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SUMMARY WITH CRITICAL APPRAISAL

Identification of Tuberculosis: A Review of the Guidelines

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Abbreviations

AGREE II	Appraisal of Guidelines for Research & Evaluation 2
ATS	American Thoracic Society
BCG	Bacillus Calmette-Guérin
CADTH	Canadian Agency for Drugs and Technologies in Health
CDC	Centers for Disease Control and Prevention
ECDC	European Centre for Disease Prevention and Control
ERS	European Respiratory Society
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
IDSA	Infectious Disease Society of America
IGRA	Interferon-gamma release assay
LTBI	Latent tuberculosis infection
MOH	Ministry of Health
NICE	National Institute for Health and Care Excellence
NTAC	National Tuberculosis Advisory Committee
NTCA	National Tuberculosis Controllers Association
PHAC	Public Health Agency of Canada
TB	Tuberculosis
TB-LAMP	Tuberculosis- Loop-Mediated Isothermal Amplification
TST	Tuberculin skin test
USPSTF	United States Preventive Services Task Force Recommendation Statement
WHO	World Health Organization

Context and Policy Issues

Tuberculosis (TB) is an infectious disease caused by the bacteria Mycobacterium tuberculosis and is transmitted through the air by those who are infected with the bacteria (i.e., coughing). According to the World Health Organization (WHO),[1] roughly a quarter of the world's population is infected with M. tuberculosis and may be at risk for developing the disease. TB typically affects the lungs of a person (i.e., pulmonary TB) but can also spread to other parts of the body (i.e., extrapulmonary TB).

TB is prevalent in low and middle income countries, as the disease is associated with poverty, poor sanitation or hygiene practices and being easily transmissible from person to person.[1] However, high income countries, including Canada, still report cases of TB and it is considered an important public health matter. According to the Public Health Agency of Canada (PHAC),[2] Canada has one of the lowest rates of active TB in the world. However, annual rates of TB have remained the same in the country since the 1980's rather than steadily declining.[2] In 2017, PHAC reported 1,796 cases of active TB in Canada with migrants and Indigenous peoples bearing the highest rates of active TB in the country and approximately 70% of cases being pulmonary TB.[2,3] Migrants and Indigenous peoples are not the only populations that are at higher risk of TB infection in Canada. Workers travelling to areas with a high incidence of TB, and those individuals who are immunocompromised (e.g., patients living with HIV, children, infants) or workers (e.g., health care professional) who are in direct contact with immunocompromised people are also at high risk of TB infection.[2] Additionally, homeless persons, prison staff and inmates are considered high-risk populations due to the proximity to others and conditions that enable the transmission of TB bacteria.[2]

Individuals with TB are categorized into latent TB infection (LTBI) and active TB disease.[1,4] LTBI refers to an individual who has the M. tuberculosis infection in which the bacteria are alive but are not currently causing active TB disease .[4] Persons with LTBI do not possess any symptoms and are not considered infectious. However, those with the LTBI can develop active TB disease if they do not receive proper treatment or have a compromised immune system. [4]

Active TB disease (also known as active TB) occurs when the TB bacteria begins to multiply and the individual's immune system is compromised, leading to infection.[4] Symptoms can progress right away or can develop long after infection, depending on the individual. Symptoms can vary between individuals who have TB infection but often experience weight loss, fever, fatigue, chills, excessive coughing and chest pain.[4] In comparison to LTBI, persons with TB disease can spread the TB bacteria to others and are considered infectious.[4]

Early identification of TB is critical to receive timely treatment, reduce poor health outcomes, and to reduce the transmission of TB. Many people with LTBI initially go undetected and are often only diagnosed when they develop symptoms from developing active TB. Screening LTBI may be selectively done in groups of individuals who have a higher-risk of either being exposed to TB (e.g., health care workers, prison staff, people living in areas with high TB incidence) or of developing active TB diseases (e.g., immunosuppressed individuals, patient living with HIV), or in people who have been come into contact with a person with TB (i.e., contact tracing).[5] The identification of LTBI is done through tuberculin skin test (TST) and the interferon-gamma release assay (IGRA); these diagnostic tools cannot differentiate between latent and active TB.[6,7] The TST is performed by injecting a small amount of tuberculin into the lower part of the arm and to see whether the patient has a reaction to the injection, while the IGRA is a blood test that measures the person's immune response to TB proteins.[7] Diagnosing active TB disease is more involved, and can include recognizing the signs and symptoms of TB, chest radiography, sputum samples, and microbiologic testing.[6] Active case finding can also be used to systematically search for cases of active TB disease in populations with a high risk of TB rather than waiting for individuals to present symptoms of the disease.[5]

There are multiple guidelines published about TB, and these guidelines may vary in quality and the topics covered on identifying TB.[8] The purpose of this report is to review and critically appraise the evidence-based guidelines regarding interventions for the identification of TB. This report is part of series of evidence reviews on TB guidelines and can serve as a guidance document to identify which guidelines include recommendations for specific identification methods and specific populations of interest, and the strength of the guidelines. This report does not cover recommendations regarding the identification of multi-drug resistant TB, or diagnostic tests in people with HIV or conditions that compromise the immune system, as these topics are covered in separate reports.[9,10] This report focuses on identification strategies and diagnostic tests for the identification of LTBI and active TB diagnosis.

This report is a component of a larger CADTH Condition Level Review on TB. 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 TB, please visit the project page (https://www.cadth.ca/tuberculosis).

Research Questions

1. What are the evidence-based guidelines regarding the identification of latent tuberculosis infection?

2. What are the evidence-based guidelines regarding the identification of active tuberculosis disease?

Key Findings

Fourteen evidence-based guidelines for the identification of tuberculosis (TB) were identified and included in this report.

Nine guidelines include recommendations regarding screening strategies for TB. Six guidelines include recommendations regarding diagnostic tests to identify latent TB infection. Nine guidelines include recommendations regarding diagnostic tests for active TB disease.

Overall, there are five high-quality and nine low-quality guidelines that include between one and 64 recommendations on the identification of TB. The recommendations vary in strength and the quality of the evidence. The population and setting of interest may determine which guideline(s) and which recommendation(s) are of interest.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, 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 was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was tuberculosis. Search filters were applied to limit retrieval to guidelines. The search was also limited to English language documents published between Jan 1, 2014 and Nov 7, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1 Evidence-based guidelines including information regarding the identification of TB were considered eligible.

Table 1: Selection Criteria

Population	People who have or may have been exposed to pulmonary tuberculosis or people with suspected pulmonary tuberculosis infection
Intervention	Any intervention for the identification of tuberculosis
Comparator	Any other intervention for the identification of tuberculosis
Outcomes	Recommendations regarding the identification of tuberculosis
Study Designs	Evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included guidelines were assessed with the AGREE II instrument.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included guideline were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 446 citations were identified in the literature search. Following screening of titles and abstracts, 377 citations were excluded and 69 potentially relevant reports from the electronic search were retrieved for full-text review. Seven potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 62 publications were excluded for various reasons, and 14 evidence-based guidelines met the inclusion criteria and were included in this report Appendix 1 presents the PRISMA[12] flowchart of the study selection.

Additional publications that did not meet the inclusion criteria for an evidence-based guideline, but may be of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Fourteen evidence-based guidelines were identified and included in this report.[13-26] Detailed characteristics and methods of the guidelines are available in Appendix 2, Table 2 and Table 3.

Study Design

Fourteen relevant evidence-based guidelines were identified.[13-26] Three of these guidelines were developed by PHAC and were published in 2014.[17,21,22] These three guidelines from PHAC represent three chapters from a larger report by PHAC: the 7th edition of the Canadian Tuberculosis Standards.[27] Two guidelines were developed by the WHO; one was published in 2018[20] and the other was published in 2016.[13] One guideline was published in 2019 by the United States National Tuberculosis Controllers Association and the Centers for Disease Control and Prevention (NTCA-CDC).[25] One guideline was prepared by the European Respiratory Society (ERS) and European Centre for Disease (ECDC) and published in 2018.[19] Two guidelines were published in 2017; the Australian National Tuberculosis Advisory Committee (NTAC) position statement[14] and a joint guideline by the American Thoracic Society (ATS), CDC, and Infectious Diseases Society of America (IDSA).[18] Five guidelines were published in 2016; they were developed by the Italian Pediatric TB Study Group,[15] the Singapore Ministry of Health,[24] the National Institute for Health Care Excellence (NICE),[26] the Spanish Society of Infectious Diseases and Clinical Microbiology and the Spanish Society of Respiratory Diseases and Thoracic Surgery (SEIMC/SEPAR),[23] and the United States Preventive Services Task Force Recommendation Statement (USPSTF).[16]

Four guidelines followed standardized methodology for guideline development available online from their institution.[13,16,20,26] The Italian Pediatric guideline for diagnosing TB reported having followed the 'Consensus Conference Method' for the developing the recommendations, but did not provide a reference.[15] The other nine guidelines provided brief details of their guideline development process, but did not cite published methodology. Six guidelines reported their methods for critically appraising the evidence, and provided ratings of the quality of evidence and strength of recommendation.[13,16,18,20,23,26] Five guidelines provided ratings of the quality of evidence and strength of recommendation, but did not provide the methods for evaluating the evidence.[15,17,21,22,24] Three guidelines did not provide ratings of the quality of evidence or the strength of the recommendations.[14,19,25] Decisions about the recommendations were reached through consensus in nine guidelines,[13-15,18-20,23,24,26] and by attaining at least two-thirds of the vote in one guideline.[16] In the other four guidelines, the methods for reaching consensus on the recommendations were unclear or not reported.[17,21,22,25]

Country of Origin

The three PHAC guidelines are meant to apply to Canada.[17,21,22] The two guidelines from the WHO are meant to apply globally.[13,20] Three guidelines are meant to apply to the United States.[16,18,25] Four guidelines are meant to apply to Europe; the ERS/ECDC Standards[19] is for all of Europe, while the others are specific to the United Kingdom,[26] Italy,[15] and Spain.[23] The other two guidelines were developed for Australia[14] and Singapore.[24]

Patient Population

The main target populations covered by the guidelines included populations at high risk of LTBI (e.g., health care workers, people from area with high TB incidence),[14,16-18,20,21,23-26] patients suspected of having active TB disease,[13-15,17-19,22-24,26] and people in close contact with someone with TB.[14,19,20,25,26] Intended users of all fourteen guidelines were health care workers and other key TB stakeholders.[13-26]

Interventions

Nine guidelines included recommendations regarding contact tracing, the screening of specific populations for LTBI, or active case finding in specific populations.[14,16,17,19,20,23-26] Six guidelines included recommendations regarding the use of the TST or the IGRA for identifying LTBI in various populations.[14,18,20,21,24,26] Nine guidelines included recommendations regarding the identification of active TB disease.[13-15,18,19,22-24,26]

Outcomes

The number recommendations regarding identifying TB ranged from 1 to 64 recommendations across the different guidelines. Eight of the guidelines contain fewer than 10 recommendations.[13,14,16,19-21,23,25] The ATS/IDSA/CDC Guideline[18] has 15 recommendations; the Italian Pediatric guideline for diagnosis[15] and the Singapore Guideline[24] each have 30 recommendations; the NICE Guideline[26] has 64 recommendations; and the PHAC guideline for active TB[22] has 11 recommendations, and the PHAC guideline on screening high-risk populations[17] has 14 recommendations.

Five of the guidelines reported which outcomes were considered in the systematic reviews that were used for developing the recommendations.[13,16,20,26] The other nine guidelines[13-15,17-19,21,22,24,25] did not specify which outcomes were considered when developing the recommendations.

Summary of Critical Appraisal

This report includes five high-quality guidelines,[13,16,20,23,26] and nine low-quality guidelines.[14,15,17-19,21,22,24,25] Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 4 and Table 5.

Five guidelines were high-quality; these were the two WHO guidelines,[13,20] the NICE Guideline,[26] the SEIMC/SEPAR Guideline,[23] and the USPSTF Recommendation.[16] These high-quality guidelines have clear descriptions of the scope of the guideline, the health questions, the populations covered, and the target users of the guideline, and have clear, unambiguous recommendations.[13,16,20,23,26] These guidelines used high-quality, systematic methods for developing the recommendations: systematic reviews were conducted with transparent search methodology and eligibility criteria, the quality of the evidence was evaluated and well described; and the process for developing the recommendations was clear. The guideline development group for the NICE Guideline[26] included members from all relevant disciplines, as well as four patient or caregiver members. For the two WHO guidelines,[13,20] and the SEIMC/SEPAR Guideline[23] the guideline development group involved numerous experts from different professional groups, however, the specific roles or expertise of each member was not described. For the USPSTF Recommendation,[16] a list of the members of the guideline development group and authors of the systematic review were provided, but the areas of expertise were not reported, thus it is unclear whether all areas of expertise were included. The potential conflicts of interest of the guideline development group members were recorded in all five high-quality guidelines, with no conflicts of interest declared in four guidelines,[13,20,23,26] however, in the conflict of interest declaration for the USPSTF Recommendation[16] was not available, thus it is unclear whether any potential conflicts were addressed appropriately. No conflict of interest from the funding body was declared by the SEIMC/SEPAR Guideline[23] and the USPSTF Recommendation[16], while the other three high-quality guidelines reported the funder, but it was unclear whether the funding agency influenced the recommendations.[13,20,26]

Nine guidelines were assessed to be low-quality due to poor reporting of methods, creating uncertainty in the recommendations.[14,15,17-19,21,22,24,25]

The ATS/IDSA/CDC Guideline[18] is limited by the strategy used to search for evidence; the authors reported using a pragmatic evidence synthesis, but their methods did not qualify as a systematic review. This guideline used GRADE methodology to assess the quality of the evidence and the strength of the recommendations, however, there was no report of the quality of the primary studies, and no evidence tables, thus it was unclear how the evidence was evaluated and synthesized. Other methodological details that were not reported included: whether the views of the patients were sought; what the eligibility criteria were for the evidence selection; whether the guideline was externally peer reviewed; and whether there is a procedure for updating the guideline. This guideline provided adequate descriptions of the objectives, health questions, population, and target users of the guideline, as well as detailed and specific recommendations that are easy to identify. In addition, the funding body was not reported, thus it is unknown if there is a conflict of interest with the funder. It was also reported that members were eligible for the guideline committee if they were free of disqualifying conflicts of interest, but some of the authors reported conflicts of interests (e.g., fees from manufacturers) that the editor of the guideline considered relevant to the guideline. Thus, it is not clear whether any potential conflicts of interest from the authors influenced the recommendations.

The Singapore Guideline[24] had clear descriptions of the scope and target users of the guideline, and clear, easily identifiable recommendations, however, it did not provide sufficient methodological details and the roles and areas of expertise of the members of the guideline development group were not clear. It was unclear whether a systematic approach was used to search for and evaluate the evidence, and there was a lack of detail regarding the process for formulating the recommendations. The Singapore guideline reported the level of evidence and the grade of the recommendation for each recommendation but did not provide the methods for grading the evidence. In addition, this guideline did not report the risk of bias of the individual studies or include evidence-to-decision tables, thus the specific link between strengths and limitations of the evidence and the recommendations was unclear. It was not reported whether this guideline was externally reviewed by experts, thus the level of certainty in the recommendations is unclear. The funding body was not reported, and the authors did not disclose whether they had any conflicts, thus it is unclear whether there were any conflicts of interest from the funder or the authors.[24]

The Italian Pediatric guideline for diagnosis[15] had clear descriptions of the scope and health questions covered by the guideline, however, the guideline lacks details of the development of the recommendations, leading to uncertainty in the recommendations. The guideline development group included numerous experts from relevant disciplines, but the area of expertise and the role of each member was unclear, and it was not reported whether the views of the target population were considered. The guideline reports that a systematic review was conducted, however, no details were provided for selecting the evidence, nor did they report the quality of the primary studies. This guideline provided a narrative summary of the evidence for each health question, but did not clearly outline the benefits and harms, and it is unclear how the recommendations were formulated from the evidence. Additionally, the guideline did not report whether it was externally reviewed or a procedure for updating the guideline. The authors and panel members declared no conflicts of interest, however, it was not reported whether the funding agency had any influence on the guideline.

The three PHAC guidelines[17,21,22] have clear and specific recommendations that are easily identified in the guidelines, however, limited detail on the process for developing the recommendations was provided, creating a lack of certainty in the recommendations. The overall scope of these guidelines was not explicitly stated, but could be inferred from the title of the documents. None of the PHAC guidelines reported the health questions covered in the guideline, thus it is unclear what questions guided the development of the recommendations. The populations to whom the PHAC guidelines apply were well described. The PHAC guidelines listed a small (i.e., five or fewer) number of authors and their institutions (3 authors for identification in high-risk populations; 4 authors for LTBI, and 5 authors for active TB), but their specific roles were unclear. It was not reported whether a larger guideline development group was involved in the process, thus is unknown if individuals from all relevant professional groups were involved or whether the views of the target population were sought. The PHAC guidelines did not report any methods regarding the search for evidence, thus the quality of the search strategy and eligibility criteria for selecting the evidence is unknown. The PHAC guidelines report the strength of the recommendation and the quality of evidence for each recommendation, and the scores are explained in the preface document,[28] however, there is no explanation as to how these criteria were applied. It is unknown how the quality of the primary studies was evaluated, and no evidence tables were provided, thus the strengths and limitations of the evidence are unclear, and no methods for formulating the recommendations were reported. A list of external reviewers was reported for the whole set of PHAC TB Standards, but it was

unclear who reviewed these specific sets of recommendations, or what the process was for the external review. The funding body was disclosed for the PHAC guidelines, but there is no explicit statement that the views of the funding body have not influenced the guideline, and the authors did not disclose whether they had any conflicts, thus it is unclear whether there were any conflicts of interest from the funder or the authors.

Of the nine guidelines assessed to be low-quality, three guidelines did not evaluate the strength of the recommendations or the quality of the evidence; these were the NTCA-CDC Recommendations,[25] the ERS/ECDC Standards[19] and the NTAC Position Statement.[14]

Overall, the low-quality NTCA-CDC Recommendations[25] lacked methodological detail and clarity. The objectives of this guideline are not clearly described, and it was not clear which health questions were addressed or who the target users are for the guideline. The guideline development group was missing relevant professional groups (e.g., a methodologist), and the area of expertise it was not clear for each member. In addition, there was no involvement of the target population (in this case health care workers), which could have provided valuable insight in developing the recommendations. A systematic review of the evidence was conducted with a good search and eligibility criteria, however, the authors did not report whether the risk of bias or the quality of the evidence was assessed. The guideline briefly describes how the recommendations were formulated, but there is no explicit link between the evidence and the recommendations, and the recommendations are not graded. The funding body was not disclosed, and it is unclear whether there was an influence by the funder on the recommendations. Some authors declared potential conflicts of interest, but it was not reported how these were handled or if they influenced the recommendations.

The scope of the ERS/ECDC Standards[19] is clear, but the limited detail on the development process for the standards, contributes to a lack of certainty in the standards. The health questions covered by the guideline were not reported, thus it is unclear what guided the development of the recommendations. This guideline listed various authors that were involved and their roles in the development of the recommendations. In addition, the guideline states that a task force was created but it was not clear who was part of this task force and their role, only the organizations that were involved. This guideline reported that a non-systematic search was conducted through various databases, but no other methods were provided regarding the search for evidence. The quality of evidence was not reported, and it was not stated whether individual studies were assessed or evaluated, and no evidence tables were provided. Summaries of the evidence were included but there was no indication that the benefits and adverse effects were considered in developing the recommendations, however, the guideline reports that the standards were based on evidence. This guideline did not report the strength and the quality of evidence for each standard, thus limiting the certainty in the recommendations. The funding body was disclosed, but there is no explicit statement that the views of the funding body have not influenced the guideline, and all authors except for one author disclosed they did not have any conflicts of interest.

The NTAC Position Statement[14] provides limited detail on the methodology, and it is unclear whether a systematic approach to searching for and synthesizing the evidence was used. It was not reported how the evidence was used to formulate the recommendations, or whether the benefits and risks were considered when the recommendations were formulated. In addition, the quality of the evidence is not reported, and the guideline specifically stated that the recommendations were not graded. The guideline also lacked

detail on the scope, health questions, and populations covered by the guideline. A list of the committee members was reported, but no other details were provided (e.g., institution, area of expertise), thus is it unknown whether the guideline development group included the relevant professional groups. The funding body was not reported, and it was not reported whether the guideline was externally reviewed, thus adding uncertainty to the guideline. In a previous version of the guideline, some committee members declared the receipt of funding from manufacturers, but it was not addressed how these conflicts were handled.

Summary of Findings

Guidelines

Fourteen evidence-based guidelines were identified that made recommendations regarding the identification of TB.[13-26] Nine guidelines made recommendations regarding screening targeted populations for LTBI, active case finding (i.e., systematically identifying active or latent TB), or contact tracing (i.e., identifying those who may have come into contact with a person with TB).[14,16,17,19,20,23-26] Six guidelines made recommendations regarding which test (e.g., TST or IGRA) to use for identifying LTBI in various populations.[14,18,20,21,24,26] Nine guidelines made recommendations regarding which tests to use for the identification of active TB disease.[13-15,18,19,22-24,26] A summary of the topics covered by the recommendations within the guidelines are presented in Appendix 4, in Table 6 (screening, contact tracing, active case finding), Table 7 (tests for identifying LTBI), and Table 8 (tests for identifying active TB disease). Given the vast number of recommendations across multiple different populations, identification strategies, and identification tests, the specific recommendations from each guideline are not included in this report. The recommendations from each guideline can be viewed by obtaining a copy of the guideline (the hyperlinks to the guidelines are provided in the references section).

Recommendations regarding Contact Tracing, Screening, and Active Case Finding

The high-quality WHO consolidated LTBI guideline[20] covered TB testing in household contacts of those with active TB disease and targeted screening for LTBI in high-risk populations (e.g., immigrants from areas with high TB incidence). This guideline included both conditional and strong recommendations, with evidence varying from very low to high quality, depending on the topic.[20]

The high-quality NICE Guideline[26] included recommendations regarding contact tracing (in general, in children, and in household contacts), screening for LTBI in populations with higher risk of TB (e.g., prisons, injection drug users), screening of health care workers, and active case finding in specific populations (e.g., people who are homeless). For this guideline, the certainty of the recommendation is reflected in the wording of the recommendation, and the strength of the evidence varied across the different recommendations, varying from weak to strong evidence.

The high-quality SEIMC/SEPAR Guideline[23] made weak recommendations based on very low- to moderate-quality evidence regarding contact tracing in children, which tests to use for contact tracing, and screening for LTBI in people with medical conditions that increase the risk of TB, as well as LTBI screening in health care workers.[26]

The high-quality USPSTF Guideline[16] includes one recommendation with moderate certainty regarding screening for LTBI in high-risk populations.

The low-quality Singapore Guideline[24] covered which test to use for contact tracing and screening various high-risk populations for LTBI. The evidence used in developing these recommendations ranges from expert opinion to high quality evidence, and the strength of the recommendations range from weak to strong, and the guideline also includes some good practice points, where there is a lack of evidence.[24]

The low-quality PHAC guideline on screening high-risk populations[17] includes mostly conditional recommendations, with three strong recommendations, based on weak to strong quality evidence. This guideline makes recommendations regarding screening for LTBI in high-risk populations (e.g., homeless people, people misusing drugs and alcohol) and screening for LTBI in travelers.[17]

The low-quality NTCA-CDC Guideline[25] made recommendations regarding LTBI screening in US health care personnel, including baseline screening, post-exposure screening, and serial screening, however, the strength of the recommendation and the quality of the evidence were not reported.

The low-quality ERS/ECDC Standards[19] covered contact tracing in general and for household contacts, however, the strength of recommendations and quality of evidence was not reported.

The low-quality NTAC Position Statement[14] included recommendations regarding which test to use for contact tracing, screening of LTBI in immigrants from high TB incidence areas and those with medical conditions that increase the risk of TB, as well as serial screening of health care workers, however, the strength of the recommendation and the quality of the evidence were not reported.

Recommendations regarding Identifying LTBI

The high-quality WHO consolidated LTBI guideline[20] includes a strong recommendation based on very low-quality evidence regarding the use of the TST or IGRA for testing for LTBI in the general population.

The high-quality NICE Guideline[26] also includes recommendations regarding the use of the TST or IGRA for testing for LTBI in the general population and children. In this guideline the strength of the evidence varies from weak to strong evidence, depending on the topic, and the certainty of the recommendation is reflected in the wording of the recommendation.[26]

The low-quality ATS/IDSA/CDC Guideline[18] made conditional and strong recommendations, based on very low-quality to moderate quality evidence, regarding the use of the TST or IGRA for identifying LTBI, as well as situations where IGRA is preferred over the TST.

The low-quality Singapore Guideline[24] covered the use of the TST or IGRA in the general population, in people who have received the BCG vaccine, and in children. The recommendations in this guideline range from weak to strong, as well as good practice points, and are based on evidence ranging from expert opinion to high quality evidence.

The low-quality PHAC guidelines on the diagnosis of LTBI[21] made conditional and strong recommendations, based on evidence of moderate to strong quality, regarding the use of the TST or IGRA in the general population, as well as situations where one test is preferred

over the other, situations where neither test is appropriate, and situations when both tests should be use.

The low-quality NTAC Position Statement[14] covered the use of the TST or IGRA in the general population, however, the strength of the recommendation and the quality of the evidence were not reported.

Recommendations regarding Identifying Active TB

The high-quality NICE Guideline[26] includes recommendations based on weak to strong evidence regarding the use of multidisciplinary TB teams, recognizing the signs and symptoms of TB, and the use of various diagnostic tools including chest radiography, sputum specimens, gastric aspirate samples, mycobacterial cultures, nucleic acid amplification tests (NAATs), in the general population and in children.

The high-quality SEIMC/SEPAR Guideline[23] made a strong recommendation based on low quality evidence regarding the use of IGRAs for diagnosing active TB in adults, and a weak recommendation based on very low quality evidence regarding the use of IGRAs for the diagnosis of active TB in children younger than 5 years.

The high-quality WHO policy guidance on TB-LAMP[13] made conditional recommendations, based on very low-quality evidence, regarding the use of TB-LAMP for diagnosing pulmonary TB.

The low-quality ATS/IDSA/CDC Guideline[18] included recommendations about sputum sampling methods, acid-fast bacilli smear microscopy, mycobacterial cultures (in adults and children), genotyping culture isolates, and drug sensitivity testing. This guideline includes conditional and strong recommendations, based on very low-quality to moderate quality evidence.

The low-quality Italian pediatric guideline for the diagnosis of active TB[15] included recommendations covering the various diagnostic tools for identifying active TB disease specifically in children, including the use of the TST or IGRA, signs and symptoms of TB, chest radiography, CT scans, sputum samples, smear microscopy, mycobacterial cultures, genotyping, and NAATs. The recommendations in this guidelines had strong, moderate, and marginal support, based on evidence from very low- and low-quality studies.[15]

The low-quality Singapore Guideline[24] includes weak to strong recommendations, and some good practice points, based on evidence ranging from expert opinion to high quality evidence, regarding the various diagnostic tools for identifying active TB in adults and children.

The low-quality PHAC guideline on the diagnosis active TB[22] made conditional and strong recommendations, based on moderate to strong evidence, regarding recognizing when to test for active TB, whether the TST or IGRA should be used to diagnose active TB, and the diagnostic tools to diagnose active TB (e.g., chest radiography, sputum samples, smear microscopy, NAATs, drug sensitivity testing.

The low-quality ERS/ECDC Standards[19] provided recommendations regarding the use of various diagnostic tools for active TB in adults and children, but did not report the strength of the recommendations or the quality of the evidence.

The low-quality NTAC Position Statement[14] covered whether the TST or IGRA should be used for diagnosing active TB disease on adults and children, however, the strength of the recommendation and the quality of the evidence were not reported.

Limitations

There are limitations associated with the evidence in this report on guidelines for the identification of TB.

This report includes nine low-quality guidelines,[14,15,17-19,21,22,24,25] including three guidelines[14,19,25] that did not grade the strength of recommendations or quality of evidence. While most topics covered by the recommendations were discussed in more than one guideline, and usually included a high-quality guideline and a low-quality guideline, not all topics were covered by high-quality guidelines. Some of the topics (e.g., diagnostics tests for active TB in children, screening for LTBI in travelers, certain active TB tests for adults) were only covered in one or more low-quality guideline(s), and thus may have reduced reliability. Additionally, three topics were covered only in guidelines that did not grade the strength of the recommendations or the quality of evidence, and are associated with a high amount of uncertainty; these topics are serial screening and post-exposure screening of health care workers, and drug-sensitivity testing for active TB children.

The three PHAC guidelines[17,21,22] were developed for the Canadian context. These PHAC guidelines were assessed to be low-quality due to poor reporting of the methodology, however, for two of the PHAC guidelines (diagnosis of active TB, and diagnosis of LTBI) the recommendations were based on moderate to strong evidence (no low quality evidence)[21,22], thus increasing the certainty of the recommendations. The PHAC guideline on surveillance and selected high-risk populations, does not include recommendations for specific populations or settings that may be of interest to Canadian health care providers, such as Indigenous peoples, or screening in rural or remote health care settings. It was reported by this PHAC guideline[17] that information specific to targeted LTBI screening in Indigenous peoples is provided in Chapter 14 of the Tuberculosis Standards (Tuberculosis Prevention and Care in First Nations, Inuit and Métis Peoples[29]), however, no specific recommendations were identified.

With regards to the generalizability of the other guidelines, two high-quality guidelines are intended for global use,[13,20] three guidelines were developed for the United States,[16,18,25] four guidelines are meant to apply to Europe[15,19,23,26] and the other two guidelines were developed in Australia Australia[14] and Singapore.[24] It is unknown if the guidelines developed outside of Canada are generalizable to the Canadian context, as there may be differences in the populations that require for screening for latent and active TB in Canada, as well as geographic differences in the availability of diagnostic tools.

This report was also limited by the large volume of recommendations covering the identification of TB published in the guidelines (i.e., between one and 64 recommendations per guideline), as it was not possible to compare and contrast the recommendations made across the various guidelines. Thus, it is unclear whether any of the recommendations contradict each other or whether there is agreement in the evidence across guidelines.

Conclusions and Implications for Decision or Policy Making

The report was comprised of fourteen guidelines regarding the identification of latent and active TB.[13-26]

Nine guidelines covered selective screening for LTBI, active case finding, or contact tracing.[14,16,17,19,20,23-26] Four guidelines[16,20,23,26] that used high-quality, systematic methods for searching for evidence and formulating the recommendations, made regarding contact tracing in different situations, LTBI screening in high-risk populations, and active case-finding. The recommendations from these high-quality guidelines varied in strength (weak to strong recommendations) and were developed from evidence ranging from very low- to high-quality. For the Canadian context, the PHAC guideline on screening TB in selected populations,[17] made conditional and strong recommendations regarding screening certain high risk populations, such as travelers, migrants, and people who are homeless. However, this guideline did not publish the methods for searching for evidence or formulating the recommendations, limiting the overall quality of the guideline. A low-quality guideline from Singapore[24] that did not provide sufficient methodological detail on the process of developing the recommendations also made recommendations on contact tracing and screening various high-risk populations for LTBI. Three other low-quality guidelines with unclear methodology[14,19,25] also covered contact tracing,[14,19] screening in high-risk populations,[14] and screening in US health care workers,[25] however, these guidelines did not report the strength of the recommendations or the quality of the evidence, limited the certainty of the recommendations.

Six guidelines made recommendations regarding the appropriate test for identifying LTBI in various populations.[14,18,20,21,24,26] Two high-quality guidelines with strong methodology make recommendations regarding the use of the TST and IGRA for identifying LTBI in the general population[20,26] and children,[26] based on very low- to high-quality evidence. The Canadian PHAC guideline for identifying LTBI[21] made recommendations regarding the use of the TST or IGRA including situations where one test is preferred, where neither test is appropriate, and when both tests should be used. This includes conditional and strong recommendations, however, this guideline did not publish their methodology, limiting the certainty of the recommendations. The low-quality guideline from Singapore[24] also made recommendations regarding the use of the TST and IGRA to identify TB in the adults, children, and those who have received the BCG vaccine, however, this guideline did not provide sufficient methodological detail on the process of developing the recommendations. The low-quality ATS/IDSA/CDC Guideline[18] made conditional and strong recommendations regarding the use of the TST or IGRA, as well as situations where IGRA is preferred, but this guideline did not use a systematic approach to developing the recommendations. The low-quality NTAC Position Statement[14] also covered the use of TST and IGRA, although the methods used to formulate the recommendations were unclear, the strength of the recommendations and the quality of the evidence were not reported, thus it is not clear whether the recommendation should be trusted.

Nine guidelines made recommendations covering various tests for the identification of active TB disease.[13-15,18,19,22-24,26]

The high-quality NICE Guideline,[26] which followed a systematic approach to developing the recommendations, includes regarding the use of multidisciplinary TB teams, recognizing the signs and symptoms of TB, and the use of various diagnostic tools in the general population and in children (e.g., chest radiography, sputum and gastric aspirate samples, NAATs). The high-quality SEIMC/SEPAR Guideline[23] covered whether IGRAs should be used for diagnosing active TB in adults and children younger than 5 years. The other high-quality WHO guideline[13] made recommendations specific to the use of TB-LAMP for diagnosing active TB. The PHAC guideline on the diagnosis active TB[22] covered multiple different diagnostic tests for the identification of active TB in adults, however, this guideline lacked

methodological detail and was assessed to be low-quality. Two other low-quality guidelines (ATS/IDSA/CDC Guideline[18] and Singapore Guideline[24]) that did not provide sufficient methodological detail also made recommendations regarding various diagnostic tests for active TB in the general population. Recommendations regarding diagnostic tests for active TB in children were covered in the low-quality Italian pediatric guideline for the diagnosis of active TB[15] and the low-quality ATS/IDSA/CDC Guideline.[18] Additionally, two guidelines with poor reporting of their methodology and that did not report the strength of the recommendations or the quality of the evidence also provided recommendations on active TB diagnostic tests for adults and children[19] and the use of the TST or IGRA for diagnosing active TB.[14]

Overall, this report identified five high-quality guidelines,[13,16,20,23,26] that included recommendations for selective TB identification strategies, testing for LTBI, and diagnosis active TB disease. This report also identified nine low-quality guidelines[14,15,17-19,21,22,24,25] that may provide additional guidance on identifying latent and active TB, however, there is uncertainty associated with these low-quality guidelines and the recommendations should be interpreted with caution.

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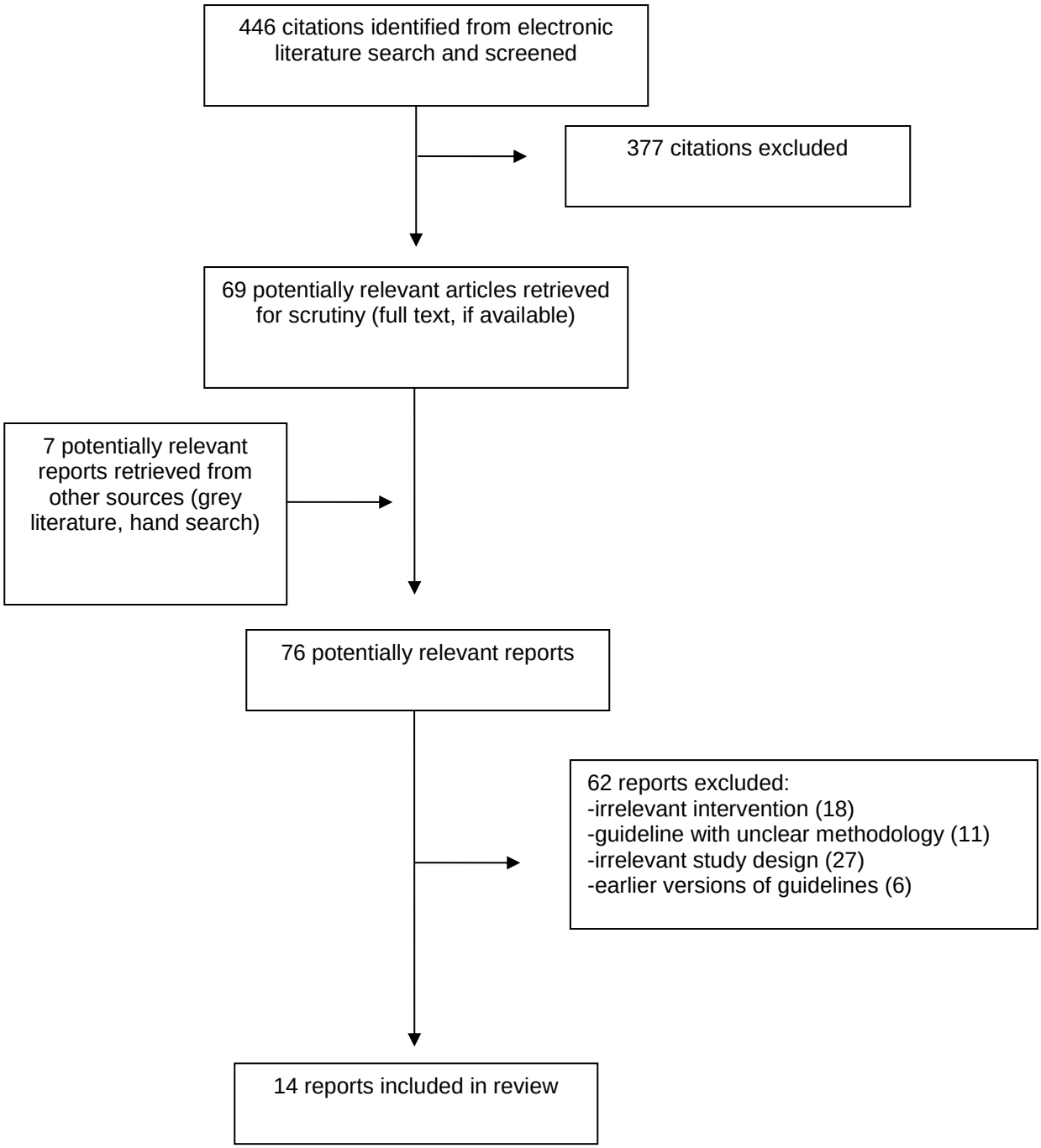
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Guidelines

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
					Identification of LTBI	**Identification of Active TB**
Tuberculosis, Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC NTCA-CDC[25] 2019	**Country:** United States **Funding:** Not specified **Developing Institution:** NTAC, CDC	Guidelines for preventing TB transmission in health care settings including baseline and annual TB screening of all U.S. health care personnel	**Primary users:** U.S health care personnel, academia, public health departments, health associations	**Technologies**: Identification of LTBI - baseline screening - TST - IGRA - postexposure screening - risk assessment Treatment of LTBI - Evaluation and treatment of positive test results **Total # of recommendations:** 4	**Main population**: U.S health care personnel without prior LTBI/TB or tested positive for TB or have and symptoms of TB **Subgroups:** - temporary or permanent residence - Current or planned immunosuppression (e.g., HIV/AIDS, organ transplant) - Those in close contact with someone who has had TB (3)	Not applicable
Latent tuberculosis infection Updated and consolidated guidelines for programmatic management WHO LTBI[20] 2018	**Country:** Global **Funding**: The US CDC, US Agency for International Development, and the Ministry of Health of the Republic of Korea **Developing Institution:** World	Six previous WHO guidelines were consolidated and updated to provide the most recent and most comprehensive set of WHO recommendations for the management of LTBI.	**Primary users**: National TB and HIV control programs, ministries of health, and policy-makers working on TB and HIV. **Other users**: Health officials in other areas including prison services, social	**Technologies**: Identification populations for testing and treatment of TB -TST - symptom screening - preventive treatment Identification of LTBI -TST -IGRA	**Main population:** General population (1) **Subgroups**: Household contacts of patient with TB (3) High-risk groups (immunocompromised, incarcerated,	Not applicable

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
					Identification of LTBI	**Identification of Active TB**
	Health Organization	This guideline can be adapted to the national and local level based on epidemiology of TB, and the availability of resources.	services, immigration, and clinicians and public health practitioners working on TB or HIV.	**Total # of recommendations:** 7	health care workers, immigrants from high TB countries, homeless, those who use illicit drugs, people with diabetes, smokers) (3)	
ERS/ECDC Statement: European Union standards for tuberculosis care, 2017 update ERS/ECDC Standards[19] 2018	**Country:** Europe **Funding:** European Respiratory Society (ERS) **Developing institution:** ERS and European Centre for Disease Prevention and Control (ECDC)	Incorporate the new scientific evidence that has become available since the publication of the European Union Standards for Tuberculosis Care in 2012.	Clinicians; health care professionals	Technologies: -Recognizing signs and symptoms -Sputum specimen -microscopic examinations - culture-based techniques, species identification) -Chest radiography -Bronchoscopy -TST -IGRA -contact tracing **Total # recommendations:** 9	**Main populations:** Contacts of people with TB (3)	**Main populations:** Patients with symptoms, signs, risk factors or history of TB (4) **Subgroups**: Individuals with HIV or immune compromising decisions; children with intrathoracic TB (2)
Position statement on interferon-gamma release assays for the detection of latent tuberculosis infection NTAC[14] 2017	**Country:** Australia **Funding:** Not specified **Developing Institution:** The National Tuberculosis Advisory	The use of TST and IGRA for the investigation of LTBI	TB community, Communicable Diseases Network Australia, Department of Health (Australian Government)	**Technologies**: Identification of LTBI - TST - IGRA - history - chest x-ray Identification of active TB - TST - IGRA	**Main population:** General population (adults and children) (2) **Subgroups**: Immigrants from high-incidence setting (1)	**Main population:** General population (adults and children) (4)

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
					Identification of LTBI	**Identification of Active TB**
	Committee (NTAC)			- Chest x-ray - sputum examination Contact tracing - TST - IGRA **Total # of recommendations:** 8	Healthcare workers (1)	
Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children ATS/IDSA/CDC [18] 2017	**Country:** United States **Funding:** Not specified **Developing Institution:** Task force supported by the American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America	Clinical practice guidelines on the diagnosis and classification of tuberculosis in adults and children.	**Primary users**: Clinicians in high-resource countries with a low incidence of TB disease and LTBI (e.g., the United States) **Other users**: Countries with medium- or high-incidences of TB (although the guideline suggests that the recommendations may be less applicable)	**Technologies**: Testing for LTBI: - TST -IGRA Testing for active TB: - acid-fast bacilli smear microscopy -liquid and solid mycobacterial cultures - nucleic acid amplification test - rapid molecular drug susceptibility testing for rifampin with or without isoniazid - mycobacterial culture of respiratory specimens - sputum induction - flexible bronchoscopic sampling - post-bronchoscopy sputum specimens - culture isolate	**Main population:** - General population (adults and children) (5) **Subgroups**: - Patients with high risk of progression to active TB (1)	**Main population:** General population (adults and children) (8) **Subgroups**: Patients with high risk of active TB (1)

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
					Identification of LTBI	**Identification of Active TB**
				Total # of recommendations: 15		
Recommendations for the diagnosis of pediatric tuberculosis Italian Pediatric TB diagnosis [15] 2016	**Country:** Italy **Funding:** Italian Ministry of Health **Developing Institution:** Italian Pediatric TB Study Group	"…Recommendations of a group of scientific societies concerning the signs and symptoms suggesting pediatric TB, and the diagnostic approach towards children with suspected disease" (pg. 2)	**Primary users**: Clinicians and health care professionals and policy-makers	**Technologies**: Identification of active TB - signs and symptoms - TST - chest radiograph - immunological testing - radiology - microbiological testing **Total # of recommendations:** 30	Not applicable	**Main population:** Children, general population (27) **Subgroups**: Children with T lymphocyte immunodepression (3)
Prevention, Diagnosis and Management of Tuberculosis MOH Singapore[24] 2016	**Country:** Singapore **Funding:** Not specified **Developing Institution:** Ministry of Health, Singapore	Diagnosis and treatment of active and latent TB, and public health actions required by physicians treating patients with TB	**Primary users**: All healthcare practitioners in Singapore **Other users**: Public health service providers who treat patients with TB.	**Technologies**: Identification of LTBI - TST - IGRA - chest x-ray Identification of active TB - chest x-ray - sputum samples - microscopy and mycobacterial cultures - acid-fast bacilli smear and culture - nucleic acid amplification tests - adenosine deaminase **Total # of recommendations:** 30	**Main populations:** General population (5) Children (7) **Subgroups**: Immigrants (2) Exposed to patient with active TB (1)	**Main population:** General population (12) **Subgroups**: Pregnant women (1) Immigrants (2)

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
					Identification of LTBI	**Identification of Active TB**
Tuberculosis NICE[26] 2016	**Country:** United Kingdom **Funding:** Not specified **Developing Institution:** National Institute for Health and Care Excellence	Preventing, identifying and managing latent and active TB in children and adults	Healthcare professionals and TB multidisciplinary teams Substance misuse services, prisons and immigration removal centers Local government and commissioners TB control boards, directors of public health and public health consultants Public Health England and NHS England Voluntary sector workers People with TB and their carers	**Technologies**: Identification of LTBI - TST - risk assessment - IGRA - contact tracing - case finding Identifying active TB - TB culture samples - clinical signs and symptoms - chest x-ray - respiratory samples - nucleic acid amplification tests - care pathways **Total # of recommendations:** 64	**Subgroups**: Adults (general) (1) Immunocompromised adults (3) Healthcare workers (4) Children (general) (5) Immunocompromised children (1) Immigrants from high-incidence countries (4) Contact tracing (9) High-risk (under-served) groups (9) People using homeless or substance misuse services (6) People in prisons (5)	**Main population:** General population (all ages) (12) **Subgroups**: Adults, high risk (1) Children (4)
Guidelines for the use of interferon-γ release assays in the diagnosis of tuberculosis infection	**Country:** Spain **Funding:** Spanish Society of Respiratory Diseases and Thoracic Surgery	Recommendation on the use of IGRAs for diagnosing TB infection and to minimize the uncertainty and	**Primary users**: Clinicians and health care professionals and policy-makers	**Technologies**: Identification of LTBI -TST -IGRA Identification of active TB -TST	**Main population:** General population (adults and children) (3)	**Main population:** General population (2)

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
					Identification of LTBI	**Identification of Active TB**
SEIMC/SEPAR Guideline [23] 2016	and the Spanish Society of Infectious Diseases and Clinical Micro-biology **Developing Institution:** Spanish Society of Respiratory Diseases and Thoracic Surgery and the Spanish Society of Infectious Diseases and Clinical Micro-biology	variability in the diagnosis of TB infection by the IGRAs.		-IGRA **Total # of recommendations:** 9	**Sub-group(s):** Health care workers (1) People with HIV (1) People with chronic inflammatory diseases (1) Patients requiring transplant (1)	
Screening for Latent Tuberculosis Infection in Adults US Preventive Services Task Force Recommendation Statement USPSTF[16] 2016	**Country:** United States **Funding:** Agency for Healthcare Research and Quality **Developing Institution:** Not specified	Screening and treatment for LTBI among adults in primary care settings	**Primary users**: Clinicians and health care decision makers (e.g., patients, health system leaders, policymakers)	**Technologies**: Identification of LTBI - TST - IGRA - chest x-ray **Total # of recommendations: 1**	**Main population:** asymptomatic adults 18 years and older at increased risk for TB (e.g., people born in, or former residents of areas with high TB incidence; people who live in or have lived in high-risk congregate settings such as homeless shelters) (1)	Not applicable
The use of loop-mediated isothermal amplification (TB-LAMP)	**Country**: Global **Funding**: The United States	Recommendations on using TB-LAMP to diagnose pulmonary TB in	**Primary users:** Clinicians treating patients with TB	**Technologies**: Identification of active TB - TB-LAMP	Not applicable	**Main population:** Adults with signs and symptoms of TB (2)

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
					Identification of LTBI	**Identification of Active TB**
for the diagnosis of pulmonary tuberculosis WHO TB-LAMP[13] 2016	Agency for International Development **Developing Institution:** World Health Organization	adults with signs and symptoms of TB	**Other users:** Those working in TB programs (e.g., managers, laboratory technicians, advisers), relevant government departments working on TB.	**Total # of recommendations:** 2		
Canadian Tuberculosis Standards Chapter 4: Diagnosis of Latent Tuberculosis Infection PHAC Identification LTBI[21] 2014	**Country:** Canada **Funding:** Jointly funded by the Canadian Thoracic Society of the Canadian Lung Association, and the Public Health Agency of Canada **Developing institution:** Jointly produced by the Canadian Thoracic Society of the Canadian Lung Association, and the Public Health Agency of Canada	Testing for LTBI	Public health and clinical professionals	Technologies: - TST -IGRA **Total # of recommendations:** 8	**Subgroups**: - people at low risk of TB (1) -people at high risk or infection or progression to active TB (1) - people suspected of having active TB disease (1) - immigrants (1) - infancy (1) - people unlikely to return for TST reading (1) - people needing repeat or serial testing (1) - children (1)	
Canadian Tuberculosis Standards	**Country:** Canada **Funding:** Jointly funded by the	Diagnosis of active TB	Public health and clinical professionals	Technologies: - recognizing signs and symptoms of TB	Not applicable	**Main population:** - people suspected of having TB (11)

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
					Identification of LTBI	**Identification of Active TB**
Chapter 3: Diagnosis of Active Tuberculosis and Drug Resistance PHAC Identification Active TB[22] 2014	Canadian Thoracic Society of the Canadian Lung Association, and the Public Health Agency of Canada **Developing institution:** Jointly produced by the Canadian Thoracic Society of the Canadian Lung Association, and the Public Health Agency of Canada			- microbiological diagnosis - chest radiography - sputum samples - smear microscopy - nucleic acid amplification tests - serology, TST, IGRA - phenotypic drug susceptibility testing (for drug resistant-TB) **Total # of recommendations:** 11		
Canadian Tuberculosis Standards Chapter 13: Tuberculosis Surveillance and Screening in Selected High-Risk Populations PHAC Identification High-Risk[17] 2014	**Country:** Canada **Funding:** Jointly funded by the Canadian Thoracic Society of the Canadian Lung Association, and the Public Health Agency of Canada **Developing institution:** Jointly produced by the Canadian Thoracic Society	Targeted TB surveillance and screening of specific population subgroups at higher risk of TB: immigrants and refugees; people with non-HIV immune suppression and other medical, social and behavior risk factors for TB; and long-term visitors to countries	Public health and clinical professionals	Technologies: - LTBI screening **Total # of recommendations:** 14	**Main population:** - specific populations wither higher incidence of TB (2) **Subgroups**: - foreign-born (7) - homeless people (2) - injection drug users (2)	**Main population:** - specific populations wither higher incidence of TB (1)

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
					Identification of LTBI	Identification of Active TB
	of the Canadian Lung Association, and the Public Health Agency of Canada	with higher incidence of TB.				

ATS = American Thoracic Society; CDC = Centers for Disease Control and Prevention; ECDC= European Centre for Disease Prevention and Control; ERS = European Respiratory Society; ESTC = the European Union Standards for Tuberculosis Care; HIV = human immunodeficiency virus; IDSA = Infectious Diseases Society of America; IGRA = interferon-gamma release assay; LTBI = latent tuberculosis; MOH = Ministry of Health; NICE = National Institute for Health and Care Excellence; NTAC = National Tuberculosis Advisory Committee; NTCA = National Tuberculosis Controllers Association; PHAC = Public Health Agency of Canada ;TB = tuberculosis; TB-LAMP = Tuberculosis- Loop-Mediated Isothermal Amplification; TST= Tuberculin skin test; UK = United Kingdom; US = United States; USPSTF = United States Preventive Services Task Force Recommendation Statement; WHO = World Health Organization

Table 3 Methods used in the Guidelines

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
Tuberculosis, Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC NTCA-CDC[25] 2019	A working group comprised of experts in TB, infection control, and occupational health was established to update the 2005 recommendations for health care personnel TB screening and testing. The group met periodically to discuss which updates were needed then conducted a systematic review on the topic. Findings of the systematic review were discussed during a web conference. A second web conference was used to develop the recommendations.	The authors conduced a systematic review of relevant evidence published in MEDLINE, EMBASE, and Scopus between 2006 and 2017. Evidence meeting the eligibility criteria was abstracted by two reviewers. Not reported.	Recommendations were drafted based on the findings from the systematic review and expert opinion from the working group.	Not applicable (recommendations not graded)	The draft recommendations were presented publicly at three meetings tuberculosis and infectious disease meetings, and members could provide feedback. Feedback was addressed and incorporated by the working group. Process for updating not reported.
Latent tuberculosis infection Updated and consolidated guidelines for programmatic management WHO LTBI[20] 2018	Development of the guidelines followed the process outlined in the WHO Handbook for Guideline Development.[30] Three groups were established: 1. The steering group, composed of WHO staff, who oversee the guideline development process. 2. Guideline development group (GDG), composed of methodologists, external content experts, national TB program	The steering group prepared a scoping document which identified 7 key questions in the PICO format. A list of potential outcomes for each question was circulated to the GDG, who scored the importance of each outcome, which was used to prioritize and select the most important outcome for each question. Seven new or updated SRs were conducted for these guidelines to address the 7 PICO questions. The SRs were conducted by SR teams composed of	The evidence for each PICO question was appraised and used to formulate recommendations. The GRADE "evidence-to-decision" tables were used to guide discussions on the benefits and harms, the quality of evidence, the cost, feasibility, acceptability,	Four levels of evidence quality:[30] High: Very confident that the true effect lies close to that of the estimate of the effect. Moderate: Moderately confident that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different. Two levels of strength of the recommendation: Strong: the GDG was confident that the desirable effects of adherence would	The external review group reviewed the draft of the final guideline, and remarks were evaluated by the steering group and incorporated into the final version of the guidelines. WHO will update the guideline 5 years after publication, or earlier if new evidence becomes available and a

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
	managers, academics, and representatives from patient groups and civil society. The GDG formulates recommendations, the general scope and content of the guideline. 3. External review group, composed of experts with an interest in LTBI, who reviewed the draft guidelines.	researchers from the WHO or other organizations with the relevant expertise. The SR team did not participate in formulating the recommendations. The WHO Handbook for Guideline Development[30] outlines specific methods for conducting SRs. An online survey was also conducted to determine the preferences and values of affected populations. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of the body of evidence and the strength of the recommendations for each PICO question. The strength of the recommendation reflected the degree of confidence of the GDG that the desirable effects outweighed the undesirable effects. As this guideline is an update and consolidation of previous guidelines, the recommendations were classified as: Existing: published in a previous guideline and	equity, values, and preferences. The GDG used these factors to determine the recommendations and the strength of the recommendations. Recommendations were formulated a consensus process. When consensus could not be reached, a voting process was used. The recommendations and supporting documents were reviewed and endorsed by all GDG members.	outweigh the undesirable effects. Could be either in favour of or against an intervention. Conditional: the GDG concluded that the desirable effects of adherence would probably outweigh the undesirable effects, but the GDG was not confident about the trade-off. Reasons for lack of confidence included: absence of high-quality evidence; imprecise estimates of benefit or harm; uncertainty or variation in the value of the outcomes for different individuals; and small benefits or benefits that might not be worth the cost.	revision is necessary.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
		approved by the review committee and are still valid Updated: published in a previous guideline, and the evidence was reviewed, discussed, and updated, including for clarity. New: made for the current guideline			
ERS/ECDC Statement: European Union standards for tuberculosis care, 2017 update ERS/ECDC Standards[19] 2018	A task force was created including the ERS and the ECDC to revise the 2016 guideline. The task force included a panel of experts representing the ERS, other international societies and organizations, national TB programs, civil society, and affected communities. A writing committee, consisting of six experts, led the process of the document. After three discussion rounds, consensus was reached. All co-authors participated in the entire process and contributed to the final document.	The task force conducted an initial scoping search, it was determined that sufficient relevant evidence was already available for an update of ESTC. No systematic reviews were conducted as part of the ESTC updating process. A targeted non-systematic search was conducted. Databases and other sources were searched including relevant evidence was retrieved after consulting the expert panel, institutional websites and selected electronic databases, i.e. Medline, PROSPERO and the Cochrane Database of Systematic Reviews The guideline did not state whether the evidence was critically appraised by experts or committee members.	Task force members assessed the synopsis of the evidence and provided their written input for the revision of the 21 standards and their supporting enablers for implementation. Recommendations were listed as “Standards” and noted whether the standard changed or unchanged from the first version of the ETSC.	Not applicable (recommendations not graded)	The guideline was peer-reviewed by the European Respiratory Journal Process for updating not reported.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
Position statement on interferon-gamma release assays for the detection of latent tuberculosis infection NTAC[14] 2017	This is an update to a previous position statement. Each committee member reviewed one sub-section of the report.	Unclear if formal systematic reviews were conducted by committee members. They "cited meta-analyses where possible and has provided a few key references for each sub-section" (pg. E323) The committee did not formally grade the quality of the evidence for each recommendation.	The committee discussed each member's literature review, and proposed recommendations for each section. A consensus position was reached for each section.	Not applicable (recommendations not graded)	No external review reported. To be updated when significant developments occur in the field
Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children ATS/IDSA/CDC [18] 2017	A committee was selected based on qualifications in the area, involvement in one of the organizations, and absence of conflicts of interest. The committee was divided into 4 subcommittees based on topic. Meetings were held in person on via teleconference.	Each subcommittee developed research questions and performed a "pragmatic evidence synthesis" for each question. According to the authors, this search was comprehensive, but should not be considered a systematic review of the evidence. The approach involved first searching for studies directly comparing two diagnostic strategies. If comparative evidence was not available, diagnostic accuracy studies were sought. If there was a lack of published evidence, collective clinical experience was used to inform the recommendations. The quality of the evidence was evaluated using GRADE. [31]	Recommendations were formulated using the GRADE approach. The following was considered when formulating the recommendations: the balance of the benefits and harms, the quality of the evidence, patient values and preferences, cost, resource use, and feasibility. The subcommittees used an open discussion to reach consensus on the recommendation	Grading recommendations:[31] "Grade of Recommendation: Strong recommendation = Benefits clearly outweigh harms and burdens, or vice versa Weak (conditional) recommendation = benefits may be closely balances with harms and burdens Quality of Supporting Evidence: High-quality = Consistent evidence from well-performed RCTs, or exceptionally strong evidence from unbiased observational studies Moderate-quality = Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or unusually strong evidence from unbiased observational studies Low-quality = Evidence for at least once critical outcome from observational studies, from RCTs with serious flaws or indirect evidence	No external review reported. No process for updating reported.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
			s. If a consensus could not be reached via discussion, an open voting system was used (although not needed for any of the recommendations in this guideline)	Very-low-quality = evidence for at least one critical outcome from unsystematic clinical observations or very indirect evidence“ (pg. 612)	
Recommendations for the diagnosis of pediatric tuberculosis Italian Pediatric guideline for diagnosis [15] 2016	Followed the “Consensus Conference method”. The Working Group developed a list of clinical problems related to diagnosing TB, and evidence reviews were conducted to address the questions. A multidisciplinary panel of clinicians and experts was selected to review the evidence and formulate the recommendations.	Systematic review of MEDLINE and the Cochrane Database of Systematic Reviews, from inception to December 2014. Also reviewed the clinical recommendations in the international guidelines. Primary studies in the systematic review were appraised using the Scottish Intercollegiate Guidelines Network methodological checklists. Quality of the evidence, and the strength of the recommendations was graded, although no methodology was reported	The evidence and draft documents were provided to the panel prior to the meetings. The Delphi method was used to reach a consensus when the evidence did not provide consistent, clear recommendations. Final recommendations were revised based on discussions, and reviewed by participants at the Consensus Conference for final approval.	“Quality of Evidence: I = Evidence from more than one properly designed, randomized, controlled study and/or systematic review of randomized studies II = Evidence from one properly designed, randomized, controlled study III = Evidence from cohort studies or their meta-analysis IV = Evidence from retrospective case-controlled studies or their meta-analysis V = Evidence from case series without control group VI = Evidence from opinions of respected authorities, based on clinical experience Strength of recommendation A = The panel strongly supports a recommendation for use B = The panel moderately supports a recommendation for use C = The panel marginally supports a recommendation for use“ (pg. 3)	Not reported.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
Prevention, Diagnosis and Management of Tuberculosis MOH Singapore[24] 2016	Guidelines were produced by a committee experts, including physicians, infectious disease experts, and the ministry of health. The guidelines were developed by adapting the existing guidelines, a review of the relevant literature, and expert clinical consensus.	Not described The critical appraisal of the individual studies as not described. The recommendations were appraised by scoring the strength of the evidence, and the grade of the recommendation. (No other details provided)	The development of the recommendations were guided by two principles: - recommendations were supported by evidence and expert consensus - treatment should maximize benefit and minimize harm	"*Levels of Evidence:* *1++ = High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias.* *1+ = Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.* *1- = Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias* *2++ = High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal* *2+ = Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal* *2- = Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal* *3 = Non-analytic studies, e.g. case reports, case series* *4 = Expert opinion* *Grades of recommendation:* *A = At least one meta-analysis, systematic review of RCTs, or RCT rated as 1+ + and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results* *B = A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1+ + or 1+* *C = A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall*	No external review process reported. Recommends that guidelines are updated within 5 years, or sooner, if evidence is available.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
				consistency of results; or Extrapolated evidence from studies rated as 2+ + *D = Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+* *GPP (good practice point) = Recommended best practice based on the clinical experience of the guideline development group*." (pg 2)	
Tuberculosis NICE[26] 2016	Update to a previous 2011 guideline. Developed in accordance to the NICE manual for developing guidelines.[32] A technical team drafted PICO questions during scoping, which were refined and validated by the guideline development group. Both teams jointly prepared a protocol for each question, which were used to draft the SRs.	35 SRs were conducted to address the questions. Evidence published up to December 2014 was identified from the following databases: Medline (1950 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 onwards), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and Health Technology Assessment Database. Evidence was limited to publications in English. Publications were screened and extracted by one reviewer, and a second reviewer randomly checked 10% of publications for accuracy. 24 of the SRs included evidence from SRs and RCTs. The other 11 SR included evidence from SRs, RCTs, and NRS.	The results of the meta-analyses were sent to the guideline development group prior to each meeting. At the meetings, the findings were presented in evidence tables, excluded study tables, GRADE profiles, and evidence statements on the findings. Statements summarizing the groups interpretation of the findings was used to form the recommendations. A consensus method was used to formulate the recommendations. Specific 'linking evidence to recommendation' criteria were used to guide the	The wording used in the recommendations denotes the certainty in the recommendations. The terms used in this guideline are: "Offer' – for the vast majority of patients, an intervention will do more good than harm 'Do not offer' – the intervention will not be of benefit for most patients 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient." (pg. 90)	The guideline was published online for two formal rounds of public and stakeholder consultation prior to publication. This process involves responding to each comment, and maintaining an audit trail. NICE follows a protocol for partial and full updates of guidelines. Areas not updated in this guideline may be addressed 2 years after publication. Updates of specific areas of the guideline may be updated if relevant evidence is published.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
		For each SR, detailed eligibility criteria were reported. For the critical appraisal of the primary studies: For RCTs, the NICE methodological checklist for RCTs was used. For NRS, the NICE methodological checklist for cohort studies was used. The QUADAS checklist was used for diagnostic accuracy studies. For the critical appraisal of the body of evidence: GRADE evidence profiles were prepared. Criteria considered included risk of bias, inconsistency, indirectness, imprecision, and other considerations. Evidence synthesis: meta-analyses were conducted where it was possible to combine the evidence for the outcomes. An extensive network meta-analysis was conducted for synthesize the evidence for the treatment of LTBI.	development of the recommendations. Recommendations consider the tradeoff of benefits and harms, and the quality of the evidence.		

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
Guidelines for the use of interferon-y release assays in the diagnosis of tuberculosis infection SEIMC/SEPAR Guideline [23] 2016	Guidelines were developed by a multidisciplinary panel of experts in collaboration with a guidelines methodology expert. All panel members were assigned a subgroup based on their expertise. The methodologist guided the panel in the methodology, performed the literature search, guided the discussions, and summarized the recommendations. The panel members participated in discussions of the evidence and formulated the recommendations, and reviewed the final version of the guideline. A coordinator drafted the manuscript.	Clinical questions were formulated with the PICO structure, and outcomes of interest were prioritized. Systematic review was conducted of MEDLINE and EMBASE, until 2013, with the complete search strategy provided in the appendix. They searched for relevant systematic reviews and primary studies. Where possible they prioritized evidence from countries with low TB incidence, and used evidence from intermediate- or high-prevalence countries when necessary. They excluded studies non-commercial IGRAs or older versions of the assays. Also searched for publications on cost and resource use in the NHS EED database until October 2014. Two panel members from each subgroup independently compiled the evidence. The quality of the evidence was assessed using GRADE. The panel assessed the quality of the evidence for all outcomes, by examining the following: limitations, consistency, availability of direct evidence, precision, and publication bias.	When available, the panel formulated the recommendations based on the two outcomes with the highest level of importance (efficacy of chemoprophylaxis based on the IGRA results, and predictive values if IGRAs for the development of active TB). Panel formulated the recommendations based on the evidence for each clinical question. To determine the strength and direction of the recommendation, the panel considered the overall quality of the evidence, the balance of harms and benefits, the importance of the outcomes, and the resource implications. Recommendations were established by	Four GRADE categories for the quality of evidence: High, moderate, low, and very low.[33] "High = Further research is very unlikely to change our confidence in the estimate of effect Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Very low = Any estimate of effect is very uncertain" (pg. 672)	External reviewers listed at the end of the document. Recommended that the guideline is updated within 5 years, or earlier if relevant information becomes available.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
			consensus between panel members.		
Screening for Latent Tuberculosis Infection in Adults US Preventive Services Task Force Recommendation Statement USPSTF[16] 2016	The US Preventive Services Task Force has standardized methods for developing recommendations.[28] This document does not reference the procedure manual, but it is assumed that it was followed. The development process involves four steps: 1. topic nomination 2. develop a research/ project plan 3. drafting an evidence review and recommendation statement 4. Finalize evidence review and recommendation statement There are several workings groups involved in the development of the recommendations. These include the following groups: methods; topic prioritization; subpopulation; conflict of interest; modeling; and	A SR was commissioned of the evidence on screening for LTBI in asymptomatic adults in primary care settings. PubMed/ MEDLINE and the Cochrane Library were searched from inception to May 2016 for English language articles. The search strategies are available online. The search was supplemented by reviewing reference lists. Two reviewers independently screened the publications, using pre-defined eligibility criteria. Data extraction was conducted by one reviewer, and checked for accuracy by another. Two independent reviewers assessed the quality of the primary studies using predefined criteria developed by the US Preventive Services Task Force. Only studies assessed to be fair or good quality were included. Findings for each question were summarized in tables	Steps to arrive at a recommendation: 1. Assess the adequacy of evidence to address the question, and critically appraise the evidence (including internal and external validity) 2. Evaluate the benefits and harms 3. Evaluate the certainty of the evidence 4. Estimate the net benefit 5. Develop a recommendation grade for the service All recommendations are based on scientific evidence. Recommendations are based on the evidence for	Grade and Definition: “A = The USPSTF recommends the service. There is high certainty that the net benefit is substantial B = The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial. C = The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small. D = The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. I Statement = The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.” (pg. 2) Levels of certainty regarding net benefit: High = available evidence is consistent, from good quality studies, and conclusions are unlikely to be strongly affected by future studies. Moderate = available evidence is sufficient to determine its effects, but the confidence is constrained. The magnitude or direction of	The Task Force shares drafts of its research plans, SRs, and recommendation statements for public comment and expert review. The documents are subsequently revised following review. The Task Force process for updating recommendations is to update every 5 years, unless there is evidence to support an earlier update.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
	dissemination and implementation.	and narratively. Meta-analyses were conducted where appropriate, following standard methods. Body of evidence was appraised based on the level of certainty regarding the net benefit, and graded. Assessing the certainty of the evidence followed methods in the procedure manual.	the benefits and harms, and an assessment of the balance. It does not consider the cost of providing the service. Voting on draft recommendations occurs at meetings. A 'yes' vote from at least two thirds of the current Task Force is needed to pass the motion.	the effect could change with additional studies. Low = insufficient evidence is available. More information may allow for an estimation of effect.	
The use of loop-mediated isothermal amplification (TB-LAMP) for the diagnosis of pulmonary tuberculosis WHO TB-LAMP[13] 2016	Update to a previous 2012 WHO guideline, which recommended additional studies be conducted. Since then, 20 additional studies were conducted, and the WHO convened a Guideline Development Group via webinar to review the evidence for TB-LAMP. In accordance with the WHO Handbook for Guideline Development,[30] the development of this guideline included a Steering Group (who was responsible for scoping, drafting PICO questions, and oversight), a Guideline Development Group (who formulated	One systematic review was conducted to address four PICO questions developed for the guideline on a specific technology (TB-LAMP). The systematic review followed standard methodology, with a comprehensive search, well defined eligibility criteria, and well described data analysis. This review also provides evidence for a cost-effectiveness analysis. The quality of the included studies in the systematic review were appraised using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. This tool assesses risk of bias and applicability in four domains:	The Steering Group prepared an initial list of relevant outcomes (e.g., benefits and harms) for consideration when drafting the outcomes. The Steering Group helped the Guideline Development Group formulate recommendations based on the evidence. Decisions were based on consensus.	Four levels of evidence quality:[30] High: Very confident that the true effect lies close to that of the estimate of the effect. Moderate: Moderately confident that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different. Two levels of strength of the recommendation: Strong: the GDG was confident that the desirable effects of adherence would outweigh the undesirable effects. Could be either in favour of or against an intervention. Conditional: the GDG concluded that the desirable effects of adherence would probably outweigh the undesirable effects,	Findings and recommendations were sent to an External Review Group of international TB experts. This group did not identify any major errors or missing data in the guideline, and had no concerns regarding the recommendations. Guideline will be updated in 2020, or earlier, if additional evidence becomes available.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
	the recommendations), a separate group a reviewers who conducted the systematic review, and an external review group. A guideline methodologist participated in the initial planning of the guideline, and the development of the key questions, but did not participated in the guideline development meeting.	patient selection, index test, reference standard, and flow and timing. The GRADE approach was used to assess the evidence prior to formulate the recommendations. This system determines the quality of the evidence and determines the strength of the recommendation. GRADE evidence-to-decision tables were created from the systematic review evidence to guide the development of the recommendations. The evidence that contributed to the recommendations was also summarized narratively in the guideline.		but the GDG was not confident about the trade-off. Reasons for lack of confidence included: absence of high-quality evidence; imprecise estimates of benefit or harm; uncertainty or variation in the value of the outcomes for different individuals; and small benefits or benefits that might not be worth the cost.	
Canadian Tuberculosis Standards Chapter 4: Diagnosis of Latent Tuberculosis Infection PHAC Identification LTBI[21] 2014	This 7th edition of the Canadian Tuberculosis Standards builds off previous versions and has been revised to include new information. Each chapter is written by experts from across Canada.	The authors synthesized and rated the evidence. No other details provided	Not reported	"Quality of Evidence Strong = Evidence from multiple randomized controlled trials (RCTs – for therapeutic evidence), or cohort studies (etiologic evidence) with strong designs and consistent results. Moderate = Evidence from only one RCT or RCTs with an inadequate number participants or inconsistent results, or multiple observational studies of strong design providing consistent results. Weak = Evidence from observational analytic studies that had weak designs, weak effect estimates or inconsistent results, or generalization from a randomized trial that involved one type of patients to a different group of patients. Very weak = Evidence from published case series and/or opinion of the authors and other experts	Process for external review not reported. Process for updating the guidelines not reported.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
				Strength of Recommendations Strong = The recommendation implies that the desirable effects clearly outweigh undesirable effects, was based on strong/moderate evidence and was considered unlikely to change with additional published evidence. Conditional = The recommendation implies that the desirable effects are closely balanced with undesirable effects, and/or was based on moderate/weak/very weak evidence and was considered likely to change with additional published evidence." (pg. 3-4, from Preface[28])	
Canadian Tuberculosis Standards Chapter 3: Diagnosis of Active Tuberculosis and Drug Resistance PHAC Identification Active TB[22] 2014	This 7th edition of the Canadian Tuberculosis Standards builds off previous versions and has been revised to include new information. Each chapter is written by experts from across Canada.	The authors synthesized and rated the evidence. No other details provided	Not reported	"Quality of Evidence Strong = Evidence from multiple randomized controlled trials (RCTs – for therapeutic evidence), or cohort studies (etiologic evidence) with strong designs and consistent results. Moderate = Evidence from only one RCT or RCTs with an inadequate number participants or inconsistent results, or multiple observational studies of strong design providing consistent results. Weak = Evidence from observational analytic studies that had weak designs, weak effect estimates or inconsistent results, or generalization from a randomized trial that involved one type of patients to a different group of patients. Very weak = Evidence from published case series and/or opinion of the authors and other experts Strength of Recommendations Strong = The recommendation implies that the desirable effects clearly outweigh undesirable effects, was based on strong/moderate evidence and was considered unlikely to change with additional published evidence.	Process for external review not reported. Process for updating the guidelines not reported.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
				Conditional = The recommendation implies that the desirable effects are closely balanced with undesirable effects, and/or was based on moderate/weak/very weak evidence and was considered likely to change with additional published evidence." (pg. 3-4, from Preface[28])	
Canadian Tuberculosis Standards Chapter 13: Tuberculosis Surveillance and Screening in Selected High-Risk Populations PHAC Identification High-Risk[17] 2014	This 7th edition of the Canadian Tuberculosis Standards builds off previous versions and has been revised to include new information. Each chapter is written by experts from across Canada.	The authors synthesized and rated the evidence. No other details provided	Not reported	"Quality of Evidence Strong = Evidence from multiple randomized controlled trials (RCTs – for therapeutic evidence), or cohort studies (etiologic evidence) with strong designs and consistent results. Moderate = Evidence from only one RCT or RCTs with an inadequate number participants or inconsistent results, or multiple observational studies of strong design providing consistent results. Weak = Evidence from observational analytic studies that had weak designs, weak effect estimates or inconsistent results, or generalization from a randomized trial that involved one type of patients to a different group of patients. Very weak = Evidence from published case series and/or opinion of the authors and other experts Strength of Recommendations Strong = The recommendation implies that the desirable effects clearly outweigh undesirable effects, was based on strong/moderate evidence and was considered unlikely to change with additional published evidence. Conditional = The recommendation implies that the desirable effects are closely balanced with undesirable effects, and/or was based on moderate/weak/very weak evidence and was considered likely to change with additional published evidence."	Process for external review not reported. Process for updating the guidelines not reported.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
				(pg. 3-4, from Preface[28])	

CDC = Centers for Disease Control and Prevention; ECDC = European Centre for Disease Prevention and Control; ERS = European Respiratory Society; ESTC = European Union Standards for Tuberculosis Care; GDG= guideline development group; GRADE = Grading of Recommendations Assessment, Development and Evaluation; IDSA = Infectious Diseases Society of America LTBI = latent tuberculosis infection; MOH = Ministry of Health; NHS = national health system; NICE = National Institute for Health and Care Excellence; NTAC = National Tuberculosis Advisory Committee; NTCA = National Tuberculosis Controllers Association; PHAC = Public Health Agency of Canada; PICO = population, intervention, comparator, outcome; QUADAS: quality assessment of diagnostic accuracy studies; RCT = randomized-controlled trial; SR = systematic review; TB = Tuberculosis; TB-LAMP = Tuberculosis- Loop-Mediated Isothermal Amplification; USPSTF = United States Preventive Services Task Force Recommendation Statement; WHO = World Health Organization

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Guidelines using AGREE II[11](part 1; first seven guidelines)

Item	Guideline						
	NTCA-CDC[25]	WHO LTBI[20]	ERS/ECDC Standards[1] [9]	NTAC[14]	ATS/IDSA/CDC [18]	Italian Pediatric TB diagnosis [15]	MOH Singapore[2] [4]
Domain 1: Scope and Purpose							
1. The overall objective(s) of the guideline is (are) specifically described.	Partially	Yes	Yes	Partially	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Partially	Yes	No	Partially	Yes	Yes	No
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Partially	Yes	Yes	Partially	Yes	Partially	Partially
Domain 2: Stakeholder Involvement							
4. The guideline development group includes individuals from all relevant professional groups.	Partially	Partially	Partially	No	Partially	Partially	Partially
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No	Yes	No	No	No	No	No
6. The target users of the guideline are clearly defined.	No	Yes	Partially	No	Yes	No	Yes
Domain 3: Rigour of Development							
7. Systematic methods were used to search for evidence.	Yes	Yes	Partially	No	No	Yes	No
8. The criteria for selecting the evidence are clearly described.	Yes	Yes	No	No	No	No	No
9. The strengths and limitations of the body of evidence are clearly described.	No	Yes	No	No	Partially	No	Partially
10. The methods for formulating the recommendations are clearly described.	Partially	Yes	No	Partially	Partially	Partially	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	No	Yes	No	No	Partially	Partially	No

Item	Guideline						
	NTCA-CDC[25]	WHO LTBI[20]	ERS/ECDC Standards[19]	NTAC[14]	ATS/IDSA/CDC [18]	Italian Pediatric TB diagnosis [15]	MOH Singapore[24]
12. There is an explicit link between the recommendations and the supporting evidence.	No	Yes	Yes	Partially	Yes	Partially	Partially
13. The guideline has been externally reviewed by experts prior to its publication.	Partially	Yes	Yes	No	No	No	No
14. A procedure for updating the guideline is provided.	No	Yes	No	Partially	No	No	Yes
Domain 4: Clarity of Presentation							
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Partially	Yes	Partially	Yes
16. The different options for management of the condition or health issue are clearly presented.	not applicable	Yes	Partially	not applicable	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Partially	Yes	Yes	Yes
Domain 5: Applicability							
18. The guideline describes facilitators and barriers to its application.	No	Yes	No	No	No	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Partially	Partially	No	No	No	No	No
20. The potential resource implications of applying the recommendations have been considered.	No	Partially	No	Partially	Partially	No	No
21. The guideline presents monitoring and/or auditing criteria.	No	Yes	No	No	No	No	Partially
Domain 6: Editorial Independence							
22. The views of the funding body have not influenced the content of the guideline.	No	Partially	Partially	No	No	Partially	No

Item	Guideline						
	NTCA-CDC[25]	WHO LTBI[20]	ERS/ECDC Standards[19]	NTAC[14]	ATS/IDSA/CDC [18]	Italian Pediatric TB diagnosis [15]	MOH Singapore[24]
23. Competing interests of guideline development group members have been recorded and addressed.	Partially	Yes	Partially	Partially	Partially	Yes	No

ATS= American Thoracic Society; CDC = Centers for Disease Control and Prevention; ECDC = European Centre for Disease Prevention and Control; ERS = European Respiratory Society; IDSA = Infectious Disease Society of America; LTBI = latent tuberculosis infection; MOH = Ministry of Health; ; NTAC = National Tuberculosis Advisory Committee; NTCA = National Tuberculosis Controllers Association; PHAC = Public Health agency of Canada; TB = tuberculosis; USPSTF = United States Preventative Services Task Force; WHO = World Health Organization

Table 5: Strengths and Limitations of Guidelines using AGREE II[11] (part 2; next seven guidelines)

Item	Guideline						
	NICE[26]	SEIMC/SEPAR Guideline [23]	USPSTF[16]	WHO TB-LAMP[13]	PHAC Identification LTBI[21]	PHAC Identification Active TB[22]	PHAC Identification High-Risk[17]
Domain 1: Scope and Purpose							
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	No	No	No
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	No	No	No
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Domain 2: Stakeholder Involvement							
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Partially	Partially	Partially	Partially	Partially	Partially
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Partially	Partially	No	No	No	No
6. The target users of the guideline are clearly defined.	Yes	Yes	Yes	Yes	Partially	Partially	Partially
Domain 3: Rigour of Development							
7. Systematic methods were used to search for evidence.	Yes	Yes	Yes	Yes	No	No	No
8. The criteria for selecting the evidence are clearly described.	Yes	Yes	Yes	Yes	No	No	No
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Partially	Yes	Yes	No	No	No
10. The methods for formulating the recommendations are clearly described.	Yes	Yes	Yes	Partially	No	No	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes	Yes	Yes	No	Partially	Partially
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Yes	No	No	No

Item	Guideline						
	NICE[26]	SEIMC/SEPAR Guideline [23]	USPSTF[16]	WHO TB-LAMP[13]	PHAC Identification LTBI[21]	PHAC Identification Active TB[22]	PHAC Identification High-Risk[17]
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Partially	Partially	Yes	Partially	Partially	Partially
14. A procedure for updating the guideline is provided.	Yes	Yes	Yes	Partially	No	No	No
Domain 4: Clarity of Presentation							
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	not applicable	not applicable	Yes	not applicable	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Domain 5: Applicability							
18. The guideline describes facilitators and barriers to its application.	No	Partially	Yes	Yes	No	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Partially	No	No	Partially	Partially	No	No
20. The potential resource implications of applying the recommendations have been considered.	Yes	Partially	Partially	Yes	No	No	No
21. The guideline presents monitoring and/or auditing criteria.	Yes	No	No	Partially	No	No	No
Domain 6: Editorial Independence							
22. The views of the funding body have not influenced the content of the guideline.	Partially	Yes	Yes	Partially	Partially	Partially	Partially
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Partially	Yes	No	No	No

LTBI = latent tuberculosis infection; PHAC = Public Health agency of Canada; TB = tuberculosis; TB-LAMP = Tuberculosis- Loop-Mediated Isothermal Amplification; USPSTF = United States Preventative Services Task Force

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of the topics regarding Screening and Contact Tracing in the Included Guidelines

Topics Covered by the recommendation	NTCA-CDC[25]	WHO LTBI[20]	2018 – ERS/ECDC Standards[19]	NTAC[14]	MOH Singapore[24]	NICE[26]	SEIMC/SEPAR Guideline [23]	USPSTF [16]	PHAC Identification High-Risk[17]
Contact tracing (i.e., identifying those who may have come into contact with a person with TB)			X			X			
Use of TST or IGRA for contact tracing				X	X		X		
Contact tracing in children						X	X		
TB testing in household contacts of people with TB		X	X			X			
TB testing in neonates in close contact to people with TB						X			
Screening for LTBI in high-risk populations		X			X	X		X	X
Screening for LTBI in low-risk populations					X				
Screening for LTBI in immigrants from countries with high TB incidence		X		X	X	X			X
Screening for LTBI in people with medical conditions that increase TB risk (e.g., HIV, immunocompromised)		X		X	X	X	X		X
Screening for LTBI in the homeless									X
Screening for LTBI in people misusing substances (e.g., injection drugs, alcohol)						X			X
Screening for LTBI in high-incidence areas (e.g., prisons)						X			
Screening for LTBI in travelers									X

Topics Covered by the recommendation	NTCA-CDC[25]	WHO LTBI[20]	2018 – ERS/ECDC Standards[19]	NTAC[14]	MOH Singapore[24]	NICE[26]	SEIMC/SEPAR Guideline [23]	USPSTF [16]	PHAC Identification High-Risk[17]
Baseline LTBI screening and testing of health care workers (includes clinical students, and others in contact with patients)	X					X	X		
Post-exposure screening and testing for health care workers	X								
Serial screening and testing of health care workers	X			X					
Active case finding in immigrants from countries with high TB incidence						X			
Active case finding in people who are homeless						X			
Active case finding in people using misuse services (e.g., injection drugs, alcohol)						X			
Active case finding in prisons or immigration removal centers						X			
Active case finding following a TB outbreak						X			

CDC = Centers for Disease Control and Prevention; ECDC = European Centre for Disease Prevention and Control; ERS = European Respiratory Society; HIV = human immunodeficiency virus; IGRA = interferon gamma release assay; LTBI = latent tuberculosis infection; MOH = Ministry of Health; NICE = National Institute for Care and Health Excellence; NTAC = National Tuberculosis Advisory Committee; NTCA = National Tuberculosis Controllers Association; PHAC = Public Health agency of Canada TB = tuberculosis; TST = Tuberculin skin test; USPSTF = United States Preventative Services Task Force; WHO = World Health Organization

X = the guideline made a recommendation on this topic

Table 7: Summary of the topics regarding identifying LTBI covered in the Included Guidelines

Topics Covered by the recommendation	WHO LTBI[20]	NTAC[14]	ATS/IDSA/ CDC [18]	MOH Singapore[2] [4]	NICE[26]	PHAC Identification LTBI[21]
Use of TST or IGRA for identifying LTBI (general population)	X	X	X	X	X	X
Use of TST or IGRA in people who have received the BCG vaccine				X		
Use of TST or IGRA in children				X	X	
Situations in which neither TST nor IGRA should be used for LTBI testing						X
Situations where IGRA is preferred over TST			X			X
Situations where TST is recommended and IGRA is not acceptable						X
Situations to use both TST and IGRA to enhance sensitivity						X

ATS= American Thoracic Society; CDC = Centers for Disease Control and Prevention; IDSA = Infectious Disease Society of America; IGRA = interferon gamma release assay; LTBI = latent tuberculosis infection; MOH = Ministry of Health; NTAC = National Tuberculosis Advisory Committee; NICE = National Institute for Care and Health Excellence; PHAC = Public Health agency of Canada TB = tuberculosis; TST= Tuberculin skin test; USPSTF = United States Preventative Services Task Force; WHO = World Health Organization

X = the guideline made a recommendation on this topic

Table 8: Summary of the topics regarding Identifying Active TB covered in the Included Guidelines

Topics Covered by the Recommendations	2018 – ERS/ECDC Standards[19]	NTAC[14]	ATS/IDSA/CDC[18]	Italian Pediatric TB diagnosis[15]	MOH Singapore[24]	NICE[26]	SEIMC/ SEPAR Guideline[23]	WHO TB-LAMP[13]	PHAC Identification Active TB[22]
General population									
When to test for active TB	X								X
Referral to multidisciplinary TB teams for diagnosis						X			
Use of TST or IGRA to diagnose active TB (general population)		X					X		X
Signs and symptoms of TB	X				X	X			
Chest radiography	X				X	X			X
Chest radiography in pregnant patients					X				
Use of sputum specimens	X				X	X			X
Use of gastric aspirate samples						X			
Sputum sampling methods			X		X				
Smear microscopy	X								X
Use of acid-fast bacilli smear microscopy			X		X				
Use of liquid and solid mycobacterial cultures	X		X		X	X			
Genotyping of culture isolates			X		X				
Nucleic Acid Amplification Tests (NAAT) or Rapid molecular test	X		X		X	X			X
Use of serologic, antibody-based TB tests									X
Drug sensitivity testing	X		X		X				X

Topics Covered by the Recommendations	2018 – ERS/ECDC Standards[19]	NTAC[14]	ATS/IDSA/CDC[18]	Italian Pediatric TB diagnosis[15]	MOH Singapore[24]	NICE[26]	SEIMC/SEPAR Guideline[23]	WHO TB-LAMP[13]	PHAC Identification Active TB[22]
TB-LAMP to diagnose pulmonary TB								X	
Children									
Use of TST or IGRA to diagnose active TB in children		X		X	X	X	X		
Signs and symptoms of TB in children				X	X				
Chest radiography in children				X	X				
CT scan with contrast medium in children < 5 years old					X				
Use of sputum specimens (children)				X					
Use of gastric aspirate samples (children)				X					
Sputum sampling methods (children)				X					
Smear microscopy (children)	X			X					
Use of liquid and solid mycobacterial cultures (children)			X	X					
Genotyping of culture isolates (children)				X					
Nucleic Acid Amplification Tests (NAAT) or Rapid molecular test in children	X			X		X			
Drug sensitivity testing (children)	X								

CDC = Centers for Disease Control and Prevention; ECDC = European Centre for Disease Prevention and Control; ERS = European Respiratory Society; IGRA = interferon gamma release assay; LTBI = latent tuberculosis infection; MOH = Ministry of Health; NICE = National Institute for Care and Health Excellence; NTAC = National Tuberculosis Advisory Committee; NTCA = National Tuberculosis Controllers Association; PHAC = Public Health agency of Canada; TB = tuberculosis; TB-LAMP = Tuberculosis- Loop-Mediated Isothermal Amplification; TST = Tuberculin skin test; WHO = World Health Organization

X = the guideline made a recommendation on this topic

Appendix 5: Additional References of Potential Interest

Guidelines with Unclear Methodology

Bielecka T, Augustynowicz-Kopec E, Gonerko P, et al. Recommendations for the management of tuberculosis in children - KOMPASS TB. Part 1: Tuberculosis prevention. Adv Respir Med. 2018;86(3)
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