

APPENDIX I

Tuberculin Skin Testing Contraindications, Administration and Interpretation

The following persons should not receive a TST:

- Those who had severe blistering TST reactions in the past or with extensive burns or eczema present over TST testing sites, because of the greater likelihood of adverse or severe reactions
- Those with documented TB disease or a well-documented history of adequate treatment for TB infection or disease in the past. In such patients the test is of no clinical utility.
- Those currently with major viral infections e.g. varicella (chickenpox), measles, mumps, infectious mononucleosis *BUT* not the common cold or minor viral infections.
- Those who received MMR vaccines in the previous four weeks as this has been shown to increase the likelihood of false negative TST results. No data are available in relation to the effect of other live virus vaccines e.g. varicella or yellow fever but it would be prudent to follow the same four-week guidance (1).

The following persons can receive a TST:

- Those with a common cold
- Those who are pregnant or breastfeeding
- Those immunised with any vaccine on the same day
- Those immunised within the previous 4 weeks with inactivated vaccines
- Those who give a history of a positive TST reaction (other than blistering) that is not documented
- Those taking low doses of systemic corticosteroids, < 15mg prednisolone (or equivalent) daily. It generally takes a steroid dose equivalent to ≥15mg prednisolone daily for 2-4 weeks to suppress tuberculin reactivity (1, 2).

Advantages and disadvantages of TST (Adopted from US Centers for Disease Control and Prevention (CDC) [Guidance](#)) (3)

Advantages

- Relatively simple to perform by those who have received training in its administration
- Low cost
- No need for phlebotomy
- Well-established definitions of TB skin test conversions
- Legacy of decades of clinical and epidemiological research

Disadvantages

- Requires trained personnel to administer and interpret
- Requires correct refrigeration and an inventory plan for the skin test solution
- Requires two or more patient visits
- Previous BCG vaccination or infection with nontuberculous mycobacteria can cause false-positive results
- Concurrent infections can cause false-negative results
- Rare adverse effects
- Can cause booster phenomenon
- Subject to biases and errors with TB skin test placement and reading.

Administration of the Mantoux test

In all cases, the Mantoux test should be administered intradermally. This is also sometimes referred to as intracutaneous administration. The Mantoux test is normally performed on the flexor surface of the left forearm at the junction of the upper third and the lower two-thirds. If the skin is visibly dirty, it should be washed with soap and water. The Mantoux test is performed using a 0.1ml tuberculin syringe or alternatively a 1ml graduated syringe fitted with a short bevel 26G (0.45x10mm) needle. A separate syringe and needle must be used for each subject to prevent cross-infection. Then 0.1ml of PPD should be drawn into the tuberculin syringe and the 25G or 26G short-bevelled needle attached to give the injection. The needle should be firmly attached, and the intradermal injection administered with the bevel facing uppermost.

The operator stretches the skin between the thumb and forefinger of one hand and with the other hand slowly inserts the needle with the bevel upwards for about 5mm into the superficial layers of the dermis almost parallel to the surface. The needle can usually be seen through the epidermis. A correctly given intradermal injection results in a tense blanched raised bleb

and considerable resistance is felt when the fluid is being injected. A bleb is typically of 7mm diameter following a 0.1ml intradermal injection. If little resistance is felt when injecting and a diffuse swelling occurs rather than a tense bleb the needle is too deep and should be withdrawn and reinserted intradermally on the opposite forearm or on the same forearm at a site at least 10cm away from the previous injection. Do not cover the site with a bandage. Inform the patient that he or she should not scratch the site but may perform all normal activities including showering or bathing. Record the following details: a) date of injection; b) dose (2TU, 0.1ml); c) manufacturer; d) lot number; e) expiry date; f) site of injection and g) person who administered the injection.

Storage

Care should be taken to store PPD Mantoux tests and BCG vaccine in separate areas of the fridge to ensure the correct product is administered. If using the vial of Tuberculin PPD (Mantoux) on more than one patient, it is recommended that once the vial is in use, it should be used immediately. Otherwise, it should not be in use for longer than 24 hours and stored between 2 and 8°C as per Tuberculin PPD product specific details from Statens Serum Institut (SSI) in Copenhagen (4). In light of the need for the immediate use of the vial of PPD as indicated above, it is recommended that where possible a clinic should be arranged to undertake Mantoux testing on more than one person.

Reading the TST (Mantoux test)

The TST should be read **by a trained health professional**. Individuals without experience in reading a TST may not feel slight induration and the result may be mistakenly recorded as 0mm.

TST interpretation depends on a number of factors as follows:

- Measurement of the induration in millimetres
- The person's risk of being infected with TB and of progression to disease if infected
- Prior BCG vaccination or exposure to non-tuberculous mycobacteria (NTM)
- Conditions resulting in a false negative result.

The results should be read **within 48 to 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 and not the erythema at the injection 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.

It is recommended that the following items are recorded:

- Date the induration was read
- Measurement of the induration if any in millimetres
- Any adverse reactions e.g. blistering (can occur in 3-4% of subjects) and
- The name of the individual who read the test.

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. The predictive value can be enhanced by using cut-off points dependent on the infection risk. The reaction to a TST is classified as positive based on the individual's risk factors (see [Appendix Table 1](#)). In general, a negative TST result is $\leq 5\text{mm}$.

The TST (Mantoux test) result should be read within 48 to 72 hours of receiving the test. The transverse diameter of the area of induration (and not the erythema at the injection site) is measured with a ruler and the result recorded using millimetres.

Note:

- A delay in reading the TST if the result is positive i.e. $>5\text{mm}$ 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.

Deciding that a TST is positive

The health professional reading the TST must decide whether the test result is positive. This is based on the size using the criteria listed in [Appendix Table 1](#). Once a TST is considered positive the individual should be referred for a medical evaluation. There is no clinical utility in performing a TST in the future once a test that was properly performed and read is considered positive (1).

Medical evaluation

This should include assessment of symptoms suggestive of possible TB disease, risk factors for TB such as contact history or other medical illness and a chest X-ray. In the event of symptoms or an abnormal chest X-ray, sputum for acid-fast bacteria smear and culture should be taken. In persons with no evidence of TB disease, treatment of TB infection should be considered.

Appendix Table 1: Categories of response to TSTs (Mantoux tests) based on individual's risk factor(s) for development of TB disease ^ψ

An induration of >5 mm is considered positive in:	• Person(s) living with HIV • A recent contact of a person with TB disease. • Persons with fibrotic changes on chest X-ray consistent with prior TB and no documented treatment • Persons with organ transplants and other immunosuppressed persons e.g. those taking the equivalent of $\geq 15\text{mg/day}$ of prednisolone for one month or longer or taking TNF-alpha antagonists • Children aged < 5 years (with no BCG) from a country with a high incidence of TB ($\geq 40/100,000$ per year)
An induration of ≥ 10 mm is considered positive in:	• Migrants, including refugees and applicants seeking protection: Persons (aged 16 to 35 years) who have immigrated within the past 5 years from countries with a very high TB incidence ($>500/100,000$) and children aged 5 to 15 years who have immigrated (within the past 5 years) from countries with TB incidence $\geq 40/100,000$ per year • All children <5 years of age or children/adolescents exposed to adults in high-risk categories* • People who inject drugs • Residents or employees of high-risk congregate settings e.g. prisons or places of detention, homeless shelters or hubs, State-provided (IPAS/UCTAT) congregate accommodation for refugees and applicants seeking protection • Mycobacteria laboratory personnel • Persons with clinical conditions which place them at increased risk of progression to TB disease e.g. silicosis, diabetes mellitus

	• HCWs from high incidence countries (≥ 40 cases per 100,000 population per year)^{†‡}
An induration of ≥ 15mm is considered positive in:	• HCWs from countries (including Ireland) where the annual rate of TB is < 40 per 100,000[§] • All others i.e. any person including persons with no known risk for TB. However, targeted skin testing programmes should only be conducted among high-risk groups.

^ψ In the context of serial tuberculin skin testing an increase of > 5 mm represents conversion and recent exposure.

* Recent converters, person(s) living with HIV, persons receiving immunosuppressive therapy i.e. tumour necrosis factor- α (TNF- α) antagonist, persons with evidence of old healed TB lesions on chest X-ray i.e. fibronodular disease/non-calcified fibrotic lesions (if not previously treated or if treated, and not adequately treated), foreign-born persons from countries with high TB endemicity, people experiencing homelessness, IDUs and HCWs

[†] Such patients should generally be referred to a respiratory or infectious disease clinician for assessment. However, an occupational medicine consultant may wish to treat these patients if appropriate protocols, audit of care and resources are in place

[‡] HCWs from countries of high TB incidence have a higher risk of having TB, hence the lower cut-off point for considering TB infection

[§] Such patients should generally be referred to a respiratory or infectious disease clinician for assessment. However, an occupational medicine consultant may wish to treat these patients if appropriate protocols, audit of care and resources are in place

Factors Affecting the Result of the Tuberculin Skin Test

False positive TST results

Although for persons with TB infection and normal immune responses the test sensitivity approaches 100% (5), false positive results can occur because of the sensitising effect on the immune system of either prior BCG vaccination or exposure to non-tuberculous mycobacteria (NTM).

BCG and NTM have important effects on the predictive value of the TST when the expected prevalence of true TB infection is low such as in Western Europe or North America. In contrast, when the expected prevalence of tuberculous infection is high, such as close contacts of a person with sputum smear positive pulmonary TB or persons from high TB incidence countries, then the predictive value of a positive TST result is high. A study by Menzies *et al* in 1992 showed that BCG leading to a false positive TST was more common among participants from low-incidence countries compared to those from countries of high endemicity for TB (6).

Menzies and Doherty (7) state that although all recipients of BCG will have positive tuberculin reactions within two months of vaccination with BCG, these reactions will wane over time. Studies by Menzies *et al* (1992, 1994) indicate that for those vaccinated with BCG in infancy, only 3-5% manifest a positive TST when tested 5 years after the vaccination (8, 9). This may reflect the relative immaturity of the immune system in infants although protective efficacy if anything is higher (10, 11). Of those vaccinated at an older age, tuberculin reactions are larger and wane more slowly. In this older cohort, on average 30-35% will have BCG-related positive TST results even after an interval of more than 10 to 15 years (8-10, 12-14). Post-BCG vaccination can account for up to 10mm of induration, and there is no published evidence to suggest that this sensitivity correlates with immunological protection (15-18).

Note:

Care should be taken when attributing BCG vaccination as a cause of a positive TST if (1):

- BCG vaccine was given in infancy and the person tested is now aged 10 years or older
- There is a high probability of TB infection i.e. close contacts of an infectious TB case or immigrants (including HCWs) from countries with high annual TB incidence (see [Appendix Table 1](#))

- There is a high risk of progression from TB infection to disease (see [Appendix Table 1](#))
- Any TST ≥ 15 mm induration should not be attributed to BCG vaccination.

False negative TST results

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

- Cutaneous anergy (anergy is the inability to react to skin tests because of a weakened immune system)
- Recent TB infection (within eight to 10 weeks of exposure)
- Old TB infection
- Age: very young age (less than three months old) and the elderly
- Major viral infections e.g. varicella (chickenpox), measles, mumps, infectious mononucleosis • Recent live viral vaccination e.g. measles, mumps, rubella, varicella and yellow fever (tuberculin testing should not be undertaken within four weeks of having received a live viral vaccine) • Malnutrition, particularly when there has been recent weight loss (19).
- Extensive TB disease (pulmonary or miliary) can itself also temporarily depress immunity and can lead to a paradoxically negative TST (20).
- Other illnesses e.g. malignancies especially lymphoma, renal failure, sarcoidosis, diabetes mellitus
- Immunosuppression due to disease including HIV infection
- Immunosuppression due to treatment including cytotoxics, corticosteroid therapy (≥ 15 mg prednisolone daily for four weeks or longer), transplant therapy and infliximab
- Incorrect method of TST administration (21). This should be avoidable.
- Incorrect interpretation of the TST reaction
- Insufficient dose of PPD
- Inactive tuberculin PPD: tuberculin PPD vials must be used within 24 hours of opening.

Subjects who have a negative test but who may have had one of the major viral infections (excluding the common cold) outlined above at the time of testing or at the time of reading the test should be re-tested two to three weeks after clinical recovery before being given BCG.

REFERENCES

1. Campbell JR, Pease C, Daley P, Pai M, Menzies D. Chapter 4: Diagnosis of tuberculosis infection. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2022;6(sup1):49-65.
2. Schatz M, Patterson R, Kloner R, Falk J. The prevalence of tuberculosis and positive tuberculin skin tests in a steroid-treated asthmatic population. Ann Intern Med. 1976;84(3):261-5.
3. Centers for Disease Control and Prevention (CDC). Clinical Testing Guidance for Tuberculosis: Tuberculin Skin Test. 2024. Available from: <https://www.cdc.gov/tb/hcp/testing-diagnosis/tuberculin-skin-test.html>.
4. Statens Serum Institut. Product Specific Details for Tuberculin PPD RT 23 SSI, 2 T.U./0.1ml. . Copenhagen, Denmark, Statens Serum Institut. 2006.
5. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Journal of Respiratory and Critical Care Medicine. 2000;161(supplement_3):S221-S47.
6. Menzies R, Vissandjee B, Amyot D. Factors associated with tuberculin reactivity among the foreign-born in Montreal. Am Rev Respir Dis. 1992;146(3):752-6.
7. Menzies D, Doherty TM. Diagnosis of latent tuberculosis infection. Reichman and Hershfield's tuberculosis: CRC Press; 2006. p. 265-314.
8. Menzies R, Vissandjee B. Effect of bacille Calmette-Guerin vaccination on tuberculin reactivity. American Review of Respiratory Disease. 1992;145(3):621-5.
9. Menzies R, Vissandjee B, Rocher I, St. Germain Y. The booster effect in two-step tuberculin testing among young adults in Montreal. Annals of internal medicine. 1994;120(3):190-8.
10. Bahr G, Chugh T, Behbehani K, Shaaban M, Abdul-Aty M, Al Shimali B, et al. Unexpected findings amongst the skin test responses to mycobacteria of BCG vaccinated Kuwaiti school children. Tubercle. 1987;68(2):105-12.
11. Rodrigues LC, Diwan VK, Wheeler JG. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. International journal of epidemiology. 1993;22(6):1154-8.
12. Horwitz O, Bunch-Christensen K. Correlation between tuberculin sensitivity after 2 months and 5 years among BCG vaccinated subjects. Bulletin of the World Health Organization. 1972;47(1):49.
13. Joncas J, Robitaille R, Gauthier T. Interpretation of the PPD skin test in BCG-vaccinated children. Canadian Medical Association Journal. 1975;113(2):127.
14. Comstock GW, Edwards LB, Nabangxang H. Tuberculin sensitivity eight to fifteen years after BCG vaccination. American Review of Respiratory Disease. 1971;103(4):572-5.

15. Hart PA, Sutherland I, Thomas J. The immunity conferred by effective BCG and vole bacillus vaccines, in relation to individual variations in induced tuberculin sensitivity and to technical variations in the vaccines. *Tubercle*. 1967;48(3):201-10.
16. al-Kassimi FA, al-Hajjaj MS, al-Orainey IO, Bamgboye EA. Does the protective effect of neonatal BCG correlate with vaccine-induced tuberculin reaction? *American journal of respiratory and critical care medicine*. 1995;152(5):1575-8.
17. Fine PE, Sterne JA, Pönnighaus JM, Rees RJ. Delayed-type hypersensitivity, mycobacterial vaccines and protective immunity. *The Lancet*. 1994;344(8932):1245-9.
18. Comstock GW. Identification of an effective vaccine against tuberculosis. 1988.
19. Kardjito T, Donosepoetro M, Grange J. The Mantoux test in tuberculosis: correlations between the diameters of the dermal responses and the serum protein levels. *Tubercle*. 1981;62(1):31-5.
20. Stead WW, To T. The significance of the tuberculin skin test in elderly persons. *Annals of Internal Medicine*. 1987;107(6):837-42.
21. Guld J. Quantitative aspects of the intradermal tuberculin test in humans. II. The relative importance of accurate injection technique. 1954.