22 Tuberculosis

BCG introduced in 1950s

NOTIFIABLE

In some circumstances, advice in these guidelines may differ from that in the product Summary of Product Characteristics (SmPC). When this occurs, NIAC advises that the recommendations in these guidelines, which are based on current expert advice from NIAC, are followed.

Contents

Key changes:

Section 22.5 (universal neonatal BCG vaccination discontinued, targeted vaccination recommended).

22.1 Introduction

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis*. The organism typically infects the lungs, but may infect other sites (extrapulmonary TB), particularly in children. The organism remains dormant in most of those infected (latent TB infection, LTBI), but can cause disease particularly in young children and in those with immunocompromise.

22.2 Epidemiology

Globally, TB is a major cause of ill-health and death. Estimates of TB incidence in 2020 suggest that one third of the world's population is infected with *M. tuberculosis*, and a global total of about 10 million people fell ill with TB in 2020.

Note: there is a decrease in recent data quality due to pandemic resource re-allocation, so recent data should be interpreted with caution.

Most cases were in the WHO regions of South-East Asia (43%), Africa (25%) and the Western Pacific (18%). Estimates of the number of TB deaths in 2020 suggest that the global number of TB deaths increased between 2019 and 2020 from 1.2 million to 1.3 million. This is the first annual increase in the number of people dying from TB since 2005, and has been caused by disruptions to provision of and access to essential TB diagnostic and treatment services during the COVID-19 pandemic. It is anticipated that TB will rank second as a cause of death from a single infectious agent, after COVID-19, when figures for 2021 are available.

TB affects people of both sexes and all age groups. The highest burden is in adult men, who accounted for 56% of all TB cases in 2020; by comparison, adult women accounted for 33% and children for 11%.

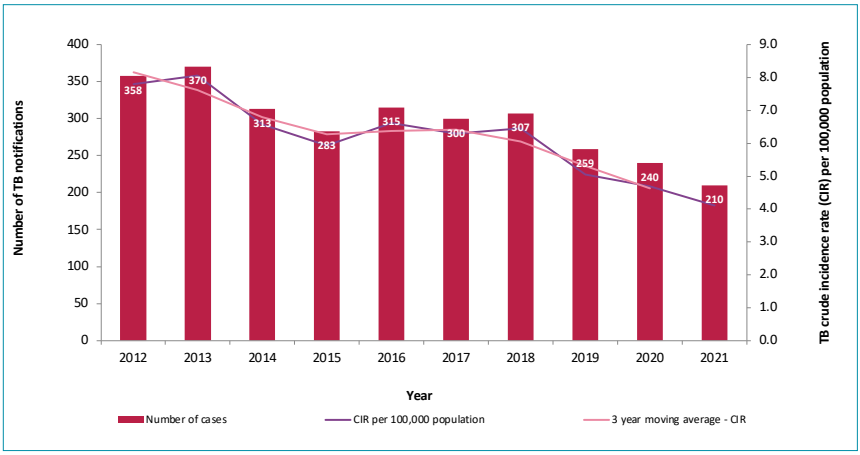
In children, TB is most common in those aged under five years. Infants and young children, especially those aged under two years, are at risk of developing severe disseminated disease with a short incubation period and acute onset.

Ireland is a low TB incidence country (TB notification rate of under 10 cases (all forms) per 100,000 population per year). The number of cases of TB decreased from 358 in 2012 to 211 in 2021. This corresponds to a decline in the crude incidence rate from 7.8 per 100,000 in 2012 to 4.6 per 100,000 in 2021. In 2021, 17% of notified TB cases were in Irish-born people (38 cases).

Cases born outside Ireland accounted for 49% of notified cases (107 cases). There has been no significant increase in paediatric TB rates reported, despite absence of BCG vaccine since 2015. One meningitis case in an infant was reported in 2021.

Migrant TB rates remained stable despite the COVID-19 pandemic. There has been an increase in M/XDR TB in 2021 and 2022 associated with TB in migrants. There was an increase in reports of multidrug-resistant tuberculosis (MDR TB) and extensively drug-resistant TB (XDR TB) in 2021 and 2022.

Figure 22.1 Notified cases of TB in Ireland with crude rates per 100,000 population, 2012 to 2021* and 3-year moving averages, 2012 to 2021
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 one 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 more than three 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.

The risks for TB transmission are greatest for:

- those who have cumulative close contact for eight hours or more in an indoor environment that is poorly ventilated, with patients diagnosed with TB, particularly multidrug-resistant TB (MDR TB).
- healthcare workers (HCWs) who carry out high risk procedures while unprotected, including:
  - cough inducing procedures (e.g., sputum induction, bronchoscopy)
  - autopsy
  - pathology examination
  - bronchoscopy
  - designated TB laboratory procedures, especially handling TB cultures.
- those staying more than three months in a country with a high TB burden including:
  - those in close contact with the local population in a country with a high TB burden.
  - those visiting relatives or friends are at higher risk.

22.3 Effects of tuberculosis

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

22.3.1 Latent tuberculosis infection (LTBI)

Latent tuberculosis infection (LBTI) is defined by WHO as a state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically manifested active TB disease. There is no gold standard test for LTBI; either tuberculin skin testing (TST) or an interferon gamma release assay (IGRA) can be used. (See section 22.3.1)

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 significantly increased in those with HIV infection and in children less than five years of age.

Interferon-γ–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.

22.3.2. Active Tuberculosis Disease

TB disease is classified as pulmonary, extrapulmonary or both. In Ireland, approximately 70% of TB cases are pulmonary cases. Non-respiratory forms of TB are more common in those with impaired immunity.

Symptoms and signs of TB vary depending on age, immune status, site of infection and disease severity. 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 under five years of age, have a much higher risk of progression to disseminated (miliary) TB and TB meningitis after primary infection.

Active pulmonary TB can be diagnosed by X-ray changes and bacterial positivity. Examination and culture of clinical specimens (e.g., sputum, urine, cerebrospinal fluid, gastric aspirate) are of critical diagnostic importance. The specimens should be examined and cultured in a laboratory that specialises in testing for *M. tuberculosis.*

Note: For full information on definitions and diagnosis, refer to the HPSC Guidelines on the Prevention and Control of Tuberculosis in Ireland, 2010 - Amended 2014

22.4. Bacillle Calmette Guérin (BCG) vaccine

The efficacy of BCG in preventing TB varies. 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. A meta-analysis showed that BCG vaccinated children exposed to TB had 19% (95% CI 8-29) less TB infection than non-vaccinated children. This represents a significant additional benefit of BCG vaccination.

A recent UK study of adults with a median age of 32 years (interquartile range 25–43) concluded that BCG is associated with lower prevalence of LTBI in adult contacts of tuberculosis.

The BCG vaccine licensed in Ireland (SSI) contains a live attenuated Danish strain 1331 derived from *M. bovis*. Full details can be found in the SmPC.

Vaccine effectiveness
It is 70-80% effective against the most severe forms of TB, such as TB meningitis. However, it is less effective in preventing pulmonary TB.

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

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 aged 12 months and over
The recommended dose is 0.1 ml, by intradermal injection over the middle of the left deltoid muscle.

Detailed instructions for intradermal injection technique 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.

No further vaccination should be given in the arm used for BCG vaccination for at least three months because of the risk of regional lymphadenitis.

22.5 Recommendations

Note: for testing prior to BCG see section 22.3.1

BCG vaccine is recommended for:

- Neonates born to parents (or with other regular close contacts[1]) with untreated sputum smear-positive pulmonary or laryngeal tuberculosis (TB), once the neonate has completed chemoprophylaxis and is Mantoux negative
- Neonates born in households with contacts[1] from countries with a high TB, TB/HIV, or multidrug-resistant TB (MDR TB) burden[2]
- Neonates in any locally identified high risk group with TB, TB/HIV, or MDR TB
- Unvaccinated TST- or IGRA-negative[3] children aged under five years born in a country with a high TB, TB/HIV, or MDR TB burden[3] or living with a person who has been born in a high burden country.

BCG vaccine should be considered for the following, after a risk-benefit assessment:

- Unvaccinated TST- or IGRA-negative[3] people aged five years and older moving or travelling to high TB, TB/HIV or MDR TB incidence settings
- Unvaccinated TST- or IGRA-negative[3] persons at risk of unprotected occupational exposure (e.g., healthcare workers, laboratory workers, medical students, prison workers and others with occupational exposure).

Contraindications

- Anaphylaxis to any of the vaccine constituents.
- Previous BCG vaccine.
- Past history of TB.
- TST or IGRA positive.
- Family history of primary immunodeficiency, e.g., inherited severe

[1] Those who have cumulative close contact for eight hours or more in an indoor environment that is poorly ventilated, with patients diagnosed with TB, particularly MDR TB

[2] WHO (2021). Global lists of high burden countries for tuberculosis (TB), HIV-associated TB and multidrug/rifampicin-resistant TB (MDR/RR-TB) for 2021-2025

[3] Either tuberculin skin testing (TST) or an IFN-γ release assay (IGRA) may be used. See section 22.3.1

combined immunodeficiency (SCID), chronic granulomatous disease (CGD) etc. until evaluation is complete.

- TB exposed neonates. BCG vaccine should be deferred in neonates requiring chemoprophylaxis until treatment is completed and Mantoux is negative.
- HIV exposed neonates. If two HIV PCR tests, one at ≥ six weeks of age, are negative the infant can be given BCG.
- Infants up to 12 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) and fusion proteins (e.g., etanercept), calcineurin inhibitors (e.g., cyclosporin), cytotoxics (e.g., azathiaprin, methotrexate) and mesalazine.
- Infants up to 28 days born to mothers using topical tacrolimus.
- Infants up to three months of age born to mothers who received high dose steroid therapy for two weeks or more in the second and/or third trimester.
- Breastfed infants whose mother is taking immunomodulating drugs should be assessed on a case by case basis (See Chapter 3).
- Persons with blood dyscrasias, malignant neoplasms involving bone marrow or the lymphoreticular system, or with gamma globulin deficiency or abnormality.
- HIV positivity.
- Generalised infected dermatosis.
- Pregnancy.

Precautions

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

Preterm and low birth weight infants

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

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

Previous BCG vaccination

BCG vaccine for prevention of TB 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. The scar may be in a site other than the deltoid area, e.g., the forearm, in children vaccinated outside Ireland.

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. There may be enlargement of a regional lymph node, usually less than one 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:	Common: irritation, pain, pruritus
	Very rare: induration, pustule, ulceration and scab formation within 10 days are associated with concurrent TB infection. They are more likely following subcutaneous administration
General:	Uncommon: fever
	Rare: regional lymphadenopathy

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 a relevant medical specialist, and will normally require systemic anti-tuberculous treatment and mandate a detailed immunological investigation.

22.6 Tuberculin skin testing (TST) prior to BCG vaccination

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.

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

The TST and IGRA tests are used to diagnose LTBI.

The TST is a test of delayed cell-mediated hypersensitivity to tuberculin, a purified protein derived from cultures of tubercle bacilli. TST conversion occurs within eight weeks of mycobacterial infection. A positive TST test is of low specificity and cannot differentiate between *M. tuberculosis* infection, prior BCG vaccination, infection with, or exposure to non tuberculous mycobacteria. It also has a low sensitivity in those with immunosuppression such as people living with HIV. The strength of TST recommended for use in Ireland is 2TU.

Precaution
MMR vaccination and measles infection in the previous four weeks increases the likelihood of false negative TST results; testing should be delayed for four weeks. No data are available in relation to the effect of other live virus vaccines or infections, e.g., varicella, yellow fever but the same guidance to delay the TST test by four weeks should be followed. Full details regarding administration, interpretation and adverse reactions of the TST can be found in the SmPC.

The IGRA test detects interferon-gamma produced by white blood cells in those infected with *M. tuberculosis*. Sensitivity is approximately 90%, and specificity approximately 85%. IGRAs are not affected by prior BCG vaccination or by prior exposure to non tuberculous mycobacteria.

A negative reaction to either test does not outrule TB infection. Neither test can be used to diagnose active TB disease.

The TST is preferred in children aged under two years. IGRAs can be used but the test sensitivity is reduced.

The IGRA is preferred if the person is:

- aged two years or older
- has received the BCG vaccine
- unlikely to return to have their TST evaluated
- immunocompromised.

BCG can be given up to three 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 of 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
<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*
≥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 - Amended 2014

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:

- Infectious mononucleosis
- Viral infections including upper respiratory tract infections
- Live viral vaccines. TST should not be undertaken within four weeks of having received a live viral vaccine except rotavirus
- Sarcoidosis
- 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.

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