CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Treatment of Tuberculosis: A Review of Guidelines

Abbreviations

2HRZE/4HR	Initial phase of 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by continuation phase of 4 months of isoniazid and rifampicin;
3HP	Once-weekly isoniazid and rifapentine for 12 weeks
9INH	9 months of daily isoniazid;
AGREE II	Appraisal of Guidelines for Research & Evaluation 2
ATS	American Thoracic Society
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
LTBI	Latent tuberculosis infection
NICE	National Institute for Health and Care Excellence
NTCA	National Tuberculosis Controllers Association
PHAC	Public Health Agency of Canada
TB	Tuberculosis
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 disease 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]

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 contagious. However, those with the LTBI can develop active TB disease if they do not receive proper treatment.[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] Active TB disease can develop shortly or long after infection, depending on the individual. Symptoms of active TB disease can include excessive coughing, chest pain, weight loss, fever, and fatigue.[4] Persons with active TB disease can spread the TB bacteria to others and are considered contagious.[4]

The treatment of TB, both LTBI and active TB disease, is a priority for public health officials. The overall goal of TB treatment is to eradicate the M. Tuberculosis infection. Treating patients for LTBI is done to prevent LTBI from developing into active TB.[5] Treatment for active TB disease is focused on improving the patient's clinical condition, preventing the development or worsening of drug-resistance, and preventing relapse of the disease.[6]

The treatments differ for LTBI and active TB disease, although there may be some overlap across therapies. It is important that an individual receives the correct diagnosis of either latent or active TB for the individual to receive optimal treatment.[7] There are several drug options for the treatment of LTBI and active TB disease, and treatment regimens may depend on the age of the individual (e.g., pediatric, adult, elderly patients etc.), co-morbidities (e.g., hepatitis, HIV, renal insufficiency), availability of drugs, the ability to adhere to treatment, and whether the TB is drug-susceptible.[5,6]

There are numerous guidelines published on TB treatment, and these guidelines may vary in quality and the topics covered, which may make it difficult for health care professionals to select the optimal treatment for patients with TB.[8] The purpose of this report is to review and critically appraise the evidence-based guidelines regarding the treatment 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 the treatment of latent and active TB and the strength of the guidelines. This report does not cover recommendations regarding the treatment of multi-drug resistant TB, or treating TB 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 treatment strategies for LTBI and active TB disease.

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 treatment of latent tuberculosis infection?

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

Key Findings

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

Four guidelines include recommendations regarding therapies for treating latent TB infection. Seven guidelines include recommendations regarding the treatment options for active TB disease. Nine guidelines include recommendations about different approaches for administering TB treatments.

Overall, there were four high-quality and seven low-quality guidelines that include between one and 23 recommendations on the treatment 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 with recommendations regarding the treatment of TB were considered eligible.

Table 1: Selection Criteria

Population	People who have been diagnosed with active or latent pulmonary tuberculosis infection
Intervention	Any intervention for the treatment of tuberculosis
Comparator	Any other intervention for the treatment of tuberculosis
Outcomes	Recommendations regarding the treatment of latent or active 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. Five potentially relevant publications

were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 63 publications were excluded for various reasons, and 11 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 references of potential interest are provided in Appendix 5

Summary of Study Characteristics

Eleven evidence-based guidelines were identified and included in this report.[13-23] Detailed characteristics and methods of the guidelines are available in Appendix 2, Table 2 and Table 3.

Study Design

Eleven evidence-based guidelines were identified.[13-23] One guideline published in 2019 was developed by the United States National Tuberculosis Controllers Association and the Centers for Disease Control and Prevention (NTCA-CDC).[23] Two guidelines were developed by the WHO; one was published in 2018[22] and one was published in 2017.[19] Two other guidelines were published in 2018; these were developed by the Centers for Disease Control and Prevention (CDC),[20] and the European Respiratory Society (ERS) and European Centre for Disease (ECDC).[21] Four guidelines were published in 2016; these were developed by the Italian Pediatric TB Study Group,[16] the Singapore Ministry of Health,[17] the National Institute for Health Care Excellence (NICE),[18] and a joint guideline by the American Thoracic Society (ATS), CDC, and Infectious Diseases Society of America (IDSA).[15] Two guidelines were developed by PHAC and were published in 2014.[13,14] These two guidelines from PHAC represent three chapters from a larger report by PHAC: the 7th edition of the Canadian Tuberculosis Standards.[24]

Four guidelines followed standardized methodology for guideline development that is available online.[15,18,19,22] The Italian Pediatric guideline for treating TB reported following the 'Consensus Conference Method' to develop the recommendations, but did not provide a reference.[16] The other four guidelines provided brief details of their guideline development process, but did not cite published methodology.[13,14,17,20] Four guidelines reported their methods for critically appraising the evidence, and provided ratings of the quality of evidence and strength of recommendation.[15,18,19,22] Four guidelines provided ratings of the quality of evidence and strength of recommendation, but did not provide the methods for evaluating the evidence.[13,14,16,17] Three guidelines did not provide ratings of the quality of evidence or the strength of the recommendations.[20,21,23] Decisions about the recommendations were reached through consensus in seven guidelines.[15-19,21,22] In the other guidelines, the methods for reaching consensus on the recommendations were unclear or not reported.[13,14,20,23]

Country of Origin

The two PHAC guidelines are meant to apply to Canada.[13,14] The two guidelines from the WHO are meant to apply globally.[19,22] Three guidelines are meant to apply to the United States.[15,20,23] The other guidelines are meant to apply to Europe,[21] the United Kingdom,[18] Italy,[16] and Singapore.[17]

Patient Population

The main target populations covered by the guidelines are people with LTBI[13,18,20,22,23] and people with active TB disease.[14-19,21] Other populations covered include children,[16,18,20,22]

pregnant persons,[13,14,17,18] people with renal insufficiency,[14,17,18] people with hepatic disease,[14,17,18] and US health care workers.[23] The intended users for all eleven guidelines are health care workers and other key TB stakeholders.[13-23]

Interventions and Comparators

Four guidelines include recommendations for the treatment of LTBI (i.e., drugs and regimens).[13,18,20,22] Seven guidelines include recommendations regarding the treatment of active TB disease (i.e., drugs and regimens).[14-19,21] Nine guidelines have recommendations that cover different options for administering treatment for LTBI or active TB disease (e.g., direct observational therapy (DOT), treatment adherence, patient follow-up).[14-21,23]

Outcomes

The number of recommendations regarding the treatment of TB ranged from one to 23 recommendations across the guidelines. Five of the guidelines contain five or fewer recommendations.[15,20-23] The other guidelines contain between 10 and 23 recommendations.[13,14,16-19]

Five of the guidelines reported which outcomes were considered in the systematic reviews that were used for developing the recommendations.[15,18-20,22] In the other six guidelines it was not reported which outcomes were considered when developing the recommendations.[13,14,16,17,21,23]

Summary of Critical Appraisal

This report includes four high-quality guidelines,[15,18,19,22] and seven low-quality guidelines.[13,14,16,17,20,21,23] Additional details regarding the strengths and limitations of included guidelines are provided in Appendix 3, Table 4 and Table 5.

Four guidelines were high-quality; these were the two WHO guidelines,[19,22] the NICE guideline,[18] and the ATS/CDC/IDSA treatment guideline.[15] These 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.[15,18,19,22] A systematic approach to developing the recommendations was reported in these high quality guidelines: systematic reviews with transparent search methodology and eligibility criteria were conducted; the quality of the evidence was evaluated; the evidence was clearly presented; and the process for formulating the recommendations was clear; and there is an explicit link between the evidence and the recommendations. The guideline development group for the NICE Guideline[18] included members from all relevant disciplines, as well as four patient or caregiver members. For the WHO guideline on drug-susceptible TB[19] the guideline development group included members from all relevant disciplines, and the role of each member was clear. One patient was involved in the external review of the WHO drug-susceptible TB guideline,[19] but otherwise it was not clear whether the views of the target population were incorporated into formulating the recommendations. The ATS/CDC/IDSA guideline,[15] had a multidisciplinary guideline development group, but it was not reported whether the views of the target population were sought when developing the recommendations. For the WHO consolidated LTBI guidelines,[22] a list of all members of the guideline development group was provided, but it was unclear who was responsible for what components of the process, and an online survey was conducted to determine the preferences and values of the target population. The potential conflicts of interest from the authors were declared and well managed in all four high-quality guidelines. No conflict of interest from the funding body was declared by

the ATS/CDC/IDSA guideline,[15] while the other three high-quality guidelines reported the funder, but it was unclear whether the funding agency influenced the recommendations.[18,19,22]

Seven guidelines were assessed to be low-quality due to poor reporting of methods, creating uncertainty in the recommendations.[13,14,16,17,20,21,23]

The Italian Pediatric TB Treatment guideline[16] reported clear descriptions of the scope and health questions covered by the guideline, however, the guideline lacked detail on the process of developing the recommendations, leading to uncertainty in the recommendations. The guideline development group included multiple 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 reported that a systematic review was conducted to search for evidence, however, no methods were provided for selecting the evidence, nor did they report the quality of the included studies. A narrative summary of the evidence was provided for each health question, but the benefits and harms were not clearly outlined, and there is not explicit link between the evidence and the recommendations. It was not reported whether the guideline was externally reviewed or a process 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 Singapore Guideline[17] had clear descriptions of the scope and target users of the guideline, and the recommendations were clear and easy to identify. However, the guideline did not report sufficient methodological detail, leading to uncertainty in the recommendations. It was not clear whether a systematic approach was used to search for and evaluate the evidence, and the process for formulating the recommendations was not clearly described. The Singapore guideline reported the level of evidence and the grade of the recommendation for each recommendation and the scores are explained at the beginning of the document, but it did not report the methods for grading the evidence. In addition, this guideline did not report the risk of bias of the primary studies or include evidence-to-decision tables, thus the link between strengths and limitations of the evidence and the recommendations was unclear. Furthermore, the roles and areas of expertise of the members of the guideline development group were not clear. It was not reported whether this guideline was externally reviewed by experts, thus reducing the level of certainty in the recommendations. The funding body was not reported, and the authors did not disclose whether they had any conflicts, and it is unclear whether there were any conflicts of interest from the funder or the authors.[17]

The two PHAC guidelines[13,14] have clear and specific recommendations that are easy to identify, however, limited detail on the process for developing the recommendations was reported, leading to a lack of certainty in the recommendations. The overall scope was not explicitly stated but could be inferred from the title of these guidelines. The health questions covered in the guidelines were not reported, thus it is unclear what questions guided the development of the recommendations. The population to whom the PHAC LTBI treatment guideline applies was well described,[13] and the population for the PHAC active TB treatment guideline[14] could be inferred from the content of the guideline. These guidelines listed a small number of authors (i.e., fewer than four) and their institutions (2 authors for active TB, 3 authors for LTBI), but their specific roles were unclear. It was not reported whether a larger guideline development group was involved in developing the recommendations, 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 for searching for evidence, thus the quality of the search strategy and eligibility criteria is unknown, limiting the certainty in the evidence. The strength of the recommendation and the quality of evidence for each recommendation is reported, and the scores are explained in the preface document for the PHAC TB Standards,[25] however, there are no methods explaining how these criteria were applied. How the quality of the primary studies was evaluated was not reported, and no evidence tables were provided, thus the strengths and limitations of the evidence are unclear. In addition, it is unclear how the recommendations were developed, as no methods for formulating the recommendations were reported. A list of external reviewers was reported for the larger PHAC TB Standards report, but it was unclear who reviewed these two guidelines, or what the process was for the external review. The funding body was disclosed, but there is no explicit statement that the views of the funding body have not influenced the guideline. The authors did not disclose whether they had any conflicts, thus it is unclear whether there were any conflicts of interest from the authors.

Of the seven 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,[23] the CDC treatment guideline,[20] and the ERS/ECDC Standards.[21]

With regards to the NTCA-CDC Recommendations,[23] there was an overall lack of detail and clarity. The objectives of the guideline are not clearly described, and it is not clear which health questions were addressed or who are the target users for the guideline. The area of expertise was not clear for each member of the guideline development group, and it did not include all relevant professional groups (e.g., no methodologist). In addition, there was no involvement of the target population (i.e., health care workers), who could have provided valuable insight towards the recommendations. A systematic search of the evidence was conducted, and the authors reported the search strategy and eligibility criteria, however, the risk of bias and the quality of the evidence was not assessed. The guideline briefly describes the process for formulating the recommendations, but there is no explicit link between the evidence and the recommendations, and the recommendations are not graded. It is unclear whether there was an influence by the funder on the recommendations as the funding body was not reported. 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 CDC treatment guideline[20] was not clearly described, and the health questions covered by the guideline were not reported, thus it is unclear what guided the development of the recommendations. This guideline did not report all of the names, institutions, or areas of expertise of the members of the guideline development group, and it is unknown if members from all relevant professional groups were involved. It was reported that 'patient advocacy' was involved at a development meeting, but no other details were provided, thus it is unclear how patients were involved in the process. A systematic review was conducted with a comprehensive search strategy and detailed eligibility criteria, and the internal and external validity of the primary studies was evaluated and reported in the systematic review. However, the overall strengths and limitations of the body of evidence were not evaluated or reported. An explicit link between the evidence and the recommendations was not apparent, and the guideline did not report any methods for formulating the recommendations, nor did they grade the recommendations (i.e., quality of evidence, strength of recommendations). The guideline did not indicate the funding source

thus it is unclear whether there was any influence by the funder on the recommendations. The authors reported no conflicts of interest.

For the ERS/ECDC Standards,[21] the scope of the guideline is clear, but there is limited detail on the development process, resulting in a lack of certainty in the standards. The health questions were not reported, thus it is unclear what guided the development of the recommendations. This guideline listed various authors and their roles in the development of the recommendations, and the guideline also reported that a task force was created, but it was not clear who was part of this task force as only the organizations were reported. This guideline reported that they conducted a non-systematic search through various databases, but no other methods were provided regarding the search or selection of evidence. It was not reported whether the quality of individual studies was assessed, and no evidence tables were provided. The guideline included summaries of the evidence, but there was no indication that the benefits and adverse effects were considered in developing the recommendations. This guideline did not report the strength of the recommendations or 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.

Summary of Findings

Guidelines

Eleven evidence-based guidelines were identified that made recommendations regarding the treatment of TB.[13-23] Four guidelines include recommendations regarding the drugs and drug regimens for the treatment of LTBI.[13,18,20,22] Seven guidelines include recommendations regarding the treatment options for active TB disease.[14-19,21] Nine guidelines have recommendations that cover different options and approaches for administering TB treatment.[14-21,23] A summary of the topics covered by the recommendations within each guideline is presented in Appendix 4, Table 6 (LTBI treatment), Table 7 (active TB treatment), and Table 8 (treatment approaches). Given the vast amount of recommendations across multiple different populations and prevention strategies, 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 LTBI treatment

The low-quality CDC treatment guideline[20] from 2018 included recommendations for the use of 3HP (i.e., once-weekly isoniazid and rifapentine for 12 weeks) as standard therapy in people of all ages with LTBI, however, the strength of the recommendation and the quality of the evidence were not reported.

The high-quality guideline from the WHO on LTBI[22] published in 2018, included recommendations regarding the use of daily isoniazid for 6 months as standard therapy for adults and children with LTBI, as well as recommendations for alternatives to this therapy for people in countries with high and low incidences of TB. There are three strong recommendations and one conditional recommendation (alternative therapies for people in countries with high TB incidence), based on low- to high-quality evidence.

The recommendations regarding LTBI treatment in the high-quality NICE Guideline[18] refer to choosing the treatment based on person's clinical circumstances. In this guideline, the

certainty of the recommendation is reflected in the wording of the recommendation, and the quality of the evidence varies according to the topic.

The low-quality 2014 guideline from PHAC on the treatment of LTBI,[13] includes conditional and strong recommendations, based on evidence ranging from weak to strong quality, for daily isoniazid therapy for 9 months (9INH) as standard therapy, as well as recommendations regarding shorter alternatives to 9INH, and recommendations for treating certain higher risk subgroups (e.g., pregnancy, adults older than 65, contacts of patients with drug-resistant TB).

Recommendations regarding active TB treatment

The low-quality ERS/ECDC Standards[21] from 2018 includes recommendations regarding the use of 2HRZE/4HR (i.e., initial phase of 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E), followed by a continuation phase of 4 months of isoniazid and rifampicin) as a first line treatment regimen for active TB disease, as well as fixed dose combination tablets, however, the strength of recommendations and quality of evidence was not reported.

The high-quality 2017 WHO guideline for drug-susceptible TB[19] has recommendations regarding the use of 2HRZE/4HR as first line treatment for active TB disease, fixed dose combination tablets, and shorter treatment regimens. This guideline contains conditional and strong recommendations, derived from evidence with very low to high certainty in the estimates of the effects.

The high-quality ATS/CDC/IDSA treatment guideline[15] has a strong recommendation based on moderate quality evidence regarding the frequency of dosing of TB medication for active TB. This guideline also includes detailed information on treatment regimens (drugs and dose), but this information is not graded for quality.

The low-quality Italian guideline for treating TB in pediatric patients[16] makes recommendations regarding the treatment of active TB disease in pediatric patients with limited or extensive lung involvement, dose recommendations, and vitamin supplementation. The recommendations in this guideline have moderate and strong support, based on evidence ranging from expert opinion to high quality studies.

The low-quality guideline from Singapore[17] includes recommendations regarding the use of 2HRZE/4HR as first line treatment for active TB disease, alternative treatments for those unable to tolerate 2HRZE/4HR, and treatment recommendations for specific conditions (i.e., pregnancy, renal disease, hepatic disease). These recommendations range from weak to strong recommendations, based on expert opinion to high quality evidence. This guideline also includes 'good practice points' (i.e., suggested best practices; see grading system in) based on clinical experience when no evidence was available.

The recommendations regarding treating active TB disease in the high-quality NICE guideline[18] covered the use of 2HRZE/4HR as first line treatment, fixed dose combination tablets, frequency of dosing of TB medication, and recommendations for specific conditions (i.e., pregnancy, renal disease, hepatic disease). The strength of the evidence differs across recommendations, varying from weak to strong, and the certainty of the recommendation is reflected in the wording of the recommendation.

The low-quality 2014 guideline from PHAC on the treatment of active TB disease[14] includes recommendations regarding the use of use of 2HRZE/4HR as first line treatment, fixed

dose combination tablets, frequency of dosing of TB medication, and recommendations for specific conditions (i.e., pregnancy, renal disease, hepatic disease, adults > 65 years). This guideline includes conditional and strong recommendations, based on evidence ranging from weak to strong quality.

Recommendations regarding approaches to administering TB treatment

The high-quality WHO guideline on drug-susceptible TB[19] includes conditional and strong recommendations, based on evidence with very low to high certainty in the estimates of the effect, regarding the use of DOT, the method of administering DOT, video observed therapy, and different approaches to treatment adherence. This guideline also includes one good practice point regarding drug-susceptibility testing prior to retreatment of LTBI.

The high-quality ATS/CDC/IDSA treatment guideline[15] has conditional and strong recommendations, based on evidence with very low to high certainty, regarding DOT, self-administered therapy, and the use of case management interventions.

The high-quality NICE Guideline[18] includes recommendations regarding DOT for adults and pediatric patients, treatment adherence, monitoring the response to therapy, establishing care plans, and strategies for care in specific scenarios (e.g., prisons, interruptions in care). The strength of these recommendations differs across topics, varying from weak to strong evidence.

The low-quality Italian guideline for treating TB in pediatric patients[16] makes recommendations regarding DOT and monitoring treatment compliance in pediatric patients. These recommendations have moderate and strong support, based on evidence ranging from expert opinion to high quality studies.

The low-quality guideline from Singapore[17] includes weak to strong recommendations, as well as some good practice points based on expert opinion to high quality evidence, regarding initiating treatment, DOT, treatment adherence, and monitoring the response to therapy.

The low-quality PHAC guideline on the treatment of active TB disease[14] includes conditional and strong recommendations based on evidence ranging from weak to strong quality regarding DOT, treatment adherence, monitoring the response to therapy, and managing adverse events due to treatment of active TB.

The low-quality NTCA-CDC guideline[23] provides a recommendation regarding treating LTBI in health care workers, however this guideline did not evaluate the strength of the recommendation or the quality of the evidence.

The low-quality CDC treatment guideline[20] has recommendations concerning DOT and self-administered therapy, however, the strength of the recommendation and the quality of the evidence were not reported.

The low-quality ERS/ECDC Standards[21] includes recommendations regarding treatment adherence, monitoring responses to therapy, record keeping during TB treatment, however, the strength of recommendations and quality of evidence was not reported.

Limitations

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

This report includes seven low-quality guidelines,[13,14,16,17,20,21,23] including three guidelines[20,21,23] that did not evaluate the quality of the evidence and the strength of the recommendations. The low-quality guidelines may limit the reliability of the findings of this report, however, most of the topics covered by the recommendations were covered in at least one high-quality guideline in addition to one or more low-quality guideline(s). Eighteen of the 47 topics were only covered in guidelines assessed to be low-quality, and these recommendations should be interpreted with caution, particularly if the recommendations are not graded for strength and quality of evidence. Topics with higher uncertainty due to the quality of the guideline are the use of 3HP[20] or 9INH[13] as standard therapy for LTBI; active TB treatment recommendations for pediatric patients[16] or the elderly;[14] and some topics with regards to monitoring treatment.[16,21]

With regards to generalizability, the two guidelines from PHAC[13,14] were developed for use in Canada and two other guideline are intended for global use,[19,22] however, it is unknown if the other seven guidelines developed for countries outside of Canada are generalizable to the Canadian context. There may be geographical differences in the populations that require treatment for TB as well as differences in resources for treating TB, including the availability of drugs and health care personnel.

This report was also limited by the large number of recommendations regarding the treatment of TB published in the guidelines (i.e., between one and 23 recommendations per guideline), as it was not possible to directly compare all of the different recommendations made across the various guidelines. Therefore, it is not clear whether the recommendations are consistent across guidelines, or whether there is disagreement in the evidence or recommendations across topics.

Conclusions and Implications for Decision or Policy Making

This report was comprised of eleven guidelines[13-23] that contain recommendations regarding the treatment of latent and active TB.

Four guidelines (two high-quality and two low-quality) included recommendations regarding how to treat LTBI.[13,18,20,22] These guidelines covered topics such as which therapy was recommended as the standard therapy for LTBI, [13,20,22] alternatives to the standard therapy,[13,22] the choice of treatment regimens,[18] and treatment recommendations for specific populations (e.g., during pregnancy).[13] With regards to the standard treatment for LTBI, the recommended standard therapy differed across the three guidelines that provided a recommendation on this topic.[13,20,22] In the 2014 guideline from PHAC,[13] the recommended first line therapy is 9 months of daily isoniazid (i.e., 9INH), however, this guideline did not publish their methodology, limiting the certainty of the recommendations. In the guidelines from 2018, shorter courses of treatment are recommended. The standard therapy in the high-quality WHO LTBI guideline[22] is 6 months of daily isoniazid, and the standard therapy in the low-quality guideline from the CDC[20] is 3 months (i.e., 3HP) however, this guideline did not grade the strength of the recommendation or the quality of the evidence. Both of these shorter treatment courses were covered as alternative therapies in the PHAC guideline, and it is possible that new evidence on shorter treatments became available after the recommendations were made in the 2014 PHAC guideline, thus contributing to the different standard therapy recommendations in the guidelines.

Seven guidelines (three high-quality, four low-quality) made recommendations regarding specific treatments for active TB disease.[14-19,21] Six of the guidelines made recommendations regarding the use 2HRZE/4HR as the standard therapy for treating

active TB disease in adults[14,17-19,21] and pediatric patients.[16] Recommendations regarding fixed dose combination tablets were made in four guidelines (two high- and two low-quality),[14,18,19,21] and recommendations regarding the use of intermittent or daily dosing strategies were also made in four guidelines (three high- and one low-quality).[14,15,18,19] The Italian guideline[16] also covered alternative treatments for active TB in pediatric patients, however, this guideline lacked detail on the process of developing the recommendations, leading to uncertainty in the recommendations. In addition, three guidelines (one high- and two low-quality) included recommendations for treating active TB in specific populations (i.e., pregnancy, renal disease, hepatic disease), with the strength of the recommendations varying across populations and guidelines.

Nine guidelines (six low-quality and three high-quality) discussed different approaches to administering and monitoring therapies for TB.[14-21,23] Seven guidelines covered the use of DOT for adults[14,15,17-20] or pediatric patients.[16,18] In addition, recommendations regarding the use of self-administered therapy[15,20] and video observed therapy[19] were also covered. Six guidelines also included recommendations about approaches to improve treatment adherence[14,17-19,21] and five guidelines covered methods of monitoring the response to therapy.[14,17,18,21] The high-quality NICE Guideline[18] also includes recommendations regarding establishing care plans and strategies for care in specific scenarios (e.g., prisons, interruptions in care).

Overall, this report identified four high-quality guidelines,[15,18,19,22] that included recommendations for treating latent and active TB, and approaches for administering TB therapies. This report also identified seven low-quality guidelines[13,14,16,17,20,21,23] that may provide additional guidance on these topics, however, given the uncertainty associated with these low-quality guidelines, the recommendations should be interpreted with caution given.
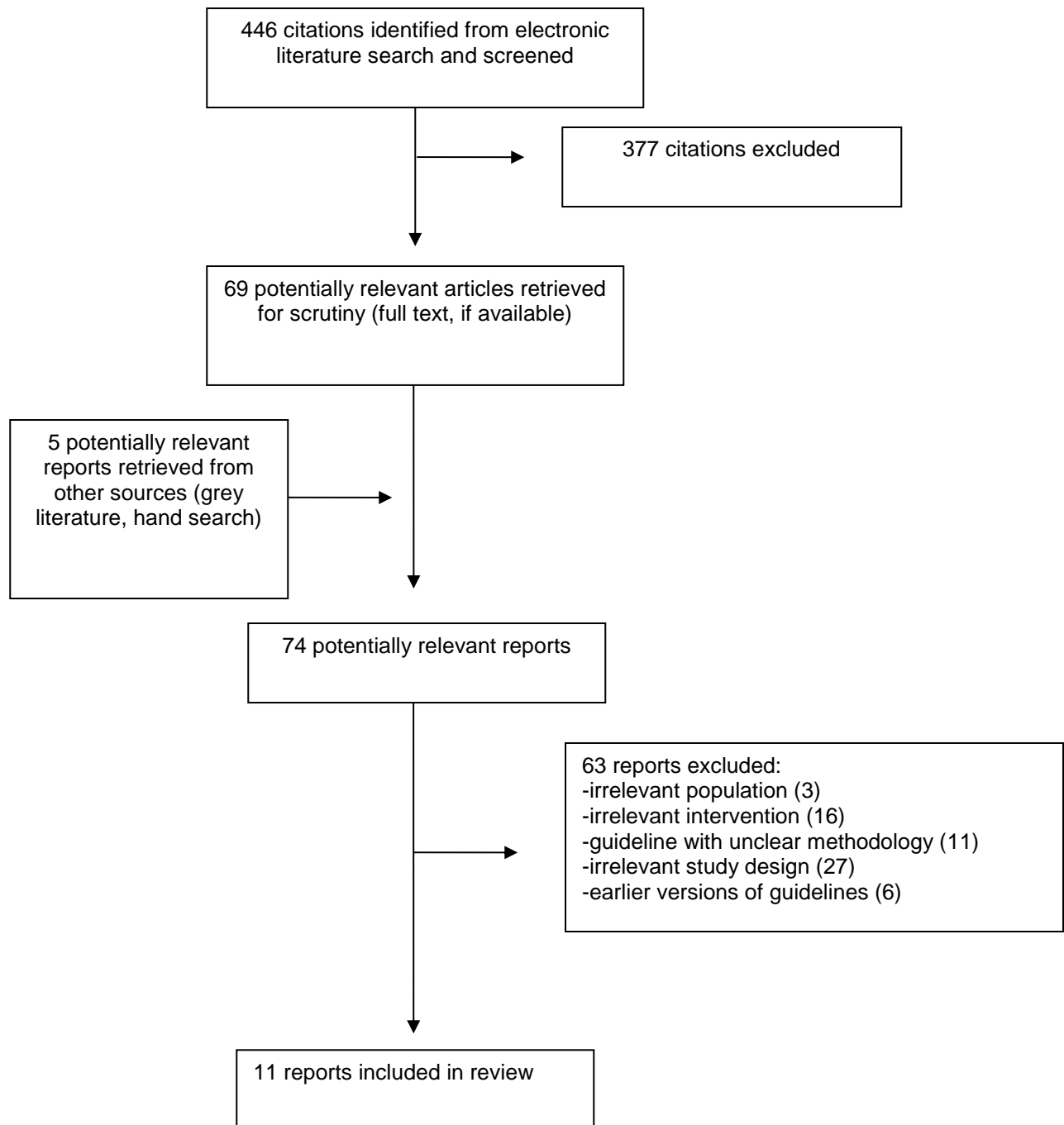
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CADTH

Appendix 1: Selection of Included Studies

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┌──────────────────────────────────────┐
│ 446 citations identified from         │
│ electronic literature search and      │
│ screened                              │
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        │         ┌──────────────────────────────┐
        ├────────▶│ 377 citations excluded        │
        │         └──────────────────────────────┘
        ▼
┌──────────────────────────────────────┐
│ 69 potentially relevant articles      │
│ retrieved for scrutiny (full text, if │
│ available)                            │
└──────────────────────────────────────┘
        │
┌─────────────────────────┐
│ 5 potentially relevant   │
│ reports retrieved from   │────┐
│ other sources (grey      │    │
│ literature, hand search) │    │
└─────────────────────────┘    ▼
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┌──────────────────────────────────────┐
│ 74 potentially relevant reports       │
└──────────────────────────────────────┘
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        │         ┌──────────────────────────────────────────┐
        │         │ 63 reports excluded:                      │
        │         │ -irrelevant population (3)                │
        ├────────▶│ -irrelevant intervention (16)             │
        │         │ -guideline with unclear methodology (11)  │
        │         │ -irrelevant study design (27)             │
        │         │ -earlier versions of guidelines (6)       │
        │         └──────────────────────────────────────────┘
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┌──────────────────────────────────────┐
│ 11 reports included in review         │
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Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of the Guidelines

Guideline and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
					Treatment of LTBI	**Treatment of Active TB**
Tuberculosis, Screening, Testing, and Treatment of US Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC NTCA-CDC Recommendations [23] 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:** Treatment of LTBI - Evaluation and treatment of positive test results **Total # of Recommendations: 1**	**Main population:** U.S health care personnel with LTBI (1)	Not applicable
Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium tuberculosis Infection CDC treatment guideline[20] 2018	**Country:** United States **Funding:** United States Centers for Disease Control and Prevention **Developing institution:** Not specified	CDC Work Group conducted a systematic review and meta-analyses of the 3HP regimen using methods adapted from the Guide to Community Preventive Services	**Primary users:** Clinicians and health care professionals, public health departments **Other users:** Patients with LTBI	**Technologies:** Treatment of LTBI - 3HP - DOT - self-administered therapy **Total # of Recommendations: 3**	**Main population:** General population (≥ 2 years) (3)	Not applicable
ERS/ECDC Statement: European Union	**Country:** Europe **Funding:** European	Incorporate the new scientific evidence that has become available since	Clinicians; health care professionals	Technologies: -drugs and regimen - promote adherence	Not applicable	**Main population:** Patients with active TB (5)

Guideline and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
standards for tuberculosis care, 2017 update ERS/ECDC Standards[21] 2018	Respiratory Society (ERS) **Developing institution:** ERS and European Centre for Disease Prevention and Control (ECDC)	the publication of the European Union Standards for Tuberculosis Care in 2012.		- patient centered treatment - monitoring - record keeping **Total # recommendations:** 5		
Latent tuberculosis infection Updated and consolidated guidelines for programmatic management WHO LTBI[22] 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 Health Organization	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. This guideline can be adapted to the national and local level based on epidemiology of TB, and the availability of resources.	**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 services, immigration, and clinicians and public health practitioners working on TB or HIV.	**Technologies:** Treatment of LTBI - drugs and regimens **Total # of Recommendations:** 5	**Main population:** Adults and children with LTBI (5)	Not applicable
Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update)	**Country:** Global **Funding:** United States Agency for International Development (USAID)	The objective of the guideline is to provide updated recommendations for the treatment of drug-susceptible TB based on new evidence	**Users:** All health professionals (e.g., doctors, nurses) who treat patients with TB, and key TB policy-makers	**Technologies:** - drugs, dosing, and regimens - patients care and support (e.g., education, treatment adherence)	Not applicable	**Main population:** Patients with drug-susceptible pulmonary TB (15)

Guideline and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
WHO drug-susceptible[19] 2017	**Developing institution:** World Health Organization			- treatment administration options (e.g., DOT, video observed treatment) **Total # of Recommendations:** 15		
Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis ATS/CDC/IDSA treatment guidelines[15] 2016	**Country:** United States **Funding:** The American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America **Developing institution:** American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America**,** European Respiratory Society, and US National Tuberculosis Controllers Association	Recommendations on the clinical and public health management of drug-susceptible TB in children and adults in settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis.	**Primary users**: National TB programs, or their equivalents in ministries of health, and for other policy-makers working on TB	**Technologies**: Treatment of active TB - regimen, dosing, drug-drug interactions - DOT - self-administered therapy **Total # of Recommendations: 5**	Not applicable	**Main population:** General population (5)

Guideline and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
Recommendations Concerning the First-Line Treatment of Children with Tuberculosis Italian Pediatric TB Treatment [16] 2016	**Country:** Italy **Funding:** Italian Ministry of Health **Developing institution:** Not specified	*"This document describes the recommendations of a group of scientific societies concerning the first-line therapeutic approach to paediatric TB"* (p. 1)	**Primary users:** Clinicians, health care professionals and policy-makers	**Technologies:** Treatment of active TB - drug regimen and dosing - Steroid administration - Vitamins - Monitoring drug regimen - Treatment compliance **Total # of Recommendations: 10**	Not applicable	**Main population:** Children with TB (10)
Prevention, Diagnosis and Management of Tuberculosis MOH Singapore[17] 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:** Treatment of active TB - treatment regimen - DOT **Total # of Recommendations:** 16	Not applicable	**Main population:** General population (11) **Subgroups:** Pregnant women (1) Renal insufficiency (3) Hepatic disease (1)
Tuberculosis NICE[18] 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	**Technologies:** Treatment of LTBI - drug regimens - monitoring - social support - testing for co-infection Treating active TB - drugs - dosing - surgery Adherence to treatment and follow-up	**Subgroups:** Adults (general) (3) High-risk groups (in general) (6) Patients with liver disease (1) Children (1)	**Main population:** General population (all ages) (8)

Guideline and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies , total # of recommendations	Populations covered by the recommendations (# of recommendations)	
			health and public health consultants. People with TB and their carers	- DOT (8) - other strategies (3) - strategies for prisons (8) - re-establishing treatment after an interruption (3) - follow- up (3) **Total # of Recommendations:** 19		
Canadian Tuberculosis Standards Chapter 6: Treatment of Latent Tuberculosis Infection PHAC Treatment LTBI[13] 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	Treatment of LTBI	Public health and clinical professionals	Technologies: - drug regimen and dosing Total # of Recommendations: 13	**Main population:** - patients with TB (11) **Subgroups:** - pregnancy (2)	

Guideline and year	Country, Funding body, Developer	Scope or Objective	Target Users	Health Technologies, total # of recommendations	Populations covered by the recommendations (# of recommendations)
Canadian Tuberculosis Standards Chapter 5: Treatment of Tuberculosis Disease PHAC Treatment Active TB[14] 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	Treatment of active TB disease	Public health and clinical professionals	Technologies: - drug regimen and dosing - intermittent therapy - DOT - therapeutic drug monitoring - management of adverse events **Total # of Recommendations:** 23	**Main population:** - people with drug sensitive TB (20) **Subgroups:** - people with severe liver disease (1) - pregnancy (2) - people with risk factors for altered drug absorption

3HP = once-weekly isoniazid and rifapentine for 12 weeks; ATS = American Thoracic Society; CDC = Centers for Disease Control and Prevention; DOT = directly observed treatment; ECDC= European Centre for Disease Prevention and Control; ERS = European Respiratory Society; HIV = human immunodeficiency virus; IDSA = Infectious Diseases Society of America; LTBI = latent tuberculosis; MOH = Ministry of Health; NICE = National Institute for Health and Care Excellence; NTCA = National Tuberculosis Controllers Association; PHAC = Public Health Agency of Canada; TB = tuberculosis; US = United States; WHO = World Health Organization.

Table 3: Characteristics of the 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 US Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC NTCA-CDC Recommendations [23] 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 reported.	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.
Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium tuberculosis Infection CDC treatment guideline[20] 2018	A multidisciplinary Work Group was convened to conducted a systematic review. The systematic review and proposed recommendations were later presented at a meeting of experts, including patient advocacy. The experts provided feedback on: individual perspectives and viewpoints and experience with implementation. Additional input was sought from members of the public, and an advisory council, and	The systematic review was published elsewhere.[26] Systematic review searched MEDLINE, Embase, CINAHL, Cochrane Library, Scopus, and Clinicaltrials.gov, for evidence published through 2006 to June 2017, with complete search strategy provided. Reference lists were also reviewed. Primary studies were assessed for their internal and external validity.	Not described.	Not reported.	Input was gathered from members of the public and the Advisory Council for the Elimination of Tuberculosis. 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
	incorporated into the final recommendations.	Appraisal of body of evidence not conducted.			
ERS/ECDC Statement: European Union standards for tuberculosis care, 2017 update ERS/ECDC Standards[21] 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.	The guideline did not use a grading system.	The guideline was peer-reviewed by the European Respiratory Journal
Latent tuberculosis infection Updated and consolidated guidelines for programmatic management	Development of the guidelines followed the process outlined in the WHO Handbook for Guideline Development.[27] Three groups were established:	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	The evidence for each PICO question was appraised and used to formulate recommendations. The GRADE "evidence-to-decision" tables were used to guide	Four levels of evidence quality:[27] 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	The external review group reviewed the draft of the final guideline, and remarks were evaluated by the steering group and incorporated

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
WHO LTBI[22] 2018	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 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.	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 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[27] 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	discussions on the benefits and harms, the quality of evidence, the cost, feasibility, acceptability, 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.	effect, but there is a possibility that it is substantially different. <u>Low</u>: Our confidence in the effect estimate is limited: the true effect may be substantially different. <u>Very low</u>: 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: <u>Strong</u>: 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. <u>Conditional</u>: 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.	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 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
		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 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 | | | |
| Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update)

WHO drug-susceptible[19]

2017 | This is an update to the 2010 guideline/
The WHO Guidelines Steering Group and the Guidelines Development Group considered priority questions and topics for the guideline update. For recommendations from the previous guideline for which no new evidence has emerged, the recommendations are considered still valid and included in this update. | The evidence collection was guided by 9 PICO questions regarding the treatment of drug-susceptible TB and 2 PICO questions on patient care and support.
The systematic reviews were commission by independent reviewers. The reviews were conducted using standard methodology, and are available online.

Teams of experts were commissions to assess the evidence for the PICO | GRADE evidence-to-decision tables were prepared and presented to the guideline development group for formulation of the recommendations.

The following criteria were considered in evaluating the evidence: study design, risk of bias, imprecision, inconsistency, | Certainty of the evidence
"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 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. | An external review group, composed of experts and end-users from national programs, technical agencies and WHO regional offices, reviewed the draft guideline and provided comments.

Guideline will be reviewed and updated in 4 to 5 |

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
		questions and their outcomes. The GRADE approach was used to assess the quality of the evidence and the strength of the recommendations. The GRADE assessment was conducted in line with the considerations outlined in the WHO Handbook for Guideline Development[27].	indirectness, publication bias, magnitude of effect, dose–effect relations and residual confounding. All decisions on the recommendations were reached by discussion and consensus, including the strength of the recommendations. There was no need to vote on any of the recommendations.	Very low = Any estimate of effect is very uncertain." (p4) Strength of the recommendation (patient perspective): "Strong = Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. Conditional = Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences." (p5)	years, or earlier if new evidence becomes available.
Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of	A multi-disciplinary panel of experts (including methodologists), screened for conflicts of interest, was selected to develop the guideline. The development of the guideline followed procedures and methods outlined in a "Guideline Development Checklist" (available online) and the	For each PICO question, systematic reviews were conducted. They searched MEDLINE and Cochrane, using search terms specific to the PICO, and specific selection criteria were provided for each review. The methodologists prepared evidence profiles for each systematic review.	The guideline panel used the evidence summaries and the evidence-to-decision tables to formulate the recommendations. For each recommendation, the panel agreed on the quality of the evidence, the balance of benefits	"Strong recommendation For patients: Most individuals in this situation would want the recommended course of action, and only a small proportion would not. For clinicians: Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal	A final draft of the guideline was peer reviewed by experts in the field, and the document was revised to incorporate the comments. 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
Drug-Susceptible Tuberculosis ATS/CDC/IDSA treatment guidelines[15] 2016	'Guideline Development Tool' by GRADE. The panel developed 9 PICO questions to address in the guideline. The writing committee selected priority outcomes for each question. Systematic reviews were conducted for each PICO question. Two face-to-face meetings were conducted, during which the panel discussed specific questions, the evidence, and drafted recommendations.	For the primary studies included in the systematic reviews, the risk of bias at the outcome level was assessed using Cochrane's risk of bias tool. The certainty of the evidence for each outcome was then assessed using GRADE, based on risk of bias, precision, consistency, magnitude, directness, risk of publication bias, the dose-effect relationship, and confounding. Certainty of the evidence was categorized into 4 levels (e.g., very low to high). Evidence-to-decision tables were prepared based on benefits, harms, patient values and costs.	and harms, and the patient preferences. The panel also considered resource implications. Recommendations were decided by consensus, and none required voting. Recommendations were rated as either "strong" or "weak/conditional"	decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. For policy makers: The recommendation can be adopted as policy in most situations. Weak/Conditional recommendation. For patients: The majority of individuals in this situation would want the suggested course of action, but many would not. For clinicians: Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences. For policy makers: Policy-making will require substantial debate and involvement of various stakeholders." (p. 9, Appendix A)	
Recommendations Concerning the First-Line Treatment	Followed the "Consensus Conference method". The Working Group developed a list of clinical questions about the	Systematic review of MEDLINE and the Cochrane Database of Systematic Reviews, from inception to December 2014.	The evidence and draft documents were provided to the panel prior to the meetings.	"Quality of Evidence: I = Evidence from more than one properly designed, randomized, controlled study	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
of Children with Tuberculosis Italian Pediatric TB Treatment [16] 2016	therapeutic management of TB (excluding drug resistant TB).	Also reviewed the clinical recommendations in the international guidelines. Trained personal critically appraised the literature 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 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.	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" (p. 14)	
Prevention, Diagnosis and Management of Tuberculosis MOH Singapore[17] 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	"*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.*	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
			- treatment should maximize benefit and minimize harm	*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++,*	

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
				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 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."* (p. 2)	
Tuberculosis NICE[18] 2016	Update to a previous 2011 guideline. Developed in accordance to the NICE manual for developing guidelines.[28] 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.	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	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	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

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
		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. 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,	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 development of the recommendations. Recommendations consider the trade off of benefits and harms, and the quality of the evidence.	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." (p. 90)	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
		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.			
Canadian Tuberculosis Standards Chapter 6: Treatment of Latent Tuberculosis Infection PHAC Treatment LTBI[13] 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." (p. 3-4, from Preface[29])	
Canadian Tuberculosis Standards Chapter 5: Treatment of Tuberculosis Disease PHAC Treatment Active TB[14] 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	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
				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." (p. 3-4, from Preface[29])	

ATS = American Thoracic Society; 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; NRS = non-randomized study; 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; US = United States; 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 six guidelines)

Item	Guideline					
	NTCA-CDC[23]	CDC treatment guideline[20]	ERS/ECDC Standards[21]	WHO LTBI[22]	WHO guideline of drug-susceptible TB[19]	ATS/CDC/IDSA treatment guidelines[15]
Domain 1: Scope and Purpose						
1. The overall objective(s) of the guideline is (are) specifically described.	Partially	Partially	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Partially	No	No	Yes	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Partially	Partially	Yes	Yes	Partially	Yes
Domain 2: Stakeholder Involvement						
4. The guideline development group includes individuals from all relevant professional groups.	Partially	Partially	Partially	Partially	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No	Partially	No	Yes	Partially	No
6. The target users of the guideline are clearly defined.	No	Partially	Partially	Yes	Yes	Yes
Domain 3: Rigour of Development						
7. Systematic methods were used to search for evidence.	Yes	Yes	Partially	Yes	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes	No	Yes	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	No	Partially	No	Yes	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Partially	No	No	Yes	Yes	Yes

Item	Guideline					
	NTCA-CDC[23]	CDC treatment guideline[20]	ERS/ECDC Standards[21]	WHO LTBI[22]	WHO guideline of drug-susceptible TB[19]	ATS/CDC/ IDSA treatment guidelines[15]
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	No		No	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	No	Partially	Yes	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Partially	Partially	Yes	Yes	Yes	Yes
14. A procedure for updating the guideline is provided.	No	No	No	Yes	Yes	No
Domain 4: Clarity of Presentation						
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	not applicable	not applicable	Partially	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes	Yes	Yes
Domain 5: Applicability						
18. The guideline describes facilitators and barriers to its application.	No	No	No	Yes	Partially	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Partially	No	No	Partially	Yes	Partially
20. The potential resource implications of applying the recommendations have been considered.	No	No	No	Partially	Partially	Partially
21. The guideline presents monitoring and/or auditing criteria.	No	No	No	Yes	Yes	No
Domain 6: Editorial Independence						
22. The views of the funding body have not influenced the content of the guideline.	No	No	Partially	Partially	Yes	Yes

Item	Guideline					
	NTCA-CDC[23]	CDC treatment guideline[20]	ERS/ECDC Standards[21]	WHO LTBI[22]	WHO guideline of drug-susceptible TB[19]	ATS/CDC/ IDSA treatment guidelines[15]
23. Competing interests of guideline development group members have been recorded and addressed.	Partially	Yes	Partially	Yes	Yes	Yes

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; NTCA = National Tuberculosis Controllers Association; TB = tuberculosis; WHO = World Health Organization.

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

Item	Guideline				
	Italian Pediatric TB Treatment [16]	MOH Singapore[17]	NICE[18]	PHAC Treatment LTBI[13]	PHAC Treatment Active TB[14]
Domain 1: Scope and Purpose					
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	No	No
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	No	Yes	No	No
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Partially	Yes	Yes	No
Domain 2: Stakeholder Involvement					
4. The guideline development group includes individuals from all relevant professional groups.	Partially	Partially	Yes	Partially	Partially
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No	No	Yes	No	No
6. The target users of the guideline are clearly defined.	No	Yes	Yes	Partially	Partially
Domain 3: Rigour of Development					
7. Systematic methods were used to search for evidence.	Yes	No	Yes	No	No
8. The criteria for selecting the evidence are clearly described.	No	No	Yes	No	No
9. The strengths and limitations of the body of evidence are clearly described.	No	Partially	Yes	No	No
10. The methods for formulating the recommendations are clearly described.	Partially	No	Yes	No	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Partially	No	Yes	Partially	Partially

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

LTBI = latent tuberculosis infection; MOH = ministry of health; NICE = National Institute for Health and Care Excellence; PHAC = Public Health agency of Canada; TB = tuberculosis.

Appendix 4: Main Study Findings

Table 6: Summary of the topics regarding the treatment of LTBI

Topics Covered by the recommendation	CDC treatment guideline[20]	WHO LTBI [22]	NICE[18]	PHAC Treatment LTBI[13]
3HP as standard therapy (adults and children)	X			
Isoniazid daily for 6 months (adults and children) as standard therapy		X		
Isoniazid daily for 9 months (9INH) as standard therapy				X
Alternatives to 6 months of isoniazid monotherapy in countries with high TB incidence (e.g., Rifampicin plus isoniazid daily, Rifapentine and isoniazid)		X		
Alternatives to 6 months of isoniazid monotherapy in countries with low TB incidence (e.g., 9INH, 3HP, 3 to 4 months of isoniazid and rifampin, 3 to 4 months of rifampin alone)		X		
Choice of treatment regimen for LTBI based on a person's clinical circumstances			X	
Treatment regimen for people (<65 years) with LTBI who have been in contact with people with active TB disease			X	
Inform and advise approach for people with LTBI			X	
Shorter alternatives to 9INH (e.g., 6 months daily isoniazid, 3 to 4 months of isoniazid and rifampin daily, 3HP, 4 months daily rifampin)				X
Intermittent, directly observed regiments with isoniazid or isoniazid and rifampin				X
LTBI treatment to adults <65 years with no comorbidities who are at moderate or high risk				X
LTBI treatment during pregnancy or breastfeeding				X
LTBI treatment for re-exposure				X
LTBI treatment for contacts of patients with drug-resistant TB				X

3HP = once-weekly isoniazid and rifapentine for 12 weeks; 9INH = 9 months of daily isoniazid; CDC = Centers for Disease Control and Prevention; LTBI = latent tuberculosis infection; NICE = National Institute for Health and Care Excellence; PHAC = Public Health Agency of Canada; TB = tuberculosis; WHO = World Health Organization.

Note: X = the guideline made a recommendation on this topic

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Table 7: Summary of the topics regarding the treatment of active TB disease

Topics Covered by the recommendation	ERS/ECDC Standards[21]	WHO drug-susceptible[19]	ATS/CDC/ IDSA treatment guidelines[15]	Italian Pediatric TB Treatment [16]	Singapore Guideline[17]	NICE[18]	PHAC Treatment Active TB[14]
First-line treatment regimen (2HRZE/4HR)	X	X			X	X	X
Treatment for patients unlikely to tolerate pyrazinamide					X		
Fixed dose combination tablets	X	X				X	X
Shortened fluoroquinolone-containing regimens (i.e., 4 months)		X					
Frequency of dosing of TB medication (i.e., intermittent or daily dosing)		X	X			X	X
Treatment regimens (drugs and dosage)			X				
2 months of isoniazid, rifampin and pyrazinamide (intensive phase), followed by 4 months of isoniazid and rifampin (continuation phase) (pediatric patients with limited lung involvement)				X			
2HRZE/4HR for pediatric patients with extensive lung involvement				X			
Dose recommendations for pediatric patients				X			
Vitamin supplements in children with TB				X			
Treatment during pregnancy and breastfeeding					X	X	X
Treatment during renal insufficiency and end stage renal failure					X	X	X
Treatment for patients with hepatic disease					X	X	X

Topics Covered by the recommendation	ERS/ECDC Standards[21]	WHO drug-susceptible[19]	ATS/CDC/IDSA treatment guidelines[15]	Italian Pediatric TB Treatment[16]	Singapore Guideline[17]	NICE[18]	PHAC Treatment Active TB[14]
Treatment of active TB in the elderly (>65 years old)							X

2HRZE/4HR = initial phase of 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E), followed by continuation phase of 4 months of isoniazid and rifampicin; ATS = American Thoracic Society; CDC = Centers for Disease Control and Prevention; ECDC = European Centre for Disease Prevention and Control; ERS = European Respiratory Society; IDSA = Infections Disease Society of America; LTBI = latent tuberculosis infection; NICE = National Institute for Health and Care Excellence; PHAC = Public Health Agency of Canada; TB = tuberculosis; WHO = World Health Organization.

Note: X = the guideline made a recommendation on this topic

Table 8: Summary of the topics regarding treatment administration options

Topics Covered by the Recommendations	NTCA-CDC Recommendations[23]	CDC treatment guideline[20]	ERS/ECDC Standards[21]	WHO drug-susceptible[19]	ATS/CDC/IDSA treatment guidelines[15]	Italian Pediatric TB Treatment[16]	Singapore[17]	NICE[18]	PHAC Treatment Active TB[14]
Treatment of health care personnel for LTBI	X								
DOT		X		X	X		X	X	X
DOT for pediatric patients						X		X	
DOT administration options (e.g., community- or home-based, by health care workers, by family members)				X					
Self-administered therapy (SAT)	X				X				
Video observed therapy				X					
Treatment adherence approaches and interventions			X	X			X	X	X

Topics Covered by the Recommendations	NTCA-CDC Recommendations[23]	CDC treatment guideline[20]	ERS/ECDC Standards[21]	WHO drug-susceptible[19]	ATS/CDC/IDSA treatment guidelines[15]	Italian Pediatric TB Treatment [16]	Singapore[17]	NICE[18]	PHAC Treatment Active TB[14]
Monitoring response to therapy			X				X	X	X
Monitoring treatment compliance in pediatric patients						X			
Record keeping of medications, adverse reactions, treatment outcomes			X						
Drug-susceptibility testing prior to TB retreatment				X					
Use of case management interventions (e.g., DOT, SAT)					X			X	
Initiation of treatment						X			
Explain risks and benefits of preventive LTBI treatment								X	
Linking people receiving LTBI treatment who also have social risk factors to social services								X	
Establishing a health and social care plan								X	
Care for active TB disease through multidisciplinary TB specialists								X	
Strategies for caring for patients with TB in prisons or immigration removal centers								X	
Re-establishing treatment for active or latent TB after interruptions due to adverse events								X	

Topics Covered by the Recommendations	NTCA-CDC Recommendations[23]	CDC treatment guideline[20]	ERS/ECDC Standards[21]	WHO drug-susceptible[19]	ATS/CDC/ IDSA treatment guidelines[15]	Italian Pediatric TB Treatment [16]	Singapore[17]	NICE[18]	PHAC Treatment Active TB[14]
Management of adverse events from active TB treatment									X

3HP = once-weekly isoniazid and rifapentine for 12 weeks; ATS = American Thoracic Society; CDC = Centers for Disease Control and Prevention; DOT = directly observed therapy; ECDC = European Centre for Disease Prevention and Control; ERS = European Respiratory Society; IDSA = Infections Disease Society of America; LTBI = latent tuberculosis infection; NICE = National Institute for Health and Care Excellence; NTCA = National Tuberculosis Controllers Association; PHAC = Public Health Agency of Canada; SAT = self-administered therapy; TB = tuberculosis; WHO = World Health Organization.

Note: X = the guideline made a recommendation on this topic

Appendix 5: Additional References of Potential Interest

Guidelines with Unclear Methodology

Krause V, National Tuberculosis Advisory C. Policy recommendation: latent tuberculosis infection screening and treatment in children in immigration detention. Commun Dis Intell Q Rep. 2015;39(4):E597-598.

Specific to children in immigration centers.

Newfoundland Labrador. Guideline for Preventing the Transmission Of Mycobacterium tuberculosis across the Continuum of Care. 2019 July.
https://www.health.gov.nl.ca/health/publichealth/cdc/tuberculosis_management.pdf

Canadian context: Newfoundland

Nicholson EG, Geltemeyer AM, Smith KC. Practice guideline for treatment of latent tuberculosis infection in children. J Pediatr Health Care. 2015;29(3):302-307.

Specific to children.

Stock D, National Tuberculosis Advisory C. National position statement for the management of latent tuberculosis infection. Commun Dis Intell Q Rep. 2017;41(3):E204-E208.