

# 2012 Antigen Review for the New Zealand National Immunisation Schedule: Tuberculosis

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# Executive summary

TB infection of humans has been recognised for many thousands of years. The disease exists in all countries in the world and is endemic in most of the poorer countries. TB is estimated to currently infect around one third of the current world population. Most of those infected carry the organism with no symptoms, called latent tuberculosis infection (LTBI). Of the LTBI approximately 5-10% will reactivate and develop clinical disease sometime over their life course. Most new cases occur in the developing countries and infection is usually acquired in childhood. The Bacille Calmette-Guérin (BCG) vaccines have been in use for over 80 years, routinely since the 1960s, in almost all countries except the United States (US) and the Netherlands, and have been given to over four billion people.

## Epidemiology

Worldwide the incidence rate of TB now appears to be stable or falling, but as the global population grows the number of new cases is still increasing, predominantly in developing countries in Africa and Asia, and amongst immunocompromised, particularly with human immunodeficiency virus (HIV) infection. The World Health Organization (WHO) estimates that there continue to be more than eight million new cases a year and over 1.8 million deaths.

The peak age for TB infection in most Western countries is adults over 50 years. However, among ethnic and racial minorities rates are higher and often in young adults and children. Certain environments tend to make TB incidence much higher: poverty, poor nutrition, poor access to healthcare and crowded conditions

Cases of TB in New Zealand (NZ) has declined substantially between 1980 and 2007, but has remained relatively stable since then. Most cases in 2011 were associated with people born in Asia, Africa and the Pacific Islands. The most common age of diagnosis was aged 20 – 29 years. There is significant regional variation in rates with the highest incidence occurring in the Auckland region. Risk factors for being diagnosed with TB included being born overseas in a high prevalence country, recent immigrant, prior or recent contact with TB, and identified as living in an area of higher deprivation.

## Safety

The safety profiles of BCG vaccines are well established. Complications are rare, but depend on vaccinator skill, method of administration used, type, strength and dose of vaccine, and age and immune status of the vaccinee. Local reactions are more common in women and older people, and vaccines are better tolerated in young infants less than six months of age.

BCG vaccination early in life does not appear to offer protection against allergy sensitisation, but may have a protective effect against asthma. It is unknown if BCG can offer protection against cancers. There is no effect on the incidence of multiple sclerosis.

Severe local reactions occur in less than 1% in immunocompetent persons and serious systemic reactions are rare. Case reports highlight some rare reactions to be aware of: BCG bacteraemia, BCG osteomyelitis, necrotising fasciitis, local tumours at the scar site, lichen striatus, late onset suppurative lymphadenopathy and disseminated lupus vulgaris.

The incidence of vaccine reactions vary with different BCG strains.

Immunocompromised individuals are at higher risk of BCG adverse events, both for increased incidence of local reactions and disseminated BCG-TB, which occasionally leads to death. Newborn infants of immunocompromised mothers, such as those with HIV-infection or taking immunosuppressive therapeutics in pregnancy, may be at risk of severe reactions to BCG given in early infancy. HIV-infected children are likely to be at higher risk of severe adverse events, but not HIV-exposed children.

## Immunogenicity, efficacy, effectiveness

The exact immune response elicited by BCG vaccination and the mechanism of action in the host are still not well understood. There is no reliable established laboratory correlate for immunity to *Mycobacteria tuberculosis*. While it is unlikely that any single, simple measure of cellular immune function will be useful as a direct correlate of protection, new breakthroughs in technology are on the horizon that could improve the diagnostic tools available.

Efficacy for BCG vaccines varies from zero - 80%. The vaccines have documented protective effect against meningitis and disseminated TB in children, particularly in newborn and young infants. However, BCG vaccines do not prevent primary infection, are only partially effective against severe infection in children, are unreliable against adult pulmonary TB, and not effective against reactivation of latent pulmonary infection. In persons infected with TB, subsequent vaccination with BCG does not augment the level of immune response.

BCG vaccines do not appear to prevent infection with *M. tuberculosis*, but can prevent disease in the host, associated with dissemination of the organism, in particular. Therefore, the vaccines offer a higher level of protection against the most serious forms of TB, such as meningitis and disseminated disease, than against the more moderate forms of disease, usually pulmonary.

There are significant differences in efficacy across populations and geographical areas. Maternal factors, genetic factors, nutritional factors and environmental factors all appear to influence efficacy. Efficacy and immune responses vary considerably across strains, but the data to date does not differentiate which strains are more effective overall.

HIV-exposed infants show a blunting of the immune response to early infancy BCG. Efficacy in HIV-infected infants is unknown.

In developing countries, a birth dose of BCG significantly reduces overall infant mortality. One possible aspect of this effect may be that BCG appears to enhance the production of vitamin D.

BCG offers no impact on disease transmission and there are no herd immunity effects. Duration of protection is unknown, possibly 10 to 15 years or longer in some populations.

## Vaccine options

As of early 2013, there are seven sites throughout the world that produce BCG vaccine. The vaccines are known by the location where they are produced. Although there are many different strains in use, four main strains account for more than 90% of the vaccine in use worldwide. BCG vaccine strains have and continue to evolve from the original BCG first used in 1921, and from each other. There is no worldwide consensus about which strain of BCG is optimal for general use. The use of a more attenuated strain gives fewer side effects, however it may also have lower efficacy.

There is large international effort behind looking for new options. By 2011, there were 12 TB vaccine candidates that had entered clinical trials. The first new TB vaccine could become available in 2018 at the earliest.

## Options for scheduling

BCG vaccines have not, and cannot, lead to the elimination of the disease from the human population, and are not considered a reliable tool for TB control. TB can only be eliminated if new, more effective vaccines are developed. Vaccination of children with BCG vaccine prevents severe forms of TB in children, such as TB meningitis, but is less effective in preventing pulmonary TB in adults.

The WHO recommends a single dose of BCG vaccine to newborn infants in developing countries with a high prevalence of infectious TB. Countries with lower rates of TB have already discontinued or are considering discontinuing BCG vaccination. However, in countries where there are childhood cases from high-risk

immigrant communities, BCG vaccination selectively targeted programmes continue. The current NZ strategy of offering vaccination to newborn infants from immigrant families coming from countries with endemic TB rates  $\geq 40$  per 100 000 is consistent with this approach.

In many developed countries the strategy for adults has moved to protecting high-risk adults, such as those who work with patients who have multidrug resistant TB. Some commentators now recommend, in low prevalence settings, to consider BCG vaccination for adolescents who are at risk of exposure such as high risk occupations and are tuberculin skin test negative. However, this is not a consistent recommendation and opinion remains divided.

## Implementation Issues

Intradermal administration in the deltoid using a syringe and needle is now the internationally accepted route for all current BCG vaccines, because the dosage can be measured precisely and the administration can be controlled. Percutaneous multipuncture devices may offer advantages with lower rates of adverse events and are currently offered in Japan and South Africa.

The recommended dosage differs by vaccine strain and the age of the recipient. Most manufacturers recommend a 0.05ml dose for infants and a 0.1ml dose for children and adults.

The use of tuberculin tests prior to BCG vaccination is not recommended for newborns and remains controversial for older ages.

The WHO currently recommends not giving BCG vaccination to HIV-infected infants, although this is challenged by some authors. Some commentary now recommends that neonatal BCG vaccine should be delayed for a few months in families with a history of recurrent infection, or any history of primary immunodeficiency as this could suggest a genetic underlying immunodeficiency in the child.

Repeat vaccination with BCG is not recommended. International advice on post-exposure vaccination is inconsistent.

## International Policy

Most countries that continue national policies use neonatal or early infant BCG. Very few countries use repeated doses. Most developed countries now have moved to targeted policies with vaccination of high risk infants and/or high risk people of other ages, such as healthcare workers.

As TB rates continue to decline in developed countries, it is expected that trends will continue to limit BCG vaccination to even more selective use and to discontinue universal immunisation programmes.

This report summarises new research on TB vaccines and vaccination published between 2009 and 2012. During an edit of this review in 2014, reference updates were inserted where the data referenced had been published since 2013. A full review of publications and vaccination schedules was not conducted.

# **2012 Antigen Review for the New Zealand National Immunisation Schedule: Tuberculosis**

Prepared as part of a Ministry of Health contract

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This review is one of a series of 18 antigen reviews presented in 15 individual reports.

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# Abbreviations

ACIP	Advisory Committee on Immunisation Practices (US)
AEFI	Adverse Event Following Immunisation
BCG	Bacille Calmette-Guérin Vaccine against TB
ELISA	Enzyme-Linked Immunosorbent Assay
IgE	Immunoglobulin E
HIV	Human Immunodeficiency Virus
IFN- $\gamma$	Interferon gamma, a cytokine produced by CD4 T cells
IL	Interleukin: cytokines produced by CD4 T cells
IUATLD	International Union against Tuberculosis and Lung Disease
LTBI	Latent Tuberculosis infection
MSMD	Mycobacterial diseases
<i>Mycobacterium bovis</i>	A bovine mycobacterium strain in BCG vaccines
NZ	New Zealand
SAE	Serious Adverse Event
TB	Tuberculosis
TNF- $\alpha$	Tumour necrosis factor- alpha
UK	United Kingdom
US	United States
WHO	World Health Organization
IVR	WHO Initiative for Vaccine Research
UNICEF	United Nations Children's Fund

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# 1. Background – tuberculosis and vaccination

This report summarises new research on Tuberculosis (TB) vaccines and vaccination published during the past four years (2009-2012). During an edit of this review in 2014, reference updates were inserted where the data referenced had been published since 2013. A full review of data and vaccination schedules was not conducted.

New Zealand (NZ) has excellent recent national resources covering advice around the control and management of TB:

- *The NZ Communicable Diseases Control Manual 2012 (1)*. This manual describes the standard practice that public health services should follow in NZ for the prevention and control of notifiable diseases including TB.
- *The Guidelines for Tuberculosis Control in New Zealand 2010 (2)*. These guidelines produced in August 2010 contain detailed NZ information based on latest international evidence and covers epidemiology, treatment and management of patients, infection control and best practice.

## 1.1 Introduction

TB infection of humans has been recognised for many thousands of years. The disease exists in all countries in the world and is endemic in most of the poorer countries. It is estimated to infect around one third of the current world population. Many carry the organism with no symptoms, known as latent tuberculosis infection (LTBI). Of the LTBI cases, approximately 5-10% will reactivate and develop clinical disease sometime over their life course. Most new cases occur in the developing countries and infection is usually acquired in childhood. Much of the increase in global TB infection during 1980 to 2005 was attributable to the spread of Human Immunodeficiency Virus (HIV) in Africa and Asia (3). The World Health Organization (WHO) estimates there are more than eight million new cases a year and over 1.8 million deaths (4).

The Bacille Calmette-Guérin (BCG) vaccines have been in use for over 80 years, routinely since the 1960s in almost all countries except the United States (US) and the Netherlands, and have been given to over four billion people (3). The WHO estimates that BCG is given currently to more than 80% of neonates and infants in low income countries, where it is a routine part of their national childhood immunisation schedule (4).

## 2. Methodology for review

### 2.1 Objectives

The objectives for this review have been informed by the general specifications for the 2012 NZ antigen review and the specific specifications for tuberculosis vaccines. These are listed below. The dates for publication are between 2009 and 2012 as per the brief. This is not a systematic review or a critique of the literature. The choice of articles reviewed is based on the purposeful selection of recent reviews and studies that may best inform policy discussions around tuberculosis vaccines for New Zealand.

- General specifications
  - Safety
  - Effectiveness
  - Implementation issues (practicality and possible impact on uptake)
  - The differences that need to be considered for each age group such as the variable severity of diseases and issues for vaccination
  - Different options of placement on the schedule, based on international findings and best practice
  - Different vaccine options and comparisons between the options

### 2.2 New Zealand epidemiology

In NZ, TB disease is notifiable to Medical Officers of Health under the Tuberculosis Act 1948. The NZ epidemiological information presented is based on national notification and laboratory-based surveillance summarised in the Tuberculosis in New Zealand Annual Report 2011 (5).

### 2.3 Literature search strategy

The points below have formed the focus of the literature search:

1. Safety
2. Effectiveness in disease control
  - a. Effect on
    - i. Indirect effects/herd immunity
    - ii. Duration of protection
  - b. Immunogenicity
3. Implementation issues (practicality of and possible impact on uptake)
4. Differences that need to be considered for each age group, and groups with particular needs
  - a. Age
  - b. High-risk groups – definition of which groups most likely to benefit and which vaccines/s
5. Different option for placement on the schedule, based on international findings and best practice
6. Different vaccine options and comparison between the options
7. Current international research and evidence around use of vaccines

#### 2.3.1 Medline search terms and strategy

**MeSH term: Tuberculosis vaccin\***

14956

Limit to Humans, English, 2009 – current

932

NOT Costs and Cost analysis

887

NOT qualitative, interview, parent, physician, survey, attitudes

873 (keep and view)

### 2.3.2 Cochrane Library search terms and strategy

Search term Tuberculosis vaccin\*

Limit to Cochrane Reviews, Other Reviews, and Trials  
2009-present

2 results (keep and view)

### 2.3.3 Scopus search terms and strategy

Tuberculosis vaccin\* Published 2011 – present

1881

Limit to: Medicine, Humans, English

1225

Exclude Letter, short survey, editorial and erratum

1087

Reject Veterinary, Agricultural and Biological, Arts and Humanities, Social science articles.

814 (keep and view)

Delete duplicates

Final Endnote Library 1432 Articles

### 2.3.4 Grey literature

Conference abstracts were sought to include data that has not yet been published, particularly from the key infectious diseases conferences for 2011 and 2012 – there were no abstracts or posters accessed.

### 2.3.5 Additional searches

Where questions arose additional searches were undertaken to ensure there was no further available data. Where articles were missing they were accessed and added to the library. A further 5 articles were accessed.

### 2.3.6 Final library

The final library includes 1437 references. Where systematic reviews and/or meta-analysis were available the preceding literature has been excluded from the review.

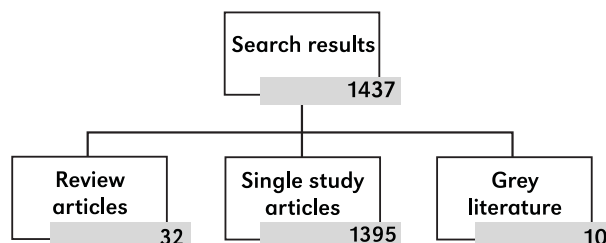


Figure 1. Flow of selection of articles for review

## 2.4 Participants/populations

The population for a universal programme are Infants and targeted vaccination all ages, children and adults.

## 2.5 The interventions included are:

- BCG OncoTICE
- BCG Vaccine SSI

### 2.5.1 BCG OncoTICE

OncoTICE vaccine contains live, attenuated bacilli of *Mycobacterium bovis*, prepared from a culture of Bacillus of Calmette-Guérin (BCG, strain Tice) and distributed by Merck Sharp & Dohme (NZ) Ltd.

The composition includes lactose, asparagine, citric acid (E330), potassium phosphate (dibasic), magnesium sulphate, iron ammonium citrate, glycerin (E422), ammonium hydroxide (E527), zinc formate.

The freeze-dried BCG preparation each dose contains approximately  $2.8 \times 10^8$  colony forming units (CFU) of Tice BCG. After reconstitution in 50ml saline the suspension contains  $0.4\text{--}1.6 \times 10^7$  CFU/ml.

No preservatives have been added.

### 2.5.2 BCG Vaccine SSI

The licensed BCG vaccine SSI (CSL Biotherapies) is a live attenuated vaccine containing *Mycobacterium bovis* BCG, Danish strain 1331.

- For adults and children aged 12 months and over 1 dose (0.1 ml) contains *Mycobacterium bovis* BCG (Bacillus Calmette-Guérin), Danish strain 1331, live attenuated,  $2 - 8 \times 10^5$  CFU.
- For infants under 12 months of age, 1 dose (0.05 ml) contains *Mycobacterium bovis* BCG (Bacillus Calmette-Guérin), Danish strain 1331, live attenuated,  $1 - 4 \times 10^5$  CFU.

The formulation includes magnesium sulphate heptahydrate, dipotassium phosphate, citric acid, monohydrate, L-asparagine monohydrate, ferric ammonium citrate, glycerol 85% and water for injection.

## 2.6 Study designs

The studies included in this update are meta-analysis, systematic reviews, reviews, randomised controlled trials, and observational studies using database matching.

## 3.0 Recent epidemiology

Worldwide the incidence of TB infection now appears to be stable or falling, but as the global population grows, the number of new cases is still increasing, predominantly, in developing countries in Africa and Asia and amongst the immunocompromised, particularly, those infected with HIV infection (6). Global TB incidence has been decreasing by 1.3% per year since 2002, and the absolute numbers of incident cases has fallen since 2006. Deaths from TB have fallen by 40% globally since 1990, and achievement of the WHO 50% reduction target by 2015 is likely (7).

### 3.1 Vulnerable populations

The peak age of TB incidence in most Western countries occurs in adults over 50 years. However, among ethnic and racial minorities rates are higher, often occurring in children and young adults. Environments of poverty, poor nutrition, limited access to healthcare and crowded conditions are associated with a higher incidence of TB. Prisons, nursing homes, homeless populations and migrant camps have all been identified as higher risk environments. However, independent of socioeconomic conditions, ethnicity is the strongest risk factor for TB (3)

#### 3.2.1 Age specific:

The highest rates are in those aged 20 – 29 years (13.1/100,000). Age and sex-specific rates are listed below in Table 1.

**Table 1. Age-sex distribution of tuberculosis disease cases, 2011**

Age group (years)	Male		Female		Total	
	Cases	Rate <sup>1</sup>	Cases	Rate <sup>1</sup>	Cases	Rate <sup>1</sup>
<1	0	-	3	-	3	-
1 to 4	3	-	3	-	6	2.4
5 to 9	1	-	2	-	3	-
10 to 14	2	-	6	4.2	8	2.7
15 to 19	8	4.9	10	6.5	18	5.7
20 to 29	45	14.3	36	11.8	81	13.1
30 to 39	23	8.5	21	7.2	44	7.8
40 to 49	24	7.9	20	6.1	44	7.0
50 to 59	12	4.4	16	5.6	28	5.0
60 to 69	16	7.8	21	9.9	37	8.9
70+	23	12.8	13	5.7	36	8.8
<b>Total</b>	<b>157</b>	<b>7.3</b>	<b>151</b>	<b>6.7</b>	<b>308</b>	<b>7.0</b>

<sup>1</sup> Rate per 100 000 based on 2011 mid-year population estimates; not shown for counts less than 5 cases

### 3.2 Recent NZ epidemiology

Previous epidemiological data is well described in the NZ publication *The Guidelines for Tuberculosis Control in New Zealand 2010*.

Data below is accessed from the ESR report *Tuberculosis in New Zealand Annual Report 2011 (5)*. Data from 2012 was yet not available in early 2013.

In 2011, there were 626 cases of TB reported:

- 308 case of TB disease, both new and relapse/reactivation
- 318 cases of TB infection; treatment of latent and old disease on preventive treatment.

The 2011 disease rate was 7.0 cases per 100,000, which was unchanged from the rate reported in 2010. Overall annual TB disease rates have more than halved from 1980, when there were rates of 15.1/100,000.

### 3.2.2 Ethnic specific

- Middle Eastern/Latin American/African ethnic group: 42.5/100,000
- Asian ethnic group: 40.6/100,000
- Pacific peoples: 18.0/100,000
- Maori: 6.2/100,000
- European/Other: 1/100,000

#### 3.2.2.1 Country of Origin

Of the 308 TB disease cases in 2011, birth country was recorded for 301 cases (97.7%). Seventy four cases (24.6%) were born in NZ, and 227 cases (75.4%) were born overseas. The highest disease rate was among those born in Asia: 61.7/100,000, followed by those born in Sub-Saharan Africa: 38.9/100,000 and thirdly, in the Pacific Islands 27.2/100,000 (see Table 2).

**Table 2. Tuberculosis disease cases by birth country, 2011**

Birth country region (n = 301)	Number of cases <sup>2</sup>	Rate <sup>1</sup>
Asia	155	61.7
Australia	0	-
New Zealand	74	2.5
North Africa & the Middle East	2	-
North America	0	-
North-West Europe	6	2.0
Pacific Islands	37	27.2
South & Central America	0	-
Southern & Eastern Europe	4	-
Sub-Saharan Africa	23	38.9

<sup>1</sup> Rate per 100 000 based on census 2006 birthplace for the usually resident population counts; rates not shown for counts less than 5 cases

<sup>2</sup> Seven cases with no country information were excluded

Table 3 illustrates TB cases NZ born or overseas born by ethnicity. Cases for NZ born showed the proportion of Māori (50.0%) was the highest, followed by European or Other (24.3%) and Pacific Peoples (17.6%) ethnicities. For overseas born cases, the largest proportion were classified as Asian ethnicity (70.5%), followed by those of Pacific Peoples ethnicity (14.5%).



**Table 3. New Zealand-born and overseas-born tuberculosis disease cases by ethnicity, 2011**

Ethnicity <sup>1</sup>	Born in New Zealand		Born overseas	
	No.	%	No.	%
Māori	37	50.0	0	-
Pacific Peoples	13	17.6	33	14.5
Asian	5	6.8	160	70.5
MELAA	1	1.4	15	6.6
European or other	18	24.3	11	4.8
Unknown	0	-	8	3.5
<b>Total</b>	<b>74</b>	<b>100</b>	<b>227</b>	<b>100</b>

<sup>1</sup> Ethnic groups were prioritised in the following order: Māori, Pacific Peoples, Asian, Middle Eastern/Latin American/African (MELAA), European or Other Ethnicity (including New Zealander)

### 3.2.2.2 Region-specific

More than half of all the cases were reported in the three DHB in the Auckland region.

- Auckland DHB: 17.7/ 100,000
- Capital and Coast DHB: 11.9/100,000
- Hawkes Bay DHB: 10.90/100,000
- Counties Manukau 10.2/100,000
- MidCentral 7.1/100,000
- Waitemata 6.4/100,000

### 3.2.3 Risk factors

- The most common risk factor was being born overseas with 75.4% of cases and current or recent residence with a person born outside of NZ in 74% of cases.
- More than half of the cases born overseas (52.5%) reported TB less than five years after arriving in NZ.
- Prior contact with a confirmed case of TB was recorded in 28% of cases.
- People from the four most deprived deciles by the NZDep rating (decile 7-10) comprised 58.5% of cases.

## 3.3 Summary of epidemiology

Worldwide the incidence rate of TB now appears to be stable or falling, but as the global population grows the number of new cases is still increasing, particularly in developing countries in Africa and Asia and amongst the immunocompromised, predominantly, by HIV infection.

The peak age of TB incidence in most Western countries occurs in adults over 50 years. However, among ethnic and racial minorities rates are higher and often in young adults and children. Certain environments tend to make TB incidence much higher: poverty, poor nutrition, poor access to healthcare and crowded conditions

The rate of TB in NZ declined substantially between 1980 and 2007, but has remained relatively stable since then. Most cases in 2011 were associated with people born in Asia, Africa and in the Pacific Islands. The most common age of diagnosis was aged 20 – 29 years. There is significant regional variation in rates with the highest incidence occurring in the Auckland region. Risk factors for being diagnosed with TB, included being born overseas in a high prevalence country, recent immigrant, prior or recent contact with TB, and identified as living in an area of higher deprivation.

## 4. Safety

### 4.1 Objective

The objective of this section is to review any recent safety data for currently licenced BCG vaccines.

### 4.2 Outcomes

Outcomes are general vaccine safety including adverse events following immunisation (AEFI) and serious adverse events (SAE).

### 4.3 Review

BCG vaccine was first used in 1921, and a range of BCG vaccines have been extensively used since that time. It is estimated that more than four billion people have received BCG vaccines.

The rate of complications, which are rare, vary depending on the skill of the vaccinator; the administration method used; the vaccine type, dose and strength; and the age and immune status of the recipient. Infants less than six months of age is better tolerate vaccination than older infants. Development of local reactions and abscesses is, in general, more likely in women and older people (3).

Local reactions are common: 90-95% of BCG recipients develop a local reaction followed by healing and scar formation within three months. An accelerated response to the vaccine is often observed in those with LTBI, as characterised by having induration within one-two days and scab formation and healing within 10-15 days.

After local skin reactions, the most common complications are local ulceration and regional, which occur in less than 1% of immunocompetent recipients with good intradermal administration. These reactions can appear from a few weeks to months after vaccination, symptoms can be delayed for months in immunocompetent persons and for years in some immunocompromised patients. Suppurative lymphadenitis is more common among newborns than older infants and children, especially when a full dose of vaccine is given; hence, the WHO recommends a reduced dose of 0.05ml in children younger than 30 days.

Although resolution may take several month, nonsuppurative lymph nodes usually improve spontaneously. A meta-analysis of the treatment of

adenitis found the literature lacking for consensus, but that based on currently available studies, oral antibiotics or antituberculosis drugs did not reduce the frequency of suppuration (3).

A recent study from Saudi Arabia reported on 145 patients presenting with BCG lymphadenitis between January 2005 and December 2010 (8). In the majority of cases (n=103), the lymphadenitis involved the left axillary nodes. Eight (27%) of the patients had positive cultures for *Mycobacterium bovis* (the BCG mycobacterium). The authors recommended that in the context of Saudi Arabia, a time later than at birth may be preferable for BCG as this reaction is more common in newborns. Another Saudi Arabian study followed the records of 26,000 newborns given BCG vaccination from 2008 - 2011 and found 81 complications (3.12 complications/1000 newborns). There were 64 cases of axillary lymphadenitis, nine supraclavicular lymphadenitis, six collections at the immunisation site and one each of cervical lymphadenitis, left arm abscess. In total, two of the children were immunocompromised. The simple lymphadenitis were treated expectantly, the suppurative lymphadenitis were excised, or incised and drained. The authors recommend conservative treatment of non-suppurative lymphadenitis and excision of suppurative to avoid rupture and shorten the recovery period, without using antituberculosis treatment (9).

There is no evidence that children who experience local complications are more likely to have immune deficits (3).

#### 4.3.1 Allergy and BCG vaccination

A systematic review and meta-analysis was published in 2011, which reviewed the relationship between BCG vaccination and the risk of sensitisation, eczema/atopic dermatitis, allergic rhinoconjunctivitis, asthma and other allergic conditions, including food allergy and anaphylaxis. The review identified 767 articles, of which 17 satisfied the inclusion criterion. The results did not show any protective effect of BCG vaccination against the risk of sensitisation, as measured by specific Immunoglobulin E (IgE) tests (OR 1.33, 95% CI 1.07-1.60), skin prick testing (OR 0.87, 95% CI 0.67-1.13), the risk of atopic eczema/dermatitis (OR 0.84, 95% CI 0.64-1.09), or the risk of allergic rhinoconjunctivitis (OR 1.07, 95% CI 0.89-1.28). BCG was associated with a protective effect against asthma (OR 0.73, 95% CI 0.56-0.95), although, this

might be explained by publication bias. The reviewers concluded that BCG is unlikely to be associated with protection against the risk of allergic sensitisation (10).

An international cross-sectional study investigated whether TB infection and BCG may have a protective effect on allergic disease risk. Data and physical examinations were undertaken on a randomly selected subset of 23,901 school children, aged 8–12 year old, in 20 centres in developed and developing countries. No protective association was found for early BCG vaccination on asthma, rhinitis or eczema (11).

### 4.3.2 Asthma

A 2010 systemic review appraised 23 studies to review the effect of BCG on asthma outcomes. Three studies were excluded due to poor quality. Results show that the epidemiological evidence was in support of the hypothesis that exposure to BCG vaccine in early life prevents asthma and the authors speculated that this was possibly through a modulation of the immune maturation process (12).

A retrospective cohort study involving 2,311 individuals who had received BCG vaccine classified them according to the number of BCG vaccines they had received: one, two or three doses. Overall, 1,317 had received one, 644 received two, and 350 had received three or more. There were no significant differences in the prevalence of asthma between the three groups (13). Multiple doses of BCG do not appear to be associated with further reductions in the incidence of asthma.

### 4.3.3 Serious adverse events

The major serious vaccine safety concern for BCG vaccine is the possibility of the vaccine associated infection in immunocompromised people, both if an immunocompromised person receives BCG themselves, or from shedding of the attenuated organism from other people (4). Generalised BCG disease is extremely rare in immunocompetent patients, although there have been occasional case reports (3).

Use of BCG vaccination in persons already infected with TB may actually promote reactivation of the TB – this is called the Koch reaction (3).

Some experts have raised questions about a possibly increased or decreased risk of certain types of cancer, particularly, lymphomas among vaccinated compared to unvaccinated persons: to date, this has not been definitively shown. Other studies have suggested that BCG in newborns may reduce certain childhood cancers, but the data to date is insufficient to answer this.

A meta-analysis of published data from 1956 – 2011 showed no change in the risk of developing multiple sclerosis after vaccination with BCG (OR 0.96, 95% CI 0.69-1.34) (14).

#### 4.3.3.1 Case reports

A Thai study reported four cases of immunocompetent newborns vaccinated with BCG and all hospitalised with high fever and/or jaundice within 72 hours of vaccination. One isolate was identified as the BCG bacterium, *Mycobacterium bovis*. The similar clinical presentation and temporal association suggested to the authors that all four infants probably had BCG bacteraemia shortly following vaccination (15). This has not been previously described.

Cases of BCG osteomyelitis have been reported: in a nine month old girl in South Korea, presenting with BCG osteomyelitis following vaccination with BCG – Tokyo strain at birth; in the femur of an infant in Hong Kong; and in the tibia of a ten month old in China (16-18). A Saudi study reports three immunocompetent children who developed osteomyelitis after BCG vaccination. With surgical intervention and chemotherapy the prognosis was good (19). A case study of an infant with osteomyelitis of the proximal tibia undertook a review of BCG osteomyelitis in infants. The authors found seven studies reporting 14 cases of BCG osteomyelitis extending to the grown plate and epiphysis. There was a high recurrence rate with just over a half requiring reoperation, but there were no significant risk factors associated with recurrence. The authors recommend early curettage of the entire lesion to eradicate it and avoid recurrence (20).

A newborn in India was reported with necrotizing fasciitis after BCG vaccination that required extensive debridement and intravenous antibiotics (21).

Another case report published in 2012 was of a 59 year old man in Finland who developed a superficial basal cell carcinoma on a prior BCG site (22). A lipoma was reported on the BCG scar of a 14 month old girl that had been rapidly growing for four months and was restricting movement and causing pain: it was fully resected (23).

Severe local reactions with large cutaneous necrotic ulcers are very occasionally reported following BCG vaccination and considered to be extremely rare (24).

A child was reported with a 7mm erythematous nodule at a distance of 4cm from the BCG injection site which histologically defined as a necrotizing granulomatous reaction. This specific complication is called *BCG-itis* in the literature (25).

A seven month old Indian girl given BCG at two ½ months of age presented with a hypopigmented lesion linearly arranged along the lateral aspect of her left upper limb which was diagnosed as lichen striatus. This was expected to resolve in seven to nine months (26).

A healthy young Japanese boy presented at two years and five months of age with late onset suppurative lymphadenopathy more than two years after having a BCG at three months of age. *Mycobacterium bovis* was identified. The lesion was fully excised with no complications. While late complications have been associated with impairment of cell mediated immunity, this has not been previously identified in children with normal cell-mediated immunity (27).

An otherwise healthy seven year old Indian boy presented with skin lesions over the left upper limb, forehead and back for six years and a large fleshy mass over the left arm for two years. He had been given BCG at six weeks of age. This was diagnosed as BCG-disseminated lupus vulgaris complicated by a squamous cell carcinoma. It was treated with excision and antitubercular medication (28). BCG-disseminated lupus vulgaris is estimated to occur in five per 1 million vaccinations, but increases after multiple BCG vaccinations.

#### 4.3.3.2 Immunocompromised

HIV-infected children and any others with severe defects in cell-mediated immunity including chronic granulomatous disease, severe combined immunodeficiency, malnutrition, cancers, complete Di George syndrome, interferon gamma (IFN- $\gamma$ ) production or receptor deficiency have a higher chance of disseminated BCG disease that can, rarely, be fatal (3, 29).

A case study reported on severe axillary lymphadenitis following BCG vaccination given to newborns in three infants with primary immunodeficiencies: one with a partial recessive interferon-receptor 1 deficiency who developed BCG dissemination and two relatives with ZAP70 deficiency, which is a severe combined immunodeficiency, who presented with regional and distant BCG disease. This case study highlights the importance of considering the diagnosis of immunodeficiency in a child with severe axillary lymphadenitis after BCG vaccination and of the risks of disseminated BCG disease in an immunodeficiency child. The authors recommended that BCG vaccination should be delayed in every newborn with a family history of primary immunodeficiency until the condition has been ruled out (30).

A fatal case was reported of disseminated BCG disease given to an infant that was exposed *in utero* to infliximab. The infliximab, an anti-tumour necrosis factor alpha (anti-TNF- $\alpha$ ) agent, was given to the mother for Crohn's disease throughout pregnancy. The infant was healthy when he received a BCG at three months of age and died of disseminated BCG TB at 4.5 months of age. This case highlights that infants born to mothers who have received anti-TNF $\alpha$  drugs in the third trimester may be unable to develop an appropriate immune response to live vaccines and the authors recommend postponing all live vaccines in these infants until at least seven months of age (31).

A Turkish case study reports on a five month old infant with severe combined immunodeficiency who was given BCG at birth and presented with recurrent diarrhoea, respiratory infection and lymphadenopathy (32).

A case report of an infant with the rare condition of Mendelian susceptibility to mycobacterial diseases (MSMD) was identified by the symptoms of recurrent mucocutaneous candidiasis and BCG lymphadenitis (33).

##### 4.3.3.2.1 HIV infection and exposure

Studies from South Africa and Argentina reported a much higher risk of disseminated BCG disease among HIV-infected children, with rates approaching 1%. The median age of onset was 98 months with a range of 3 – 35 months, and in the reports that included outcome data, 81% died; survival was improved with the use of antiretroviral treatment. There is no apparent increase in risk for infants of mothers who are HIV-infected, although long term follow-up studies are not yet available (3).

In contrast, data from Brazil looking at both HIV-infected children and HIV-exposed children concluded that BCG was safe to recommend universal vaccination with BCG of newborns regardless of HIV infection or exposure (34). A seven year prospective study, which followed 141 HIV-exposed and 66 HIV-infected children given BCG at birth, found no localised disease in the HIV-exposed group, 3/66 (4.5%) of adverse local events in the HIV-infected group and no disseminated BCG disease in either group. Further data from the Brazilian National Programme of Immunizations supported the overall safety by estimating a rate of 0.387/1000 adverse events, such as ulcers, abscesses and suppurative regional lymphadenopathy, among BCG vaccinated group with no disseminated BCG disease.

#### 4.3.3.3 Undernourished

An animal model using dietary restricted mice was used to test whether the BCG vaccine is safe for undernourished children. A much higher proportion of undernourished mice exhibited bacterial dissemination to lymph nodes, spleen and liver following being immunised with BCG, and they had lower production of cytokines. These animal study results suggest that disseminated BCG disease may be more likely in malnourished children (31).

#### 4.3.4 Vaccine strains

BCG types vary widely with different strains. Refer to Section 5.3.1

The incidence of adverse events with BCG vaccination differs between strains that are considered 'strong' i.e. those that elicit stronger immune responses in animal models, and strains that are considered 'weak'. The strong strains have been associated with a higher rate of lymphadenitis and osteitis, especially among neonates. Reducing the vaccination dosage for the strong strains also reduces the incidence of lymphadenitis (3).

The Danish BCG strain is the most common strain reported in immunocompromised patients with disseminated disease, but the Pasteur strain has also been associated. Disseminated disease has not been reported with the Moreau and Japanese strains (3).

Certain BCG strains, particularly the Tokyo and Moreau strains in Brazil, appear to be very rarely associated with lymphadenitis - whereas the French (Pasteur) strain appears to have a higher incidence of lymphadenitis (3). Outbreaks of lymphadenitis have been noted following the introduction of a new BCG strain. A study reported from Saudi Arabia undertook a retrospective chart review and prospective follow-up of 19,402 infants who had received four different strains of BCG vaccine during 2002 – 2007. Over the study period, eight infants developed BCG lymphadenitis and all were associated with the BCG SSI vaccine. The authors concluded that caution is needed to be exercised in switching from one BCG vaccine to another (35).

A large cohort study in Uganda of 1,341 infants given BCG-Russia, BCG-Bulgaria or BCG-Denmark at birth found that the BCG-Denmark has the highest incidence of adverse events ( $p=0.025$ ) and the highest rate of scar with 92.6% of infants having BCG scars compared to 52.2% of the BCG-Russia and 64.1% of the BCG-Bulgaria groups (36).

## 4.4 Summary vaccine safety

More than four billion people have received BCG vaccines. The safety profile is well established; complications are rare, but depend on vaccinator skill, method of administration used, type, strength and dose of vaccine and age and immune status of the vaccinee. Local reactions are more common in women and older people, and vaccines are better tolerated in young infants less than six months of age.

BCG vaccination early in life does not appear to offer protection against allergy sensitisation, but may have a protective effect against asthma. It is unknown if BCG may offer protection against cancers. There is no effect on the incidence of multiple sclerosis.

Severe local reactions occur in less than 1% in immunocompetent recipients and serious adverse systemic reactions are rare. Case reports highlight some rare reactions to be aware of: BCG bacteraemia, BCG osteomyelitis, necrotising fasciitis, local tumours at the scar site, lichen striatus, late onset suppurative lymphadenopathy and disseminated lupus vulgaris.

The incidence of vaccine reactions vary with different BCG strains.

Immunocompromised are at higher risk of BCG adverse events, both an increased incidence of local reactions and disseminated BCG-TB, which occasionally leads to death. Newborns of immunocompromised mothers, such as HIV-infected mothers or mothers taking immunosuppressives in pregnancy, may be at risk of severe reactions to BCG given in early infancy. HIV-infected children are likely to be at higher risk of severe adverse events, but not HIV-exposed children.



# 5. Immunogenicity, efficacy, effectiveness and vaccine impact

## 5.1 Objective

The objective of this section is to review the most recent performance data for currently licenced BCG vaccines. Consideration is given to relevant immunogenicity data, efficacy and effectiveness studies that contribute to the current understanding of the effectiveness of BCG vaccines and evidence of their impact in populations.

## 5.2 Outcomes

The outcomes considered for this review are:

- Immunogenicity markers
- Pulmonary TB
- Latent TB
- Disseminated TB

Note that there is still no consensus on single primary end-point definitions for standard case definitions for tuberculosis for clinical trials (37).

## 5.3 Review

### 5.3.1 Immunogenicity

#### 5.3.1.1 Immunogenicity measures

There is no reliable, established laboratory correlate for immunity to *Mycobacteria tuberculosis*. The exact immune response elicited by BCG vaccination and the mechanism of action in the host are still not well understood, and there is a lack of studies about the immunologic events that occur in the human host after BCG vaccination (3).

Tuberculin skin test conversion has for a long time been used as evidence of TB infection or as a sign of adequate response to BCG vaccine. However, the relationship between protective immunity and the tuberculin response is controversial, with no clear relationship established. Neither the presence, nor the size of the post vaccination tuberculin skin test reaction reliably predicts the degree of protection given by BCG. A recent study of 376 first year school children in Madagascar, all given tuberculin skin tests,

showed that TB infection either latent or active is associated with a positive tuberculin result, but there was no association with past BCG vaccination (38).

Some studies have suggested that IFN- $\gamma$ , a cytokine produced by CD4 T cells, may be a better marker for vaccine-induced immunity (39). Several hundred new proteins, antigens and cell-mediated mechanism have recently been identified with particular interest in T-helper cell cytokine responses, the production of IFN- $\gamma$  and its relationship to protective immunity against TB. A number of new antigens in the *Mycobacterium tuberculosis* organism have been identified, including AG85, MPT64, ESAT-6 and CFP-10, and studies are ongoing as to their possible use as tools for diagnostic tests in the future (40). Some of these have cross-reactivity with other environmental mycobacteria making it difficult to interpret. The whole-blood assay QuantiFERON-TB test measures IFN- $\gamma$  and tests for latent TB infection. The T-SPOT.TB test is also based on measuring the IFN- $\gamma$  released by T cells stimulated with ESAT-6 and CFP-10 using an ELISPOT assay. Neither of these tests can differentiate latent TB from active disease.

Smith, Orme & Starke consider that new breakthroughs in technology are on the horizon, which should improve the diagnostic tools available and will be important in future vaccine trials (3, 41, 42). It is unlikely that any single, simple measure of cellular immune function will be useful as a direct correlate of protection. An immune correlate may need to be vaccine-specific and also disease-stage specific, for example a correlate in naïve infants may be very different to one in infected adults (43).

#### 5.3.1.2 Immune responses children versus adults

Earlier studies have suggested that the protective efficacy of BCG vaccines is better for children than adults, with a potential explanation that BCG induces a better protective immune response in children. A small study measured Th1 cytokines in 26 children and adults immunised with BCG, before and 10 weeks after vaccination. It showed that both children and adults had comparable proportions of CD4 T cells; although concentrations of secreted cytokines were comparable, the proportion of polyfunctional cells was greater in children. The authors concluded that the specific

cell-mediated immune response induced by BCG immunisation is similar in children and adults, and the implication of a shift to a more polyfunctional immune response in children is unclear (31).

### 5.3.1.3 HIV exposed infants

A cross sectional study compared three groups of HIV-1-exposed infants given BCG at birth with age-matched (to youngest group) unexposed infants: infants exposed to, but not infected by HIV, were placed into three age groups: from 6.1 – 8.8 months, 9.1 - 17.1 months and 18.1 - 26.3 months. Overall, results showed that BCG-specific T cell proliferation was reduced in HIV-exposed infants and the IFN- $\gamma$  levels were lower in the younger exposed infants. The authors concluded that this showed a delay in the immune system maturation of HIV-exposed infants (44).

Similar findings were seen in a study of 31 HIV-negative infants, born to 21 HIV-negative and 16 HIV-positive mothers in Malawi, which measured their response to BCG given at birth. At two weeks of age, maternal HIV status did not influence the CD4 T cell responses, but by 10 weeks of age, the CD4 counts in infants born to HIV-positive mothers fell to a level seen in HIV-positive infants. The authors concluded that the reduced CD4 counts and other cytokine effects measured indicated a deficiency in their ability to develop immunological memory (45).

### 5.3.1.4 The elderly

A small study in Indonesia tested efficacy and immune markers in 34 elderly participants, aged 60 – 75 years, following BCG vaccination given monthly for three consecutive months. They measured prevention of acute upper respiratory tract infections, IFN- $\gamma$  levels and interleukin (IL)-10 levels. There was a significant reduction in the prevalence of acute upper respiratory tract infections and increase in IFN- $\gamma$  levels in the vaccinated group compared to placebo (46).

### 5.3.1.5 Immune responses and BCG strain types

A study of the immune response of 164 infants, immunised at birth with either BCG-Denmark (n=54), BCG-Japan (n=54) and BCG-Russia (n=57), measured CD4 T cells ten weeks after immunisation. The study showed that the proportion of polyfunctional CD4 T cells was significantly higher in infants immunised with BCG-Denmark vaccine (0.013%) or BCG-Japan (0.016%) than with BCG-Russia (0.007%;  $p=0.018$

and  $p=0.003$ , respectively). Those vaccinated with BCG-Japan had higher concentrations of secreted Th1 cytokines, those immunised with BCG-Denmark had higher proportion of CD107-expressing cytotoxic CD4 cells. This study highlights that there is significant variation in immunological responses induced by different BCG strains (31).

A large cohort of 1341 infants in Uganda, from the Entebbe Mother and Baby Study who were given BCG-Russia, BCG-Bulgaria or BCG-Denmark at birth, were analysed by BCG strain. At one year of age, IFN- $\gamma$ , IL-5, IL-3 and IL-10 responses to mycobacterium-specific antigens and non-mycobacterial stimuli (tetanus toxoid and phytohaemagglutinin) were measured using enzyme-linked immunosorbent assay (ELISA) testing. Results showed that BCG-Denmark vaccinated infants had the highest cytokine responses. Infants with more scarring had higher cytokine responses. The BCG-Denmark group had the highest frequency of adverse events ( $p=0.025$ ). There were no significant mortality differences. The authors concluded that both specific and non-specific immune responses to the BCG vaccine differ by strain (47).

## 5.3.2 Efficacy and effectiveness

### 5.3.2.1 Protection against disease outcomes

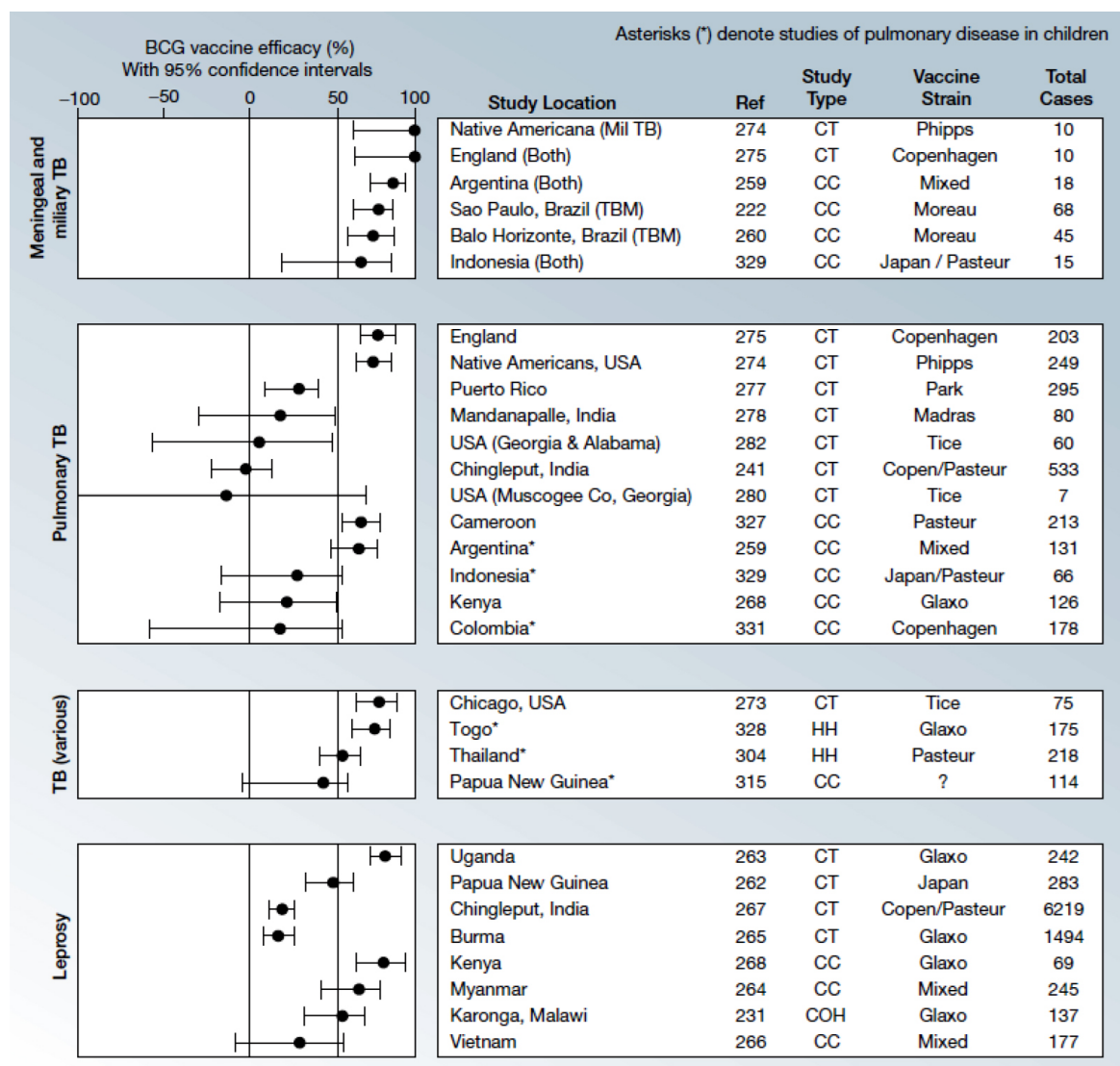
The true effectiveness of BCG vaccines has been debated for years. The original efficacy studies gave estimates ranging from 0% – 80% (3). There are marked differences in efficacy between age groups on the basis of previous mycobacterium priming. A recent commentary article summarising a 2002 re-analysis of four prospective trials of BCG given to mycobacterium-naïve newborns indicated that immunisation was 73% effective against disease and 87% effective against death in the era prior to antibiotics being available (48).

The recent analysis from a large substudy of the BCG REVAC trial, in 20,622 school-age children in Brazil (aged seven -14 years), who did not have a BCG scar, and therefore, were considered to be BCG-naïve. Following their first BCG immunisation, they showed an efficacy against subsequent TB development in the next nine years of 25% (95% CI 3-43%). However, it was estimated that about 30% of the population were tuberculin reactive (although not tested), and hence, previously exposed to a mycobacterium. The large group in this trial and other trials may lower the estimate of efficacy of BCG for mycobacterial naïve persons (49).

Possible explanations for low efficacy in trials in adults and children beyond infancy include differences in vaccine strain, latitude, method of administration, and the rate of previous infection with *Mycobacterium tuberculosis* or non-tuberculosis mycobacteria. Previous infection appears to reduce observed efficacy (48).

Most of the major trials and meta-analyses of BCG vaccines have demonstrated that they offer a higher level of protection against the most serious forms of TB, particularly meningitis and disseminated disease, than against the more moderate forms of disease usually pulmonary disease (3). This is probably because the protective effect of BCG derives from its interference with the blood borne spread of the organism from the primary focus i.e. the vaccination does not prevent infection, but helps the host to retard the growth of organisms at the primary site of infection in the lungs and lymph nodes and to prevent massive dissemination.

The overall question of efficacy remains unanswered despite a range of on-going studies; case-control, cohort, household contact and meta-analysis (3).



**Figure 2. Estimates of Bacille Calmette-Guérin (BCG) vaccine efficacy against different forms of tuberculosis (TB) and leprosy from clinical trials (CT), case-control (CC), cohort (COH) and household (HH) studies.**  
Adapted by (3) from Fine et al for WHO (50)

Figure 2 displays the estimates of efficacy from the major BCG field trials. At least six different vaccines were used in these trials. Some vaccines have given inconsistent results between trials. Strains have changed over time, yet the trends in efficacy of BCG vaccination have not increased or decreased over time, so definitive conclusions cannot be drawn about the protective effect of the different BCG strains (3, 50).



In summarising the literature, BCG vaccines do not prevent infection with *Mycobacterium tuberculosis*, but can prevent disease in the host associated with dissemination of the organism. The vaccines have a documented protective effect against meningitis and disseminated TB in children, particularly, in newborns and young infants. However, BCG vaccines do not prevent primary infection, are only partially effective against severe infection in children, are unreliable against adult pulmonary TB and are not effective against reactivation of latent pulmonary infection. In persons infected with TB, subsequent vaccination with BCG does not augment the immune response (49). However, there is still no consensus as to the mechanism of how this works. The original belief was that BCG simply establishes immune memory, and this is all that is needed to protect the individual over the long term, but BCG immunity clearly wanes in some, but not all populations, so this belief is now challenged (43).

Despite the recognised effectiveness against severe disease, TB is still reported in BCG vaccinated children. A recent study reported on the outcomes for 16 Tunisian children, aged two – 168 months, all of whom presented with tuberculosis meningitis despite being given BCG vaccination at birth. Three died and nine of the remaining 13 developed permanent sequelae (51).

Due to limitations in controlling infection, BCG vaccines do not have impact on transmission of the organism (4).

### 5.3.2.1.1 Revaccination

There is little evidence that BCG revaccination confers any additional protection. A randomised control trial in Guinea-Bissau followed 2871 children for up to five years, who had been given an infant dose of BCG and revaccinated at 19 months. Over that time, 250 were admitted to hospital for the first time between enrolment and the end of the study, with an incidence rate ratio for BCG-revaccinated children versus controls of 1.04 (95% CI 0.81-1.33). The trial was stopped prematurely due to a cluster of deaths in the revaccinated arm of the study. The hazard ratio for BCG-revaccinated children compared with controls was 2.69 (95% CI 1.05-6.88). Throughout the trial, the effect of BCG revaccination on mortality was significantly higher in children who had received diphtheria-tetanus-pertussis booster vaccination before

enrolment than for children who had not receive the booster before enrolment ( $p=0.006$ ). The authors concluded that there was no overall beneficial effect of being revaccinated with BCG and the effect of BCG revaccination on mortality might depend on other health interventions (52).

An extension study of the BCG-REVAC trial in Brazil followed up over 200,000 children, aged seven-14 years, to evaluate the efficacy of BCG revaccination in children who had received neonatal vaccination and were revaccinated at school age. With a nine year follow-up, overall vaccine efficacy on prevention of diagnosed TB was 12% (95% CI -2 to 24%) compared to 9% (95% CI -16 to 29%) at five years. With revaccination, vaccine efficacy was 19% (95% CI 3-33%), 1% (95% CI -27 to 27%) and 33% (95% CI 3-54%) in three different cities. Efficacy was only significant in Salvador, the city furthest from the Equator and confined to a small subgroup of children less than 11 years at vaccination. The authors suggested that revaccination can offer weak protection in selected subgroups (53).

### 5.3.2.1.2 Population differences

A small study comparing 40 Malawian infants with 28 UK infants given the same BCG strain vaccine, between three and 13 weeks of age, demonstrated differences in 27 cytokine responses for infants between the two countries. The authors proposed that the pattern of cytokines produced by Malawian infants following vaccination, and after contact with infectious diseases, is already predetermined *in utero*, at birth or within the first few months of life and may be due to maternal factors, genetic factors, epigenetic factors, nutritional factors and environmental factors (54).

### 5.3.2.1.3 Low birth weight

A small study reported on mortality outcomes for 105 low-birth weight infants (< 2.5 Kg) in The Gambia. BCG vaccine was randomised to give at birth with 51 infants or at more than a month of age in 54 infants. Overall, lower mortality was seen in the group given the birth dose. At two months follow-up, the group given BCG at birth had significantly lower mortality (mortality relative risk [MRR] 0.27, 95% CI 0.07-0.98), and the effect was stronger in boys (MRR 0.21, 95% CI 0.04-1.03) than with girls (MRR 0.81, 95% CI 0.19-3.36) (55).

### 5.3.2.2 BCG strains and effectiveness

The original BCG strain was maintained at the Pasteur Institute and then distributed to dozens of laboratories in many countries. Each laboratory produced its own BCG line and maintained it by serial passage. This has resulted in many daughter BCG strains that differ widely. In an attempt to standardise production and vaccine characteristics the production laboratories adopted a seed lot system in the mid-1950s, and in the 1960s the WHO recommended standards for the stabilisation of the biologic characteristics of the daughter strains. Despite this, strains in use still vary widely in many characteristics (3).

A recent study in a guinea-pig model, on the genetic stability of Japanese BCG vaccine, showed that there were no significant differences between seed lot, the product manufactured by normal procedures and the 20<sup>th</sup> passage product indicating the maximum number of passages, currently required by WHO for BCG vaccines (12 passages), is adequate for the Japanese BCG vaccine (56).

A retrospective cohort study followed four years of birth cohorts for infants born in Kazakhstan, where birth BCG coverage is over 95 % and BCG are used from three different sources. The infants were followed for three years and outcomes were notifications of clinical TB, culture-confirmed TB and TB meningitis. Effectiveness was measured based on vaccinated versus non-vaccinated cohorts. All three BCG vaccines showed effectiveness for TB notifications: the Japanese-BCG was 69% effective, the Serbian vaccine 43% effective and the Russian vaccine 22% effective. For culture confirmed TB, the Japanese BCG was 92% effective, Serbian 82% and Russian 51% effective. All three were >70% effective against TB meningitis. While there was a range of limitations in this study, it does highlight the considerable differences between different vaccine strains (57).

Most recent expert opinion is that based on the evidence to date the loss of genes in different BCG strains does not confer any difference in protective efficacy (43).

### 5.3.2.3 Birth dose

Smith et al. summarised the data for the effectiveness of a birth dose and comment that there are only three prospective community trials evaluating the efficacy of BCG vaccine given at birth (3). The limited data shows that there are much higher rates of immunogenic sensitisation in children if BCG vaccination is delayed from the first week to nine months of life. One clinical

trial has demonstrated good T cell responses in infants vaccinated at 10 weeks compared with being vaccinated at birth. Infants, even preterm infants vaccinated at 34 to 35 weeks, develop lymphocyte proliferation and interleukin IL-2 production in response to a BCG vaccine (58). A small trial of BCG in Guinea Bissau with 105 low birth weight infants (<2.5kg) randomised to BCG at birth (n=1182) or later, at a median of 7.7 weeks (n=1161), showed a 45% (95% CI 11%-66%) lower mortality for those given the BCG at birth versus being delayed to after two months of age. While the methodology was challenged with questions around inadvertent bias, the authors are clear that the suggested possible biases were unlikely to produce these results (59).

A widely accepted hypothesis is that natural immunity to nontuberculous mycobacteria in the environment renders BCG vaccine less effective or masks its protective effect. Enhanced immunogenicity in neonates vaccinated prior to nontuberculous mycobacteria has been observed. It is thought that the reduced efficiency of BCG vaccine may be explained by over attenuation of the vaccine due to negative regulatory immune mechanisms, suppressor responses can be induced by BCG vaccine, and regulatory T-cells and IL-10 have been shown to play a role in this suppression. A Gambian study assessed whether exposure to nontuberculous mycobacteria attenuated BCG immunogenicity by the induction of specific regulatory T-cells. One hundred and three infants were randomised to receive BCG at birth or at 4.5 months and immune responses were assessed at both 4.5 and nine months of age. Vaccination at birth significantly enhanced Th1, Th2, IL-6, IL-17 and regulatory T cell responses measured at 4.5 months compared with the BCG naïve group (no birth dose). Responses waned by nine months, leading to comparable immunity in both groups at nine months of age. The authors commented that vaccination at birth induces a broad cellular response, which was reduced when delaying the vaccination, and that at nine months outcomes are similar (60).

### 5.3.2.4 HIV-infected

Efficacy of the BCG vaccines in HIV-infected children is unknown (3).

### 5.3.3 All-cause mortality

There is good evidence from six randomised controlled trials that the BCG vaccine reduced mortality from infections, other than TB, in developed countries in the 1940s and 1950s, and more recently, in developing countries (59, 61). Other studies have shown possible protective effects against leukaemia in childhood (62). The protective effect of BCG varies greatly from region to region, and generally, appears more protective when given earlier in life (62).

A recent study in Guinea-Bissau showed potent non-specific effects on mortality in low birth weight neonates, who were randomized to receive BCG at birth or at an older age (median 7.7 weeks). BCG administered at birth reduced mortality (mortality risk ratio [MRR] 0.43; 95% CI 0.21–0.85) with fewer deaths from fever, sepsis and acute respiratory tract infections in the first month of life (59). Combining data from the two neonatal studies in Africa shows that neonatal mortality rate ratio was just over 50% (MRR 0.52, 95% CI 0.33–0.82) (63).

Commentators have suggested possible reasons, including that vaccination may generate cross-reactive T cells that recognise epitopes, such as those presented on cancer cells, or the vaccine could substitute for microorganisms that lead to the development of immune regulatory pathway (62).

#### 5.3.3.1 Vitamin D

An observational study collected blood samples from 47 infants in the UK, at three months post BCG birth vaccination, and 37 infants at 12 months post BCG birth vaccination, which were compared with age-matched unvaccinated infants as a control group (n=60). Overall, 58% of all infants have low vitamin D levels (<30ng/ml). BCG vaccinated infants were almost six times more likely to have sufficient vitamin D levels than the matched controls (95% CI 1.8–18.6). The authors suggested these effects may be due to TB antigens in BCG activating toll-like receptors on macrophages, resulting in increased production of enzymes that lead to increased production of 25(OH)D (Vitamin D). Vitamin D has been shown to play a role in immune-regulation and is thought to be involved in many autoimmune and inflammatory diseases. It is possible that part of the non-specific effects attributed to BCG vaccination may be due to increased vitamin D levels (64).

### 5.3.4 Herd immunity

Since BCG vaccines do not have impact on transmission of the organism, they do not offer any herd immunity protection.

### 5.3.5 Duration of protection

The duration of immunity after BCG vaccination is unknown. A systematic review found no evidence of substantial protection against TB after 10 years, although the authors also report a UK study suggesting around 59% protection at 10–15 years after vaccination in school-age children (65). Most of the data to date, as of early 2013, suggests that there is decreasing protection with increasing age, and waning immunity is seen 15–20 years after vaccination. Although, protection in just over 50% of patients, aged 50–60 years after a single dose of BCG vaccination, has also been reported (3). BCG clearly wanes in some populations, but not others, and there is no data on the stability or longevity of the induced memory T cells, or what happens to them beyond the point on initial exposure to mycobacteria. Memory T cells may be subject to different rates of attrition in different geographical areas e.g. different TB prevalence, low population density, levels of exposure of environmental mycobacteria (43).

Recent data suggest that there are two broad subsets of memory CD4 and CD8 T cells – effector memory T cells generated by the BCG in large numbers in the lung, and central memory T cells that BCG induces in only relatively low numbers. Whether the failure of BCG to generate any appreciable levels of central memory has any relevance to protection is still unclear (43).

### 5.3.6 BCG and leprosy

BCG is now well recognised as inducing protection against leprosy, although, with considerable heterogeneity in results. This meta-analysis by Merle et al. summarises the efficacy data to date (66).

## 5.4 Summary of immunogenicity, efficacy and effectiveness

The exact immune response elicited by BCG vaccination and the mechanism of action in the host are still not well understood. There is no reliable established laboratory correlate for immunity to *Mycobacteria tuberculosis*. While it is unlikely that any single, simple measure of cellular immune function will be useful as a direct correlate of protection, new breakthroughs in technology are on the horizon that could improve the diagnostic tools available.

Efficacy for BCG vaccines varies from 0 - 80%. The vaccines provide protection against meningitis and disseminated TB in children, particularly in newborns and young infants. However, BCG vaccines do not prevent primary infection, are only partially effective against severe infection in children, are unreliable against adult pulmonary TB, and not effective against reactivation of latent pulmonary infection. In persons infected with TB subsequent vaccination with BCG does not augment the immune response.

BCG vaccines do not appear to prevent infection with *Mycobacterium tuberculosis*, but can prevent disease in the host, particularly associated with dissemination of the organism. Therefore, the vaccines offer a higher level of protection against the most serious forms of TB, particularly meningitis and disseminated disease, than against the more moderate forms of disease, usually pulmonary.

There are significant differences in efficacy across populations and geographical areas. Maternal factors, genetic factors, nutritional factors and environmental factors all appear to influence efficacy. Efficacy and immunogenicity responses vary considerably across strains, but the data to date cannot differentiate which strains are more effective, overall.

HIV-exposed infants show a blunting of the immune response to early infancy BCG. Efficacy in HIV-infected infants is unknown.

In developing countries, a birth dose of BCG significantly reduces overall infant mortality. One possible aspect of this effect may be that BCG appears to enhance the production of vitamin D.

BCG offers no impact on disease transmission and hence, there are no herd immunity effects. Duration of protection is unknown, possibly 10 to 15 years; it may be much longer in some populations.

## 6. Age-specific issues

### 6.1 Objective

The objective of this section is to consider the evidence for offering the vaccine to different age groups.

### 6.2 Review

#### 6.2.1 Vaccine issues for different age groups

BCC vaccines are more effective if given to mycobacterium naïve persons. Efficacy and effectiveness data shows that the vaccine works most effectively in young infants, but is less effective and more variable in older children and adults. Lower efficacy in older children and adults is due to a large range of factors, but particularly that they may have already been exposed to environmental mycobacterium.

In developing countries, where there is a high burden of disease in young infants, vaccination programmes are recommended to be directed at newborns or very young infants. Vaccination of newborns appears to reduce all-cause mortality and neonatal vaccination is more effective than with delayed vaccination in these developing countries. Vaccination of the newborn with BCG may also act as an adjuvant for other vaccines given during the newborn period (3).

Revaccination appears in the majority of cases not to be effective, so BCG has little role in the management of older child and adult vaccination in developing countries.

The epidemiology of the disease is very different in more affluent countries, compared with poorer countries, where disease is more likely to occur in adults, particularly in high risk groups – immigrants from TB endemic areas and those in close living proximity to them and is associated with other factors such as poverty, overcrowding and poor nutrition. The efficacy of BCG is not well established in older children and adults, and does not prevent severe or disseminated TB disease, or the spread of disease.

The most common age of diagnosis in NZ is aged 20–29 years, with most cases in this age group or older, and the majority of cases in immigrants from TB endemic-areas where they were likely to have been infected younger and arrived in NZ with LTBI that reactivated. Strategies therefore need to be targeted at high risk groups and there appears little gain for universal strategies in the NZ context.

# 7. Vaccine options

## 7.1 Objective

The objectives for this section are to consider the different vaccine options available to NZ in terms of available vaccines and schedules.

## 7.2 Review

### 7.2.1 BCG vaccines

As of early 2013, there are seven sites throughout the world that produce BCG vaccine. Since the mid-1970s to 1997, an international system for the production and quality control of BCG vaccines was centred at the WHO. Quality control of BCG vaccines is now the responsibility of individual manufacturers, overseen by the independent National Regulatory Authorities in the country of manufacture.

The vaccines are known by the location where they are produced. Although there are many different strains in use, four main strains account for more than 90% of the vaccine in use worldwide (3):

- The French (Pasteur) strain 1173 P2
- The Danish strain 1331
- The Glaxo strain 1077, derived from the Danish strain 1331 but different from it substantially (The English Evans vaccine and French Merieux vaccine are the Glaxo strain)
- The Tokyo strain 172

These vaccines are not identical, there are known differences in molecular and genetic characteristics. It is not known to what extent that creates any differences in efficacy or safety (4).

Comparative genomic studies have documented that BCG vaccine strains have and continue to evolve from the original BCG, first used in 1921, and from each other. Because these genetic differences affect the antigenic proteins, changes are likely to translate into differences in efficacy and effect.

While differences between BCG strains have been noted, data has been limited and with small numbers, so far. The largest study, published in 2012, is an observational study based in Uganda following 1341 infants and comparing by BCG-strain group. There were three groups who received BCG-Russia (n=1124), BCG-Bulgaria (n= 788) or BCG-Denmark

(n=169) at birth. At one year, all infants were tested for IFN- $\gamma$ , IL-5, IL-13 and IL-10 responses to Tb-specific antigens and non-TB stimuli (tetanus toxoid and phytohaemagglutinin) measured using ELISA. Cytokine responses, scar frequency, BCG associated adverse event frequency and mortality rates were compared across groups, and adjusted for potential confounders. The results show that both specific and nonspecific immune responses varied between strains, including responses to stimulation with tetanus toxoid. BCG-Denmark immunised infants had the highest cytokine responses. Scarring differed significantly with BCG scars occurring at one year of age in 52.2% of BCG-Russia vaccinated, 64.1% BCG-Bulgaria and 92.6% of infants vaccinated with BCG-Denmark ( $p < 0.001$ ). Scarred infants had higher IFN- $\gamma$  and IL-13 responses to TB antigens than infants without a scar. It is possible, but not proven, that the greater immunogenicity of BCG-Denmark may lead to better protection against TB; however, the authors noted that IFN- $\gamma$  alone is an insufficient protective marker and it is feasible that higher regulatory IL-10 noted in the same group may counteract its effects (47).

#### 7.2.1.1 Choice of BCG strain

There is no worldwide consensus about which strain of BCG is optimal for general use. The use of a weaker strain gives less side effects, particularly adenitis, however they may also have lower efficacy (3).

### 7.2.2 Alternative vaccine options

The widespread challenge of TB and the limitations of the BCG vaccines have made the development of new vaccine options a very high international priority. There is large effort behind looking for new options, including the WHO Initiative for Vaccine Research (IVR) which acts as a facilitator (41). There has been recent renewed interest in developing novel vaccines for TB. According to the Global Plan to Stop TB, 2006–2015, “effective TB vaccines will be an essential component of any strategy to eliminate tuberculosis (TB) by 2050” (67). Novel vaccine candidates include both live and sub-unit vaccines. Many use a “prime-boost” strategy that is intended to complement the existing immune response to BCG. Either the existing BCG or a new recombinant BCG is administered first, and then the new vaccine serves as a “booster”.



There has been more than US\$600 million invested between 2005 and 2012 which has allowed more than 15 vaccines to be tested in more than 50 human trials and joint international priorities (61, 68).

The options for new TB vaccines include (4):

- Priming vaccines intended for newborns to replace BCG and to prevent TB in people who have not been infected with the organism.
- ‘Early’ booster TB vaccines that can be delivered with other childhood vaccines in early infancy to amplify the immune response induced by the priming vaccine.
- ‘Late’ booster TB vaccines that are administered after infancy, typically to school-aged children, adolescents or adults who are potentially infected, but show no sign of disease. These vaccines are intended to reduce progression from latent to active disease.
- Therapeutic vaccines given to people with active TB alongside drug therapy and aim to shorten the duration of the therapy or reduce relapses after completion of treatment.

The WHO reports that, by 2011, there were 12 TB vaccine candidates had entered clinical trials (69).

There are currently two adjuvanted protein subunit vaccines, called fusion proteins, in phase IIa trials.

There are two virus vectored vaccines that express one or more TB antigens in phase IIb trials:

- MVA-85A, based on the ‘modified vaccinia Ankara’ vector and expresses TB antigen 85A (61, 70-75).
- Aeras 402 based on the adenovirus 35 virus vector and expresses several TB antigens (76).

There are five vaccines in pre-clinical development and an additional 33 novel candidates in early pre-clinical development (61). There is early animal data on DNA vaccines and recombinant virus-based vaccines (77-80).

The WHO predicts that, assuming one of the most advanced vaccine candidates shows sufficient efficacy, the first new TB vaccine could become available at the earliest around 2018.

## 7.3 Summary for vaccine options

Currently, there are seven sites throughout the world that produce BCG vaccine. The vaccines are known by the location where they are produced. Although there are many different strains in use, four main strains account for more than 90% of the vaccine in use worldwide. BCG vaccine strains have and continue to evolve from the original BCG first used in 1921 and from each other. There is no worldwide consensus about which strain of BCG is optimal for general use. The use of weaker strains give fewer side effects, however, they may also have lower efficacy.

There is large international effort behind looking for new options. The options include:

- Priming vaccines intended for newborns to replace BCG, and to prevent TB in people who have not been infected.
- ‘Early’ booster TB vaccines that can be delivered with other childhood vaccines in early infancy to amplify the immune response induced by the priming vaccine.
- ‘Late’ booster TB vaccines that can be administered after infancy to, school-aged children, adolescents or adults who are potentially infected, but show no sign of disease. These vaccines are intended to reduce progression from latent to active disease.
- Therapeutic vaccines given to people with active TB alongside drug therapy and aim to shorten the duration of the therapy or reduce relapses after completion of treatment.

By 2011, there were 12 TB vaccine candidates that had entered clinical trials. The first new TB vaccine could become available at the earliest around 2018.

# 8. Options for scheduling

## 8.1 Objective

This section will review the evidence for different options for placement of TB vaccine on the national immunisation schedule and/or for special groups.

## 8.2 Review

BCG vaccines have not, and cannot, lead to the elimination of the disease from the human population and are not considered a reliable tool for TB control (81). Despite the use in over four billion people, there has been almost no effect on the worldwide prevalence of TB. TB can only be eliminated if new, more effective vaccines are developed. However, despite that, it is likely that millions of cases of severe TB, meningeal and disseminated, have been prevented by its widespread use, particularly in children. Of note, it has also reduced rates of leprosy, especially in Africa.

The BCG vaccine prevents severe forms of TB in children, such as TB meningitis; it is less effective in preventing pulmonary TB in adults, because the protection appears to be limited. In developed countries, the strategy for adults has moved to protecting high-risk adults such as those who work with patients who have multidrug resistant TB. However, there is no data on the effectiveness of using BCG vaccines in adults (3).

The WHO recommends a single dose of BCG vaccine to newborns in developing countries with a high prevalence rate of infectious TB. Countries with lower rates of TB have already discontinued or are considering to discontinue BCG vaccination. However, in countries where there are cases from high-risk immigrant communities, BCG vaccination selectively targeted programmes continue. The current NZ strategy of offering vaccination to newborn infants from immigrant families coming from countries with endemic TB rates  $\geq 40$  per 100 000 is consistent with this approach.

The worldwide epidemic of HIV infection has had a significant effect on the epidemiology of TB. However, the risk of disseminated BCG disease prevents its use in HIV-infected children, currently.

Many studies have noted markedly different cytokine responses following BCG vaccine across countries. It is possible that different settings and populations will require variation in vaccines, vaccine doses or immunisation schedules. It is anticipated that the new generation of vaccines will improve upon the variability in effectiveness seen in BCG across populations, but time will tell (82).

In many developed countries, exposure to TB is now unlikely in infancy or childhood. A recent study of non-vaccinated Swedish healthcare students showed that nearly all of them were tuberculin skin test non-reactive, indicating low exposure to TB. Hence, some commentators now recommend, in low prevalence settings, to consider BCG vaccination for adolescents who are at risk of exposure such as high risk occupations and are tuberculin skin test negative (83). However, this is not a consistent recommendation and opinion remains divided.



# 9. Implementation issues

## 9.1 Objective

The objective of this section is to consider the issues around implementation.

## 9.2 Review

### 9.2.1 Route of delivery

While traditionally a range of delivery routes have been used, including oral administration which has not been used since the 1970s, intradermal injection in the deltoid using a syringe and needle is now the internationally accepted route for all current BCG vaccines; this is because the dosage can be measured precisely and the administration can be controlled (3, 84). Despite there being higher rates of local reactions, including ulcers and lymphadenitis with the intradermal route, this remains the method recommended by the WHO and the United Nations Children's Fund (UNICEF) (3).

Japan and South Africa use a percutaneous administration with a multipuncture device, apparently, with a low rate of adverse events. No conclusive trial has been reported that compares the various techniques, although opinion is that local complication rates are generally lowest with multipuncture devices (3).

### 9.2.2 Dosage

The recommended dosage differs by vaccine strain and the age of the recipient. Most manufacturers recommend a 0.05ml dose for infants and a 0.1 ml dose for children and adults (3).

### 9.2.3 Use of Tuberculin skin test

A 2012 review article reviewed and discussed current international guidelines and recommendations on the need to screen children for LTBI prior to BCG vaccination. The authors concluded that there was lack of evidence on which to base recommendations for the undertaking of tuberculin tests, and suggested that an alternative strategy, using a risk assessment questionnaire, to identify children more likely to have LTBI and who could then have a tuberculin skin test; this would reduce the number of unnecessary screens on children (85).

### 9.2.4 HIV Infection

People with untreated HIV infection previously infected with TB, develop TB disease at a rate of 5-10% per year, compared with the lifetime risk of 5-10% in immunocompetent adults (3). The efficacy of BCG in adults and children with HIV infection is not well established, and there are strong safety concerns about the use of the vaccine in infants with HIV infection.

In 2007, the WHO revised its policy on BCG vaccination of children with HIV, making HIV infection in infants a full contraindication for BCG vaccination, even in settings highly endemic for TB (86). They recommend delaying immunisation in HIV-exposed infants until HIV infection has been ruled out. However, this has been challenged by some authors (34).

### 9.2.5 Immunodeficiency

Vaccination of immunocompromised individuals can lead to severe disseminated disease. Some commentary authors recommend that BCG vaccine should be delayed for a few months in families with a history of recurrent infection, or any history of primary immunodeficiency, as this could suggest a genetic underlying immunodeficiency in the child (6, 30).

### 9.2.6 Risk of spread to contacts

Ulceration and drainage at the vaccination site can culture viable mycobacteria for up to two months after vaccination, raising the potential for spread to contacts, particularly immunocompromised. There are no reported cases of organisms becoming airborne from BCG ulcerated sites.

### 9.2.7 Concomitant administration at birth with hepatitis B vaccination

A blinded randomised controlled trial of 76 healthy infants in India compared neonatal pain during injection and showed that pain was reduced when the BCG was administered before the hepatitis B vaccine in neonates undergoing routine vaccination (87).

### 9.2.8 Repeat vaccination

Repeat BCG vaccination is not recommended, even when travelling to countries with a high TB burden, as revaccination of individuals after initial vaccination does not seem to offer substantial additional protection (65). The UK recommendations are to be aware that, the best estimate of duration of protection by BCG is currently about 10 years and the level of protection seems to fall with time. People vaccinated 10 years or more before coming into close contact with infectious tuberculosis might have no BCG derived protection against active disease. BCG does not protect when given to people who are already infected (65).

### 9.2.9 Post-exposure vaccination

The international advice on post-exposure vaccination is not consistent (3). The UK recommends BCG vaccination for unvaccinated contacts with negative tuberculin skin tests. The US recommends BCG vaccination for young children who are continually exposed to TB and cannot be removed from the exposure, or cannot be treated with prophylaxis.

### 9.2.10 Vitamin A and BCG

A trial in 1717 low birth weight infants (<2.5Kg) in Guinea Bissau showed that there was no interaction observed between the use of vitamin A and birth and the delivery of BCG at birth versus giving BCG later (88).

## 9.3 Summary for implementation issues

Intradermal administration in the deltoid using a syringe and needle is now the internationally accepted route for all current BCG vaccines because the dosage can be measured precisely and the administration can be controlled. Percutaneous multipuncture devices may offer advantages with lower rates of adverse events and are currently offered in Japan and South Africa.

The recommended dosage differs by vaccine strain and the age of the recipient. Most manufacturers recommend a 0.05ml dose for infants and a 0.1 ml dose for children and adults.

The use of tuberculin tests prior to BCG vaccination is not recommended for newborns and remains controversial for older ages. A risk assessment questionnaire to identify those likely to have latent TB may be more useful.

The WHO currently recommends not giving BCG vaccination to HIV-infected infants, although this is challenged by some authors. Some commentary authors now recommend that neonatal BCG vaccine should be delayed for a few months in families with a history of recurrent infection, or any history of primary immunodeficiency as this could suggest a genetic underlying immunodeficiency in the child.

Repeat vaccination with BCG is not recommended.

International advice on post-exposure vaccination is inconsistent. In light of this, the current NZ advice as listed in the Guidelines for Tuberculosis Control in New Zealand 2010 advising BCG vaccination only for unvaccinated Mantoux-negative contacts under five years of age seems currently sensible advice.

# 10. International policy and practice

## 10.1 Objective

The objective to this section is to summarise international practice with regard to the use of BCG vaccines.

## 10.2 Review

There is wide disparity among countries concerning vaccine schedules. The official recommendation of the WHO is a single dose given in infancy.

The International Union against Tuberculosis and Lung Disease (IUATLD) has suggested criteria for countries to consider when shifting from routine universal BCG vaccination to selective vaccination of high-risk groups. They recommend that BCG be discontinued only if, 1) an efficient notification system is in place, and 2) either the average annual notification rate of smear-positive pulmonary tuberculosis is less than five per 100,000, the average annual notification rate of tuberculous meningitis in children under five years of age is less than one in 10 million population over the previous five years, or the average annual risk of tuberculosis infection is less than 0.1% (3).

A website has been created, which is sponsored by the public health agency of Canada, because TB vaccination policies and practices vary markedly across time and countries. This “BCG World Atlas” is a searchable, online, open-access database of global BCG vaccination policy and practices (<http://www.bcgatlas.org/>). It contains detailed information on current and past BCG policies and practices for over 180 countries, covering 86% of all countries (89).

Among the 180 countries with available data, as of early 2013, 157 recommend universal BCG vaccination, while the remaining 23 countries have either stopped BCG vaccination, due to a reduction in TB incidence, or never recommended mass BCG immunisation and instead focus on selective vaccination of more ‘at risk’ groups. Nine countries have ceased universal BCG vaccination programs; Spain in 1981, then Denmark in 1986, Austria in 1990 and Germany in 1998. The Isle of Man, Slovenia, UK,

Finland and France all ceased their BCG vaccination campaigns between 2005 and 2007. Most of these countries do continue to provide BCG vaccination selectively to high-risk individuals, including those involved in high TB risk occupations and/or travel, and infants born into high TB risk environments. In the past, 33 countries had multiple vaccination programmes, but have since ceased revaccination and now use a single BCG vaccination schedule, usually for newborns. In 16 countries, an additional BCG vaccination after the initial BCG vaccination continues. Four countries, Kazakhstan, Belarus, Uzbekistan and Turkmenistan, continue to recommend three BCG vaccinations, with the third given between the ages of 12 and 15. Of the 19 countries that do not recommend universal BCG vaccination, vaccine is offered to certain at-risk groups, most frequently healthcare workers and infants living in high-risk TB settings.

### 10.2.1 United States

The US has never had a universal TB vaccination strategy. BCG vaccination is only used for selected persons who meet specific criteria:

- Infants and children who reside in settings in which the likelihood of TB transmission and subsequent infection is high, provided no other measures can be implemented.
- Healthcare workers (HCW) who are employed in settings in which the likelihood of transmission and subsequent infection with TB strains resistant to isoniazid and rifampicin is high.

BCG vaccination is not recommended for children and adults who are infected with HIV.

### 10.2.2 United Kingdom

The UK initiated a single dose BCG for 10 – 14 year olds in 1957, as well as to certain groups at higher risk of exposure to TB. In 2005, this was discontinued and vaccination is now recommended for infants living in high-risk areas or with high-risk persons.

### 10.2.3 Australia

BCG is recommended in Australia for (90):

- Aboriginal neonates in areas of high incidence of TB, such as the Northern Territory, Far North Queensland, northern areas of Western Australia and South Australia;
- Neonates and children five years and under who will be travelling or living in countries or areas with a high prevalence of TB for extended periods;
- Neonates born to parents with leprosy or a family history of leprosy;

In addition to these recommendations BCG may be considered in the following:

- children over five years who will be travelling or living in countries or areas with a high prevalence of TB for extended periods;
- Healthcare workers who may be at high risk of exposure to drug resistant cases.

## 10.3 Summary of international policy and practice

Most countries that continue national policies use neonatal or early infant BCG. Very few countries use repeated doses.

Most developed countries now have moved to targeted policies with vaccination of high risk infants and/or high risk people of other ages, such as healthcare workers.

As TB rates continue to decline in developed countries, it is expected that trends will continue to limit BCG vaccination to even more selective use and to discontinue universal immunisation programmes.

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