Section 2: Understanding Tuberculosis

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Etiology, Transmission and Pathogenesis

Etiology

TB disease is caused by mycobacteria, specifically those in a grouping called the *Mycobacterium tuberculosis* complex (MTB complex). Of these, *Mycobacterium tuberculosis* is the most common cause of TB disease (active TB) in humans. Mycobacteria that cause TB disease are referred to as 'TB bacteria' throughout this manual.

Mycobacteria that **DO NOT** cause TB disease are known as 'nontuberculous mycobacteria' (NTM). In the past, NTM were called 'atypical mycobacteria' or 'mycobacteria other than tuberculosis' (MOTT). NTM are found in soil and water, and do not usually cause disease in people with healthy immune systems. NTMs are not thought to spread from person-to-person therefore information on diagnosis and management of NTM disease is not included in this manual. Refer to the *Canadian Tuberculosis Standards* for information on NTM.

Characteristics of TB Bacteria

TB Bacteria are:

- Tiny (1 to 5 microns in size)
- Rod-shaped
- Slow-growing (divide once every 15 to 20 hours) and therefore difficult to culture

TB bacteria are identified in a clinical specimen with an acid-fast bacilli (AFB) smear under a microscope and a mycobacterial culture. They cannot be identified with routine culture and sensitivity testing (i.e. 'routine C&S').

Figure 2.1: *Mycobacterium tuberculosis* (violet rods), Ziehl-Neelsen stain

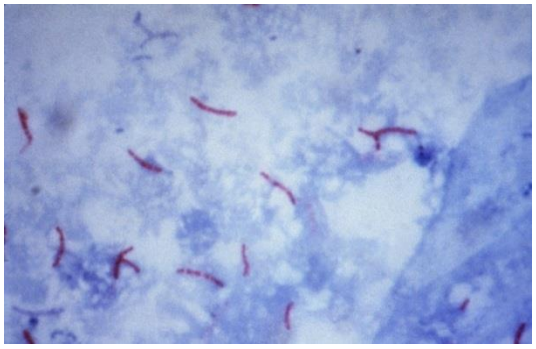


Image from: http://www.museumofhealthcare.ca/explore/exhibits/breath/diagnosis.html#hc5

Transmission

Transmission of TB bacteria is primarily person-to-person, through inhalation of airborne droplets (droplet nuclei) that contain TB bacteria.

Droplet nuclei are released by a person with infectious TB during forceful expirations such as coughing, sneezing, singing and playing wind instruments. A person with TB disease affecting his/her larynx (laryngeal TB) can release droplet nuclei while talking.

Less commonly, TB bacteria are transmitted when droplet nuclei are aerosolized during:

- Pressurized irrigation or debridement of open TB wounds.
- Handling of specimens containing TB bacteria in the laboratory.
- Autopsies of people with active TB.

TB bacteria (specifically *Mycobacterium bovis*) can also be transmitted in unpasteurized milk or other food products from animals with active TB.

Factors that influence the risk of transmission include:

- **Concentration of droplet nuclei in the shared airspace**, which is influenced by:
    - Degree of infectiousness of the person with TB (the case).
    - Degree of air circulation/ventilation.
    - Physical proximity to the case.
    - Behavior of the case (e.g. covering his/her mouth when coughing or sneezing).
- **Whether the exposed person was previously infected with TB bacteria.**

  Some studies suggest healthy people who were previously infected with TB bacteria might be protected against re-infection during subsequent exposures. However, this is an outstanding question.
- **Duration and frequency of exposure(s).**

  In general, risk increases with longer and/or more frequent exposures.
- **Whether the person is/was adequately protected against inhaling TB bacteria during the exposure.**

Wearing a properly sealed, disposable N95 respirator (commonly referred to as an 'N95 mask') can protect a health care provider from inhaling TB bacteria while caring for an infectious case.

- **Age and immune status of the exposed person.**

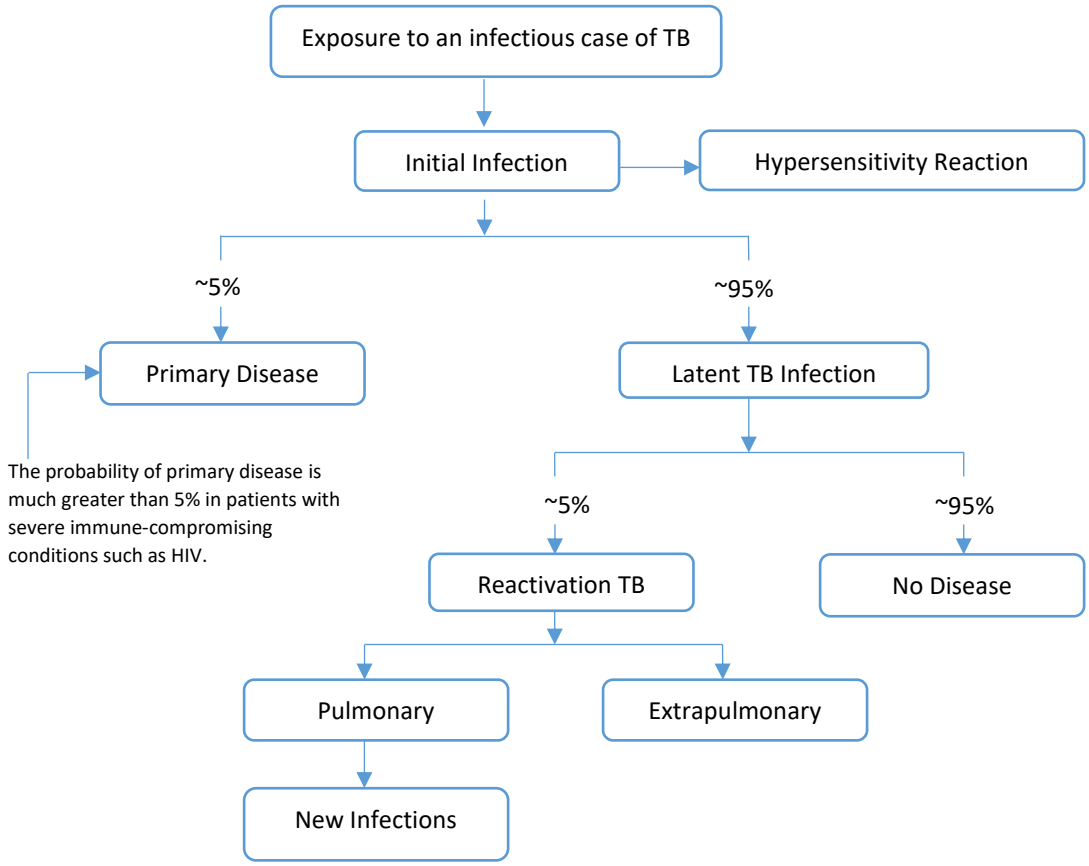
  Very young contacts, elderly contacts and immunosuppressed contacts might be at higher risk for becoming infected with TB bacteria during exposures to infectious cases.

Some strains of TB bacteria might also be more easily transmitted than others.

Pathogenesis

Figure 2.2: The pathogenesis of tuberculosis in an infected host

(From the 7th Edition of the Canadian Tuberculosis Standards)



Primary TB and Reactivation TB

Some people will develop active TB within the first 18-24 months after becoming infected with TB bacteria. This is known as **primary TB**. TB meningitis, miliary TB and pleural TB are often (but not always) presentations of primary TB.

Contacts under five years of age and those with severe immunosuppression are at high risk for developing primary TB rather than latent infection after becoming infected with TB bacteria. Window period prophylaxis (WPP), also known as primary prophylaxis, is used in contact investigations to protect young and severely immunosuppressed contacts from developing primary TB (see **Section 12: Contact Investigation and Source Case Investigation**). Active TB that develops more than 18 to 24 months after initial infection with TB bacteria is known as **reactivation TB**.

Although it is not always possible to do so, making distinctions between cases with primary TB and those with reactivation TB can be important for public health management. For example, when a young child is diagnosed with active TB, it could mean there is someone with undiagnosed infectious TB among the people s/he spends time with. The CDCN may request that household members and others who spent time regularly with the child be assessed for TB. This practice is known as 'source case investigation' (see **Section 12: Contact Investigation and Source Case Investigation**).

Latent TB Infection

Latent TB infection (LTBI) is the condition where a person is infected with TB bacteria but does not have active TB. **Table 2.1** outlines some similarities and differences between LTBI and active TB. **Treating LTBI can prevent active TB from developing in the future**.

Table 2.1: Latent TB infection (LTBI) compared to active TB

Latent TB Infection (LTBI)	Active TB
○ TB bacteria in the body ○ TST and/or IGRA **USUALLY** positive ○ TB bacteria are **DORMANT (not multiplying)** ○ **NO** TB signs/symptoms ○ **NOT** infectious ○ At risk for development of active TB in future unless LTBI treatment is completed ○ **NOT a "TB case"** ○ **May** have an abnormal chest x-ray ○ Negative sputum culture	○ TB bacteria in the body ○ TST and/or IGRA **USUALLY** positive ○ TB bacteria are **ACTIVE (multiplying)** ○ **USUALLY** TB signs/symptoms but may be asymptomatic ○ **POTENTIALLY** infectious (respiratory forms of active TB) ○ **A "TB CASE"** ○ **USUALLY** abnormal chest x-ray ○ **USUALLY** positive sputum culture

It is not possible to know which people with LTBI will develop active TB. Impaired immunity can substantially increase the risk of developing active disease, whether it exists at the time a person is infected with TB bacteria or develops later.

Table 2.2: Risk factors and estimated risk for development of active TB among people with positive tuberculin skin tests

Risk factor	Estimated risk for TB relative to people with no known risk factor
High risk	
Acquired immunodeficiency syndrome (AIDS)	110 – 170
HIV infection	50 – 100
Transplantation (related to immune-suppressant treatment)	20 – 74
Silicosis	30
Chronic renal failure requiring hemodialysis	10 – 25
Carcinoma of the head and neck	11.6
TB infection within the prior two years	15.0
Abnormal chest x-ray – fibronodular disease	6 – 19
Moderate risk	
Tumour necrosis factor alpha inhibitors	1.5 - 4
Diabetes mellitus (all types)	2 - 3.6
Treatment with glucocorticoids (≥ 15 mg/day of prednisone)	4.9 - 7.7
Young age when infected (zero to four years of age)	2 - 2.5
Slightly increased risk	
Alcohol consumption ≥ three drinks/day	3 - 4
Underweight (< 90% ideal body weight; for most people, this is a body mass index ≤ 20)	2 – 3
Cigarette smoker (one pack/day)	1.8 – 3.5
Abnormal chest x-ray – granuloma	2
Low risk	
Person with a positive TST, no known risk factor, and a normal chest x-ray	1
Very low risk	
Person with a positive two-step TST (booster), no other known risk factor, and a normal chest x-ray	0.5

Presentation

Although active TB most often involves the lungs, TB disease can develop in almost any site in the body, including:

- Lymph nodes
- Genitourinary system
- Central nervous system
- Gastrointestinal system
- Bones and joints
- Eyes

Presentations of active TB are divided into two main categories:

1. **Respiratory TB** – TB disease occurring **within** the respiratory system. In Canada, respiratory TB includes primary TB, pulmonary TB, tuberculosis pleurisy (non-primary) and TB of the intrathoracic lymph nodes, mediastinum, nasopharynx, nose (septum) and any nasal sinus.

2. **Non- respiratory TB** – TB disease occurring **outside** of the respiratory system. Some sites of non-respiratory TB includes peripheral lymph nodes (TB lymphadenitis), the central nervous system (e.g. TB meningitis), the genitourinary system, the abdominal cavity, and the bones and joints.

It is possible to have concurrent respiratory TB and non-respiratory TB. Thus, when a person is diagnosed with non-respiratory TB, chest x-rays are done, and sputum specimens are tested for TB to determine whether s/he also has respiratory TB.

TB Signs and Symptoms

Signs and symptoms of active TB vary depending on:

- Which site(s) are involved?
- How advanced the disease is?
- How old the client is?
- How well the client's immune system is working?

Classic **systemic** TB symptoms include:

- Unexplained weight loss (or failure to gain weight in a growing child)
- Fever
- Night sweats

- Loss of appetite
- Fatigue

In addition to systemic TB symptoms, people with **respiratory TB** might report:

- Cough (dry or productive) for at least two to three weeks
- Bloody sputum (hemoptysis)
- Chest pain
- Hoarse voice and/or sore throat (with laryngeal TB)
- Wheezing (rare but potential symptom of respiratory TB in children)

In addition to systemic TB symptoms, people with **non-respiratory TB** might also report pain, swelling or dysfunction of involved sites. Typical signs and symptoms of some of the more common non-respiratory presentations of active TB are shown in **Table 2.3**.

Table 2.3: Typical signs/symptoms of some presentations of non-respiratory TB

Involved site	Typical signs/symptoms
Peripheral lymph nodes	○ Isolated, unilateral, non-tender mass ○ Often involves anterior and posterior triangles of the neck, supraclavicular or axillary regions
TB meningitis *treat as a medical emergency*	○ Headache ○ Malaise ○ Personality changes, confusion ○ Irritation of the brain and spinal cord (meningismus) ○ Cranial nerve palsies ○ Seizures/coma
Miliary or disseminated TB	○ Fever of unknown origin ○ Occurs most commonly in childhood (especially under one year of age) ○ 'Miliary' disease pattern might be present on chest x-ray ○ Chest x-ray results can be normal and tuberculin skin test can be negative
Abdominal TB Gastrointestinal TB Peritoneal TB	○ Abdominal pain/swelling ○ Diarrhea, weight loss ○ Can mimic inflammatory bowel disease, Crohn's disease
Genitourinary TB	○ Bloody urine ○ Sterile pus in urine ○ Frequent and/or painful urination
Bone TB	○ Pain at involved site

Adapted from Menzies R, Wong T. *Canadian Tuberculosis Standards*. 7th ed. Canadian Thoracic Society and the Public Health Agency of Canada; 2013.

TB Assessment

A TB assessment is done to identify or rule out active TB or LTBI, or to document a client's TB status at a given point in time (e.g. pre-employment TB screening for health care providers).

There are two flowcharts to guide how a TB assessment is done:

- General TB Testing Flowchart (see **Section 3: General TB Assessment**)
- TB Contact Testing Flowchart (see **Section 12: Contact Investigation, Window Period Prophylaxis and Source Case Investigation**)

Any or all of the following tests might be included in a TB assessment, depending on why the assessment is being done, and whether the client has TB signs/symptoms or is at increased risk for developing active TB. **Every TB assessment begins with an assessment for TB signs/symptoms and risk factors to ensure the appropriate tests are done.**

The TB clinic at the Labrador Health Centre provides timely and appropriate clinical follow-up of individuals with a positive Tuberculin Skin Test (TST), those who have been recently diagnosed with active or latent TB infection and/or those currently receiving treatment for active or latent TB infection and follow up during the surveillance period or any other situation requiring TB related assessment by a physician.

Tuberculin Skin Test (TST)

The tuberculin skin test (TST) is also known as a 'Mantoux test' or a 'TB skin test'. The TST is used to test for infection with TB bacteria. **TST is not used to diagnose active TB because people with LTBI can also have a positive TST result.**

During a TST, a small amount of purified protein derivative (PPD, also known as 'tuberculin') is injected intradermally on the client's inner forearm. If the client is infected with TB bacteria, s/he will develop a discrete area of swelling and firmness (induration) at the injection site within 48 to 72 hours.

The accuracy of TST results can be affected by a number of factors, including:

- Improper storage and handling of the testing solution.
- Errors in giving the test or measuring the results, which is why TSTs should only be given by health care providers with training in this skill.
- Limitations in the ability of the client's immune system to respond to the testing solution (e.g. infants, clients with immunosuppression).

- Recent infection with TB bacteria, as it can take up to eight weeks after infection with TB bacteria for the immune system to respond accurately to a TST.

- Cross-reactivity to the testing solution due to infection with non-tuberculous mycobacteria (NTM) or prior Bacille Calmette-Guérin (BCG) vaccine.

Indications and Contraindications

A TST is included in a TB assessment **unless**:

- The client is under six months of age,

- TST is contraindicated, or

- There is a reason to defer the TST (see **Table 2.4**).

Table 2.4: TST contraindications and when to defer TST

Adapted from Menzies R, Wong T. *Canadian Tuberculosis Standards*. 7th ed. Canadian Thoracic Society and the Public Health Agency of Canada; 2013.

Contraindications to TST	Situations when TST should generally be deferred
○ Allergy to any component of Tubersol® (Tuberculin Purified Protein Derivative [Mantoux]) or its container, or an anaphylactic or other allergic response to a previous TST ○ Previous active TB or LTBI ○ Documented prior positive TST or IGRA result ○ Prior blistered TST reaction	○ Measles or other live virus immunization within past four weeks. (Note: TST may be given before or on the same day as live virus vaccines but at a different site) ○ TST should be deferred until the client reaches six months of age

Unless contraindicated or there is a reason to defer, TST **CAN** be given to a client:

- With a history of BCG vaccination(s).
- With a common cold.
- Who is pregnant or breastfeeding.
- Who was immunized with any vaccine on the same day.
- Who was immunized within the previous four weeks with any inactivated vaccine(s).
- Who gives a history of a prior positive TST reaction, but the result is not documented.

Interpreting TST skin test results

Interpretation and follow-up of TST results is client-specific. See **Table 2.5** for cut-points in various risk groups.

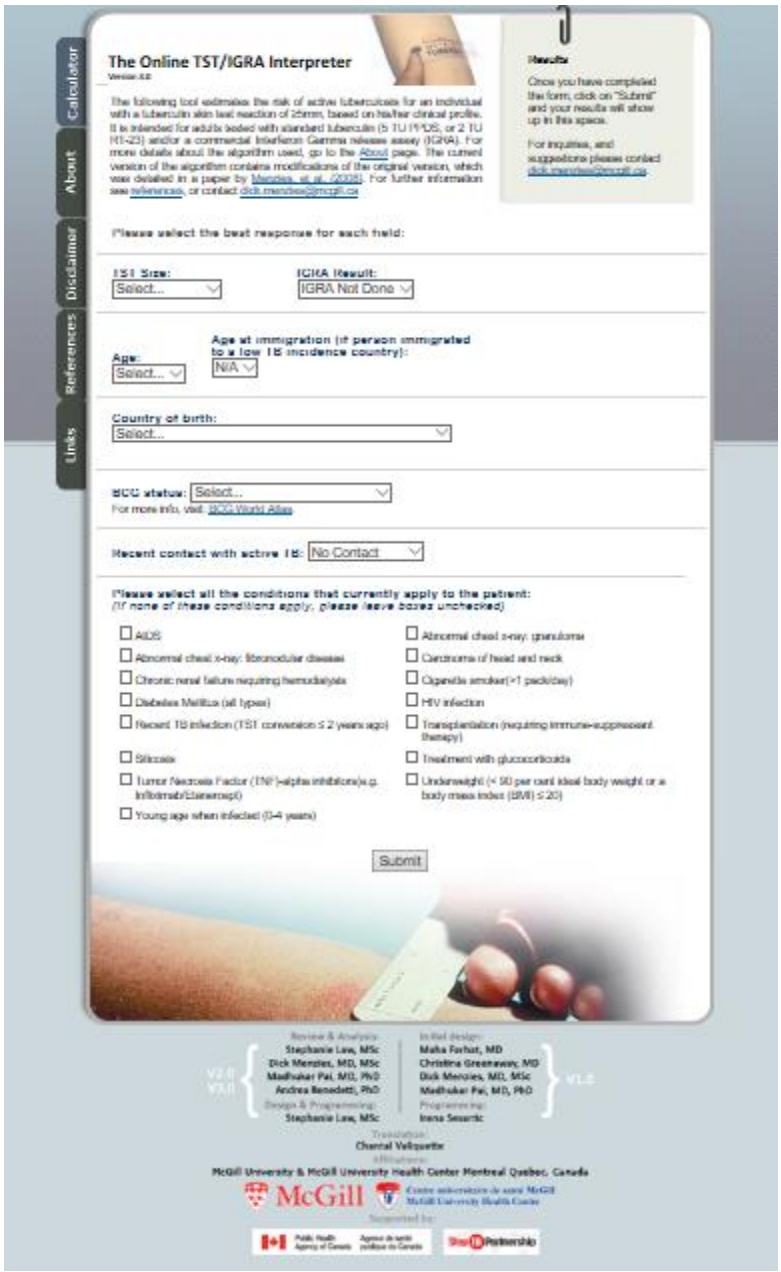
Table 2.5: Interpretation of tuberculin skin test results and cut-points in various risk groups. (From the Canadian Tuberculosis Standards, 7th Edition, 2014, page 75)

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)

Note that Anti-TNF agents currently licensed in Canada include adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), golimumab (Simponi) and infliximab (Remicade). Etanercept is a soluble TNF receptor, which binds competitively with circulating TNF: the other agents are monoclonal anti-TNF antibodies. These agents are used for the treatment of autoimmune, inflammatory conditions, notably rheumatic diseases such as rheumatoid arthritis and inflammatory bowel disease.

The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of ≥5mm, based on his/her clinical profile. The tool can be used to decide on treatment for LTBI based on the TST result and the client's risk factors.

http://www.tstin3d.com/en/calc.html



<u>Bacille Calmette-Guérin (BCG) Vaccination and TST Results</u>

BCG is a live, attenuated vaccine derived from *Mycobacterium bovis*. Bacille Calmette-Guérin (BCG) is the only anti-TB vaccine currently available. **BCG does not protect against infection with TB bacteria, nor will administering BCG protect someone already infected with TB bacteria from developing TB disease**. However, it is widely accepted that BCG reduces the risk of the most serious forms of TB in young children (e.g., TB meningitis, miliary TB).

Prior BCG vaccination **IS NOT** a contraindication to TST. However, it is important to note whether a client undergoing TST had BCG in the past because the vaccine can affect TST results.

BCG vaccination is no longer used in the province of Newfoundland & Labrador. The routine BCG program was discontinued in Newfoundland in 1975 and in the Labrador region in 1979.

Identifying BCG Scars

BCG scars are typically raised, dimpled and shiny (see **Figure 2.3**). They are usually found on the upper left or right deltoid. If two scars are present, the BCG scar is usually the smaller, raised one. Look on the lower back for parallel scratch-like scars for BCG given in Quebec or Newfoundland ("back scratch scars").

Figure 2.3: Typical BCG Vaccination scar

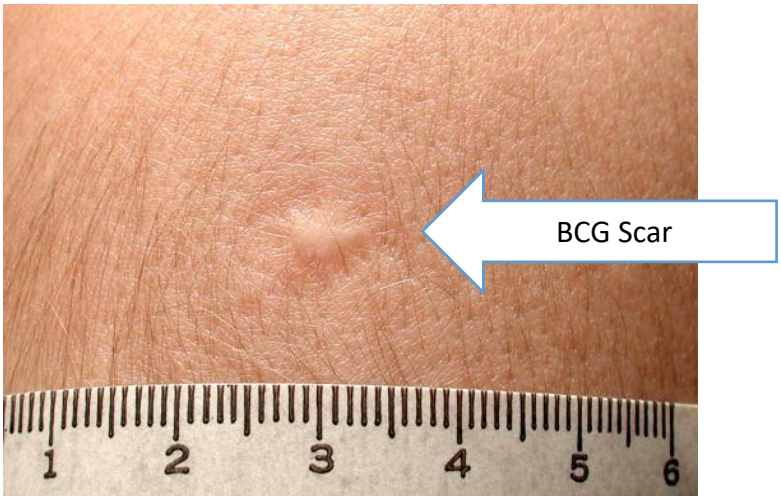


Image from: *http://www.phac-aspc.gc.ca/tbpc-latb/pdf/recognition-bcg-scars_e.ppt*

Two-Step TST

A two-step TST is done to establish an accurate baseline TST result for a person who will have tuberculin skin testing done at regular intervals (e.g. a health care provider). **Two-step TSTs are NOT DONE during TB contact investigations or source case investigations.**

During a two-step TST, two TSTs are done; an initial TST followed by a second TST one to four weeks later if the initial TST result is negative. The two-step TST procedure is described in **Section 4: Tuberculin Skin Testing (TST)**. After a client has a negative two-step TST documented, future TSTs can be single-step (a single TST) regardless of how many years have passed since the two-step TST was done.

Chest X-Rays

Chest x-rays are used to detect abnormalities that **COULD BE** TB-related, including but not limited to:

- Infiltrates in the upper lobes or in the superior segments of lower lobes
- Cavities, cavitary disease, granuloma
- Hilar and/or mediastinal lymphadenopathies
- Diffuse miliary nodules/patterns
- Pleuritis, pleurisy and pleural effusions

Indications and Contraindications

Unless a client is or might be pregnant, posterior/anterior (PA) and lateral chest x-rays are included in TB assessments when:

- TST is contraindicated (see **Table 2.4**).
- There are TB signs/symptoms.
- TST result requires follow-up according to **Table 2.5** or the appropriate TB testing flowchart.
- An interferon gamma release assay (IGRA) result is positive.
- The client is at high risk for developing active TB (e.g., immunosuppressed contact, contact under five years of age).
- The client was referred for Immigration, Refugees and Citizenship Canada (IRCC) medical surveillance.

A physician order is required prior to taking shielded chest x-rays of a client who is or might be pregnant.

Examination of Clinical Specimens for TB Bacteria

Almost any bodily fluid or tissue can be tested for TB bacteria. Respiratory TB is usually confirmed with sputum or specimens collected during bronchoscopy or gastric lavage. Non-respiratory TB is confirmed with specimens from the involved area such as pleural fluid, cerebrospinal fluid, urine, blood or a tissue biopsy.

Initial examinations of specimens submitted for TB testing include acid-fast bacilli (AFB) smear and mycobacterial culture. Follow-up testing of culture-positive specimens typically includes drug susceptibility testing and TB genotyping. **Submission of multiple, good-quality specimens is important for ensuring accurate test results.**

Testing of clinical specimens is essential for guiding clinical and public health management of people infected with TB bacteria and those with TB signs/symptoms or other findings consistent with active TB. Results are used to:

- Confirm whether mycobacteria are present.
- Identify which mycobacteria are present (if any).
- Inform estimates on how infectious TB cases might be.
- Monitor response to treatment for active TB.
- Guide decisions on treatment for active TB (e.g. drug susceptibility testing).
- Monitor the occurrence and prevalence of strains of TB bacteria in Nunatsiavut.
- Identify potential TB outbreaks.
- Identify (or disprove) epidemiologic links and chains of transmission between or among TB cases.

Indications

Sputum specimens are included in TB assessments for clients with:

- Signs or symptoms consistent with **ANY** site of active TB.
- Chest x-ray abnormalities consistent with active or inactive (old, healed) TB (**see Chest X-Rays**).
- Non-respiratory TB (to rule out concurrent respiratory TB).
- Immunosuppression.
- New positive TST or IGRA results.
- Histories of active TB or LTBI, or prior positive TST or IGRA results.

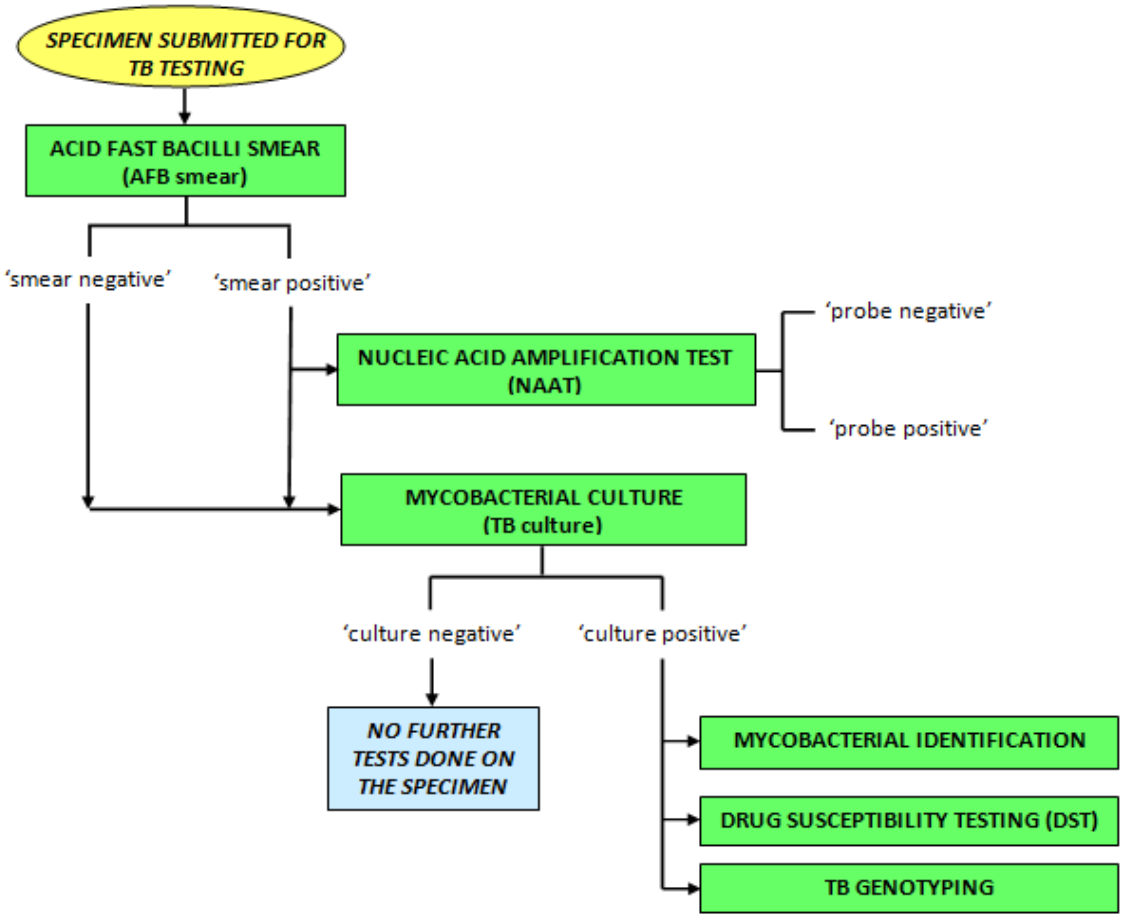
The CDCN may, after consultation with the TB physician, recommend testing of sputum specimens for TB **instead** of shielded chest x-rays for pregnant women in need of clinical investigations for active TB. See **Figure 2.4** for the sputum specimen testing pathway.

When a client is not able to provide sputum specimens spontaneously, other methods might be ordered to obtain material for testing (e.g., gastric aspiration, sputum induction, bronchoscopy).

See **Section 5: Collection of Specimens for TB Testing** for information on collecting specimens for TB testing.

See **Appendix E: TB Fact Sheets** for client instructions on collecting sputum specimens.

Figure 2.4: Sputum specimen testing pathway



<u>Acid-Fast Bacilli (AFB) Smear</u>

AFB smear results are often available within 24 hours of when the specimen is received by the laboratory. Results are reported as "**no AFB seen**" (smear-negative), or "**AFB seen**" (smear-positive). **A positive AFB smear result indicates POSSIBLE active TB**.

Smear-positive reports also include a description of how many bacteria were seen in the specimen (quantification). In Nunatsiavut/LGH, AFB smear quantification is reported as:

- 1+ (rare)
- 2+ (few)
- 3+ (moderate)
- 4+ (many)

A case with high numbers of AFB noted in his/her sputum specimen smears is considered potentially more infectious than a case with fewer AFB noted (see **Table 2.6**).

Mycobacterial Cultures (TB Cultures)

A mycobacterial culture that is positive for MTB complex is considered the "gold standard" for the definitive diagnosis of active TB. All specimens sent for TB testing undergo mycobacterial culture (i.e. mycobacterial culture is done even when the AFB smear result is negative).

TB culture results are reported as "**positive**" or "**negative**". Results are typically reported two to eight weeks after the specimen is received at the laboratory.

Culture results from specimens with high numbers of TB bacteria (e.g. smear-positive specimens) will usually be reported sooner than specimens with fewer TB bacteria. Thus, a case whose TB culture was reported positive early (e.g. after two weeks) is considered potentially more infectious than a case whose culture was reported positive later (e.g. after seven weeks). More information on relative levels of infectiousness is shown in **Table 2.6**.

Nucleic Acid Amplification Tests (NAAT)

NAATs can provide additional information on whether there are TB bacteria in specimens that are AFB smear-positive (smear-positive) or mycobacterial culture-positive (culture- positive).

When a smear-positive specimen has a 'positive' NAAT result ('probe-positive'), the client likely has active TB. However, a negative NAAT result does not rule out active TB.

NAATs (e.g. Gen-Probe™ Accuprobe) are used on positive TB cultures to help identify which mycobacteria are growing.

Drug Susceptibility Testing (DST)

DST is done to confirm which TB drugs should be used for cases and their contacts. DST can only be done when there is a positive mycobacterial culture to work from. **Thus, DST cannot be done for people with LTBI.**

DST can take one to three weeks to complete, so cases and contacts generally begin treatment before DST results are available but are later adjusted according to the results.

TB Genotyping

TB genotyping is a method for identifying which strain of TB bacteria a TB case is infected with. TB genotyping can only be done when there is a positive mycobacterial culture to work from. **Thus, TB genotyping cannot be done for people with LTBI.**

Infectivity

Infectivity refers to the ability of a pathogen to spread from one host to another. TB cases with smear positive, culture positive (S+C+) sputum are highly infectious. Cases whose sputum is smear negative, culture positive (S-C+) are less infectious, but still demonstrate infectivity.

Table 2.6: Relative levels of infectiousness of TB

Sputum smear positive, culture positive	Sputum smear negative, culture positive	Extrapulmonary TB Sputum smear negative, culture negative
Highly contagious	Less contagious, but still infectious	Rarely contagious
AFB seen under the microscope directly from the sputum sample.	AFB not seen under the microscope but grow in culture	Blood or biopsy sample positive for TB
Often symptomatic	May or may not be symptomatic	Localized or systemic symptoms

Other Tests - Interferon Gamma Release Assay (IGRA) and GeneXpert®

Interferon Gamma Release Assay (IGRA)

IGRA is a blood test to detect if a person is infected with TB bacteria; more specifically, IGRAs measure a person's immune response to *M. tuberculosis*. **IGRAs are not used to diagnose active TB because people with LTBI can also have a positive (reactive) IGRA result.**

IGRA results are not influenced by prior BCG vaccination or by exposure to most NTM. This means IGRA results can be more reliable than TST results in some circumstances. In Canada, IGRA is not considered a replacement for TST. Instead, IGRA results are used to supplement or complement TST results. In Nunatsiavut/LGH, IGRA is currently only available when ordered by a TB physician.

GeneXpert®

GeneXpert® is an automated, cartridge-based nucleic amplification assay test (NAAT). It can simultaneously detect TB bacteria in a clinical specimen and resistance to rifampin (an important 'first line' TB drug). GeneXpert® is performed directly from the testing material (versus requiring a positive mycobacterial culture).

GeneXpert® results can take as little as two hours once the testing process is underway. Results are reported as 'positive' or 'negative'. The test is used only during the initial clinical investigation of a potential new case. GeneXpert® is not repeated on confirmed cases to monitor the effectiveness of TB treatment. (GeneXpert® is currently unavailable in this region)

Treatment

Treatment of active TB and LTBI are essential components of TB care, prevention and control programming.

Treating active TB improves outcomes for those who are ill and stops transmission from infectious cases. Treating LTBI prevents progression to active TB in those infected with TB bacteria.

Drugs used to treat active TB and LTBI (TB drugs) are available in every community. In our Labrador-Grenfell Health Region, active TB and LTBI are treated with directly observed therapy (DOT).

When treatment for active TB or LTBI is provided outside the clinical setting the parent/guardian must sign a **Medication Administration Consent Form** (see **Appendix D - TB Forms and Client Letters**).

Treatment of Active TB

Active TB is almost always curable when appropriate treatment is prescribed and adhered to. The objectives of active TB treatment are to:

- Rapidly reduce the number of TB bacteria, which will:
  - Provide relief from symptoms
  - Lower the risk for TB-related death or disability
  - Reduce the risk of transmission of TB bacteria from infectious cases
- Prevent the development or worsening of TB drug resistance, and
- Prevent relapse of active TB after completion of treatment.

Drug-resistant TB is rare in our region, therefore standardized treatment regimens are used initially and adjusted when necessary once results from drug susceptibility testing become available (usually four to six weeks from date of initial positive TB culture).

The overall duration of active TB treatment is informed by:

- Which treatment regimen is used,

- How well the client responds to treatment, and
- How long it takes for the client to take all of the prescribed doses.

Treatment for active TB is divided into two phases: the initial phase (first two months) and the continuation phase (month three until treatment end).

Initial Phase of TB Treatment

During the initial phase, at least three TB drugs are used, usually isoniazid (INH), rifampin (RIF) and pyrazinamide (PZA). Ethambutol (EMB) is included in the treatment regimen for most cases until results from drug susceptibility tests confirm there is no TB drug resistance. Results from drug susceptibility tests are usually available four to six weeks after the first positive TB culture. Supplemental pyridoxine (vitamin B6) is included in regimens with INH to prevent peripheral neuropathy (numbness/tingling in fingers and/or toes).

Treatment is taken daily. **Adherence to treatment during the initial phase is extremely important.**

The full number of doses ordered by the treating physician must be observed before the client can advance to the next phase of treatment (the continuation phase). Therefore, missed doses can result in the initial phase of treatment taking longer than two calendar months to complete.

Continuation Phase of TB Treatment

The continuation phase begins once all doses prescribed for the initial phase have been observed and an updated prescription has been received.

Typically, two TB drugs are used (usually INH and rifampin), supplemented with vitamin B6. PZA and ethambutol are not usually used in the continuation phase unless the client has drug-resistant TB or is not taking **BOTH** INH and rifampin. Treatment is generally given **AT LEAST** three times a week (Monday, Wednesday, Friday). Thrice-weekly dosing is recommended over twice-weekly dosing to ensure cases continue to receive adequate treatment and protection against developing TB drug resistance, should they miss a dose in a treatment week. The duration of the continuation phase for most cases with drug-susceptible TB is four calendar months, during which **AT LEAST** 54, thrice-weekly doses are observed. An extended continuation phase is necessary for some cases, including those:

- With forms of active TB that require longer treatment (e.g., bone TB, TB meningitis).
- Whose initial treatment phase did not include PZA throughout.
- Whose treatment regimens did not include INH and rifampin (or rifabutin) throughout.
- With HIV infection who are not taking antiretroviral therapy.

- With risk factors for relapse of TB disease, specifically:
    - Extensive disease and/or cavities on chest x-ray in the first two months of treatment,
    - Culture-positive sputum specimens after two months of treatment, and/or
    - Cavities on chest x-rays taken after six months of treatment.

Regular monitoring throughout TB treatment is required to identify and respond to adverse effects promptly. Monitoring during TB treatment also includes testing to confirm the effectiveness of the treatment, specifically chest x-rays and testing of sputum specimens for TB.

Follow-up requirements after completion of TB treatment are determined by the treating physician. In general, cases that complete treatment and whose clinical evaluations are satisfactory at the end of treatment do not require follow-up. Exceptions include:

- Pediatric cases (cases under 13 years of age).
- Cases treated with non-standard regimens.
- Cases with:
    - Advanced disease (e.g. cavitary TB) and/or substantially abnormal end-of-treatment chest x-rays,
    - Inconsistent adherence,
    - Substantial immunosuppression (e.g. HIV infection),
    - Diabetes, and/or
    - Drug-resistant TB.
- Cases that require follow-up after treatment are placed on TB surveillance (see **Section 13: TB Surveillance**).

See **Section 7: Care of Clients with Active TB** for information on TB treatment regimens, TB drug doses and monitoring requirements during treatment for active TB.

Treatment of Latent TB Infection (LTBI)

Once a person is infected with TB bacteria, s/he is at risk for developing active TB. The risk is greatest within the first two to three years after the infection occurs.

Treating LTBI can prevent development of active TB. LTBI treatment (also known as 'preventive treatment' or 'TB prophylaxis' or 'DOP' when directly observed), is prescribed for clients with positive tuberculin skin test (TST) results and/or positive interferon gamma release assays (IGRA), once active TB has been ruled out.

Treating LTBI is especially important for TB contacts and others at high risk for progression to active TB, such as infants and other children under five years of age, and people with immunosuppression. For some contacts, LTBI treatment might be started even before tuberculin skin testing (or IGRA testing) can reliably indicate whether they are infected with TB bacteria, once active TB has been ruled out. This practice is known as 'window period prophylaxis' (see **Section 12: Contact Investigation, Window Period Prophylaxis and Source Case Investigation**).

LTBI treatment is not mandatory but is strongly recommended. Clients who decline treatment or who do not complete LTBI for other reasons may be placed on TB surveillance (see **Section 13: TB Surveillance**).

The duration of LTBI treatment is determined by which treatment regimen is used and how long it takes for the client to take all of the prescribed doses. There are several options for treatment of LTBI.

LTBI is often treated with a single TB drug: isoniazid (INH). INH is taken until 78, twice-a-week doses have been observed. Vitamin B6 is included in regimens with INH to prevent peripheral neuropathy (numbness/tingling in fingers and/or toes). Treatment is typically given twice a week, on Mondays and Thursdays. With regular adherence, it takes about nine months to complete treatment.

LTBI treatment with rifampin (instead of INH and vitamin B6) might be prescribed for some clients, such as contacts of cases with INH-resistant TB.

Although INH and rifampin are well-tolerated by most clients, both are hepatotoxic drugs. Adverse effects can include liver failure (and potentially, death), particularly when treatment continues after signs or symptoms of hepatotoxicity become apparent. Regular monitoring throughout LTBI treatment is required to identify and respond to adverse effects promptly.

A recent addition to the treatment options for LTBI is the combination of rifapentine and INH (along with vitamin B6) once a week for twelve weeks. This is a significantly shorter course and may lead to increased acceptance and compliance with treatment. While taking rifapentine many people experience a change in the color of body fluids (tears, breast milk, and urine) to a red-orange colour. Contact lens and dentures may be permanently stained. Rifapentine may

also reduce the effectiveness of hormonal contraceptives. This may not be the best option for women who are pregnant or plan to become pregnant. Breastfeeding is not recommended while rifapentine is being taken.

Follow-up is usually not needed once LTBI treatment has been completed. Exceptions include contacts of cases with drug-resistant TB and clients with:

- Abnormal chest x-rays at baseline or three-month follow-up,
- Intermittent adherence, or
- Substantial immune suppression.

See **Section 8: Care of Clients with Latent TB Infection (LTBI)** for information on LTBI treatment regimens, TB drug doses and monitoring requirements during LTBI.

Special Considerations in the Treatment of Active TB and LTBI

Table 2.7: Conditions that require special consideration during treatment of active TB or LTBI

Condition	Considerations
Hepatic disease	Many TB drugs are hepatotoxic (e.g., INH, rifampin, PZA). Baseline liver function testing is required for all clients, along with regular clinical and laboratory monitoring throughout treatment to promptly identify adverse effects. More frequent monitoring may be ordered by the treating physician for clients with pre-existing liver disease.
Renal disease	Dosing of PZA and ethambutol may require adjustment for clients with renal disease.
Pregnancy and breastfeeding	INH, rifampin and ethambutol are considered safe in pregnancy, The WHO recommends use of PZA in pregnancy, although there remains some uncertainty about its safety in pregnancy. To date there have been no reports of teratogenicity even though this drug has been given to millions of pregnant women worldwide. Due to potential for increased risk of hepatotoxicity during pregnancy and the first three months postpartum, treatment of LTBI is usually delayed unless a woman is considered very high risk for progression to active TB.

	HIV-negative breastfeeding women with active TB who have been treated appropriately for at least two weeks and who are not considered infectious can breastfeed. The concentration of TB drugs in breast milk is not sufficient to protect the child. Supplemental pyridoxine (vitamin B6) should be given to the nursing mother and to the breastfeeding child.
HIV infection	Treatment of LTBI or active TB is done in consultation with a specialist.
TB drug resistance	LTBI treatment for contacts to drug-resistant TB cases and treatment of active cases with known or suspected TB drug resistance are done in consultation with a specialist.

Supporting Adherence to Active TB and LTBI Treatment

Directly Observed Treatment (DOT)

In the Labrador-Grenfell Health Region, all treatment of active TB and LTBI is directly observed. With DOT, each dose of treatment is observed by a trained health care provider (e.g., nurse, community health aide). Using DOT helps clients to complete treatment safely and as quickly as possible.

For clients with active TB, supporting adherence to treatment is especially important to prevent:

- Treatment failure.
- Recurrence of active TB.
- Development or worsening of TB drug resistance.

DOT visits also provide opportunities for:

- Clients to ask questions about their diagnosis and their care plan.
- Health care providers to monitor how well clients are responding to treatment, and to promptly identify and respond to potential adverse effects.
- Asking the client how they are coping and if they perceive any barriers to treatment or require referrals for other services (e.g. social worker, etc.).

Incentives and Enablers

Incentives and enablers may be given to a client to encourage or acknowledge adherence to treatment. Enablers are practical items given to a client to facilitate adherence to treatment, such as food vouchers. Incentives and enablers are available to support clients on DOT. This option requires careful consideration and collaboration amongst the TB treatment team.

Treatment Refusal and Non-adherence

LTBI and WPP

Clients recommended for LTBI treatment or WPP (or their parents/guardians) may decline treatment or choose to discontinue treatment at any point after starting.

Every effort should be made to support adherence to LTBI treatment and WPP, and to encourage clients to complete LTBI treatment when it is recommended. Although non-adherence to LTBI or WPP treatment **DOES NOT** lead to development of TB drug resistance, it can lead to development of active TB. However, TB drug resistance can develop when treatment for LTBI (or WPP) is given to someone with active TB (i.e. incorrect treatment).

Active TB

Although it is very rarely necessary to do so, clients with infectious TB can be compelled to adhere to treatment and to comply with isolation precautions.

Before assistance from the Medical Officer of Health (MOH) is sought, all efforts made to support adherence/compliance must be thoroughly and clearly documented and the principles of reasonableness and due process must be met. These principles include:

- Educating the client about TB and why isolation and treatment are necessary.
- Making multiple attempts to support the client to adhere/comply.
- Attempting to find out why the client is not adhering/complying.
- Attempting to overcome any issues that may be barriers to adherence/compliance, and negotiating with the client accordingly.
- Consider using enablers and/or incentives when appropriate to support or encourage adherence/compliance.

Contact Investigation and Source Case Investigation

A TB contact investigation is a systematic process for identifying, prioritizing and screening people who have been exposed to infectious TB disease.

A source case investigation (also called 'reverse contact investigation') is done to identify how a person became infected with TB bacteria (i.e. the 'source' of the TB bacteria the person is infected with).

Contact investigations and source case investigations are an important component of our TB Program because they can identify people with active TB or LTBI.

Contact Investigation

Contact investigations are planned on a case-by-case basis and informed by factors such as:

- Age of the case.
- How infectious the case is.
- Date of onset of TB signs/symptoms.
- Date of the first chest x-ray finding suggestive of active TB or first positive laboratory results (e.g. AFB smear or mycobacterial culture).
- Case's travel history since and immediately prior to the onset of TB signs/symptoms, abnormal chest x-ray, or positive laboratory results.
- Size and complexity of the case's social network (e.g. family, friends, work/school environments).
- Circumstances that might require enhanced/alternate approaches (e.g. under-housed or highly transient case and/or contacts).
- Whether the case can/will provide details of his/her activities and identities of his/her contacts.

Generally:

- Only people exposed to the case during the infectious period are included in the investigation.
- Contact investigations for highly infectious cases (e.g. cases with AFB smear-positive TB, cavitary pulmonary TB or laryngeal TB) include a wider range of contacts than contact investigations for less infectious cases.

- Contact investigations for cases with drug-resistant TB follow the same steps as those for cases with drug-susceptible TB.

Once an infectious period has been established for the case, the case is interviewed to identify people who were exposed to the case during that time. They are then grouped into categories based on the characteristics of their exposures to the case (contact categories). The following contact categories are based on those recommended in the *Canadian Tuberculosis Standards 7th Edition.*

Contact Categories

Type 1 - Household: people who slept in the same household as the case, such as:

- Family,
- Room-mates and boarders,
- Overnight visitors, and
- "Couch surfers".

Type 2 - Close, Non-household: people who shared breathing space with the case daily, such as:

- Caregivers,
- Regular sexual partners,
- Close friends and extended family,
- Daycare or primary/secondary school classroom contacts, and
- Coworkers who work in close proximity, particularly in a small room.

Type 3 - Casual/community: people who spent time with the case less frequently than household or close non-household contacts, such as:

- High school classmates who share fewer courses with the case than Type 2 contacts,
- Classmates in college/university classes,
- Coworkers with less exposure than Type 2 contacts,

- Members of a club, team, weekly children's playgroup or other social/recreational/religious group,

- Extended family members who are seen occasionally, and

- Other students on a school bus.

Once categorized, contacts are then prioritized for screening and follow-up in consultation with the CDCN, based on risk for developing active TB if infected with TB bacteria.

High- priority contacts generally include:

- **Type 1** contacts,

- Symptomatic contacts (e.g. **ANY** contact with: a cough for longer than three weeks, or weight loss, or fever/night sweats),

- Contacts under five years of age, and

- Immunosuppressed contacts, such as those with: HIV infection; end-stage renal disease; organ transplant (related to immune suppressive therapy); and/or treatment with TNA alpha inhibitors and/or other immune suppressive drugs/therapies, such as corticosteroids (equivalent of equal to or more than 15 mg/day of prednisone for one month or more) or chemotherapy.

Contact Screening and Follow-up

Contacts are prioritized in the first round of screening based on case characteristics and contact classification.

See **Section 12: Contact Investigation, Window Period Prophylaxis and Source Case Investigation** for the steps in contact screening and the ***TB Contact Testing Flowchart*** which describes how to test and follow-up contacts.

Most contact investigations involve two rounds of screening. The first round begins when the new case is identified. The second round is done once at least eight weeks have passed since the date of last contact with the case while the case was infectious. This is when a TST or interferon gamma release assay [IGRA] can reliably indicate whether the contact was infected with TB bacteria. Note that this is different than a two-step TST which NOT DONE in contact tracing but is used for individuals who are starting a serial testing program to rule out the second TST being positive due to the booster effect.

Some contacts **DO NOT** require a second round of screening **UNLESS** they present with TB signs/symptoms. These include contacts:

- With prior active TB or LTBI (treated or untreated),
- Diagnosed with active TB or LTBI during the first round of screening, and
- Whose first round of screening was done at least eight weeks after their last exposure to the case while the case was infectious.

The time between exposure to a case and when a TST or IGRA result is considered reliable is referred to as the 'window period'. Treatment is given during the window period to contacts at very high risk for developing active TB, such as contacts under five years of age and contacts who are severely immunosuppressed. This practice is known as 'window period prophylaxis' (see **Section 12: Contact Investigation, Window Period Prophylaxis and Source Case Investigation**).

Narrowing or Expanding the Scope of a Contact Investigation

The scope of a contact investigation can be narrowed or expanded in response to new information about the case or to findings from the initial groups of contacts tested. Decisions on when and how to expand a contact investigation are made by the CDCN, in consultation with the Regional Medical Officer of Health (RMOH).

A contact investigation is usually expanded if evidence of recent transmission is found. Evidence of transmission can include:

- Contacts found to have active TB,
- Positive TST results in contacts that had documented negative TST results within the prior two years (TST conversions),
- A greater-than-expected number of contacts with LTBI, and
- LTBI in contacts under five years of age.

Contact investigation might also be expanded if active TB is diagnosed in a contact from a category or group not initially included in the contact investigation. This could include contacts with very limited exposure to the case or contacts whose last exposures to the case were prior to the infectious period originally established for the contact investigation.

A contact investigation is usually closed once the majority of contacts have completed screening **unless** evidence of transmission is found. Decisions on when to close a contact investigation are made by the CDCN, in consultation with the RMOH.

See **Section 12: Contact Investigation, Window Period Prophylaxis and Source Case Investigation** for the Contact Investigation Protocol.

Source Case Investigation

A source case investigation might be recommended when a client is believed to have been recently infected with TB bacteria, without a known TB exposure. The purpose of the investigation is to look for an infectious TB case (a 'source case') among people the client spends time with.

Source case investigations are usually limited to household members and others who spend time with the client on a daily basis. A single round of screening is done. Emphasis is placed on identifying and testing people with TB signs/symptoms, and those with a history of LTBI or active TB.

See **Section 12: Contact Investigation, Window Period Prophylaxis and Source Case Investigation** for the source case investigation protocol.

TB Surveillance

The Nunatsiavut/LGH TB Surveillance Program is a mechanism to monitor for active TB in at risk clients. TB surveillance is an important component of the TB Program because early detection of active TB can improve outcomes for cases and prevent or reduce TB transmission from cases with infectious TB.

TB surveillance is generally recommended for:

- Clients with untreated or incompletely treated LTBI.
- Cases of active TB post-treatment.
- High priority contacts with a past history of active TB or LTBI who were re-exposed (close contact) to a smear positive pulmonary active TB.

Surveillance guidelines for individual clients are determined by the TB physician.

See **Section 13: TB Surveillance** for the TB Surveillance Protocol.

Immigrant, Refugee and Citizenship Canada (IRCC) Medical Surveillance

Some newcomers are required by IRCC to complete an immigration medical examination (IME). Those with histories of active TB or abnormal IME chest x-rays must undergo periodic monitoring for active TB under the IRCC medical surveillance program.

IRCC medical surveillance is coordinated by the CDCN. Outcomes of medical surveillance assessments are reported to the provincial disease control division, Department of Health and Community Services.

See **Section 14: Immigration, Refugees and Citizenship Canada Medical Surveillance** for the IRCC medical surveillance protocol.