7. BCG Vaccination

The Bacillus Calmette-Guerin (BCG) vaccine was derived by in-vitro attenuation of the bovine tubercle bacillus between the years 1908 and 1918 in France. WHO encouraged widespread use of the vaccine starting in the 1950s and as a result more than 70% of the world's children now receive BCG. However, the policies on BCG vaccination differ greatly both nationally and internationally, reflecting differences of expert opinion as to the mechanism of action and effectiveness of the vaccine.[242] The potential loss of the tuberculin test as an indicator of natural infection with tubercle bacilli when BCG is routinely used may be a disadvantage that has to be weighed against the benefits of the vaccine.

7.1 Clinical Efficacy

The clinical efficacy of a vaccine is measured in terms of the percentage reduction in disease among vaccinated individuals that is attributed to vaccination i.e. the proportion of those vaccinated who gain protective immunity from the vaccine.[243] BCG vaccines are generally given to protect against TB. BCG vaccine does not give 100% protection but it does protect against the more serious forms of the disease, e.g. TB meningitis especially in the young. The NICE guidelines cite evidence from both randomised controlled trials and case control studies for the efficacy of BCG vaccination in infancy in preventing pulmonary TB infection, TB deaths, TB meningitis, laboratory-confirmed TB cases and disseminated TB.[26] BCG vaccine is probably most consistently effective against tuberculous meningitis and miliary TB with protection lasting approximately 15 years. It is universally agreed that BCG vaccine protects small children from severe forms of childhood TB especially in areas with a high risk of infection.[244;245] In such areas with high infection risk, WHO EPI programme reports a global coverage of BCG in children less than one year at around 85%.[246]

An extensive study by Tala *et al.* attempted to interpret variations in the efficacy of BCG vaccine. Factors considered to be important are age at administration, prior exposure to environmental non-tuberculous mycobacteria, efficacy of BCG vaccine including vaccine quality, host genetics and nutrition, infection incidence, the study design and the route of administration.[247] A meta-analysis of large numbers of BCG efficacy trials revealed a protection rate against pulmonary TB of 86% in randomised trials and 75% in case control studies despite extensive use of the vaccine.[40] Colditz *et al.* in a meta-analysis estimated the overall efficacy of BCG in preventing pulmonary TB to be approximately 50%. Against TB meningitis the efficacy was 64% and against TB deaths 71%.[248] In summary, there is overall agreement that the efficacy of BCG is at its best about 80%[249] and of 15-20 years duration.[250] Kritski *et al.* reported a protection rate of 69% against MDR-TB in a recent study in 1996.[251]

7.2 Criteria for Discontinuation of a Universal BCG Vaccination Programme

In 1994, the International Union against Tuberculosis and Lung Disease (IUATLD) expert group published criteria for discontinuing BCG vaccination programmes in countries with a low prevalence of TB.[252] These criteria are outlined as follows:

IUATLD criteria

Before consideration is given to whether a country stops or modifies its BCG programme, the following requirements must be met:

- There is a well functioning TB control programme
- There has been a reliable reporting system over the previous five or more years, enabling the estimation of the annual incidence of active TB by age and risk groups, with particular emphasis on TB meningitis and sputum smear positive pulmonary TB. In Ireland, national data enabling a detailed epidemiological analysis for the country, as a whole was first produced by HPSC in the 1998 National TB Report. The 2006 National TB Report is the ninth national TB report.
- Due consideration has been given to the possibility of an increase in the incidence of TB resulting from the epidemiological situation of AIDS in that country.

With one of the following

- The average annual notification rate of sputum smear positive pulmonary TB should be 5 per 100,000 or less during the previous three years

or

- The average annual notification rate of TB meningitis in children under five years of age should be less than one case per ten million general population over the previous five years
  or
- The average annual risk of TB infection should be 0.1% or less. This is not applicable to Ireland.

The national rate for sputum smear positive pulmonary TB has been under 5 per 100,000 for the three years prior to 2006. In 2005 the rate was 3.3 per 100,000, while in 2004, 2003 and 2002, the rates were 3.5 per 100,000, 3.7 per 100,000 and 3.1 per 100,000 respectively. However, data from between 2001 and 2006 indicate that there were four cases of TB meningitis notified in children aged less than five years, of whom two were culture positive and three had not received BCG vaccine.[20]

When considering the importance of neonatal BCG vaccination, it is worth considering the practice in other European countries. For example, Sweden discontinued routine neonatal BCG vaccination in 1975 when they had a total notification rate of 20 per 100,000 population and an age-specific incidence rate for children aged 0-14 years of 0.3 per 100,000. While the national crude rate in Ireland is less than 20 per 100,000 population, the 2006 age-specific incidence rate for children 0-14 years was 2.4 per 100,000, eight times the rate recorded in Sweden when they discontinued neonatal BCG vaccination. In 2005, 2004, 2003, 2002, 2001 and 2000, the age-specific incidence rate for children aged 0-14 years was 3.0 per 100,000, 1.2 per 100,000, 2.9 per 100,000, 2.2 per 100,000, 1.9 per 100,000 and 1.9 per 100,000 respectively. In 1999, the age-specific incidence rate for children aged 0-14 years was 5.1 per 100,000 population, almost seventeen times the rate recorded in Sweden. In 1998, the corresponding figure was 3.5 per 100,000 population almost twelve times the rate recorded in Sweden when they discontinued BCG.[20]

It is also notable that Finland who moved from a universal newborn BCG vaccination programme to a targeted risk group programme in September 2006 had only five notified cases of TB in the 0-2 year olds between 1997 and 2001 and no cases of TB meningitis in the 0-14 year olds notified in this period. Since 1970, only two cases of TB meningitis have been notified nationally in Finland. The national incidence rate for TB is 11 per 100,000 and 65% of cases occur in those aged over 60 years. Foreign-born patients represent 6 to 9% of the total.[253]

When Canada discontinued universal BCG in 2002, the national TB notification rate was 5.2 per 100,000 and the notification rate was 1.6 per 100,000 in 0-14 year olds.[254]

Also, rates of TB notifications in 1998 in the following Nordic countries that have discontinued neonatal BCG programmes are much lower than in Ireland and among the best in the world as outlined below:

- Sweden = 5.0 per 100,000
- Norway = 5.0 per 100,000
- Denmark = 9.6 per 100,000
- Iceland = 5.8 per 100,000.

As well as the IUATLD criteria, there are additional considerations which should also be reviewed when deciding to modify or stop a universal BCG programme as outlined below:

- Costs
- Adverse reactions to BCG
- Risk groups: In the event of discontinuation of the BCG vaccination programme for the general population, it may be advisable to continue it in certain well-defined population groups with a known high notification rate of active TB.[253]

While Ireland meets the IUATLD criteria on the basis of overall smear positive pulmonary TB reporting rates, the number of TB meningitis cases in children and general rates of TB in children remain a concern. Also, the TB control programme is currently under review and it is likely that recommendations will be made for strengthening the programme. In light of these findings, the continuation of the universal programme of neonatal BCG vaccination is recommended in Ireland at this time.

Recommendation:

The continuation of a universal programme of neonatal BCG vaccination is recommended in Ireland at this time.

7.3 Dose and Route of Administration

BCG Vaccine Statens Serum Institut (SSI) is the only available licensed BCG vaccine in Ireland. It contains the Danish strain 1331. It does not contain thiomersal or any other preservatives. It may be given concurrently with another live vaccine, but if they are not given at the same time an interval of at least four weeks should be allowed between such vaccines. It can also be given at the same time as killed vaccines e.g. DTaP/IPV/Hib/Hepatitis B, PCV (pneumococcal conjugate vaccine) or Men C.

Recommendation:

When BCG is given to infants there is no need to delay the primary immunisations. No further immunisation should be given in the arm used for BCG immunisation for at least three months because of the risk of regional lymphadenitis.

Infants under 12 months of age

The recommended dose is 0.05ml by **intradermal** injection of the reconstituted vaccine at one site over the middle of the deltoid muscle.

Adults and children 12 months and over

The recommended dose is 0.1ml by **intradermal** injection of the reconstituted vaccine and given at one site over the middle of the deltoid muscle.

Although the protection afforded by BCG vaccine may wane with time, there is no evidence that repeat vaccination offers significant protection and repeat BCG is not recommended. If re-immunisation with BCG is being considered expert advice should be sought.

Detailed instructions including illustrations are available from the Immunisation Guidelines for Ireland prepared by the National Immunisation Advisory Committee.[255]

7.4 Indications for BCG Vaccine

Recommendation:

Training for health professionals in the correct administration of BCG vaccine is recommended. Those administering vaccine should be aware of indications, contraindications, immunisation and adverse reactions associated with BCG.

Groups in whom BCG vaccine is indicated:

1. Newborn babies
2. Unvaccinated children aged one to 15 years (i.e. those with no documented evidence of BCG or without a characteristic scar)
    i. Children aged three months to less than six years who are not in an at-risk environment[Π] do

[Π] Children in at-risk environments include those who are contacts of a pulmonary TB case, who are from an area of high endemnicity (annual TB rates of ≥ 40/100,000) or whose parents are from an area of high endemnicity or who have household contacts who belong to an at-risk group for TB

not need a TST (Mantoux test) prior to receiving BCG vaccine℘
ii. Children in at-risk environments should have a TST (Mantoux test) prior to BCG.[256]

3. Unvaccinated (that is without adequate documentation or a characteristic scar) Mantoux negative immigrants under 16 years of age who were born or who have lived for a prolonged period (at least three months) in a high incidence country♦ OR aged 16-35 years from a sub-Saharan African country or country with a TB incidence of 500 per 100,000[26]
4. Unvaccinated Mantoux negative contacts aged 35 years and under of cases with active pulmonary TB. Children under five years of age in contact with smear positive TB should be referred to a contact tracing clinic for investigation and then immunised with BCG as indicated.
5. Members of special at-risk groups such as the travelling community due to the logistical difficulties of providing alternative control measures and follow up of contacts
6. Unvaccinated Mantoux negative persons under 16 years of age intending to live or work with local people in high incidence countries for more than one month[257]
7. BCG is indicated for unvaccinated healthcare workers (HCWs) aged <35 years who are TST negative and who will have contact with patients or with clinically contaminated materials. Not all HCWs are at equal risk of TB. A risk assessment should be carried out to see if BCG is indicated for unvaccinated HCWs aged 35 years and older who are TST negative, taking into account their country of origin and the nature of their work. For more details see page 114.

8. Those more likely than the general population to come into contact with someone with infectious sputum smear positive TB. Unvaccinated Mantoux negative persons aged 35 years and under in the following occupations should be offered BCG vaccination:[26]
   i. Veterinary laboratory staff who handle animal species known to be susceptible to TB and abattoir workers who handle animal species, carcasses and products known to be susceptible to TB
   ii. Prison staff working directly with prisoners
   iii. Staff of facilities for the elderly
   iv. Staff of hostels for homeless people and facilities accommodating refugees and asylum seekers.

7.5 Contraindictions

BCG vaccine should not be given to:

1. Neonates in a household where an active TB case is suspected or confirmed
2. Those with a past history of TB
3. Those receiving systemic corticosteroid therapy (other than as replacement) or other immunosuppressive treatment including x-irradiation. Inhaled steroids are not a contraindication.
4. Those suffering from blood dyscrasias, lymphoma, or malignant neoplasms involving bone marrow or the lymphoreticular system, or with gamma globulin deficiency or abnormality
5. Those with a family history of primary immunodeficiency e.g. inherited severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), etc. until evaluation is complete
6. BCG should not be given to adults or children known to be HIV positive (asymptomatic or symptomatic). However, lack of knowledge of maternal HIV status is not a reason to defer routine BCG inoculation in healthy newborns.
7. Those with pyrexia ≥ 38°C
8. Those with generalised infected dermatosis. The effect of BCG vaccine may be exaggerated in these patients and a more generalised infection is possible. If the person has eczema, an immunisation site should be chosen that is free from skin lesions. Eczema is not a contraindication.
9. Those who are pregnant. Breast-feeding does not constitute a contraindication to BCG vaccine.
10. Those with positive tuberculin tests (or positive IGRA)
11. Those who have had a confirmed anaphylactic reaction to a component of the vaccine
12. Those who received a live vaccine e.g. MMR within the previous four weeks.

℘ In extremely rare instances, an accelerated local response to BCG vaccine known as Koch's Phenomenon characterised by induration that is more than 5mm (within 24-48 hours), early pustule formation (within 3 to 5 days), an ulcer (at seven day) and a scab (within 10-15 days) can occur and indicates concurrent TB

♦ High incidence refers to countries where the annual rate of TB is 40/100,000 or greater

7.6 Interactions

Administration of blood or plasma transfusions, hepatitis B vaccine, hepatitis B immunoglobulin and normal immunoglobulin are thought not to reduce the effectiveness of BCG vaccine.[258-261] A baby who has received blood or plasma transfusions can be subsequently immunised with BCG, after the observation period (24 hours) for transfusion reactions has ended. A baby who has received hepatitis B vaccine, hepatitis B immunoglobulin or normal human immunoglobulin can be subsequently immunised with BCG without delay.

7.7 Administration of BCG Vaccination

Detailed instructions are available in chapter 2 of the Immunisation Guidelines for Ireland available at www.immunisation.ie and also on the Staten Serum Institut (Denmark) website at www.ssi.dk/sw4145.asp.

7.8 Immunisation Reaction and Care of the Immunisation Site

The expected reaction to a successful BCG vaccination seen in 90-95% of recipients is induration at the injection site followed by a local lesion which starts as a papule two or more weeks after vaccination. It may ulcerate and then slowly subside over several weeks or months to heal leaving a small flat scar. It may also include enlargement of a regional lymph node to less than 1cm.

It is not necessary to protect the site from becoming wet during washing and bathing. The ulcer should be encouraged to dry and abrasion (for example by tight clothes) avoided. Should any oozing occur a temporary dry dressing may be used until a scab forms. It is essential that air is not excluded. If absolutely necessary (e.g. to allow swimming), an impervious dressing may be applied but only for a short period as it may delay healing and cause a larger scar.

Further observation after routine vaccination with BCG is not necessary, other than as part of monitoring of the quality of the programme, nor is further tuberculin testing recommended.

Severe injection site reactions, large discharging ulcers, abscesses and keloid scarring are most commonly caused by faulty injection technique, excessive dosage or vaccinating individuals who are tuberculin positive. It is essential that all healthcare professionals be properly trained in all aspects of the process involved in tuberculin skin tests and BCG vaccination.

7.9 Adverse Reactions

Local: Side effects include local induration, pain and occasionally ulceration, enlargement of a regional lymph node greater than 1cm, abscess formation, lupoid reaction and inflammatory and suppurative adenitis.[109]

General: Headache, fever and generalised lymphadenopathy can rarely occur (in less than one in 1,500 vaccinated). Anaphylactic reaction and disseminated BCG complications (such as osteitis, osteomyelitis or disseminated BCG infection) are also very rare. Disseminated BCG infection occurs in approximately two per one million persons, primarily in persons with severely impaired immune systems.[109]

Management of adverse reactions

Local adverse reactions to BCG vaccine occur in 1-2% of immunisations. Severe local reactions (ulceration greater than 10mm, caseous lesions, abscesses or drainage at the injection site) or regional suppurative lymphadenitis with draining sinuses following BCG vaccination should be discussed with a respiratory physician or consultant paediatrician.[255]

Most experts do not recommend treatment of draining skin lesions or chronic suppurative lymphadenitis caused by BCG vaccine because spontaneous resolution occurs in most cases. Large needle aspiration of suppurative lymph nodes may hasten resolution. There is little evidence to support the use of either locally instilled anti-mycobacterial agents or systemic treatment of patients with severe persistent lesions.

Disseminated BCG infection should be referred to a respiratory or infectious disease consultant for specialist advice and will normally require systemic anti-tuberculous treatment and mandate a detailed immunological investigation.[255]

7.10 Tuberculin Testing prior to BCG Immunisation

BCG vaccine should not be administered to an individual with a positive tuberculin test. Those with strongly positive tests should be referred to a respiratory or infectious disease physician for assessment of the need for further investigation and treatment.

A TST (Mantoux test) is necessary prior to BCG vaccination for:

1. Children aged three months to aged under six years in at-risk environments[Π]
2. Persons aged six years and older
3. Infants and children under six years of age with a history of ever having lived or had a prolonged stay (more than one month) in a country of high endemnicity (i.e. an annual TB rate of ≥ 40/100,000)
4. Those who have had close contact with a person with known TB and
5. There is a history of TB in a household contact in the last five years.

BCG can be given up to three months following a negative tuberculin test.

The standard skin test for use in Ireland is the Mantoux 2TU/0.1ml tuberculin PPD (see chapter 2).

Recommendation:

BCG should not be administered to an individual with a positive tuberculin (or IGRA) test.

For further detail on BCG, see the Immunisation Guidelines for Ireland available at www.immunisation.ie

[Π] Children in at-risk environments include those who are contacts of a pulmonary TB case, who are from an area of high endemnicity (annual TB rate ≥ 40/100,000) or whose parents are from an area of high endemnicity or who have household contacts who belong to an at-risk group for TB.