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Interferon Gamma Release Assay for the Identification of Latent Tuberculosis Infection in Rural and Remote Settings

Rapid Review

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

BCG	bacillus Calmette-Guérin
IGRA	interferon gamma release assay
LTBI	latent tuberculosis infection
SR	systematic review
TST	tuberculin skin test

Key Messages

- There is a lack of evidence on the clinical utility of the interferon gamma release assay for identifying latent tuberculosis infection in rural and remote settings.
- In remote Indigenous communities with known history of bacillus Calmette-Guérin vaccination, more positive tests results were reported with the tuberculin skin test than with the interferon gamma release assay.

Context and Policy Issues

There are 2 accepted tests for the identification of latent tuberculosis infection (LTBI): the tuberculin skin test (TST) and the interferon gamma release assay (IGRA).[1] There are some logistical challenges to the IGRA test (e.g., infrastructure, transporting the blood), but the test can be more accurate than the TST in certain populations (e.g., those who have received the bacillus Calmette-Guérin [BCG] vaccine).[1] Despite the desire to use the IGRA test in many jurisdictions in Canada, the test may not always be available, particularly in rural or remote areas.[2]

In August 2020, CADTH searched the literature for evidence on the clinical utility, the cost-effectiveness, and guidelines regarding the use of IGRA for the identification of LTBI in rural and remote settings.[3] This report identified 1 systematic review[4] regarding the clinical utility of IGRA in rural and remote settings, but no relevant economic evaluations or guidelines were identified.[3] The purpose of the current report is to summarize and critically appraise this systematic review.[4]

This report is a component of a larger CADTH condition-level review on tuberculosis. A condition-level review is an assessment that incorporates all aspects of a condition, from prevention, detection, treatment, and management. For more information on CADTH's condition-level review of tuberculosis, please visit the project page (https://www.cadth.ca/tuberculosis).

Research Question

What is the clinical utility of the interferon gamma release assay for identifying latent tuberculosis infection in rural and remote settings?

Methods

Literature Search Methods

A limited literature search was conducted for a previous CADTH report[3] by an information specialist on key resources including MEDLINE via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian

and major international health technology agencies, as well as a focused Internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were the interferon gamma release assay and people in rural and remote settings who may have been exposed to tuberculosis. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2015 and July 26, 2020.

Selection Criteria and Methods

The evidence in this report was identified in a previous CADTH report,[3] where 1 reviewer screened citations and abstracts. For this report, the full-text articles were reviewed and the final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1.

Critical Appraisal of Individual Studies

The included publication was critically appraised by 1 reviewer using the following tool as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2).[5] Summary scores were not calculated; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 107 citations were identified in the literature search for the previous CADTH report.[3] No potentially relevant publications were retrieved from the grey literature search. One potentially relevant report was identified and retrieved for full-text review. This systematic review met the inclusion criteria and was included in this report.

Additional details regarding the study characteristics, and the main study findings and authors' conclusions, are provided in Appendix 1, in Table 2 and Table 3, respectively.

Table 1: Selection Criteria

Criteria	Description
Population	People in rural and remote settings who may have been exposed to tuberculosis
Intervention	Interferon gamma release assay
Comparator	Tuberculin skin test
Outcomes	Clinical utility (e.g., detection outcomes, people who obtain screening in accordance with guidelines, patients receiving treatment for infection, need for additional latent tuberculosis infection screening)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

Summary of Study Characteristics

The systematic review (SR) by Faust et al.[4] was published in 2018, but the authors did not include the date restrictions for their literature search. The eligible population and interventions for this SR were broader than that of the current report and 2 diagnostic accuracy studies relevant to this report were identified. This SR was led by authors in Canada and the 2 relevant primary studies were conducted in Canada. The populations of the 2 included studies were individuals from Indigenous communities in remote areas in Canada (i.e., Iqaluit, Nunavut; and Sioux Lookout, Ontario). One of the studies included 256 participants; the other study included 11 participants. Both relevant studies in the SR compared IGRA to the TST and the relevant outcomes reported in the SR were sensitivity, specificity, and discordant results.

Summary of Critical Appraisal

Overall, this SR was poorly reported, with some methodological weaknesses that reduce the certainty in the findings. The authors of this SR did not mention whether they followed an a priori protocol and there was no published protocol, which increases the risk of reporting bias. The research questions and inclusion criteria described the population and intervention of interest, but the comparators and outcomes were not well-defined. Thus, the focus of the SR was unclear. The source of funding for the SR was reported, but it was not reported whether the funding agency influenced the content of the review. All authors declared no conflicts of interest.

The literature search strategy involved searching 2 databases, with no limits on publication date, language, or study design; and it included a search of the grey literature. The search terms were provided but not the entire search strategy, which reduces the reproducibility of the search. As well, the search date was not reported; thus, it is unclear whether the search was recent. It was not reported how many authors performed study selection and only a single reviewer performed data extraction; thus, it is possible that relevant studies were missed or that relevant evidence was omitted. The number of full texts excluded and the reasons for exclusion were reported, but the authors did not provide a full list of the excluded studies; thus, it is uncertain whether the exclusion of these potentially relevant studies was correct.

There was lack of detail in the description of the primary studies included in the SR; the population, intervention, and comparators were described but lacked sufficient detail, and the outcomes and study designs were listed but not described. In addition, the source of funding for the primary studies was not reported and it is unclear if the source of funding may have biased the results of these primary studies. The quality of the diagnostic accuracy studies relevant to this report were assessed using an appropriate tool and the quality assessments were reported for the individual studies. As well, the authors discussed the quality of the studies when discussing the results. However, it was unclear whether the quality assessments were done in duplicate, reducing the certainty of these assessments.

Summary of Findings

Detection Outcomes

In Indigenous communities in remote areas of Canada, both of the performance and feasibility studies included in the SR found discordant results between the TST and IGRA tests. In both studies, there was a higher proportion of positive TST tests versus the IGRA

test, particularly among those vaccinated with BCG. The authors of both studies recommend the use of IGRA in these communities because of the high proportion of individuals vaccinated with BCG.

Limitations

This report is limited by the quantity of evidence, with 1 low-quality SR identified in the previous report[3] and summarized here. This SR included 2 relevant studies, which were assessed by the authors as having moderate to high methodological quality. However, 1 study included only 11 participants, which may limit the internal and external validity of this study. This small quantity of evidence may limit the strength and reliability of the findings.

In addition, the evidence in this report was limited by outcomes reported. Both primary studies in the SR reported discordant results, but they did not report other measures of diagnostic test accuracy, such as sensitivity or false-positive results. However, there is no gold standard test for LTBI and true diagnostic accuracy studies are not feasible for the identification of LTBI.

Conclusions

Overall, the evidence from this SR found that, in rural and remote communities with known vaccination with BCG, there are discordant results between TST and IGRA tests, with a higher proportion of positive tests identified using the TST test.

This SR did not report any other clinical utility outcomes (e.g., subsequent treatment or testing) and the clinical utility of IGRA versus TST is unknown in rural and remote settings. However, the authors of the SR did suggest that, in BCG-vaccinated communities, the IGRA could potentially save resources dedicated to TB prophylaxis, as there may be fewer people who would be falsely identified as positive for LTBI.

References

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Appendix 1: Characteristics of Included Publications

Table 2: Characteristics of the Systematic Review

Study citation, country, funding	Study designs and number of primary studies	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Faust et al. (2018)[4] Canada Funding: First Nations and Inuit Health Branch, Health Canada	36 studies in total: 2 studies that evaluated the feasibility and performance of IGRA and TST were relevant to this report	**Eligible populations**: Pediatric populations that are epidemiologically similar to Canadian Indigenous communities (i.e., high-risk populations within low-burden countries), as well as Canadian Indigenous settings (including non-pediatric populations) **Excludes**: Studies that did not focus on high-incidence communities within otherwise low-burden countries **Relevant populations**: Indigenous populations in remote settings	**Eligible interventions**: Strategies or tools for LTBI screening in pediatric populations **Relevant interventions**: IGRA **Eligible comparators**: Alternative strategies or tools **Relevant comparators**: TST	Discordant results

IGRA = interferon gamma release assay; LTBI = latent tuberculosis infection; TST = tuberculin skin test.

Table 3: Summary of Findings of the Systematic Review

Main study findings	Systematic review authors' conclusion
Study from Iqaluit, Nunavut (N = 256) 44/256 (17%) of results were discordant (most of which occurred in people with multiple BCG vaccinations) Positive results: 18% IGRA vs. 32% TST Study author's recommendation regarding screening tools: "IGRAs are a valid screening tool for LTBI in Nunavut, as most of the community is BCG vaccinated, making IGRAs more specific." (p. 8) Quality assessment: 6/6 **Study from Sioux Lookout, Ontario (N = 11)** Positive TST = 7/11 (63%) Positive IGRA = 0/11 (0%) None of the participants developed symptoms of active TB disease Study author's recommendation regarding screening tools: "Recommends use of IGRA due to high proportion of false-positive TST in BCG vaccinated adolescents." (p. 8) Quality assessment: 5/6 (did not describe execution of index test in sufficient detail to allow replication)	"As an alternative to LTBI screening via TST, a study assessing the effectiveness of the use of IGRAs for LTBI screening among an Indigenous population in Nunavut concluded that IGRAs are a valid screening tool for LTBI in this setting, as most of the community was BCG-vaccinated, making IGRAs more specific, and thereby saving resources dedicated to TB prophylaxis" (p. 20) "In the Canadian context, a study among Indigenous adolescents in northern Ontario province reports that prior BCG vaccination was associated with false-positive TST results." (p. 20) "The results of this review suggest that targeted rather than universal screening is warranted in high-risk communities within low TB-incidence countries, and that the consideration of both community-level or location-based as well as individual risk factors have merit as determinants of targeted screening strategies." (p. 22) "The choice of a context-appropriate screening tool in the case of the pediatric Indigenous population in northern Canadian communities is complicated by the history of BCG vaccination in some regions, which may result in high false positive TST readings. IGRAs may therefore represent a more accurate screening tool in this population, although their accuracy in children remains contested and it should thus be kept in mind that their implementation may lead to increased missed cases." (p. 22)

BCG = bacillus Calmette-Guérin; IGRA = interferon gamma release assay; LTBI = latent tuberculosis infection; TB = tuberculosis; TST = tuberculin skin test; vs. = versus.