

# 22

## Tuberculosis

BCG introduced in 1950s

NOTIFIABLE

In some circumstances, advice in these guidelines may differ from that in the Summary of Product Characteristics of the vaccines. When this occurs, the recommendations in these guidelines, which are based on current expert advice from NIAC, should be followed.

### Introduction

Human tuberculosis (TB) is caused by infection with bacteria of the *Mycobacterium tuberculosis complex* (including *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. canetti*, *M. caprae* and *M. pinnipedii*). The organism may infect any part of the body. However, the majority of cases involve the respiratory system. The risk of progression to active TB is highest in those with HIV coinfection.

One third of the world's population is estimated to be infected with *M. tuberculosis*, representing a huge reservoir of potential TB disease. The Millennium Development Goal target to halt and reverse the TB epidemic by 2015 has already been achieved. The TB mortality rate decreased by 41% between 1990 and 2011, and the world is on track to achieve the global target of a 50% reduction by 2015. However, the global burden of TB remains enormous, and the European region is not on track to halve 1990 levels of mortality by 2015.

A number of new vaccines against TB are entering advanced clinical trials.

## Epidemiology

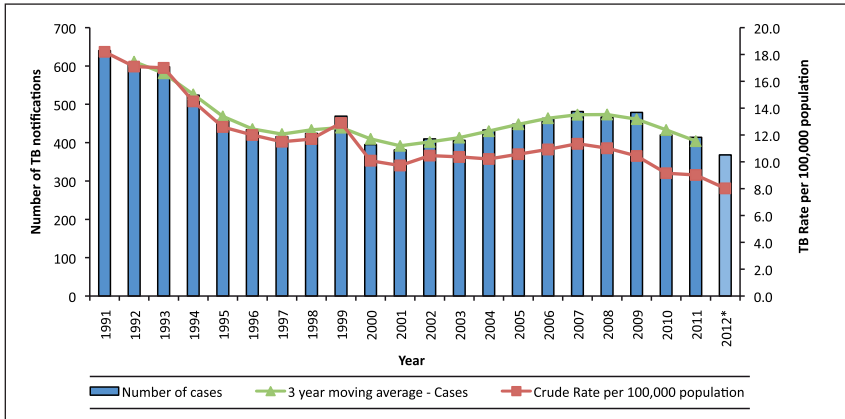
In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease (including 320 000 deaths among HIV-positive people). India and China account for almost 40% of the world’s TB cases. The WHO African region has the highest rates of cases and deaths per capita. The reported incidence of TB in Ireland declined from 230 cases per 100,000 in 1952 to 9.2 cases per 100,000 in 2011 (see Figure 22.1).

In 2011 globally there were about 310, 000 cases of Multi Drug Resistant (MDR) TB among patients with pulmonary TB. Almost 60% of these cases were in India, China and the Russian Federation. It is estimated that about 9% of MDR-TB cases had Extensively Drug Resistant (XDR) TB.

In Ireland, MDR-TB remains very uncommon, with 1-3 cases reported per year since 2008. Just 1 case of XDR-TB has been reported in Ireland (in 2005).

**Figure 22.1** Notified cases of TB in Ireland with crude rates per 100,000 population, 1991 to 2012\* and 3-year moving averages, 1992-2011

Source: HPSC



\* 2012 figures are provisional.

## Transmission

TB is primarily an airborne disease, transmitted by a person with respiratory TB through coughing, sneezing, speaking, laughing or spitting. Infected particles are inhaled during close contact (usually within 1 metre) and prolonged or repeated contact with an infected family member, friend, childminder, co-worker, or classmate.

Transmission is most likely when the index case has smear positive sputum for the bacillus on microscopy. One person with pulmonary TB infects >3 people before diagnosis and treatment and can infect 10–15 other people per year. Most cases of infectious TB become non-infectious after a few weeks of treatment. TB in other parts of the body such as the kidney or spine is very rarely infectious.

## Effects of tuberculosis

When infection with *M. tuberculosis* occurs, the result may be elimination of the organism, latent infection or active disease.

### Latent tuberculosis infection (LTBI)

This is defined as *M. tuberculosis* complex infection in a person with a positive Tuberculin skin test (TST) or Interferon gamma release assay (IGRA), who has no symptoms or physical signs of TB disease, and a chest X-ray which is either normal or shows evidence of healed infection.

In the majority of infected people, immune responses control and limit the infection, such that individuals remain free from disease for prolonged periods of time. Approximately 10-15% of those with LTBI may develop active disease at some point in their lives. Around 50% of those who develop active disease do so within five years of infection. The risks of developing disease are very significantly increased in those with HIV infection, and in children aged <5 years.

The diagnosis of LTBI is most commonly based on a positive tuberculin skin test (TST), the Mantoux test. For further information see section below on Tuberculin skin testing (TST) prior to Bacille Calmette-Guérin (BCG) immunisation.

Interferon- $\gamma$ -release assays (IGRA) may be used to detect interferon-gamma generated by T cells in response to *M. Tuberculosis* antigens. Sensitivity is approximately 90% and specificity approximately 85%. IGRAs are not affected by prior BCG vaccination and are less likely to be influenced by previous exposure to nontuberculous mycobacteria. There are some concerns about their reproducibility and test variability around cut-off from negative to positive results.

The role of IGRA in children is unclear, especially in young children. IGRAs should not replace standard diagnostic methods including microbiology, molecular tests, and clinical and radiological assessment.

### Active Tuberculosis Disease

TB 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 depend on the site of infection. General symptoms include fever, fatigue or weakness, 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 rarely haemoptysis.

Children, particularly infants and those < 5 years of age, have a much higher risk of progression to disseminated (miliary) tuberculosis and tuberculous meningitis after primary infection.

Note: For full information on definitions and diagnosis, refer to the HPSC Guidelines on the Prevention and Control of Tuberculosis in Ireland (2010) available at <http://www.hpsc.ie/hpsc/A-Z/VaccinePreventable/TuberculosisTB/Guidance/File,4349,en.pdf>

### BCG vaccine

The reported efficacy of BCG in preventing TB has varied. BCG vaccination protects against disseminated forms of childhood tuberculosis (particularly TB meningitis) in up to 80% of children with protection lasting 15 years or longer. There are few data on the protection afforded by BCG vaccine given to those 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 their risk of exposure is high (see Indications below).

The BCG vaccine licensed in Ireland (SSI) contains a live attenuated Danish strain 1331 derived from *M bovis*.

BCG vaccine should be stored at +2°C to +8°C. If BCG vaccine has been frozen it should not be used.

**Dose and route of administration**

In all cases, BCG must be administered intradermally.

*Infants under 12 months of age*

The recommended dose is 0.05 ml, by intradermal injection over the middle of the left deltoid muscle.

*Adults and children 12 months and over*

The recommended dose is 0.1 ml, by intradermal injection over the middle of the left deltoid muscle.

Detailed instructions including illustrations are available in Chapter 2.

Booster doses are not recommended.

BCG vaccine may be given at the same time as or at any interval before or after all live and non live vaccines.

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.

**Indications.**

**Note:** “Unvaccinated” is defined as absence of documentation of having received BCG, or absence of a characteristic BCG scar.

1. Newborn infants.
2. All unvaccinated children aged 1 month to <16 years.

Children aged less than 6 years who are not in an at-risk environment do not need a TST prior to BCG vaccination.

Children from 3 months up to 6 years of age in at risk environments should have a TST test prior to BCG vaccination. These include

- children who are contacts of a pulmonary TB case
- children from a country of high TB endemicity ( $\geq 40/100,000$ )
- children whose parents are from a country of high TB endemicity.

3. Unvaccinated TST negative individuals under 16 years of age who were born or lived for >3 months in a country with an annual incidence TB incidence of  $\geq 40/100,000$ .
4. Unvaccinated new entrants aged 16-35 years from a country with a TB incidence of  $\geq 500$  per 100,000.
5. Unvaccinated persons aged <35 years who are contacts 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 immunised with BCG as indicated.
6. Members of at risk groups e.g. the Traveller community (due to the logistical difficulties of providing alternative control measures and follow-up of contacts).
7. Unvaccinated persons under 16 years of age intending to live with local people in countries with an annual TB incidence of  $\geq 40/100,000$  for more than 3 months.
8. Unvaccinated TST negative persons aged <35 years in the following at risk occupations:
  - Veterinary laboratory staff who handle animals susceptible to TB
  - Abattoir workers who handle animal species, carcasses and products 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 residences for homeless people, refugees and asylum seekers.
9. Unvaccinated health-care workers aged <35 who are TST negative and who will have contact with patients or with clinically contaminated material.
10. Not all HCWs are at equal risk of TB. A risk assessment should be carried out to see if BCG should be given to unvaccinated HCWs aged 35 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 of the Guidelines on the Prevention and Control of Tuberculosis in Ireland 2010. <http://www.hpsc.ie/A-Z/VaccinePreventable/TuberculosisTB/Publications/File,4349,en.pdf>

**Contraindications**

1. Anaphylaxis to any of the vaccine constituents.
2. Previous BCG vaccine.
3. Past history of TB.
4. TST or IGRA positive.
5. Family history of primary immunodeficiency, e.g. inherited severe combined immunodeficiency (SCID), Chronic Granulomatous Disease (CGD) etc. until evaluation is complete.
6. Neonates in a household where an active TB case is suspected or confirmed.
7. HIV exposed neonates. If two HIV PCR tests, one at  $\geq 6$  weeks of age, are negative the infant can be given BCG.
8. Infants up to 6 months of age 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 (e.g. infliximab, etc) and fusion proteins (e.g. etanercept); calcineurin inhibitors (e.g. cyclosporin); cytotoxics (e.g. azathioprin, methotrexate); and mesalazine. BCG should be deferred for 28 days in infants born to mothers using topical tacrolimus.
9. Infants up to 3 months of age born to mothers who received high dose steroid therapy for two weeks or more in the second and/or third trimester.
10. Breast fed infants whose mother is taking immunomodulating drugs should be assessed on a case by case basis (See Chapter 3).
11. Persons with blood dyscrasias, malignant neoplasms involving bone marrow or the lymphoreticular system, or with gamma globulin deficiency or abnormality.
12. HIV positivity.
13. Generalised infected dermatosis.
14. Pregnancy.

**Precautions**

1. Acute severe febrile illness-defer until recovery.
2. Eczema. - give at a site clear of eczema.
3. Locally applied anaesthetic preparations should not be applied prior to BCG, because of possible effects on the immune response.

The following are NOT contraindications or precautions

1. Phototherapy.
2. Treatment with Palivizumab, a respiratory syncytial virus (RSV) specific monoclonal antibody.

### ***Preterm and low birth weight infants***

Preterm infants can be vaccinated with BCG when they have reached the equivalent of 34–35 weeks gestational age.

Low birth weight infants (<2500g) show a good immune response to BCG irrespective of their weight.

BCG vaccine can be given to low birth weight infants when they have reached the equivalent of 34–35 weeks gestation irrespective of their weight at birth or at the time of vaccination.

### ***Previous BCG vaccination***

BCG should not be administered to previously vaccinated individuals as there is an increased risk of adverse reactions and no additional protection.

Evidence of previous BCG vaccination includes: documentary evidence, a reliable history of vaccination or presence of a characteristic scar.

### ***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. There may be enlargement of a regional lymph node, usually less than 1 cm in diameter.

The ulcer should be allowed to dry and abrasion (e.g. by tight clothes) avoided. Should oozing occur, a dry dressing may be applied until a scab forms. It is essential that air is not excluded. If 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.

### ***Adverse reactions***

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

Severe injection site reactions, such as large discharging ulcers, abscesses and keloid scarring are most commonly caused by inadvertent subcutaneous injection, excessive dosage or vaccinating individuals who are tuberculin positive.

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



*General:* Headache, fever, and generalised lymphadenopathy are rare. Anaphylaxis and disseminated BCG complications (such as osteitis, osteomyelitis or disseminated BCG infection) are very rare. Disseminated BCG infection occurs in approximately 2 per 1 million persons.

### **Management of adverse reactions**

Discharging skin lesions and chronic suppurative lymphadenitis usually resolve spontaneously. 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 an appropriate specialist, and will normally require systemic anti-tuberculous treatment and mandate a detailed immunological investigation.

### **Tuberculin skin testing (TST) prior to BCG immunisation**

The Tuberculin skin test (TST), also known as the Mantoux test, involves intradermal injection of Purified Protein Derivative (PPD). The local skin reaction to PPD injected into the skin is used to assess sensitivity to PPD. The greater the reaction, the more likely it is that an individual has TB infection or disease.

The PPD recommended for use in Ireland is 2TU/0.1 ml.

PPD should be stored at +2°C to +8°C. If PPD has been frozen it should not be used.

A TST is necessary prior to BCG vaccination for:

- Persons aged 6 years and older
- Children from 3 months up to 6 years of age
  - who have ever lived or stayed more than 3 months in a country of high endemicity
  - whose parents are from a country of high endemicity
  - who are contacts of a pulmonary TB case
- Children under 3 months of age in whom TB disease is suspected

Measles vaccination may temporarily suppress PPD reactivity. If MMR has been given the TST should be postponed for at least 4 weeks. However, the TST may be administered before or on the same day as MMR.

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There is currently no information on the effect of varicella vaccine on reactivity to the TST. Until information is available, it is prudent to apply the same rules to varicella vaccine.

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

### Administration of PPD

Detailed instructions are available in Chapter 2.

Care should be taken to store PPD 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).

### Reading the TST

The results should be read within 48-72 hours the test but a valid reading can be obtained up to 96 hours. The transverse diameter of the area of induration (not the erythema) at the injection site is measured with a ruler and the result recorded in millimetres. As several factors affect interpretation of the test, the size of the induration should be recorded and NOT just a positive or negative result, see Table 22.1. The TST is subject to interobserver variability in the measurement of induration.

#### Note:

- A delay in reading the TST if the result is positive i.e.  $\geq 6$  mm does not affect the validity of the results.
- A strongly positive TST resulting from inadvertent subcutaneous administration does not affect the validity of the reading.

**Table 22.1** Interpretation of the TST

Diameter of induration	Interpretation	Action
Less than 6 mm	Negative	Previously unvaccinated individuals may be given BCG.
6 to <15 mm	Previous TB infection, BCG vaccine, or exposure to atypical mycobacteria	Should not be given BCG*
$\geq 15$ mm	Suggestive of TB infection or disease	Refer for further investigation and management .

\* For more information, refer to Guidelines on the Prevention and Control of Tuberculosis in Ireland 2010

### ***Factors affecting the result of the TST***

The TST is neither very sensitive nor specific.

False positives can be caused by prior exposure to non-tuberculous mycobacteria, by serial TSTs and cross-reactivity with the BCG vaccine.

False negatives are seen in young children, the immunocompromised and in people with overwhelming tuberculosis disease.

The reaction to PPD may be suppressed by:

1. Infectious mononucleosis.
2. Viral infections including upper respiratory tract infections.
3. Live viral vaccines. TST should not be undertaken within 4 weeks of having received a live viral vaccine except rotavirus.
4. Sarcoidosis.
5. Immunosuppression due to disease or treatment.

Persons who have a negative TST but who had a viral infection at the time of testing or of reading the test should be re-tested 2-3 weeks after recovery. This second test should be done on the other arm.

### Bibliography

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