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# Tuberculosis

INFORMATION FOR HEALTHCARE PROVIDERS



6<sup>TH</sup> EDITION

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## Information for HealthCare Providers

This booklet has been prepared by members of the Lung Health Foundation's Tuberculosis Committee and is published by the Lung Health Foundation. The Lung Health Foundation is a registered charity that provides public information and lung health services across the country. One of Canada's oldest and most respected health promotion organizations, it began more than a century ago to prevent and stop the spread of tuberculosis. Today, it focuses primarily on the prevention and management of asthma, chronic obstructive pulmonary disease and lung cancer, tobacco cessation and prevention, and the effects of air quality on lung health. Tuberculosis continues to be addressed provincially through the work of the TB Committee. Nationally, the Lung Health Foundation is involved in the development of the Canadian Tuberculosis Standards, international TB programs and the work of StopTB Canada and the International Union Against Tuberculosis and Lung Disease (IUATLD).

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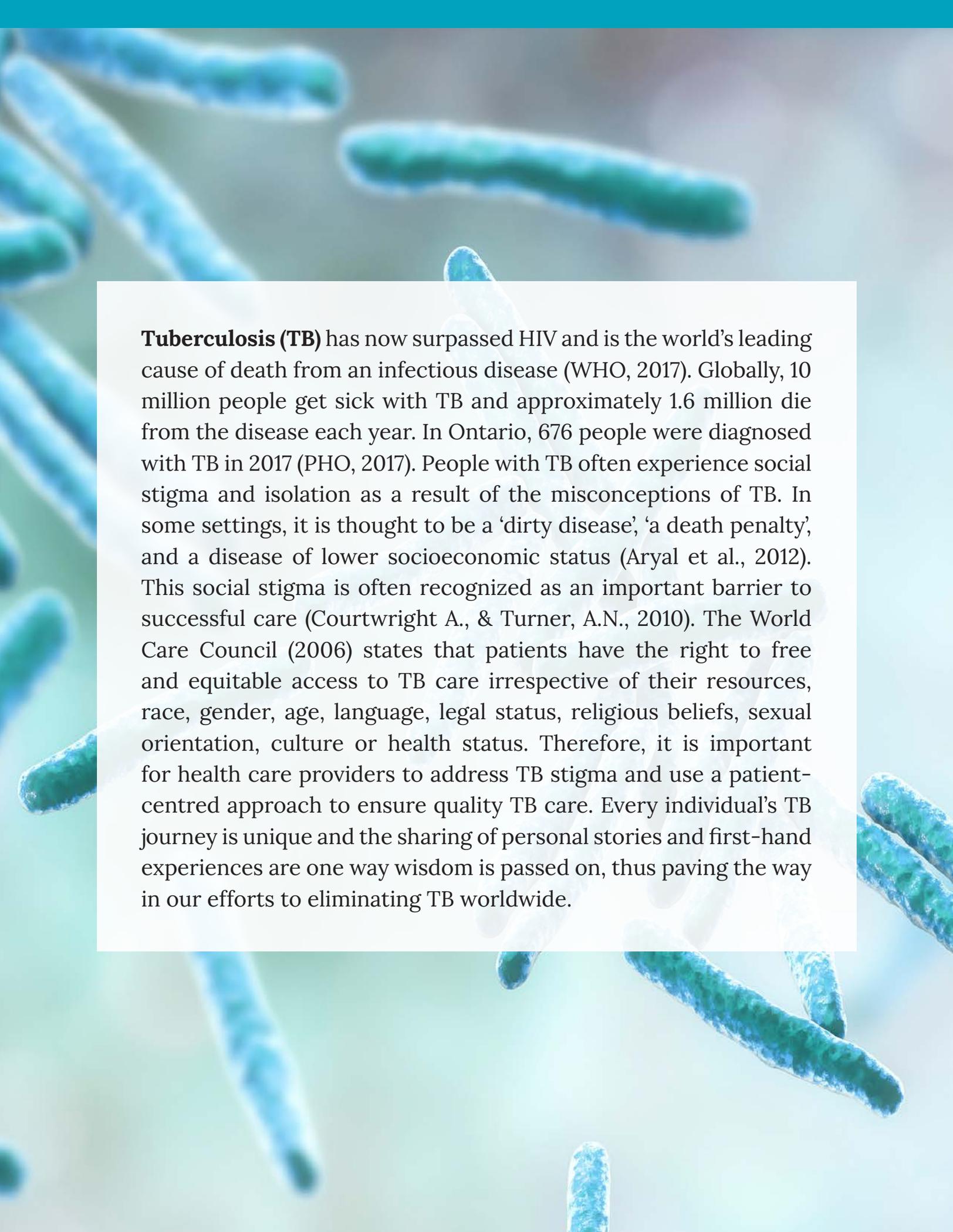
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**Tuberculosis (TB)** has now surpassed HIV and is the world's leading cause of death from an infectious disease (WHO, 2017). Globally, 10 million people get sick with TB and approximately 1.6 million die from the disease each year. In Ontario, 676 people were diagnosed with TB in 2017 (PHO, 2017). People with TB often experience social stigma and isolation as a result of the misconceptions of TB. In some settings, it is thought to be a 'dirty disease', 'a death penalty', and a disease of lower socioeconomic status (Aryal et al., 2012). This social stigma is often recognized as an important barrier to successful care (Courtwright A., & Turner, A.N., 2010). The World Health Organization (2006) states that patients have the right to free and equitable access to TB care irrespective of their resources, race, gender, age, language, legal status, religious beliefs, sexual orientation, culture or health status. Therefore, it is important for health care providers to address TB stigma and use a patient-centred approach to ensure quality TB care. Every individual's TB journey is unique and the sharing of personal stories and first-hand experiences are one way wisdom is passed on, thus paving the way in our efforts to eliminating TB worldwide.

A microscopic view of several blue, rod-shaped bacteria, likely Mycobacterium tuberculosis, against a light blue background. The bacteria are arranged in various orientations, some parallel and some at angles.

# Old Disease. New Face.

## Have no fear, it's *only* Tuberculosis

By Priya Amin, TB Patient Advocate

**Tuesday, September 8, 2015** should have been the official start to a new school year, with a new employer, in my new role as a Program Manager. Instead I was at home in quarantine and was on day four of the mandatory first line drugs that were prescribed to me for active pulmonary, and *presumed* extra pulmonary, Tuberculosis (TB). Sputum tests revealed I was +2 smear positive. According to my statistics, I had a better chance at winning the lottery. I also exhibited some of the symptoms associated with TB: persistent dry cough, fatigue, loss of appetite, swollen lymph node, and weight loss.

Daily routines would be suspended. There would be no going to work, the grocery store, bank, restaurants, social functions, or having the occasional glass of wine. Sharing this new world of mine with my loved ones was not easy. The hardest part was seeing their fear. My sickness was not a prevalent one here in Canada and *Google* could be your best or worst friend. My incredible nurse who visited me daily during this time of quarantine wisely said to me, *“the relationships in my life will be tested and those I thought were always there for me, may not be, and those who haven't been around, may come*

*out and shine brightly.”* In the end, I am blessed for the relationships in my life.

*“The blessings of the support and relationships I formed with my nurse and case manager had me feeling like I wasn't alone in this stigmatized illness...”*

I was born and raised in Toronto to parents who immigrated to North America from India and Zimbabwe in the early 1970s. I lived in Toronto for most of my life and did not know anyone with Tuberculosis nor had I traveled to an endemic country since my last negative TB test in October 2013. Having TB in Canada (which in 2015 meant I was one of 1,500 people nationwide and one of 300 in Toronto) has its distinct benefits with the supportive directly observed treatment (D.O.T) program. The blessings by means of the support and relationships I formed with my

nurse and case manager had me feeling like I wasn't alone in this stigmatized illness and reminded me that though my case seemed 'bad' to me, it really wasn't that bad. I would learn about the dire experiences of others in Canada and Toronto and couldn't imagine what that would feel like for me.

I will never forget the time I was waiting to pick up my meds from the pharmacy (this was in the summer of 2016), when a young lady approached me and said, *Do you have TB too? Is this your first time picking up your medication too?* In that moment, I was compelled to keep her spirits as high as possible (I remember being her, my first time and how daunting it was) and as such, I replied, "No, it's not my first time, I've been on meds for about six months and you know what, it's all going to be okay. You may feel a little nauseous after you take these meds, but you will keep going". She shared that she was 21, had just moved here from Africa, had a one year old at home and would have to take medicine for six months (she had latent TB). Her distress and fear was evident as she wondered if she could handle it all. I replied, "*Yes you can and you will. All is temporary and this too shall pass*".

*"The need for live contact (in-person or via phone), in my opinion, can ease the hardships of having TB. The physical effects are one thing, the emotional and mental toll is another."*

As a patient, the ability to connect with TB patients (past or present) is vital to the journey that one goes through. Reading case stories online, mainly from those living in other countries, is eye-opening and provides some

solace. However the need for live contact (in-person or via phone), in my opinion, can ease the hardships of having TB. The physical effects are one thing, the emotional and mental toll is another. My course of treatment had many ups and downs and finally I was officially cleared as a TB patient in October 2017.

Throughout this chapter of my life, denial, joy, anger, sadness, fear, gratitude, strength, acceptance, unconditional support from a cherished few and lots of humour propelled me forward to rise and conquer TB. So many people, from my family and friends, my health-care treatment team, the strangers I would see in the clinic, to the people at Toronto Public Health, and now The Lung Association - Ontario came into my life. And, I consider my life to be far richer for this experience. Talk about turning lemons into lemonade! I'm now a part of The Lung Association's TB committee as a patient representative and I am excited and inspired for all that lies ahead!

Change is inevitable.  
Growth is optional



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# Introduction

**Tuberculosis (TB)** remains a major cause of illness and death worldwide, especially in Asia and Africa. Although rates have begun to decrease globally, the original declaration of the World Health Organization (WHO) in 1993 that TB is a “global emergency” remains true today. Over the past two decades, the clinical presentation of TB cases has become increasingly complex. The human immunodeficiency virus (HIV) pandemic has escalated the spread of TB drug-resistant strains of TB – including XDR-TB (extensively drug-resistant TB) – an increasing concern worldwide. In developed countries, advancements in medical care are allowing people to live longer with immunocompromising conditions, and others are rendered immunocompromised by medical treatments for other conditions. Concurrently, new methods for diagnosing TB have been introduced and approaches to case management and public health practice have been revised.

In Canada, many healthcare providers have little or no experience with TB. The incidence of TB in Canada has declined over the last 100 years due to improvements in the standard of living, and since the 1950s due to the availability of effective antibiotics and improved disease management. Although Canada is

a low incidence country overall, TB is increasingly concentrated in specific sub-populations: immigrants from high-burden countries, VFR (Visiting Friends and Relatives), travelers to such countries, and Indigenous Canadians in the northern prairies and the Arctic.

The aim of this booklet is to:

- Increase healthcare provider awareness of TB as a possible diagnosis
- Provide guidelines for case management and referral to specialists
- Guide the appropriate use and choice of preventative therapy for latent TB infection, and
- Increase understanding of the interconnecting roles of primary care providers, hospitals, TB clinics, public health, the Ministry of Health and Long-Term Care and public health labs in providing optimal TB care for all Ontario residents.

This booklet contains basic information about TB and is intended to be a reference for healthcare providers. It is not meant to provide detailed answers to all questions about TB. Further consultation with a TB specialist, infectious disease specialist or your local health unit is recommended.

# Epidemiology

## 2.1 Incidence

The World Health Organization estimates that ¼ of the world's population is infected with *Mycobacterium tuberculosis*. In 2016, an estimated 10.4 million people fell ill with TB worldwide, and 1.3 million died of TB. In the same year, the top 20 countries reported more than 80 per cent of TB cases. Rates of TB are highest in countries where poverty, crowding and lack of healthcare programs are characteristic. The largest number of new TB cases occurred in the South-East Asia region (45 per cent), the African Region (25 per cent) and Western Pacific Region (7 per cent), accounting for 60 per cent of new cases globally. However, sub-Saharan Africa continued to have the highest rate of new cases per population, with more than 255 cases per 100,000 people in 2012. Country TB rates are published annually by the WHO and can be found at in the Global TB Report.<sup>1</sup>

By contrast, in 2016, Canada had a rate of 4.8 new cases per 100,000 (a total of 1,737 new cases). This is a small increase; over the previous decade. TB case counts were roughly stable around 1,600 per year. A large, prolonged TB outbreak has affected Inuit communities in Nunavut as well as northern Quebec and Labrador since about 2010. Outbreaks of TB have also occurred in homeless shelters in several provinces/territories. In 2016, 70 per cent of all reported TB cases were foreign-born individuals, 20 per cent were Canadian-born Indigenous peoples and 10 per cent were Canadian-born non-Indigenous people.<sup>2</sup>

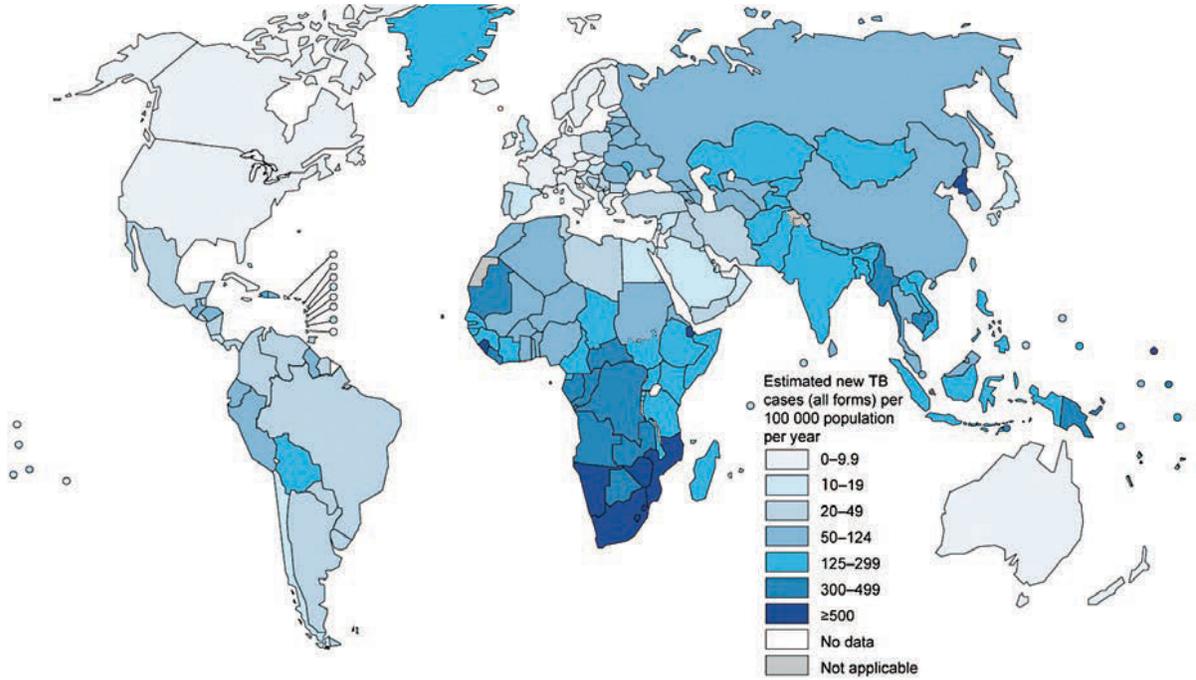
Ontario continues to have the most TB cases of any province: in 2016, Ontario had 635 reported new cases for a rate of 4.5 per 100,000. However, 90 per cent of Ontario cases occur in foreign-born, so cases are concentrated in areas with high immigration; 75 per cent (about 1/3 of the total Canadian TB cases) live in the Greater Toronto Area. Less than one per cent of Ontario cases involved Indigenous people.

## 2.2 Drug Resistance

Tuberculosis is preventable, treatable and curable. However, the emergence of drug-resistant strains of TB is a global threat to TB prevention and control efforts. A drug-resistant strain can be transmitted to others in the same way as any other TB strain – the drug resistance is a characteristic of the TB strain, not the patient. Thus “primary resistance” occurs in individuals who became infected with a resistant strain tuberculosis. “Acquired drug resistance” can occur during treatment, if the drug regimen does not include enough active medications, or there are problems with the length and/or consistency of treatment. Acquired drug resistance is rare in Canada. Nevertheless, the situation underlines the critical importance of:

- obtaining samples for culture and sensitivities
- treatment guided by sensitivity results
- support for all patients to complete adequate treatment (which also means involving public health TB programs in the care of all patients with active TB, whether respiratory or non-respiratory).

**FIGURE 1** Estimated TB Incidence Rates, 2016<sup>3</sup>

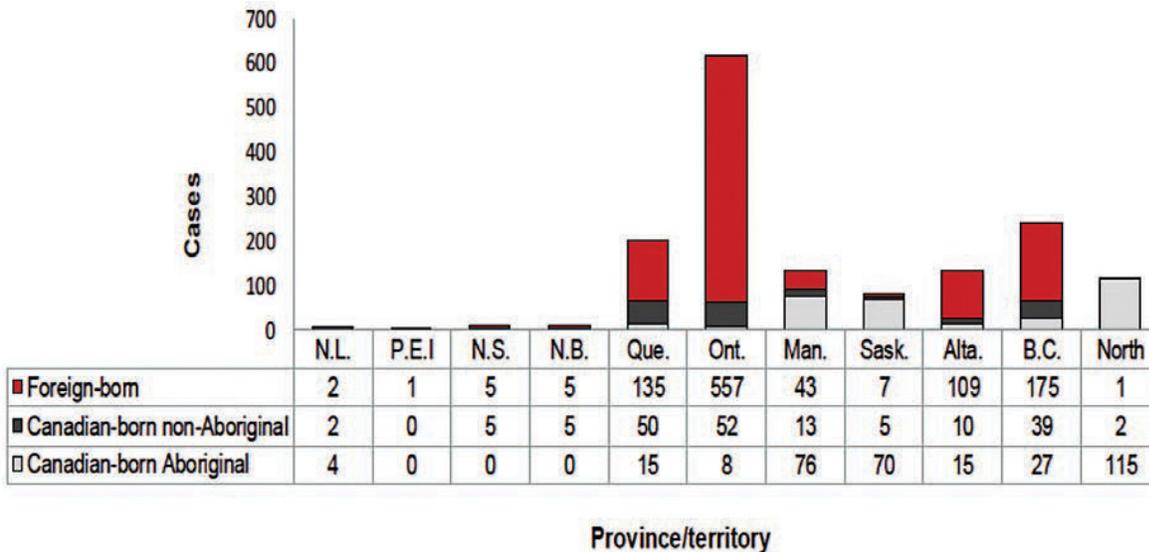


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2013*. WHO, 2013.  
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**FIGURE 2** Number of TB Cases in Canada, By Province/Territory and Population Group, 2016



Public Health Agency of Canada CCCR March 2018. Tuberculosis in Canada: 2016 Supplementary Data Tables. Note BC does not report Canadian born cases separately for Indigenous and non-Indigenous origins.

Multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid (INH) and rifampin (RMP), the two most effective anti-tuberculosis drugs. Treatment for MDR-TB is more complicated and much longer, involving less-effective medications with more side effects overall. Cure rates for MDR-TB are about 75 per cent<sup>4</sup> compared to 95 per cent for fully sensitive TB. Drug-resistant TB is difficult and very expensive to treat.<sup>5</sup> It requires specialist treatment with individualized treatment regimens.

The WHO estimates that there were 490,000 new cases of MDR-TB worldwide in 2016, 4.1 per cent of newly diagnosed TB cases and 19 per cent of individuals previously treated for TB had an MDR-TB strain. Almost half of MDR-TB cases lived in India, China and the Russian Federation. The highest levels of MDR-TB are found in Eastern Europe and central Asia, where in some countries more than 20 per cent of new TB cases and more than 50 per cent of those previously treated for TB have MDR-TB.<sup>6</sup>

In Canada, most TB strains are sensitive to all four first-line medications (92 per cent of all TB cases in 2017). Drug-resistant TB is most commonly diagnosed in foreign-born persons, especially those with a past history of TB (i.e. previously treated or relapsed cases). In 2017, 6 per cent of all TB cases had an INH mono-resistant strain and 0.9 per cent had an MDR strain.<sup>7</sup> However, in Ontario and in particular the Greater Toronto Area (GTA), the rate of drug resistance tends to be higher, linked to the higher proportion of foreign-born TB. In 2017, 9 per cent of TB diagnosed in Ontario was resistant to at least one drug, mainly mono-resistance to INH; half of the MDR-TB cases in Canada were diagnosed in Ontario. MDR-TB rates in the GTA have been stable at approximately two per cent for over a decade.<sup>8</sup>

One hundred and twenty-three countries including Canada reported at least one case of extensively drug-resistant TB (XDR-TB) by the end of 2016. XDR-TB is MDR-TB which is also resistant to at least two second-line groups of drugs, the fluoroquinolones (e.g. moxifloxacin) and the injectable TB medications (e.g. amikacin, capreomycin). As of 2016, seven cases of XDR-TB have been diagnosed in Canada. Five of these were in Ontario.

## 2.3 TB & HIV Co-Infection

HIV is a major risk factor for progression to active TB in individuals who have been exposed to TB. While HIV-infected individuals respond well to standard TB treatment, globally the HIV epidemic has had a dramatic impact on TB rates and control. In Canada, about 5 per cent of TB cases are co-infected with HIV (personal communication from the Public Health Agency of Canada, 2014). All patients with TB should be tested for HIV, and vice versa.

## 2.4 Risk Factors

### Risk Factors for Latent TB Infection (LTBI)<sup>9</sup>

- Close contacts of a recently diagnosed infectious case of TB
- Immigrants and travellers from countries with high TB incidence
- Persons who are homeless or underhoused
- Indigenous communities with high rates of LTBI or infection
- Persons at risk due to occupational exposure, e.g., hospital, shelter, correctional facility, long-term care home staff and volunteers
- Residents of communal living settings, e.g., long-term care facilities, shelters and correctional facilities

### Risk Factors for Development of Active TB Among Persons with Latent TB Infection

#### HIGH RISK:

- Acquired immunodeficiency syndrome (AIDS)
- HIV infection
- Silicosis
- Transplantation (related to immune-suppressant therapy)
- Chronic renal failure requiring hemodialysis
- Carcinoma of head and neck
- Recent TB infection
- Abnormal chest x-ray – fibronodular disease

#### INCREASED RISK:

- Treatment with glucocorticoids
- Tumor necrosis factor (TNF) – alpha inhibitors
- Diabetes (all types)

- Underweight (< 90 per cent ideal body weight for most people this is a body mass index  $\leq$  20)
- Young age when infected (0-4 years)
- Cigarette smoker (1 pack/day)
- Abnormal chest x-ray – granuloma
- Heavy alcohol consumption  $\geq$  3 drinks per day

#### LOW RISK:

- Infected persons, no known risk factor, normal chest x-ray
- (“low risk reactor”)

Some of the medical risk factors listed above have extremely high relative risks among AIDS patients with LTBI, the risk of developing active TB is up to 170 times that of a low risk person with LTBI.<sup>10</sup> Nevertheless, the majority of people with active TB disease in Ontario are relatively young individuals without any of the major medical risks above. The main TB risk factor for these persons is simply birth/residence in a country with higher rates of TB.<sup>11</sup>

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Canadian Tuberculosis Standards, 7<sup>th</sup> Edition, Public Health Agency of Canada and the Canadian Lung Association/Canadian Thoracic Society, 2013<sup>®</sup>: Chapters 1, 6 & 13

# 3

## Transmission

TB is spread by infected droplet nuclei when a person with respiratory TB coughs or sneezes. Infection is almost exclusively transmitted by the airborne route, although *M. bovis* can be spread from diseased cows to humans through unpasteurized dairy products. Non-respiratory TB is not infectious. However, transmission may also occur rarely from non-respiratory TB when infected fluid becomes aerosolized during a procedure (e.g. high-pressure irrigation). Young children are rarely infectious.

TB is not a highly infectious disease. Transmission usually requires close, frequent and prolonged exposure to a source case. Nevertheless, over time a person with active respiratory TB can potentially infect a large number of individuals, particularly if he or she has advanced symptomatic TB disease.

The probability of transmission increases with the following:

- Bacterial burden (positive sputum AFB smear), cavitory and upper lung zone disease, and laryngeal disease
- Amount and severity of cough in the source case
- Duration of exposure proximity to the source case
- Crowding and poorer room ventilation
- Delays in diagnosis and/or effective treatment
- Smoking (by index case or by contact).<sup>12</sup>

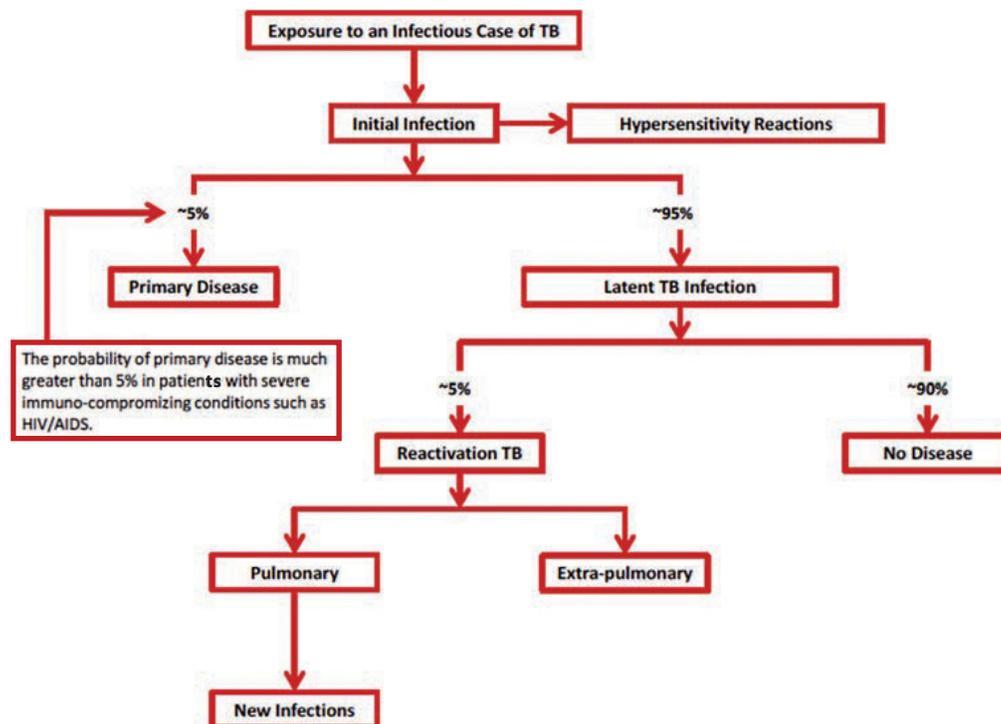
The most effective way to reduce transmission is to diagnose and treat patients with active TB disease as soon as possible.<sup>13</sup>

# Pathogenesis

Moist droplets containing the tubercle bacillus are generated during forceful expirations (coughing, sneezing, singing, etc.). Larger particles fall to the ground, while the smaller ones rapidly evaporate, leaving infected droplet nuclei small enough to be carried by air currents and inhaled deep into the alveoli. Viable bacilli must reach the lung tissue for infection to be established. Infected droplets landing higher up in the airways (nose, trachea) will usually be

cleared from the body by the innate immune system (ciliary action, cough, and swallowing of contaminated mucus). If local alveolar macrophages do not immediately kill the bacteria, the primary infection grows and spreads through the blood and lymphatic systems. It settles in secondary locations anywhere in the body (the lungs, lymph nodes, bones, central nervous system, genitourinary tract, etc.).

**FIGURE 3** The Pathogenesis of Tuberculosis in the Infected Host



Canadian Tuberculosis Standards, 7<sup>th</sup> Edition, Chapter 2, Figure 1, Public Health Agency of Canada and the Canadian Lung Association/Canadian Thoracic Society, 2013. © Canadian Tuberculosis Standards, 7<sup>th</sup> Edition. Public Health Agency of Canada, 2013. Reproduced with permission from the Minister of Health, 2015.

Latent TB infection (LTBI) and active TB may be considered as two ends of a spectrum ranging from asymptomatic infection to overt disease.<sup>14</sup> Status at any point in time depends on the cellular immune system's ability to contain the primary infection. The TB bacilli may be killed, infection may progress directly to active disease over a number of weeks or months ("primary TB"), live bacteria may persist but remain dormant for years (this is the classic concept of LTBI), or active disease may develop years later if/when the immune system fails to contain replicating TB bacilli ("reactivation TB"). A positive tuberculin reaction indicates the development of cell-mediated immune response to the tubercle bacillus and supports the diagnosis of LTBI, though this response does not provide full "immunity" to TB. In Canada, most TB disease is thought to be reactivation TB, i.e., occurring more than two years following initial infection.<sup>15</sup> This is consistent with the high proportion of Canadian TB cases occurring in individuals who immigrated to Canada from high-burden countries. Reinfection with TB is possible, though less common in Canada because of the smaller number of infectious cases.

Tubercle bacilli can survive in the dormant stage (LTBI) for years. Approximately five per cent of persons who have been infected with tuberculosis will progress to active disease within two years of exposure to the disease. Another five per cent will go on to develop active disease sometime later in their lifetime.<sup>16</sup> Persons with immunocompromising conditions will be much more likely to progress to active disease after being infected with TB. The risk of an individual with AIDS (advanced HIV with severe immunocompromise) progressing to active disease is 10 per cent per year.<sup>17</sup>



## 5

# Screening for TB: Diagnosing TB Infection and Preventing Disease

### **TB is Preventable**

The goal of screening for latent TB infection (LTBI) is to identify and treat individuals who are at an increased risk of developing active disease and thus would benefit from prophylactic treatment. A decision

to test is a decision to treat if the test is positive. Therefore, assess whether the person is a candidate for treatment prior to testing. This section discusses the tests available for diagnosing TB infection and the indications for those tests.

All positive tuberculin skin tests (TSTs) and Interferon Gamma Release Assays (IGRAs) must be reported to public health as required by the Health Protection and Promotion Act of Ontario, whether or not LTBI treatment is planned.

## 5.1 TB Skin Testing

### General Information

TB skin testing is a useful tool for diagnosing tuberculosis infection. There are three general situations when risk of disease is increased:

1. Recent infection: contacts of persons with recent diagnosis of active, contagious respiratory TB or immigrants and visitors from countries with high TB incidence within two years of arrival in Canada
2. Risk of reactivation due to impaired immunity: HIV infection and other immunosuppressive conditions, diabetes, renal failure, immunosuppressive medication, and pulmonary silicosis
3. Untreated infection: when there is radiographic evidence of old, healed inactive TB but no prior treatment.

A TST is NOT as helpful in the diagnosis of active tuberculosis and can produce a 'false negative' result in up to 25 per cent of patients with active disease.

Who should be tested?

- Close contacts of an active case of pulmonary TB
- Persons who live in Indigenous communities with high incidence of TB
- Immigrants from countries with high TB incidence
- Injection drug users
- Homeless or underhoused persons
- Healthcare workers (HCW)
- Residents of long-term care facilities
- Residents of correctional facilities
- Travelers to countries where TB is endemic.

Tubersol® 5 tuberculin units (5-TU) of PPD (purified protein derivative-standard) is used for TB skin testing in Canada. Ensure the testing solution is stored between 2° to 8°C and that the solution does not freeze. Discard if frozen. The solution is adversely affected by light, so PPD must be kept in a dark place. Do not preload syringes as the potency of the PPD may be diminished. Do not use EMLA® cream or similar local anesthetic creams prior to testing.

FIGURE 4 TB Skin Testing Method

1. Cleanse the skin and allow it to air dry. With the bevel up, approach the skin at a 5-15° angle. The injection should be placed on the palm-side up surface of the forearm, about 5-10 cm below the elbow. Inject 0.1 mL of tuberculin using 5-TU PPD intradermally. A wheal 6-10 mm in diameter should appear at the needle point. If no wheal appears or if the fluid substantially leaks out, inject again at another site 5-10 cm from the original site. This wheal will usually disappear in 10-15 minutes.
2. All TB skin tests should be measured and interpreted by a trained healthcare practitioner. Read the test at 48-72 hours. Use fingertips to find the edges and mark the border of the induration on each side with a pen. Measure the transverse diameter of the induration and document its size in millimeters (mm). No induration is recorded as 0 mm. Only the indurated area should be measured, not erythema (redness). Record the measurement. Redness with no induration is recorded as 0 mm.

**Note:** A punctured vial of 5-TU PPD should be discarded after one month due to possible contamination and loss of potency (Date the vial when opened). Failure to store and handle the tuberculin preparation as recommended will result in loss of potency and inaccurate test results or false negative results.

**FIGURE 5** Technique of Administering and Reading Tuberculin Skin Tests



## Contraindications to Tuberculin Skin Testing

**DO NOT** conduct skin testing for persons with:

- A previous severe reaction (e.g. blistering, necrosis or ulceration) to a TST
- Known active TB or known treatment in the past (TST does not distinguish between prior and recent infection, and will not yield any useful information in this case)
- Extensive burns or eczema (choose an alternate site if available, avoiding bony prominences)
- Documented previous positive reaction read by a knowledgeable healthcare worker
- Persons with viral infections (e.g. rubeola, mumps, influenza), which may temporarily depress the reactivity to TST. Defer skin testing for four weeks after infection
- Recent immunization with measles, mumps, rubella (MMR), varicella and/or yellow fever or other live virus vaccines within the last four weeks. Measles vaccine has been shown to increase the likelihood of false negative TST results. Although no data are available regarding the effect on TST on other live virus immunizations, it would be prudent to follow the same four week deferral guideline. However, if the opportunity to test may be missed, the TST should not be delayed for these vaccines.

**Options:** either administer TST before or simultaneously with live viral vaccine or defer skin testing for four weeks after immunization with live viral vaccine.

The following persons **CAN** receive a TST:

- People who have been immunized with a non-live-virus vaccine (e.g. diphtheria, tetanus, polio, pertussis) which does not suppress the reaction
- Women who are pregnant or breastfeeding
- Anyone with a previous Bacille Calmette-Guérin (BCG) vaccination
- Anyone who has a history of a “positive TST” (without blistering, ulceration, or necrosis at the site) but the reaction was not documented in millimeters
- Anyone with a common cold
- Those taking low dose corticosteroids daily. It generally takes a steroid dose equivalent to  $\geq 15$  mg prednisone daily for two to four weeks to suppress tuberculin reactivity.

## 5.2 Interpretation of Skin Test Reactions

### Positive Skin Test Reactions

A positive skin test reaction should be considered according to three dimensions – size, positive predictive value and risk of disease.

## 1. SIZE

**FIGURE 6** Interpretation of Tuberculin Skin Test Results and Cut-Points in Various Risk Groups

TST RESULT	Situation in which reaction is considered positive*
<b>0-4 mm</b>	<ul style="list-style-type: none"> <li>In general this is considered negative, and no treatment is indicated</li> </ul>
<b>≥ 5 mm</b>	<ul style="list-style-type: none"> <li>HIV infection</li> <li>Contact with infectious TB case within the past 2 years</li> <li>Presence of fibronodular disease on chest x-ray (healed TB, and not previously treated)</li> <li>Organ transplantation (related to immune suppressant therapy)</li> <li>TNF alpha inhibitors</li> <li>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 doses and longer duration)</li> <li>End-stage renal disease</li> </ul>
<b>≥ 10 mm</b>	<p>All others, including the following specific situations:</p> <ul style="list-style-type: none"> <li>TST conversion (within 2 years)</li> <li>Diabetes, malnutrition (&lt;90 per cent ideal body weight), cigarette smoking, daily alcohol consumption (&gt;3 drinks per day)</li> <li>Silicosis</li> <li>Hematologic malignancies (leukemia, lymphoma) and certain carcinomas (e.g., head and neck)</li> </ul>

\*The goal of testing for LTBI is to identify individuals who are at increased risk for the development of tuberculosis 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

Canadian Tuberculosis Standards, 7<sup>th</sup> edition 2013, Chapter 4, Table 2. © Canadian Tuberculosis Standards, 7<sup>th</sup> Edition. Public Health Agency of Canada, 2013. Reproduced with permission from the Minister of Health, 2015.

## 2. POSITIVE PREDICTIVE VALUE

This number refers to the pre-TB skin test probability that a positive test represents the true presence of TB infection. This probability can be affected by issues such as the following:

**Nontuberculous mycobacteria (NTM):** Sensitivity to NTM is uncommon in Canada and is not an important cause of TST reactions of 10 mm or more. Some small positive TST reactions (5-9 mm) may be due to cross-reactivity with these antigens.

**BCG Vaccination:** Many populations in Canada will have had BCG vaccinations, i.e., immigrants from Europe and the developing world, Indigenous Canadians, especially from northern communities (routine BCG at birth was discontinued in most of the southern reserves in the 1970s), and people born in Quebec or Newfoundland between the 1940s and 1970s. The prevailing opinion is that BCG does not prevent infection but does increase the resistance to uncontrolled multiplication and dissemination of *M. tuberculosis* throughout the body. The effectiveness in adulthood is likely lower than in children.

The interpretation of the TST result should ignore the history of vaccination with BCG (as a cause of a positive skin test reaction) when:

- BCG was given in infancy, and the person tested is now aged 10 years or older
- There is a high probability of TB infection: e.g., close contacts of an infectious TB case, Indigenous Canadians from high TB prevalence communities, or immigrants/visitors from countries with a high burden of TB
- There is a high risk of progression from TB infection to TB disease (HIV/AIDS, cancer, diabetes, etc.).

BCG should be considered the likely cause of a positive TST if:

- BCG vaccine was given after 12 months of age; AND
- The person is either Canadian-born non-Indigenous OR an immigrant/visitor from a low TB incidence country; AND
- The person is not a recent contact of an infectious case.

### 3. RISK OF DEVELOPMENT OF ACTIVE TB DISEASE

Many illnesses and treatments can increase the risk of reactivation and this is generally related to the immuno-suppressive effects. HIV infection is the strongest factor in reactivation, but others include diabetes, renal failure, immuno-suppressive medications (such as those used in the treatment of severe Crohn's disease and rheumatoid arthritis), certain malignancies, excessive alcohol use and cigarette smoking.<sup>18</sup>

A very helpful web-based interactive algorithm is available to assist in TST interpretation at [tstin3d.com](http://tstin3d.com).

#### Potential Causes of False Negative Reactions

Technical:

- Injection not intradermal
- Injection of too much or too little PPD solution
- Inexperienced reader or error in recording
- Administration > 20 minutes after drawing up the syringe
- Improper storage or contamination of PPD solution

Biological:

- Active TB disease, especially if advanced
- Other severe bacterial infection
- HIV infection especially if CD4 count < 200
- Other viral infection, e.g., measles
- Fungal infection (South American blastomycosis)
- Live virus vaccination within past four weeks (MMR/MMRV)
- Immunosuppressive drugs, e.g., corticosteroids, tumour necrosis factor (TNF) inhibitors
- Metabolic disease, e.g., chronic renal failure, severe malnutrition
- Diseases of lymphoid organs, e.g., lymphoma
- Age – infants < 6 months or the elderly

Close household contacts who are under the age of five or are severely immunosuppressed (even if the initial tuberculin skin test is negative) should be investigated immediately for active disease. Contacts under five years of age with a negative skin test and no evidence of active TB by examination or radiology should be started on 'window' prophylactic therapy immediately after the initial TST is done. This is to prevent the development of TB while waiting for the definitive repeat TST (performed at least four weeks after the last exposure to the infectious case). If the repeat TST is negative, treatment for window

prophylaxis can be discontinued. This should be done in consultation with a pediatrician or a TB specialist. If the repeat TST is positive, the full course of treatment for LTBI should be completed.

Interpretation of TB Skin Tests: Contacts of Respiratory TB Conversion of the skin test from negative to positive after exposure to tuberculosis may take at least eight weeks. Therefore if skin testing is performed before eight weeks from the last exposure and the result is negative, a second skin test must be done at least eight weeks after a contact's last possible exposure to the infectious case. A two-step TST in the setting of a contact investigation is not recommended.<sup>19</sup>

A TST result is considered positive in contacts:

- With a TST result of  $\geq 5$  mm at initial or repeat testing
- Who have an increase of at least 6 mm from a previous TST
- TST result of 5-9 mm

Other indicators of transmission include:

- Active TB identified in a contact
- The prevalence rate of TST results  $\geq 10$  mm among contacts is higher than expected in the population\*
- A contact < 5 years of age has a positive TST without another possible source of infection

A history of BCG vaccination should be disregarded in the interpretation of TST results for recent contacts.

Contacts with a previously documented TST result of  $\geq 10$  mm should not have the TST repeated. These contacts should be assessed with a symptom screen and a chest x-ray to rule out active TB. If treatment for LTBI was not completed in the past, it should be considered.

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\* See Canadian TB Standards Chapter 12 for expected range of prevalence in various Canadian populations.<sup>20</sup>

#### Interpretation of Two-Step Skin Tests

The two-step TST is used to detect the booster phenomenon in people who are starting serial testing for TB.

A positive tuberculin skin test may gradually wane over the years. The first skin test may be negative in persons whose TB exposure (or BCG) was many years ago. However, this initial test may stimulate the individual's immune response and a positive reaction

may occur when the person is retested one or more weeks later. This delayed response is termed the “booster” phenomenon. The two-step TST provides an accurate baseline for individuals who will have future serial testing. If a true baseline is not obtained with a two-step test and the individual is tested again at a future date, a positive result may be misinterpreted as a new infection or “conversion”, when it may really represent a “booster” phenomenon.

The two-step TST requires the administration of two tuberculin (5-TU PPD) skin tests one to four weeks apart. If the reaction to the first test is negative, a second test is given one to four weeks later (up to 1 year). Repeated tuberculin testing does not sensitize the uninfected person.

The two-step TST needs to be done only once if properly performed and documented. Subsequent skin tests can be one-step regardless of how long it has been since the two-step test was done.

### Indications for the Two-Step Skin Test

Perform two-step TST only if subsequent testing will be conducted at regular intervals, i.e., among HCW and correctional service workers.

### Interferon-Gamma Release Assays (IGRAs) Testing

IGRAs in-vitro blood tests of cell-mediated immune response measure T-cell release of interferon-gamma following stimulation by antigens specific to MTB, similar to a TST. However, they are very specific to MTB. Because they are not affected by BCG vaccination status, they are useful in evaluating people with a history of BCG vaccination, especially if vaccination occurred after infancy or when multiple vaccinations were administered. They can also clarify LTBI diagnosis in low-risk reactors (e.g. Canadian-born individuals with no history of TB exposure).

Two types of IGRAs are approved by Health Canada for use: QuantiFERON-TB Gold In-Tube (QFT) and TSPOT. QFT testing is available on a limited basis through

Gamma-Dynacare Medical Laboratories. IGRA tests are not currently covered by OHIP.

### Recommendation for Use of IGRAs and TST

Both the IGRA and TST are acceptable alternatives for LTBI diagnosis. Either test can be used for screening.

#### 1. SITUATIONS IN WHICH NEITHER TST NOR IGRAS SHOULD BE USED FOR TESTING:

- If the person has a low risk of infection and a low risk to progress to active disease
- To diagnose active TB disease in adults
- For routine or mass screening for LTBI of all immigrants
- To monitor anti-TB drug treatment response.

#### 2. SITUATIONS IN WHICH IGRAS ARE PREFERRED FOR TESTING BUT TST IS ACCEPTABLE:

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

#### 3. SITUATIONS IN WHICH TST IS RECOMMENDED FOR TESTING BUT IGRA IS NOT ACCEPTABLE:

- Serial TB testing. Do not use IGRA if there is a plan to repeat the test later to assess the risk of new infection.

#### 4. SITUATIONS IN WHICH BOTH TESTS CAN BE USED TO ENHANCE SENSITIVITY:

- When the risk of infection or progression to disease and of a poor outcome are high
- In children < 18 years of age with suspected TB disease, IGRA may be used as a supplementary diagnostic aid, along with the TST and other diagnostic tools. A negative IGRA does not rule out active TB disease at any age, especially not in young children.

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Canadian Tuberculosis Standards, 7<sup>th</sup> Edition, Public Health Agency of Canada and the Canadian Lung Association/Canadian Thoracic Society, 2013<sup>©</sup>, Chapters 4, 9, 12 & 13.

**FIGURE 7** Tuberculosis (TB) Infection or Disease?

<b>TB INFECTION</b>	<b>OR</b>	<b>TB DISEASE</b>
TB germ has entered the body but is not growing (dormant/inactive)	<b>Status</b>	TB germ has entered the body and is growing (replicating/active)
Positive Skin Test	<b>Skin Test</b>	May be positive or negative
No active TB disease	<b>Chest x-ray (or e.g., CT scan, MRI)</b>	Most show active TB on x-ray of chest OR on x-ray/CT scan/MRI of other parts of the body (e.g. lymph node, spine, kidney)
No TB germs in sputum	<b>Sputum</b>	May have TB germs in sputum
No symptoms	<b>Symptoms</b>	Symptoms which become worse over time (e.g. cough, chest pain, chills, weakness, weight loss, night sweats, coughing up blood, swollen lymph node)
<b>Not contagious</b> Cannot pass TB germ to anyone else	<b>Infectiousness</b>	<b>Contagious</b> If disease is in the lungs and not properly treated with medication
Person is at risk of developing disease in the future	<b>Associated Risks</b>	Person has disease and must be treated to prevent disease from getting worse or spreading to others
May be prescribed medication to prevent disease from developing	<b>Treatment</b>	Needs treatment with several medications for 6 months or longer to cure the disease



# Diagnosis

The Canadian national TB case definitions include either

## A) LABORATORY CONFIRMED CASE

Mycobacterium tuberculosis complex isolated in culture from clinical specimens, specifically *M. tuberculosis*, *M. africanum*, *M. canetti*, *M. caprae*, *M. microti*, *M. pinnipedii*, *M. orygis* or *M. bovis* (excluding *M. bovis* BCG strain)

## B) CLINICAL CONFIRMED CASE

In the absence of a TB culture, a diagnosis of active TB is made based on:

- i. Chest x-ray changes compatible with active TB;
- ii. Active non-respiratory TB (meningeal, bone, kidney, peripheral lymph nodes), etc.;
- iii. Pathologic or post-mortem evidence of active TB;
- iv. Favourable response to therapeutic trial of anti-TB drugs.

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PHAC Cases Reported to the Canadian TB Reporting System

## Diagnosis Overview

The diagnostic process for active TB includes:

- Symptom presentation;
- Radiographic presentation;
- Microbiological evidence (i.e. specimen collection for AFB smear and culture).

TB skin tests and IGRAs are unable to differentiate active TB. Hence, neither is recommended for diagnosing active TB.<sup>21</sup> Skin tests in particular can demonstrate up to 25 per cent false negativity in individuals with active disease, due to anergy. The “gold standard” of active TB diagnosis is culture.

## 6.1 Signs and Symptoms

The presentation of TB can be subjective, though is dependent upon on the site and severity of disease. Classic symptoms for respiratory TB include a new or worsening cough for two to three weeks duration, fever and night sweats. The cough may or may not be productive. Hemoptysis, anorexia, weight loss and pleuritic chest pain are generally associated with advanced disease. Very young children and the elderly may present with non-specific symptoms.

It is also possible to be asymptomatic. Respiratory TB can occur without a cough and in some cases, individuals may present with no symptoms especially early on in the disease process or in the case of an incidental diagnosis. The physical examination findings for active respiratory TB can also be non-contributory, or within normal limits, even with advanced disease.

Approximately 35 per cent of active cases in Canada are non-respiratory.<sup>22</sup> Diagnosing active non-respiratory TB is challenging as symptom presentation is highly variable when compared to pulmonary symptoms. Thus, there is often a delay in diagnosis. The clinical presentation is site-specific. These may include lymph node swelling in lymphatic disease, neurological changes (i.e. headache or neck stiffness) in meningeal disease, bone pain/joint swelling in osteomyelitis, chronic back pain in Pott’s disease (spinal compression or abscess), recurrent sterile pyuria (urinary tract infections) in renal disease, abdominal pain or ascites in gastrointestinal disease, or infertility in genitourinary disease.

Respiratory and non-respiratory TB can occur concurrently. Hence, it is important to rule out respiratory TB when a diagnosis of non-respiratory TB is made. Assessment should include both thoracic imaging and collection of sputum for TB culture,

even if the x-ray appears normal. Although drug therapy does not change with a concurrent diagnosis, airborne isolation precautions and contact tracing are necessary with respiratory disease.

HCWs caring for patients who have immunosuppressive conditions or are on immunosuppressant medications (i.e. steroids, biologics, chemotherapy, etc.) should maintain a high degree of suspicion for TB, particularly in patients with an increased epidemiological likelihood of either recent or remote TB exposure. TB should be in the differential diagnosis when investigating any unexplained illness, even in the absence of typical features of TB disease.

## Special Populations: Symptom Presentation

### IMMUNOCOMPROMISED INDIVIDUALS

The symptom presentation of TB in the immunocompromised individual depends largely on the degree of immunosuppression. In individuals with HIV/AIDS, presentation is dependent on the CD4 count, with counts < 200 cells/microliter being most likely to present with atypical or systemic manifestations such as increased risk of non-respiratory TB, or disseminated disease with lymph node, pleural, pericardial or meningeal TB involvement. In some cases, symptoms may appear to be consistent with TB, but may be caused by other opportunistic infections like bacterial pneumonia or *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*).

### PEDIATRICS

Most children who have TB disease in North America are asymptomatic and are discovered as part of the contact investigation of adult cases, especially children under five years of age. Typically these children appear entirely well without any clinical signs, but may have x-ray abnormalities. TB disease in a very young child is a sentinel event indicating recent transmission. When such a diagnosis is made outside of a contact investigation, a source case investigation should be performed.

Epidemiologic risk factors, such as living or travelling in an endemic country, and/or a clinical picture compatible with TB, should prompt appropriate testing. After infection, children under five years of age have a high risk of progression to more severe forms of TB.

Young infants may present with nonspecific findings such as hepatosplenomegaly, respiratory distress, fever, lymphadenopathy, abdominal distention, weight loss, hemophagocytosis, lethargy or irritability. The

skin test is often negative. Older children and adolescents present with similar symptoms as adults, with the classic symptoms of fever, weight loss and night sweats, and associated respiratory symptoms of pulmonary TB. Symptoms can still be quite subtle and atypical. These unusual presentations in adolescents may lead to a delay in the diagnosis and subsequent treatment of TB.

Children with HIV infection and TB disease tend to present as non-HIV children do, but with more advanced disease. Active TB disease in this population is ideally managed by a specialist.

## 6.2 Radiographic Presentation

Chest x-rays (both posterior-anterior [PA] and lateral views) are an effective tool for diagnosing respiratory TB. Classic radiographic presentation of TB in an immunocompetent individual includes infiltrates, nodules and/or cavities in the upper lobes of the lungs, or superior segments of the lower lobes. TB can also have atypical radiographic presentations such as infiltrates in the lower lobes and/or hilar and mediastinal lymphadenopathy. These may occur especially during primary infection and in individuals who are immunocompromised. Other abnormalities include fibrosis, scarring, granulomas or volume loss as the TB bacillus destroys lung tissue and causes remaining tissue to contract. Chest x-rays can have a sensitivity of up to 80 per cent in diagnosing active TB. However, chest x-rays have poor specificity in ruling out active TB disease. Although uncommon, individuals with normal chest x-rays can also have active disease, especially in early disease and in close contacts of active cases or immunosuppressed populations.

Radiological presentation does not determine disease activity. Clinical and microbiological correlation is required to rule out active disease.

### Special Populations: Radiographic Presentation

#### PREGNANCY

Pregnancy is not a contraindication for diagnostic investigations for active TB disease, including chest x-rays. Women who are or may be pregnant should have all x-rays done with appropriate protection.

## IMMUNOCOMPROMISED INDIVIDUALS

Chest x-rays may have typical or atypical presentations in the immunocompromised individual. The greater the level of immunosuppression, the less likely these individuals will have upper lobe findings or cavitation. Hilar lymphadenopathy, lower lobe infiltrates, pleural effusion and miliary presentations are also apparent in this population. Individuals with HIV/AIDS can also have completely normal chest x-rays approximately 10 per cent of the time.

## PEDIATRICS

Chest x-rays are important in diagnosing pediatric TB, but can be difficult to interpret in a young child. Technique (inadequate inspiration, over-penetration, child is rotated) and the radiologist's experience in reading pediatric chest x-rays are variables that can influence the utility of the film. Therefore, before ordering a chest x-ray, the clinician should check that the facility has experience with positioning and interpretation of pediatric TB films.

Both posterior-anterior and lateral views are recommended as it is important to evaluate for hilar lymphadenopathy, a hallmark of primary TB. In primary disease, lung lesions can be found anywhere. Abnormalities found in the lung apices tend to indicate reactivation TB disease. Lastly, the age of the child must be considered when interpreting chest x-rays. Miliary disease is much more common in young infants and in the immunocompromised. Miliary refers to diffuse tiny nodules similar in size to millet seeds visualized on x-ray. Radiographic presentations in older children and adolescents can be similar to those of adults, with upper lobe or cavitary involvement. Abnormalities on imaging can appear to worsen initially on treatment before improving.<sup>23</sup>

## 6.3 Mycobacteriological Evidence: Testing for Acid Fast Bacilli (AFB) Smear and Culture

The causative agent of TB is *Mycobacterium tuberculosis* Complex (MtbC) [excluding *M. bovis* BCG], which is a slow growing mycobacterium that may take several weeks to grow in culture. The laboratory requisition must specifically request acid-fast smear and culture for TB, as routine culture/sensitivity and Gram stain tests do not detect TB.

## The Microbiology of Acid-Fast Bacilli (AFB) Smears

The term “smear” refers to the laboratory technique for visualizing mycobacteria. The specimen is smeared onto a microscope slide, stained, and examined.

“Acid-fast” refers to mycobacteria's resistance to decolourization in the staining process of the bacilli. Mycobacteria are rod-shaped organisms that have a cell wall largely composed of fatty acids (mycolic acids). The cell wall prevents penetration by the stains used for other bacteria (e.g. Gram stain). The stain used to visualize mycobacteria is a highly concentrated phenolic dye. After the smear has been stained using this dye, the smear is then “decolourized” using acid-alcohol.

Mycobacteria will resist decolourization due to their complex cell wall and will retain the stain. Thus, the term “acid-fast” refers to the mycobacterium's ability to retain the stain in the presence of weak acids. Laboratories now routinely use fluorescent stains (e.g. Auramine O), which greatly improve the sensitivity of smear microscopy.

Both MtbC and nontuberculous mycobacteria (NTM) will stain AFB smear positive, although only MtbC is infectious. It is important to determine whether a positive AFB smear is due to MtbC or NTM. This may be determined by direct detection, using molecular assays (nucleic acid amplification tests or NAATs) and culture.

All NAATs are presumptive, and results must be confirmed by culture (gold standard). However, until TB or *Mycobacterium avium* Complex (MAC), the most common NTM is ruled out, all positive smears should be considered to be MtbC and appropriate infection control precautions taken.\* In Ontario, all fresh specimens sent for AFB smear are also cultured for both MtbC and nontuberculous mycobacteria.

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\* For further information on NTM, please refer to section 10 in this booklet and Chapter 11 of the CTS 2013.

## AFB Smears in Clinical Practice

AFB smear is a rapid test used to examine specimens for possible active TB disease. Each specimen sent for AFB is stained, and the number of AFB visualized is quantified using a numerical scale as shown in Figure 8.

Some laboratories perform a direct or unconcentrated AFB smear (without digestion, decontamination and concentration steps), for rapid results. An

unconcentrated specimen smear lacks specimen processing steps that yield more sensitive smear results. Unconcentrated smear results are considered to be preliminary until a concentrated AFB smear is performed. A minimum of 5,000–10,000 bacterial/mL are required for a positive smear result, whereas culture can detect a much lower bacillary load of approximately 10 bacteria/mL.<sup>24</sup>

Smear results are a rough indicator of the infectiousness of the active TB case. Hence, they must be interpreted within the context of an individual's symptoms and radiological presentation. Smear results are influenced by numerous factors including the quality of the specimen, the number of samples obtained, and the individual's burden of disease.

**FIGURE 8** AFB Smear Report Interpretation

Number of AFB seen in smear	PHOL Reporting (b)	CTS Reporting
None	No AFB seen	No AFB seen
3-9 / smear	Few (a)	Inconclusive, repeat (a)
1-9 / ten fields	1+	1+ (rare) (c)
1-9 / field	2+	2+ (few)
10-90 / field	3+	3+ (moderate)
> 90 / field	4+	4+ (numerous)

- Few as designated by the Public Health Ontario Laboratories (PHOL) is reported only after a repeat second smear is read confirming the presence of acid-fast bacilli on the smear. PHOL does not use the “inconclusive, repeat” terminology.
- The criteria set in the Canadian Tuberculosis Standards are enumerated by reading smears at 250x magnification. PHOL smears are read at 200x magnification with the same number of fields as in the CTS. Results correlate with the same enumeration as indicated in the chart above.
- The PHOL does not use the terminology as described in the CTS (rare, few, etc.). *Please refer to the chart above regarding smear enumeration.*

A negative AFB smear result does not rule out the diagnosis of TB, as the culture can still be positive for MtbC. Individuals with negative AFB smears, but positive cultures may still be infectious and transmit TB.<sup>25</sup>

If non-respiratory TB is suspected, tissue biopsies or other samples should be tested from non-respiratory sites for AFB and culture. The PHOL has specific requirements for the collection and transport of specimens. *Please refer to the Public Health Ontario website for specimen collection instructions.\**

Sputa or other specimens that are submitted for AFB smear and culture must clearly specify testing for TB on the microbiology requisition. Routine bacterial culture and sensitivity does not include AFB smear and culture for TB.

\* <https://www.publichealthontario.ca/en/laboratory-services/additional-mycobacterium-collection-details>

## Molecular Testing (NAATs)

Molecular tests are available for the direct detection of MtbC from specimens. These assays amplify target sequences of DNA or RNA from MtbC and have a rapid

turn-around time of 2–24 hours. These results are presumptive and must be confirmed where possible by conventional culture. Nucleic Acid Amplification Tests (NAATs) have a high degree of specificity.

The NAAT currently in use for respiratory specimens at the PHOL is the real time polymerase chain reaction (TB/MAC NAAT) assay for the direct detection of Mycobacterium tuberculosis complex and Mycobacterium avium complex DNA (implemented June 1<sup>st</sup>, 2016). This assay detects the presence of Mycobacterium tuberculosis complex and Mycobacterium avium complex DNA in specimens. This real time PCR has replaced the AMTD (Amplified Mycobacterium Direct Test, Hologic, Marlborough, MA), the previous assay in use at PHOL). Some hospital laboratories in Ontario have also implemented the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA) for direct detection of MtbC in undigested and unconcentrated respiratory specimens.

NAATs are recommended for respiratory specimens (excluding pleural fluid) though under special circumstances they can be used on non-respiratory specimens. The Hain GenoType MTBDRplus (Hain Lifesciences, Nehren, Germany) will also detect

common mutations associated with rifampin (RMP) and isoniazid (INH) resistance, and the Xpert MTB/RMP will detect common mutations associated with RMP resistance.

AFB smear-positive respiratory specimens are routinely tested using the TB/MAC NAAT in patients for whom there has been no previous smear-positive respiratory sample (i.e. “new smear positive”). PHOL will not perform the TB/MAC NAAT on multiple specimens or any specimens from patients known to be on treatment. Please consult with the Medical Microbiologist as required.

AFB smear-negative respiratory specimens will be tested using the TB/MAC NAAT assay only upon request which must be made within 72 hours of the date and time the specimen was received at the laboratory to ensure specimen integrity. Requests should be considered for patients in whom TB is highly likely and have significant risk factors for TB.

PHOL Customer Service must be contacted in order to obtain the Medical Microbiologist’s approval to request NAAT testing on AFB smear negative specimens.

Confirmation by detection and identification of MtbC in culture and conventional phenotypic drug susceptibility testing (DST) is necessary (gold standard). Phenotypic drug susceptibility testing is performed routinely on all new culture positive case MtbC isolates.

The performance of the TB/MAC NAAT assay is monitored routinely at the PHOL. In 2017, the TB/MAC NAAT performance statistics were:

	AFB Positive	AFB Negative
MtbC: Sensitivity	98.6%	50%
MtbC: Specificity	97.9%	97.8%
MAC: Sensitivity	77.5%	0%
MAC: Specificity	96.5%	100%

## Culture and Anti-Tuberculous Drug Susceptibility Testing

Culture is the gold standard for the laboratory diagnosis of TB. MtbC is a slow growing organism, and cultures are held for seven weeks before a final report is issued. If a positive culture is identified as MtbC, the first isolate from the patient will automatically be tested for susceptibility to the first-line TB drugs (i.e. INH, RMP, PZA, and Ethambutol). Susceptibility testing results are usually available 7-10 days after the culture

has grown. First-line anti-tuberculous drug susceptibility testing (DST) results are automatically repeated if a patient’s cultures remain positive at three months or greater.

If the isolate is identified as resistant to INH (low-level), it is then automatically tested for high-level INH resistance, and for resistance to fluoroquinolones (moxifloxacin and ofloxacin). Second-line DST is automatically performed if resistance is detected to Rifampin or to two or more of the other first line drugs. Species determination, including identification of *M. bovis* and *M. bovis* BCG is performed if susceptibility testing indicates pyrazinamide (PZA) resistance.

If a specimen does not grow MtbC in culture, phenotypic drug susceptibility testing cannot be performed.

## Pathology

Histopathological examination is often helpful for determining TB disease in tissue biopsies or specimens. Acid-fast organisms and/or caseating granulomata may be seen on microscopic examination, and should prompt further investigation, as these findings are highly suspicious for the diagnosis of TB.

## 6.4 Specimen Collection

Diagnostic specimens should ideally be collected before starting drug therapy for TB. Specimens are usually sent to private or hospital laboratories, and from there are sent to the PHOL for processing. Specimens must be collected in a leak-proof, sterile, and appropriately labeled container.

*Please refer to the Public Health Ontario website for specimen collection and labelling instructions.\** Specimens lacking required information or inappropriately collected will be rejected for processing.

\* [http://www.publichealthontario.ca/en/ServicesAndTools/LaboratoryServices/Pages/Additional\\_Specimen\\_Collection\\_Details\\_-\\_Mycobacterium.aspx](http://www.publichealthontario.ca/en/ServicesAndTools/LaboratoryServices/Pages/Additional_Specimen_Collection_Details_-_Mycobacterium.aspx)

## Spontaneous and Induced Sputum

Three sputum specimens should be collected (5-10 mL each) to facilitate diagnosis. In order to prevent overgrowth by other contaminating bacteria, sputum samples must be refrigerated if not transported to the laboratory within one hour of collection. Morning specimens may be easiest for the patient to provide.

Sputum samples must be refrigerated if not transported to the laboratory within one hour, in order to prevent overgrowth by other contaminating bacteria. Instruct the patient to not rinse his/her mouth with tap water or other rinses such as mouth-wash prior to obtaining the specimen. Tap water may contain environmental mycobacteria (non-tuberculous mycobacteria or NTM) which may contaminate the specimen and cultures.

If an individual is unable to produce sputum spontaneously, induced sputum is also an effective way of obtaining a specimen. It has a sensitivity of 75 per cent. A sputum induction involves inhaling 3 per cent or 5 per cent hypertonic saline mist to irritate the airways, causing the individual to cough up sputum. The mist is created by a nebulizer. It is normal for an induced sputum sample to look watery. Sputum induction must be done in a negative pressure room, as it is considered an aerosolizing generating procedure. Please indicate on the PHOL test requisition that the specimen is an induced sputum, due to the watery nature of the specimen.

## Bronchoscopy

If the initial series of sputum smears are negative, and the clinical and/or radiological suspicion for TB remains high, then a bronchoscopy should also be considered in order to rule out TB. Bronchoscopy should also be done if the individual is unable to produce a specimen either spontaneously or via induction.

Bronchoscopy is also helpful in diagnosing other respiratory diseases such as malignancy or other infectious etiologies. When bronchoscopy specimens are submitted for TB testing, always submit a post-bronchoscopy spontaneous sputum specimen. It is always preferable to submit more than one specimen where possible.

## Biopsy

Fresh tissue specimens should be submitted to the laboratory for AFB smear, culture and susceptibility testing. Tissue and biopsy specimens must be placed in a small amount of sterile saline and submitted in a

sterile container to the laboratory. Do not submit on gauze. Frozen specimens are not optimal for culture.

Formalin-fixed paraffin-embedded specimens can only be tested for the presence of MTB DNA by the TB/MAC NAAT assay. The laboratory must be notified prior to submission for instructions. Formalin-fixed tissue, or tissue from paraffin blocks (histopathology specimens) cannot be cultured, and anti-tuberculous drug susceptibility testing (DST) cannot be performed on these specimens.

## Gastric Aspirate

Gastric aspirate is performed on individuals who cannot expectorate sputum, and is primarily done on very young children, or elderly patients with dementia, in whom TB is suspected. A recent systematic review in children with gastric aspirate or lavage for TB diagnosis revealed positive AFB smears 0-21 per cent (median 7 per cent), and culture positive in 0-75 per cent (median 20 per cent).<sup>26</sup>

A gastric aspirate consists of inserting a tube through an individual's nose through to the stomach. During sleep, the mucociliary mechanism in their respiratory tract sweeps mucus, which may contain TB bacilli, into the mouth. The material is swallowed and the gastric aspirate may be a source to obtain organisms, especially if the stomach has not emptied. Gastric aspirates are commonly done in hospitals as it is an uncomfortable procedure, and must be done immediately after awakening. This usually involves an overnight admission. The PHOL provides gastric lavage collection kits (N-0043). Specimens not submitted in the gastric lavage collection kit (contains buffer to neutralize stomach acids) will be rejected.

*Please refer to the Public Health Ontario website for specimen collection information and how to obtain kits.\**

\* [http://www.publichealthontario.ca/en/ServicesAndTools/LaboratoryServices/Pages/Mycobacterium\\_Gastric\\_Lavage.aspx](http://www.publichealthontario.ca/en/ServicesAndTools/LaboratoryServices/Pages/Mycobacterium_Gastric_Lavage.aspx)

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Canadian Tuberculosis Standards, 7<sup>th</sup> Edition, Public Health Agency of Canada and the Canadian Lung Association/Canadian Thoracic Society, 2013<sup>©</sup>, Chapters 3, 4, 9, 10 and Appendix D

**FIGURE 9** Specimen Requirements for Mycobacterial Isolation and Acid-Fast Stain\*

SPECIMEN TYPE	SPECIMEN REQUIREMENTS	SPECIAL INSTRUCTIONS	UNACCEPTABLE SPECIMENS
<b>Abscess contents, aspirated fluid</b>	As much as possible in sterile plastic container.	Cleanse skin with alcohol before aspirating sample. If volume is insufficient for aspiration by needle and syringe, collect specimen on swab and place in multi organism (Amico or Stuarts) aerobic transport medium.	Dry swab. Swabs in anaerobic transport medium.
<b>Blood</b>	7mL SPS (yellow top) or 7mL heparin (green top) blood collection tube or 10mL Isolator tube or 5mL inoculated directly into Myco/F Lytic Medium.	Disinfect site as for routine blood culture. Mix tube contents immediately after collection.	Blood collected in EDTA, which greatly inhibits mycobacterial growth even in trace amounts coagulated blood serum or plasma.
<b>Body fluids (pleural, pericardial, peritoneal, etc.)</b>	As much as possible (10–15mL minimum) in sterile container.	Disinfect site with alcohol if collecting by needle and syringe.	
<b>Bone</b>	Bone in sterile container without fixative or preservative.		Specimen submitted in formalin.
<b>Bone marrow</b>	As much as possible in sterile collection tube or SPS or heparin tube.	Collect aseptically. Mix heparinized or SPS tube contents immediately following collection.	
<b>Bronchoalveolar lavage or bronchial washing</b>	≥ 5mL in sterile container.	Avoid contaminating bronchoscope with tap water. Saprophytic mycobacteria may produce false-positive culture or slide results.	
<b>Bronchial brushing</b>	Sterile container. If small amount of specimen then add sterile saline.		
<b>Corneal Scrapings</b>	Physician to inoculate cultures during procedure.	Contact the laboratory before the procedure. Laboratory to send one MGIT tube, two LJ slants and a microscope slide to the physician's office.	Specimen submitted in formalin.
<b>CSF</b>	≥ 2mL in sterile container.	Send maximum volume attainable.	< 0.5mL
<b>Gastric lavage fluid</b>	≥ 5 – 10mL in gastric lavage container. Collect in the morning soon after patient awakens in order to obtain sputum swallowed during sleep.	Collect fasting early-morning specimen on three consecutive days. Use sterile water. Adjust to neutral pH with 100 mg of sodium carbonate immediately following collection. The PHOL provides collection jars for gastric lavage (N-0043).	Specimen that has not been neutralized.
<b>Lymph node</b>	Node or portion in sterile container without fixative or preservative. A small amount of sterile saline may be added.	Collect aseptically. Select caseous portion if available. Do not wrap in gauze. Do not freeze.	Specimen submitted in formalin.
<b>Skin lesion material</b>	Submit biopsy specimens in sterile containers without fixative or preservative. Submit aspirate in syringe with needle removed and Luer Lock cap in place.	Swabs in transport medium (Amies or Stuarts) are acceptable only if biopsy sample or aspirate is not obtainable. For cutaneous ulcer, collect biopsy sample from periphery of lesion, or aspirate material from under margin of lesion. If infection was acquired in Africa, Australia, Mexico, South America, Indonesia, New Guinea or Malaysia, note on requisition, because <i>Mycobacterium ulcerans</i> may require prolonged incubation for primary isolation.	Dry swab. Swabs in anaerobic transport medium.
<b>Sputum</b>	5 – 10mL in sterile, wax-free, disposable container. Three specimens should be submitted, collected at least one hour apart. Early morning specimens may be the easiest for patients to produce. Do not pool specimens. To obtain a sufficient volume of specimen (5mL) the patient may expectorate several times per collection. For follow-up of patients on therapy, submit three specimens after two months and again on completion of therapy.	Saprophytic mycobacteria in tap water may produce false- positive culture or slide results. For expectorated sputum, instruct patient on how to produce specimen as distinct from saliva or nasopharyngeal discharge. Do not have patient rinse mouth with tap water which may contain environmental mycobacteria. For induced sputum, use sterile hypertonic saline. Avoid sputum contamination with nebulizer reservoir water. Indicate on request if specimen is induced sputum, as these watery specimens resemble saliva and risk rejection as inadequate.	24 hour pooled specimens saliva.
<b>Feces</b>	≥ 1g in sterile, wax-free, disposable container.	Collect specimen directly into container, or transfer from bedpan or from plastic wrap stretched over toilet bowl.	Frozen specimen. Specimen that has been in contact with water in toilet.
<b>Tissue biopsy sample</b>	1g of tissue, if possible, in sterile container without fixative or preservative.	Collect aseptically, and avoid indigenous microbiota. Select caseous portion if available. Do not wrap in gauze. Do not freeze.	Specimen submitted in formalin.
<b>Transtracheal aspirate</b>	As much as possible in syringe with needle removed and Luer Lock cap in place. Aspirate can be sent in sterile container.	Do not submit specimens in endotracheal tubes these are unsuitable for processing.	

**FIGURE 9** Specimen Requirements for Mycobacterial Isolation and Acid-Fast Stain\* (*continued*)

SPECIMEN TYPE	SPECIMEN REQUIREMENTS	SPECIAL INSTRUCTIONS	UNACCEPTABLE SPECIMENS
<b>Urine</b>	Catheter or midstream urine as much as possible (minimum, 40mL) of first morning specimen. For suprapubic tap, as much specimen as possible with needle removed and Luer Lock cap in place. Aspirate can be sent in sterile container.	Collect first morning specimen on three consecutive days. PHOL will accept only one specimen/day. Organisms accumulate in bladder overnight, so first morning void provides best yield. Specimens collected at other times are dilute and are not optimal.	24 hour pooled specimens urine from catheter bag specimens of <40mL unless larger volume is not obtainable. Urine specimens should only be tested if renal TB is suspected, not used for as routine screen.
<b>Wound material</b>	(See biopsy or aspirate)	(See biopsy or aspirate)	Dry swabs in anaerobic transport medium.

# 7

## Reporting Requirements

Under the Health Protection and Promotion Act (HPPA) of Ontario, physicians and nurses registered in the Extended Class (Nurse Practitioners) are required to report **all cases of active TB disease and latent TB infection** to the local Medical Officer of Health in the jurisdiction in which the professional services are provided. In addition, the following disciplines are required to report when a person has been diagnosed with TB infection or disease:

- Hospital administrators
- Superintendents of an institution (based on entry in the records of the institution that TB is suspected or diagnosed)
- Chiropractors
- Nurses
- Pharmacists
- Optometrists
- Persons registered as drugless practitioners

- School principals
- Operators of laboratories
- Dentists
- Naturopaths

Patient consent is not required for reporting this information. The Personal Health Information Protection Act (PHIPA) explicitly allows healthcare providers to disclose health information without consent where permitted or required by law.

Report all latent TB infection (LTBI) and TB disease to Public Health

- Report patients with clinical or lab confirmed TB disease (respiratory and non-respiratory) as soon as possible. Culture confirmation is not necessary for reporting of a TB case
- Report patients with LTBI, indicated by a positive TST or IGRA blood test, regardless of plans for prophylaxis.

It is important to report all cases of TB disease in a timely manner to ensure that the follow-up of contacts and Public Health supports such as DOT for TB patients can begin without delay. Physicians and other healthcare professionals who undertake the clinical management of TB patients must report any non-adherence to treatment and missed appointments. Under the HPPA, the Medical Officer of Health or designate can order an individual with active infectious TB disease to comply with treatment, to isolate themselves and to keep their medical appointments.

The order is written to minimize the public health risk posed by any non-compliance. (See section 12.6 for non-adherence).

The healthcare professional reporting must provide information requested by the Medical Officer of Health or designate, including chest x-ray, CT scan, MRI findings, smear/culture results and demographic information such as date of birth, gender, address and telephone number. (See also Chapter 12 *The Role of Public Health in TB Prevention and Control*)

# 8

## Treatment of Active Tuberculosis Disease

### 8.1 General Information and Principles

All cases of active tuberculosis should be treated by a clinician with tuberculosis (TB) experience. In jurisdictions where this is not possible, the treating practitioner should consult with a TB clinic or TB specialist. The decision to treat implies a decision to help ensure treatment completion and monitor for side effects. Pregnant women, children < 15 years,<sup>27</sup> drug-resistant cases, HIV co-infected cases and cases with known or suspected treatment failure, should be referred to a TB clinic or TB specialist.

The objectives of treatment and management of TB disease are to achieve a lifetime cure while preventing drug resistance, and limiting transmission. To accomplish these objectives, the treating clinician should follow these principles:

- All patients with respiratory TB should be managed with airborne precautions and/or home isolation until no longer infectious; clinicians should consult with their Infection Prevention and Control Department and local Public Health unit, with prompt referral made to local Public Health or primary healthcare provider;
- Patients with non-respiratory TB should also be managed with airborne precautions until respiratory TB has been ruled out;
- Most patients with TB can be managed as outpatients;
- Initiate treatment with all four anti-tuberculosis medications, (Isoniazid, Rifampin, Pyrazinamide, Ethambutol) until sensitivity results are obtained (see specific treatment regimens below). The drug sensitivity reports follow the culture results within one to two weeks. The treatment regimen should always be guided by drug sensitivity results. If drug sensitivities are not available, all 4 first-line medications should be continued throughout treatment.

In special circumstances and on request only, the Public Health Ontario Laboratories can perform molecular testing on smear positive samples for potential rifampin and isoniazid resistance. The results are preliminary only and should be confirmed by final phenotypic sensitivities;

- **Promptly** refer every TB patient to Public Health for free-of-charge TB medications, TB nursing support and education, contact tracing, and Directly Observed Therapy (DOT) support to facilitate compliance. The treating healthcare provider and local public health authorities share responsibility for case management;
- Every patient diagnosed with TB disease should have HIV testing. It should be stressed that this is “routine” as the management of TB is different in individuals infected with HIV;
- Patients with drug resistant or active TB should be referred to an Infectious TB Specialist or a TB Clinic;
- **Never** add a single drug to a failing regimen. Referral to a TB specialist is essential with patients experiencing treatment failure;
- At **every** visit with the patient:
  - assess for drug side effects;
  - review education about TB disease and how drug resistance occurs;
  - emphasize the need for adherence to drug treatments and isolation requirements;
  - ensure that patients take their medication correctly.

**Notify** your Public Health unit if non-adherence with treatment or isolation is suspected. Refer to section 12, *The Role of Public Health in Prevention and Control of TB*, for more detail.

Drugs for the treatment of active tuberculosis disease and latent tuberculosis infection are provided or covered by local public health units, free of charge to patients in Ontario. This includes first-line and second-line drugs and pyridoxine (Vitamin B<sub>6</sub>). Contact the local Public Health unit to arrange for TB medication.

## 8.2 Standard Treatment for Active Tuberculosis

The standard treatment regimens for fully sensitive TB for adults and children are shown in Table 1. Non-respiratory TB is treated with the same regimens as respiratory TB. Treatment is commonly extended to

12 months in disseminated and meningeal TB – consult with a TB specialist in these situations.

- Pregnant women, children < 15 years\*, drug-resistant cases, HIV co-infected cases and cases with known or suspected treatment failure or other complex co-morbidities should be referred to a TB clinic or experienced TB specialist;
- Ethambutol (EMB) is generally included in the initial phase until drug resistance is ruled out. A baseline ophthalmological assessment (visual acuity and red-green colour discrimination) should be done before starting EMB and repeated regularly during treatment with EMB;
- During active TB treatment, follow the patient at least monthly to assess adherence and response to therapy and to detect adverse events:
  - Response to treatment should be gauged clinically, radiographically and biologically;
  - If the patient is AFB positive, obtain two sputum every 2-4 weeks to monitor for smear conversion (and removing airborne precautions/home isolation);
  - Culture conversion to negative should be documented as a key indicator of treatment progress;
- Sputum collection to monitor progress may not be possible for small children or adults who are no longer able to produce sputum:
  - If treatment failure is suspected, obtain two sputum samples;
  - Chest x-rays should be done after two and six months of therapy to assess response;
  - Liver function testing: all adults and children should receive baseline testing at the beginning of treatment, and follow up, as necessary, to ensure hepatic stability on medications. Closely monitor liver enzymes of patients with underlying hepatic disease and the elderly.
- Routine liver function testing in children is not always indicated but advise parents that the TB medication should be immediately held and medical attention sought if anorexia, nausea, vomiting or jaundice occurs;<sup>28</sup>
- INH/RMP containing regimens that include Pyrazinamide (PZA) for the first two months of treatment may be discontinued after 6 months;

- INH/RMP containing regimens without PZA for the first two months should continue for a total of nine months;
- Extend six month treatment regimens to nine months in patients with the combination of positive cultures after two months of treatment and extensive disease or cavities on CXR within

the first two months; or HIV positive and not on antiretroviral therapy (ART);

\* The World Health Organization (WHO) defines pediatric tuberculosis as TB in persons less than 15 years of age (WHO, 2013, Roadmap for Childhood Tuberculosis).

**FIGURE 10** Standard Treatment Regimens for Active TB Disease

**TABLE 1: TREATMENT REGIMENS FOR FULLY DRUG-SENSITIVE TUBERCULOSIS**

Regimen	Initial Phase (months)	Continuing Phase (months)	Total (months)
INH/RMP/PZA + EMB*	2	4	6
INH/RMP + EMB*	2	7	9

INH=Isoniazid, RMP=Rifampin, PZA=Pyrazinamide, EMB=Ethambutol\* (See Table 2 re: Ethambutol use in children).

**Note:** even though this may be the normal protocol for treatment, extensive disseminated disease is treated longer than a minimally infectious PTB and that a consult with a TB/ID specialist is warranted, i.e.: Table highlights the minimum duration of therapy.

**TABLE 2** Dosage Recommendation for the Treatment of Tuberculosis in Adults and Children

	Daily		Thrice Weekly	
	By Weight*	Max (mg)	By Weight	Max (mg)
<b>First-line Drugs</b>				
INH	Adult: 10 mg/kg Children: 10-15 mg/kg	300	Adult: 10 mg/kg Children: 20-30 mg/kg	Adult: 600 Children: 600-900
RMP	Adult: 10 mg/kg Children: 10-20 mg/kg	600	Adult: 10 mg/kg Children: 10-20 mg/kg	Adult: 600 Children: 600
PZA	Adult: 20-25 mg/kg Children: 30-40 mg/kg	2000	Adult: 30-40 mg/kg Children: 60-80 mg/kg	Adult: 4000 Children: 2000-3000
EMB	Adult: 15-20 mg/kg** Children: 15-25 mg/kg	Adult: 1600 Children: 1600-2500	Adult: 25-40 mg/kg Children: 30-50 mg/kg	Adult: 2400 Children: 2400-2500

\* Doses for children are based on weight.

In general, daily therapy is preferred over intermittent therapy<sup>29</sup>

\*\* Ethambutol optimal dosing is unclear. It is clear that eye toxicity is dose dependent, and its risk is higher at 25 mg/kg than at 15 mg/kg.

For further information about ETH dosing, see Pediatric TB, Chapter 9 of the Canadian Tuberculosis Standards, 7<sup>th</sup> Edition, Public Health Agency of Canada and the Canadian Lung Association/Canadian Thoracic Society, 2013<sup>®</sup>. And for more detailed information, see Chapter 5.

**WARNING:** Every effort has been made to ensure the accuracy of the dosages of drugs and the prescribing information included in this book. Nevertheless, those prescribing these drugs are urged to follow carefully the manufacturers' printed instructions.

**TABLE 3 Anti-Tuberculosis Drug Information<sup>30</sup>**

Drug	Major Adverse Reactions	Monitoring	Remarks
<b>Isoniazid (INH)</b>	<ul style="list-style-type: none"> <li>Hepatotoxicity/ hepatitis</li> <li>Hypersensitivity reactions (e.g. rash, drug induced fever, thrombocytopenia)</li> <li>Peripheral neuritis (due to vitamin B6 deficiency)</li> <li>Drug interactions</li> </ul>	<ul style="list-style-type: none"> <li>Symptoms of hepatitis, hypersensitivity, or peripheral neuritis.</li> <li>Baseline CBC, and liver enzymes (ALT, ALP) and bilirubin. Monitor monthly for patients with pre-existing liver disease, concurrent use of other hepatotoxic drugs, history of chronic or excessive alcohol use, prior drug induced hepatitis, age &gt; 35 years, pregnant or within 3 months post- partum.</li> </ul>	<ul style="list-style-type: none"> <li>Do not use INH alone in the presence of suspected/confirmed active TB disease as monotherapy may lead to the development of drug resistance.</li> <li>Do not use INH where there is a high likelihood that patient has been exposed to an INH-resistant organism.</li> <li>Asymptomatic minor elevations in AST level are common and not an indication for discontinuation of treatment.</li> <li>Withdraw hepatotoxic drugs and consult a TB specialist when AST or ALT exceeds five times the upper limit of normal without symptoms, or when AST or ALT exceeds three times upper limit of normal with symptoms or whenever clinical jaundice develops.</li> <li>Consult/refer to a TB specialist, and do not initiate INH, in patients with history of INH-induced hepatitis, severe adverse reactions, acute/active liver disease.</li> <li>Avoid alcohol consumption.</li> <li>Best absorbed if taken on empty stomach (1 hour before meals or 2 hours after meals) but may be taken with foods that are low in fat and sugar if stomach upset occurs.</li> <li>Can increase the serum concentration of both drugs if given with Phenytoin (Dilantin) and some other anticonvulsant medications, and doses may have to be adjusted.</li> <li>May lead to behaviour and coordination disturbances if given with Disulfiram (Antabuse).</li> <li>Administer INH at least one hour before antacids containing aluminum salts to avoid decreased gastro-intestinal absorption of INH.</li> <li>Pyridoxine (25 mg) is given to prevent peripheral neuritis. It should routinely be prescribed with INH to adults/children with nutritional deficiencies, (including infants, children and adolescents on meat- and milk-deficient diets), alcoholism, diabetes, renal failure, HIV infection, seizure disorders, pregnant or breastfeeding women/teens.</li> <li>Advise patient to notify healthcare provider if any of the following symptoms appear: nausea, vomiting, anorexia, fatigue, weakness, fever lasting more than 3 days, persistent paraesthesia of hands and/or feet, rash, dark urine, jaundice, abdominal pain or tenderness especially in right upper quadrant, arthralgia.</li> </ul>
<b>Rifampin (RMP)</b>	<ul style="list-style-type: none"> <li>Hepatitis / Hepatotoxicity</li> <li>Hypersensitivity reactions (e.g. rash, drug induced fever, thrombocytopenia)</li> <li>Drug interactions</li> <li>Flu-like illness</li> </ul>	<ul style="list-style-type: none"> <li>Same as for INH</li> </ul>	<ul style="list-style-type: none"> <li>Presents similar risks for hepatotoxicity as INH therefore follow the same precautions</li> </ul> <p>In addition:</p> <ul style="list-style-type: none"> <li>Orange-red discolouration of body fluids e.g., urine, sweat, tears, saliva and feces is harmless, but permanently stain soft contact lenses</li> <li>May accelerate clearance of many drugs metabolized by the liver, e.g., estrogens (i.e., oral contraceptives), coumadin, anticonvulsants, glucocorticoids, digoxin, antiarrhythmics, sulfonyleureas, theophylline, cyclosporine, methadone, ketoconazole and others therefore: <ul style="list-style-type: none"> <li>Advise patients using oral contraceptive pill to use other methods of birth control</li> <li>Increases anti-coagulant drug requirement</li> <li>May precipitate Addisonian crisis in patients with marginal adrenal function</li> </ul> </li> <li>Advise patient to notify healthcare provider if symptoms/adverse reactions appear</li> <li>Memory impairment, thrombocytopenia, leukopenia and haemolytic anaemia have been observed</li> </ul>
<b>Pyrazinamide (PZA)</b>	<ul style="list-style-type: none"> <li>Arthralgia (joint pain)</li> <li>Hepatotoxicity</li> <li>Hypersensitivity reactions</li> <li>Hyperuricemia</li> <li>Gastric irritation</li> <li>Drug interactions</li> </ul>	<ul style="list-style-type: none"> <li>Same as for INH</li> </ul> <p>In addition:</p> <ul style="list-style-type: none"> <li>Uric Acid level if gout is suspected</li> </ul>	<ul style="list-style-type: none"> <li>Avoid alcohol consumption</li> <li>Discontinue for severe adverse reactions</li> <li>Absorption is not influenced by food intake</li> <li>Use with caution in patients with gout, renal failure and diabetes mellitus consult a TB specialist <ul style="list-style-type: none"> <li>PZA may increase serum uric acid levels and decrease efficacy of gout therapy, requiring dosage adjustments of these medications</li> <li>Dosing intervals may require adjustment in patients with impaired renal function and/or dialysis</li> </ul> </li> <li>PZA can be given in women who do not tolerate first-line drugs and/or with extensive disease</li> <li>Withdraw hepatotoxic drugs and consult a TB specialist when AST or ALT exceeds five times the upper limit of normal without symptoms, or when AST or ALT exceeds three times upper limit of normal with symptoms or whenever clinical jaundice develops</li> <li>Assess for interactions with other drugs, e.g., Allopurinol, sulfinpyrazone, cyclosporine</li> <li>Advise patient to notify healthcare provider if symptoms/adverse reactions appear</li> </ul>

**TABLE 3** Anti-Tuberculosis Drug Information<sup>41</sup> (continued)

Drug	Major Adverse Reactions	Monitoring	Remarks
<b>Ethambutol (EMB)</b>	<ul style="list-style-type: none"> <li>Optic neuritis (most commonly seen in those receiving &gt; 25 mg/kg but can occur with lesser dose, especially in patients with impaired renal function)</li> <li>Hypersensitivity reactions</li> </ul>	<ul style="list-style-type: none"> <li>Baseline and periodic assessment of visual acuity, visual field, and red-green colour perception</li> <li>Monthly monitoring recommended for patients receiving &gt; 15 mg/kg</li> </ul>	<ul style="list-style-type: none"> <li>Must be used in conjunction with at least one other anti-tuberculosis drug</li> <li>Contraindicated in known hypersensitivity, and known optic neuritis</li> <li>Use with caution in patients with decreased renal function                             <ul style="list-style-type: none"> <li>Dosing intervals may require adjustments in patients with impaired renal function and/or dialysis</li> </ul> </li> <li>Use with caution in children, especially children too young for ophthalmologic monitoring – risk of optic neuritis is dose dependent. Consult with a TB specialist</li> <li>EMB related visual changes are usually reversible if the drug is stopped promptly, although resolution can take several months</li> <li>Advise patient to notify healthcare provider if symptoms or adverse reactions appear, e.g., Patient should report any visual changes to physician immediately (usually occurs after taking drug for months)</li> </ul>

**Warning:** For complete information about the above drugs, their side effects, precautions and directions for use, healthcare professionals should always consult the manufacturers' printed materials or an equivalent pharmaceutical resource, e.g., Compendium of Pharmaceuticals and Specialties (CPS).

See also: Curry International TB Centre, Drug-Resistant Tuberculosis – A Survival Guide for Clinicians, 3<sup>rd</sup> ed. Chapter 4, [http://www.currytbccenter.ucsf.edu/drtb/drtb\\_ch4.cfm](http://www.currytbccenter.ucsf.edu/drtb/drtb_ch4.cfm).<sup>31</sup> For more detailed information, consult the Canadian Tuberculosis Standards, 7<sup>th</sup> Edition, Public Health Agency of Canada and the Canadian Lung Association/Canadian Thoracic Society, 2013<sup>9</sup>.

### 8.3 Drug-Resistant Tuberculosis

Refer suspected or confirmed drug-resistant TB cases to a TB specialist/TB clinic because the management can be complex, lengthy and requires specific expertise from a full treatment team. All patients in Ontario with MDR-TB or XDR-TB must be treated by or in consultation with West Park Healthcare Centre or SickKids. They are often hospitalized for their initial treatment and must have DOT support upon discharge.

TB treatment must always be guided by drug sensitivity results. The possibility of drug resistance should always be considered, especially in patients:

- with a previous history of tuberculosis – patients previously treated for TB are at high risk for drug resistance and should be referred to a TB specialist prior to initiating treatment;
- who are from areas with a high prevalence of drug-resistant tuberculosis such as India, China, the Russian Federation and other countries of the former Soviet Union, Philippines, Korea, and southern Africa.

Treatment regimens for drug-resistant TB must be tailored to the drugs to which the organism is susceptible by phenotypic DST.

Second-line TB medications may be less effective and have more side effects than first-line medications. Thus, the patient with drug-resistant respiratory disease may be infectious for longer periods than drug-susceptible cases. MDR-TB and XDR-TB cases

should remain isolated on airborne precautions for the duration of hospital stay or until three sputum cultures are negative after six weeks of incubation.

### 8.4 Pediatric Tuberculosis

Refer children promptly for assessment, diagnosis and treatment by a pediatric TB specialist. The diagnosis of TB disease in children can be difficult and is often based on a clinical presentation of a positive TB skin test, abnormal physical examination and/or chest x-ray, and a link to a suspect or known infectious TB case. In young children, the signs and symptoms are often non-specific. Asymptomatic child cases are typically found when investigated as contacts of patients with infectious TB.

Young children (< 5) are more likely to develop severe forms of TB including TB meningitis and miliary disease; the younger the child, the greater the risk. Children, especially those under 5 years of age, often present with non-specific or absent symptoms, they may have few bacilli present, and they may be unable to produce sputum. Epidemiologic risks factors and/or a clinical picture compatible with TB should prompt appropriate testing and referral to a TB specialist.

Tuberculosis disease in children is treated in the same manner as disease in adults. The child's weight should be monitored monthly and anti-tuberculosis drug doses adjusted according to weight. Pyridoxine (B<sub>6</sub>) supplementation is given to selected children receiving INH.

## 8.5 Treatment of Active TB in Pregnancy and Breastfeeding

Refer pregnant patients promptly for assessment and treatment by a TB specialist. **The risk of untreated active TB to a pregnant woman and her fetus is far greater than the risk of any side effects of the drugs used in its treatment.** Isoniazid, rifampin and ethambutol are considered safe in pregnancy based on strong evidence. PZA is also recommended by the WHO for treatment during pregnancy and there is no evidence of fetal adverse effects, though some clinicians prefer to avoid it for patients with minimal disease. All first-line drugs are considered safe with breastfeeding. However, the trace amounts of medication in breast milk are inadequate to provide prophylaxis for a breastfeeding infant. Vitamin B<sub>6</sub> is recommended for pregnant and breastfeeding women. Most second-line drugs are not considered safe in pregnancy.

## 8.6 Treatment of Active TB in People With HIV/AIDS

All persons with TB disease should have HIV testing. All persons with HIV should have TB testing. Treatment of TB in HIV-infected patients should be guided by a physician with expertise in the management of both diseases.

Co-infected patients not already on anti-retroviral therapy (ART) should be started on ART once TB treatment is established. Specialist consultation is essential. Treatment of co-infected patients may be complicated by:

- adherence problems with polypharmacy;
- overlapping side effects;
- drug interactions, and
- the occurrence of immune reconstitution inflammatory syndromes (IRIS).

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Rifampin may interact with ART. Rifabutin, with appropriate dose adjustment, can be substituted for rifampin in TB treatment when required. Pyridoxine (Vitamin B<sub>6</sub>) should be given to HIV-infected TB patients receiving INH.



# Treatment and Management of Latent Tuberculosis Infection (LTBI)

## 9.1 General Information

Treatment for latent tuberculosis infection (LTBI) is undertaken to prevent active disease in infected persons thereby preventing potential transmission to others. The decision to offer treatment for LTBI should include:

- Interpretation of TST in context of patient's history
- Consideration of medical contraindications, e.g., patients under 65 years old with no comorbidities have low rates of hepatotoxicity
- Likelihood of adherence to full length of LTBI treatment
- Discussion of risks/benefits with the patient
- Ensuring that active **pulmonary or non-pulmonary** TB has been ruled out (i.e., history, risk factors and physical examination, negative sputum cultures if the patient is symptomatic, has abnormal chest x-ray or is being treated with Rifampin).

## 9.2 Recommended Treatment Regimen for LTBI

Medications can be ordered free of charge through the local Public Health Unit. LTBI treatment is usually a self-administered daily regimen. If staff resources are available, in situations where the patient may have difficulty with adherence, consider providing intermittent Direct Observed Prophylactic Therapy

(DOPT). Intermittent dosing for the treatment of LTBI should be undertaken only with the assistance of a TB specialist and must be directly observed.<sup>32</sup>

### INH

INH is the standard first-line treatment for LTBI. It has been used since Ferebee et al first reported its effectiveness in 1957. While the drug has been shown to be safe, cheap, easy to take and well-tolerated, its effectiveness is dependent on adherence to treatment and adequate duration. The optimal protection is probably achieved by nine months of therapy. However, six months of INH is an acceptable alternative.<sup>33</sup>

### RMP

Four months of daily RMP has been shown to be not inferior to the nine month regime of INH described above for the prevention of active TB and is now recommended as a first line treatment for LTBI.<sup>34</sup> It is useful in situations where compliance to longer regimes is a concern.

### INH / RMP

Alternative regimens of INH/RMP can be used to treat LTBI. Three or four months of daily, self-administered INH/RMP provides similar efficacy and safety to six to nine months of INH alone. Active TB should be ruled out by sputum collection prior to initiation to avoid drug resistance.

## RIFAPENTINE / INH

Rifapentine and INH are being used in combination for the treatment of LTBI. This combination has been shown to be as effective as the current standard regimes. At the time of writing, rifapentine is not yet licensed in Canada but can be obtained for individuals through the federal Special Access Programme, and by provincial/territorial TB programs through the federal regulations on “Access to Drugs in Exceptional Circumstances”.

### 9.3 Contraindications, Side Effects, Adverse Events and Clinical Monitoring

Please refer to section 8 – Table 3 for a summary of adverse events, side effects and monitoring recommendations for INH/RMP. If symptoms such as those listed below develop, the patient should be advised to stop

taking the medication and to consult with a healthcare provider:

- Anorexia
- Nausea
- Vomiting
- Abdominal pain
- Unexplained fatigue
- Dark coloured urine
- Scleral icterus (jaundice)

RMP is associated with significant drug interactions and contraindications related to its action as an inducer of P450 isoenzymes. Thus the rate of many drugs can be accelerated resulting in reduced effect or toxicity when RMP is discontinued. The risk of hepatic dysfunction is similar to that of INH. Consultation with a TB expert is recommended.

FIGURE 11 Recommended Treatment of LTBI

First-Line Regimen	Interval & Duration	Oral Dose
Isoniazid (INH)	Daily for 9 months	Adult: • 5 mg/kg/day to a maximum of 300 mg/day Children: • 10 - 15 mg/kg/day to a maximum of 300mg day
Vitamin B6 (Pyridoxine)	Daily with INH	Adult: • 25 mg Children: proportional according to weight: • 1 mg/kg (maximum of 25 mg) daily • < 10 kg = 6.25 mg (1/4 tab) • 10 - 30 kg = 12.5 mg (1/2 tab) • > 30 kg = 25 mg (1 tab)
Rifampin (RMP)	Adult: Daily for 4 months Children: Daily for 4 months	<b>Adult:</b> • <b>10 mg/kg/day to a maximum of 600 mg/day</b> <b>Children</b> • <b>10-20 mg/kg/day to a maximum of 600 mg/day</b>
Second-Line/Alternative Regimen	Interval & Duration	Oral Dose
Isoniazid and Rifampin	Daily for 3-4 months	Adult: • INH – 5 mg/kg/day to a maximum of 300 mg/day • RMP – 10 mg/kg/day to a maximum of 600 mg/day Children: • Currently this combination is not recommended for children.

## 9.4 HIV and Other Immunocompromising Conditions

HIV positive or severely immunocompromised individuals with LTBI are at high risk for progression to active TB disease. This group includes patients being treated with biologicals for conditions such as severe rheumatoid arthritis, psoriasis and Crohn's Disease. LTBI treatment is not indicated for individuals who are immunocompromised and TST negative (less than 5 mm induration). Immunocompromised persons with LTBI should be prescribed the standard dose and duration of INH.

## 9.5 Pregnancy and Breastfeeding

INH/RMP are considered safe in pregnancy and when breastfeeding. However, due to the increased risk of hepatotoxicity during pregnancy and the first three months postpartum, it is recommended to defer LTBI treatment until after this period. LTBI treatment should not be deferred when there is a high risk of progression to active disease, e.g., HIV, recent TB contact. The possibility of active disease must be ruled out. When treatment for LTBI is deferred, both the patient and physician should watch for any symptoms of active TB disease.<sup>35</sup>

## 9.6 Pediatrics

LTBI in children should be treated with INH for nine months. Consultation with a TB specialist is recommended. Treatment for LTBI should be initiated immediately once active disease has been ruled out. Children do not need baseline liver function tests

unless they have a known or suspected underlying liver disease and are not taking any other hepatotoxic drugs. When children begin drug therapy, inform parents or guardians about symptoms associated with the most common adverse reactions and signs of hepatotoxicity. A clear plan for monitoring should be implemented.<sup>36</sup>

## 9.7 Managing Close Contacts Exposed to Drug-Resistant Active Cases

When an infectious TB patient has a drug-resistant TB organism, infected contacts (those with positive TST through screening) should be referred to a TB clinic or TB specialist for follow-up. Consult your local Public Health unit for assistance with clinic referrals.

## 9.8 Managing LTBI When Treatment is Refused, Contraindicated or Stopped Before Completion

Patients who cannot or will not complete LTBI treatment should be instructed carefully regarding the symptoms of active TB and be instructed to return for medical assessment if symptoms develop. Routine chest x-ray or follow up is not recommended unless there is a very high risk of progression to active TB disease (i.e., severe immunocompromised, recent TB contact). In this situation, consider regular follow up of two years as this is the period of highest risk (e.g., at 6, 12 and 24 months).<sup>37</sup>

# Nontuberculous Mycobacteria (NTM)

Nontuberculous Mycobacteria (NTM) are species of myco- bacteria sometimes called “mycobacteria other than tuberculosis” (MOTT), “atypical”, “environmental” or “opportunistic” mycobacteria. NTM species include all mycobacterial species except those that cause TB. Some examples of NTM are *M. avium* complex (MAC), non-pigmented rapid growers (e.g., *M. abscessus*), *M. fortuitum*, *M. chelonae*, *M. goodii*, *M. kansasii*, *M. malmoense* and *M. xenopi*. These organisms may present with symptoms suggestive of pulmonary TB. They appear to be acquired from the environment and occur naturally in water, soil and food and also in association with animals. They are generally non-contagious and their transmission from person to person is extremely rare. Contact follow-up is not necessary. They are not reportable diseases in Ontario.

A positive NTM culture in an asymptomatic patient is not an indication for treatment.

Treatment of NTM disease is lengthy and complex and is determined on a case by case basis, and where indicated benefits only the patient. Management by a specialist is recommended. NTM are resistant to a wide range of anti- microbial agents and the resistance develops rather readily hence single drug therapy must be avoided. Treatment is not mandatory and is determined on a case-by-case basis. Decisions to treat NTM should be based on clinical presentations and demonstrating three consecutive sputum specimens that grow the organism.

Drugs for the treatment of NTM are not supplied through Public Health and are not provided free-of-charge.<sup>38</sup>



# In-Hospital and Institutional Management of TB

TB is largely managed in the outpatient setting but TB disease is often diagnosed in hospital. When hospitalization is indicated, patients should be managed in facilities with adequate airborne precautions.

Indications for Hospitalization:

- To investigate or treat symptoms of TB, e.g., life-threatening hemoptysis
- To establish a treatment regimen in patients with significant adverse events or known drug resistance
- To manage associated medical conditions complicating the management of TB such as HIV infection or congestive heart failure
- To provide airborne isolation if this cannot be provided in the community as an outpatient
- As involuntary admission for non-compliant patients.

## 11.1 Preventing Spread of TB

It is essential that all facilities have a TB management program. These programs should be supported at the highest administrative level. The goal of the TB management program is to prevent TB transmission to HCWs, patients and visitors.

The recommendations involve a hierarchical approach to infection prevention and control measures, including:

- Administrative controls, such as rapid isolation in an airborne infection isolation room (AIIR), diagnosis and treatment of patients with suspected or active TB
- Environmental (engineering) controls, such as improved ventilation in patient care areas and the use of ultraviolet germicidal irradiation (UVGI) and high-efficiency particulate air (HEPA) filters and

- Personal protection controls, such as the use of respirators, i.e., fit-tested N95 masks.

In healthcare facilities where TB is uncommon and airborne infection isolation rooms (AIIR) are not available, there should be at least one separate, well-ventilated area or single room with the door closed, away from high-risk patients, where patients can be kept in isolation until they are transferred. Patients should wear a procedure/surgical mask and staff should wear a fit-tested N95 mask.

Early identification of patients with suspected TB is essential for early diagnosis, treatment and prevention of transmission of TB disease.

The presence of cough of two to three weeks duration with or without weight loss and fever in a person belonging to one of the risk groups listed below should prompt a thorough investigation to rule out TB:

- People with a history of active TB
- Persons born in, or history of travel to, areas where TB is endemic
- Indigenous Canadians residing in communities with high rates of TB
- Staff and residents of homeless shelters (current and former)
- The urban poor
- Staff and inmates of correctional facilities and persons who have a history of previous incarceration
- Injection drug users
- Persons with HIV
- People born in Canada or other low incidence countries prior to 1966
- HCWs serving at-risk groups.

- Suspected or confirmed infectious TB patients should **immediately** be placed in appropriate airborne (isolation) precautions. For the recommended steps for isolation for suspected or confirmed active respiratory TB diseases in hospital, see Figure 12.

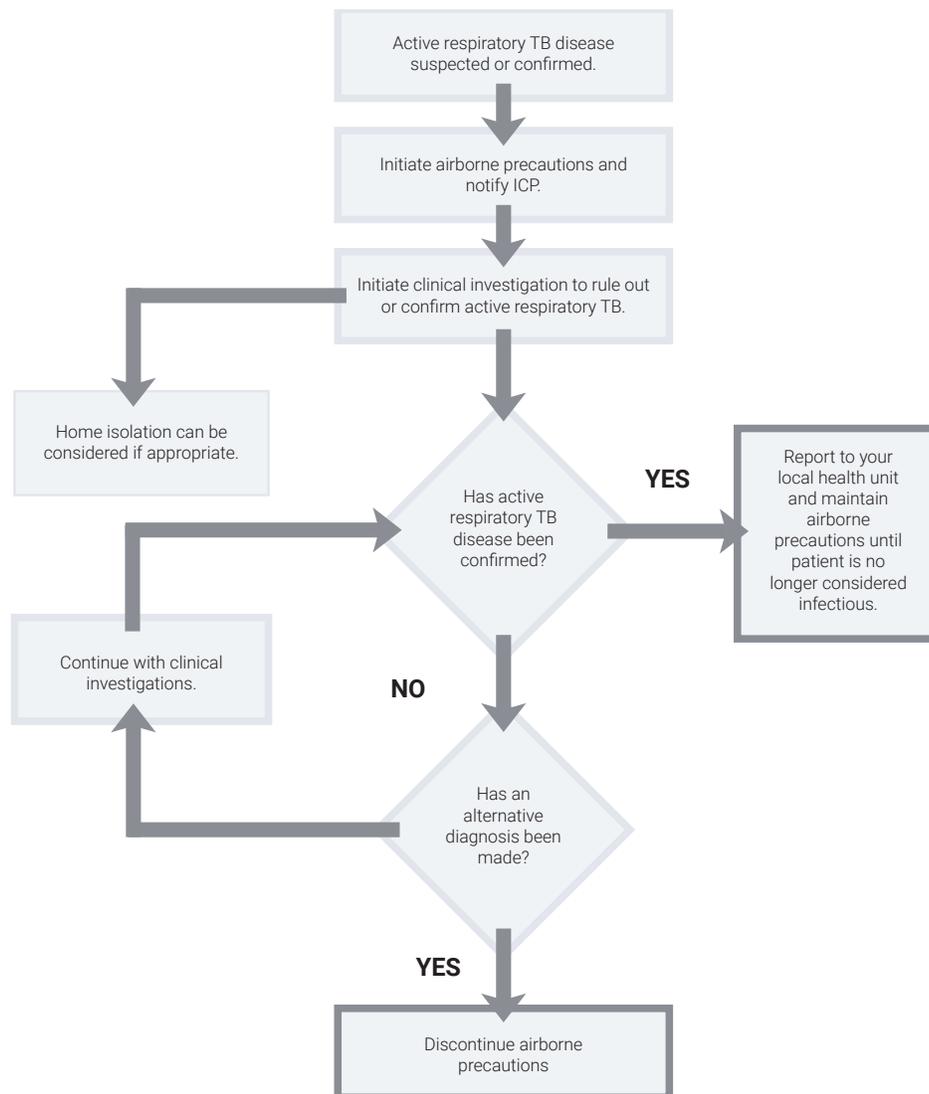
## 11.2 Preventing TB Transmission in Hospitals

A person with suspected or confirmed respiratory TB should wear a procedure/surgical mask as a source control measure to prevent the spread of TB, until the patient can be placed in an airborne infection isolation room (AIIR).

- Once airborne precautions have been initiated, the patient should stay in AIIR until isolation is discontinued by the infection prevention control program (see Criteria for Discontinuing Isolation)
- Patients in AIIR can leave the room with a surgical/procedure mask on to attend medical appointments or diagnostic tests only
- HCWs in hospitals must wear fit-tested N95 respirators with patients suspected or with confirmed TB disease when transferring patients and providing direct patient care until respiratory TB has been ruled out. Visitors should be provided with an N95 to mask to wear while in the room with the patient.

For detailed information on infection prevention and control in institutional settings, refer to Tables 5 & 6 in Chapter 15, *Canadian TB Standards 2013*.

**FIGURE 12** Recommended Steps for Isolation for Suspected or Confirmed Active Respiratory TB Disease in Hospital (Includes inpatient in correctional facilities.)



Canadian Tuberculosis Standards, 7<sup>th</sup> Edition. Public Health Agency of Canada, 2013. Figure 1. Reproduced with permission from the Minister of Health, 2015.

## 11.3 Discontinuation of Airborne Precautions

Criteria for discontinuation of precautions should never be based on a fixed interval of treatment (e.g., two weeks) but rather on evidence of clinical and bacteriological improvement and evidence of the adequacy of the treatment regimens. Airborne isolation precautions should be continued until patients are highly likely to be non-infectious. Sputum specimens can be collected on the same day, a minimum of one hour apart.

### Criteria for Discontinuing Airborne Isolation Precautions

#### 1. SUSPECTED TB CASES:

- Three successive sputum samples (spontaneous or induced) are smear-negative, unless pulmonary TB is still strongly suspected on clinical and radiological findings.

#### 2. CONFIRMED TB PATIENTS WHO ARE AFB SMEAR POSITIVE:

- At least two weeks of effective multi-drug therapy based on the patient's phenotypic DST pattern AND
- 3 consecutive negative AFB sputum smears AND
- Evidence of clinical improvement.

#### 3. CONFIRMED TB PATIENTS WHO ARE AFB SMEAR NEGATIVE AT DIAGNOSIS:

- At least two weeks of effective multi-drug therapy based on the patient's phenotypic DST pattern AND
- Evidence of clinical improvement.

### Cleaning of Rooms

Staff should wear a fitted respirator (N95) to enter and clean a room still in use to isolate a client with TB infection. A room previously occupied by a patient with respiratory TB disease including an Airborne Infection Isolation Room (AIIR) that has been ventilated for the appropriate amount of time as shown in Table 5 below can be entered and cleaned routinely.

**Table 5:** Time Needed (By Number of Air Exchanges Per Hour) to Remove Airborne Microorganisms After Generation of Infectious Droplet Nuclei Has Ceased.

Air changes per hour	Minutes required for removal of airborne microorganisms	
	99 per cent removal	99.9 per cent removal
2	138	207
4	69	104
6	46	69
12	23	35
15	18	28
20	14	21
50	6	8

Adapted from CDC recommendations [CTS 7th Edition, p383]

## 11.4 Discharge Planning

Discharge planning should begin as soon as the diagnosis is made, and in collaboration with the local public health unit.

Most individuals with active TB can be successfully treated as outpatients. Infectious patients can be discharged as long as they can be safely isolated at home. They need to remain in isolation until the criteria for discontinuing isolation are met as listed above. Isolation in the home is only appropriate if there are no

children under the age of five or persons with immunocompromising conditions (e.g., HIV) residing in the household, unless those people are already receiving treatment for TB disease or LTBI. Also, household air must not circulate to other housing units, (e.g., older apartment buildings). Infectious TB patients should not be discharged to congregate settings such as a rooming house, shelter, long-term care facility or group home.

Collaboration with the local public health unit is essential for the patient to be successfully transitioned into the community.

Prior to discharge, the following steps should be arranged for community transition:

- Notify your local Public Health department in order to implement DOT and follow-up
- Confirm outpatient appointment with the provider who will manage the patient
- Provide the patient with the healthcare provider's phone number in case complications arise
- Give a sufficient supply of TB medications until the next appointment. All TB medications are free through Public Health – check with your local health department
- For isolation in the home, review isolation precautions with the infectious patient and provide surgical masks for the patient
- Assess if the patient requires absentee documentation for school/employer.

## 11.5 Personal Controls

The level of routine personal controls should correspond to the following risk classifications:

**Risk classification:** healthcare workers (HCW).<sup>39</sup>

### HIGH-RISK ACTIVITIES:

- Aerosolizing procedures, e.g., sputum inductions, bronchoscopy, autopsy, morbid anatomy and pathology examination and designated mycobacteriological laboratory procedures.

### INTERMEDIATE-RISK ACTIVITIES:

- Work requiring regular direct patient contact on units (such as emergency departments) where patients with TB may be present
- Any work involving prolonged periods in the rooms of patients with respiratory TB.

### LOW-RISK ACTIVITIES:

- Work requiring minimal direct patient contact on units with active TB patients, i.e., medical records, administration, maintenance, etc.
- Work on units where patients with respiratory TB are unlikely to be present.

## Tuberculin Skin Testing (TST)

The importance of proper baseline tuberculin skin testing upon starting work for all HCWs cannot be overemphasized. Facilities are strongly encouraged to meet the minimum standard of baseline two-step upon hire and post-exposure tuberculin skin testing for all employees. Routine repeat skin testing programs should be implemented according to the risk classifications. If a HCW has a documented prior two-step TST, a single TST only should be given. Do not repeat the TST if there is a documented previous positive skin test. Workers who require further medical assessment should be seen by a healthcare provider experienced in the interpretation of TSTs and the treatment of LTBI.

Screening of HCWs is usually completed prior to starting employment. Routine follow-up (CXR's/symptom review) of HCWs in low risk settings with previous positive TSTs or previous treatment for LTBI is generally not recommended unless there are significant risk factors for developing active TB disease. If there are significant risk factors, follow-up during the first two years (6/12/24 months) is recommended. Similarly, this would also apply to individuals with recent re-exposure to TB that are already known to have LTBI.

## Interferon-Gamma Release Assays (IGRA)

The use of IGRA for repeated testing of HCWs is not recommended but it may be useful for confirming a positive TST in a low-risk HCW who is found to be TST positive on baseline TST pre-employment testing. See Section 5 for recommended use of IGRAs.

## TST Following Unprotected Exposure

All healthcare facilities must have a process in collaboration with Public Health to contact and assess all workers, including contractors, volunteers and agency workers who had unprotected exposure to infectious TB. If appropriate, a single TST may be performed soon after the contact is identified. If this TST is negative then a second TST is performed no sooner than eight weeks after the last known exposure to detect TST conversion.<sup>40</sup>

# The Role of Public Health in TB Prevention and Control

Public Health has many roles in decreasing the morbidity, mortality and transmission of TB in our communities. This work is carried out under the mandate of the Provincial Health Protection and Promotion Act (HPPA) and includes:

- Case management for all individuals with TB to ensure access to high-quality TB care and treatment
- Provision of publicly-funded TB drugs at no charge to the patient for treatment of active or latent TB
- Identification, assessment, and management of contacts of active TB
- Identification and management of individuals with LTBI (*refer back to previous chapter LTBI*)
- To carry out post-landing Medical Surveillance for individuals identified by Immigration, Refugees and Citizenship Canada (IRCC)
- To provide education on TB infection control, screening and other issues as needed
- Epidemiologic surveillance of TB.

## 12.1 Case Management

Public Health legislation provides local health units with the authority to ensure that suspected or confirmed cases of active TB receive timely diagnosis and treatment. The fundamental purpose of case management is to ensure access to high-quality TB care, completion of treatment and to minimize the risk of additional TB transmission.

A Public Health case manager investigates suspected and confirmed cases of active TB and coordinates diagnostic services, infection control measures and treatment. Each person with active TB should be educated about

TB treatment including the potential for side effects. Public Health monitors for side effects and adherence to medications, provides support and problem-solving for psychosocial issues related to TB, and can also supervise therapy with the use of DOT. In addition to the above, the case manager assists the treating healthcare provider by identifying or providing any update on the cases' progress or assessment findings.

The case manager also identifies and follows up with potential close contacts of individuals with infectious TB to ensure they are assessed for active TB and offered TB prophylaxis if it is determined that they have LTBI.

## 12.2 Provision of Medication

All TB medications are provided by the Ministry of Health and Long-Term Care at no cost for the treatment of both active and latent TB. This includes both first-line and second-line TB drugs. Each health unit has their own mechanism by which these medications are provided to the patient. Medication for non-mycobacterium TB is not covered. Contact your local Public Health unit for information on accessing free TB medications for your patient.

## 12.3 Directly Observed Therapy (DOT)/Video-Directly Observed Therapy (VDOT)

Adherence to an effective treatment regimen is essential to cure TB, reduce the risk of transmission and prevent the development of drug-resistant strains. The best way to ensure adherence to treatment is to observe a person

with TB taking all of their prescribed medications. In Ontario, DOT is available through Public Health. Contact your local health unit for the availability and criteria of VDOT.

The Purpose of DOT/VDOT is not only to observe the person taking their medication but to also monitor for side effects of the drugs, watch for signs indicating relapse, ensuring the person attends appointments, educate about TB and provide ongoing support and assistance for other issues (e.g. housing, welfare). In some jurisdictions, incentives and enablers (e.g. bus tickets, food supplements and clothing) may be available for persons on (V)DOT.

All persons with active TB disease should be assessed for (V)DOT therapy; persons on intermittent regimens **must** receive (V)DOT. At a minimum, individuals with known risk factors for non-adherence and/or whose TB has major individual and public health implications if they fail treatment should be considered for (V)DOT throughout their treatment.

## 12.4 Limitations on Activities While in Isolation

The infectious patient should NOT return to work, school, or usual social activities, nor have visitors. The patient should also refrain from going into any other indoor environment or using public transportation. The patient should be instructed to wear a mask while attending essential healthcare appointments. The patient can walk outdoors without a mask provided they are not in close contact with others. Public Health and the treating healthcare provider will determine when these precautions can be discontinued.

## 12.5 Resumption of Normal Activities

Isolation may be discontinued when the patient has clinical evidence of improvement, three consecutive negative sputum smears for AFB and there is evidence of adherence to at least two weeks of effective therapy when drug-resistant TB is not suspected.

The decision regarding when a person with active respiratory TB can resume normal activities, i.e., return to school or work, must be made in consultation between Public Health and the treating healthcare provider.

## 12.6 Non-Adherence to TB Treatment

It can be difficult for patients to adhere to the prolonged treatment required for TB disease, particularly as symptoms resolve. However, when individuals fail to take their medications as prescribed, they are at risk of infecting others, relapsing and/or developing drug-resistant TB. If a person is not on (V)DOT, it is important for Public Health to maintain regular contact to ensure adherence.

Other methods that Public Health will use to monitor adherence include:

- Contacting the treating healthcare provider/clinic on a regular basis to ensure that the person has kept their follow-up appointments and that they are making appropriate clinical improvement (e.g. sputum conversion, x-ray has improved)
- Conducting a home visit to assess compliance
- Carrying out pill counts.

It is also important to address any barriers to adherence when possible, such as the need for convenient appointment times, or assistance with transportation to appointments, etc. If measures to achieve treatment adherence have failed and the patient is deemed to be a public health risk, the Medical Officer of Health has the legal authority under the HPPA to order the patient to comply with treatment and/or isolation. Public Health should be contacted when a healthcare professional has concerns regarding lack of adherence and cooperation from a patient with active TB, or if an infectious TB patient intends to travel by public transport, (e.g. airplane, train).

If necessary, the Medical Officer of Health can apply to provincial court for a detention order, whereby a TB patient may be detained in hospital for treatment in order to protect the public.

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See Sections 22 and 35 of the HPPA at: [http://www.e-laws.gov.on.ca/html/statutes/english/elaws\\_statutes\\_90h07\\_e.htm#BK72](http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_90h07_e.htm#BK72)

## 12.7 Contact Follow-Up

**Contact follow-up is the responsibility of Public Health.** The purpose of contact follow-up is to identify secondary cases promptly and offer LTBI treatment to contacts who are infected.

Usually only respiratory TB is infectious. Contact follow-up should be carried out for both sputum smear-negative and smear-positive cases. Priority for contact follow-up is based on: infectiousness of the source case, the extent of exposure and the susceptibility of those exposed (i.e. immunologic vulnerability). Thus, the greatest effort is to reach contacts that are most at risk of being infected and/or most at risk of developing active TB disease if infected. The identity of the index case remains confidential throughout the contact investigation.

Contact assessment involves TB history and symptom assessment. An initial skin test may be performed (if no contraindications); if this is negative it is repeated no sooner than eight weeks after the last exposure to the infectious case. Contacts who are symptomatic or have a positive TST should have a chest x-ray (and sputum TB testing if symptomatic). Once active TB has been ruled out, LTBI treatment should be offered unless there are contraindications.

Contacts deemed to be at risk are most often referred for follow-up to their own healthcare provider. However, in group settings such as schools, shelters for the homeless, or workplaces, public health staff may hold screening clinics to facilitate the follow-up of large numbers of people. Individuals who test positive during these screening clinics are referred to their healthcare provider for further assessment and management. Contact follow-up in hospitals is undertaken in collaboration with the hospital IPAC and occupational health programs. TST is not recommended as a primary contact assessment tool for contacts 65 years of age and over. When the index case has drug-resistant TB, contacts should be referred to a TB specialist who has experience in dealing with drug-resistant TB.

## 12.8 Investigation and Management of TB Outbreaks

TB outbreaks are rare but may occur in marginalized communities and in crowded/congregate settings. TB outbreaks generally last for several years; response and control are major undertakings requiring additional resources and close collaboration between Public Health and healthcare providers. Community outreach and education are especially important in the context of an outbreak.

Genotyping (DNA fingerprinting to identify matching strains) of TB specimens can be conducted by the Ontario Public Health Laboratory (PHOL) to assist in identifying TB transmission.

## 12.9 Patient, Family and Community Education

Myths, misinformation and stigma about TB continue to present problems. Common myths include:

- I will be deported if I am found to have TB
- People who have TB are dirty, poor or immoral
- TB is usually fatal and,
- TB is not found in Canada.

It is thus very important for the individual with newly diagnosed infection or active disease and their families/contacts to receive accurate and timely information. Education should begin at the time of diagnosis and continue until all of the patient's questions have been answered and he/she is knowledgeable about:

- The cause of tuberculosis
- How to prevent transmission to others
- Side effects to watch for with anti-tuberculosis medication
- Why prolonged treatment is required and why it is important to take anti-tuberculosis medication as prescribed (adherence to therapy)

Health promotion activities extend from the TB client and family to the community and can include provision of resources, presentations, acknowledgment of World TB Day (March 24) and collaboration with organizations to develop policies and initiatives for topics such as TB-HIV co-infection.

## 12.10 Immigration Medical Surveillance

Canada, with an overall TB disease rate of 4.8 new cases per 100,000 (in 2016), is considered a low TB incidence country. The majority of reported cases in Canada (70 per cent) occur in the foreign-born population. Canada accepts approximately 250,000 new permanent residents from countries with high TB incidence each year. Approximately 50 per cent of these have latent TB infection. The strongest predictors of active TB

development in the immigrant populations are: TB rate in the country of origin, refugee claimants, presence of underlying medical comorbidities, and amount of time lived in Canada post-arrival and recent travel to high TB incidence countries.

All immigrant applicants to Canada and visitors staying more than six months must undergo an Immigration Medical Examination (IME). In most cases, the IME is carried out prior to arrival in Canada. It includes a comprehensive medical history, targeted physical examination guided by the history and available laboratory data, and other investigations considered relevant, including chest x-ray for all individuals 11 years and older. The IME does not include a TST, as the goal is only to detect active, infectious TB. When an individual applying to immigrate is found to have active TB they must complete a course of treatment consistent with Canadian standards and provide proof of completion.

Applicants identified as having inactive (LTBI) or previously treated TB are permitted to enter Canada but may be placed under medical surveillance by Immigration, Refugees and Citizenship Canada (IRCC) and referred to provincial public health authorities. The applicant must report to or be contacted by a public health authority for post-landing surveillance within 30 days of landing.

The medical surveillance assessment includes symptom screening, physical examination and a chest x-ray to look for active disease. If any of these is positive, sputum samples should be submitted for

TB testing. If no active disease is found, testing for LTBI (TST or IGRA), unless previously known positive, should be completed. Those identified as having LTBI should be offered treatment.

Discharge from medical surveillance follow-up should include education about:

- The risks of potential reactivation
- Seeking medical attention promptly should symptoms arise and
- Informing their healthcare provider of their history of medical surveillance for TB.

## 12.11 TB Diagnostic and Treatment Services for Uninsured Persons (TB-UP) Program

TB-UP is a program funded by the MOHLTC and offered only in Ontario. It ensures that persons who are not covered by OHIP, Interim Federal Health (IFH) or any other provincial, territorial or private health insurance plan can be assessed and/or treated for active TB, and for contact assessment. Contact your local Public Health Unit to enroll someone prior to providing service. TB-UP will not issue retroactive payments. TB-UP is intended mainly for outpatient care but may cover some inpatient services directly related to the diagnosis and/or management of TB (13).

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Canadian Tuberculosis Standards, 7th Edition, Public Health Agency of Canada and the Canadian Lung Association/ Canadian Thoracic Society, 2013©, Chapters 5, 12 & 13



# Summary

Neither healthcare providers nor Public Health officials can achieve control of TB without each other. It is important that we work together.

## **Additional TB Resources:**

The Lung Health Foundation has useful TB resources for healthcare providers and the public.

To order, call 1-888-344-LUNG (5864).

[hcp.lunghealth.ca/patient-resources](http://hcp.lunghealth.ca/patient-resources)

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