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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Prevention of Tuberculosis: A Review of Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	January 29, 2020
Report Length:	40 Pages

CADTH

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Cite As: Prevention of Tuberculosis: A Review of Guidelines. Ottawa: CADTH; 2020 Jan. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AGREE II	Appraisal of Guidelines for Research & Evaluation 2
BCG	Bacillus Calmette-Guérin
CADTH	Canadian Agency for Drugs and Technologies in Health
CDC	Centers for Disease Control and Prevention
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
LTBI	Latent tuberculosis infection
MDR-TB	Multi-drug resistant tuberculosis
NICE	National Institute for Health and Care Excellence
PHAC	Public Health Agency of Canada
RCT	Randomized controlled trial
SR	Systematic Review
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,[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). Individuals with TB are categorized into latent TB infection (LTBI) and active TB disease.[1,2] LTBI refers to an individual whom does not have TB disease and may not possess any symptoms but has the *M. tuberculosis* infection. [2] Persons with LTBI cannot spread TB infection to others and are not considered infectious. However, those with the LTBI can develop TB disease if they do not receive proper treatment or have a compromised immune system. [2] 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. [2] Symptoms can progress right away or can develop long after infection, depending on the individual. Symptoms can vary between individuals who have TB infection but often experience weight loss, fever, fatigue, chills, excessive coughing and chest pain. [2] In comparison to LTBI, persons with TB disease can spread the TB bacteria to others and are considered infectious. [2]

TB continues to be burdensome in developing countries as the disease is associated with poverty, poor sanitation or hygiene practices and being easily transmissible from person to person. [1] Although TB is more common and prevalent in low and middle income countries, 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),[3] Canada has one of the lowest rates of active TB in the world. However, annual rates of TB have remained the same in the country since the 1980's rather than steadily declining.[3] 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.[3,4] Migrants and Indigenous peoples are not the only populations that are at higher risk of TB infection in Canada. Workers travelling to areas with a high incidence of TB, and those individuals who are immunocompromised (e.g., patients living with HIV, children, infants) or workers (e.g., healthcare professional) who are in direct contact with immunocompromised people are also at high risk of TB infection.[3] Additionally, homeless persons, prison staff and inmates are considered high-risk

populations due to the proximity to others and conditions that enable the transmission of TB bacteria.[3]

Prevention and infection control are necessary to reduce the spread of TB. There are a variety of preventative mechanisms used by public health organizations to reduce the transmission of TB. For example, the Bacillus Calmette-Guérin (BCG) vaccine, which is approved for the prevention of TB, may be administered at birth in countries with high incidence of TB. While educating health care staff about TB and screening health care workers for LTBI may be appropriate preventative measures to reduce the spread of TB disease in hospital settings. Depending on the setting and the population at risk, the interventions used for the prevention of TB may differ. There are multiple guidelines published about TB, and these guidelines may vary in quality and the topics covered.[5] The purpose of this report is to review and critically appraise the evidence-based guidelines regarding interventions for the prevention of TB. This report is part of series of evidence reviews on TB guidelines. This report can serve as a guidance document to identify which guidelines include recommendations for specific prevention methods and specific populations of interest, and the strength of the guidelines.

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 for the prevention of tuberculosis infection?

Key Findings

Nine evidence-based guidelines for the prevention of tuberculosis (TB) infection were identified and included in this report.

Five guidelines include recommendations regarding the use of the Bacillus Calmette-Guérin (BCG) vaccine for the prevention of TB. Six guidelines include recommendations regarding risk reduction measures to reduce the risk of TB transmission.

Overall, there are three high-quality, one moderate-quality, and five low-quality guidelines that include between one and 71 recommendations on the prevention of TB. The recommendations vary in strength and the quality of the evidence. The population and setting of interest may determine which guideline(s) and which recommendation(s) are of interest.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was tuberculosis.

Search filters were applied to limit retrieval to guidelines. The search was also limited to English language documents published between Jan 1, 2014 and Nov 7, 2019.

Selection Criteria and Methods

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

Table 1: Selection Criteria

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

Exclusion Criteria

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

Critical Appraisal of Individual Studies

The included guidelines were assessed with the AGREE II instrument.[6] 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, 65 publications were excluded for various reasons, and 9 evidence-based guidelines met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[7] 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

Nine evidence-based guidelines were identified and included in this report.[8-14] Detailed characteristics and methods of the guidelines are available in Appendix 2, Table 2 and Table 3.

Study Design

Nine relevant evidence-based guidelines were identified.[8-16] Three of these guidelines were developed by the World Health Organization (WHO); one was published in 2019[13] and the other two were published in 2018.[8,12] Three guidelines were published in 2016, and they were developed by the National Institute for Health and Care Excellence (NICE),[9] the Italian Pediatric TB Study Group[10] and the Singapore Ministry of Health.[14] Two guidelines were developed by the Public Health Agency of Canada (PHAC) and were published in 2014.[15,16] These two guidelines from PHAC represent two chapters from a larger report by PHAC: the 7th edition of the Canadian Tuberculosis Standards.[17] The other guideline was published in the 2014 and was prepared by members of the US Centers for Disease Control and Prevention (CDC).[11]

Three guidelines followed standardized methodology for guideline development available online from their institution;[18,19] there were the WHO Guideline on TB Infection Prevention,[13] the WHO consolidated LTBI guidelines,[12] and the NICE Guideline.[9] The other WHO Position Paper on the BCG vaccine[8] followed the development process outlined for WHO vaccine position papers.[20] The Italian Pediatric guideline[10] reported following the 'Consensus Conference Method' for the developing the recommendations, but did not provide a reference. The Singapore Guideline[14] the PHAC guidelines,[15,16] and the CDC guideline[11] provided brief details of their guideline development process, but did not cite published methodology. Four guidelines used systematic searches of various electronic databases to identify evidence (WHO Guideline on TB Infection Prevention,[13] WHO consolidated LTBI guidelines,[12] Italian Pediatric guideline,[10] and the NICE Guideline[9]). Five guidelines did not provide the specific details of the methods used to identify evidence (WHO Position Paper on the BCG vaccine,[8] Singapore Guideline,[14] both PHAC guidelines,[15,16] and the CDC guideline[11]). The three WHO guidelines[8,12,13] and the NICE Guideline[9] used the GRADE approach to assess the quality of the evidence, and included evidence-to-decision tables. The WHO Guideline on TB Infection Prevention[13] and the WHO consolidated LTBI guidelines[12] both provided ratings of the quality of evidence and strength of recommendation, whereas the WHO Position Paper on the BCG vaccine[8] did not. The NICE Guideline[9] included a discussion of the quality of the evidence, and the wording of recommendations reflects the certainty in the recommendations. The Italian Pediatric guideline,[10] the Singapore Guideline,[14] and both PHAC guidelines[15,16] provided ratings of the quality of evidence and strength of recommendation, but did not provide the methods for grading the evidence. The CDC guideline[11] did not described any critical appraisal methods, and did not report the quality of evidence or the strength of the recommendations. The rating systems, where available, are reported in Table 3. Decisions about the recommendations were reached through consensus in six guidelines,[8-10,12-14] and the methods for formulating the recommendations were unclear in the PHAC guidelines[15,16] and the CDC guideline.[11]

Country of Origin

The two PHAC guidelines are meant to apply to Canada.[15,16]The three guidelines from the WHO are meant to apply globally.[8,12,13] The NICE guideline[9] is meant to apply to the United

Kingdom. The other guidelines are meant to apply to Singapore,[14] Italy,[10] and the United States.[11]

Patient Population

The main target populations covered by the guidelines included populations at risk of TB[8,9,13,14,16] and health care workers.[9,13-15] Other populations covered included travelers to countries with high incidence of TB,[8,16] contacts of patients with multi-drug resistant TB (MDR-TB),[12] pediatric patients in Italy,[10] and US workers travelling for health care or humanitarian work.[11] For four guidelines, the population covered by whole guideline is broader (e.g., also included people with latent or active TB) than the population of interest for this review, and only the populations covered by the relevant components of the guidelines are included in this report.[9,12-14]. The intended users for the three WHO guidelines,[8,12,13] the NICE guideline,[9] the Singapore guideline,[14] and the two PHAC guidelines[15,16] were health care workers and other key TB stakeholders. The intended users of the CDC guideline were US health care workers,[11] and the Italian Pediatric guideline[10] did not specify who the intended users were.

Interventions

Five guidelines covered the use of the BCG vaccine.[8-11,16] Six guidelines covered other risk reduction interventions for the prevention of TB.[9,11-15]

The WHO Guideline on TB Infection Prevention[13] considered administrative controls (e.g., triage, isolation, respiratory hygiene), environmental controls (e.g., ventilation systems) and respiratory protection (e.g., particulate respirators). The WHO consolidated LTBI guidelines[12] considered preventive treatments for contacts of MDR-TB. The NICE Guideline[9] considered TB education and awareness, screening of health care staff, administrative controls, infection control in different settings, and contact tracing. The Singapore Guideline[14] covered air travel, administrative controls, environmental controls, and respiratory protection. The PHAC Prevention and Control Guideline[15] covered administrative, environmental, and personal protective controls. The CDC guideline.[11] covered risk reduction measures for before and after travel, respiratory protection, screening for TB, and control measures for resource limited settings.

Outcomes

The number recommendations on prevention or infection control in the guidelines ranged from one to 71 recommendations. Five of the guidelines contain fewer than 10 recommendations;[10,12-14,16] the WHO Position Paper on the BCG vaccine[8] has 24 recommendations; the CDC guideline[11] has 32 recommendations, the PHAC Prevention and Control Guideline[15] has 57 recommendations, and the NICE Guideline[9] contains 71 recommendations.

Four of the guidelines reported which outcomes were considered in the SRs that were used for developing the recommendations.[8,9,12,13] The other five guidelines[10,11,14-16] did not specify which outcomes were considered when developing the recommendations.

Summary of Critical Appraisal

This report includes three high-quality guidelines,[9,12,13] one moderate-quality guideline,[8] and five low-quality guidelines,[10,11,14-16] Additional details regarding the AGREE assessment of the included guidelines are provided in Appendix 3, Table 4.

Three guidelines were high-quality; these were the WHO Guideline on TB Infection Prevention,[13] the WHO consolidated LTBI guidelines,[12] and the NICE Guideline.[9] These high quality guidelines provided clear descriptions of the scope of the guideline, health questions, populations covered, and target users of the guideline.[9,12,13] The methodology for developing the recommendations was strong in each of the high-quality guidelines: [9,12,13] multiple SRs were conducted with transparent search methodology and eligibility criteria; the strengths a limitations of the body of evidence were well described; the recommendations were formulated following a detailed process that involved evaluating the evidence and reaching a consensus among experts. In addition, the recommendations were clear and easy to identify in all three high quality guidelines, with explicit links between the recommendations and the supporting evidence.[9,12,13] Although, in the WHO consolidated LTBI guidelines[12] the recommendation for preventive treatment lacked detail on the type of treatment to be provided. The guideline development group included members from all relevant disciplines for the WHO Guideline on TB Infection Prevention[13] and the NICE Guideline,[9] although the exact area of expertise for all panel members was unclear in the WHO guideline. The guideline development group for the NICE Guideline also included four members who were patients or caregivers.[9] For the WHO consolidated LTBI guidelines, [12] a list of all members of the guideline development group was provided, but it was unclear who was responsible for what components of the guideline development. The potential conflicts of interest of the guideline development group members were recorded and addressed in all three high quality guidelines.[9,12,13] The WHO Guideline on TB Infection Prevention[13] reported no influence of the funding agency on the development or content of the guideline. The other two guidelines reported the source of the funding but did not provide information on the potential influence of the funder on the guideline; however, these guidelines were funded by health authorities[12] and NICE,[9] thus the potential influence of the funder is not likely to be biased. The three high-quality guidelines are available for free online,[9,12,13] and the WHO guidelines are published (or have plans to be published) in multiple languages,[12,13] which may facilitate the dissemination and implementation of these guidelines.

The WHO Position Paper on the BCG vaccine[8] was of moderate quality. One of the main limitations of this guideline was the lack of clear, easy to identify information with regards to the process for identifying the evidence and formulating the recommendations. Systematic reviews were commissioned to address some of the health questions addressed in this guideline, but it was unclear if this was done for all questions. In addition, some of the systematic reviews used to identify the evidence were listed as 'unpublished', so it was not possible to determine if the methods were systematic and reproducible. There was limited detail provided on the methods used to formulate the recommendations, although the benefits and risks of the intervention were considered when formulating the recommendations. The key recommendations are clear, although they are not easily identifiable in the document and the strength or confidence in the individual recommendations was not reported. The guideline development group included members from different countries, but the exact role or area of expertise for each member was unclear. The competing interests of the funding body and the guideline development group were reported and determined to not be a conflict of interest.[8]

Five guidelines were assessed to be low-quality due to the poor reporting of methods, creating uncertainty in the recommendations.[10,11,14-16]

The scope and health questions in the Italian Pediatric guideline[10] were clear, and the recommendations were specific and easy to identify in the report, however, there was

insufficient detail on the development of the recommendations, creating uncertainty. The guideline development group included experts from numerous relevant disciplines, but the area of expertise and the role for each member was unclear, and it was not reported whether the views of the target population were considered. This guideline conducted a systematic review with a high-quality search strategy, but did not report the criteria for selecting the evidence, or the quality of the included studies. For each health question, the number and type of relevant studies was reported and summarized, but there was no comparison of the benefits and harms, and the quality of the evidence was not reported. The Delphi method was used to reach a consensus, but otherwise the process for formulating the recommendations was unclear. In addition, while it was reported that an external review was conducted, the process was not explained. The authors and panel members declared no conflicts of interest, however, funding was provided through a grant from one of the societies directly involved in development of the guideline, and it is not clear whether this influenced the guideline development.[10]

The Singapore Guideline[14] had clear descriptions of the scope and target users of the guideline, and clear, easily identifiable recommendations, however, it did not provide sufficient methodological details and the roles and areas of expertise of the members of the guideline development group were not clear. It was unclear whether a systematic approach was used to search for and evaluate the evidence, and there was a lack of detail regarding the process for formulating the recommendations. The Singapore guideline reported the level of evidence and the grade of the recommendation for each recommendation but did not provide the methods for grading the evidence. In addition, this guideline did not report the risk of bias of the individual studies or include evidence-to-decision tables, thus the specific link between strengths and limitations of the evidence and the recommendations was unclear. It was not reported whether this guideline was externally reviewed by experts, thus the level of certainty in the recommendations is unclear. The funding body was not reported, and the authors did not disclose whether they had any conflicts, thus it is unclear whether there were any conflicts of interest from the funder or the authors.[14]

Both PHAC guidelines[15,16] have clear and specific recommendations, that are easy to identify in the guideline, however, the guidelines have limited detail on the development process for the recommendations, creating a lack of certainty in the recommendations. The overall scope of the PHAC Prevention and Control Guideline[15] was described, whereas the scope of the PHAC BCG Guideline[16] was not explicitly stated, but could be inferred from the title of the document. Neither PHAC guideline reported the health questions, thus it is unclear what questions guided the development of the recommendations. The population and settings covered by the PHAC Prevention and Control Guideline[15] were clearly described, whereas the populations to whom the PHAC BCG Guideline[16] applies is not explicitly stated. Both PHAC guidelines listed a small number (i.e., fewer than four) of authors and their institutions (two authors for BCG, 3 authors for prevention and control), but their specific roles were unclear. In addition, 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. Neither PHAC guideline reported any methods with regards to the search for evidence, thus the quality of the search strategy and eligibility criteria for selecting the evidence is unknown. The PHAC guidelines report the strength of the recommendation and the quality of evidence for each recommendation, and the scores are explained in the preface document[21] 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. For the PHAC Prevention and Control Guideline,[15] it was reported that the recommendations were based on available evidence, but no other methods for formulating the recommendations were reported. A list of external reviewers was reported for the whole set of PHAC TB Standards, but it was unclear who reviewed these specific sets of recommendations, or what the process was for the external review. The funding body was disclosed for both 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.

The CDC guideline.[11] had clear descriptions of the scope and population of the guideline, however, it was unclear which health questions were addressed and the methodology for guideline development lacked sufficient detail. It was unclear whether systematic methods were used to search for, select and evaluate the evidence and how the recommendations were formulated. The CDC guidelines also did not report the overall quality of the evidence or the strength of recommendations. The members of the guideline development group were not clearly reported, the views of the target population were not sought, and it was not reported whether the guideline was externally reviewed by experts. While this guideline did provide specific recommendations that covered different options for reducing the risk of TB for healthcare workers, due to the lack of detailed methodology, there is uncertainty with these recommendations. All authors of the manuscript declared no competing interests, although it was not clear whether the authors of the report served in the guideline development group. The funding body was not reported, thus it is unknown whether it had any influence on the content of the guideline.[11]

Summary of Findings

Guidelines

Nine evidence-based guidelines were identified that made recommendations for the prevention of TB.[8-16] Five guidelines made recommendations on the use of the BCG vaccine for the prevention of TB.[8-11,16] Six guidelines made recommendations for other risk reduction measures for the prevention of TB transmission.[9,11-15] A summary of the topics covered by the recommendations within the guidelines is presented in Table 5 (BCG vaccine) and Table 6 (risk reduction measures). 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 the BCG Vaccine

The WHO Position Paper on the BCG vaccine[8] and the NICE Guideline[9] include multiple recommendations on the BCG vaccine, covering multiple different subgroups.

The recommendations in the low-quality WHO Position Paper on the BCG vaccine[8] covered topics such universal and selective BCG vaccine strategies at birth (depending on the areas incidence of TB) and revaccination, as well as BCG vaccination of other populations such as children, adults, migrants, pregnant women, travelers, and high-risk groups. The recommendations in the WHO Position Paper[8] were not graded, and the quality of the evidence from which the recommendations are based is unknown.

The high-quality NICE Guideline,[9] covered topics such as the identification of groups eligible for vaccination, and the vaccination of specific populations, such as neonates (depending on their risk for TB), children, adults, migrants, travelers, health care workers, and workers in other high risk groups (e.g., prison staff, veterinary staff, people working with the homeless or refugees). For the NICE Guideline,[9] 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 PHAC BCG Guideline[16] covered vaccination of infants in First Nations and Inuit communities with high incidence of TB, as well as vaccination of people planning to travel and stay in areas with high TB incidence for an extended period of time (in particular infants born in Canada). Both were strong recommendations based on moderate quality evidence.

The other two guidelines focus on specific populations.[10,11]

The low-quality Italian Pediatric guideline[10] included strong and moderately strong recommendations for pediatric patients (including neonates, school children, immunocompromised patients, and revaccination), although it was unclear how the quality of the evidence was evaluated.

The low-quality CDC guideline[11] made recommendations on the BCG vaccine specifically for people from the US travelling for work, however, the strength of the recommendation and the quality of the evidence were not reported.

Recommendations Regarding the Prevention of TB Transmission through Risk Reduction Measures

The high-quality WHO Guideline on TB Infection Prevention[13] includes conditional and strong recommendations covering a variety of administrative, environmental, and respiratory controls for the prevention and control of TB infection. These recommendations were based on evidence with very low to moderate certainty in the estimates of effects.[13]

The high-quality WHO consolidated LTBI guidelines[12] provided one conditional recommendation, based on very low-quality evidence for preventative TB treatment for contacts of patients with MDR-TB.

The high-quality NICE Guideline[9] made recommendations on multiple risk reduction measures, including isolation, respiratory hygiene, education, infection control, and contact tracing. For the NICE Guideline, the certainty of the recommendation is reflected in the wording of the recommendation, and the strength of the evidence varied across the different recommendations.

The low-quality Singapore Guidelines[14] also provides recommendations for a variety of administrative, environmental, and respiratory controls for the prevention of TB infection, as well as a recommendation against air travel for people with TB, however, these recommendations were mostly based off of expert opinion or non-analytic studies.

The low-quality PHAC Prevention and Control Guideline[15] made recommendations for triaging patients with suspected TB, airborne precautions, ventilation systems, respirators, and transporting patients with TB. This PHAC guideline also covered screening health care workers, and precautions that can be taken in other settings, such as correctional facilities, homeless shelters, and remote health care settings. This guideline includes a mix of strong and conditional recommendations that were based off very weak to strong quality evidence.

The low-quality CDC guideline[11] made a number of recommendations for risk reduction measures before and after travel, control measures for resource limited settings, the use of respirators, and LTBI screening in people travelling for work, however, the strength of the recommendation and the quality of the evidence were not reported.

Limitations

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

This report includes five low-quality guidelines[10,11,14-16] which may limit the reliability of the findings, however, most of the topics covered by the recommendations were discussed in more than one guideline, and were usually covered by a high-quality guideline in addition to the low-quality guideline(s). However, some topics were only covered in a low-quality guideline, such as some of the topics specific to US workers traveling for health care or humanitarian work (e.g., risk reductions measures for before and after travel to high TB incidence, LTBI screening), and thus may have reduced reliability.[11] In addition, some topics which may be of interest to Canadian health care providers given the high rates of TB borne by Indigenous peoples living in Canada (e.g., BCG vaccination of infants in First Nations and Inuit communities,[16] precautions for TB transmission in remote or isolated heath care settings[15]) were only covered in the PHAC guidelines, which were assessed to be low-quality due to the absence of reported methodology.

With regards to the generalizability of the other guidelines, three of the guidelines (two high-quality, one moderate-quality) are intended for global use,[8,12,13] two of the guidelines were developed in the context of very specific populations (i.e., pediatric patients in Italy[10] and US workers travelling for health care and humanitarian work[11]), and the other two guidelines were developed in Singapore[14] and the United Kingdom.[9] It is unknown if the guidelines developed outside of Canada are generalizable to the Canadian context, as there may be geographical differences in the risks of TB transmission in Canada.

In addition, we did not evaluate the extent to which guidelines directed toward specific populations (e.g. Indigenous peoples, migrants) had been developed in collaboration with people from those populations. As such, it is important to consider how histories of colonial and racial aggression toward the diversity of peoples typically subsumed within these broad categories may affect the utility of guidelines developed without their direction or discretion.

This report was also limited by the large volume of recommendations about TB prevention published in the guidelines (i.e., between one and 71 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 nine guidelines[8-16] regarding the prevention and infection control of TB.

Five guidelines covered the use of the BCG vaccine.[8-11,16] Recommendations regarding the use of the BCG vaccine for the prevention of TB across multiple different populations were covered in one high-quality guideline[9] and one moderate-quality guideline.[8] These guidelines covered topics such as the identification of groups eligible for vaccination and

the use of universal and selective BCG vaccine strategies, as well as made recommendations for specific populations, including different at-risk groups (e.g., travelers, migrants, prison staff).[8,9] The recommendations in the NICE guideline[9] were based on evidence ranging from weak to high-quality, whereas the quality of the evidence and strength of the recommendations were not reported in the WHO Position Paper.[8] The low-quality Italian Pediatric guideline[10] included strong and moderately strong recommendations specifically for pediatric patients in Italy, although the methods used to evaluate the quality of the evidence was unclear. For the Canadian context, the PHAC BCG Guideline[16] made strong recommendations on BCG vaccination of infants in First Nations and Inuit communities with high incidence of TB, and for people planning extended travel to areas with high TB incidence, however, this guideline did not publish their methodology, limiting the certainty of the recommendations. In addition, specific recommendations for the BCG vaccine for people from the US travelling for work were identified in one low-quality CDC guideline,[11] but did not report the strength of the recommendations or the quality of the evidence, and did not provide sufficient methodological detail on the development process.

Six guidelines discussed other measures to reduce the risk of TB transmission,[9,11-15] three of which were considered to be high-quality guidelines,[9,12,13] and three were considered low-quality guidelines.[11,14,15] Five of the guidelines[9,11,13-15] covered multiple different risk reduction measures, including administrative (e.g., isolation), environmental (e.g., ventilation), and respiratory controls (e.g., respirators), as well as some public health interventions (e.g., education programs). Whereas the high-quality WHO consolidated LTBI guidelines[12] provided one recommendation for preventative TB treatment for contacts of patients with MDR-TB, based on very low-quality evidence. For both high-quality guidelines (the WHO Guideline on TB Infection Prevention[13] and the NICE Guideline[9]) the strength of the evidence varied by recommendation, with evidence ranging from very low to high quality evidence. For the low-quality CDC guideline specific to people from the US travelling for work,[11] the strength of the recommendations and the quality of the evidence were not reported, thus it is not clear whether the recommendation should be trusted. In the other low-quality Singapore Guideline,[14] insufficient methods were reported and the recommendations were mostly based off of expert opinion or non-analytic studies, thus resulting in low-quality recommendations. With regards to the Canadian context, the PHAC Prevention and Control Guideline[15] includes conditional and strong recommendations for numerous topics, such airborne precautions, ventilation systems, transporting patients with TB, and precautions for correctional facilities, homeless shelters, and remote health care settings. However, this guideline did not publish the methods for searching for evidence or formulating the recommendations, limiting the overall quality of the guideline.

Overall, this report identified three high-quality guidelines[9,12,13] that cover interventions for prevention and infection control of TB, that may serve as useful resources for those seeking guidance of specific populations or circumstances. This report also identified six guidelines of low- to moderate-quality[8,10,11,14-16] that may provide additional guidance on TB prevention, however, there is uncertainty associated with these guidelines and the recommendations should be interpreted with caution.

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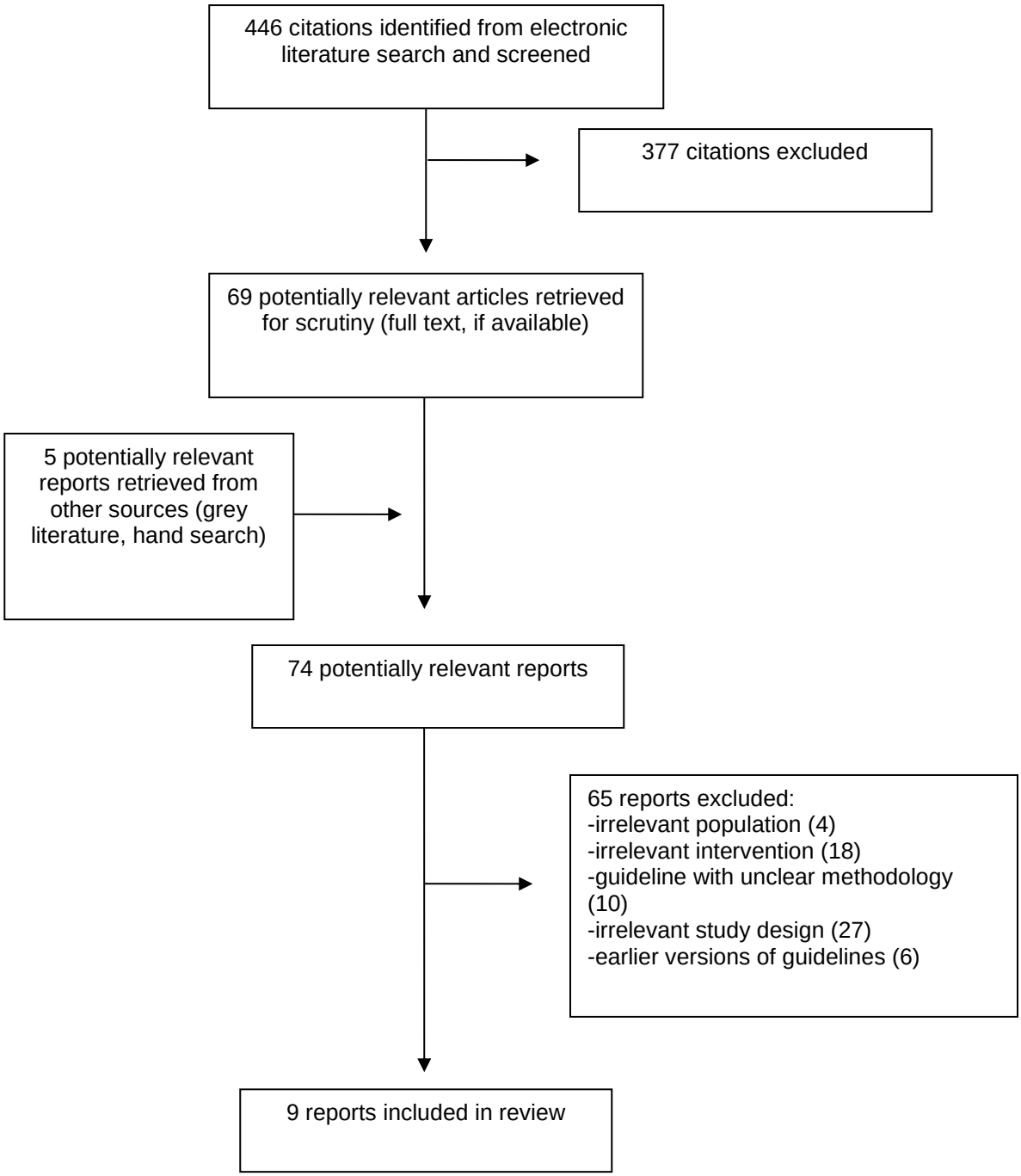
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Guidelines

Table 2: Characteristics of the Guidelines

Guideline title, author, and year	Country, Funding body, Developing Institution	Scope or Objective	Target Users	Health Technologies, total # of recommendations	Populations covered by the recommendations (# of recommendations)
WHO guidelines on tuberculosis infection prevention and control WHO[13] 2019	**Country:** Global **Funding:** USAID **Developing Institution:** WHO	Provide evidence-based recommendations on a public health approach to TB infection prevention and control for health care services and other settings where the risk of TB transmission is high	Users: key TB stakeholders; policymakers; health officials; healthcare workers; health system managers for TB and HIV disease programs; managers of infection prevention and control; managers of penitentiary facilities.	**Technologies:** Prevention of infection - administrative controls (triage, isolation, respiratory hygiene) - environmental controls (Upper-room germicidal ultraviolet systems, ventilation systems) - respiratory protection (particulate respirators) **Total # of Recommendations:** 7	**Main populations**: People with or suspected of having TB (4) Healthcare workers (3)
BCG vaccines: WHO position paper WHO[8] 2018	**Country:** Global **Funding:** not reported **Developing Institution:** WHO	Guidance on the BCG vaccine for children, including those infected with HIV	Primary users: National public health officials and managers of immunization programs Other users: international funding agencies, healthcare providers and researchers, vaccine advisory groups and manufacturers.	**Technologies:** Prevention of TB - BCG vaccine - revaccination **Total # of Recommendations:** 24	**Main population**: Neonates in areas with high incidence of TB (4) **Subgroups:** Neonates from areas of low TB incidence born in households with higher risk of TB (3) Countries with declining TB rates (2) Unvaccinated adults and children in areas with high incidence of TB (1) Unvaccinated adults and children moving from low to high TB incidence areas (1)

Guideline title, author, and year	Country, Funding body, Developing Institution	Scope or Objective	Target Users	Health Technologies, total # of recommendations	Populations covered by the recommendations (# of recommendations)
					Unvaccinated persons at risk of occupations exposure to TB (1) Migrants from high TB areas (1) General population (1) Pregnant and lactating women (1) Immunocompromised and HIV infected adults and children (6) Travelers (1) Preterm and low birth weight infants (1) Neonates born to mothers with TB (1)
Latent tuberculosis infection Updated and consolidated guidelines for programmatic management WHO[12] 2018	**Country:** Global **Funding:** The US CDC, USAID, and the Ministry of Health of the Republic of Korea **Developing Institution:** WHO	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	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:** Preventive treatments of contacts of MDR-TB (1) **Total # of Recommendations:** 1	**Main population**: Contacts of MDR-TB (1)

Guideline title, author, and year	Country, Funding body, Developing Institution	Scope or Objective	Target Users	Health Technologies, total # of recommendations	Populations covered by the recommendations (# of recommendations)
		and local level based on epidemiology of TB, and the availability of resources.			
Recommendations for pediatric tuberculosis vaccination in Italy Montagnani[10] 2016	**Country:** Italy **Funding:** Supported by a grant from the Italian Society for Pediatric Infectious Diseases **Developing Institution:** Italian Pediatric TB Study Group	Recommendations on the use of the BCG vaccine in pediatric patients in Italy	Not specified	**Technologies:** Prevention of TB - which patients should be vaccinated - administration of BCG vaccine Identification of LTBI (prior to vaccination) - TST **Total # of Recommendations:** 8	**Main population**: Pediatric patients who will receive BCG vaccine (2) **Subgroups:** Infants and children from areas with high TB incidence (2) Infants and children with contact with family member with TB (2) Children previously vaccinated with BCG (1) Infants with a possible HIV infection or immunodeficiency (1)
Tuberculosis NICE[9] 2016	**Country:** United Kingdom **Funding:** Not specified **Developing Institution:** NICE	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:** Preventing TB - education - BCG vaccine - screening of healthcare staff Infection control - identification - isolation - limiting contact - respiratory hygiene - contact tracing - incident and outbreak response	**Subgroups:** People and organizations working with at-risk for TB populations (8) General population (8) (1) Healthcare staff (15) (1) Neonates (0 to 4 weeks) (7) Children (0 to 15 years) (2) Immigrants from high-incidence areas (3)

Guideline title, author, and year	Country, Funding body, Developing Institution	Scope or Objective	Target Users	Health Technologies, total # of recommendations	Populations covered by the recommendations (# of recommendations)
			health and public health consultants Public Health England and NHS England Voluntary sector workers People with TB and their carers	**Total # of Recommendations:** 71	Contacts of people with TB (1) Other at-risk groups (people working with animals susceptible to TB, prison staff, staff of care homes, staff at facilities for homeless persons and refugees, people going to a high-incidence country for more than 3 months) (1) Setting: - Healthcare setting (13) - Non-healthcare setting (2) - Cases on an aircraft (5) - Cases in schools or childcare (7) - Cases in inpatient hospitals (6)
Prevention, Diagnosis and Management of Tuberculosis MOH Singapore[14] 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:** Prevention of infection - air travel - healthcare settings - cough etiquette **Total # of Recommendations:** 6	**Main populations**: General population (2) Healthcare facilities (4)
Canadian Tuberculosis Standards Chapter 16: Bacille Calmette-Guérin (BCG) Vaccination in Canada PHAC BCG[16]	**Country:** Canada **Funding:** Jointly funded by the Canadian Thoracic Society of the Canadian Lung Association, and the Public	BCG vaccine in Canada	Public health and clinical professionals	**Technologies:** BCG vaccine **Total # of Recommendations:** 2	**Subgroups:** - infants in Frist Nations and Inuit communities, or infants in groups with high incidence of TB (1) - travelers planning extended stays in areas of high TB incidence (1)

Guideline title, author, and year	Country, Funding body, Developing Institution	Scope or Objective	Target Users	Health Technologies, total # of recommendations	Populations covered by the recommendations (# of recommendations)
2014	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				
Canadian Tuberculosis Standards Chapter 15: Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings PHAC Prevention and Control[15] 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	Review factors associated with the transmission of TB within hospitals, other health care settings, community care settings and correctional facilities, and formulate recommendations for the prevention of TB transmission to health care workers, patients, and visitors.	Public health and clinical professionals	**Technologies:** -administrative controls (e.g., institutional policies, diagnosis, isolation) - environmental controls (e.g., ventilation, filters) - personal protection controls (e.g., respirators) **Total # of Recommendations:** 57	**Subgroups:** - health care workers (13) - patients with confirmed or suspected TB (9) - patients with TB with outpatient care (4) - paramedics (1) **Settings**: - hospitals and other health care settings(17) - remote or isolated health care settings (3) - home care settings (4) -homeless shelters (2) - correctional facilities (4)

Guideline title, author, and year	Country, Funding body, Developing Institution	Scope or Objective	Target Users	Health Technologies, total # of recommendations	Populations covered by the recommendations (# of recommendations)
Multidrug-Resistant Tuberculosis Recommendations for Reducing Risk during Travel for Healthcare and Humanitarian Work Seaworth[11] 2014	**Country:** United States **Funding:** Not reported **Developing Institution:** US CDC	Recommendations for infection control and worker vaccination for workers travelling to international sites where the risk of MDR-TB is high	Primary users: Personnel from the United States serving in high-risk (for TB) international settings	**Technologies:** Prevention of TB - risk reduction before and after travel - control measures for resource limited settings - respirators - frequent screening the TB - BCG vaccine **Total # of Recommendations:** 32	**Main populations**: Workers traveling to areas with a high incidence of TB (32)

BCG = Bacillus Calmette–Guérin; CDC= Centre for Disease Control; HIV= Human immunodeficiency virus; LTBI= Latent tuberculosis infection; MDR-TB= Multi-drug resistance tuberculosis; MOH = ministry of health; NICE = National Institute for Health and Care Excellence; PHAC = Public Health Agency of Canada; TB= Tuberculosis; TST= Tuberculin skin test; US = United States; USAID= US Agency for International Development; WHO= World Health Organization

Table 3: Methods used in the Guidelines

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
WHO guidelines on tuberculosis infection prevention and control WHO[13] 2019	Development of the guidelines followed the process outlined in the WHO Handbook for Guideline Development.[18] The process included identifying questions and outcomes, systematically	The guideline development process was guided by three background questions and four PICO questions. Seven systematic reviews of the evidence were used to inform the recommendations. These systematic reviews were conducted by an outside	GRADE evidence-to-decision tables were developed and used to support the formulation of the recommendations. These frameworks take into account the condition, the balance of the benefits and harms of the	Four levels of evidence quality[18]: 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.	The External Review Group received full guideline document to peer-review. The WHO Steering Group then assessed the feedback received by the peer-reviewers, and incorporated revisions and suggestions.

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
	searching and synthesizing the evidence, formulating recommendations, and providing ideas for dissemination and implementation of the guideline. The process included three groups: 1. A Guideline Development Group of international experts was formed to advise WHO in the process, and to provide input on the scope of the project. 2. The WHO Steering Group developed the key questions that guided the document. 3. External Review Group who peer reviewed the final guideline document	group, and the protocols were evaluated and endorsed by the guideline steering group. The WHO Handbook for Guideline Development [18] outlines specific methods for conducting SRs. The GRADE approach was used to assess the quality of the evidence and the strength of the recommendations. Based on certain criteria (i.e., limitations of the study design, inconsistency, imprecision, indirectness, and publication bias) the certainty of the evidence was for all critical outcomes was rates as 'high', 'moderate', 'low', or 'very low'.	intervention, values, resources, equity, acceptability, and feasibility. The GDG formulated the recommendations through a consensus process that was informed by the evidence, and the expertise of the group members. When consensus could not be reached, a voting process was used.	Low: Our confidence in the effect estimate is limited: the true effect may be substantially different. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different. Two levels of strength of the recommendation: Strong: the GDG was confident that the desirable effects of adherence would outweigh the undesirable effects. Could be either in favour of or against an intervention. Conditional: the GDG concluded that the desirable effects of adherence would probably outweigh the undesirable effects, 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.	Guideline did not report a process for updating, but the standard methodology for WHO guidelines indicates that guidelines should regularly updated.
BCG vaccines: WHO position paper WHO[8]	The GDG for this WHO Vaccine Position Paper included SAGE and supported by a SAGE working group.	The Working Group gathers, examines, and synthesizes the evidence, including background information, the quality of	Evidence to recommendation tables are provided in an appendix that detail the evidence for each	Not reported.	Reviewed by external experts, WHO staff, and reviewed and endorsed by the WHO Strategic Advisory

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
2018	SAGE working Groups consist of two members, with an additional 8-12 additional subject matter experts. SAGE develops PICO questions for the guideline, which are further refined by the Working Group.	the evidence, and evidence-to-recommendation tables, as well as proposed recommendations. GRADE methodology was used to assess the quality of the evidence. Evidence to recommendation tables are prepared with the evidence for each PICO.	question, and evaluate the problem, benefits and harms, values and preferences, resource use, equity, acceptability, feasibility, and the balance of the consequences. The Working Group drafts the recommendations and SAGE accepts or modifies the proposed recommendations. Decisions are reached by consensus, rather than voting, to ensure an in-depth discussion of the issues.		Group of Experts on immunization. Decision to update will be made within two years, or sooner, if evidence is available.
Latent tuberculosis infection Updated and consolidated guidelines for programmatic management WHO[12] 2018	Development of the guidelines followed the process outlined in the WHO Handbook for Guideline Development.[18] Three groups were established: 1. The steering group, composed of WHO staff, who oversee the guideline development process.	The steering group prepared a scoping document which identified seven key questions in the PICO format. A list of potential outcomes for each question was circulated to the GDG, who scored the importance of each outcome, which was used to prioritize and select the most important outcome for each question.	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.	Four levels of evidence quality[18]: 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	The external review group reviewed the draft of the final guideline, and remarks were evaluated by the steering group and incorporated into the final version of the guidelines. WHO will update the guideline five years after publication, or earlier if new evidence

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
	2. 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.	Seven new or updated SRs were conducted for these guidelines to address the seven 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[18] outlines specific methods for conducting SRs. An online survey was also conducted to determine the preferences and values of affected populations. 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	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.	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 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.	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
		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			
Recommendations for pediatric tuberculosis vaccination in Italy Montagnani[10] 2016	Recommendations developed using the "Consensus Conference method". The Working Group developed a list of clinical questions about the prevention of TB through vaccination.	Systematic review of MEDLINE and the Cochrane Database of Systematic Reviews, from inception to December 2014 and also reviewed the clinical recommendations in the international guidelines. Trained personal critically appraised the literature using the Scottish Intercollegiate Guidelines	The evidence and draft documents were provided to the panel prior to the meetings. The Delphi method was used to reach a consensus when the evidence did not provide consistent, clear recommendations. Final recommendations were revised based on	"Quality of Evidence: I = Evidence from more than one properly designed, randomized, controlled study and/or systematic review of randomized studies II = Evidence from one properly designed, randomized, controlled study III = Evidence from cohort studies or their meta-analysis IV = Evidence from retrospective case-controlled studies or their meta-analysis	External reviewers from Italy and other European countries evaluated the final report. 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
		Network methodological checklists. Quality of the evidence, and the strength of the recommendations was graded, although no methodology was reported.	discussions and reviewed by participants at the Consensus Conference for final approval.	V = Evidence from case series without control group VI = Evidence from opinions of respected authorities, based on clinical experience Strength of recommendation A = The panel strongly supports a recommendation for use B = The panel moderately supports a recommendation for use C = The panel marginally supports a recommendation for use“ (pg. 645)	
Tuberculosis NICE[9] 2016	Update to a previous 2011 guideline. Developed in accordance to the NICE manual for developing guidelines[19] 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 of the findings was used to form the recommendations. A consensus method was used to formulate	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	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

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 SRs 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.	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.	spend more time considering and discussing the options with the patient." (pg. 90)	areas of the guideline may be updated if relevant evidence is published.

Guideline and year	Development Process	Evidence collection and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
		For the critical appraisal of the body of evidence: GRADE evidence profiles were prepared. Criteria considered included risk of bias, inconsistency, indirectness, imprecision, and other considerations. Evidence synthesis: meta-analyses were conducted where it was possible to combine the evidence for the outcomes. An extensive network meta-analysis was conducted for synthesize the evidence for the treatment of LTBI.			
Prevention, Diagnosis and Management of Tuberculosis MOH Singapore[14] 2016	Guidelines were produced by a committee experts, including physicians, infectious disease experts, and the ministry of health. The guidelines were developed by adapting the existing guidelines, a review of the relevant literature, and expert clinical consensus.	Not described. The critical appraisal of the individual studies as not described. The recommendations were appraised by scoring the strength of the evidence, and the grade of the recommendation. (No other details provided)	The development of the recommendations were guided by two principles: - recommendations were supported by evidence and expert consensus - treatment should maximize benefit and minimize harm	Levels of Evidence: "1++ = High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias. 1+ = Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias. 1- = Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias 2++ = High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of	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 and selection, Critical appraisal of evidence and synthesis	Recommendation formulation and validation	Grading system	External review of guideline, Process for updating
				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+	

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
				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." (pg. 2)	
Canadian Tuberculosis Standards Chapter 16: Bacille Calmette-Guérin (BCG) Vaccination in Canada PHAC BCG[16] 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	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
				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[21])	
Canadian Tuberculosis Standards Chapter 15: Prevention and Control of Tuberculosis Transmission in Health Care and Other Settings	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 reviewed all published evidence, particularly the most recent studies. No details of search strategy reported. The authors synthesized and rated the evidence. No other details provided	Recommendations were based on published evidence, if possible. However, there was a lack of evidence of strong quality on this topic, with the majority evidence coming from observational studies, and from qualitative analyses of outbreaks.	"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	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
PHAC prevention and control[15] 2014				studies of strong design providing consistent results. Weak = Evidence from observational analytic studies that had weak designs, weak effect estimates or inconsistent results, or generalization from a randomized trial that involved one type of patients to a different group of patients. Very weak = Evidence from published case series and/or opinion of the authors and other experts Strength of Recommendations Strong = The recommendation implies that the desirable effects clearly outweigh undesirable effects, was based on strong/moderate evidence and was considered unlikely to change with additional published evidence. Conditional = The recommendation implies that the desirable effects are closely balanced with undesirable effects, and/or was based on moderate/weak/very weak evidence and was considered likely to change with additional published evidence." (pg. 3-4, from Preface[21])	
Multidrug-Resistant Tuberculosis	The CDC gathered a panel of experts on TB from various disciplines. The panel	Evidence from 1961 to 2011 was considered, but no details provided on how	The panel selected which evidence to included based on its relevance to reduce the	Not reported.	The recommendations were approved by the Advisory Council for

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
Recommendations for Reducing Risk during Travel for Healthcare and Humanitarian Work Seaworth[11] 2014	reviewed findings from reports, guidelines, surveillance, and other summary reports from 1961 to 2011, as well as conducted interviews with experts, held discussions, and summarized the evidence.	this evidence was searched for or selected. Not described.	risk of MDR-TB for US personnel serving in high-risk settings.		Elimination of Tuberculosis. No procedure to update was reported.

CDC = Centers for Disease Control; GDG = guideline development group; GRADE = Grades of Recommendation, Assessment, Development and Evaluation; LTBI = latent tuberculosis infection; MDR-TB = multi-drug resistance tuberculosis; MOH = ministry of health; NICE = National Institute for Health and Care Excellence; NRS = non-randomized studies; PHAC = Public Health Agency of Canada; PICO = population, intervention, comparator and outcome; QUADAS = Quality Assessment of Diagnostic Accuracy Studies; RCT = randomized controlled trial; SAGE = Strategic Advisory Group of Experts on Immunization; 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[6]

Item	Guideline								
	WHO Infection Prevention 2019 [13]	WHO BCG 2018 [8]	WHO LTBI 2018 [12]	Italian Pediatric [10]	NICE[9] 2016	Singapore[14]	PHAC BCG[16] 2014	PHAC Prevention Control[15] 2014	US CDC[11] 2014
Domain 1: Scope and Purpose									
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Partially	Yes	Yes	Yes	Yes	No	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	Yes	No	No	No	No
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Partially	Yes	Partially	Yes	Partially	Partially	Yes	Yes
Domain 2: Stakeholder Involvement									
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Partially	Partially	Partially	Yes	Partially	Partially	Partially	Partially
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Partially	No	Yes	No	Yes	No	No	No	No
6. The target users of the guideline are clearly defined.	Yes	Yes	Yes	No	Yes	Yes	Partially	Partially	No
Domain 3: Rigour of Development									
7. Systematic methods were used to search for evidence.	Yes	Partially	Yes	Yes	Yes	No	No	No	No
8. The criteria for selecting the evidence are clearly described.	Yes	Partially	Yes	No	Yes	No	No	No	No
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Partially	Yes	No	Yes	Partially	No	No	No

Item	Guideline								
	WHO Infection Prevention [13] 2019	WHO BCG [8] 2018	WHO LTBI [12] 2018	Italian Pediatric [10]	NICE[9] 2016	Singapore[14]	PHAC BCG[16] 2014	PHAC Prevention Control[15] 2014	US CDC[11] 2014
10. The methods for formulating the recommendations are clearly described.	Yes	Partially	Yes	Partially	Yes	No	No	No	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Partially	Yes	Partially	Yes	No	Partially	No	Partially
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Partially	Yes	Partially	Yes	Partially	No	No	Partially
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Partially	Yes	Partially	Yes	No	Partially	Partially	No
14. A procedure for updating the guideline is provided.	Partially	Yes	Yes	No	Yes	Yes	No	No	No
Domain 4: Clarity of Presentation									
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	NA	Yes	NA	Yes	Yes	NA	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Partially	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Domain 5: Applicability									
18. The guideline describes facilitators and barriers to its application.	Yes	Yes	Yes	No	No	No	No	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Partially	No	Partially	No	Partially	No	No	No	No
20. The potential resource implications of applying the recommendations have been considered.	Yes	Partially	Partially	No	Yes	No	No	No	Partially

Item	Guideline								
	WHO Infection Prevention [13] 2019	WHO BCG [8] 2018	WHO LTBI [12] 2018	Italian Pediatric [10]	NICE[9] 2016	Singapore[14]	PHAC BCG[16] 2014	PHAC Prevention Control[15] 2014	US CDC[11] 2014
21. The guideline presents monitoring and/or auditing criteria.	No	Yes	Yes	No	Yes	Partially	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	Partially	Partially	No	Partially	Partially	No
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes

BCG = Bacillus Calmette–Guérin vaccine; NA = not applicable; WHO = World Health Organization;

Appendix 4: Main Study Findings

Table 5: Summary of BCG Vaccine Specific Topics Covered by the Recommendations in the Included Guidelines

Topics Covered by the recommendation	WHO BCG [8] 2018	Italian Pediatric [10]	NICE[9] 2016	PHAC BCG 2014[16]	US CDC[11] 2014
Universal BCG vaccination strategy at birth (areas with high incidence of TB)	X	X	X		
Selective BCG vaccination strategy at birth for high risk groups in countries with low TB incidence - neonates with parents or close contacts with TB -neonates in households with contacts to countries with high TB incidence -neonates in other locally identified risk group with TB	X	X	X		
Switching from universal to selective BCG vaccination strategy at birth (countries with declining TB incidence)	X				
Infants in First Nations and Inuit communities with high rates of TB				X	
BCG vaccination in school children	X	X	X		
BCG vaccination in older children, adolescents, and adults	X		X		
BCG vaccination of migrants from areas with high TB incidence	X		X		
Revaccination with BCG	X	X			
BCG vaccination in pregnant and lactating women	X				
BCG vaccination in immunocompromised and HIV infected patients	X	X			
BCG vaccination in Travellers	X		X	X	
BCG vaccination in preterm infants and low birth weight infants	X				
BCG vaccination in neonates born to mothers with pulmonary TB	X				
BCG vaccination for workers travelling to areas with high incidence of TB			X		X
Identification of eligible groups for BCG vaccination			X		
BCG vaccination for health care workers with direct contact with patients with TB			X		
BCG vaccination for health care workers from countries with high TB incidence			X		
BCG vaccination for contacts of people with active TB			X		
BCG vaccination for other at risk groups:			X		

Topics Covered by the recommendation	WHO BCG [8] 2018	Italian Pediatric [10]	NICE[9] 2016	PHAC BCG 2014[16]	US CDC[11] 2014
- veterinary staff - prison staff - staff of care homes -people working with the homeless, refugees, or asylum seekers					

BCG = Bacillus Calmette–Guérin; CDC= Centre for Disease Control; HIV= Human immunodeficiency virus; NICE = National Institute for Health and Care Excellence; PHAC = Public Health Agency of Canada; US = United States; WHO= World Health Organization

X = the guideline made a recommendation on this topic

Table 6: Summary of Risk Reduction Topics Covered by the Recommendations in the Included Guidelines

Topics Covered by the Recommendations	WHO Infection Prevention [13] 2019	WHO LTBI [12] 2018	Singapore[14]	NICE[9] 2016	PHAC Prevention and Control[15] 2014	US CDC[11] 2014
Triage people with signs or symptoms of TB	X		X	X	X	X
Isolation or respiratory separation	X			X	X	X
Prompt treatment initiation	X					X
Respiratory hygiene (e.g., cough etiquette)	X		X	X		X
Use of upper-room germicidal ultraviolet systems	X					
Ventilation systems	X		X	X	X	
Particulate respirators	X		X		X	X
Preventative treatment for contacts of patients with MDR-TB		X				
Air travel restrictions			X			
Infection control plan			X			
Risk reduction measures before travelling to areas with high TB incidence (e.g., education, fit testing respirator, risk assessment)						X
Risk reduction measures after returning from areas with high TB incidence (e.g., TB screening)						X
LTBI screening for workers with extended or frequent travel to areas with high-risk of MDR-TB						X

Topics Covered by the Recommendations	WHO Infection Prevention [13] 2019	WHO LTBI [12] 2018	Singapore[14]	NICE[9] 2016	PHAC Prevention and Control[15] 2014	US CDC[11] 2014
Educational programs to raise awareness for TB - for health care professionals and those working with high-risk groups - for high-risk groups - information to the public				X		
Screening new health care staff for TB (including clinical students, agency, and locum staff)				X	X	
Screening health care workers who have been exposed to people with TB					X	
Assessment of visitors to children with TB				X		
Admission and discharge from the hospital for patients with TB				X		
Infection control in non-health care settings with large numbers of at risk people				X		
Infection control in correctional facilities				X	X	
Infection control for patients with MDR-TB				X		
Contact tracing - general - cases on an aircraft - cases in school - cases in community childcare - cases in hospital in patients				X		
Transportation of patients with TB					X	
Outpatient health care visits for people with TB					X	
Precautions for remote or isolated health care settings					X	
Precautions for home health care					X	
Precautions for homeless shelters					X	

CDC= Centre for Disease Control; LTBI= Latent tuberculosis infection; MDR-TB= Multi-drug resistance tuberculosis; NICE = National Institute for Health and Care Excellence; PHAC = Public Health Agency of Canada; TB= Tuberculosis; US = United States; WHO= World Health Organization

X = the guideline made a recommendation on this topic

Appendix 5: Additional References of Potential Interest

Guidelines with Unclear Methodology

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

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

Coulter C, and the National Tuberculosis Advisory C. Infection control guidelines for the management of patients with suspected or confirmed pulmonary tuberculosis in healthcare settings. *Commun Dis Intell Q Rep.* 2016;40(3):E360-E366