12 Tuberculosis

12.1 Introduction

The history of tuberculosis (TB) in New Zealand has been well documented.[1] The present control programme took shape with the introduction of the Tuberculosis Act 1948. Under this Act the medical officer of health is given wide powers to investigate and control all TB cases and their contacts, while district health boards are required to make provision for the treatment and supervision of patients and their contacts.

The TB control programme, including some aspects of Bacille Calmette-Guérin (BCG) immunisation, are outlined in the Ministry of Health publication *Guidelines for Tuberculosis Control in New Zealand*, 2003 (see www.moh.govt.nz). The local medical officer of health can advise on local TB control programmes, including BCG immunisation. Under the Tuberculosis Regulations 1951, BCG immunisation in New Zealand may legally be performed only by gazetted BCG vaccinators. A detailed technical description for the administration of the BCG vaccine is provided in the Ministry of Health publication *Technical Guidelines for Tuberculin Testing and BCG Vaccination*, 1996.

12.2 The illness

Human TB is caused by infection with *Mycobacterium tuberculosis* or *Mycobacterium bovis*. It most commonly causes disease in the lungs, but any part of the body may be affected. The initial infection with *M. tuberculosis* often goes unnoticed, and most of those infected enter a latent phase. The lifetime risk for infected people progressing from this latent phase to active TB disease is commonly stated to be 5–15 percent,[2] but this risk is strongly affected by the size of the infecting dose and the strength of the infected person's immunity.[3] For example, the risk of disease in young children is up to 40 percent. A small proportion of those infected progress directly to pulmonary TB, or by lympho-haematogenous dissemination of bacilli to miliary, meningeal or other extrapulmonary involvement. Infants, young children, older people and the immune compromised are more likely to progress to severe generalised infection.

TB infection and BCG immunisation lead to the development of a cellular immune response, which can be detected by the injection of tuberculin purified protein derivative. A positive 5 international tuberculin unit (TU) Mantoux test may be an indication of current infection, previous natural infection, or prior BCG immunisation. However, the reaction may be depressed if the patient is seriously ill from TB, is suffering from certain infectious diseases (notably human immunodeficiency virus (HIV) or measles), or has recently been administered live virus vaccines, and in those in whom disease or drugs have led to immune suppression. The interpretation of a positive Mantoux test must take account of all the above factors and the disease risk of the person being tested.[4] This interpretation and the consequent clinical advice are therefore complex, and are discussed fully in the Ministry of Health publications described above.

12.3 Epidemiology

TB remains an important cause of death in non-industrialised countries. However, there has been a resurgence of TB in the industrialised world. The frequency of TB in certain population groups is increasing worldwide, partly in association with the HIV/AIDS epidemic. At present in New Zealand TB is not common in patients with HIV infection.

New Zealand epidemiology

The overall incidence rate of TB in New Zealand is low compared with most countries, but has not declined over the last 20 years (see Figure 12.1). TB is still one of the most common notifiable infectious diseases. Reasons for the persistence of TB as a public health problem in New Zealand are complex, and include immigration from countries where there is a high incidence of TB, social conditions favouring transmission, and the fact that identification and prophylaxis for all infected people is not practicable. High rates of TB exist in New Zealand among population groups from Asia, Africa and the Pacific, particularly recent immigrants from these areas.

In 2000 the incidence rates in New Zealand were 1.7 per 100,000 for Europeans, 13.8 for Māori, 36.4 for Pacific, and 91.8 for other ethnic groups.[5] The proportion of TB cases born in New Zealand was stable at about 40 percent between 1995 and 2000. In 2004[6] there were 372 (new and reactivated) cases of TB notified, a rate of 10.0 per 100,000. As in previous years, rates were low in Europeans (1.5 per 100,000) and higher in Māori (13.9 per 100,000) and Pacific peoples (32.9 per 100,000). Rates were highest in those of 'other' ethnicity, with a rate of 78.1 per 100,000.

In 2004 there were 27 cases of tuberculosis reported, a rate of 3.2 per 100,000, in children aged 0–14 years. The age groups with highest rates of disease were females aged 20–29 years (52 cases, or 20.8 per 100,000) and males over 70 years (21 cases, or 15.7 per 100,000), and a high rate was especially seen in Pacific males over 70 years. In general the rates of disease increased with age, although in people of 'other' ethnicity there was a bimodal peak, with a high rate in those from 20 to 49 years as well as in older people.

Extrapulmonary TB (particularly miliary and meningeal), which is vaccine preventable in children, continues to occur in New Zealand (see Figure 12.2). Pacific, African and Asian children are disproportionately affected (see Figure 12.3). Figure 12.4 shows the number of hospitalisations for tuberculosis in children age 0–14 years from 1989–2004.

Bovine infection with *M. bovis* has spread to feral opossums, placing dairy herds, other cattle and deer at risk from the contamination of pastures. At present, because of herd testing and the widespread pasteurisation of milk, this causes very few cases of human *M. bovis* disease.

History of the New Zealand Immunisation Schedule

BCG immunisation was first introduced to New Zealand in 1948 and later extended to all adolescents. BCG immunisation of neonates was introduced in 1976, initially in high risk districts, but has been variably implemented throughout New Zealand.

Universal screening and vaccination of 13 year olds was discontinued in the South Island in 1963, was phased out in regions of the North Island in the 1980s, and had ceased by 1990. It was stopped because TB had declined to a point at which the advantages of vaccination (limited efficacy) were outweighed by the disadvantages (cost, side effects and reduced diagnostic value of the Mantoux test). An increase in TB transmission in particular districts or subpopulations would warrant reconsideration of this policy. Routine immunisation of adolescents with BCG is not regarded as necessary at present, although BCG could be reconsidered if the population specific rate rises to over 10 per 100,000.[7]

There have been different approaches to using BCG in the control of TB in developed countries. The United States (US) has not had a programme of universal BCG for adolescents, whereas New Zealand until 1990 (see above) and the United Kingdom (UK) have had programmes. The UK programme was discontinued in autumn 2005[8] because the annual risk of infection had fallen to less than 1 in 1000, and of people reported with TB in 2003 two-thirds were born outside the UK. The adolescent programme has been replaced by a neonatal BCG programme, whereby BCG is offered to high risk infants, defined as infants from communities where the incidence of TB is at least 40 per 100,000 and individuals who come from or whose parents or grandparents come from a country where the rate of TB exceeds 40 per 100,000 population.

Figure 12.1: Number of notifications of TB, 1970–2004

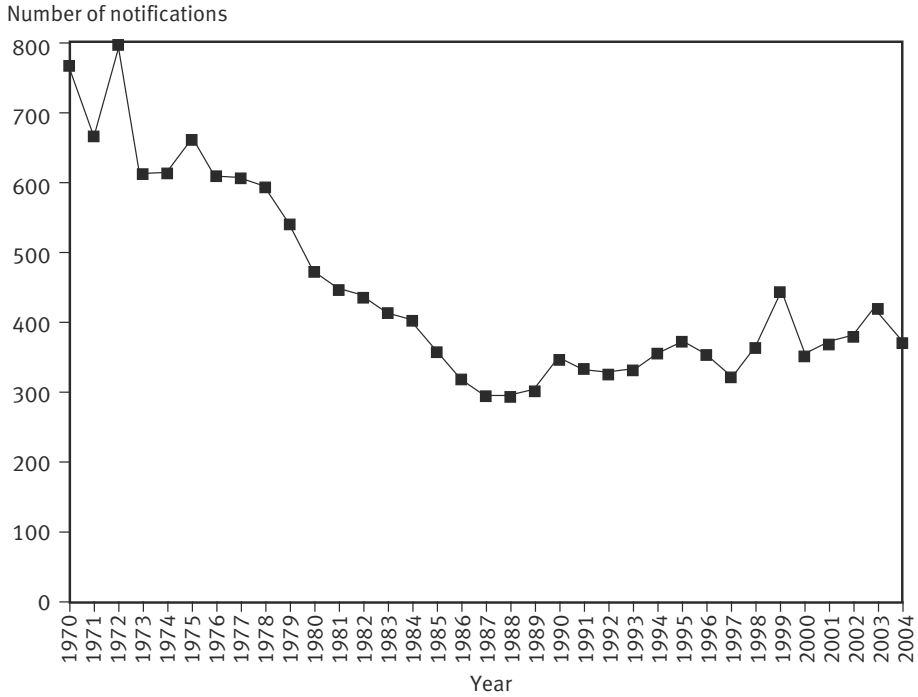


Figure 12.2: New Zealand miliary and meningeal TB admissions, by age, 1970–98

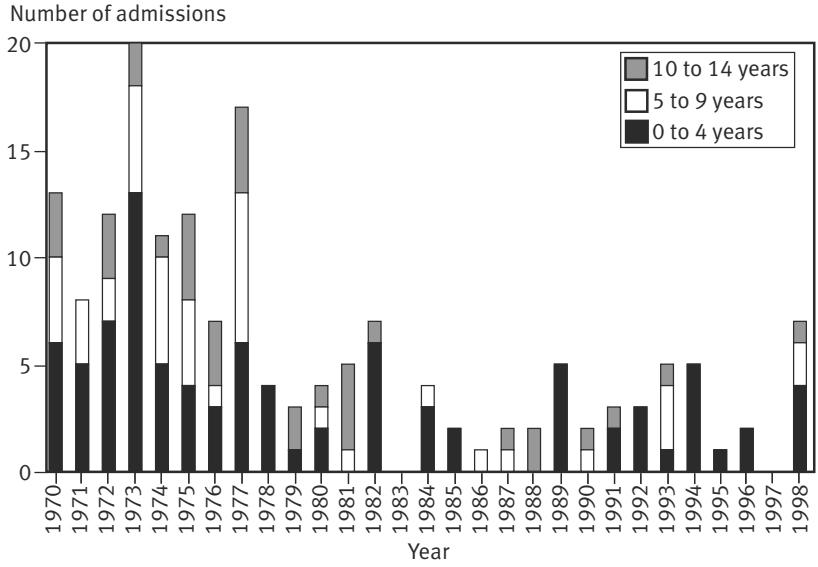


Figure 12.3: New Zealand extrapulmonary TB, by ethnicity, 0–14 years, 1990–98

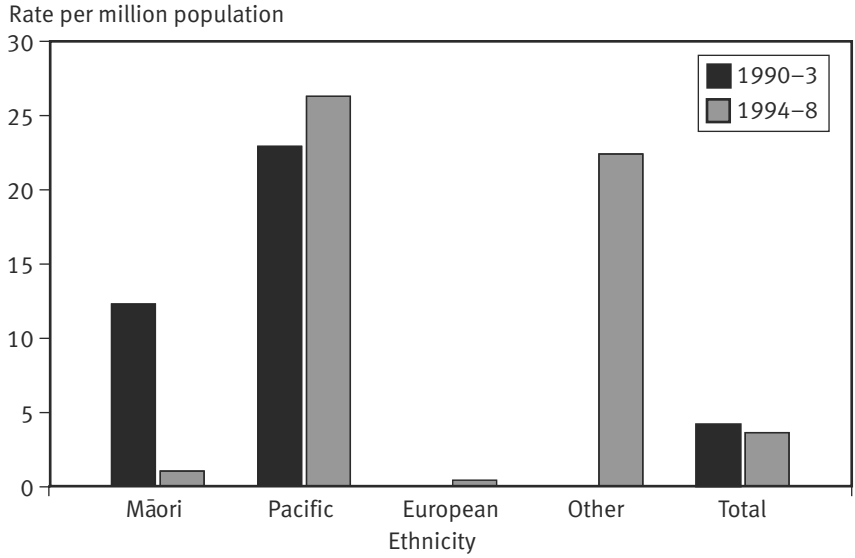
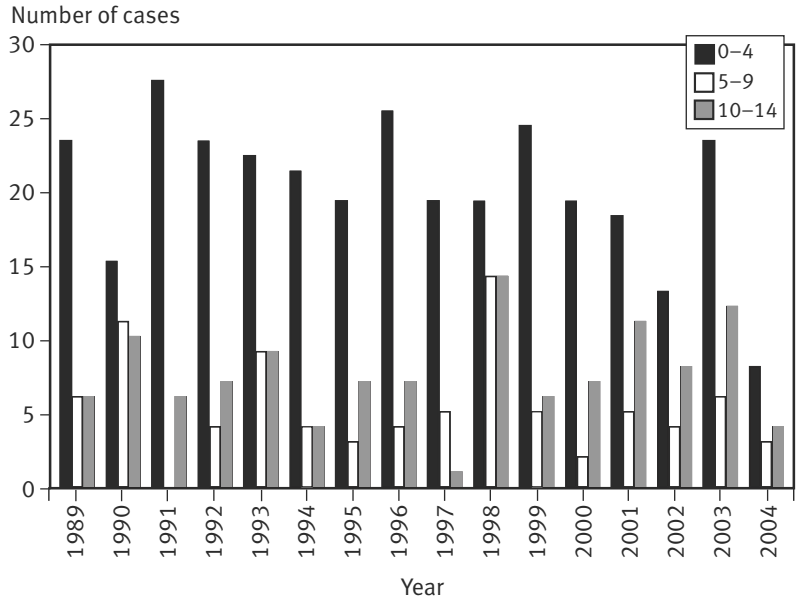


Figure 12.4: Hospitalisations of TB in children age 0–4, 5–9 and 10–14 years, from 1989–2004



12.4 Vaccines

The BCG vaccine was first derived in France from an attenuated strain of *M. bovis* in 1921. Originally the vaccine was given orally, but this was found to be ineffective and the intradermal route was introduced in Sweden in 1927. The current BCG vaccine contains a live attenuated strain of *M. bovis*. It is presented as freeze dried material with a diluent in a separate ampoule, and must be protected from heat and light. Reconstituted vaccine should be stored at 4˚C and used within four hours.

Efficacy

The principal role of BCG is to protect individuals at high risk of intensive exposure, but it does not have a significant impact on the incidence of the disease. Efficacy has varied in different trials between 0 and 90 percent.[9] This has been attributed to variations in methodology, differences in vaccines used, and the prevalence of environmental mycobacteria in the areas where trials have taken place. However, it is widely regarded as efficacious in preventing serious extrapulmonary disease in neonates.[10,11,12]

Although it is reported there is no good evidence that BCG provides protection more than 10 years after vaccination,[13] some evidence has since been found that in certain populations protection has lasted for up to 60 years after BCG immunisation.[14] Although the evidence is limited, BCG revaccination does not appear to offer any additional protection so no more than one immunisation should be given in a lifetime.[15,16]

A recent study from Turkey,[17] where BCG is recommended at two to three months of age and at age six to seven years, looked at the incidence of TB infection in children aged 16 or under, living in households where an adult had been diagnosed with smear positive TB. This prospective community study used both a tuberculin skin test and a T-cell based blood test (ELISpot) to assess the exposed children, and found that the amount of TB exposure in the household and the age of the child were risk factors for TB infection. The ELISpot test also identified that absence of a BCG scar was an independent risk factor for TB infection in the TB-exposed children. BCG vaccinated children had a 24 percent reduction in their risk of having TB infection compared with unvaccinated children (odds ratio 0.6, 95 percent confidence interval 0.43–0.83). This suggests that BCG offered some protection against TB infection.

BCG given with other vaccines

BCG can be given simultaneously with any other vaccine. However, it must be administered into a separate site and not in the same syringe. Because of the risk of local lymphadenitis, no further immunisations should be given into the arm used for BCG for at least three months.

Hepatitis B immunoglobulin (given at birth to babies of hepatitis B carrier mothers) or normal immunoglobulin is thought not to reduce the effectiveness of BCG immunisation, which principally acts through cell-mediated immunity.

Administration

Only gazetted vaccinators may give BCG immunisations. The vaccine is given by intradermal injection over the point of insertion of the left deltoid muscle. This is not much higher than the mid-point of the upper arm. For full details about administration, please refer to the *Technical Guidelines for Tuberculin Testing and BCG Vaccination*.

A local reaction usually develops at the site of a BCG immunisation within two to six weeks. This begins as a small papule, which increases in size for a few weeks and may break down into a shallow ulcer approximately 10 mm in diameter. The lesion may be covered by a dry dressing until a scab forms. It is essential that air is not excluded. The site should not be squeezed, incised or treated with antibiotic or steroid ointment.

If an impermeable dressing is necessary to allow activities such as swimming, the dressing should be left in place for only a short time. Prolonged occlusive coverage gives rise to a large, unsightly scar. The lesion usually subsides over several months and will usually leave only a small scar.

There is no relationship between the presence or absence of a post-vaccination tuberculin reaction and protective immunity.[18] Nor are there any data relating to the presence or absence of a scar and protective immunity.[19] Therefore, follow up of vaccinees is not recommended.

The 2003 *Guidelines for Tuberculosis Control in New Zealand*, chapter 8, p.11, offer advice on determining whether an individual has been previously vaccinated:

> *Often it is uncertain whether an individual has been previously vaccinated or not. Previous BCG vaccination is defined as documented evidence of a BCG vaccination (including date), or history of BCG vaccination supported by a compatible scar. A compatible scar is considered to be one of at least 4 mm diameter at a likely site. The scar is usually at the insertion of the deltoid, but it may be elsewhere, such as scapula, thigh or buttock. Persons not meeting these criteria may be offered a vaccination. Inadvertent repeat vaccination is not harmful.*

12.5 Recommended immunisation schedule

Mantoux testing before BCG immunisation

Mantoux testing is done before immunisation to exclude prior infection. It is not needed if BCG is given before the age of three months unless a history of contact with a known or possible case of TB is obtained. Because the Mantoux test is usually positive following BCG vaccination it has lower utility for diagnosing TB infection in a vaccinated individual.

BCG immunisation in New Zealand

The incidence of TB in Māori has been declining for many years, although there was a temporary increase in 1999 largely because of one outbreak. If there is a sustained increase in rates in Māori, then the re-introduction of universal neonatal vaccination for Māori will be considered either nationally or in affected districts. BCG immunisation is generally not recommended for people five years of age or older unless they are expected to be at very high risk of TB infection. This is because the efficacy of the vaccination is highest against extrapulmonary forms of TB, which mostly affect those under five years of age.

Neonatal BCG eligibility criteria

TB is more common in non-Māori and non-European people in New Zealand. However, all pregnant women should be assessed by their lead maternity carer as to the risk of TB for their baby. Neonatal BCG should be offered to infants at increased risk of TB, defined as those who:

- will be living in a house or family/whānau with a person with either current TB or a past history of TB
- have one or both parents who identify as being Pacific people
- have parents or household members who within the last five years lived for a period of six months or longer [a] in countries where there is a high incidence of TB.[b]
- during their first five years will be living for three months or longer in a high-incidence country.[c]

Neonates at risk should be identified antenatally by lead maternity care providers, including midwives, general practitioners, practice nurses and obstetricians. Immunisation is desirable before infants leave hospital. If this does not happen, immunisation should be arranged through the local medical officer of health.

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a This indication is not absolute. Vaccination is usually advisable if the adult is foreign born and has spent at least six months in a high incidence country within the past five years. The decision is not so clear cut when the adult is a New Zealand resident who has travelled to a high incidence country. The vaccinator must assess the adult's actual risk of exposure to TB during the past five years. For example, it is reasonable not to vaccinate the baby of a businessperson who has spent a year in a Hong Kong bank with a low risk of TB exposure. On the other hand, a baby living with a person who has returned recently from six months' volunteer work in a poor rural Indian community should be vaccinated. Vaccination may even be appropriate for a baby living with an adult who has travelled to a high risk setting (eg, patient care in a hospital in a high incidence country) for less than six months in the past five years. In cases where there is difficulty assessing the level of risk, advice should be sought from the medical officer of health.

b All countries 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, the UK and US.

c All countries except those listed above.

Children who have missed immunisation at birth should be immunised at any time up to five years of age. If the child is 12 weeks or older they should have a pre-vaccination Mantoux test to detect whether they have already been infected.

If an infant meeting the criteria is born prematurely, vaccination should not be delayed until discharge from hospital or he/she reaches 'term'. The evidence on the effectiveness of BCG given to premature infants at birth is conflicting, and is based on studies of post-vaccination Mantoux reactivity,[20,21,22,23,24,25] which is known to have no clear relationship to protective efficacy. Low birthweight in term infants is not a contraindication.[26]

If the baby has not been vaccinated before leaving hospital, and if there is a history of *current* TB in a relative who has had contact with the baby, **do not vaccinate immediately**. Withhold vaccination, conduct Mantoux testing, seek paediatric advice and vaccinate only after the possibility of infection in the baby has been excluded. This is because the baby may have been infected. Vaccination may not protect the baby who is incubating disease, and will prevent the Mantoux test from assisting with the diagnosis of disease.

A parent's/caregiver's request in itself should not be accepted as an indication for immunisation. Parents/caregivers seeking vaccination of their children who do not meet the above criteria should be referred to the local medical officer of health to discuss the risks and benefits of immunisation before a final decision is made.

Following implementation of the National Immunisation Register birth cohort in district health boards, information will be collected on BCG immunisation (see section 2.3).

Other high risk individuals or groups

BCG should be offered to the following at risk persons if they have not had a previous BCG immunisation and if a pre-vaccination 5 TU Mantoux test is negative (less than 5 mm):

- contacts of active TB cases less than five years of age (note that a contact exposed to TB in the preceding three months will need two negative Mantoux tests, 8–12 weeks apart, before vaccination)
- immigrants less than five years of age from high incidence countries
- health care workers, depending on their risk of exposure (refer to the *Guidelines for Tuberculosis Control in New Zealand*) – a baseline two-step Mantoux test is essential before health care workers have contact with patients or infectious materials; vaccination is recommended only for those working regularly with known TB patients, or who may be seconded to care for TB patients in institutions with high rates of multi-drug resistant TB, or in institutions where local epidemiology demonstrates a high annual risk of occupationally acquired infection
- people exposed to animals that are likely to be infected.

The medical officer of health may recommend vaccination programmes for specific populations with a high risk of TB, depending on local epidemiology. Staff and residents of rest homes, prisons and other closed populations may be recommended for vaccination, from time to time, depending on local epidemiology and in consultation with the medical officer of health.

Vaccination for overseas travel (even prolonged travel in high incidence areas) should be discouraged. It is more useful to ensure that a pre- and post-travel Mantoux test is documented and to carry out investigations and treatment or chemoprophylaxis in the event of Mantoux conversion. An exception to this is a child under five years of age travelling for prolonged residence in high incidence areas. In this instance, vaccination should be considered.

BCG immunisation in other countries

BCG is one of the vaccines that are part of the World Health Organization (WHO) Expanded Programme on Immunization. It is given at birth in non-industrialised countries. Revaccination with BCG is not recommended by the WHO[27] but is still practised in many countries.

Tuberculosis and measles vaccine

There has been some concern that the measles vaccine could exacerbate TB. This concern is effectively addressed in the 2003 *Red Book*,[28] p. 428 (see chapter 9: Measles):

> *Tuberculin skin testing is not a prerequisite for measles immunization, and measles vaccine does not exacerbate tuberculosis. If tuberculin skin testing is otherwise indicated, it can be done on the day of immunization. Otherwise testing should be postponed for 4 to 6 weeks because measles immunization may temporarily suppress tuberculin skin test reactivity.*

12.6 Expected responses and adverse events following immunisation (AEFI)

Expected responses

Ninety to 95 percent of people vaccinated with BCG develop a local reaction, followed by healing and scar formation within three months. A minor degree of adenitis developing in the weeks following immunisation should be regarded as normal, not a complication. It may take months to resolve. Suppurative adenitis should be regarded as a complication.

Adverse events following immunisation

Adverse events following immunisation with BCG vary with age and vaccine strain and are summarised in Table 12.1.

Table 12.1: Age specific estimated risks for complications after administration of Bacille Calmette-Guérin vaccine[29]

Complication	Incidence per 1 million vaccinations	
	Age < 1 year	Age 1–20 years
Local subcutaneous abscess; regional lymphadenopathy	387	25
Musculoskeletal lesions	0.39–0.89	0.06
Multiple lymphadenitis; non-fatal disseminated lesions	0.31–0.39	0.36
Fatal disseminated lesions	0.19–1.56	0.06–0.72

Source: Lotte A, Wasz-Hockert O, Poisson N, et al. 1988. Second IUATLD study on complications induced by intradermal BCG-vaccination. *Bull Int Union Tuberc Lung Dis* 63: 47–59.

Severe injection site reactions, large ulcers and abscesses are most commonly caused by faulty injection technique, where part of or the entire dose is administered too deeply (ie, subcutaneously instead of intradermally). Immunisation of individuals who are tuberculin positive may also give rise to such reactions. Special care is needed both in interpreting initial Mantoux results and in delivering the BCG vaccine.

Keloid scars at the injection site, although not uncommon, are largely avoidable. Some sites are more prone to keloid formation than others and vaccinators should adhere to the site recommended (mid-upper arm). Most experience has been with the upper arm site and it is known that the risk of keloid formation increases greatly if the injection is given higher than the insertion of the deltoid muscle into the humerus.

Rarely, osteitis and osteomyelitis, lupoid and other types of skin disorders, and neurological disorders have been reported following BCG immunisation. A few cases have been described of widespread dissemination of the vaccine organism in immune compromised people, such as children with primary immune deficiency.

Between 1965 and 2001 there were 91 cases reported to the Centre for Adverse Reactions Monitoring (CARM), with 124 adverse events following BCG vaccination, as follows: injection site reactions including abscess (53), lymphadenopathy (12), skin reactions (12), alimentary (10), anaphylaxis (4) and other reactions (33).

Every effort should be made to recover and identify the causative organism from any lesions constituting a serious complication.

Adverse BCG events will usually resolve spontaneously. Isoniazid, isoniazid/rifampicin and erythromycin prescribed for lymphadenitis are little better than observation.[30] If reactions persist for longer than one to two months, seek specialist opinion.

It is important that all complications are recorded and reported to a paediatrician or chest physician. Abscesses and more serious complications should be reported to the local medical officer of health in the interests of quality control of BCG immunisation technique, and to CARM, PO Box 913, Dunedin, using the prepaid postcard HP3442 (see section 2.4) or via online reporting at http://carm.otago.ac.nz. If the patient or parent/caregiver does not consent to being identified, the report should be made without personal identification.

12.7 Contraindications

See section 1.9 for general contraindications for all vaccines.

BCG vaccine should not be given to individuals:

- receiving corticosteroids or other immune suppressive treatment, including radiotherapy (see chapter 1: General Considerations)
- suffering from malignant conditions such as lymphoma, leukaemia, Hodgkin's disease or other tumours of the reticulo-endothelial system
- in whom an immune compromising disease is known or suspected, such as individuals with hypogammaglobulinaemia – primary immune deficiencies in children are often not detected until after the first few weeks of life (ie, after BCG vaccine is given) so a family history of immune deficiency should be sought and, if present, discussed with a paediatrician before vaccination
- known to be infected with HIV, including neonates with suspected HIV infection
- with a positive Mantoux reaction (5 mm or more)
- with a significant fever
- with generalised septic skin conditions – in the case of eczema, an immunisation site should be chosen which is free of skin lesions
- who are pregnant (this is a counsel of caution, as no harmful effects to the fetus have been observed following immunisation of the mother during pregnancy).

12.8 Control measures

The principal control measures for TB are case finding, treatment (directly observed, if necessary) of active and latent infection, contact tracing and selective screening. All cases of TB should be notified to the local medical officer of health.

A consideration of the diagnosis, management and public health follow up of TB is outside the scope of this document. For further information, please refer to *Guidelines for Tuberculosis Control in New Zealand,* or the *Control of Communicable Diseases Manual*.[31]

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