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ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Interferon-Gamma Release Assay Testing for Latent Tuberculosis Infection

A Health Technology Assessment

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Ontario Health

Key Messages

What Is This Health Technology Assessment About?

Tuberculosis (TB) is a disease caused by bacteria that primarily affects the lungs and can be spread through an infected person's breath, especially through coughing or speaking. Symptoms include respiratory distress, organ failure and eventual death, but is curable when caught and treated early. Many people infected with TB bacteria experience a symptomless, inactive stage of infection. This stage is known as "latent tuberculosis infection" (LTBI). Screening for – and treating people with – LTBI can reduce the risk of symptoms appearing and spreading TB to others.

The interferon-gamma release assay (IGRA) can determine if an individual has been exposed to the bacteria that causes TB. This technology involves testing a blood sample for an immune system response in a laboratory. Currently in Ontario, only the tuberculin skin test (TST) is publicly funded as a test for LTBI. The IGRA test is considered an acceptable alternative to the TST for people who may have LTBI by the Canadian Tuberculosis Standards, published in 2022.

This health technology assessment looked at how accurate and cost-effective IGRA testing is for LTBI. It also evaluates the budget impact of publicly funding IGRA. We reached out to people with LTBI to learn about their experiences, preferences, and values, but were unable to complete interviews. Instead, we spoke to 53 health care providers who prescribe and rely on the results of TB tests.

What Did This Health Technology Assessment Find?

We found good evidence for the diagnostic accuracy of IGRA when used to test for LTBI. Compared with TST, IGRA may yield fewer false-positive findings (results showing that a person has LTBI when they don't), particularly in people who had previously received the BCG vaccine against TB. IGRA may also be informative for people with immunocompromising conditions who are at risk of a false-negative finding (results showing a person does not have LTBI when they do) by a TST.

Using IGRA (either as a standalone test or in sequence with TST) for LTBI was found to be cost-effective or cost-saving compared with TST alone in populations identified by Canadian TB Standards for being recommended for IGRA testing. We estimated that publicly funding IGRA in Ontario (for populations in alignment with the current Canadian TB Standards) over the next 5 years would cost between $2.99 million and $18.80 million, depending on how the test is used. These figures represent the final costs after considering the costs of IGRA testing and treatment for people who might otherwise be misdiagnosed as not having LTBI as well as the savings from avoiding unnecessary testing and treatment in people who might be incorrectly identified as having LTBI.

Health care providers we surveyed explained that most patients prefer IGRA as a standalone test. This is mainly due to the single visit to the clinic required by IGRA compared to the two visits required for TST. Providers also noted the perceived positive impact of having IGRA as an accessible test for patients.

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The statements, conclusions, and views expressed in this report do not necessarily represent the views of those we consulted.

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Citation

TBD

Abstract

Background

Many people infected with the *Mycobacterium tuberculosis* complex (the bacteria that cause tuberculosis [TB]) have an inactive stage of infection known as latent tuberculosis infection (LTBI). A person with LTBI is at risk of developing active TB. Screening for, and treating people with, LTBI is an important part of preventing adverse health outcomes, reducing the risk of reactivation and the further spread of tuberculosis in a community. We conducted a health technology assessment of interferon gamma release assay (IGRA) for the detection of LTBI, compared to the standard tuberculin skin test (TST) to evaluate the diagnostic accuracy, cost-effectiveness, the budget impact of publicly funding, and health care provider preferences and values.

Methods

We performed a systematic literature search of the clinical evidence as an overview of systematic reviews. We reported the findings of the identified reviews, including their quality assessment of the body of evidence. To contextualize the potential value of IGRA, we spoke with health care providers about people requiring TB testing for LTBI. We attempted to reach out to people who had experience with IGRA or TST but did not receive any feedback. We performed a systematic literature search of the economic evidence and included published Canadian cost-effectiveness studies. We assessed the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We developed a probabilistic decision-tree model to estimate the incremental costs of IGRA strategies versus TST alone over 1 year in eligible population subgroups. IGRA was examined as a single test and in a sequential pathway with tuberculin skin test (TST; the test order depended on the type of population). We considered subpopulations at high risk of LTBI for whom IGRA would be preferred, as indicated by the Canadian TB Standards published in 2022 (hereinafter, the Standards); e.g., people who received a Bacille Calmette-Guérin (BCG) vaccine, such as BCG-vaccinated immigrants and people identified in contact investigations. We also considered people with comorbid conditions or who were undergoing treatments that may cause low immune function and, hence, may test incorrectly negative. We estimated the total 5-year budget impact (in 2024 CAD) for publicly funding IGRA testing in Ontario. To contextualize the potential value of IGRA, we spoke with health care providers about people requiring TB testing for LTBI.

Results

We included 12 systematic reviews that included over 500 unique primary studies in the clinical evidence overview of reviews and found good evidence aligned with the uses of IGRA outlined in the Standards.

We included 5 economic studies from Canada (using a public payer perspective), which found that IGRA, either as a sequential test following TST or as a standalone test, was cost-effective or cost-saving compared with TST alone for LTBI in high-risk populations as identified in the Standards. All reviewed studies were of good quality and 3 studies were directly applicable to the Ontario context (GRADE: High). Therefore, we did not conduct a primary economic evaluation for Ontario.

Our reference case budget impact analysis showed that publicly funding IGRA in Ontario in all examined subpopulations over the next 5 years was associated with additional costs ranging from $2.99 million (IGRA alone) to $18.80 million (IGRA in sequential pathways with TST). These overall estimates include potential savings in some subpopulations and additional costs in others. In the population-specific analyses, we estimated cost savings of over $1.63 million over 5 years with publicly funded IGRA testing in BCG-vaccinated immigrants and BCG-vaccinated people identified via contact investigations (who are therefore susceptible to a false positive result with the TST alone). These cost-savings resulted from reductions in costs of follow-up evaluation and treatment (due to prevention of reactivated LTBI). We found additional costs of about $6.26 million or higher over 5 years with publicly funded IGRA testing in immunocompromised people due to increased appropriate medical evaluations for immunocompromised people who were previously incorrectly identified as negative. In sensitivity analyses, if we assumed a high chance of reactivation of LTBI into active TB in immunocompromised populations, then IGRA testing resulted in cost savings.

Health care providers we surveyed had positive comments about IGRA, and expressed it as patients' preferred test for LTBI, partly because this test requires only 1 office visit (compared to the multiple visits needed for TST), thus reducing the effect of barriers such as transportation, language, childcare and employment arrangements.

Conclusions

Interferon gamma release assay testing was found to have good diagnostic accuracy and to be cost-effective or cost-saving for LTBI in populations aligned with the recommended uses of the Standards. We estimate that publicly funding IGRA in Ontario would result in additional costs of around $2.99 million over 5 years (up to $18.80 million if IGRA is used sequentially with TST). We estimate a cost savings of over $1.63 million with IGRA testing for BCG-vaccinated populations. There was a preference for IGRA among health care practitioners, particularly to support people who may have challenges with the available alternative tests (e.g., TST).

Table of Contents

List of Tables

List of Figures

Objective

This health technology assessment summarizes the clinical and economic evidence for interferon gamma release assay (IGRA) testing for latent tuberculosis infection. It also evaluates the budget impact of publicly funding IGRA and the experiences, preferences, and values of health care providers who prescribe and rely on the results of tuberculosis (TB) tests.

Background

Health Condition

Tuberculosis is an infectious disease caused by bacteria in the *Mycobacterium tuberculosis* complex.[1] Symptoms of TB disease include respiratory distress (i.e., bad cough with phlegm and sometimes blood), lack of appetite, weight loss, weakness, fatigue, and fever.[1] While it is well known that TB disease commonly impacts the lungs, it may also affect other organs and body systems, including the brain, kidneys, spine, bones, and lymphatic system.[1] If left untreated, it can lead to organ failure and eventual death.[1] Tuberculosis disease is highly infectious and is airborne—TB can spread through an infected person's cough, speech, or through singing. Young children (under 5 years) are particularly vulnerable for TB infection to progress to a severe form of TB disease.[2]

Tuberculosis is curable when caught early. Treatment can prevent adverse health outcomes, but it can also reduce the risk of reactivation and the further spread of TB in a community.[1] Treatment for TB disease can be burdensome for patients, requiring a regimen of multiple antibiotics that typically lasts 6–12 months, but can continue for over 18 months (email communications, Robin Taylor, MD, Melissa Greenblatt, PhD, Kevin Schwartz, MD, and Ministry of Health, December 2023; Elizabeth Rea, January 2024).

Latent TB Infection

Many people infected with TB-causing bacteria have an inactive stage of infection, also known as latent tuberculosis infection (LTBI).[3] People with LTBI have the bacteria in their body, but there are no symptoms and they are at no risk for spreading TB to others in their community.[3] However, a person with LTBI is still at risk of developing active TB. There is an effective preventive treatment targeting the *M. tuberculosis* bacteria at the LTBI stage to substantially reduce the risk of LTBI developing into TB disease.[4] Preventive treatment in people with LTBI is less arduous and with a shorter treatment period (typically 4 months or less) than the treatment for people with active TB disease (email communications, Robin Taylor, MD, December 2023; Elizabeth Rea, MD and Kevin Schwartz, MD, May 2024). However, not everyone will complete treatment. While estimates in Ontario are uncertain, 1 study from the United States found about 70% of patients complete their treatment for LTBI.[5]

Clinical Need and Target Population

In 2022, TB was the second greatest cause of mortality by infectious disease, behind only COVID-19.[6] The World Health Organization (WHO) estimated that 1.3 million people died from tuberculosis disease and 10.6 million were ill because of it.[6] The key risk factor for acquiring *M. tuberculosis* (Mtb) is direct exposure to others with infectious active TB, which occurs at higher rates in congregate living settings

such as crowded housing, prisons, long-term care homes, homeless shelters, and hospitals.[7] People with medical conditions that weaken the immune system are at higher risk of developing TB disease.[8]

Tuberculosis disease was reported in 1,829 people in Canada in 2021[9] and in 2022, there were 119 deaths due to tuberculosis.[10] The incidence rate has been relatively stable, between 4.6 and 5.1 cases per 100,000 people from 2012 to 2021.[9] The highest rates of TB in Canada are seen among Canadian-born Indigenous Peoples, at 12.7 cases per 100,000 people (almost triple the average rate), with the highest rates among Inuit Canadians, at 135 cases per 100,000 people.[9] However, the majority of cases (76.7% of active TB cases) are among those in Canada who are foreign born.[9] In Ontario, foreign-born individuals make up 89% of people with active TB disease, with the median time of diagnosis of TB being around 8 years after arrival in Canada.[11] There is a national goal for TB elimination in Canada.[6]

There is a vaccine available to protect against TB infection, known as the Bacille Calmette-Guérin (BCG) vaccine. The BCG vaccine is only 51% effective in preventing TB disease overall, though up to 78% effective in protecting newborns from disseminated or meningeal TB.[7] The BCG vaccine is not routinely given in Canada due to the overall low rates of TB; however, it may be given under certain local circumstances (e.g., high-risk community or a local outbreak).[7] As well, most foreign-born Canadians have arrived vaccinated due to differing policies around the world.[12] Ending the global tuberculosis epidemic by 2030 is one of the key health targets of the United Nations Sustainable Development Goals.[6] To support efforts to achieve this goal, many countries are using the BCG vaccine to control population spread of tuberculosis.[6]

Latent TB Infection

Because TB can persist for many years in an inactive form, it is difficult to get an accurate estimate of how many people in Ontario are currently infected with TB bacteria, but the global burden is estimated at 23% (in 2014) and 1 Canadian study estimated the prevalence in Ontario among foreign-born people is 22% (in 2016).[13,14] There are no standard monitoring or reporting practices for LTBI in Canada.[15] Most people with LTBI will remain unaffected, however 5% to 15% of patients will experience a 'reactivation' which will become active TB disease.[16] The highest risk of reactivation is within the first 2 years after an initial infection.[17] Some immunocompromising health conditions and lifestyle factors may put people at higher risk for developing active TB, namely living with HIV, silicosis, diabetes, being an organ transplant recipient, having advanced stage chronic kidney disease, receiving immunosuppressing drugs (including chemotherapy), and heavy alcohol or cigarette use.[18] It is recommended that people are tested and treated for LTBI when there is potential for preventing active TB and reducing the risk of spread.[18,19]

One large public health unit in Ontario monitors their cases through various epidemiological methods, including TB genotyping, and has estimated that 5% to 8% of their active TB cases arise due to contact with a TB case, known as "secondary cases" (email communication, Elizabeth Rea, MD, January 2024). It is also well understood that this number is an underestimate of the true spread due to transmission between people, as pre-existing positive cases exist in Ontario and some individuals identified as contacts will take preventative treatment while others will not. Some of those will go on to become active TB cases themselves in the future (email communication, Elizabeth Rea, MD, January 2024).

Current Testing Options

People are tested for LTBI for several reasons, including having had close contact with a person who has TB disease, has arrived from a high TB incidence country, or is about to undergo certain

immunosuppressant therapies.[20,21] As well, screening is a requirement for certain employment scenarios, such as in a health care setting.[20]

In Ontario, there is currently only 1 publicly funded test for LTBI, the tuberculin skin test (TST).[22] The TST has been in use for over a century and today's version (sometimes referred to as the Mantoux) is conducted by injecting a small amount of a purified protein derivative extract of the *M. tuberculosis* bacteria into the forearm under the skin.[18] This spot is marked and checked by a health care provider 48 to 72 hours later, thus requiring a second clinic visit.[18] If there is an induration (i.e., a reddish bump) of a specific size, then the injected person is having an immune system response, indicating they have been infected.[18] The TST is an imperfect test. If a person has received the BCG vaccine, they may display a false-positive immune response, and if they are immunocompromised, they may display a false-negative response. There is no gold-standard test to confirm LTBI, the only true confirmative test is clinically confirmed TB (or absence of developing active TB), which is diagnosed through a variety of methods, such as sputum microbiologic tests and x-rays.[2,12,18,23]

In addition to TB testing with TST, Ontario publicly funds any required additional diagnostic test and treatments for LTBI and active TB disease. There is also some public funding for those who may not qualify for OHIP, Interim Federal Health (IFH), or any other provincial/territorial/private health insurance plan through a program known as the TB Diagnostic and Treatment Services for Uninsured Persons (TB-UP).[24] Individuals who are uninsured and who may be eligible for TB-UP typically include those with vulnerable social determinants of health, either being a recently landed immigrant (<3 months), homeless, a foreign visitor or student, or a person without legitimate immigration (long-term visitor) or recently discharge from prison.[24]

A person may access testing through a variety of different clinical pathways. Some people will go to their primary care provider to conduct the TST or be referred to a community lab, while others may access testing through a hospital or community specialist physician, or through public health units as part of contact tracing investigations (email communication, Ministry of Health and Robin Taylor, MD, December 2023; Elizabeth Rea MD, January 2024) The most recent version of the Canadian Tuberculosis Standards, 8th edition (hereinafter, the Standards) was published in 2022. It considers testing for tuberculosis infections a key feature of identifying individuals who are at greater risk of developing TB disease and who would benefit from LTBI treatment.[2,18,19] Similarly, there are recommendations for people to be tested for TB infection regularly for employment environments with high potential exposure, such as in health care, or upon a known exposure to someone with active TB.[18] Public Health Ontario,[20] Ontario Ministry of Health,[19] and Health Canada[7] documents about tracking and managing tuberculosis all refer to the Standards as a key resource.

Health Technology Under Review

In the early 2000s, a new test known as the interferon-gamma release assay (IGRA) was developed to determine if an individual was previously exposed to the *M. tuberculosis* bacteria by measuring their immune response.[25] To conduct an IGRA test, a sample of blood is drawn from the patient and tested for a response to specific antigens in a laboratory.[26]

As with a positive TST, a positive finding with IGRA cannot distinguish between active TB disease and LTBI. Further diagnostic tests such as sputum microbiology or chest x-ray may be required.[20,26] Unlike with TST, this type of assessment of the antibody immune response at the cellular level does not cause a false-positive result among people who have previously received the BCG vaccine.[26] People who are

immunocompromised, who are at risk for a false negative with a TST, may receive an 'indeterminate' result from IGRA. An indeterminate result may be an indication of LTBI, which might be otherwise missed.[27]

The IGRA test has been considered an acceptable alternative to the TST for people who may have LTBI by the Standards (summarized below),[2,18] as well as many other jurisdictions around the world.[12]

Canadian Tuberculosis Standards

For the use of IGRA for the diagnosis of tuberculosis, the Canadian Tuberculosis Standards, 8th edition states:

> *We strongly recommend both the tuberculin skin test and interferon-gamma release assay as acceptable alternatives for TB infection diagnosis. Either test can be used for TB infection screening in any of the situations in which testing is indicated. However, there are preferences and exceptions detailed in subsequent recommendations (good evidence).*[18]

IGRA is recommended for adults and children, with the understanding there may be a higher false-negative rate for very young children related to immune system immaturity.[2] The preferences and exceptions are summarized in Table 1.

Table 1: Summary of Recommended Uses of IGRA as Per the Canadian Tuberculosis Standards, 8th Edition[18]

Timing in the clinical pathway	Recommended uses for IGRA
IGRA as the preferred first line test in certain populations (Figure 1, A)	For people who have been previously vaccinated with BCG or exposed to non-tuberculosis mycobacteria infection (as the TST can give false-positive results) • Specifically, for children who have been vaccinated and aged 2–10 years, and for those aged > 10 years if they received their BCG vaccine after infancy (aged > 1 year) When TST is unavailable, such as when there is a lack of trained personnel When a person is considered unlikely or unable to return to have their TST results read, as required When TST is otherwise contraindicated
IGRA as part of sequential testing in certain circumstances (Figure 1, B)	After a negative TST result if the risk for infection or a poor outcome from progression to TB is high • Includes circumstances where a person's conditions or habits may reduce the sensitivity of the TST (e.g., people living with HIV or other immunocompromising conditions) After a positive TST result if the likelihood of TB infection is low or there is a risk of a false positive, such as due to BCG vaccine
Serial testing	IGRA is not considered acceptable for infection monitoring, or for workplace monitoring

Abbreviations: BCG, Bacille Calmette-Guérin; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

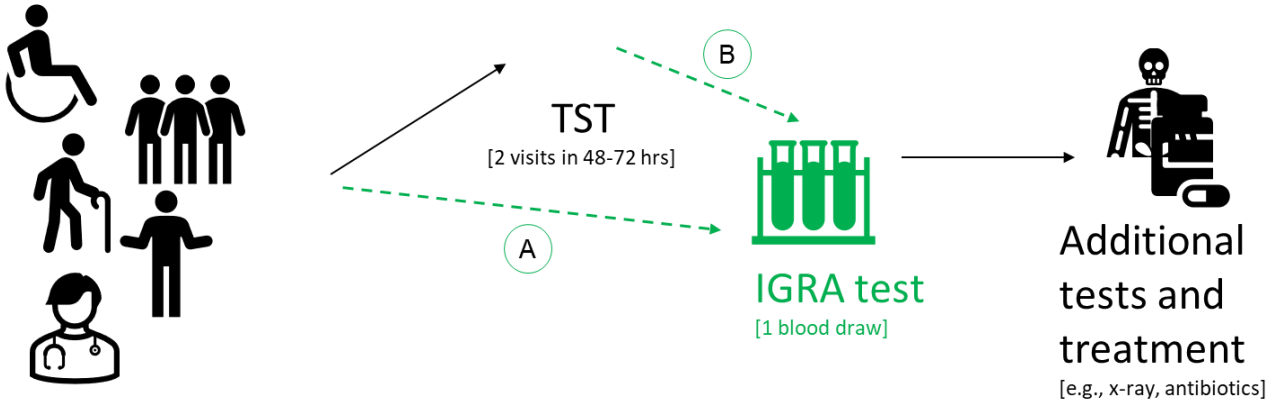

Figure 1: Simplified clinical pathway of people recommended for IGRA testing in Canada

In accordance with the Canadian Tuberculosis Standards, 8th edition,[2,18] IGRA is recommended as a first line test (A) for people who have previously been vaccinated with BCG (common in high-incidence countries around the world; Canadian Tuberculosis Standards includes additional details defining specific ages and vaccine status); capacity or training for TST is not available, but is available for IGRA; when a person is unable or unlikely to return to have their TST result read; or when TST is otherwise contraindicated. Sequential testing (B) is used when TST is positive and there are concerns of a false positive (e.g., the person may have been BCG vaccinated), when TST is negative and there is a high risk for infection (e.g., person has been exposed to active TB, progression to TB is elevated, a poor outcome from active TB is anticipated, or there are other conditions or habits that may reduce the sensitivity of the test).

Abbreviations: BCG, Bacille Calmette-Guérin; IGRA, interferon-gamma release assay; TB, tuberculosis; TST, tuberculin skin test.

Regulatory Information

There are 2 companies that make IGRA tests for LTBI, both have Health Canada approval as class 3 devices: the T-SPOT by Oxford Immunotec LTD (Health Canada License No. 69598)[28] and the QuantiFERON-TB Gold Plus by Qiagen Sciences (Health Canada License No. 72209).[29] These tests have had several iterations over the years and remain the leading brands internationally. We've been able to confirm T-SPOT having the CE mark (Europe) and FDA approval (United States), as well as regulatory approval in China, Japan, Taiwan, Russia, Singapore, Thailand, Peru, Nigeria, and Mexico.[30] QuantiFERON-TB Gold Plus is recognized by the WHO, the Centers for Disease Control (CDC, United States), and the European Centre for Disease Prevention and Control (ECDC, Europe).[31] New IGRA tests are in development, but to our knowledge, none currently have Health Canada approval.[32]

Ontario, Canadian, and International Context

In Ontario, IGRA is available as an out-of-pocket expense (~$95 to $105 CAD) for patients through community labs such as Dynacare and Lifelabs.[33,34] Additionally, we have been informed by clinical experts that The Hospital for Sick Children (SickKids) covers the expense of IGRA testing within their hospital, and their volumes have grown nearly 6-fold since 2019 (personal communication, Melissa Richard-Greenblatt, PhD, November 2023). We have also heard reports of other Ontario hospitals paying SickKids to perform IGRA testing on inpatients and select outpatients (e.g., on dialysis or with HIV; email communication, Kevin Schwartz, MD, December 2023). Toronto Public Health's TB Program covers the cost of IGRA testing for some contacts of people with infectious TB as part of their contact follow-up (email communication, Elizabeth Rea, MD, January 2024).

Ten Canadian provinces/territories publicly fund IGRA (email communication, Ministry of Health, May 2024). We are unable to confirm the detailed criteria for the various funding models, with the exception of British Columbia, which publicly funds the use of IGRA[35] in general alignment with the recommendations of the Standards,[36] including the use of IGRA prior to commencing dialysis.[37]

Internationally, IGRA is widely available; however, public funding is uncertain. In the United Kingdom, certain visa applications require people to pay for their own testing, while other people may have access to testing for free.[38,39] The use of IGRA is recommended in documents about tuberculosis from the United Kingdom[40] and Australia,[41] and is funded by the BlueCross BlueShield[42] in parts of the United States. In a 2018 summary of 18 international guidelines, the ECDC a found that there was a trend towards including IGRA as part of screening strategies.[23]

Equity Context

We use the PROGRESS-Plus framework to help explicitly consider health equity in our health technology assessments.[43] PROGRESS-Plus is a health equity framework used to identify population and individual characteristics across which health inequities may exist. These characteristics include place of residence, race or ethnicity, culture or language, gender or sex, disability, occupation, religion, education, socioeconomic status, social capital, and other key characteristics (e.g., age) that stratify health opportunities and outcomes.[43] We also used the Benkatli et al[44] checklist to guide equity considerations in HTAs to explore potential factors related to inequities, as available in the published evidence.

In Ontario, there is currently inequity in access to LTBI testing as health units across the province report that many primary care clinicians have stopped offering TST over the last decade for a variety of reasons, notably the logistics of the second visit, and particularly for children (email communication, Elizabeth Rea, MD, January 2024; Meb Rashid, MD, April 2024). Additionally, the TST requires a person to be seen by a clinical professional to inject and re-check the injection site 48 to 72 hours later, which is not always feasible for people who may have to take time off work, have caregiver responsibilities, or for whom traveling to a doctor's office is a burden. In Ontario, this includes many low-paid health care workers such as personal support workers who are required to have TB screening for work; many of whom are immigrants and BCG-vaccinated (email communication, Elizabeth Rea, MD, January 2024). The IGRA test requires only a single visit for a blood draw.

The use of IGRA testing would streamline the process for the individual, and from a public health perspective as well. When public health officials track all individuals to confirm the results, with IGRA results would be known after a single visit and only those considered for treatment would require the resourcing efforts for follow-up (email communication, Elizabeth Rea, MD, January 2024; Innocent Magocha, MPH, and Jo Ann Majerovich, MD, June 2024). The Standards take into consideration challenges patients may have by including a recommendation for the use of IGRA when a person is unable or unlikely to return to have their result read.[18]

Screening for latent tuberculosis has been recommended for people immigrating to Ontario from countries with a high incidence of TB[45] because they may have been previously vaccinated with BCG. Thus there are equity concerns due to out-of-pocket costs for IGRA testing. Notably, the population that would most benefit from access to IGRA (i.e., people who, as immigrants to Canada, have had a prior BCG vaccine) are also more likely to be unable to afford the cost (i.e., recent immigrants are more likely to belong to lower income groups).[46] People who have been vaccinated with BCG have a higher rate of a false-positive findings from TST. Positive findings require additional testing and false-positives may lead to unnecessary treatment while further investigations are conducted to confirm the result.

Conversely, the experience of the Toronto Public Health TB program, and others, is that some patients and clinicians who know about the concerns with BCG vaccination discount the results of a positive TST. Those people may in fact they have LTBI, as the vaccine is only partially effective over the long-term. Without treatment, they are at risk of developing TB disease (email communication, Robin Taylor, MD, December 2023; Elizabeth Rea, MD, May 2024). IGRA is suggested to be less likely to give a false-negative result in people who are immunocompromised. Compared with the TST, IGRA tests provide results that are more nuanced and may lead to appropriate further investigations in circumstances where a negative TST might be the end of the diagnostic journey. Overall, access to IGRA testing is proposed to streamline this process and the health care system considerably.

Canadian Indigenous populations have the highest rates of TB in the country (along with immigrants from high incidence countries), and as such many Indigenous communities opted to provide universal BCG vaccines for their population until around 2014 (email communication, Jo Ann Majerovich, MD, Innocent Magocha, MPH, June 2024). Appreciating there is diversity among the First Nations, Inuit, Métis, and urban Indigenous populations,[47] concerns around LTBI testing among the Canadian Indigenous populations are anticipated to be aligned with other BCG vaccinated Canadians. IGRA may offer improved accuracy while reducing follow-up appointments (as these are needed to review results for TST). The IGRA test is currently being used with limited public funding in 1 Indigenous community in Ontario with an active TB outbreak. However, access is limited and hindered by the expense required to ship samples far distances to a laboratory that can process the test.

Implementation of publicly funded IGRA, and the need for education for health care providers and patients, may look different across the province. For example, clinicians in areas with more TB or with higher populations of immigrants (who may have false positive results on a TST), are likely more familiar with IGRA tests; clinicians in remote areas where even non–publicly funded IGRA is not currently available are less likely to be familiar. Certain public health units, such as Toronto, are already doing limited IGRA testing for contacts and already have internal protocols in place that may allow them to adopt testing more readily than other regions (personal and email communication, Elizabeth Rea, MD, Patrick Galange, MD, and Rehannah Khan, April to May 2024).

At least 1 rural Ontario hospital that services remote and First Nations communities has purportedly expressed interest in offering IGRA testing in their region (email communication, Jo Ann Majerovich, MD, Innocent Magocha, MPH, June 2024). This would not only improve access, but also reduce shipping costs, which dominate budgets in this space and thus limit the number of tests available to communities in need. Current funding for TB testing for First Nations communities is provided through a patchwork of provincial and federal funding. Current access to IGRA tests for select First Nations communities is limited and is being supported out of the Canadian Federal budget as a TB outbreak response (email communication, Jo Ann Majerovich, MD, Innocent Magocha, MPH, June 2024).

Implementation of programs to access IGRA should respect the diversity of individuals and groups across the province. This includes diversity in preferred language as English and French are not the first language for many potentially affected Ontarians, including Indigenous peoples.[47] Consulted experts surmise that if IGRA were to become broadly publicly funded in Ontario, local hospitals would build the capacity to conduct IGRA testing, and thusly greatly reduce the expense of transportation while increasing capacity and access to the people in need (personal and email communication, Jo Ann Majerovich, MD, Innocent Magocha, MPH, January and June 2024, respectively).

Finally, advancements in recent versions of IGRA tests have improved the pre-analytics steps, allowing for easier operationalization of transporting samples from collection-to-laboratory.[30,31] This improves the potential accessibility of IGRA in geographical regions where courier services may be extended or delayed and laboratories are not available to meet the short turn-around requirements for processing.[30,31]

Expert Consultation

We engaged with experts in the specialty areas of public health, microbiology, pediatric and adult infectious disease, primary care, and health justice to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42024504025), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Purpose

Because IGRA is already accepted and recommended for use by current Canadian Tuberculosis Standards, 8th edition (hereinafter, the Standards), the purpose of this review is to summarize existing evidence on diagnostic accuracy and clinical utility.

Research Questions

- What is the diagnostic accuracy of interferon gamma release assay (IGRA) for latent tuberculosis infection when used: (1) as first line diagnostic test, and (2) in sequential testing (after a tuberculin skin test [TST])?
- What is the clinical utility of IGRA for assessing latent tuberculosis infection compared with TST?

The population of interest is adults and children, with a focus on the assessment of IGRA when used for the diagnosis of latent tuberculosis infection (LTBI) in circumstances aligned (at least in part) with the recommended population for IGRA testing as per the Standards.[18]

Methods

Clinical Literature Search

We performed a clinical literature search on January 9, 2024, to retrieve studies published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Database of Systematic Reviews, and the National Health Service Economic Evaluation Database (NHS EED). We used the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. A methodological filter to limit retrieval to systematic reviews, meta-analyses, and health technology assessments was used in keeping with the overview of reviews methodology, since several systematic reviews that potentially answered our research question were identified during the scoping period. The final search strategy was peer-reviewed using the PRESS Checklist.[48]

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them until April, 2024. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Systematic reviews that met the inclusion criteria were prioritized based on the consideration of multiple factors, in alignment to the Cochrane methods for overview of reviews,[49] including:

- Recency and comprehensiveness (i.e., are sufficiently up-to-date)
- Sufficiently homogenous so that they are aligned to the HTA research questions criteria and contextually relevant to Ontario
- Sufficiently homogenous in their reporting of the outcomes of interest and how the data are presented
- Present sufficient data (amount and type) to inform the HTA research questions
- Report risk of bias and quality assessment of primary studies (e.g., using GRADE)
- Are considered to be sufficiently low risk of bias and of high methodological quality (as supported by using ROBIS).

Inclusion Criteria

- English-language full-text publications
- Systematic reviews reported as standalone publications, or within HTAs, meta-analyses, or guidelines
    - Included systematic reviews must have transparent, defined inclusion criteria, and a description of the search terms and databases searched

Exclusion Criteria

- Narrative reviews, primary studies (i.e., diagnostic accuracy studies, randomized controlled studies)
- Editorials, commentaries, case reports, conferences abstracts, letters
- Animal and in vitro studies

Participants

Inclusion Criteria

- Adults >18 years old and children >2 year old
- Assessment of IGRA when used for the diagnosis of LTBI, in circumstances aligned (at least in part) with the recommended population for IGRA testing as per the Canadian TB standards – 8th edition.[18]

Exclusion Criteria

- People undergoing testing with IGRA for conditions other than LTBI (e.g. active TB)

- People undergoing testing in circumstances that are not aligned with the 8th Edition Canadian TB standard including use for screening (e.g. general populations, for employment such as health care workers and serial testing) and for confirming active TB disease.

Interventions

Inclusion Criteria

- Interferon Gamma Release Assay (IGRA)

Exclusion Criteria

- Laboratory developed IGRA, non-commercially available tests

Reference Test (for diagnostic accuracy)

Inclusion Criteria

- Clinically confirmed such as through microbiological testing.
  - Development of active TB may be used as the reference test when comparing accuracy of IGRA to TST.

Comparators

Inclusion Criteria

- Tuberculin skin test (TST)

Exclusion Criteria

- No testing
- Comparisons between types of IGRA

Outcome Measures

- Diagnostic accuracy:
  - Sensitivity, specificity, and predictive values (PPV/NPV)
- Clinical utility:
  - Impact on clinically-important outcomes, including but not limited to progression to active TB and subsequent clinical effects for patients
- Indirect measures of clinical utility:
  - Impact on health services resources (e.g., diagnostic tests such as X-rays)
  - Impact on medical decision making (e.g., antibiotic use, and adherence to taking prescribed medications)

Literature Screening

Two reviewers screened titles and abstracts to assess the eligibility of a sample of 100 citations to validate the inclusion and exclusion criteria. A greater than 80% agreement was achieved and all disagreements were discussed until consensus reached. The process would have been repeated with a further sampling of 50 until sufficient agreement was reached. A single reviewer then screened all remaining citations using Covidence[50] and obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

One reviewer extracted relevant data on study characteristics of the systematic reviews and their included primary studies (as reported within the systematic reviews). The reviewer also extracted risk-of-bias, results and PICOTS (population, interventions [reference-standard], comparator, outcomes, time and setting) of the primary studies, as reported by the systematic reviews.

Equity Considerations

Equity issues related to the effect of IGRA for LTBI across various populations including those with immune compromising conditions and/or are BCG vaccinated are reported to the extent that information was available in the included studies (see subgroup analyses section for full list of groups considered).

Statistical Analysis

As an overview of reviews, we narratively summarize findings of the individual systematic reviews. Systematic reviews were considered for the presence and extent of clinical, methodological and statistical heterogeneity as part of the inclusion selection and when interpreting and reporting the results. Meta-analyses conducted within the included systematic reviews were reported where considered appropriate and relevant.

Subgroup Analyses

To explore the differences in accuracy based on known biological principals that may affect the accuracy, the following subgroups were considered and reported where present in the included systematic reviews:

- Specific IGRA test (with a preference for findings most relevant to Ontario, where currently only the QFT gold-plus is available).
- Confounding immunocompromising health conditions and lifestyle factors that put people at higher risk for developing active TB disease (e.g. living with HIV, diabetes, being an organ transplant recipient, having advanced stage chronic kidney disease, receiving immunosuppressing drugs (including chemotherapy), heavy alcohol or cigarette use.[18]
- Specific age groups (e.g. children <18 years; older adults >65 years)

- Settings (e.g. high-prevalence countries with annual incidence >40 per 100 000; congregate living settings; others as defined by individual reviews)
- BCG vaccination status (which is often associated with high-incidence countries; BCG status unknown)
- Pre-test probability (e.g. general screening vs close-contacts)

Critical Appraisal of Evidence

We assessed the risk of bias of any eligible systematic reviews using ROBIS[51]. We also limited the overview of reviews to individual systematic reviews which reported their own critical appraisal of evidence of the primary studies, and reported their findings where possible.

Due to this being an overview of reviews which relied on others compilation and interpretation of the body of primary evidence we were unable to evaluate the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[52]

Results

Clinical Literature Search

The search of the clinical literature yielded 467 citations published between database inception and January 9, 2024, including grey literature searches and after duplicates were removed. We identified no additional eligible studies from other sources, including database alerts (monitored until April, 2024). In total, we identified 49 systematic reviews that met our inclusion criteria, of which 12 were considered to represent the most comprehensive body of evidence for the purposes of this overview of reviews as they were most recently published (from 2020 onwards). See Appendix 4 for a list of selected studies excluded after full-text review. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

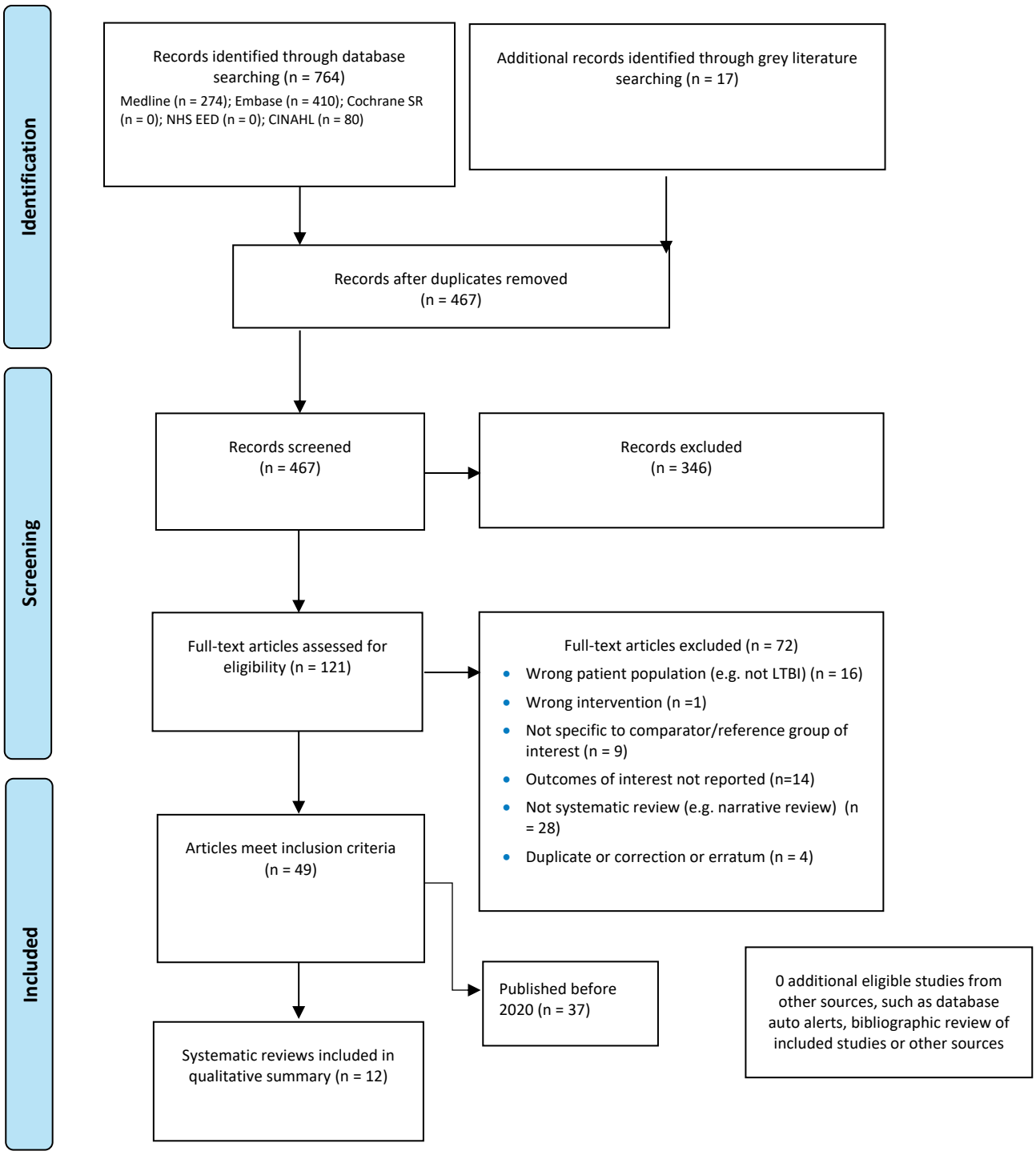

Figure 2: PRISMA Flow Diagram – Clinical Systematic Review

PRISMA flow diagram showing the clinical systematic review. The clinical literature search yielded 467 citations, including grey literature results and after removing duplicates, published up to January 9, 2024. We screened the abstracts of the 449 identified studies and excluded 328. We assessed the full text of 121 articles and excluded a further 72. In the end, we applied a date limit of 2020 and ultimately included 12 systematic reviews in the qualitative synthesis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[50]

Characteristics of Included Systematic Reviews

The systematic search full text screening identified 49 systematic reviews which met our inclusion criteria. After consideration of the identified individual reviews, it was found that the body of evidence was well captured within the 12 reviews published from 2020 onwards. All older systematic reviews (i.e., published before 2020; see appendix 5) were reviewed in detail and considered to contain evidence that was directly or indirectly updated by more recently published reviews, or focused on versions of IGRA that are older. Therefore, the results from the 12 systematic reviews are reported.

One of the 12 included systematic review was identified to have two publications, one grey literature report and one peer review journal publication.[53,54] Both publications were consulted for the purposes of this overview of review, but they are counted as 1 systematic review onwards.

Across the 12 included systematic reviews (Table 2), there were more than 500 unique primary studies. The reviews applied various inclusion and exclusion criteria: some focused on unique populations (e.g., adults, children, people with select immunocompromising conditions such as HIV, excluding primary studies with people who are immunocompromised), while some reviews applied different limits to acceptable TST induration cut-offs, anti-tubercular treatment use as well as TB incidence country of origin. All systematic reviews acknowledged there is no gold-standard for the diagnosis of LTBI, given such, reviews also differed in how they managed primary study reference standards. Some systematic reviews limited to only longitudinal development of active TB, while others accepted primary studies that confirmed with sputum culture-positive TB, and others did not specify limits to the inclusion criteria.

The included reviews reported primary studies from a balanced mix of sexes (male/female) of a variety of ages from very young to elderly. As well, primary studies included in the systematic reviews were found to have representation from countries around the world including the Americas, Europe, Asia, Africa and Oceana. The systematic reviews considered BCG status differently, with some reviews simply mentioning BCG vaccination rates in supplemental tables describing the primary studies, while other reviews conducted subgroup analyses by BCG status. None of the reviews addressed the aspect of our research question related to timing of IGRA versus TST testing. They all examined IGRA as an alternative replacement to TST.

Table 2: Characteristics of the Systematic Reviews Included in the Clinical Literature Review

	Review design			IGRA Inclusion criteria	Characteristics of included studies	
Author, year	**Search dates; Databases searched**	**Review methods**	**Population(s)**	**[Actual included IGRA tests]**	**N Studies (n participants)**	**Quality assessment**
Volkman et al, 2024[55]	1998 to June 27 2023 MedLINE, EMBASE, and Cochrane databases	English language Excluded case reports	Children <5yrs old, with *no* immune compromising conditions (e.g. HIV) Subgroup: BCG vaccination status	QFT-GIT	17 (4335)	QUADAS Review considered them 'high' quality [all fulfilling ≥10 of 14 criteria]
Zhou et al, 2023[56]	Up to November 2022 Pubmed, Embase, Cochrane Library databases	Excluded abstracts, letters, case reports, reviews If invalid results due to technical errors were accounted as indeterminate	Adult and children populations considered high-risk for TB (recent contacts, immunocompromised, occupational risk, possible immunosuppression such as children, nursing home residents and homeless).[a]	Commercially available IGRAs [Included: QFT-Plus; QFT-GIT (3rd gen); QFT-Gold (2nd gen); T-SPOT.TB	403 (486 886)	QUADAS-2 315 studies, high quality and 53 moderate quality
Yahav et al, 2023[57]	Up to June 2022 Medline, Embase, and Cochrane CENTRAL	English language Excluded case reports and case series with <10 participants	Adults who had ≥1 solid organ transplant (lung, heart, kidney, liver, pancreas, small bowel)	Commercially available IGRAs [included: QFT-GIT; QFT-G; T-SPOT.TB]	17 (5510)[b]	QUADAS-2 [12 had risk of bias, 5 were found to have low risk of bias]
Jonas et al, 2023[54]	Up to January 20, 2023 PubMed/MEDLINE, Cochrane Library, trial registries, references, experts, literature surveillance	English language Excluded screening close-contacts of active TB	Adults at increased risk for LTBI [c], but also no underlying immunosuppression (e.g. HIV)	Commercially available IGRAs [included QFT- Plus, QFT-GIT; T-SPOT.*TB*]	79 (13493)[b]	Fair or good quality [quality assessed with 8 point questions about study design including patient selection and analyses methodologies]
Zhou et al, 2022[58]	Up to March 12, 2022 EMBASE, PubMed, and Cochrane Library	No population or language restrictions Head-to-Head Comparative studies within 4 week for receiving both tests; TST Excluded study if only IGRA or TST positive/negative patients were included, non-commercially available IGRAs	Adult and children populations considered high-risk for TB (recent contacts, immunocompromised, occupational risk, possible immunosuppression such as children, nursing home residents and homeless).[a]	Commercially available IGRAs [included QFT; T-SPOT.TB]	458 (204 787)	QUADAS-2 [~75% were considered high and moderate quality]

	Review design			IGRA Inclusion criteria	Characteristics of included studies	
Author, year	**Search dates; Databases searched**	**Review methods**	**Population(s)**	**[Actual included IGRA tests]**	**N Studies (n participants)**	**Quality assessment**
Park et al, 2022[59]	Up to November 2021 Medline, EMBASE, Cochrane Library databases	English language Excluded abstracts, studies focused on pediatric patients;	Inflammatory Bowel Disease Subgroups: People on immunosuppressants vs not [and subgroups within based on IGRA device, BCG status etc..]	Commercially available IGRAs [Included: QFT-GIT; T-SPOT.TB]	20 (4045)	Newcastle Ottawa Scale [all studies considered high quality with combined scores >7)
Chen et al, 2022[60]	Up to September 30, 2021 PubMed, Web of Science, Cochrane and Embase	No population restrictions Included articles, briefs, conference abstracts in any language	People living with HIV	IGRA, no limits specified [Included: QFT-GIT; T-SPOT]	7 (1267)[b]	QUADAS-2 [overall low risk of bias[d]]
Oh et al, 2021[61]	January 2013 to May 2020 MEDLINE, Embase, Web of Science, Cochrane Database of Systematic Reviews	Original full text reports, that were conducted with blind assessment Excluded editorials, narrative reviews, letters and conference abstracts.	Adults at higher risk for TB[e] [excluded studies with very low risk of LTBI: age <50yrs, life long residents in counties with <25/100000 TB incidence, no known exposure, healthcare workers]	QFT-Plus [Also included as comparators: QFT-GIT T-SPOT.TB]	24 (6357)	QUADAS-2 [Low to high risk of bias]
Zhou et al, 2020[62]	Up to October 18, 2019 PubMed, Embase, Web of Science, Cochrane Library	No language restriction, cohort design Excluded abstracts, letters, case reports and reviews, or if LTBI progressed to active TB within 3 months	High risk population for TB, according to WHO recommendations, (e.g. people living with HIV infection, transplantation, dialysis, health-case workers and immigrants)[a]	IGRA, no limits specified [Included: QFT-G; QFT-GIT; T-SPOT.TB]	40 (50,592)	Modified Newcastle-Ottawa Scale [moderate to low risk of bias]
Yamasue et al, 2020[63]	August 1992 to October 22, 2018 PubMed, Cochrane Central Register of Controlled Trials, EMBASE database	English language, multivariate analysis assessing risk factors that influence false negatives of IGRA Excluded abstracts, children only,	Adults Subgroups explored: Gender, advanced age, low peripheral lymphocyte counts, HIV positivity, extrapulmonary TB and BMI Also classified by low incidence TB country vs middle and high incidence country (as per WHO criteria)	Commercially available IGRAs [Included: QFT-GIT; T-SPOT.TB; QFT-Gold; ELISPOT]	17 (9470)	Cochrane handbook, and MOOSE guidelines; Modified Heyden's criteria: [Studies averaged meeting 3.5 of 6 criteria indicating moderate quality]

	Review design			IGRA Inclusion criteria	Characteristics of included studies	
Author, year	**Search dates; Databases searched**	**Review methods**	**Population(s)**	**[Actual included IGRA tests]**	**N Studies (n participants)**	**Quality assessment**
Campbell et al, 2020[64]	January 1, 1990 to May 17, 2019 Medline, Embase, Cochrane Controlled Register of Trials	English or French >12 month follow up, at least 10 participants, untreated Excluded BCG vaccinated; excluded studies of people with HIB in high TB incidence countries	People in higher risk groups for developing TB	QFT-Gold QFT-GIT T-SPOT.TB	102 (116197)	MOOSE, QUADAS-2 [60% moderate to high quality]
Alrajhi et al 2020[65]	June 2011 to April 2018 Medline, Embase, Cochrane databases	Adults, English, abstract, letters and full texts included. Excluded if less than 10 IBD patients.	Inflammatory bowel disease Subgroups: People on immunosuppression vs not	QFT-QFT-G QFT-GIT	16 (2488)	QUADAS-2 [Most studies had low risk of bias, 3 studies possible high risk of bias]

Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; mm, millimeter; QFT, QuantiFERON-TB; QFT-G, QuantiFERON-TB Gold; QFT-GIFT, QuantiFERON-TB Gold-In-Tube; QFT-Plus, QuantiFERON-TB Gold-Plus; TST, tuberculin skin test; yrs, years

[a] We have opted to include this review in our overview of reviews as the majority of studies were in our population of interest.

[b] Review included additional studies, beyond the scope of this overview of review

[c] according to WHO criteria

[d] Risk of bias only reported on full cohort of studies

[e] One included study had age limits of 15yrs and older

Risk of Bias in the Included Studies

Risk of bias of reviews was assessed using ROBIS, see appendix 2. This overview of reviews selected for systematic reviews that were considered well done, and this is reflected in the high quality ROBIS scores of the included publications.

Of the 12 systematic reviews from which we extracted data, all conducted quality assessment of the primary studies comprising their respective bodies of evidence and generally found moderate to low risk of bias across the included studies (table 2). However, they did not report quality for each individual outcome, except for Jonas et al[54] and Oh et al[61], for the outcomes of sensitivity and specificity (table 3).

Diagnostic Accuracy

Diagnostic accuracy was reported in 6 systematic reviews. Sensitivity and specificity, as well as positive and negative predictive values were pooled in a number of different reviews. There were high values reported for specificity across all reviews and subpopulations explored, however sensitivity was found to be lower amongst those who had immunosuppression such as HIV, in alignment with clinical expectations due to the supressed immune response of a person overall; results are summarized in tables 3 and 4 below.

Additionally, Volkman et al, 2024[55] reported a **pooled diagnostic odds ratio of 18.84 (95%CI 7.33 to 48.41)** and a summary receiver operating characteristic (SROC) curve of 0.7812, which they reported as good diagnostic accuracy. Yamasue et al[63] explored risk factors associated with false negative findings of IGRA and reported that advanced age as well as immunosuppressive conditions such as HIV positivity, lower peripheral lymphocyte counts, being on immunosuppressive therapy (including cancer immunotherapies) were all significantly associated with false-negatives.

Table 3: Sensitivity and Specificity of IGRA

Author, year [population details]	Population	Study group details N studies (n participants)	Pooled Sensitivity	Pooled Specificity	Quality assessment as reported
Volkman et al, 2024[55]	Children <5, with no underlying immunosuppression	Overall 17 (4335)	0.45 (95%CI 0.42 to 0.48)	0.96 (95%CI 0.96 to 0.97)	Not reported by outcome, overall high quality
Yahav et al, 2023[57]	Adults with ≥1 solid organ transplant	QFT-GIT 10 (NR)	37.5%	77.9%	
		T.SPOT 3 (NR)	82.3%[a]	73.5%	
Jonas et al, 2023[54]	Adults at increased risk for LTBI, with no underlying immunosuppression	QFT-Plus Total 11 studies Sens: 11 (939) Spec: 1 (211)]	0.89 (95%CI 0.84 to 0.94)	0.98 (95%CI 0.95 to 0.99)	Moderate for sensitivity; low for specificity
		QFT-GIT Total 51 studies Sens: 48 (7 055) Spec: 3 (2 090)	0.81 (95%CI 0.79 to 0.84)	0.99 (95%CI 0.98 to 0.99)	High for sensitivity, moderate for specificity

Author, year [population details]	Population	Study group details N studies (n participants)	Pooled Sensitivity	Pooled Specificity	Quality assessment as reported
		Studies with BCG vaccination prevalence >50%	0.78 (0.73 to 0.83)	Not estimable	
		T-SPOT.TB Total 39 studies Sens: 37 (5 367) Spec. 2 (1664)	0.90 (95%CI 0.87 to 0.92)	Ranges: 0.95 (95%CI 0.91 to 0.97) to 0.97 (95%CI 0.96 to 0.98)	High for sensitivity, moderate for specificity
		Studies with BCG vaccination prevalence >50%	0.89 (0.86 to 0.92)	Not estimable	
Chen et al, 2022[60]	People living with HIV	7 studies[b] 1267 participants	0.64 (95% CI 0.61 to 0.66)	Not estimable	
		QFT 5 studies 691 participants	0.66 (95%CI 0.56 to 0.70)[c]	Not estimable	
		T-SPOT 3 studies 576 participants	0.60 (95%CI 0.56 to 0.64)	Not estimable	
Oh et al, 2021[61]	Adults at higher risk for TB	QFT-Plus 7 studies in sensitivity; 2 studies in specificity	91.4% (95%CI 87.5 to 94.2%)	97.8% (95%CI 95.5 to 98.9)	QUADAS-2 Sensitivity: high risk of bias Specificity: Low risk of bias
		QFT-GIT 7 studies in sensitivity; 2 studies in specificity	91.4% (95%CI 88.9 to 93.4)	98.7 (95%CI 96.7 to 99.5)	QUADAS-2 Sensitivity: low risk of bias Specificity: Low risk of bias
		T-SPOT.TB 2 studies in sensitivity; 1 study in specificity	90.2% (95%CI 61.9 to 98.1)	98.1% (95%CI not applicable)	QUADAS-2 Sensitivity: low risk of bias Specificity: Low risk of bias

Abbreviations: CI, confidence interval; NR, not reported; TB, tuberculosis

[a] Systematic review authors suggested findings are skewed due to very limited studies

[b] One publication results for QFT and T-Spot were extractable separately

[c] data reported here comes from the supplemental information of the systematic review and differs slightly from the published abstract

Table 4: Positive and Negative Predictive Value of IGRA

Author, year	Population	Study group details, if specified N studies (n participants)	Diagnostic Accuracy of IGRA PPV (95% CI)	 NPV (95% CI)
Yahav et al, 2023[57]	Adults with solid organ transplant	All IGRA	1.2% (NR)	99.6% (NR)
		QFT	0.86% (NR)	99.6% (NR)
		T-Spot	1.59%(NR)	97.6% (NR)
Zhou et al, 2020[62]	High risk population for TB, according to WHO recommendations	All IGRA tests PPV: 38 studies (4212 people) NPV: 40 studies (23607 people)	4.5% (3.5 to 5.8)	99.7% (99.5 to 99.8)
		QFT	4.8% (3.3 to 6.7)	99.6% (99.4 to 99.8)
		T-SPOT.TB	3.9% (2.7 to 5.4)	99.8% (99.6 to 100)

Abbreviation: IGRA, interferon gamma release assay; NR, not reported; TB, tuberculosis.

Concordance between IGRA and TST:

Given the absence of a gold-standard concordance likely represents similarities between the tests, while discordance might be suggestive of improved accuracy of IGRA compared to TST. Lower positivity rates with IGRA when compared to TST are seen by the field to represent fewer false positive rates, and thus a consideration in favour of IGRA for certain populations.

Table 5 summarizes reported risk difference in positivity rates between the IGRA and TST tests, as conducted by one systematic review. It reports overall lower positive rates in IGRA compared to TST to varying degrees across different subpopulations, a selection of which are included below. Particularly notable due to its applicability to the Ontario context is the observed lower rates amongst BCG vaccinated people in low-TB burden areas (risk difference of -0.19) which can be indicative of lower false-positive rates with IGRA, especially when taken together with the outcomes of clinical utility reported later in this report.

Table 5: Risk difference of positivity rates comparing IGRA and TST findings

Author, year	Population	N studies (n people)	Risk Difference (95%CI)
Zhou et al, 2022[58]	General population of adults at higher risk for TB	66 studies (53,799)	−0.11 (−0.15 to −0.07)
	Immunocompromised patients	130 studies (24,143)	0.05 (0.02 to 0.07)
	Children	7 studies (5226)	−0.26 (−0.46 to −0.05)
	Nursing home residents	3 studies (427)	−0.26 (−0.36 to −0.17)
	Low TB-burden area (<100 per 100,000)		
	Not-BCG vaccinated	33 studies (23,213)	−0.02 (−0.07 to 0.02)
	BCG vaccinated	66 studies (27,851)	−0.19 (−0.25 to −0.14)

	High TB-burden area (>100 per 100,000)		
	Not-BCG vaccinated	11 studies (2825)	0.02 (−0.08 to 0.11)
	BCG vaccinated	15 studies (5574)	−0.05 (−0.09 to −0.01)

Abbreviations: CI, confidence interval; TB, tuberculosis

Zhou et al, 2020[58] also reported discordance when IGRA was used there were significantly higher pooled PPV and NPV than when TST was used (*P* = 0.002); however Yahav et al,2023[57] reported no differences in PPV and NPV between IGRA and TST results (mean different 0.000 to 0.001). Additional measures of concordance and discordance are reported in Appendix 3, Table A2.

Indeterminate rate

Zhou et al, 2023[56] conducted a systematic review focused on indeterminate findings rates of IGRA. In their review they reported from 403 studies (486,886 individuals), that the pooled indeterminate rate for IGRA was 3.9% (95%CI 3.5% to 4.2%).

They conducted various subgroups, and reported there were slightly higher rates of indeterminate findings of 5.7% (95%CI 4.8% to 6.6%) amongst the 48,379 people within 134 studies who are immunocompromised (e.g., HIV, hemodialysis, transplant, cancer, drug and alcohol abusers).[56] As well as children having higher rates (4.3%) than adults (odds ratio 2.56; 95%CI 1.79 to 3.57). There were some differences between the IGRA brands, with the lowest rates of indeterminate findings observed in the newest generation.[56]

Indeterminate rates are also reported within other systematic reviews, reporting similar findings ranging from 0% up to 4.5%;[54,55] and having higher indeterminate rates in people with IBD, on immunosuppressive therapy (compared to not on therapy) OR 2.91 (95%CI 1.36 to 6.24).[59]

Clinical Utility

One key measure of clinical utility is the progression to active TB disease. As there is no reference standard for LTBI, part of the concern about the TST test is that there is a high rate of false positives and therefore people going on treatment unnecessarily. Thus, it is clinically important to determine if both tests are able to predict development into active disease, and how IGRA compares to TST at doing so. Table 6 summarizes the findings from the 2 systematic review which report this outcome. While each review chose slightly different metrics to measure it by, findings are consistently demonstrating that a positive finding with IGRA is associated with a higher likelihood of a person going on to experience active TB disease, than when the TST has a positive finding; therefore, suggesting that IGRA may have a higher rate of true positives than TST.

Zhou et al,2020 reported differences in IGRA and TST to be statistically significant (P = 0.008), and findings were similar in a sensitivity analysis which limited to the body of evidence of the direct head-to-head studies.

Table 6: Disease progression among *positive* LTBI test results

Author, year	Population	N studies (n people)	Results (subgroup of various TST induration cut-off)	
			Risk Ratio (95%CI)	
Zhou et al, 2020[62]	Adults at higher risk for TB	33 studies (26, 212)	With IGRA	9.35 (6.48 to 13.49)
		16 studies (22120)	With TST (>10mm)	4.28 (3.29 to 5.56)
	Subgroup of head-to-head studies of tests being used in the same population	10 studies (5337)	With IGRA	7.12 (3.39 to 14.94)
		5 studies (3828)	With TST (>10mm)	4.30 (2.03 to 9.10)
		5 studies (1454)	With TST (>5mm)	2.81 (0.69 to 11.42)
			Incident Rate Ratio (95%CI)	
Campbell et al, 2020[a] [64]	Exposed contacts, at higher risk for TB	20 studies (4078)	With IGRA	11.6 (6.6 to 20.5)
		29 studies (18446)	With TST (>10 mm)	4.1 (2.6 to 6.5)
	Recent immigrant or refugee	4 studies (1597)	With IGRA	10.9 (6.3 to 18.9)
		4 studies (10785)	With TST (>10 mm)	4.0 (2.1 to 7.7)
	Immune suppressing medication	4 studies (141)	With IGRA	4.5 (0.1 to 262.8)
		7 studies (234)	With TST (>5mm)	6.0 (2.0 to 17.6)

Abbreviations: CI, confidence interval; IGRA, interferon gamma release assay; mm, millimeter; TB, tuberculosis; TST, tuberculin skin test

[a] Campbell et al, 2020 also conducted many subgroups and reported similar conclusions for people with various immune compromising conditions including HIV positive status, transplant recipients, and over the age of 65 years.

Indirect measures of clinical utility

No systematic reviews were identified that reported on the measures of impact on health services resources such as reduction in the number of unnecessary tests such as X-rays. Nor were any identified that reported on impact on medical decision making such as changes to antibiotics prescribed or adherence by patients to prescribed medications.

Ongoing Studies

While there are many ongoing studies in the field of tuberculosis, and many include the use of IGRA and other novel tests, we are not aware of any pivotal ongoing study that has the potential to substantially impact the relevance of this review.

Discussion

This overview of reviews identified a large body of evidence comprising many well-done systematic reviews reporting moderate to high quality primary studies. The evidence supports the diagnostic accuracy of IGRA. While there were some differences in reported accuracy outcomes, we observed consistently high specificity and NPV values, thus making IGRA especially useful as a rule-in test. This is in alignment with the current recommendations from the Canadian Tuberculosis Standards – 8th edition.[2,18]

Concordance between IGRA and TST was inconsistent. However, it is well acknowledged that there is no gold-standard test for LTBI and accepted that TST has false positives. Therefore, discordance is thought to be representative of improved accuracy of IGRA compared to TST, particularly because of the observed lower rates of positivity with IGRA. It is believed to be reflective of reducing potentially unnecessary treatment in people with otherwise false-positive findings with TST. There is a well accepted false-positive reaction with TST among people who have BCG vaccination, and differences in rates of positivity between IGRA and TST, as demonstrated in this overview, are in alignment with other bodies of evidence.[66]

Clinical utility, measured as the progression to active TB after a positive IGRA or positive TST result, is a key clinically important outcome. We observed with this overview of reviews that there was higher predictive value of a positive IGRA leading to active TB disease by approximately 2-fold compared with TST. Taken together with the findings from this overview of reviews of lower positivity rates among those who received IGRA compared to TST we can reasonably conclude IGRA has lower false-positive tests, particularly for certain populations such as those who have been BCG vaccinated. Findings are particularly notable in the subgroup analyses by Zhou et al 2020[62] which limited to head-to-head studies where all patients received both IGRA and TST and therefore isolates the likely impact of the differences in tests as it eliminates the potential impact of differences in after-test treatment access being the cause of observed differences.

Finally, IGRA tests are intended to yield binary results (yes/no) but there are a number of results that return as indeterminate findings. Indeterminate results with IGRA can be a sign towards some underlying immunodeficiency, hyperactivity of interferon gamma release, or a compromised state (e.g. the mitogen tube not having a reaction), among other possibilities.(Email communication, Angela Ma, PhD, May 21, 2024) It was observed that there are higher rates of indeterminate findings among those with immunocompromising disorders (e.g. transplant recipients and people living with HIV). Clinical experts informed us that an indeterminate finding within this group would be clinically meaningful as it

is a flag for further investigation, unlike a TST, which may simply yield a false negative finding.(email communication, Kevin Schwartz, MD, May 16, 2024, Elizabeth Rea, MD May 22, 2024)

Strengths and Limitations

The decision to conduct an overview of reviews was made after an exhaustive scoping effort including consultation with clinical experts. In identifying systematic reviews for inclusion, we considered their overall quality, ensuring the systematic reviews were well done with low risk of bias, comprehensiveness, and alignment with our research question. We followed methods for conducting an overview of reviews as outlined by Cochrane.[49]

We do acknowledge there may be missing systematic reviews due to our limitations to English language only, and we relied on other reviews having broader inclusion criteria to capture as broad body of evidence as possible which included non-English language primary studies. Due to the use of an overview of reviews approach, we were also not able to capture the most recent primary studies. For example, we are aware of a recent publication of a large population very similar and relevant to the Ontario population as well as an update to that paper very recently published publication on the clinical utility of progression to disease within findings from these two primary studies demonstrating alignment the results reported in this overview of reviews.[67,68]

The technology surrounding IGRAs and TST is continually advancing, and we are limited to that which has been published and included in other systematic reviews, potentially making our overview a few years behind the most current advancements in this space. With that said, this overview of reviews included many versions of IGRA tests over the years including the most recent versions that are currently in use in Ontario (Email communication, Elizabeth Rea, MD, May 22, 2024, Angela Ma, PhD May 21, 2024), and have been demonstrated to have similar concordance between IGRA versions.[32] It does not however account for the newest developments of laboratory methods for IGRA[69], or new types of skin testing based on antigen testing as an alternative to both IGRA and TST.[70]

Additionally, the TB population is broad, and heterogeneous, and LTBI does not have a gold reference-standard. This has led to an equally broad and heterogenous body of primary studies of evidence. Each review managed this diversity slightly differently and thus differences in conclusions and interpretations and resulting in many more subgroup and sensitivity analyses within the included reviews than presented in this overview of reviews. We selected and reported analyses that best aligned to our research question and relevance to the Ontario context. However, none of the reviews we included examined the optimal timing of multiple tests where conducting TST before or after IGRA may influence the overall diagnostic accuracy of test findings. We do recognize there is a booster effect from both tests, and this is already a consideration in the current Canadian Tuberculosis Standards – 8th edition.[18]

There are also limitations with the body of evidence to be considered. The absence of a proper reference-standard has led to some studies using microbiologically confirmed LTBI as their reference, while others have active-TB as their reference. The included reviews acknowledge this limitation of not having a direct test being problematic as it requires extrapolation for both sensitivity with active TB and specificity with low-risk populations.[54] Additionally, active TB is a different clinical immunologically distinct form of LTBI and therefore not seen as an appropriate adequate reference.[71]

Additionally, there is no universal standard for the TST test, with accuracy depending on the induration cut-off used by the primary studies. Many reviews limited the primary study inclusion criteria to a

specific cut off (e.g., >5mm) or conducted subgroup analyses based on 5, 10 or 15mm cut-offs. The higher the cut-off used the more accurate the TST becomes with regards to positivity, meaning there is more certainty around when a positive is a true positive. Thus, when comparing TST to IGRA the manner in which TST was conducted may change the interpretation of how different IGRA is compared to it. TST relies on clinical skills for both placement and reading, and is prone to interrater reliability errors.[72] Additionally, the TB incidence of a region influences the pre-test probability and therefore the calculations around accuracy of a diagnostic test. In regions with high TB incidence (e.g. >100 per 100,000 people) there will be fewer false positives and thus results may appear more similar compared to the IGRA test even for populations with known accuracy concerns such as those BCG vaccinated. This is reflected by many of the systematic reviews included and in this overview of review. [54,55,57,58,65]

Finally, there are many other factors that were not consistently accounted for across the included systematic reviews. For example, Yamasue et al[63] identified that advanced age is a risk factor associated with a false-positive finding of an IGRA test, however this factor is rarely accounted for in the identified included reviews of this overview of reviews. As well, a review that did not meet this overview's inclusion criteria, by Saag et al, 2018 [73] reflect that low BMI was a risk factor for LTBI, but we did not see this explicitly accounted for in our included body of evidence. In addition to the uses of IGRA that fell beyond the scope of this review such as for the diagnosis of active TB.

Conclusions

This overview of reviews summarizes the existing evidence on diagnostic accuracy and the clinical utility of IGRA for LTBI.

Interferon-gamma release assay was found to have good evidence as a rule-in test for LTBI due to consistently high specificity. The reviews reported slightly lower sensitivity among people who have underlying immunosuppression conditions (e.g., HIV positive, organ transplant, on cancer treatment, on dialysis) compared to a more general population. However, compared to TST (the standard test for TB), IGRA appears to have fewer false-positive results, as signaled by a lower risk difference of developing active TB among those who tested positive on both LTBI tests in head-to-head comparisons. This was particularly notable for the immunocompromised populations, as well as observed in children and the elderly (e.g., people in nursing homes) and those who have received an anti-tuberculin vaccination known as the BCG vaccine. Additionally, IGRA may be informative for people with immunocompromising conditions who are at risk for a false-negative result from a TST, as it yields indeterminate findings, signaling that further clinical investigation may be needed.

Therefore, the evidence supports the use of IGRA as a viable option compared to TST for testing LTBI, in accordance with situations outlined in the Standards.

Economic Evidence

Research Question

Based on the published evidence in a Canadian health care setting, what is the cost-effectiveness of the interferon-gamma release assay (IGRA) used alone (as a single test) or in sequential testing pathways with the tuberculin skin test [TST] compared with TST alone for supporting the diagnosis of latent tuberculosis infection (LTBI) in eligible populations, aligned with the recommendations of the 8th Edition Canadian Tuberculosis (TB) Standards[74]?

The population of interest is adults aged ≥18 years and children aged 2 to 17 years, with a focus on the assessment of IGRA when used for supporting the diagnosis of LTBI, in circumstances aligned (at least in part) with the recommended population for IGRA testing as per the Canadian TB Standards, 8th edition (hereinafter, the Standards).[74] The Standards proposed a strong recommendation for the use of IGRA as an alternative or additional test to TST for people who previously received a Bacille Calmette-Guérin (BCG) vaccine, immunocompromised people, people unable or unlikely to return to have their TST read, and people who are contraindicated for TST.

Methods

Economic Literature Search

We performed an economic literature search on January 10, 2024, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied. In addition to the databases used for the clinical search, we also used the Ovid interface in the Cochrane Central Register of Controlled Trials.

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them until June 18, 2024. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Cost-utility, cost-effectiveness, cost-benefit, or cost-consequence analyses

Exclusion Criteria

- Narrative or systematic reviews, non-comparative costing (feasibility) studies or cost-of-illness studies, letters/editorials, case reports, commentaries, abstracts, posters, unpublished studies

Study Setting

Inclusion Criteria

- Comparative primary economic analyses conducted from a public healthcare payer perspective of the government of Canada or of a Canadian province

Exclusion Criteria

- Comparative economic analyses conducted in a non-Canadian setting
- Comparative economic analyses conducted in Canadian settings from a wider (e.g., societal) or narrower perspective (e.g., hospital), not reporting cost-effectiveness outcomes by the payer perspective (i.e., not able to extract outcomes from the perspective of the Ministry of Health)

Participants/Population

Inclusion Criteria

- Adults 18 years and older and individuals > 2 years, undergoing testing with IGRA for the diagnosis of latent tuberculosis infection (LTBI), with a preference for the circumstances recommended by the 8th Edition Canadian Tuberculosis (TB) Standards[74]

Exclusion Criteria

- People undergoing testing with IGRA in circumstances that are not aligned with the 8th Edition Canadian Tuberculosis Standards including its use for screening (e.g., general populations, for employment such as health care workers or for confirming active cases of TB disease)

Interventions

Inclusion Criteria

- Interferon Gamma Release Assay (IGRA), as a single test (IGRA alone) or in combination with TST (e.g., IGRA as a follow-up test to TST as part of sequential testing)

Exclusion Criteria

- Laboratory developed IGRA, non-commercially available or non-Health Canada approved tests

Comparators

Inclusion Criteria

- Tuberculin skin test (TST)

Exclusion Criteria

- No testing
- IGRA test (e.g., studies comparing various commercial types of IGRA tests)

Outcome Measures

- Costs
- Health outcomes (e.g., life-years, cases of active TB, quality-adjusted life years [QALYs])
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios (ICERs, expressed as additional costs (in Canadian dollars [CAD, $]) per one active TB case averted, or $ per one QALY gained)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[75] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom. [76] The NICE checklist has two sections: the first is for assessing study applicability, and the second is for assessing study limitations. We modified the wording of the questions of the first section to make it specific to Ontario. Using this checklist, we assessed the applicability of each study to the research question and Ontario context (directly, partially, or not applicable). Next, we assessed the limitations (minor, potentially serious, or very serious) of the studies that we found to be applicable.

Results

Economic Literature Search

The search of the economic literature yielded 487 citations published between database inception and January 10, 2024, including grey literature searches and after duplicates were removed. We did not identify any additional eligible studies from other sources, including database alerts (monitored until June 18, 2024). In total, we identified 5 studies that met our inclusion criteria. See Appendix 6 for some examples of studies excluded after full-text review. Figure 3 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

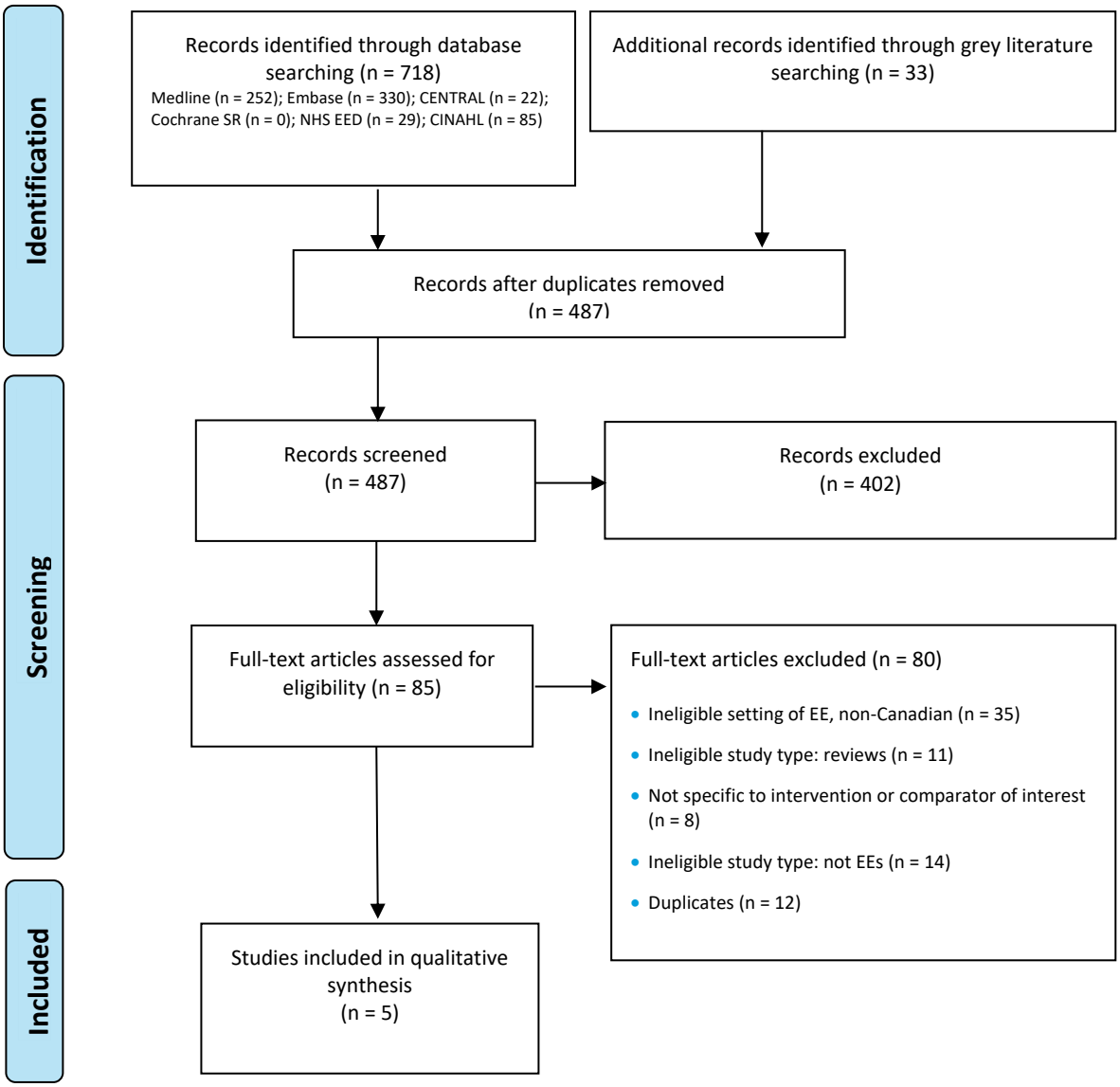

Figure 3: PRISMA Flow Diagram – Economic Systematic Review

PRISMA flow diagram showing the economic search strategy. The database search of the economic literature yielded 487 citations published from inception until January 10, 2024, including grey literature searches and after duplicates were removed. We identified no additional eligible

studies from other sources. After removing duplicates, we screened the abstracts of 485 studies and excluded 402 citations. We assessed the full text of 85 articles and excluded a further 80. In the end, we included 5 articles in the qualitative synthesis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; EE, economic evaluation.
Source: Adapted from Page et al.[50]

Overview of Included Economic Studies

Tables A3 and A4 in the Appendix 7 present study designs, populations, outcomes, and results of the 5 included studies that were published between 2007 and 2019.[77-81] Below, we summarize their findings.

Review of Methods of Included Economic Studies

Analysis Characteristics: Study Type, Perspective, Time Horizon and Discounting

All included economic evaluations were model-based cost-effectiveness analyses. Four studies [77-80] were conducted from the Canadian third-party payer perspective (i.e., the Ministry of Health, British Columbia). One study [81] did not specify the perspective used; instead, the authors reported that they considered government and health system costs (reflecting the Ontario Ministry of Health perspective) such as those related to LTBI screening and treatment, as well as patients' out-of-pocket costs. However, costs associated with TB-related death or disability were excluded.

The included studies modeled the natural and clinical history of LTBI and TB across two distinct populations. For the general population (immigrants and contacts),[77,79-81] studies projected outcomes over 10 to 25-year time horizons. For the immunocompromised population (i.e., patients with chronic kidney disease),[78] a shorter 5-year time horizon was used. All studies appropriately discounted both costs and health outcomes using the same discount rate, which was 3% in three studies.[77,80,81] and 1.5% in two studies.[78,79]

Study Populations

All studies considered populations that conformed to the recommended eligibility criteria for LTBI screening by the Canadian TB standards (the 7th and 8th editions[74,82]). Thus, study populations included a general population without comorbid conditions: all immigrants seeking permanent residence status,[77,79,81] a subgroup of immigrants who were flagged for post-medical TB surveillance,[79] or individuals who were close or casual contacts of confirmed or suspected active TB cases.[80,81] One study considered immunocompromised individuals, such as immigrants who had late-stage chronic kidney disease (CKD) and/or had initiated dialysis treatment.[78] Notably, no Canadian study specifically examined vulnerable populations such as people who experience homelessness, or children and young adults, as a separate population.

All studies addressed heterogeneity of the study populations regarding a potential risk of LTBI and used complex statistical procedures such as cohort stratification or variable adjustment to account for differences in age, BCG vaccination status, and incidence of TB in the country of origin. Data needed for these adjustments were sourced from the published literature or estimated from provincial databases of British Columbia and Ontario and from federal immigration data. The populations were stratified as following:

- Oxlade et al.[81] stratified the population by annual incidence of TB in the country of origin using the following categories: low (2/100,000), intermediate (60/100,000), and high (120/100,000)

- Campbell et al.[77,79] accounted for differences in TB incidence in the country of origin using the following categories: low (<30 cases/100,000 persons/year), moderate (>30 and <100 cases/100,000 persons/year), high (>100 and <200 cases/100,000 persons/year), and very high (>200 cases/100,000 persons/year)[78]
- Marra et al.[80] examined contacts exposed to a TB case and categorized their cohort by ethnicity to foreign-born, non-aboriginal Canadian-born and Aboriginal

For these cohorts sub-grouped by the risk of TB, the authors further estimated the LTBI prevalence:

- indirectly by using formulas to combine age of immigrants and incidence of TB in the country of origin, [81] or age of contacts, TST-positivity rate in British Columbia and country-specific incidence of TB [80]
- directly from linkages of the federal and provincial administrative database registry data [77-79]

Strategies: Interventions and Comparators

The intervention strategies across all studies included IGRA either as a single stand-alone test or combined with TST (as part of sequential testing). In the sequential testing pathway, individuals who tested positive on TST were subsequently assessed with IGRA. If IGRA yielded an indeterminate finding, a second IGRA test was included. All models included the therapy for LTBI or for active TB (if LTBI reactivated), following the positive test finding and additional work-up (where it was required).

In two studies in a general population of migrants[80,81] and in one study in people with CKD,[78] therapy with isoniazid (INH) was modeled (either as a preventative treatment for LTBI or therapy for active TB, depending on the modeled health state). The other two studies in migrants considered preventative treatment with either rifampin (RIF, 4 months) or INH (9 months) for LTBI. Therefore, these two studies included more interventions with IGRA to delineate the difference in LTBI treatment following positive IGRA test (e.g., IGRA/RIF, IGRA/INH, or sequential [SEQ] TST/IGRA testing: SEQ/RIF and SEQ/INH [77-79]).

The main comparator of interest was TST in two studies,[79,80] while the remaining studies considered TST as the intervention and compared it to no testing. Given that TST was the main comparator for our review, we excluded results pertaining to the no-testing strategy and reported results only for the comparisons between IGRA and TST strategies.

Outcomes: Health Outcomes and Costs

Long-term decision models predicted two key health outcomes, by the number of future active TB cases prevented (reported by three studies)[78,79,81] and QALYs (four studies)[77-80]. Utility weights used to estimate QALYs were sourced from published literature[77-79] and the British Columbia Centre for Disease Control (BC CDC) administrative databases.[80] Most studies indirectly estimated health utility weights using the Short-Form Six-Dimension (SF-6D) from the SF-36 questionnaire. These studies included individuals from British Columbia, Ontario or Quebec (sample size range: 71 to 162) with active TB or LTBI. Utility weights were reported for various health states or events considered in the models: e.g., LTBI (0.81-0.83, where the weights for LTBI and full health were assumed to be equal), active TB (0.68-0.69), utility decrements due to hepatotoxicity of the treatment (adverse effect of the INH therapy: —0.2), or due to hospitalization (—0.5). The model that examined LTBI screening in CKD patients

included additional utility weights related to late-stage CKD (e.g., living with CKD: 0.66; and initiation of dialysis: 0.62).

The second important outcome was the expected average total medical costs, often presented per person, in Canadian dollars. The total costs were predicted by simulating various cost categories such as costs of screening with TST or IGRA, costs of diagnostic workup (e.g., X-ray, initial and follow-up physician visits, blood tests, sputum test where appropriate), and treatment costs for LTBI or active TB. The section below describes details on the model structures, sourcing and estimation of key cost input parameters.

Analytic (Modeling) Technique and Model Inputs

The included economic analyses were supported by the complex decision-analytic models that simulated the natural and clinical course of LTBI and its progression to active TB over the long term (5-25 years), including a possibility of a secondary transmission. Thus, Oxlade et al. and Marra et al. developed Markov (state-transition) cohort models,[80,81] and Campbell et al. created individual-level discrete event simulation (DES) models for a general migrant population [77,79] and for people with late-stage CKD.[78] All models started with screening or diagnostic testing with IGRA or TST which was incorporated within the overall model structure [77-79,81] or distinguished as a separate decision tree followed by different state-transition sub-models.[80] For example:

- Oxlade et al.[81] developed a model with four distinct TB-health states (i.e., non-infected, recent LTBI, active TB, and long-standing LTBI and the death state) and all diagnostic and treatment activities occurred in the first year of simulation. Depending on the test or treatment results, people who survived the first year remained in the same health state or moved to another state such as LTBI, active TB or long-standing LTBI
- Marra et al.[80] modeled the progression of LTBI in contacts by simulating firstly the diagnostic pathways stratified by ethnicity and BCG status; each of these sub-cohorts had different probabilities of recent LTBI, remote LTBI, active TB or no infection. LTBI was confirmed with IGRA or TST and the cohort transitioned into the Markov sub-model (named "reactivation of TB") including 4 health states: at-risk of reactivation, active TB, previous TB, and death. The progressions of those with active TB or with no infection were simulated through another two sub-models ("active TB" and "normal life" models, which health states were not reported in the article).

The DES models in migrants by Campbell et al [77-79] simulated individual-level event pathways for each migrant accounting for various events and health states following immigration. Two cohorts were separated from the beginning of the simulation:

- A bigger cohort (i.e., healthy), not flagged for immigration TB surveillance (by a formal program at Immigration, Refugees, and Citizenship Canada (IRCC)
- A smaller cohort, flagged for immigration TB medical surveillance (i.e., about 6,100 individuals or 2.4% of the whole cohort of 260,600 people):
    - People flagged for the TB surveillance followed the screening steps (i.e., screening for LTBI with TST or IGRA), after testing transitioning into the healthy or LTBI state, depending on the test result. From these two health states, they could further transitioned to:

- Active TB (could occur from: 1) LTBI because of reactivation, and 2) full health because of secondary transmission; also, third option was a relapse after TB treatment), or
- Death state (dead due to background [all-cause] mortality, TB itself or adverse reaction to TB therapy)

The DES model for a CKD population simulated individual treatment pathways of LTBI or TB in people with CKD by including 4 health states after TST/IGRA screening: late-stage CKD, dialysis, active TB and dead (all-cause or TB-related).[78]

Model Inputs

The model inputs in all studies represented the risk of LTBI or of active TB for the Canadian population. They accounted for medical evaluations associated with the screening (e.g., clinic visits, X-ray, additional workup for those that tested positive on X-Ray) or the treatment based on Canadian data. They included the costs of LTBI or TB therapies, likelihoods of adherence to and completion of the initiated treatments and simulated a possibility of the major TB treatment side effect such as hepatotoxicity and its consequences (e.g., hospitalization or death). As mentioned above, the models also accounted for a possibility of secondary transmission. We below discuss in detail inputs related to diagnostic testing of LTBI with IGRA or TST.

Uptake of LTBI Screening

Modeling of the uptake of IGRA or TST testing differed among the included studies. Both Oxlade and Marra et al. assumed 100% uptake of the initial IGRA or TST test, [80,81] but Marra et al.[80] accounted for some probability of not returning for TST reading (i.e., second TST visit, 8% of the cohort) or not returning for the additional (second) screening test if recommended (30%). Campbell et al.[77-79] assumed that all migrants would be offered LTBI screening but accounted for their incomplete participation in surveillance (completed by 60% of the flagged cohort)[79] and by 76.7% of migrants with CKD)[78] and non-adherence to a full medical evaluation following the screening (e.g., 78% of migrants and 88% of migrants with CKD). They also accounted for incomplete rates of reading of the TST test (completion rate: 72%, migrants to Canada; 91%, migrants with CKD). [78,79]

Sensitivity and Specificity of IGRA and TST for LTBI

In two studies by Oxlade et al (in healthy migrants) and Marra et al (in contacts), [80,81] the sensitivity of TST and IGRA was assumed to be the same for both tests and close to perfect (0.95[81] and 0.99 [80]. In the remaining three studies,[77-79] the sensitivity of IGRA was higher than that of TST: for example, in migrants, it was 0.89 vs. 0.78; in people with CKD and dialysis (i.e., immunocompromised), the sensitivity of IGRA was 0.78 (CKD) and 0.68 (dialysis) versus the sensitivity of TST, 0.65 and 0.52, respectively. Also, the sensitivity of these two tests did not depend on BCG vaccination status.

The BCG-vaccination status affected the specificity of TST, while it did not change the specificity of IGRA in all examined populations (e.g., healthy migrants or people with CKD). The specificity of TST in BCG-vaccinated people, ranged between 0.60 to 0.69 in four studies.[77-80] One study additionally differentiated TST specificity by the age of vaccination: thus, the specificity was 0.60 for those vaccinated in older childhood/adolescence compared with 0.92 for those vaccinated in infancy.[81] In contrast, the specificity of TST in non-vaccinated was almost perfect (0.97-0.99), and similar to the specificity of IGRA (0.96-0.98).[77-81]

The accuracy inputs for TST and IGRA for diagnosis of LTBI were informed by the published studies and the BC CDC registry. Oxlade et al. and Marra et al. ascertained the accuracy of one commercial brand of IGRA (i.e., QuantiFERON), while Campbell et al. conducted their own systematic reviews with meta-analyses that combined two commercial types of IGRA tests (i.e., QuantiFERON and T.SPOT which had similar diagnostic accuracies).[77-81] In addition, the four of five modeling studies[77-80] considered a possibility of indeterminate results with IGRA (probability range: 0.02 to 0.07 based on the published data) and a need for the second testing to resolve the indeterminate test result.

Costs of IGRA and TST

The type of IGRA test costed in all studies was the QuantiFERON-TB or QuantiFERON-Gold. The assumed cost was between $41 (2004, CAD[81] and $54 (2016, CAD [77-80]) in the reference case, and it ranged between $31 and $62 (2016, CAD) in the sensitivity analysis. This cost included components related to the costs of commercial kits, labour (staff time), equipment and consumables. The IGRA cost was based on data from the BC CDC registry [77-80] or the manufacturer[81]. The cost of a complete TST test was between $12 (2004, CAD) and $31 (2016, CAD) in the reference case, and it ranged between $24 and $38 (2016, CAD) in the sensitivity analysis. This cost included the test cost and labour time (2 visits with nurses: skin injection and test reading) and was sourced from the literature[81] or BC CDC registry.[77-80] Campbell et al. included a separate cost for an incomplete TST test at $21 (2016, CAD) in the reference case, ranging between $17 and $25 (2016, CAD) in the sensitivity analysis. [77-80] None of the included studies reported if the IGRA or TST test costs were adjusted for the mark-ups.

Statistical Analyses: Reference Case and Sensitivity Analysis

All studies used a deterministic approach for estimation of the expected mean costs and mean effects (i.e., the mean number of TB cases averted and mean QALYs) in the reference case analysis (also known as base case). The sensitivity analyses examined changes in numerous input parameter values or assumptions related to the accuracy of IGRA, prevalence of LTBI or active TB, reactivation, secondary transmission or relapse rates, completeness of screening or adherence to therapy, effectiveness of LTBI and TB therapy, utilities, costs of tests and therapies, discount rate, duration of time horizon and willingness-to-pay values. Two studies published in 2007 and 2008[80,81] also used numerous deterministic one-way or two-way sensitivity analyses to address uncertainty in the model input values. Three more recent studies [77-79] (published in 2017 and 2019) assigned probability distributions to the input parameters and conducted probabilistic sensitivity analyses for individual-level state-transition models (including between 50,000 and 100,000 individuals [iterations] in the inner loop, and between 1,000 and 2,000 replications in the outer loop). In addition to this, they used one-way deterministic analyses on the assigned range values for important input parameters to address robustness of the reference case model results. Lastly, the included studies reported estimates for all included strategies; thus, we were able to report these values as is or to estimate incremental costs and effects from the data reported for IGRA and TST strategies. Also, results of the sensitivity analyses that were compared with the results of the base case analyses which considered TST as a main comparator were deemed fully relevant to our review.

Summary of Findings: Incremental Cost-Effectiveness of IGRA versus TST for LTBI

Reference Case Results

General Population: Migrants

Studies conducted in migrants suggested that IGRA as part of sequential diagnostic testing with TST or a single test was cost-saving or cost-effective compared with TST alone, particularly for BCG-vaccinated people or those coming from countries with intermediate (moderate) to very high TB incidence rates (Tables A3 and A4, Appendix 7).

A study by Oxlade et al.[81] showed that diagnostic testing with the IGRA QuantiFERON Gold (QFT) and TST as a single option was equally effective in preventing active TB, regardless of differences in the country-specific TB incidence rates:

- QFT alone was cost-saving for individuals receiving BCG vaccines in older childhood or adolescence because the specificity of TST for this group was 0.60 compared to 0.92 in BCG-vaccinated in infancy or 0.99 in non-vaccinated (—$6,220 to —$64,740 per 1,000 persons). For the later two groups, IGRA (QFT) alone was associated with an increase in costs ($16,110 to $35,790, per 1,000).
- For the sequential TST/QFT testing (i.e., initial test with TST, followed by QFT in those who were TST-positive) compared with TST alone, the study showed equal health benefit only for those migrating from low-TB incidence; sequential testing resulted in cost-savings for all people coming from low-incidence countries regardless of BCG-vaccination status (savings per 1,000 ranged between —$2,951[non-vaccinated] and —$102,291 [BCG-vaccinated when older, namely, older childhood/adolescence]).
- TST/QFT vs TST alone in non-vaccinated or vaccinated in infancy migrating from countries with the medium or high incidence of TB sequential resulted in:
  - additional costs ($3,632 to $27,412 per 1,000 persons) in general
  - cost-savings only for groups of migrants who were BCG-vaccinated in older childhood/adolescence (—$49,498 and —$14,598 per 1,000 persons, for migrants from countries with intermediate and high TB incidences, respectively].

Two studies by Campbell et al.[77,79] accounted for BCG-vaccination status but differently stratified the population of migrants which caused slightly different and more nuanced findings:

- The first 2017 study considered immigrants to Canada and reported results for the cohort flagged for TB medical surveillance (2.4% of the whole cohort—6,100 people):[79]
  - Compared with TST (with INH), IGRA alone (combined with therapy: INH or RIF) was slightly more effective (small increments in QALYs) and more cost-saving than the sequential TST/IGRA options (but for this sub-group in general all IGRA options were less costly than TST).
  - For the whole cohort (N=260,600 people), none of the IGRA interventions were less costly or cost-effective (ICERS > $100,000/QALY) compared with the reference case (IGRA vs. TST/INH for those flagged for surveillance).

- The second 2019 study by Campbell et al.[77] stratified migrants by incidence of TB in back-home countries.
  - Compared to TST/INH (i.e., TST alone combined with INH in test-positive), all IGRA options were associated with lower costs and small QALYs gains regardless of TB incidence.
  - These findings differed slightly when IGRA options were compared to TST alone combined with RIF (TST/RIF), which was cheaper and more effective comparator than TST/INH.
  - When the cost-effectiveness of all IGRA strategies was compared to TST/RIF and among themselves, the cost-effectiveness of IGRAs depended on the country-specific TB incidence. The best option for migrants coming from:
    - low-, moderate- or high-TB-incidence countries was sequential testing with TST/IGRA followed by RIF therapy for LTBI (i.e., SEQ/RIF)
    - very-high-TB incidence countries, it was IGRA alone followed by RIF.

We also estimated that for migrants coming from moderate and high-incidence TB countries, IGRA alone was cost-effective because the ICERs of IGRA/RIF vs. sequential TST/IGRA [SEQ/RIF] were less than $25,000/QALY gained (estimated ICERs for people coming from moderate TB-incidence, high TB-incidence and very-high TB-incidence countries, respectively were $23,620/QALY, $10,162/QALY and $4,170/QALY).

General Population: Contacts

Findings of two studies [80,81] in populations of contacts with undiagnosed LTBI exposed to active TB cases suggested that IGRA for BCG-vaccinated contacts only (and not for all) was the most economically viable option.

Oxlade et al.[81] examined use of TST and IGRA compared with no screening in close and casual contacts. Because of lack of detailed reporting (mean costs/effects per strategy), we were not able to estimate cost-savings with QFT as compared with TST. However, this study showed that both QFT and TST were cost saving options but for close contacts who are BCG-vaccinated when in older childhood or adolescence, QFT was the preferred option (more saving than TST).

Marra et al.[80] found very small changes in QALYs (0.00 to 0.0004) with IGRA as a single diagnostic option or in the sequential testing (following TST-positive results) compared with TST alone in foreign-born, Canadian-born and Aboriginal contacts. Compared with TST alone, savings ranged from $0.61 per contact for the strategy with IGRA alone in BCG-positive contacts and TST for the rest to $2.54 per contact for sequential TST/IGRA testing in BCG-positive contacts, and TST for the rest. Compared with TST, IGRA alone for all contacts was associated with additional costs of $30.08 per person, and small increase in QALYs of 0.0004 and was ranked as a the least cost-effective option. The option with the highest net monetary benefit was selective use of IGRA for BCG-vaccinated people and reserving TST for all others.

Immunocompromised Populations

We found favorable economic evidence for the use of IGRA versus TST in Canada for the diagnosis and prevention of LTBI in one type of immunocompromised people such as people with late-stage CKD. One Canadian study compared no LTBI testing with testing with IGRA or TST (both tests combined with INH for treatment of LTBI) in migrants with late-stage CKD and/or dialysis.[78] Based on the data reported in

this study, we estimated that IGRA/INH dominated TST/INH because it was associated with small increments in QALYs and cost savings in both patient groups, and regardless of the age or incidence of TB in back-home country. The QALY gains ranged between 0.00004 to 0.0009 in people with late-stage CKD and between 0.0001 and 0.0014 in people with CKD initiating dialysis. The cost savings ranged from $46.05 to $79.32 per person, for people with late-stage CKD and from $53.04 to $112.22 for those with dialysis.

Sensitivity Analysis Results

In two studies that included the probabilistic sensitivity analysis, the testing with IGRA (combined with the LTBI therapy) remained highly likely to be cost-effective in a sub-group of migrants flagged for medical TB surveillance (probability ranged from about 99% at willingness-to-pay of $10,000/QALY, 95% at $50,000/QALY to about 65% at $100,000/QALY, Cambel 2017), and in migrants with late-stage CKD (>75% at $50,000/QALY, Campbell 2019). As in the base-case, IGRA screening of the whole population of migrants immigrating to Canada was not likely to be cost-effective.

The deterministic sensitivity analyses of the two studies[79,80] used TST as the main comparator rather than no screening.

- In migrants, Campbell et al. [79] found that IGRA would not be cost-effective at $100,000/QALY with the following input parameter changes: high sensitivity and specificity of TST (0.95 and 1.00 vs. 0.78 and 0.60 in base case), perfect completion of TST testing (100% vs.72%), high cost of treatment of LTBI/TB ($686 vs. $575), high probability of dying from TB (8% vs. 4%), low proportion of people adherent with TB treatment (high proportion of indeterminate IGRA results (18% vs. 6%), smaller probability of BCG vaccination in countries with high prevalence of LTBI and TB (50% vs. 94%) and higher cost of IGRA ($62 vs. $54 [2016 CAD])
- In contacts, Marra et al. [80] found that IGRA for all contacts (not only BCG-vaccinated) would be cost-effective at $50,000/QALY if they assumed a higher prevalence of LTBI (30% vs. 10% in base case), higher completion rate of LTBI therapy (75% vs. 61%), higher rate of TB reactivation (0.24 to 0.60% vs. 0.18-0.55% in base case) or a higher willingness-to-pay value (>$100,000/QALY vs. $50,000/QALY). They also found a threshold price for IGRA at $57 (vs. $45 [2005 CAD] in base case), above which IGRA testing would not be cost-effective (at willingness-to-pay of $50,000/QALY).

In summary, favorable cost-effectiveness of IGRA versus TST testing in specific migrant populations or groups of contacts remained robust; it could vanish if some important parameters take values at their less likely extremes.

Applicability and Limitations of the Included Studies

Appendix 8 provides the results of the quality appraisal checklist for economic evaluations applied to the included studies (Tables A5 and A6). Three studies[78-80] were directly applicable to the Canadian/Ontario setting and our research question because they:

- examined populations that are recommended for IGRA testing under the Canadian TB standards,[74,82]
- the incremental cost-effectiveness of IGRA versus TST could be estimated from the published data,
- were done from the third-party payer perspective and used the population, resource, and cost parameters transferable to the Ontario health care system, and
- used the discount rate for cost and utility outcomes, as recommended at the time of publication

Thus, two more recently published studies discounted the future costs and QALYs at the currently recommended rate of 1.5% by the CADTH guidelines, [78,79] while the 2008 study used the previously recommended rate of 3%. The discount rate was not suggested to be the major driver of the cost-effectiveness results in these studies.

Two other published studies judged as partially applicable were downgraded because they used "no screening/no testing" comparator, and we were not able to estimate the incremental cost-effectiveness versus TST alone for some populations considered in the analysis, and were not able to extrapolate the applicability of the sensitivity analyses results; these studies also applied the higher (3%) discount rate for their outcomes. [77,81]

We found that all studies used very complex, comprehensive and valid methods for modeling of the natural and clinical courses of LTBI and active TB and IGRA or TST testing and for assessing parameter and decision uncertainty. Therefore, we found all studies associated with minor limitations. Few limitations such as use of the probabilistic versus deterministic approach to the analysis are related to older modeling practice guidelines available at the time of publication. Also, all studies were done by academic groups recognised in the Canadian TB research field that reported no conflicts of interest. We did not detect any risk of publication bias.

In general, all studies were consistent in the overall conclusion pertinent to use of IGRA testing to support the diagnosis of LTBI and prevention of future active TB in populations at high-risk of LTBI reactivation in Canada.

Discussion

We reviewed five model-based economic studies that examined the cost-effectiveness of IGRA testing for supporting the diagnosis of LTBI in high-risk populations (i.e., migrants without or with co-morbid conditions and contacts), from the perspective of a third-party payer in Canada. [77-81] All included studies were of good quality (i.e., only minor methodological limitations) and three studies[78-80] were directly applicable to the Ontario context and the research question.

We found that compared to TST alone, the cost-effectiveness of IGRA as a single test or in combination with TST (sequential testing) is the most favourable for BCG-vaccinated adults or those at high risk of LTBI migrating from countries with intermediate (moderate) to very high incidences of TB. Other research studies indicated (i.e., BCG-vaccination Atlas[83,84]) that countries with moderate to very-high

incidences of TB generally implement nation-wide BCG vaccination policies; this suggests that categorizing the cost-effectiveness findings by the number of active TB cases per country (or country-specific TB incidence) could serve as a proxy measure for the BCG vaccination status.

Restricting access to IGRA testing to specific populations at high risk is in agreement with the current 8th Edition Canadian TB standards[74] that recommend consideration of IGRA as an alternative to TST for the following people or situations such as:

- previously vaccinated with BCG in infancy (IGRA recommended for ages 2-10 years) or after infancy (IGRA recommended at any age)
- limited TST capacity
- high chance of no return for 2nd follow-up with TST (TST reading)
- high concerns of a false negative result with TST (e.g., immunocompromised conditions or associated therapies)

These recommendations are also aligned with the findings of one economic study included in our review that showed IGRA screening of all immigrants to Canada to be cost prohibitive.[79]

All studies included adult populations. One of the included studies stratified the results by the age of BCG vaccination which was closely related to differences in the specificity of TST: it was 0.92 if BCG vaccine was given in infancy versus 0.60 if received when older (childhood or adolescence).[81] IGRA has been recommended for individuals > 2 years that received BCG vaccine because TST alone was found to result in a higher rate of false-positive results.[85] In addition, Marra et al [80] considered Canadian-born Aboriginal people as part of the study population of contacts exposed to active TB and estimated input parameters from the British Columbia data: IGRA combined with TST for all BCG-vaccinated people was the most cost-effective strategy, regardless of subgrouping for the ethnicity.

We identified only one economic study in people with late-stage CKD and/or dialysis who could be considered immunocompromised because of their underlying comorbid condition.[78] Compared to TST, IGRA testing was cost-effective in this population. In this study, the model inputs related to the test performance of IGRA were assumed to be higher for BCG-vaccinated people. Although the rationale behind this assumption remains unclear, this may be due to the ability of IGRA to provide indeterminate results in instances of an insufficient immune response, leading to less false negatives in the detection of LTBIs. In addition, research studies have also suggested higher sensitivity of IGRA in patients with CKD compared to TST.[86,87] Assuming similarities in relevant inputs related to the diagnostic cost-effectiveness modeling of IGRA and TST, we can expect similar direction of cost-effectiveness findings for other patient populations with underlying immunocompromised conditions such as people with human immunodeficiency virus (HIV), CKD, and organ transplant patients.

Although the cost-effectiveness of IGRA across the included studies had a favorable direction for populations of interest, in sensitivity analyses, assessments of the parameter uncertainty suggested some influential drivers of cost-effectiveness results especially when extreme values were applied. For example, Marra et al.[80] found that IGRA would be the optimal strategy if its sensitivity was at least 0.80 (even if the specificity was at 0.90); given that the IGRA tests accuracies could only increase over time for the next generations of the test, these threshold cost-effectiveness findings related to the lower sensitivity and specificity of IGRA might not be applicable. Furthermore, in a sensitivity analysis relatively large increases in the cost of IGRA were associated with overall cost increases and lack of cost savings; nevertheless, if high volumes of IGRA tests were to be offered to testing LTBI in the populations of

interest, the cost of IGRA would have been contained. Also, substantial decreases in screening participation and completion of LTBI treatment could affect the cost-effectiveness of IGRA. While these results are hypothetical in nature, they show that barriers to IGRA testing (such as participation) ought to be considered seriously by policy and decision-makers, and additional supports need to be ensured for successful implementation.

Findings of Other Systematic Reviews and Non-Canadian Economic Studies

Several systematic reviews were identified in the literature.[71,75,88-92] The most recent reviews found that the addition of IGRA for screening and supporting the management of LTBI in people at high risk represented good value for money. For example, Mahon et al.[90] continued with the methods 2011 Nienhaus review[91] and examined methods and results of 32 economic studies, published between 2011 and 2021 (3 studies from Canada, Campbell et al.: 2017-2019); these studies assessed the cost-effectiveness of LTBI testing (with IGRA and TST) in high-risk groups populations such as migrants, contacts of people with active TB, children, healthcare workers, immunocompromised and people with HIV. They found quality of the primary studies to be high, while recognizing concerns in the variability of input parameters across the studies as did Nienhaus et al.[91] in their previously conducted 2011 review. Mahon et al.[90] concluded that the inclusion of IGRA in LTBI screening in people at high risk was cost-effective for high-income countries, and that the cost-effectiveness of IGRA depended on the prevalence of LTBI. Yoopetch et al[75] reviewed 11 economic evaluations on LTBI screening of contacts of TB patients published until 2022 (2 studies from Canada (Marra et al., 2008 and Oxlade et al., 2007)) and found that the use of either IGRA alone or IGRA as a confirmatory test for a positive TST was cost-effective in high-income countries (such as Germany, Switzerland, Canada, Japan, France, US, UK). Greenaway et al.[89] reviewed the effectiveness and cost-effectiveness of screening for LTBI among migrants to the European Union to inform migrant screening guidelines. They included 16 economic studies of which 8 were model-based analyses (1 study from Canada: Oxlade et al., 2007 [81]). They concluded that the economic evidence was limited and that the most cost-effective approach could be targeting young migrants from high TB incidence countries. They found that the cost-effectiveness of screening strategies was dependent on the test characteristics, comparative options, cost of tests and BCG-vaccination status. The sequential approach to LTBI screening (TST followed by IGRA) was preferred over TST and IGRA as a single test, especially in people who had a high likelihood of a true positive TST (i.e., LTBI prevalence > 5%) and were BCG-vaccinated after infancy.

In addition to these reviews, in 2016, Auguste et al. published a NICE heath technology assessment from the UK health care system perspective.[71] They investigated the clinical effectiveness and cost-effectiveness of screening tests (IGRAs [QFT-GIT[Gold-In-Tube] and T-SPOT.TB] and TST) for LTBI diagnosis in three populations at higher risk of progression from LTBI to active TB: 1) children, 2) immunocompromised people and 3) individuals who have recently arrived in the UK from high-incidence countries. The economic analysis showed that the most-cost-effective option for children and people with low immunity was the sequential testing including IGRA (i.e., children: TST (≥ 5 mm) followed by IGRAs if TST-negative, ICER [vs. TST]: £18,900 per QALY gained; and immunocompromised people: IGRA followed by TST if IGRA-negative: ICER of £18,700 per QALY gained). The analysis in all recently arrived migrant cohorts to the UK did not categorize IGRA's diagnostic accuracy by BCG-vaccination status; thus, they found that TST alone (≥ 5 mm) was the most cost-effective strategy with an ICER of approximately £1,500 per QALY gained compared with IGRA (QFT-GIT). More recently, in 2021, Sousa et al.[93] compared two-step TST/IGRA (QuantiFERON Gold Plus) with the current IGRA-only screening strategy in a total of 1,125 close contacts residing in Porto, Portugal between (IGRA-only contacts included 578 immune-competent individuals exposed to individuals with respiratory TB). Using medical records registry data,

they estimated clinical effectiveness and costs (direct and non-direct medical costs related to LTBI screening, excluding treatment costs) of the two strategies. The cost of IGRA (QuantiFERON-TB Gold Plus) was estimated at €38.23 (€37.66 for the test and €0.57 for disposables) and the cost of TST at €1.31 ((€1.00 for tuberculin and €0.31 for disposables). The IGRA-only strategy was costlier than the sequential option (e.g., total mean costs: €55.21 vs. €42.71, per screened person), but was associated with increased odds of establishing the LTBI diagnosis, hence preventing more TB cases (adjusted OR = 2.12, 95% CI = 1.53 to 2.94). The authors reported the ICER of €106 per LTBI diagnosis.

Several original non-Canadian economic analyses found favorable results for the cost-effectiveness of IGRA in immunocompromised people due to their underlying condition such as people with HIV or organ transplant patients. For instance, Auguste et al.[94] in their 2022 cost-effectiveness analysis in people with HIV (the UK health care system perspective) found that sequential testing with IGRA (QFT-GIT) followed by TST was the most cost-effective option at the NICE threshold of £20,000 per QALY but they warned on the paucity of test accuracy studies in this population. Also, Kowada et al. examined the cost-effectiveness of IGRAs versus TST and no screening in kidney, liver and lung transplant adult recipients using a societal Japanese perspective and found IGRA (QFT) to be the most cost-effective option, regardless of BCG-vaccination status.[95]

Equity Considerations

LTBI and active TB disease represent serious public health conditions frequently associated with stigma.[45] As mentioned in the clinical review (background), there is inequity in access to IGRA testing in Ontario because it is only available to those who can pay it out of pocket or can access laboratories offering this testing. IGRA testing requires a single visit and is more likely to be completed by some people compared to TST– in particular, those with low-paying jobs are more likely to be unable to take time off work twice (TST) vs once (IGRA), and/or suffer financially if they do so. Also, the accuracy of IGRA is not affected by a person's BCG-vaccination and delivers less false negative results in immunocompromised patients. Therefore, IGRAs may represent better clinical choice in certain populations as defined by the current Canadian TB Standards[74]. The economic studies in this review accounted for many important factors indirectly related to inequities such as variability in the LTBI prevalence, BCG-vaccination status, ethnicities, completion of TST reading (and costs associated with incomplete readings) and participation in screening.

Strengths and Limitations

We thoroughly assessed the published economic studies in Canada and found consistency in their methods and their results with respect to cost-effectiveness of IGRA compared to TST for some high-risk populations. This review fills in some gaps in the literature suggested by the most recent CADTH assessment of the evidence including the TB guidelines.[96-98] The majority of the included studies considered the public-payer perspective; if they were to use the societal perspective and to account for indirect (productivity loss) and non-medical direct costs, then the incremental cost-effectiveness of IGRA (as a sequential or single test) versus TST alone would have been likely larger.

Limitations of our study are related to the limitations of the current evidence which relate to the lack of Canada-based economic studies in immunocompromised people, people unlikely to return for TST reading or children. Our review suggests that IGRA (as a sequential test to TST or a single test) in certain populations likely represents good value for money, but our inferences are conditional on the parameter assumptions of the published studies. Thus, in a new analysis, changes in QALYs would likely be similar

to those reported, but the current list price of IGRA in Ontario could be similar or higher than the one used in the published studies, even after adjustment for the inflation (e.g., $90-$100); therefore, the reported savings could be smaller. Therefore, an Ontario-based budget impact analysis is needed to estimate the costs needed to support publicly funding of IGRA testing as an alternative option to TST in certain eligible populations in Ontario. Lastly, this review did not consider newly developed TST tests[99] which may have similar accuracy as IGRA for all populations of interest because this test is not currently unavailable in Ontario and Canada.

Conclusions

Based on our review of the 5 economic studies from Canada, IGRA (either as a stand alone or in sequence with TST) is cost-effective compared with TST alone for supporting the diagnosis of LTBI in high-risk populations that are aligned with the current Standards[74].

Primary Economic Evaluation

Based on our review of 5 economic studies from Canada,[77-81] the interferon-gamma release assay (IGRA), used either as a sequential test following the tuberculin skin test (TST) or as a stand-alone test, is considered a cost-effective testing approach compared with TST alone for supporting the diagnosis and management of latent tuberculosis infection (LTBI) in high-risk populations, as recommended by the current Canadian Tuberculosis Standards, 8th edition (hereinafter, the Standards).[74] All reviewed studies were of good quality (i.e., minor methodological limitations) and 3 studies[78-80] were directly applicable to the Ontario context and our research question.

We evaluated the certainty of this body of evidence (i.e., directly applicable studies) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. We did not identify any serious limitations in the following GRADE[100,101] domains (Appendix 9, Table A7; GRADE: High):

- Methodological quality of published models, including modeling (structural), method, and parameter assumptions (i.e., credibility of the models and their limitations)[101]
- Inconsistency and imprecision of the reported cost-effectiveness estimates[101] (e.g., variability of estimates in probabilistic and other sensitivity analyses, switch in the cost-effectiveness of the compared strategies)
- Applicability of the published study findings to the Ontario context and our research question (i.e. indirectness)[100,101]
- Publication bias[101]

If we were to conduct a primary economic evaluation, it would be highly likely that our cost-effectiveness analysis would use similar model structures and input parameter values as the existing studies.[77-81] Therefore, limitations in the currently published evidence would likely recur in our evaluations. Furthermore, we anticipate a very small difference in QALYs between IGRA and TST across all populations of interest; consequently, the cost-effectiveness of IGRA would primarily hinge on the differences in expected mean costs between the strategies. Therefore, we leveraged the existing directly applicable economic evidence[78-80] instead of conducting a primary economic evaluation for Ontario. We conducted a budget impact analysis to estimate the total costs, resources, and net budget impact of publicly funding IGRA testing for supporting the diagnosis and management of LTBI in certain eligible populations in Ontario, as defined by the Standards.[74]

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding an interferon-gamma release assay (IGRA) test, as single test or in combination with TST, for latent tuberculosis (TB) infection in eligible people (below) according to the Canadian Tuberculosis Standards, 8th edition (hereinafter, the Standards)?[74]

We estimated the budget impact of publicly funding IGRA testing in the following subgroups of people at high risk of latent TB infection (LTBI)[74] in whom IGRA is the preferred test as per the Standards[74]:

- People who have previously received a Bacille Calmette-Guérin (BCG) vaccine (e.g., immigrants to Ontario, certain First Nation communities), including:
    - Children aged 2 to 10 years who had previously received a BCG vaccine against tuberculosis
    - Persons aged ≥10 years who received a BCG vaccine after infancy (>1 year of age), or who received a BCG vaccine more than once and/or are uncertain about when they received it
- Contacts (people recently exposed to active TB cases) who have been BCG vaccinated or who are unable or unlikely to return for the TST reading (their second TST visit)
- People with comorbid conditions and/or who are undergoing treatments that may cause low immune function and who may test incorrectly as negative (false negative) with TST, such as people with HIV, late-stage kidney disease, or cancer, or who are organ-transplant recipients or are taking immunosuppressant drugs

Methods

Analytic Framework

We estimated the budget impact of publicly funding IGRA testing using the cost difference between two scenarios: (1) current clinical and public health practice without public funding for IGRA testing (the current scenario), and (2) anticipated clinical practice with public funding for IGRA testing (the new scenario). Figure 4 presents a schematic of estimation of the budget impact. More details about the budget impact model structure can be found in a later section.

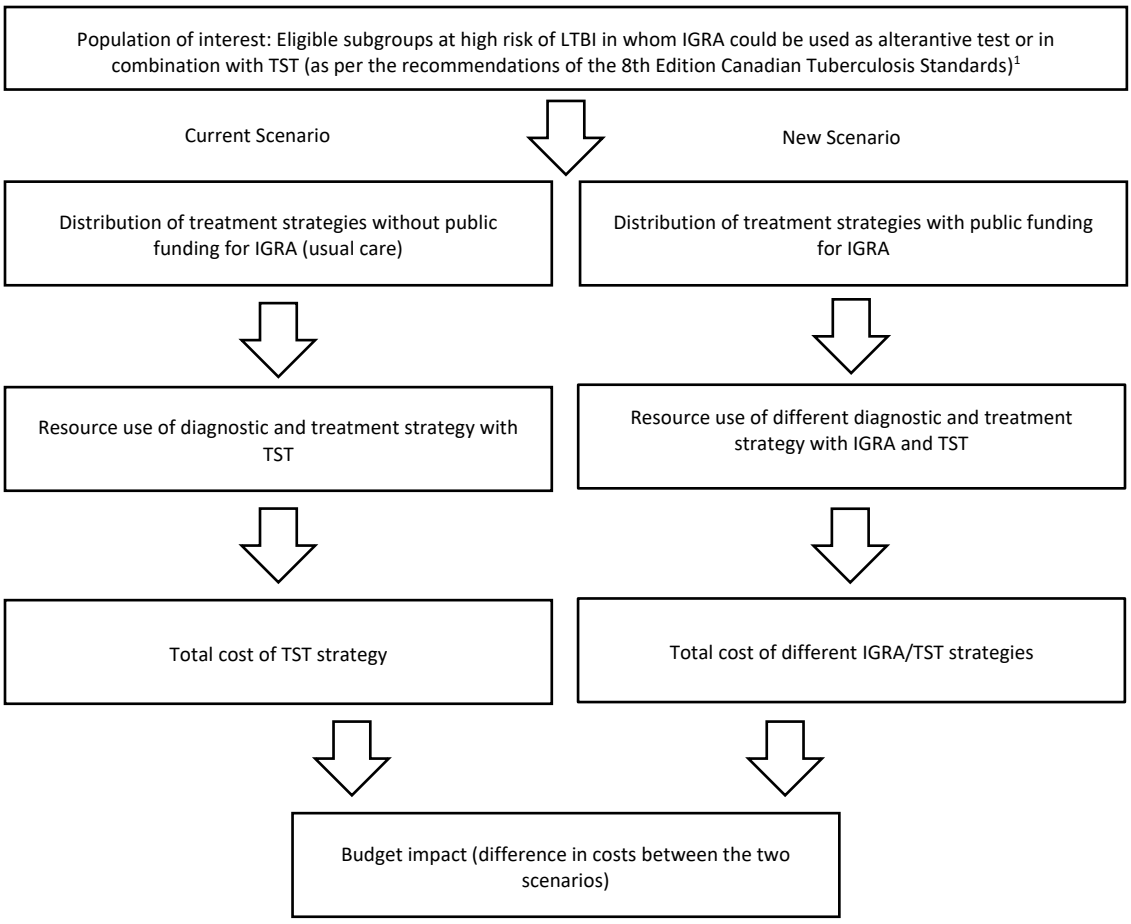

Figure 4: Schematic of Budget Impact Estimation

Flow chart describes a simplified model for estimation of the budget impact analysis. For a specific population of interest, we created two scenarios: the current scenario, which would explore the distribution of diagnostic and treatment strategies, resource use and total costs without public funding for IGRA (usual care); and the new scenario, which would explore the distribution of diagnostic and treatment strategies, resource use and total costs with public funding for IGRA. The budget impact would represent the difference in costs between the two scenarios.

Key Assumptions

The assumptions that apply to the budget impact analysis are listed under the two main categories:

Modeling assumptions related to clinical parameters

- Situations where IGRA is the preferred method of testing as defined by the Canadian TB standards[74] reflects the currently accepted best-practice and is determined at the discretion of treating, primary responsible physicians or public health units/programs; of note, occupational health screening program for healthcare providers is out of scope of this HTA; however, some healthcare providers who belong to the pre-defined population subgroups in this HTA[74] would be considered eligible for IGRA testing

- Results of diagnostic testing for TB infection (i.e., LTBI) combined with additional clinical and/or laboratory medical evaluations are used to predict (justify) the initiation of the drug treatment for LTBI
- One year is generally sufficient for LTBI testing, diagnosis and treatment
- Test accuracies (IGRA or TST) are based on the published evidence that is generalizable to our populations of interest, and they remain constant over the next five years
- Population-wide screening is not within the scope of this topic; thus, some people unaware of their risk for LTBI (this is an asymptomatic condition) would not be diagnosed
- People identified would accept the diagnostic testing - this assumption of 100% participation in the testing was examined in sensitivity analysis
- Uptake of IGRA strategies over 5 years was assumed to be different between the populations of interest, with a small annual uptake in immigrant populations (increase of 3% per year) and a large uptake in contact or immunocompromised populations (starting with 75% in year 1 and growing to 100% in year 5) (oral expert consultation, April 25 , 2024, E. Rea, MD); this assumption was examined in sensitivity analysis

Assumptions related to determination of the test cost and organization of testing

- IGRA test cost is assumed from the cost of QuantiFERON®–TB Gold Plus (QFT-Plus) which is the only currently available and used IGRA test in the province; this cost (list price of $100 per person, available at LifeLab website) includes all important cost components related to equipment, test kit, consumables, transportation/shipping, turnaround time, and labour
- Testing costs (TST or IGRA) would stay constant over 5 years
- No expansion of currently existing laboratory infrastructure in the next five years; start-up and implementation costs, including training, lab infrastructure or renovation, and accreditation or organizations of LTBI screening were not considered
- IGRA testing is assumed to be de-centralized and done as needed, on the request of treating physicians/public health units and per indications recommended by the Canadian TB standards[74]
- In this analysis, IGRA is examined as an additional or optional test to TST, indicated in the same circumstances as TST without any assumption on investments for IGRA/TST implementation in a large-scale (mass) screening programme
- Our analyses assumed that the billing codes for IGRA are already in place for funding; however, in reality, additional policy work would be required:
    - OHIP Fee Billing Code: No changes to the specific OHIP fee codes would be required (oral and email communications, Infectious Diseases Policy and Programs Unit, Ministry of Health, Nov 16, 2023, April 09, and April 30 2024) ; however, with public funding for IGRA, an expansion and more detailed explanation of the eligibility criteria in the Physicians' Services Schedule of Benefits would be needed[102]
    - Lab Fee Billing Code: For publicly funding of IGRA, a new lab fee code for an IGRA test would be required to establish in the Schedule of Benefits for Laboratory Services[103]

Population of Interest

The population of interest includes several subgroups of people who are eligible for testing with either IGRA or TST based on the the recommendations of the 8th Edition Canadian Tuberculosis Standards.[74] These population subgroups are:

1. Individuals at high risk of exposure to TB (for primary care screening):
    a. Children >2 years and less than 10 years of age that previously received the BCG vaccine in infancy (<1 year of age)
    b. Persons >10 years of age received a BCG vaccine after infancy (>1 year of age), or received a BCG vaccine more than once and/or are uncertain about when they received a BCG vaccine (but are likely to have had BCG vaccine based on routine immunizations schedules)
2. Individuals with known high risk of TB exposure: e.g., people identified as contacts through public health contact investigations, have been BCG-vaccinated as described above (1a and 1b), or who meet criteria above for LTBI screening or for occupational health LTBI screening, but are unable or unlikely to return for TST reading, or are contraindicated for TST
3. Individuals at high risk of adverse outcomes if TB disease develops (as part of care for high-risk medical conditions):
    - People (adults or children) with confounding immunocompromising health conditions and receiving immunosuppressive treatments are likely to be misdiagnosed as not having LTBI (false negative results with TST) and therefore not receive proper treatment. As a result, they are at higher risk for developing active TB disease. This includes individuals living with human immunodeficiency virus (HIV), cancer, diabetes, having advanced stage chronic kidney disease, being an organ transplant recipient, receiving immunosuppressing drugs including chemotherapy

IGRA is currently being used in some circumstances and on a case-by-case basis for investigation of TB infection:

- in children with immunocompromising conditions or low immunity where a TST is highly likely to give a false negative result because of their underlying conditions (email and oral expert communications, 10 April, 2024, M. Richard-Greenblatt, PhD, FCCM)
- in children born in a TB endemic country or Indigenous Canadian children who have received a previous BCG vaccination (expert communication, 10 April, 2024, M. Richard-Greenblatt, PhD, FCCM)
- in contacts who are part of epidemiologic public health field investigations (expert communication, 25 March, 2024, E. Rea, MD)
- after informed consent discussion with the assessing physician when the patient is able to pay out of pocket and IGRA is currently recommended over TST by the Canadian TB Standards (expert communication, April 11 and June 03, 2024, R. Taylor, MD).

In addition, estimation of patient volumes from the IntelliHealth's OHIP claims data for identification of eligible patients with TB infection may not be reliable because the OHIP fee codes that may be used to

render TST testing could be also used for other purposes (e.g., combination of OHIP fee codes: A001, G372 and G373 for the diagnosis of LTBI/TB, and the diagnostic code for pulmonary TB: 011).

Therefore, we used the currently available data and published literature to make assumptions and estimate the size of each potentially eligible patient subgroup. In general, we assumed the following:

- No overlap or double counting of eligible persons between the subgroups
- BCG vaccination rate was based on the published studies and World Health Organization data,[78,79] with the assumption that the most recent immigration is mostly driven by migrants coming from the countries with high incidence of TB and population-wide BCG vaccination policies
- Immunocompromised people are eligible for IGRA irrespective of their BCG vaccination status,[74] and the size of this population included previous volumes of IGRA done at Hospital for Sick Kids and also assumed from data published for people with HIV, cancer, CKD and dialysis and organ kidney transplants

Overall Estimates

Table 7 presents the overall size of the population and three subgroups. We present the estimation of each subgroup in the sections below (Tables 8A–8C). Our assumptions were validated in expert consultation (oral and email communications, April to June 2024: E. Rea, MD; R. Taylor, MD; L. Macdonald, MD; N. Persaud, MD; M. Richard-Greenblatt, PhD; A. Ma, PhD; S. Patel, PhD; M. Muhammad, MD; Victoria J. Cook, MD; I. Kitai, MB; Infectious Diseases Policy and Programs Unit, Ministry of Health). In summary, over the next 5 years, we estimated that a total of 294,234 people would be eligible for testing with TST or IGRA for supporting the diagnosis of LTBI.

Table 7: Populations of interest eligible for IGRA/TST testing: Overall estimates

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total population, n	**55,339**	**57,059**	**58,812**	**60,595**	**62,429**	**294,234**
Immigrants, n	38,588	39,901	41,257	42,660	44,110	206,516
Contacts, n	1,817	1,872	1,928	1,986	2,045	9,648
Immunocompromised, n	14,934	15,286	15,627	15,949	16,273	78,069

Abbreviations: n, number; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

Immigrant Populations

We estimated the number of new immigrants who may be eligible for LTBI (IGRA) testing in Table 8A as following:

- First, based on published Ministry of Finance statistics for immigration to Ontario in 2023 (N=194,982) and assuming a general annual growth rate of 3.4% established for 2023,[104] we projected the number of new immigrants coming to Ontario in the next 5 years (201,611 in year 1 to 230,461 in year 5).
- Next, we assumed that IGRA testing would only be offered to those who are at risk or suspected of having LTBI.[74] It is highly uncertain how many people could potentially receive IGRA testing as this depends on many factors and the specific eligibility criteria (e.g.,

whether the individual comes from countries with moderate to high incidence of TB, is BCG-vaccinated and is flagged for further immigration medical TB surveillance based on risk factors[79]).

- To estimate what proportion of new immigrants could be offered the testing, we used data reported by a 2023 Canadian study by Jordan et al,[14] which estimated an overall prevalence of TB infection of 22% among foreign-born Canadians who immigrated to Ontario between 2001 and 2021.
- Lastly, to estimate the number of people who are BCG vaccinated, we applied a published BCG-vaccination rate of about 87% to these population estimates,[105] assuming that the majority of immigrants to Canada are coming from the countries where the incidence of TB is moderate to very high and the nation-wide BCG vaccination policy is in place.[83,84]

Given these assumptions, we arrived at an estimate of about 39,000 to 44,000 people per year (Table 8A). In addition, based on expert consultation, likely not all immigrants would require IGRA testing since this is a large population and we are not suggesting screening. The specific size of population would depend on the policy and could be just a proportion of this population.

Table 8A: Immigrant Population: Assumptions and Calculations

Immigrants to Ontario	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Forecasted new immigrant population (2024-2028), growth per year of 3.4%, n	201,611	208,466	215,554	222,883	230,461	1,078,975
Immigrants at risk of LTBI, assuming a prevalence of 22% for LTBI[14], n	44,354	45,863	47,422	49,034	50,701	237,374
Total: BCG-vaccinated immigrants at risk of LTBI, eligible for testing with IGRA (assuming a BCG vaccination rate of 87%[105])[a], n	**38,588**	**39,901**	**41,257**	**42,660**	**44,110**	**206,516**

Abbreviations: n, number; LTBI, latent tuberculosis infection; BCG-vaccine, Bacille Calmette-Guérin vaccine; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

[a] Calculated as the following example: 201,611 *0.22*0.87= 35,588.

Contact Investigations

All contacts that could have been exposed to the index case, need to be screened for TB infection and further evaluated for active TB. [106] The contact investigations are particularly important when children or young people are the index case (with active TB). [106] As shown in Table 8B, we estimated the size of this sub-group as following:

- The number of contacts screened with TST by the Toronto Public Health Units ranged from 1,689 to 2,054 per year in 2017-2019 (email communication, January 12, 2024, E. Rea, MD). Based on these data, we assumed that there would be about 2,000 contacts tested for LTBI per year in Toronto.
- According to clinical experts, Toronto has about 40-45% provincial caseload (email communication, January 12, 2024, E. Rea, MD). Therefore, we estimated that about 4,444 contacts per year (2000/45%) who could be screened in Ontario for LTBI.

- We then assumed that about 47% of screened contacts are foreign-born, based on the estimates from the BC CDC reports that presented contact investigations in British Columbia.[107]
- Lastly, we assumed that 87%[105] of these individuals are BCG-vaccinated and estimated that between 1,817 and 1,986 contacts would be screened with IGRA per year, for a total of 9,648 over the next five years.

Table 8B: Contacts: Assumptions and calculations

Contacts (people exposed to actve TB cases, eligible for LTBI testing)	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Contacts tested for LTBI per year in Toronto, n (ballpark number, expert email communication, 12 Jan 2024, E. Rea, MD)	2,000	2,000	2,000	2,000	2,000	10,000
Contacts to be tested for LTBI per year in Ontario, estimate, n (assuming the Toronto caseload is 45% of the provincial caseload)	4,444	4,444	4,444	4,444	4,444	22,222
Contacts to be tested for LTBI, foreign-born (based on assumption that 47% of contacts are foreign-born[107])	2,089	2,089	2,089	2,089	2,089	10,444
BCG-vaccinated contacts at risk (87%),[105] eligible for testing with IGRA, n (estimate: 4,444*0.47*0.87) , assuming 3% increase per year	**1,817**	**1,872**	**1,928**	**1,986**	**2,045**	**9,648**

Abbreviations: n, number; LTBI, latent tuberculosis infection; IGRA, interferon-gamma release assay; TST, tuberculin skin test; BCG-vaccine, Bacille Calmette-Guérin vaccine.

Immunocompromised Populations

We used published data from Ontario to estimate the size of potential immunocompromised populations represented by people with HIV, cancer (all non-solid tumors in the reference case: e.g., leukemias, Hodgkin and non-Hodgkin lymphoma and myeloma), those with late-stage kidney disease and kidney transplant recipients (Table 8C). For instance, we predicted the number of people with HIV from the study that reported incident cases and prevalent cases of HIV between 2011 and 2020.[108](Appendix 10). We also used the CIHI data to estimate the population from the reported incident cases with late stage chronic kidney disease (CKD) and kidney transplants between 2013 and 2022 (Appendix 10).[109] To estimate number of people with cancer, we used CCO projections for all non-solid tumors in Ontario (adults and children) in the reference case and for all cancers combined in a scenario analysis (Appendix 10).[110]

In addition, based on expert consultation, the Hospital for Sick Children (Toronto, Ontario) has been using IGRA tests for nearly a decade. In recent years, IGRA testing volumes have increased from 147 since 2019, to 699 (2021) and 865 (2023) (expert consultation, email communications, 24 Nov 2023 and 10 April 2024, M. Richard-Greenblatt, PhD). We estimated that these volumes would increase by 30 tests per year and included these data into our calculations.

In summary, as shown in Table 8C, we estimated about 78,100 people with immunocompromised conditions who could be eligible for IGRA testing over the next 5 years.

Table 8C: Immunocompromised People, Assumptions and Calculations

Immunocopromised populations	Year 1	Year 2	Year 3	Year 4	Year 5	Total
HIV positive , n	797	793	789	785	780	3,943
Organ transplant recipient (kidney, adults and children), n	3,507	3,563	3,618	3,674	3,729	18,092
End-stage CKD and dialysis, n	733	745	757	769	782	3,786
Cancer (non-solid tumors) ,all ages, n	9,032	9,291	9,538	9,766	9,997	47,624
Volumes based on the current use*, n	865	895	925	955	985	4,625
Immunocompromised, total , n	**14,934**	**15,286**	**15,627**	**15,949**	**16,273**	**78,069**

Abbreviations: n, number; CKD, chronic kidney disease; HIV, human immunodeficiency virus.

* Hospital for Sick Children

Budget Impact Model

We developed a standalone budget impact model to estimate the total costs for the current scenario with TST and for the new scenarios with IGRA used as an alternative or additional test to TST (see below Table 9: *Interventions and Comparator*). The budget impact model considered the population-specific diagnostic test accuracy of IGRA and TST, probability of test completion, costs of the tests, of additional medical evaluations and of treatment for LTBI or of active TB disease following the positive test results. As in prior economic analyses,[77-81] we assumed that the testing for supporting the diagnosis of LTBI and its treatment would occur within one year. The structure of this diagnostic decision-analytic model and model parameters are described in Figure 5 and sections below. All analyses were done from the third-party payer perspective (i.e., the Ministry of Health). The budget impact was estimated per year and over a 5-year time horizon for the reference case and scenario analyses. We did not use the discount rate for costs in the calculations.

Interventions and Comparator

We considered two types of testing strategies with IGRA which are in line with the current TB Standards[74] and currently available IGRA strategies in British Columbia:

- *IGRA as a single test*: this would lead to substitution or replacement of some volumes of TST tests with IGRA tests in the eligible populations (and no follow-up test with TST)
- *IGRA in sequential pathways (in combination) with TST*:
  - IGRA as a follow-up test in those who tested positive with TST (i.e., BCG-vaccinated populations: immigrants and contacts)
  - Combination of TST and IGRA (i.e., immunocompromised people):
    - TST used as the first test, followed by IGRA in those who test negative with TST
    - IGRA used as the first test, followed by TST in those who test negative with IGRA
- If the first IGRA test result is indeterminate, a second IGRA test should be conducted and is expected to produce a definitive result

Table 9: Interventions and Comparators for Specific Population Subgroups Used in the Economic Models

Interventions	Comparator	Population Subgroups	Outcomes
1. IGRA alone 2. TST as the first test, followed by IGRA in those who test positive with TST	TST alone	Immigrants and contacts, BCG vaccinated (healthy people at risk of LTBI)	Total costs in 2024 CAD
1. IGRA alone 2. TST as the first test, followed with IGRA in those who test negative with TST 3. IGRA as the first test, followed by TST in those who test negative with IGRA	TST alone	Immunocompromised people due to their underlying comorbid conditions at risk of LTBI	Total costs in 2024 CAD

Abbreviations: IGRA, interferon-gamma release assay; TST, tuberculin skin test; CAD, Canadian dollars

Model Structure

In brief, we developed a probabilistic decision-tree model to estimate testing and treatment costs for LTBI, both in the new scenario (using IGRA as a single test or in combination with TST) and the current scenario (using TST alone). Figure 5 presents a simplified diagnostic testing model that accounted for the prevalence of LTBI and the test accuracies of TST and IGRA. As described in Table 9, in the new scenario, we explored various hypothetical IGRA testing pathways to explore changes in the total costs with a single test approach versus the sequential approaches. We also accounted for the costs of treatment for those who tested true or false positive and additional testing costs for indeterminate IGRA results.

Sections below describe the input parameters that are used in the model.

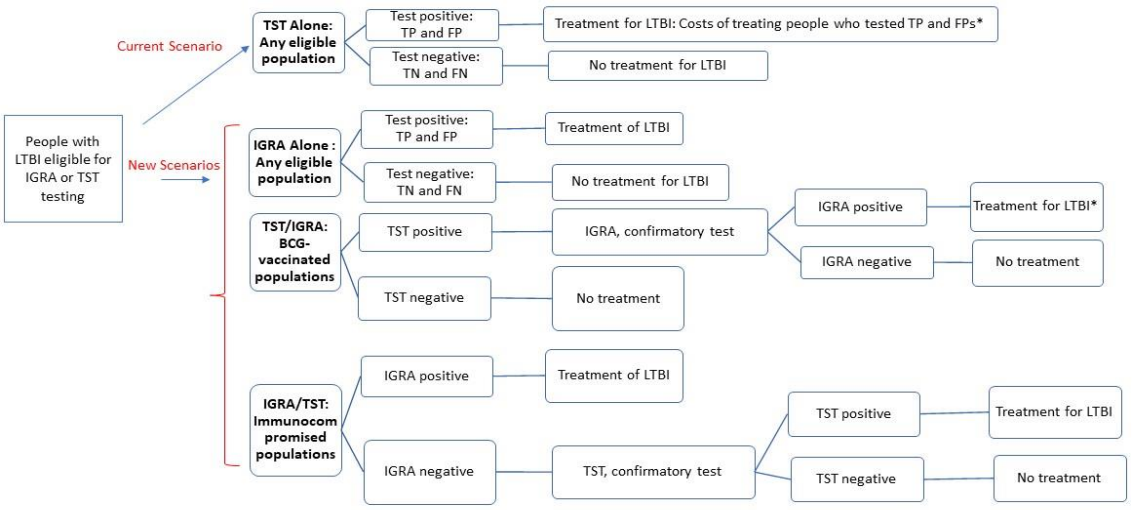

Figure 5: Structures of Simplified Model Pathways

We developed probabilistic decision-tree models for each sub-population. This schematic summarized the approach in general; it represents a simplified representation of the strategies and pathways that were included in the models for people eligible for IGRA testing or TST. Under the current scenario, people receive TST alone. People with a positive result, whether a true or false positive, receive treatment for LTBI. In a simplified schematic encompassing various models for different populations, 3 new scenarios are presented: IGRA alone for any eligible population, TST and IGRA for the BCG-vaccinated population, and IGRA and TST for immunocompromised populations. Under the IGRA alone scenario, all positive test results lead to treatment for LTBI and all negative test results lead to no treatment for LTBI. Under the TST and IGRA for BCG vaccinated people, the TST is given first and people with positive results are given a confirming IGRA test before treatment is given for LTBI. Among immunocompromised populations, the IGRA test is given first and all people with positive results receive treatment for LTBI. People with negative results are given a TST for confirmation, with all people receiving a positive result from the confirming test given treatment for LTBI.

Abbreviations: BIA, Budget Impact; FN, false negative; FP, false positive; TN, true negative; TP, true positive; LTBI, latent tuberculosis infection; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

Clinical Parameters

We obtained model parameter values from published studies identified in our clinical evidence review and economic evidence review. We simplified the natural and clinical history of LTBI and accounted only for major clinical inputs that could affect the total costs:

- Variables related to the natural and clinical course of LTBI such as prevalence of LTBI in Ontario and Canada, probability of reactivation of LTBI into active TB, probabilities of initiating and completing the preventative LTBI therapy and therapy for acute TB (see Table 10A)
- Variables related to diagnostic testing with IGRA and TST such as test accuracy, and probability of indeterminate results (see Table 10B)

Table 10A: Natural and Clinical History Inputs Used in the Economic Model

Model parameter	Reference Case Mean (95% CI) [a,b]	Sensitivity analysis	Sources
Prevalence of LTBI (pre-test probability), based on Canadian/Ontario data	0.22 (0.18-0.26)	0.36	Reference case: Jordan, 2023 [14] Sensitivity analysis: Campbell , 2017[79]
Participation in LTBI testing with TST	1.00 (NA)	0.60-0.70	Assumption
- Immigrants		0.60-0.70	Campbell,2017 [79]
- Contacts		1.00	
- Immunocomompromised			
Probability of developing active TB disease in people with LTBI (reactivation) [c]	0.0011[c] (NR)	NA	Campbell , 2017[79]
Probability of initiating and completing LTBI preventative therapy	0.55 (NR)	0.81	Reference case: PHO data request[111] Sensitivity analysis: Campbell, 2017;[79,80] Alsdurf, 2016[112]
Probability of initiation TB therapy in those diagnosed with TB:		NA	Campbell , 2017[79]
- Immigrants	0.94 (NR)		
- Contacts	1.00 (NA)		
- Immunocompromised	1.00 (NA)		

Abbreviations: TST, tuberculin skin test; LTBI, latent tuberculosis infection.

[a]Standard errors were estimated whenever data are available. We assumed 10%–25% around the mean, where data were not available.

[b]Beta distributions were assigned to the probability estimates in probabilistic analysis.

[c]This assumption is relevant for people who are false negative on the test, and in whom TB has been reactivated. In such case, full cost of TB treatment was applied.

Diagnostic Accuracy: IGRA and TST

As shown in Table 10B, we obtained the reference case inputs from the clinical evidence review and additional published literature. The systematic reviews included in the clinical evidence review were of very high methodological quality. We sourced the inputs related to the sensitivity and specificity of TST or IGRA by a sub-population:

- The diagnostic accuracy of TST and IGRA was assumed to be the same *for immigrant and contact sub-populations*:
    - The sensitivity and specificity values of TST for these two populations were obtained from Pai et al [113] because this review accounted for BCG-vaccination status.
    - The sensitivity and specificity values of IGRA (QFT-Plus) were sourced from Jonas et al [53,54]
- The diagnostic accuracies of TST and IGRA *for immunocompromised populations* were taken from a systematic review by Yahav et al [57] showing that the diagnostic accuracy of IGRA (QFT-GIT) was slightly higher than the accuracy of TST. The sensitivity of IGRA or TST were markedly lower in immunocompromised populations compared with those in healthy immigrant/contacts populations.
- The percentage of indeterminate results with IGRA was based on a review by Zhou et al,[56] which also categorized this result by the type of sub-population.

In the sensitivity analysis, we examined the robustness of the reference case cost and budget impact estimates to various values for the diagnostic accuracies of TST and IGRA.

Table 10B: Inputs Related to Accuracy of TST and IGRA, Reference Case

Model parameters	Mean (95% CI) [a]	Source
TST		
Sensitivity		
- Immigrants, BCG-vaccinated	0.77 (0.71-0.82)	Pai, 2008 [113]
- Contacts, BCG-vaccinated	0.77 (0.71-0.82)	Pai, 2008 [113]
- Immunocompromised	0.309 (0.218-0.417)	Yahav, 2023 [57]
Specificity		
- Immigrants, BCG-vaccinated	0.59 (0.46-0.73)	Pai, 2008 [113]
- Contacts, BCG-vaccinated	0.59 (0.46-0.73)	Pai, 2008 [113]
- Immunocompromised	0.779 (0.727-0.825)	- Yahav, 2023 [57]
Completion of the TST test (both visits)		
- Immigrants, BCG-vaccinated	0.75 (NR)	- Sester , 2010 [114]
- Contacts, BCG-vaccinated	0.91 (NR)	- BC CDC, Marra 2008, Campbell 2017 2019 [78-80]
- Immunocompromised	0.91 (NR)	- BC CDC, Marra 2008, Campbell 2017 2019 [78-80]
IGRA		
Sensitivity		
- Immigrants, BCG-vaccinated	- 0.89 (0.84-0.94)	- Jonas, 2023 [53,54]
- Contacts, BCG-vaccinated	- 0.89 (0.84-0.94)	- Jonas, 2023 [53,54]
- Immunocompromised	- 0.375 (0.117-0.631)	- Yahav, 2023[57]
Specificity		-
- Immigrants, BCG-vaccinated	- 0.98 (0.95;0.99)	- Jonas, 2023 [53,54]
- Contacts, BCG-vaccinated	- 0.98 (0.95;0.99)	- Jonas, 2023 [53,54]
- Immunocompromised	- 0.799 (0.715-0.863)	- Yahav, 2023 [57]
Indeterminate results		
- Immigrants, BCG-vaccinated	- 0.019 (0.016- 0.022)	- Zhou, 2023 [56]
- Contacts, BCG-vaccinated	- 0.019 (0.016- 0.022)	- Zhou, 2023 [56]
- Immunocompromised	- 0.057 (0.048-0.066)	- Zhou, 2023 [56]
Completion of the IGRA test, all populations	100%	Assumption

Abbreviation: IGRA, interferon-gamma release assay; TST, tuberculin skin test; BCG-vaccine, Bacille Calmette-Guérin vaccine.
[a]Standard errors were estimated whenever data are available. We assumed 10%–25% around the mean, where data were not available.
[b]Beta distributions were assigned to the probability estimates in probabilistic analysis.
[c]This assumption was based on the fact that this test being the reference standard.

Resources and Costs: Model Inputs

We estimated costs related to resource use and services for LTBI testing and management of LTBI and active TB (Tables 11A–11C and 12). The data were estimated through consultations with experts and from published literature sources. All costs are expressed in 2024 Canadian dollars; when up-to-date costs were not available, we used the Consumer Price Index to adjust the values to 2024 Canadian dollars.[115]

As mentioned in *Main Assumptions*, our analyses assumed that the billing codes for IGRA are already in place for publicly funding and are considered under the OHIP billing codes for TST (e.g., A001 (visit) and

G372 (injection); (expert consultation, oral and email communications, Infectious Diseases Policy and Programs Unit, Ministry of Health, April 09, and April 30, 2024). In reality, additional policy work will be required with respect to the following:

- Expansion and more detailed explanation of the eligibility criteria in the Physicians' Services Schedule of Benefits[102] under the current OHIP billing codes for TST
- For publicly funding of a new test, a new lab fee code for the IGRA test would have to be assigned and listed in the Schedule of Benefits for Laboratory Services[103]

Cost Parameters

Cost of Testing: TST and IGRA

Table 11A and B (and Appendix 11) present the estimation of the cost inputs relevant to testing with either TST or IGRA. In our costing approach, we assumed that TST or IGRA would be likely done differently between the examined sub-populations:

- For *contact investigations and healthy immigrants*, testing could be shared between public health units and MDs. For simplicity, we assumed this share in Ontario to be 50-50 for the reference case, and tested this assumption in sensitivity analysis (see Table A14, Appendix 12, Scenarios 8 and 9)
  - When the testing was assumed to be done at a public health unit, the nurse labour time was included in the cost; if it was done at an MD's office, the labour was fully billed via OHIP fees (may include MD's and nurse's labour time, depending on the organization of the MD's office)
  - Additionally, for the contact investigations, we accounted for the nurse labour associated with the travel time; this is because of a specific approach used for contact investigation testing, which accounts for identification of all possible contacts exposed to an active TB case. In this estimation, we used a conservative approach and for the travel time cost component, we estimated it per person and not per a total number of people included in the field investigation visit
- For *immunocompromised populations*, the testing would likely be done by physicians (MDs) (expert consultation, email and via proposal communication April 03-June 10: E. Rea, MD; P. Galange, MD; M. Richard-Greenblatt, PhD, R. Taylor, MD)

Costing: TST

Appendix 11 and Table 11A describes the approach and inputs used to estimate a total cost of TST for sub-populations. The ***cost of testing with TST*** included the cost of test and relevant consumables, labour time and where appropriate the cost of the initial TST visit (counted as referral, depending on the type of population). As per expert opinion (email communication, I. Kitai, MD, April 30, 2024), the reference case accounted for the cost of TST vials wastage when TST was done at an MD's office.

As shown in Table 11A, *the total cost of fully completed TST* for:

- Immigrant population: about $71 per test (i.e., weighted cost by the share of PHU: MD test setting: 50:50, reference case)

- Contact investigations: about $141 per test (i.e., weighted cost by the share of PHU: MD test setting: 50:50, reference case)
- Immunocompromised populations: about $74 (at MD's office, 100%, reference case)

The total *cost of incompletely done TST* which included only the components related to the first visit (e.g., cost of initial visit and TST planting) was estimated at about:

- $65, $100 and $67 per test for immigrant, contact and immunocompromised populations, respectively.

Table 11A: Testing for LTBI with TST Testing — Per-Person Costs Used in in the Reference Case

Costs inputs	Unit cost, $[a]	Quantity /Duration	Total cost, $[a]	Source
TST: immigrant populations and contacts perfomed by MDs and PHUs				
TST at MD's office				
Referral for TST: physician visit	23.75	1	23.75	GP visit, minor assessment, Physician SoB[102]: A001
Nurse's time, 1st visit: if nurse plants TST, time is covered by the OHIP billing code	0	NA	NA	Expert oral consultation, E Rea, MD; R, Khan, RN; P Galange, MD; April 25, 2024
TST, injection	3.89	1	3.89	Injection, with visit, Physician SoB[102]: G372
TST, PPD consumable, 1 vial	206	NA	206	Each vial can provide 10 doses, with 1 dose per person, if there is no wastage (expert email communications, E Rea, MD/ R. Khan, RN: January 12 and April 10, 2024)
TST, PPD consumable, per dose	NA	1	37.08	Estimation of the cost of PPD per dose including the wastage at MD's office (Assuming about 44% wastage of the whole vial due to low uptake of patients in MD's office)
TST, other consumables (e.g., swabs, bib, syringe, containers)	2.47	1	2.47	Estimate, expert email communications, E Rea, MD/ R. Khan, RN: January 12 and April 10, 2024
TST, second visit: reading	6.75	1	6.75	Reading visit, Physician SoB[102]: G 373
Additional nurse's time for travel	0	NA	NA	No additional travel time (both contacts and immigrants, TST at MD's office)
TST: Total cost, test done at MD's office	-	-	**73.94**	Calculated
TST at PHU				
Referral for TST physician visit	0	1	0	No visit claimed by PHU unit, according to the Medical Act (expert oral consultation, E Rea, MD; R, Khan, RN; P Galange, MD; April 25, 2024
Nurse's time, 1st visit: set-up, consent, review, TST plant, post-TST monitoring	1.01	40 min	40.40	Estimate, expert email communications, E Rea, MD/ R. Khan, RN: January 12 and April 10, 2024
Nurse's time, 2nd visit: TST reading	1.01	5 min	5.05	Estimate, expert email communications, E Rea, MD/ R. Khan, RN: January 12 and April 10, 2024)

Costs inputs	Unit cost, $[a]	Quantity /Duration	Total cost, $[a]	Source
TST, PPD consumable , vials	206	1/10	20.60	Estimate, PPD cost of 10-dose vial, expert email communications, E Rea, MD/ R. Khan, RN: January 12 and April 10, 2024
TST, other consumables(e.g., swabs, bib, syringe, containers)	2.47	1	2.47	Estimate, expert email communications, E Rea, MD/ R. Khan, RN: January 12 and April 10, 2024
Contact investigation only: Additional nurse's time for travel, contact investigation only, mileage for 2 visits per single contact)	-	-	139.02	Assumed only for contact investigation: Estimated total, 80 minutes, 30 km: $0.68/km ((expert email communications, E Rea, MD/ R. Khan, RN: January 12, 2024 and April 10, 2024)
TST: Total cost, test done at PHU:	-	-		Calculated
Immigrants			**68.52**	Immigrants
Contacts			**207.54**	Contacts
Adjustment of the total test cost, based on test-market share				
Test cost at MD's office (share 50%)	73.94	50%	36.97	Calculations, to include the share; simplifying assumption made for % share which was tested in sensitivity analysis (expert oral and email consultations, E Rea, MD; R, Khan, RN; P Galange, MD; April 25, and June 13, 2024)
Test cost at PHU (share 50%)		50%		Calculations, to include the share; simplifying assumption made for % share which was tested in sensitivity analysis (expert oral and email consultations, E Rea, MD; R, Khan, RN; P Galange, MD; April 25, and June 13, 2024)
- Immigrants	68.52		34.26	
- Contacts	207.54		103.77	
Completed TST: Overall total test cost, adjusted for the share:		1		Calculated, adusted for the share
			71.23	Immigrants
- **Immigrants**	-		**140.74**	Contacts
- **Contacts**				
Incomplete TST test: MDs and PHU, immigrants and contacts				
Incomplete TST: MD's office	-	1	67.19	Estimated, as the cost of 1 TST visit (inlcuding initial visit, but excluding 2nd visit: TST reading)
Incomplete TST: PHU	-	1		Estimated, as the cost of 1 TST visit and travel time for 1 visit (no TST reading and ½ of travel cost
- Immigrants			63.47	
- Contacts			132.98	
Incomplete TST: Overall total test cost , adjusted for the share:		**50%**		Calculated
	130.66		**65.33**	Immigrants
- **Immigrants**	**200.17**		**100.09**	Contacts
- **Contacts**				
TST, 100% tests perfomed by MDs: immunocompromized populations				
TST, initial visit	23.75	1	23.75	GP visit, minor assessment, Physician SoB[102]: A001

Costs inputs	Unit cost, $[a]	Quantity /Duration	Total cost, $[a]	Source
TST, injection	3.89	1	3.89	Injection, with visit, Physician SoB[102]: G 372
TST, PPD consumable, 1 vial	206	NA	206	Each vial can provide 10 doses, with 1 dose per person, if there is no wastage (expert email communications, E Rea, MD/ R. Khan, RN: January 12 and April 10, 2024)
TST, PPD consumable, per dose	NA	1	37.08	Estimation of the cost of PPD per dose including the wastage at MD's office (Assuming about 44% wastage of the whole vial due to low uptake of patients in MD's office)
TST, other consumables (e.g., swabs, bib, syringe, containers)	2.47	1	2.47	Estimate, expert email communications, E Rea, MD/ R. Khan, RN: January 12 and April 10, 2024
TST, second visit: reading	6.75	1	6.75	Reading visit, Physician SoB[102]: G 373
Completed TST: total cost, immunocompromised	-	1	**73.94**	Calculated
Incomplete TST: total cost, immunocompromised	-	1	**67.19**	Calculated

Abbreviations: GP, general practitioner; OHIP, Ontario Health Insurance Plan; MOH, Ministry of Health; SoB, Schedule of Benefits; TST, tuberculin skin test.

[a]All costs are in 2024 Canadian dollars. The input parameters related to the physician fees, lab fees and the list price of IGRA are treated as fixed and were not assigned the distribution in probabilistic analysis. For the rest of the cost inputs, we assigned gamma distribution.

Costing: IGRA

Appendix 11 and Table 11B describes the approach and inputs used to estimate a total cost of IGRA for sub-populations. The ***cost of IGRA testing*** in the reference case considered the list price of IGRA (i.e., QFT-Plus at LifeLab website). The list price of IGRA includes all important cost components such as the cost of equipment, test kit/reagents, consumables, labor and shipping cost (expert oral communication, M. Richard-Greenblatt, PhD, April 11, 2024) As shown in Table 11B, we estimated *the total cost of fully completed IGRA* for:

- Immigrant population: about $125 per test (i.e., weighted cost by the share of PHU: MD test setting: 50:50, reference case)
- Contact investigations: about $160 per test (i.e., weighted cost by the share of PHU: MD test setting: 50:50, reference case)
- Immunocompromised populations: about $135 (at MD's office, 100%, reference case)

The total *cost of indeterminate IGRA* result, requiring the second IGRA test was estimated at about:

- $113, $148 and $111 per test repeat for immigrant, contact and immunocompromised populations, respectively.

Table 11B: Testing for LTBI with IGRA Testing — Per-Person Costs Used in the Reference Case

Costs inputs	Unit cost, $[a]	Quantity /Duration	Total cost, $[a]	Source
IGRA, reference case: immigrant populations and contacts perfomed by MDs and PHUs				
IGRA at MD's office				
Referral for LTBI	23.75	1	23.75	GP visit, minor assessment, Physician SoB[102]: A001
Blood sampling	10.76	1	10.76	L700, Ontario Schedule of Benefits: Laboratory Services
List price for IGRA, inlcudes all cost components sich as kits, consumables and shipping and handling	100.00	1	100.00	List price, LifeLab website
Shipping and handling	0	1	0	Included in the list price (expert oral consultation, E Rea, MD; R, Khan, RN; April 25, 2024; Mellisa Richard-Greenblatt, PhD, April 15, 2024)
Additional nurse's time for travel	0	NA	NA	No additional travel time (both contacts and immigrants, TST at MD's office)
IGRA: Total cost, MD's office	-	-	**134.51**	Calculated
IGRA at PHU				
Referral for TST physician visit	0	1	0	No visit claimed by PHU unit, in accordance with the Medical Act, expert oral consultation, E Rea, MD; R, Khan, RN; P Galange, MD; April 25, 2024
Blood sampling, nurse time	1.01	15 min	15.15	Estimate, expert email communications, E Rea, MD/ R. Khan, RN: January 12 and April 10, 2024
List price for IGRA, inlcudes all cost components sich as kits, consumables and shipping and handling	100.00	1	100.00	List price, **LifeLab website**
Shipping and handling	0	1	0	Assumed to be included in the list price, expert, consultation: E Rea, MD; R, Khan, RN; April 25, 2024; M. Richard-Greenblatt, PhMD, April 15, 2024
Contact investigation only: Additional nurse's time for travel, contact investigation only, mileage for 1 visit per single contact)	139.02	1/2	69.51	Estimated to be half the cost for TST visit (expert email communication: E. Rea, MD, R, Khan, RN, January 12, 2024 and April 25, 2024)
IGRA: Total cost, PHU	-	-		Calculated
Immigrants			**115.15**	Immigrants
Contacts			**184.66**	Contacts
Adjustment of the total test cost, based on test-market share				
Test cost at MD's office (share 50%)	**134.51**	50%	67.255	Calculations, to include the share; simplifying assumption made for % share which was tested in sensitivity analysis (expert oral and email consultations, E Rea, MD; R, Khan, RN; P Galange, MD; April 25, and June 13, 2024)

Costs inputs	Unit cost, $[a]	Quantity /Duration	Total cost, $[a]	Source
Test cost at PHU (share 50%)		50%		Calculations, to include the share; simplifying assumption made for % share which was tested in sensitivity analysis (expert oral and email consultations, E Rea, MD; R, Khan, RN; P Galange, MD; April 25, and June 13, 2024)
Immigrants	**115.15**		57.55	
Contacts	**184.66**		92.33	
Completed IGRA: Overall, total test cost, adjusted for the share:	-	1		Calculated, adjusted for the share
Immigrants			**124.83**	Immigrants
Contacts			**159.585**	Contacts
Test repeat, indeterminate IGRA result:	1	1		Estimated, as the cost of 1 IGRA test without the initial MD visit
At MD's office			110.76	
Test repeat, indeterminate IGRA result, at PHU :	1	1		Estimated, as the cost of 1 IGRA test without the initial MD visit
Immigrants			115.15	
Contacts			184.66	
Test repeat, indeterminate IGRA result, adjsuted for the share of 50%		50%		Calculated, adjusted for the share
Immigrants	225.91		**112.96**	Immigrants
Contacts	295.42		**147.71**	Contacts
IGRA, reference case: immunocompromised populations, 100% by MDs				
Referral for LTBI	23.75	1	23.75	GP visit, minor assessment, Physician SoB[102]: A001
Blood sampling	10.76	1	10.76	L700, Ontario Schedule of Benefits: Laboratory Services
List price for IGRA, inlcudes all cost components sich as kits, consumables and shipping and handling	100.00	1	100.00	List price, LifeLab website
Shipping and handling	0	1	0	Included in the list price: expert oral consultation, E Rea, MD; R, Khan, RN; April 25, 2024; M. Richard-Greenblatt, PhMD, April 15, 2024
Completed IGRA: Total cost, MD's office	-	-	**134.51**	Calculated
Test repeat, indeterminate IGRA result, immunocompromised		1	**110.76**	Estimated, as the cost of 1 IGRA test without the initial visit

Abbreviations: GP, general practitioner; OHIP, Ontario Health Insurance Plan; MOH, Ministry of Health; SoB, Schedule of Benefits; IGRA, interferon-gamma release assay.

[a]All costs are in 2024 Canadian dollars. The input parameters related to the physician fees, lab fees and the list price of IGRA are treated as fixed and were not assigned the distribution in probabilistic analysis.

Costs of Further Medical Evaluation

People who were identified in the testing (e.g., positive with TST or IGRA) underwent additional medication evaluations. We costed this clinical care pathway for Ontario based on previously suggested algorithm including specialist visits and diagnostic assessments (X-ray and microbiology).[80] As shown in Table 11C, the total cost of follow-up was estimated at $267 per person.

Table 11C: Medical Evaluation, Test Positive — Per-Person Costs

Costs inputs	Unit cost, $[a]	Quantity /Duration	Total cost, $[a]	Source
Follow-up, medical evaluation				
Post-test visit with specialist, test positive	108.95	1	108.95	Limited consultation: respirologist (e.g., Physician SoB: A575)[102]
Chest X-ray (PA and lateral)	H: 21.90 P: 10.70	1	32.60	SoB: X091, two ro more views : (H and P components) [102]
Lab testing: Sputum – culture and smear for tuberculosis, including ZN or fluorescent smear	19.95	3	59.85	Lab Schedule Fee: L631 [103]
Follow-up visit, specialist	65.90	1	65.90	Medical specific re-assessment, respirologist (e.g., Physician SoB: A474)[102]
Total cost, follow-up	-	1	**267.30**	Calculated

Abbreviations: SoB, Schedule of Benefits.

[a]All costs are in 2024 Canadian dollars. The input parameters related to the physician fees, lab fees and the list price of IGRA are treated as fixed and were not assigned the distribution in probabilistic analysis. For the rest of the cost inputs, we assigned gamma distribution.

Treatment Costs: LTBI and Active TB

Table 12 presents the cost inputs relevant to the management of LTBI and active TB. We estimated the cost of treatment of LTBI (often referred as TB infection) and drug-susceptible TB from a 2022 costing study by Campbell et al.[116] This study provided the estimates for the total cost and cost components (in 2020 CAD) relevant to LTBI and various types of active TB incurred at 3 treatment centres in Canada (BC CDC, West Park Healthcare Centre [Ontario] and Montreal Chest Institute [Quebec]). For the purpose of our analysis, we used the cost estimates reported for those who completed the treatment in Ontario:

- The total cost of treatment of LTBI, estimated at $978 per person, included the cost of drugs (INH (isoniazid) or RIF (rifampin)) and the cost of post-treatment monitoring (Note: the cost of hospitalization for LTBI is $0).
- The total cost of management of an active TB case, estimated at $18,063 per person, included the costs of diagnosis, therapy (i.e., for drug-susceptible TB, medications: INH and RIF), post-treatment monitoring, hospitalization and public health interventions.
- In our model, we also accounted for the costs incurred for people who did not complete the treatment (see Table 10A: 0.55-0.81). This cost was based on the median cost estimates reported across all 3 centers.

Table 12: Per-Person Treatment Costs for LTBI and Active TB

Costs inputs	Total mean cost, $[a]	Total mean cost (median [IQR range], $ (2020 CAD) [b]	Source
LTBI			
Completed treatment			
Preventative treament, test positive	916.41	791 (778 [558-1,085])	Campbell, 2022:[116] Appendix Table 8, Table 12
Post-treatment monitoring	61.40	53 (18 [0-93])	Campbell, 2022:[116] Appendix Table 8, Table 12

Costs inputs	Total mean cost, $[a]	Total mean cost (median [IQR range], $ (2020 CAD) [b]	Source
Total costs, treatment	**977.81**	NA	Estimated
Not completed treatment [c]			
Total cost, not completed treatment[c]	244.45	NR (211 [150-481])	Campbell, 2022:[116] Appendix Table 4
Active drug-suspectiable TB			
Completed treatment			
Total cost, management of TB	**18,062.88**	15,591 (13,328 [7,921-19,080])	Campbell, 2022:[116] Appendix Table 8, Table 14
Not completed treatment			
Total cost, management of TB, treatment not completed	14,413.46	NR (12,441 [10,104-18,574])	Campbell, 2022:[116] Appendix Table 4

Abbreviations: LTBI, latent tuberculosis infection; TB, tuberculosis; IQR, interquartile range; CAD, Canadian dollars.

[a]All costs are in 2024 Canadian dollars. We assigned gamma distributions (with 25% SE around the mean) in probabilistic analysis.

[b]These are reported costs in the original publication, based on data reported for Ontario (for those who completed the treatment). We adjusted the cost inputs for inflation using the CPI for January 2024 (159.3), ratio: 159.3/137.5=1.158.

[c]The mean costs were not reported for those who did not complete the treatment and were calculated as the median cost across all 3 Canadian sites (Table 4, Appendix, original publication[116]); the mean estimate for our analysis was based on the reported median.

Resources and Costs: Model Outputs, Reference Case

We simulated probabilistically the inputs described in prior sections in the budget impact model and estimated the total costs and relevant cost components (i.e., model outputs) by the population. The cost data by the population (further used for the budget impact estimations, results section) are shown below in Table 13A–13C.

In probabilistic analyses, we also estimated incremental mean changes in the costs per person between IGRA and TST strategies, by the type of tested population as following:

- Immigrant population: IGRA alone vs. TST alone, —$85.93 (95% Credible Interval (CrI): —$193.63 to $14.37); Sequential TST/IGRA vs TST alone, —$181.75 (95% CrI: —$262.86 to —$111.80)
- Contact population: IGRA alone vs. TST alone, —$189.04 (95% CrI: —$313.20 to —$50.59); Sequential TST/IGRA vs TST alone, —$203.97 (95% CrI: —$296.26 to —$120.36)
- Immunocompromised population: IGRA alone vs. TST alone, $89.77 (95% CrI: —$15.52 to $206.43); Sequential TST/IGRA vs TST alone, $276.77 (95% CrI: $188.87 to $361.03); Sequential IGRA/TST vs TST alone, $344.62 (95% CrI: $273.39 to $435.54)

Table 13A: Reference Case – Per-Person Cost Estimates: Immigrant Sub-Population

	Cost per person, $[a]		
	Current scenario: TST[b] Mean (95% CrI)[d]	**New scenario: IGRA alone[c]** Mean (95% CrI) [d]	**New scenario: Sequential TST/IGRA (TST+ then IGRA)[c]** Mean (95% CrI) [d]
Total	**408.53 (308.06-518.59)**	**322.60 (282.67-366.78)**	**226.78 (185.52-269.92)**
Testing	69.75	126.98	115.83
Follow-up	98.08	56.49	31.50
Treatment – LTBI	237.75	136.94	76.36

	Cost per person, $[a]		
	Current scenario: TST[b] Mean (95% CrI)[d]	**New scenario: IGRA alone[c]** Mean (95% CrI)[d]	**New scenario: Sequential TST/IGRA (TST+ then IGRA)[c]** Mean (95% CrI)[d]
Treatment – active TB	2.94	2.20	3.09
Treatment – total cost	240.69	139.16	79.45

Abbreviations: IGRA, interferon-gamma release assay; TST, tuberculin skin test; 95% CrI, 95% credible interval.
[a]2024 Canadian dollars.
[b]*Current scenario* refers to the existing testing with TST.
[c]*New scenarios* refers to new testing strategies with IGRA
[d]95% CrI provided for the total cost only

Table 13B: Reference Case – Per-Person Costs Estimates: Contact Sub-Population

	Cost per person, $[a]		
	Current scenario: TST[b] Mean (95% CrI)[d]	**New scenario: IGRA alone[c]** Mean (95% CrI)[d]	**New scenario: Sequential TST/IGRA (TST+ then IGRA)[c]** Mean (95% CrI)[d]
Total	**547.03 (407.17-674.75)**	**357.98 (318.48-401.69)**	**343.06 (273.92-395.03)**
Testing	137.09	162.39	209.35
Follow-up	118.94	56.47	38.21
Treatment – LTBI	288.32	136.89	92.63
Treatment – active TB	2.68	2.23	2.87
Treatment – total cost	291.00	139.12	95.50

Abbreviations: IGRA, interferon-gamma release assay; TST, tuberculin skin test; 95% CrI, 95% credible interval.
[a]2024 Canadian dollars.
[b]*Current scenario* refers to the existing testing with TST.
[c]*New scenarios* refers to new testing strategies with IGRA
[d]95% CrI provided for the total cost only

Table 13C: Reference Case – Per-Person Costs Estimates: Immunocompromised Sub-Population

	Cost per person, $[a]			
	Current scenario: TST[b] Mean (95% CrI)[d]	**New scenario: IGRA alone[c]** Mean (95% CrI)[d]	**New scenario: Sequential TST/IGRA (TST- then IGRA)[c]** Mean (95% CrI)[d]	**New scenario: Sequential IGRA/TST (IGRA- then TST)[c]** Mean (95% CrI)[d]
Total	**318.56 (242.12-385.15)**	**408.33 (320.93-507.65)**	**595.33 (444.12-708.93)**	**663.17 (578.70-750.25)**
Testing	73.33	140.82	170.71	197.08
Follow-up	58.45	63.91	102.00	112.07
Treatment – LTBI	183.40	200.55	320.08	351.67
Treatment – active TB	3.37	3.04	2.54	2.36
Treatment – total cost	186.78	203.59	322.61	354.02

Abbreviations. IGRA, interferon-gamma release assay; TST, tuberculin skin test; 95% CrI, 95% credible interval.
[a]2024 Canadian dollars.
[b]*Current scenario* refers to the existing testing with TST.
[c]*New scenarios* refers to new testing strategies with IGRA
[d]95% CrI provided for the total cost only

Current Intervention Mix

IGRA testing is not publicly funded in Ontario. It is offered at a few sites to selected patients such as Toronto PHU (contacts only, free of charge) or the Hospital for Sick Children, and lab testing is done at the Hospital for Sick Children (where it is publicly funded from the hospital global budget). IGRA testing is also offered at private labs (e.g., LifeLabs), where individuals pay for IGRA out-of-pocket. For simplicity, we assumed that at present, only TST is used for LTBI screening in all subgroups described in the section *Population of Interest*.

Uptake of the New Intervention and New Intervention Mix

In this section, we estimated how quickly IGRA testing may be adopted if it is publicly funded. The uptake of IGRA in Ontario is uncertain and likely different between the populations (e.g., uptake of the test for people identified in contact investigations or with immunocompromised conditions could be larger and faster than for immigrants because these populations could be easily identified in the system). Hence, we assumed that the uptake of IGRA testing strategies (as a replacement or in combination with TST) was different between the populations of interest, with a small annual uptake in immigrant populations (increase of 3% per year) and a large uptake in the contact or immunocompromised populations (starting with 75% in year 1 and growing to 100% in year 5) (oral expert consultations April 2024). We tested this assumption in sensitivity analysis.

A small annual uptake in the reference case for immigrant population was justified by a similar experience with a small and steady upward uptake of IGRA in British Columbia. In British Columbia, IGRA test officially lunched on for a select group of patients in October 2009. In 2010, the IGRA volumes were less than 1000 and they grew to about 7,000 in 2023 (expert consultation, 30 Jan, 2024, and May 22, 2024, V. Cook, MD, BC CDC and M. Morshed, MD, BC CDC). In addition, the participation of people in the TST or IGRA testing strategies was assumed to be 100% in the reference case, but this assumption was tested in sensitivity analysis. As shown in Table 14A–C, we estimated the uptake of IGRA strategies by the population as following:

- *Immigrant population* (at uptake rate of 3% per year, Table 14A): the total number of people to be tested by the new strategy including IGRA would about 19,000 over the next five years (from about 1,160 in year 1 to 6,620 in year 5)
- *Contacts* (at uptake rate of 75% in year 1 and 100% in year 5, Table 14B): the total number of people to be tested the new strategy including IGRA would about 8,620 over the next five years (from about 1,363 in year 1 to 2,045 in year 5)
- *Immunocompromised populations* (at uptake rate of 75% in year 1 and 100% in year 5, Table 14C): the total number of people to be tested by the new strategy including IGRA would about 69,700 over the next five years (from about 11,200 in year 1 to 16,300 in year 5)

Table 14A: Uptake of IGRA and TST in Ontario: Immigrant Populations

	Year 1	Year 2	Year 3	Year 4	Year 5	Total

Current scenario						
IGRA, n[b]	**0**	**0**	**0**	**0**	**0**	**0**
TST, n	38,588	39,901	41,257	42,660	44,110	206,516
New scenario[a]						
Uptake rate for the New Strategy with IGRA, %	3%	6%	9%	12%	15%	
IGRA, n[b]	**1,158**	**2,394**	**3,713**	**5,119**	**6,617**	**19,001**
TST, n	37,430	37,507	37,544	37,541	37,493	187,515
Total, both, n	38,588	39,901	41,257	42,660	44,110	206,516

Abbreviations: n, number; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

[a]The volume of interventions was calculated from the total number multiplied by the uptake rate of the New Intervention. For example, in the New Scenario, the total volume in year 1 is 38,588 and the uptake rate of IGRA is 3%, so the volume of IGRA in year 1 is 1,158 (38,588 × 3%).

[b] IGRA represents the new testing strategy that includes testing with IGRA (depending on the type of intervention, this could be IGRA as a single test or IGRA in combination with TST).

Table 14B: Uptake of IGRA and TST in Ontario: Contacts

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
IGRA, n[b]	**0**	**0**	**0**	**0**	**0**	**0**
TST, n	1,817	1,872	1,928	1,986	2,045	9,648
New scenario[a]						
Uptake rate for the New Strategy with IGRA, %	75%	85%	90%	95%	100%	
IGRA, n[b]	**1,363**	**1,591**	**1,735**	**1,887**	**2,045**	**8,621**
TST, n	454	281	193	99	0	1,027
Total, both, n	1,817	1,872	1,928	1,986	2,045	9,648

Abbreviations: n, number; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

[a]The volume of interventions was calculated from the total number multiplied by the uptake rate of the New Intervention.

[b] IGRA represents the new testing strategy that includes testing with IGRA (depending on the type of intervention, this could be IGRA as a single test or IGRA in combination with TST).

Table 14C: Uptake of IGRA and TST in Ontario: Immunocompromised Populations

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
IGRA, n[b]	**0**	**0**	**0**	**0**	**0**	**0**
TST, n	14,934	15,286	15,627	15,949	16,273	78,069
New scenario[a]						
Uptake rate for the New Strategy with IGRA, %	75%	85%	90%	95%	100%	
IGRA, n[b]	**11,200**	**12,993**	**14,064**	**15,151**	**16,273**	**69,681**
TST, n	3,734	2,293	1,563	798	0	8,388

Total, both, n	14,934	15,286	15,627	15,949	16,273	78,069

Abbreviations: n, number; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

[a]The volume of interventions was calculated from the total number multiplied by the uptake rate of the New Intervention.

[b] IGRA represents the new testing strategy that includes testing with IGRA (depending on the type of intervention, this could be IGRA as a single test or IGRA in combination with TST).

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a model-based reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions. As shown in the section above (Model Outputs), the undiscounted mean cost estimates were estimated probabilistically by running 100,000 simulations that simultaneously captured the uncertainty in the majority of the model parameters that were expected to vary. The probabilistic analyses were conducted using TreeAge Pro 2023.[117] The budget impact calculations were done using Microsoft Excel for Office 365.[118]

Sensitivity Analysis

We conducted the following scenarios to address uncertainty in the budget impact estimates (see Appendix 12 for details):

- Two scenarios related to *changes* in *the estimation of the populations of interest*:
  - ***Scenario 1***: Immigrant and contact sub-populations estimated from latent TB infection episode data recorded in the integrated Public Health Information System (iPHIS) extracted by and obtained from Public Health Ontario (email communication, A. Saunders, MSc, 01 Apr 2024, Public Health Ontario (PHO) Data Request #2024-011,[111] and expert oral and email communications June 10-14, 2024, L. Macdonald, MD, A. Saunders, MSc, M. Whelan, MSc and E. Rea, MD). The estimation and assumptions shown in Appendix 13 and Table 15.

Table 15: Scenario 1 – Overall population estimates for budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total population, n	**42,503**	**43,793**	**45,103**	**46,427**	**47,787**	**225,614**
Immigrants, n [a]	17,203	17,788	18,393	19,018	19,665	92,068
Contacts, n [a]	10,366	10,718	11,083	11,460	11,849	55,477
Immunocompromised, n	14,934	15,286	15,627	15,949	16,273	78,069

Abbreviations: n, number.

[a] Estimates calculated from latent tuberculosis infection data for extracted from iPHIS by Public Health Ontario[111]. See Appendix 13 for explanations of assumptions and calculations.

- ***Scenario 2***: Inclusion of *all types of cancers* into estimation of the size of immunocompromised population as shown in Table 16 (also in Appendix 10)

Table 16: Scenario 2 – Overall population estimates for budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Total population, n	**146,139**	**149,848**	**153,546**	**157,383**	**161,255**	**768,171**
Immigrants, n	38,588	39,901	41,257	42,660	44,110	206,516
Contacts, n	1,817	1,872	1,928	1,986	2,045	9,648
Immunocompromised, n[a]	105,734	108,075	110,361	112,737	115,099	552,006

Abbreviations: n, number.

[a] All cancers considered in the estimation of the immunocompromised populations.

- Four scenarios related to *changes in the uptake of IGRA strategies*:
  - ***Scenario 3***: *Same, large uptake for all* sub-populations starting from 75% in Year 1 – this is a substantial change in the uptake for the immigrant populations (which was 3%/year, the reference case)
  - ***Scenario 4***: *Same, low uptake for all* sub-populations of interest of 5% per year – this is a large change in the uptake for contacts and immunocompromised population (which was 75% in Year 1 -100% in Year 5, the reference case)
  - ***Scenario 5***: *Evenly spread uptake for immunocompromised* population of 20% per year (reaching 100% in Year 5) and the same uptake for the rest as in the reference case
  - ***Scenario 6***: *Smaller uptake for immunocompromised* population of 10% per year (reaching 50% in Year 5) and the same uptake for the rest as it was in the reference case

- Four scenarios related to *uncertainty in the testing pathway* with respect to:
  - ***Scenario 7:*** *No cost of referral* when the testing is done by MDs, thus, assuming no cost of referral visit for all sub-populations (vs. no cost of referral for testing done by PHU in the reference case)
  - ***Scenarios 8 and 9:*** *The share of TST and IGRA test settings* between MDs and PHUs for immigrant and contact sub-populations assuming:
    - ***Scenario 8:*** All tests for immigrants and contacts done by PHUs (MD:PHU, 50%-50%, reference case)
    - ***Scenario 9:*** All tests for immigrants done by MDs (MD:PHU, 50%-50%, reference case); we assumed that it would not be plausible to exclude PHUs from the testing for the contact investigations
  - ***Scenarios 10 (10a and 10b)***: No waste of the PPD vial at MD's office (Scenario 10a, the cost of PPD per dose: $20.6) and 80% of the vial wastage (Scenario 10b, the cost of PPD per dose: $103 vs. reference case, $37.08, about 44% of the PPD vial wastage)

- Two scenarios related to the *cost of IGRA:*

- ***Scenario 11***: The *cost of IGRA decreased by 25%* to $75/test (vs. $100/test, reference case)
- ***Scenarios 12 (12a and 12b)***: IGRA *done at an established hospital laboratory*

We estimated the ***cost of testing with IGRA*** **done at an established hospital lab** (e.g., Hospital for Sick Children), based on inputs obtained from the expert (expert consultation, email and oral communications, Nov-April 2024, M. Richard-Greenblatt, PhD). As shown in Table 17, we estimated *the total cost of IGRA test* for:

- Immigrant population: about $130 per test (i.e., weighted cost by the share of PHU: MD test setting: 50:50)
- Contact investigations: about $165 per test (i.e., weighted cost by the share of PHU: MD test setting: 50:50)
- Immunocompromised populations: about $138 (at MD's office, 100%)

The total *cost of indeterminate IGRA* result, requiring the second IGRA test was estimated at about:

- $119, $153 and $114 per test repeat for immigrant, contact and immunocompromised populations, respectively.

We conducted *additional analyses under this scenario* that accounted for the cost of shipping/handling of IGRA samples only for immigrant and contact populations (see Tables 17 and 24, Scenarios 12a and 12b). We assumed that immunocompromised populations would be tested at hospitals, and therefore, there would be no need for additional shipping costs required if testing is offered at the collection site (email and oral communications, April 03-May 31, 2024, M. Richard-Greenblatt, PhD).

Table 17: Testing for LTBI with IGRA — Per-Person Costs Used in a Scenario, IGRA done at an Established Hospital Laboratory

Costs inputs	Unit cost, $[a]	Quantity /Duration	Total cost, $[a]	Source
IGRA, immigrant populations and contacts perfomed by MDs and PHUs				
IGRA at MD's office				
Referral for LTBI	23.75	1	23.75	GP visit, minor assessment, Physician SoB[102]: A001
Blood sampling	10.76	1	10.76	L700, Ontario Schedule of Benefits: Laboratory Services
Test cost inlcudes all cost components sich as kits, consumables and shipping and handling , done by personnel at the hospital laboratory	103.00	1	103.00	Cost, Sick Kids Hospital , M. Richard-Greenblatt, PhD 11 April 2024
Shipping and handling	0	1	0	Included in the list price, expert oral consultation, E Rea, MD; R, Khan, RN; April 25, 2024; M. Richard-Greenblatt, PhD, April 15, 2024
Additional nurse's time for travel	0	NA	NA	No additional travel time (both contacts and immigrants, TST at MD's office)
IGRA: Total cost, MD's office	-	-	**137.51**	Calculated
IGRA at PHU				

Costs inputs	Unit cost, $[a]	Quantity /Duration	Total cost, $[a]	Source
Referral for TST physician visit	0	1	0	No visit claimed by PHU unit, expert oral consultation, E Rea, MD; R, Khan, RN; P Galange, MD; April 25, 2024
Blood sampling, nurse's time	1.01	15 min	15.15	Estimate, expert email communications, E Rea, MD/ R. Khan, RN: January 12 and April 10, 2024
Other consumables (needles, syringes, heparin, swabs, gauze, band aid, containers, if it is done at the PHU or hospital site) - scenario	4.63	1	4.63	Estimate (expert email communication: E. Rea, R, Khan, January 12, 2024 and April 25, 2024)
Test cost inlcudes all cost components such as equipment, overheads, labour, kits, consumables and shipping and handling, done by personnel at the hospital laboratory	103.00	1	103.00	Cost, Hospital for Sick Children, expert communication, M. Richard-Greenblatt, PhD, 11April 2024
Shipping and handling (Scenario 12a)*	0	1	0	Assumed to be covered by the current trasportation routes , expert, consultation: E Rea, MD; R, Khan, RN; April 25, 2024; M.Mellisa Richard-Greenblatt, PhD, April 15, 2024 Will be tested in additional scenario
*Shipping and handling added to the cost of test, if it is shipped from the site to the lab, included in an additonal scenario (Scenario 12b)	6.025	1	6.025	Tsiplova, 2016
Contact investigations only: Additional nurse's time for travel, contact investigation only, mileage for 1 visit per single contact)	139.02	1/2	69.51	Estimated to be half the cost for TST visit (expert email communication: E. Rea, MD, R, Khan, RN, January 12, 2024 and April 25, 2024)
IGRA: Total cost, PHU **Immigrants** **Contacts**	-	-	 **122.78** **192.29**	Calculated **(no shipping cost)**
IGRA: Total cost, PHU* **Immigrants** **Contacts**	-	-	 **128.805** **198.315**	Calculated **(shipping cost inlcuded)***
Adjustment of the total test cost, based on test-market share				
Test cost at MD's office (share 50%)	**137.51**	50%	68.755	Calculations, to include the share; simplifying assumption made for % share which was tested in sensitivity analysis (expert oral and email consultations, E Rea, MD; R, Khan, RN; P Galange, MD; April 25, and June 13, 2024
Test cost at PHU (share 50%) **Immigrants** **Contacts**	 **122.78** **192.29**	50%	 61.39 96.15	Calculations, to include the share; simplifying assumption made for % share which was tested in sensitivity analysis (expert oral and email consultations, E Rea, MD; R, Khan, RN; P Galange, MD; April 25, and June 13, 2024)

Costs inputs	Unit cost, $[a]	Quantity /Duration	Total cost, $[a]	Source
Completed IGRA: Overall, total test cost, adjusted for the share: **Immigrants** **Contacts**	-	1	 **130.455** **165.21**	Calculated (no shipping cost), adjusted for the share: Immigrants Contacts
Completed IGRA*: Overall, total test cost, adjusted for the share, additional scenario (with shipping cost) **Immigrants** **Contacts**	**MD: 137.51** **PHU*:** **128.81/ 198.32***	50%	**133.16** **167.91**	Calculated (shipping cost for PHU included), adjusted for the share, additional scenario Immigrants Contacts
Test repeat, indeterminate IGRA result: At MD's office	1	1	 113.76	Estimated, as the cost of 1 IGRA test without the initial MD visit
Test repeat, indeterminate IGRA result, at PHU : Immigrants Contacts	1	1	 122.78 192.29	Estimated, as the cost of 1 IGRA test without the initial MD visit
Test repeat, indeterminate IGRA result, adjsuted for the share of 50% **Immigrants** **Contacts**	 236.54 306.05	50%	 **118.27** **153.025**	Estimated, as the cost of 1 IGRA test without the initial MD visit and no shipping costs to PHU, adjusted for the share
Test repeat, indeterminate IGRA result, immigrants and contacts, additional scenario (with shipping cost):* **Immigrants** **Contacts**	MD: 113.76 PHU*: 128.81/ 198.32*	50%	**121.285** **156.04**	Estimated, as the cost of 1 IGRA test without the initial MD visit and with shipping costs to PHU, additional scenario
IGRA: immunocompromised populations, 100% by MDs				
Referral for LTBI	23.75	1	23.75	GP visit, minor assessment, Physician SoB[102]: A001
Blood sampling	10.76	1	10.76	L700, Ontario Schedule of Benefits: Laboratory Services
Test cost inlcudes all cost components sich as kits, consumables and shipping and handling, done by personnel at the hospital laboratory	103.00	1	103.00	Cost, Sick Kids Hospital , expert communication, M. Richard-Greenblatt, PhD, 11 April 2024
Shipping and handling	0	1	0	Included in the list price, expert oral consultation, E Rea, MD; R, Khan, RN; April 25, 2024; M. Richard-Greenblatt, PhD, April 15, 2024
IGRA: Total cost, immunocompromised	-	-	**137.51**	Calculated
IGRA test repeat, indeterminate IGRA result, immunocompromised		1	113.76	Estimated, as the cost of 1 IGRA test without the initial visit

Abbreviations: GP, general practitioner; OHIP, Ontario Health Insurance Plan; MOH, Ministry of Health; SoB, Schedule of Benefits; IGRA, interferon-gamma release assay.

[a]All costs are in 2024 Canadian dollars. The input parameters related to the physician fees, lab fees and the list price of IGRA are treated as fixed and were not assigned the distribution in probabilistic analysis.

We also conducted a set of **one-way sensitivity analyses** on the incremental cost of IGRA strategies versus TST alone to examine the influence of the following model inputs: screening participation, TST

completion, prevalence of LTBI, the diagnostic accuracy of TST and IGRA, reactivation of LTBI into active TB in untreated patients, completion of LTBI and active TB treatment, cost of shipping. These analyses were presented using tornado diagrams. We used a threshold parameter value for probability of reactivation of LTBI in immunocompromised population to examine costs and budget impact in **Scenario 13.**

Results

Reference Case: Overall Budget Impact – All Sub-Populations

Error! Reference source not found. presents the overall budget impact of publicly funding IGRA for supporting the diagnosis of LTBI (TB infection) in the three populations (immigrants, contacts, and immunocompromised people). These are overall estimates for the eligible populations that were calculated altogether, and they are result of averaging potential savings in some populations, and additional costs in other populations.

With the current scenario (current practice with TST), the total costs ranged from $21.52 million in year 1 to about 24.32 million in year 5, with a total 5-year cost of $114.52 million.

In the new scenario with IGRA alone (as a single test), the total costs were:

- In immigrants, between $15.66 million and 17.45 million per year, with a total 5-year cost of $82.73 million
- In contacts, about $0.73-$0.74 million per year, with a total 5-year cost of $3.65 million
- In immunocompromised, between $5.76 million and $6.64 million per year, with a total 5-year cost of $31.12 million

In this analysis for all populations, the budget impact of publicly funding IGRA alone (as a single test) was between $0.51 and $0.65 million per year, for a total of $2.99 million over the next 5 years. The cost associated with the IGRA test itself was $6.01 million. The overall budget impact is lower than the cost of testing because of downstream cost savings (reductions of follow-up costs and treatment costs, see next sections by the cost component).

Table 18: Budget Impact Analysis Results, Reference Case - IGRA alone vs TST, all populations

All populations	Total costs and budget Impact, in millions ($)[a,b]					
Scenarios: Total costs (millions)	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total 5-year Cost**
Current Scenario, TST alone, all populations	21.52	22.19	22.89	23.59	24.32	114.52
Cost of test	4.04	4.16	4.29	4.42	4.55	21.45
NEW Scenario: IGRA alone, Immigrants	15.66	16.09	16.54	16.99	17.45	82.73
Cost of test	2.76	2.92	3.09	3.27	3.46	15.49
NEW Scenario: IGRA alone, Contacts	0.74	0.73	0.73	0.73	0.73	3.65
BI: Cost of test	0.28	0.30	0.31	0.32	0.33	1.54

NEW Scenario: IGRA alone, Immunocompromised	5.76	6.04	6.24	6.44	6.64	31.12
BI: Cost of test	1.85	2.00	2.10	2.19	2.29	10.43
Total BI: IGRA alone vs TST alone	**0.65**	**0.66**	**0.62**	**0.56**	**0.51**	**2.99**
BI: Cost of test	0.86	1.05	1.21	1.36	1.53	6.01

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

[a]In 2024 Canadian dollars.

[b]Results may appear inexact due to rounding.

Error! Reference source not found. presents the overall budget impact of publicly funding the new testing including IGRA as a sequential testing for supporting the diagnosis of LTBI (TB infection) in all examined sub-populations (immigrants, contacts and immunocompromised people). In this estimation, we included the costs of IGRA testing sequentially with TST, done as follow-up to TST-positive results in immigrants/contact populations and as follow-up to TST-negative results in immunocompromised people.

In the new scenario with IGRA as part of sequential testing, the total cost depended on the population:

- In immigrants, was between $15.55 million and 16.82 million per year, with a total 5-year cost of $80.91 million
- In contacts, was about $0.70-$0.72 million per year, with a total 5-year cost of $3.52 million
- In immunocompromised, was between $7.86 million and $9.69 million per year, with a total 5-year cost of $44.16 million

In this analysis for all populations, the total additional costs of testing with IGRA as a sequential test to TST were between $2.61 and $2.88 million per year, with an overall additional cost of about $14.07 million over the next 5 years. The total cost associated with the testing alone was about $8.28 million.

Table 19: Budget Impact Analysis Results, Reference Case - IGRA in Sequential Testing* vs TST, all populations

All populations	**Total costs and budget Impact, in millions ($)[a,b]**					
Scenarios : Total costs (millions)	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5-year Cost
Current Scenario, TST alone, all populations	21.52	22.19	22.89	23.59	24.32	114.52
Cost of test	4.04	4.16	4.29	4.42	4.55	21.45
NEW Scenario: SEQ, Immigrants	15.55	15.87	16.18	16.50	16.82	80.91
Cost of test	2.75	2.89	3.05	3.21	3.38	15.28
NEW Scenario: SEQ, Contacts	0.72	0.70	0.70	0.70	0.70	3.52
Cost of test	0.35	0.37	0.39	0.41	0.43	1.95
NEW Scenario: SEQ with initial TST, Immunocompromised*	7.86	8.47	8.87	9.27	9.69	44.16
Cost of test	2.19	2.39	2.52	2.64	2.78	12.51
Total BI: SEQ- TST/IGRA vs TST alone	**2.61**	**2.84**	**2.86**	**2.88**	**2.88**	**14.07**
BI: Cost of test	1.24	1.49	1.67	1.85	2.04	8.28

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways.

[a]In 2024 Canadian dollars.
[b]Results may appear inexact due to rounding.
* TST followed by IGRA, in TST-negative in immunocompromised people.

Table 20 presents the overall budget impact of publicly funding the new testing including IGRA as a sequential testing for supporting the diagnosis of LTBI (TB infection) in all examined sub-populations (immigrants, contacts and immunocompromised people). In this estimation, we included the costs of IGRA testing sequentially with TST, done as follow-up to TST-positive results in immigrants/contact populations. In immunocompromised populations, IGRA was done as the first test followed-up with TST in those who tested IGRA-negative. In the new scenario with IGRA in sequential testing, the total cost depended on the population:

- In immigrants, was between $15.55 million and 16.82 million per year, with a total 5-year cost of $80.91 million
- In contacts, was about $0.70-$0.72 million per year, with a total 5-year cost of $3.52 million
- In immunocompromised, was between $8.62 million and $10.79 million per year, with a total 5-year cost of $48.88 million

In this analysis for all populations, the total additional costs of testing with IGRA were between $3.37 and $3.99 million per year, with an overall additional cost of about $18.80 million over the next 5 years. The total cost associated with the testing alone was about $10.12 million.

Table 20: Budget Impact Analysis Results, Reference Case - IGRA in Sequential Testing** vs TST, all populations

All populations	**Total costs and budget Impact, in millions ($) [a,b]**					
Scenarios: Total costs (millions)	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5-year Cost
Current Scenario: TST alone	21.52	22.19	22.89	23.59	24.32	114.52
Cost of test	4.04	4.16	4.29	4.42	4.55	21.45
NEW Scenario: SEQ, Immigrants	15.55	15.87	16.18	16.50	16.82	80.91
Cost of test	2.75	2.89	3.05	3.21	3.38	15.28
NEW Scenario: SEQ, Contacts	0.72	0.70	0.70	0.70	0.70	3.52
Cost of test	0.35	0.37	0.39	0.41	0.43	1.95
NEW Scenario: SEQ with initial IGRA, Immunocompromised **	8.62	9.35	9.82	10.30	10.79	48.88
Cost of test	2.48	2.73	2.89	3.04	3.21	14.35
Total BI: SEQ TST/IGRA &IGRA/TST (immunocompromised) vs TST alone	**3.37**	**3.72**	**3.82**	**3.91**	**3.99**	**18.80**
BI: Cost of test	1.54	1.83	2.04	2.25	2.47	10.12

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways.
[a]In 2024 Canadian dollars.
[b]Results may appear inexact due to rounding.
**IGRA for all then TST in IGRA negative for immunocompromised people

Reference Case: Budget Impact – By Sub-Population

Immigrant Populations

As shown in Table 21A, for the immigrant population, IGRA testing was associated with savings ranging from —$1.63 million (IGRA alone) to —$3.45 million (IGRA as sequential test) over the 5 years. Respectively, the total cost associated with the testing including IGRA was between $1.09 and 0.88 million.

Table 21A: Budget Impact Results, Reference Case – Immigrant Sub-Population

Immigrants	**Total costs and budget Impact, in millions ($) [a-c]**					
Scenarios: Total costs (millions)	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total 5-year Cost**
Current Scenario: TST alone	15.76	16.30	16.85	17.43	18.02	84.37
Cost of test	2.69	2.78	2.88	2.98	3.08	14.41
New Scenario: SEQ - TST/IGRA	15.55	15.87	16.18	16.50	16.82	80.91
Cost of test	2.75	2.89	3.05	3.21	3.38	15.28
New Scenario: IGRA alone	15.66	16.09	16.54	16.99	17.45	82.73
Cost of test	2.76	2.92	3.09	3.27	3.46	15.49
Total BI: IGRA alone vs TST alone	**-0.10**	**-0.21**	**-0.32**	**-0.44**	**-0.57**	**-1.63**
BI: Cost of test	0.07	0.14	0.21	0.29	0.38	1.09
Total BI: SEQ- TST/IGRA vs TST alone	**-0.21**	**-0.44**	**-0.67**	**-0.93**	**-1.20**	**-3.45**
BI: Cost of test	0.05	0.11	0.17	0.24	0.30	0.88

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways.

[a]In 2024 Canadian dollars.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

As shown in Table 21B, savings with IGRA testing were the result of downstream savings in the follow-up costs (—$0.79 to —$1.27 million over 5 years) and treatment costs (—$1.92 to —$3.07 million over 5 years).

Table 21B: Budget Impact Results, Reference Case – Immigrant Sub-Population, by Cost Component

	Total costs and budget Impact, in millions ($)[a-c]					
Current scenario: TST	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total 5-year Cost**
Total costs, current scenario	**15.76**	**16.30**	**16.85**	**17.43**	**18.02**	**84.37**
Cost of test	2.69	2.78	2.88	2.98	3.08	14.41
Cost of FU	3.78	3.91	4.05	4.18	4.33	20.26
Cost of LTBI treatment	9.17	9.49	9.81	10.14	10.49	49.10
Cost of TB treatment	0.11	0.12	0.12	0.13	0.13	0.61
New Scenario: IGRA alone						
Total costs, future scenario	**15.66**	**16.09**	**16.54**	**16.99**	**17.45**	**82.73**
Cost of test	2.76	2.92	3.09	3.27	3.46	15.49
Cost of FU	3.74	3.81	3.89	3.97	4.05	19.47

Cost of LTBI treatment	9.06	9.25	9.43	9.63	9.82	47.18
Cost of TB treatment	0.11	0.12	0.12	0.12	0.12	0.59
New Scenario: SEQ: TST/IGRA						
Total costs, future scenario	**15.55**	**15.87**	**16.18**	**16.50**	**16.82**	**80.91**
Cost of test	2.75	2.89	3.05	3.21	3.38	15.28
Cost of FU	3.71	3.75	3.80	3.84	3.89	18.99
Cost of LTBI treatment	8.99	9.10	9.21	9.32	9.42	46.03
Cost of TB treatment	0.11	0.12	0.12	0.13	0.13	0.61
BI: IGRA alone vs. TST						
Total Budget Impact	**-0.10**	**-0.21**	**-0.32**	**-0.44**	**-0.57**	**-1.63**
Cost of test	0.07	0.14	0.21	0.29	0.38	1.09
Cost of FU	-0.05	-0.10	-0.15	-0.21	-0.28	-0.79
Cost of LTBI treatment	-0.12	-0.24	-0.37	-0.52	-0.67	-1.92
Cost of TB treatment	0.00	0.00	0.00	0.00	0.00	-0.01
BI: SEQ (TST/IGRA) vs. TST						
Total Budget Impact	**-0.21**	**-0.44**	**-0.67**	**-0.93**	**-1.20**	**-3.45**
Cost of test	0.05	0.11	0.17	0.24	0.30	0.88
Cost of FU	-0.08	-0.16	-0.25	-0.34	-0.44	-1.27
Cost of LTBI treatment	-0.19	-0.39	-0.60	-0.83	-1.07	-3.07
Cost of TB treatment	0.00	0.00	0.00	0.00	0.00	0.00

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways.
[a]In 2024 Canadian dollars.
[b]Negative costs indicate savings.
[c]Results may appear inexact due to rounding.

Contacts

As shown in Table 22A, for the contact investigations, IGRA testing was associated with savings ranging from —$1.63 million (IGRA alone) to —$1.76 million (IGRA as sequential test) over the 5 years. Respectively, the total cost associated with the testing including IGRA ranged between $0.22 and $0.62 million.

Table 22A: Budget Impact Analysis Results, Reference Case – Contacts Sub-Population

Contacts	**Total costs and budget Impact, in millions ($)[a-c]**					
Scenarios : Total costs (millions)	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5-year Cost
Current Scenario: TST alone	0.99	1.02	1.05	1.09	1.12	5.28
Cost of test	0.25	0.26	0.26	0.27	0.28	1.32
New Scenario: IGRA alone	0.74	0.72	0.73	0.73	0.73	3.65
Cost of test	0.28	0.30	0.31	0.32	0.33	1.54
New Scenario: SEQ - TST/IGRA	0.72	0.70	0.70	0.70	0.70	3.52
Cost of test	0.35	0.37	0.39	0.41	0.43	1.95
Total BI: IGRA vs TST alone	**-0.26**	**-0.30**	**-0.33**	**-0.36**	**-0.39**	**-1.63**
BI: Cost of test	0.03	0.04	0.04	0.05	0.05	0.22
Total BI: SEQ, TST/IGRA vs TST alone	**-0.28**	**-0.32**	**-0.35**	**-0.38**	**-0.42**	**-1.76**
BI: Cost of test	0.10	0.11	0.13	0.14	0.15	0.62

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways.

[a]In 2024 Canadian dollars.
[b]Negative costs indicate savings.
[c]Results may appear inexact due to rounding.

As shown in Table 22B, savings with IGRA testing were the result of downstream savings in the follow-up costs (—$0.54 to —$0.70 million over 5 years) and treatment costs (—$1.31 to —$1.69 million over 5 years).

Table 22B: Budget Impact Results, Reference Case – Contact Sub-Population, by Cost Component

	Total costs and budget Impact, in millions ($)[a-c]					
Current scenario: TST	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total 5-year Cost**
Total costs, current scenario	0.99	1.02	1.05	1.09	1.12	5.28
Cost of test	0.25	0.26	0.26	0.27	0.28	1.32
Cost of FU	0.22	0.22	0.23	0.24	0.24	1.15
Cost of LTBI treatment	0.52	0.54	0.56	0.57	0.59	2.78
Cost of TB treatment	0.00	0.01	0.01	0.01	0.01	0.03
New Scenario: IGRA alone						
Total costs, future scenario	0.74	0.72	0.73	0.73	0.73	3.65
Cost of test	0.28	0.30	0.31	0.32	0.33	1.54
Cost of FU	0.13	0.12	0.12	0.12	0.12	0.61
Cost of LTBI treatment	0.32	0.30	0.29	0.29	0.28	1.48
Cost of TB treatment	0.00	0.00	0.00	0.00	0.00	0.02
New Scenario: SEQ: TST/IGRA						
Total costs, future scenario	0.72	0.70	0.70	0.70	0.70	3.52
Cost of test	0.35	0.37	0.39	0.41	0.43	1.95
Cost of FU	0.11	0.09	0.09	0.08	0.08	0.45
Cost of LTBI treatment	0.26	0.23	0.22	0.20	0.19	1.09
Cost of TB treatment	0.01	0.01	0.01	0.01	0.01	0.03
BI: IGRA alone vs. TST						
Total Budget Impact	**-0.26**	**-0.30**	**-0.33**	**-0.36**	**-0.39**	**-1.63**
Cost of test	0.03	0.04	0.04	0.05	0.05	0.22
Cost of FU	-0.09	-0.10	-0.11	-0.12	-0.13	-0.54
Cost of LTBI treatment	-0.21	-0.24	-0.26	-0.29	-0.31	-1.31
Cost of TB treatment	0.00	0.00	0.00	0.00	0.00	0.00
BI: SEQ (TST/IGRA) vs. TST						
Total Budget Impact	**-0.28**	**-0.32**	**-0.35**	**-0.38**	**-0.42**	**-1.76**
Cost of test	0.10	0.11	0.13	0.14	0.15	0.62
Cost of FU	-0.11	-0.13	-0.14	-0.15	-0.17	-0.70
Cost of LTBI treatment	-0.27	-0.31	-0.34	-0.37	-0.40	-1.69
Cost of TB treatment	0.00	0.00	0.00	0.00	0.00	0.00

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways.
[a]In 2024 Canadian dollars.
[b]Negative costs indicate savings.
[c]Results may appear inexact due to rounding.

Immunocompromised Populations

As shown in Table 23A, for the immunocompromised populations, IGRA testing was associated with additional costs ranging from $6.26 million (IGRA alone) to $19.29 and $24.01 million (IGRA as sequential test) over the 5 years. The total cost associated with the testing including IGRA ranged from $4.70 and $8.62 million.

Table 23A: Budget Impact Results, Reference Case – Immunocompromised Populations

Immunocompromised	**Total costs and budget Impact, in millions ($)[a,b]**					
Scenarios: Total costs (millions)	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5-year Cost
Current Scenario: TST alone	4.76	4.87	4.98	5.08	5.18	24.87
Cost of test	1.10	1.12	1.15	1.17	1.19	5.73
New Scenario: IGRA alone	5.76	6.04	6.24	6.44	6.64	31.12
Cost of test	1.85	2.00	2.10	2.19	2.29	10.43
New Scenario: SEQ - TST/IGRA	7.86	8.47	8.87	9.27	9.69	44.16
Cost of test	2.19	2.39	2.52	2.64	2.78	12.51
New Scenario: SEQ - IGRA/TST	8.62	9.35	9.82	10.30	10.79	48.88
Cost of test	2.48	2.73	2.89	3.04	3.21	14.35
Total BI: IGRA alone vs TST alone	**1.01**	**1.17**	**1.26**	**1.36**	**1.46**	**6.26**
BI: Cost of test	0.76	0.88	0.95	1.02	1.10	4.70
Total BI: SEQ- TST/IGRA vs TST alone	**3.10**	**3.60**	**3.89**	**4.19**	**4.50**	**19.29**
BI: Cost of test	1.09	1.27	1.37	1.48	1.58	6.79
Total BI: SEQ- IGRA/TST vs TST alone	**3.86**	**4.48**	**4.85**	**5.22**	**5.61**	**24.01**
BI: Cost of test	1.39	1.61	1.74	1.87	2.01	8.62

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways.

[a]In 2024 Canadian dollars.

[b]Results may appear inexact due to rounding.

As shown in Table 23B, IGRA testing was associated with some downstream savings in the treatment costs (—$0.02 to —$0.07 million over 5 years, depending on the strategy).

Table 23B: Budget Impact Results, Reference Case – Immunocompromised Sub-Population, by Cost Component

	Total costs and budget Impact, in millions ($)[a-c]					
Current scenario: TST	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total 5-year Cost**
Total costs, current scenario	4.76	4.87	4.98	5.08	5.18	24.87
Cost of test	1.10	1.12	1.15	1.17	1.19	5.73
Cost of FU	0.87	0.89	0.91	0.93	0.95	4.56
Cost of LTBI treatment	2.74	2.80	2.87	2.93	2.98	14.32
Cost of TB treatment	0.05	0.05	0.05	0.05	0.05	0.26
New Scenario: IGRA alone						

Total costs, future scenario	5.76	6.04	6.24	6.44	6.64	31.12
Cost of test	1.85	2.00	2.10	2.19	2.29	10.43
Cost of FU	0.93	0.96	0.99	1.01	1.04	4.94
Cost of LTBI treatment	2.93	3.03	3.11	3.18	3.26	15.51
Cost of TB treatment	0.05	0.05	0.05	0.05	0.05	0.24
New Scenario: SEQ: TST all/ IGRA in TST (-)						
Total costs, future scenario	7.86	8.47	8.87	9.27	9.69	44.16
Cost of test	2.19	2.39	2.52	2.64	2.78	12.51
Cost of FU	1.36	1.46	1.53	1.59	1.66	7.60
Cost of LTBI treatment	4.27	4.58	4.79	5.00	5.21	23.84
Cost of TB treatment	0.04	0.04	0.04	0.04	0.04	0.21
New Scenario: SEQ: IGRA all/TST in IGRA (-)						
Total costs, future scenario	8.62	9.35	9.82	10.30	10.79	48.88
Cost of test	2.48	2.73	2.89	3.04	3.21	14.35
Cost of FU	1.47	1.59	1.67	1.74	1.82	8.30
Cost of LTBI treatment	4.62	4.99	5.23	5.47	5.72	26.04
Cost of TB treatment	0.04	0.04	0.04	0.04	0.04	0.19
BI: IGRA alone vs. TST						
Total Budget Impact	**1.01**	**1.17**	**1.26**	**1.36**	**1.46**	**6.26**
Cost of test	0.76	0.88	0.95	1.02	1.10	4.70
Cost of FU	0.06	0.07	0.08	0.08	0.09	0.38
Cost of LTBI treatment	0.19	0.22	0.24	0.26	0.28	1.19
Cost of TB treatment	0.00	0.00	0.00	-0.01	-0.01	-0.02
BI: SEQ (TST/IGRA) vs. TST						
Total Budget Impact	**3.10**	**3.60**	**3.89**	**4.19**	**4.50**	**19.29**
Cost of test	1.09	1.27	1.37	1.48	1.58	6.79
Cost of FU	0.49	0.57	0.61	0.66	0.71	3.03
Cost of LTBI treatment	1.53	1.78	1.92	2.07	2.22	9.52
Cost of TB treatment	-0.01	-0.01	-0.01	-0.01	-0.01	-0.06
BI: SEQ (IGRA/TST) vs. TST						
Total Budget Impact	**3.86**	**4.48**	**4.85**	**5.22**	**5.61**	**24.01**
Cost of test	1.39	1.61	1.74	1.87	2.01	8.62
Cost of FU	0.60	0.70	0.75	0.81	0.87	3.74
Cost of LTBI treatment	1.88	2.19	2.37	2.55	2.74	11.72
Cost of TB treatment	-0.01	-0.01	-0.01	-0.02	-0.02	-0.07

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways.

[a]In 2024 Canadian dollars.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

Sensitivity Analysis

Our scenario analyses showed that IGRA as a single test strategy was the least costly option of all IGRA testing options (Table 24). The results of sensitivity analyses by the populations are presented in the

Appendices 14–16. The total budget for all populations considered together was mostly affected by the uptake, size of populations of interest, lack of the share between PHU and MD settings and the cost of the test:

- The largest savings in the total budget were seen in scenarios that assumed a large increase in the uptake of IGRA in immigrant populations, small uptakes of IGRA for all populations (5% per year), with 25% lower cost of IGRA test or a large chance of reactivation of LTBI in immunocompromised.
- The largest increase in the total budget was observed in scenarios that considered the testing for all people diagnosed with cancer in addition to those already indicated in the reference case population (e.g., selected non-solid cancers), and the testing setting (i.e., immigrant and immunocompromised people testing done at MDs offices assuming the waste of PPD).

Table 24: Budget Impact Results—Sensitivity Analysis: All Populations

Scenario	Total 5-year budget impact (BI) (IGRA strategies vs. TST alone), $ million [a,b]		
	IGRA alone	**SEQ: TST/IGRA** (all subpopulations)	**SEQ: TST/IGRA & IGRA/TST*** (*immunocompromised only)
Reference case, Total BI	**2.99**	**14.07**	**18.80**
Reference case, BI – Test cost	6.01	8.28	10.12
Change in Population Size			
Scenario 1: Ontario's number of people for testing based on iPHIS LTBI data obtained from PHO, and published LTBI prevalence estimates, **Total BI**	-3.85	7.63	12.36
Scenario 1: BI – Test cost	6.44	10.76	12.60
Scenario 2: All cancer types, Total BI	**40.96**	**131.15**	**164.58**
Scenario 2: BI – Test cost	34.56	49.48	62.47
Change in the uptake of IGRA			
Scenario 3: Large uptake for immigrants (all: 75% Y1-100% Y5), **Total BI**	**-11.24**	**-16.03**	**-11.30**
Scenario 3: BI – Test cost	15.49	15.92	17.75
Scenario 4: Low uptake for all (all: 5% per year), **Total BI**	**-1.93**	**-2.77**	**-1.96**
Scenario 4: BI – Test cost	2.65	2.72	3.04
Scenario 5: Evenly spread uptake for immunocompromised (20%/y), **Total BI**	**1.00**	**7.94**	**11.16**
Scenario 5: BI – Test cost	4.51	6.12	7.38
Scenario 6: Smaller uptake for immunocompromised (10%/y), Total BI	**-1.13**	**1.36**	**2.97**
Scenario 6: BI – Test cost	2.91	3.81	4.44
Change in the testing pathway			
Scenario 7: No cost of referral, Total BI	**1.34**	**11.15**	**15.76**

Scenario	Total 5-year budget impact (BI) (IGRA strategies vs. TST alone), $ million [a,b]		
	IGRA alone	**SEQ: TST/IGRA** (all subpopulations)	**SEQ: TST/IGRA & IGRA/TST*** (*immunocompromised only)
Scenario 7: BI – Test cost	4.35	5.36	7.08
Scenario 8: All tests done by PHUs, Total BI	**2.53**	**14.11**	**18.83**
Scenario 8: BI – Test cost	5.54	8.32	10.15
Scenario 9: Tests done by MDs in immigrants/immunocompromised, Total BI	**3.44**	**14.14**	**18.87**
Scenario 9: BI – Test cost	6.46	8.35	10.19
Scenario 10a: No waste of the PPD vial (no TST vial waste at MD's office), Total BI	**4.37**	**14.07**	**19.08**
Scenario 10a: BI – Test cost	7.38	8.28	10.40
Scenario 10b: 80% waste of the PPD vial (most of the TST vial wasted at MD's office), Total BI	**-2.36**	**13.92**	**17.55**
Scenario 10a: BI – Test cost	1.19	7.60	8.33
Change in the cost of IGRA			
Scenario 11: IGRA cost 25% lower, Total BI	**0.45**	**12.53**	**16.69**
Scenario 11: BI – Test cost	3.46	6.74	8.01
Scenario 12a: IGRA at hospital lab, cost of shipping and handling included in the test cost, Total BI	**3.36**	**14.28**	**19.08**
Scenario 12a: BI – Test cost	6.38	8.49	10.40
Scenario 12b: IGRA at hospital lab, additional cost of shipping and handling to the test cost, Total BI	**3.45**	**14.32**	**19.11**
Scenario 12b: BI – Test cost	6.46	8.53	10.43
Change in the probability of reactivation of LTBI into active TB, immunocompromised			
Scenario 13: high probability of reactivation of LTBI (threshold value of 30%, hypothetical scenario), **Total BI**	**-3.27**	**-0.40**	**-45.03**
Scenario 13: BI – Test cost	6.01	10.12	10.12

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways; iPHIS, Public Health Information System; PHO, Public Health Ontario.

[a]In 2024 Canadian dollars.

[b]Negative costs indicate savings.

In additional one-way sensitivity analyses in immigrant and contact sub-populations, the incremental savings of IGRA alone compared with TST alone would be switched to incremental costs if there were substantial changed in the sensitivity and specificity of IGRA, specificity of TST, completion of TST test, and prevalence of LTBI (See Figures 6 and 7).

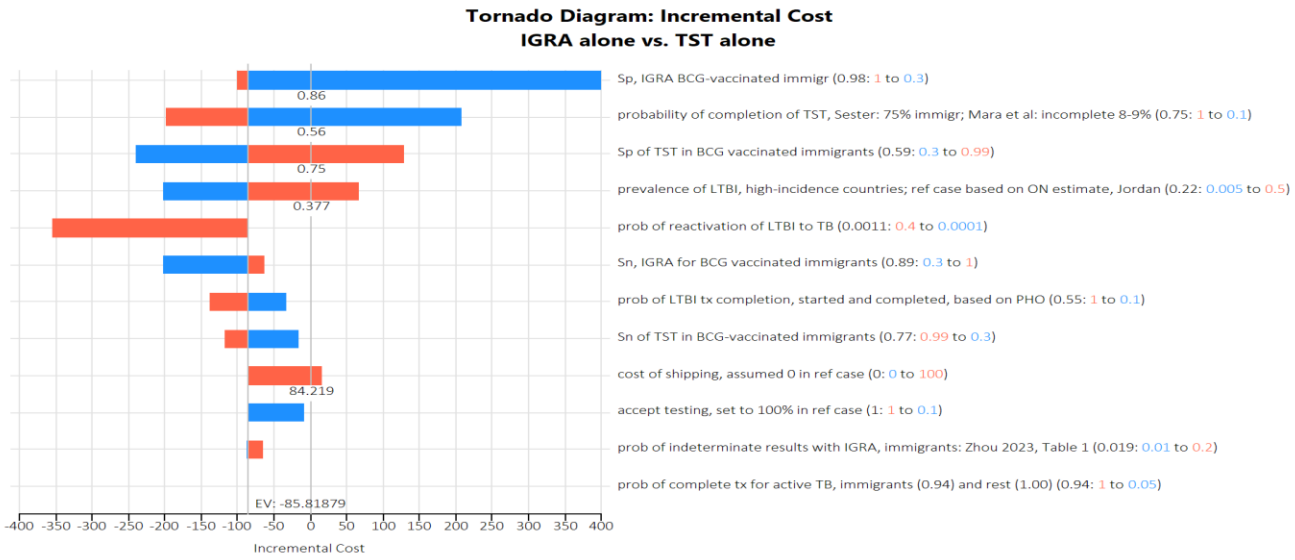

Figure 6. Tornado Diagram: Changes in Incremental Savings of IGRA alone vs. TST alone, Immigrant Populations

A tornado diagram showing changes in the incremental cost of IGRA alone versus TST alone, with changes in the initial values of clinical and cost parameters used for the reference case analysis in the BCG-vaccinated immigrant population. For example, varying the value of participation in IGRA testing (the parameter labeled “acceptance of testing”) from 0.1 to 1.0 did not change the direction of the incremental cost estimates, while the budget impact estimates were sensitive to the parameter estimates for the sensitivity and specificity of IGRA, specificity of TST, completion of TST, and prevalence of LTBI.

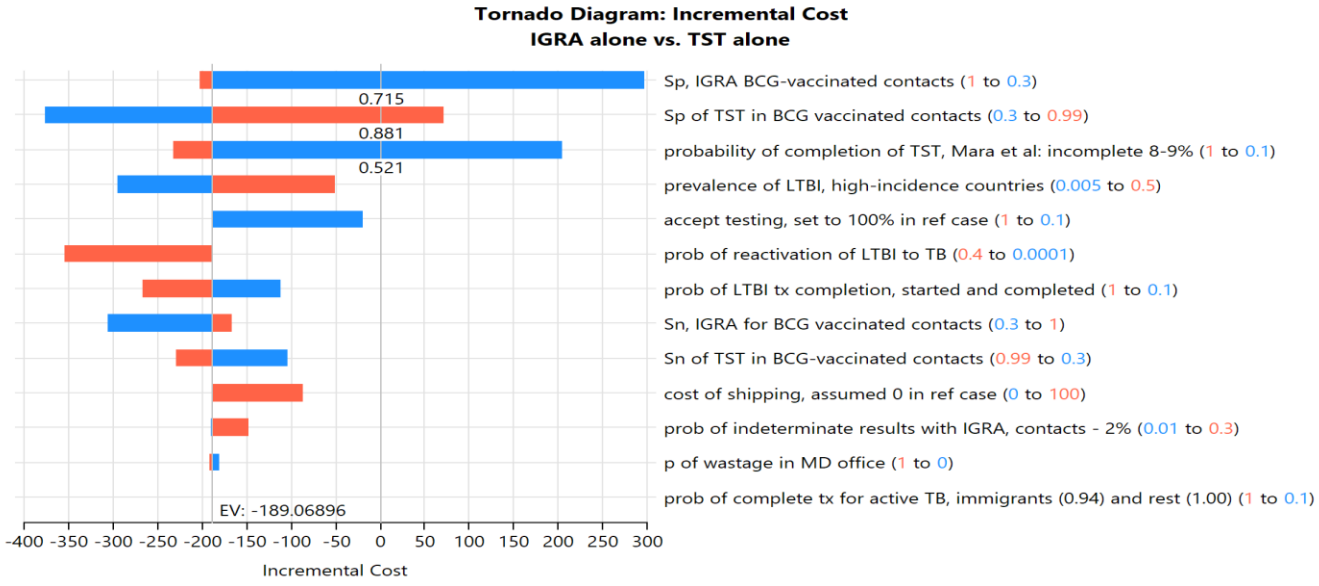

Figure 7. Tornado Diagram: Changes in Incremental Savings of IGRA alone vs. TST alone, Contacts

A tornado diagram showing changes in the incremental cost of IGRA alone versus TST alone, with changes in the initial values of clinical and cost parameters used for the reference case analysis in the BCG-vaccinated people identified via contact investigations. For example, varying the

value of participation in IGRA testing (the parameter labeled "acceptance of testing") from 0.1 to 1.0 did not change the direction of the incremental cost estimates, while the budget impact estimates were sensitive to the parameter estimates for the specificity of IGRA and TST, and completion of TST.

In immunocompromised populations, the incremental costs of IGRA alone compared with TST alone, would switch to savings with increasing sensitivity and specificity of TST (thresholds of 72% and 66%), specificity of IGRA (threshold of 90%) and probability of LTBI reactivation (threshold of 30%).

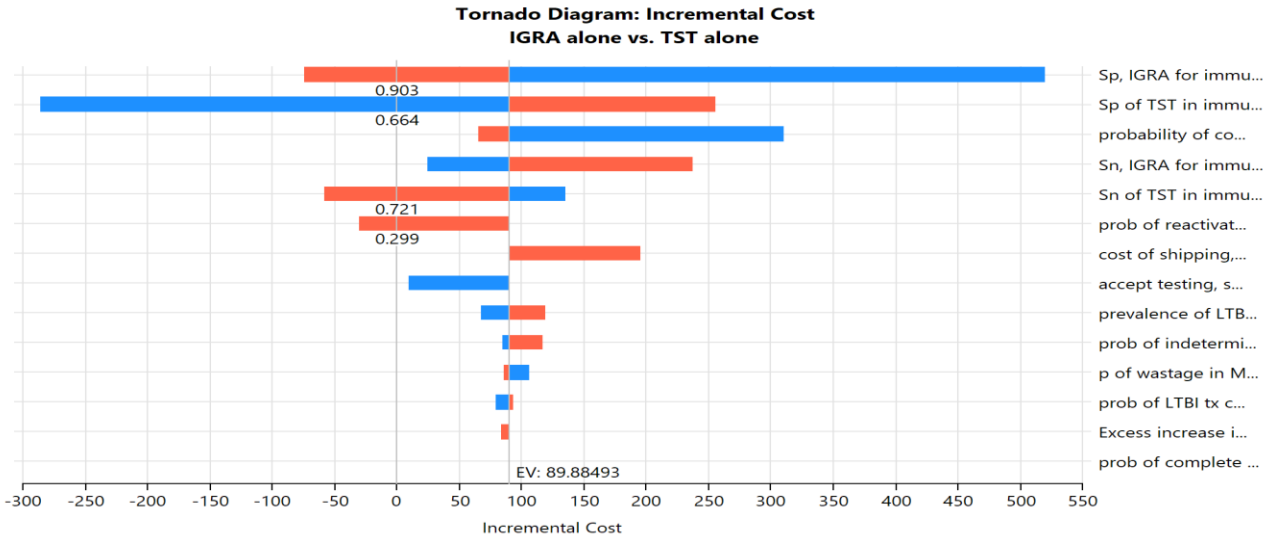

Figure 8. Tornado Diagram: Changes in Incremental Costs of IGRA alone vs. TST alone, Immunocompromised Populations

A tornado diagram showing changes in the incremental cost of IGRA alone versus TST alone, with changes in the initial values of clinical and cost parameters used for the reference case analysis in immunocompromised populations. For example, varying the value of participation in IGRA testing (the parameter labeled "acceptance of testing") from 0.1 to 1.0 did not change the direction of the incremental cost estimates, while the budget impact estimates were sensitive to the parameter estimates for the sensitivity and specificity of TST (the threshold values of 72% and 66%), specificity of IGRA (the threshold value of 90%), and probability of LTBI reactivation (the threshold value of 30%).

Discussion

We conducted model-based budget impact analyses to estimate the total 5-year budget for publicly funding IGRA testing in Ontario for the eligible subgroups of people at high risk of LTBI[74] in whom IGRA would be preferred test, as per the 8th Edition Canadian TB Standards.[74] We provided budget impact estimates for the overall population of interest and by a population subgroup (i.e., which we for simplicity divided into immigrant, contact and immunocompromised populations). We explored additional costs or savings with IGRA used as a single test or in sequential pathways with TST (serial testing), where the sequence of the tests depended on the population, as recommended by the Standards, and confirmed by experts[74]. Of note, we did not examine the use of both IGRA and TST at the same time (parallel testing) because this is not considered a good clinical practice and is not recommended by the Canadian TB Standards.[74]

In the reference case considering all populations, the total additional costs of testing with IGRA as a single test, IGRA as the follow-up test to TST for all subgroups, and IGRA in various sequential pathways (follow-up test to TST in BCG-vaccinated immigrants and contacts and as an initial test in

immunocompromised populations) were estimated at about $2.99 million, $14.07 million and $18.80 million, respectively, over the next 5 years. The corresponding additional costs over 5 years associated solely with the testing was about $6.01 million, $8.28 million and $10.12 million.

When we examined the budget impact by population, we found:

- Cost savings of over $1.63 million over 5 years with IGRA strategies in eligible BCG-vaccinated immigrant populations (assuming a 3% uptake of IGRA per year) and eligible BCG-vaccinated people identified via contact investigations (assuming a 75% uptake of IGRA in year 1 rising to 100% in year 5). The savings were result of reductions of the costs related to unnecessary follow-up evaluation and unnecessary use of costly TB treatments in those identified as incorrectly positive (false positive) by TST
- Additional costs of over $6.26 million over 5 years with IGRA strategies in selected groups of immunocompromised people including people with CKD, organ transplants, HIV-positive, and non-solid cancers investigations (assuming a 75% uptake of IGRA in year 1 rising to 100% in year 5). In this populations, IGRA was used to identify people at high risk of TB who were missed by TST (incorrectly tested negative)

We explored changes in the estimates of the budget in sensitivity analysis. The scenario analyses corroborated that IGRA as a single test was the least costly option of all IGRA testing options. The total budget estimated for all subgroups together was mostly affected by the uptake of an IGRA strategy, size of population (e.g., estimated based on Ontario data), the cost of the IGRA test, and the percentage-share of the testing between public health units and physicians. For instance:

- When we assumed the estimate of the eligible immigrant and contact populations based on the iPHIS LTBI data obtained from Public Health Ontario,[111] and published LTBI prevalence estimates,[14] we found a switch in the budget impact estimates for IGRA alone testing from additional costs ($2.99 million) to cost savings (-$3.85 million); also, a lower additional costs were estimated for sequential strategies (Table 24, scenario 1). This is because of decreased estimates of immigrant and increased estimates of the contact subpopulations. However, our estimates of the population size based on the number of identified true positive results of TST testing in Ontario (i.e., LTBI episodes) are associated with data limitations related to reporting and most likely represent an underestimate of the true burden of LTBI in Ontario (expert oral and email communications June 10-14, 2024, L. Macdonald, MD, A. Saunders, MSc, M. Whelan, MSc and E. Rea, MD). For example, positive TST results may be under-reported to local public health units by those that administer the TST and interpret the results; data entry practices for LTBI diagnosed by a positive TST may vary across public health units and over time; and, some LTBI episodes may be diagnosed via a IGRA result rather than a positive TST result, although to date this is expected to be a very small proportion of reported LTBI episodes. Overall, the number of LTBI episodes reported in iPHIS annually most likely underestimate the true burden of LTBI in Ontario. In addition, this estimate is limited by additional data-related assumptions that we had to make to calculate an overall TST-screened population for Ontario (see Appendix 13).
- If the uptake of IGRA in immigrant population changed from small (3% per year) to very high (75% in year 1), then the cost savings in immigrant and contact populations together would prevail cost increases in immunocompromised populations and the overall budget would be between saving of $11.24 million (IGRA alone) to saving of $16.03 million (sequential strategies) over 5 years (Table 24, scenario 3)

- Interestingly, if the uptake of IGRA changed but remained constant and small for all populations (5% per year for all), then we would see overall savings for all strategies across all populations (Table 24); this is because of the savings in BCG-vaccinated populations and small additional costs in immunocompromised populations – thus the savings would prevail additional costs in the budget estimation for all populations (Table 24, scenario 4: e.g., overall 5-Y budget impact for IGRA alone: -$2.72 million [immigrant]+ (-$0.28) million [contacts]) + $1.07 million [immunocompromised]= -$1.93 million, see data in Appendix 14–16)
- Also, we showed that the total additional costs of IGRA testing could be lowered by $2 million to $7 million if a slower evenly spread roll-out of IGRA intervention was used in a relatively large immunocompromised population (Table 24, scenario 5: uptake of 20% per year in immunocompromised populations).

In addition, we did not separately estimate the size of populations who are unlikely to return for testing because the reasons for this could be very different. However, as pointed in expert consultations (oral and email communication April 10-25, E. Rea, MD), these populations still need to have an indication for testing and are thus already included within the estimated immigrant and contact populations (therefore, considered by our analyses).

Lastly, funding of TST testing in Indigenous populations (First Nations) in Ontario would likely combine federal and provincial sources (e.g., PPD vials are provided by Infectious Diseases Policy and Programs Unit, Ministry of Health, April 10, 2024). Until 2014 many Indigenous people communities offered universal BCG vaccination for their population, thus, making them more likely BCG-vaccinated than Canadian-born people, because of their high risk of LTBI and high incidence of TB. Therefore, testing with IGRA could be more sensible approach to be used in this population. In addition, costs estimated for these populations are likely to be greater due to need for timely couriers and limited access to facilities for blood draw as well as laboratories capable of processing IGRAs. Also, the cost of IGRA is very high currently because of lack of nearby hospital with a lab that could perform this test. In our scenario analyses (Scenarios 12a and 12b), we estimated the additional costs of IGRA testing (with or without inclusion of the shipping cost) assuming that the test was done at a local hospital with established equipment and trained personnel to conduct the IGRA test.

Equity Considerations

As mentioned in previous sections, there is inequity in access to IGRA testing in Ontario because it is only available to those who can pay it out of pocket or can access laboratories offering this testing. Our budget impact analyses addressed that inequity in access for people who are considered eligible and at high-risk by the current Canadian TB standards.[74] The additional personal costs incurred in the 2 visits for a TST vs single visit for IGRA, such as additional (often unpaid) time off work and travel costs, are also significant equity considerations, as the burden of these personal costs falls more heavily on the same population that is most likely to need LTBI diagnosis and treatment (e.g., immigrants and contacts). However, they have not been included in this provincial budget impact analysis (estimated from a public payer perspective). Moreover, we examined various assumptions related to IGRA testing and provided insight how much investment the province would need to make to enable full (100%) access to IGRA testing over the next 5 years or conduct IGRA in an established Ontario-based hospital lab. Overall, publicly funding IGRA would address and mitigate the issues around unequal access to IGRA testing.

Strengths and Limitations

Our budget impact analysis was associated with several strengths:

- The budget-impact estimates were calculated from outputs of our probabilistic model which accounted for the diagnostic accuracy of IGRA and TST tests, follow-up and treatment costs associated with LTBI and future active TB, and completion of the testing and therapy.
- We examined the use of IGRA as a single test or in a sequential pathway with TST which are the testing strategies recommended by the current Canadian TB Standards.[74]
- Our model parameter inputs were informed by our up-to-date clinical evidence review which considered the most recent systematic reviews of the highest quality.
- We derived the costs associated with TST and IGRA testing through expert consultations from the Ontario sources and established costs related to follow-up medical evaluations and treatment of LTBI and active TB from the relevant Canadian and Ontario-based economic studies.
- We validated our assumptions and estimates with clinical experts with expertise in the use of IGRA and TST in supporting the diagnosis of LTBI.
- Lastly, findings of our reference case and sensitivity analyses are generally aligned with the results of the published Canadian economic studies included in our economic evidence review.[77-81] They are generalizable to all populations currently recommended for IGRA testing as an alternative or preferred test to TST by the current Canadian TB Standards[74].

There are some limitations to our analysis:

- First, our analyses are restricted by uncertainty in the overall population size particularly for the size of immunocompromised populations.
- In addition, the Canadian TB Standards[74] distinguish recommendations for BCG-vaccinated population by their age of vaccination, while we considered previously vaccinated individuals altogether.
- Next, the uptake of IGRA testing in contact investigations and immunocompromised populations could be smaller because of limited healthcare system capacity to rapidly adopt the new technology in the implementation stage.
- Also, with a higher chance of reactivation of LTBI in exposed immunocompromised populations, the downstream treatment costs could be much higher (Table 24, scenario 13); therefore, it is possible that we overestimated the budget impact for this sub-population.
- In addition, because of uncertainty in the test settings for the populations of interest, we made a simplifying assumption regarding the share of testing between PHUs and MDs (50-50% in the reference case). However, it is more likely that a small proportion of selected immigrants could be likely tested by designated physicians (MDs) and not by PHUs. In a scenario analysis, we showed that this assumption slightly affected the budget impact because the test costs assumed for immigrant population in the reference case (adjusted for the 50-50 share) are not substantially different from

those used in a scenario which assumed no share (100% of tests done by MDs, Table A14, Appendix 12 and Scenarios 8 and 9).

In summary, our analyses provide rough cost estimates of possible pathways, and because of uncertainty in many factors, we conduct sensitivity analyses to address implications of important assumptions or parameter values and explore changes in the budget estimates. Therefore, we conducted several scenarios related to changes in the population size, uptake of IGRA or test settings to address potential uncertainties. In the implementation stage, further work would be needed to establish a clinically inclusive and fiscally reasonable approach to IGRA testing if it is recommended for publicly funding.

Conclusions

Over the next 5 years, the total additional costs of publicly funding testing with IGRA in Ontario for all examined population subgroups ranged between $2.99 million (IGRA as a stand-alone test) and $14.07 to $18.80 million (IGRA in sequential pathways with TST). In the population-specific analyses, we estimated cost savings of $1.63 million or higher with publicly funded testing with IGRA in eligible BCG-vaccinated immigrant populations or people identified via contact investigations. We found additional costs of $6.26 million or higher with publicly funded testing with IGRA in immunocompromised people.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the preferences and values of patients who have experience with the tuberculosis skin test (TST) and the interferon-gamma release assay (IGRA) testing for latent tuberculosis infection (LTBI).

Methods

Partnership Plan

The partnership plan for this health technology assessment focused on engagements to examine the experiences of patients who have experience with TST and/or IGRA testing for latent tuberculosis infection (LTBI).

Participant Outreach

We used an approach called purposeful sampling, which involves engaging participants who are especially knowledgeable or experienced with the health technology under review. We also used snowball sampling to identify additional contacts from interview participants and Ontario Health. We distributed our recruitment poster through 15 clinician and 1 public health contact who serve the community with testing for LTBI. We also reached out to TB awareness and support groups to further facilitate patient recruitment.

Inclusion Criteria

We sought to interview patients with direct experience with TST and/or IGRA.

Exclusion Criteria

We did not set exclusion criteria for participants who otherwise met the inclusion criteria.

Participants

Despite our recruitment efforts, we did not hear back from interested patients by the deadline for recruitment. The clinician contacts we reached out to for recruitment explained that this could be due to language barriers of the typical populations for LTBI testing (immigrants, refugees,).

As a contingency plan, we decided to engage with healthcare providers across clinical sites in Ontario who have experience with skin test (TST) and/or blood test (IGRA) for LTBI. We sought to capture the preferences and values of patients indirectly through provider engagement via an online survey.

Our survey was completed by 53 providers ranging from primary care physicians, nurse practitioners, respirologists, pediatricians and public health personals. All participants were familiar and had direct experience with TST and/or IGRA.

Approach

At the beginning of the survey, we included a written description of the role of our organization, the purpose of this health technology assessment. Questions focused on the pros and cons of TST and IGRA as well as providers preference and perceived impact on patients towards these tests for LTBI. Please see Appendix 18 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze survey results. This approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[119,120] We used the qualitative data analysis software program NVivo[121] to identify and interpret patterns in the data. The patterns we identified allowed us to describe the impact of IGRA testing for LTBI.

Results

Patient population for LTBI testing

Providers described the populations that they serve for LTBI testing. Recently arrived immigrants and immunocompromised patients were mentioned by most participants. In addition, healthcare workers who need LTBI testing for work/study purposes, as well as persons living in congregate settings such as shelters, long term care and correction facilities were mentioned as highly susceptible group for LTBI, and therefore required testing. Participants also mentioned that they refer multiple patients at their clinic for TST or IGRA.

TST Skin Test

The TST, being the only publicly funded test in Ontario, is the conventional method for LTBI testing. It involves the injection of a derivative protein on under the patient's skin on their forearm. This spot is then checked by a healthcare provider during a second appointment 48-72 hours later. Participants commented on the challenges of TST including delayed care caused by missed appointments for the second/ follow-up visit, inter-reader variability of results and the risk for false positives in patients with prior BCG vaccination history which is common in newcomer population (immigrants and refugees). Administration difficulties in young children and those with comorbidities was also highlighted as a challenge by providers.

Delayed care

Participants described that there is a significant delay in care due to missed follow up visits for the second TST reading. The requirement of a second visit for TST was also highlighted as a challenge for healthcare resource utilization.

> *TST has high rate of non return for the second day reading (even despite very good education to patients)*

> *[TST] is inefficient for clinic workflow (leads to more work for clinic admin staff, waiting room crowding, low-value use of precious RN resource).*

Client needs to come back for reading causing substantial delay [in care].

Subjective reading

Participants mentioned that TST is difficult to interpret and is often dependent on the user for accurate reading specially in immunocompromised patients leading to misdiagnosis.

TST is difficult to interpret and frequently interpreted incorrectly.

Dependent on the clinician's visual inspection. Not all clinicians can accurately read the test.

Also, some challenges with interpreting TST / inconsistency about reading between providers especially in immunocompromised / HIV patients.

I have also seen many patients misdiagnosed with LTBI based on false positive results and clinician's experience with planting and reading the TST.

False positives and negatives (BCG vaccinated and immunocompromised)

Participants explained that TST is not as sensitive with BCG vaccine which most patients that get tested for LTBI have. This leads to high rate of false positives. In addition, people who are immunocompromised tend to get false negatives.

[TST] not as sensitive with BCG vaccine (which most patients have had).

It is difficult to interpret positive results in the context of prior BCG vaccination which most patients have had.

Have high false positive [for BCG vaccinated].

Risk of false negatives in immunocompromised patients.

Administrative challenges

Participants described the various administrative challenges with TST including difficulty scheduling appointments with patients, high healthcare resource utilization as well as difficulty with administering the test in children and people with comorbidities such as ADHD.

TST can be difficult to schedule especially for transient populations (e.g. underhoused), vs if we could use an IGRA we could test more opportunistically.

Difficulty in test administration especially if very young or have other co-morbidities, e.g., ADHD.

Education lacking in the community about appropriate TST administration and reading (measuring induration correctly and providing that in the referral), leads to unnecessary referrals More resources for staff required.

IGRA

All participants highlighted the advantages of IGRA over TST citing multiple reasons such as the streamlining of care, determinate results in BCG vaccinated populations, patient and provider preference, and improved equity.

Streamlining Care

Providers explained that IGRA improves clinical workflow as it is done through bloodwork. They mentioned IGRA could be done as part of the routine initial intake of bloodwork for newcomers (immigrants or refugees) leading to streamlining of care and avoiding delays. Moreover, participants noted that IGRA only requires a single visit to the clinic which would allow for a better patient adherence and healthcare resource utilization.

> *All the newcomer clients seen at the clinic have some screening blood tests if this test was covered, we could Add it to the screening tests. Less invasive for the clients and improved workflow.*
>
> *It would ideal if IGRA could be covered for our client group - This would expedite screening process (not have to wait for next nursing apt which can take up to 6- 12 months based on our wait list), allow better compliance with screening by patients doing bloodwork vs waiting for appointment.*
>
> *IGRA is much better than TST - we do bloodwork for all newly arrived refugees anyway so it's easy to add on.*
>
> *IGRA also improves compliance significantly since its one blood test and many patients are lost to follow up to read the TST.*

Determinate results

Participants explained that IGRA is not reliant on the user for accurate reading. Furthermore, it eliminates the risk for false positives in patients with prior BCG vaccination. This is particularly important in populations that are susceptible for LTBI as they are not aware of their vaccination status, and for newcomers who are mostly BCG vaccinated.

> *[IGRA is a] simple blood test without inter reader variability.*
>
> *Removal of biases and inter-readability concerns.*
>
> *IGRA is more accurate and would give better picture/ numbers of those at risk of TB.*
>
> *IGRA is also not affected by prior vaccination, which is very important as many clients are completely unsure of their vaccine records from childhood and/or are illiterate.*
>
> *IGRA is especially useful in those who have been BCG vaccinated which is majority of patients seen in our TB clinic.*

Provider Preferences

Furthermore, all providers emphasized their preference towards IGRA for the diagnosis of LTBI. They explained that IGRA should be the standard of care and offered to patients without cost. They also implied that having IGRA as an accessible test to patients would increase accurate diagnosis of LTBI and reduce inequities in healthcare.

> *QFT [type of IGRA] needs to be the gold standard for TB screening and testing and needs to be publicly funding.*
>
> *This [IGRA] is the standard of care, should be offered as an insured test to all who need it.*
>
> *IGRA is standard of care for screening for LTBI, and is the most appropriate test for use in certain populations and in certain clinical/logistical circumstances. At this point in time, not giving providers funded access to this test implies, that inequitable health outcomes for certain cohorts of people, is indeed the goal.*
>
> *I would also like to point out that IGRA is the preferred test over TST in a number of clinical situations as outlined in Chapter 4 of the current Canadian TB standards of which I am a co-author. As such, performing an IGRA is the expected standard of care but yet is not available to patients who cannot afford it.*

Some participants also mentioned that IGRA is the preferred test for children under the age of 10.

> *[IGRA] can be drawn with other bloodwork as part of a workup leading to fewer painful procedures for children.*
>
> *We see a lot of children under 10y.o. where IGRA's are the preferred test.*
>
> *[IGRA is] reliable in children.*

Challenges with IGRA

Participants explained the challenges with IGRA including implementation challenges and risk for false negatives in immunocompromised patients. Implementation challenges with IGRA included delays in lab shipment and collection process of blood samples leading to indeterminate results.

> *Problems in collecting and transporting blood especially if batched and processed at an outside facility.*
>
> *[IGRA results in] objective measurement; but I've seen issues with discordant results and lab shipment/collection problems.*
>
> *Time constraints leading to indeterminate results.*
>
> *[IGRA is] dependent on lab hours.*

One participant mentioned that IGRA, same with TST, poses a risk for false negatives in immunocompromised patients.

> *[IGRA has] false negatives in immunocompromised patients (same as for TST).*

Perceived Impact on Patients

IGRA is mostly preferred by patients according to providers who shared their insights from their interactions with patients. This was mainly due to the convenience of IGRA such as not requiring multiple visits to the clinic.

> *QFT [type of IGRA] is an EXTREMELY VALUABLE tool/test to have for our patient population. I have spoken informally to many patients, and they would agree with this statement.*

> *Most patients prefer IGRA as no need for return visit.*

> *This is an important equity issue, particularly for immigrants and refugees-- IGRA is a preferred option by many patients.*

Participants also explained that IGRA testing is especially important when considering treatment for LTBI.

> *We have had situations where, should we have had an IGRA available, we would have been able to diagnose LTBI much earlier than we were able to, and possibly start therapy and prevent negative health outcomes.*

> *IGRA is more accurate, helps in a much more robust way in decision making re management of LTBI. Would make life easier for patients, providers and system.*

> *IGRA preferred especially if considering treatment for LTBI*

> *IGRA tests would allow us to more accurately counsel patients on the importance of treating latent TB.*

Equity

Participants highlighted that having IGRA as an accessible diagnostic test would improve equity for newcomer populations and those with lower income as they are a common group to be affected by LTBI. They mentioned that these patients face difficulties traveling to the clinic for multiple appointments that the TST requires.

> *This [IGRA] would improve equity for migrant populations and those who are lower income. [IGRA] would be of great benefit to those in shelters, street involved people who may have difficulty with that second visit [for TST].*

> *Thinking about the families and children that are most affected by having IGRAs available, this is an issue of equity. Perpetuation of harm by not being able to complete the workup that is recommended for these children is real. We have had situations where, should we have had an IGRA available, we would have been able to diagnose LTBI much earlier than we were able to, and possibly start therapy and prevent negative health outcomes.*

However, due to its expensiveness, patients are not able to afford IGRA which leads to delay in diagnosis and treatment.

> *I feel this is an equity issue - the IGRA is currently only available to those who can afford it, but often would be most useful in our patients who cannot afford such a costly test.*
> *Many of my immigrants and refugees find cost of IGRA a barrier if they have previously been BCG vaccinated.*
>
> *Expensive test to do, specially for vulnerable, marginalized population who are the ones at risk of TB.*
>
> *Cost is prohibitive for many patients.*

For the TST, patients face different barriers such as childcare arrangements, having to take time off from work, transportation, and language barriers, therefore resulting in non-adherence and delayed care.

> *TST is very inefficient for patients (2nd visit for skin test reading is disruptive, expensive and difficult -- parking, transportation, kids out of school -- and patients often do not show up leading to need for repeat testing).*
>
> *[TST] entails two visits sometimes more... with a vulnerable population with poor access to transportation, health literacy and other barriers this testing often is not completed.*
>
> *Multiple visits are a burden for patients (take time off work, travel distances, childcare-- more significant burden for ppl in lower paid jobs or with other financial strain) and a burden for healthcare workers (takes up precious appointment time that can delay care for other patients)*

Preferences and Values Evidence Discussion

Outreach for this provider perspectives summary yielded engagement with 53 healthcare providers who had expertise with IGRA and/or TST. Participants reported the strengths of IGRA testing for LTBI including the streamlining of care and improved accuracy. They also explained the perceived positive impact of IGRA on patients including improved equity and access to care. Cost was highlighted as a major barrier for accessing IGRA. Participants also commented on the challenges that patients face with TST due to the multiple visits needed. They noted barriers such as transportation, language, childcare arrangements and taking time off from work which resulted in non-adherence and delayed care.

Limitation

There is a lack of direct patient engagement. The patient populations that get tested for LTBI commonly include newcomers and people living in congregate settings (such as shelters, long term care, correctional facilities). Speaking to our clinical experts, we learnt that it would be difficult to directly engage with this population due to language barriers. During our recruitment stage, we reached out to 14 clinicians, 1 public health contact as well as 2 TB awareness organizations to distribute our recruitment posters, however, by the deadline for recruitment, we did not hear back from interested participants. To mitigate this limitation, we engaged with healthcare providers who gave us insight on the perceived impact of IGRA on patients' lives as well as patients' preferences and decision-making factors for LTBI testing.

Preferences and Values Evidence Conclusions

Overall, participants had positive comments about IGRA testing for LTBI. They expressed that IGRA is their preferred test for LTBI; however, they highlighted cost as a barrier to accessing the test. Furthermore, participants reflected on the downsides of TST related to perceived impact on patients and equity.

Conclusions of the Health Technology Assessment

The interferon gamma release assay was found to have good evidence as a rule-in test for LTBI due to consistently high specificity. Compared to TST, IGRA appears to have fewer false-positives among those who tested positive on both LTBI tests in head-to-head comparisons, which was particularly notable in the population that has had the BCG vaccine. Additionally, IGRA may be informative for people with immunocompromising conditions, who are at risk for a false-negative from a TST, as it yields indeterminate findings, signaling that further clinical investigation may be needed.

Based on our review of the 5 economic studies from Canada, IGRA (either as a stand alone or in sequence with TST) is cost-effective compared with TST alone for supporting the diagnosis of LTBI in high-risk populations that are aligned with the Canadian TB Standards, published in 2022. All reviewed studies were of good quality and 3 studies were directly applicable to the Ontario context and our research question. Therefore, we did not conduct a primary economic evaluation.

Over the next 5 years, the total additional costs of publicly funding testing with IGRA in Ontario for all examined population subgroups ranged between $2.99 million (IGRA as a stand-alone test) and $14.07 to $18.80 million (IGRA in sequential pathways with TST). In the population-specific analyses, we estimated cost savings of $1.63 million or higher with publicly funded testing with IGRA in eligible BCG-vaccinated immigrant populations or people identified via contact investigations. We found additional costs of $6.26 million or higher with publicly funded testing with IGRA in immunocompromised people.

Health care professionals who we spoke with expressed that IGRA is patients' preferred test for LTBI; however, they highlighted cost as a barrier to access the test. Furthermore, participants reflected on the downsides of TST related to perceived impact on patients and equity, particularly the need for a second office visit to read the test results.

Abbreviations

BCG: Bacille Calmette-Guérin

CI: confidence interval

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

ICER: incremental cost-effectiveness ratio

IGRA: interferon gamma release assay

LTBI: Latent TB infection

NICE: National Institute for Health and Care Excellence

OR: odds ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

QALY: quality-adjusted life-year

RR: relative risk

SD: standard deviation

TB: Tuberculosis

TST: tuberculin skin test

WTP: willingness-to-pay

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Base case: In economic evaluations, the base case is the "best guess" scenario, including any assumptions, considered most likely to be accurate. In health technology assessments conducted by Ontario Health, the reference case is used as the base case.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cohort model: In economic evaluations, a cohort model is used to simulate what happens to a homogeneous cohort (group) of patients after receiving a specific health care intervention. The proportion of the cohort who experiences certain health outcomes or events is estimated, along with the relevant costs and benefits. In contrast, a microsimulation model follows the course of individual patients.

Cost–benefit analysis: A cost–benefit analysis is a type of economic evaluation that expresses the effects of a health care intervention in terms of a monetary value so that these effects can be compared with costs. Results can be reported either as a ratio of costs to benefits or as a simple sum that represents the net benefit (or net loss) of one intervention over another. The monetary valuation of the different intervention effects is based on either prices that are revealed by markets or an individual or societal willingness-to-pay value.

Cost–consequence analysis: A cost–consequence analysis is a type of economic evaluation that estimates the costs and consequences (i.e., the health outcomes) of two or more health care interventions. In this type of analysis, the costs are presented separately from the consequences.

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness acceptability curve: In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.

Cost-effectiveness acceptability frontier: In economic evaluations, a cost-effectiveness acceptability frontier is a graph summarizing the probability of a number of health care interventions being cost-

effective over a range of willingness-to-pay values. Like cost-effectiveness acceptability curves, cost-effectiveness acceptability frontiers plot willingness-to-pay values on the horizontal axis and the probability of the interventions being cost-effective at particular willingness-to-pay values on the vertical axis.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost-effectiveness plane: In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.

Cost-minimization analysis: In economic evaluations, a cost-minimization analysis compares the costs of two or more health care interventions. It is used when the intervention of interest and its relevant alternative(s) are determined to be equally effective.

Cost–utility analysis: A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Deterministic sensitivity analysis: Deterministic sensitivity analysis is an approach used to explore uncertainty in the results of an economic evaluation by varying parameter values to observe the potential impact on the cost-effectiveness of the health care intervention of interest. One-way sensitivity analysis accounts for uncertainty in parameter values one at a time, whereas multiway sensitivity analysis accounts for uncertainty in a combination of parameter values simultaneously.

Disability-adjusted life-year (DALY): The disability-adjusted life-year (DALY) is a health-related quality-of-life measure used to quantify the burden of disease from ill health, disability, or premature death. One disability-adjusted life-year represents the loss of one year of full health. Disability-adjusted life-years enable comparisons across different diseases, such that a disease that may cause premature death (e.g., measles) can be compared with a disease that may cause disability (e.g., cataracts).

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Disease-specific preference-based measures: Disease-specific preference-based measures are instruments used to obtain the quality-adjusted weight (i.e., the utility value) of being in a particular health state or having a specific health condition. Disease-specific preference-based measures are often thought to be more sensitive than generic preference-based measures in capturing condition-specific health effects. Like generic preference-based measures, disease-specific preference-based measures typically consist of a self-completed questionnaire, a health-state classification system, and a scoring formula that calculates the utility value. The key difference is that health states in disease-specific preference-based measures are important for the health condition of interest but may not apply to all patient populations. Examples of disease-specific preference-based measures include the Diabetes Utility Index (DUI) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

Disutility: A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Equity: Unlike the notion of equality, equity is not about treating everyone the same way.[122] It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

Extended dominance: A health care intervention is considered to be extendedly dominated when it has an incremental cost-effectiveness ratio higher than that of the next most costly or effective comparator. Interventions that are extendedly dominated are ruled out.

Generic preference-based measures: Generic preference-based measures are generic (i.e., not disease specific) instruments used to obtain the quality-adjusted weight (i.e., the utility value) of being in a given health state. Generic preference-based measures typically consist of a self-completed questionnaire, a health-state classification system, and a scoring formula that calculates the utility value. Examples include the Health Utilities Index Mark 3 (HUI3), the EQ-5D, and the Short Form–Six Dimensions (SF-6D). The quality-adjusted weights are obtained from the public or from patients, who are provided with a descriptive profile of each predefined health state and asked to fill out a questionnaire. The benefit of using a generic instrument is the ability to obtain utility values that are comparable across different health care interventions and diseases.

Health inequity: Health inequities are avoidable inequalities in health between groups of people within countries and between countries.[123] These inequities arise from inequalities within and between

societies. Social and economic conditions and their effects on people's lives determine their risk of illness and the actions taken to prevent them becoming ill or treat illness when it occurs.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Health Utilities Index Mark 3 (HUI3): The HUI3 is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The HUI3 was developed in Canada and is used in major Canadian population health surveys. The HUI3 comprises eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain and discomfort. Each attribute is associated with five or six defined functional levels, thus producing a total of 972,000 unique health states. A predefined scoring formula is used to convert HUI3 scores to utility values.

Horizontal equity: Horizontal equity requires that people with like characteristics (of ethical relevance) be treated the same.

Human capital approach: In economic evaluations, the human capital approach is used to estimate a monetary value that represents a person's loss of productivity due to disability, illness, or premature death.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Incremental net benefit: Incremental net benefit is a summary measure of cost-effectiveness. It incorporates the differences in cost and effect between two health care interventions and the willingness-to-pay value. Net health benefit is calculated as the difference in effect minus the difference in cost divided by the willingness-to-pay value. Net monetary benefit is calculated as the willingness-to-pay value multiplied by the difference in effect minus the difference in cost. An intervention can be considered cost-effective if either the net health or net monetary benefit is greater than zero.

Market distribution: When evaluating more than two technologies, the market distribution is the proportion of the population that uses each technology.

Markov model: A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.

Microsimulation model: In economic evaluations, a microsimulation model (e.g., an individual-level or patient-level model) is used to simulate the health outcomes for a heterogeneous group of patients (e.g., patients of different ages or with different sets of risk factors) after receiving a particular health care intervention. The health outcomes and health events of each patient are modelled, and the outcomes of several patients are combined to estimate the average costs and benefits accrued by a group of patients. In contrast, a cohort model follows a homogeneous cohort of patients (e.g., patients of the same age or with the same set of risk factors) through the model and estimates the proportion of the cohort who will experience specific health events.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Monte Carlo simulation: Monte Carlo simulation is an economic modelling method that derives parameter values from distributions rather than fixed values. The model is run several times, and in each iteration, parameter values are drawn from specified distributions. This method is used in microsimulation models and probabilistic analysis.

Multiway sensitivity analysis: A multiway sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying a combination of model input (i.e., parameter) values simultaneously between plausible extremes to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Natural history of a disease: The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.

One-way sensitivity analysis: A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying one model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Return on investment: Return on investment is a type of economic evaluation that values the financial return, or benefits, of a health care intervention against the total costs of its delivery. Return on investment is the benefit minus the cost, expressed as a proportion of the cost.

Risk difference: Risk difference is the difference in the risk of an outcome occurring between one health care intervention and an alternative intervention.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses involve varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Short-Form–Six Dimensions (SF-6D): The SF-6D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The classification system consists of six attributes (physical functioning, role limitations, social functioning, pain, mental health, and vitality), each associated with four to six levels, thus producing a total of 18,000 possible unique health states. A scoring table is used to convert SF-6D scores to health state values.

Social capital: Social capital refers to the connections among people's social networks and the reciprocity and trust arise from them. More social capital is generally seen as better than less, but some kinds are more societally productive (for example, bridging) and others are more valuable for individuals (for example, bonding). It is also important to note that the effects of social capital are not always positive. For example, some communities' social bonding can make them exclusionary, wealth concentrated, and restrictive of freedoms.

Societal perspective: The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).

Standard gamble: In economic evaluations, standard gamble is a direct method of measuring people's preferences for various health states. In a standard gamble, respondents are asked about their preference for either (a) remaining in a certain health state for the rest of their life, or (b) a gamble scenario in which there is a chance of having optimal health for the rest of one's life but also a chance of dying immediately. Respondents are surveyed repeatedly, with the risk of immediate death varying each time (e.g., 75% chance of optimal health, 25% chance of immediate death) until they are indifferent about their choice. The standard gamble is considered the gold standard for eliciting preferences as it incorporates individual risk attitudes, unlike other methods of eliciting preferences.

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Time trade-off: In economic evaluations, time trade-off is a direct method of measuring people's preferences for various health states. In a time-trade off, respondents are asked about their preference for either (a) living with a chronic health condition for a certain amount of time, followed by death, or (b) living in optimal health but for less time than in scenario (a). That is, respondents decide how much time in good health they would be willing to "trade off" for more time spent in poorer health. Respondents are surveyed repeatedly, with the amount of time spent in optimal health varying each time until they are indifferent about their choice.

Tornado diagram: In economic evaluations, a tornado diagram is used to determine which model parameters have the greatest influence on results. Tornado diagrams present the results of multiple one-way sensitivity analyses in a single graph.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Value-of-information analysis: In economic evaluations, value-of-information analysis is used to estimate the value of investing in future research to minimize uncertainty in input parameters.

Vertical equity: Vertical equity allows for people with different characteristics (of ethical relevance) to be treated differently.

Visual analogue scale (VAS): The visual analogue scale (VAS) is a direct method of measuring people's preferences for various health states. Respondents are first asked to rank a series of health states from least to most preferable. Then, they are asked to place the health states on a scale with intervals reflecting the differences in preference among the given health states. The scale ranges from 0 (worst imaginable health) to 100 (best imaginable health). The value of a respondent's preference for each health state is given by their placement of each health state on the scale.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search Date: January 9, 2024

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database; and EBSCO Cumulative Index to Nursing and Allied Health Literature

Database segments: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 3, 2024>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2024 Week 01>, Ovid MEDLINE(R) ALL <1946 to January 08, 2024>
Search Strategy:
---
1 Tuberculosis/ (239899)
2 tuberculo*.ti,ab,kf. (481399)
3 Mycobacterium tuberculosis/ (132231)
4 Latent Tuberculosis/ (12300)
5 Tuberculosis, Pulmonary/ (98534)
6 (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) adj3 TB) or LTB or LTBI or koch*).ti,ab,kf. (67013)
7 or/1-6 (576360)
8 Interferon-gamma Release Tests/ (7433)
9 (((interferon* or IFN) adj3 gamma* adj3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) adj3 (release or test* or assay*)) or IGRA or IGRAs).ti,ab,kf. (20757)
10 (quantiferon* or QFT* or gold plus* or "gold in tube*").ti,ab,kf. (7987)
11 (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*).ti,ab,kf. (2616)
12 (QIAreach* or standard e TB feron* or "T-cell select*").ti,ab,kf. (1256)
13 (qiagen gmbh* or oxford immunotec* or diasorin inc*).ti,ab,kf. (449)
14 or/8-13 (30103)
15 7 and 14 (15430)
16 exp Animals/ not Humans/ (16422933)
17 15 not 16 (11293)
18 Congress.pt. (67511)
19 17 not 18 (11289)
20 limit 19 to english language [Limit not valid in CDSR; records were retained] (10575)
21 20 use coch (0)
22 (Systematic Reviews or Meta Analysis).pt. (192867)
23 Systematic Review/ or Systematic Reviews as Topic/ or Meta-Analysis/ or exp Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (1025393)
24 ((systematic* or methodologic*) adj3 (review* or overview*)).ti,ab,kf. (764529)
25 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab,kf. (700186)

26 (evidence adj2 (review* or overview* or synthes#s)).ti,ab,kf. (104994)
27 (review of reviews or overview of reviews).ti,ab,kf. (2705)
28 umbrella review*.ti,ab,kf. (3606)
29 GRADE Approach/ (3796)
30 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).ti,ab,kf. (669376)
31 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (800250)
32 cochrane.ti,ab,kf. (336370)
33 (meta regress* or metaregress*).ti,ab,kf. (34648)
34 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).ti,ab,kf. (41688)
35 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (77778)
36 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).ti,ab,kf. (60629)
37 or/22-36 (1927703)
38 20 and 37 (618)
39 38 use medall,cleed (274)
40 or/21,39 (274)
41 tuberculosis/ (239899)
42 tuberculo*.tw,kw,kf. (481755)
43 Mycobacterium tuberculosis/ (132231)
44 latent tuberculosis/ (12300)
45 (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) adj3 TB) or LTB or LTBI or koch*).tw,kw,kf. (67691)
46 or/41-45 (563934)
47 interferon gamma release assay/ (7417)
48 (((interferon* or IFN) adj3 gamma* adj3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) adj3 (release or test* or assay*)) or IGRA or IGRAs).tw,kw,kf,dv. (20794)
49 (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*).tw,kw,kf,dv. (2958)
50 (QIAreach* or standard e TB feron* or "T-cell select*").tw,kw,kf,dv. (1269)
51 (qiagen gmbh* or oxford immunotec* or diasorin inc*).tw,kw,kf,dv. (779)
52 or/47-51 (26148)
53 46 and 52 (12625)
54 (exp animal/ or nonhuman/) not exp human/ (12005527)
55 53 not 54 (11738)
56 conference abstract.pt. (5013227)
57 55 not 56 (10080)
58 limit 57 to english language [Limit not valid in CDSR; records were retained] (9350)
59 Systematic review/ or "systematic review (topic)"/ or exp Meta Analysis/ or "Meta Analysis (Topic)"/ or Biomedical Technology Assessment/ (996097)
60 (meta analy* or metaanaly* or health technolog* assess* or systematic review*).hw. (1000098)
61 ((systematic* or methodologic*) adj3 (review* or overview*)).tw,kw,kf. (775173)
62 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).tw,kw,kf. (708173)

63 (evidence adj2 (review* or overview* or synthes#s)).tw,kw,kf. (107391)
64 (review of reviews or overview of reviews).tw,kw,kf. (2926)
65 umbrella review*.tw,kw,kf. (3637)
66 ((pool* adj3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) adj2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*).tw,kw,kf. (678847)
67 (medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus).ab. (800250)
68 cochrane.tw,kw,kf. (339807)
69 (meta regress* or metaregress*).tw,kw,kf. (35638)
70 (((integrative or collaborative or quantitative) adj3 (review* or overview* or synthes*)) or (research adj3 overview*)).tw,kw,kf. (42780)
71 (cochrane or (health adj2 technology assessment) or evidence report or systematic review*).jw. (77778)
72 ((comparative adj3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) adj comparison*)).tw,kw,kf. (61968)
73 or/59-72 (1931962)
74 58 and 73 (698)
75 74 use emez (410)
76 40 or 75 (684)
77 76 use medall (274)
78 76 use coch (0)
79 76 use cleed (0)
80 76 use emez (410)
81 remove duplicates from 76 (451)

CINAHL

#	Query	Results
S1	(MH "Tuberculosis")	17,678
S2	TI tuberculo* OR AB tuberculo*	28,056
S3	(MH "Mycobacterium Tuberculosis")	4,404
S4	(MH "Latent Tuberculosis")	86
S5	(MH "Tuberculosis, Pulmonary")	5,813
S6	TI (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) N3 TB) or LTB or LTBI or koch*) OR AB (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) N3 TB) or LTB or LTBI or koch*)	4,960
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	35,509
S8	(MH "Interferon-Gamma Release Tests")	0
S9	TI (((interferon* or IFN) N3 gamma* N3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) N3 (release or test* or assay*)) or IGRA or IGRAs) OR AB (((interferon* or IFN) N3 gamma* N3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) N3 (release or test* or assay*)) or IGRA or IGRAs)	884
S10	TI (quantiferon* or QFT* or gold plus* or "gold in tube*") OR AB (quantiferon* or QFT* or gold plus* or "gold in tube*")	577
S11	TI (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*) OR AB (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*)	303
S12	TI (QIAreach* or standard e TB feron* or "T-cell select*") OR AB (QIAreach* or standard e TB feron* or "T-cell select*")	22

S13 TI (qiagen gmbh* or oxford immunotec* or diasorin inc*) OR AB (qiagen gmbh* or oxford immunotec* or diasorin inc*)	30
S14 S8 OR S9 OR S10 OR S11 OR S12 OR S13	1,413
S15 S7 AND S14	1,118
S16 (PT "Meta Analysis") or (PT "Systematic Review")	169,900
S17 (MH "Systematic Review") OR (MH "Meta Analysis")	160,941
S18 ((systematic* or methodologic*) N3 (review* or overview*))	211,094
S19 (meta analy* or metaanaly* or met analy* or metanaly* or meta review* or metareview* or health technolog* assess* or HTA or HTAs or (technolog* N1 (assessment* or overview* or appraisal*)))	133,276
S20 (evidence N2 (review* or overview* or synthes#s)))	28,737
S21 ((review or overview) N2 reviews)	9,325
S22 umbrella review*	817
S23 ((pool* N3 analy*) or published studies or published literature or hand search* or handsearch* or manual search* or ((database* or systematic*) N2 search*) or reference list* or bibliograph* or relevant journals or data synthes* or data extraction* or data abstraction*)	131,349
S24 AB(medline or pubmed or medlars or embase or cinahl or web of science or ovid or ebsco* or scopus)	127,553
S25 cochrane	73,494
S26 (meta regress* or metaregress*)	5,329
S27 (((integrative or collaborative or quantitative) N3 (review* or overview* or synthes*)) or (research N3 overview*))	14,011
S28 SO(cochrane or (health N2 technology assessment) or evidence report or systematic review*)	12,464
S29 ((comparative N3 (efficacy or effectiveness)) or relative effectiveness or ((indirect or indirect treatment or mixed-treatment) N1 comparison*))	10,291
S30 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29	370,831
S31 S15 AND S30	80
S32 PT Proceedings	76,098
S33 S31 NOT S32	80
S34 S31 NOT S32	
Limiters - English Language	80

Economic Evidence Search

Search Date: January 10, 2024

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database; and EBSCO Cumulative Index to Nursing and Allied Health Literature

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 3, 2024>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2024 Week 01>, Ovid MEDLINE(R) ALL <1946 to January 09, 2024>
Search Strategy:
---
1 Tuberculosis/ (241779)
2 tuberculo*.ti,ab,kf. (488390)
3 Mycobacterium tuberculosis/ (132680)
4 Latent Tuberculosis/ (12491)
5 Tuberculosis, Pulmonary/ (99758)
6 (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) adj3 TB) or LTB or LTBI or koch*).ti,ab,kf. (68489)
7 or/1-6 (584407)
8 Interferon-gamma Release Tests/ (7464)
9 (((interferon* or IFN) adj3 gamma* adj3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) adj3 (release or test* or assay*)) or IGRA or IGRAs).ti,ab,kf. (21102)
10 (quantiferon* or QFT* or gold plus* or "gold in tube*").ti,ab,kf. (8200)
11 (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*).ti,ab,kf. (2661)
12 (QIAreach* or standard e TB feron* or "T-cell select*").ti,ab,kf. (1256)
13 (qiagen gmbh* or oxford immunotec* or diasorin inc*).ti,ab,kf. (474)
14 or/8-13 (30655)
15 7 and 14 (15698)
16 exp Animals/ not Humans/ (16426259)
17 15 not 16 (11561)
18 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6595888)
19 17 not 18 (10407)
20 limit 19 to english language [Limit not valid in CDSR; records were retained] (9778)
21 20 use cleed,coch (29)
22 economics/ (265027)
23 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (1077454)
24 economics.fs. (470475)
25 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1321816)
26 exp "costs and cost analysis"/ (701070)
27 (cost or costs or costing or costly).ti. (340597)
28 cost effective*.ti,ab,kf. (467555)

29 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kf. (319787)
30 models, economic/ (16214)
31 markov chains/ or monte carlo method/ (110219)
32 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (70391)
33 (markov or markow or monte carlo).ti,ab,kf. (184752)
34 quality-adjusted life years/ (57484)
35 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (116403)
36 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (204003)
37 or/22-36 (3475185)
38 20 and 37 (638)
39 38 use medall,cctr (274)
40 21 or 39 (303)
41 tuberculosis/ (241779)
42 tuberculo*.tw,kw,kf. (489148)
43 Mycobacterium tuberculosis/ (132680)
44 latent tuberculosis/ (12491)
45 (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) adj3 TB) or LTB or LTBI or koch*).tw,kw,kf. (69167)
46 or/41-45 (572234)
47 interferon gamma release assay/ (7424)
48 (((interferon* or IFN) adj3 gamma* adj3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) adj3 (release or test* or assay*)) or IGRA or IGRAs).tw,kw,kf,dv. (21157)
49 (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*).tw,kw,kf,dv. (3003)
50 (QIAreach* or standard e TB feron* or "T-cell select*").tw,kw,kf,dv. (1269)
51 (qiagen gmbh* or oxford immunotec* or diasorin inc*).tw,kw,kf,dv. (804)
52 or/47-51 (26555)
53 46 and 52 (12792)
54 (exp animal/ or nonhuman/) not exp human/ (12011811)
55 53 not 54 (11905)
56 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11529012)
57 55 not 56 (8785)
58 limit 57 to english language [Limit not valid in CDSR; records were retained] (8114)
59 Economics/ (265027)
60 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (150591)
61 Economic Aspect/ or exp Economic Evaluation/ (563928)
62 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1342226)
63 exp "Cost"/ (701070)
64 (cost or costs or costing or costly).ti. (340597)
65 cost effective*.tw,kw,kf. (476420)
66 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog* or increment*)).ab,kw,kf. (329680)
67 Monte Carlo Method/ (85478)
68 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (73811)
69 (markov or markow or monte carlo).tw,kw,kf. (188224)
70 Quality-Adjusted Life Years/ (57484)

71 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (119757)
72 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (224844)
73 or/59-72 (2987441)
74 58 and 73 (595)
75 74 use emez (330)
76 40 or 75 (633)
77 76 use medall (252)
78 76 use coch (0)
79 76 use cctr (22)
80 76 use cleed (29)
81 76 use emez (330)
82 remove duplicates from 76 (449)

CINAHL

#	Query	Results
S1	(MH "Tuberculosis")	17,680
S2	TI tuberculo* OR AB tuberculo*	28,062
S3	(MH "Mycobacterium Tuberculosis")	4,404
S4	(MH "Latent Tuberculosis")	86
S5	(MH "Tuberculosis, Pulmonary")	5,814
S6	TI (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) N3 TB) or LTB or LTBI or koch*) OR AB (((mycobacteri* or bacteri* or laten* or active or disease* or infection*) N3 TB) or LTB or LTBI or koch*)	4,962
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	35,517
S8	(MH "Interferon-Gamma Release Tests")	0
S9	TI (((interferon* or IFN) N3 gamma* N3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) N3 (release or test* or assay*)) or IGRA or IGRAs) OR AB (((interferon* or IFN) N3 gamma* N3 (release* or test* or assay* or diagnos* or screen*)) or ((interferon-y or y-interferon*) N3 (release or test* or assay*)) or IGRA or IGRAs)	884
S10	TI (quantiferon* or QFT* or gold plus* or "gold in tube*") OR AB (quantiferon* or QFT* or gold plus* or "gold in tube*")	577
S11	TI (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*) OR AB (tspot* or t spot* or "t-spot.tb*" or tb assay* or tb blood test*)	303
S12	TI (QIAreach* or standard e TB feron* or "T-cell select*") OR AB (QIAreach* or standard e TB feron* or "T-cell select*")	22
S13	TI (qiagen gmbh* or oxford immunotec* or diasorin inc*) OR AB (qiagen gmbh* or oxford immunotec* or diasorin inc*)	30
S14	S8 OR S9 OR S10 OR S11 OR S12 OR S13	1,413
S15	S7 AND S14	1,118
S16	(MH "Economics")	14,117
S17	(MH "Economic Aspects of Illness")	11,218
S18	(MH "Economic Value of Life")	666
S19	MH "Economics, Dental"	153
S20	MH "Economics, Pharmaceutical"	2,414
S21	MW "ec"	193,215
S22	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*)	347,734

S23	(MH "Costs and Cost Analysis+")	135,962
S24	TI cost*	63,755
S25	(cost effective*)	52,246
S26	AB (cost* N2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*))	40,804
S27	(decision N1 (tree* or analy* or model*))	11,983
S28	(markov or markow or monte carlo)	7,950
S29	(MH "Quality-Adjusted Life Years")	6,090
S30	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs)	15,569
S31	((adjusted N1 (quality or life)) or (willing* N2 pay) or sensitivity analysis or sensitivity analyses)	25,991
S32	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	481,999
S33	S15 AND S32	88
S34	PT (Case Study or Commentary or Editorial or Letter or Proceedings)	1,281,856
S35	S33 NOT S34	85
S36	S33 NOT S34 Limiters - English Language	85

Grey Literature Search

Performed on: January 10 – 17, 2024

Websites searched:
Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), University Of Calgary Health Technology Assessment Unit, Ontario Health Technology Assessment Committee (OHTAC), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Contextualized Health Research Synthesis Program of Newfoundland (CHRSP), Health Canada Medical Device Database, International HTA Database (INAHTA), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), National Health Service England (NHS), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Adelaide Health Technology Assessment, Australian Government Medical Services Advisory Committee, Monash Health Centre for Clinical Effectiveness, The Sax Institute, Australian Government Department of Health and Aged Care, Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S), Pharmac, Italian National Agency for Regional Health Services (Aegnas), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment (Austria), The Regional Health Technology Assessment Centre (HTA-centrum), Swedish Agency for Health Technology Assessment and Assessment of Social Services, Norwegian Institute of Public Health - Health Technology Assessments, The Danish Health Technology Council, Ministry of Health Malaysia - Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, Sick Kids PEDE Database, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used:

tuberculosis, TB, latent, LTBI, LTB, interferon gamma, interferon gamma release assay, IGRA, IFN, quantiferon, QFT, gold plus, gold in tube, t.spot, tspot, t spot, tuberculose

Clinical results (included in PRISMA): 17
Economic results (included in PRISMA): 33
Ongoing HTAs (PROSPERO/EUnetHTA/NICE/MSAC): 38
Ongoing clinical trials: 0

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Systematic Reviews (ROBIS Tool)

	Phase 2				Phase 3
Author, year	**Study eligibility criteria**	**Identification and selection of studies**	**Data collection and study appraisal**	**Synthesis and findings**	**Risk of bias in the review**
Volkman et al, 2024	Low	Low	Low note: unclear if two reviewers were involved in the extraction but based on overall reporting of study methodology consdiered low risk of bias	Low	Low
Zhou et al, 2023	Low	Low	Low	Low	Low
Yahav et al, 2023	Low	Low	Low	Low	Low
Jonas et al, 2023	Low	Low	Low	Low	Low
Zhou et al, 2022	Low	Low	Low	Low	Low
Park et al, 2022	Low	Low	Low	Low	Low
Chen et al, 2022	Low included conference abstracts and briefs	Low	Low	Low	Low
Oh et al, 2021	Low	Low	Low	Low	Low
Zhou et al, 2020	Low	Low	Low unclear if duplicate data extract and quality assessment, used 'we' in description	Low unclear if duplicate data extract and quality assessment, used 'we' in description	Low
Yamasue et al, 2020	Low	Low	Low	Low	Low
Campbell et al 2020	Low	Low	Low	Low	Low
Alrajhi et al, 2020	Low	Low Sensitivity analyses were conducted to assess the inclusion of studies published as abstracts and letter to editor	Low	Low	Low

Abbreviation: ROBIS, Risk of Bias in Systematic Reviews.

[a]Possible risk-of-bias levels: low, high, unclear.

Appendix 3: Other Measures to Compare Findings

Campbell et al, 2020[64] reported differences in incidence rate ratio by level of agreement between IGRA and TST positive and negative findings; Zhou et al, 2020[62] reported rates of progression to TB disease based on alignments in IGRA and TST; Alrajhi et al, 2020[65] reported the odds ratio of testing positive when on an immunosuppressant versus not; and 4 studies reported concordance as a rate of agreement between IGRA and TST test results.[55,59,61,65]

Table A2: Other Measures Comparing IGRA and TST Findings

Author, year	Population	Test agreement scenario	Results
		Group 1 and Group 2 descriptions of scenarios	**Incidence rate ratio of progressing to TB disease (95%C)**
Campbell et al, 2020[64]	Higher risk for TB	Group 1: IGRA and TST both positive Group 2: IGRA and TST both negative	19.1 (2.9 to 127.3)
		Group 1: IGRA and TST both positive Group 2: IGRA positive, but TST negative	3.0 (0.2 to 40.7)
		Group 1: IGRA and TST both positive Group 2: IGRA negative and TST positive	7.6 (1.6 to 36.7)
		Group 1: IGRA positive and TST negative Group 2: IGRA and TST both negative	5.1 (2.4 to 10.8)
		Group 1: IGRA negative and TST positive Group 2: IGRA and TST both negative	3.6 (1.8 to 7.2)
		Scenarios	**Proportion progress to TB disease**
Zhou et al, 2020[62]	High risk population for TB	IGRA and TST both positive	6.1% (2.3 to 11.5)
		IGRA and TST both negative	0.5% (0.2 to 1.1)
		IGRA negative and TST positive	0.8% (0.2 to 1.6)
		IGRA positive and TST negative	1.7% (0.3 to 4.2)
		LTBI test	**Odds Ratio of testing positive when on immunosuppressants, vs not**
Alrajhi et al, 2020[65]	Adults with inflammatory bowel disease	With IGRA	0.57 (95%CI 0.31 – 1.03; P = 0.006)
		With TST	1.14 (95%CI 061 to 2.12)
		Scenarios	**Rate of agreement occurrence (95%CI)**
Volkman et al, 2024[55]	Children <5, with no underlying immunosuppression	IGRA and TST both positive or both negative	50% (ranges 17% to 80%)
Park et al, 2022[59]	Adults with inflammatory bowel disease	IGRA and TST both positive or both negative	83.3% (95%CI 78.5% to 88.1%)
		IGRA negative and TST positive	9.5% (5.8 to 13.2)
		IGRA positive and TST negative	5.8% (4.0 to 7.7)

Oh et al, 2021[61]	Adults at higher risk for TB	IGRA and TST both positive or both negative	46% (95%CI 38% to 54%)
Alrajhi et al, 2020[65]	Adults with inflammatory bowel disease	IGRA and TST both positive or both negative	84.8% (95%CI 81.4% to 88.3%)

Appendix 4: Selected Excluded Studies – Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Brett K, Severn M. Interferon Gamma Release Assay for the Identification of Latent Tuberculosis Infection in Rural and Remote Settings. Canadian Agency for Drugs and Technologies in Health CADTH Health Technology Review2021. 2021;04:04.	Wrong study design. This publication is a dive into relevant primary studies from a systematic review that was identified during a rapid review.
Ghosh S, Dronavalli M, Raman S. Tuberculosis infection in under-2-year-old refugees: Should we be screening? A systematic review and meta-regression analysis. Journal of Paediatrics and Child Health. 2020;56(4):622-9.	Wrong study design. Had high risk of bias according to ROBIS assessment and did not report quality assessment of primary studies.
Hamada Y, Gupta RK, Quartagno M, Izzard A, Acuna-Villaorduna C, Altet N, et al. Predictive performance of interferon-gamma release assays and the tuberculin skin test for incident tuberculosis: an individual participant data meta-analysis. EClinicalMedicine. 2023;56:101815.	Population not specific to our population of interest
Krutikov M, Faust L, Nikolayevskyy V, Hamada Y, Gupta RK, Cirillo D, et al. The diagnostic performance of novel skin-based in-vivo tests for tuberculosis infection compared with purified protein derivative tuberculin skin tests and blood-based in vitro interferon-gamma release assays: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2022;22(2):250-64.	Wrong intervention
Ortiz-Brizuela E, Apriani L, Mukherjee T, Lachapelle-Chisholm S, Miedy M, Lan Z, et al. Assessing the Diagnostic Performance of New Commercial Interferon-gamma Release Assays for Mycobacterium tuberculosis Infection: A Systematic Review and Meta-Analysis. Clinical Infectious Diseases. 2023;76(11):1989-99.	Results for population of interest could not be extracted.
Saag LA, LaValley MP, Hochberg NS, Cegielski JP, Pleskunas JA, Linas BP, et al. Low body mass index and latent tuberculous infection: a systematic review and meta-analysis. Int J Tuberc Lung Dis. 2018;22(4):358-65.	Population outside of scope

Appendix 5: Systematic reviews which met the inclusion criteria, published before 2020

For transparency, we provide a list of systematic reviews that met the inclusion criteria, but were not included in the core results of this overview of reviews.

Citation
Al-Ghafli H, Al-Hajoj S. QuantiFERON-TB Gold In-Tube in Saudi Arabia benchmarked with other sites of the Middle East: A meta-analysis review. Journal of Infection in Developing Countries. 2018;12(9):687-99.
Anonymous. Use of Tuberculosis Interferon-Gamma Release Assays (IGRAs) in Low- and Middle- Income Countries: Policy Statement. World Health Organization WHO Guidelines Approved by the Guidelines Review Committee2011. 2011.
Auguste P, Madan J, Tsertsvadze A, Court R, McCarthy N, Sutcliffe P, et al. Identifying latent tuberculosis in high-risk populations: systematic review and meta-analysis of test accuracy. International Journal of Tuberculosis and Lung Disease. 2019;23(11):1178-90.
Auguste P, Tsertsvadze A, Pink J, Court R, McCarthy N, Sutcliffe P, et al. Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis: systematic review and meta-analysis. BMC Infectious Diseases. 2017;17(1):200.
Auguste P, Tsertsvadze A, Pink J, Court R, Seedat F, Gurung T, et al. Accurate diagnosis of latent tuberculosis in children, people who are immunocompromised or at risk from immunosuppression and recent arrivals from countries with a high incidence of tuberculosis: systematic review and economic evaluation. Health Technology Assessment (Winchester, England). 2016;20(38):1-678.
Ayubi E, Doosti-Irani A, Mostafavi E. Do the tuberculin skin test and the QuantiFERON-TB Gold in-tube test agree in detecting latent tuberculosis among high-risk contacts? A systematic review and meta-analysis. Epidemiology and health. 2015;37:e2015043.
Ayubi E, Doosti-Irani A, Sanjari Moghaddam A, Khazaei S, Mansori K, Safiri S, et al. Comparison of QuantiFERON-TB Gold In-Tube (QFT-GIT) and tuberculin skin test (TST) for diagnosis of latent tuberculosis in haemodialysis (HD) patients: a meta-analysis of kappa estimates. Epidemiology and Infection. 2017;145(9):1824-33.
Ayubi E, Doosti-Irani A, Sanjari Moghaddam A, Sani M, Nazarzadeh M, Mostafavi E. The Clinical Usefulness of Tuberculin Skin Test versus Interferon-Gamma Release Assays for Diagnosis of Latent Tuberculosis in HIV Patients: A Meta-Analysis. PLoS ONE [Electronic Resource]. 2016;11(9):e0161983.
Campbell JR, Chen W, Johnston J, Cook V, Elwood K, Krot J, et al. Latent tuberculosis infection screening in immigrants to low-incidence countries: a meta-analysis. Molecular Diagnosis & Therapy. 2015;19(2):107-17.
Campbell JR, Krot J, Elwood K, Cook V, Marra F. A systematic review on TST and IGRA tests used for diagnosis of LTBI in immigrants. Molecular Diagnosis & Therapy. 2015;19(1):9-24.
Cattamanchi A, Smith R, Steingart KR, Metcalfe JZ, Date A, Coleman C, et al. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. Journal of Acquired Immune Deficiency Syndromes: JAIDS. 2011;56(3):230-8.
Chang KC, Leung CC. Systematic review of interferon-gamma release assays in tuberculosis: focus on likelihood ratios. Thorax. 2010;65(3):271-6.
Chang KC, Leung ECC, Leung CC. Interferon-gamma release assays in childhood tuberculosis: A systematic review. Hong Kong Journal of Paediatrics. 2009;14(2):86-95.
Diel R, Goletti D, Ferrara G, Bothamley G, Cirillo D, Kampmann B, et al. Interferon-gamma release assays for the diagnosis of latent Mycobacterium tuberculosis infection: a systematic review and meta-analysis. European Respiratory Journal. 2011;37(1):88-99.
Diel R, Loddenkemper R, Nienhaus A. Predictive value of interferon-gamma release assays and tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis. Chest. 2012;142(1):63-75.
Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment (Winchester, England). 2007;11(3):1-196.
Doan TN, Eisen DP, Rose MT, Slack A, Stearnes G, McBryde ES. Interferon-gamma release assay for the diagnosis of latent tuberculosis infection: A latent-class analysis. PLoS ONE [Electronic Resource]. 2017;12(11):e0188631.
Doosti-Irani A, Ayubi E, Mostafavi E. Tuberculin and QuantiFERON-TB-Gold tests for latent tuberculosis: a meta-analysis. Occupational Medicine (Oxford). 2016;66(6):437-45.
Eisenhut M, Fidler K. Performance of Tuberculin Skin Test Measured against Interferon Gamma Release Assay as Reference Standard in Children. Tuberculosis Research & Treatment Print. 2014;2014:413459.

Citation
Ferguson TW, Tangri N, Macdonald K, Hiebert B, Rigatto C, Sood MM, et al. The diagnostic accuracy of tests for latent tuberculosis infection in hemodialysis patients: a systematic review and meta-analysis. Transplantation. 2015;99(5):1084-91.
Ge L, Ma JC, Han M, Li JL, Tian JH. Interferon-gamma release assay for the diagnosis of latent Mycobacterium tuberculosis infection in children younger than 5 years: a meta-analysis. Clinical Pediatrics. 2014;53(13):1255-63.
Greveson K. Can ELISpot replace the tuberculin skin test for latent tuberculosis? British Journal of Nursing. 2009;18(20):1248-54.
Jonas DE, Riley S, Lee L, Coffey C, Wang SH, Asher GN, et al. Screening for Latent Tuberculosis Infection in Adults: An Evidence Review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality. 2023:05.
Kahwati LC, Feltner C, Halpern M, Woodell CL, Boland E, Amick HR, et al. Screening for Latent Tuberculosis Infection in Adults: An Evidence Review for the U.S. Preventive Services Task Force. Agency for Healthcare Research and Quality. 2016:09.
Lu P, Chen X, Zhu LM, Yang HT. Interferon-Gamma Release Assays for the Diagnosis of Tuberculosis: A Systematic Review and Meta-analysis. Lung. 2016;194(3):447-58.
Machingaidze S, Wiysonge CS, Gonzalez-Angulo Y, Hatherill M, Moyo S, Hanekom W, et al. The utility of an interferon gamma release assay for diagnosis of latent tuberculosis infection and disease in children: a systematic review and meta-analysis. Pediatric Infectious Disease Journal. 2011;30(8):694-700.
Mamishi S, Pourakbari B, Marjani M, Mahmoudi S. Diagnosis of latent tuberculosis infection among immunodeficient individuals: review of concordance between interferon-gamma release assays and the tuberculin skin test. British Journal of Biomedical Science. 2014;71(3):115-24.
Maung Myint T, Rogerson TE, Noble K, Craig JC, Webster AC. Tests for latent tuberculosis in candidates for solid organ transplantation: A systematic review and meta-analysis. Clinical Transplantation. 2019;33(8):e13643.
Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Annals of Internal Medicine. 2007;146(5):340-54.
Munoz L, Santin M. Interferon-gamma release assays versus tuberculin skin test for targeting people for tuberculosis preventive treatment: an evidence-based review. Journal of Infection. 2013;66(4):381-7.
Nasiri MJ, Pormohammad A, Goudarzi H, Mardani M, Zamani S, Migliori GB, et al. Latent tuberculosis infection in transplant candidates: a systematic review and meta-analysis on TST and IGRA. Infection. 2019;47(3):353-61.
Overton K, Varma R, Post JJ. Comparison of Interferon-gamma Release Assays and the Tuberculin Skin Test for Diagnosis of Tuberculosis in Human Immunodeficiency Virus: A Systematic Review. Tuberculosis & Respiratory Diseases. 2018;81(1):59-72.
Pyo J, Cho SK, Kim D, Sung YK. Systematic review: Agreement between the latent tuberculosis screening tests among patients with rheumatic diseases. Korean Journal of Internal Medicine. 2018;33(6):1241-51.
Rogerson TE, Chen S, Kok J, Hayen A, Craig JC, Sud K, et al. Tests for latent tuberculosis in people with ESRD: a systematic review. American Journal of Kidney Diseases. 2013;61(1):33-43.
Ruan Q, Zhang S, Ai J, Shao L, Zhang W. Screening of latent tuberculosis infection by interferon-gamma release assays in rheumatic patients: a systemic review and meta-analysis. Clinical Rheumatology. 2016;35(2):417-25.
Sadatsafavi M, Shahidi N, Marra F, FitzGerald MJ, Elwood KR, Guo N, et al. A statistical method was used for the meta-analysis of tests for latent TB in the absence of a gold standard, combining random-effect and latent-class methods to estimate test accuracy. Journal of Clinical Epidemiology. 2010;63(3):257-69.
Shahidi N, Fu YT, Qian H, Bressler B. Performance of interferon-gamma release assays in patients with inflammatory bowel disease: a systematic review and meta-analysis. Inflammatory Bowel Diseases. 2012;18(11):2034-42.

Appendix 6: Selected Excluded Studies – Economic Evidence

For transparency, we provide an example list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Gosce, L.; Allel, K.; Hamada, Y.; Korobitsyn, A.; Ismail, N.; Bashir, S.; Denkinger, C. M.; Abubakar, I.; White, P. J.; Rangaka, M. X.. Economic evaluation of novel Mycobacterium tuberculosis specific antigen-based skin tests for detection of TB infection: A modelling study. 2023	Wrong intervetion/comparator
Deuffic-Burban, S.; Atsou, K.; Viget, N.; Melliez, H.; Bouvet, E.; Yazdanpanah, Y. Cost-effectiveness of QuantiFERON-TB test vs. tuberculin skin test in the diagnosis of latent tuberculosis infection. 2010	Wrong setting: Non-Canadian economic evalution
Auguste, P. E.; Mistry, H.; McCarthy, N. D.; Sutcliffe, P. A.; Clarke, A. E.. Cost-effectiveness of testing for latent tuberculosis infection in people with HIV. 2022	Wrong setting: Non-Canadian economic evalution
Kowada, A. Interferon-gamma release assay for tuberculosis screening of solid-organ transplant recipients is cost-effective. 2019	Non-Canadian economic evalution: wrong setting
Campbell, J. R.; Sasitharan, T.; Marra, F.A. Systematic Review of Studies Evaluating the Cost Utility of Screening High-Risk Populations for Latent Tuberculosis Infection. 2015	Systematic review: wrong study type
Brett, K.; Severn, M. Interferon Gamma Release Assay for Identifying Latent Tuberculosis Infection in People With Bacillus Calmette-Guerin Vaccination. 2021	Not economic study: wrong study type
Brett, K.; Severn, M. Interferon Gamma Release Assay for Identifying Latent Tuberculosis Infection in People With Bacillus Calmette-Guerin Vaccination. 2021	Not economic study: wrong study type

Appendix 7: Economic Literature Review – Cost-Effectiveness of IGRA vs. TST for LTBI

Table A3: Characteristics of Studies Included in the Economic Literature Review: Summary of Methods

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs
Oxlade, 2007, Canada[81]	Cost-effectiveness analysis, Markov (state-transition) model	1) Interventions for *immigrantion entry screening*:	1) *Immigrants* at entry to Canada (mean age 35 years) 2) *Close and causal contacts* (mean age 35 years)	- State transition model, 4 health states: non-infected, recent LTBI, long-standing LTBI and active TB disease - Prevalence of LTBI different between two screened cohorts, and dependent on the incidence of TB - Diagnostic and treatment activities completed at the end of the first year
	Perspective: Not clearly reported[a]	• CXR (chest X-rays)	Both populations stratified by: • Incidence of TB in the home country into 3 sub-cohorts: low, intermediate or high incidence of TB (with 2/60/120 active TB cases per 100,000 persons, respectively) • BCG- vaccination status	- Medical evaluation for test positive (TST, cut-off >10 mm or QFT) included: initial clinic visit, consultation, chest X-ray and blood test - Patients with active TB or LTBI received full or preventative TB therapy with INH - Costs of treating TB (active or infection) included
	Time horizon, years (discount rate, %): 20 ys (3%)	• TST • QFT (IGRA)[b] • TST followed by QFT[b] if TST-positive 2) Interventions for *contact screening*: • TST • QFT (IGRA)[b] 3) Comparator for both cohorts: • No screening	All cohorts assumed to be HIV-negative	Test accuracy, TST/QFT: • Sn, TST/QFT: 0.95 • Sp, TST by BCG-vaccination status: 1) non-BCG vaccinated - 0.98; 2) vaccinated in infancy – 0.92; 3) vaccinated in older age - 0.60 • Sp, QFT: 0.98, regardless of BCG vaccination status Test, unit cost, CAD (2004) • CXR: $25.74 • TST: $12.73 • QFT: $41.32[b]

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs
Marra, Canada, 2008 [80]	Cost-effectiveness analysis, Markov (state-transition) model	1) Interventions [c]:	Contacts (age 20 ys and older) with undiagnosed LTBI, exposed to confirmed or suspected cases of active TB Population divided in subgroups by: 1) *BCG vaccination status*: positive, negative and unknown, and 2) *Ethnicity*: foreign-born, non-aboriginal Canadian-born and Aboriginal	- Diagnostic tree followed by the state-transition model with several Markov sub-models: reactivation of TB (described 4 health states: at-risk of reactivation, active TB, previous TB and death); active TB (health states not decribed), healthy (health states not decribed); - Accounted for secondary spread of TB from each active TB case, diagnostic assessemnts, and treatment of active TB or LTBI with INH: compliance, costs and side effects - Most data inputs based on BC CDC registry
	Perspective:Third party payer (British Columbia [BC])	• *QFT-G (IGRA)*[d] • Medical evaluation same as for TST alone (second test is QFT)	Population assumed to be HIV-negative	Test accuracy, TST/QFT by ethicity and BCG-vaccination status :

	Time horizon, years (discount rate, %): 20 ys (3%)	• *Sequential TST/QFT-G*: TST followed by QFT-G [d]
		• Medical evaluation:
		TST-positive further testing with QFT-G and begin the treatment for LTBI if postive result confimed .
		TST-negative at 1st TST, then a second TST done after 8–12 weeks
		TST is positive and QFT-G is negative or *QFT-G indeterminate* (2%): QFT-G was the second test, done 8-12 weeks later
			Close and casual contacts were not separately modeled (weighted proportion average used, based on BC data)	• Sn, TST or QFT-G: 0.99
				• Sp, TST:
				  ○ Canadian-born, BCG-(+): 0.685
				  ○ Foreign-born, BCG(+): 0.608
				  ○ Aboriginal, BCG (+): 0.608
				  ○ Canadian-born, BCG (-): 0.999
				  ○ Foreign-born, BCG (-): 0.990;
				  ○ Aboriginal, BCG (-): 0.999
				• Sp, QFT-G: 0.96, regardless of BCG-vaccination status or ethnicity

		2) Comparator: • *TST alone* (current practice): • Medical evaluation: *TST-positive* (cut-off >5 mm) inlcuded: clinic visits, CXR, additional follow-up and workup if CXR+ (active TB case); *TST negative:* second TST test after 8-12 weeks		Test, unit cost, CAD (2005): • TST: $25.41 • QFT-G [d]: $45.32

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs
Campbell, Canada, 2017 [79]	Cost-effectiveness analysis, Discrete-event simulation model	1) Interventions [e] :	Two populations: 1) *Flagged for post-landing medical surveillance*: a subgroup the whole 2014 cohort of new permanent residents to Canada (n=6,100, about 2.4% of the total; mean age: NR) - Flagging for surveillance based on age and TB incidence in the country of origin, and BCG vaccination status (numbers derived from Ontario data) 2) Whole cohort*: all new permanent residents to Canada immigrated in 2014 (N= 260,600, mean age: NR) - *this group was examined in sensitivty analysis, and the results between two cohorts were compared	- Descrete-event simulation model simulating individual event pathways for immigrants after arrival to Canada; part of the full cohort was being *flagged for surveillance* (2.4%) - Initial part of the model accounted for the completion of screening for LTBI with TST or IGRA - 4 health states after the screening: either healthy or with LTBI (considered healthy), transitioning from these two states to: - active TB (from LTBI or healthy), - healthy (from TB) and - dead (due to TB, adverse event of therapy [hepatotoxicity] or background mortality) ; - the model accounted for: adherence to screening, incompletion of TST, treatment of LTBI (medical evaluation, treatment with INH or RIF – the medication effectivness, side effects and costs) - the model accounted for: reactivation of LTBI, relapse from active TB and people and secondary trasmission - LTBI prevalence estimated by the TB incidence in the country of origin (4 categores) for people under surveillance (flagged cohort) and those who were not flagged - the model accounted for the probability of BCG vaccination depending on LTBI prevalnce and number of cases: 93.8% if >30 cases, and 0.605 if <30 cases Test accuracy, TST and IGRA
	Perspective: Third party payer (British Columbia [BC]) Time horizon, years (discount rate, %): 10 ys (1.5%)	• *IGRA/INH* [f]: IGRA • IGRA-positive followed by 9 months of treatment with INH • *IGRA/RIF*: IGRA • IGRA-positive followed by 4 months of treatment with RIF • *Sequential TST/IGRA/INH* (*SEQ/INH*): Sequential testing, TST first, followed by IGRA for confirmation of TST-positive test • Test-positive: 9 months of INH • *Sequential TST/IGRA/RIF (SEQ/RIF)*: Sequential testing, TST followed by IGRA in TST-positive • Test-positive: 4 months of RIF		• Sn, TST: 0.78, ○ Completion of TST: 72% • Sn IGRA: 0.89 • Sp, TST: ○ BCG-(+): 0.602 ○ BCG-(-) : 0.974

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs

		• *TST/RIF*: TST alone
		• TST-positive (>=10 mm) followed by 4 months of RIF
		• *No intervention:* No testing
		2) Comparator:
		• *TST/INH*: TST alone
		• TST-positive (>=10 mm) followed by 9 months of INH
				• Sp, IGRA: 0.957
				• IGRA, indeterminate: 6%
				
				Test, unit cost, CAD (2016)
				• TST, completed : $31
				  ○ $11 tuberosol
				  ○ $20 (2 visits by nurses)
				• TST, incomplete: $21
				• IGRA[f]: $54.00

Campbell, Canada, 2019 [77]	Cost-effectiveness analysis, Discrete-event simulation model	1) Interventions (same as in the 2017 study): • IGRA/INH • IGRA/RIF • Sequential TST/IGRA/INH (SEQ/INH) • Sequential TST/IGRA/RIF (SEQ/RIF) • TST/RIF • TST/INH	Prospective migrants with permanet resident status coming from countries (mean age: NR; assumed age distribution of permanent residents to Ontario/Canada in 2014)	- Similar descrete-event simulation model as in the prior 2017 study, some model inputs updated
	Perspective: Third party payer (British Columbia [BC]) Time horizon, years (discount rate, %): 25 ys (3%)	2) Comparator: No intervention (no testing) - only CXR and treatment if needed -**for our review, we estimated ICER/INB for TST optons vs IGRA options and we could not use sn results because the compartor was different*	Classified into 4 categories (n of cases of active TB per 100,000 per y), same as in prior 2017 study: • low TB incidence: <30 • moderate TB incidence: >30 &<100 • high TB incidence: >100 & <200 • very high TB incidence: >200 Populations of interest were further adjusted for patient age, BCG vaccination status, chest radiograph results, and LTBI prevalence.	- Estimated LTBI prevalence by country of origin for 4 populations: same estimates as reported in prior paper for the whole cohort of interest - *Same input estimates* as in the 2017 study for: - Test accuracies: Sn and Sp of TST/IGRA - Test costs - Costs of treatments (INH/RIF) - Utilitiy values - Updated inputs: 1) 4 types of populations - their characteristics further adjusted to the prevalence of abnormal CXR results (based on a reference cohort of permanent residents who came to Ontario during 2002–2011)

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs
				2) TST completion assumed to be 100% 3) higher efficacy of LTBI treatment with INH and RIF 4) different discount rate 5) longer time horizon
Campbell, Canada, 2019 (CKD)[78]	Cost-effectiveness analysis, Discrete-event simulation model	1) Interventions:	People who migrated to Canada who have had **1) diagnosed late-stage chronic kidney disease (CKD)** and/or **2) initiated dialysis therapy**	- Descrete-event simulation model accommodated modeling of multiple competing events for each individual alonside the clinical pathway : screened for LTBI with TST or IGRA, treated for LTBI if test-postive (accepatance of screening: 0.77 and adhereencetherapy accounted for, medical evaluation, treatment with INH : its effectivness, side effects and costs of tx and hospitalizations; death due to TB or hepatotoxicity). - 4 health states after screening: late-stage CKD, dilysis, active TB and dead (all-cause or TB-specific).
	Perspective: Third party payer (British Columbia [BC]) Time horizon, years (discount rate, %): 5 ys (1.5%)	• *IGRA/INH*[f]: IGRA • IGRA-positive followed by 9 months of treatment with INH (INH is the best treatment option for CKD population) • *TST/INH*: TST alone • TST-positive (>=10 mm) followed by 9 months of INH	Patient mean age was not reported but age was categorized into **2 age groups: <60 ys and >=60 ys** Classified into 4 categories (n of cases of active TB per 100,000 per y): • *low TB incidence*: <30 • *moderate TB incidence*: >30 &<100 • *high TB incidence*: >100 & <200 • *very high TB incidence*: >200	- Inputs related to patient charactristcs and treatment were obtained from BC admin data (competing-risk analysis applied to admin data, with 3 outcomes: active TB, in the case of those with late-stage CKD, the progression outcome was dialysis; and death) - Multi-state utilities : CKD (0.66), dialysis (0.62) and event of hospitalization (0.4) adjusted for the diagosis of LTBI (*1) and treatment of LTBI (AE: *0.8) or active TB (*0.75)
		2) Comparator: No intervention (no testing) - only CXR and treatment if needed -**for our review, we estimated ICER/INB for TST optons vs IGRA options and we could not use sn results because the compartor was different*	Admin database linkages were used to identify the patient cohort and their characteristics Further adjustment made for diagnosis of diabetes, use of immunosupressants or diagnosis of HIV (immuno-compormosied effects), BCG vaccination status, and LTBI prevalence.	Tes accuracy: IGRA or TST

Author, year, country	Study and analysis characteristics	Interventions and comparator	Populations	Model description and main inputs
				• Sn, TST (specific to CKD/dialysis) : 0.651/0.519 ○ Completion of TST: p=0.913 • Sp, TST: ○ BCG-(+): 0.602 ○ BCG- (-): 0.974 • Sn, IGRA (specific to CKD/dyalisis): 0.780/0.670 • IGRA indeterminate (specific to CKD/dyalisis): 4.1%/6.7% • Sp, IGRA : 0.957 Tests, unit cost, CAD (2016): same as in their 2017 study

Abbreviations: CXR, X-ray; TST, tuberculin skin test; QFT, QuantiFERON®-TB Gold; IGRA, interferon-gamma release assay; n, number; BCG, bacillus Calmette-Guérin ; CAD, Canadian dollars; LTBI, latent tuberculosis infection; INH, isoniazid; RIF, rifampin; Sn, sensitivity; Sp, specificity.

[a] Oxlade et al[81] did not clearly defined and reported the perspective: costs included government, health system costs (relevant to Ontario), and out of pocket costs (type of cost not clearly reported).

[b] Oxlade et al[81]: IGRA test was QuantiFERON®-TB Gold, the test cost included the manufacturer's current unit cost for the test plus tax ($19.00; 2004 CAD), and costs for clinical personnel, transportation, laboratory personnel and reporting ($22.32; 2004 CAD)

[c] Marra et al[80]: Strategies were further categorized by population subgroups: BCG vaccination status, and ethnicity: foreign-born, non-aboriginal Canadian-born and Aboriginal; results were reported by the subgroup, and per strategy.

[d] Marra et al[80]: IGRA test was QuantiFERON®-TB Gold, the test costs included staff time, equipment, consumables and commercial kits (a total of $45.32, 2005 CAD).

[e] Campbell et al (2017)[79]: IGRA and TST diagnostic strategies followed by treatment with INH or RIF. In the original paper, no testing strategy included as an intervention strategy and compared with TST/INH. We focused on reporting the results for the comparison between IGRA and TST strategies.

[f] Campbell et al (2017)[79]: IGRA test was not specified (QFT or T-SPOT). The test accuracy based on the source including both types of IGRA tests. The test cost was based on the cost of QuantiFERON®-TB Gold, it was referenced back to Marra et al (BC CDC)[80] and it included the cost of kit and labor ($ 47, 2016 CAD) and cost of nurse visits ($7, 2016 CAD) , for a total of $54 (2016 CAD).

Table A4: Characteristics of Studies Included in the Economic Literature Review: Results

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
Oxlade, 2007, Canada	Incremental effectiveness , TST vs QFT : future active TB cases prevented with: *reported only for immigrant entry screening	Total mean cost and incremental cost (estimated from reported data, only for IGRA and TST strategies, immigrant entry screening by BCG status), per 1,000 people; CAD (2004)	**1) Immigrant entry screening** (reporting only results relevant to TST and QFT): Commpared to TST alone, QFT alone was equally effective and associated with cost savings in people who were BCG vaccinated in older ages (TST specificty : 60%), regadless of incidence of TB from various countries. For other two groups, BCG vaccinated in infancy or not vaccinated, QFT was more expensive, incremental costs ranged from $16,110 to $35,790.
	QFT or TST screening, country with low/intermediate/high TB incidence: 0.05 / 1.3 / 2.1; incremental effectivness =0 same values for both strategies]	TST alone, country with low/intermediate/high TB incidence (BCG non-vaccinated, Sp: 0.98), *total mean cost:* $30,320 / $267,250 / $423,250	**Sequential screeing with TST followed by QFT vs TST** alone was equally effective in low-incidence countries , but was less effective in countries with intermediate or high incidence of TB: intermediate: 1.3[TST]-0.05[IGRA/SEQ]=12.5 cases averted with TST; high: 2.1-0.05=2.05 cases averted with TST
	TST followed by QFT if TST-positive, all countries: reported as 0.05	TST alone, country with low/intermediate/high TB incidence (BCG vaccinated in infancy, Sp: 0.92), *total mean cost:* $48,810/ $279,390 / $431,060	**Sequential testing (QFT only in TST-positive persons)** would result in savings in populations with a low prevalence of TB infection and in those who were BCG-vacinated as older (TST specificty low, 60%); in these populations ICER was: cost svaing (low)/ 49,498/12.5=$3,959.84 per case averted (intermediate); 14,598/12.5=$7,120.97 per case averted (high)
		TST alone, country with low/intermediate/high TB incidence (BCG vaccinated, older ages, Sp: 0.60), *total mean cost:* $129,660/ $332,520 / $465,260	**2) Contact screening**: No mean cost data reported for TST and QFT strategies, so we were unable to estimate the difference of QFT vs TST, compared to no screening , close contact testing - QFT or TST was cost saving (smaller savings among contacts originally from high-incidence TB countries [high prevalence of prior LTBI associated with protective effect against disease following re-infection]). QFT was more cost-effective than TST in close and casual contacts who had received BCG vaccination after infancy because of reduced TST specificity
		QFT alone , country with low/intermediate/high TB incidence (Sp: 0.98), *total mean cost:* $64,920 / $303,020 / $459,040;	Additional deterministic analyses varied the QFT sensitivity for active disease (0.70 to 0.90) , discount rate (0 to 6%), and found no impact on the findings, no change in relative order of the screening strategies in any of the populations or scenarios
		TST followed by QFT if TST-positive, country with low/intermediate/high TB incidence (**non-vaccinated, TST Sp: 0.98**), *total mean cost: $27,369/ $283,022 / $450,662*	Probabilistic sensitivity analysis: Not done

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
		TST followed by QFT if TST-positive, country with low/intermediate/high TB incidence (**vaccinated in infancy, TST Sp: 0.92**), *total mean cost: $30,793/ $285,281 / $452,115*	
		TST followed by QFT if TST-positive, country with low/intermediate/high TB incidence **(vaccinated - older ages, TST Sp: 0.60),** *total mean cost:* $45,827/ $295,164 / $458,475	
		QFT alone vs. TST alone, country with low/intermediate/high TB incidence **(non-vaccinated, TST Sp: 0.98),** incremental cost :$34,600 / $35,770; $35,790	
		QFT alone vs. TST alone, country with low/intermediate/high TB incidence **(BCG-vaccinated in infancy, TST Sp: 0.92),** incremental cost :$16,110 / $23,630; $27,980	
		QFT alone vs. TST alone, country with low/intermediate/high TB incidence **(BCG vaccinated - older ages, TST Sp: 0.60), i**ncremental cost : **savings (—$64,740) / (—$29,500); (—$6,22**0)	
		TST/QFT vs. TST alone, country with low/intermediate/high TB incidence **(non-vaccinated, TST Sp: 0.98),** incremental cost :(—$2,951) / $15,772; $27,412	
		TST/QFT vs. TST alone, country with low/intermediate/high TB incidence **(BCG-vaccinated in infancy, TST Sp: 0.92),** incremental cost :(—$21,441) / $3,632; $19,602	
		TST/QFT vs. TST alone, country with low/intermediate/high TB incidence **(BCG vaccinated - older ages, TST Sp: 0.60), i**ncremental cost : **savings (—$102,291) / (—$49,498); (—$14,598**)	
Marra, Canada, 2008	Incremental effectiveness of 8 QFT-G interventions, QALYs (active TB averted) compared with TST alone (15.1143 QALYs [0.012 cases averted])	Incremental cost (compared with TST alone: $442.6), per person; CAD (2005)	ICER and Incremental Net Monetary Benefit (INMB at WTP of $50,000 QALY gained): **Best option- QFT-G in BCG-positive contacts, TST for others**, ICER - cost saving (dominant), INB=$3.70 (the highest value of all);
	QFT-G in BCG-positive contacts, TST for others: 0.0001 QALYs (*# of cases averted not reported clearly)	QFT-G in BCG-positive contacts, TST for others: –$0.61	QFT-G for all: ICER: $79,443/QALY and INMB= –$11.15 (negative sig indicates not cost-effective at $50K/QALY)

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
	TST/QFT-G in BCG-positive contacts, TST for others: 0.0000 QALY	TST/QFT-G in BCG-positive contacts, TST for others: –$2.54	Authors conclusions: The most economically attractive strategy - administer QFT-G in BCG-vaccinated contacts, and to reserve TST for all others (INMB CA$3.70/contact). The least cost-effective strategy was QFT-G for all contacts.
	QFT-G in foreign born, aboriginal, and BCG-positive contacts, TST in others: 0.0002 QALYs	QFT-G in foreign born, aboriginal, and BCG-positive contacts, TST in others: $5.00	Deterministic sensitivity analysis/scenarios: QFT-G for all with positive INB (cost-effective) if prevalence of LTBI up to 30% (vs. 10% in ref case), single-step QFT-G (fast-conversion), higher rate of start and completion of LTBI treatment (75% vs. 61%), a higher rate of TB reactivation (0.24 to 0.60% vs. 0.18-0.55% in base case), higher WTP (>$100K/QALY vs. $50K/QALY)
	QFT-G in foreign-born and aboriginal, TST for Canadian-born: 0.0001 QALYs	QFT-G in foreign-born and aboriginal, TST for Canadian-born: $5.58	The cost of QFT-G on the INMB of the optimal strategy: below the ***threshold price of QFT-G of $57***, none of QFT-G intervetions was cost-effective
	TST/QFT-G in foreign-born, aboriginal, and BCG-positive contacts, TST in others: 0.0000 QALY	TST/QFT-G in foreign-born, aboriginal, and BCG-positive contacts, TST in others: –$1.67	Diagnostic accuracy of QFT-G: as long as Sn was >80%, the optimal strategy remained cost-effective even if Sp of QFT-G = 90%.
	TST/QFT-G in foreign-born and aboriginal, TST for Canadian-born: 0.0000 QALY	TST/QFT-G in foreign-born and aboriginal, TST for Canadian-born: –$0.67	Probabilistic sensitivity analysis: Not done
	TST/QFT-G for all: —0.0001 QALYs	TST/QFT-G for all: $5.34	
	QFT-G for all: 0.0004 QALYs	QFT-G for all: $30.08	
Campbell, Canada, 2017	Mean and incremental effectiveness of IGRA interventions (compared with TST/INH), expressed as QALYs or active TB averted (per population) **for "flagged" cohort for medical surveillanc**e (n=6,100)	Mean and incremental cost (compared with TST/INH), per population (flagged cohort, n=6, 100); CAD (2016)	ICER : Flagged cohort - b**est options- IGRA/INH and IGRA/RIF**, ICER - cost saving (dominant vs. TST/INH); INMB higher with IGRA/RIF than with IGRA/INH ($753,658 vs. $676,330); SEQ/INH or SEQ/RIF less effective and less costly: ICERs, $1.06M/QA:Y and $308,919/QALY, ; WTP assumed for for any intervetion being cost-effectivness: $100,000/QALY or $20,000/TB case averted [mean cost of treating TB]
	TST/RIF, flagged cohort - total TB cases (and change in TB cases vs. TST/INH) and total QALYs (change in QALY): TB cases - 100.58 (1.17) ; QALYs - 45,025.4 (—0.7)	**TST/RIF, flagged cohort** - total mean cost (change in cost, vs. TST/INH): $2,914,913 (—$222,762)	In analysis for the whole cohort (N=260,600), none of the interventions were less costly, or cost-effective compared with ref case with TST/INF for those flagged for surveilance: ICERS > $100,000/QALY
	IGRA/INH, flagged cohort - total TB cases (and change in TB cases vs. TST/INH) and total QALYs (change in QALY): TB cases - 92.70(—6.71) ; QALYs - 45,030.9 (4.8)	**IGRA/INH, flagged cohort** - total mean cost (change in cost, vs. TST/INH): $2,946,383 (—$191,292)	If completion of treatment improved by 30% and there were 100% adherence to surveillance after screening, then INMb would be hiher (adding more QALYs) but there would be added costs of screening and treatment with IHN as compared to treatment with RIF so that there would be no cost saving anymore seen with IGRA/INH and only with IGRA/RIF. Thus, IGRA/RIF would remain as most cost-effective

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
	IGRA/RIF, flagged cohort - total TB cases (and change in TB cases vs. TST/INH) and total QALYs (change in QALY): TB cases - 94.51(—4.90) ; QALYs - 45,030.1 (4.0)	**IGRA/RIF, flagged cohort** - total mean cost (change in cost, vs. TST/INH): $2,784,661 (—$353,014)	Deterministic sensitivity analysis: IGRA/RIF would have negative INMB (not cost-effective at WTP of $100,000/QALY) if TST sn and Sp Increased to 0.95 (vs. 0.78, ref case) and 1 (vs. (0.60, ref case) , respestively, or if TST completion was 100% (vs. 0.72 , ref case); same if cost of IGRA was assumed to be $62 (vs. $54, ref case) or cost of threatment with RIF was assumed to be $686 (vs. $575, ref case), when healthy HSU was 1.0 (vs. 0.81, ref case, assumed to be the same as for LTBI), p of dying from TB twice higher (ref case: 4.7% vs. 8%), p of indeterminate IGRA higher (ref: 6% vs. 18%), completion of med evalution after screening lower (ref: 78% vs. 60%); completion of therapy with RIF lower (ref: 81.4% vs. 70%), proportion of BCG vaccinated lower if high-risk of LTBI (prevalnce >=30 cases/100,000): ref: 94% vs. 50%
	SEQ/INH, flagged cohort - total TB cases (and change in TB cases vs. TST/INH) and total QALYs (change in QALY): TB cases - 100.58(1.17) ; QALYs - 45,025.8 (—0.3)	**SEQ/INH, flagged cohort** -total mean cost (change in cost, vs. TST/INH): $2,853,649 (—$284,026)	Probabilistic sensitivity analysis: 1) flagged cohort analysis: best option, IGRA/RIF had a probability of being cost-effective of 99.4% at a WTP of $10,000/QALY lowering down to about 97% at $40k/QALY and to 64.9% at $100K/QALY gained
	SEQ/RIF, flagged cohort - total TB cases (and change in TB cases vs. TST/INH) and total QALYs (change in QALY): TB cases - 101.73(2.32) ; QALYs - 45,016.0(—1.3)	**SEQ/RIF, flagged cohort** - total mean cost (change in cost, vs. TST/INH): $2,756,316 (—$381,359)	The whole cohort: In efficiency frontier analysis, IGRA/RIF for all immigrants maximized QALYs. In migrants from countries >=30 cases per 100,000, IGRA/RIF was the most cost-effective option in deterministic analysis, had a probability of being cost-effective of 43.3% at a WTP of $100,000 per QALY, however use of SEQ/RIF in migrants from countries >= 200 cases per 100,000 had the highest probability of being cost-effective at this threshold of 47.8%
	TST/INH, flagged cohort - total TB cases and total QALYs (change: NA), comparator : TB cases - 99.41 (NA:0) ; QALYs - 45,026.1 (NA, 0)	**TST/INH, flagged cohort** - total mean cost (change in cost, NA), comparator : $3,137,675 (NA, 0)	
Campbell, Canada, 2019	Mean and incremental effectiveness of IGRA interventions (compared with TST/RIF* estimated by us), expressed as QALYs per 1,000 persons; categorized by 4 population subgroups based on incidence of TB: 1) low TB incidence; 2) moderate TB incidence; 3) high TB incidence; and 4) very high TB incidence	Mean and incremental cost (compared with TST/RIF**, estimated), per 1,000 persons; CAD (2016)	Best options [our estimation] when compared vs. TST/RIF, for migrants coming from countries with: 1) low TB incidence : **all IGRA options with more QALYs and less costy than TST**, but **SEQ/RIF: most QALYs and most savings** ; 2) moderate TB incidence: a**ll IGRA options with less QALYs and less costy than TST, but cost-effective because the INBs for all comparisons were positive** (at WTP f $50,000/QALY); **SEQ/RIF, and IGRA/RIF** with the highest cost savings and the highesst INBs; 3) high TB incidence: **all IGRA options were cost-effective vs TST**, with **SEQ/RIF, IGRA/RIF and SEQ/INH with more QALYs and cost savings** and IGRA/INH,with more QALYs and additional costs (INB>0; ICER: ~$27 K/QALY) ; 4) very high TB incidence: **all IGRA options cost-effective (INB>0**), **only IGRA/RIF with additional QALYs and cost savings**

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
	Low TB Incidence, total QALYs (change in QALYs vs. TST/RIF*, estimated) for: **SEQ/RIF -13,761.3 (0.65)**; SEQ/INH - 13,761.08 (0.43); **IGRA/RIF - 13,761.22 (0.57)** ; and IGRA/INH: - 13,761.07 (0.42)	**Low TB Incidence,** total mean costs (change in costs vs. TST/RIF*, estimated) for: **SEQ/RIF - 60,996 (—59,914)**; SEQ/INH - 67,309 (—53,601); **IGRA/RIF - 80,107 (—40,803)** ; and IGRA/INH: - 91,056 (—29,854)	Best options [our estimation] when IGRA options compared (sequential comparisons), for migrants coming from countries with: 1) low TB incidence: SEQ/RIF 2) moderate TB incidence: SEQ/RIF; ICER of IGRA/RIF vs. SEQ/RIF=$23,620/QALY) ; 3) high TB incidence: SEQ/RIF and IGRA/RIF;ICER of IGRA/RIF vs. SEQ/RIF=$10,161/QALY ; 4) very high TB incidence: IGRA/RIF
	Moderate TB Incidence, total QALYs (change in QALYs vs. TST/RIF*, estimated) for: SEQ/RIF -13,736.36 (—0.48); SEQ/INH - 13735.71 (—1.13); **IGRA/RIF - 13736.66 (—0.18)** ; and IGRA/INH: - 13736.69 (—0.15)	**Moderate TB Incidence,** total mean costs (change in costs vs. TST/RIF*, estimated) for: **SEQ/RIF - 121,950 (—84,195)**; SEQ/INH - 142,739 (—63,406); **IGRA/RIF - 129,036 (—77,109)** ; and IGRA/INH: - 154,804 (—51,341)	Results of deterministic or PSA presented vs. no intervention (no testing); based on reported data unable to explore drivers of cost-effectiveness of IGRA strategies vs TST strategies
	High TB Incidence, total QALYs (change in QALYs vs. TST/RIF*, estimated) for: SEQ/RIF -13,704.93 (0.58); SEQ/INH - 13704.38 (0.03); **IGRA/RIF - 13705.48 (1.13)** ; and IGRA/INH: - 13704.93 (0.58)	**High TB Incidence,** total mean costs (change in costs vs. TST/RIF*, estimated) for: **SEQ/RIF - 194,289 (—53,199)**; SEQ/INH - 231,835 (—15,653); **IGRA/RIF - 199,878 (—47,610)** ; and IGRA/INH: - 263,572 (16,084)	
	Very High TB Incidence, total QALYs (change in QALYs vs. TST/RIF*, estimated) for: SEQ/RIF -13,670.25 (—0.07); SEQ/INH - 13671.23 (0.91); **IGRA/RIF - 13671.50 (1.18)** ; and IGRA/INH: - 13671.02 (0.70)	**Very High TB Incidence,** total mean costs (change in costs vs. TST/RIF*, estimated) for: **SEQ/RIF - 263,628 (—54,394)**; SEQ/INH - 318,435 (410); **IGRA/RIF - 268,840 (—49,185)** ; and IGRA/INH: - 337,716 (19,691)	
	TST/RIF, comparator of interest for our evaluation (TST/INH was dominated by TST/RIF in all for populations : higher costs and lower QALYs), mean QALYs: 1) low incidence: 13760.65 ; 2) moderate TB incidence:13736.84 ; 3) high TB incidence: 13704.35; 4) very high TB incidence: 13670.32	**TST/RIF,** total mean costs (change in costs : NA) for: 1) low incidence: 120,910 ; 2) moderate TB incidence: 206,145 ; 3) high TB incidence: 247,488; 4) very high TB incidence: 318,025	
	TST/INH, comparator of interest for our evaluation (TST/INH was dominated by TST/RIF in all for populations), mean QALYs: low incidence: 13760.59 ; moderate TB incidence: 13735.98; high incidence:13704.15 ; very high incidence: 13669.91	**TST/INH,** total mean costs (change in costs : NA) for: 1) low incidence: 162, 233 ; 2) moderate TB incidence: 277,998 ; 3) high TB incidence: 348,686; 4) very high TB incidence: 415,877	

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
Campbell, Canada, 2019 (CKD)	Mean effectiveness, expressed as QALYs per person, 1) people starting with dyalisis and 2) those with late-satge CKD ; further categorized by 2 age groups and 4 population subgroups based on incidence of TB: 1) low ; 2) moderate ; 3) high ; and 4) very high	Mean cost, per person; CAD (2016)	When compared to TST, for people <60 ys or those >= 60, at late CKD stage or those initiating dyalsis, IGRA was associated with more QALYs (small increments) and lower costs , so was cost saving * original paper compared these two vs. no screening
	IGRA/INH, In **Dialysis**, AGE**<60 ys**, total mean QALY: **low TB incidence**: 2.79946 ; **moderate TB incidence**: 2.77393 ; **high TB incidence**: 2.79260 ; **very high TB incidence**: 2.78464	**IGRA/INH**, In **Dialysis**, AGE**<60 ys**, total mean cost ($): **low TB incidence**: 148.22 ; **moderate TB incidence**: 555.95 ; **high TB incidence**: 656.54 ; **very high TB incidence**: 1,063.92	PSA, efficiency fronitier for IGRA, people in dialysis: IGRA screening at a willingness-to-pay threshold of $100,000 was highly probable to be the most cost-effective option, with probabilities >79% among those > 60 years from countries with a moderate, high, and very high TB incidence
	TST/INH, **In Dialysis**, AGE**<60 ys**, total mean QALY: **low TB incidence**: 2.79932 ; **moderate TB incidence**: 2.77337; **high TB incidence**: 2.79189 ; **very high TB incidence**: 2.78347	**TST/INH**, **In Dialysis**, AGE**<60 ys**, total mean cost ($): **low TB incidence**: 203.50 ; **moderate TB incidence**: 663.30; **high TB incidence**: 759.94 ; **very high TB incidence**: 1,165.36	PSA, efficiency fronitier for IGRA, people in late-sateg CKD: IGRA screening at a willingness-to-pay threshold of $50,000 was highly probable to be the most cost-effective option, >75% -80% for those (both age groups) coming from countries with a moderate, high, and very high TB incidence
	IGRA/INH, **In Dialysis**, AGE**>=60 ys**, total mean QALY: **low TB incidence**: 2.30436 ; **moderate TB incidence**: 2.23593; **high TB incidence**: 2.25267 ; **very high TB incidence**: 2.22301	**IGRA/INH**, **In Dialysis**, AGE**>=60 ys**, total mean cost ($): **low TB incidence**: 122.96 ; **moderate TB incidence**: 477.11; **high TB incidence**: 561.89 ; **very high TB incidence**: 973.03	Results of deterministic or PSA presented vs. no intervention (no testing); based on reported data unable to explore drivers of cost-effectiveness of IGRA strategies vs TST strategies
	TST/INH, **In Dialysis**, AGE**>=60 ys**, total mean QALY: **low TB incidence**: 2.30425 ; **moderate TB incidence**: 2.23534; **high TB incidence**: 2.25197; **very high TB incidence**: 2.22163	**TST/INH**, **In Dialysis**, AGE**>=60 ys**, total mean cost ($): **low TB incidence**: 176.00 ; **moderate TB incidence**: 585.22; **high TB incidence**: 666.85 ; **very high TB incidence**: 1,085.25	
	IGRA/INH, **Late-Stage CKD**, AGE**<60 ys**, total mean QALY: **low TB incidence**: 2.99247 ; **moderate TB incidence**: 2.98910; **high TB incidence**: 2.98710 ; **very high TB incidence**: 2.98398	**IGRA/INH**, **Late-Stage CKD**, AGE**<60 ys**, total mean cost ($): **low TB incidence**: 90.04 ; **moderate TB incidence**: 206.61; **high TB incidence**: 245.65; **very high TB incidence**: 364.77	
	TST/INH, **Late-Stage CKD**, AGE**<60 ys**, total mean QALY: **low TB incidence**: 2.99243 ; **moderate TB incidence**: 2.98893; **high TB incidence**: 2.98684 ; **very high TB incidence**: 2.98352	**TST/INH**, **Late-Stage CKD**, AGE**<60 ys**, total mean cost ($): **low TB incidence**: 140.95 ; **moderate TB incidence**: 285.93; **high TB incidence**: 317.05 ; **very high TB incidence**: 410.82	

Author, year, country	Results		
	Health outcomes	**Costs**	**Cost-effectiveness**
	IGRA/INH, **Late-Stage CKD**, AGE**>=60 ys**, total mean QALY: **low TB incidence**: 2.55380 ; **moderate TB incidence**: 2.51397; **high TB incidence**: 2.53277 ; **very high TB incidence**: 2.51147	**IGRA/INH**, **Late-Stage CKD**, AGE**>=60 ys**, total mean cost ($): **low TB incidence**: 98.81 ; **moderate TB incidence**: 271.95; **high TB incidence**: 321.74 ; **very high TB incidence**: 507.19	
	TST/INH, **Late-Stage CKD**, AGE**>=60 ys**, total mean QALY: **low TB incidence**: 2.55371 ; **moderate TB incidence**: 2.51347; **high TB incidence**: 2.53229 ; **very high TB incidence**: 2.51061	**TST/INH**, **Late-Stage CKD**, AGE**>=60 ys**, total mean cost ($): **low TB incidence**: 147.60 ; **moderate TB incidence**: 351.18; **high TB incidence**: 394.09 ; **very high TB incidence**: 558.75	

Abbreviations: CXR, X-ray; TST, tuberculin skin test; QFT, QuantiFERON®-TB Gold; IGRA, interferon-gamma release assay; n, number; BCG, bacillus Calmette-Guérin ; CAD, Canadian dollars; LTBI, latent tuberculosis infection; INH, isoniazid; RIF, rifampin; Sn, sensitivity; Sp, specificity.

Appendix 8: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A5: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of IGRA vs TST for LTBI

Author, year, country	Is the study population appropriate for the review question?	Are the interventions appropriate for the review question?	Is the system in which the study was conducted sufficiently like the current Ontario context?	Is the perspective of the costs appropriate for the review question (e.g., Canadian public payer)?	Is the perspective of the outcomes appropriate for the review question?	Are all future costs and outcomes discounted appropriately (as per current CADTH guidelines)?	Are QALYs derived using CADTH's preferred methods, or is an appropriate social care–related equivalent used as an outcome? (If not, describe rationale and outcomes used in line with the analytical perspective taken)	Overall judgment[a]
Oxlade, 2007, Canada	Yes	Yes	Yes	Yes, Canada & Ontario government and limited societal	Yes	Yes, 3% (ranged from 0-6%)	No, case prevented	Partially applicable
Marra, 2008, Canada	Yes	Yes	Yes	Yes, third party payer (BC)	Yes	Yes, 3%	Yes	Directly applicable
Campbell, 2017, Canada	Yes	Yes	Yes	Yes, third party payer (BC)	Yes	Yes, 1.5%	Yes	Directly applicable
Campbell, 2019, Canada	Yes	Yes(IGRA could be compared with TST given broken down results)	yes	Yes, third party payer (BC)	Yes	Yes, 3%	Yes	Partially applicable
Campbell, 2019, Canada	Yes (immunocopromised)	Yes (IGRA could be compared with TST given broken down results)	Yes	Yes, third party payer (BC)	Yes	Yes, 1.5%	Yes	Directly applicable

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; QALY, quality-adjusted life-year.

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Table A6: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of IGRA vs. TST for LTBI

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputsa match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment[b]
Oxlade, 2007, Canada	Yes	Yes	Partially, QALYs not inlcuded but the effectivness is the same between the TST and QFT strategies	Yes, Sn of TST (cut-off >10 mm) and IGRA same	Yes	Yes	Yes	Yes	Yes, for migrants - recalculated ; for contacts not able	Partially, PSA not done	NA (not reported)	Minor Limitations
Marra, 2008, Canada	Yes	Yes	Yes	Yes, Sn of TST (cut-off >5 mm, not clearly reported) and IGRA same	Yes	Yes	Yes	Yes	Yes	Yes, PSA not done	No	Minor Limitations
Campbell, 2017, Canada	Yes	Yes	Yes	Yes, Sn of TST (cut-off:>10 mm) smaller than Sn of IGRA, QFT type not specified?	Yes	Yes	Yes	Yes	Yes	Yes, PSA done	No	Minor Limitations

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputsa match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment[b]
Campbell, 2019, Canada	Yes	Yes	Yes	Yes, Sn of TST (cut-off:>10 mm) smaller than Sn of IGRA, QFT type not specified?	Yes	Yes	Yes	Yes	Yes, estimated from data (IGRA vs TST)	Yes, PSA	No	Minor Limitations
Campbell, 2019, Canada	Yes	Yes	Yes	Yes, Sn of TST (cut-off:>10 mm) smaller than Sn of IGRA	Yes	Yes	Yes	Yes	Yes, estimated from data (IGRA vs TST)	Yes, PSA done	No	Minor Limitations

Abbreviations: Sn, sensitivity, QF, QuantiFERON, PSA, probabilistic analysis, CKD, chronic kidney diseases; IIGRA, TST, LTBI

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA” (not applicable).

[a]Clinical inputs include relative treatment effects, natural history, and utilities.

[b]Overall judgment may be “minor limitations,” “potentially serious limitations,” or “very serious limitations.”

Appendix 9: Economic Evidence - GRADE

Table A7: GRADE Evidence Profile for the Comparison of IGRA and TST — Directly Applicable Economic Studies

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
3 economic studies,[78-80] deemed as directly applicable	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected		⨁⨁⨁⨁ High

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

Note: Assessments done by a single reviewer for directly applicable studies. We used the NICE quality appraisal checklist for economic evaluations, which consists of two sections (Tables A5 and A6, Appendix 8). The quality assessment (Appendix 8, Table A6) was used for assessing the methodological quality or risk of bias (credibility of the published models and their limitations including modeling (structural), method and parameter assumptions), inconsistency, and imprecision of the reported cost-effectiveness estimates (variability in probabilistic and other sensitivity analyses). The applicability assessment (Appendix 8, Table A5) was used to examine indirectness (applicability of the study findings to the Ontario context/our question). Study details are described in the main text of the report.

Appendix 10: Estimation of Immunocompromised Population

Table A8: Annual Estimates for Number of People with HIV in Ontario[108]

HIV positive	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Year 1	Year 2	Year 3	Year 4	Year 5
Actual, first time HIV diagnosis[108]	834	707	666	696	686	716	697	738	683	515					
Actual, past HIV diagnosis[108]	107	113	87	100	112	113	157	201	239	146					
Actual, overall	941	820	753	796	798	829	854	939	922	661					
Forecast[b]	—	—	—	—	—	—	—	—	—	—	797	793	789	785	780

Table A9: Annual Estimates for Incident Number of People with End-Stage CKDs in Ontario[109]

End-stage CKD	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Year 1	Year 2	Year 3	Year 4	Year 5
Actual [109]	2,828	2,912	3,039	3,071	3,102	3,285	3,300	3,376	3,308	3,252					
Forecast[b]	—	—	—	—	—	—	—	—	—	—	3,507	3,563	3,618	3,674	3,729

Table A10: Annual Estimates for Number of People with Kidney Transplants in Ontario[109]

Kidney transplants (pediatric and adult recepients)	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Year 1	Year 2	Year 3	Year 4	Year 5
Actual [109]	521	604	597	730	696	673	747	609	652	699					
Forecast[b]	—	—	—	—	—	—	—	—	—	—	733	745	757	769	782

Table A11: Annual Estimates for Number of People with Cancers in Ontario[110]

Cancer, all sexes and all ages , Ontario	2023	2024	2025	2026	2027	2028
Projection, all non-solid tumors (reference case)	**8,781**	**9,032**	**9,291**	**9,538**	**9,766**	**9,997**
Leukemia	2,872	2,934	3,000	3,057	3,115	3,179
Hodgkin lymphoma	451	458	469	473	483	492
Non-Hodgkin lymphoma	5,458	5,640	5,822	6,008	6,168	6,326
Myeloma	1,844	1,915	1,986	2,056	2,126	2,195
Projection, all cancers combined (Scenario 2)	97,586	99,832	102,080	104,272	106,554	108,823

Appendix 11: Costing Components, Contact and Immigrant Populations: TST and IGRA

The cost and cost components were based on consultations with experts (email and oral expert consultations, January 12 to April 25, 2024, E. Rea, MD; R. Khan, RN; P. Galange, MD).

We made a simplifying assumption regarding the share of testing between PHUs and MDs (50-50% in the reference case). This was tested in sensitivity analysis (see Table A14, Appendix 12 and Scenarios 8 and 9).

Table A12. Costing components when the tests are requested and done at MD's office

Test	Referral	Blood sampling	Test fee:	Test Supplies	Need for incubators to transport samples	Transportation of specimens (shipping cost)	Travel time (nurse)
TST	Yes (fee 1st visit: applied)	No	• 1st visit, OHIP fee (nurse labour included in the fee) • 2nd visit: Fee for TST reading (2nd visit, OHIP fee, no nurse time)	Yes	NA	No	No
IGRA	Yes (fee applied)	Yes (lab fee)	Yes (list price) Includes all costs: equipment, tubes, supplies, transportation/ shipping	No (included in test fee)	No	No	No

Table A13. Costing components when the tests are requested and done at Public Health Unit (PHU)

Test	Referral	Blood sampling	Test fee:	Test Supplies	Need for incubators to transport samples	Transportation of specimens (shipping cost)	Travel time (nurse)
TST	No: billing not allowed because of the Medical Act (no physician's fee)	No	• 1st visit: Nurse plants the test (the nurse labour time) • 2nd visit: Nurse reads the test (the nurse labour time)	Yes	NA	No	Yes, full cost for nurse's time
IGRA	No	Yes (nurse's time)	Yes (list price) Includes all costs: equipment, tubes, supplies, transportation	No (included in test fee)	No (already available across the majority of PHU units)	No (established workflow system at PHUs), - shipping cost accounted in a scenario 12b	Smaller: half cost assumed

Appendix 12: Sensitivity Analysis – Description of Scenarios

Table A14: Summary of Changes in Parameter Input Values or Assumptions in Scenario Analyses Compared with Reference Case

Scenarios	Reference Case	Description of changes (vs. reference case)
Change in population size		
Scenario 1: Number of people for testing *in immigrant and contact populations* estimated from PHO data	Initial population for immigrant and contact populations based on reported demographic data, expected population growth, and expected number of contact investigations (Table 8A and B), details described in the main report Model parameter values and uptakes described in Tables 10–12 and Table 14A-C	• Estimation of the initial population size and assumptions described n Appendix 13 • No changes to the model parameter values • No changes to the uptake rates
Scenario 2: Inclusion of all types of cancers in *immunocompromised population*	Non-solid cancer types included in estimation of immunocompromised population (Table 8C)	• All cancer types included in the estimation (Table 16 and Appendix 10, Table A11) • No changes to the model parameter values • No changes to the uptake rates
Change in uptake rates for IGRA		
Scenario 3: Large uptake in immigrant population (same large uptake for all)	Uptake of IGRA strategies in immigrant population: 3 % per year (3% in Year 1 to 15% in Year 5, Table 14A)	• Change in the uptake of IGRA for immigrant population to 75% in Year 1 to 100% in Year 5, and same uptake as in the reference case for the rest (contacts/immunocompromised: 75%-100%, Table 14B–C) • No change in the population size • No changes to the model parameter values
Scenario 4: Same low uptake in all populations	Uptake of IGRA strategies in: • Immigrant population: 3% in Year 1 to 15% in Year 5 (Table 14A) and • Contact / immunocompromised populations: 75% in Year 1 to 100% in Year 5 (Table 14B–C)	• Low uptake of IGRA in all populations: 5% in Year 1 to 25% in Year 5 (5% per year) • No change in the population size • No changes to the model parameter values
Scenario 5: Evenly spread uptake for immunocompromised population	Uptake of IGRA strategies in immunocompromised population: 75% in Year 1 to 100% in Year 5 (Table 14C)	• Evenly spread uptake of IGRA in immunocompromised population: 20% in Year 1 to 100% in Year 5 (20% per year), no chnages to the uptakes of IGRA for the rest • No change in the population size • No changes to the model parameter values
Scenario 6: Smaller uptake of IGRA for immunocompromised population	Uptake of IGRA strategies in immunocompromised population: 75% in Year 1 to 100% in Year 5 (Table 14C)	• Smaller uptake of IGRA in immunocompromised population: 10% in Year 1 to 50% in Year 5 (10% per year), no chnages to the uptakes of IGRA for the rest • No change in the population size • No changes to the model parameter values
Changes in the testing pathway		

Scenarios	Reference Case	Description of changes (vs. reference case)
Scenario 7: No cost of referral	If testing is done by MDs, the cost of referral visit inlcuded ($23.75, Table 11A and B)	• Parameter value change, referral visit cost: 0$ for the referral visit regadless of the setting (MD or PHU) • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates
Scenario 8: Share of TST/IGRA testing between MDs and PHUs	• *Immigrant and contact populations*: Simplifying assumtion of the share - 50-50 between MDs and PHUs, and estimated and adjusted the overall costs of testing (Tables 11A and B, reference case: complete TST in immigrants and contacts: $71.23 and $140.74, respectively; IGRA in immigrants and contacts: $124.83 and $159.59, respectively) • Immunocompromised population: no share, 100% done by MDs	• Parameter value change for immigrants and contacts, no share, 100% testing done by PHUs: we used unadjusted costs estimated for PHU setting (Table 11A: TST in immigrants and contacts by PHUs: $68.52 and $207.54, respectively; and Table 11B: IGRA in immigrants and contacts by PHUs: $115.15 and $184.66, respectively) • No change of the setting for immunocompromised population • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates
Scenario 9: All testing *for immigrants* done by MDs	*Immigrant population*: Simplifying assumtion of the share - 50-50 between MDs and PHUs, adjusted the overall costs of testing (Tables 11A and B, reference case in *immigrants*: complete TST: $71.23 and IGRA: $124.83)	• Parameter value *change for immigrants only*, no share between MDs and PHUs, 100% testing done by MDs and used unadjusted cost estimated for MD setting (Table 11A: TST in immigrants by MDs: $73.94; and Table 11B: IGRA in immigrants by MDs: $134.51) • No change of the setting for contact and immunocompromised population • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates
Scenarios 10: No waste of PPD (no TST vials waste, consumables, scenario 10a) or large waste (80% of the doses wasted in the vial, scenario 10b) when testing done by MDs	TST cost adujsted for the wastage of the TST vial if testing done at MDs (Table 11A: TST consumable cost related to PPD: $37.08, 44.4% wastage of the vial)	• Parameter value change for the TST vial wastage (i.e., consumable cost related to PPD): Scenario 10a, no wastage of the vial (Table 11A: TST consumable cost related to PPD: $20.60); Scenario 10b, large (80%) wastage of the vial (TST consumable cost per dose: $103) • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates
Changes in the cost of IGRA		
Scenario 11: Lower cost of IGRA test	Cost of IGRA (list price): $100 per test, the test cost inlcudes all cost components such as equipment, overheads, labour, kits, consumables and shipping and handling	• Parameter value change for the cost of IGRA: the cost decreased by 25%, to $75 per test • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates

Scenarios	Reference Case	Description of changes (vs. reference case)
Scenario 12a: IGRA provided by a hospital lab	Cost of IGRA (list price): $100 per test, the test cost inlcudes all cost components such as equipment, overheads, labour, kits, consumables and shipping and handling	• Parameter value change for the cost of IGRA if done at a hospital lab: $103 per test, the test cost inlcudes all cost components such as equipment, overheads, labour, kits, consumables and shipping and handling (Table 17) • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates

Scenario 12b: IGRA provided by a hospital lab	Cost of IGRA (list price): $100 per test, the test cost inlcudes all cost components such as equipment, overheads, labour, kits, consumables and shipping and handling	• Parameter value change for the cost of IGRA if done at a hospital lab with additional inclusion of the cost of shipping and handling:
		  ○ Cost of IGRA: $103 per test, the test cost inlcudes all cost components such as equipment, overheads, labour, kits, consumables but it does not cover shipping and handling, may be applicable to remote areas (Table 17)
		  ○ Assumed additional cost of shipping and handling (Table 17: $6.025 per test)
		• No changes to other model parameter values
		• No changes in the population size
		• No changes to the uptake rates

Change in the probability of reactivation of LTBI into active TB, immunocompromised population		
Scenario 13: High probabiity of reactivation of LTBI into active TB in immunocompromised populations	Probability of reactivation of LTBI same for all populations and based on the inputs form the literature[79] (Table 10A: 0.0011)	• Parameter value change for the probabilty of reactivation of LTBI into active TB in immunocompromised population only • Hypothetical treshold value of 0.30 used in this scenario (Figure 8) • No changes to other model parameter values • No changes in the population size • No changes to the uptake rates

Abbreviations: LTBI, latent tuberculosis (TB) infection; IGRA, interferon-gamma release assay; TST, tuberculin skin test. MD, medical doctor (physician); PHU, public health unit.

Appendix 13: Estimation of Immigrant and Contact Sub-Populations from Reported LTBI episodes in Ontario

To estimate the populations of interested, we used unpublished aggregate, non-identifiable data on the number of reported latent tuberculosis infection (LTBI)episode data per year recorded in the integrated Public Health Information System (iPHIS) extracted by and obtained from Public Health Ontario Ontario's (PHO) (email communication, A. Saunders, MSc, 01 Apr 2024, PHO Data Request #2024-011,[111] and expert oral and email communications June 10-14, 2024, L. Macdonald, MD, A. Saunders, MSc, M. Whelan, MSc and E. Rea, MD).

Estimation of Number of People for LTBI Testing in Ontario

Based on the PHO data (Table A15 as presented in the unpublished report,[111] the annual number of LTBI episodes in Ontario between January 1, 2015 and December 31, 2023 ranged from **4,307 (in 2020)** to **7,995 (in 2015).** Data reported between 2020 and 2022 should be interpreted with caution because these were pandemic years and access to care, including for TB infection testing and treatment, as well as iPHIS data entry practices were likely impacted by the COVID-19 pandemic response.

For the purpose of estimating the size of immigrant and contact subpopulations in a scenario analysis (**sensitivity analysis: scenario 1**), we used the largest estimated annual number of LTBI episodes which was reported for people born outside of Canada of **4,884 LTBIs in 2019**. We assumed that this estimate was a true positive estimate for LTBI in Ontario for these populations and used it as a starting point to calculate the overall number of tested immigrants and contacts annually.

Next, we applied the Bayesian approach to diagnostic assessment with TST, and used the published sensitivity and specificity of TST[113] and modelled estimated of the prevalence of LTBI in Ontario (among those born outside of Canada)[14] to estimate the number of false-positives and number of test-negative as following:

- The Bayesian formulas for estimation of the test-positive and test-negative results:
    - True-positive = (Prevalence*Sensitivity_TST)/ ((Prevalence * Sensitivity_TST)+((1-Prevalence)*(1- Specificity_TST))
    - False-positive = ((1- Prevalence)*(1- Specificity_TST)/((Prevalence* Sensitivity_TST)+((1-Prevalence)*(1- Specificity_TST))
    - Test-positive = (Prevalence* Sensitivity_TST)+((1- Prevalence)*(1-Specificty_TST))
    - Test-negative = ((Prevalence *(1- Sensitivity (TST))+((1- Prevalence)* Specificity(TST)),

  where Sensitivity of TST (10mm) was 0.77, specificity of TST was 0.59[113] and prevalence of LTBI was 0.22[14]

  Using these formulas, we estimated proportions of true-positives (0.346), false-positives (0.654), test positives (0.49) and test-negatives (0.51)

- Assuming there would be 4,884 true-positive test results (LTBI episodes for people born outside of Canada (in 2019), as the largest reported estimate (excluding missing data) Table A14), we estimated 9,232 people with false-positive results and a total of 14,116 people who were testing positive

- We then estimated that 14,692 people tested negative (from the number of people who tested-positive as 14,116*0.51/0.49)
- Thus, overall size of tested foreign-born immigrant and contact populations was about 28,808 people
- Next, we assumed that the proportion of incomplete TST tests was about 10% (n= 2,881), which in result increased the total estimate to **31,689 screened people (immigrant and contacts – foreign born)**.
- For the purpose of estimating the budget impact by sub-population (immigrant and contact), we assumed that about 37.6% of screened people was identified via contact investigations in 2019 (PHO data request, Table A16), and estimated the size of two subpopulations:
    - 11,915 people screened via contact investigations and
    - the rest of 19,774 people screened via immigration screening
- Next, we adjusted these two populations for the WHO-reported BCG-vaccination rate of 87% [105]and arrived with a total of 27,569 people to be screened in year 1: immigrants, 17,203; and, contacts, 10,366 (Table A17).
- Lastly, we accounted for a growth rate of 3.4% [104] and estimated a total population of about 147,600 (immigrants and contacts) to be tested over the next 5 years (Table A17).

Limitations of iPHIS Data

Based on our expert consultations, the iPHIS data that we used for this calculation likely represent underestimates of the true numbers of LTBI episodes in the eligible population for the following reasons **(**expert oral and email communications, June 10-14, 2024, L. Macdonald, MD, A. Saunders, MSc, M. Whelan, MSc and E. Rea, MD):

- It is assumed that, although notifiable to local public health units in Ontario, not all positive TB infection test results are reported to public health units
- Reporting practices may vary considerably by providers
- Missing place of birth information also reduced the number of LTBI episodes included in this calculation. Close to 30% of LTBI cases were missing information on place of birth, overall 5% cases were reported to have been born in Canada and over 65% of cases were born outside of Canada. Therefore, it could be possible that many of those cases that are missing were likely born outside of Canada.

In addition, estimation of the population size for scenario 1 need to be interpreted with caution because of additional caveats of iPHIS data reporting and extraction [111]:

- iPHIS is a dynamic disease reporting system which allows ongoing updates to data previously entered. As a result, data extracted represent a snapshot at the time of extraction and may differ from previous or subsequent reports.
- The data only represent cases reported to public health and recorded in iPHIS. As a result, all counts will be subject to varying degrees of underreporting due to a variety of factors, such

as disease awareness and medical care seeking behaviours, which may depend on severity of illness; access to medical care; clinical practice; and changes in laboratory testing and reporting.

- Overall, LTBI episodes reported in iPHIS may be under-reported by clinicians administering and reading positive TSTs, or be under-recorded in iPHIS, so may under-estimate the number of trust positive TSTs performed in Ontario for a given year, even when accounting for the potential for small number of these LTBI episodes to have been identified via IGRA rather than TST results.
- LTBI episodes generally do not have a diagnosis status reported in iPHIS, however, those with a diagnosis status entered as 'Does Not Meet Definition' are excluded from the counts.
- Only provincial case classifications as listed in the Ontario Ministry of Health surveillance case definitions are included in the report counts. Cases are excluded if they do not meet the provincial case classifications that were in effect at the time that they were reported.
- Cases are reported based on 'episode date'. The episode date is an estimate of the onset date of disease for a case. In order to determine this date, the following hierarchy is in place in iPHIS: Onset Date > Specimen Collection Date > Lab Test Date > Reported Date. If an onset date exists it will be used as the episode date. If not available, then the next available date in the hierarchy will be used.
- Cases for which the Disposition Status was reported as entered in error, does not meet definition, duplicate-do not use, or any variation on these values have been excluded.
- Duplicate case records may be included if they were not identified and resolved at either the local or provincial level prior to data extraction from iPHIS.
- The assessment of LTBI varies by health care providers and public health units. Comparisons of LTBI incidence reported between public health units and the province should be made with caution.

Table A15. Number and percentage of LTBI episodes by origin of birth and episode year: Ontario, 2015 – 2023

Origin of birth	2015 n (%)	2016 n (%)	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	2021 n (%)	2022 n (%)	2023 n (%)
Born outside Canada	**4,375 (54.7)**	**4,641 (58.8)**	**4,799 (60.1)**	**4,826 (61.5)**	**4,884 (65.6)**	**2,736 (63.5)**	**2,521 (58.2)**	**3,313 (59.9)**	**4,075 (58.2)**
Born in Canada	384 (4.8)	432 (5.5)	389 (4.9)	386 (4.9)	372 (5.0)	186 (4.3)	150 (3.5)	187 (3.4)	170 (2.4)
Unknown/missing	3,236 (40.5)	2,825 (35.8)	2,794 (35.0)	2,641 (33.6)	2,191 (29.4)	1,385 (32.2)	1,657 (38.3)	2,029 (36.7)	2,761 (39.4)
Total	**7,995 (100.0)**	**7,898 (100.0)**	**7,892 (100.0)**	**7,853 (100.0)**	**7,447 (100.0)**	**4,307 (100.0)**	**4,328 (100.0)**	**5,529 (100.0)**	**7,006 (100.0)**

Data source: Ontario. Ministry of Health. iPHIS (Database; extracted 4 Mar 2024).[111]

Table A16. Number and percentage of TSTs administered by reason for testing and year given: Ontario, 2015 – 2023

Reason for testing	2015 n (%)	2016 n (%)	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	2021 n (%)	2022 n (%)	2023 n (%)
Routine screening	5,850 (49.9)	6,015 (48.1)	5,548 (46.0)	5,174 (42.0)	5,175 (43.5)	2,709 (45.1)	3,285 (51.6)	4,230 (51.9)	5,218 (54.7)
Contact tracing	**3,788 (32.3)**	**4,274 (34.1)**	**4,284 (35.5)**	**4,805 (39.0)**	**4,467 (37.6)**	**2,133 (35.5)**	**2,054 (32.3)**	**2,034 (25.0)**	**2,397 (25.1)**
Immigration screening	788 (6.7)	1,051 (8.4)	1,164 (9.7)	1,087 (8.8)	1,192 (10.0)	590 (9.8)	514 (8.1)	1,069 (13.1)	921 (9.7)
Targeted screening	906 (7.7)	751 (6.0)	639 (5.3)	763 (6.2)	613 (5.2)	282 (4.7)	192 (3.0)	400 (4.9)	507 (5.3)
Symptoms	88 (0.8)	77 (0.6)	74 (0.6)	75 (0.6)	67 (0.6)	36 (0.6)	43 (0.7)	31 (0.4)	40 (0.4)
Unknown/missing	295 (2.5)	349 (2.8)	351 (2.9)	427 (3.5)	379 (3.2)	262 (4.4)	273 (4.3)	387 (4.7)	461 (4.8)
Total	**11,715 (100.0)**	**12,517 (100.0)**	**12,060 (100.0)**	**12,331 (100.0)**	**11,893 (100.0)**	**6,012 (100.0)**	**6,361 (100.0)**	**8,151 (100.0)**	**9,544 (100.0)**

Data source: Ontario. Ministry of Health. iPHIS (Database; extracted 4 Mar 2024).[111]

Table A17: Estimation of Immigrant and Contact Sub-Populations for Budget Impact, Based on the reported LTBI episodes for Ontario and additional assumptions

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Forecasted BCG-vaccinated **immigrant population** for IGRA testing, growth per year of 3.4%, n	17,203	17,788	18,393	19,018	19,665	92,068
Forecasted BCG-vaccinated **contact population** for IGRA testing, growth per year of 3.4%, n	10,366	10,718	11,083	11,460	11,849	55,477
Total (both populations), n	**27,569**	**28,507**	**29,476**	**30,478**	**31,514**	**147,545**

Abbreviations: n, number; BCG; IGRA, interferon-gamma release assay; TST, tuberculin skin test.

Appendix 14: Sensitivity Analysis: Immigrant Subgroup Population

Table A18: Budget Impact Results—Sensitivity Analysis: Immigrant Sub-Population

Scenario	Total 5-year budget impact (BI) (IGRA strategies vs. TST alone), $ million[a]	
	IGRA alone vs TST	**SEQ: TST/IGRA vs TST alone**
Reference case, Total BI, all populations	2.99	14.07
Reference case, BI – Test cost, all populations	6.01	8.28
Reference case, Total BI, Immigrant	**-1.63**	**-3.45**
Reference case, BI – Test cost, Immigrant	1.09	0.88
Change in Population Size		
Scenario 1: Ontario's number of people for testing based on iPHIS LTBI data obtained from PHO, and published LTBI prevalence estimates**, Immigrants, Total BI**	-0.73	-1.54
Scenario 1: BI – Test cost	0.48	0.39
Scenario 2: All cancer types, Immigrants, Total BI	**NA**	**NA**
Scenario 2: BI – Test cost	-	-
Change in the uptake of IGRA		
Scenario 3: Large uptake for all, Immigrants (75%, year 1), Total BI	-15.86	-33.56
Scenario 3: BI – Test cost	10.56	8.51
Scenario 4: Low uptake for all, Immigrants (5% per y), Total BI	-2.72	-5.76
Scenario 4: BI – Test cost	1.81	1.46
Scenario 5: Smaller uptake for immunocompromised (20%/y), Immigrants, Total BI	**NA**	**NA**
Scenario 5: BI – Test cost	-	-
Scenario 6: Smaller uptake for immunocompromised (10%/y), Immigrants, Total BI	**NA**	**NA**
Scenario 6: BI – Test cost	-	-
Change in the testing pathway		
Scenario 7: No cost of referral, Immigrants, Total BI	-1.63	-3.54
Scenario 7: BI – Test cost	1.09	0.79

Scenario	Total 5-year budget impact (BI) (IGRA strategies vs. TST alone), $ million[a]	
	IGRA alone vs TST	**SEQ: TST/IGRA vs TST alone**
Scenario 8: All tests done by PHUs, Immigrants, Total BI	-1.77	-3.52
Scenario 8: BI – Test cost	0.95	0.81
Scenario 9: Tests done by MDs in immigrants/immunocompromised (with PPD waste), Immigrants, Total BI	-1.50	-3.39
Scenario 9: BI – Test cost	1.22	0.94
Scenario 10a: No waste of PPD (no TST vials waste at MD's office), Immigrants, Total BI	-1.48	-3.45
Scenario 10a: BI – Test cost	1.24	0.88
Scenario 10b: Large waste of PPD (80% of the TST vial wasted at MD's office), Immigrants, Total BI	-2.26	-3.45
Scenario 10b: BI – Test cost	0.46	0.88
Change in cost of IGRA		
Scenario 11: IGRA cost 25% lower, Immigrants, Total BI	-2.12	-3.63
Scenario 11: BI – Test cost	0.60	0.70
Scenario 12a: IGRA at hospital lab, no shipping cost, Immigrants, Total BI	-1.53	-3.42
Scenario 12a: BI – Test cost	1.19	0.91
Scenario 12b: IGRA at hospital lab, with shipping cost in immigrant and contact testing, Immigrants, Total BI	-1.47	-3.39
Scenario 12b: BI – Test cost	1.25	0.93
Scenario 13: Change in probability of reactivation of LTBI into active TB for immunocompromised (hypothetical threshold value), **Immigrants, Total BI**	NA	NA
Scenario 13: BI-test cost	NA	NA

Abbreviations: BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways; iPHIS, Public Health Information System; PHO, Public Health Ontario.

Note: * Remains the same as in the reference case for this subpopulation.

[a]All costs are in 2024 CAD.

Appendix 15: Sensitivity Analysis: Contact Subgroup Population

Table A19: Budget Impact Results—Sensitivity Analysis: Contact Sub-Population

	Total 5-year budget impact (BI) (IGRA strategies vs. TST alone), $ million[a]	
Scenario	**IGRA alone vs TST**	**SEQ: TST/IGRA vs TST alone**
Reference case, Total BI, all populations	2.99	14.07
Reference case, BI – Test cost, all populations	6.01	8.28
Reference case, Total BI, Contacts	**-1.63**	**-1.76**
Reference case, BI – Test cost, Contacts	**0.22**	**0.62**
Change in Population Size		
Scenario 1: Ontario's number of people for testing based on iPHIS LTBI data obtained from PHO, and published LTBI prevalence estimates, Contacts, **Total BI**	-9.38	-10.12
Scenario 1: BI – Test cost	1.25	3.58
Scenario 2: All cancer types, Contacts, Total BI*	**NA**	**NA**
Scenario 2: BI – Test cost*	-	-
Change in the uptake of IGRA		
Scenario 3: Large uptake for all, Contacts, Total BI *	**NA**	**NA**
Scenario 3: BI – Test cost*	-	-
Scenario 4: Low uptake for all, Contacts (5%/y), Total BI	-0.28	-0.30
Scenario 4: BI – Test cost	0.04	0.11
Scenario 5: Smaller uptake for immunocompromised (20%/y), Contacts, Total BI *	**NA**	**NA**
Scenario 5: BI – Test cost	-	-
Scenario 6: Smaller uptake for immunocompromised (10%/y), Contacts, Total BI *	**NA**	**NA**
Scenario 6: BI – Test cost	-	-
Change in the testing pathway		
Scenario 7: No cost of referral, Contacts, Total BI	-1.63	-1.80
Scenario 7: BI – Test cost	0.22	0.58
Scenario 8: All tests done by PHUs, Contacts, Total BI	-1.96	-1.66

Scenario	Total 5-year budget impact (BI) (IGRA strategies vs. TST alone), $ million[a]	
	IGRA alone vs TST	**SEQ: TST/IGRA vs TST alone**
Scenario 8: BI – Test cost	-0.11	0.72
Scenario 9: Tests done by MDs in immigrants/immunocompromised , Contacts, Total BI *	**NA**	**NA**
Scenario 9: BI – Test cost	-	-
Scenarios 10a: No waste of PPD (no TST vials waste at MD's office), Contacts, Total BI	-1.56	-1.76
Scenario 10a: BI – Test cost	0.29	0.62
Scenario 10b: Large waste of PPD (80% of the TST vial wasted at MD's office), Contacts, Total BI	-1.76	-1.91
Scenario 10b: BI – Test cost	0.62	-0.07
Change in cost of IGRA		
Scenario 11: IGRA cost 25% lower, Contacts, Total BI	-1.85	-1.86
Scenario 11: BI – Test cost	0.00	0.53
Scenario 12a: IGRA at hospital lab, no shipping cost , Contacts, Total BI	-1.58	-1.74
Scenario 12a: BI – Test cost	0.26	0.64
Scenario 12b: IGRA at hospital lab, with shipping cost only in immigrant and contact testing , Contacts, Total BI	-1.56	-1.73
Scenario 12b: BI – Test cost	0.29	0.66
Scenario 13: Change in probability of reactivation of LTBI into active TB in immunocompromised (hypothetical threshold value) **, Contacts, Total BI**	NA	NA
Scenario 13: BI-test cost	NA	NA

BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways; iPHIS, Public Health Information System; PHO, Public Health Ontario.

Note: * Remains the same as in the reference case for this subpopulation.

[a]All costs are in 2024 CAD.

Appendix 16: Sensitivity Analysis: Immunocompromised Subgroup Population

Table A20: Budget Impact Results—Sensitivity Analysis: Immunocompromised Sub-Populations

	Total 5-year budget impact (BI) (IGRA strategies vs. TST alone), $ million[a]		
Scenario	**IGRA alone**	**SEQ: TST/IGRA vs TST alone**	**SEQ: TST/IGRA & IGRA/TST[b]**
Reference case, Total BI, all populations	**2.99**	**14.07**	**18.80**
Reference case, BI – Test cost, all populations	6.01	8.28	10.12
Reference case, Total BI, Immunocompromised Population	6.26	19.29	24.01
Reference case, BI – Test cost, Immunocompromised Population	4.70	6.79	8.62
Change in Population Size			
Scenario 1: Ontario's number of people for testing based on iPHIS LTBI data obtained from PHO, and published LTBI prevalence estimates, **Immunocompromised, Total BI ***	NA	**NA**	**NA**
Scenario 1: BI – Test cost*	-	-	-
Scenario 2: All cancer types, Immunocompromised, Total BI	44.23	136.36	169.79
Scenario 2: BI – Test cost	33.25	47.98	60.97
Change in the uptake of IGRA			
Scenario 3: Large uptake for all, Immunocompromised, Total BI *	NA	**NA**	**NA**
Scenario 3: BI – Test cost*	-	-	-
Scenario 4: Low uptake for all, Immunocompromised (5%/y), Total BI	1.07	3.29	4.09
Scenario 4: BI – Test cost	0.80	1.16	1.47
Scenario 5: Smaller uptake for immunocompromised (20%/y), Immunocompromised, Total BI	4.26	13.15	16.37
Scenario 5: BI – Test cost	3.21	4.63	5.88
Scenario 6: Smaller uptake for immunocompromised (10%/y), Immunocompromised, Total BI	2.13	6.57	8.19
Scenario 6: BI – Test cost	1.60	2.31	2.94
Change in the testing pathway			

Scenario	Total 5-year budget impact (BI) (IGRA strategies vs. TST alone), $ million[a]		
	IGRA alone	**SEQ: TST/IGRA vs TST alone**	**SEQ: TST/IGRA & IGRA/TST[b]**
Scenario 7: No cost of referral, Immunocompromised, Total BI	4.60	16.49	21.10
Scenario 7: BI – Test cost	3.05	3.99	5.71
Scenario 8: All tests done by PHUs in contacts and immigrants, Immunocompromised, Total BI *	NA	**NA**	**NA**
Scenario 8: BI – Test cost	-	-	-
Scenario 9: Tests done by MDs in immigrants/immunocompromised, Immunocompromised, Total BI *	NA	**NA**	**NA**
Scenario 9: BI – Test cost	-	-	-
Scenario 10a: No waste of PPD (no TST vials waste at MD's office), Immunocompromised, Total BI	7.40	19.29	24.29
Scenario 10: BI – Test cost	5.85	6.79	8.90
Scenario 10b: Large waste of PPD (80% of the TST vial wasted at MD's office), Immunocompromised, Total BI	1.66	19.29	22.91
Scenario 10b: BI – Test cost	0.11	6.79	7.52
Change in cost of IGRA			
Scenario 11: IGRA cost 25% lower, Immunocompromised, Total BI	4.41	18.01	22.17
Scenario 11: BI – Test cost	2.86	5.51	6.78
Scenario 12a: IGRA at hospital lab, no shipping cost, Immunocompromised, Total BI	6.48	19.44	24.23
Scenario 12a: BI – Test cost	4.92	6.94	8.84
Scenario 12b: IGRA at hospital lab, with shipping cost only for immigrants and contacts, Immunocompromised, Total BI	6.48	19.44	24.23
Scenario 12b: BI – Test cost	4.92	6.94	8.84
Scenario 13: p of reactivation of LTBI (at threshold value of 30%, hypothetical), Total BI	0.00	4.81	-39.82
Scenario 13: BI – Test cost	4.70	8.62	8.62

BI, budget impact; IGRA, interferon-gamma release assay; TST, tuberculin skin test; SEQ, sequential pathways; iPHIS, Public Health Information System; PHO, Public Health Ontario

Note: * Remains the same as in the reference case for this subpopulation, because of inability to differentiate specific TST count data for immunocompromised people. Remains the same as large uptake already considered in the reference case (from 75% in year 1)

[a]All costs are in 2024 CAD.

[b]IGRA/TST vs TST alone, the strategy applicable only to immunocompromised population.

Appendix 17: Letter of Information

Thank you for participating in Ontario Health's Health Technology Assessment (HTA) on "Interferon Gamma Release Assay for Latent Tuberculosis Infection (IGRA for LTBI)".

What is a Health Technology Assessment (HTA)?

An HTA is a review of scientific evidence about health care services and interventions. This includes speaking with care providers to find out about the perceived benefits and disadvantages of health interventions and technologies.

What is this survey about?

We would like to know your perspective and opinion about TB skin test and blood test (IGRA) for the diagnosis of LTBI (latent tuberculosis infection).

IGRA is a blood test used for the diagnosis of LTBI. In Ontario, there is currently no standardized funding or access to the use of IGRA. Our HTA will conclude in a recommendation about public funding for IGRA in Ontario.

The last day to participate in this assessment is April 30, 2024.

Important note

Your participation in this HTA is completely voluntary. You are under no obligation to participate, and you can withdraw from the HTA at any time and/or refuse to answer any questions without any negative consequences.

If you choose to participate, please note that all information collected from participants will be kept confidential and your privacy will be protected, except as required by law. The overall findings from this survey will be published, however, we will not use your name or any personally identifiable information (e.g., names of clinics or doctors) in any presentations or publications related to this HTA.

If you have any questions about the survey or would like to submit your feedback in another format, please contact:

Thank you for your time and input! Your experience is valued and appreciated.

Appendix 18: Interview Guide

1. What is your job title?
2. Where is the location of your clinic/hospital?
3. Does your clinic/hospital currently offer TB skin test? (bullet)
    - Yes, on site
    - Yes, by referral
    - No

    a. (If yes) On average, how many TB skin tests (on site/referral) do you offer to your patients per month?
4. Does your clinic refer patients for IGRA (blood test)? (bullet)
    - Yes
    - No

    a. (If yes) On average, how many IGRA (blood test) referrals do you do per month?

5. What population do you serve for LTBI (latent tuberculosis infection) testing? (checkbox)
    - Immunocompromised patients
    - Healthcare workers who recently immigrated to Canada and are BCG vaccinated.
    - People living in congregate settings such as long-term care homes, homeless shelters, and hospitals.
    - Other (please specify)

6. What are the pros and cons of each test (TST skin test and IGRA-blood test) in your opinion? (consider the following: patient preference, workflow, equity)

7. Is there anything else to add that you feel would be important to our health technology assessment regarding IGRA (blood test)?

What happens next?

The Ontario Health Technology Advisory Committee (OHTAC), a group of scientific experts and people with lived experience, reviews our findings and, after careful deliberation, makes their draft recommendation. At that time, the report will be published on our website and available for public comment.

Following public comment, the review will conclude with a formal recommendation to the Ministry of Health and Long-Term Care on whether this intervention should be publicly funded.

For more information about Ontario Health and our health technology assessments, please go to: http://www.hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment

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About Us

We are an agency created by the Government of Ontario to connect, coordinate, and modernize our province's health care system. We work with partners, providers, and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and well-being.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

For more information about Ontario Health, visit OntarioHealth.ca.

Ontario Health
500–525 University Avenue
Toronto, Ontario
M5G 2L3
Toll Free: 1-877-280-8538
TTY: 1-800-855-0511
Email: OH-HQO_HTA@OntarioHealth.ca
hqontario.ca

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