytopenia)	330 children develop thrombocytopenia
Very rare complications	
Up to four children get a severe allergic reaction (anaphylaxis). This is readily treated with complete recovery	No anaphylaxis cases
No children will get subacute sclerosing panencephalitis (SSPE). SSPE causes progressive brain damage and death	10 children get SSPE several years later
Uncertain; a maximum of one child may develop inflammation of the brain (encephalitis). Encephalitis from any reason may result in permanent brain damage or death	2000 children may develop encephalitis

BOX 11

Is vaccination during pregnancy safe, and if so for what diseases?

It is safe to give inactivated vaccines in pregnancy [1]. The rates of side effects among pregnant women are similar to those in the general population, and no link has been established between vaccination with inactivated vaccines in pregnancy and birth defects [80, 81]. The use of inactivated vaccines in pregnancy is particularly desirable for infections, such as influenza, that affect pregnant women or their babies more frequently and severely than the general population [82]. This is because vaccination during pregnancy not only protects the mother against infection, but also provides protection to the unborn baby as a result of transfer of maternal antibodies (see Question 1).

Live attenuated vaccines, such as MMR or varicella vaccines, are not recommended during pregnancy, as the live viruses could in theory be transmitted from pregnant mother to their foetus. However, there is no evidence of an increased incidence of birth defects in children whose mothers inadvertently received live attenuated vaccines while pregnant [83].

5 How are vaccines shown to be safe?

Safety testing is an integral component of vaccine development and use

Careful testing of safety is an essential part not only of vaccine development and manufacture, but also of ongoing surveillance programs after vaccines have been introduced into the community.

The importance of strict routine testing is illustrated by an incident that occurred in 1955, before such testing, when a batch of polio vaccine had not been fully inactivated and still contained live virus. As a result, some recipients and their close family members developed polio infections, leading to paralysis and some deaths [84].

Vaccine safety is always assessed before licensing for use

During vaccine development, initial safety testing procedures occur in two stages (see Figure 5.1). The first stage involves preclinical assessment in the laboratory [85]. If a vaccine is not shown to be safe in the lab, it cannot progress into clinical trials. Vaccines are then evaluated in three phases of clinical trials. In phase I clinical trials, the vaccine candidate is given to small numbers (25–50) of healthy adults with the primary goal of assessing safety.

Phase II trials involve hundreds of participants and are designed to demonstrate how effective a vaccine is in mounting an immune response, and to determine the optimal dose regimen. Phase III clinical trials aim to demonstrate protection against the target disease and safety, and this usually requires administration of the vaccine to many thousands of potentially susceptible people. Only after the vaccine has passed each of these safety and efficacy hurdles is it approved for widespread community use.

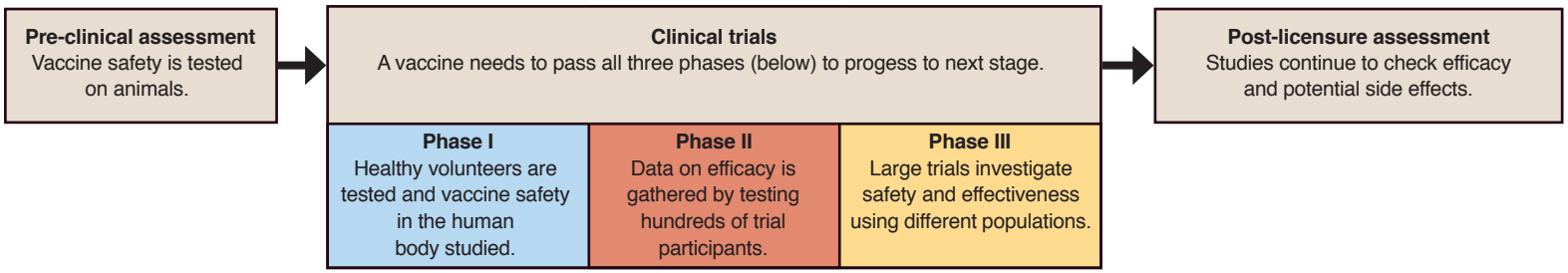
Safety assessments continue once a vaccine is licensed for use

Some side effects of vaccines are so uncommon, they are not detected during the extensive safety testing before vaccine licensure. To ensure that authorities can detect such unanticipated side effects, careful surveillance continues even after a vaccine candidate has proven to be effective and has passed all safety checks in thousands of people. The formal term for this systematic collection of data and analysis of reports of any suspected adverse events is post-licensure assessment (see Figure 5.1).

The value of ongoing safety testing of licensed vaccines is demonstrated by the successful identification of potential clinical problems. The most recent example is the detection of an increased risk of febrile seizures that unexpectedly occurred in young children given a particular influenza vaccine in Australia in 2010 [86]. When the problem first became apparent, the use of all influenza vaccines in young children was suspended to allow time for authorities to identify the one type of vaccine preparation causing the problem. The exact cause is still being investigated, but in the meantime, influenza vaccines shown not to be associated with unacceptable rates of febrile seizures have been reintroduced to ensure protection against influenza is available for children, who are at high risk of complications from the disease.

Likewise, in adults, long-term surveillance has been used to determine the risk of developing Guillain–Barré syndrome (GBS), a rare (one to two cases per 100,000 people) but serious condition characterised by temporary paralysis which has occasionally been reported to occur after influenza vaccination. The conclusion of these long-term studies was that, at most, one additional case of GBS occurs for every million people vaccinated against influenza [87]. On the other hand, the risk of developing GBS after influenza infection is much greater [12].

Figure 5.1 The phases of vaccine safety testing.



BOX 12

If vaccines are so rigorously tested, why are some withdrawn from the market after introduction into the community?

Withdrawal of vaccines from the market is very rarely required. Occasionally, adverse events may occur too infrequently to be detected during phase III trials. For example, rotavirus is a viral infection that causes severe diarrhoea among infants and young children. One specific vaccine against rotavirus called Rotashield was shown to be effective and generally well tolerated in clinical trials [88]. Intussusception, a blockage of the small bowel, was noted during a phase III trial but was not found to be statistically significant [89]. As a normal precaution, doctors were encouraged to report cases of intussusception when Rotashield was introduced. Within a year this reporting revealed a small but significant increase in the number of cases of intussusception, leading to withdrawal of the vaccine.

Rotavirus vaccines were redeveloped and further tested in clinical trials sensitive enough to rule out the risk of intussusception at the level reported following use of the Rotashield vaccine. When the new vaccines were introduced, active surveillance in Australia detected a slightly higher number of cases of intussusception [90]. When the risk was balanced against the benefits of the vaccines, which prevent an estimated 1–2 deaths and nearly 8,000 hospitalisations each year in Australia [91], continued use was recommended. Similarly, the World Health Organisation, based on the benefits of new rotavirus vaccines greatly exceeding the risk of intussusception, has recommended continued use globally [92].

6 What does the future hold for vaccination?

The benefits of vaccination worldwide will continue

Vaccination represents the most successful form of disease prevention [11, 93]. In the past 20 years, vaccine technology has improved, resulting in production of vaccines against a broad range of infectious diseases.

Nevertheless, the burden of infectious diseases worldwide remains high, particularly in developing countries. According to the World Health Organisation, infections still account for about 40% of all recorded deaths worldwide [94].

Future strategies to meet this challenge include extending the use of existing vaccines, new technologies to deliver vaccines and generating new vaccines. Priority targets for future vaccines include viruses, bacteria and parasites (see Figure 6.1).

Existing vaccines will be used in new ways

Using existing vaccines in different ways shows promise. One example is administration of a killed vaccine, normally given during childhood, to a pregnant woman. This immunisation boosts antibody levels in the mother, and the extra antibodies also reach her baby by crossing the placenta, and in the mother's breast milk. Doing this protects her newborn baby while the baby's immune system is still maturing [26]. In the future, giving a malaria vaccine in this way could be beneficial to protect newborns from becoming chronically infected from birth [93].

Another way of applying existing vaccines more effectively is to target them to elderly people, who make up a growing proportion of the population. For instance, elderly people in hospitals are more prone to infections with vaccine-preventable diseases such as *Streptococcus pneumoniae*, influenza virus and shingles-causing varicella [93].

New technologies will change vaccine delivery

Many technologies under development will improve the simplicity and effectiveness of vaccine delivery.

To make a vaccine that only needs to be given once, it must either be very powerful, or be packaged in such a way that its contents are released intermittently once it has been administered. Under development are multilayer particle technologies [95, 96] and alternative adjuvants, which have the potential to remove the need for multiple shots [97].

Needle-free administration is already possible for some vaccines, such as live vaccines given orally (polio vaccine) or via a nasal spray (influenza vaccines). Currently, many vaccines need to be injected, but researchers are working on edible (plant-based) vaccine materials [98], needle-free skin patches and microneedle injection technologies to get the vaccine through the skin without discomfort [95, 96].

Technologies for delivering multiple vaccines in one injection are improving – many different killed vaccines can already be given in one injection without impairing the immune response to each [99], and some live virus vaccines can also be given together [100].

Novel vaccines

Most successful vaccines protect against acute infections largely through production of antibodies. Vaccines for chronic infections, in particular malaria, HIV and tuberculosis remain a problem. One of the major reasons for this is the viruses, bacteria and parasites that cause these infections 'hide' from the immune system in the person's own cells. This requires an immune response mediated by T-cells (see Question 1), instead of, or in addition to, an antibody response [93, 101].

There are effective vaccines to target infections that predispose people to long-term complications, such as cancer [102]. Examples include vaccines to the human papillomavirus (HPV) [103], hepatitis B and the shingles-causing varicella virus. On the other hand, there are still no vaccines for other infections associated with many serious long-term complications. For instance, infection with the bacterium *Helicobacter pylori* predisposes patients to stomach cancer [104], group A streptococcus infection is responsible for rheumatic fever [38] – still a major cause of death and disability in developing countries, and chlamydia infection can lead to infertility and blindness [105] (see Figure 6.1).

Vaccines have the potential to be used to treat rather than prevent infectious and non-infectious diseases. Such therapeutic vaccines are being targeted at persistent infections, such as shingles, and also at non-infectious conditions, including autoimmune disorders, allergies and cancers not related to infections. In the case of tumours, the vaccine can be directed against parts of the tumour itself. For autoimmune or allergic disorders, the vaccines are being designed to switch off unwanted immune responses, so-called negative vaccination – rather than switching on the useful immune response needed for infections and cancer [106].

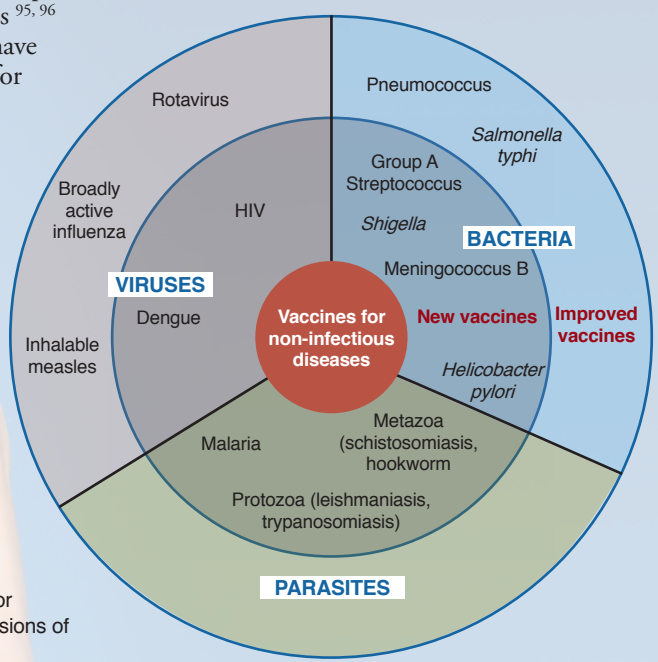


Figure 6.1 Current research is aiming for entirely new vaccines and improved versions of existing vaccines.

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Figure sources

Figure 1.2
Based on information in: Murphy, K., Travers, P., and Walport, M. (2007) *Janeway's Immunobiology*. 7th edition. Garland Science: 928.

Figure 3.1 and Figure 3.2
Source: Chiu, C., et al. Vaccine preventable diseases in Australia, 2005 to 2007. *Commun Dis Intell* 2010; **34** Suppl: S1–S167.

Figure 4.1
Peltola, H., and Heinonen, O.P. (1986) Frequency of true adverse reactions to measles–mumps–rubella vaccine. A double-blind placebo-controlled trial in twins. *Lancet* **1** (8487), 939–42.

Figure 4.2
Plotkin, S.A., Orenstein, W.A., and Offit, P.A. eds. (2007). *Vaccine*. 5th edition. Saunders Elsevier.
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Figure 6.1
Derived from Nossal, G.J. (2011) Vaccines of the future. *Vaccine* **29** Suppl 4: D111–5.

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