Canadian Tuberculosis Standards

7th Edition

Chapter 4: Diagnosis of Latent Tuberculosis Infection

Public Health Agency of Canada
Agence de la santé publique du Canada

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Canadian Tuberculosis Standard, 7th edition

Également disponible en français sous le titre :
Normes canadiennes pour la lutte antituberculeuse, 7ième édition

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PDF Cat.: HP40-18/2014E-PDF
ISBN: 978-1-100-23171-6
Pub.: 140199

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CHAPTER 4

DIAGNOSIS OF LATENT TUBERCULOSIS INFECTION

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KEY MESSAGES/POINTS

- The goal of testing for latent tuberculosis infection (LTBI) is to identify individuals who are at increased risk for the development of active tuberculosis (TB) and therefore would benefit from treatment of LTBI.
- Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive.
- There are two accepted tests for identification of LTBI: the tuberculin skin test (TST) and the interferon gamma release assay (IGRA).
- When interpreting a positive TST, it is important to consider much more than simply the size of the reaction. Rather, the TST should be considered according to three dimensions: size of induration, positive predictive value and risk of disease if the person is truly infected.
- As with the TST, IGRAs are surrogate markers of *Mycobacterium tuberculosis* infection and indicate a cellular immune response to *M. tuberculosis*.
- In general, IGRAs are more specific than the TST in populations vaccinated with Bacille Calmette-Guérin (BCG), especially if BCG is given after infancy or multiple times.
- Neither the TST nor IGRAs can separate LTBI from TB disease and therefore have no value for active TB detection. Both tests have suboptimal sensitivity in active TB, especially in HIV-infected people and children.
- Both tests appear to correlate well with the gradient of exposure. Both tests are associated with nonspecific variations and reproducibility issues, and borderline values need careful interpretation.
- Neither IGRAs nor the TST have high accuracy for the prediction of active TB, although use of IGRAs might reduce the number of people considered for preventive treatment.

MAJOR RECOMMENDATIONS

Both the TST and IGRA are acceptable alternatives for LTBI diagnosis. Either test can be used for LTBI screening in any of the situations in which testing is indicated, with preferences and exceptions noted below.

1. Situations in which neither TST nor IGRAs should be used for testing

- Neither the TST nor the IGRA should be used for testing people who have a low risk of infection and a low risk that there will be progression to active TB disease if they are infected. However, low-risk individuals are commonly tested before exposure, when repeat testing is likely. In this situation TST is recommended (see recommendation 3 below); if the TST is positive then an IGRA may be useful to confirm a positive TST result to enhance specificity.
- Neither TST nor IGRA should be used for active TB diagnosis in adults (for children, see recommendation 4).
- Neither TST nor IGRA should be used for routine or mass screening for LTBI of all immigrants (adults and children).
- Neither TST nor IGRA should be used for monitoring anti-TB treatment response.

2. Situations in which IGRAs are preferred for testing but a TST is acceptable

- People who have received BCG as a vaccine after infancy (1 year of age) and/or have received BCG vaccination more than once.
- People from groups that historically have poor rates of return for TST reading.

3. Situations in which TST is recommended for testing but an IGRA is NOT acceptable

- The TST is recommended whenever it is planned to repeat the test later to assess risk of new infection (i.e. conversions), such as repeat testing in a contact investigation or serial testing of health care or other populations (e.g. corrections staff or prison inmates) with potential for ongoing exposure.

4. Situations in which both tests can be used (sequentially, in any order) to enhance sensitivity

Although routine dual testing with both TST and IGRA is not recommended, there are situations in which results from both tests may be helpful to enhance the overall sensitivity:

- When the risks of infection, of progression to disease and of a poor outcome are high.
- In children (under age 18 years) with suspected TB disease, IGRAs may be used as a supplementary diagnostic aid in combination with the TST and other investigations to help support a diagnosis of TB. However, IGRA should not be a substitute for, or obviate the need for, appropriate specimen collection. A negative IGRA (or TST) does not rule out active TB at any age and especially not in young children.
- In addition, repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline or invalid, and a reason for testing persists.

INTRODUCTION: DIAGNOSIS OF LATENT TUBERCULOSIS INFECTION

While diagnosis and treatment of individuals with active TB is the first priority for TB control, an important second priority is identification and treatment of individuals with LTBI. In most individuals, *M. tuberculosis* infection is contained initially by host defences, and infection remains latent. However, latent infection can develop into active disease at any time. Identification and treatment of LTBI can substantially reduce the risk of development of disease (See Chapter 6, Treatment of Latent Tuberculosis Infection) and so have the potential to protect the health of the individual as well as the public by reducing the number of possible sources of future transmission.

There are two tests for identification of LTBI: the TST and the IGRA. Both tests evaluate cell-mediated immunity, and neither test can distinguish between LTBI and active TB disease.[1] The TST consists of the intradermal injection of a small amount of purified protein derivative (PPD) from *M. tuberculosis* bacteria. In a person who has cell-mediated immunity to these tuberculin antigens, a delayed hypersensitivity reaction will occur within 48 to 72 hours. The reaction will cause localized swelling and will be manifest as induration of the skin at the injection site.[2]

IGRAs are *in vitro* blood tests of cell-mediated immune response; they measure T cell release of interferon-gamma (IFN-gamma) following stimulation by antigens specific to *M. tuberculosis*.[1,3] Previous Advisory Committee Statements (ACSs) have provided guidance on the use of IGRAs in Canada.[4-6] This chapter supersedes these statements and serves as the updated guideline on the use of both IGRAs and TST in Canada.

INDICATIONS FOR LTBI TESTING AND GOAL OF TESTING

The goal of testing for LTBI is to identify individuals who are at increased risk for the development of active TB and therefore would benefit from treatment of latent TB infection (formerly termed preventive therapy or prophylaxis). Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive. This means that screening for LTBI in people or groups who are healthy and at low risk of active disease development is discouraged, since the positive predictive value of TST or IGRA is low and the risks of treatment will often outweigh the potential benefits. Moreover, screening for LTBI should be undertaken only when there is an *a priori* commitment to treatment or monitoring should test results be positive.[7]

In general, testing for LTBI is indicated when the risk of development of disease, if the patient is infected, is increased. The specific populations targeted for LTBI testing and the risk categories are described in Chapter 13, Tuberculosis Surveillance and Screening in High-Risk Populations, and Chapter 6, Treatment of Latent Tuberculosis Infection.

TUBERCULIN SKIN TESTING

The only internationally recommended method of tuberculin skin testing is the Mantoux technique, which consists of intradermal injection of tuberculin material into the inner surface of the forearm. It has been adapted and reproduced,[2,7] as described below.

ADMINISTRATION

Handling the tuberculin solution

- Tubersol® 5 tuberculin units (5-TU) of PPD-S (purified protein derivative – standard) is recommended in Canada. Use of one tuberculin unit (1-TU) is not recommended as it leads to too many false-negative reactions. Use of 250-TU is not recommended as this is associated with a very high rate of false-positive reactions.[8]
- Store at 2° to 8° C, but do not freeze. Discard the solution if frozen.
- Remove the tuberculin solution from the vial under aseptic conditions. A little more than 0.1 mL of PPD solution should be drawn into the TB syringe. Hold the syringe upright and lightly tap out the air, then expel one drop. Check that a full 0.1 mL remains in the syringe.
- Do not transfer the solution from one container to another (the potency of the PPD may be diminished).
- Draw up the solution just before injecting it. Do not preload syringes for later use as the potency of the PPD may be diminished.
- The solution can be adversely affected by exposure to light. PPD should be stored in the dark except when doses are actually being withdrawn from the vial.
- Discard the solution if the vial has been in use for longer than 1 month or for an undetermined amount of time (the potency of the solution may be diminished).
- Use the solution within 1 month after opening. Label each bottle with the discard date when it is opened.

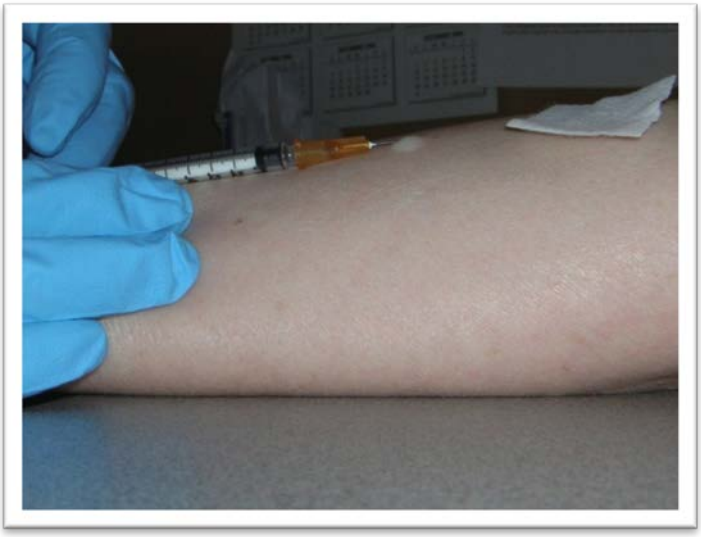
Preparing the person to be tested

- Seat the person comfortably, and explain the procedure.
- Use the inner aspect of the forearm, preferably the nondominant arm (where administration and reading of the reaction is easiest), about 10 cm (4 inches) below the elbow; avoid areas with abrasions, swelling, visible veins or lesions. If there is a localized rash, a burn or localized eczema, avoid this area.
- If neither forearm is suitable, use the outside of the forearm or the upper arm. In this case mark the location clearly in the record.
- Cleanse the area to be injected with an alcohol swab and let it dry.
- Do not use EMLA® cream (or similar local anesthetic cream), as application of this cream has been reported to cause localized edema, which could easily be confused with a positive TST result.[7]

Injecting the PPD tuberculin solution

- Use a 0.6 to 1.3 cm (¼ to ½ inch), 26- or 27-gauge needle with a disposable plastic tuberculin syringe.
- Position the bevel of the needle so that it opens facing up.
- While holding the skin of the inner aspect of the forearm taut, insert the needle at a 5°-15° angle to the skin without aspirating. The tip of the needle will be visible just below the surface of the skin. The needle is inserted until the entire bevel is covered (see Figure 1).
- Administer the PPD by the slow intradermal injection of 0.1 mL of 5-TU.
- A discrete, pale elevation of the skin (a wheal) 6-10 mm in diameter should appear. The wheal will typically disappear in 10-15 minutes. The size of the wheal is not completely reliable, but if a lot of liquid runs out at the time of injection and there is no wheal, then repeat the injection on the opposite forearm, or on the same forearm as before, but at least 5 cm from the previous injection site.
- A drop of blood may be seen – this is normal. The person tested should be offered gauze to remove the blood but should be advised not to massage the site in order to avoid squeezing out the PPD and disrupting the test.
- Do not cover the site with a bandage.
- Tell the patient that he or she should not scratch the site but may perform all normal activities, including showering or bathing.
- Place uncapped disposable needles and syringes in appropriate puncture-resistant containers immediately after use.
- If the TST is accidentally given as a subcutaneous or an intramuscular injection, this should not pose a serious problem. It is possible that tuberculin-sensitive people would have localized inflammation, which should be self-limited. It would not be possible to take a measurement of or clinically interpret any such reaction, so the TST should be administered again *but using proper intradermal technique* on the volar surface of the forearm. This should be done immediately (as soon as it is realized that the injection was too deep).

Figure 1. Technique of administration of TST



Record the following:

- date of injection;
- dose of PPD (5 TU, 0.1 mL);
- PPD manufacturer;
- PPD lot number;
- expiration date of the PPD reagent;
- site of injection;
- person administering the TST.

PRECAUTIONS

- Acute allergic reactions, including anaphylaxis, angioedema, urticaria and/or dyspnea, have been very rarely reported following skin testing with Tubersol®, see "Risk of Serious Allergic Reactions Following Tubersol® [Tuberculin Purified Protein Derivative (Mantoux)] Administration" (available from: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2005/14373a-eng.php).
- These reactions may occur in people without a history of a TST.
- Epinephrine hydrochloride solution (1:1000) and other appropriate agents should be routinely available for immediate use in case an anaphylactic or other acute hypersensitivity reaction occurs. Health care providers should be familiar with the current recommendations of the National Advisory Committee on Immunization on monitoring the patient for immediate reactions over a period of at least 15 minutes after inoculation and for the initial management of anaphylaxis in non-hospital settings (http://www.phac-aspc.gc.ca/publicat/cig-gci/p02-03-eng.php).

The following people should not receive a TST:

- Those with positive, 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 reactions or severe reactions.
- Those with documented active TB 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 with current major viral infections (e.g. measles, mumps, varicella).
- Those who have received measles or other live virus immunization within the past 4 weeks, as this has been shown to increase the likelihood of false-negative TST results. Note that only measles vaccination has been shown to cause false-negative TST results, but it would seem prudent to follow the same 4-week guideline for other live virus immunizations – mumps, rubella, varicella (chickenpox) and yellow fever. However, if the opportunity to perform the TST might be missed, the TST should not be delayed for live virus vaccines since these are theoretical considerations. (NOTE that a TST may be administered before or even on the same day as the immunizations but at a different site.)

The following people can receive a TST:

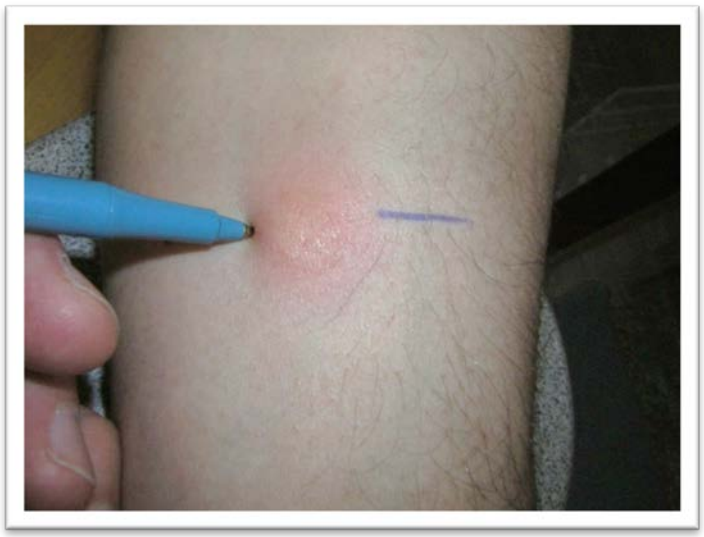
- Those with a history of receiving BCG vaccination(s);
- Those with a common cold;
- Those who are pregnant or are breastfeeding;
- Those immunized with any vaccine on the same day;
- Those immunized within the previous 4 weeks with vaccines other than the ones listed earlier;
- Those who give a history of a positive TST reaction (other than blistering) that is not documented;
- Those taking low doses of systemic corticosteroids, <15 mg prednisone (or equivalent) daily. It generally takes a steroid dose equivalent to ≥15 mg prednisone daily for 2-4 weeks to suppress tuberculin reactivity.[9,10]

MEASURING INDURATION

- The TST should be read by a trained health professional. Individuals without experience in reading a TST may not feel slight induration, and the TST would be mistakenly recorded as 0 mm.
- Self-reading is very inaccurate and is strongly discouraged.[11]
- Reading should be performed 48 to 72 hours after administration, as maximum induration can take up to 48 hours to develop, but after 72 hours it is difficult to interpret a reaction. Reactions may persist for up to 1 week, but for as many as 21% of individuals with a positive reaction at 48 to 72 hours the reaction will be negative after 1 week.[12] If the TST cannot be read within 72 hours because of unforeseen circumstances, it should be repeated at an injection site far enough from that of the previous test that the reactions do not overlap. No minimum wait is required before the repeat test.

- The forearm should be supported on a firm surface and slightly flexed at the elbow. Induration is not always visible. Palpate with fingertips to check whether induration is present. If there is induration, mark the border of induration by moving the tip of a pen at a 45° angle laterally toward the site of the injection (Figure 2). The tip will stop at the edge of the induration, if present. Repeat the process on the opposite side of the induration. This pen method has the advantages of being as reliable as the traditional palpation method (which relies entirely on fingertips) among experienced readers and of being easier for new readers to learn and use.
- Using a caliper, measure the distance between the pen marks, which reflects the diameter of the induration at its widest transverse diameter (at a right angle to the long axis of the forearm). A caliper is recommended because readings will be more precise and, most important, if the reader has to set the caliper and then read the diameter the rounding error is reduced. If a caliper cannot be found a flexible ruler could be used.
- Disregard and do not record erythema (redness). Approximately 2%-3% of people tested will have localized redness or rash (without induration) that occurs within the first 12 hours. These are minor allergic reactions, are not serious and do not indicate TB infection. They are not a contraindication to future TSTs.[13]
- Blistering, which can occur in 3% to 4% of subjects with positive tests, should be recorded.
- Record the result in millimetres (mm). Record no induration as “0 mm.” Recordings of positive, negative, doubtful, significant and non-significant are not recommended.
- Do not round off the diameter of the induration to the nearest 5 mm. as this can interfere with determining whether TST conversion has occurred in the event of a future TST. If the measurement falls between demarcations on the rules, the smaller of the two numbers should be recorded.

Figure 2. Ball-point method for reading transverse diameter of TST induration



Record the following:

- dates the induration was read;
- measurement of the induration, if any, in millimetres (mm);
- any adverse reactions, e.g. blistering;
- name of the individual reading the test.

Provide a record of the TST result to the individual tested.

INTERPRETATION OF A NEGATIVE TST RESULT

False-negative reactions

False-negative reactions can be caused by technical or biologic reasons (see Table 1).

Table 1. Potential causes of false-negative tuberculin tests[2,14-16]

Technical (potentially correctable)
Tuberculin material: - Improper storage (exposure to light or heat) - Contamination, improper dilution, or chemical denaturation **Administration:** - Injection of too little tuberculin or injection made too deeply (should be intradermal) - Administration more than 20 minutes after drawing up into the syringe **Reading:** - Inexperienced or biased reader - Error in recording
Biologic (not correctable)
Infections: - Active TB (especially if advanced) - Other bacterial infection (typhoid fever, brucellosis, typhus, leprosy, pertussis) - HIV infection (especially if CD4 count <200) - Other viral infection (measles, mumps, varicella) - Fungal infection (South American blastomycosis) **Live virus vaccination: measles, mumps, polio** **Immunosuppressive drugs:** **corticosteroids, tumour necrosis factor (TNF) inhibitors, and others** **Metabolic disease:** **chronic renal failure, severe malnutrition, stress (surgery, burns)** **Diseases of lymphoid organs:** **lymphoma, chronic lymphocytic leukemia, sarcoidosis** **Age: infants <6 months, the elderly**

MANAGEMENT OF A POSITIVE TST RESULT

Management of a positive TST should occur in two distinct steps:

STEP 1 – Deciding that a TST is positive

The health professional reading the TST should decide whether the test is positive. This is based on the size, using the criteria listed in Table 2. Once a TST is considered positive, the individual should be referred for medical evaluation. There is no clinical utility in performing a TST in the future once a test is considered positive, as long as the TST was properly performed and read.[2,7]

STEP 2 – Medical evaluation

This should include assessment of symptoms suggestive of possible active TB, risk factors for TB, such as contact history or other medical illnesses, as well as chest radiography. In the presence of symptoms or abnormal chest x-ray, sputum for acid-fast bacteria smear and culture should be taken. In subjects without evidence of active TB, a recommendation should be made regarding therapy for LTBI, based on interpretation of the TST.[2,7]

INTERPRETATION OF A POSITIVE TST

When interpreting a positive TST, it is important to consider much more than simply the size of the reaction. Rather, the TST should be considered according to three dimensions:[17]

1. size of induration;
2. positive predictive value; and
3. risk of disease if the person is truly infected.

A web-based interactive algorithm,[17] The Online TST/IGRA Interpreter (Version 3.0), which incorporates all three dimensions, is available (http://www.tstin3d.com) to assist in TST and IGRA interpretationhttp://www.tstin3d.com/index.html (Figure 3).

FIRST DIMENSION – SIZE OF INDURATION

This dimension (Table 2) is the easiest to understand (but the least important).[17] A criterion of 5 mm for a diagnosis of LTBI has a sensitivity of >98%, but the specificity is lower. This criterion is used when maximum sensitivity is desirable because the risk of development of active disease is high. A criterion of 10 mm has a sensitivity of 90% and specificity of >95%, and is recommended for most clinical situations. A criterion of 15 mm or more has sensitivity of only 60%-70% but has high specificity (>95%) in most parts of the world. However, this criterion is not appropriate for use in Canada, because specificity is not much higher than with 10+ mm, yet the sensitivity is reduced considerably.[2,7]

Figure 3. Screenshot of the Online TST/IGRA Interpreter (Version 3.0)

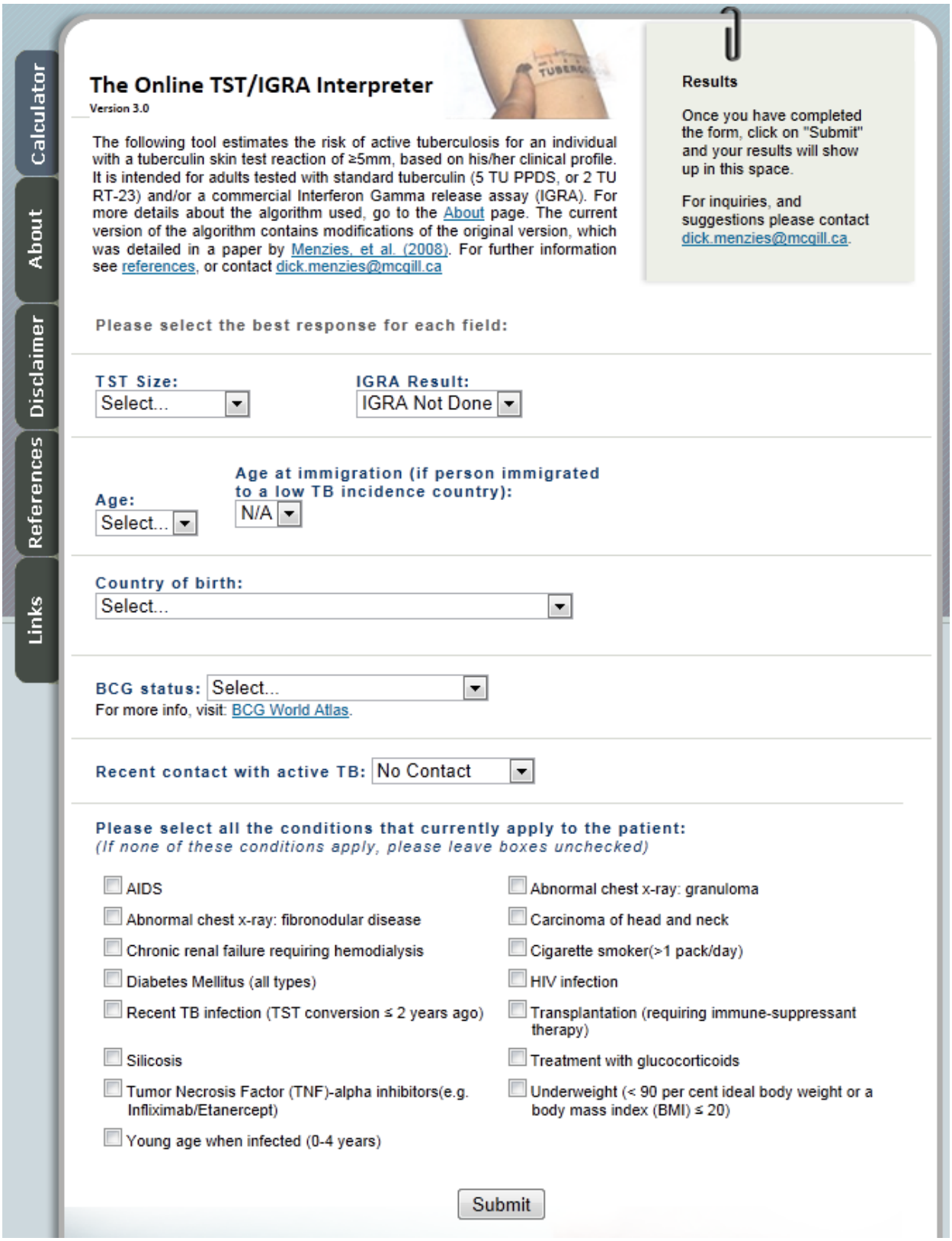


Table 2. Interpretation of tuberculin skin test results and cut-points in various risk groups[2,7]

TST result	Situation in which reaction is considered positive*
0-4 mm	In general this is considered negative, and no treatment is indicated.
	Child under 5 years of age and high risk of TB infection
≥5 mm	HIV infection
	Contact with infectious TB case within the past 2 years
	Presence of fibronodular disease on chest x-ray (healed TB, and not previously treated)
	Organ transplantation (related to immune suppressant therapy)
	TNF alpha inhibitors
	Other immunosuppressive drugs, e.g. corticosteroids (equivalent of ≥15 mg/day of prednisone for 1 month or more; risk of TB disease increases with higher dose and longer duration)
	End-stage renal disease
≥10 mm	All others, including the following specific situations: - TST conversion (within 2 years) - Diabetes, malnutrition (<90% ideal body weight), cigarette smoking, daily alcohol consumption (>3 drinks/day) - Silicosis - Hematologic malignancies (leukemia, lymphoma) and certain carcinomas (e.g. head and neck)

*The goal of testing for LTB is to identify individuals who are at increased risk for the development of tuberculosis and therefore would benefit from treatment of LTB. Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive (see text).

SECOND DIMENSION – Positive predictive value

The positive predictive value of the TST is the probability that a positive test result represents the true presence of TB infection. This differs from the TST sensitivity, which reflects the probability of a positive TST result in the presence of known TB infection. Positive predictive value is primarily influenced by the pretest probability or prevalence of TB infection, as well as the specificity of the TST. Thus, the positive predictive value is low and the utility of the TST is limited in populations at low risk of TB infection, those with previous exposure to nontuberculous mycobacteria (NTM) or those with a previous BCG vaccination, each of which can reduce the specificity of the TST.[18]

NTM: In parts of the world with tropical, subtropical or warm, temperate climates NTM are frequently found in soil and water, and most adults will have evidence of exposure and sensitization to some NTM antigens. Because the antigens of NTM are similar to those of *M. tuberculosis*, in people who are sensitized to NTM antigens there will be cross-reactivity with PPD-S, causing small tuberculin reactions, most of 5-9 mm and some of 10-14 mm, although almost none of 15+ mm. In most of Canada, sensitivity to NTM antigens is uncommon and is not an important cause of TST reactions of 10 mm or greater.[19] A study in Quebec demonstrated that less than 5% of all reactions of 10 mm or greater to standard PPD were due to this cross-reactivity.[20,21] This is why, in Canada, 10 mm remains the standard cut-point to determine whether TB infection is present.[7]

BCG vaccination: Several population groups in Canada are likely to have received BCG vaccination. These include immigrants from many European countries and most developing countries.[22] In Canada, many Aboriginal Canadians have been vaccinated, as have people born in Quebec and Newfoundland and Labrador between the 1940s and the 1970s (see the Public Health Agency of Canada's website for a summary of the provincial and territorial usage of BCG vaccine over time: http://www.phac-aspc.gc.ca/tbpc-latb/bcgvac_1206-eng.php).

Studies conducted in Canada and several other countries show that if BCG was received in infancy (the first year of life) only 1% had a TST result of ≥10 mm if tested >10 years later.[18] Therefore, a history of BCG vaccination received in infancy can be ignored in all people aged 10 years and older when interpreting an initial TST reaction of 10 mm or greater.[18,23-26]

If the BCG vaccination was received after 12 months of age, 42% had a false-positive TST of ≥10 mm after 10 years. If the vaccine was received between the ages of 1 and 5 years, persistently positive TST reactions were seen in 10%-15% of subjects up to 25 years later.[26] Of subjects vaccinated at the age of 6 years or older, up to 40% had persistent positive reactions. BCG-related reactions may be as large as 25 mm or even greater.[27,28] Therefore, if BCG vaccination was received after 12 months of age, it can be an important cause of false-positive TST reactions, particularly in populations whose expected prevalence of latent TB infection (i.e. true positive reactions) is less than 10%.

In summary, BCG vaccination can be ignored as a cause of a positive TST under the following circumstances:[2,7]

- BCG vaccination was given in infancy, and the person tested is now aged 10 years or older;
- there is a high probability of TB infection: close contacts of an infectious TB case, Aboriginal Canadians from a high-risk community or immigrants/visitors from a country with high TB incidence;
- there is high risk of progression from TB infection to disease.

BCG should be considered the likely cause of a positive TST under the following circumstances:[2,7]

- BCG vaccine was given after 12 months of age AND
  - There has been no known exposure to active TB disease or other risk factors AND
    - the person is either Canadian-born non-Aboriginal OR
    - an immigrant/visitor from a country with low TB incidence.

International TB incidence rates are available at: http://www.phac-aspc.gc.ca/tbpc-latb/itir-eng.php.

"Recognition of BCG (versus smallpox) scars" offers some tips on identifying BCG scars and may be viewed at http://www.phac-aspc.gc.ca/tbpc-latb/pubs-eng.php.

BCG vaccination policies in different countries can be found in the *BCG World Atlas*[22] at http://www.bcgatlas.org (Figure 4).

Figure 4. Screenshot of the *BCG World Atlas*

THIRD DIMENSION – Risk of development of active TB disease

After primary TB infection, the lifetime cumulative risk for the development of active TB is generally estimated to be 10%. Half of these cases will occur in the first 2 years after infection. Certain factors increase the risk of TB reactivation because of diminished local or systemic immunity, as summarized in Chapter 6, Treatment of Latent Tuberculosis Infection.

Many medical illnesses and therapies can increase the risk of reactivation, but the strongest risk factor is HIV infection.[2,7] The other problems have in common a reduction or suppression of immune function and include diabetes, renal failure, malnutrition, certain cancers, alcohol overuse and cigarette smoking. Medical therapies that suppress immune function, described in Chapter 6, are increasingly important indications for LTBI treatment.

Example of three-dimensional interpretation

As an example, consider a young woman aged 20, referred because of apical fibronodular scarring as observed on her chest x-ray. This is unchanged from previous chest radiographic results obtained 6 months earlier. She was vaccinated with BCG as an infant, recently (a year ago) immigrated to Canada from the Philippines, a country with high TB incidence, and is asymptomatic. The TST reaction is measured as 8 mm. Using the Online TST/IGRA Interpreter (www.tstin3d.com) algorithm, her annual risk of development of active tuberculosis disease is estimated to be about 1%, and the likelihood that this is a true positive test (PPV) is estimated as 77%. After consideration of the likelihood of a true- versus false-positive TST result and the risk of disease development, the prescription of isoniazid (INH) may or may not be indicated, depending on the balance between the risk of disease and the risks of therapy (see Chapter 6, Treatment of Latent Tuberculosis Infection).

INTERPRETATION WHEN SERIAL (REPEATED) TST IS PERFORMED

Nonspecific variation

Because of differences in the technique of administering or reading the TST or because of biologic differences in response, there may be differences in the same individual from test to test of as much as 5 mm in reaction size. Therefore, 6 mm has been selected as the criterion to distinguish a real increase from nonspecific variation.[29]

Conversion

The most helpful guide in distinguishing conversion from the booster effect described in the next section is the clinical situation. If there has been recent exposure, such as close contact with an active case or occupational TB exposure, then conversion will be more likely than when there has been no exposure. Conversion is defined as a TST of 10 mm or greater when an earlier test resulted in a reaction of less than 5 mm. If the earlier result was between 5 and 9 mm, the definition of conversion is more controversial.

There are at least two criteria in use, although neither have strong supportive evidence:

1. An increase of 6 mm or more – this is a more sensitive criterion, which is suggested for those who are immune compromised with increased risk of disease or for an outbreak;
2. An increase of 10 mm or more – this is a less sensitive but more specific criterion. In general, the larger the increase, the more likely that it is due to true conversion.[29]

All available experimental and epidemiologic evidence consistently shows that TST conversion occurs within 8 weeks of exposure.[29] Therefore, adopting 8 weeks as the maximum interval for conversion following exposure allows newly infected contacts to be identified a month sooner. It is also more practical for casual contacts, who can be tested once only after 8 weeks, and it results in fewer problems of interpretation because of the booster effect.

Two-step TST and the booster effect

A single TST may elicit little response yet stimulate an anamnestic immune response, so that a second TST at any time from 1 week to 1 year later will elicit a much greater response.[29] This phenomenon is important to detect, as it could be confused with TST conversion. The booster effect was first described in older people in whom it was felt to show LTBI acquired many years before (remotely) with subsequent waning of immunity.[30] It has also been described in people with prior BCG vaccination or sensitivity to nontuberculous mycobacterial antigens.[21,31,32]

Indications for 2-step tuberculin testing

A two-step TST should be performed if subsequent TSTs will be conducted at regular intervals or after exposure to an infectious TB case, for instance among health care or correctional service workers.[29] This is to reduce the chance of a false-positive TST conversion when the TST is repeated. One controversial area is whether travellers should be given two-step TST before and/or after travel to a region with high TB incidence. Please refer to Chapter 13, Tuberculosis Surveillance and Screening in High-Risk Populations, for recommendations.

The two-step protocol needs to be performed ONCE only if properly performed and documented. It never needs to be repeated. Any subsequent TST can be one step, regardless of how long it has been since the last TST.[2,7]

Repeat TST in a contact investigation: In a contact investigation, a single TST should be performed as soon as possible after the diagnosis has been made in the source case and the contact is identified. If this first TST is negative and it was performed less than 8 weeks after contact with the source case was broken, then a second TST should be performed no sooner than 8 weeks after the contact was broken. This is done to detect very recent infection that occurred just before contact was broken, since it will take anywhere from 3 to 8 weeks for the TST to become positive after new infection.[2,7]

Technique[2,7,29]

The same material and techniques of administration and reading should be used. The second test should be performed 1 to 4 weeks later. Less than 1 week does not allow enough time to elicit the phenomenon, more than 4 weeks allows the possibility of a true TST conversion to occur. Both tests should be read and recorded at 48 to 72 hours. In some centres, to reduce the total number of visits required to three, the first TST is read at 1 week, so that people with a negative TST can have a second TST immediately. However, reading performed at 1 week is less accurate and is not recommended.

Interpretation

The only two longitudinal studies of the risk of TB following a booster reaction defined the reaction simply as a second TST result of 10 mm or more induration.[16,33] Therefore, it is recommended that a second TST result of 10 mm or more should be considered significant and the patient referred for medical evaluation and chest radiography.

In the elderly, a significant booster effect most likely represents remotely acquired LTBI. In longitudinal studies, subjects with a second TST response of 10 mm or more had a risk of TB that was approximately half that of subjects in whom the first TST response was 10 mm or more.[33] Therefore, it is recommended that individuals with a reaction of 10+ mm on a second TST should be considered to have a risk of TB disease that is intermediate between individuals with initial positive and individuals with initial negative TST results from the same population group.

Management

All subjects with a reaction of 10+ mm on the second TST of a two-step TST do not need a TST in the future. There is no clinical utility.[2,7] They should be referred for medical evaluation, as performed for those with a positive first TST. Since the risk of TB is about half that of patients whose initial TST result is positive, the decision to give INH should be individualized.

A common question is how to manage a person in whom first TST measured 5-9 mm and the second test measured 10+ mm but increased by less than 6 mm from the first test. This should be managed as a positive TST, meaning referral for medical evaluation and no further TSTs. While appropriate epidemiologic data are lacking, it seems reasonable to suggest that the risk of active TB development would be lower than in people whose second TST increased by at least 6 mm. The decision to give INH should be individualized.

INTERFERON-GAMMA RELEASE ASSAYS (IGRAS)

The development of IGRAs is a new advance in the diagnosis of LTBI. IGRAs are *in-vitro* blood tests of cell-mediated immune response; they measure T cell release of interferon-gamma (IFN-gamma) following stimulation by antigens specific to *Mycobacterium tuberculosis* – early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10). These antigens are encoded by genes located within the region of difference 1 (RD1) segment of the *M. tuberculosis* genome.[1] They are more specific for *M. tuberculosis* than PPD because they are not shared with any BCG vaccine strains or most species of nontuberculous mycobacteria other than *M. marinum*, *M. kansasii*, *M. szulgai* and *M. flavescens*.[1]

TYPES OF ASSAYS

Two IGRAs are available in many countries: the QuantiFERON-TB Gold In-Tube (QFT-GIT) assay (Cellestis/Qiagen, Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Abingdon, United Kingdom). Both tests are approved by Health Canada and the United States Food and Drug Administration (FDA).

The QFT-GIT assay is an ELISA (enzyme-linked immunosorbent assay)-based, whole-blood test that uses peptides from three TB antigens (ESAT-6, CFP-10 and TB7.7) in an in-tube format. The result is reported as quantification of IFN-gamma in international units (IU) per millilitre. An individual is considered positive for *M. tuberculosis* infection if the IFN-gamma response to TB antigens is above the test cut-off (after subtracting the background IFN-gamma response in the negative control, see Appendix D, Tuberculosis and Mycobacteriology Laboratory Standards: Services and Policies).

The T-SPOT.TB is an enzyme-linked immunospot (ELISPOT) assay performed on separated and counted peripheral blood mononuclear cells; it uses ESAT-6 and CFP-10 peptides. The result is reported as number of IFN-gamma producing T cells (spot-forming cells). An individual is considered positive for *M. tuberculosis* infection if the spot counts in the TB antigen wells exceed a specific threshold relative to the control wells (see Appendix D).

IGRAs require laboratories with adequate equipment and trained personnel to perform the assays. In addition, IGRAs require fresh blood samples: pre-analytical steps and transportation delays can affect test performance.[34] Blood specimens for the QFT assay should be collected and shaken as per the manufacturer's instructions. They should be placed in an incubator as soon as possible and within 16 hours of blood collection. For the standard T-SPOT.TB assay, blood should be processed within 8 hours of collection. However, if the T-Cell Xtend® reagent is used, whole blood can be stored overnight prior to processing in the T-SPOT.TB assay.[35] Test kits should be transported and stored in optimum conditions to prevent exposure to excessive heat. Strict quality assurance is necessary to detect unusual patterns in results (such as a spike in the number of indeterminate results due to low mitogen response or high negative control responses), and it is important to run both positive and negative controls with each assay. The appendix on TB laboratory standards provides technical information on how to perform and interpret IGRA results, and how to achieve high quality.

In the recommendations that follow, both commercial IGRAs (QFT and T-SPOT.TB) are treated as acceptable alternatives, acknowledging that these assays differ in terms of laboratory expertise required, cost, pre-analytical steps and ease of use (see Appendix D). The decision regarding which commercial IGRA to offer is left to the discretion of provincial, commercial and hospital laboratories in Canada.

SENSITIVITY AND SPECIFICITY OF IGRAs

When measured using active TB as a surrogate reference standard, IGRAs have a specificity of >95% in the diagnosis of LTBI, and specificity is not affected by BCG vaccination.[36,37] The sensitivity for T-SPOT.TB appears to be higher than for QFT-GIT or TST (approximately 90%, 80% and 80% respectively).[37] TST specificity is high in populations not vaccinated with BCG (97%). In populations administered BCG it is much lower, although variable (approximately 60%).[37]

Because IGRAs are not affected by BCG vaccination status, they are useful for evaluating LTBI in BCG-vaccinated individuals, particularly in settings in which BCG vaccination is administered after infancy or when multiple (booster) BCG vaccinations are given. In contrast, as discussed previously, the specificity of TST varies depending on the timing of BCG and whether repeated (booster) vaccinations are given.[18] Further, although the finding is based on limited evidence, IGRAs appear to be unaffected by most infections with nontuberculous mycobacteria, which can cause false-positive TSTs. However, two nontuberculous mycobacteria that affect humans, *Mycobacterium marinum* and *Mycobacterium kansasii*, contain gene sequences that encode for ESAT-6 or CFP-10, antigens used in the new IGRAs. Infection with either of these NTMs has been shown to produce positive results in IGRAs using these antigens, as with the TST.[38,39]

IGRA sensitivity is diminished by HIV infection.[40,41] Lower CD4 counts have been associated with higher rates of indeterminate IGRA results; this is especially the case with QFT-GIT.[40,41] T-SPOT.TB appeared to be less affected by immunosuppression than QFT-GIT, likely because the testing procedure requires that an adequate number of peripheral blood mononuclear cells are placed in each test well, even if the overall peripheral blood lymphocyte count is low. An "indeterminate result" implies that the test cannot produce a valid result; often this is because of immune suppression, which leads to lack of T-cell response to the positive control. The likelihood of indeterminate results increases as CD4 count levels decrease in HIV-infected individuals. An indeterminate IGRA result should be repeated to make sure there are no technical or laboratory flaws. If the repeat result is also indeterminate, then the clinician cannot rely on IGRA for clinical decision-making. Other tests, risk factors and clinical information will be informative.[42]

EVIDENCE BASE ON IGRA PERFORMANCE IN VARIOUS SUBGROUPS

A large number of studies have evaluated IGRAs, and these have been summarized in several systematic reviews and guidelines (see Table 3 on the next page). As with the TST, IGRAs are surrogate markers of *M. tuberculosis* infection and indicate a cellular immune response to *M. tuberculosis*. IGRAs (like the TST) cannot distinguish between latent infection and active TB disease.

Table 3. Key findings of recent systematic reviews of IGRAs

Subgroup or focus of the review	Key findings	Reference
Active TB (pulmonary as well as extrapulmonary TB)	IGRAs have limited accuracy in diagnosing active TB. Their sensitivity is not high enough to rule out TB disease, and since they do not distinguish active from latent TB, specificity for active TB is low and cannot be used as a “rule in” test.	43,44
Children	TST and IGRAs have similar accuracy for the detection of TB infection or the diagnosis of disease in children. Both tests have similar correlations with exposure gradient in children. However, the ability of either TST or IGRAs was suboptimal to "rule in" or "rule out" active TB.	45,46
HIV-infected people	Current evidence suggests that IGRAs perform similarly to the TST in identifying HIV-infected individuals with LTBI. Both tests have modest predictive value and suboptimal sensitivity. Although T-SPOT appeared to be less affected by immunosuppression than QFT-GIT and the TST, overall, differences among the three tests were small or inconclusive.	40,41,47
Immune-mediated inflammatory diseases (IMID)	Current evidence does not clearly suggest that IGRAs are better than TST in identifying individuals with IMID who could benefit from LTBI treatment. To date, no studies have been done on the predictive value of IGRAs in IMID patients. Among patients receiving biologic therapy, in regions of moderate or high TB prevalence, or in patients with TB risk factors there is some evidence that a dual testing strategy of TST and IGRA improves sensitivity.	48-50
Health care workers (HCWs)	The use of IGRAs instead of TST for one-time screening may result in a lower prevalence of positive tests and fewer HCWs who require LTBI treatment, particularly in settings of low TB incidence. However, when the manufacturer’s cut-offs are used, IGRAs had high rates of conversions (2%-5%), which were frequently much higher than the rates of TST conversions and higher than the annual risk of TB infection expected in these low-incidence settings. IGRAs also had high rates of spontaneous reversions, which ranged from about 20%-40% in most studies.	51,52
Predictive value for progression to active TB disease	Neither IGRAs nor the TST have high accuracy for the prediction of active TB, although use of IGRAs in some populations might reduce the number of people considered for preventive treatment.	53
Reproducibility, within-person variation of IGRA results, and boosting effect of TST on IGRA results	Although the finding was based on limited data, within-subject variability was present in all studies, but the magnitude varied (16%-80%) across studies. A TST-induced ‘‘boosting’’ of IGRA responses was demonstrated in several studies and although more pronounced in IGRA-positive (i.e. sensitized) individuals it also occurred in a smaller but not insignificant proportion of IGRA-negative subjects.	54
Use of IGRAs for monitoring response to anti-TB therapy	Monitoring changes in IGRA response during anti-TB treatment has no utility in adults. Data in children are limited but are in line with results reported in adults.	55

IGRAs FOR ACTIVE TB DIAGNOSIS

For the diagnosis of active TB, IGRA sensitivity and specificity are poor, particularly in people from settings with high TB incidence.[43] Specificity is poor because these populations (e.g. recent immigrants) will have a high prevalence of LTBI, and the immune-based tests cannot distinguish between active disease and latent infection.[43] Sensitivity is reduced because of the temporary anergy of the acute illness. A positive IGRA result may not necessarily indicate active TB, and a negative IGRA result may not rule out active TB. Therefore, IGRAs should not be used for diagnosis of active TB in adults.[43]

CHILDREN

Available data from systematic reviews suggest that the TST and IGRAs have similar accuracy for the detection of TB infection or the diagnosis of disease in children.[45,46] Both tests have similar correlations with exposure gradients in children. However, the ability of either the TST or IGRAs was suboptimal to "rule in" or "rule out" active TB, reinforcing the appropriate use of these tests as adjuncts (rather than isolated tests) in the clinical diagnosis of active TB. In children with suspected active TB, every effort should be made to collect appropriate clinical specimens for microbiological testing, and IGRAs should be used with other clinical data (e.g. TST results, chest radiographic findings, history of contact) to support a diagnosis of active TB.[56]

HIV-INFECTED PERSON

Systematic reviews show that in HIV-infected people with active TB (a surrogate reference standard for LTBI), pooled sensitivity estimates were heterogeneous but higher for T-SPOT.TB (72%; 95% confidence interval [CI] 62%-81%) than for QFT-GIT (61%; 95% CI 47%-75%) in low-/middle-income countries.[5] However, neither IGRA assay was consistently more sensitive than the TST in head-to-head comparisons. Although T-SPOT.TB appeared to be less affected by immunosuppression than QFT-GIT and the TST, overall, differences among the three tests were small or inconclusive. Thus, current evidence suggests that IGRAs perform similarly to the TST at identifying HIV-infected individuals with LTBI, and both tests have suboptimal sensitivity for active TB.[5,6,47]

REPRODUCIBILITY

A systematic review published in 2009 found limited data on reproducibility but reported that within-subject variability was present in all studies, the magnitude varying (16%-80%) across studies.[54] More recent studies have confirmed this finding and expanded the type of evidence on test reproducibility.

There are now studies that show five important sources of variability in IGRA results:

1. pre-analytical steps (e.g. tube shaking, time to incubation, actual incubation time);[34]
2. test-retest variation (i.e. same sample tested twice);[57]
3. within-person variations over time (i.e. same person tested on separate days with separate samples);[58]
4. interlaboratory variations (i.e. same sample tested in different laboratories);[59]
5. TST-induced variations in QFT results (i.e. effect of a prior PPD placement on subsequent IFN-gamma values).[60]

The importance of pre-analytical factors, such as the time lapse between blood collection and sample processing and/or incubation at 37° C, was brought out by a recent study in the United States.[34] Compared with immediate incubation, 6- and 12-hour delays resulted in positive-to-negative reversion rates of 19% (5/26) and 22% (5/23) respectively.

A recent large US study on the repeatability of QFT performed multiple IGRA tests using leftover stimulated plasma.[57] This study reported substantial variability in TB response when QFT tests were repeated using the same patient sample. The normal expected range of within-subject variability in TB response upon retesting included differences of +/–0.60 IU/mL for all individuals (coefficient of variation [CV]) 14%) and +/–0.24 IU/mL (CV 27%) for individuals whose initial TB response was between 0.25 and 0.80 IU/mL. The authors recommended that test results should be interpreted cautiously among individuals with a positive IFN-gamma value of less than 0.59 IU/mL.[57]

Another recent study compared results from the same subjects when QFT ELISAs were performed in different laboratories in the United States.[59] This study reported substantial within-subject interlaboratory variability in QFT interpretations and IFN-gamma measurements when blood samples collected from the same person at the same time were tested in three different laboratories. Of the 97 subjects tested in three laboratories, 11% had discordant QFT interpretations based on the original reported data. A portion of the variability in test interpretation was associated with manual data entry errors.[59]

All of these studies have argued for a borderline zone (conceptually similar to the interpretation of a TST result of 5 to 9 mm) for the interpretation of IGRAs, rather than a simplistic negative/positive interpretation. Currently, the FDA- and Health Canada-approved versions of QFT Gold In-Tube do not provide a borderline zone, and laboratories do not routinely report absolute values of IFN-gamma or spot-forming cells.

There is currently no consensus on the exact borderline zone that should be used, and this an active area of debate and research. Until more definitive evidence and consensus emerges, on the basis of existing literature it appears that IFN-g values of 0.20-1.00 IU/mL for QFT should be interpreted cautiously, as nonspecific and reproducibility issues can easily result in false conversions and reversions if the initial value fell in this borderline zone. If results do fall in this borderline zone, care providers could choose to repeat the test, depending on the clinical context and other information available (e.g. on risk factors). To facilitate the interpretation of such values, laboratories should provide quantitative results in addition to the dichotomous (positive/negative) results. This is particularly critical for interpretation of repeated IGRA results (see Appendix D).

Laboratories should also ensure that there is standardization of pre-analytical procedures such as tube shaking, time interval between the drawing of blood and incubation, and exact duration of incubation. If portable incubators are used, it is important to make sure that such incubators can accurately stabilize the temperature at 37° C. Laboratories should avoid manual entry of results to avoid additional variability and errors (see Appendix D).

HEALTH CARE WORKERS AND OTHER GROUPS THAT MIGHT BENEFIT FROM SERIAL TESTING

Serial (repeated) testing for TB infection is indicated in specific populations, such as HCWs in high-risk settings, prison inmates and staff, and close contacts.

Several studies have evaluated the use of IGRAs in HCWs, and these have been summarized in systematic and narrative reviews.[52,55,61] In settings of low TB incidence the pooled prevalence of positive IGRA in HCWs was significantly lower than for a positive TST. However, in high-incidence settings there were no consistent differences in the prevalence of positive tests. IGRAs showed good correlation with occupational risk factors for TB exposure in low-incidence settings. Only 10 studies assessed the use of IGRA for serial testing, and all showed large variation in the rates of conversions and reversions, with no data suggesting that IGRAs are better than the TST at identifying the incidence of new TB infection.[51]

Thus, the use of IGRAs instead of TST for one-time screening may result in a lower prevalence of positive tests and fewer HCWs who require LTBI treatment, particularly in settings of low TB incidence. However, when simple negative/positive changes were used as cut-offs, IGRAs had high rates of conversions (2%-15%), which were frequently higher than the rates of TST conversions and higher than the annual risk of TB infection expected in these low-incidence settings. IGRAs also had high rates of reversions, which ranged from about 20% to 40% in most studies.[52] Thus, the use of IGRAs for serial testing is complicated by lack of data on optimum cut-offs for serial testing, issues with reproducibility, and unclear interpretation and prognosis of conversions and reversions.[61]

On the basis of a growing number of serial IGRA testing studies, several observations can be made:[44]

- IGRAs are inherently dynamic in a serial testing context, and this is reflected in the literature, which consistently shows high rates of both conversions and reversions.
- This dynamic pattern is seen in settings of low, intermediate and high TB incidence, suggesting that at least some of the observed variations may be intrinsic to the assay, independent of the risk of exposure. These include nonspecific variations due to biological reasons as well as assay reproducibility issues (reviewed earlier).
- While IGRAs are not prone to the subjectivity that adversely affects the reading of TST, other factors affect their reproducibility, including pre-analytical delays (e.g. time to incubation and length of incubation), procedures such as tube shaking (for QFT), and test-retest and inter-laboratory variations.
- When the manufacturer's cut-offs are used for conversions, the result will likely be conversion rates that are incompatible with what is epidemiologically expected for a given setting.
- IGRA reversions are highly likely to occur among those with interferon-gamma values (or spot counts) just above the diagnostic threshold (i.e. borderline zone), and reversion rates

can exceed 40%-50% in some settings. Reversions can occur spontaneously, even in the absence of treatment.

- While a previous IGRA will not boost the results of the subsequent IGRA result, a previous TST can boost the subsequent IGRA result, and this is mostly seen among those who are already sensitized to mycobacteria (i.e. TST positive) but is not due to BCG.
- When tests are repeated more frequently on the same individuals, more complex patterns or phenotypes are seen, including stable and unstable (transient) conversions, persistent positives and negatives, and other complex patterns that defy description.
- There are no longitudinal data on the prognosis of such phenotypes, and it is unclear which subgroup should be targeted for preventive therapy.

Overall, routine implementation of IGRAs in serial testing programs offers some benefits (e.g. higher specificity and easier logistics) but also poses significant challenges in the interpretation of test results – for the individual and for the health care provider. This is evident from recent experiences of North American hospitals that began implementing IGRAs for employee screening after publication of the 2005 Centers for Disease Control and Prevention guidelines.[62-64] Similar findings have been reported from Canadian hospitals.[65]

There is limited evidence on the timing of IGRA conversions. Available evidence suggests that most IGRA conversions occur within 4 to 7 weeks after TB exposure.[66,67] However, in some cases conversion may be delayed longer than 3 months; agreement between TST and IGRA show a better concordance after this window period.

PREDICTION OF ACTIVE DISEASE

As shown in a recent systematic review, neither IGRAs nor the TST have high accuracy for the prediction of active TB, although use of IGRAs in some populations might reduce the number of people considered for preventive treatment (because of higher specificity).[53] Several longitudinal studies show that incidence rates of active TB, even in IGRA-positive individuals in countries with a high burden of TB, are low, suggesting that in a vast majority (>95%) of IGRA-positive individuals there is no progression to TB disease during follow-up. This is similar to the TST. Compared with test-negative results, IGRA-positive and TST-positive results were much the same with regard to the risk of TB (pooled incidence rate ratios in the five studies that used both was 2.11 [95% CI 1.29-3.46] for IGRA versus 1.60 [0.94-2.72] for TST at the 10 mm cut-off).[53]

Only one study has evaluated the risk of progression to TB associated with an IGRA conversion.[68] This study, conducted among adolescents in South Africa, compared the incidence rate of TB disease following recent QFT conversion with the incidence among non-converters. Recent QFT conversion was indicative of an approximately 8-fold higher risk of progression to TB disease (compared with non-converters) within 2 years of conversion in a cohort of adolescents. For QFT converters, the TB incidence rate (all cases) was 1.46 cases per 100 person years. A significantly lower TB incidence rate (0.17 cases per 100 person years) was observed for QFT non-converters.[68] It is noteworthy that even among QFT convertors, the overall TB incidence was about 3% within 2 years of conversion. This is consistent with other studies showing that in a vast majority of IGRA- or TST-positive individuals there is no progression to TB disease. Thus, further research is needed to identify biomarkers that are highly predictive and can identify latently infected individuals who are at highest risk of disease progression.[69]

TREATMENT MONITORING

A recent systematic review on the use of IGRAs for monitoring TB treatment found that reversion from positive to negative IGRA occurred in a minority of treated patients and monitoring IGRA changes over time had no clinical utility in adults.[55] Data in children were limited but in line with results reported for adults.

REVISED RECOMMENDATIONS FOR USE IN CANADA

Available evidence suggests that both the TST and IGRAs are acceptable, but imperfect, tests for LTBI. In general, IGRAs are more specific than the TST in BCG-vaccinated populations, especially if BCG is given after infancy or multiple times. Neither test can distinguish LTBI from TB disease and therefore has no value for active TB detection in adults. Both tests have suboptimal sensitivity in active TB, especially in HIV-infected people and children. Both tests appear to correlate well with gradient of exposure. Neither IGRAs nor the TST have high accuracy for the prediction of active TB, although use of IGRAs in some populations might reduce the number of people considered for LTBI treatment. IGRAs do offer some improvements over the TST, but the improvement is incremental rather than transformational.[70]

In 2010, the Canadian Tuberculosis Committee issued an updated Advisory Committee Statement on IGRAs,[4] which recommended the use of IGRA as a confirmatory test when false-negative or false-positive TST results are suspected. The following new recommendations will supersede the previous ACS:

Both the TST and IGRA are acceptable alternatives for LTBI diagnosis. Either test can be used for LTBI screening in any of the situations in which testing is indicated, with preferences and exceptions noted below.

New Recommendations

1. Situations in which neither TST nor IGRAs should be used for testing

- Neither the TST nor the IGRA should be used for testing people who have a low risk of infection and a low risk that there will be progression to active TB disease if they are infected. However, low-risk individuals are commonly tested before exposure, when repeat testing is likely. In this situation TST is recommended (see recommendation 3); if the TST is positive then an IGRA may be useful to confirm a positive TST result to enhance specificity.
- Neither TST nor IGRA should be used for active TB diagnosis in adults (for children, see recommendation 4).
- Neither TST nor IGRA should be used for routine or mass screening for LTBI of all immigrants (adults and children).
- Neither TST nor IGRAs are useful tools for monitoring anti-TB treatment response.

  (Strong recommendations, based on strong evidence)

Rationale

The goal of testing for LTBI is to identify individuals who are at increased risk for the development of active TB and therefore would benefit from treatment of LTBI. Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive. This is the rationale for not using either TST or IGRA for screening low-risk individuals. However, in some settings, low-risk individuals might get tested with TST. In such situations, it may be helpful to rule out a false-positive TST result by performing an IGRA test. This strategy will improve the overall specificity of the testing process in low-risk individuals and may also be cost-effective, as shown in a Canadian study.[71]

Neither the TST nor the IGRA can distinguish latent infection from active TB disease, and therefore these tests should not be used for adults with suspected active TB.[43] In children with suspected active TB disease, every effort must be made to collect specimens for microbiological testing. IGRAs can be used as a supplementary diagnostic aid, along with TST and other investigations and clinical data (e.g. chest radiography, history of contact) to support a diagnosis of TB in children.[56]

Neither the TST nor IGRAs are useful tools for monitoring anti-TB treatment response, and their use for this purpose should be avoided.[55]

2. Situations in which IGRAs are preferred for testing but a TST is acceptable

- People who have received BCG as a vaccine after infancy (1 year of age) and/or have received BCG vaccination more than once.
- People from groups that historically have poor rates of return for TST reading.

(Conditional recommendations, based on moderate evidence)

Rationale

Among people with a history of post-infancy BCG vaccination or of multiple BCG vaccinations, the specificity of the TST is likely to be poor. IGRAs are therefore the preferred tests, although a TST can still be used. In populations that are known to have poor rates of return for TST reading (e.g. homeless individuals and injection drug users), use of IGRAs can help achieve a higher rate of test completion and follow-up, although completion of LTBI treatment may still be challenging in these populations.

3. Situations in which TST is recommended for testing but an IGRA is NOT acceptable

- The TST is recommended whenever it is planned to repeat the test later to assess risk of new infection (i.e. conversions), such as repeat testing in a contact investigation, or serial testing of health care or other populations (e.g. corrections staff or prison inmates) with potential for ongoing exposure.

(Conditional recommendation, based on moderate evidence)

Rationale

IGRAs are not recommended in these situations because serial testing studies have shown high rates of conversions and reversions, unrelated to exposure or treatment. There is no consensus on the appropriate cut-offs or borderline zones for deciding on IGRA conversions and reversions, although the literature suggests that IFN-gamma values of 0.20-1.00 IU/mL for QFT should be interpreted cautiously, as nonspecific and reproducibility issues can easily result in false conversions and reversions if the initial value fell in this borderline zone. If results do fall in this zone, care providers could choose to repeat the test, depending on the clinical context and other information available (e.g. risk factors). To facilitate the interpretation of such borderline values, laboratories should provide quantitative results in addition to the dichotomous (positive/negative) results.

4. Situations in which both tests can be used (sequentially, in any order) to enhance sensitivity

Although routine dual testing with both TST and IGRA is not recommended, there are situations in which the results from both tests may be helpful to enhance the overall sensitivity:

- When the risk of infection, of progression to disease and of a poor outcome are high. See Chapter 6, Treatment of Latent Tuberculosis Infection.
- In children (under age 18 years) with suspected TB disease, IGRAs may be used as a supplementary diagnostic aid in combination with the TST and other investigations to help support a diagnosis of TB. However, IGRA should not be a substitute, or obviate the need, for appropriate specimen collection. A negative IGRA (or TST) does NOT rule out active TB at any age and especially not in young children.
- In addition, repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline or invalid and a reason for testing persists.

  (Conditional recommendations, based on moderate evidence)

In these situations, it is recommended that health care providers use either a TST or IGRA as the initial test and if it is negative consider a second test using the alternative format. If the initial test is positive, then no second test is required.

For example, if the initial TST is positive, then the testing process stops because LTBI is diagnosed. If the initial TST is negative, then an IGRA test can be performed (or vice-versa, if testing was started with an initial IGRA).

IMPORTANCE OF CONSIDERING THE CLINICAL CONTEXT

The results of both TST and IGRA should be interpreted with other relevant clinical information, such as age, BCG status, history of contact with active TB and factors that increase the risk of progression to active disease. An online TST/IGRA algorithm (www.tstin3d.com) has been developed to facilitate the three-dimensional interpretation of these tests. All individuals with positive TST or IGRA results should undergo evaluation to determine whether they have LTBI or active TB disease and be managed according to the recommendations in Chapters 5, Treatment of Tuberculosis Disease and 6, Treatment of Latent Tuberculosis Infection.

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