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Drug-Resistant Tuberculosis: A Review of the Guidelines

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Abbreviations

AGREE II	Appraisal of Guidelines for Research & Evaluation 2
ATS	American Thoracic Society
BCG	Bacillus Calmette-Guérin
CADTH	Canadian Agency for Drugs and Technologies in Health
CDC	Centers for Disease Control and Prevention
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility testing
ECDC	European Centre for Disease Prevention and Control
ERS	European Respiratory Society
IDSA	Infectious Disease Society of America
IGRA	Interferon-gamma release assay
LTBI	Latent tuberculosis infection
MDR-TB	Multi-drug resistant tuberculosis
NICE	National Institute for Health and Care Excellence
PHAC	Public Health Agency of Canada
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

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] Active TB disease occurs when the TB bacteria begins to multiply and the individual's immune system is compromised, leading to disease.[4] Moreover, patients with active TB disease can have drug-resistant TB (DR-TB). DR-TB refers to cases of TB where the bacteria are resistant to one of the first-line therapies for TB (e.g., isoniazid).[5] More specifically patients can be categorized as having multi-drug resistance (MDR-TB) when the bacteria are resistant to at least isoniazid and rifampicin, the two most commonly used drugs for TB treatment.[5] They can also be categorized as extensively drug-resistant TB (XDR-TB) when the bacteria are resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs.[6,7] Patients with MDR-TB and XDR-TB have fewer treatment options. According

to the WHO, there are approximately 490,000 cases of MDR-TB worldwide.[6,7] MDR-TB and XDR-TB cases are on this rise and may be due to mismanagement of treatment or person-to-person transmission, leading to higher drug resistance. Proper diagnosis and treatment regimens for DR-TB, MDR-TB and XDR-TB can help control drug-resistant cases.[6,7]

There are numerous guidelines published on TB that may vary in quality and the topics covered, which may make it difficult for health care professionals to select the optimal care for patients with DR-TB. The purpose of this report is to review and critically appraise the evidence-based guidelines regarding DR-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 DR-TB. This report does not cover LTBI and drug-susceptible TB, which can be found in separate reports.[8-10] This report focuses on strategies for the prevention, identification, and treatment of DR-TB.

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 Question

What are the evidence based-guidelines regarding the prevention, identification, or treatment of drug-resistant pulmonary tuberculosis?

Key Findings

Ten evidence-based guidelines regarding drug-resistant tuberculosis were identified and included in this report.

Seven guidelines include recommendations regarding the identification of drug-resistant tuberculosis. Nine guidelines include recommendations regarding the treatment of drug-resistant tuberculosis. Two guidelines include recommendations for infection control practices for caring for patients with drug-resistant tuberculosis.

Overall, there are three high-quality guidelines and seven low-quality guidelines that include between three and 29 recommendations on drug-resistant tuberculosis. The recommendations vary in strength and the quality of the evidence. The population and setting of interest may determine which guideline(s) and which recommendation(s) are of interest.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was tuberculosis. Search filters were applied to limit retrieval to guidelines. The search was also limited to English language documents published between Jan 1, 2014 and Nov 7, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1. Evidence-based guidelines including recommendations regarding the prevention, identification, or treatment of DR-TB were considered eligible. For the purpose of this report, all forms of DR-TB (e.g., single-drug resistant, multi-drug resistant, or extensively drug resistant) were considered eligible.

Table 1: Selection Criteria

Population	People who have or may have been exposed to drug-resistant pulmonary tuberculosis, people with suspected drug-resistant pulmonary tuberculosis, or people who have been diagnosed with drug-resistant pulmonary tuberculosis
Intervention	Any intervention for the prevention, identification, or treatment of drug-resistant tuberculosis
Comparator	Any other intervention for the prevention, identification, or treatment of drug-resistant tuberculosis
Outcomes	Recommendations regarding the prevention, identification, or treatment of drug-resistant 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, 64 publications were excluded for various reasons, and 10 evidence-based guidelines met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[12] flowchart of the study selection.

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

Summary of Study Characteristics

Ten evidence-based guidelines were identified and included in this report.[13-22] Detailed characteristics and methods of the guidelines are available in Appendix 2, in Table 2 and Table 3.

Four of these guidelines[13,15,21,22] include recommendations for both drug-susceptible TB and DR-TB, and are also included in the CADTH reports on guidelines for TB identification and treatment.[8,10] This report includes the publication details and recommendations specific to DR-TB for these four guidelines.[13,15,21,22]

Study Design

Ten relevant evidence-based guidelines were identified.[13-22] Two guidelines were published in 2019; one was developed they the World Health Organization (WHO)[17] and one was a joint guideline by the American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), the European Respiratory Society (ERS), and the Infectious Diseases Society of America (IDSA).[16] One guideline, prepared by ERS and the European Centre for Disease (ECDC), was published in 2018.[22] One guideline published in 2017 was prepared on behalf of the Sentinel Project on Pediatric Drug-Resistant Tuberculosis.[20] Three guidelines were published in 2016; they were developed by the Italian Pediatric TB Study Group,[19] the Singapore Ministry of Health,[15] and the National Institute for Health Care Excellence (NICE).[21] Two guidelines were developed by PHAC[13,14] and are two chapters from a larger report by PHAC that was published in 2014: the 7th edition of the Canadian Tuberculosis Standards.[23] One guideline was developed by the Tuberculosis Network European Trials Group (TBNET) in 2014.[18]

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

Country of Origin

The two PHAC guidelines are meant to apply to Canada.[13,14] The guideline from the WHO is meant to apply globally.[17] One guideline is meant to apply to the United States,[20] while one guideline is meant to apply to the United States and Europe.[16] Four guidelines are meant to apply to Europe; the ERS/ECDC Standards[22] is for all of Europe, while the others are specific to the United Kingdom,[18,21] Germany,[18] and Italy.[19] The other guideline was developed for Singapore.[15]

Patient Population

The main target populations covered by the guidelines were adults suspected of having DR-TB,[13,15,18,21,22] adults with DR-TB, MDR-TB, or XDR-TB,[14-18,21,22] pediatric patients with MDR-TB or suspected of having DR-TB,[19,20] and contacts of patients with MDR-TB (i.e., people who may have been exposed to DR-TB).[18] The intended users for six guidelines were health care workers and other key TB stakeholders.[13-16,20,21] For the other four guidelines, the intended users were health care professionals.[17-19,22]

Interventions

Seven guidelines include recommendations regarding the identification of DR-TB, such as drug susceptibility testing (DST).[13-15,18,19,21,22] Nine guidelines include recommendations regarding the treatment of DR-TB, such as the composition and duration of drug regimens, care models, and treatment adherence.[14-22] Two guidelines also include recommendations for infection control practices when caring for patients with DR-TB.[18,21]

Outcomes

The number of recommendations regarding DR-TB ranges from three to 29 recommendations across the different guidelines.[13-22] Six guidelines contain ten or fewer recommendations[13,15,19-22] The ATS/CDC/ERS/IDSA guideline[16] has 25 recommendations; the WHO DR-TB guideline[17] has 29 recommendations; the TBNET guideline[18] has 15 recommendations; and the PHAC DR-TB guideline[14] has 11 recommendations.

Four of the guidelines[16,17,20,21] reported which outcomes were considered in the systematic reviews that were used for developing the recommendations. The other six guidelines did not specify which outcomes were considered when developing the recommendations. [13-15,18,19,22]

Summary of Critical Appraisal

This report includes three high-quality guidelines,[16,17,21] and seven low-quality guidelines.[13-15,18-20,22] Additional details regarding the strengths and limitations of the included guidelines are provided in Appendix 3, Table 4: Strengths and Limitations of Guidelines using AGREE II[11] (part 1; first five guidelines)Table 4 and Table 5.

Four guidelines[13,15,21,22] are included in the other CADTH reports on TB guidelines, and the detailed critical appraisal of these guidelines can be found in the TB identification guidelines report[8] and in the TB treatment guidelines report.[10] In brief, the NICE Guideline[21] followed a detailed process for developing the recommendations, and was assessed to be high-quality. The Singapore Guideline[15] did not report sufficient methods for developing the recommendations and was assessed to be low-quality. The PHAC guideline for diagnosing active TB[13] was assessed to be low-quality, as it provided limited detail on the process for developing the recommendations thus creating uncertainty in the recommendations. The ERS/ECDC Standards[22] had limited methodological detail and did not evaluate the strength of the recommendations or the quality of the evidence, and the guideline was assessed to be a low-quality.

The ATS/CDC/ERS/IDSA guideline[16] and the WHO DR-TB guideline[17] were high-quality. The overall objective and the health questions covered of these guidelines are clear and well described, the they have clear, unambiguous recommendations. The populations to whom the recommendations apply are clearly outlined, and the target users of the guidelines were well described. A list of all members of the guideline development group

was provided, with the specific roles or expertise of each member was described. These guidelines used high-quality, systematic methods for developing the recommendations: systematic reviews were conducted with transparent search methodology and eligibility criteria, the quality of the evidence was evaluated and well described; and the process for developing the recommendations was clear. The WHO guideline[17] also conducted an online survey to determine the preferences and values of the target population. Both guidelines underwent external peer review. There were no conflicts of interest from the members of the guideline development group for either guideline. Both guidelines reported the source of their funding; the ATS/CDC/ERS/IDSA guideline[16] noted that the funding would likely not have influenced the content of the guideline, but the WHO guideline[17] did not report the potential influence of the funding bodies on the content of the guideline.

Four guidelines were assessed to be low-quality due to poor reporting of methods, creating uncertainty in the recommendations.[14,18-20]

The Italian Pediatric DR-TB guideline[19] has a clear description of the scope of the guideline, and the research questions can be inferred from the content of the guideline, however, the guideline lacks details of the development of the recommendations, leading to uncertainty in the recommendations. The guideline development group included numerous experts from relevant disciplines, but the area of expertise and the role of each member was unclear, and it was not reported whether the views of the target population were considered. The authors conducted a systematic literature search, with high quality search methods but the eligibility criteria were not well-described, nor did they report the quality of the primary studies (although they reported using Scottish Intercollegiate Guidelines Network to assess the quality of the primary studies). The guideline states that they used the 'consensus conference method' to develop the recommendations, however, the method was not described. This guideline presented a narrative summary of the evidence for each health question, but did not clearly outline the benefits and harms, and it is unclear how the recommendations were formulated from the evidence. It is not clear whether the guideline underwent an external or peer review prior to publication. The authors declared no conflicts of interest, but it was not reported whether the funding agency had any influence on the guideline.

The PHAC DR-TB guideline[14] has clear and specific recommendations that are easily identified in the guidelines, however, there is limited detail on the process for developing the recommendations, creating a lack of certainty in the recommendations. The overall scope of these guidelines was not explicitly stated, but could be inferred from the title of the documents. The health questions covered in the guideline were not reported, thus it is unclear what questions guided the development of the recommendations. The population to whom the guidelines applies was not described, but could be inferred from the content. This guideline listed a small number of authors (i.e., two authors) and their institutions, but their specific roles were unclear. It was not reported whether a larger guideline development group was involved in the process, thus is unknown if individuals from all relevant professional groups were involved or whether the views of the target population were sought. This guideline did not report any methods regarding the search for evidence, thus the quality of the search strategy and eligibility criteria for selecting the evidence is unknown. The strength of the recommendation and the quality of evidence for each recommendation was reported, and the scores are explained in the preface document,[24] however, there is no explanation as to how these criteria were applied. It is unknown how the quality of the primary studies was evaluated, and no evidence tables were provided, thus the strengths and limitations of the evidence are unclear, and no methods for

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

Of the four guidelines assessed to be low-quality, two guidelines did not evaluate the strength of the recommendations or the quality of the evidence; these were the Sentinel Project guideline[20] and the TBNET guideline.[18]

The Sentinel guideline[20] has clear descriptions of the scope of the guideline, the population to whom the guideline applies, and the target users, but the research questions were not reported, thus it is unclear what guided the development of the recommendations. It was not clear if all relevant stakeholders were included in the guideline development group, and the roles of the committee members were not stated. This guideline cited a separate guideline[25] as their methods, which provided the citation for the systematic review[26] that was used as the evidence base for the Sentinel guideline. This systematic review used a systematic search strategy and reported the eligibility criteria, however, the search was conducted in 2011, suggesting that more recent evidence may not have been considered, thus reducing the certainty in the evidence. The systematic review did not formally evaluate or report the quality of the primary studies, and the guideline did not critically appraise the quality of the body of evidence. A narrative summary of the efficacy and safety evidence was provided, but there was no clear comparison of the evidence, and no explicit link to the recommendations. The process for formulating the recommendations was not clearly described, and the authors of the guideline acknowledged their process for formulating recommendations was unique and did not follow the same process as other guidelines. The recommendations were more so based on consensus by experts rather than a framework tool to interpret assess the evidence, which limits the certainty in the recommendations. The competing interests of members involved in developing the guidelines were recorded and addressed. The funding body was not disclosed and it is unknown if the funder influenced the guideline.

The scope of the TBNET guideline[18] is clear, however, there is a lack of detail on the process of developing the recommendations, contributing to a lack of certainty of the guideline. The health questions covered by the guideline were not reported, but the topics that guided the development of the recommendations could be inferred from the content of the evidence summaries. A literature search was conducted, but it was explicitly stated by the guideline authors that a systematic review was not conducted, and no other details were provided, including the eligibility criteria, or the search strategy. It was reported that coordinating authors together with the TBNET steering committee developed the standards and reviewed all sections of the guideline, although limited detail was given on this. It was not reported whether the views of the target population were sought, and the target users were not clearly defined. The quality of the primary studies and the body of evidence were not reported, and no evidence tables were provided, thus, the strengths and limitations of the evidence that contributed to the standards is unclear. The process for developing the recommendations involved proposing the recommendations, voting on statements, and having the authors indicate their agreement or disagreement with the recommendation. However, the recommendations were not graded. Narrative evidence summaries were included, but it was difficult to identify which section supported which recommendation. An

external process was not reported. The funding body was disclosed but there is no explicit statement that the views of the funding body have influenced the guideline. Conflicts of interests of the authors were disclosed in a supplemental document.

Summary of Findings

Guidelines

Ten evidence-based guidelines were identified that made recommendations regarding DR-TB.[13-22] Seven guidelines made recommendations regarding the identification of DR-TB.[13-15,18,19,21,22] Nine guidelines made recommendations regarding the treatment of DR-TB.[14-22] A summary of the topics covered by the recommendations within the guidelines are presented in Appendix 4, in Table 6 (identification of DR-TB) and Table 7 (treatment of DR-TB). Given the vast number of recommendations across multiple different identification tests, and treatments, 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 the Identification of DR-TB

Three low-quality guidelines[13-15] include recommendations regarding phenotypic DST for suspected DR-TB; these include conditional and strong recommendations based on very weak to moderate evidence from the two PHAC guidelines[13,14] and a strong recommendation from the Singapore guideline.[15]

Five guidelines[13,15,18,21,22] include recommendations regarding rapid molecular tests for DST for suspected DR-TB. This includes a recommendation in the high-quality NICE guideline,[21] in which the certainty of the recommendation is reflected in the wording of the recommendation. Recommendations were also made by the low-quality Singapore guideline[15] and PHAC guideline on active TB,[13] as well as the low-quality ERS/ECDC Standards,[22] and TBNET guideline, [18] however, these two guidelines did not report the strength of recommendations or the quality of the evidence.

The low-quality PHAC guideline on active TB,[13] also included a conditional recommendation based on moderate evidence regarding the use of nucleic acid amplification tests in remote settings.

The low-quality Italian Pediatric guideline for DR-TB[19] includes strong and moderate recommendations based on very low- to moderate-quality evidence regarding when to suspect DR-TB in children.

The low-quality TBNET guideline[18], which did not report the strength of the recommendations, includes a recommendation regarding screening close contacts of people with MDR-TB for latent or active TB.

Recommendations regarding the Treatment of DR-TB

The high-quality ATS/CDC/ERS/IDSA guideline[16] includes conditional and strong recommendations, based on evidence with very low- to low-certainty, regarding drug regimens for isoniazid resistant TB and MDR-TB, surgery for MDR-TB, the administration of injectable drugs, and preventive therapy for close contacts of people with MDR/XDR-TB.

The high-quality WHO DR-TB guideline[17] includes recommendations regarding drug regimens (composition and duration) for isoniazid resistant TB and MDR-TB, surgery for

MDR-TB, models of care for patients with MDR-TB, and treatment adherence methods for patients with MDR-TB (e.g., directly observed therapy, education). The recommendations in this guideline are mostly conditional based on evidence with very low to moderate certainty in estimates of effect, with some strong recommendations based on evidence with low to moderate certainty in estimates of effect.

The low-quality ERS/ECDC Standards[22] that did not report the strength of recommendations or the quality of the evidence, includes recommendations regarding individualized treatments regimens and models of delivering service for treatment MDR-TB.

The low-quality Sentinel guideline[20] covered regimens for new and repurposed drugs for children and adolescents with MDR-TB, however, these recommendations were not evaluated for strength or quality of the evidence.

The low-quality Italian Pediatric guideline for DR-TB[19] made a strong recommendation based on very low-quality evidence regarding who should treat pediatric patients with MDR-TB.

The low-quality Singapore guideline[15] includes recommendations regarding drug regimens for isoniazid resistant TB and MDR-TB, surgery for MDR-TB, and who should treat adults with MDR-TB. This guideline includes weak to strong recommendations, based on evidence ranging from expert opinion to high quality evidence.

The high-quality NICE guideline[21] includes recommendations regarding how to treat patients based on the results of the DST, treatment regimens for patients who are resistant to one TB drug, who should treat patients with MDR-TB, surgery for MDR-TB, clinical follow-up for patients with MDR-TB, and infection control practices when treating patients with MDR-TB. For this guideline, the certainty of the recommendation is reflected in the wording of the recommendation, and the strength of the evidence differs across recommendations, varying from weak to strong evidence.

The low-quality TBNET guideline[18] that did not report the strength of the recommendations or the quality of the evidence includes recommendations on how to treat patients based on the results of the DST, drug regimens for MDR-TB, monitoring the response to treatment for MDR-TB, treatment adherence, and infection control practices when treating patients with MDR-TB (e.g., isolation, respiratory controls).

The low-quality PHAC guideline for DR-TB[14] includes a strong recommendation based on moderate evidence regarding the treatment of isoniazid resistant TB (i.e., drug regimen and directly observed therapy). The other recommendations are conditional, based on weak to very weak evidence, and cover who should treat adults with MDR-TB, outpatient care for MDR-TB, drug regimens and individualized treatment for MDR-TB, the administration of injectable drugs, and directly observed therapy for MDR-TB.

Limitations

There are limitations associated with the evidence in this report on guidelines for DR-TB.

This report includes seven low quality guidelines,[13-15,18-20,22] with three guidelines[18,20,22] that did not grade the strength of the recommendations or the quality of the evidence. Most of the topics covered by the recommendations were discussed in two or more guidelines, including a high- and low-quality guidelines, however, some topics were only covered by recommendations in low-quality guidelines. The topics not covered in the high-quality

guidelines may have reduced reliability due to the uncertainty of the low-quality guidelines; these topics include: phenotypic DST, nucleic acid amplification tests in remote settings, who should treat pediatric patients with MDR-TB, and individualized treatment regimens for MDR-TB. In addition, treatment regimens for children and adolescents with MDR-TB were only covered in one low-quality guideline that did not grade the strength of the recommendations or the quality of evidence, thus there is a high amount of uncertainty associated with treating pediatric patients with MDR-TB.

The two PHAC guidelines[13,14] were developed for the Canadian context, but were assessed to be low-quality based on limited reporting of the methods. The PHAC guideline for active TB[13] includes a conditional recommendation for DST in remote settings, "*for example, hospitals in northern regions of Canada serving Aboriginal populations*" (p12) which may be of interest to Canadian health care providers given the high rates of TB borne by Indigenous peoples living in Canada;[2,3] however, due to the absence of reported methods, there is uncertainty associated with this recommendation. With the exception of this recommendation for DST, there are no other recommendations (Canadian or otherwise) regarding DR-TB specific to these populations (e.g., Indigenous peoples) or settings (e.g., rural or remote) of potential interest to Canadian health care providers. The recommendations in the PHAC DR-TB guideline[14] were developed for Canada, but are not specialized for specific populations or settings.

With regards to the generalizability of the other guidelines, one high-quality guideline is intended for global use,[17] six guidelines are meant to apply to the United States or Europe,[16,18-22] and one guideline was developed for Singapore.[15] It is unknown if the guidelines developed outside of Canada are generalizable to the Canadian context, as there may be geographical differences in resources and practices used for identifying and treating DR-TB compared to Canada.

This report was also limited by the large volume of recommendations about DR-TB published in the guidelines (i.e., between three and 29 recommendations per guideline), as it was not possible to compare and contrast the recommendations made across the various guidelines. Thus, it is unclear whether any of the recommendations contradict each other or whether there is agreement in the evidence across guidelines

Conclusions and Implications for Decision or Policy Making

This report was comprised of 10 guidelines[13-22] regarding DR-TB.

Seven guidelines covered the identification of DR-TB.[13-15,18,19,21,22] Three low-quality guidelines[13-15] made conditional and strong recommendations regarding phenotypic DST for suspected DR-TB. Five guidelines, including one high-quality guideline[21] and four low-quality guidelines[13,15,18,22] include recommendations regarding rapid molecular tests for DST for suspected DR-TB, however, two of these guidelines[18,22] did not report the strength of recommendations or the quality of the evidence. One low-quality[19] guideline includes moderate and strong recommendations regarding when to suspect DR-TB in Italian children. For the Canadian context, the PHAC guideline on active TB,[13] also included a conditional recommendation regarding DST in remote settings, however, this guideline did not publish the methods for searching for evidence or formulating the recommendations, limiting the quality of the guideline. The low-quality TBNET guideline[18], also covers screening close contacts of people with MDR-TB for TB, but did not grade the recommendations.

Nine guidelines discussed approaches to treating patients with DR-TB.[14-22] The three high-quality guidelines (i.e., ATS/CDC/ERS/IDSA guideline,[16] WHO DR-TB guideline,[17] and NICE guideline[21]) include conditional and strong recommendations regarding who should treat patients with DR-TB, how to treat patients based on the results of the DST, drug regimens (composition and duration) for isoniazid resistant TB and MDR-TB, surgery for MDR-TB, surgery for MDR-TB, the administration of injectable drugs, models of care for patients with MDR-TB, treatment adherence methods, infection control practices, and preventive therapy for close contacts of people with MDR/XDR-TB. Recommendations regarding who should treat adults with MDR-TB, drug regimens isoniazid resistant TB and MDR-TB, surgery for MDR-TB, outpatient care for MDR-TB, the administration of injectable drugs, and treatment adherence were also included in the low-quality guidelines from Singapore[15] and the PHAC guideline for DR-TB.[14] One low-quality guideline[19] includes a strong recommendation regarding who should treat pediatric patients in Italy. For the three low-quality guidelines that did not grade their recommendations,[18,20,22] the topics covered by the recommendations include drug regimens for MDR-TB,[18,22] monitoring treatment response, treatment adherence, infection control practices,[18] service models,[22] and regimens for new and repurposed drugs for children and adolescents with MDR-TB.[20] However, it is not clear whether these recommendation should be trusted.

Overall, this report identified three high-quality guidelines[16,17,21] that include recommendations for DR-TB. This report also identified seven low-quality guidelines[13-15,18-20,22] that may provide additional guidance on identifying and treating DR-TB, however, there is uncertainty associated with these low-quality guidelines and the recommendations should be interpreted with caution.

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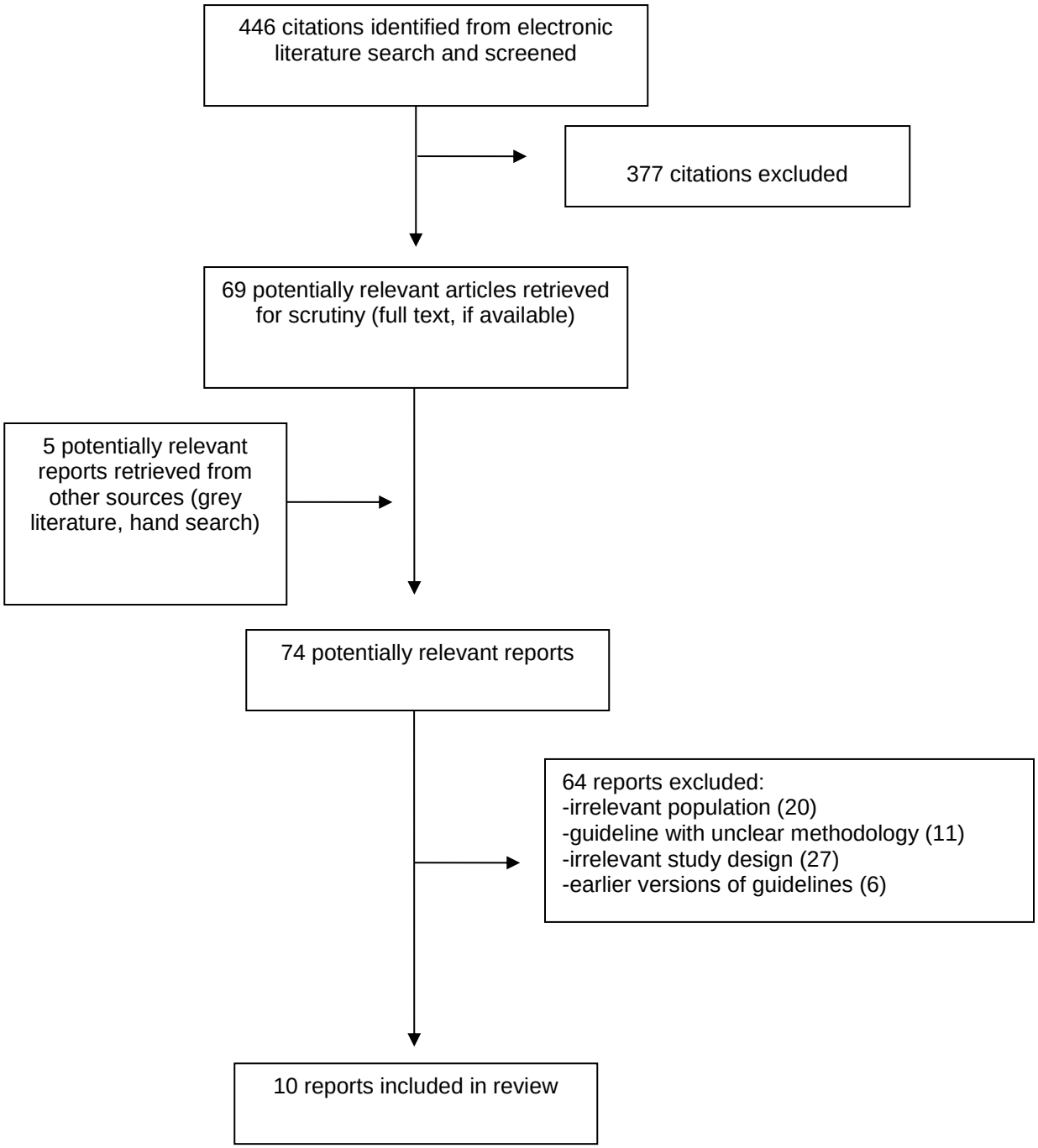
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Guidelines

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Technologies , Number of recommendations	Populations (# of recommendations)
Treatment of Drug-Resistant Tuberculosis An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline ATS/CDC/ERS/IDSA [16] 2019	**Country:** United States and Europe **Funding:** ATS, U.S. CDC, ERS, and IDSA **Developing institution:** ATS, CDC, ERS, IDSA	The treatment of DR-TB, including MDR-TB, and isoniazid-resistant but rifampin-susceptible TB.	Healthcare providers working with patients with TB, in settings where treatment is individualized and where mycobacterial cultures, drug susceptibility testing, and radiographic facilities are available.	Treatment of MDR-TB: - drugs and regimens - surgery **Total # of Recommendations:** 25	**Main population:** Patients with MDR-TB (25)
WHO consolidated guidelines on drug-resistant tuberculosis treatment WHO DR-TB[17] 2019	**Country:** Global **Funding:** USAID supported the guideline development process. McGill University coordinated he consolidation of the patient level database, which was funded by ATS, IDSA and the U.S. CDC. **Developing institution:** World Health Organization	Consolidation of 8 previous WHO guidelines (with no update), for a comprehensive set of recommendations for the treatment and care of DR-TB. (Replaces the other WHO recommendations relating to the treatment of multidrug- and rifampicin-resistant tuberculosis)	Health professionals who care for patients with DR-TB	Treatment of DR-TB: - drugs and regimens - surgery - DOT **Total # of Recommendations:** 29	**Main population:** Patients with MDR-TB (26) **Subgroups**: Isoniazid-resistant TB (2) Patients with HIV (1)
ERS/ECDC Statement: European Union standards for tuberculosis care, 2017 update ERS/ECDC Standards[22] 2018	**Country:** Europe **Funding:** European Respiratory Society (ERS) **Developing institution:** ERS and European Centre for Disease Prevention and Control (ECDC)	Incorporate the new scientific evidence that has become available since the publication of the European Union Standards for Tuberculosis Care in 2012.	Clinicians; health care professionals	Identification: -tests to identify DR-TB Treatment of DR-TB: - drugs and regimen **Total # recommendations:** 3	**Subgroups**: Patients suspected of DR-TB (1) Patients with DR-TB (2)

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Technologies , Number of recommendations	Populations (# of recommendations)
New and Repurposed Drugs for Pediatric Multidrug-Resistant Tuberculosis: Practice-based Recommendations Sentinel Project[20] 2017	**Country:** United States **Funding:** Not specified **Developing institution:** Sentinel Project on Pediatric Drug-Resistant Tuberculosis	Recommendations for new and repurposed drugs for treating pediatric patients with MDR-TB	**Primary users**: clinicians and health care professionals and policy-makers	Treatment of active MDR-TB - drugs and regimen **Total # of Recommendations: 5**	**Main population:** Children and adolescents with MDR-TB (5)
Recommendations for treating children with drug-resistant tuberculosis Italian Pediatric DR-TB[19] 2016	**Country**: Italy **Funding**: grant from the Italian Ministry of Health **Developing institution:** Italian Pediatric TB Study Groups	Recommendations for identifying and treating pediatric patients with MDR-TB and extensively DR-TB	**Primary users:** Those who care for pediatric patients with TB	Identifying MDR-TB in children Treatment of MDR-TB in children **Total # of Recommendations:** 4	**Main populations:** Children who may have DR-TB (3) Children with MDR-TB (1)
Prevention, Diagnosis and Management of Tuberculosis MOH Singapore[15] 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.	Identification of MDR-TB: - rapid molecular tests -drug susceptibility testing Treatment of DR-TB: - treatment regimen - surgery **Total # of Recommendations:** 5	**Main populations:** People suspected of having MDR-TB (2) People with MDR-TB (3)
Tuberculosis NICE[21] 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, TB control boards, directors of public health, volunteers, people with TB and their caregivers.	Infection control practices Identification of MDR-TB: - rapid molecular tests Treating DR-TB - drugs and regimen **Total # of Recommendations:** 10	**Main populations:** People suspected of having MDR-TB (1) People with MDR-TB or DR-TB (16)

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Technologies , Number of recommendations	Populations (# of recommendations)
Management of patients with multidrug resistant/ extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement TBNET[18] 2014	**Country:** Germany, United Kingdom **Funding:** Not specified **Support:** EU FP7 project, German Center for Infection Research, Federal Ministry of Education and Research, UK Medical Research Council, National Institute for Medical Research and National Institute of Health Research **Developing institution:** Tuberculosis Network European Trials Group (TBNET)	To summarize the current knowledge on the prevention, diagnosis and treatment of adults and children with MDR/XDR-TB and their contacts, and provides expert consensus recommendations on questions where scientific evidence is still lacking.	Clinicians; health care professionals	Infection control practices Identification of MDR/XDR-TB Treating MDR-XDR-TB **Total # of recommendations: 15**	**Main population:** Individuals with MDR/XDR -TB (10) **Subgroups:** Individuals suspected of MDR/XDR -TB (3) Individuals in contact with MDR/XDR patients (2)
Canadian Tuberculosis Standards Chapter 8: Drug-Resistant Tuberculosis PHAC DR-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 DR-TB	Public health and clinical professionals	Identification of DR-TB - drug susceptibility testing Treatment of DR-TB - DOT - drugs and regimen - care provider and location **Total # of Recommendations**: 11	**Main population:** - patients with DR-TB (11)
Canadian Tuberculosis Standards Chapter 3: Diagnosis of Active Tuberculosis and Drug Resistance PHAC Identification Active TB[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	Diagnosis of active TB	Public health and clinical professionals	Identification of DR-TB: - drug susceptibility testing **Total # of Recommendations**: 3	**Subgroups**: - people suspected of DR-TB (3)

Guideline title, author, and year	Country, Funding body, Developer	Scope or Objective	Target Users	Technologies , Number of recommendations	Populations (# of recommendations)
	Lung Association, and the Public Health Agency of Canada				

ATS = American Thoracic Society; CDC = Centers for Disease Control and Prevention; DOT = direct observed therapy; DR-TB = drug resistant TB; ECDC= European Centre for Disease; ERS = European Respiratory Society; IDSA = Infectious Diseases Society of America; MDR = multi-drug resistant; MOH = Ministry of Health; NICE = National Institute for Health Care Excellence; PHAC = Public Health Agency of Canada; TB = tuberculosis; TBNET = Tuberculosis Network European Trials; WHO = World Health Organization; XDR-TB = extensively drug resistant TB.

Table 3: Methods used in the Guidelines

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
Treatment of Drug-Resistant Tuberculosis An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline ATS/CDC/ERS/IDSA [16] 2019	A multi-disciplinary panel of experts (including methodologists), screened for conflicts of interest, was selected to develop the guideline. The panel also included a patient representing the views of the community. The development of the guideline followed procedures and methods outlined in a guideline development commitee (available online) and the Guideline Development Tool by GRADE. The panel developed 21 PICO questions to address in the guideline. The writing committee selected priority outcomes for each question. Systematic reviews were conducted for each PICO question. Face-to-face meetings were held between May 2016 to May 2017, during which the panel discussed specific questions, the evidence, and drafted recommendations.	For each PICO question, SRs were conducted. They searched MEDLINE, Embase 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 SR. Individual patient data level meta-analysis was used that has been published. The quality of studies were assessed using ROBINS-1 tool and Cochrane Collaboration risk of bias tool. Studies of high quality met at least four of the six selection criteria and moderate quality studies met at least two of the six selection criteria. All of studies were considered low quality. Certainty of the evidence was	The guideline panel used the GRADE approach, evidence summaries and the evidence-to-decision tables to formulate and decide on the recommendations. For each recommendation, the panel agreed on the quality of the evidence, the balance of benefits and harms, and the patient preferences. The panel also considered resource implications. Recommendations were voted on by the panel and agreed upon the final wording of the recommendation. The final recommendations approved by all members of the guideline panel. Recommendations were rated as either “strong” or “weak/ conditional”	*“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 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*	The final draft was reviewed and approved for all the member of the committees and peer reviewed my experts for supporting organizations. The guideline also sought opinion from the public and incorporated all comment prior to final publication. The guideline will be reviewed every three years which will determine if it needs updating.

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
		categorized into 4 levels (e.g., very low to high). Evidence-to-decision tables were prepared based on benefits, harms, patient values and costs.		*decisions consistent with their values and preferences.* *For policy makers: Policy-making will require substantial debate and involvement of various stakeholders"* • *(pg 6, Supplementary material)*	
WHO consolidated guidelines on drug-resistant tuberculosis treatment WHO DR-TB[17] 2019	Development of the guidelines followed the process outlined in the WHO Handbook for Guideline Development.[27] Three groups were established: 1. The steering group, composed of WHO staff, who oversee the guideline development process. 2. GDG, composed of methodologists, external content experts, researchers, and representatives from patient groups and civil society. The GDG formulate recommendations, the general scope and content of the guideline. 3. External review group, composed of experts with an interest in DR-TB, who reviewed the draft guidelines.	The steering committee drafted and scoped the research questions and PICO criteria. The PICO criteria and research questions were summarized for each guideline was summarized. The SR team coordinated the consolidation of individual patient data for analysis (meta-analysis) The GRADE approach was used to assess the quality of the body of evidence and the strength of the recommendations for each PICO question. The strength of the recommendation reflected the degree of confidence of the GDG that the desirable effects	The evidence for each PICO question was appraised and used to formulate recommendations. The GRADE "evidence-to-decision" tables were used to guide discussions on the benefits and harms, the quality of evidence, the cost, feasibility, acceptability, equity, values, and preferences. The GDG used these factors to determine the recommendations and the strength of the recommendations. The recommendations and supporting documents were reviewed and	Four levels of evidence quality: High: Very confident that the true effect lies close to that of the estimate of the effect. Moderate: Moderately confident that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different. Two levels of strength of the recommendation: Strong: the GDG was confident that the desirable effects of adherence would outweigh the undesirable effects. Could be either in favor of or against an intervention. Conditional: the GDG concluded that the desirable effects of adherence would probably outweigh the undesirable effects, but the	The external review group reviewed the draft of the final guideline, and remarks were evaluated by the steering group and incorporated into the final version of the guidelines. The guideline does not indicate when an update will take place.

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
		outweighed the undesirable effects. Implications of the strength of the recommendation for different users was taken into consideration.	endorsed by all GDG members.	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.	
ERS/ECDC Statement: European Union standards for tuberculosis care, 2017 update ERS/ECDC Standards[22] 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	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

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
		Cochrane Database of Systematic Reviews The guideline did not state whether the evidence was critically appraised by experts or committee members.			
New and Repurposed Drugs for Pediatric Multidrug-Resistant Tuberculosis: Practice-based Recommendations Sentinel Project [20] 2017	These guidelines were developed using a process previously described.[25] A writing committee wrote the initial draft of guidelines and an expert panel facilitated the process by providing insight regarding TB clinical studies.	A SR[26] was conducted using a comprehensive literature search of PubMed, PubMed, Ovid, Embase, Cochrane Library, PsychINFO, and BioMed Central databases from inception to October 31, 2011. A review of recent WHO guidelines was conducted. The SR did not assess the risk of bias of the individual primary studies. The guideline did not critically appraise the evidence. Efficacy and safety was summarized narratively.	Recommendations from available guidelines were reviewed, and, where evidence was lacking, expert consensus was reached. An expert panel formulated the recommendation through a consensus process which included clinical health professionals within the Sentinel Project on Pediatric DR-TB.	The guideline did not use a grading system.	Process for external review not reported. Process for updating the guidelines not reported.
Recommendations for treating children	Followed the “Consensus Conference method”.	Systematic review of MEDLINE and the Cochrane Database of	The evidence was presented and discussed at various	The quality of evidence was broken down into six categories:	No details were given if the guideline underwent an

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
with drug-resistant tuberculosis Italian Pediatric DR-TB [19] 2016	The Working Group agreed on a list of clinical problems for the guideline. An expert panel responsible for formulating the recommendations and assessing the evidence consisted of a variety of experts from various fields and backgrounds.	Systematic Reviews, from inception to December 2014. The evidence review focused on clinical problems related to MDR and XDR-TB for patient between 0 and 18 years. A targeted search was conducted in addition to the SR through a Consensus Conference method. The Working Group critically appraised the guideline using the SIGN checklist.[28]	meetings, and the Delphi method was used to reach a consensus if the evidence did not provide unambiguous recommendations. The final text for the recommendations was revised based on the discussions and submitted by email to participants for final approval at the Consensus Conference. The Scottish Intercollegiate Guidelines Network checklist[28] was used but no further detail was given	I = Well- designed, randomized, controlled study and/or SR II = Well-designed RCTs III = Cohort studies or their MA IV = Retrospective case-controlled studies or their MA V = Case series without control group VI = Opinions from authorities based on clinical experience The strength of the recommendations were categorized by: A = Panel strongly supports a recommendation for use B = Panel moderately supports a recommendation for use C = Panel marginally supports a recommendation for use	external review process or will undergo an update
Prevention, Diagnosis and Management of Tuberculosis MOH Singapore[15] 2016	Guidelines were produced by a committee expert, including physicians, infectious disease experts and the ministry of health. The guidelines were developed by adapting the existing guidelines, a review of the relevant literature, and expert clinical consensus.	Not described The critical appraisal of the individual studies as not described. The recommendations were appraised by scoring the strength of the evidence, and the grade of the recommendation. (No other details provided)	The development of the recommendations were guided by two principles: - Recommendations were supported by evidence and expert consensus - Treatment should maximize benefit and minimize harm	"*Levels of Evidence:* *1++ = High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias.* *1+ = Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.* *1- = Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias* *2++ = High quality systematic reviews of case control or cohort studies. High quality*	No external review process reported. Recommends that guidelines are updated within five years, or sooner, if evidence is available.

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
				case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal *2+ = Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal* *2- = Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal* *3 = Non-analytic studies, e.g. case reports, case series* *4 = Expert opinion* *Grades of recommendation:* *A = At least one meta-analysis, systematic review of RCTs, or RCT rated as 1+ + and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results* *B = A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1+ + or 1+* *C = A body of evidence including studies rated as 2+, directly applicable to the target*	

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
				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[21] 2016	Update to a previous 2011 guideline. Developed in accordance to the NICE manual for developing guidelines[29] A technical team drafted PICO questions during scoping, which were refined and validated by the guideline development group. Both teams jointly prepared a protocol for each question, which were used to draft the SRs.	35 SRs were conducted to address the questions. Evidence published up to December 2014 was identified from the following databases: Medline (1950 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 onwards), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and Health Technology Assessment Database. Evidence was limited to publications in English.	The results of the meta-analyses were sent to the guideline development group prior to each meeting. At the meetings, the findings were presented in evidence tables, excluded study tables, GRADE profiles, and evidence statements on the findings. Statements summarizing the groups interpretation of the findings was used to form the recommendations. A consensus method was used to formulate the recommendations. Specific 'linking evidence to	The wording used in the recommendations denotes the certainty in the recommendations. The terms used in this guideline are: "Offer' – for the vast majority of patients, an intervention will do more good than harm 'Do not offer' – the intervention will not be of benefit for most patients 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient." (pg. 90)	The guideline was published online for two formal rounds of public and stakeholder consultation prior to publication. This process involves responding to each comment and maintaining an audit trail. NICE follows a protocol for partial and full updates of guidelines. Areas not updated in this guideline may be addressed two 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, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
		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	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.		

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
		prepared. Criteria considered included risk of bias, inconsistency, indirectness, imprecision, and other considerations. Evidence synthesis: meta-analyses were conducted where it was possible to combine the evidence for the outcomes. An extensive network meta-analysis was conducted for synthesize the evidence for the treatment of LTBI.			
Management of patients with multidrug resistant/ extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement TBNET[18] 2014	The document structure and outline were conducted by the two coordinating authors and agreement by the TBNET steering committee, co-authors and international experts in the field. The writing committee searched available evidence.	A systematic search of the literature was not conducted. A review of the available literature was accomplished by the members of the writing committee and the search for evidence included handsearching journals, reviewing previous guidelines, and searching electronic databases including MEDLINE and PubMed.	Final decisions for formulating recommendations were based upon the result of literature review and practical experience by committee members. Final recommendations were developed by coordinating authors. Consensus statements were developed in a stepwise approach: 1. 15 preliminary recommendations	The guideline did not use a grading system.	Process for external review not reported. Process for updating the guidelines not reported.

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
		The guideline did not state if the evidence was critically appraised by experts.	were drafted by the authors 1. alternative statements were collected 3. chapter leaders selected one preferred statement among the suggested statements 4. For each recommendation, the statement that received the most votes was included 5. All authors indicated their agreement, disagreement, or abstinence from a decision on the recommendations. These decisions are reported with the recommendations.		
Canadian Tuberculosis Standards Chapter 8: Drug-Resistant Tuberculosis PHAC DR-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 of participants or inconsistent results, or multiple observational studies of strong	Process for external review not reported. Process for updating the guidelines not reported.

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
				design providing consistent results. Weak = Evidence from observational analytic studies that had weak designs, weak effect estimates or inconsistent results, or generalization from a randomized trial that involved one type of patients to a different group of patients. Very weak = Evidence from published case series and/or opinion of the authors and other experts Strength of Recommendations Strong = The recommendation implies that the desirable effects clearly outweigh undesirable effects, was based on strong/moderate evidence and was considered unlikely to change with additional published evidence. Conditional = The recommendation implies that the desirable effects are closely balanced with undesirable effects, and/or was based on moderate/weak/very weak evidence and was considered likely to change with additional published evidence." (pg. 3-4, from Preface[30])	
Canadian Tuberculosis Standards Chapter 3: Diagnosis of Active	This 7th edition of the Canadian Tuberculosis Standards builds off previous versions and has been revised to include new information. Each chapter is	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	Process for external review not reported. Process for updating the guidelines not reported.

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
Tuberculosis and Drug Resistance PHAC Identification Active TB[13] 2014	written by experts from across Canada.			(etiologic evidence) with strong designs and consistent results. Moderate = Evidence from only one RCT or RCTs with an inadequate number of participants or inconsistent results, or multiple observational studies of strong design providing consistent results. Weak = Evidence from observational analytic studies that had weak designs, weak effect estimates or inconsistent results, or generalization from a randomized trial that involved one type of patients to a different group of patients. Very weak = Evidence from published case series and/or opinion of the authors and other experts Strength of Recommendations Strong = The recommendation implies that the desirable effects clearly outweigh undesirable effects, was based on strong/moderate evidence and was considered unlikely to change with additional published evidence. Conditional = The recommendation implies that the desirable effects are closely balanced with undesirable effects, and/or was based on moderate/weak/very weak evidence and was considered	

Guideline and year	Development Process	Evidence collection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
				likely to change with additional published evidence." (pg. 3-4, from Preface[30])	

ATS = American Thoracic Society; CDC = Centers for Disease Control and Prevention; DR-TB = drug resistant TB; ECDC= European Centre for Disease; ERS = European Respiratory Society; ESTC= the European Union Standard for Tuberculosis Care; GDG = guideline development group; GRADE = Grades of Recommendation, Assessment, Development and Evaluation; IDSA = Infectious Diseases Society of America; LTBI = latent TB infection; MA = meta-analysis; MDR = multi-drug resistant; NICE = National Institute for Health Care Excellence; NRS = non-randomized studies; PHAC = Public Health Agency of Canada; PICO = population, intervention, comparator, outcomes; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RCT = randomized controlled trial; SR = systematic review; TB = tuberculosis; TBNET = Tuberculosis Network European Trials; WHO = World Health Organization; XDR-TB = extensively-drug resistant TB.

Appendix 3: Critical Appraisal of Included Publications

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

Item	Guideline				
	ATS/CDC/ERS/IDSA [16]	WHO DR-TB[17]	ERS/ECDC Standards[22]	Sentinel Project[20]	Italian Pediatric DR-TB [19]
Domain 1: Scope and Purpose					
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	No	Yes	Partially
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes	Yes
Domain 2: Stakeholder Involvement					
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Partially	Partially	Partially
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Yes	No	Partially	No
6. The target users of the guideline are clearly defined.	Yes	Yes	Partially	No	Partially
Domain 3: Rigour of Development					
7. Systematic methods were used to search for evidence.	Yes	Partially	Partially	Partially	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Partially	No	Yes	Partially
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes	No	No	No
10. The methods for formulating the recommendations are clearly described.	Yes	Yes	No	No	Partially
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes	No	Partially	Partially
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Partially	Partially

Item	Guideline				
	ATS/CDC/ERS/IDSA [16]	WHO DR-TB[17]	ERS/ECDC Standards[22]	Sentinel Project[20]	Italian Pediatric DR-TB [19]
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Yes	Yes	No	No
14. A procedure for updating the guideline is provided.	Yes	No	No	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	Partially	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes	Partially
Domain 5: Applicability					
18. The guideline describes facilitators and barriers to its application.	Yes	Yes	No	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes	No	Partially	No
20. The potential resource implications of applying the recommendations have been considered.	Yes	Partially	No	Partially	No
21. The guideline presents monitoring and/or auditing criteria.	No	Yes	No	No	No
Domain 6: Editorial Independence					
22. The views of the funding body have not influenced the content of the guideline.	Yes	Yes	Partially	No	Partially
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Partially	Yes	Yes

ATS= American Thoracic Society; CDC = Centers for Disease Control and Prevention; DR-TB = drug resistance TB; ECDC = European Centre for Disease Prevention and Control; ERS = European Respiratory Society; IDSA = Infectious Disease Society of America; LTBI = latent tuberculosis infection; MOH = Ministry of Health; TB = tuberculosis; WHO = World Health Organization.

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

Item	Guideline				
	MOH Singapore [15]	NICE[21]	TBNET[18]	PHAC DR-TB[14]	PHAC Identification Active TB[13]
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.	No	Yes	Partially	No	No
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Partially	Yes	Yes	Partially	No
Domain 2: Stakeholder Involvement					
4. The guideline development group includes individuals from all relevant professional groups.	Partially	Yes	Yes	Partially	Partially
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No	Yes	No	No	No
6. The target users of the guideline are clearly defined.	Yes	Yes	No	Partially	Partially
Domain 3: Rigour of Development					
7. Systematic methods were used to search for evidence.	No	Yes	Partially	No	No
8. The criteria for selecting the evidence are clearly described.	No	Yes	No	No	No
9. The strengths and limitations of the body of evidence are clearly described.	Partially	Yes	No	No	No
10. The methods for formulating the recommendations are clearly described.	No	Yes	Yes	No	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	No	Yes	No	Partially	Partially
12. There is an explicit link between the recommendations and the supporting evidence.	Partially	Yes	Partially	No	No
13. The guideline has been externally reviewed by experts prior to its publication.	No	Yes	No	Partially	Partially
14. A procedure for updating the guideline is provided.	Yes	Yes	No	No	No
Domain 4: Clarity of Presentation					

Item	Guideline				
	MOH Singapore [15]	NICE[21]	TBNET[18]	PHAC DR-TB[14]	PHAC Identification Active TB[13]
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	Partially	Yes	Yes
Domain 5: Applicability					
18. The guideline describes facilitators and barriers to its application.	No	No	Partially	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No	Partially	No	No	No
20. The potential resource implications of applying the recommendations have been considered.	No	Yes	Partially	No	No
21. The guideline presents monitoring and/or auditing criteria.	Partially	Yes	No	No	No
Domain 6: Editorial Independence					
22. The views of the funding body have not influenced the content of the guideline.	No	Partially	Yes	Partially	Partially
23. Competing interests of guideline development group members have been recorded and addressed.	No	Yes	Yes	No	No

MOH = Ministry of Health; NICE = National Institute for Health Care Excellence; PHAC = Public Health Agency of Canada; TB = Tuberculosis; TBNET = TB Network European Trials

Appendix 4: Main Study Findings

Table 6: Summary of the topics regarding the identification of DR-TB

Topics Covered by the recommendation	ERS/ECDC Standards[2] [2]	Italian Pediatric DR-TB[19]	MOH Singapore[1] [5]	NICE[21]	TBNET[18]	PHAC DR-TB[14]	PHAC Identification Active TB[13]
Phenotypic DST			X			X	X
Rapid molecular tests for DST	X		X	X	X		X
NAAT in remote settings, for DST							X
When to suspect DR-TB in children		X					
Screening close contacts of people with MDR-TB for active and latent TB					X		

CDC = Centers for Disease Control and Prevention; DST = drug susceptibility testing; DR-TB = drug resistant TB; ECDC= European Centre for Disease; ERS = European Respiratory Society; MDR = multi-drug resistant; NAAT = Nucleic Acid Amplification Test; NICE = National Institute for Health Care Excellence; PHAC = Public Health Agency of Canada; TB = tuberculosis; TBNET = Tuberculosis Network European Trials; WHO = World Health Organization.

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

Table 7: Summary of the topics regarding the treatment of DR-TB

Topics Covered by the Recommendations	ATS/CDC/ERS/IDSA [16]	WHO DR-TB[17]	ERS/ECDC Standards[22]	Sentinel Project[2] [0]	Italian Pediatric DR-TB[19]	MOH Singapore[15]	NICE[21]	TBNET[1] [8]	PHAC DR-TB[14]
How to treat patients based on results of rapid molecular testing							X	X	
Treatment based on definitive phenotypic susceptibility results							X		
Treatment regimens for DR-TB (i.e., isoniazid, pyrazinamide, ethambutol, or rifampicin resistance, but not MDR or XDR TB)							X		
Drug regimen for isoniazid resistant TB	X	X				X			X
Who should treat MDR-TB (adults)						X	X		X
Who should treat DR-TB (pediatric patients)					X				
Outpatient (ambulatory) care for MDR-TB		X							X
Model for service delivery for MDR-TB		X	X						
Individualized treatment regimens for MDR-TB			X						X
Drug regimens (duration and drug selection) for MDR-TB	X					X		X	X
Composition and duration of longer drug regimens for MDR-TB		X							

Topics Covered by the Recommendations	ATS/CDC/ERS/IDSA [16]	WHO DR-TB[17]	ERS/ECDC Standards[22]	Sentinel Project[20]	Italian Pediatric DR-TB[19]	MOH Singapore[15]	NICE[21]	TBNET[18]	PHAC DR-TB[14]
Shorter regimen for MDR-TB	X	X							
New and repurposed drugs and regimens for MDR-TB in children and adolescents				X					
Surgery for MDR-TB	X	X				X	X		
Administration of injectable drugs	X								X
Monitoring response to treatment for MDR-TB		X						X	
Clinical follow-up for patients with MDR-TB							X	X	
Education and counselling for patients with DR or MDR-TB		X							
Treatment adherence interventions for patients with DR or MDR-TB		X						X	
DOT for isoniazid resistant TB									X
DOT for MDR-TB		X							X
Video observed therapy for patients with DR or MDR-TB		X							
Preventive TB therapy for close contacts of people with MDR/XDR-TB	X							X	
Isolation of patients with MDR/XDR-TB							X	X	
Respiratory controls: ventilation, respirators, cough hygiene for MDR/XDR-TB							X	X	
When to discharge patients with MDR/XDR-TB							X	X	

ATS = American Thoracic Society; CDC = Centers for Disease Control and Prevention; DR-TB = drug resistant TB; DOT = directly observed treatment; ECDC= European Centre for Disease; ERS = European Respiratory Society; IDSA = Infectious Diseases Society of America; MDR = multi-drug resistant; NAAT = Nucleic Acid Amplification Test; NICE = National Institute for Health Care Excellence; PHAC = Public Health Agency of Canada; TB = tuberculosis; TBNET = Tuberculosis Network European Trials; WHO = World Health Organization; XDR-TB = extensively-drug resistant TB.

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

Appendix 5: Additional References of Potential Interest

Guidelines with Unclear Methodology

Piubello A, Aït-Khaled N, Caminero JA, et al. Field guide for the management of drugresistant tuberculosis. Paris (FR): International Union Against Tuberculosis and Lung Disease, 2018; http://www.tbonline.info/media/uploads/documents/theunion_dr-tb-guide.pdf Accessed 2020 Mar 9.