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Interferon Gamma Release Assay for Identifying Latent Tuberculosis Infection in People With Bacillus Calmette-Guérin Vaccination

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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Table of Contents

CADTH

List of Tables

CADTH

Abbreviations

BCG	Bacillus Calmette-Guérin
IGRA	interferon gamma release assay
LTBI	latent tuberculosis infection
TB	tuberculosis
TST	tuberculin skin test

Key Messages

- In people who have been vaccinated with Bacillus Calmette-Guérin, the interferon gamma release assay appears to be related to fewer diagnoses for latent tuberculosis infection, fewer prescriptions of preventive tuberculosis therapy, and no difference in the number of active TB cases compared to the tuberculin skin test (findings based on 1 [non-randomized study] of low quality).
- No evidence-based guidelines were found regarding the identification of latent tuberculosis infection in people with previous Bacillus Calmette-Guérin vaccination.

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] TST involves an intradermal injection of a purified protein derivative into the lower part of the arm and waiting to see whether the patient has a reaction to the injection; whereas, IGRA is a blood test that measures the person's immune response to TB proteins.[2] There are differences with regard to the cost, ease of use, skill, and laboratory equipment required for these 2 tests.[1] There may be differences in the accuracy of these tests in specific populations, such as those with previous Bacillus Calmette-Guérin (BCG) vaccination.

In August 2020, CADTH searched the literature for evidence on the clinical utility, the cost-effectiveness, and evidence-based guidelines regarding the use of the IGRA for identifying LTBI in people with previous BCG vaccination.[3] That report[3] identified 1 non-randomized study[4] and 1 evidence-based guideline[5] that were potentially relevant, but no economic evaluations. The purpose of the current report is to review the full texts of these publications, and to summarize and critically appraise the eligible publications.

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, including 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 Questions

1. What is the clinical utility of the interferon gamma release assay for identifying latent tuberculosis infection in people with previous Bacillus Calmette-Guérin vaccination?
2. What are the evidence-based guidelines regarding the identification of latent tuberculosis infection in people with previous Bacillus Calmette-Guérin vaccination?

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 All via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination 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 interferon gamma release assay and people with a history of Bacillus Calmette-Guérin vaccination who may have been exposed to tuberculosis. Search filters were applied to limit retrieval to guidelines for Question 3 only. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and August 3, 2020. Internet links were provided, where available.

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 by 1 reviewer 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, they were duplicate publications, or were published before 2015. Guidelines with unclear methodology were also excluded.

Table 1: Selection Criteria

Criteria	Description
Population	People with a history of Bacillus Calmette-Guérin vaccination who may have been exposed to tuberculosis
Intervention	Q1: Interferon gamma release assay Q2: Interferon gamma release assay, tuberculin skin test
Comparator	Q1: Tuberculin skin test Q2: not applicable
Outcomes	Q1: 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) Q2: Recommendations regarding the best practices for screening for latent tuberculosis infection in this population
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: the Downs and Black checklist[6] for non-randomized studies and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[7] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

For the previous CADTH report,[3] a total of 356 citations were identified in the literature search and 1 potentially relevant publication was retrieved from the grey literature. Two potentially relevant reports were identified and retrieved for full-text review, of which 1 non-randomized study[4] met the inclusion criteria and was included in this report.

The following is a summary and critical appraisal this study. Additional details regarding the study characteristics, the main study findings, and the authors' conclusions are provided in tables in Appendix 1.

Summary of Study Characteristics

This retrospective cohort by Munoz et al. (2017)[4] was conducted in Spain and compared LTBI screening strategies for contacts of people with TB from 2 distinct time periods. From January 2006 to May 2008 only the TST was used, and from June 2008 to December 2010 both the TST and IGRA were used simultaneously to screen for LTBI. The study included individuals with and without BCG vaccination, but only the findings from the 290 individuals with BCG vaccination are relevant to this report. There were 124 individuals screened with the TST alone, and 166 individuals who were screened with the TST and IGRA simultaneously. The relevant outcomes were the diagnosis of LTBI, the prescription of preventive TB therapy, and the development of active TB.

Summary of Critical Appraisal

There are some concerns with the population included in this study. The aim of this study was to assess the utility of using IGRA in BCG-vaccinated contacts of people with TB versus using the TST to test for LTBI; however, the population that was included in the study comprised both BCG-vaccinated individuals and unvaccinated individuals. It is unclear why the authors chose to include both populations, as the inclusion of the unvaccinated population adds unnecessary confusion to the findings of the study, and the results are not always clearly reported by BCG vaccination status. In addition, although the main population of interest for this study was those who were vaccinated with BCG, the baseline characteristics were reported by cohort (i.e., TST test period versus IGRA test period), but not by BCG vaccination status. This retrospective cohort study compares 2 cohorts recruited over 2 separate time periods based on when the approach the testing for LTBI was changed in their institution. There is a risk that confounding factors due to these 2 different time periods could contribute to difference in the results between the cohorts. There were some significant differences in

baseline characteristics between the cohorts, including the percent of foreign-born individuals, and it is unclear how these differences may have influenced the outcome of the study.

The quality of the reporting for this non-randomized study was mixed. The objective, hypothesis, interventions, and eligibility criteria were clearly described, including the cut-off values and time frames for both diagnostic tests. However, minimal information was reported for the baseline characteristics of the populations, for instance the study did not report potential socioeconomic or health risk factors for TB, which may have influenced the outcomes. The reporting of some results was unclear, limiting the conclusions that can be formed from the data. For instance, simple outcome data were not always reported, 1 finding was reported in the abstract but not in the main body of the report, and for 1 outcome the raw data were reported but detection outcomes were not calculated and statistical tests were not reported, limiting the interpretation of the findings.

Due to the nature of the interventions (i.e., blood test, skin reaction), it was not possible to blind the patients or those measuring the main outcomes; however, it is unlikely that unblinded participants or outcome assessors would influence the outcomes of tests. However, it was not reported whether those assessing the outcomes were blinded to the patient's BCG vaccination status, which could potentially influence the outcome. The appropriate statistical tests were conducted for comparing continuous and categorical variables, but it is unclear whether a statistical power calculation was done.

Summary of Findings

Clinical Utility of the Interferon Gamma Release Assay in People with Bacillus Calmette-Guérin Vaccination

Diagnosis of LTBI

A statistically significantly higher proportion of BCG-vaccinated individuals were diagnosed with LTBI during the TST period (96 of 124 individuals tested; 77.4%) compared to the IGRA test period (85 of 166 individuals tested; 51.2%).

During the IGRA test period, out of the 166 BCG-vaccinated individuals who were tested simultaneously with the TST and IGRA tests, there were more positive TST results (60%) versus positive IGRA results (39%), and both tests were positive in one-third of the people. Of the positive IGRA test results, the TST was negative in 14% of cases. With the positive TST results the IGRA test was negative in 44% of cases.

Prescription of Tuberculosis Therapy

In BCG-vaccinated individuals, preventive TB therapy (i.e., treatment for LTBI to prevent the possible development of active TB) was prescribed to a statistically significantly higher proportion of individuals during the TST period (62.1%) compared to the IGRA period (48.2%).

Development of Active TB

Of those vaccinated with BCG, over the median follow-up of 5 years, 2 individuals (1.6%) developed active TB in the TST period and none in the IGRA test period.

Guidelines

No relevant evidence-based guidelines regarding the identification of LTBI in people with previous BCG vaccination were identified.

Limitations

This report is limited by the quantity and quality of evidence, with 1 non-randomized study identified and summarized. There are some concerns with the quality of reporting of the findings, and the appropriateness of the included population. This small quantity of low-quality evidence may limit the strength and reliability of the findings.

In addition, there is no gold standard test for LTBI and true diagnostic accuracy studies are not feasible for the identification LTBI, which may have limited the types of outcomes that were reported.

The findings in this report are based on 1 study conducted in Spain, and it is unknown whether the findings are generalizable to the Canadian clinical practice as there may be geographical differences in access to care for TB.

Furthermore, this report did not identify any evidence-based guidelines regarding the identification of LTBI in people with previous BCG vaccination; thus, the recommendations regarding the best practices for screening for LTBI in this population are unknown.

Conclusions

This report comprised 1 non-randomized study. The evidence from this retrospective cohort study found that in individuals vaccinated with BCG, that a testing strategy for LTBI with TST alone resulted in a higher percentage of people with a positive LTBI diagnosis and a higher proportion of people that were prescribed preventive TB therapy, when compared to a testing strategy that uses both IGRA and TST. There were 2 BCG-vaccinated people who later developed active TB in the TST period, and none in the IGRA period.

Overall, using IGRA to test for LTBI in BCG-vaccinated individuals resulted in a lower percentage of people prescribed preventive TB therapy, and no difference in the development of active TB. This conclusion is based on the results from 1 poorly reported cohort study and should be interpreted with caution.

No relevant evidence-based guidelines were identified; thus, no conclusions can be formed.

References

1. Pai M, Kunimoto D, Jamieson F, Menzies D. Canadian Tuberculosis Standards, Chapter 4 - Diagnosis of Latent Tuberculosis Infection. 7th ed. Ottawa: Public Health Agency of Canada; 2014: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-16.html. Accessed 2021 March 15.
2. Menzies D. Approach to diagnosis of latent tuberculosis infection (tuberculosis screening) in adults. UpToDate. Waltham (MA): UpToDate; 2019: www.UpToDate.com. Accessed 2020 Jan 8.
3. Interferon Gamma Release Assay for the Identification of Latent Tuberculosis Infection in People with Previous Bacille Calmette-Guérin Vaccination: Clinical Utility, Cost-Effectiveness, and Guidelines. Ottawa: CADTH; 2020 Aug. (CADTH rapid response report: summary of abstracts). https://cadth.ca/sites/default/files/pdf/htis/2020/RB1513%20IGRA%20vs%20TST%20BCG%20Final.pdf. Accessed 2021 Apr 21.
4. Muñoz L, Gonzalez L, Soldevila L, Dorca J, Alcaide F, Santin M. QuantiFERON®-TB Gold In-Tube for contact screening in BCG-vaccinated adults: A longitudinal cohort study. *Plos one.* 2017;12(8):e0183258. PubMed
5. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018: https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/. Accessed 2021 Jan 27.
6. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. PubMed
7. Agree Next Steps C. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2021 Apr 21.

Appendix 1: Characteristics of Included Publications

Table 2: Characteristics of the Included Primary Clinical Study

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Munoz et al. (2017)[4] **Spain** **Funding: none**	Retrospective cohort study Compared 2 consecutive 30-month periods TB unit of a teaching hospital	**Inclusion criteria**: Immunocompetent individuals 15 years or older, with no history of TB infection, who were contacts of a patient with pulmonary TB **Relevant population:** those with a history of BCG vaccination **Excludes**: those with known history of TB infection, contacts of people with multi-drug resistant TB or non-pulmonary TB, those with known active TB N = 290 BCG-vaccinated people (across both time periods) TST period, n = 124 BCG vaccinated IGRA period, n = 166 BCG vaccinated	Compared 2 screening strategies for LTBI **Intervention:** IGRA test period (QuantiFERON1-TB Gold In-tube). Approach varied by BCG vaccination status: non-BCG patients were screened with TST; BCG patients were simultaneously screened with TST and IGRA. Preventive therapy started if IGRA was positive, or TST was ≥ 15 mm. If IGRA was negative, and TST < 15 mm, then a second IGRA test was performed 8 weeks later. **Comparator**: TST test period; with no difference in testing strategy regardless of BCG vaccination status. Preventive therapy started if TST was ≥ 5 mm.	Outcome: rate of positive latent TB infection, prescription of TB therapy, development of TB Length of follow-up: 5 years

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

Table 3: Summary of Findings of the Included Primary Clinical Study

Main study finding	Authors' conclusion
Munoz et al. (2017)[4]	
Diagnosis of LTBI in BCG-vaccinated people, n (%) 96 (77.4%) in the TST period vs. 85 (51.2%) in the IGRA test period, P < 0.01 Comparison of IGRA test vs. TST results in BCG-vaccinated people, n (%): In the IGRA screening strategy period (n = 166) Positive TST = 99/166 (60%) Positive IGRA test = 64/166 (39%) Both tests positive = 55/166 (33%) Positive TST with a negative IGRA test = 44/99 (44%) Positive IGRA test with negative TST = 9/64 (14%) (No other calculations or comparisons were reported) Preventive therapy prescribed to BCG-vaccinated patients %: 62.1% in the TST period vs. 48.2% in the IGRA test period, P = 0.02 Development of active TB in BCG-vaccinated patients, n TST period = 2 IGRA period = 0	"In BCG-vaccinated TB contacts, the addition of IGRA safely reduced TB diagnosis and treatment rates without increasing the risk of subsequent active TB." (p. 1) "The results of this observational study support our hypothesis that the use of IGRA for targeting BCG-vaccinated TB contacts for preventive therapy is as effective as a TST-based strategy for preventing subsequent development of TB, while allowing a substantial reduction of treatment prescriptions" (p. 5) "Despite the conservative approach of treating close contacts with TST ≥ 15 mm and negative IGRA result, we attained a significant reduction of 26% in TB diagnoses among BCG-vaccinated contacts, without increasing the risk of active TB." (p. 6)

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