

## Current Practice

# Tuberculin Test

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**Abstract.** Although tuberculin test is widely used for detection of tuberculous infection among children, there is no clear understanding about its performance and interpretation. This article has been written with the purpose of elucidating the performance and interpretation of standard tuberculin test, based on the experiences gained at the National Tuberculosis Institute, Bangalore and other centres.

The standard tuberculin test involves intradermal injection of '1TU PPD RT23 with Tween 80' on the mid-volar aspect of forearm and measurement of the maximum transverse diameter of induration after 3 days. Larger the size of induration, higher is the probability of it being due to tuberculous infection. The majority of reactions with induration size of 15 mm and above are attributable to infection with tubercle bacilli, irrespective of BCG-vaccination status. While inductions of less than 5 mm indicate absence of any kind of tuberculin sensitivity, the majority of inductions in 5-9 mm range are usually of non-tuberculous nature. An induration of 10-14 mm requires more careful interpretation. It is more likely to be attributable to infection with tubercle bacilli in case of history of contact with smear positive case or among children with clinical findings of tuberculosis. However, the size of induration in an infected child may be diminished in the presence of immuno-suppressive conditions. One should also consider the purpose of the test while interpreting the test results.

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**Key words :** *Tuberculin test; Size of Induration; Infection with tubercle bacilli; Non-specific sensitivity; BCG-induced sensitivity; Purpose of the test.*

The Tuberculin test has been the traditional method for detection of infection with tubercle bacilli. Epidemiologists have used it extensively for assessment of tuberculosis situation in different communities. In clinical practice, it is used to find out the presence or absence of tuberculous infection. This aids in the differential diagnosis of TB among children and to decide about administration of chemoprophylaxis.

The usefulness of the test lies not only on proper technique of administering a standard dose of a standard tuberculin and reading of the reactions by trained personnel but also in its careful interpretation. However, there is no clear understanding among some of the

medical practitioners and health workers regarding the performance and interpretation of the test.

The purpose of this article is to present guidelines on conducting the standard tuberculin test and its interpretation in pediatric practice, based on the experiences gained at the National Tuberculosis Institute (NTI), Bangalore and those of other TB workers in the country and abroad.

## THE STANDARD TUBERCULIN TEST

### Product and Dosage

One tuberculin unit (1TU) of *Purified Protein Derivative (PPD) RT23 with tween 80* is recommended for use in India. Tween 80 is a stabilizing agent to protect the absorption of tuberculin to glass surfaces. PPD RT23 with tween 80 was prepared by Statens Serum Institute, Denmark (SSI) from *Mycobacterium tuberculosis (M. tuberculosis)* and the seed-lot

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was supplied in freeze-dried form to laboratories of the individual countries. In India, it is reconstituted and supplied by BCG Vaccine Laboratory, Guindy, Chennai as an isotonic buffer solution. Other tuberculin available in the market may not be standardized.

Though some countries use 2TU of PPD RT23 with tween 80, it is recommended to use 1TU in India<sup>1</sup>, as this is more specific in our situation and better suited to differentiate tuberculin sensitivity induced by infection with *M. tuberculosis* from that of non-specific sensitivity induced by infection with *environmental Mycobacteria* i.e. *Mycobacteria* other than *M. tuberculosis* (MOTT).

Some other countries like USA use PPD-S (Siebert) which is also called as of Mammalian tuberculin and is considered as the international standard. All other tuberculins are standardized for biological activity against this preparation. Older preparations like old tuberculin (OT) and PPD RT22 are no longer in use. Other tuberculins like PPD-B (Battey) and PPD-G are used only in epidemiological studies for finding the prevalence of infection with *environmental mycobacteria*, which are usually non-pathogenic. These antigens are not used in clinical practice in this country.

Tuberculin vials should always be stored at 2-8° C and used before the expiry period, which is about one year after reconstitution and dilution. Exposure to sunlight and heat must be avoided.<sup>2</sup> The tuberculin should never be allowed to freeze or kept at temperatures exceeding 20° C except for short periods. The vials once used may be re-used within a maximum of 48 hours.

### Administration of Test

Tuberculin is injected in a measured amount of 0.1 ml intradermally on the mid-volar aspect of the forearm (*Mantoux method*). Conventionally, the test is given on the left forearm to avoid errors in reading. However, right arm may be used in case of any contra-indication to use the left arm.

The skin is lightly stretched and the

needlepoint is inserted with its bevel facing upward into the superficial layers of the skin. The skin area chosen should be free of scars, veins and areas of inflammation. The test site need not be sterilized before injection.<sup>3</sup> It can be simply cleaned with soap and water and should be dried before injection. The injection is given with the standard 1-ml tuberculin syringe graduated to hundredth of a mm, fitted with 26-gauge needle of half an inch length and 20 degree bevel. A tuberculin syringe is required to be absolutely airtight since lot of pressure is required to be exerted on the plunger for intradermal injection. If the syringe is not air tight, the amount of tuberculin injected will not be precise. A glass tuberculin syringe or a disposable tuberculin syringe can be used. No other syringe like insulin syringe should be used for the purpose.

A satisfactory test should raise a flat pale pea-sized wheal with clear pits of hair follicles and there should be no leakage of tuberculin. If the test is unsatisfactory i.e., the correct amount has not been injected or the injection has been made into the sub-cutaneous tissue, then another injection can be given either at a sufficient distance from the first injection or on the other forearm. The site chosen for the second test should be appropriately recorded.

*Adverse effects* : In some atopic individuals, an urticarial wheal may appear within minutes of injection. It usually disappears in 1-2 hours. The formation of vesicles, bullae, lymphangitis, ulceration or necrosis at the test site, which may occur in a proportion of children, indicates a high degree of tuberculin sensitivity.<sup>4</sup>

### Reading of the Test

The injection of the tuberculin antigen leads to migration and proliferation of the sensitized T-cell lymphocytes to the test site. These T-cells release lymphokines, which further attract other lymphocytes and monocytes.<sup>5</sup> These reactions along with increased permeability of the local blood capillaries lead to an induration at the test site. The size of this induration is

maximum between 48-96 hours after the test.<sup>6</sup> The reading of the test is done by measuring the maximal transverse diameter of this induration during this period. The erythema at the test site due to increased vascular permeability extends beyond the induration and is not considered for interpretation of the test results.

The reading of the test should be done in good day light with flexed forearm, by carefully palpating the site of injection using one finger. Since PPD RT23 with tween 80 has been found to result in softer reactions, the small indurations may be missed if not sought carefully. The transverse margins of the induration are marked with the ballpoint pen and the maximum transverse diameter is measured in millimetres with a transparent ruler, as followed internationally. The test result should never be recorded as 'positive' or 'negative' and must always be recorded in millimeter of size. Indurations upto 40 mm in diameter are found in practice. Record should also be made of formation of vesicles, bullae, lymphangitis, ulceration and necrosis at the test site.

A very high degree of inter-reader variation has been observed in the measurement of the induration sizes and more commonly, there is a tendency towards under-reading.<sup>7</sup> Therefore, in any institution, the required number of health workers may be appropriately trained in tuberculin testing and reading to perform the test. The training for tuberculin testing and reading requires a period of 6 weeks during which, each trainee is given to perform about 1,500 tests and readings in different phases. The measurements of indurations by the trainee reader are compared against those of standard reader.<sup>1,8</sup> Only those workers who give less than 2% unsatisfactory tests qualify as testers. Similarly, those who achieve a high correlation of more than 90% with the standard reader in reading and a minimal intra-reader variation are considered eligible for reading of the tests.

### SKIN SENSITIVITY TO TUBERCULIN

The tuberculin injection gives rise to a delayed-type of hypersensitivity reaction in the form of induration at the test site in a sensi-

tized host. This may occur due to one or more of the following:

### Infection with Environmental Mycobacteria

Infection with environmental mycobacteria also leads to sensitization of the host. The sensitivity induced by these generally non-pathogenic mycobacteria cross reacts with tuberculin and is known as non-specific sensitivity (NSS). This non-specific sensitivity is highly prevalent in most parts of India as in other tropical countries. In fact, it is more prevalent than true infection with tuberculosis causing organisms. In a survey conducted by NTI, about half of the children were found to be infected with environmental mycobacteria by the age of 10 years and two thirds by 14 years.<sup>9,10</sup> During the Tuberculosis Prevention Trial at Chingleput, 61% of children were found to be infected with environmental mycobacteria by the age of 9 years and almost all by 19 years.<sup>11</sup> Therefore, much of tuberculin sensitivity in the community is due to frequent contact with ubiquitous environmental mycobacteria. However, sensitivity induced by these mycobacteria will lead to smaller reactions to tuberculin than from true infection with tubercle bacilli<sup>12</sup>.

### BCG - induced sensitivity

Under universal immunization programme (UIP), multipurpose workers administer a reduced dose of 0.05 ml of the reconstituted freeze-dried BCG-vaccine during early infancy. In a study conducted by NTI, 70% of the children aged 0-9 years, vaccinated under UIP, elicited either no reaction or a reaction less than 10 mm to 1TU of PPD RT23 with tween 80.<sup>13</sup> Even in the immediate post-vaccination period i.e., during infancy and second year of age, same proportion of children elicited reactions below 10 mm. On the other hand, BCG induced tuberculin sensitivity was found to be highly satisfactory when full dose (0.1 ml) of BCG was administered under controlled experimental conditions during the Tuberculosis Prevention Trial at Chingleput<sup>11</sup>. Many factors might have been responsible for results obtained in the NTI study, such as administration of reduced dose of the vaccine given during early infancy

and difficulty in maintenance of high standards in the technique of vaccination under programme conditions. Even during the Mass BCG Vaccination Programme in India, tuberculin reactions due to BCG induced sensitivity were found to be smaller than those due to true infection with tubercle bacilli.<sup>14</sup>

Therefore, BCG induced sensitivity to tuberculin is generally weaker than sensitivity induced by infection with tubercle bacilli. It has also been confirmed experimentally that the sensitivity to the heterologous antigen is weaker than to a homologous antigen.<sup>12</sup>

Even during the Chingleput trial, BCG induced sensitivity was found to wane with time since vaccination.<sup>11</sup> Therefore, higher the age of the child, lesser the probability of the reaction attributable to BCG.

**Sensitivity induced by infection with tubercle bacilli.** The specific tuberculin sensitivity induced by infection with tubercle bacilli is more pronounced compared to the non-specific sensitivity induced by infection with environmental mycobacteria or BCG-vaccination as explained above. Therefore, most of the individuals harbouring tuberculous infection usually elicit a larger reaction to tuberculin. However, it is difficult to distinguish the sensitivity induced by *M.tuberculosis* and *M.bovis*. In this country, the infection due to *M.bovis* is rare as compared to *M. tuberculosis* because of the practice of boiling milk before consumption.

### INTERPRETATION OF TUBERCULIN TEST

The tuberculin test is based on the principle that the individuals who have been infected with tubercle bacilli respond with a delayed type hypersensitivity reaction at the test site. However, the interpretation of the test is complicated by cross-sensitivity induced by environmental mycobacteria and/or BCG-vaccination as explained earlier. Based on the above and the experience gained during various tuberculin surveys conducted by NTI and other organizations in various parts of India, the following general interpretations can be made :

1. Not all reactions to tuberculin are attributable to infection with tubercle bacilli.

2. Larger the size of induration at the test site, higher is the probability of presence of infection with tubercle bacilli. This is supported by the observation that tuberculosis morbidity increased with the size of induration.<sup>15</sup>

3. Almost all reactions with induration of 15 mm or more in size may be considered attributable to infection with tubercle bacilli, irrespective of the presence or absence of BCG-scar.

4. The formation of vesicles, bullae or necrosis at the test site indicates high degree of tuberculin sensitivity and thus presence of infection with tubercle bacilli.<sup>4</sup>

5. The reactions with induration of less than 5 mm in size usually indicate lack of tuberculin sensitivity and thus absence of infection either with tubercle bacilli or with environmental mycobacteria. Simple trauma of the needle has been observed to give rise to induration usually in the range of 1-4 mm.<sup>16</sup> However, some individuals infected with tubercle bacilli but suffering from severe degree of immune-suppression may show induration in this range.

6. Among children without BCG-scar, the majority of reactions with indurations in the range of 5-9 mm. are attributable to cross-sensitivity to environmental mycobacteria. Some of these children might actually have been vaccinated with BCG but do not show the BCG-scar.<sup>17,18</sup> Thus, in a proportion of children without BCG-scar, the indurations in this range may be attributable to BCG-vaccination. Among children with BCG scar, the reactions with indurations, in this range may be attributable to BCG vaccination and/or infection with environmental mycobacteria.

7. A reaction with induration between 10 to 14 mm could be attributable to infection with tubercle bacilli or due to cross sensitivity to environmental mycobacteria and/or BCG-induced sensitivity. It is mainly the proportion of true infections in this range that varies from com-

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munity to community and in different epidemiological groups. An induration in this size range is more likely to be attributable to infection with tubercle bacilli among high risk contacts e.g., infants of mothers suffering from tuberculosis, other children who have a history of contact with smear positive case of pulmonary tuberculosis or anti-TB treatment in the family, presence of symptoms or clinical findings suggestive of tuberculosis. The probability of a reaction in this range attributable to infection with tubercle bacilli is relatively higher among children without BCG-scar compared to those with scar, *Population surveys have shown that there are two groups of individuals in any community, one consisting of those 'infected with tubercle bacilli' and the rest having no tuberculin sensitivity or sensitivity due to other causes.*<sup>11,19-22</sup> *The majority of the reactions above a particular cut off point obtained from tuberculin surveys in respective areas signify infection with tubercle bacilli and majority of reactions below this cut off are due to other causes as explained above. However, there is always some degree of overlapping between the infected group and the rest even around these cut off points. Thus at any cut off point, some true infections will be missed and some others falsely included. These cut off points as obtained during epidemiological surveys have been found to vary between 10 to 15 mm in different parts of the country. However, it is impracticable to conduct tuberculin surveys all over the country to find suitable cut off points in respective areas. Therefore, the interpretation of reactions in 10-14 mm range requires more careful interpretation. In general, as the cut-off point moves to the left, there is increase in sensitivity of the test at the expense of specificity and vice versa. In clinical practice, it is best to consider other circumstances of the child as explained above to decide on the significance of the reactions with induration in this range.*

8. The tuberculin reaction may be suppressed in the presence of immuno-suppressive states. The size of induration has been observed to be diminished among children who are suffering from tuberculosis disease specially those

suffering from disseminated tuberculosis.<sup>23,24</sup> This is because a few sensitized circulating T cells are available to participate in the reaction since most of these may be collected in the tuberculous lesions. The mean reaction size of tuberculin test has also been found to decrease with increasing grade of undernutrition.<sup>25</sup> Tuberculin induration size may similarly be diminished in presence of cancer, Hodgkin's disease, sarcoidosis and cortico-steroid therapy.<sup>3</sup> During HIV infection, though tuberculin sensitivity is not affected at the initial stages, a greater proportion of individuals show suppression of test reactions as the CD4+ counts decline.<sup>26</sup> The above observations do not imply that the test should not be carried out in the presence of these conditions. The size of induration depends upon the degree of immune-suppression and the level of immunodeficiency should be considered while interpreting tuberculin reactions.

9. The hypersensitivity takes about 4-8 weeks to develop after initial infection and thus infection with tubercle bacilli may be missed in the *window period*'. Therefore, there should be a minimum period of 8 weeks between exposure and tuberculin test for detecting infection.

10. The interpretation of tuberculin test also depends on *the purpose of the test* WC5. In case the test is used for screening apparently healthy children for subjecting to further investigations for diagnosis of tuberculosis, it is more desirable to have a higher sensitivity by deciding on a lower cutoff point of 10-mm. For a decision on preventive chemotherapy, it is desirable to have a higher cut-off point of 15 mm, to be more specific. Though chemoprophylaxis is not routinely recommended in our country, it may, be considered in particular situations e.g. HIV positive contact of a case of tuberculosis. Under the Revised National Tuberculosis Control Programme (RNTCP), every 0-6 year old asymptomatic child in contact with smear positive case is put on preventive chemotherapy.<sup>27</sup> This is because the tuberculin test may not be available at every place and there is high risk of such children acquiring tuberculous infection. It is also well known that

the risk of breakdown into disease is maximum in the period immediately following acquisition of infection especially among children.<sup>28</sup>

It does not need to be emphasized that the tuberculin test detects only the presence or absence of tuberculous infection. The presence of infection is not synonymous with disease and only about 10% of the infected children break down into disease over their lifetime. Half of this risk occurs within one to two years of getting infected.<sup>29</sup> Thus, *tuberculin test should never be the sole criteria for diagnosing tuberculosis.*

### REPEAT TEST

It is usually unnecessary to repeat the test unless the test injection or reading was performed unsatisfactorily. The repeat test should be given at a different site within 1 week of the first test.<sup>30</sup> This is because the small amount of tuberculin injected for the first test can boost the size of the second test though it per-se does not sensitize the individual. This

boosting results from 'recall' of sensitivity induced by BCG vaccination or infection with environmental mycobacteria. In a study conducted by NTI, the boosting effect was observed when the test was repeated after two months.<sup>31</sup> The boosting phenomena was not observed when the test was repeated after 18 months.<sup>32</sup> However, when the boosting effect disappeared could not be ascertained. In another study, boosting was observed within three weeks of the first test.<sup>33</sup> Therefore, previous history of the individual taking the test should always be ascertained while interpreting the test result.

Repeating the test with higher doses may result in larger reactions which are attributable to non-specific sensitivity.<sup>9,10</sup> Same may be the case with BCG induced sensitivity. Therefore, a repeat test with higher dose is of no value for detection of infection with tubercle bacilli.

### DETECTION OF THE NEWLY INFECTED

The tuberculin test does not distinguish between past and new infection. As stated

**TABLE 1. Summary for Interpretation of the Tuberculin Test**

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#### **Size of induration 15 mm & above**

- Signifies infection with tubercle bacilli, irrespective of BCG vaccination

#### **Size of induration 10-14 mm**

- could be attributable to one or more of the following :
  - i. Cross-sensitivity induced by environmental mycobacteria.
  - ii. BCG-induced sensitivity
  - iii. Infection with tubercle bacilli
- It is more likely to be attributable to infection with tubercle bacilli in case of history of contact with smear positive case of pulmonary TB; clinically confirmed TB; X-ray consistent with active TB

#### **Size of induration 5-9 mm**

- Majority of such reactions are attributable to cross-sensitivity induced by environmental mycobacteria and/or BCG-vaccination
- Could be attributable to infection with tubercle bacilli in the presence of immuno-suppressive conditions.

#### **Size of induration less than 5 mm**

- Indicates absence of any type of mycobacterial infection except in children with severe degree of immune- suppression
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above, the incidence of disease among recently infected is much higher compared to the incidence among previously infected especially in the pediatric age group.<sup>28,29</sup> Therefore, detection of newly infected may be important in some situations e.g. among children who showed a reaction of less than 10 mm at an earlier test but have been exposed to a smear positive case thereafter. For detection of such new infection occurring in the intervening period between the two tests, there should be a significant increase in reaction size. Studies conducted in NTI have shown an increase of 14 mm and above among those infected during the intervening period when two tests were conducted 1 1/2 to 3 years apart.<sup>21,34</sup> In clinical practice, it would be more useful to consider an increase of 10 mm between the two tests as indicative of new infection. There should be a minimum period of 8 weeks between exposure and the second test. This applies to BCG-vaccinated as well as unvaccinated children.

### BCG TEST

Some medical practitioners use BCG vaccination for detection of tuberculous infection by assessment of local reactions. However, the interpretation of BCG test has not been standardized since the number of injected viable and dead organisms is highly variable. Moreover, the vaccine has not been prepared for the purpose of eliciting tuberculin sensitivity. Therefore, BCG test is not recommended to be used for detecting tuberculous infection.

### NEWER TUBERCULINS

PPD though more specific than old tuberculin is not a fully species-specific antigen and is widely crossreacting to sensitivity induced by environmental mycobacteria and BCG vaccination. Attempts are thus being made by various scientists to develop newer tuberculins, which are more species-specific.

### CONCLUSION

The usefulness of the tuberculin test lies in performing a standard test and its careful interpretation. The significance of the test

result cannot always be decided from the reaction size and depends upon other circumstances including the purpose of the test.

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