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Effectiveness and safety of available preventive tuberculosis treatment regimens for children and adolescents: protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction Approximately 5%–10% of individuals with untreated latent tuberculosis infection (LTBI) will progress to active tuberculosis (TB). Children are at a higher risk for progression to TB disease than adults. Isoniazid prophylaxis treatment period is long and can cause liver damage. Alternatives to isoniazid, such as rifamycin containing regimens, should be considered for prophylaxis. Previous systematic reviews, with different study designs and data combining results on children and adults, have evaluated the comparative efficacy and harms of LTBI treatment regimens. We aim to determine the effectiveness and safety of all the different regimens available for the treatment of LTBI for children and adolescents less than 18 years of age, contacts of drug-susceptible TB, without HIV infection.

Methods and analysis MEDLINE, Embase and Cochrane Central Register of Controlled Trials will be systematically searched for randomised controlled trials without any language or publication date restriction. Screening and extraction will be performed in duplicate. Risk of bias will be performed in duplicate with Cochrane Risk of Bias tool V.2. Pairwise meta-analysis of direct comparisons and network meta-analyses (NMAs) will be performed. Heterogeneity will be assessed using I^2 and Cochrane thresholds. Direct and indirect estimates in an NMA will be combined if justifiable. Subgroups analyses will be performed in different mean age and study year groups. Sensitivity analysis based on the risk of bias will be conducted. Publication bias will be investigated using funnel plots and Egger's regression test. Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria will assess certainty of the evidence for the direct comparisons. GRADE approach for NMA will assess the quality of the evidence from the indirect and NMA.

Ethics and dissemination Ethical approval is not required as no primary data are collected. This systematic review will be disseminated in a peer-reviewed journal.

PROSPERO registration number CRD42021271512.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Children have a higher risk for progression to tuberculosis disease than adults, due to vaccination, nutritional and immune status, and age.
⇒ Isoniazid prophylaxis non-compliance can be due to long treatment duration, hepatotoxicity, adverse events and forgetting to take or administer the tablets by caregivers.
⇒ Short-term regimens should also be considered in children.

WHAT THIS STUDY ADDS

⇒ There is no evidence synthesis on the best preventive tuberculosis regimens for children and adolescents.
⇒ This project aims to provide a summary of the best available evidence on the effectiveness and safety of the available preventive treatment.
⇒ If the assumptions of homogeneity, coherence and transitivity are judged to be justifiable, we will determine the relative effectiveness among regimes to highlight the best and the worst ones for our outcomes of interest.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our project will present an updated synthesis of the best available evidence about preventive treatments in children.
⇒ Our findings will be key to inform clinicians, decision-makers, guideline developers from international organizations and patients/caregivers. about the best interventions to implement in different contexts.

INTRODUCTION

Latent tuberculosis infection (LTBI) is a state of persistent bacterial viability, immune control and no evidence of clinically manifested active tuberculosis (TB),[1] constituting a public health problem requiring effective

interventions. Since up to 2014, nearly 1.7 billion individuals were reported as latently infected with *Mycobacterium tuberculosis*.[2]

Most infected individuals are asymptomatic and do not develop active TB. Nevertheless, if untreated, approximately 5%–10% of persons with LTBI will progress to active TB or TB disease.[3–5] Moreover, children are at a higher risk for progression to TB disease than adults.[6] Several factors appear to influence the balance of risk between LTBI or progression to active disease, including age and nutritional, vaccination and immune status.[7] For instance, in the absences of preventive measures, approximately 50% of infants, even those delivered at term, develop active TB after infection.[8] Children under 4 years of age have the highest risk of progression with development of severe forms of TB, such as miliary or disseminated and meningeal or central nervous system TB.[9] Safe and effective preventive treatment strategies as part of global TB control[10] should be targeted to those population groups at highest risk for progression to active disease.

Among first-line antituberculous medication, isoniazid is also used as a single drug to prevent *M. tuberculosis* infection and progression from latent infection to active TB.[11] Isoniazid prophylaxis has traditionally been used for decades; it has showed high efficacy and proved risk reduction for TB among children.[12] However, the treatment period with isoniazid is long, can cause liver damage and only approximately 50% of patients complete the treatment.[10] Compliance to isoniazid regimen can be a challenge, especially in high-risk populations. Noncompliance has been reported due to forgetting to take or administer the tablets by caregivers, adverse events, migration or travelling, among others.[13]

Alternatives to isoniazid, such as rifamycin containing regimens (rifampicin and rifapentine), should be considered for prophylaxis. Trials comparing short-term rifampicin alone with long regimes of isoniazid, mostly in adults, have not shown higher rates of active TB, and compliance is probably higher and adverse events rates may be lower.[10] Furthermore, a combination of rifapentine and isoniazid supervised weekly for 3 months has demonstrated to be as effective in preventing TB as self-administered isoniazid for 9 months, increased treatment completion and caused less liver toxicity, though treatment-limiting adverse events were more frequent.[10]

Previous systematic reviews and network meta-analyses have evaluated the comparative efficacy and harms of LTBI treatment regimens. However, these studies have combined data from both, adults and children, to estimate the comparative effectiveness of several regimens.[14] Other previous reviews have included different study types, such as non-randomised studies and trials, to answer one structured clinical question about LTBI treatment options in children.[15] Moreover, a meta-analysis of randomised controlled trials (RCTs) has exclusively evaluated the efficacy of isoniazid, compared with placebo or no prophylaxis, in the prevention of TB morbidity and mortality in children.[12] As a result, to date, there is not a systematic review that had synthesised all the available evidence from RCTs comparing all the available prophylaxis regimes in children to determine whether there are differences among them. We aim to evaluate the effectiveness and safety of all the different regimens available for the treatment of LTBI for children and adolescents less than 18 years of age, contacts of drug-susceptible TB and without HIV infection.

METHODS AND ANALYSIS
Review method
The protocol of this systematic review was developed based on Participants, Interventions, Comparators and Outcomes components of the review method and prepared according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.[16] The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration No. CRD42021271512) on 2 August 2021. The final report of this review will follow the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for systematic reviews incorporating network meta-analyses (NMAs).[17]

Eligibility criteria
Participants
We are interested in RCT studies including children and/or adolescents under 18 years of age, with LTBI and who are contacts of individuals with drug-susceptible TB, regardless of the definition the authors used for LTBI. We will exclude studies with combined results for adults and children/adolescents, from which the information on children could not be extracted, and studies with HIV-infected children/adolescents.

Interventions and comparators
The interventions of interest are listed in table 1. Studies must compare at least one drug regimen listed in table 1 with another drug regimen and/or placebo and/or no treatment.

We will not include pyrazinamide regimens due to the known risk of severe hepatotoxicity as recommended by the Centers for Disease Control and Prevention (CDC) and the American Thoracic Society, since 2003.[18] On the basis of multiple reports and investigations from 2000 to 2002, the entities recommended in 2003 that rifampin and pyrazinamide regimens should generally not be offered to persons with LTBI for either HIV-negative or HIV-infected persons, which is also endorsed by the Infectious Diseases Society of America.[18] Clinicians are advised to use the preferred or alternative regimens for treatment of LTBI and only can be considered in carefully selected patients.[18] We will include studies that compared all the mentioned regimens among them, or with placebo.

Table 1	Interventions of interest	
Drug regimen	**Dose**	**Duration**
Rifampin	15 mg/kg/day (10–20 mg)	3–4 months
Isoniazid with rifampin	10 mg/kg/day (7–15 mg) 15 mg/kg/day (10–20 mg)	3–4 months
Rifapentine with isoniazid	Rifapentine weekly dose: 300 mg (10–14 kg) 450 mg (14.1–25 kg) 600 mg (25.1–32 kg) 750 mg (32.1–50 kg) 900 mg (>50 kg)	3 months
	Isoniazid weekly dose: 25 mg (2–11 years) 15 mg (≥12 years)	
Isoniazid	10 mg/kg/day (7–15 mg)	6 months
Isoniazid	10 mg/kg/day (7–15 mg)	9 months
Isoniazid	10 mg/kg/day (7–15 mg)	12 months
Placebo		
No treatment		

Outcomes

The primary outcomes are incidence of active TB at 2 years of follow-up and treatment compliance/adherence. We defined active TB as the disease caused by being infected with *M. tuberculosis*,[19] confirmed bacteriologically or diagnosed clinically based on the TB diagnostic criteria of the American Thoracic Society/Infectious Diseases Society of America/CDC Clinical Practice Guidelines.[20] Treatment adherence/compliance is included as used and reported by the authors of the primary studies.

Our secondary outcomes are incidence of active TB at 1 year and 5 years of follow-up, bacteriological confirmation of TB within the first 2 years after exposure, adverse reactions, hepatotoxicity, discontinuation of treatment due to adverse event and mortality at 5 years of follow-up. Bacteriological confirmation is obtained when TB is diagnosed in a biological specimen by smear microscopy, culture or molecular test (such as Xpert MTB/RIF).[19]

Adverse events, as defined by the study authors, include all signs and symptoms that can be expressions of organic or physiological alteration in the child/adolescent, as a result of the administration of the medication at indicated doses. These events can be detected during questioning of the children and/or their caregivers, during medical evaluations (clinically) or through laboratory test, and can lead to treatment discontinuation according to the seriousness of the event. Serious adverse events can result in death, are life threatening, require or prolong hospitalisation, result in persistent or significant disability or incapacity, or result in a congenital anomaly.[21] While unexpected adverse events are previously unobserved or undocumented, expected events typically do not require expedited reporting to the regulatory authorities.[21] Related adverse events indicate a reasonable possibility of an event being related to exposure to the product, based on biological plausibility, prior experience, temporal relationship between product exposure and onset of the event, as well as dechallenge and rechallenge.[21] Even though there is no standard nomenclature to describe the degree of causality, terms such as certainly, definitely, probably, possibly or likely related or not related have been used.[21]

Information sources and search strategy

We will search MEDLINE via Ovid, Embase via Ovid and the Cochrane Central Register of Controlled Trials (The Cochrane Library – current) without any language or publication date restriction and limited to human studies. The MEDLINE strategy was developed with input from the project team. To build the search strategy, MEDLINE and Embase via Ovid were used to identify an extensive list of keywords and MeSH terms related to "latent tuberculosis", "children", and "isoniazid" or "rifampin" or "rifamycins". The search strategy was revised and approved by all authors. A draft MEDLINE search strategy is available in online supplemental appendix 1. The MEDLINE strategy will be adapted to the syntax and subject subheadings of the other databases. PROSPERO database was also searched for ongoing or recently completed systematic reviews. The search will be updated towards the end of the review, after being validated to ensure that the MEDLINE strategy retrieves a high proportion of eligible studies found through any means but indexed in MEDLINE. The full search strategies and study selection process will be presented in a PRISMA flow diagram.

Selection process

Citations retrieved from the searches from all the databases will be merged using EndNote V.X9.1 software, and duplicate records will be removed. References will be then exported to a Microsoft Excel (V.14.1.0, Redmond, Washington, USA: Microsoft, 2011) spreadsheet to continue the selection process. Title and abstract screening will be performed in duplicate by two reviewers (VS-J and YHM). We will obtain full-text articles for all titles identified as potentially eligible by at least one of the reviewers, which appear to meet the inclusion criteria or when there is any uncertainty.

The potentially eligible full-text articles will also be reviewed independently and in duplicate by two reviewers (VS-J and YHM) to determine their inclusion. We will seek additional information and contact the corresponding authors to resolve questions about eligibility when needed. Studies considered eligible by both reviewers will be included. Data extraction of included will also be performed independently and in duplicate (VS-J, YHM and AFE-B). Disagreements in the full-text or the data extraction stages will be resolved by consensus discussion or by seeking adjudication from a third reviewer (JA-R). Extracted data will include information on study design (title, author information, year of publication, recruitment stage, country in which the study was conducted, language,

study design, sample size and funding), population characteristics (age, percentage of children less than 5 years old, body weight/body mass index, sex, case source identification, intrafamilial infection, TB incidence, endemicity and population type), trial characteristics (tuberculin skin testing cut-off point for inclusion, interferon gamma release assay result and type as inclusion criteria, number of patients per trial arms, allocation and information of interventions (dose, details and duration)), risk of bias assessment and outcome measurements (number of events, per arms, for dichotomous outcomes).

Risk of bias (RoB) in individual studies
The RoB of each randomised control trial will be performed with the Cochrane Risk of Bias tool V.2.[22] The following domains will be assessed per outcome (primary and secondary outcomes): RoB in randomisation process, deviations from the intended intervention (effect of assignment and adhering to intervention), missing outcome data, measurement of the outcome and selection of the reported result. Each domain will be assigned an RoB judgement of 'low risk of bias', 'high risk of bias' or 'some concerns'. The overall risk of bias domain will be classified as: 'low risk of bias' when all domains are judged as low risk, 'some concerns' when at least one domain is some concern but was not high risk for any domain and 'high risk' if at least one domain was high risk or if multiple domains were judged as some concerns.[22] Two independent reviewers (VS-J, YHM and AFE-B) will perform the RoB assessment. Possible discrepancies between the two reviewers regarding bias appraisal will be solved by consensus. Nevertheless, if consensus cannot be reached, a third reviewer will resolve it (IDF).

Statistical analysis
We will first describe the results narratively and using tables. If possible, we will conduct a pairwise meta-analysis of the available direct comparisons and network meta-analyses. Since we expect clinical and methodological heterogeneity among the studies, we plan to pool direct evidence for each treatment comparison using a frequentist random-effects model, applying the Hartung-Knapp-Sidik-Jonkman method.[23] Effect estimates along with 95% CIs will be estimated using OR for dichotomous outcomes. Heterogeneity will be assessed using the I^2 statistic to quantify the percentage of variability that is due to true differences between studies rather than sampling error.[24 25] The I^2 will be interpreted following the Cochrane thresholds.[26]

NMA synthesises both direct and indirect evidence, estimates the relative effectiveness among pairs of interventions, even if specific interventions have never been compared directly in RCTs, and provides a ranking of interventions.[27] When direct evidence for a given comparison is not available, an indirect comparison will provide an effect estimate. In the presence of direct evidence, the NMA will provide a combined estimate (ie, the statistical combination of direct and indirect evidence).[28] We will combine direct and indirect estimates in an NMA if the coherence and transitivity assumptions across treatment comparisons are judged to be justifiable. By combining direct and indirect evidence, we may obtain estimates with increased precision. We will present the network geometry and the results in probability statements as well as forest plots. We will calculate the surface under the cumulative ranking curve values for each intervention, per outcome. The NMA will be performed in Statistical Software for Data Science (STATA) V.15.0.

We will conduct additional analyses to investigate potential reasons for heterogeneity. We plan to conduct subgroups analyses based on potential effect modifiers if sufficient data are available. We have identified age as a potential effect modifier, as well as study year (the year the recruitment began), due to the likelihood of TB infection. We will also conduct a sensitivity analysis based on the risk of bias, excluding articles with high risk of bias to assess the robustness of results. Lastly, we will conduct network meta-regression to evaluate the potential impact of age on the effect estimates. Publication bias will be investigated using funnel plots, and Egger's regression test will be applied to statistics when the funnel plots show asymmetry and there are five or more studies available.[29]

Certainty of the evidence
The confidence in the estimates for each reported outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach.[30] We will assess the certainty of the evidence for the direct available comparisons following the traditional GRADE criteria: risk of bias, inconsistency, imprecision, indirectness and publication bias.[31] The assessment of the quality of the evidence from the indirect and NMA will be performed using the specific GRADE approach for NMA. This approach considers, in addition to the traditional GRADE criteria, the assessment of intransitivity and incoherence criteria.[32 33] Lastly, to optimise the results interpretation, we will present a summary using a novel approach recommended by GRADE to draw conclusions from the NMA using a minimally contextualised framework.[34]

Patient and public involvement
There was no patient or public involvement in the development of the systematic review protocol.

Ethics and dissemination
Ethical approval is not required for this study; this review is based on the analysis of published evidence. No personal data of patients were required. The results of the review will be disseminated by the publication

of the manuscript in a peer-reviewed journal focusing on infectious diseases and paediatrics for publication.

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Contributors IDF, DB-B and YHM conceptualised and designed the study; VS-J, AFE-B and IDF developed the search strategy. VS-J wrote the manuscript under the supervision of DB-B, JA-R and IDF. VS-J, YHM, DB-B, AFE-B, JA-R and IDF critically reviewed the protocol and manuscript submitted. All authors provided substantive feedback on the manuscript and have read and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing interests VS-J attended a Master Class on Reproductive and Evidenced-Based Medicine financed by Abbott Laboratories, a Medical Health Update Conference financed by Sanofi Aventis, and was a speaker for Virtual Training in Primary Healthcare financed by Lafrancol S.A.S. The other authors certify that they have no affiliations with or involvement in any organisation or entity with any financial or non-financial interest in the subject matter or materials discussed.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

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Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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REFERENCES

1 Getahun H, Matteelli A, Chaisson RE, *et al*. Latent *Mycobacterium tuberculosis* infection. *N Engl J Med* 2015;372:2127–35.
2 Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med* 2016;13:e1002152.
3 Sutherland I. The ten-year incidence of clinical TB following conversion in 2,550 individuals aged 14 to 19 years. In: *Tuberculosis surveillance research unit progress report*. The Hague, the Netherlands: The Royal Netherlands Tuberculosis Foundation, 1968.
4 Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. *Adv Tuberc Res* 1976;19:1–63.
5 Kritski AL, Marques MJ, Rabahi MF, *et al*. Transmission of tuberculosis to close contacts of patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 1996;153:331–5.
6 Sterling TR, Njie G, Zenner D, *et al*. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National tuberculosis controllers association and CDC, 2020. *MMWR Recomm Rep* 2020;69:1–11.
7 Newton SM, Brent AJ, Anderson S, *et al*. Paediatric tuberculosis. *Lancet Infect Dis* 2008;8:498–510.
8 Marais BJ, Gie RP, Schaaf HS, *et al*. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis* 2004;8:392–402.
9 Cruz AT, Starke JR. Pediatric tuberculosis. *Pediatr Rev* 2010;31:13–26.
10 Sharma SK, Sharma A, Kadhiravan T, *et al*. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. *Cochrane Database Syst Rev* 2013;2013:CD007545.
11 International Union against tuberculosis Committee on prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull World Health Organ* 1982;60:555–64.
12 Ayieko J, Abuogi L, Simchowitz B, *et al*. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta-analysis. *BMC Infect Dis* 2014;14:91.
13 Gomes VF, Wejse C, Oliveira I, *et al*. Adherence to isoniazid preventive therapy in children exposed to tuberculosis: a prospective study from Guinea-Bissau. *Int J Tuberc Lung Dis* 2011;15:1637–43.
14 Zenner D, Beer N, Harris RJ, *et al*. Treatment of latent tuberculosis infection: an updated network meta-analysis. *Ann Intern Med* 2017;167:248–55.
15 Gwee A, Coghlan B, Curtis N. Question 1: what are the options for treating latent TB infection in children? *Arch Dis Child* 2013;98:468–74.
16 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
17 Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
18 Centers for Disease Control and Prevention (CDC), American Thoracic Society. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection--United States, 2003. *MMWR Morb Mortal Wkly Rep* 2003;52:735–9.
19 Latent tuberculosis infection. Updated and consolidated guidelines for programmatic management [Internet]. Geneva World Health Organization; 2018.
20 Lewinsohn DM, Leonard MK, LoBue PA, *et al*. Official American thoracic Society/Infectious diseases Society of America/Centers for disease control and prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. *Clin Infect Dis* 2017;64:111–5.
21 Gliklich RE, Dreyer NA, Leavy MB. Chapter 12: Adverse Event Detection, Processing, and Reporting. In: Gliklich RE, Dreyer NA, Leavy MB, eds. *Registries for Evaluating Patient Outcomes: A User's Guide*. 3rd ed. Rockville (MD): Agency for Healthcare Research and Quality (US), 2014. https://www.ncbi.nlm.nih.gov/books/NBK208615/
22 Higgins JPT, Savović J, Page MJ, *et al*. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, *et al*, eds. *Cochrane Handbook for systematic reviews of interventions version 6.3 (updated February 2022)*. Cochrane, 2022. http://www.training.cochrane.org/handbook
23 Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat Med* 2001;20:3875–89.

24 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.

25 Higgins JPT, Thompson SG, Deeks JJ. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.

26 Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, *et al*, eds. *Cochrane Handbook for systematic reviews of interventions version 6.3 (updated February 2022*. Cochrane, 2022. www.training.cochrane.org/handbook

27 Al Khalifah R, Florez ID, Guyatt G, *et al*. Network meta-analysis: users' guide for pediatricians. *BMC Pediatr* 2018;18:180.

28 Mills EJ, Thorlund K, Ioannidis JPA. Demystifying trial networks and network meta-analysis. *BMJ* 2013;346:f2914.

29 Egger M, Smith GD, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.

30 Guyatt G, Oxman AD, Akl EA, *et al*. Grade guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.

31 Puhan MA, Schunemann HJ, Murad MH, *et al*. A grade Working group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:g5630.

32 Balshem H, Helfand M, Schünemann HJ, *et al*. Grade guidelines: 3. rating the quality of evidence. *J Clin Epidemiol* 2011;64:401–6.

33 Brignardello-Petersen R, Bonner A, Alexander PE, *et al*. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol* 2018;93:36–44.

34 Brignardello-Petersen R, Florez ID, Izcovich A, *et al*. Grade approach to drawing conclusions from a network meta-analysis using a minimally contextualised framework. *BMJ* 2020;371:m3900.