CADTH Health Technology Review

Prevention of Tuberculosis Reactivation

Rapid Review

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Abbreviations

EMB   ethambutol

INH   isoniazid

LTBI   latent tuberculosis infection

NICE   National Institute for Health and Care Excellence

NMA   network meta-analysis

PZA   pyrazinamide

RFB   rifabutin

RMP   rifampin

RPT   rifapentine

TB   tuberculosis

USPSTF   US Preventive Services Task Force

Key Messages

- It is not known if screening for latent tuberculosis infection (LTBI) is useful for reducing the risk of tuberculosis reactivation among people at risk (no evidence was found).
- In people with LTBI, providing treatment for the latent infection may be helpful for preventing the development of active tuberculosis disease. (In addition, LTBI treatments do not appear to increase the risk for hepatotoxicity.) Treatment effectiveness may depend on the specific LTBI treatment regimen used.
- For people at an increased risk for tuberculosis — including those from areas with high rates of tuberculosis — guidelines recommend screening and treatment for LTBI, as this may help prevent TB reactivation. Treatment is recommended for those who are 65 years old or younger and with a positive LTBI result (recommendation from 1 high-quality guideline).

Context and Policy Issues

In Canada, where the incidence of tuberculosis (TB) is low and the risk of exposure to TB is low, most cases of active TB are due to the reactivation of a latent TB infection (LTBI) rather than a new TB infection.[1] Certain factors are associated with an increased risk of reactivation of active TB and include HIV infection, diabetes, renal failure, certain cancers, and treatment with immunosuppressants.[2] There is a need for a better understanding of measures that can be taken to prevent TB reactivation.

In July 2020, CADTH searched the literature for evidence on the prevention of TB reactivation.[3] This previous CADTH report[3] identified 1 network meta-analysis (NMA),[4] 1 non-randomized study,[5] and 2 guidelines[6,7] that met the inclusion criteria based on their titles and abstracts. The purpose of the current report is to review the full texts of these publications and to summarize and critically appraise the eligible publications.

This report is a component of a larger CADTH condition-level review on TB. A condition-level review is an assessment that incorporates all aspects of a condition, from prevention and detection to treatment and management. For more information on CADTH's condition-level review of TB, please visit the project page (https://www.cadth.ca/tuberculosis).

Research Questions

1. What is the clinical utility of screening for latent tuberculosis infection in people at risk of tuberculosis reactivation?

2. What is the clinical effectiveness of treating latent tuberculosis infection to prevent tuberculosis reactivation?

3. What are the evidence-based guidelines for the prevention of tuberculosis reactivation?

Methods

Literature Search Methods

A limited literature search was conducted for a previous CADTH report[3] by an information specialist on key resources including MEDLINE, 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 comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were latent tuberculosis and reactivation. Search filters were applied to limit retrieval to guidelines for Question 3, only. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2015 and June 24, 2020. Internet links were provided, where available.

Selection Criteria and Methods

The evidence in this report was identified in a previous CADTH report,[3] where 1 reviewer screened citations and abstracts. For this report, the full-text articles were reviewed by 1 reviewer and the final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Q1: Individuals at risk of LTBI or TB reactivation
	Q2: Individuals with LTBI
	Q3: Individuals with LTBI or who are at risk of LTBI or TB reactivation
Intervention	Q1: Screening for LTBI using the tuberculin skin test or interferon-gamma release assay
	Q2: Treatment for LTBI
	Q3: Strategies and approaches to prevent TB reactivation
Comparator	Q1: No screening for LTBI
	Q2: No treatment for LTBI
	Q3: Not applicable
Outcomes	Q1: Clinical utility (e.g., patients receiving treatment for LTBI, TB reactivation, adverse effects of treatment)
	Q2: Clinical benefits and harms (e.g., TB reactivation, need for subsequent treatment for active TB, adverse effects of LTBI treatment, anxiety)
	Q3: Recommendations regarding strategies to reduce the TB reactivation
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, guidelines

LTBI = latent tuberculosis infection; Q = question; TB = tuberculosis.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or they were published before 2015. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[8] for systematic reviews, the "Questionnaire to assess the relevance and credibility of a network meta-analysis"[9] for NMAs, the Downs and Black checklist[10] for randomized and non-randomized studies, and the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument[11] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Additional details regarding the study characteristics, and the main study findings and authors' conclusions, are provided in tables in Appendix 2.

Quantity of Research Available

In the previous CADTH report,[3] a total of 603 citations were identified in the literature search and 3 potentially relevant publications were retrieved from the grey literature. Four potentially relevant reports were identified and retrieved for full-text review, of which 1 SR with NMA,[4] 1 retrospective cohort,[5] and 2 guidelines[6,7] met the inclusion criteria and were included in this report.

Summary of Study Characteristics

The SR with NMA[4] was published in 2017 and is an update of a previous SR with NMA published in 2014.[12] It was led by authors in England. The SR with NMA[4] included randomized controlled trials (RCTs) that compared any LTBI treatment to any alternative LTBI treatment, no treatment, or placebo; this is broader than the inclusion criteria for this report where only studies that compare LTBI treatments to no treatment are eligible (i.e., comparisons between LTBI treatments are not relevant to this report). The SR[4] included literature that was searched from inception to May 8, 2017 and RCTs were eligible for inclusion. Overall, 61 RCTs were identified and included in the SR with NMA (53 from the original SR[4] and 8 RCTs from the update), of which 40 RCTs were directly relevant to this report.[4] The NMA used a Bayesian approach.[4] Direct pairwise, random-effects meta-analyses were also conducted if relevant RCTs were available.[4] The SR with NMA[4] included RCTs of people with LTBI; 140,723 individuals were included in the NMA and of the RCTs that were directly relevant to this report, there were 51,671 individuals. The relevant outcomes were the development of active TB and hepatotoxicity.

The retrospective cohort[5] was led by authors and conducted in England. This study used data from screening databases collected between 2009 and 2013, and linked this data with the UK TB surveillance system. The population of interest were individuals younger than 35 years

who were recent migrants to England from an area with high rates of TB and were screened for LTBI using an interferon-gamma release assay, and tested positive. This cohort study compared the number of active TB cases identified at least 60 days after the positive LTBI test (i.e., incident TB cases) between the two groups: those who received treatment for LTBI and those who did not receive treatment for LTBI.

One guideline was developed by the National Institute for Health and Care Excellence (NICE) in the UK in 2016.[6] The scope of the guideline is broad, covering all individuals with — or at risk of TB — and the guideline is intended to be used by health care professionals or public health professionals working with TB. The recommendations in this guideline that were relevant to this report included those covering the screening and preventive treatment for LTBI to prevent TB reactivation. This guideline was an update to a previous version of the guideline, and systematic reviews were conducted to address specific research questions in this update and the previous version of the guideline. The wording of the recommendations in the NICE guideline reflects the certainty in the recommendations; direct language (e.g., "offer," "do not offer") is used to indicate more certainty than less direct language (e.g., "consider").

One guideline was published in 2016 by the US Preventive Services Task Force (USPSTF).[7] The guideline is meant to be used by clinicians and health care decision-makers in the US. The population covered by the guideline is asymptomatic adults who have an increased risk of LTBI. A systematic review was conducted as part of the guideline development, which searched for evidence on the effectiveness of identifying and treating LTBI to prevent progression to active TB disease (i.e., TB reactivation). The recommendations in the USPSTF guideline[7] are graded based on whether the USPSTF recommends for or against the service (i.e., grade A to D, or I for insufficient), as well as the level of certainty in the net benefit of the intervention (i.e., high, moderate, or low).

Summary of Critical Appraisal

Systematic Reviews

The SR with NMA[4] was an update to a previous SR with NMA[12] and the authors reported that they used the same methodology as the previous report. The protocol for the update is registered in the PROSPERO database (CRD42016037871); however, minimal details were provided and it is unclear what approach will be used to update the previous review (e.g., how the findings will be integrated). The research question and eligibility criteria are well-described. A comprehensive search strategy was used (e.g., searched multiple databases, no language restrictions, provided keywords) and 2 reviewers performed study selection in duplicate, reducing the likelihood that relevant literature was missed. The number of excluded studies was reported and the reason for excluding studies at the full-text level was provided, but the authors did not include a full list of excluded studies. Data extraction and the quality assessment were done in duplicate, and an appropriate tool was used to assess the risk of bias, including the risk of selection bias, the blinding of participants and outcome assessors, and reporting bias. A brief description of the included studies was provided (e.g., number of participants, intervention groups, which outcomes were included). However, some details were lacking, such as the dose or length of treatment, or a complete description of how outcomes were assessed, thus limiting the ability to assess the heterogeneity of the studies. In addition, although the authors report that length of follow-up was extracted, it is not reported by RCT nor is it summarized per treatment group; this information limits the interpretation of the outcome "development of active TB" with respect to TB reactivation, as longer follow-up periods may increase the likelihood of new TB infections. The authors also

did not report on the source of funding of the RCTs and it unclear whether the reporting in these trials may be biased because of their source of funding. The authors reported that there was no direct source of funding for the SR; however, 2 of the authors declared funding from pharmaceutical companies and it was not reported how these potential conflicts were managed. Thus, it is unclear whether the reporting of the findings is biased due to these potential conflicts.

The NMA conducted as part of the SR[4] used a Bayesian approach and report 95% credible intervals with the effect estimates, which is an appropriate statistical model. However, limited information was provided on the methods used for the NMA; thus, the quality of the methods is unclear. For instance, the authors did not report whether informative or non-informative priors were used, nor did they report how the outcomes were modelled (e.g., normal likelihood, Poisson likelihood). The authors grouped treatments together that were clinically similar based on the drugs and duration of treatment (e.g., regimens containing isoniazid of 3 to 4 months), and they grouped treatments together based on the drug(s) regardless of the length of treatment (e.g., regimens containing rifampin alone, any duration). However, insufficient information was reported on the treatment regimens used in the individual RCTs and it is not possible to determine the clinical heterogeneity of these groups. The authors reported direct pairwise meta-analysis comparisons and indirect comparisons from the NMA, and consistency was demonstrated for some, but not all, comparisons, which suggests some uncertainty in the findings of the NMA. To account for variation across treatments, the authors used random-effects models but did not report measures of between-study variance or statistical heterogeneity for the NMA, and it is unclear whether there are concerns with the level of heterogeneity across the network. The authors also conducted pre-planned meta-regressions that stratified the groups by predefined variables of interest (i.e., age of participants, immunosuppression status, or TB incidence in the country of study), but did not report the odds ratios for these comparisons. Instead, treatment rankings were reported, as well as the ratios of odds ratios for comparisons that pooled all of the treatment groups together compared to a pooled estimate that combined no treatment and placebo. The results from the meta-regressions suggest that the effectiveness of the treatments was reduced in people with an HIV infection and in high TB incidence areas. However, it is not possible to compare the main findings of the NMA with those of the meta-regressions because of differences in the way the findings were reported and it unclear whether these variables may have influenced the results.

Non-Randomized Studies

The quality of the reporting in the retrospective cohort[5] was mixed. The aim, eligibility criteria, and outcomes of interest were clearly described, simple outcomes data were provided for the main findings together with estimates of random variability, and actual P values were reported. However, minimal information was reported for the interventions of interest (e.g., no details on the LTBI treatment regimen were provided), the list of potential confounders was not described, and it is unclear whether a statistical power calculation was done. The source of funding is reported and there is a statement that the views of the authors were not influenced by the funding agency. It is reported that author disclosure forms are available online, but they were not accessible, and it is unknown whether there were any potential conflicts of interest for the authors. Because of the retrospective cohort design of this study, randomization of the interventions was not possible; rather, all patients were selected from the same retrospective database where the choice of intervention already occurred and was not influenced by the authors of this study. In addition, a retrospective cohort design does not allow for the blinding of participants. However, it is unlikely that this would have influenced the

outcome of interest (i.e., TB reactivation). It was not reported whether those who extracted the information from the databases or those who conducted the statistical analysis were blinded to the intervention and it is unclear whether this would have influenced the findings of this study. This cohort study calculated the incidence rate ratio for the risk of TB reactivation, whereby values greater than 1 indicate an increased risk relative to the comparator. This is reported as a multivariable analysis; however, the authors did not report which variables were included in the analysis and it is unknown whether potential confounders were included in the analysis. For instance, it is unclear whether the length of follow-up, which varied across participants, was included in this analysis. Less than 1% of patients in the whole study were lost to follow-up and the findings were unlikely to be affected by their inclusion.

Guidelines

Both guidelines[6,7] were previously included in a CADTH report on guidelines for the identification of TB.[13] The detailed critical appraisal of these guidelines can be found in that report.[13] In brief, both the NICE guideline[6] and the USPSTF guideline[7] used high-quality systematic methods to search for evidence and to develop the recommendations.

Summary of Findings

Clinical Utility of Screening for LTBI in People at Risk of TB Reactivation

There was no relevant evidence found regarding the clinical utility of screening for LTBI in people at risk of TB reactivation; therefore, no summary can be provided.

Clinical Effectiveness of Treating LTBI to Prevent TB Reactivation

One SR with NMA[4] and 1 retrospective cohort[5] were identified regarding the clinical effectiveness of treating LTBI to prevent TB reactivation.

Development of Active TB

In patients with LTBI, indirect comparisons from the SR with NMA[4] found that, when compared to placebo, the following regimens were favoured for preventing the development of active TB: isoniazid (INH) alone for 6 months, INH alone for 12 to 72 months, INH and ethambutol (EMB) for 12 months, rifampin (RMP) alone, RMP and INH for 3 to 4 months, RMP with INH and pyrazinamide (PZA), and RMP and PZA. No specific therapy was favoured when INH alone for 3 to 4 months, INH alone for 9 months, INH and EMB, rifabutin (RFB) and INH, higher doses of RFB and INH, rifapentine (RPT) and INH, or RMP and INH for 1 month were compared to placebo. In addition, when compared to no treatment, the following regimens were favoured for preventing the development of active TB: INH alone for 6, 9, or 12 to 72 months; INH and EMB for 12 months; RFB and INH; higher doses of RFB and INH; RPT and INH; RMP alone; RMP and INH for 3 to 4 months; RMP with INH and PZA; and RMP and PZA. No specific therapy was favoured when INH alone for 3 to 4 months, INH and EMB, or RMP and INH for 1 month were compared to no treatment.

In recent migrants from areas with high TB rates who tested positive for LTBI, 1 retrospective cohort study found treatment for LTBI resulted in statistically significantly fewer cases of active TB identified at least 60 days after the LTBI test and that the risk of TB reactivation was lower in those treated for LTBI compared to those who were not treated for LTBI.[5]

Hepatotoxicity

In patients with LTBI, indirect comparisons from the SR with NMA[4] found treatment with RMP alone was favoured compared to no treatment with regard to the odds of hepatotoxicity and that no specific therapy was favoured when no treatment was compared to the other treatment groups (i.e., INH alone for 6 months, INH alone for 9 months, INH alone for 12 to 72 months, RPT and INH, RMP and INH for 3 to 4 months, RMP with INH and PZA, or RMP with PZA).

In addition, indirect comparisons from the SR with NMA[4] found treatment with INH alone for 6 months, RPT and INH, RMP alone, or RMP and INH for 3 to 4 months were favoured compared to placebo with regard to the odds of hepatotoxicity and that no specific therapy was favoured when placebo was compared to the other treatment groups (i.e., INH alone for 9 months, INH alone for 12 to 72 months, RMP with INH and PZA, or RMP with PZA).

Guidelines

Two evidence-based guidelines[6,7] included recommendations regarding the prevention of TB reactivation.

For new migrants to the UK from countries with a high incidence of TB, the NICE guideline[6] recommends that individuals are offered testing for LTBI and that individuals 65 or younger who test positive should be offered treatment for LTBI. This recommendation was based on evidence that, with increasing age, there is an increased risk of TB reactivation and a possible increased risk of hepatotoxicity from LTBI treatment; the recommendation is made with the certainty that for most patients this approach will do more good than harm.

The USPSTF guideline[7] recommends screening for LTBI in populations at increased risk of TB, such as those from areas with a high prevalence of TB; this is a moderate strength recommendation and is based on evidence that screening tests for LTBI are accurate and that the treatment of LTBI has a moderate benefit in preventing TB reactivation.

Limitations

This report did not identify any evidence regarding the clinical utility of screening for LTBI in people at risk of TB reactivation; therefore, no conclusions can be made on these research questions.

The clinical evidence in this report is limited by the heterogeneity and the lack of detail regarding the different LTBI treatments. In the SR with NMA,[4] 14 different groups of treatments were included in the analysis and these groups differed by the drug(s) used and the duration of treatment (e.g., any duration, 6 months, 9 months). However, there was a lack of detail on the specifics of the treatments (e.g., dose was not reported) and some of the groups were broad in their length of treatment (e.g., any duration, 12 to 72 months). In addition, the retrospective cohort[5] did not report the drugs, dose, or duration of treatment for LTBI. This lack of detail and variability in the treatment regimens may impact the generalizability of the findings from this report to the clinical context, as it is more challenging to determine the regimen that could be used to prevent TB reactivation.

The findings in this report are based on 1 SR with NMA[4] and 1 retrospective cohort[5] led by authors in England, and 2 guidelines that are meant to apply to the UK[6] and the US.[7] While 4 of the 61 studies that contributed to the NMA[4] were conducted in Canada, these 4 studies compared 2 different treatment for LTBI and were not directly relevant to this report (i.e., LTBI treatment versus no treatment). Thus, it is unknown if the findings in this report are generalizable to the Canadian clinical practice.

Conclusions

This report comprised 1 SR with NMA[4] and 1 retrospective cohort[5] with clinical evidence regarding treating LTBI to prevent TB reactivation and 2 evidence-based guidelines[6,7] with recommendations regarding the prevention of TB reactivation. No relevant evidence was identified regarding the clinical utility of screening for LTBI in people at risk of TB reactivation.

Overall, the findings from 1 SR with NMA[4] and 1 retrospective cohort[5] suggest that treatment for LTBI may lower the risk of TB reactivation in those individuals who test positive for LTBI when compared to those who were not treated for LTBI. However, the effectiveness may depend on which treatment for LTBI is used. None of the LTBI treatments were associated with an increased likelihood of hepatotoxicity compared to no treatment or placebo.[4]

To prevent TB reactivation, it is recommended that populations at an increased risk of TB, such as those from areas with a high prevalence of TB, be screened for LTBI[6,7] and that those 65 years and younger who test positive for LTBI be offered treatment for LTBI.[6]

The limitations of the included literature[4-6,14] (e.g., uncertainty in the methods for the NMA, heterogeneity of the LTBI treatment) should be considered when interpreting the findings of this report. Future work conducted from the Canadian perspective or that identifies specific LTBI treatment regimens (e.g., dose and duration) may be useful to further inform clinical and policy decisions.

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Appendix 1: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Review and Network Meta-Analysis

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Zenner et al. (2017a)[4] England Funding: support through a postdoctoral fellowship through the UK National Institute for Health Research	**Study design**: SR with NMA; also includes pairwise meta-analyses. This is an update to a 2014 SR with NMA.[12] New studies were identified and incorporated into the NMA. RCTs were eligible for inclusion in the SR and NMA **Included studies**: 61 RCTs identified in the SR and included in the NMA overall **Studies relevant to this report**: 40 RCTs	**Includes**: people with LTBI Overall population in NMA: N = 140,723 Population relevant to this report: N = 51,671 No other summary statistics reported for population	**Eligible interventions**: LTBI treatments **Relevant interventions**: 16 different regimens for LTBI **Relevant comparators**: No treatment, placebo	Development of active TB, hepatotoxicity Follow-up not reported

LTBI = latent tuberculosis infection; NMA = network meta-analysis; RCT = randomized controlled trial; SR = systematic review; TB = tuberculosis.

Table 3: Characteristics of Included Primary Clinical Study

Study citation, country, funding source	Study design	Population characteristics	Relevant Intervention and comparator	Clinical outcomes, length of follow-up
Zenner et al. (2017b)[5] England Funding: National Institute for Health Research Health Protection Research Unit	Retrospective cohort study Used data collected between 2009 and 2013 Screening databases linked with the UK enhanced TB surveillance system	Individuals < 35 years who were recent migrants to England from areas with high TB rates, who were screened with IGRA and tested positive Excluded: those with active TB N = 366 Follow-up years, median (IQR): 2.2 (1.8 to 2.7) Age at screening, median (IQR): 26.4 (22.8 to 27.9) Initiated treatment, n (%) = 243 (66.4)	Intervention: Treatment for LTBI Comparator: No treatment for LTBI	Incident TB cases (i.e., active TB identified > 60 days after LTBI test date) Follow-up ended when patient died, tested positive for active TB, emigrated from the UK, or the study ended (December 31, 2014)

IGRA = interferon-gamma release assay; IQR = interquartile range; LTBI = latent tuberculosis infection; TB = tuberculosis

Table 4: Characteristics of Included Guidelines

Intended users, target population	Relevant interventions and outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
NICE (2016)[6]					
Intended users: Health care professional working with patients with TB. Government and public health professionals. People with TB and their carers. **Target population:** General population, including new entrants from countries with high incidence of TB	**Interventions:** screening for LTBI, preventive LTBI treatment **Outcomes:** progression from LTBI to active TB, detection outcomes, harms	Update to a 2011 version of the guideline. Follows method in the NICE guidelines manual.[15] SRs were conducted to address specific research questions for the guideline update. Not all recommendations were updated from previous versions. Comprehensive search strategies. For each SR, detailed eligibility criteria were reported. GRADE evidence profiles were prepared.	NICE methodological checklists were used to critically appraise RCTs and cohort studies. GRADE was used to critically appraisal the body of evidence. Criteria considered included risk of bias, inconsistency.	Recommendations balance the benefits and harms, and the quality of the evidence. They are based off the findings from the evidence reviews, GRADE profiles, and a discussion of the evidence statements. Specific criteria are used to link evidence to the recommendations. Consensus is needed to formulate the recommendations. The wording of the recommendations reflects the certainty in the recommendations (as outlined in the full guideline[16]) Direct language (e.g., "offer," "advise," "do not offer") indicates that benefits of the intervention are more certain. If the benefit of the intervention is less certain, "consider" is used.	Online stakeholder feedback and public consultation is conducted twice. An audit trail is used to track responses to feedback.

Intended users, target population	Relevant interventions and outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
USPSTF (2016)[7]					
Intended Users: Clinicians and health care decision-makers **Target Population:** Adults at increased risk for LTBI (e.g., people born in or former residents of high TB prevalence countries, people living in or who have lived in high-risk congregate settings).	**Interventions:** Screening tests for LBTI (i.e., TST, IGRA), preventive LTBI treatment **Outcomes**: sensitivity, specificity, development of active TB, harms, mortality	Development of the guideline followed the USPSTF standardized methods,[14] and includes a published SR on the topic.[17] The SR used a comprehensive search strategy and approach to evidence collection. Evidence was summarize in tables and narratively.	Body of evidence was appraised based on the level of certainty regarding the net benefit, and graded. Assessing the certainty of the evidence followed methods in the procedure manual. Evidence grades: A = High certainty that the net benefit is substantial (recommend the service) B = High certainty that the net benefit is moderate, or moderate certainty that the benefit is moderate to substantial (recommend the service) C = At least moderate certainty the net benefit is small (selectively offer) D = moderate to high certainty that there is no net benefit or that harms outweigh the benefits (recommend against) I = insufficient evidence	Recommendations were developed by assessing the adequacy of the evidence, critically appraising the evidence, evaluated the benefits and harms, evaluating the certainty of the evidence, then developing the recommendations based on evidence. Voting on draft recommendations takes place at meetings. At least 2 thirds of Task Force members must vote yes to approve the recommendation. Levels of certainty of net benefit: High = available evidence is consistent, from good quality studies, and conclusions are unlikely to be strongly affected by future studies. Moderate = available evidence is sufficient to determine its effects, but confidence in the effect estimate is constrained. The magnitude or direction of the effect could change with additional studies. Low = insufficient evidence is available to assess effects on health outcomes.	Drafts of the research plan, SR, and recommendation are posted online for stakeholder feedback. Documents are revised post-feedback.

GRADE = Grading of Recommendations Assessment, Development and Evaluation; IGRA = interferon-gamma release assay; LTBI = latent tuberculosis infection; NICE = National Institute for Health and Care Excellence; SR = systematic review; TB = tuberculosis; TST = tuberculin skin test; USPSTF = US Preventive Services Task Force.

Table 5: Strengths and Limitations of Guidelines Using AGREE II[11]

Item	NICE (2016)[6]	USPSTF (2016)[7]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Partially
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	Partially
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes
13. The guideline has been externally reviewed by experts before its publication.	Yes	Partially
14. A procedure for updating the guideline is provided.	Yes	Yes
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Not applicable
17. Key recommendations are easily identifiable.	Yes	Yes
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	No	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Partially	No
20. The potential resource implications of applying the recommendations have been considered.	Yes	Partially
21. The guideline presents monitoring and/or auditing criteria.	Yes	No
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Partially	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Partially

AGREE II = Appraisal of Guidelines for Research and Evaluation II; NICE = National Institute for Health and Care Excellence; USPSTF = US Preventive Services Task Force.

Appendix 2: Main Study Findings and Authors' Conclusions

Note that this appendix has not been copy-edited.

Summary of Findings Included Systematic Review and Network Meta-Analysis

Zenner et al. (2017a)[4]

Main Study Findings

Treatment groups are grouped by drug(s) and length of treatment. Groups that do not specify duration include all the treatment regimens that contain the single drug or combination of drugs, regardless of length of treatment.

Indirect comparisons from NMA of 61 studies —

Active TB:

Comparisons were made between: no treatment, placebo, INH 3 to 4 months, INH 6 months, INH 9 months, INH 12 to 72 months, INH-EMB, INH-EMB 12 months, RFB-INH, RFB-INH (high), RPT-INH, RMP, RMP-INH 1 month, RMP-INH 3 to 4 months, RMP-INH-PZA, RMP-PZA

Relevant comparisons where 1 treatment was favoured compared to another at preventing active TB, odds ratio (OR) (95% credible interval [CrI]):

- INH 6 months versus placebo: 0.65 (0.50 to 0.83)
- INH 6 months versus no treatment: 0.40 (0.26 to 0.60)
- INH 9 months versus no treatment: 0.46 (0.22 to 0.95)
- INH 12 to 72 months versus placebo: 0.50 (0.41 to 0.62)
- INH 12 to 72 months versus no treatment: 0.31 (0.21 to 0.47)
- INH-EMB 12 months versus placebo: 0.20 (0.04 to 0.82)
- INH-EMB 12 months versus no treatment: 0.12 (0.02 to 0.54)
- RFB-INH versus no treatment: 0.18 (0.03 to 0.95)
- RFB-INH (high) versus no treatment: 0.19 (0.03 to 0.98)
- RPT-INH versus no treatment: 0.36 (0.18 to 0.73)
- RMP versus placebo: 0.41 (0.19 to 0.85)
- RMP versus no treatment: 0.25 (0.11 to 0.57)
- RMP-INH 3 to 4 months versus placebo: 0.53 (0.36 to 0.78)
- RMP-INH 3 to 4 months versus no treatment: 0.33 (0.20 to 0.54)
- RMP-INH-PZA versus placebo: 0.35 (0.19 to 0.61)
- RMP-INH-PZA versus no treatment: 0.21 (0.11 to 0.41)
- RMP-PZA versus placebo: 0.53 (0.33 to 0.84)
- RMP-PZA versus no treatment: 0.33 (0.18 to 0.58)

Hepatotoxicity:

Comparisons were made between: no treatment, placebo, INH 6 months, INH 9 months, INH 12 to 72 months, RPT-INH, RMP, RMP-INH 3 to 4 months, RMP-INH-PZA, RMP-PZA

Relevant comparisons where 1 treatment was favoured compared to another with regard to hepatotoxicity, OR (95% CrI):

- INH 6 months versus placebo: 0.27 (0.10 to 0.60)
- RPT-INH versus placebo: 0.27 (0.03 to 0.42)
- RMP versus placebo: 0.03 (< 0.02 to 0.16)
- RMP versus no treatment: 0.14 (0.02 to 0.81)
- RMP-INH 3 to 4 months versus placebo: 0.17 (0.05 to 0.46)

Authors' Conclusion

"This review confirms that all currently recommended regimens are safe and efficacious and provides more robust evidence to demonstrate the efficacy of rifamycin-containing regimens, including 3- to 4-month RMP monotherapy, to prevent active TB." (p. 252)

"Placebo ranked poorly for hepatotoxicity, which seems highly unusual. The evidence for this result is not based on a single, unusual, result it was reported from several trials." (p. 34 of online supplement)

Table 6: Summary of Findings of Included Primary Clinical Study

Main study findings	Authors' conclusion
Zenner et al. (2017a)[5]	
Incident TB cases, n (%) LTBI treatment vs. untreated: 4 (1.7) vs. 13 (10.6), P = 0.001 **Risk of TB reactivation** LTBI treatment vs. untreated, IRR (95% CI): 0.225 (0.051 to 0.997). P = 0.049 **Multivariable analysis (variables included not reported)**	"After adjusting for confounders, treatment for LTBI therefore reduced the risk of reactivation by an estimated 83%." (p. 6)

IRR = incidence rate ratio; LTBI = latent tuberculosis infection.

Table 7: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
NICE (2016)[6]	
"Assess and manage TB in new entrants from high incidence countries who present to healthcare services as follows: • offer testing for LTBI • offer treatment to people aged 65 years or younger in whom active TB has been excluded but who have a positive Mantoux test or a positive interferon-gamma release assay for LTBI." (p. 51) **Evidence for age:** **With increasing age, there is an increased risk of progressing from LTBI to active TB, and a possible increase in risk of hepatotoxicity from treatment. The increased risk of TB reactivation with age supports the recommendation that everyone up to the age of 65 should be eligible for treatment for LTBI.**	The wording of the recommendations reflects the certainty in the recommendation Offer = for the vast majority of patients, the intervention will do more good than harm
USPSTF (2016)[7]	
"Screen for latent tuberculosis infection (LTBI)" (p. 964) **Evidence summary by the USPSTF:** • adequate evidence was identified that accurate screening tests for LTBI are available (e.g., TST, IGRA) • no evidence was found that evaluated the direct benefits of screening for LTBI • adequate evidence was found that treatment of LTBI provides a moderate health benefit in preventing progression to active disease • no evidence found on the direct harms of screening for LTBI • adequate evidence was found that the harms of treating LTBI are small	Grade: B, moderate certainty "The USPSTF concludes with moderate certainty that the net benefit of screening for LTBI in persons who are at increased risk for tuberculosis is moderate." (p. 964)

IGRA = interferon-gamma release assay; LTBI = latent tuberculosis infection; NICE = National Institute for Health and Care Excellence; TST = tuberculin skin test; USPSTF = US Preventive Services Task Force.