

CADTH POLICY INSIGHTS

Supports to Enhance Adherence to the Treatment of Latent Tuberculosis Infection

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Issue

Although Canada has one of the lowest rates of active tuberculosis (TB) in the world, its progress in eliminating the disease has plateaued since the 1980s.¹ Untreated latent tuberculosis infection (LTBI) is one of the major sources of active TB infection and transmission, and accounts for the majority of new TB cases in Canada.^{2,3} Given that the successful treatment for LTBI requires prolonged medication regimens, knowledge of and good adherence to treatment is recognized as a key factor in TB control. The causes of nonadherence are complex and may be influenced by factors such as economic barriers, available treatments, or occurrence of adverse reactions.

Purpose

This briefing note describes factors that influence low LTBI treatment adherence in Canada, summarizes evidence related to current practices that support adherence, and discusses potential implications and considerations to optimize the use of interventions aimed to support completion of LTBI treatment.

Key Messages

- There are currently no consistent and standardized formal mechanisms to support the monitoring and reporting of LTBI cases across Canada. As, LBTI accounts for most of the new TB cases in Canada, the monitoring and reporting of LTBI cases would be highly beneficial to our overall response in eliminating the disease.
- Implementation of existing interventions with promising efficacy in enhancing adherence to LTBI treatment (e.g., directly observed preventive therapy [DOPT] and video directly observed therapy) has proved difficult and their adoption in Canada's LTBI treatment adherence efforts has been limited.
- At a health-system level, inter-governmental and multi-sectoral collaboration is needed to ensure customized care that meets the needs, values, and resources of patients while addressing the underlying societal and personal factors that disproportionately affect certain populations who are at risk of nonadherence to LTBI treatment. It is essential that this collaborative approach fully engages Indigenous governments, leaders, and services and allows for respective leadership in many areas.

Background

Prevalence and Incidence of TB in Canada

- In 2017, there were 1,796 cases of active TB reported in Canada with 71.8% of the cases reported among foreign-born populations, 17.4% among Canadian-born Indigenous populations, and 7.0% among Canadian-born non-Indigenous populations.¹
 - The prevalence of active TB in Canada is also greater in some communities and among certain age groups. For instance, the average annual rate of TB for the Inuit population in Canada is almost 300 times higher than that of Canadian-born non-Indigenous people.⁴ Additionally, those 75 years or older have a higher incidence of active TB as a result of cumulative exposure and because of an elevated risk due to comorbid conditions.⁵ A 2017 report also revealed that incident rates of TB among Nunavut's infants was 1,020 cases per 100,000 people, compared to the rest of Canada, which is just three infants per 100,000 people.⁶

- The majority of cases with active TB in 2016, reported successful completion of treatment. In particular, treatment completion rate was highest among Canada's Inuit and Metis populations with 92.8% and 88.9% of the population respectively reportedly cured or had completed treatment in 2017.⁵ Treatment success rates were also high among Canada's First Nations (78.3%) and foreign born (79.1%) and Canadian-born non-Indigenous populations (78.0%).⁵ These numbers are based on the most current publicly available data available on active TB cases in the country.
- Similar data pertaining to the rates of LTBI among Canada's population are limited; however, the [Canadian Tuberculosis Standards 7th Edition](#) highlights that almost 50% of the 6 million migrants in the country are estimated to have LTBI. In a systematic review of studies on LTBI screening and treatment in post-landing surveillance programs in Canada and the US, only 26% of immigrants who have positive tuberculin skin test (TST) completed LTBI treatment.⁷ This raises the risk of progressing from LTBI to active TB disease, a process called reactivation, and highlights a need for measures to enhance adherence to treatment among high-risk populations.
 - Populations at risk of reactivation include those who have lowered immunity through the presence of other comorbidities such as diabetes, chronic renal failure, transplant, and HIV infection.² Risk can also increase when individuals have prolonged close contact with someone who has active TB, face conditions of poverty, are homeless, and have substance misuse problems.²

Factors That Influence Low Adherence to LTBI Treatment

Complexity and Duration of Treatment

- The standard regimen in Canada for patients with LTBI consists of a nine-month, daily, self-administered isoniazid (INH9). The length of the treatment and its potential to cause hepatotoxicity is a leading factor in nonadherence in the treatment of LTBI.⁸ Shorter alternative regimens such as three to four months of daily self-administered isoniazid and rifampin is also authorized for use in Canada along with a four-month daily rifampin regimen.⁸ Medical and patient considerations, such as potential for drug-drug interaction, complications due to comorbidities, drug-sensitivity, and drug-resistance are some factors that are reviewed to guide health care practitioners in determining the best LTBI treatment option.⁹
 - Recently, a 12-dose weekly regimen of isoniazid plus rifapentine (3HP), administered by directly observed therapy (DOT), has been shown to be as effective as INH9.⁸ This regimen has also been proven to result in reduced hepatotoxicity and higher treatment completion rates.^{10,11} However, rifapentine is not yet authorized for regular use in Canada.⁸

Access to Drugs

- Consistent supply of and access to anti-TB drugs is important to maintain ongoing treatment of LTBI, and to avoid reactivation from untreated LTBI. However, maintaining adequate supply of certain anti-TB drugs such as rifampin¹² has been challenging in Canada, leading to a number of drug shortages.¹³ This is also particularly concerning as there are limited substitutions for rifampin, providing minimal alternative regimens for patients. While there are many factors that can influence the occurrence and severity of drug shortages, the most frequently cited reasons include issues relating to securing the supply of raw and bulk materials, manufacturing disruptions, and strict regulatory processes.^{14,15}
 - Some policies and strategies that have been identified to mitigate drug shortages and ensure adequate access to drugs include encouraging the development of new manufacturing technologies, ensuring that supply guarantee clauses are included and respected in contractual obligations, developing ethical tools for allocating scarce

resources, and ensuring mechanisms to enable the monitoring and measuring of shortages to allow for the proactive identification of substitutes and alternate sources.^{15,16}

- Rifampentine, although not approved in Canada, is used by many provinces such as Ontario, Manitoba, British Columbia, and Alberta to treat high-risk patients, as it requires a shorter treatment regimen as noted above, compared to the standard nine-month treatment option.¹⁷ To access the drug, health practitioners utilize the federal Special Access Program to acquire rifampentine for individual patients on a case-by-case basis. Public health officials also seek access to rifampentine through the Access to Drugs in Exceptional Circumstances regulatory pathway for importation of larger quantities to serve jurisdictional needs. Both of these programs are aimed at providing access to drugs that are not authorized for sale in Canada, and has a limited restriction of one year.¹⁸

Social Determinants of Health

- Inequities in social determinants of health leave some populations more susceptible to acquiring TB and TB spread. This includes access to safe housing that is not overcrowded; access to affordable and adequate nutrition including safe drinking water; and an empowering, culturally safe environment that places individuals at the centre of their health care team.
- The current Canadian practice of TB treatment, prevention and management endorses a patient-centred approach, recognizing that many health system, personal and societal factors contribute toward progress in TB control.^{19,20} There is increasing evidence in the role of these factors in hindering completion of LTBI treatment and consequently increasing the potential progression from LTBI to active TB.
 - Economic constraints: The inability to pay for the modalities that are required for adherence such as transportation to clinic, childcare expenses, and the costs of other medications to manage side effects are some known factors that contribute to low adherence to LTBI treatment.²¹ Furthermore, fear about loss of employment and income as a result of missed workdays is also a contributor to low adherence to LTBI treatment.^{22,23} These concerns are exacerbated by conditions of poverty among some populations who already experience precarious living and employment conditions.
 - Stigma: Fear of discrimination due to one's ethnicity and having an infectious disease can be significant contributing factors in individuals avoiding contact with (western) health care providers due to colonial experiences, especially for Indigenous populations.^{24,25} In addition, the use of health messaging that may inadvertently attach blame on individuals for spreading TB disease continues to result in resistance toward TB treatment among some populations.²⁵
 - Access to health services: Many Indigenous peoples, new migrants, and refugees face unique barriers in obtaining health care when needed, that may affect adherence to LTBI treatment, including jurisdictional differences in program delivery, lack of provincial health insurance or personal identification cards, long wait times, and competing health priorities.²⁶ Furthermore, many rural and remote communities in Canada continue to experience under-resourced health care clinics (resources and personnel), which can result in delays in patients receiving treatment.²¹ In addition, effective communication between government departments and agencies could contribute to reduced barriers to patients in getting timely, efficient, and safe care.
 - Language and cultural barriers: Unfamiliarity of health care workers with the language or culture of the patient has been identified as a barrier of LTBI treatment adherence as it hinders health care workers' ability to describe treatment regimes, risk factors associated with incomplete treatment, symptoms, or address misconceptions of TB; thereby reducing a patient's understanding of the disease and the importance of completing treatment.¹⁹

- Comorbidities: Concurrent issues such as HIV, diabetes, and renal failure can increase the risk for and severity of side effects and complications of TB disease and can also increase a patient's pill burden, placing stress on the patient to take a high number of pills daily.²¹

Existing Interventions Aimed at Improving Treatment Adherence

DOT and/or DOPT

- DOT and DOPT is the act of witnessing someone with TB or LTBI, respectively, take their daily medication(s). Across the country, a variety of approaches to this have evolved, each with strengths and weaknesses. For example, where done by public health nurses, other health conditions can be addressed, but there is a limit in health nurse availability and this approach can be expensive. While patient surveillance by health care providers has been criticized as being authoritarian, the interaction is also seen as a source of support and builds trust.²⁷
- Historically, DOTs have been recommended as the standard of care to promote compliance of TB treatment regimens for patients with suspected or confirmed active TB.^{8,28-30}
 - There is conflicting evidence on the associated improved treatment outcomes with the use of DOT as noted in CADTH's Rapid Response report, [Direct Observational Therapy of the Treatment of Tuberculosis: Clinical Evidence and Guidelines](#).
- As TB treatments can take several months or more for completion, DOPT is resource and labour-intensive, and can interfere with one's daily activities, employment, and it involves the time and travel of both health care providers and patients. This is especially a challenge for people living in rural and remote areas.
 - While all Canadian jurisdictions have some capacity to provide DOPT, decisions regarding the use of DOPT are based on the resources available at the public health departments. Public health departments assess patients need for DOPT based on risk factors for nonadherence, and complex social or clinical need (e.g., patients with pre-existing respiratory conditions).³⁰
- Monetary incentives such as snacks, transportation, and food stipends are offered by some health facilities to increase patients' clinic attendance, particularly for marginalized populations.⁸

Video Directly Observed Therapy (VDOT)

- VDOT is available in Ontario through the Ontario Telemedicine Network to support treatment adherence, although it is unclear whether this option is available for patients with both active TB and LTBI. However, using VDOT, patients have the option to use their own mobile devices to log into a secure video link with Toronto Public Health Staff.²⁷ The recorded videos allow patients the flexibility of choosing the best time and place to take their medication.
 - While there are limited studies on the effectiveness of VDOT in improving adherence in Canada, other studies of VDOT in the US, Mexico, and the UK showed adherence ranging from 77% to 98% among TB patients.³¹⁻³³
 - While VDOT may alleviate some of the inconvenience and costs associated with DOT and DOPT, the feasibility and opportunities for video-assisted therapy for active TB and LTBI in other jurisdictions across Canada is still being considered.³⁴ For patients in rural and remote communities, challenges pertaining to limited broadband internet or cell phone network access make the implementation of VDOT challenging.

Analysis and Implications

Eliminating TB in Canada will continue to be an ongoing challenge if the high prevalence of undiagnosed and untreated LTBI among high-risk populations remain unaddressed. As a “social disease with a medical aspect,”¹⁹ treatment of LTBI requires addressing health system, social system, other government systems, as well as societal and personal factors that can potentially create vulnerabilities to acquiring TB and/or inhibit people from adhering to treatment. The WHO framework for TB elimination in low-incidence countries advocates for an individual-level, multi-sectoral approach to TB elimination.³ This is motivated, in part by an understanding that TB demands that treatment efforts provide a tailored approach to ensure adequate supports are provided for populations that remain vulnerable and without the resources to address this serious health matter. Below are some health-system level interventions aimed at optimizing adherence of LTBI treatment. Given that TB is known as a “biological expression of social inequality,”³⁵ the implementation of any health-system intervention should be accompanied by interventions applicable to the social context of the individual as well as address upstream risks and inequities.

Monitoring and Reporting LTBI

While provinces and territories must legally report all cases of active TB to the Public Health Agency of Canada, the reporting and monitoring of LTBI is not mandatory.⁸ This has resulted in a lack of data on the background prevalence of LTBI, making it challenging for jurisdictions to implement targeted programming for LTBI treatment. This further complicates efforts to detect, understand disease epidemiology, and ultimately eliminate TB in Canada. This is a significant concern as some studies on LTBI treatment completion rates suggest that Canada currently experiences low LTBI treatment adherence rates,^{26,36,37} and the majority of TB cases in Canada are generated through reactivation of LTBI acquired domestically or abroad.³⁸

A formal, systematic and mandatory post-arrival screening program for LTBI in immigrants has been recognized as a key factor in eliminating TB in low-incidence countries, especially as ongoing migration from higher-incidence countries continues.^{3,39} In addition, while data on HIV and TB coinfection in Canada is limited, screening for HIV and LTBI infection together is critical as an individual with both infections has a 100 times higher risk of developing active TB.² This is particularly important now as Canada has seen a 25.3% jump between 2014 and 2018 in the number of new HIV cases.⁴⁰ As TB treatment and prevention is a shared responsibility among the federal, provincial, and territorial governments, a coordinated approach to monitoring and reporting efforts, supplemented by data-sharing agreements, can allow for consistent, timely and complete reporting of LTBI infection, reactivation, and relevant risk factors for nonadherence.

A TB screening program for government-sponsored refugees after arrival in Edmonton has demonstrated that early integration of LTBI programming into refugees’ medical care can result in a high acceptance and completion of LTBI treatment.⁴¹ The program offers supports such as “prompt evaluation within two weeks of arrival, integration of TB services with a general refugee health clinic, and placement of a TST in most refugees.”⁴¹ These supports can serve as an example on the development of similar programs for LTBI among immigrant and refugee populations.

Engage Community Leaders, Foster Community Involvement, and Allow for Culturally Appropriate Treatment Plans

As the lack of knowledge about the nature of TB and stigmatization is a contributing factor of poor treatment adherence, several studies note that effective community and patient involvement is essential in improving both active and LTBI treatment outcomes.^{42,43} For instance, efforts to develop a shared knowledge of LTBI, which includes Indigenous and Western scientific health beliefs and practices, has been suggested to improve treatment adherence.⁴⁴ For Indigenous communities, ensure any approach involves Indigenous governments, leaders, and health care providers. Allow for the incorporation and use of traditional healing practices as directed by Indigenous leaders. These may include smudging and accessing sweat lodges in patient treatment plans.⁴⁴

In addition, local community, and worship centres may serve as facilitators in raising awareness of TB and can provide environments for patients to seek the necessary supports to help relieve the burden of LTBI treatment, in particular for individuals facing competing economic, health, and social challenges.

Workforce Planning

Recruitment and retention of health practitioners in Canada's remote and isolated communities remains an ongoing challenge. Many First Nations and Inuit communities for whom DOPT would be beneficial, do not have access to health professionals or specialists with TB expertise or awareness of the community in which they are entering.⁴⁴ As LTBI treatment is lengthy, presence of health practitioners is required for many months to support patient adherence to treatment and can be costly for public health departments. Strategies such as rural medical education/training, targeted physician recruitment for remote and isolated communities, expanding scope of non-physician practitioners may enhance access to care over the longer term. In addition, a system to facilitate referral for patients requiring additional supports such as mental health, housing, food, and addictions may further facilitate adherence of LTBI treatment.

In some communities with a low incidence of TB overall, TB programs and services have been integrated with services for other communicable diseases. Many of these communities identify adequate human health resources as a significant challenge; however, the use of telemedicine within these communities may offer a less resource-intensive and cost-effective alternative to deliver TB treatment programming.

Overcrowded and Poor-Quality Living Conditions

There is a growing body of evidence that suggests that patients with LTBI increase their chances of reactivation the infection if they are living in unsuitable, substandard and overcrowded housing, especially if there is already an active case of TB in the household.^{45,46} This can become a significant concern in areas that have not developed, supported, and maintained adequate housing programs. The adverse health impact of overcrowded housing on the progression from latent to active TB requires new approaches to housing affordability policies as developed through a public health lens. Provincial, territorial, Indigenous, and municipal decision-makers could consider strategies such as ensuring proper ventilation in housing, provide rent subsidies, increase funding for affordable housing construction, and implement rent control in private rental buildings to help

stabilize rent. The federal government has acknowledged that greater flexibility in federal funding could better meet the housing needs of Indigenous communities.⁴⁷

Monetary Incentives

While there is contradictory evidence on the role of monetary incentives to improve treatment completion rates⁴⁸, this practice provides a solution to lessen the immediate financial stresses that are associated with nonadherence of LTBI treatment. The Canadian Tuberculosis Standards identifies incentives as a key element to supporting adherence and response to LTBI and TB treatment regimens.⁸ However, there are limited formal mechanisms such as grants, and specific funding attributed to public health departments to provide such incentives to all patients and on a consistent basis. Allocation of public health funding toward incentivizing adherence behaviour would enable public health departments to provide incentives to improve adherence to LTBI treatment.

Continued Investment in TB Treatment, Research, and Adherence Tools

Research is required to produce evidence around clinical advances to meet the challenges of TB. Health decision-makers have expressed interest in shorter and more effective treatment regimens to enhance adherence of LTBI.^{49,50} In addition, development of new tools and guidance is needed to assist health care providers to determine patients at risk of nonadherence to LTBI treatment in communities where health human resources are limited. The use of digital technologies to send reminders and record video using smartphone applications may be further explored and studied as options to promote adherence.^{51,52}

In addition, a coordinated approach to prioritize TB research opportunities among key stakeholders, interest groups, and organizations in collaboration with federal, provincial, and territorial governments can encourage the sharing of resources and insights and help reduce the duplication of efforts.

Other Resources

CADTH has compiled evidence related to the diagnosis, identification, management, and prevention of TB that may be of interest, including:

- [a rapid response search on guidelines related to the treatment or management of TB](#)
- [a rapid response search on the management of discontinued TB treatment](#)
- [a rapid response search on guidelines related to DOT for the treatment of TB](#)
- [a rapid response search on the effectiveness of shortened drug regimens for the treatment of active TB](#)

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