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## Immunity and how vaccines work

### Introduction

Immunity is the ability of the human body to protect itself from infectious disease. The defence mechanisms of the body are complex and include innate (non-specific, non-adaptive) mechanisms and acquired (specific, adaptive) systems.

Innate or non-specific immunity is present from birth and includes physical barriers (e.g. intact skin and mucous membranes), chemical barriers (e.g. gastric acid, digestive enzymes and bacteriostatic fatty acids of the skin), phagocytic cells and the complement system.

Acquired immunity is generally specific to a single organism or to a group of closely related organisms. There are two basic mechanisms for acquiring immunity – active and passive.

### Active immunity

Active immunity is protection that is produced by an individual's own immune system and is usually long-lasting. Such immunity generally involves cellular responses, serum antibodies or a combination acting against one or more antigens on the infecting organism. Active immunity can be acquired by natural disease or by vaccination. Vaccines generally provide immunity similar to that provided by the natural infection, but without the risk from the disease or its complications. Active immunity can be divided into antibody-mediated and cell-mediated components.

#### Antibody-mediated immunity

Antibody-mediated responses are produced by B lymphocytes (or B cells), and their direct descendants, known as plasma cells. When a B cell encounters an antigen that it recognises, the B cell is stimulated to proliferate and produce large numbers of lymphocytes secreting an antibody to this antigen. Replication and differentiation of B cells into plasma cells is regulated by contact with the antigen and by interactions with T cells (a type of lymphocyte), macrophages and complement. The antibody provides immunity against infection in a variety of ways. These ways include neutralising toxins, blocking adhesion and cell entry by organisms, neutralising and preventing viral replication or complement-mediated killing.

#### Cell-mediated immunity

Cell-mediated immunity is controlled by a subset of lymphocytes called T lymphocytes or T cells. T cells mediate three principal functions: help, suppression and cytotoxicity. T-helper cells stimulate the immune response of other cells (i.e. T cells stimulate B cells to produce antibodies). T-suppressor cells play an inhibitory role and control the level and quality of the immune response. Cytotoxic T cells recognise and destroy infected cells and activate phagocytes to destroy pathogens they have taken up.

These two components of specific immunity are closely related to each other, and T cells interact with B cells in the production of antibodies against most antigens. Specific antibodies and cell-mediated responses are induced for all infections, but the magnitude and quality of these two components vary in different infections.

## Passive immunity

Passive immunity is protection provided from the transfer of antibodies from immune individuals, most commonly across the placenta or less often from the transfusion of blood or blood products including immunoglobulin. Protection provided by the cross-placental transfer of antibodies from mother to child is more effective against some infections (e.g. tetanus and measles) than for others (e.g. polio and whooping cough). This protection is temporary – commonly for only a few weeks or months.

## How vaccines work

Vaccines produce their protective effect by inducing active immunity and providing immunological memory. Immunological memory enables the immune system to recognise and respond rapidly to exposure to natural infection at a later date and thus to prevent or modify the disease. Antibodies can be detected in blood or serum, but, even in the absence of detectable antibodies, immunological memory may still be present. Cell-mediated responses to some vaccines (e.g. BCG, see Chapter 32) may be detectable by skin testing but do not necessarily indicate protection.

Vaccines can be made from inactivated (killed) or attenuated live organisms, secreted products, recombinant components or the constituents of cell walls.

Vaccines such as pertussis and inactivated poliomyelitis virus (IPV) contain inactivated bacteria or viruses. Other vaccines contain only the antigens that are important for protection. For example, tetanus and diphtheria vaccines contain inactivated toxins (toxoids), influenza vaccine contains a surface protein called haemagglutinin, and pneumococcal vaccine contains the polysaccharide from the capsule. Live attenuated vaccines include yellow fever; measles, mumps and rubella (MMR); and BCG.

From birth and in early infancy and childhood, humans are exposed to countless numbers of foreign antigens and infectious agents in the everyday environment. Responding to these stimuli helps the immune system to develop and mature. Compared with exposure in the natural environment, vaccines provide specific stimulation to a small number of antigens. Responding to these specific antigens uses only a tiny proportion of the capacity of an infant's immune system (Offit *et al.*, 2002). If an infant's immune system could be exhausted by multiple vaccines, one would expect vaccinated children to be at a higher risk of serious infections. Studies to investigate whether vaccines increase susceptibility to serious infections have shown no evidence of such an effect, with infection rates generally being lower in vaccinated children (Hviid *et al.*, 2005, Miller *et al.*, 2003).

## Inactivated vaccines

A first injection of an inactivated vaccine or toxoid in an individual without prior exposure to the antigen produces a primary antibody response. This response is dominated by IgM antibody initially, followed by IgG antibody. Two or more injections may be needed to elicit such a response in young infants. This is usually called the primary course. Depending on

the potency of the product and the time interval, further injections will lead to an accelerated response dominated by IgG – the secondary response. Following a primary course of vaccination, antibodies may persist for months or years. Even if the level of detectable antibody subsequently falls, the immune system has been primed and an individual may be protected. Further reinforcing doses of vaccine are used to boost immunity and to provide longer-term protection. Inactivated vaccines cannot cause the disease that they are designed to prevent.

Plain polysaccharide antigens do not stimulate the immune system as broadly as protein antigens such as tetanus, diphtheria or influenza. Therefore, protection from such vaccines is not long-lasting and response in infants and young children is poor. Some polysaccharide vaccines have been enhanced by conjugation – where the polysaccharide antigen is attached to a protein carrier (e.g. Hib and MenC vaccines). This enables the immune system to respond more broadly to the antigen to provide immunological memory, even in young children. Some inactivated vaccines contain adjuvants, substances that enhance the antibody response. Most combination vaccines contain adjuvants such as aluminium phosphate or aluminium hydroxide.

### Live vaccines

Live attenuated virus vaccines, such as MMR, usually promote a full, long-lasting antibody response after one or two doses. To produce an immune response, the live organism must replicate (grow) in the vaccinated individual over a period of time (days or weeks). The immune system responds in the same way as it does to natural infection. It usually does this without causing the disease itself (because the vaccine virus is weakened or 'attenuated') but, for some vaccines, a mild form of the disease may rarely occur (e.g. a rash following measles-containing vaccines).

### Vaccine failure

No vaccine offers 100% protection and a small proportion of individuals get infected despite vaccination. Vaccines can fail in two main ways – known as primary or secondary vaccine failures. Primary failure occurs when an individual fails to make an initial immunological response to the vaccine. Infection can therefore occur at any point after vaccination. A good example of primary vaccine failure is the 5–10% of children who do not respond to the measles component of the first dose of MMR. The risk of measles in such children is reduced by offering an additional dose of vaccine, usually before school entry.

Secondary failure occurs when an individual responds initially but then protection wanes over time. The incidence of secondary vaccine failure therefore increases with time. Individuals who acquire infection despite vaccination may have a modified, milder form of disease and are less likely to suffer serious complications than those who have never been vaccinated. An example of secondary vaccine failure is pertussis vaccine, when protection against whooping cough after three doses is initially high but declines as a child gets older. A fourth (booster) dose is given to improve protection during the school years.

### Population immunity

The primary aim of vaccination is to protect the individual who receives the vaccine. Vaccinated individuals are also less likely to be a source of infection to others. This reduces the risk of unvaccinated individuals being exposed to infection. This means that individuals

who cannot be vaccinated will still benefit from the routine vaccination programme. This concept is called population (or 'herd') immunity. For example, babies below the age of two months, who are too young to be immunised, are at greatest risk of dying if they catch whooping cough. Such babies are protected from whooping cough because older siblings and other children have been routinely immunised as part of the childhood programme.

When vaccine coverage is high enough to induce high levels of population immunity, infections may even be eliminated from the country, e.g. diphtheria. But if high vaccination coverage were not maintained, it would be possible for the disease to return. Vaccination against smallpox enabled the infection to be declared eradicated from the world in 1980. The World Health Organization (WHO) is currently working towards the global eradication of poliomyelitis.

## Immunoglobulins

Passive immunity can be provided by the injection of human immunoglobulin which contains antibodies to the target infection and temporarily increases an individual's antibody level to that specific infection. Protection is afforded within a few days but may last only a few weeks.

Human normal immunoglobulin (HNIG) is derived from the pooled plasma of donors and contains antibodies to infectious agents that are currently prevalent in the general population. HNIG is used for the protection of immunocompromised children exposed to measles and of individuals after exposure to hepatitis A.

Specific immunoglobulins are available for tetanus, hepatitis B, rabies and varicella zoster. Each specific immunoglobulin contains antibodies against the target infection at a higher titre than that present in normal immunoglobulin. Specific immunoglobulins are obtained from the pooled blood of donors who:

- are convalescing from the target infectious disease, or
- have been recently immunised with the relevant vaccine, or
- are found on screening to have sufficiently high antibody titres

Recommendations for the use of normal and specific immunoglobulins are given in the relevant chapters.

## References

- Hviid A, Wohlfahrt J, Stellfeld M and Melbye M (2005) Childhood vaccination and non-targeted infectious disease hospitalization. *JAMA* **294**(6): 699–705.
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