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Tuberculosis

BCG introduced in 1950s

NOTIFIABLE

Introduction

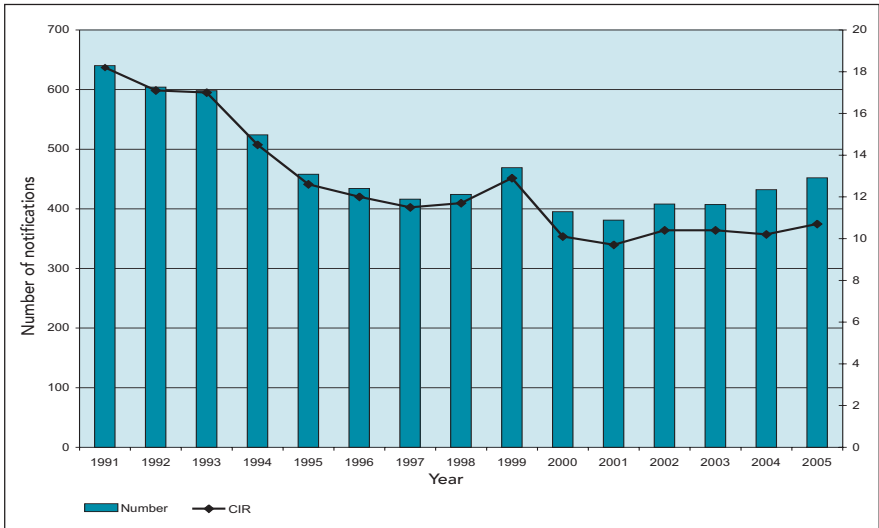
Human tuberculosis is caused by infection with bacteria of the *Mycobacterium tuberculosis complex* (*M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti* or *M. canettii*, *M. caprae*, *M. pinnipedii*). The organism may infect any part of the body. However, the majority of cases involve the respiratory system.

The World Health Organization (WHO) declared TB a global health emergency in 1993. In 2006 WHO launched the Global Plan to Stop TB 2006-2015 in collaboration with public and private partners. This plan is a comprehensive assessment of the action and resources needed for implementation and to make an impact on the global TB burden. It aims at global elimination of TB by 2050.

Epidemiology

The incidence of tuberculosis in Ireland has declined from a recorded rate of 230 cases per 100,000 in 1952 to a rate of 10.6 per 100,000 in 2005. The number of notified cases declined each year from 1991 to 1997 but increased in 1998 and 1999. The number of cases fell to 9.7 per 100,000 in 2001 with a total of 450 cases. Since 2001 the rate has slowly increased to the current rate of 10.6 per 100,000 (432 cases). Multidrug-resistant (MDR) isolates remain very uncommon, with 1-3 reported per year. Extensively drug-resistant (XDR) isolates remain very uncommon worldwide, with only 1 case reported in Ireland in 2005.

Figure 16.1 Number and crude incidence rates (per 100,000 total population) of tuberculosis notifications in Ireland, 1991-2005. Source: HPSC



Transmission

The infection is usually acquired by the respiratory route through breathing in infected droplets from a person with infectious pulmonary TB. Such transmission is more likely when the index case has sputum, which is smear positive for the bacteria on microscopy, and often occurs after prolonged close contact such as living in the same household as the case.

Effects of tuberculosis

A notified case of tuberculosis refers to clinically active disease due to infection with *M. tuberculosis* complex. Tuberculosis disease is classified as pulmonary, extrapulmonary or both. In Ireland, approximately 70% of all TB cases are pulmonary cases. Non-respiratory forms of TB are more common in those with impaired immunity.

The symptoms of TB are varied and depend on the site of infection. General symptoms may include fever, lassitude, loss of appetite, weight loss and night sweats. Pulmonary TB typically causes a persistent productive cough, which may be accompanied by blood-streaked sputum or more rarely frank haemoptysis.

The initial TB infection may be eliminated or remain latent or progress to active TB disease. Latent TB infection (LTBI) occurs where a person

has no symptoms and no evidence of TB disease but the TB bacteria remain in the body. LTBI may reactivate in later life in approximately 5% of persons particularly if an individual's immune system becomes weakened, e.g. by disease (HIV), due to certain medical treatments such as cancer chemotherapy, corticosteroids, TNF- α antagonists, or in old age. Currently a diagnosis of LTBI is most commonly based on a positive tuberculin skin test (Mantoux test). Interferon gamma release assays (IGRA) may be used (where they are available) as an adjunct to the tuberculin skin test in the diagnosis of LTBI.¹

BCG vaccine

Bacille Calmette Guerin (BCG) vaccine contains a live attenuated strain derived from *Mycobacterium bovis*. 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.

The efficacy of BCG in preventing tuberculosis has varied in reported studies over the years, but is probably most consistently effective against tuberculous meningitis and miliary TB, with protection lasting approximately 15 years. Two meta-analyses of published clinical trials and case control studies have shown the vaccine to be 70-80% effective against the most severe forms of disease such as TB meningitis in children. International and Irish studies have also indicated a protective efficacy of the vaccine against childhood tuberculosis.

BCG is less effective in preventing respiratory disease, which is the more common form in adults and more important for the transmission of the disease. There are few data on the protection afforded by BCG vaccine when it is given to adults (aged 16 years and older) and virtually no data for persons aged over 35 years.

BCG is not usually recommended for people over 16 years of age unless the risk of exposure is great, e.g. new entrants from areas where the annual rates of tuberculosis are high and those at occupational risk, in which case it is given up to and including age 35 years, except in the case of health-care workers when it is given at any age.

Indications for BCG vaccine continue to be re-evaluated by the National

¹ Interferon Gamma Release Assays (IGRA) are new whole blood tests for screening for latent TB infection (LTBI) and active TB disease. These tests measure the release of interferon-gamma from white blood cells in response to stimulation by the tuberculin antigens ESAT-6 and CFP-10 which are not present in BCG or the vast majority of non-TB mycobacteria. They aim to be more specific by removing false positive results and to be better correlated with LTBI.

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TB Advisory Committee. At present it is recommended that universal neonatal BCG be continued.

Dose and route of administration

BCG vaccine may be given concurrently with another live vaccine, but if it is not given at the same time an interval of at least 4 weeks should be allowed between such vaccines. It can also be given at the same time as killed vaccines, e.g. DTaP/IPV/Hib or MenC. 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 3 months because of the risk of regional lymphadenitis.

Infants under 12 months of age

The recommended dose is 0.05 ml, by **intra**dermal 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 0.1 ml, by **intra**dermal 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.

Indications

The vaccine is indicated for prophylactic immunisation in Mantoux (or interferon-gamma) negative individuals.

Groups in whom BCG vaccine is indicated

- a. Newborn babies
- b. Unvaccinated children aged 1-15 years (i.e. those with no documented evidence of BCG or without a characteristic scar)
 - Children aged 3 months to less than 6 years who are not in an at-risk environment² do not need a Mantoux test prior to receiving BCG vaccine
 - Children in at-risk environments should have a Mantoux test prior to BCG
- c. Unvaccinated Mantoux negative immigrants with a history of ever living in a high incidence country (Appendix 2) and their children who are previously unvaccinated (that is without adequate

² Children in at-risk environments include those who are contacts of a pulmonary TB case, who are from an area of high endemicity or whose parents are from an area of high endemicity.

- documentation or a characteristic scar) and aged younger than 16 years OR aged 16-35 years who ever lived in a sub-Saharan African country or country with a TB incidence of 500 per 100,000
- d. Unvaccinated Mantoux negative contacts aged 35 years and under, of cases with active respiratory tuberculosis. Children under 5 years of age in contact with smear positive tuberculosis should be referred to a contact tracing clinic for investigation and then immunised with BCG as indicated
 - e. Members of special at-risk groups such as the Traveller community – due to the logistical difficulties of providing alternative control measures and follow-up of contacts
 - f. Unvaccinated Mantoux negative persons under 16 years of age intending to live with local people in high-incidence countries for more than 1 month (Appendix 2)
 - g. All health-care workers who are previously unvaccinated (i.e. without adequate documentation or a characteristic scar) and will have contact with patients or clinical materials and are Mantoux (or interferon-gamma, if available) negative should be offered BCG vaccination irrespective of age. Health-care workers include the following:
 - Those who will have contact with patients or clinical materials
 - Laboratory staff who will have contact with patients, clinical materials or derived isolates
 - h. Those more likely than the general population to come into contact with someone with infectious sputum positive TB. Unvaccinated Mantoux negative persons aged 35 years and under in the following occupations should be offered BCG vaccination.
 - 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 tuberculosis. Agricultural officers and veterinary inspectors may require BCG vaccination based on individual risk assessment
 - Prison staff working directly with prisoners.
 - Staff of facilities for the elderly
 - Staff of hostels for homeless people and facilities accommodating refugees and asylum seekers.

Contraindications

BCG vaccine should not be given to:

- 1 Neonates in a household where an active TB case is suspected or confirmed
- 2 BCG vaccination is contraindicated for up to 6 months in infants born to mothers who received immunomodulating drugs in the second and/or third trimesters of pregnancy. Immunomodulators include

TNF-alpha inhibitors such as monoclonal antibodies (eg. infliximab, etc) and fusion proteins (eg enbrel); calcineurin inhibitors (eg cyclosporin); cytotoxics (eg azathiaprin, methotrexate); and steroids. A decision regarding giving BCG to a breast-feeding infant whose mother is receiving immunomodulators can be made on a case-by-case basis.

- 3 Those suffering from blood dyscrasias, lymphoma, or malignant neoplasms involving bone marrow or the lymphoreticular system, or with gamma globulin deficiency or abnormality
- 4 Those with a family history of primary immunodeficiency, e.g. inherited severe combined immunodeficiency (SCID), Chronic Granulomatous Disease (CGD) etc. until evaluation is complete
- 5 Those with pyrexia $\geq 38^{\circ}\text{C}$
- 6 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
- 7 Those who are pregnant. Breast feeding does not constitute a contraindication to BCG vaccine
- 8 Those with positive tuberculin tests (or gamma interferon tests)
- 9 Those who have had a confirmed anaphylactic reaction to a component of the vaccine.

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HIV

BCG should not be given to children known to be HIV positive. However lack of knowledge of maternal HIV status is not a reason to defer routine BCG inoculation in healthy newborns.

Low-birth weight infants

A number of studies of the safety and efficacy of BCG given to low-birth weight and/or preterm infants have been published. Some limitations of these studies are that they involved small numbers, were carried out in different ethnic groups, and used different BGG strains. Taking these limitations into account, the studies suggest that:

- BCG elicits an immune response in preterm infants from 28 weeks gestation.
- The response increases with increasing gestational age.

³ In extremely rare instances, an accelerated local response to BCG vaccine known as Koch's Phenomenon characterised by induration that is more than 5 mm (within 24-48 hours), early pustule formation (within 3 to 5 days), an ulcer (at day 7) and a scab (within 10-15 days) can occur and indicates concurrent TB.

- Preterm babies can be vaccinated effectively with BCG at 34–35 weeks gestation.
- Low birth weight newborns (<2500g) show a good immune response to BCG.

BCG vaccine can be given to low-birth weight infants before discharge from neonatal facilities when they have reached 34-35 weeks gestation, irrespective of their weight.

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Adverse reactions

Local: Side-effects include local induration, pain and occasionally ulceration, enlargement of a regional lymph node greater than 1 cm, abscess formation, lupoid reaction and inflammatory and suppurative adenitis.³

General: Headache, fever, and generalised lymphadenopathy can occur on rare occasions (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 2 per 1 million persons.

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. A baby who has received blood or plasma transfusions can be subsequently immunised with BCG, after the observation period for transfusion reactions has ended (24 hours). A baby who has received hepatitis B vaccine, hepatitis B immunoglobulin or normal human immunoglobulin can be subsequently immunised with BCG without delay.

Administration of BCG vaccination

Detailed instructions including illustrations are available in Chapter 2.

Note: In all cases, BCG must be administered strictly intradermally.

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 2 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 1 cm.

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 health-care professionals be properly trained in all aspects of the process involved in tuberculin skin tests and BCG vaccination.

Management of adverse reactions

Local adverse reactions to BCG vaccine occur in 1-2% of immunisations. Severe local reactions (ulceration greater than 10 mm, 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 paediatrician.

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.

² Children in at-risk environments include those who are contacts of a pulmonary TB case, who are from an area of high endemicity or whose parents are from an area of high endemicity.

Tuberculin testing prior to BCG immunisation

BCG should not be administered to an individual with a positive tuberculin test. It is unnecessary and may cause a more severe local reaction. Those with strongly positive tests should be referred to a respiratory physician for assessment of the need for further investigation and treatment.

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

- Children aged 3 months to under 6 years in at-risk environments²
- Persons aged 6 years and older
- Infants and children under 6 years of age with a history of ever having lived or had a prolonged stay (more than 1 month) in a country of high endemicity (Appendix 2)
- Those who have had close contact with a person with known TB
- When there is a history of TB in a household contact in the last 5 years.

BCG can be given up to 3 months following a negative tuberculin test.

The Mantoux test is used as a screening tool for tuberculosis infection or disease and as an aid to diagnosis. The local skin reaction to tuberculin purified protein derivative (PPD) injected into the skin is used to assess an individual's sensitivity to the tuberculin protein. The greater the reaction, the more likely it is that an individual is infected or has active TB disease. The standard test for use in Ireland is the Mantoux 2TU/0.1 ml tuberculin PPD.

Administration of the Mantoux test

Detailed instructions are available in Chapter 2.

Care should be taken to store PPD Mantoux tests and BCG vaccine in separate areas of the fridge to ensure that the correct product is administered (see section on cold chain for storage of PPD and BCG).

Mantoux testing can be undertaken at the same time as inactivated vaccines are administered. Live viral vaccines can suppress the tuberculin response and so testing should not be undertaken within 4 weeks of having received a live viral vaccine such as MMR.

Reading the Mantoux test

The results should be read within 48-72 hours of receiving the test but a valid reading can usually be obtained up to 96 hours later. The transverse diameter of the area of induration but not the erythema at the injection

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site is measured with a ruler and the result recorded using millimetres. As several factors affect interpretation of the test, the size of the induration should be recorded and NOT just as a positive or negative result, see Table 16.1.

There is some variability in the time at which the test develops its maximum response. The majority of tuberculin sensitive subjects will be positive at the recommended time of reading.

Note:

- A delay in reading the Mantoux test if the result is positive i.e. ≥ 6 mm does not affect the validity of the results.
- A strongly positive Mantoux test resulting from inadvertent subcutaneous administration does not affect the validity of the reading.

Table 16.1 Interpretation of the Mantoux test

Diameter of induration	Interpretation	Action
Less than 6 mm	Negative	Previously unvaccinated individuals may be given BCG provided there are no contraindications
6 mm or greater but less than 15 mm	Hypersensitive to tuberculin protein. May be due to previous TB infection, BCG or exposure to atypical mycobacteria	Should not be given BCG*
≥ 15 mm	Strongly hypersensitive to tuberculin protein Suggestive of TB infection or disease	Refer for further investigation and supervision which may include preventive chemotherapy

* When Mantoux tests are being performed as part of an immunisation programme, no further action is required for people with a reaction in this range (6-<15 mm). In other contexts (e.g. new immigrant screening, contact tracing programmes) where the subject has not been previously vaccinated with BCG and taking account of the precise size of the reaction and the circumstances of the case, referral to a respiratory physician may be indicated for further investigation.

Factors affecting the result of the tuberculin test

The reaction to tuberculin protein may be suppressed by the following:

- 1 Infectious mononucleosis
- 2 Viral infections in general including upper respiratory tract infections
- 3 Live viral vaccines (tuberculin testing should not be undertaken within 4 weeks of having received a live viral vaccine)
- 4 Sarcoidosis
- 5 Corticosteroid therapy
- 6 Immunosuppression due to disease or treatment including HIV infection

Subjects who have a negative test but who may have had an upper respiratory tract or other viral infection at the time of testing or at the time of reading the test should be re-tested 2-3 weeks after clinical recovery before being given BCG. This second test should be done on the other arm; repeat testing at one site may alter the reactivity either by hypo- or more often hyper-sensitising the skin and a changed response may only reflect local changes in skin sensitivity.

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