# Alberta Public Health Disease Management Guidelines

Tuberculosis

Alberta

This publication is available online at https://open.alberta.ca/publications/tuberculosis-tb

For further information on the use of this guideline contact:

Health.CD@gov.ab.ca

Health and Wellness Promotion Branch

Public Health and Compliance Division

Alberta Health

**Tuberculosis** | Alberta Health, Government of Alberta

# Contents

# Case Definition

## Confirmed Case (Active Disease)

*A confirmed case can be either of the following.*

### Laboratory Confirmed Case [(A)]

- A person on whom, laboratory testing has detected *Mycobacterium tuberculosis* (MTB) complex on culture, specifically *M. tuberculosis, M. africanum, M. canetti, M. caprae, M. microti, M. pinnipedii* or *M. bovis* (excluding BCG strain)

OR

- A person on whom, laboratory testing has detected MTB complex (excluding *M. bovis*) by nucleic acid amplification testing (NAAT) AND who meets the clinically diagnosed case definition

*Additionally, all laboratory confirmed cases can also be further categorized based upon susceptibility and resistance testing.* [(1)]

  - Multi-drug resistant (MDR) TB: strains resistant to at least isoniazid and rifampicin
  - Pre-extensively drug resistant (pre-XDR) TB: fulfill MDR TB definition and resistant to a fluroquinolone
  - Extensively drug resistant (XDR) TB: fulfill pre-XDR TB definition and resistant to one additional second line drug (i.e. levofloxacin, moxifloxacin, bedaquiline, linezolid)

### Clinically Confirmed Case [(B)]

- A person for whom microbiological confirmation is absent and who meets at least two or more of the following criteria:
  - Signs or symptoms clinically compatible with active TB (pulmonary or extrapulmonary)
  - diagnostic imaging compatible with active TB
  - pathologic evidence of active TB (e.g., necrotising granuloma on histology)
  - post-mortem evidence of active TB
  - favourable response to therapeutic trial of anti-TB drugs
  - epidemiological characteristics of case (e.g., foreign-born, recent contact, Indigenous)

## Possible Case

High index of suspicion (clinical and/or epidemiological) of TB in whom empiric treatment is being contemplated

[(A)] Refer to the Public Health Laboratories (ProvLab) Guide to Services for current specimen collection and submission information.
[(B)] In Alberta, determination of a clinical case of TB diagnosis is undertaken by specialist physicians within the Alberta TB Control Program.

# Case Classification

## New Case

No documented evidence or history of previously active TB

## Re-treatment Case [C]

Documented evidence or adequate history of previously active TB that was declared cured or treatment-completed by current standards and at least six months have passed since the last day of previous treatment[D] and diagnosed with a subsequent episode of TB that meets the confirmed (laboratory or clinical) TB Case definition.

**OR**

- Documented evidence or adequate history of previously active TB that cannot be declared cured or treatment-completed by current standards and inactive[E] for six months or longer after the last day of previous treatment[D] and diagnosed with a subsequent episode of TB which meets the active TB case definition

# Outbreak Case Definition

*This definition is provided for reporting purposes.*

- During and because of a contact investigation, 2 or more of the identified contacts are diagnosed as secondary cases of active TB (confirmed by genotyping or whole genome sequencing (WGS) if available

OR

- TB cases occurring within a 12 month period of time that are discovered to be epidemiologically linked (and matched by genotyping/WGS if available), but the linkage is recognized outside of a direct contact investigation. [F(2)]

---

[C] Prior to 2008 in Canada, re-treatment cases were known as relapsed cases.

[D] If less than six months have passed since the last day of previous treatment and the case was not previously reported in Canada, report as a re-treatment case. If less than six months have passed since the last day of previous treatment and the case was previously reported in Canada, do not report as a re-treatment case. Submit an additional *Treatment Outcome of New Active or Re-treatment Tuberculosis Case* form at the end of treatment.

[E] Inactivity for a respiratory TB case is defined as three negative TB smears and cultures with a three-month duration of stability in serial chest radiographs or in the event of overseas screening, the absence of mycobacteriology and a six-month duration of stability in serial chest radiographs. Inactivity for a non-respiratory TB case is to be documented bacteriologically, radiologically and/or clinically as appropriate to the site of disease.

[F] When determining what cases are included in the outbreak, use the earliest diagnosis date as a reference point.

# Reporting Requirements

## Health Practitioners

Health practitioners shall notify the Medical Officer of Health (MOH) or designate in the zone where a patient resides by Fastest Means Possible (FMP):

- all laboratory and clinically confirmed cases OR
- possible cases who have initiated treatment with anti-TB drugs

## Laboratories

All specimens must be forwarded to Alberta Precision Laboratories Public Health Laboratory (ProvLab) for smear and culture identification and susceptibility testing.

The ProvLab must report positive smear and culture results by FMP via direct voice communication to Alberta Health Services (AHS) TB Services (TBS) (geographically dependent)[G] If the Individual is determined to reside in a First Nations Community, Central TBS then notifies First Nations and Inuit Health Branch (FNHIB) MOH or designate.

Any rifampicin resistance (RR) detected in specimens should be notified by FMP via direct voice communication to the medical director of the TB Service that serves the case's geographic location.

## Alberta Health Services (AHS)

- AHS TBS is responsible for reporting and follow-up and shall direct AHS public health staff in investigation activities.
  - All laboratory confirmed and clinically confirmed and possible cases that may be cause for community concern (e.g., smear positive case with multiple contacts and high probability of transmission) and outbreaks shall be reported to the Chief Medical Officer of Health (CMOH) (or designate) by FMP.
  - All data points for reportable cases and their outcomes are provided to Alberta Health for surveillance and reporting purposes. [H]
- The MOH (or designate) shall notify the appropriate TB Specialist (AHS Provincial TB Consultant; or Medical Director, Edmonton or Calgary TB Clinics) by FMP of case reports for all remaining clinically confirmed or possible cases. Notification will include:
  - name of individual (full name and any aliases if known),
  - date of birth,
  - country of birth,
  - personal health number,
  - address of individual,
  - phone number of individual,
  - date of any tests (including AFB specimen collection, radiographic investigations, etc.,),
  - any identified high risk medical conditions, and
  - signs and symptoms consistent with active TB.

---

[G] The Medical Director of the Edmonton TB Clinic (or designate) if the individual lives in the Edmonton Zone, or
The Medical Director of the Calgary TB Clinic (or designate) if the individual lives in the Calgary Zone, or
TB Medical Consultant of the Centralized TB Program (or designate) if the individual lives outside of Calgary/Edmonton Zones or if the individual lives in a First Nations Community.

[H] Reportable data points are listed on the Public Health Agency of Canada reporting forms: Active Tuberculosis Case Report Form and Treatment Outcome of a New Active or Re-treatment Tuberculosis Case.

# Additional Reporting Requirements

## Citizenship and Immigration Canada

- All immigration applicants, refugees or students who plan to remain in the country for more than six months, as well as certain visitors, are required to undergo an immigration medical at their point of application.
  - Those applying from outside of Canada, with evidence of active disease, are denied entry until treatment has been completed.
  - Individuals who do not have active disease but have a past history of TB or those who have evidence of past disease on their chest x-ray are reported to AHS TBS for medical surveillance. As a condition of entry, these individuals are required to report to or be contacted by a public health authority within 30 days of their arrival in Canada.
  - Anyone with a high risk medical condition[I] is further screened at their immigration medical with a tuberculin skin test (TST) or interferon gamma release assay (IGRA) and all positive reactors are also referred for medical surveillance to AHS TBS.

[(I)] High-risk medical condition has been defined as: i) close contacts of active infectious pulmonary TB case diagnosed within the last 2 years, ii) HIV/AIDS, iii) advance chronic renal failure and end stage kidney disease (ESRD) with a GFR less than 30 ml/min, iv) history of treatment for head/neck cancer in the last 5 years, v) solid organ or bone marrow transplant recipient on immunosuppressant therapy.

# Epidemiology

## Etiology

*Mycobacterium tuberculosis* is the etiologic agent of TB in humans.[3] The organism is a slightly curved bacillus, 0.2–0.5 micrometres in diameter and approximately two to four micrometres in length.[4] Mycobacteria are aerobic, non-spore forming and non-motile.[3] Growth rates are very slow, with a doubling time of 15–20 hours. [3,5]

## Clinical Presentation

Active TB (when the bacilli are actively multiplying) predominantly presents as respiratory disease, although almost any organ system can be infected.[5–7] Clinical presentation varies depending upon the site of disease. Symptoms usually begin insidiously and progress over a period of many weeks or months prior to diagnosis.

Systemic symptoms consistent with TB include:

- weight loss,
- fever,
- night sweats.[4]

Symptoms of respiratory TB include:

- persistent cough (of three weeks or more),
- sputum production, sometimes with hemoptysis,
- chest pain (TB pleurisy).[4]

Symptoms of non-respiratory TB are dependent on the site affected.

- TB of the spine might produce back pain.
- TB of the kidney may cause flank pain, frequency and dysuria.
- TB of the lymph nodes can result in lymphadenopathy (which may be painful if enlargement occurs rapidly).[4,6]

Individuals can also have concurrent involvement of multiple sites.

## Diagnosis

Definitive diagnosis of TB disease is made by isolation of the MTB in culture. As such, efforts to obtain a microbiological diagnosis is preferred when possible.[7]

  - As MTB grows slowly, it can take up to six weeks to show definitive results. However, molecular detection by NAAT in parallel with clinical symptoms is also used to diagnose disease. Further, drug susceptibility testing (DST) should be routinely performed for all first positive culture isolates. Any resistance detected in specimens shall be notified by FMP via direct voice communication to the medical director of the TB Service that serves the case's geographic location.

As TB can infect any tissue, any symptom of infection is reflected in site of disease, which would guide further investigation i.e. urinary symptoms prompt urine specimen collection.[7–9]

When it is not possible to safely obtain a specimen for culture, a clinical diagnosis of TB is made for a minority of cases on the basis of appropriate clinical and/or radiological and/or pathological presentation as well as treatment response. **Epidemiological links can also support clinical diagnosis, notably in children.**[6,10–12]

## Treatment

**NOTE:** TB treatment regimens are coordinated by AHS TBS. For more information, refer to the AHS TB Clinical Operations Manual and the current Canadian TB standards.

Fundamental goals for treatment of active TB disease are:

- Reduce contagiousness, morbidity and mortality by rapid killing of bacilli,
- Prevent emergence or worsening of drug resistance, and
- Prevent relapse of disease and achieve long-lasting cure. [13]

Medication used to treat and prevent active TB disease is provided at no cost to the patient.

A combination of medications provided over several months or longer are required to cure active TB. Specific treatment regimens are dependent upon disease site, drug susceptibility and patient tolerance. In Alberta, Directly Observed Treatment (DOT) is the standard of care. Traditional (in-person health provider) and variations of DOT (video, community based etc.) and other approaches are used as a way to monitor treatment adherence and achieve treatment completion. (R. Cooper, personal communication) To encourage adherence, patient centered care is critical to achieving treatment goals and may require use of a combination of strategies including treatment incentives or other supports. [14–17]

## Reservoir

The reservoir for *M. tuberculosis* is humans whereas animals are the primary reservoir for *M. bovis.* [3–5]

## Transmission

Infection of *M. tuberculosis* is transmitted almost exclusively by inhalation of airborne tubercle bacillus in droplet nuclei form. Droplet nuclei are created by individuals with active TB through breathing, coughing, sneezing, singing and other forceful expiratory efforts. Duration of exposure needed for transmission is usually prolonged, but in highly infectious individuals, duration can be as short as a few minutes. Person-to-person transmission of *M. tuberculosis* is affected by the following:

- characteristics of the illness in the source case (i.e. presence of cough)
- characteristics of the person(s) exposed (i.e. presence of immunocompromising conditions)
- environment where exposure occurs (i.e. crowded home). [2,5]

The usual route of transmission of *M. bovis* is in unpasteurized milk or milk products from a diseased animal. [4,8]

## Incubation Period

Detection of infection can occur 2 – 10 weeks after exposure. Both the TST and IGRA are used to detect latent TB infection, although the IGRA has a higher specificity than the TST in those who have received BCG vaccination. An individual is at highest risk of disease development in the first 2 years following infection. Approximately 5-10% who are infected will develop active TB disease in their lifetime. [5,8,12]

## Period of Communicability

As long as viable tubercle bacilli are being aerosolized, untreated or inadequately treated individuals with active respiratory disease are contagious. Adequate treatment with drugs renders most individuals non-infectious within a matter of weeks. [2,4,5]

Young children (less than 11 years) with active pulmonary TB often have pauci-bacillary disease and considered non-infectious. [18]

Non-respiratory TB is not usually infectious. [6]

## Host Susceptibility

All persons are susceptible to this disease if exposed, however, the degree of vulnerability varies with personal health status and history.[5] Previous TB disease does not confer immunity, although risk of repeat disease incident after re-exposure is considered low.[5]

Several medical conditions place individuals, once infected, at moderate to very high risk of disease. These include:

- HIV infection (increasing risk as CD4 count falls),
- stage 4 or 5 chronic kidney disease, regardless of dialysis
- cancer (lung, sarcoma, leukemia, lymphoma or gastrointestinal),
- silicosis
- recent TB infection (≤ two years),
- abnormal chest radiograph – fibronodular disease or granuloma,
- transplant recipients
- receiving immunosuppressing treatment.
- diabetes
- heavy alcohol use (3+ drinks per day)
- heavy Tobacco smoker (1+ pack per day) [5,12]

**NOTE:** Bacille Calmette-Guérin (BCG) vaccine does not provide a high degree of protection against TB. [5,10,12] It is not currently recommended for routine use by the Canadian National Advisory Committee on Immunization (NACI) in Canada, however, it may be considered in geographic locations where TB epidemiology suggests merit. It is not offered in Alberta as part of public vaccination programs.

## Incidence

TB continues to be one of the world's leading infectious causes of death. [19] However, Canada is considered a low incidence country for TB with rates remaining relatively stable over the past decade. [20] In Alberta, incidence rates of TB disease is highest in persons born outside of Canada (14.1 per 100 000). Incidence of TB disease in Alberta's Indigenous populations is the lowest among prairie provinces at 4.8 per 100 000 but remains higher than the general Alberta population.[21]

See the Interactive Health Data Application here for more information.

# Public Health Management

## Key Investigation

Consult with AHS TBS regarding immediate management and risk of transmission.

- Confirm that the client warrants investigation
- Facilitate collection of all appropriate specimens i.e. 3 sputa samples or specimens from other sites and appropriate radiographic investigations (Chest X-ray, CT, MRI or others) should be performed
- HIV testing should be performed at the time of TB diagnosis or during the period of active TB disease.
- Obtain a history of illness, including onset date of signs and symptoms
- Determine potential source of infection
- Obtain travel history
- Determine whether there was a recent contact with a confirmed or possible case
- Assess for similar symptoms in other members of the household or close contacts
- Determine period of communicability
- Assess if high risk settings involved in exposure
- Identify household, close and casual contacts that may have had a significant exposure to the case during the period of communicability.

Active TB disease in a child is considered a sentinel event that should prompt investigation for a source case, typically an adult. [18]

## Management of a Case

Management of active TB disease in Alberta involves a partnership between the patient, their physician, the zone MOH and/or FNIHB MOH and the Alberta TB Program (including the public health program) that serves their geographic location.

- TBS provides provincially (Alberta Health) funded medications to all patients in the province; TBS also prescribes the treatment regime, monitors adherence with and response to treatment (all at no additional cost to patient).
- In addition to the fundamental goals for treatment, the Canadian TB standards include the goal “to optimize long term health by ensuring linkage to care for treatment of co-morbidities, and helping mitigate social and economic vulnerability”. [13]

## Recalcitrant Patients

- The *Public Health Act* (sections 39 through 52) authorizes detention of recalcitrant patients for medical examination, investigations, treatment and/or counselling.
- The CMOH [or designate (section 13(3) of the *Public Health Act*)] or MOH may issue a certificate to detain an individual who is believed to be infected and refuses or neglects to comply with examination and/or treatment.
- To issue a certificate of detention, there must be sufficient evidence of infection, or contact with an infected person and documentation of failure to comply with prescribed treatment and medical examination, or non-adherence for testing and/or treatment.

## Management of Contacts

- Determine the type of exposure, the setting and the time since last exposure
- Provide information about TB disease including signs and symptoms.

- A contact investigation is necessary for all potentially infectious active cases of TB. AHS TBS provides coordination and guidance for contact investigations for all cases of active TB disease. Goals of a contact investigation are to:
  - Identify and treat any secondary cases of disease
  - Identify and offer preventive therapy to any contacts considered at higher risk of disease progression (i.e. children up to and including 5 years old, immunosuppressed persons)
  - Identify contacts who have been infected but do not have active disease and offer preventive therapy. [2]

- Prioritize management of contacts based upon the following:
  - Infectiousness of index case
  - Extent of exposure
  - Vulnerability of contacts (i.e. immunosuppressed persons, children up to and including 5 years of age)

- A symptom inquiry should be completed for all contacts. For those with previous documentation of TB disease or infection, assessment should include chest X-ray and sputum collection.
- For contacts with no previous documentation of TB disease or infection, a TST or IGRA can be used up to 8 weeks post exposure to identify those with infection. [2,12]

## Outbreak Management

*See reporting section for definitions*

- In Alberta, TB outbreaks are reportable by FMP. Instructions for completing the form can be found here. The reporting form is available here.
- Genotyping/whole genome sequencing and social network analysis have been used to inform outbreak management.[2]

## Preventive Measures

Strategies needed to prevent ongoing TB cases include:

- Early detection and prompt diagnosis, isolation and treatment of individuals with active disease
- Infection protection and control measures in health care facilities and settings:
  - Administrative controls e.g. TB infection control plan
  - Environmental controls e.g. ventilation
  - Respiratory/personal protection controls e.g. training HCW on respiratory protection.[22]
- Identification and treatment of individuals with latent TB infection who are at higher risk of reactivation and recent infection.[22–24]
- Adequately addressing underlying social determinants of health can positively impact vulnerability, transmission and progression to active disease. [19]

# Screening for Latent TB Infection

In most individuals infected with MTB, host defenses are able to contain the bacilli and the infection remains latent. The goal of screening for LTBI is to identify individuals who are at increased risk for the development of active disease. Only those individuals who would be offered or benefit from preventative treatment should be screened. For use of Tuberculin in these populations, refer to the *Alberta Immunization Policy* biological page for Tuberculin. IGRA use is under direction by an internal medicine specialist or infectious disease expert, typically in consultation with the TB program.

Targeted testing can be beneficial in high risk populations including the following individuals who are:.

- Identified as contacts of infectious TB disease
- From countries with endemic rates of TB
- Living with medical co-morbidities
- People who inject drugs
- Underhoused
- Living in Indigenous Communities
- Health Care Workers
- Residents of correctional facilities
- Travelers to countries with endemic rates of TB
- HIV-positive individuals
- Long term care residents

Active TB disease should always be ruled out prior to any treatment for LTBI. [12,24]

# Appendix 1: Revision History

| Revision Date | Document Section | Description of Revision |
|---|---|---|
| November 2021 | General | • Updated Template<br>• Etiology, Clinical Presentation, Diagnosis and Treatment sections moved to Epidemiology<br>• Key Investigation section moved to Public Health Management (formerly called Control)<br>• Updated web links |
| | Reporting Requirements | • Updated to reflect current processes |
| | Incidence | • Surveillance weblinks added |
| September 2022 | Case Definition | • Updated to align with PHAC |
| | Reporting | • Clarification of reporting for those residing in First Nations Communities<br>• Addition of additional screening undertaken during immigration medical |
| | Diagnosis | • Discussion on role of molecular detection in diagnosing active TB<br>• Discussion of drug susceptibility testing<br>• Addition of “pre-XDR TB” to FMP |
| | Treatment | • Updated fundamental goals to align with Canadian TB Standards |
| | Incubation Period | • Updated to include role of Interferon gamma release assays |
| | Host Susceptibility | • Updated to include high and very high risk categories |
| | Incidence | • Updated to include more recent epidemiological information for Alberta<br>• Link to IHDA |
| | Public Health Management | • Clarify role of Alberta Health Services, Tuberculosis Services<br>• Importance of HIV testing of all Active TB Cases<br>• New section on Recalcitrant Patients<br>• New section on Outbreak Management<br>• Updated Preventive Measures<br>• New section on Screening for Latent TB Infection |

# References


1. WHO announces updated definitions of extensively drug-resistant tuberculosis [Internet]. [cited 2022 Sep 1]. Available from: https://www.who.int/news/item/27-01-2021-who-announces-updated-definitions-of-extensively-drug-resistant-tuberculosis

2. Rea E, Huard J, Lee R. Chapter 11: Tuberculosis contact investigation and outbreak management. Can J Respir Crit Care, Sleep Med [Internet]. 2022 Mar 24 [cited 2022 Mar 30];6(sup1):167–83. Available from: https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2037909

3. American Academy of Pediatrics. Tuberculosis. In: Commitee on Infectious Diseases, editor. Red Book: 2018-2021 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018. p. 829–53.

4. Fitzgerald DW, Sterling TR, Haas DW. Mycobacterium tuberculosis. In: Mandell GL, Bennett JE, Dolin D, editors. Mandell, Douglas and Bennett's principles and practice of infectious diseases. Phildelphia, PA: Churchill Livingston; 2015. p. 2787–843.

5. Long R, Divangahi M, Schwartzman K. Chapter 2: Transmission and pathogenesis of tuberculosis. Can J Respir Crit Care, Sleep Med [Internet]. 2022 Mar 24 [cited 2022 Mar 30];6(sup1):22–32. Available from: https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2035540

6. Barss L, Connors WJA, Fisher D. Chapter 7: Extra-pulmonary tuberculosis. Can J Respir Crit Care, Sleep Med [Internet]. Taylor & Francis; 2022;6(sup1):87–108. Available from: https://doi.org/10.1080/24745332.2022.2036073

7. Behr MA, Lapierre SG, Kunimoto DY, Lee RS, Long R, Sekirov I, et al. Chapter 3: Diagnosis of tuberculosis disease and drug-resistant tuberculosis. Can J Respir Crit Care, Sleep Med [Internet]. 2022 Mar 24 [cited 2022 Mar 30];6(sup1):33–48. Available from: https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2035638

8. Committe on Infectious Diseases (American Academy of Pediatrics). Tuberculosis. In: Red Book: 2018-21 Report of the Committee on Infectious Diseases. 31st ed. American Academy of Pediatrics; 2018. p. 829–53.

9. Todar K. Mycobacterium tuberculosis and tuberculosis. Textbook of Bacteriology. 2008.

10. Pearce EC, Woodward JF, Nyandiko WM, Vreeman RC, Ayaya SO. A systematic review of clinical diagnostic systems used in the diagnosis of tuberculosis in children. AIDS Res Treat. 2012;2012.

11. Barss L, Connors WJA, Fisher D. Chapter 7: Extra-pulmonary tuberculosis. Can J Respir Crit Care, Sleep Med [Internet]. 2022 Mar 24 [cited 2022 Mar 30];6(sup1):87–108. Available from: https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2036073

12. Campbell JR, Pease C, Daley P, Pai M, Menzies D. Chapter 4: Diagnosis of tuberculosis infection. Can J Respir Crit Care, Sleep Med [Internet]. 2022 Mar 24 [cited 2022 Mar 30];6(sup1):49–65. Available from: https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2036503

13. Johnston JC, Cooper R, Menzies D. Chapter 5: Treatment of tuberculosis disease. Can J Respir Crit Care, Sleep Med [Internet]. 2022 Mar 24 [cited 2022 Mar 30];6(sup1):66–76. Available from: https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2036504

14. Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2015.

15. CADTH. Direct Observational Therapy for the Treatment of Tuberculosis : Clinical Evidence and Guidelines. 2020.

16. Müller AM, Osório CS, Silva DR, Sbruzzi G, De Tarso Roth Dalcin P. Interventions to improve adherence to tuberculosis treatment: Systematic review and meta-analysis. Int J Tuberc Lung Dis. 2018;22(7):731–40.

17. Alipanah N, Jarlsberg L, Miller C, Linh NN, Falzon D, Jaramillo E, et al. Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. 2018; Available from: https://doi.org/10.1371/journal.pmed.1002595

18. Dwilow R, Hui C, Kakkar F, Kitai I. Chapter 9: Pediatric tuberculosis. Can J Respir Crit Care, Sleep Med [Internet]. 2022 Mar 24 [cited 2022 Mar 30];6(sup1):129–48. Available from: https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2043055

19. Tuberculosis E. in Canada FROM CANADA ' S CHIEF.

20. Tuberculosis: Monitoring - Canada.ca [Internet]. [cited 2022 May 2]. Available from: https://www.canada.ca/en/public-health/services/diseases/tuberculosis/surveillance.html

21. Public Health Agency of Canada. Tuberculosis in Canada 2008-2018. 2018;

22. Johnston BL, Ogunremi T, Defalco K, Savard N, Smith SW. Chapter 14: Prevention and control of tuberculosis transmission in healthcare settings. Can J Respir Crit Care, Sleep Med [Internet]. Taylor & Francis; 2022;6(sup1):205–28. Available from: https://doi.org/10.1080/24745332.2022.2043677

23. Greenaway C, Diefenbach-Elstob T, Schwartzman K, Cook VJ, Giovinazzo G, Njoo H, et al. Chapter 13: Tuberculosis surveillance and tuberculosis infection testing and treatment in migrants. Can J Respir Crit Care, Sleep Med [Internet]. 2022 Mar 24 [cited 2022 Mar 30];6(sup1):194–204. Available from: https://www.tandfonline.com/doi/full/10.1080/24745332.2022.2035544

24. Alvarez GG, Pease C, Menzies D. Chapter 6: Tuberculosis preventive treatment in adults. Can J Respir Crit Care, Sleep Med [Internet]. Taylor & Francis; 2022;6(sup1):77–86. Available from: https://doi.org/10.1080/24745332.2022.2039498