1 General immunisation principles

It is not necessary to have an in-depth knowledge of the immune system to understand the first principles of vaccinology. The immune system is an extremely complex inter-connected system, but certain aspects involved in the process of inducing specific immunity through vaccination inform vaccination practice.

As protective immunity develops over time, the timing of vaccine doses, along with a basic understanding of the different types of vaccines, becomes important.

1.1 Immunity and immunisation

Immunity is the biological state of being able to resist disease: the primary objective of vaccination is to induce an immunological memory against specific diseases, so that if exposure to a disease-causing pathogen occurs, the immune response will neutralise the infection before disease can occur.

1.1.1 Immune recognition

One of the primary ways in which the immune system achieves elimination of pathogens and other unwanted foreign material is through a 'self' tag. Each cell in the body is equipped with a type of molecule that identifies the individual from any other, much like a barcode. Pathogens not only lack a 'self' tag, they also contain a range of material termed 'virulence factors' that the immune system recognises as danger signals.

Antigens (antibody generators) are the drivers of an immune response. Antigens are usually part of a foreign protein or glycoprotein; molecular shapes that the immune system recognises as foreign and trigger an adaptive immune response. While some vaccines contain the entire weakened or attenuated organism (such as measles, mumps and rubella vaccines), increasingly vaccines now contain purified antigens (as in acellular pertussis, HPV or pneumococcal vaccines).

The first process that occurs when a foreign antigen, such as a vaccine antigen, is introduced to the body is the recognition that the antigen is non-self. The antigen is taken up at the local site (such as the injection site) by professional phagocytic cells called antigen-presenting cells; for example, macrophages and dendritic cells. Once inside the antigen-presenting cells, degradation of the foreign protein (or microbe) occurs and tiny fragments are carried to the cell surface and displayed along with a 'self' tag molecule. These antigen-presenting cells then make their way through the lymph to the local lymph node where the adaptive immune response is initiated.

1.1.2 Induction of the adaptive immune response

> The response that occurs the first time an antigen is 'seen' by the immune system is called the primary immune response.

The adaptive immune response occurs in lymphoid tissue, primarily the lymph nodes, of which there are 500–600 distributed throughout the body, including the spleen.

The adaptive immune response to most vaccines occurs at the draining lymph node proximal to the site of injection. The spleen and lymph nodes are densely populated with important effector lymphocytes of the immune response: the T-cells and B-cells. The lymph that flows through the nodes brings with it the vaccine antigen that has been captured at the injection site by the specialised antigen-presenting cells. Once in the lymph node the vaccine antigen, in combination with the cell that has carried it there, comes into contact with the specific T-cells and B-cells.

Among the trillions of specific T and B lymphocytes (~10^{16} possibilities) there (usually) exists a match for the antigen. The process that occurs once these cells recognise each other is the primary immune response and it matures over a period of four to six weeks.

An early outcome of the interaction between these antigen-presenting cells and T and B lymphocytes is the production of antibody-producing B-cells. Antibody can be measured in the blood as soon as 4–7 days, but is usually more effectively measured weeks to months later. Initially, this is low in quantity and of low affinity for the antigen (binds weakly to the antigen), and primarily consists of the antibody subtype immunoglobulin M (IgM), often referred to as 'early antibody'. It peaks at around 7–10 days then declines relatively quickly (see Figure 1.1).

For most vaccine-preventable diseases this process is too slow following infection, and disease occurs before an effective immune response can be mounted. Injecting a subunit part of the disease in the form of vaccine readies the immune response so an effective immune response can be mounted more rapidly when the wild disease is encountered.

1.1.3 Development of immune memory and the secondary response

The response that occurs the second time an antigen is 'seen' by the immune system is called the secondary immune response.

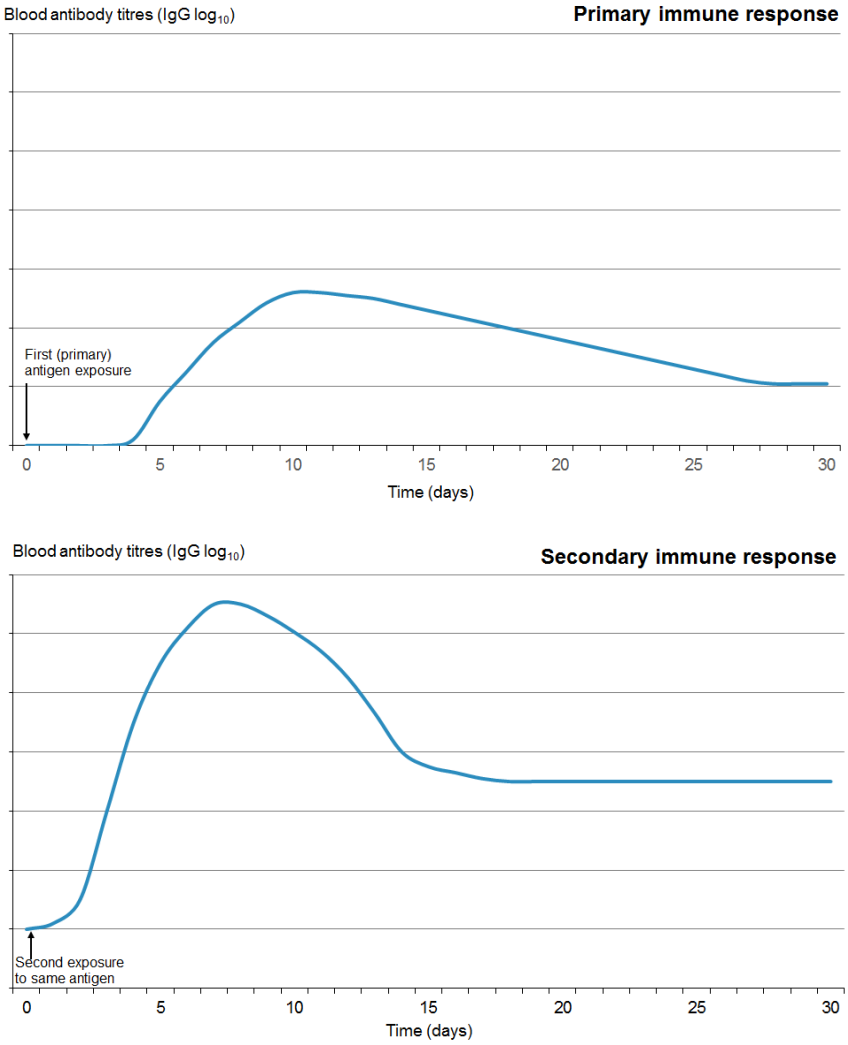
Following the primary immune response, a reaction occurs within the lymph node. Over a period of around two months, cells that are less specific for the specific antigen are deleted, and those that are highly specific are retained and divide. During this time immunological memory cells also develop.

The next time the same antigen is introduced, either as a pathogen component or as a further dose of vaccine subunit, the immunological memory cells will recognise it and begin to proliferate. Highly specific antibody (primarily of the IgG subtype, but also IgA) is rapidly produced in large amounts. The lag phase is much shorter than the primary immune response (see Figure 1.1), just 1–4 days; the antibody peaks very quickly and lasts much longer.

The immune system has been readied by the vaccine; if the actual disease pathogen enters the body, then it is recognised by the immune system and is prevented from causing disease.

Figure 1.1: Comparison of primary and secondary immune responses to protein-containing vaccines

Secondary responses are faster (peaking at day 7) than the primary immune response and the antibody titres are higher, more prolonged and of higher neutralising capacity.

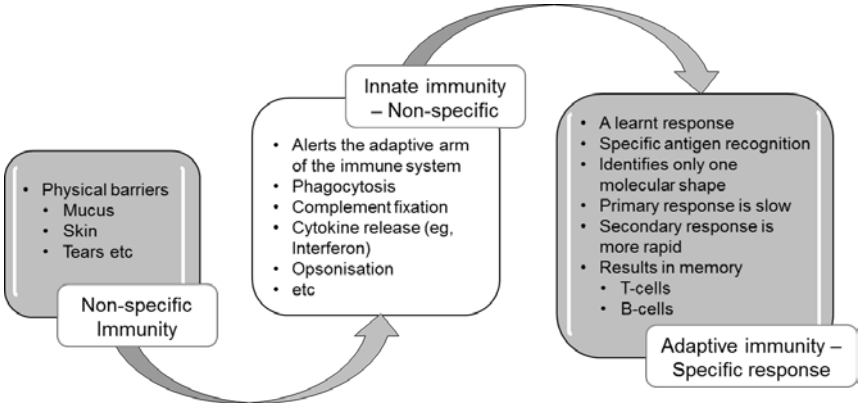


Innate immunity

Most infectious microbes (also known as micro-organisms) are prevented from entering the body by barriers such as skin, mucosa, cilia and a range of anti-microbial enzymes. Any microbes that breach these surface barriers are then attacked by other components of the innate immune system, such as polymorphonuclear leucocytes (neutrophils), macrophages and complement.

This non-specific immune response termed 'innate' is robotic and does not involve learnt or adaptive mechanisms. The cells and proteins of the innate immune system are able to recognise common microbial fragments and can kill microbes without the need for prior exposure. The cells of the innate immune system also interact with the cells of the adaptive immune system (eg, lymphocytes) to induce a cascade of events that results in the development of adaptive immunity and immune memory, as summarised in Figure 1.2.

Figure 1.2: Summary of non-specific innate and adaptive (specific) immunity



1.1.4 Acquisition of adaptive immunity

Specific antibody can be acquired either naturally via infection or 'artificially' using vaccines by teaching the immune system to respond to specific parts of the potential pathogenic antigens. This is termed adaptive or learnt immunity.

Naturally acquired immunity

Naturally acquired immunity occurs either actively by experiencing the infection or passively through the transfer of maternal antibodies from mother to fetus or infant (transplacentally or in breastmilk).

Artificially acquired immunity

'Artificially' acquired immunity occurs either actively through vaccination or passively through administration of immunoglobulin (IG) (see Appendix 6).

While actively acquired immunity lasts from years to life, passively acquired immunity lasts from weeks to months as the transferred antibodies decay and are not renewed.

1.1.5 Maternally derived immunity

The passive transfer of antibody from mother to fetus provides an opportunity to provide protection to the neonate against several diseases before they are old enough to be vaccinated themselves. Maternal vaccination boosts the immunity of the mother, inducing high levels of maternal antibody. This antibody is actively transported across the placenta to concentrate at protective levels by birth (in term infants).

Important diseases that maternal vaccination is effective at preventing include neonatal tetanus, influenza and pertussis in the infant for the first weeks or months of life (see section 4.1 and the relevant disease chapters).

1.1.6 Summary

- Successful immune responses occur following the recognition of, and appropriate response to, a foreign antigen.
- Specialised but non-specific cells, called antigen-presenting cells, take up, transport and present the vaccine antigen to antigen-specific T-cells and B-cells within the lymph nodes and spleen.
- The first wave of antibodies produced are short lived and of low affinity.

- Immune memory takes at least four months to fully develop, but the antibody and memory cells that arise are of high affinity.
- Immune memory can be boosted. This is called a secondary immune response.
- Adaptive immunity is learnt and acquired actively through disease or vaccination.
- Passive immunity is acquired through maternal transfer and administration of IG.
- Maternal vaccination offers passive protection to infants for the first weeks or months of life.

1.2 From personal protection to community (herd) immunity

By protecting individuals, vaccination can also protect the wider community. This herd immunity occurs when the vaccine coverage is high, meaning an infectious case is unlikely to encounter susceptible contacts, so transmission stops.

When a vaccine is able to prevent carriage and transmission of a human-only pathogen such as polio virus, measles virus or *Streptococcus pneumoniae*, the whole population benefits, and these agents can be reduced and even eliminated. This phenomenon, called herd or community immunity, can prevent infections spreading and therefore protect vulnerable members of the population, such as the very young, very old, or those with underlying conditions that increase their risk from infectious diseases (immunocompromised). These individuals may not themselves be able to receive some vaccines (eg, live vaccines) or may not mount an effective immune response to other vaccines.

The population benefits depend on the disease itself and the nature of the vaccine. A recent example of herd immunity in New Zealand is the significant reduction in rotavirus hospital discharge rates in children aged under 5 years following the July 2014 introduction of rotavirus vaccine for infants (see section 17.3.2).

1.2.1 Reproduction number (R_0) and herd immunity threshold (H)

A measure of the infectiousness of a disease is the basic reproduction number (R_0). This is the number of secondary cases generated by a typical infectious individual when the rest of the population is susceptible. In other words, R_0 describes the spreading potential of an infection in a population.[1] Measles is one of the most infectious diseases, with an R_0 of 12–18 (Table 1.1). In other words, one person with measles is likely to infect up to 18 other susceptible people. Pertussis is similarly infectious.

If a significant proportion of the population are immune, then the chain of disease transmission is likely to be disrupted. The herd immunity threshold (H) is the proportion of immune individuals in a population that must be exceeded to prevent disease transmission. For example, to prevent measles or pertussis transmission, 92–94 percent of the population must be immune (Table 1.1).

R_0 must remain above 1 in order for an infection to continue to exist. Once R_0 drops below 1 (such as in the presence of an effective vaccination programme), the disease can be eliminated. The greater the proportion of the population that is immune to the infection, the lower the R_0 will be. For example, data[2] indicates that a quadrivalent HPV vaccine programme with 70 percent coverage in young women may lead to the near disappearance of genital warts from the heterosexual population because the R_0 for HPV types 6 and 11 (causing genital warts) falls to below 1 (see 'Herd immunity' in section 9.4.2).

Table 1.1: Approximate basic reproduction numbers (in developed countries) and implied crude herd immunity thresholds[a] for common vaccine-preventable diseases[b]

Infection	Basic reproduction number (R_0)	Crude herd immunity threshold, H (%)
Diphtheria	6–7	83–85
Influenza[c]	1.4–4	30–75
Measles[d]	12–18	92–94
Mumps	4–7	75–86
Pertussis	5–17	92–94
Polio[e]	2–20	50–95
Rubella	6–7	83–85
Varicella	8–10	Not defined

Notes

a The herd immunity threshold (H) is calculated as $1-1/R_0$.

b The values given in this table are approximate: they do not properly reflect the range and diversity among populations, nor do they reflect the full immunological complexity underlying the epidemiology and persistence of these infections.

c The R_0 of influenza viruses varies among subtypes.

d Herd immunity thresholds as low as 55% have been published.

e This is complicated by uncertainties over immunity to infection and variation related to hygiene standards.

Adapted from: Fine PEM, Mulholland K. 2013. Community immunity. In: Plotkin SA, Orenstein WA, Offit PA (eds). *Vaccines* (6th edition). Philadelphia, PA: Elsevier Saunders. Table 71.2.

1.2.2 Summary

- Vaccines provide not only individual protection, but for many of the diseases we vaccinate against there is also a population effect called herd/community immunity.
- Some diseases are extremely infectious and require a very high proportion of the community to be immune to prevent transmission (particularly measles and pertussis).

1.3 The importance of immunisation coverage

High immunisation coverage not only means more individuals are protected but is vital to achieve herd immunity. High coverage reduces the spread of disease to those who have not been vaccinated for medical reasons (eg, children with leukaemia while receiving treatment) or because of age (eg, infants who are too young to respond to some vaccines). High coverage also reduces the spread of disease to those who may not mount an effective immune response to vaccines because of an underlying condition (eg, those on immunosuppressive regimes).

The World Health Organization (WHO) and the New Zealand government target for immunisation coverage is for at least 95 percent of children to be fully vaccinated by age 2 years. The New Zealand target includes a marker for on-time immunisation of 95 percent by age 8 months, as well as at age 2 years. This target is based on the need for:

- on-time immunisation coverage, particularly three doses of pertussis-containing vaccine for infants in the primary series and the first dose of measles vaccine at age 15 months
- achieving high herd immunity, particularly to prevent measles transmission.

For the three months ending 31 December 2017, 92.2 percent of New Zealand children were fully immunised by age 8 months and 92.3 percent were fully immunised by age 2 years. Up-to-date national and DHB immunisation coverage data is available on the Ministry of Health website (www.health.govt.nz/national-and-dhb-immunisation-data).

1.4 Classification of vaccines

There are three broad categories of vaccine type: live attenuated (weakened), killed/inactivated, and subunit. Examples of the different types of vaccines are summarised in Table 1.2.

Table 1.2: Classification of vaccines, with examples

Live attenuated	Inactivated or whole killed	Subunit
Measles Mumps Rubella Varicella Rotavirus Tuberculosis (BCG) Zoster	Poliomyelitis (IPV) Hepatitis A Some influenza vaccines	Toxoid: • diphtheria • tetanus Polysaccharide: • pneumococcal (23-valent) Conjugate: • pneumococcal (10- and 13-valent) • *Haemophilus influenzae* type b • meningococcal (monovalent and quadrivalent) Recombinant: • hepatitis B • human papillomavirus Other subunit: • pertussis, acellular • influenza

Note: Travel vaccines have been omitted from the above table.

1.4.1 Live attenuated vaccines

Live vaccines contain pathogens, usually viruses, which have been weakened (attenuated) so that they are able to replicate enough to induce an immune response but not cause disease. Immunity from live vaccines is usually very long-lived. The live vaccines on the National Immunisation Schedule are MMR, varicella, rotavirus and herpes zoster vaccines.

1.4.2 Killed and inactivated vaccines

Killed vaccines contain whole bacteria that have been killed. The whole-cell pertussis vaccine is an example of a killed vaccine. There are no killed vaccines on the Schedule.

Inactivated vaccines contain viruses that have been inactivated in some way, such as splitting, so they are unable to replicate or cause disease. Examples of inactivated vaccines are influenza and polio vaccines.

1.4.3 Subunit vaccines

Subunit vaccines contain microbial fragments or particles that can induce an immune response which protects against disease. These are produced using a range of methods including recombinant engineering, detoxification processes and splitting and purification.

Toxoid vaccines

In some bacterial infections (eg, diphtheria, tetanus), the clinical manifestations of disease are caused not by the bacteria themselves but by the toxins they secrete. Toxoid vaccines are produced by harvesting a toxin and altering it chemically (usually with formaldehyde) to convert the toxin to a toxoid. The toxoid is then purified. Toxoid vaccines induce antibodies that neutralise the harmful exotoxins released from these bacteria.

Recombinant vaccines

Recombinant vaccines, such as those used against HBV and HPV, are made using a gene from the (disease-causing) pathogen. The gene is inserted into a cell system capable of producing large amounts of the protein of interest. The protein produced is capable of generating a protective immune response. For example, the gene for the hepatitis B surface antigen (HBsAg) is inserted into yeast cells, which replicate and produce large amounts of HBsAg. This is purified and used to make vaccine. The advantage of this approach is that it results in a very pure vaccine that is efficient to produce.

Polysaccharide and conjugate vaccines

Polysaccharides are strings of sugars. Some bacteria, such as *Streptococcus pneumoniae* and *Neisseria meningitidis*, have large amounts of polysaccharide on their surface, which encapsulate the bacteria. The polysaccharide capsules protect the bacteria from the host's immune system and can make the bacteria more virulent. Historically, it has been difficult to stimulate an effective immune response to these polysaccharide capsules using vaccines, particularly in children aged under 2 years.

First-generation capsular polysaccharide vaccines contained antigens isolated from the different polysaccharide capsules (eg, 23PPV, see chapter 15). Polysaccharide vaccines are poorly immunogenic, and they only induce a primary immune response. They produce low affinity antibodies (which do not bind well to the antigen) and, because they do not elicit T-cell responses, immune memory is not strong. Multiple priming doses (even a single dose) can cause hyporesponsiveness in both children and adults to further doses. There is also concern that repeated doses could result in 'clonal deletion' where the specific B-cell pool becomes depleted due to successive primary responses.

The new generation conjugate vaccines (eg, PCV13 and MCV4-D) contain carrier proteins that are chemically attached to the polysaccharide antigens. Attaching relatively non-immunogenic polysaccharides to the highly immunogenic carrier proteins means that by activating a T-cell response, conjugate vaccines induce both high-affinity antibodies against the polysaccharide antigens, and immune memory.

Examples of carrier proteins and vaccines that use them are:

- tetanus toxoid, used in the meningococcal C conjugate vaccine (MenCCV; NeisVac-C)
- a non-toxic recombinant variant of diphtheria toxin (CRM197), used in the 13-valent pneumococcal conjugate vaccine (PCV13; Prevenar 13)
- diphtheria toxoid (D), used in the quadrivalent meningococcal conjugate vaccine (MCV4-D; Menactra)
- outer membrane protein, used in some Hib vaccines.

The new generation conjugate vaccines are limited by the number of polysaccharides that can be covalently linked to the carrier molecule, so there is still a role for polysaccharide vaccines to broaden the number of serotypes recognised. For example, PCV13 has 13 serotypes, compared to 23PPV with 23 serotypes. Conjugate vaccine technology is expected to improve so that polysaccharide vaccines can eventually be phased out.

Principles and implications for using polysaccharide and conjugate vaccines

- Because of their improved immune response, where possible use protein conjugate polysaccharide vaccines in preference to plain polysaccharide vaccines.
- To ensure broad protection against disease, use a conjugate vaccine to prime the immune system before using the polysaccharide vaccine to increase the number of serotypes recognised. For example, high-risk children are primed with PCV13 then boosted with 23PPV (see section 15.5).
- To avoid or minimise hyporesponsiveness, individuals should have a maximum of three lifetime doses of polysaccharide vaccine.
- Children aged under 2 years should not receive polysaccharide vaccines as they are likely to be ineffective.

1.4.4 Summary

- Vaccines introduce antigens to the immune system in the form of live, killed/inactivated or subunit vaccines.
- Polysaccharide vaccines do not induce immune memory and have been associated with hyporesponsiveness to later doses. Polysaccharide-conjugated vaccines overcome these problems.

1.5 Vaccine ingredients

In addition to the antigen, a vaccine may contain a range of other substances; for example, an immune enhancer (adjuvant) and/or a preservative. Traces of residual components from the manufacturing process may also be present in the vaccine. For further information on vaccine content, see chapter 3 and the vaccine sections within the disease chapters of this *Handbook*.

1.5.1 Adjuvants

Adjuvants are substances that enhance the immune response to an antigen through a range of mechanisms, including improving the delivery of the antigen to the innate immune system and to the lymphoid organs. Use of adjuvants also means that less antigen (which can be difficult to produce) is needed (antigen sparing).

Adjuvants licensed for human use include aluminium salts (eg, aluminium hydroxide and aluminium phosphate), oil-in-water emulsions (MF59, Novartis; AS03, GSK) and a bacterial endotoxin (AS04, GSK). Most non-live vaccines require an adjuvant, and most vaccines still use aluminium adjuvants. The amount of aluminium contained in a vaccine is very small compared with that present in our daily intake from food and water, including breastmilk.

1.5.2 Preservatives

Preservatives prevent the contamination of vaccines, particularly in multi-dose vials. 2-phenoxyethanol is an example of a preservative used in some vaccines. It is also used in many cosmetics and baby care products. Many vaccines do not contain a preservative. Mercury-based preservatives (thiomersal) are not used in vaccines on the New Zealand National Immunisation Schedule.

1.5.3 Stabilisers

Stabilisers protect the vaccine from adverse conditions (such as exposure to heat), inhibit chemical reactions and prevent components from separating. Examples include sucrose, lactose, albumin, gelatin, glycine and monosodium glutamate (MSG).

1.5.4 Surfactants/emulsifiers

These are wetting agents that alter the surface tension of a liquid, like a detergent does. Surfactants assist particles to remain suspended in liquid, preventing settling and clumping. A commonly used surfactant is polysorbate 80, made from sorbitol (sugar alcohol) and oleic acid (an omega fatty acid). It is also commonly used in foods such as ice-cream.

1.5.5 Residuals

Residuals are traces of substances that remain in the vaccine as an inevitable consequence of the manufacturing process. Regulatory bodies vary as to which trace substances must be specified. Residuals may include virus-inactivating agents (such as formaldehyde), antibiotics and other substances used in the manufacturing process, such as egg protein and gelatin.

1.6 Safety monitoring of vaccines in New Zealand

1.6.1 The approval of vaccines for use in New Zealand

Vaccines, like all medicines, have benefits and risks of harm. Before a medicine or vaccine is approved for use, it must be tested in clinical trials to determine its efficacy and safety profile. Information about efficacy and potential risks of harm is identified from the clinical trial data and assessed before the medicine or vaccine is approved for use.

Known information about each medicine and vaccine is published for health professionals in a manufacturer's data sheet, available on the Medsafe website (www.medsafe.govt.nz). Consumer medicine information is usually also published.

Once the vaccine is used freely (ie, outside of the clinical trials), further information becomes available on its safety profile. Some adverse reactions are rare and may not be seen until a very large number of people have received the medicine or vaccine. This is one of the reasons why it is important to monitor all medicines and vaccines after they have been approved (registered). Note that some vaccines that are approved for use by Medsafe may not have been made available for distribution by the manufacturer or supplier.

Most countries (including New Zealand) have a safety monitoring system, which includes a voluntary spontaneous reporting scheme, to help identify any possible safety concerns. These reporting systems feed into the WHO Collaborating Centre for International Drug Monitoring, called the Uppsala Monitoring Centre, located in Sweden. This means

that international data, often covering millions of doses, is available for Medsafe, which is the medicines regulator responsible for monitoring information to ensure that approved vaccines remain acceptably safe for use in New Zealand. Vaccine safety is never reviewed in isolation from the expected benefits of the vaccine; it is always looked at in terms of the risk–benefit balance.

In addition, the WHO plays an important role in vaccine safety through its Strategic Advisory Group of Experts on Immunization and the Global Advisory Committee on Vaccine Safety.

1.6.2 The New Zealand spontaneous reporting scheme

Two terms are used to describe spontaneous reports. *Adverse events* are undesirable events experienced by a person, which may or may not be causally associated with the vaccine. *Adverse reactions* are undesirable effects resulting from medicines or vaccines (ie, they are causally associated).

Spontaneous reports are case reports of adverse events that people have experienced while or after taking a medicine or having a vaccine. Medsafe contracts the collection, review and analysis of this information to the New Zealand Pharmacovigilance Centre at the University of Otago in Dunedin.

Health care professionals and consumers are encouraged to report adverse events following immunisation (AEFIs) to the Centre for Adverse Reactions Monitoring (CARM), which is part of the New Zealand Pharmacovigilance Centre. Pharmaceutical companies also submit adverse event reports.

Further information about suspected adverse reactions (and events following immunisation) reported in New Zealand can be found in the *Suspected Medicine Adverse Reaction Search* (SMARS) on the Medsafe website (www.medsafe.govt.nz/projects/B1/ADRDisclaimer.asp). See below for details about how to report to CARM and what information should be reported.

1.6.3 AEFI reporting process – notifying CARM

When obtaining consent for immunisation, vaccinators should also seek consent to report any adverse events that may occur, because AEFI reporting is considered part of immunisation programme quality control monitoring and public safety.

How to report to CARM

Adverse events may be reported to CARM by:

- the electronic adverse reaction reporting tool available in practice management software programmes
- online reporting at https://nzphvc.otago.ac.nz/report/
- using the iPhone/iPad iOS application (available at https://nzphvc.otago.ac.nz/app)
- downloading and printing a reporting form (https://nzphvc.otago.ac.nz/reporting), then mailing the completed form to the address below
- completing a Freepost Yellow Card (available from CARM), and also found in the *MIMS New Ethicals* and inside the back cover of some editions of *Prescriber Update*
- by telephone, email or fax (see below). Outside office hours, a telephone-answering machine will take messages.

Send reporting forms to:

Freepost 112002
The Medical Assessor
Centre for Adverse Reactions Monitoring (CARM)
University of Otago Medical School
PO Box 913
Dunedin 9710

Telephone: (03) 479 7247
Fax: (03) 479 7150
Email: carmnz@otago.ac.nz
Website: www.otago.ac.nz/carm

In terms of guidance, the sort of information the reporting form generally requires is a patient identifier (gender, age, initial), a medicine, a reaction and the reporter's contact details.

What should be reported?

Health professionals/vaccinators should report:

- all serious suspected AEFI and other reactions of clinical concern to established vaccines, such as those described in Table 1.3 below. The AEFIs should be reported regardless of whether or not they consider the event to have been caused by the vaccination, and they should still be reported even if the effect is well recognised
- all suspected adverse reactions (including minor reactions) to newly introduced vaccines, or those being used for new indications or being delivered by a different route.

Individuals or parents/guardians should be encouraged to notify vaccinators of any AEFI that they consider may have been caused by the vaccination. Alternatively, individuals or parents/guardians may wish to notify CARM themselves, or they can contact their general practice or the Immunisation Advisory Centre (IMAC) (0800 IMMUNE / 0800 466 863) to help with notification.

If in doubt, report it.

Table 1.3: Examples of AEFIs to be reported

Timeframe	Event
All vaccines	
Within 24 hours of vaccination	Anaphylactic reaction (acute hypersensitivity reaction) Anaphylaxis Persistent inconsolable screaming (more than 3 hours) Hypotonic-hyporesponsive episode Fever >40°C
Within 5 days of vaccination	Severe local reaction Sepsis Injection site abscess
Within 12 days of vaccination	Seizures, including febrile seizures Encephalopathy
Within 3 months of vaccination	Acute flaccid paralysis* (AFP), including Guillain–Barré syndrome (GBS) Brachial neuritis (usually occurs 2–28 days after tetanus-containing vaccine) Thrombocytopenia (usually occurs 15–35 days after MMR)
Between 1 and 12 months after BCG vaccination	Lymphadenitis Disseminated BCG infection Osteitis/osteomyelitis
No time limit	Intussusception after rotavirus vaccine Any death, hospitalisation, or other severe or unusual events of clinical concern that are thought by health professionals or the public to possibly be related to vaccination
Newly introduced vaccines, or those with new indications or being delivered by a different route	
No time limit	All suspected adverse reactions

* AFP in children is also monitored by the New Zealand Paediatric Surveillance Unit as part of polio eradication surveillance (see chapter 16).

Seriousness of AEFIs

Reports of suspected adverse reactions or AEFIs can be categorised as serious or non-serious. This categorisation system is a tool used to try and prioritise safety concerns. It is not a reflection of the importance of the events to the consumer or their health care professional. Because a report is defined as serious based on what is reported, it is possible to have both serious and non-serious cases reporting the same type of event; for example, headache.

International convention defines the seriousness of reports based on the outcome or nature of the reported event as documented in the report, *irrespective of whether there is any association to the medicine or vaccine.*

Serious events are based on the following international criteria:

- hospitalisation (or prolonged hospitalisation) of the patient
- life-threatening event
- persisting disability of the patient
- intervention required to prevent permanent impairment
- congenital anomaly
- death of the patient.

CARM assessment of causality

The WHO recommends that individual reports of adverse reactions to vaccines are assessed for causality. This assessment is a tool used to help detect new safety concerns; it is not a determination of whether a vaccine caused an adverse reaction.

The person reporting the event will receive a letter of response from CARM commenting on the adverse effect, the causal relationship, the number of other similar events, and advice about future use of the vaccine in the individual. Also, where applicable, CARM will provide a validated AEFI code to the NIR.

The information provided by CARM:

- needs to be communicated to the individual and parent/guardian (if applicable)
- must be entered in the medical notes
- will help to identify those individuals who should receive follow-up vaccination in a controlled environment, such as a hospital.

1.6.4 What does Medsafe do with this information?

Medsafe and CARM analyse spontaneous reports in conjunction with other information to determine whether there are any new potential safety signals. Medsafe seeks the advice of independent experts through the Medicines Adverse Reactions Committee, or may form working groups of experts to provide advice. Medsafe works closely with other regulatory authorities from around the world.

Medsafe undertakes a risk–benefit assessment of safety signals to decide if action is required. Further information on risk–benefit assessment is provided on the Medsafe website (www.medsafe.govt.nz/Consumers/Safety-of-Medicines/Medsafe-Evaluation-Process.asp).

Most safety signals are not supported by any additional information, and no action is taken, although Medsafe may continue to monitor the issue closely. A small number of possible safety signals are confirmed as real. In these cases, Medsafe has a number of regulatory actions it can take, including withdrawing the product.

In New Zealand, it is less likely that any new rare side-effects to vaccines will be detected because of the small number of people immunised compared to other countries. Therefore, Medsafe uses international data available from the WHO, other regulators and pharmaceutical companies to help assess any reports of rare events following immunisation and to determine if they may be new events linked to immunisation.

1.6.5 Advantages and limitations of spontaneous reports

Spontaneous reports have been shown to be a very simple way of identifying potential or possible safety signals with medicines, and over 90 countries have a spontaneous reporting system. They can be used to monitor the safety of medicines in real-life use over the lifetime of the medicine, and for all types of people.

The limitations of using spontaneous reports include under-reporting, a lack of reliable information on the extent of use of the medicine, and wide variations in the clinical details provided about the event and the history of the patient. Spontaneous reports are heavily subject to

reporting bias, such as media or other attention on an issue. They are also not very effective at detecting adverse reactions that occur a long time after starting the medicine.

For these reasons, such reports are only used to identify safety signals. These signals require further formal epidemiological study before they can be validated or discounted. Information obtained from spontaneous reports needs to be interpreted with caution.

Understanding vaccine safety and spontaneous reporting

Spontaneous report patterns can be variable, and they depend on many factors. Summaries of reported events following immunisation *are not* lists of known or proven adverse reactions to vaccines. They cannot be used to determine the frequency of adverse reactions to vaccines in the whole population, and they cannot be used to directly compare the relative safety of vaccines. They must not be interpreted and used as such.

Health care professionals and consumers are encouraged to report any suspicions that an event they have experienced may have been caused by vaccination. Therefore, reports sent to CARM may be:

- real adverse reactions to the vaccine
- anxiety or nervousness about needles or the process of vaccination
- coincidental events that would have occurred anyway.

With any vaccine, the adverse events that are generally reported include:

- injection-site reactions
- well-recognised events, such as headaches, dizziness, muscle aches, mild fever and tiredness
- mild allergic reactions, such as mild rashes and itching
- rare but serious allergic reactions, called anaphylaxis, which can occur in response to any medicine or vaccine and some foods – health care professionals giving vaccines are trained to recognise the symptoms of serious allergic reactions and promptly treat them
- events due to anxiety, such as fear or anticipation of the needle injection (eg, fainting)

- coincidental medical conditions
- new adverse events (ie, those not already listed in the prescribing information [data sheet]).

There will always be a number of coincidental events reported because vaccines are given to large sections of the population. In some cases, vaccines are specifically targeted at people with underlying medical conditions (eg, the influenza vaccine). The challenge is to be able to distinguish these coincidental 'background' events from those that may have been caused by the vaccine. There are a range of research methods for assessing the risk of an event after a vaccine compared with the risk with no vaccine exposure.

The time between immunisation and an event can be important in determining whether the event was coincidental. Most reactions to vaccines occur within a very short time of immunisation, usually within days.

Another important approach taken when assessing vaccine safety is comparing the number of reports for a specific event with the expected background rate for that event. When doing this, it is important to ensure that definite diagnoses of the events reported were made and to adjust the background rate for any differences in population groups and seasonal variations.[3]

References

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