SIDE EFFECTS AND COMPLETION RATES OF TREATMENT REGIMENS FOR LATENT TUBERCULOSIS INFECTION: A RAPID REVIEW WITH NETWORK META-ANALYSES

PREPARED FOR:
CHIEF MEDICAL OFFICER OF HEALTH, GOVERNMENT OF NUNAVUT; THE DRUG SAFETY AND EFFECTIVENESS NETWORK

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1. BACKGROUND

The treatment of latent tuberculosis infection (LTBI) is a vital component of the overall strategy to reduce tuberculosis (TB) in a population. Treatment prevents ongoing transmission in communities by preventing the development of active TB disease. One of the greatest impediments to the treatment is the lengthy 9 month course of treatment with Isoniazid (INH), which is the current international standard. A recent multi-centered, multi-national randomized controlled non-inferiority trial (RCT) with approximately 4,000 patients per arm demonstrated that Rifapentine and INH given once weekly for a total of 12 doses (3HP) given directly observed was as effective as 9 months (252 doses) of daily INH self administered for the treatment of LTBI. The use of 3HP was as effective as the current international standard of 9 months of INH in preventing active TB disease and resulted in a higher completion rate. Several other RCTs have been published in the past 10 years using the 3HP regimen. The most recent, published in January 2015, is an RCT in the pediatric population.[1] In this study, which included 905 patients between the ages of 2-17 years of age, 3HP was shown to be as effective as 9 months of INH for the prevention of TB disease in children. A Cochrane review[2] was reported in 2013 and a network meta-analysis was reported in the Annals of Internal Medicine in 2014 on the use of the rifamycin class of compounds in the treatment of LTBI.[3] The evidence to date supports the fact that the 3HP is as efficacious in preventing active TB disease as the international standard of 9H, however the data generated by these analyses provided only minimal insight on the adverse effects associated with 3HP.

The National Committee for Canadian TB guidelines issued in 2013 agreed to the following recommendation as a statement regarding 3HP at that time[4]: *"Three months of once weekly, directly observed INH and RPT (3INH/RPT) has acceptable efficacy, but because of high rates of poorly understood hypersensitivity reactions should be used only with very close monitoring (Conditional recommendation, based on moderate evidence)"."In summary, the evidence to date indicates that this is a very promising regimen that is well accepted, has high completion rates, and shows efficacy that is similar to that of 9 months of INH. However, every dose should be directly observed, which can be difficult to organize in some practice settings or populations. More importantly, the occurrence of hypersensitivity reactions, which can be severe, is unexplained. Until this problem is better understood, the regimen should be used __only__ under carefully monitored circumstances; patients who are prescribed this regimen should be questioned carefully, before administration of each dose, about any problems that were related to the preceding dose. Therefore, the regimen is not recommended at this time for general use. It is hoped that these adverse reactions will be better understood with more use of the regimen, allowing them to be prevented and/or managed more easily."* Therefore, the committee held back on full support of the 3HP regimen until there was more evidence presented in regards to adverse events.

Since publication of the Canadian TB guidelines and the aforementioned Cochrane review and network meta analysis,[2,3] several studies have surfaced that provide more insight on the adverse effects associated with this regimen. A large RCT reported by Sterling et al in 2015 demonstrated that 3HP exhibited statistically significantly less hepatotoxicity compared to INH standard therapy (0.4% with 3HP versus 2.7% standard INH, $p<0.001$).[5] However, they did not provide details on other adverse events associated with the regimen, specifically hypersensitivity reactions (as noted by the Canadian guidelines). Subsequently, the Cochrane systematic review as well as the network meta analysis did not have adequate data to address the remaining issue of adverse events. Since the publication of the Cochrane systematic review and the network meta-

analysis, there have been 3 more studies presenting more detailed data on adverse events related to this regimen, totaling approximately 7,000 patients that took 3HP. Additionally, in May of 2015, Sterling et al published a detailed account of the adverse event data which were unavailable from the earlier 2015 publication; this was done specifically to elucidate the hypersensitivity reactions that were observed in the initial large RCTs. Significant systemic drug reactions were more common in the 3HP regimen compared to the 9 INH regimen (138/3,893(3.5%) with 3HP vs. 15/3,659(0.4%) with 9 INH (p<0.001)), but they were mostly flu-like syndrome (83%) and cutaneous reactions (17%). Severe reactions were rare at 0.3%, and were associated with concomitant medications and white race.[6] A pediatric study published in January 2015 included approximately 1000 children.[1] Furthermore, an unpublished phase 4 post marketing study from the US Center for Disease Control (unpublished but detailed preliminary data are available on-line) gave the regimen to over 2,000 patients in the United States and demonstrated a side effect profile that was similar to the findings from the large RCT. A preliminary literature search seeking reviews addressing the aspect of safety of competing regimens for LTBI did not identify any published articles. A full literature search has not been undertaken to determine if there are more published and non-published primary data sets, however those detailed here can play a very important role in establishing whether the new 3HP regimen should be approved for use in Nunavut.

In addition to adverse events, the proposed review would study an additional key outcome which is vital to establishing a new protocol in Nunavut: the number of patients that completed the 3HP regimen compared to other common regimens (i.e. the *completion rate*). This is of high importance given that a shortened regimen will facilitate treatment to prevent disease in a region where the rate of initiation of treatment for LTBI for the standard INH regimen is only 47%, and completion rates (of those that initiated the 78 dose regimen) are only 70%.[7] In other words, for every 100 patients diagnosed with LTBI in this region, only 33 complete treatment. Therefore, we are currently missing the opportunity to treat almost two thirds of all persons diagnosed with LTBI in Iqaluit.

Knowledge generated from a review addressing these considerations will inform key stakeholders in Nunavut trying to decide if the new 3HP regimen can be adopted in the Territory. If the results are favourable, the use of this regimen could significantly impact TB prevention in Nunavut where the incidence rates of active TB disease are the highest in Canada, and also in other Canadian Aboriginal communities facing similar challenges. This rapid review will directly inform practice in this area.

Rapid reviews are a type of literature review produced using accelerated and/or modified systematic review methods in order to make concessions to accommodate an expedited turnaround time. The rapid review will be guided by this protocol and follows an iterative approach that includes allowances for modifications regarding scope and level of synthesis based upon the nature and volume of the evidence identified. Decisions will be made in consultation with all members of the research team. This protocol details several of the steps that will be taken to produce a rapid evidence synthesis of this information for policy applications in Nunavut.

2. OBJECTIVE

The objective of this rapid review is to summarize the available evidence related to the rates of toxicities and completion rates for competing treatment regimens for latent tuberculosis infection (LTBI) of relevance to the province of Nunavut. We will also provide a narrative summary of the recent systematic reviews which have addressed efficacy of competing regimens for LTBI as supplemental information for decision making.

RESEARCH QUESTIONS FOR THIS RAPID REVIEW

1. Is the 3HP regimen for latent tuberculosis associated with similar or lesser rates of adverse reactions compared to the standard 252 dose INH (9 month daily) treatment currently used in Canada, 78 dose INH (9 month) treatment used in Nunavut, 180 dose INH (6 months daily), 3-4 months daily isoniazid and rifampin, and a 4-month regimen of Rifampin given daily for 4 months?

2. Is the 3HP regimen for latent tuberculosis associated with greater rates of regimen completion compared to the standard 252 dose INH (9 month daily) treatment currently used in Canada, 78 dose INH (9 month) treatment used in Nunavut, 180 dose INH (6 months daily), 3-4 months daily isoniazid and rifampin, and a 4-month regimen of Rifampin given daily for 4 months?

Question 1 will be addressed by reviewing evidence from randomized controlled trials as well as relevant post-marketing data and observational studies, while **Question 2** will be addressed based on synthesis of data from randomized controlled trials. Methods for both questions are described in additional detail next.

3. METHODS
3.1 PICOS FRAMEWORK

To be included in this review, a study will have to meet the eligibility criteria outlined in **Table 1** as follows:

TABLE 1: PLANNED ELIGIBILITY CRITERIA, ASSESSMENT OF LTBI REGIMENS	
QUESTION COMPONENT	**SPECIFIC CRITERIA**
POPULATION	• Patients definitively diagnosed with latent TB infection. Both adults and children will be eligible.

INTERVENTION AND COMPARATORS	• For both research questions, we will focus reporting of findings to regimens identified as being of relevance to Nunavut (referred to from here on as our *primary comparators set*), which are as follows:
	    • 3 months of once weekly isoniazid and rifapentine;
	    • 252 dose isoniazid (9 months daily);
	    • 180 dose isoniazid (6 months daily);
	    • 3 to 4 months daily isoniazid and rifampin;
	    • 78 dose isoniazid (9 month twice weekly);
	    • 120 dose rifampin (4 month daily)
	• **For question 1** regarding adverse effects, we will focus summary of findings on aggregated numbers of different events of interest to decision-makers from randomized and observational studies to the regimens noted above.
	• **For research question 2** regarding completion rates, while we will focus reporting of results upon the same primary comparator set, we will include data from additional regimens from the recent Annals network meta-analysis assessing the efficacy of LTBI interventions.[3] This will be done to incorporate all direct and indirect data in anticipated network meta-analyses for these two outcomes, for which the majority of trials are already identified.

OUTCOMES	*For research question 1*, studies will be considered eligible if they report on one or more of the following measures:
	    • # discontinuing without symptoms; # discontinued with symptoms
	    • Specific harms: # with any symptom, # nausea or vomiting, # fever, # fatigue, # rash/hives/angiodema, # abdominal pain, # dizziness/fainting, # hypotension, # diarrhea, # loss of appetite, # sore muscles/joints, # numbness or tingling, # deaths, # hospitalizations, # impacting pregnancy or fetal health, # other.
	    • The most granular data available will be collected; it will later be reviewed for possible categorizations as well (flu-like symptoms, GI, respiratory, etc).
	
	For research question 2, studies will be eligible if they report on the following measure (variable definitions will be captured and assessed):
	    • <u>Completion rate</u>: amongst the # of patients who accept a treatment regimen, the completion rate reflects the # of patients who receive all treatments (or an a priori specifed amount thereof).

STUDY DESIGN	• Adverse outcomes will be gathered from both randomized trials as well as controlled observational studies and post-marketing studies. • Comparisons of completion rates will be based on randomized controlled trials only. Randomized trials will be identified from an existing 2014 systematic review, with a secondary search for RCTs to be conducted to address the amount of time that has elapsed since its final search.

• ***Rationale for choice of comparators to be considered***. Regimens in our *primary comparators set* noted above were selected based upon recommendations in the most recent Canadian guidelines for the treatment of latent TB infection (LTBI)[1]. In these

guidelines, 9 months of daily isoniazid (INH), 6 months of daily INH and 3 to 4 months of combined INH plus rifampin (RMP) are all strongly recommended regimens and were thus included in our analysis. Although more weakly recommended by Canadian guidelines, 4 months of daily rifampin alone and twice weekly INH alone will be included as primary comparators of interest in our analysis because they are currently being used for treatment of LTBI in Nunavut. A regimen of 3 months of weekly INH plus RMP is conditionally recommended but is not used in Nunavut, and thus was not included in our analysis as a primary comparator.

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- *Additional considerations.* No restrictions with regard to study setting will be in place. The selected studies will be limited to those published in English to avoid delays related to translation of foreign language articles; any foreign language studies that are screened out will be listed in an appendix to the report. We will seek grey literature in order to incorporate unpublished data.

FIGURE 1: EXISTING NETWORK OF LTBI TRIALS
(ANNALS OF INTERNAL MEDICINE REVIEW[3], SEPTEMBER 2014)
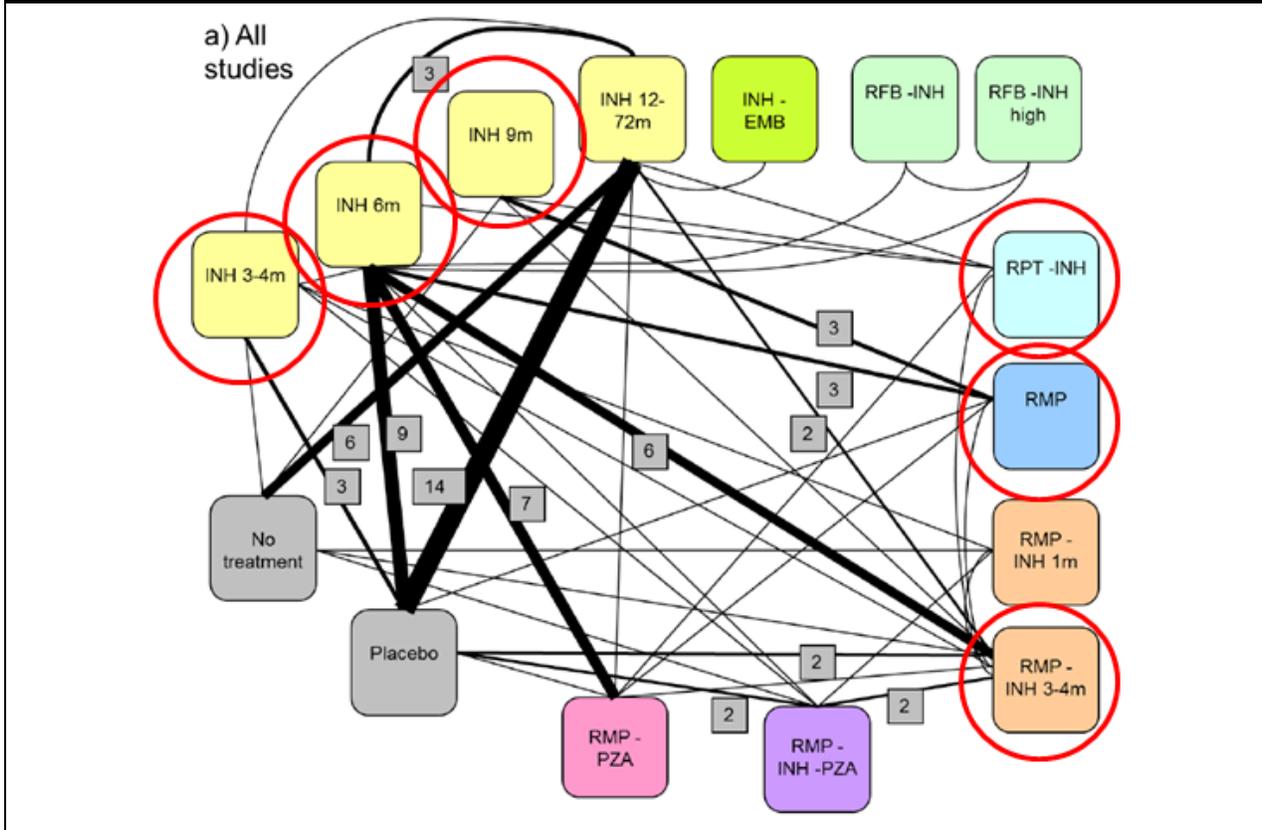
Network diagram from Stegg et al 2014 depicting comparisons between LTBI interventions from randomized trials. Edges are sized to proportionately reflect the numbers of trials informing each comparison. Classes of interventions are coded by color. Red circles highlight our primary interventions of interest for which findings will be presented for the query's knowledge users. Data from other regimens will be analyzed in network meta-analyses but related findings will be placed in appendices, with an intent to use later on in a larger peer reviewed report.

3.2   SEARCH METHODS

As the research questions in this review will be addressed using a rapid review approach, a de novo literature search for randomized trials will not be performed. We will use the 2014 network meta-analysis published in the Annals of Internal Medicine as a starting point for both research questions of interest.[3] An information specialist with expertise in systematic reviews will update the literature search (see details, **Appendix 1**) to search for studies published since the last search update from the 2014 review; an additional search for relevant observational information will also be conducted. Strategies will utilize a combination of controlled vocabulary (e.g., "Latent Tuberculosis", "Chemoprevention", "Antitubercular Agents") and keywords (e.g., inactive tuberculosis, tuberculostatic, 9INH). Vocabulary and syntax will be adjusted across databases. We will use a validated randomized controlled trial filter as well as other filters to identify observational, post-marketing and safety studies. Animal-only and opinion-pieces will be removed from the results. The core strategy will be reviewed prior to execution by another senior information specialist.

We will also present a listing of all included RCTs (see **Appendix 2**) to a group of experts in tuberculosis research who were part of the efforts to develop the Canadian guidelines for tuberculosis, querying them for any trials they feel might have been missed in order to ensure the evidence base is sound. An AMSTAR assessment of the Annals Review (**Appendix 3**) suggested the search of the Annals review was partially unclear, and our search has thus been made to be more inclusive to address this weakness.

We will selectively search web sites listed in CADTH's Grey Matters Light for grey literature. Additionally, we will search the WHO's ICTRP Search Portal and Clinical Trials.Gov for completed clinical trials, and will hand-search the bibliographies of pertinent references. A selection of relevant websites (e.g., Centers for Disease Control, Infectious Diseases Society or America) will also be searched.

3.3   STUDY SCREENING AND SELECTION

For this rapid review we intend to maximize the use of existing information from the 2014 Annals systematic review and network meta-analysis[3] to gain efficiencies. This will include building upon existing data collection and risk of bias appraisals for RCTs derived from that work. However, there remains a need to verify the existing study information, to collect additional outcome measures that were not part of that review, and to screen and gather data from new citations and grey literature, and so forth. To facilitate screening and data extraction, Distiller Systematic Review (DSR) Software© will be used. DSR is a web-based management program that enables uniformity and increases efficiency in the management of evidence flow. The DSR program enables multiple levels of relevance screening, data abstraction, data mining, mapping and table construction in unison. At level 1 screening for new literature published since the Annals 2014 review, titles and abstracts will be assessed by one reviewer for potential relevance; a second reviewer will verify those records deemed not relevant. At level 2 screening, full-text reports will be assessed for eligibility by a single reviewer with excluded records verified by a second reviewer. Disagreements during full-text screening will be resolved through consensus, or by a third team member. A PRISMA flow diagram will be included to summarize our process of study selection, reflecting the amount of information available for each research question.[8] We will also verify trials from the Annals review meet our eligibility criteria.

3.7   DATA EXTRACTION

For studies from the existing Annals systematic review, one reviewer will verify all study characteristics collected. The same reviewer will extract outcome data for new outcomes (i.e. harms, completion rates) with a second independent reviewer providing verification for at least 50% of the studies. For new studies identified from our search, the latter approach will also be followed. Extracted data will include the follow elements:

- *Population*: data related to patient age, gender, ethnicity, comorbidities (e.g. HIV), country of enrollment, and other risk factors (history of incarceration, history of drug and alcohol use, smoking status, etc) will be gathered.

- *Intervention and Comparators:* drugs provided to patients in their regimen for LTBI, including name, dose, duration and frequency of administration.

- *Outcomes:* as described earlier, data related to the following events will be gathered:

  - Side effects of interest for this review (hypersensitivity reactions, numbers of patients discontinuing treatment with and without side effects, and numbers of specific patients experiencing specific outcomes alluded to earlier such as vomiting, fever, fatigue, rash, abdominal pain, dizziness, diarrhea).
  - Rates of treatment regimen completion.
  - Definitions of some of the above outcomes may vary from study to study. Where available, we will collect outcome definitions in order to (i) ensure drastically different definitions are not combined in any analyses, and (ii) conduct appropriate sensitivity analyses related to definition.

- *Study descriptors*: A variety of relevant information including year of publication, study design, country of the corresponding authors, duration of follow-up, funding source, and so forth will be collected.

3.5   RISK OF BIAS APPRAISAL

RCTs will be evaluated using the Cochrane risk of bias tool,[9] which addresses seven domains including sequence generation, allocation concealment, blinding, missing outcome data, selective outcome reporting, attrition, and "other sources of bias." The risk of bias of included studies will be assessed by one reviewer, with subsequent comparison to assessments collected from the 2014 Annals systematic review[3] to identify any discrepancies and potential concerns. If needed, disagreements found will be addressed by consulation of a second reviewer to achieve consensus. In reflecting expertise from past work by AHRQ and the Cochrane Adverse Events Methods Group, we will also gather the following information which are relevant for risk of bias consideration when dealing with adverse outcomes:
- Listing of pre-defined adverse events to be monitored in the study;
- Use of an independent outcome assessor vs. assessment by study staff;
- Use of passive monitoring based on spontaneous reports vs. active monitoring;

- Length and frequency of monitoring;
- Completeness of outcome reporting (e.g. are patients exclude from analysis of harms?);
- Reporting of numerical data per study group (as opposed to use of vague language).

For systematic reviews that are included for summary of efficacy of comparisons of treatment regimens for LTBI, the 11-point validated AMSTAR tool (A MeaSurement Tool to Assess Reviews) will be used.[10]

All assessments will be presented in supplements to the review's main text for completeness. They will primarily be used to narratively summarize quality of data included in the review.

3.6   JUDGING STUDY HOMOGENEITY

An important step in systematic reviews combining data from different studies is the validation of the assumption that patients in the included trials are sufficiently homogeneous clinically that a patient in any one of the studies could have been a patient in any of the other included trials. We will empirically evaluate this assumption by review of the patient eligibility criteria, pertinent patient demographics, and study design information in collaboration with our participating clinical experts and other members of the research team. This will be performed by inspection of evidence tables, tabulated lists of study characteristics and boxplots of descriptive statistics for several important characteristics (i.e., means and frequency distributions as appropriate for each characteristic), as well as review of measures of statistical heterogeneity (using the I^2 statistic to identify syntheses with a value >50%, equivalent to moderate or greater heterogeneity). Characteristics of focus will include, but not be limited to, the following: mean age and/or age group, % who were contact screens, and relevant risk factors (e.g. HIV, diabetes, smoking, malnutrition, transplant, kidney failure, and liver disease).

3.7   EVIDENCE SYNTHESIS

The evidence synthesis will consist of a largely descriptive component to address research question 1 regarding adverse effects, and an analytic component incorporating network meta-analysis for research question 2 regarding treatment completion rates.

- **Descriptive Component (Question 1):**
  - The frequency of the variety of different hypersensitivity reactions outlined earlier will be presented, stratified by regimen and by type of study design, along with aggregate rates. After the data is collected, the research team will discuss whether additional quantitative approaches would provide insightful for interpretation.
  - A narrative summary of efficacy data from existing reviews in terms of prevention of active TB will be presented.

- **Analytic Component (Question 2):**
  - Treatment completion rates are commonly reported outcomes in randomized trials of interventions for LTBI. To compare this important outcome measure across interventions, we will conduct network meta-analyses to incorporate all

available direct and indirect data from available RCTs. Additional description of network meta-analysis and our planned methods are provided below.

Primary Meta-Analysis & Network Meta-Analysis for Research Question 2

Standard pairwise meta-analyses will be conducted using random-effects models in Comprehensive Meta-Analyst software (Biostat Inc; Englewood, New Jersey, USA) to generate summary estimates and to assess statistical heterogeneity. Summary estimates for the binary outcome of interest (treatment completion) will be reported as odds ratios with 95% confidence intervals. All measures of I^2 will be reported as proportions ranging from 0–100%. I^2 values of 50% or higher will be considered indicative of potentially important heterogeneity which will be explored using established methods such as subgroup analysis, meta-regression and/or exclusion of outlier studies. If necessary, similar approaches will be conducted in network meta-analyses as well to address existing heterogeneity. These efforts will be taken for each edge in the treatment network prior to progressing to network meta-analysis.

Network meta-analysis will be carried out to compare completion rates across the range of comparators of interest. Network meta-analysis is an approach to evidence synthesis that allows for the combination of both *direct* and *indirect* evidence to compare three or more treatments in a unified analysis.[11-13] Indirect comparisons between treatments A and B based on a common comparator C where no trials of A versus B exist (i.e. no direct evidence) but trials of A versus C and B versus C exist (i.e. indirect evidence) were originally proposed by Bucher et al, and Lumley and Lu and Ades subsequently developed extensions of this methodology. In addition to estimating all possible pairwise comparisons in a network (e.g. summary odds ratios), this technique can also be used to estimate probabilities of treatment superiority to rank the treatments including Surface Under the Cumulative Ranking curve (i.e., SUCRA) or median treatment rankings with corresponding 95% credible intervals.[14] These will also be reported as secondary information to help with interpretation of pairwise comparisons.

Full graphical and numeric presentations of findings along with a lay-person's summary will be provided. This will include the following: a network diagram showing the availability of evidence for all possible treatment comparisons; summary odds ratios with 95% credible intervals for all pairwise comparisons between regimens; SUCRA and median treatment rankings (with corresponding 95% CrI) for each outcome. These will be described using approaches recommended by Salanti et al.[14] We will use the PRISMA Extension Statement for Network Meta-Analysis to ensure all findings are clearly reported.[15]

Network meta-analysis will be performed using WinBUGS software version 1.4.3 (MRC Biostatistics Unit), along with the Microsoft Excel plug-in tool NetMetaXL to organize data and generate all summary figures;[15] this tool is capable of expediting the required time to complete conduct and reporting of a network meta-analsyis. Our summary will include a network diagram and forest plots, with other information provided as appendices. Approaches used for these analyses will follow existing recommendations for modeling of unadjusted and adjusted models as outlined by experts at the National Institute for Clinical Excellence.[12,16] Both fixed and random effects consistency and inconsistency models will be fit for each outcome. The fit of a model will be assessed by comparing its posterior residual deviance with the number of unconstrained data points (i.e. the number of intervention arms across all studies) for the

analysis. Selection between different models will be based upon deviance information criteria (DIC) for each competing model, with a difference of 5 or more points to be considered significant. Totals of 50,000 or more burn-in iterations and 50,000 or more sampling iterations will be used for all network meta-analyses, and model convergence will be assessed based on inspection of history plots and the Monte Carlo error of all parameters.

Additional Analyses

Dependent upon observed variations between studies (in terms of discrepancies in populations or other study-level factors) as well as perceived weaknesses in geometry of the networks under analysis (e.g. predominance of single study connections which pose threats to consider random effects models), the following supplemental analyses may be considered at the discretion of the research team as the research progresses:

- *Heterogeneity considerations*. Meta-regression analysis based on study-level traits and/or sensitivity analyses based on exclusion of potential outlier studies motivated by diversity of patient or study traits (e.g. based on extremes in terms of patient age, patient comorbidities, patient risk factors (HIV infection, immune compromised), and so forth).
- *Geometry considerations*. Removal of interventions in the network which are not a part of our primary comparators set and which are associated with single study connections only (which can limit aspects of statistical modeling).

4. PLANNED DELIVERABLES

The following deliverables will be planned for the proposed review:

1) Rapid review protocol (presented here);
2) Yield of updated search for RCTs, observational research and grey literature;
3) Rapid review summary report that will be tailored in appearance to facilitate rapid reading of findings for decision-makers, ensuring language is at an appropriate level and use of statistical jargon is minimized. This tailored report will include:
   a. Key messages from the findings;
   b. Snapshot of the evidence including PRISMA flow diagram;
   c. Brief summary of findings by outcome;
   d. Overview of the methods employed and tools used to assess risk of bias;
   e. List of included studies;
   f. List of excluded studies (with primary reason for exclusion);
   g. Summary of quantitative findings from aggregation/narrative summary of findings (for research question 1) and generated from network meta-analysis (research question 2).

More in-depth results will be provided as appendices. The report summary will not include recommendations. All deliverables will be provided in English, in electronic format (PDF).

After delivery of the report to knowledge users, we will also pursue publication of this work in a peer-reviewed journal. Dependent upon opinions of the research team at that time, additional data analyses may be pursued in order to further incorporate additional treatments and/or to provide additional analytic perspectives on the data collected. A report focused upon our set of set of primary comparators will be targeted for a Canadian journal, while a more broad report considering the additional regimens will be targeted for an international journal.

5. CONTRIBUTORS

The Knowledge Synthesis Group at the Ottawa Hospital has considerable expertise in the conduct of both rapid reviews and network meta-analyses and is well suited for this research. The research team for this review will consist of a grouping of experts in the realms of systematic reviews, meta-analysis, network meta-analysis, tuberculosis research, rapid reviews, and library sciences. Team members will include the following individuals from the Ottawa Hospital Research Institute and Ottawa Hospital: Brian Hutton, Gonzalo Alverez, Chris Pease, Fatemeh Yazdi, Dianna Wolfe, Chantelle Garritty, Becky Skidmore, Risa Shorr, David Moher. We will also work with our primary knowledge user (Dr. Maureen Baikie) and her team in terms of having regular contact during the review process.

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<u>APPENDICES</u>

- **Appendix 1**: Literature Search Considerations
- **Appendix 2**: RCTs from 2014 Network Meta-Analysis
- **Appendix 3**: AMSTAR Assessment, 2014 Network Meta-Analysis
- **Appendix 4**: Budget and Justification

APPENDIX 1. LITERATURE SEARCH CONSIDERATIONS

Description of 2014 Annals Systematic Review Search to be updated:
PubMed, EMBASE, and the Web of Science were mined by using the preestablished search terms "chemoprevention," "preventive therapy," "chemoprophylaxis," or "treatment" AND "latent tuberculosis," "tuberculous infection," or "latent TB infection," and filters to select RCTs and human studies applied wherever possible. Reference lists of included papers and review articles were also searched, as well as the Cochrane Central Register of Controlled Trials; World Health Organization International Clinical Trials Registry Platform; International Standardized Randomized Controlled Trial Number Register; ClinicalTrials.gov; and abstracts from international conferences of the International Union Against Tuberculosis and Lung Disease, American Thoracic Society, and European Respiratory Society from 2010 to 2013.

SEARCH STRATEGY, RCT DATA (OVID MEDLINE, EMBASE):

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2015 Week 26>
Search Strategy:
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1   Latent Tuberculosis/ (3605)
2   (latent adj2 (tuberculosis or TB or TBI)).tw,kw. (7631)
3   ((inactive or noninfectious or non-infectious or uninfectious) adj2 (tuberculosis or TB or TBI)).tw,kw. (606)
4   LTBI.tw,kw. (2719)
5   or/1-4 (9355)
6   (controlled clinical trial or randomized controlled trial or pragmatic clinical trial).pt. (483681)
7   clinical trials as topic.sh. (173525)
8   (randomi#ed or randomly or RCT$1 or placebo*).tw. (1561661)
9   ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (307265)
10   trial.ti. (320010)
11   or/6-10 (1973368)
12   5 and 11 (452)
13   exp Animals/ not (exp Animals/ and Humans/) (8186584)
14   12 not 13 (445)
15   (comment or editorial or interview or news).pt. (1554719)
16   (letter not (letter and randomized controlled trial)).pt. (1769674)
17   14 not (15 or 16) (434)
18   (201307* or 201308* or 201309* or 201310* or 201311* or 201312* or 2014* or 2015*).dc. (2231650)
19   17 and 18 (53)
20   19 use prmz (53)
21   latent tuberculosis/ (3605)
22   (latent adj2 (tuberculosis or TB or TBI)).tw,kw. (7631)
23   ((inactive or noninfectious or non-infectious or uninfectious) adj2 (tuberculosis or TB or TBI)).tw,kw. (606)
24   LTBI.tw,kw. (2719)
25   or/21-24 (9355)
26   randomized controlled trial/ or controlled clinical trial/ (996107)
27   exp "clinical trial (topic)"/ (152154)
28   (randomi#ed or randomly or RCT$1 or placebo*).tw. (1561661)

29   ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (307265)
30   trial.ti. (320010)
31   or/26-30 (2141547)
32   25 and 31 (583)
33   exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38570669)
34   exp humans/ or exp human experimentation/ or exp human experiment/ (30015105)
35   33 not 34 (8557150)
36   32 not 35 (576)
37   editorial.pt. (859908)
38   letter.pt. not (letter.pt. and randomized controlled trial/) (1765266)
39   36 not (37 or 38) (565)
40   (201307* or 201308* or 201309* or 201310* or 201311* or 201312* or 2014* or 2015*).dd. (3237448)
41   39 and 40 (140)
42   41 use emez (140)
43   19 or 42 (193)
44   remove duplicates from 43 (155) [TOTAL UNIQUE RECORDS]
45   44 use prmz (43) [MEDLINE UNIQUE RECORDS]
46   44 use emez (112) [EMBASE UNIQUE RECORDS]

SEARCH STRATEGY, OBSERVATIONAL DATA (OVID MEDLINE, EMBASE):

Database: Embase Classic+Embase <1947 to 2015 July 02>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
----
1   Latent Tuberculosis/ (3630)
2   (latent adj2 (tuberculosis or TB or TBI)).tw,kw. (7808)
3   ((inactive or noninfectious or non-infectious or uninfectious) adj2 (tuberculosis or TB or TBI)).tw,kw. (886)
4   LTBI.tw,kw. (2740)
5   or/1-4 (9813)
6   Latent Tuberculosis/dt (925)
7   exp Tuberculosis/pc (35601)
8   exp Antitubercular Agents/ (204983)
9   (antitubercular* or anti-tubercular* or tuberculostatic*).tw,kw. (15320)
10   Isoniazid/ (72371)
11   (Amidon or Andrazide or Antimicina or Antituberkulosum or Armazid or Armazide or Atcotibine or Azuren).tw,kw. (108)
12   (Bacillin or BP 5015 or CCRIS 351 or Cedin or Cemidon or Chemiazid or Chemidon or Cotinazin).tw,kw. (58)
13   (Defonin or Diforin or Dinacrin or Ditubin or Dow-isoniazid or Ebidene or EINECS 200-214-6 or Eralon or Ertuban or Eutizon or Evalon).tw,kw. (19)
14   (Fimalene or FSR 3 or Ftivazide or Gink or HIA or Hidranizil or Hidrasonil or Hidrulta or Hidrun or HSDB 1647 or Hycozid or Hydrazid or Hydrazide or Hyzyd).tw,kw. (11104)
15   (Ido-tebin or Idrazide dell'acido isonicotinico or Idrazil or IN-73 or INAH or INH or Inh-Burgthal or Inizid or Iscotin or Isidrina or Ismazide or Isobicina or Isocid or Isocidene or Isocotin or Isohydrazide or Isolyn or Isonerit or Isonex or Isoniazid or Isoniazide or Isonicid or Isonico or Isonicotan or Isonicotil).tw,kw. (62709)
16   (Isonicotinhydrazid or Isonicotinic acid hydrazide or sonicotinic Acid Vanillylidenehydrazide or Isonicotinic hydrazide or Isonicotinohydrazide or Isonicotinoyl hydrazide or Isonicotinoylhydrazine or Isonicotinsaeurehydrazid or Isonicotinyl hydrazide or Isonicotinylhydrazine).tw,kw. (3004)

17   (Isonide or Isonidrin or Isonikazid or Isonilex or Isonin or Isonindon or Isonirit or Isoniton or Isonizide or Isotamine or Isotebe or Isotebezid or Isotinyl or Isozid or Isozide or Isozyd).tw,kw. (53)

18   (L 1945 or Laniazid or Mybasan or Neo-tizide or Neoteben or Neoxin or Neumandin or Nevin or Niadrin or Nicazide or Nicetal or Nicizina or Niconyl or Nicotibina or Nicotibine or Nicotisan or Nicozide or Nidaton or Nidrazid or Nikozid or Niplen or Nitadon or Niteban or Nitebannsc 9659 or NSC 9659 or Nydrazid or Nyscozid).tw,kw. (821)

19   (Pelazid or Percin or Phthisen or Phthivazid or Phthivazide or Preparation 6424 or Pycazide or Pyreazid or Pyricidin or Pyrizidin or Raumanon or Razide or Retozide or Rifamate or Rimicid or Rimifon or Rimiphone or Rimitsid or RP-5015 or Stanozide or Tubazid or Tubazide or UNII-V83O1VOZ8L).tw,kw. (1324)

20   Rifampin/ (87756)

21   (Archidyn or Arficin or Arzide or "Ba 41166/E" or Benemicin or CCRIS 551 or Dione 21-acetate or Doloresum or EINECS 236-312-0 or Eremfat or Fenampicin or HSDB 3181).tw,kw. (78)

22   (L-5103 or Lepetit or NSC 113926 or "R/AMP" or RAMP or Rifa or Rifadin or Rifagen or Rifaldazin or Rifaldazine or Rifam or Rifamor or Rifampicin or Rifampicine or Rifampin).tw,kw. (56353)

23   (Rifamycin or Rifaprodin or Rifcin or Rifinah or Rifobac or Rifoldin or Rifoldine or Riforal or Rimactan or Rimactane or Rimactazid or Rimactizid or Rimazid or Sinerdol or Tubocin or UNII-VJT6J7R4TR).tw,kw. (4338)

24   (3HP or 9H or 3INH or 4INH or 6INH or 9INH or "3INH/RPT" or "RPT/INH" or "RPT-INH" or RPTINH or RMP or "RMP/INH" or "RMP-INH" or RMPINH).tw,kw. (8302)

25   or/6-24 (303759)

26   5 and 25 (3948)

27   exp Cohort Studies/ (1657272)

28   cohort$1.tw. (806754)

29   Retrospective Studies/ (951130)

30   (longitudinal or prospective or retrospective).tw. (1954271)

31   ((followup or follow-up) adj (study or studies)).tw. (94902)

32   Observational study.pt. (12018)

33   (observation$2 adj (study or studies)).tw. (134212)

34   ((population or population-based) adj (study or studies or analys#s)).tw. (28632)

35   ((multidimensional or multi-dimensional) adj (study or studies)).tw. (201)

36   Comparative Study.pt. (1714430)

37   ((comparative or comparison) adj (study or studies)).tw. (197903)

38   exp Case-Control Studies/ (827835)

39   ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (161035)

40   Cross-Sectional Studies/ (345898)

41   ((cross-sectional or frequency or prevalence) adj (analys#s or study or studies or survey$1)).tw. (273742)

42   or/27-41 (5717792)

43   26 and 42 (1024)

44   exp Product Surveillance, Postmarketing/ (38112)

45   ((drug or drugs) adj3 (surveillance* or monitor*)).tw,kw. (33491)

46   pharmacovigilan*.tw,kw. (8837)

47   (("phase 4" or "phase IV") adj3 (clinical trial$1 or evaluat*)).tw,kw. (544)

48   adverse drug reaction report*.tw,kw. (1036)

49   or/44-48 (72021)

50   26 and 49 (17)

51   43 or 50 (1039)

52   exp Animals/ not (exp Animals/ and Humans/) (8969447)

53   43 not 52 (1021)

54   (comment or editorial or interview or news).pt. (1558982)

55   (letter not (letter and randomized controlled trial)).pt. (1777771)

56   53 not (54 or 55) (1005)

57   56 use prmz (471) [MEDLINE RECORDS]

58   latent tuberculosis/ (3630)

59   (latent adj2 (tuberculosis or TB or TBI)).tw,kw. (7808)

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60 ((inactive or noninfectious or non-infectious or uninfectious) adj2 (tuberculosis or TB or TBI)).tw,kw. (886)

61 LTBI.tw,kw. (2740)

62 or/58-61 (9813)

63 latent tuberculosis/dt [Drug Therapy] (925)

64 exp tuberculosis/pc [Prevention] (35601)

65 tuberculostatic agent/ (61445)

66 (antitubercular* or anti-tubercular* or tuberculostatic*).tw,kw. (15320)

67 isoniazid/ (72371)

68 (Amidon or Andrazide or Antimicina or Antituberkulosum or Armazid or Armazide or Atcotibine or Azuren).tw,kw. (108)

69 (Bacillin or BP 5015 or CCRIS 351 or Cedin or Cemidon or Chemiazid or Chemidon or Cotinazin).tw,kw. (58)

70 (Defonin or Diforin or Dinacrin or Ditubin or Dow-isoniazid or Ebidene or EINECS 200-214-6 or Eralon or Ertuban or Eutizon or Evalon).tw,kw. (19)

71 (Fimalene or FSR 3 or Ftivazide or Gink or HIA or Hidranizil or Hidrasonil or Hidrulta or Hidrun or HSDB 1647 or Hycozid or Hydrazid or Hydrazide or Hyzyd).tw,kw. (11104)

72 (Ido-tebin or Idrazide dell'acido isonicotinico or Idrazil or IN-73 or INAH or INH or Inh-Burgthal or Inizid or Iscotin or Isidrina or Ismazide or Isobicina or Isocid or Isocidene or Isocotin or Isohydrazide or Isolyn or Isonerit or Isonex or Isoniazid or Isoniazide or Isonicid or Isonico or Isonicotan or Isonicotil).tw,kw. (62709)

73 (Isonicotinhydrazid or Isonicotinic acid hydrazide or sonicotinic Acid Vanillylidenehydrazide or Isonicotinic hydrazide or Isonicotinohydrazide or Isonicotinoyl hydrazide or Isonicotinoylhydrazine or Isonicotinsaeurehydrazid or Isonicotinyl hydrazide or Isonicotinylhydrazine).tw,kw. (3004)

74 (Isonide or Isonidrin or Isonikazid or Isonilex or Isonin or Isonindon or Isonirit or Isoniton or Isonizide or Isotamine or Isotebe or Isotebezid or Isotinyl or Isozid or Isozide or Isozyd).tw,kw. (53)

75 (L 1945 or Laniazid or Mybasan or Neo-tizide or Neoteben or Neoxin or Neumandin or Nevin or Niadrin or Nicazide or Nicetal or Nicizina or Niconyl or Nicotibina or Nicotibine or Nicotisan or Nicozide or Nidaton or Nidrazid or Nikozid or Niplen or Nitadon or Niteban or Nitebannsc 9659 or NSC 9659 or Nydrazor or Nyscozid).tw,kw. (821)

76 (Pelazid or Percin or Phthisen or Phthivazid or Phthivazide or Preparation 6424 or Pycazide or Pyreazid or Pyricidin or Pyrizidin or Raumanon or Razide or Retozide or Rifamate or Rimicid or Rimifon or Rimiphone or Rimitsid or RP-5015 or Stanozide or Tubazid or Tubazide or UNII-V83O1VOZ8L).tw,kw. (1324)

77 rifampicin/ (87756)

78 (Archidyn or Arficin or Arzide or "Ba 41166/E" or Benemicin or CCRIS 551 or Dione 21-acetate or Doloresum or EINECS 236-312-0 or Eremfat or Fenampicin or HSDB 3181).tw,kw. (78)

79 (L-5103 or Lepetit or NSC 113926 or "R/AMP" or RAMP or Rifa or Rifadin or Rifagen or Rifaldazin or Rifaldazine or Rifam or Rifamor or Rifampicin or Rifampicine or Rifampin).tw,kw. (56353)

80 (Rifamycin or Rifaprodin or Rifcin or Rifinah or Rifobac or Rifoldin or Rifoldine or Riforal or Rimactan or Rimactane or Rimactazid or Rimactizid or Rimazid or Sinerdol or Tubocin or UNII-VJT6J7R4TR).tw,kw. (4338)

81 (3HP or 9H or 3INH or 4INH or 6INH or 9INH or "3INH/RPT" or "RPT/INH" or "RPT-INH" or RPTINH or RMP or "RMP/INH" or "RMP-INH" or RMPINH).tw,kw. (8302)

82 or/63-81 (274345)

83 62 and 82 (3923)

84 cohort analysis/ (389316)

85 cohort$1.tw. (806754)

86 retrospective study/ (951130)

87 longitudinal study/ (172858)

88 prospective study/ (691542)

89 (longitudinal or prospective or retrospective).tw. (1954271)

90 follow up/ (955979)

91 ((followup or follow-up) adj (study or studies)).tw. (94902)

92 observational study/ (85980)

93 (observation$2 adj (study or studies)).tw. (134212)

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94   population research/ (73614)
95   ((population or population-based) adj (study or studies or analys#s)).tw. (28632)
96   ((multidimensional or multi-dimensional) adj (study or studies)).tw. (201)
97   exp comparative study/ (2799042)
98   ((comparative or comparison) adj (study or studies)).tw. (197903)
99   exp case control study/ (827835)
100   ((case-control* or case-based or case-comparison) adj (study or studies)).tw. (161035)
101   cross-sectional study/ (345898)
102   ((cross-sectional or frequency or prevalence) adj (analys#s or study or studies or survey$1)).tw. (273742)
103   or/84-102 (7057218)
104   83 and 103 (1353)
105   drug surveillance program/ (20141)
106   ((drug or drugs) adj3 (surveillance* or monitor*)).tw,kw. (33491)
107   pharmacovigilan*.tw,kw. (8837)
108   adverse drug reaction report*.tw,kw. (1036)
109   "phase 4 clinical trial (topic)"/ (630)
110   (("phase 4" or "phase IV") adj3 (clinical trial$1 or evaluat*)).tw,kw. (544)
111   or/105-110 (57085)
112   83 and 111 (13)
113   104 or 112 (1364)
114   exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (39538061)
115   exp humans/ or exp human experimentation/ or exp human experiment/ (30303886)
116   114 not 115 (9235832)
117   113 not 116 (1358)
118   editorial.pt. (864171)
119   letter.pt. not (letter.pt. and randomized controlled trial/) (1773360)
120   117 not (118 or 119) (1324)
121   120 use emczd (880) [EMBASE RECORDS]
122   57 or 121 (1351)
123   remove duplicates from 122 (1063) [TOTAL UNIQUE RECORDS]
124   123 use prmz (454) [MEDLINE UNIQUE RECORDS]
125   123 use emczd (609) [EMBASE UNIQUE RECORDS]

GREY LITERATURE SEARCH DETAILS:

TRIP - Latent Tuberculosis – no date limit
2015 Jul 3

1,260 results

- All Secondary Evidence
  - Systematic Reviews 52 +58
  - Evidence-based Synopses 19
  - Guidelines
    - Aus & NZ 11
    - Canada 7
    - UK 10
    - USA 37
    - Other 11
- Key Primary Research 25
- Clinical Q&A 0
- Controlled Trials 169
- Primary Research 522
- Ongoing clinical trials 335
    -
      - Open 73
      - Closed 228
      - Unknown 34
- Patient decision aids 0
- Blogs 0
- eTextbooks 62

APPENDIX 2. RCTS IDENTIFIED FROM ANNALS 2014 REVIEW

The following list presents a summary of all RCTs included in the 2014 systematic review and network meta-analysis by Stegg et al. We will incorporate these studies into our work in the proposed review as outlined earlier. We will also share this list with experts in the field to determine if any RCTs completed prior to 2014 were missed.

1. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011; 365:2155-66.

2. Gordin F, Chaisson RE, Matts JP, Miller C, de Lourdes Garcia M, Hafner R, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. JAMA. 2000;283:1445-50.

3. Gordin FM, Cohn DL, Matts JP, Chaisson RE, O'Brien RJ; Terry Beirn Community Programs for Clinical Research on AIDS. Hepatotoxicity of rifampin and pyrazinamide in the treatment of latent tuberculosis infection in HIVinfected persons: is it different than in HIV-uninfected persons? Clin Infect Dis. 2004;39:561-5.

4. Johnson JL, Okwera A, Hom DL, Mayanja H, Mutuluuza Kityo C, Nsubuga P, et al; Uganda-Case Western Reserve University Research Collaboration. Duration of efficacy of treatment of latent tuberculosis infection in HIVinfected adults. AIDS. 2001;15:2137-47.

5. Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugyenyi P, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. N Engl J Med. 1997;337:801-8.

6. Mwinga A, Hosp M, Godfrey-Faussett P, Quigley M, Mwaba P, Mugala BN, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. AIDS. 1998;12:2447-57.

7. Quigley MA, Mwinga A, Hosp M, Lisse I, Fuchs D, Porter JDH, et al. Long-term effect of preventive therapy for tuberculosis in a cohort of HIV infected Zambian adults. AIDS. 2001;15:215-22.

8. Madhi SA, Nachman S, Violari A, Kim S, Cotton MF, Bobat R, et al; P1041 Study Team. Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. N Engl J Med. 2011;365:21-31.

9. Portilla J, Jorda´ P, Esteban J, Sa´nchez-Paya´ J, Merino E, Boix V; Grupo de Estudio Protocolo-INH. [Directly observed treatment of latent tuberculosis infection: comparative study of two isoniazid regimens]. Enferm Infecc Microbiol Clin. 2003;21:293-5.

10. Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month

regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis. 2007;45:715-22.

11.   Bush OB Jr, Sugimoto M, Fujii Y, Brown FA Jr. Isoniazid prophylaxis in contacts of persons with known tuberculosis. Second report. Am Rev Respir Dis. 1965;92:732-40.

12.   del Castillo H, Bautista LD, Jacinto CP, Lorenzo CE, Lapuz S, Legaspi B. Chemoprophylaxis in the Philippines: a controlled pilot study among household contacts of tuberculosis cases. Bulletin of the Quezon Institute. 1965;7:277-90.

13.   Egsmose T, Ang'awa JO, Poti SJ. The use of isoniazid among household contacts of open cases of pulmonary tuberculosis. Bull World Health Organ. 1965;33:419-33.

14.   Ferebee SH, Mount FW. Tuberculosis morbidity in a controlled trial of the prophylactic use of isoniazid among household contacts. Am Rev Respir Dis. 1962;85:490-510.

15.   Geijo MP, Herranz CR, Van˜o D, Garcı´a AJ, Garcı´a M, Dimas JF. [Shortcourse isoniazid and rifampin compared with isoniazid for latent tuberculosis infection: a randomized clinical trial]. Enferm Infecc Microbiol Clin. 2007;25: 300-4.

16.   Gupta DK, Kumar R, Nath N, Kothari AK. Chemoprophylaxis in high-risk children—analysis of 8 years' follow-up: preliminary report. Indian Journal of Tuberculosis. 1993;40:125-7.

17.   Martı´nez Alfaro E, Solera J, Serna E, Cuenca D, Castillejos ML, Espinosa A, et al. [Compliance, tolerance and effectiveness of a short chemoprophylaxis regimen for the treatment of tuberculosis]. Med Clin (Barc). 1998;111:401-4.

18.   Mount FW, Ferebee SH. The effect of isoniazid prophylaxis on tuberculosis morbidity among household contacts of previously known cases of tuberculosis. Am Rev Respir Dis. 1962;85:821-7.

19.   Schechter M, Zajdenverg R, Falco G, Barnes GL, Faulhaber JC, Coberly JS, et al. Weekly rifapentine/ isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts. Am J Respir Crit Care Med. 2006;173:922-6.

20.   Tortajada C, Martı´nez-Lacasa J, Sa´nchez F, Jime´nez-Fuentes A, De Souza ML, Garcı´a JF, et al; Tuberculosis Prevention Working Group. Is the combination of pyrazinamide plus rifampicin safe for treating latent tuberculosis infection in persons not infected by the human immunodeficiency virus? Int J Tuberc Lung Dis. 2005;9:276-81.

21.   Veening GJ. Long term isoniazid prophylaxis. Controlled trial on INH prophylaxis after recent tuberculin conversion in young adults. Bull Int Union Tuberc. 1968;41:169-71.

22.   Magdorf K, Arizzi-Rusche AF, Geiter LJ, O'Brien RJ, Wahn U. [Compliance and tolerance of new antitubercular short-term chemopreventive regimens in childhood—a pilot project]. Pneumologie. 1994;48:761-4.

23.   Zar HJ, Cotton MF, Strauss S, Karpakis J, Hussey G, Schaaf HS, et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. BMJ. 2007;334:136.

24.   Agarwal SK, Gupta S, Dash SC, Bhowmik D, Tiwari SC. Prospective randomised trial of isoniazid prophylaxis in renal transplant recipient. Int Urol Nephrol. 2004;36:425-31.

25.   Fitzgerald DW, Severe P, Joseph P, Mellon LR, Noel E, Johnson WD Jr, et al. No effect of isoniazid prophylaxis for purified protein derivative-negative HIV-infected adults living in a country with endemic tuberculosis: results of a randomized trial [Letter]. J Acquir Immune Defic Syndr. 2001;28:305-7.

26.   Gordin FM, Matts JP, Miller C, Brown LS, Hafner R, John SL, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS. N Engl J Med. 1997;337:315-20.

27.   Halsey NA, Coberly JS, Desormeaux J, Losikoff P, Atkinson J, Moulton LH, et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. Lancet. 1998;351:786-92.

28.   Hawken MP, Meme HK, Elliott LC, Chakaya JM, Morris JS, Githui WA, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. AIDS. 1997;11:875-82.

29.   John GT, Thomas PP, Thomas M, Jeyaseelan L, Jacob CK, Shastry JC. A double-blind randomized controlled trial of primary isoniazid prophylaxis in dialysis and transplant patients. Transplantation. 1994;57:1683-4.

30.   Martı´nez Alfaro EM, Cuadra F, Solera J, Macia´ MA, Geijo P, Sa´nchez Martı´nez PA, et al. [Evaluation of 2 tuberculosis chemoprophylaxis regimens in patients infected with human immunodeficiency virus. The GECMEI Group]. Med Clin (Barc). 2000;115:161-5.

31.   Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365:11-20.

32.   Matteelli A, Olliaro P, Signorini L, Cadeo G, Scalzini A, Bonazzi L, et al. Tolerability of twice-weekly rifabutin-isoniazid combinations versus daily isoniazid for latent tuberculosis in HIV-infected subjects: a pilot study. Int J Tuberc Lung Dis. 1999;3:1043-6.

33.   Mohammed A, Myer L, Ehrlich R, Wood R, Cilliers F, Maartens G. Randomised controlled trial of isoniazid preventive therapy in South African adults with advanced HIV disease. Int J Tuberc Lung Dis. 2007;11:1114-20.

34.   Naqvi R, Naqvi A, Akhtar S, Ahmed E, Noor H, Saeed T, et al. Use of isoniazid chemoprophylaxis in renal transplant recipients. Nephrol Dial Transplant. 2010;25:634-7.

35.   Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD Jr. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet. 1993;342:268-72.

36.   Rivero A, Lo´pez-Corte´s L, Castillo R, Verdejo J, Garcı´a MA, Martı´nez-Marcos FJ, et al; Grupo Andaluz para el estudio de las Enfermedades Infecciosas (GAEI). [Randomized clinical trial investigating three chemoprophylaxis regimens for latent tuberculosis infection in HIV-infected patients]. Enferm Infecc Microbiol Clin. 2007;25:305-10.

37.   Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo- controlled trial. Lancet. 2011;377:1588-98.

38.   Swaminathan S, Menon PA, Gopalan N, Perumal V, Santhanakrishnan RK, Ramachandran R, et al. Efficacy of a six-month versus a 36-month regimen for prevention of tuberculosis in HIV-infected persons in India: a randomized clinical trial. PLoS One. 2012;7:e47400.

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APPENDIX 3. AMSTAR ASSESSMENT, STEGG ET AL (2014)

AMSTAR Assessment: Stegg et al, Annals of Internal Medicine, 2014. Treatment of latent tuberculosis infection: a network meta-analysis. 2014 Sep 16;161(6):419-28

AMSTAR Criteria	Judgement
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	Yes No Can't answer NA
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	Yes No Can't answer NA
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. *Note: the review does not mention time frames searched and the search strategy was considered potentially limited by an independent librarian assessment. We have expanded our updated search to improve this and have sought expert input to identify any missed trials prior to 2014.*	Yes No Can't answer NA
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. *Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SINGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.*	Yes No Can't answer NA
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided. *No list is provided and the references for exclusions in the main text are note complete relative to the flow diagram.*	Yes No Can't answer NA
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported. *The review's evidence table is limited and without demographics; there is a reasonable description in the text though more detail should have been provided.*	Yes No Can't answer NA
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies	Yes

AMSTAR Assessment: Stegg et al, Annals of Internal Medicine, 2014. Treatment of latent tuberculosis infection: a network meta-analysis. 2014 Sep 16;161(6):419-28	
AMSTAR Criteria	**Judgement**
if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	No Can't answer NA
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. *A narrative summary of RoB evaluations as well sensitivity analyses based on them are both provided.*	`Yes` No Can't answer NA
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?). *The authors used a random effects model for network meta-analysis, which is appropriate. They also explored pairwise meta-analyses of the edges in the network as well as I^2 values for heterogeneity. Some of the values are a bit high but not unreasonably so.*	`Yes` No Can't answer NA
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).	`Yes` No Can't answer NA
11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. *The authors report their sources of support, however they are not reported for the studies included in the systematic review.*	Yes `No` Can't answer NA