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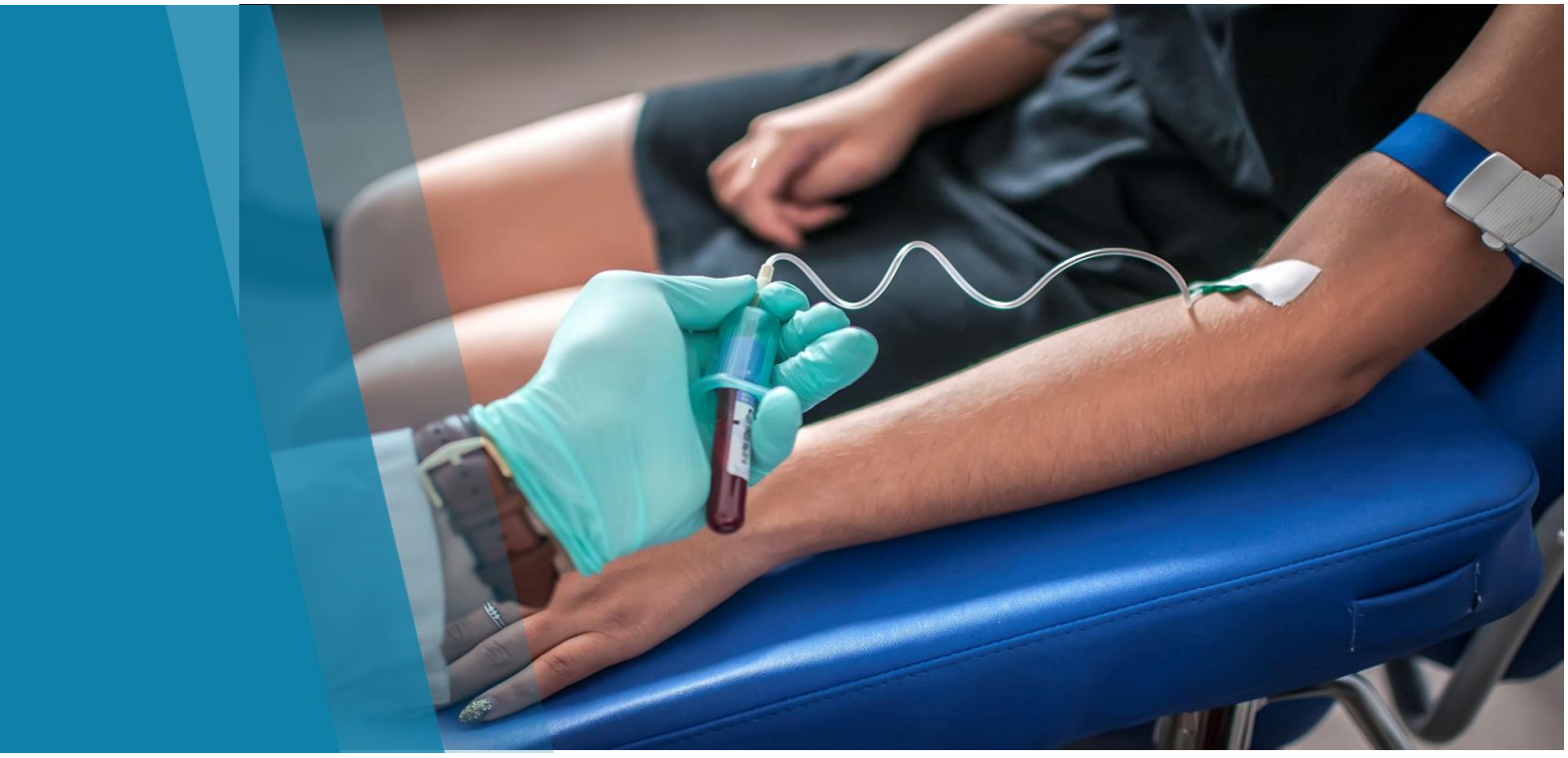
Testing for *Mycobacterium tuberculosis* infection with interferon gamma release assays



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Abbreviations

AAP: American Academy of Pediatrics

ATS: American Thoracic Society

BCG: Bacille Calmette-Guérin

CDC: Centers for Disease Control and Prevention

CXR: chest x-ray

ECDC: European Centre for Disease Prevention and Control

HIV: human immunodeficiency virus

IDSA: Infectious Diseases Society of America

IGRA: interferon gamma release assay

LTBI: latent TB infection

M. tb: Mycobacterium tuberculosis

NTM: non-tuberculous mycobacteria

PHO: Public Health Ontario

PIDAC-CD TBWG: Provincial Infectious Diseases Advisory Committee-Communicable Diseases' Tuberculosis Working Group

QFT: QuantiFERON®-TB

QFT-Gold: QuantiFERON®-TB Gold In-Tube

QFT-Plus: QuantiFERON®-TB Gold Plus

TB: tuberculosis

TNF: tumour necrosis factor

TST: tuberculin skin test

WHO: World Health Organization

Contents

Executive Summary

Purpose

This report was prepared by Public Health Ontario (PHO) with expert input from the Provincial Infectious Diseases Advisory Committee-Communicable Diseases' Tuberculosis Working Group (PIDAC-CD TBWG). It aims to summarize background information and scientific considerations relevant to the use of interferon gamma release assays (IGRAs) for detecting *Mycobacterium tuberculosis* (*M. tb*) infection, particularly in the Ontario context.

Overview of Latent TB Infection and Testing

Most people infected with *M. tb* will remain asymptomatic, but without preventive treatment, up to 15% may progress to active tuberculosis (TB) disease.[1,2] The goal of testing for latent TB infection (LTBI) is to identify those infected with *M. tb* and at increased risk of progression to active TB, so that appropriate treatment can be initiated and safely completed.[3] A gold standard test for the diagnosis of LTBI does not exist.[3-5] Two types of tests are commercially available for the detection of LTBI in Canada: the tuberculin skin test (TST) and the more recently available IGRA. Neither method performs well in immunocompromised individuals, or distinguishes LTBI from active TB.[4,5]

The TST's advantages include not requiring any specific laboratory resources, and having similar sensitivity and specificity to IGRAs in healthy individuals who have not received Bacille Calmette-Guérin (BCG) vaccine.[4,5] However, interpretation of the TST is subjective, and the test requires two clinic visits (48 to 72 hours apart), which may result in losses to follow up if patients do not return for the second visit.[4,5] Critically, the specificity of the TST is decreased in individuals who are BCG-vaccinated or were exposed to non-tuberculous mycobacteria (NTM); false-positive TST results in these individuals may lead to unnecessary LTBI treatment.[4,5]

IGRAs require only a single visit for specimen collection.[4,5] In addition, unlike TSTs, the specificity of IGRAs is not affected by previous BCG vaccination or exposure to NTM, resulting in fewer false-positive results.[4,5] The enhanced specificity of IGRA can enable clinicians to more accurately identify those for whom preventive treatment should be recommended, and helps inform patient decision-making. Potential disadvantages of IGRAs include the need for specific laboratory equipment and trained personnel, and logistical challenges related to specimen collection, processing, and transportation requirements.[4,5] However, a new iteration of the QuantiFERON® (QFT) test, an IGRA recently approved for use in Canada (i.e., QFT®-TB Gold Plus [QFT-Plus]), which allows for longer intervals between specimen collection and submission for processing (up to 53 hours), should greatly reduce some of these logistical challenges.[6,7]

Ontario Context

Ontario receives close to 40% of the permanent residents entering Canada each year, most of whom are from high TB incidence countries where universal BCG vaccination policies for infants remain in place.[8-10] From 2013 to 2017, on average, 88.7% of active TB cases reported each year in Ontario occurred in people born outside of Canada.[11] Over this five-year period, 41,211 episodes of LTBI were reported provincially; 32.8% started LTBI treatment and of those, 58.8% completed treatment.[11]

In Ontario, IGRA testing is available at the Hospital for Sick Children for children and adolescents under 18 years of age with suspected active TB disease.[12] Privately-funded IGRA testing is available through selected private medical laboratories with specimen collection locations in some Ontario communities.[13,14] The PHO laboratory does not perform any IGRA testing.

Expert Recommendations on Use of IGRAs

The 2014 *Canadian tuberculosis standards* recommend both TST and IGRA as acceptable options for LTBI diagnosis where testing is indicated, with a preference for IGRA in people who received BCG vaccine after infancy (one year of age) and/or received BCG vaccination more than once; and people from groups that historically have poor rates of return for TST reading.[15] Additionally, if active TB is suspected in a child under 18 years of age, IGRAs may also be used as a supplementary tool to support a diagnosis of TB.[15] The 2011 European Centre for Disease Prevention and Control (ECDC) recommendations also emphasize the advantages of IGRA for LTBI diagnosis in BCG-vaccinated individuals.[16]

Since the release of the *Canadian tuberculosis standards* and the ECDC recommendations, more recent clinical practice guidelines in the United States (US) have been published by the American Academy of Pediatrics (AAP) in 2018[17] and the American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention (ATS/IDSA/CDC) in 2017.[18] These guidelines also preferentially recommend the use of IGRAs rather than TSTs for those with a history of BCG vaccination (at any age) or those who are unlikely to return to have their TST read. The AAP recommendation applies to children two years of age and older; whereas, the ATS/IDSA/CDC recommendation applies to those five years of age and older.[17,18] The ATS/IDSA/CDC guidelines also suggest using IGRA instead of TST for those without a history of BCG vaccination, who are likely infected with *M. tb* and have a low or intermediate risk of disease progression.[18] Both guidelines also identify scenarios in which IGRA and TST should be used in combination to optimize sensitivity or specificity.[17,18]

Selected Evidence on Use of IGRA in Ontario and Canada

There is a growing body of peer-reviewed literature emerging on the use of IGRA in Ontario and elsewhere in Canada. For example, a study by Rose et al.[19] compared the performance of TST and IGRA in patients at a pediatric TB clinic in Toronto from 2008 to 2010, and concluded that IGRA correlated much better with TB exposure than the TST, and was most useful for detecting LTBI in BCG-vaccinated children, lower risk contacts of a TB case, and those tested for reasons other than being a contact of a case. A negative QFT test result could have helped avoid unnecessary LTBI treatment in 72% of TST-

positive lower risk contacts over five years of age.[19] A small study conducted by Kwong et al.[20] in 2014 in a remote northwestern Ontario Indigenous community found that of seven TST-positive, BCG-vaccinated 14 year-olds, none had a positive IGRA, and subsequently, did not receive unnecessary LTBI treatment. This study also highlighted implementation challenges associated with IGRA testing in this remote setting.[20]

Discussion and Conclusion

An important advantage of IGRA is its higher specificity in BCG-vaccinated individuals and those previously exposed to NTM, particularly in the context of individuals at low risk of *M. tb* infection (e.g., low risk contacts of an active TB case or those with no known contact with an infectious TB case) in a low TB incidence setting.[4,5] The specific specimen handling and laboratory testing requirements of IGRAs are key implementation considerations.

Current Canadian and American expert recommendations support the consideration of IGRA as an alternative to TST for LTBI diagnosis.[15,17,18] These recommendations align in emphasizing that IGRA should be considered preferentially over TST in the context of BCG-vaccinated individuals and in those unlikely to return for TST reading.[15,17,18] Together, these recommendations suggest that consideration of IGRA, alone or in combination with TST, has emerged as the standard of care for the detection of *M. tb* infection in many situations; exceptions include close contacts of an infectious case, individuals with no history of BCG vaccination, and serial LTBI testing.

In Ontario, individuals who are offered LTBI testing include those that are likely to be BCG-vaccinated (e.g., migrants, individuals from some Indigenous communities), and those that are unlikely to return for TST reading (e.g., individuals experiencing homelessness). Access to IGRA may help these individuals avoid unnecessary LTBI treatment.

In conclusion, we anticipate that the information summarized in this review pertaining to the use of IGRA for the detection of *M. tb* will be relevant to health care providers, public health practitioners and decision-makers.

Introduction

Purpose

This report was prepared by Public Health Ontario (PHO) with expert input from the Provincial Infectious Diseases Advisory Committee-Communicable Diseases' Tuberculosis Working Group (PIDAC-CD TBWG). It aims to summarize background information and scientific considerations relevant to the use of interferon gamma release assays (IGRAs) for the detection of *Mycobacterium tuberculosis* (*M. tb*) infection in Ontario.

Objectives

The objectives of this report are to summarize:

1. background information on:
    - latent tuberculosis infection (LTBI) and testing, including a comparison of the advantages and disadvantages of tuberculin skin tests (TSTs) and IGRAs.
    - selected demographic and epidemiologic considerations for the use of IGRAs in the Ontario context.
2. relevant expert body recommendations on the use of IGRAs.
3. selected peer-reviewed evidence on the use of IGRAs in settings/populations in Ontario and Canada.

Methods

Summary of Expert Recommendations

The most recent published recommendations on the use of IGRAs from national and international expert bodies in Canada (the *Canadian tuberculosis standards*) and other low TB incidence countries including the United States (US) (the American Academy of Pediatrics [AAP] and the American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention [ATS/IDSA/CDC]), and countries of the European Union (the European Centre for Disease Prevention and Control [ECDC]) were identified, reviewed, and summarized.

Summary of Selected Peer-Reviewed Evidence from Ontario and Canada

A rapid, focused, key-word search involving three databases (MEDLINE, Embase, and CINAHL) was performed in December 2018 by PHO's Library Services to identify peer-reviewed evidence published in English since January 1, 2012 on the use of IGRAs in settings/populations in Ontario and Canada. A

narrative summary of key findings and limitations of studies most relevant to the current Ontario context is presented in this report.

Overview of Latent TB Infection and Testing

Latent TB Infection (LTBI)

When individuals are exposed to *M. tb,* the causative agent of TB, the bacteria may either be eliminated by the host's immune responses, or remain in the body in a latent state.[1] Most of those with LTBI will remain asymptomatic, however, 5% to 15% may – in the absence of preventive treatment – progress to clinically active TB disease.[1,2] Some individuals with LTBI are at a higher risk of developing active TB disease. Factors influencing the progression from LTBI to active TB disease include:

- age: children under five years of age, particularly infants, and older adults;
- time elapsed since infection: highest risk one to two years post-infection; and
- medical co-morbidities and/or treatments that compromise the individuals' immunological status (e.g., human immunodeficiency virus infection [HIV]). [21,22]

It has been estimated that close to one-quarter of the world's population is infected with latent TB, however, this proportion varies considerably by geographic region.[23] Persons latently infected with TB serve as an important reservoir for future incident cases of active TB disease worldwide.[2] In low TB incidence settings, including Canada, the majority of active TB cases – particularly among the foreign-born population – result from the reactivation of LTBI.[24-26]

The World Health Organization (WHO) recognizes the importance of LTBI reactivation as a significant source of TB in high-income/low-incidence countries. In a recent adaptation of their global TB strategy for low incidence settings, *Towards tuberculosis elimination – an action framework for low incidence countries,* one of the eight priority actions is to "undertake screening for LTBI in TB contacts and selected high risk groups, and provide appropriate treatment."[24]

The current standard preventive treatment for LTBI in Canada is nine months of daily isoniazid, a potentially hepatotoxic medication; alternative, shorter-course LTBI treatment regimens may also be considered.[22,27]

Who to Test for LTBI

The goal of LTBI screening (i.e., testing for *M. tb* infection in the absence of clinical signs or symptoms of TB) is to identify those infected and at increased risk of progression to active TB, so that appropriate treatment can be initiated and safely completed.[3] For this reason, the *Canadian tuberculosis standards* recommend a targeted approach to LTBI screening, with the selection of individuals likely to benefit most based on their risk of prior TB exposure and risk of progression to active disease, balanced against the likelihood of safe treatment completion.[3]

Canadian populations with an increased risk of TB exposure and LTBI compared to the general population include, but are not limited to: close contacts of an active case of pulmonary TB; migrants

from high TB incidence countries; people who use injection drugs; people who are homeless/under-housed; people living in some Indigenous communities; and health care workers.[3]

How to Test for LTBI

A gold standard test for the diagnosis of LTBI does not exist.[4,5] Two types of tests are commercially available for the detection of LTBI in Canada: the TST and the IGRA. Each has its own advantages and disadvantages, which are summarized in the text below and in Table 1. Neither testing method can differentiate between LTBI and TB disease.[4,5]

Tuberculin Skin Tests

The TST was developed in the early 20th century.[4] It is an *in vivo* test that consists of an intradermal injection of purified protein derivative (a mixture of proteins drawn from *M. tb* liquid cultures).[1,4,5] In individuals who have been previously exposed to *M. tb*, it aims to induce a delayed-type hypersensitivity reaction – manifested as localized induration at the injection site – within 48 to 72 hours.[1,4,5] The size of the induration is measured by trained health care professionals. Cut-points for determining a positive TST vary between risk groups (e.g., cut-points are lower for selected groups at increased risk of progression to active TB disease).[1,5,15]

ADVANTAGES OF TSTs

The main advantages of the TST are that it does not require any special equipment or laboratory resources, and can be administered and interpreted by trained health care providers.[1] TST and IGRA also have similar sensitivity and specificity in healthy, non-Bacille Calmette-Guérin (BCG) -vaccinated populations.[5] The TST has particular advantages in remote and/or resource-limited settings because it does not require transportation of blood samples and is relatively inexpensive.[1,5]

DISADVANTAGES OF TSTs

There are, however, several disadvantages of the TST, including:

- it requires two clinic visits (one to administer the test and a second – 48 to 72 hours later – to measure and document the result), which may lead to patients not returning for the second visit and being lost to follow up;
- it can result in adverse reactions such as blistering and ulceration at the injection site;
- the interpretation of the TST is subjective; and,
- the sensitivity and specificity of the TST, as well as positive predictive value, are reduced in some populations.[1,4,5,15]

Sensitivity of the TST is decreased in individuals with LTBI who are immunosuppressed and may consequently be unable mount a cell-mediated immune response sufficient to result in a positive TST; immunosuppressed individuals are also a group at higher risk of progression from LTBI to TB, if untreated.[4,5] False-negative results may also occur due to human error, either in the administration, measurement, or interpretation of the TST.[1,5,15]

Specificity of the TST is decreased (i.e., false-positive TST results are known to occur) in individuals previously vaccinated with the BCG vaccine and/or in those previously exposed to non-tuberculous mycobacteria (NTM).[1,5,15] A false-positive TST may also occur in individuals who have received BCG immunotherapy for bladder cancer.[28,29]

The impact of previous BCG vaccination on the interpretation of TST results is largely dependent on when the BCG vaccine was given, how many doses were administered, and the interval between vaccination and TST.[5,30] For example, if BCG was administered at birth (or during infancy), was not repeated, and 10 or more years have elapsed, then its impact on the TST is minimal (i.e., a positive TST result is most likely a true positive and not due to the BCG vaccine).[30,31] However, if BCG is given after infancy and/or given multiple times, the BCG may cause the positive TST result, compromising the specificity of the TST because of the false-positive result.[30,31] This limitation of TST is particularly relevant in the context of clinical decision-making about preventive treatment in TST-positive, BCG-vaccinated individuals with a low risk of exposure to *M. tb*.

Due to the antigenic similarity between NTM and *M. tb*, those sensitized to NTM may mount a weak cell-mediated immune response to the TST that could be interpreted as positive.[1,5,15] However, a meta-analysis conducted by Farhat et al. concluded that even in populations with a high NTM prevalence, the absolute impact of NTM is very low and may only be clinically relevant if the likelihood of true *M. tb* infection is very low.[30]

Interferon Gamma Release Assays (IGRAs)

IGRAs were first licensed and available for use in the early 2000s.[1] They measure the *in vitro* response (i.e., the release of interferon-gamma) of T-cells or peripheral blood mononuclear cells to selected *M. tb* antigens.[1,4,5] These antigens are encoded by genes located in a specific region of the *M. tb* genome that does not exist in the genome of BCG vaccine strains or most species of NTM; as a result, the specificity of IGRAs is not affected by previous BCG vaccination or exposure to NTM.[1,4,5]

There are three commercially available IGRAs: QuantiFERON®-TB Gold In-Tube (QFT-Gold), QuantiFERON®-TB Gold Plus (QFT-Plus), and T-SPOT.*TB*®[6]; all three have been approved for use in Canada.[7,15]

ADVANTAGES OF IGRAs

The higher specificity (>95%) of IGRAs in BCG-vaccinated individuals and individuals sensitized to NTM is a major advantage of IGRAs over TSTs (specificity of TST is ~60% in BCG-vaccinated individuals), resulting in fewer false-positives.[32,33] Use of IGRAs can enable clinicians to more accurately identify those for whom preventive treatment should be recommended, and help inform patient decision-making. Several studies have concluded that among those with LTBI who are eligible for treatment, the proportion both initiating and completing treatment is significantly higher for those tested with IGRA compared to TST.[34-36] IGRAs are also advantageous since only a single visit is required for specimen collection leading to fewer losses to follow up compared to the TST (which requires a follow-up visit within 48 to 72 hours).[4,5]

IGRA testing is also laboratory-based and largely automated, so quantitative results are available within a relatively short turnaround-time and thus are less prone to human error in their interpretation.[4,5]

DISADVANTAGES OF IGRAs

There are, however, some disadvantages associated with IGRAs. As is the case with many assays, using IGRAs requires investment in additional laboratory equipment and training, and careful coordination of logistics to ensure specimens are processed within the acceptable timeframe. These factors contribute to overall increased costs and resource requirements for IGRA compared to the TST.[4,5] For example, both the T-SPOT.*TB*® and the QFT-Gold test should be processed within eight and 16 hours, respectively, after specimen collection.[4,5] The recently released QFT-Plus test, however, allows for a 53-hour window for specimen processing which has helped facilitate easier transportation of specimens.[6,7] Another potential disadvantage of IGRAs, highlighted in a recent study comparing the performance of IGRA and TST for serial (i.e., repeat) testing of health care workers, is that both conversions (i.e., negative to positive) and reversions (i.e., positive to negative) appear to occur more frequently with IGRAs than with TST.[15,37]

Table 1. Comparison of TSTs and IGRAs (adapted from Pai et al., 2014[5])

TST	IGRAs
Requires two visits (potential losses to follow up).	Requires single visit (fewer losses to follow up).
Between-reader variability in test interpretation (i.e., subjective).	Low between-reader variability in test interpretation (i.e., objective).
Similar sensitivity and specificity to IGRA in healthy, non-BCG-vaccinated populations.	Similar sensitivity and specificity to TST in healthy, non-BCG-vaccinated populations.
Lower specificity in BCG-vaccinated populations and those sensitized to NTM.	Higher specificity in BCG-vaccinated populations and those sensitized to NTM.
Lower likelihood of initiating and/or completing LTBI treatment.	Higher likelihood of initiating and/or completing LTBI treatment.
Recommended for serial testing for employment, school, and routine screening.	Not recommended to be used for serial testing due to the possibility of conversions and reversions (i.e., IGRA tests may vary within one individual).
Does not confirm active TB disease.	Does not confirm active TB disease (See Table 2a, Appendix B regarding potential use of IGRAs to support a diagnosis of active TB in children <18 years old).

TST	IGRAs
Estimated 5%-15% lifetime risk of developing active TB disease if LTBI detected by TST.	Clinical significance in predicting active TB disease has not been ascertained.
Accessible where health care workers are trained.	Requirement for blood drawing and processing within a defined timeframe limit locations for IGRA testing.
Should be administered on the same day (at a different site) or at least four weeks after administration of a live vaccine (unless the opportunity to perform a TST might otherwise be missed).[15]	Should be administered at least four weeks after a live vaccine (if they do not occur on the same day).[38]

Ontario Context

Population Demographics and Epidemiology of TB/LTBI

As Canada's largest immigrant-receiving province, Ontario receives close to 40% of the over 250,000 permanent residents entering the country each year.[8] The majority of these migrants are from countries deemed by the WHO as having a high TB incidence (i.e., >30 cases per 100,000 population per year), and where universal BCG vaccination policies for infants remain in place (i.e., BCG vaccine given at birth or in some countries, up to 12 months of age).[9,10]

In this context, between 2013 and 2017, on average, 88.7% (range: 86.4% to 91.3%) of TB cases reported annually in Ontario were foreign-born; of these, 70.3% (range: 65.9% to 74.2%) were from high TB incidence countries.[9,11] From 2013 to 2017, a total of 41,211 episodes of LTBI were reported in Ontario; of these, 13,505 (32.8%) started treatment and of those, 7,943 (58.8%) completed treatment.[11]

Overview of TB Prevention and Care in Ontario

TB prevention and care in Ontario is decentralized. A range of health care providers and settings provide care to individuals with LTBI and active TB, with distinct roles for clinicians and public health organizations. In this context, multiple parts of the Ontario health system are involved in the diagnosis and treatment of LTBI.

Public health programs and services are delivered locally by 35 public health units, each with a Board of Health with a mandate in respect of LTBI to "a) implement strategies to promote the identification of persons with LTBI; and b) have a mechanism in place to ensure the provision of TB medications for persons on LTBI therapy at no cost to the person with LTBI or the provider."[39]

Laboratory Testing for TB and LTBI in Ontario

Laboratory testing for infectious diseases in Ontario occurs at the PHO laboratory, hospital laboratories, and/or community or private laboratories. The PHO laboratory is the largest TB and mycobacteriology laboratory, by specimen volume, in North America.[40] The PHO laboratory provides >95% of all diagnostic testing for active TB disease and 100% of the reference testing (i.e., drug sensitivity testing, molecular diagnostics, and molecular epidemiology) for the province.[40] The PHO laboratory, however, does not perform any IGRA testing. Unlike some public health laboratories in other Canadian jurisdictions that offer IGRA testing, PHO laboratory does not have co-located facilities to support timely blood specimen collection and submission for IGRA testing.

Presently in Ontario, privately-funded IGRA testing is available through selected private medical laboratories with specimen collection locations in some Ontario communities (i.e., selected LifeLabs[13] or Dynacare[14] locations). In addition, IGRA testing is performed at the Hospital for Sick Children's Department of Pediatric Laboratory Medicine for patients under 18 years of age with suspected active

TB disease, and in some cirumstances IGRA testing for LTBI is also performed (e.g., to support public health contact investigations).[12]

At present, the TST is routinely available to test for LTBI in Ontario for the following indications:

- contacts of active TB cases;
- test deemed to be 'medically necessary' by client's primary care provider or nurse practitioner, based on level of risk as identified in the *Canadian tuberculosis standards*;
- clients under the age of 65 who are entering long-term care facilities;
- when required by an educational institution for admission or continuation in a day care or pre-school program, or a program of study in a school, community college, university, or other educational institution.[41]

Contact Management Considerations

Decision-making about whether to expand a contact investigation relies in part upon evidence suggestive of *M. tb* transmission from the infectious TB case to the exposed group(s). However, among contacts who are BCG-vaccinated, determining whether a positive TST result suggests transmission (i.e., seroconversion) can be challenging. TST also has limitations for use among contacts who are challenging for public health teams to locate and/or are unlikely to return for TST reading. In these scenarios, IGRAs can provide useful evidence to inform not only treatment decision-making, but also next steps for contact follow up.

Expert Recommendations on Use of IGRAs

Numerous expert bodies and jurisdictions have developed guidelines for health care providers and/or public health agencies on which test - TST and/or IGRA, alone or in combination - should be used in different populations.[42] The section below highlights some of the current recommendations of selected expert groups on the use of IGRAs in low TB incidence countries.

Canadian Tuberculosis Standards

The most recent (2014) edition of the *Canadian tuberculosis standards* state, "Both the TST and IGRA are acceptable alternatives for LTBI diagnosis. Either test can be used for LTBI screening in any of the situations in which testing is indicated, with preferences and exceptions noted."[15] The detailed recommendations are summarized in Appendix B, Table 2a.

Per the *Canadian tuberculosis standards*, IGRA is preferred, but TST remains acceptable in:

- people who received BCG as a vaccine after infancy (one year of age) and/or received BCG vaccination more than once; and
- people from groups that historically have poor rates of return for TST reading.[15]

Additionally, if active TB is suspected in a child <18 years of age, IGRAs may also be used as a supplementary tool to support a diagnosis of TB.[15]

European Centre for Disease Prevention and Control

The ECDC 2011 guidelines provide recommendations for use of IGRAs in a range of groups/populations (see Appendix B, Table 2b).[16] The ECDC states that IGRAs have a 'clear advantage' for LTBI diagnosis in BCG-vaccinated individuals, and should be used to inform risk assessment and treatment decisions in this group.[16] The ECDC also indicates that IGRAs 'could be used' in a two-step approach to contact tracing in low TB incidence settings (i.e., if TST is positive, perform a confirmatory IGRA).[16]

The ECDC guidelines indicate that evidence on the use of IGRAs in children is insufficient, and that there is no added value of IGRA for LTBI diagnosis in high incidence settings/populations, where active case detection is the focus.[16]

Since the 2014 release of the *Canadian tuberculosis standards* and the 2011 ECDC recommendations, more recent US clinical practice guidelines have been published.[17,18]

American Academy of Pediatrics

The AAP *2018 Report of the Committee on Infectious Diseases*[17] emphasizes several key advantages of IGRAs in children:

- increased specificity in BCG-vaccinated children who may have a false-positive TST;
- increased sensitivity, in combination with TSTs, in children at high risk for infection, progression, or poor outcome; and
- supporting the diagnosis of active TB in those with high clinical suspicion for TB disease (see Appendix B, Table 2c).

The AAP report's algorithm for use of IGRAs and TSTs in children indicates that although either TST or IGRA are acceptable tests for LTBI in children two years of age or older, IGRA is preferred over TST for those who were BCG-vaccinated, or unlikely to return for a TST reading.[17] This algorithm also identifies several criteria for which IGRA should be used in combination with TST to either increase the sensitivity of testing (e.g., to rule out LTBI in infants/young children at high risk of disease progression), or to increase the specificity of testing (e.g., to support the diagnosis of active TB).[17]

American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention

The ATS/IDSA/CDC 2017 clinical practice guidelines[18] recommend IGRA preferentially (i.e., as the standard of care) rather than TST for individuals five years of age or older who meet the following criteria (see Appendix B, Table 2d):

- likely to be infected with *M. tb;* and
- low to intermediate risk of disease progression; and
- LTBI testing is warranted; and
- history of BCG vaccination or unlikely to return for TST reading.

Even if an individual is not BCG-vaccinated or unlikely to return for TST reading, the guidelines still 'suggest' IGRA rather than TST if the other criteria listed above are met.[18] In individuals unlikely to be infected but for whom LTBI testing is mandated (e.g., for entry to health care-related educational programs or in certain workplace settings), the guidelines also suggest an IGRA instead of a TST.[18] In each of these situations, however, the guidelines still identify TST as an acceptable alternative, especially in situations where an IGRA is not available, too costly, or too burdensome.[18]

For healthy children under five years of age and for whom LTBI testing is warranted, the ATS/IDSA/CDC guidelines suggest performing a TST rather than an IGRA. However, they note that there may specific situations in which an IGRA is preferred for those over three years of age.[18]

Evidence on IGRA Use in Ontario and Canada

In this section, the key findings of selected, recent peer-reviewed studies with relevance for the use of IGRAs in the Ontario and Canadian contexts are summarized, highlighting the sub-populations of interest.

Recent Studies on the Use of IGRAs in Ontario

IGRA vs. TST in a Pediatric TB Clinic Population

Rose et al.[19] described TST and IGRA (QFT-Gold) test results in children referred to a pediatric TB clinic in Toronto, from March 2008 to September 2010. These children had different types of TB exposures, and the referral pathways and timing of TST and QFT testing also differed.

Some children were referred to the clinic by public health as identified contacts of a TB case (n=103). They were tested with TSTs and QFT after the referral, no more than 19 days apart. In this group, test agreement between the TST and QFT was very good in those who were not BCG-vaccinated (kappa=0.83) and those who were household contacts of a smear-positive TB case (kappa=0.67).[19] But TST and QFT agreement was poor in lower risk contacts, i.e., those who were not household contacts of a smear-positive TB case (k=0.34).[19]

The other group of children in this study had a known positive TST at the time of referral to the pediatric TB clinic (n=92). They were then tested with QFT. Among these TST-positive patients, QFT was positive for 78.6% of household contacts of a smear-positive case, compared to 35.0% of lower risk contacts of a case ($p < 0.003$), and just 18.2% of those with no contact with a case ($p < 0.001$).[19]

The authors concluded that in this Toronto, Ontario pediatric TB clinic population, the TST was useful for household contacts of smear-positive TB cases, and among contacts who were not BCG-vaccinated.[19] However, the QFT correlated much better with TB exposure than the TST, particularly among children who were BCG-vaccinated. They concluded that the QFT was most useful for evaluating lower risk contacts and those tested for reasons other than contact follow up. A negative QFT test result could have helped avoid unnecessary LTBI treatment in 71.7% (43/60) of TST-positive lower risk contacts over five years of age.[19]

IGRA Testing in TST-Positive Youth in a Remote Indigenous Community

Between March and August 2014, Kwong et al.[20] investigated the proportion of positive QFT among a small cohort of seven 14-year-old children undergoing routine TB testing in a remote community north of Sioux Lookout (TB incidence: 13.4 per 100,000 population). The study participants were eligible if they received the BCG vaccine as newborns (in accordance to regional policy), had a positive TST during the year of the study, and had no identifiable risk factors for acquiring TB.[20] In this study, none of the children had a positive IGRA and therefore they were not administered LTBI treatment.[20] Additionally,

chest radiographs and clinical symptom assessments ruled out active TB in all children. The authors stated that neonatal BCG vaccination may have contributed to false-positive TSTs in their study population.[20] These findings are supported by evidence in the literature that BCG vaccination contributes to false-positive TST results, favouring the IGRA as a more specific screening test for BCG-vaccinated individuals.[30,31] This study also highlighted the need for a collaborative jurisdictional approach to address challenges in the cost, collection and testing of samples in a remote community with limited capacity to facilitate IGRA screening.[20]

IGRA as Part of Admission Screening to a Provincial Correctional Facility

In 2010, Schwartz et al.[43] conducted a pilot study in an Ontario correctional facility that introduced IGRA testing as a supplement to the current TB surveillance program for screening of inmates on intake. The study population consisted of 96 male inmates with positive TST results (≥ 10 mm) on intake who agreed to undergo IGRA testing; of these, 65 (67.7%) were IGRA-negative.[43] After multivariable analysis, the independent predictive factors for TST and IGRA discordance were a history of BCG vaccination and birth in a country with low TB incidence.[43] The authors concluded that the high rates of discordance in this study population suggest that IGRAs may have an important role in TB screening programs in Canadian correctional facilities, however, further evaluations into cost-effectiveness are needed.[43]

Other Recent Canadian Studies on the Use of IGRAs

Several studies in other Canadian settings/populations have compared the performance of IGRA and TST in identifying *M. tb* infection among different groups with varying degrees of risk, and by BCG vaccination status.

Alvarez et al.[44] carried out a TB prevention campaign (Taima TB) in the residential areas of Iqaluit, Territory of Nunavut, which has one of the highest TB incidence rates in Canada. The intervention included awareness activities and offered door-to-door IGRA and TST testing to 296 individuals over six months of age. Both TSTs and IGRAs were offered to 251 participants with an unknown or previously negative TST result; as well, 45 previously positive TST participants were tested with IGRA only. As expected, a larger proportion of TSTs were positive (32.3%; 87/269) compared to the proportion of positive IGRAs (18.4%; 52/283).[44] A discordance of 17.2% in TST-positive/IGRA-negative results shows the potential of IGRA to reduce unnecessary preventive therapy for LTBI in this population.[44]

A study by Jacobs et al.[45] reported LTBI screening results in a larger cohort of 3,996 First Nations school children in Alberta aged five to 13 years between 2004 and 2009 who undergo routine TSTs. Confirmatory IGRA testing compared results between BCG-vaccinated (n=2,063) and non-BCG-vaccinated (n =1,933) children; results showed that BCG-vaccinated children were 28.5 times more likely to have a positive TST compared to non BCG-vaccinated children.[45] Of the BCG-vaccinated, TST-positive children who received an IGRA test, 7.7% (5/65) had a positive IGRA test result (95% CI: 2.5%-17.0%). The authors concluded that TST is an unreliable LTBI screening test for this population.[45]

The Montreal Children's Hospital TB Clinic implemented an IGRA follow-up program in June 2009 to confirm TST results among children categorized by varying risk of TB (i.e., active TB suspects, contact of

cases, immunocompromised, started anti-tumour necrosis factor [TNF] treatment) and reason for referral (i.e., from targeted screening programs and immigration screening).[46] Evaluation of clinical management decision-making found that a negative QFT result (TST-positive/IGRA-negative) did not change the treatment decision in 94.2% (49/52) of TB contacts; however, a negative QFT resulted in withholding isoniazid treatment in 72.1% (145/201) of TST-positive/IGRA-negative children enrolled in the targeted screening program, most of whom were immigrants and BCG-vaccinated.[46]

A descriptive study conducted in Edmonton, Alberta examined enhanced LTBI screening among 949 government-assisted refugees at a single clinic, between 2009 and 2011.[47] Individuals aged five to 50 years with a positive TST, no risk factors for progression to active TB, and no high risk chest x-ray (CXR) findings were offered an IGRA test at no cost.[47] In those with a positive TST and either an abnormal CXR or risk factors for reactivation, a TB physician performed an assessment and typically offered LTBI treatment without IGRA testing. Of those who received sequential TST/IGRA testing, 54.2% (110/203) had a TST-positive/IGRA-positive result, and therefore conversely almost half had discordant TST and IGRA results.[47] Individuals from Sub-Saharan Africa were more likely to have positive IGRA results than those from other regions; BCG vaccination status was not analyzed.[47] Only those with positive IGRAs or a positive TST, as well as risk factors for progression to active TB, were offered LTBI treatment.[47] Of 147 individuals offered LTBI treatment, 95.9% (141/147) started and 73.0% (103/141) of these completed treatment.[47] Of note, one individual in the study cohort had a positive TST and negative IGRA, was not offered LTBI treatment, and subsequently developed active TB.[47]

Similarly, a study published in 2009 by Kunimoto et al.[48] found that, among Albertan outpatients ranging in age from five to 65 years, approximately 60% of TST-positive patients were discordant (TST- positive, IGRA-negative), subsequently resulting in fewer patients receiving treatment for LTBI.

In contrast, Zwerling et al.[49] conducted sequential testing of IGRA followed by TST to determine discordance patterns and positivity rates among Canadian health care workers at low risk for TB infection. Results showed poor agreement between tests (k=0.26), specifically among TST-negative/ IGRA-positive participants.[49] IGRA positivity (6.2%, 24/388) was shown to be associated with former employment as a health care worker in a foreign country; and TST positivity (5.7%, 22/388) was associated with the number of years worked in health care, non-occupational exposure and receiving BCG vaccination.[49] Results suggested that both tests were poor identifiers of LTBI infection in this population.[49]

This emerging body of Canadian evidence generally shows IGRAs to be a more specific test than TSTs, with the potential to reduce unnecessary LTBI treatment, especially among BCG-vaccinated populations.

Discussion

This summary highlights the advantages and disadvantages of IGRAs, compared to TSTs, for the detection of *M. tb* infection. A critical advantage of the IGRA is its higher specificity in BCG-vaccinated individuals and those previously exposed to NTM, particularly in the context of individuals at low risk of infection in a low TB incidence setting. For these individuals, IGRA testing is a key tool for informing clinical decision-making, and improving appropriate use of LTBI treatment – including avoidance of unnecessary treatment in those with a low risk of *M. tb* infection. In addition, IGRA can have utility for public health follow up of contacts of infectious TB cases, particularly when it involves BCG-vaccinated populations, or individuals for whom TST reading may be logistically challenging.

However, the specific specimen handling and laboratory testing resource requirements of IGRAs are key implementation considerations. Some of the limitations may be minimized as newer IGRA tests that allow for longer transit times between specimen collection and processing become available for use in Canada and Ontario, increasing geographic access to IGRA testing from more distant specimen collection sites.

Current European, Canadian, and American expert recommendations support the consideration of IGRA as an alternative to TST for LTBI diagnosis. The Canadian and American recommendations further align in emphasizing that IGRA should be considered preferentially over TST in the context of BCG-vaccinated individuals and in those unlikely to return for TST reading. Together, these expert recommendations suggest that consideration of IGRA, alone or in combination with TST, has emerged as the standard of care for the detection of *M. tb* infection in many situations; exceptions include close contacts of an infectious case, individuals with no history of BCG vaccination, and serial LTBI testing.

In Ontario, individuals who are offered LTBI testing frequently include those who are likely to be BCG-vaccinated (e.g., some migrants, individuals from some Indigenous communities), and those that are unlikely to return for TST reading (e.g., individuals experiencing homelessness). IGRA testing may help these individuals avoid unnecessary LTBI treatment.

Conclusion

In conclusion, we anticipate that this review pertaining to the use of IGRA for the detection of *M. tb* will be relevant to health care providers, public health practitioners and decision-makers.

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Appendix A: PIDAC-CD TBWG Members

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Dr. Alanna Fitzgerald-Husek (former member)
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Dr. Rob Stirling (former member)
Senior Medical Advisor
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Appendix B: Detailed Expert Recommendations Regarding LTBI Screening Methods

Table 2a. Recommendations of the *Canadian tuberculosis standards* (2014)[15]

Recommendation	Criteria
Neither TST nor IGRAs should be used for: *Strong recommendation, based on strong evidence*	Testing people with both low risk of infection and low risk of progressing to active disease if infected. However, low risk persons are often tested before exposure, when repeat testing is likely. In this situation, TST is recommended; if TST is positive, then an IGRA may be useful to confirm a positive TST result to enhance specificity. Active TB diagnosis in adults. Routine or mass screening for LTBI of all immigrants (adults and children). Monitoring anti-TB treatment response.
IGRAs are preferred but a TST is acceptable for: *Conditional recommendation, based on strong evidence*	People who received BCG vaccine after infancy (one year of age) and/or received BCG vaccine more than once. People from groups that historically have poor rates of return for TST reading.
TST is recommended but an IGRA is not acceptable when: *Conditional recommendation, based on strong evidence*	It is planned to repeat the test later to assess risk of new infection (i.e., conversions), such as repeat testing in a contact investigation or serial testing of health care or other populations (e.g., corrections staff or prison inmates) with potential for ongoing exposure.
Both tests can be used (sequentially, in any order) to enhance sensitivity when: *Conditional recommendation, based on strong evidence*	Risks of infection, or progression to disease, and a poor outcome are high. Initial IGRA result is indeterminate, borderline, or invalid, and a reason for testing persists. Active TB is suspected in a child <18 years of age, in this case, IGRAs may be used as a supplementary diagnostic aid to support a diagnosis of TB. IGRA should not be a substitute for, or obviate the need for, appropriate specimen collection. A negative IGRA (or TST) does not rule out active TB at any age and especially not in young children.

Table 2b. Recommendations of the European Centre for Disease Prevention and Control (2011)[16]

Population/setting	Expert opinion
Immunocompromised persons (including HIV-infected patients)	As it is essential to maximise sensitivity in immunocompromised individuals, the simultaneous use of TST and IGRAs could be beneficial in identifying LTBI. Any TST- or IGRA-positive result should be taken into account in the context of an overall risk assessment when considering preventive treatment. IGRA should thus be used as part of a comprehensive risk assessment in this group of patients in view of the high risk for TB morbidity and mortality; and prevailing national/society guidelines should be maintained and followed. Note that in immunocompromised individuals, IGRAs should not be used to exclude LTBI and/or active TB.
Children	The available evidence on the use of IGRAs in children is not sufficient to change current practices and guidelines on the diagnosis and treatment of LTBI and/or active TB, particularly in children under five years of age. Regardless of the approach chosen, these three approaches should not be used to rule out LTBI and/or active TB in children under five years: TST alone, IGRAs alone, a two-step approach. If used, IGRAs needs to always be performed in the context of an overall risk assessment, and decision to treat needs to be based on this overall risk assessment.
High-TB incidence countries	There is no added value in using IGRAs to diagnose LTBI, as the focus of prevention and control is to identify and treat active cases.
Low-TB incidence countries	Given the evidence available, IGRAs could be used in contact tracing algorithms using the two-step approach (following TST, in TST-positive subjects).
BCG-vaccinated and non-vaccinated individuals	IGRAs have a clear advantage in diagnosing LTBI in BCG-vaccinated populations, as they are not influenced by BCG vaccination in terms of false-positive reactions. In a BCG-vaccinated population, IGRAs have an added value as part of an overall risk assessment, identifying individuals for whom preventive treatment should be considered.
Contact tracing	Given the available evidence, IGRAs could be used in contact tracing algorithms that use the two-step approach (following TST, in TST-positive subjects). This combined approach is based on the need to maximise specificity while improving the cost-effectiveness of contact tracing in immunocompetent adult contacts.
Occupational health care worker screening	There is insufficient evidence on the positive predictive value of IGRAs for the screening of health care workers to state an educated opinion on the topic. However, given the available evidence, the use of IGRAs in the two-step approach could increase the specificity depending on the population tested.

Table 2c. Recommendations of the American Academy of Pediatrics (2018)[17]

Recommendation	Criteria
Children for whom immediate TST or IGRA is indicated[a]:	Contacts of people with confirmed or suspected contagious TB (contact investigation). Children with radiographic or clinical findings suggesting TB disease. Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries of the former Soviet Union), including international adoptees. Children with history of significant travel to countries with endemic infection who have substantial contact with the resident population.[b]
Children who should have annual TST or IGRA:	Children with HIV infection.
Children for whom immediate and periodic TST or IGRA should be considered:	Children at increased risk of progression of LTBI to TB disease (i.e., those with other medical conditions including diabetes mellitus, chronic renal failure, malnutrition, congenital or acquired immunodeficiencies, or receiving TNF antagonists) with either a history of potential exposure to TB or where local epidemiologic factors suggest a possibility of exposure.
In any children requiring these treatments, a TST or IGRA should be performed before initiation of:	Immunosuppressive therapy, including prolonged systemic corticosteroid administration, organ transplantation, use of TNF-alpha antagonists or blockers, or other immunosuppressive therapy.

[a] Beginning as early as three months of age for TST and two years of age for IGRAs, for LTBI and TB disease.

[b] If the child is well and has no history of exposure, the TST or IGRA should be delayed for up to 10 weeks after return.

Table 2d. Recommendations of the American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention (2017)[18]

Recommendation	Criteria
An IGRA is recommended rather than a TST[a] in individuals five years of age or older who: *Strong recommendations, based on moderate evidence*	Are likely to be infected with *M. tb*; Have a low or intermediate risk of disease progression; It has been decided that testing for LTBI is warranted; and Either have a history of BCG vaccination or are unlikely to return to have their TST read.
An IGRA is suggested rather than a TST[a] in individuals five years of age or older who: *Conditional recommendations, based on strong evidence*	Are likely to be infected with *M. tb*; Have a low or intermediate risk of disease progression; and It has been decided that testing for LTBI is warranted.
There is insufficient data to recommend a preference for either a TST or an IGRA as the first-line diagnostic test in individuals five years of age or older who:	Are likely to be infected with *M. tb*; Have a high risk of disease progression; and It has been decided that testing for LTBI is warranted.
If diagnostic testing for LTBI is performed in individuals five years or older who are unlikely to be infected with *M. tb* despite guidelines to the contrary (i.e., where obliged by law or credentialing bodies):	An IGRA is suggested rather than a TST. *Conditional recommendation, based on low-quality evidence.* If the initial test is positive, a second diagnostic test is suggested. The confirmatory test may be either an IGRA or a TST. When such testing is performed, the person is considered infected only if both tests are positive. *Conditional recommendation, based on very low-quality evidence.*

[a] Note: A TST is an acceptable alternative, especially in situations where an IGRA is not available, too costly, or too burdensome.

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