

# General Considerations

## 1.1 Immunity

The immune system is a complex network of interacting cells and molecules. One of its primary purposes is to identify and remove infectious organisms and their by-products and thereby prevent infection. The immune system works by recognising small parts of microbes or their products, which are called antigens. Microorganisms contain many antigens and the immune system has an almost infinite capacity to recognise them.

Immunity to a variety of bacterial and viral antigens may be induced either actively by the disease or vaccination, or passively by antibody transfer *in utero* and through breastmilk, or by injecting serum containing antibodies.

### Active immunity

Natural active immunity occurs when the immune system responds to a foreign antigen (eg, exposure to a bacterium or virus). The antigens contained within the microorganisms are processed in local antigen presenting cells to optimise their interactions with lymphocytes. Lymphocytes are then stimulated to multiply, produce cytokines, and develop into cytotoxic cells, or into antibody producing cells.

This specific immune response amplifies and co-ordinates with other arms of the immune system, such as phagocytes and the complement system. The process takes from days to weeks to develop and fully mature, which usually results in control of the infection. In some situations there is long lasting protection against organisms and viruses of a similar type. The relative importance of cellular (T lymphocyte) and humoral (antibody) responses varies from organism to organism. Natural, active immunity depends on an individual having a relatively intact immune system to mount a full response.

Vaccine induced immunity follows a similar process, although vaccines contain either attenuated (weakened) living organisms, or components selected to produce maximum protective immunity with minimal systemic or local reactions. The response of the immune system to vaccination is essentially the same as to a 'wild type' infection. The essential goal of vaccination is to prime and prepare the immune system so that it can rapidly respond to the wild type organism, thereby preventing disease and ideally infection.

### Passive immunity

An infant naturally receives passive immunity from its mother via antibodies, which are actively and selectively transported across the placenta during the last three months of pregnancy. These antibodies provide some disease specific protection for the infant (for a few months) from the same diseases to which the mother is immune. As a result, a premature baby has a lower concentration of antibodies, and therefore a shorter duration of protection, than a full term infant.

The major antibody contained in breast milk is secretory immunoglobulin A (IgA), which is not absorbed by the baby but remains in the intestine to protect the mucosal surfaces. Some of these secretory IgA antibodies are directed against the bacterial and viral infections often present in the intestine. The protection from secretory IgA is passive and does not rely on the infant's immune system or stimulate immunologic memory.

Passive immunity can be provided by the injection of human immunoglobulin (IG), which contains high titres of antibodies to hepatitis B, cytomegalovirus, varicella, tetanus, etc. In addition, there are specific high titre globulins, such as hepatitis B immunoglobulin (HBIG), zoster immunoglobulin (ZIG), rabies immunoglobulin (RIG) and tetanus immunoglobulin (TIG). The protection provided by these injections is immediate, but lasts only a few months.

Note that passive immunity does not depend on the recipient's immune response for protection.

Recommendations for the use of immunoglobulins are outlined in the relevant specific disease sections, and in chapter 18.

## 1.2 Principles of immunisation

### What is the difference between vaccination and immunisation?

The terms 'vaccination' and 'immunisation' are often used interchangeably, but their meanings are not equivalent.

Vaccination originally referred to the inoculation of vaccinia virus to render individuals immune to smallpox. These days the term 'vaccination' means the administration (by injection, mouth or any other route) of a vaccine. Vaccination (or indeed suffering from the disease) does not always result in immunity. Immunisation is the process of converting an individual to an immune state in which the individual is protected from disease with that microbe.

### How does immunisation work?

There are many types of vaccines, but they all work in the same general way, by preparing the immune system to attack the infection. A vaccine contains components that look like the infecting organism, and so the immune system responds as it would to an infection with that organism. The most important consequence of successful vaccination is that long lived memory lymphocytes are produced. These respond more quickly and in a more co-ordinated way to subsequent infections so that the infectious microbe is destroyed more quickly. Protection is not always complete, infection may not be prevented but the severity of the illness is usually reduced.

The first exposure to a vaccine stimulates the immune response (known as priming). The immune system takes time to respond to the antigen by producing antibodies and immune cells. Initially immunoglobulin M (IgM) antibody is produced but this is in small amounts and does not bind very strongly to the antigen. After a few days the immune response begins to make immunoglobulin G (IgG) antibody, which is more specific to the microbe. Priming can take more than one dose. For example, many infants will need at least two doses of pertussis vaccine for priming to occur.

Subsequent administration of the same vaccine stimulates the secondary response. The secondary response is much faster than the primary response and produces predominantly IgG rather than IgM. The aim is to generate enough immune cells and antibodies, specific to the infectious microbe, to provide long lasting protection against the disease. The primary and secondary responses constitute the primary series of a vaccine.

If a further dose (a booster) is given some months or years later, a greater and longer lasting secondary response is stimulated, reinforcing and extending the immunologic memory for that microbe.

In assessing the immune response to vaccines, it is easier to measure circulating antibodies in the laboratory rather than cellular responses. One exception is the tuberculosis vaccine *Bacillus Calmette-Guérin* (BCG), where antibodies are not protective against infection. Here immunity is measured by the tuberculin skin test (Mantoux test), which reflects an active cellular immune response to tuberculin and not the level of antibodies.

### 1.3 National Immunisation Schedule

The National Immunisation Schedule (Schedule) from February 2006 is shown in Table 1.1.

**Table 1.1: National Immunisation Schedule from 1 February 2006**

Age	Immunisation given		Special programme**
6 weeks	DTaP-IPV	Hib-Hep B	MeNZB™
3 months	DTaP-IPV	Hib-Hep B	MeNZB™
5 months	DTaP-IPV	Hep B	MeNZB™
10 months***			MeNZB™
15 months	Hib	MMR	
4 years	DTaP-IPV	MMR	
11 years	dTap-IPV*		
45 years	Td		
65 years	Td	Influenza**** (annually)	

Key: D: diphtheria, T: tetanus, aP: acellular pertussis, d: adult diphtheria, ap: adult acellular pertussis, IPV: inactivated polio vaccine, Hib: *Haemophilus influenzae* type b, Hep B: hepatitis B, MMR: measles, mumps and rubella, Td: adult tetanus and diphtheria vaccine, MeNZB™: meningococcal B vaccine.

\* IPV will be given until the end of 2007 for those who have not previously had four doses.

\*\* MeNZB™ vaccine will be available providing provisional consent is extended. See also Table 1.2 for additional individuals eligible for MeNZB™ vaccine.

\*\*\* Infants who receive their 3<sup>rd</sup> dose between 5 to 6 months of age, have the 4<sup>th</sup> at a minimum of 10 months of age. Infants who receive their 3<sup>rd</sup> dose after 6 months of age or older, have the 4<sup>th</sup> dose at a minimum of four months after the 3<sup>rd</sup> dose.

\*\*\*\*Influenza vaccine is also recommended and funded for those under 65 years of age with chronic medical conditions.

**Table 1.2: Other publicly funded vaccines**

Vaccine	Individuals eligible for publicly funded vaccine
Hepatitis B vaccine and hepatitis B immunoglobulin (HBIG)	Babies of hepatitis B surface antigen (HBsAg) positive mothers need both hepatitis B vaccine and HBIG at birth (see chapter 3).
Hepatitis B vaccine	Household and sexual contacts of hepatitis B cases and carriers should be offered hepatitis B vaccine (see chapter 3).
BCG (Bacillus Calmette-Guérin)	<p>Neonatal BCG should be offered to infants at increased risk of tuberculosis, defined as those who:</p> <ol style="list-style-type: none"> <li>1. will be living in a house or family/whānau with a person with either current tuberculosis or a past history of tuberculosis</li> <li>2. have one or both parents who identify as being Pacific people</li> <li>3. have parents or household members who have within the last 5 years lived for a period of 6 months or longer in countries where there is a high incidence of tuberculosis**</li> <li>4. during their first 5 years will be living for 3 months or longer in a high incidence country<sup>†</sup></li> <li>5. live in specific geographical areas as defined by the medical officer of health after consultation with the Ministry of Health (see chapter 12).</li> </ol>
MeNZB™ vaccine*	<p>Children under 5 years should continue to be offered MeNZB™ vaccine opportunistically from 1 July 2006, until there is clinical or epidemiological evidence to warrant cessation.</p> <p>Individuals aged 5–19 years who have had their first dose of MeNZB™ vaccine before 30 June 2006 as part of the Meningococcal B Immunisation Programme should be encouraged to complete the course by 31 December 2006.</p> <p>MeNZB™ will also be available and funded for microbiologists and laboratory workers routinely exposed to <i>Neisseria meningitidis</i> isolates.</p> <p>Adults and children pre- or post-splenectomy.</p> <p>(See chapter 15.)</p>

MMR vaccine	Women of childbearing age who are susceptible to rubella should be offered MMR vaccine (see chapter 11).
Influenza vaccine	This should be offered annually to individuals with certain chronic medical conditions (see chapter 13).
Pneumococcal vaccine***	<p>Pneumococcal immunisation is available on the recommendation of a paediatrician or other secondary care specialist for children under 5 years of age at high risk of pneumococcal disease. Children eligible for publicly funded pneumococcal immunisation are children:</p> <ul style="list-style-type: none"> <li>• on immunosuppressive therapy or radiation therapy, when there is expected to be sufficient immune response</li> <li>• with primary immune deficiencies</li> <li>• with HIV infection</li> <li>• with renal failure, or nephrotic syndrome</li> <li>• immune suppressed following organ transplantation</li> <li>• with cochlear implants or intracranial shunts</li> <li>• with chronic cerebrospinal fluid leaks</li> <li>• receiving corticosteroid therapy for more than two weeks, who are on an equivalent daily dosage of prednisone of 2 mg/kg per day or greater, or children on a total daily dosage of 20 mg or greater.</li> </ul> <p>For further information refer to chapter 16.</p>
Pneumococcal vaccine, Hib vaccine, meningococcal A, C, Y, W135 vaccine	<p>Upon recommendation of a secondary care specialist: Adults pre- and post-splenectomy should be offered pneumococcal, Hib and meningococcal A, C, Y, W135 vaccines.</p> <p>Children under 5 years of age pre- and post-splenectomy or with functional asplenia.</p> <p>See section 1.8 plus individual vaccine chapters for more information.</p>

\* MeNZB™ will continue, providing provisional consent is extended.

\*\* All countries with high incidence of tuberculosis, except Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Holland, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, New Zealand, Norway, Slovakia, Sweden, Switzerland, United Kingdom and the United States of America.

\*\*\* It is expected that the group of eligible children for the pneumococcal vaccine will be expanded over time. Information will be sent to health practitioners and will be available on the Ministry of Health website when there are changes in pneumococcal immunisation programme eligibility.

## **Review of the National Immunisation Schedule**

The Schedule will be reviewed by the Ministry of Health and may change every two years. This is because of the rapid advances in vaccinology, the increased availability of combination vaccines, and the need to introduce new antigens to the Schedule. The Schedule review is also based on the epidemiology of vaccine preventable diseases in New Zealand.

Every effort should be made to ensure that all children are vaccinated, even if they are older than the recommended age (see Appendix 2: Immunisation Catch Up Schedules). An alternative vaccine may be necessary for older children; for example, children seven years and older require Td because it has a reduced dose of diphtheria toxoid to avoid severe local reactions (see section 4.5).

When an epidemic occurs, it may be appropriate to vaccinate a child at an earlier age than is usually recommended (see section 9.8).

## **Eligibility for publicly funded vaccines**

See Table 1.3 below.

Only vaccines given according to the National Immunisation Schedule are available free of charge, unless there is a specific funded programme in response to a recognised need.

The Ministry of Health funds providers:

- for the administration of all childhood vaccines
- for eligible adults the hepatitis B, MMR, influenza, IPV, pneumococcal, Hib and meningococcal vaccines.

Currently there is no funding provided for the administration of Td boosters or any other vaccines (see also section 1.6).

**Table 1.3: Vaccines available free of charge**

Age	Vaccines
<16 years	<ul style="list-style-type: none"> <li>• diphtheria</li> <li>• tetanus</li> <li>• pertussis</li> <li>• hepatitis B</li> <li>• <i>Haemophilus influenzae</i> type b vaccine for all children up to the 5th birthday and for individuals pre- or post splenectomy (see section 1.8 and chapter 7)</li> <li>• MMR</li> <li>• IPV</li> <li>• influenza for those meeting the chronic medical condition criteria</li> <li>• BCG for high risk individuals or groups (see Ministry of Health <i>Guidelines for Tuberculosis Control in New Zealand 2003</i>, <a href="http://www.moh.govt.nz">www.moh.govt.nz</a>)</li> <li>• Pneumococcal for those meeting the eligibility criteria</li> <li>• MeNZB™ (see chapter 15 for eligibility)</li> </ul>
> 16 years	<ul style="list-style-type: none"> <li>• tetanus diphtheria boosters</li> <li>• MMR for any individual susceptible to any one of the three diseases</li> <li>• hepatitis B for household and sexual contacts of known hepatitis B carriers</li> <li>• influenza vaccine for those <math>\geq 65</math> years</li> <li>• influenza for those <math>&lt; 65</math> years meeting the chronic medical condition criteria</li> <li>• IPV</li> <li>• BCG for high risk individuals or groups (see Ministry of Health <i>Guidelines for Tuberculosis Control in New Zealand 2003</i>, <a href="http://www.moh.govt.nz">www.moh.govt.nz</a>)</li> <li>• Hib, pneumococcal, meningococcal A, C, Y, W135 for pre- or post-splenectomy individuals only; MeNZB™ for post-splenectomy individuals while the vaccine is available</li> </ul>

### Timing of doses

The immune response to a series of vaccines is time dependent. In particular, the time interval between doses is important. A second dose of the same vaccine given less than four weeks from the first dose may result in a reduced immune response. Therefore, the general rule is for a minimum interval of four weeks between doses,

unless there are specific recommendations for rapid schedule by the manufacturer. It is not necessary to repeat prior doses.

### **Vaccination of children with inadequate vaccination records**

Research indicates that parents tend to overestimate their child's immunisation history. For this reason, children without a documented history of vaccination should be given a full course of vaccination appropriate for their age. In cases of doubt it is much safer to provide an unnecessary dose than to miss out a needed dose.

The National Immunisation Register (NIR) will assist parents and primary health care providers by providing an accurate immunisation history for a child registered on the NIR (see section 2.3).

### **Catch-up programmes for unimmunised or partially immunised children for the usual childhood schedule**

The objective of a catch-up programme is to complete a course of vaccination and provide adequate protection. Catch-up programmes should be based on documented evidence of previous vaccination. It is not necessary to repeat a vaccine dose. (See Appendix 2: Immunisation catch-up schedules.)

When children have missed vaccine doses, it is important to bring them up to date as quickly as possible. This may require more than two injections at some visits. If the vaccine provider (general practitioner or practice nurse) is uncertain about how to plan the catch-up programme, they should contact the local immunisation co-ordinator/facilitator, medical officer of health, Public Health Service or the Immunisation Advisory Centre (IMAC).

Use the following instructions to help decide what doses need to be given. Where more than one vaccine is overdue, it is preferable to give the maximum possible at the first visit. For children over 15 months of age, MMR should be the priority. (See examples of catch-up programmes in Appendix 2.) For information on the Meningococcal B Immunisation Programme see chapter 15.

For children and young people up to 16 years of age:

- 1 determine the total number of antigens required
- 2 subtract the number of previous documented doses
- 3 complete the primary programme using the minimum interval of one month between doses
- 4 when a fourth dose is required, give it not less than six months after the third dose (for the booster response to occur).

## 1.4 Notifiable diseases in New Zealand

Medical practitioners who suspect or diagnose a person with certain infectious diseases are required under the Health Act 1956 to notify the local medical officer of health, so that public health prevention and control activities can occur. All diseases prevented by vaccines on the National Immunisation Schedule are notifiable. Notification should be on clinical suspicion and should not necessarily await laboratory confirmation.

The case definitions in Table 1.4 are used by the medical officer of health to classify the notified case for surveillance purposes and to assist in identifying appropriate prevention and control activities. Table 1.5 lists the laboratory tests that confirm the diagnosis.

When cases of measles are clinically diagnosed, practitioners should notify on suspicion, and obtain laboratory confirmation of the diagnosis. Similarly, when rubella is suspected, laboratory confirmation for diagnosis should be sought, especially for any decisions involving a pregnant woman. This is because diagnosis of rash in children or adults may be confusing, and it is important to identify a vaccine preventable disease with epidemic potential. Also, the World Health Organization (WHO) is moving towards world eradication of measles, and this places a greater emphasis on laboratory confirmation of the disease.

**Table 1.4: Case definitions for vaccine preventable diseases**

Disease	Clinical description	Probable case	Confirmed case
Diphtheria	An upper respiratory tract illness characterised by pharyngitis or laryngitis, low grade fever, with or without an adherent membrane of the tonsils, pharynx and/or nose, and/or toxic (cardiac or neurological) symptoms.  Cutaneous diphtheria is not notifiable, but should be discussed with the medical officer of health.	A clinically compatible illness that is not laboratory confirmed.	A clinically compatible illness that is laboratory confirmed.

Disease	Clinical description	Probable case	Confirmed case
<i>Haemophilus influenzae</i> type b (Hib) invasive disease	Invasive disease due to Hib may cause septicaemia, meningitis, epiglottitis, cellulitis, septic arthritis, pneumonia or osteomyelitis.	A clinically compatible illness or a confident diagnosis of epiglottitis by direct vision, laryngoscope or X-ray.	A clinically compatible illness with isolation of Hib from a normally sterile site.
Hepatitis B	(The acute illness but not the carrier state is to be notified.)  An illness with variable symptoms including fever, malaise, anorexia, jaundice and/or elevated serum aminotransferase levels.	A clinically compatible illness with a positive HBsAg test.	A clinically compatible illness that is laboratory confirmed with a positive anti-HBc IgM test.
Measles	Cases must meet all the following criteria: <ul style="list-style-type: none"> <li>• fever 38°C or higher</li> <li>• generalised maculopapular rash lasting three or more days</li> <li>• cough or coryza or conjunctivitis or Koplik spots.</li> </ul>	A clinically compatible illness.	A clinically compatible illness that is epidemiologically linked to a confirmed case, or is laboratory confirmed.
<i>Neisseria meningitidis</i> invasive disease	The disease presents as an acute illness with fever, nausea, vomiting and headache, and may progress rapidly to shock and death.	A clinically compatible illness.	A clinically compatible illness with one of the laboratory tests positive.

Disease	Clinical description	Probable case	Confirmed case
Mumps	<p>An illness with acute onset of fever and unilateral or bilateral tender, self limited swelling of the parotid or other salivary glands, lasting more than two days, and without other apparent cause.</p>	<p>A clinically compatible illness.</p>	<p>A case with laboratory confirmation or a clinically compatible illness that is epidemiologically linked to another case.</p>
Pertussis	<p>A disease characterised by a cough lasting longer than two weeks, and one or more of the following:</p> <ul style="list-style-type: none"> <li>• paroxysms of cough</li> <li>• cough ending in vomiting or apnoea</li> <li>• inspiratory whoop.</li> </ul>	<p>Cough lasting longer than two weeks and one or more of the following: paroxysmal cough, cough ending in vomiting or apnoea, inspiratory whoop, for which there is no other known cause.</p>	<p>A clinically compatible illness that is laboratory confirmed or that is epidemiologically linked to a confirmed case.</p>
Rubella	<p>An illness with a generalised maculopapular rash and fever and one or more of the following:</p> <ul style="list-style-type: none"> <li>• arthralgia/arthritis</li> <li>• lymphadenopathy</li> <li>• conjunctivitis.</li> </ul> <p>Rubella often presents atypically and is difficult to diagnose clinically with certainty. If accurate diagnosis is important it must be laboratory confirmed.</p>	<p>A case that meets the clinical case definition.</p>	<p>A clinically compatible illness that is laboratory confirmed or has a close epidemiological link to a laboratory confirmed case.</p>

Disease	Clinical description	Probable case	Confirmed case
Rubella (congenital)	A live or stillborn infant with clinically compatible defects (cataracts, congenital heart disease, hearing defects, microcephaly, mental retardation, purpura, hepatosplenomegaly).	A clinically compatible illness.	A clinically compatible illness that is laboratory confirmed.
Poliomyelitis	A disease, with no other apparent cause, characterised by: <ul style="list-style-type: none"> <li>• acute flaccid paralysis of one or more limbs with decreased or absent deep tendon reflexes in affected limbs</li> <li>• no sensory or cognitive loss</li> <li>• may affect bulbar muscles.</li> </ul>	A clinically compatible illness.	A clinically compatible illness in which the neurological deficit persists 60 days after the onset of symptoms or the individual has died, with no other cause.
Tetanus	Acute onset of hypertonia and/or painful muscular contractions, most commonly of the jaw and neck, which may proceed to generalised muscle spasms. The clinical presentation of tetanus may be subtle.	Nil.	A clinically compatible case.

Source: Ministry of Health. 1998. *Communicable Disease Control Manual 1998*. Wellington: Ministry of Health. (Note: during 2006 this document is being updated, and once finalised it will be placed on the Ministry of Health website [www.moh.govt.nz](http://www.moh.govt.nz).)

**Table 1.5: Microbiological and serological tests used in the diagnosis of vaccine preventable disease**

Disease	Laboratory basis for diagnosis	Specimen	When to take specimens
Diphtheria	Isolation of toxigenic <i>Corynebacterium diphtheriae</i> from a clinical specimen.	Swab from area of the lesion (eg, throat swab, or skin in case of ulcer).	At presentation of illness: must state 'query diphtheria' to ensure appropriate laboratory testing.
<i>Haemophilus influenzae</i> type b (Hib)	Isolation of Hib from a normally sterile site OR detection of a positive antigen test in cerebrospinal fluid (CSF).	CSF and/or blood culture or aspirate from normally sterile site.	At presentation of illness.
Hepatitis B (acute)	Serology (HBsAg positive and anti-HBc IgM positive) and abnormal liver function tests (LFTs).	Blood.	At presentation of illness, but may need a second specimen one week after presentation.

Disease	Laboratory basis for diagnosis	Specimen	When to take specimens
Measles	<p>Demonstration of measles specific IgM antibody*</p> <p>OR</p> <p>a significant rise in measles antibody titre (IgG)</p> <p>OR</p> <p>isolation of measles virus from a clinical specimen.</p>	<p>Blood.</p> <p>Blood.</p> <p>Urine; nasopharyngeal swab/saliva swab for virus.</p>	<p>Single specimen taken 3–4 days after onset of rash (the preferred test; if negative a repeat test may be required).</p> <p>One specimen taken at onset of illness and a second taken at least 14 days later.</p> <p>At initial presentation of illness (note: culture of virus takes up to 35 days and viral transport medium is required). Serology is preferred.</p>
<i>Neisseria meningitidis</i> invasive disease	<p>Isolation of <i>Neisseria meningitidis</i> from blood, CSF, or other normally sterile site</p> <p>OR</p> <p>detection of gram negative intracellular diplococci in blood or CSF or skin petechiae</p> <p>OR</p> <p>detection of meningococcal antigen in CSF</p> <p>OR</p> <p>positive polymerase chain reaction (PCR).</p>	Blood, CSF, other sterile site.	At presentation of illness.

Disease	Laboratory basis for diagnosis	Specimen	When to take specimens
Mumps	<p>A positive serologic test for mumps IgM antibody except following vaccine</p> <p>OR</p> <p>a significant rise in mumps antibody level by any standard serological assay, except following vaccination</p> <p>OR</p> <p>isolation of mumps virus from a clinical specimen.</p>	<p>Blood.</p> <p>Blood.</p> <p>Saliva or viral swab taken from mouth or throat.</p>	<p>At initial presentation of illness.</p> <p>One specimen taken at onset of illness and a second taken at least 14 days later.</p> <p>At presentation. Note: viral transport medium is required.</p>
Pertussis	<p>Isolation of <i>Bordetella pertussis</i> from a pernasal swab**</p> <p>OR</p> <p>PCR.</p>	<p>Isolation: pernasal swab.</p> <p>PCR: nasopharyngeal swab; for PCR ensure correct swab is used (ie, not wooden handle and not cotton tipped).</p>	<p>At initial presentation of clinically compatible illness.</p>
Poliomyelitis	<p>Two faecal specimens collected at least 24 hours apart 0–14 days after the onset of paralysis are to be collected and sent to ESR.***</p> <p>(Acute poliomyelitis titres may assist diagnosis, but viral isolation and identification are required to confirm a case of poliomyelitis.)</p>	<p>Faeces.</p> <p>Blood.</p>	<p>At initial presentation of illness and a second specimen collected at least 24 hours later.</p> <p>At initial presentation and 14 days later.</p>

Disease	Laboratory basis for diagnosis	Specimen	When to take specimens
Rubella	<p>Demonstration of rubella specific IgM antibody, except following immunisation</p> <p>OR</p> <p>a four-fold rise in rubella antibody titre between acute and convalescent sera</p> <p>OR</p> <p>isolation of rubella virus from a clinical specimen.</p>	<p>Blood.</p> <p>Blood.</p> <p>Nasopharyngeal swab.</p>	<p>Four days after onset of illness.</p> <p>One specimen at onset of illness and second specimen 14 days later.</p> <p>Taken within three days of initial presentation of illness. (Note: rubella virus isolation rate is poor and takes four weeks. Viral transport medium is required. Serology is the preferred test.)</p>

Disease	Laboratory basis for diagnosis	Specimen	When to take specimens
Rubella (congenital)	<p>Isolation of rubella virus from a clinical specimen from the infant</p> <p>OR</p> <p>demonstration of rubella specific antibody (IgM) in the infant's serum</p> <p>OR</p> <p>persistence of rubella specific IgG antibody of titre higher than expected from passive transfer of maternal antibody</p> <p>OR</p> <p>laboratory confirmed maternal rubella infection in the first trimester of pregnancy.</p>	<p>Throat swab.</p> <p>Blood.</p> <p>Blood.</p> <p>Blood.</p>	<p>At birth. (Note: rubella virus isolation rate is poor and takes four weeks. Viral transport medium is required. Serology is preferred test.)</p> <p>Cord blood specimen.</p> <p>One specimen at birth and second specimen 14–21 days later.</p> <p>Two maternal blood tests in first trimester of pregnancy (see rubella diagnosis).</p>
Tetanus	None.	None.	

\* Measles IgM is needed to initiate public health action but viral isolation or change in IgG or PCR is needed to confirm diagnosis.

\*\* When testing for pertussis, alternative serological tests may be available. Serology is not accepted as a confirmatory test for surveillance in the *Communicable Disease Control Manual 1998* (Ministry of Health). A case diagnosed from clinical findings and positive serology would be classified as 'probable' and not 'confirmed'. Blood should be taken at the initial clinical presentation and a second specimen taken at least four days later. A positive serological test for pertussis IgA and/or IgM or rising titres would be indicative of recent infection.

\*\*\* ESR – Institute of Environmental Science and Research.

## 1.5 Vaccine types and composition

Vaccines are an antigenic preparation used to produce active immunity to a disease. There are two basic types:

- vaccines that use living, attenuated (weakened) strains of viruses or bacteria
- vaccines that use the killed whole virus or bacterial organism, or purified products derived from them.

### Live vaccines

To produce a live vaccine, such as MMR or varicella, the 'wild' or disease causing virus is attenuated or modified through repeated culture in the laboratory. This process reduces the virulence (ability to produce disease) properties of the virus so that it does not cause disease. It does, however, still generate an immune response that is protective against the wild virus. The attenuated vaccine virus multiplies to a limited extent in host tissue and induces the same immune response as the wild virus infection in the majority of subjects. Live vaccines are generally very effective and induce long lived immunity.

In some instances (eg, varicella vaccine in adults), more than one dose may be needed because replication of the vaccine virus, and hence immunity, does not always result from the first dose. Booster doses may be needed to maintain antibody levels.

### Inactivated vaccines

Whole cell, toxoid, subunit, recombinant and conjugate vaccines all come under the category of inactivated vaccines, in that they are non-infectious but retain the ability to stimulate the immune system. These are explained below.

#### *Whole cell vaccines*

Growing whole bacteria or viruses (eg, inactivated influenza or inactivated poliomyelitis vaccine) in culture media, then treating them with heat and/or chemicals, produces an inactivated, non-viable vaccine. These micro-organisms cannot cause an infection because they are dead.

#### *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 purifying the toxin and altering it chemically (usually with formaldehyde). While no longer toxic, the toxoid is still capable of inducing a specific immune response protective against the effects of the toxin.

#### *Subunit vaccines*

The whole organism is grown in culture media and then the organism is further treated to purify only those components to be included in the vaccine (eg, acellular

pertussis and the meningococcal B vaccine, MeNZB™). The use of subunit vaccines has greatly reduced the number of antigens given to children. Despite an increase in the number of vaccines given to children in the last two to three decades, the total number of antigens has significantly decreased.

### *Recombinant vaccines*

For example, the hepatitis B vaccine is made by inserting a segment of the hepatitis B virus gene into a yeast cell. The modified yeast cell produces large amounts of hepatitis B surface antigen, which is purified and harvested and used to produce the vaccine. The recombinant hepatitis B vaccine is identical to the natural hepatitis B surface antigen, but does not contain virus DNA, and is therefore unable to produce infection.

### *Conjugated vaccines*

Children under two years of age do not respond well to antigens such as polysaccharides, which produce antibodies via a T-cell independent mechanism. If these polysaccharide antigens are chemically linked (conjugated) to a protein that T-cells recognise, then these conjugate vaccines can elicit strong immune responses and immune memory in young children. For example, the *H. influenzae* type b (Hib) vaccine is made from combining the bacterial polysaccharide cell coat (PRP, which is poorly immunogenic in children) with a protein carrier – either tetanus toxoid (hence PRP-T), or an outer membrane protein from *N. meningitidis* (hence PRP-OMP). Conjugating the polysaccharide to the protein in this way makes them more easily recognised by the immune system of young children, and therefore produces long lasting immunity from an earlier age than would otherwise be possible.

The different types of vaccines are summarised in Tables 1.6 and 1.7.

**Table 1.6: Bacterial vaccines**

Inactivated	Live attenuated
Toxoid: <ul style="list-style-type: none"> <li>diphtheria</li> <li>tetanus.</li> </ul> Conjugate: <ul style="list-style-type: none"> <li><i>Haemophilus influenzae</i> type b</li> <li>meningococcal C (conjugate)</li> <li>pneumococcal conjugate.</li> </ul> Subunits: <ul style="list-style-type: none"> <li>acellular pertussis</li> <li>pneumococcal polysaccharide</li> <li>meningococcal A, C, Y &amp; W135</li> <li>MeNZB™.</li> </ul>	tuberculosis – BCG

**Table 1.7: Viral vaccines**

Inactivated	Live attenuated
Whole cell: <ul style="list-style-type: none"> <li>inactivated poliomyelitis – IPV Salk</li> <li>hepatitis A.</li> </ul> Recombinant: <ul style="list-style-type: none"> <li>hepatitis B.</li> </ul> Subunit: <ul style="list-style-type: none"> <li>influenza A and B.</li> </ul>	<ul style="list-style-type: none"> <li>measles</li> <li>mumps</li> <li>rubella</li> <li>varicella zoster</li> <li>oral polio (OPV)</li> </ul>

**Other compounds in vaccines**

Other compounds may be added to vaccines as part of their preparation as *inactivating agents* (eg, formaldehyde), as *preservatives* (eg, phenoxyethanol), as *stabilisers* (eg, human serum albumin, lactose, sorbitol, hydrolysed gelatin, neomycin, magnesium chloride), or as *adjuvants* to enhance the immune response (eg, aluminium hydroxide or phosphate). These additives are present in very small quantities and comply with WHO guidelines.

*Inactivating agents* are chemical agents used in the manufacture of certain vaccines made from components of bacteria or viruses (eg, formaldehyde is used to inactivate the tetanus toxin protein used to manufacture the tetanus vaccine). The product is then further purified to remove any contaminants and any excess formaldehyde. The resulting vaccine may contain minute traces of formaldehyde. The vaccines used in New Zealand contain well below the standard limit for traces of formaldehyde set by the WHO.

*Preservatives* are added to vaccines to prevent bacterial growth where there is risk of contamination (eg, when the vaccine is prepared in multidose vials). As a precaution, thiomersal is no longer used as a preservative in vaccines on the usual National Immunisation Schedule even though there is no evidence that it represented a danger. However, thiomersal is found in both child and adult doses of the combination diphtheria tetanus vaccines (CDT™ and ADT™; 0.01 percent w/v), and in some influenza vaccines.

*Stabilisers* are added to vaccines to maintain their effectiveness and thermal stability, because the storage and transportation of vaccines can be easily compromised. Examples are human serum albumin, lactose and sorbitol. There is no risk of transmitting blood borne viruses from human serum albumin in vaccines.

*Adjuvants* are added to vaccines to enhance the protective response. The main functions of adjuvants such as aluminium hydroxide or phosphate are to keep the antigen near the injection site and to activate the special antigen presenting cells of the immune system. The amount of adjuvant varies from 0.25 mg to 0.5 mg per dose, depending on the vaccine. There is no evidence that aluminium hydroxide or phosphate given intramuscularly causes toxic effects. They do, however, enhance the local immune response, which is essential for the induction of a good immune response. Thus a localised injection reaction may occur. They are *not* adverse events (AEFI). (See section 20.2c for further information on vaccine content.)

### **Transfer of biological products: minimising the risk from animal products**

The development of a rapidly progressive neurological disease (variant Creutzfeldt-Jakob disease, vCJD) in people presumed to be infected by exposure to tissue from cows with bovine spongiform encephalopathy (BSE) has raised concern about exposure to bovine products. The estimated risk of acquiring vCJD as a result of vaccination is generally agreed to be extremely small (or infinitesimal). (See also chapter 20: Vaccination Questions and Concerns.)

*Animal products:* vaccine manufacturers are required to source bovine products from BSE free countries. New Zealand is one of the few countries in the world certified BSE free.

*Blood products:* there is a theoretical risk of transfer of prion protein in a vaccine made using blood products. Human serum albumin is currently used during MMR manufacture. However, donors are carefully selected, and in future years synthetic human albumin will be used.

### **Concurrent administration of vaccines**

In general, it is not recommended that the schedule of vaccines or the timing of visits be changed to avoid giving multiple injections at a visit (see chapter 2). Increasing the number of visits may lead to incomplete immunisation.

Vaccines, including live virus vaccines, may be given concurrently, unless the manufacturer makes a specific recommendation against it. *Where a number of different injectable vaccines are given on the same day, they must be administered in separate syringes, at different sites.*

Some combination vaccines have a liquid and lyophilised component and are specifically designed to be mixed just prior to administration.

There are concerns about impaired immune responses to other vaccines shortly after exposure to live viral vaccines. For this reason it is suggested that other vaccines should not be administered within a four-week period after vaccination with live viral vaccines. In particular, if a live attenuated viral vaccine is given within four weeks of another viral vaccine it may result in unexpected adverse reactions due to this lowered state of immunity.

### **Use of unapproved vaccines**

#### *Vaccines unlicensed for distribution in New Zealand*

It is possible for authorised prescribers and medical practitioners to use products that are not yet licensed for distribution in New Zealand under the terms that are set out in sections 25 and 29 of the Medicines Act 1981. For further information on the risks and benefits of using an unlicensed product in New Zealand, refer to the Medsafe website: [www.medsafe.govt.nz](http://www.medsafe.govt.nz).

#### *Other vaccines licensed for distribution in New Zealand*

There are vaccines licensed for distribution in New Zealand but not publicly funded by the Ministry of Health. Health professionals can, however, purchase vaccines directly from the manufacturer. Manufacturer's contact details can be found in the back of the *MIMS New Ethicals*.

## **1.6 Adolescent and adult vaccination**

An important proportion of vaccine preventable disease now occurs in adolescents and adults. People who escaped natural infection as children, or were not vaccinated against hepatitis B, pertussis, measles, mumps, rubella, diphtheria, tetanus and poliomyelitis, are at risk of these diseases and their complications.

### **Adolescent and adult vaccination**

When adolescents and adults are seen in general practice or by vaccination providers, there is an opportunity to ensure that they have been adequately protected against the following diseases and have received at least a primary immunisation course of:

- tetanus            3 doses
- diphtheria        3 doses
- hepatitis B        3 doses (depending on age and other health factors)

- polio 3 doses
- measles 1 dose (all people born between 1969 and 1990 should have received 2 doses of measles containing vaccine, see chapter 9: Measles)
- mumps 1 dose
- rubella 1 dose.

If the requisite number of doses has not been received, catch-up vaccination should be offered. The vaccines and the administration of all Schedule vaccines are available free of charge up to the 16th birthday. Females should be offered testing to ensure that they are immune to rubella. All should be reminded of the necessity for age appropriate boosters against tetanus and diphtheria.

### *Checklist for adult vaccination*

The following vaccines are recommended and publicly funded:

- Td vaccine at 45 and 65 years of age (note: the administration charge for the Td booster is not publicly funded; see section 5.5).
- Influenza vaccine for those 65 years of age and over, and those under 65 years who meet the chronically ill criteria (see chapter 13: Influenza).
- MMR for any individual susceptible to any one of these three diseases (see relevant chapters).
- Hepatitis B vaccine for household and sexual contacts of known hepatitis B carriers (see chapter 3: Hepatitis B).
- Pneumococcal, Hib, meningococcal A, C, Y, W135 vaccines for individuals pre- and post-splenectomy (see relevant chapters).

Adult females of childbearing age should know whether or not they are immune to rubella.

The following vaccines are recommended but not publicly funded (although they may be available through hospitals):

- pneumococcal polysaccharide vaccine for those 65 years of age and over and those at risk (this includes immune competent persons at risk because of chronic illness, individuals with chronic CSF leaks and immune compromised individuals) (see chapter 16)
- hepatitis B for adults at risk (see chapter 3)
- varicella, if susceptible (see chapter 17).

All travellers should be encouraged to consider vaccination requirements well in advance of overseas travel. Information on vaccination for adults is included in the appropriate sections of this Handbook. Information can also be obtained in the Ministry of Health publication *Health Advice for Overseas Travellers* 1996.

## 1.7 Special groups: immigration, work and pregnancy

### Immigrant and refugee children

Adults and children who enter New Zealand as refugees or immigrants require assessment in regard to their vaccination requirements.

Assess the immunisation status of the presenting child and determine which catch-up vaccinations the child should receive. Children who have been previously immunised in a non-industrialised country may have received BCG, three doses of DTwP and OPV in the first six months of life, and a dose of measles vaccine between 9 and 15 months of age. However, they are unlikely to have received Hib or MMR vaccine, unless they have come from an industrialised country. Increasing numbers of countries have hepatitis B vaccine included in their national childhood immunisation schedule.

**If a refugee or immigrant child has no valid documentation of vaccination, an age appropriate catch-up programme should be commenced (see Appendix 2).**

If there is a valid record of vaccination, the history of prior doses should be taken into account when planning a vaccination catch-up that complies with the New Zealand programme.

Tuberculosis is an important public health problem for refugees. Figures from the United States (US) show that approximately 1–2 percent of refugees are suffering from active tuberculosis on arrival, and about half have positive tuberculin skin tests. The number who have received BCG immunisation is unknown. It is important that all refugee children be skin tested with the Mantoux tuberculin test at the time of the first visit and, if negative, tested again three months later to identify recently acquired infection. Previous BCG immunisation should be considered when interpreting Mantoux results. A chest X-ray is recommended if the Mantoux is > 10 mm following BCG, or > 5 mm without a previous history of BCG.

In New Zealand the policy is to provide BCG vaccination to newborns at increased risk of tuberculosis (see section 1.3 and chapter 12 for more details on the neonatal BCG eligibility criteria).

The prevalence of chronic hepatitis B infection in refugees from eastern Asia is estimated to be 10–15 percent. If a member of the family is found to have chronic hepatitis B infection, it is recommended all the family be screened and immunisation offered to all susceptibles. If no one in the family is a carrier, all children under 16 years of age should be offered immunisation against hepatitis B.

For details of immunisation schedules of other countries, contact your local immunisation co-ordinator/facilitator, medical officer of health or IMAC.

## Immunisation of those at occupational risk

Certain occupations are at increased risk of contracting some of the vaccine preventable diseases. Immunisation is recommended and *may not* be publicly funded. It may be employer funded. The following vaccines should be considered for certain occupational groups.

**Table 1.8: Recommended vaccines, by occupational group**

Occupation	Recommended vaccines	Vaccines to consider
Early childhood services staff	Hepatitis B, MMR, influenza, varicella (if susceptible)	Hepatitis A; dTap
Medical, nursing, other health professionals and students	Hepatitis B, MMR, influenza	Varicella (if susceptible and those working in high risk areas); BCG and hepatitis A; dTap for paediatric ward staff
Laboratory staff	Hepatitis B, MMR, influenza; MeNZB™ (while the vaccine is available)	
Health care assistants, long term facility carers	Hepatitis B, MMR, influenza	
Police	Influenza, hepatitis B	
Sewerage workers	IPV, hepatitis A	

## Vaccination during pregnancy

Because of the theoretical possibility of harm to the fetus, live vaccines should not be administered to a pregnant woman. In some circumstances where there is increased risk of exposure to the micro-organism, the need for immunisation may outweigh any possible risk to the fetus. Women who are to receive the rubella vaccine (as MMR) are advised to ensure they are not pregnant at the time of immunisation and for at least 28 days afterwards. There is no current evidence that rubella vaccine is teratogenic (see section 11.7). The influenza vaccine is recommended for at risk pregnant women, and may be offered to women in the second and third trimester of pregnancy (see chapter 13).

## 1.8 Special risk groups: medical conditions

Some conditions increase the risk from infectious diseases, and children with such conditions should be immunised as a matter of priority. These conditions include chronic diseases, and immune deficient and immune compromised individuals. Special care is required with some live vaccines. When considering immunising children at risk, seek advice from the child's paediatrician.

## **Preterm infants**

Preterm infants and other infants with low birthweight should be immunised at the usual chronological age with the usual vaccine dosage.

If an infant is still in hospital when immunisations are due, the DTaP-IPV and Hib-Hepatitis B vaccines should be given at the scheduled chronological age. Babies who weigh under 2 kg have a sub-optimal response to hepatitis B vaccine, so immunisation may need to be deferred (see section 3.5). In New Zealand, some neonatal units give Hib-Hepatitis B at six weeks of age (chronological age); others when the baby weighs 2 kg. However, all pre-term infants born to HBsAg positive mothers should receive immune prophylaxis (HBIG and hepatitis B vaccine) as soon as possible after birth. Available data suggests very low birthweight infants have a less adequate antibody response to Hib-OMP vaccine and an extra dose is recommended at age five months, (see chapter 7). The response may be decreased in chronically sick infants.

Preterm infants who develop chronic respiratory disease should be given influenza vaccine at six months of age, and a second dose one month later (influenza vaccine is usually available from March to June each year). Further protection of infants with these and other chronic conditions should be ensured by immunising the family and caregivers, including hospital personnel.

## **Immune deficient children**

For information on the pneumococcal immunisation programme for high risk children, see chapter 16: Pneumococcal Disease.

Diagnosis of immune deficient children is often not made before children start their immunisation schedules. However, no live virus vaccines are given in the first year of life. For children with immune suppression, consult their specialist about a suitable immunisation schedule.

The safety and effectiveness of vaccines in people with immune deficiency are determined by the nature and degree of immune suppression. Immune deficiency conditions may be divided into primary and secondary. Primary immune deficiencies that present in childhood are generally inherited, and include antibody deficiency (disorders of B lymphocytes or antibody production), defects of cell mediated immunity (disorders of T lymphocytes, which most often present as combined defects affecting antibody production as well), and defects of complement and phagocytic function. Secondary disorders of the immune system are acquired, and occur in people with human immunodeficiency virus (HIV), malignant neoplasms or transplantation, and in people receiving immune suppressive treatment or radiotherapy (see Table 1.9).

Experience with vaccine administration in immune suppressed children is limited.

*Live vaccines* (these include MMR, varicella and BCG) should not in general be given to people who are severely immune suppressed, either viral or bacterial, because of the risk of disease from vaccine strains.

*Inactivated vaccines* (IPV, DTaP, hepatitis B, Hib, pneumococcal and influenza) may be administered since the risk of adverse reactions is not increased in immune suppressed children. However, the response of immune suppressed children to these inactivated vaccines may be inadequate. In children with a secondary immune deficiency, their ability to develop an adequate immunological response depends on when immune suppression occurs. In children in whom immune suppressive therapy is discontinued, an adequate response usually occurs between three months and one year after discontinuation. Influenza vaccine should be given to immune suppressed children before each influenza season, and to children receiving chemotherapy for malignant neoplasm three to four weeks after chemotherapy is discontinued, when both the peripheral granulocyte and lymphocyte counts are  $> 1.0 \times 10^9/L$ .

#### *Primary immune deficiencies*

Live vaccines are contraindicated for most children with B lymphocyte defects (except IgA deficiency), and for all children with T lymphocyte mediated disorders of immune function. Most of these children will be on intravenous immunoglobulin (IVIG) replacement therapy, which provides passive protection against most vaccine preventable infections. Seek specialist paediatric advice. (See Table 1.9.)

#### *Secondary (acquired) immune deficiencies*

Factors to consider when immunising children with secondary immune deficiency include the underlying disease, the dose and schedule of the immune suppressive drugs, the infectious disease, and the immunisation history of the child. Live vaccines, generally, are contraindicated because of the risk of serious adverse effects. Exceptions are children with HIV infection who are not severely immune compromised, in whom MMR is recommended. Varicella vaccine is recommended for children with HIV infection with CD4+ T lymphocyte values of 25 percent or greater. Live virus vaccines should be withheld until at least three months after cessation of immune suppressive cancer chemotherapy, and tests of immune function may be used to guide safe timing. Recommendations for children on corticosteroids are given below. Seek specialist paediatric advice.

#### *Other considerations*

Children with a primary or secondary immune deficiency may not respond adequately to an immunising agent. Specific serum antibody titres should be determined to guide future management of exposures and vaccine.

People with certain immune deficiencies may benefit from specific vaccines to prevent diseases to which they are particularly susceptible. Pneumococcal and meningococcal vaccine are indicated to those with splenic dysfunction, asplenia and complement deficiencies, who are at increased risk of infection from encapsulated bacteria. Influenza vaccine is indicated for children with splenic dysfunction, asplenia, and phagocyte function deficiencies to prevent influenza and reduce risk of secondary bacterial infections.

*Household contacts*

Immunologically competent siblings and household contacts may receive all the National Immunisation Schedule vaccines, particularly IPV and MMR. There is no risk of transmission of the IPV or MMR vaccine viruses to the immune compromised individual. However, it is important to ensure that close household contacts are immune for the added protection of the immune suppressed individual. Varicella vaccine can be given safely to household contacts of immune suppressed children.

Oral polio vaccine, which was contraindicated in households where immune suppressed individuals lived, is no longer available in New Zealand.

A summary of the appropriate immunisation for children with primary and secondary immune deficiencies is given in Table 1.9.

**Table 1.9: Immunisation of children with primary and secondary immune deficiencies<sup>1</sup>**

Category	Specific immune deficiency	Vaccine contraindications	Efficacy and comments
<b>Primary</b>			
B lymphocyte (humoral)	X-linked and common variable immune deficiency	Live bacterial vaccines, MMR and varicella	The efficacy of any vaccine dependent on humoral response is doubtful; IVIG interferes with the response to live vaccines and provides passive protection.
	Selective IgA deficiency	Nil	All vaccines are probably effective.
T lymphocyte (cell mediated and humoral)	Severe combined immune deficiency	All live vaccines <sup>a,b</sup>	The efficacy of any vaccine dependent on humoral or cellular response is doubtful.

Category	Specific immune deficiency	Vaccine contraindications	Efficacy and comments
Complement	Deficiency of early components (C1, C4, C2, C3)	None	All routine vaccines are probably effective; pneumococcal and meningococcal are recommended.
	Deficiency of late components (C5–9), properdin, factor B	None	All routine vaccines are probably effective; meningococcal vaccine is recommended.
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defect, myeloperoxidase deficiency	Live bacterial vaccines <sup>b</sup>	All routine vaccines are probably effective; consider influenza vaccine.
<b>Secondary</b>			
	HIV/AIDS	BCG; withhold MMR and varicella in severely immunocompromised children	MMR, varicella and all inactivated vaccines may be effective. <sup>c</sup>
	Malignant neoplasm, transplantation, immune suppressive or radiation therapy	Live viral and bacterial, depending on immune status <sup>a,b</sup>	The effectiveness of any vaccine depends on the degree of immune suppression.

Key: IVIG: intravenous immunoglobulin; IgA: immunoglobulin A; HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; BCG: Bacille Calmette-Guérin; MMR: measles, mumps and rubella.

a Live viral vaccines (MMR, varicella).

b Live bacterial vaccines (BCG).

c HIV infected children should receive IG after exposure to measles and may receive varicella vaccine if CD4+ count  $\geq 25$  percent.

### *Children receiving corticosteroids<sup>2</sup>*

Children who receive corticosteroid therapy can become immune suppressed. The minimal amount of corticosteroid and duration of administration sufficient to cause immune suppression is not well defined, and is dependent on dose, duration and underlying disease. Many clinicians consider a daily dosage equivalent to 2 mg/kg

prednisone or greater, or a total daily dosage of 20 mg or greater, particularly when given for 14 days or more, is sufficient to raise concern about the safety of live virus vaccines.

This guide may be used for safe live virus vaccine administration to children on corticosteroids.

- Topical therapy or local injections of corticosteroids, including on skin or respiratory tract (by aerosol) or intra-articular, bursal or tendon injections, usually do not result in immune suppression, and live virus vaccines may be given after topical therapy.
- Children on maintenance physiologic doses of corticosteroids can receive live virus vaccine while on treatment.
- Children on low to moderate doses of systemic steroids given daily or on alternate days can receive live virus vaccines. This includes children receiving less than 2 mg/kg per day prednisone or less than 20 mg/day if they weigh more than 10 kg, or an equivalent dose of another short acting systemic corticosteroid.
- Children receiving high dose corticosteroids daily or on alternate days for fewer than 14 days (eg, children receiving 2 mg/kg of prednisone, or up to 20 mg if the child weighs more than 10 kg) can receive live virus vaccines immediately on discontinuation of treatment. Some experts would delay immunisation for two weeks if possible.
- Children receiving high dose corticosteroids daily or on alternate days for more than 14 days (eg, children receiving 2 mg/kg of prednisone, or 20 mg or more if the child weighs more than 10 kg) should not receive live virus vaccines until the corticosteroid therapy has been discontinued for at least one month.
- Children who have a disease process which causes immune suppression, and who are being treated with either systemic or locally administered corticosteroids, should not be offered live virus vaccines except in special circumstances.

Note: these guidelines are made to ensure safety of administration of the live virus vaccine and may not achieve optimal vaccine immunogenicity.

### **Hodgkin's disease**

Patients suffering from Hodgkin's disease should be immunised with Hib and pneumococcal vaccines (see chapters 7 and 16) according to age specific recommendations, and have their routine childhood vaccines and MeNZB™ updated as required. Quadrivalent meningococcal vaccine should also be considered. The antibody response is best if immunisation is undertaken 10–14 days prior to the initiation of any chemotherapy. If given during chemotherapy or shortly after its cessation, the antibody response will be sub-optimal. The immune system recovers quickly and immunisation can be carried out three months after chemotherapy

ceases. For children who received immunisation during therapy, the vaccines should be re-administered three months after discontinuation of therapy.

### **Children and adults receiving chemotherapy or immune suppressive therapy**

Live virus vaccines (see chapters 9–11 and 17) are generally contraindicated because of the risk of serious adverse effects. An exception appears to be the judicious use of live varicella vaccine in children with acute lymphocytic leukaemia in continuous remission of at least one year, whose total lymphocyte count is  $> 0.7 \times 10^9/L$  and in whom the risk of natural varicella far outweighs the risk from attenuated vaccine virus. Inactivated vaccines may be used where appropriate, but the immune response is likely to be sub optimal and following exposure passive immunisation with IG is likely to be required.

After cessation of immune suppressive therapy, live virus vaccines are generally withheld for an interval of not less than three months. The interval may need to be extended according to the intensity and type of the immune suppressive therapy, radiation therapy, underlying disease and other factors.

### **Bone marrow transplant**

Many factors can affect transplant recipients' immunity to vaccine preventable diseases following a successful marrow transplant. These include the donor's immunity, the type of transplant, the interval since the transplant, the continuing use of immune suppressive drugs, and graft versus host disease (GVHD). Some recipients acquire the immunity of the donor, but others lose all serological evidence of immunity. Serological tests should be carried out to establish immunological status 12 months after bone marrow transplant and prior to immunisation. If tests are not available, the patient should be reimmunised according to the appropriate catch-up schedule (see Appendix 2).

One study suggests that three doses of tetanus toxoid are required after bone marrow transplant to achieve adequate immunity. Information regarding the response to diphtheria toxoid is not available, but at least three doses will be required. As noted above, the usual childhood immunisations should be given for under seven years of age, and after the seventh birthday Td should be given. No data is available about the other inactivated bacterial vaccines (pneumococcal, meningococcal or Hib), but for maximum benefit all should be delayed for at least one year after transplant.

Healthy survivors of bone marrow transplant can be given MMR vaccine two years after transplant, but the vaccine should not be given to individuals suffering from GVHD, because of a risk of a resulting chronic latent virus infection leading to central nervous system sequelae.<sup>3</sup> It is important to ensure that household contacts are immune to infectious diseases wherever possible. Household contacts may be safely given MMR (see chapter 9). IPV can be given to transplant recipients and their household contacts (see chapter 8).

## Solid organ transplants

Children older than 12 months who have been scheduled for solid organ transplantation should receive the MMR vaccine at least one month before the transplant. Measles antibody titres should be measured one to two years after the transplant; immunisation may be repeated if titres are low. It may be advisable to check other antibody titres and reimmunise where indicated. The use of passive immunisation with IG should be based on the documentation of negative antibody titres and a positive history of exposure to the disease. See chapter 16 for further information regarding pneumococcal immunisation for these children.

## HIV infection

For children with HIV infection, discuss with their specialist the recommendations for immunisation. HIV positive children ( $CD4+ > 14$  percent), whether symptomatic or asymptomatic, should follow the routine immunisation schedule, including MMR. No ill effects have been reported following administration of MMR vaccines to HIV positive individuals, who are at increased risk from these three diseases.

The efficacy of any vaccine may be reduced in HIV positive individuals. Serological testing and the need for additional doses should be discussed with the child's specialist.

Passive immunisation with IG should be considered in HIV positive individuals exposed to measles, even if they have received measles immunisation (see section 9.8). Zoster immunoglobulin (ZIG) should be offered to HIV positive individuals who have not been infected with clinical chickenpox or who can be shown to be non-immune following exposure to chickenpox or shingles. ZIG should be given within 72 hours of exposure but may still have some effects up to seven days later (see section 17.8). For information on varicella vaccine see chapter 17. In general varicella vaccine may be safely given to children at CDC A1 or N1 ie,  $CD4+ \geq 25$  percent.

Since influenza has not caused excessive morbidity in HIV infected individuals, this vaccine is not routinely recommended for HIV positive individuals.

For other vaccines, see specific disease chapters (chapter 15 for meningococcal invasive disease, chapter 16 for pneumococcal disease).

## Asplenic children

There are three general reasons why individuals may not have a functioning spleen:

- surgical removal (eg, post trauma)
- disease (eg, sickle cell disease, thalassaemia)
- congenital asplenia.

All asplenic individuals are at increased risk of fulminant bacteraemia, which is associated with a high mortality rate. The risk is greatest for infants, and probably

declines with age and with the number of years since onset of asplenia. The degree of risk of mortality from sepsis is also influenced by the nature of the underlying disease, being increased 50 times (compared with healthy children) in asplenia after trauma, 350 times in asplenia with sickle cell disease, and even higher in asplenia with thalassaemia.

The organisms that most commonly cause fulminant sepsis in these individuals are *Streptococcus pneumoniae* (most frequent), *N. meningitidis*, *H. influenzae* type b, and *Escherichia coli*. Less commonly, infection may be caused by other streptococci, *Staphylococcus aureus* and gram-negative coliforms (eg, *Klebsiella*, *Salmonella* sp and *Pseudomonas aeruginosa*). There is an increased fatality from malaria for asplenic individuals.

If possible, splenectomy should be avoided or delayed, accessory spleens should be preserved, hemisplenectomy should be performed during staging for Hodgkin's disease, and partial splenectomy should be performed for benign splenic tumours.

The following vaccines are recommended in addition to the normal National Immunisation Schedule:

- pneumococcal vaccine – for recommendations for pneumococcal conjugate vaccine (PCV 7) and polysaccharide pneumococcal vaccine (23 PPV) for all asplenic children and adults see also below, and chapter 16.
- quadrivalent meningococcal polysaccharide vaccine for all asplenic children two years of age or older (see chapter 15 for adult recommendations); conjugate meningococcal group C vaccine may be given to children under two years of age.

Because of an increased risk of infection it is particularly important that asplenic children, whatever their age, receive the Hib vaccine schedule as per the National Immunisation Schedule.

Pneumococcal vaccine appears to reduce the risk of fulminant pneumococcal bacteraemia in asplenic children. The efficacy of other bacterial vaccines (eg, Hib) in these circumstances is not clearly established, but they are probably as effective as pneumococcal vaccine.

### *Antimicrobial prophylaxis*

The effectiveness of antimicrobial prophylaxis in asplenic children was proven only for sickle cell disease, but should be strongly considered for all children under five years of age and for at least one year after splenectomy. Monthly benzathine penicillin injections have been shown to reduce episodes of pneumococcal bacteraemia in asplenic children as compared with rates observed in untreated children. Oral penicillin daily also reduces the incidence of severe bacterial infection by 84 percent in asplenic children, compared with rates observed in placebo treated controls.

It is reasonable to extrapolate these data to other asplenic children with a high risk of bacteraemia (eg, asplenic children with malignancies, thalassaemia, etc). There is less agreement regarding the use of chemoprophylaxis in children who have been splenectomised following trauma.

Chemoprophylaxis should be recommended for:

- asplenic children five years of age and under
- for older asplenic children at least two years post-splenectomy.

There are no studies that help decide the age at which chemoprophylaxis should be discontinued. This decision has to be made according to clinical judgement.

The dosage given is as follows:

- under five years of age: 125 mg bd oral penicillin
- five years of age and older: 250 mg bd oral penicillin.

An alternative recommended by some experts is amoxicillin 20 mg/kg per day.

Parents/caregivers should be advised that all febrile illnesses are potentially serious and that they should seek immediate medical help in these circumstances. Patients should be hospitalised if bacteraemia is a possibility. In hospital, the usual treatment would be cefotaxime, ceftriaxone, or another regimen effective against *S. pneumoniae*, *H. influenzae* type b and *N. meningitis*.

## 1.9 Contraindications

No child should be denied immunisation without serious consideration of the consequences, both for the individual child and for the community. Where there is any doubt, seek advice from the child's general practitioner, a public health medicine specialist, medical officer of health, or consultant paediatrician. If there is concern about the risk of anaphylaxis, the child may be vaccinated in a controlled environment.

### General contraindications

#### *Acute febrile illness*

Minor infections without significant fever or systemic upset are not contraindications to immunisation. The decision to administer or delay immunisation because of a current or recent acute illness depends on the severity of the illness and the aetiology of the disease.<sup>4</sup> All vaccines can be administered to persons with minor acute illness (eg, diarrhoea or mild upper respiratory tract infections), but should be postponed if the subject has a significant fever over 38°C.

**Table 1.10: Examples of vaccine specific contraindications**

Vaccine	Contraindications
Any vaccine	<ul style="list-style-type: none"> <li>• Anaphylaxis/allergy to any vaccine component</li> <li>• Anaphylaxis reaction to a prior dose or to any vaccine component</li> <li>• Moderate or severe acute illness (<math>T &gt; 38.0^{\circ}\text{C}</math>)</li> </ul>
DTaP, dTap	<ul style="list-style-type: none"> <li>• Previous encephalopathy within seven days after DTWPH, DTWP or DTaP</li> <li>• Evolving (undiagnosed) neurological problem</li> </ul>
MMR	<ul style="list-style-type: none"> <li>• Live vaccine within 4 weeks</li> <li>• Immune suppressed individuals</li> <li>• If blood, plasma or immunoglobulin was given within the last 11 months (see Table 1.11)</li> </ul>
Influenza, yellow fever	<ul style="list-style-type: none"> <li>• Anaphylaxis to egg or chickens</li> </ul>

## Precautions

### *Reaction to a previous dose*

Careful consideration will be needed depending on the nature of the reaction. If in doubt about the safety of future doses, seek specialist advice. An anaphylactic reaction to a previous dose is a contraindication to further doses of that vaccine.

### *Allergy to vaccine components*

Delayed type hypersensitivity to the traces of antibiotics (eg, neomycin in MMR) is not a contraindication to the vaccine. If an individual has had anaphylaxis to an antibiotic contained in the vaccine, seek specialist advice.

Egg allergy is not a contraindication to the measles or MMR vaccines. Large studies have confirmed these children can be vaccinated safely.<sup>5</sup> Other components of the vaccine (eg, gelatin<sup>6</sup>) may be responsible for allergic reactions. Anaphylaxis to a prior dose of MMR is a contraindication to a further dose.

It is therefore recommended that any child who has a history of anaphylaxis with cardiorespiratory symptoms should be vaccinated under close supervision, with adrenaline and age appropriate resuscitation equipment immediately available. Vaccinators must be aware of the possibility that allergic reactions, including anaphylaxis, may occur after vaccination without any apparent risk factors (see chapter 2).

### *Recent receipt of another vaccine, blood or immunoglobulin product*

There are theoretical concerns about impaired immune responses if two live virus vaccines are given within four weeks of each other, and there is evidence<sup>7</sup> to substantiate these concerns. If two live virus vaccines are not given concurrently, doses should be separated by four weeks, where possible.

Live virus vaccines should be given at least three weeks before, or up to six months after, doses of human normal immunoglobulin. This is because immunoglobulin may interfere with the response to live viral vaccines. This interference may extend beyond three months for the measles vaccine, depending on the dose given. MMR should be given three weeks before or up to six months after receipt of blood or immunoglobulin, according to Table 1.11.

**Table 1.11: Suggested intervals between immunoglobulin (IG) product administration or blood transfusion and measles vaccination (MMR or monovalent measles vaccine)<sup>8</sup>**

Indication for IG	Route	Dose		Interval (mths)*
		U or mL	mg IgG/kg	
Tetanus (as TIG)	IM	250 U	~10	3
Hepatitis A prophylaxis (as IG) for contact prophylaxis	IM	0.02 mL/kg	3.3	3
Hepatitis B prophylaxis (as HBIG)	IM	0.06 mL/kg	10	3
Rabies prophylaxis (as RIG)	IM	20 IU/kg	22	4
Measles prophylaxis (as IG): • standard • immune comprised host	IM	0.25 mL/kg	40	5
	IM	0.50 mL/kg	80	6
Varicella prophylaxis (as ZIG)	IM	125 U/10kg (maximum 625 U)	20–39	5
Blood transfusion: • washed RBCs • RBCs, adenine saline added • packed RBCs • whole blood • plasma/platelet products	IV	10 mL/kg	Negligible	0
	IV	10 mL/kg	10	3
	IV	10 mL/kg	20–60	5
	IV	10 mL/kg	80–100	6
	IV	10 mL/kg	160	7
Replacement (or therapy) of immune deficiencies (as IGIV)	IV		300–400	8
ITP (as IGIV)	IV		400	8
ITP	IV		1000	10
ITP or Kawasaki disease	IV		1600–2000	11
RSV-IGIV	IV		750	9

Key:

TIG = tetanus immunoglobulin, IG = immunoglobulin, HBIG = hepatitis B immunoglobulin, RIB = rabies immunoglobulin, ZIG = zoster immunoglobulin, IV = intravenous, RBC = red blood cells, ITP = immune (formerly termed ‘idiopathic’) thrombocytopenic purpura, RSV = respiratory syncytial virus.

\* These intervals should provide sufficient time for decreases in passive antibodies in all children to allow for an adequate response to measles vaccine. Physicians should not assume that children are fully protected against measles during these intervals. Additional doses of IG or measles vaccine may be indicated after exposure to measles.

## References

- 1 American Academy of Pediatrics. 2003. In LK Pickering (ed) *Red Book: Report of the Committee on Infectious Diseases* (26th edition). Elk Grove Village, IL: American Academy of Pediatrics, p 57.
- 2 American Academy of Pediatrics. 2003. In LK Pickering (ed) *Red Book: Report of the Committee on Infectious Diseases* (25th edition). Elk Grove Village, IL: American Academy of Pediatrics, p 61.
- 3 American Academy of Pediatrics. 2003. In LK Pickering (ed) *Red Book: Report of the Committee on Infectious Diseases* (25th edition). Elk Grove Village, IL: American Academy of Pediatrics, p 63.
- 4 US Centres for Disease Control and Prevention. 2002. General recommendations on immunisation. *MMWR* 51(RR-2).
- 5 James JM, Burks W, Robertson P, et al. 1995. Safe administration of measles vaccine to children allergic to eggs. *N Engl J Med* 332: 1262–6.
- 6 Nakayama T, Aizawa C, Kuno-Sakai H. 1999. A clinical analysis of gelatin allergy and determination of its causal relationship to the previous administration of gelatin-containing acellular pertussis vaccine combined with diphtheria and tetanus toxoids. *J Allergy Clin Immunol* 103: 321–5.
- 7 American Academy of Pediatrics. 2003. In LK Pickering (ed) *Red Book: Report of the Committee on Infectious Diseases* (25th edition). Elk Grove Village, IL: American Academy of Pediatrics, p 22.
- 8 American Academy of Pediatrics. 2003. In LK Pickering (ed) *Red Book: Report of the Committee on Infectious Diseases* (25th edition), Elk Grove Village, IL: American Academy of Pediatrics, p 390.