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Original Article

Systematic review with network meta-analysis on the treatments for latent tuberculosis infection in children and adolescents

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ABSTRACT

Background: We aimed to synthesize the evidence on the efficacy and safety of different treatment regimens for latent tuberculosis infection (LTBI) in children and adolescents.
Methods: A systematic review with network meta-analysis was performed (CRD142933). Searches were conducted in Pubmed and Scopus (Nov-2021). Randomized controlled trials comparing treatments for LTBI (patients up to 15 years), and reporting data on the incidence of the disease, death or adverse events were included. Networks using the Bayesian framework were built for each outcome of interest. Results were reported as odds ratio (OR) with 95% credibility intervals (CrI). Rank probabilities were calculated via the surface under the cumulative ranking analysis (SUCRA) (Addis-v.1.16.8). GRADE approach was used to rate evidence's certainty.
Results: Seven trials (n = 8696 patients) were included. Placebo was significantly associated with a higher incidence of tuberculosis compared to all active therapies. Combinations of isoniazid (15–25 mg/kg/week) plus rifapentine (300–900 mg/week), followed by isoniazid plus rifampicin (10 mg/kg/day) were ranked as best approaches with lower probabilities of disease incidence (10% and 19.5%, respectively in SUCRA) and death (20%). Higher doses of isoniazid monotherapy were significantly associated to more deaths (OR 18.28, 95% ICr [1.02, 48.60] of 4–6 mg/kg/day vs. 10 mg/kg/3x per week).
Conclusions: Combined therapies of isoniazid plus rifapentine or rifampicin for short-term periods should be used as the first-line approach for treating LTBI in children and adolescents. The use of long-term isoniazid as monotherapy and at higher doses should be avoided for this population.

1. Introduction

Tuberculosis (TB), an infectious and chronic disease caused by *Mycobacterium tuberculosis,* is one of the leading causes of death worldwide.[1] Although considered an age-old, curable, and preventable disease, more than 10 million people are infected every year, and around 1.5 million dies. Children and adolescents are equally affected by the disease. In 2018, more than a million children were estimated to develop TB, and 250,000 died [1]. This represents 10% of the total burden of incident TB and 15% of associated total mortality [1,2].

One of the main challenges of managing the disease is that *M. tuberculosis* remains in the infected host in a latent state, causing latent TB infection (LTBI), a persistent immune response due to antigen stimulation without evident clinical manifestations of active TB [3,4]. It is estimated that up to a third of the world population is infected with *M. tuberculosis*, with most cases being asymptomatic and non-infectious. However, there are around 5–10% chances of reactivation of the bacteria and progression to active disease [5]. Moreover, patients with

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concomitant human immunodeficiency virus (HIV) infection are more prone to die due to the compromise of the immune system (i.e., preventing granuloma formation and bacillus containment at the primary infection site) and spread of the bacillus to various organs and systems [6]. This risk is even higher in children under five years old [3,5], who are more likely to progress to the most severe forms of the disease. This progression depends on the child's susceptibility, which is highest during the first years of life, probably from immunological immaturity [7–9]. Without Bacille Calmette-Guerin (BCG) vaccination, around 30% of infected infants (<1 year old) will progress to intrathoracic TB, and around 10–20% will develop disseminated disease. In children aged 1–2 years, the risk of progressing to intrathoracic TB or disseminated disease are 10–20% and 2–5%, respectively. These risks decline slowly until around ten years of age when the adult-type disease starts to emerge [10,11].

Transmission of pediatric TB is often associated with the inhalation of droplet nuclei expelled by infected in a household with active TB, but it can also be acquired congenitally [7]. Until February 2020, the World Health Organization recommended only the use of daily isoniazid (INH) (monotherapy) during 6–9 months for TB prevention. The updated guideline also includes the use of short-term regimens such as weekly rifapentine (RIP) plus INH, or daily INH plus rifampicin (RIF), both for three months [12].

Selection of the best therapeutic approach in each scenario considering drugs' clinical profile, patient's preferences, and access should be grounded in updated evidence. Currently, the comparative efficacy and safety of drug regimens for pediatric TB prevention come primarily from systematic reviews with pairwise meta-analysis [13–15]. Network meta-analysis, an extension of pairwise meta-analysis, can statistically combine in one single model both direct (i.e., available in the literature) and indirect evidence (i.e., estimated based on standard treatment comparators) across several treatments [16].

Thus, we aimed to compare the clinical profile (efficacy and safety) of all available drug regimens for LTBI in young children and adolescents (≤15 years old) through a broad and updated network meta-analysis.

2. Material and methods

This systematic review with network meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA NMA) and Cochrane Collaboration recommendations [17,18] and registered at PROSPERO (CRD142933). All steps of study selection and data extraction were performed independently by two researchers. Discrepancies were reconciled in consensus meetings, using a third researcher as a referee.

2.1. Search strategy and selection criteria

Electronic searches were conducted in the PubMed and Scopus without any time limit or language restriction (updated Nov-2021) (see full search strategy, Supplementary material 1). Clinical trial registries (ClinicalTrials.gov) and the reference lists of the included studies were manually searched to identify additional studies not retrieved in electronic databases. Primary studies that met all the following eligibility criteria were considered: 1) trials evaluating children (up to 15 years of age), living in an environment exposed or not to TB, requiring preventive treatment; 2) studies evaluating any pharmacological treatment (at any regimen) used for LTBI; 3) reporting data on TB incidence, death and main adverse events; and 4) designed as randomized controlled trial.

Two researchers independently screened titles and abstracts to identify irrelevant records. In the second stage, full-text articles were independently evaluated by these two researchers. Non-randomized controlled trial (a type of study), interventions other than pharmacological treatments, the inclusion of individuals over 16 years old, trials reported in non-Roman characters were excluded.

2.2. Data extraction and methodological quality

The following data were independently extracted by two researchers: (a) baseline characteristics (i.e., authors' names, year of publication, country, sample size, patients' gender and age, trial duration); (b) interventions (i.e., dose, regimen, treatment duration); (c) clinical efficacy outcomes assessed as the incidence of TB (i.e. active TB was confirmed bacteriologically or diagnosed using clinical or radiological criteria (pulmonary lesions), Mantoux test or alcohol-acid resistant bacillus test – BAAR; and (d) safety evaluated as the incidence of main adverse events and death.

The critical evaluation of the risk of bias of the included studies was conducted by two independent reviewers, using the Jadad Scale [19] and the Cochrane Collaboration Risk of Bias tool [20,21].

2.3. Data synthesis and quality of evidence

Network meta-analysis also called multiple treatment meta-analysis, is a technique recommended by the International Society for Pharmacoeconomics and Outcome Research to simultaneously compare safety and efficacy among different treatments [22,23]. Network meta-analyses, using a Bayesian framework for each outcome based on the Markov Chain Monte Carlo simulation method were performed. Arm-level entry data was used. For the inclusion of multiple-arm studies, correlations for the likelihood between arms were considered. A common heterogeneity parameter was assumed for all comparisons. We opted for conservative analysis of non-informative priors. A consistency model was built for each outcome, and the treatments' relative effect sizes were calculated as odds ratios (ORs) and reported with their 95% credible intervals (CrIs). Random-effect models were selected according to the lowest deviance information criteria (DIC). Convergence was attained based on visual inspection of Brooks-Gelman-Rubin plots and potential scale reduction factor (PSRF) ($1 < PSRF \leq 1.05$) [24,25]. To increase the estimate precision of the relative effect sizes of comparisons and to properly account for correlations between multi-arm trials, rank probabilities for each outcome were calculated via surface under the cumulative ranking analysis (SUCRA) [25,26]. To estimate the robustness of the network, inconsistency, defined as the difference between the pooled direct and indirect evidence for a particular comparison, was assessed using node-splitting analysis. In this analysis, the evidence on a specific node (the split node) is tested, and P-values <0.05 reveal significant inconsistencies in the network [27,28]. To better explore the results and test their robustness, we anticipated that sensitivity analyses (e.g., according to study' characteristics as year of publication, patients' eligibility criteria, patients' age, treatment duration, co-infections) could be performed by hypothetically removing studies from a given network. These results were compared with those from the original analyses aiming at better explaining the heterogeneity among studies. All analyses were conducted in the software Addis version 1.16.8 [29].

The quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group [30] for the outcomes of TB incidence and death. It was classified as high, moderate, low and very low. INH was assumed as the common comparator.

3. Results

After excluding duplicates, we identified 946 records in databases that entered the screening process, with 931 considered irrelevant. During the full-text appraisal, nine studies were excluded [31–49] (see complete reasons for exclusion in Supplementary material 2), resulting in five trials for analysis [40–44]. Other two studies [35,36] were added by manual search, finally resulting in seven randomized controlled trials

(represented by nine published articles) for evidence synthesis (see Fig. 1).

These seven trials (n = 8696 patients between 0 and 15 years) were published between 1961 and 2015, with 42% being multicentric. Treatment duration varied among studies between 12 weeks and 96 weeks. The shortest follow-up after treatment was six months, and the maximum time was 11 years [40–44]. Three studies included two independent sets of participants: Debre et al. [46] in which data were separated by age group between 5 to 9 years old and 10–14 years old; Madhi et al. [42], which divided children co-infected or not with HIV; and Egsmose et al. [40], which also evaluated adults patients (data not synthetized in this review). In the study conducted by Spyridis et al. [43], therapies were applied in two different periods with different patients. Three studies reported that the trial was performed in countries with high TB and HIV burden [40–42]; the others did not mention this information [43–46] (Table 1).

Most studies (n = 4/7; 57.1%) did not report whether patients received BCG vaccine [40,41,44,45]; in two trials the vaccine was an exclusion criterion [43,46], and in only one study the BCG vaccine was an inclusion criterion [42]. Drug resistance data in the studies were poorly reported. Zar et al. [41] provided a brief information that prophylaxis for TB does not promote an increase in bacterial resistance (data not shown); yet recommend patients' continuous monitoring. Spyridis et al. [43] stated that the association of INH with RIF is the best option for this population given the shorter treatment period, which reduces the probability of bacterial resistance. In the study of Villarino et al. [44], resistance to INH and RIF were an exclusion criteria. Debre et al. [46] reported that five out of twelve (41.6%) patients with TB from the placebo group performed resistance tests; 4 were sensitive to all antibacterials, and only 1 was resistant to all drugs (no resistance tests were performed in the treated group - INH). According to Madhi et al. [42], only five children (2 from the INH group [1 with HIV; 1 without HIV] and 3 from the placebo group [not infected with HIV]) were resistant to antituberculous drugs.

Self-administration of medication (e.g., parents or family members support) was predominant in all studies. Only Villarino et al. [44] used directly observed treatment approach (DOTS) for children who received combination therapy (INH + RIF) for 3 months; self-administration approach was applied in the INH isoniazid group for 9 months.

All trials evaluated INH monotherapy at different doses or regimens: INH from 5 to 15 mg/kg/day; 4–6 mg/kg/day; 5–10 mg/kg/day; 10 mg/kg/day; 10 mg/kg/three times a week; and 10–20 mg/kg/day. Drug combinations were reported in two trials: INH 10 mg/kg/day + RIF 10 mg/kg/day; and INH 15–25 mg/kg/week + RIP 300 a 900 mg/week. Placebo was the main comparator in four studies. In two trials, patients who had already undergone previous therapy were able to participate as long as a minimum period of wash-out was followed (see Table 1).

In all studies, tuberculin skin test or chest X-ray were performed as diagnosis and follow-up approaches (clinical evolution of the patient). No study stated to perform the interferon gamma (IFN-γ) test (IGRAs) -

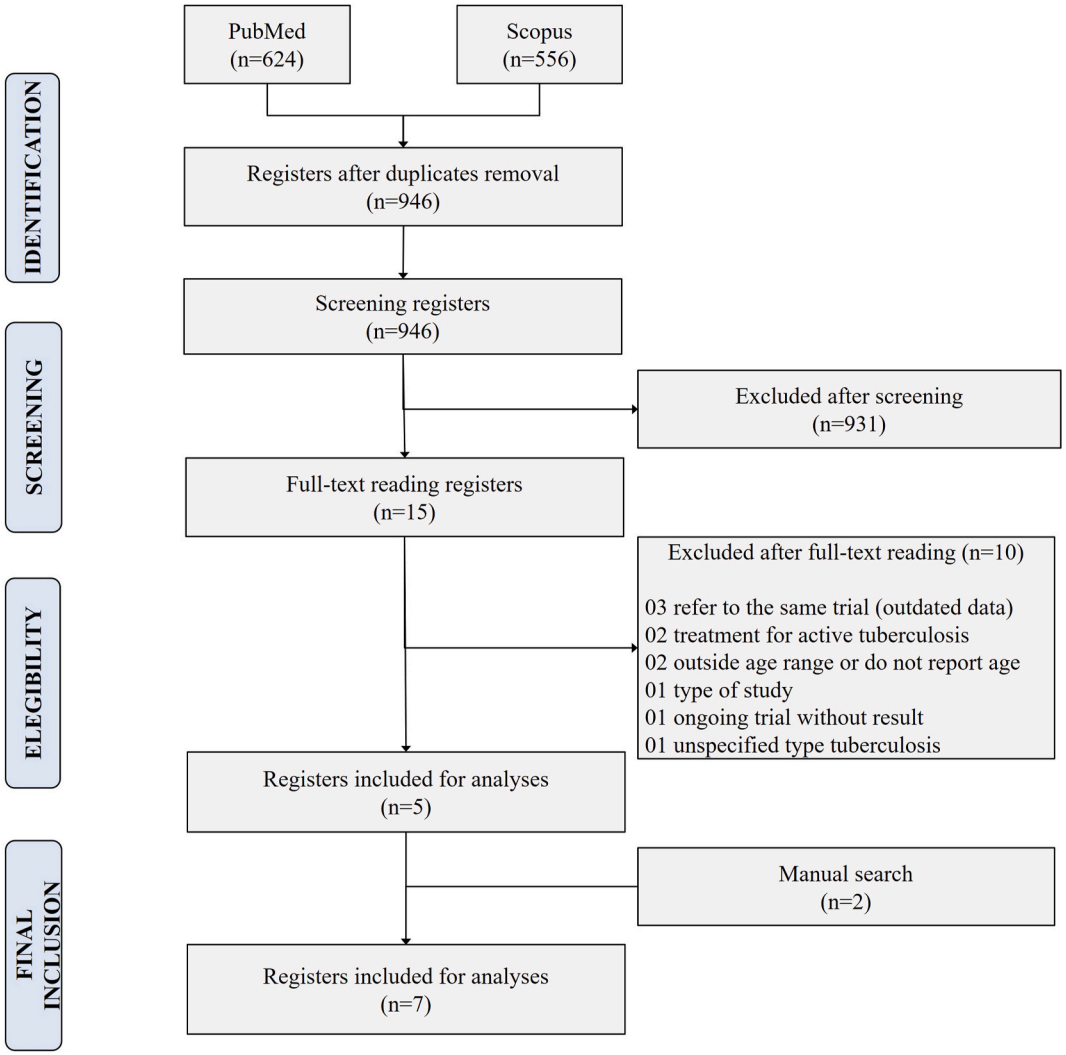

Fig. 1. Flowchart of the systematic review process.

Table 1
Characteristics of the studies included in the systematic review.

Study	Country	Rando-mized	Blind study	Duration (weeks)	High TB/ HIV Countries	BCG vaccine	HIV*	Drug	Dose	N.	Age	% Male	Incidence TB (N)	Death (N)
Debre [46][a]	France	–	No	36	–	No	No	Isoniazid	5–15 mg/kg/ day (5–9 years)	589	5–9 years	–	6	–
								Placebo		458			12	–
								Isoniazid	5–15 mg/kg/ day (10–14 years)	644	10–14 years	–	5	–
								Placebo		614			12	–
Egsmose [40]	Kenya	–	Yes	60	Yes	–	–	Isoniazid	5–10 mg/kg/ day	399	<6 years	–	2	7
								Placebo		376	6–14 years		10	7
Madhi [42][b]	South Africa and Botswana	No	Yes	96	Yes	All children received BCG within 30 days of birth	Yes	Isoniazid	10–20 mg/kg/ day	273	97 days	41.8	31	21
								Placebo		274	95 days	44.9	38	15
							No	Isoniazid	10–20 mg/kg/ day	403	96 days	49.6	28	2
								Placebo		401	96 days	52.2	31	2
Mount [45]	USA, Canada, Mexico	No	Yes	48	–	–	No	Isoniazid	4–6 mg/ kg/day	1394	0–11 years	49.6	6	4
								Placebo		1356	0–11 years	50.1	33	1
Spyridis [43]	Greece	No	No	36	–	No	–	Isoniazid	10 mg/ kg/day	200	9.1 years (median)	51.7	48	–
								Isoniazid + Rifampicin	10 mg/ kg/day	220	9.2 years (median)	47.8	26	–
Villarino [44]	USA, Canada, Brazil, China, Spain	Yes	No	48	–	–	Yes	Isoniazid + Rifapentine	15–25 mg/kg/ week+ 300–900 mg/week	471	<15 years	54	0	0
								Isoniazid	5–10 mg/kg/ day	434		48	3	2
Zar [41]	South Africa	No	Yes	24	Yes	–	Yes	Isoniazid	10 mg/ kg 3x/ week	68	29 months (11–55)	55	3	5
								Placebo	110 mg/ kg 3x/ week	71	29 months (11–55)	57	5	9
								Isoniazid	10 mg/ kg/day	64	22 months (8.9–45)	55	2	6
								Placebo	10 mg/ kg/day	60	22 months (8.9–45)	57	8	12

Note: *Studies reporting co-infected patients with HIV. [a]Results reported by subgroup according to patients' age. [b] Results reported by subgroup according to therapeutic regimen and HIV positivity. All drugs administered orally.
BCG: Bacille Calmette-Guerin vaccine; HIV: human immunodeficiency virus; TB: tuberculosis; USA: United States of America.

available since 2001 [47]. Villarino et al. [44] employed only the tuberculin test. When abnormal findings were observed in the chest X-ray, gastric aspirates and sputum induction with rapid acid staining, *M. tuberculosis* culture were performed, except in the studies of Spyridis et al. [43] and Villarino et al. [44], where patients were immediately treated for active TB.

The methodological quality of the studies was judged as low to moderate with a mean score of 3 in the Jadad Scale (Supplementary material 3) and an overall unclear risk of bias (Supplementary material 4). Although all trials were randomized, the random sequence generation was unclear in 43% of studies. Three trials were open-label [33,34,36], while the other four were double-blinded [40–42,45]. The blinding method of participants was inadequate or poorly described in all trials. All studies counted for patients' withdrawal or dropouts. The oldest studies were not financed [40,45,46], while recent trials [41–44] received grants by pharmaceutical companies or presented a conflict of interest.

We were able to build two networks for the outcomes of the incidence of TB and death (Fig. 2). The networks were found to be robust for the assessed outcomes, and no significant inconsistencies were found in magnitude or direction between the results of the direct and indirect effects. Yet, one should be aware of the heterogeneity among trials (e.g., few included studies, different sizes and slightly different designs, patients' characteristics, lack of standard outcome reporting) that hampered further analyses.

Placebo was significantly associated with a higher incidence of TB compared to the therapies: INH 10 mg/kg/day + RIF 10 mg/kg/day (OR 95% ICr 0.07 [0.01, 0.70]); INH 15–25 mg/kg/week + RIP 300–900 mg/week (0.02 [0.00, 0.50]), INH 4–6 mg/kg/day (0.16 [0.04, 0.71]) and INH 5–10 mg/kg/day (OR 95% ICr 0,16 [0,01, 0,91]). The combination INH 15–25 mg/kg/week + RIP 300–900 mg/week presented higher efficacy, significantly preventing TB, when compared to INH monotherapy 10–20 mg/kg/day (OR 95% ICr 35.70 [1.49, 171.87]). Besides, higher doses of INH monotherapy were significantly associated

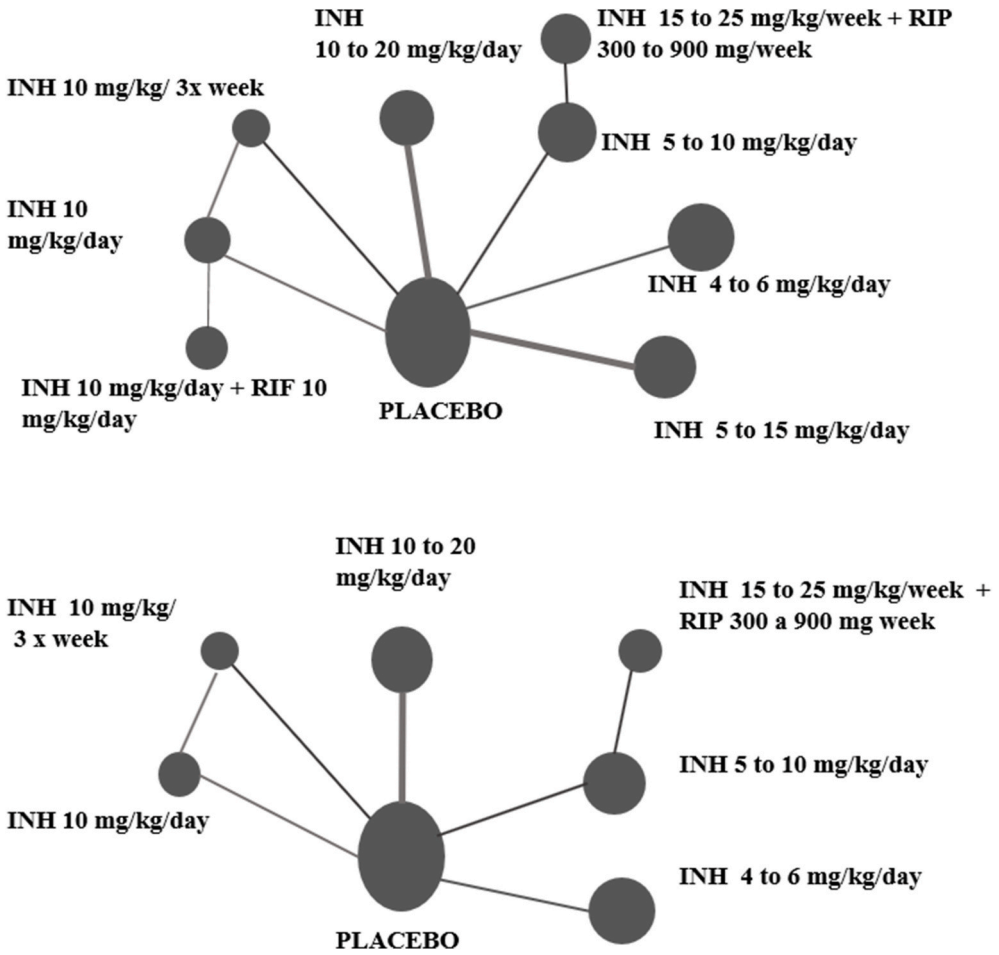

Fig. 2. Network meta-analyses for the evaluated outcomes.
(A) Incidence of tuberculosis; (B) Death. Note: Each node represents an intervention. Directly linked nodes represent the available direct evidence. The number of studies for each comparison is shown in the edges.

to more deaths when compared to lower doses (OR 95% ICr 18.28 [1.02, 483.648] of INH 10 mg/kg/3x per week vs. INH 4–6 mg/kg/day). No further differences among therapies were found as presented in Table 2.

Fig. 3 presents the SUCRA results for each outcome of intereset, (see correlation of these data for both outcomes in one single plot, Supplementary material 5). The combinations INH + RIP followed by INH + RIF were the best alternatives considering efficacy, with lower rates of incidence of TB (10% and 19.5%, respectively), and safest options (probability of death around 20%). Lower doses of INH monotherapy presented around 40% probability for the incidence of TB. INH 10–20 mg/kg/day was associated with a 70% probability of death. Placebo was the worst option considering efficacy, with the probability of 94% of causing the disease, followed by INH monotherapy at higher doses (around 86%).

Two main sensitivity analyses were possible: (i) hypothetical removal of the most older trial [45] (data not shown); (ii) hyptothetical removal of the Madhi et al. [42] study that performed subgroup analyses considering HIV patients (see Supplementary materials 6 and 7). In both scenarios, results were similar to those obtained in the original analyses. Placebo was more significantly associated with TB incidence compared to INH 10 mg/kg/day + RIF 10 mg/kg/day, INH 15–25 mg/kg/week + RIP 300–900 mg/week and INH 4–6 mg/kg/day. INH + RIP followed by INH + RIF continued to present the lowest rates for this outcome and were, thus, considered more effective (SUCRA probabilities of 10.0% and 19.7%, respectively, in the first sensitivity analysis scenario; SUCRA probabilities of 22.5% and 32.0%, respectively in the second case analysis). Placebo was again considered the worst alternative. Similar to the original analyses, no differences among therapies were found for mortality.

We were able to qualitatively gather the main adverse events reported in some of the included studies (see Supplementary material 8). Serious adverse events were more prevalent in patients using INH compared to placebo. Most common adverse events related to INH were neuropathy, gastrointestinal events, increased liver enzymes, and neutropenia. Debre et al. [46] described that patients presented rash and neurologic and digestive events. Mount et al. [45] also reported long-term complications with INH (after two years), including conjunctivitis and genitourinary infections.

The level of evidence assessment was rated as low-moderate for both outcomes (GRADE) (see GRADE, Supplementary material 9). The confidence varied mainly due to imprecision and the presence of methodological bias. Given the limitation on the number of studies included in the analysis, the confidence of the results may also be reduced. None of the comparisons in either outcome was affected by intransitivity.

4. Discussion

To our knowledge, this is the first network meta-analysis of randomized clinical trials evaluating different therapy regimens for pediatric LTBI. Previous systematic reviews with pairwise meta-analysis were limited to direct comparisons between drugs, with no assessment of different dosages and combination regimens [13,14], or included solely retrospective studies [15,47]. These reviews may not reflect the real effects of all available therapies for this population.

Table 2
Results of analysis of the comparison of multiple treatments for the result of the outcome of 'death' (white; upper quadrant) and for 'incidence of tuberculosis' (gray; lower quadrant) in children.

INH 10 mg/kg/3 x week	1.39 (0.24, 7.82)	–	4.55 (0.58, 32.40)	0.80 (0.02, 24.60)	18.28 (1.02, 48.64)	3.12 (0.32, 30.61)	–	3.42 (0.68, 17.48)
1.71 (0.16, 16.44)	**INH 10 mg/kg/day**	–	3.28 (0.46, 24.09)	0.61 (0.01, 16.89)	13.08 (0.78, 348.79)	2.32 (0.23, 23.64)	–	2.42 (0.52, 12.91)
4.08 (0.28, 53.70)	2.43 (0.63, 8.76)	**INH 10 mg/kg/day + RIF 10 mg/kg/day**	–	–	–	–	–	–
0.32 (0.03, 2.19)	0.19 (0.02, 1.64)	0.08 (0.01, 1.00)	**INH 10 to 20 mg/kg/day**	0.18 (0.00, 4.37)	3.94 (0.28, 89.83)	0.70 (0.09, 5.48)	–	0.75 (0.24, 2.54)
10.67 (0.28, 678.87)	7.43 (0.15, 460.42)	3.11 (0.05, 235.86)	**35.70 (1.49, 171.87)**	**INH 15 to 25 mg/kg/week + RIP 300 to 900 mg week**	20.94 (0.46, 3353.05)	3.80 (0.31, 109.62)	–	4.27 (0.21, 160.69)
1.69 (0.14, 15.89)	0.96 (0.06, 11.70)	0.40 (0.02, 6.59)	5.10 (0.93, 30.02)	0.15 (0.00, 4.24)	**INH 4 to 6 mg/kg/day**	0.18 (0.01, 3.48)	–	0.19 (0.01, 2.06)
1.67 (0.12, 63.79)	1.04 (0.06, 24.29)	0.44 (0.02, 10.70)	5.40 (0.76, 106.50)	0.17 (0.01, 1.74)	0.99 (0.11, 31.53)	**INH 5 to 10 mg/kg/day**	–	1.07 (0.22, 5.57)
0.69 (0.07, 5.83)	0.41 (0.04, 4.52)	0.17 (0.01, 2.51)	2.19 (0.53, 9.06)	0.06 (0.00, 1.65)	0.41 (0.07, 2.98)	0.41 (0.02, 3.57)	**INH 5 to 15 mg/kg/day**	–
0.27 (0.03, 1.51)	0.16 (0.02, 1.13)	**0.07 (0.01, 0.70)**	0.86 (0.34, 2.06)	**0.02 (0.00, 0.50)**	**0.16 (0.04, 0.71)**	**0.16 (0.01, 0.91)**	0.38 (0.12, 1.12)	**Placebo**

Note: All treatments are listed according to the doses. Comparisons between treatments should be read from left to right, and the estimated value is in the cell in common between the column definition treatment and the line definition treatment. Results are presented as odds ratios (OR) with a 95% credibility interval (ICr). For the outcome 'death', an OR <1 favors the column-defining treatment (e.g., INH 10 mg/kg/3x per week vs. INH 4–6 mg/kg/day present an OR 18.28, [95% ICr 1.02, 48.60], meaning that higher doses were significantly associated to more deaths). For the outcome 'incidence of tuberculosis', an OR >1 favors the column-defining treatment (e.g., INH 10 mg/kg/day + RIF 10 mg/kg/day vs. placebo present an OR 0.07 [95% CrI 0.01–0.70], meaning that the placebo group is significantly more prone to tuberculosis). Significant results are in bold italic.
INH: isoniazid; RIF: Rifampicin; RIP: rifapentine.

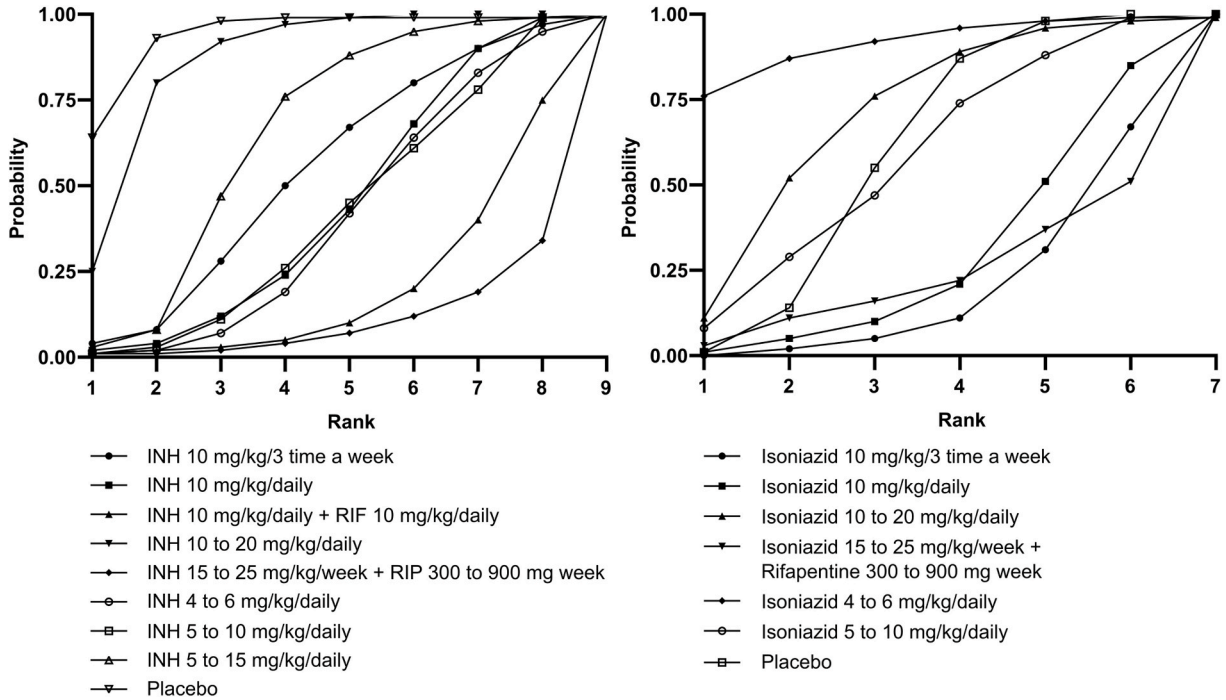

Fig. 3. Surface under the cumulative ranking curve analyses (SUCRA) for incidence of tuberculosis and death.

A previous pairwise meta-analysis reported INH monotherapy as the first-line option for TB prevention in children when compared to placebo or no treatment (RR = 0.65 [95% CI 0.47, 0.89]; p = 0.004). However, authors suggest that age might be an important effect modified of the efficacy of therapy among children, with no effect in children under four months of age (RR = 0.93 [0.71, 12.1]; p = 0,29) compared to older children between 5 and 15 years (RR = 0.53 [0.30, 0.94]; p = 0,014) [12].

We found that the combination of INH 15–25 mg/kg/week + RIP 300–900 mg/week is probably the most effective option when compared to other active drugs and placebo for preventing TB in the overall pediatric population. The combination of two bactericidal drugs with different mechanisms of action can enhance the therapeutic effect. RIF blocks gene transcription through the inhibition of the synthesis of RNA-

polymerase-DNA-dependent bacteria, which causes the cessation of protein synthesis in the cell and, consequently, death [38]. On the other hand, INH inhibits the biosynthesis of mycolic acid, which are the main components of the *M. tuberculosis* cell wall [49,50]. Previous in vitro studies demonstrated the synergistic action between these drugs [51]. However, these effects have not yet been confirmed in in vivo trials.

The combined therapies of INH + RIP and INH + RIF also proved to be more effective than the current INH monotherapy, which is still recommended by the World Health Organization. The different therapeutic regimen based on a short-term therapy, but with higher doses, may justify the superior profile of these interventions. Recent pharmacokinetic studies demonstrated that the current doses recommended by clinical guidelines are subtherapeutic [52–55], which may contribute to TB progression and bacterial resistance [56]. Also, adherence rates to complete treatment are lower in long-term therapies (6–9 months) when compared to short-term therapies (3–4 months) that are also associated with lower total costs [44,57–60]. The traditional treatment with INH monotherapy requires 180 doses for six months or 270 doses during nine months, while the combination INH + RIP is dispensed in 12 doses (1 per week) with a reduced follow-up of 3 months [44].

A cost-effectiveness analysis published by Doan et al. [61], compared the different treatment regimens for latent TB including self-administered daily INH for 6 or 9 months, self-administered daily RIF plus INH for 3 months, self-administered daily RIF for 4 months, and weekly RIP plus INH for 3 months self-administered or administered by a healthcare professional as directly observed therapy. The analysis was performed from the North American healthcare system perspective over a 20-year time horizon, including costs on drugs, medical supplies, healthcare professionals time and diagnostic procedures. All regimens reduced costs and increased quality-adjusted life-year (QALY) compared with no preventive treatment. Among active therapies, short-term INH + RIP (weekly) for 3 months was the most cost-effective option compared to long-term regimens. Also, the International Drug Purchase Facility (UNITAID) reached an agreement with the pharmaceutical industry to reduce the costs of RIP by 70%, from U$ 45 to U$ 15 for public agencies in 100 low-income countries, which may contribute to the use of combined therapies for TB [62].

The recent guideline published by the World Health Organization recommends the following options for LTBI: INH monotherapy for children <15 years (6–9 months), or a 3-month INH + RIP regimen weekly or daily, according to physicians' decision. However, authors indicate that the available evidence is still of low confidence, advising that more research on short-term regimens are needed [63]. We also found that the quality of evidence is low, primarily due to the risk of bias of the primary studies and high heterogeneity among trials (e.g., different eligibility criteria, patients' age, regions/country, co-infection rates). Therefore, caution is necessary when interpreting these results and prescribing TB therapies. The main adverse events reported when using combined therapies include the enhancement of hepatic enzymes and hepatotoxicity. Some cases of renal failure, skin rash, hematological abnormalities, may also be related to these therapies, warning of the need for patient's monitoring [64–67]. Further, well-designed randomized controlled trials directly comparing combined vs monotherapies are needed to strengthen the evidence and support recommendations for their use in clinical practice. Additionally, real-world studies, cost-effectiveness and convenience analyses should be performed to improve TB clinical guidelines for children.

Our study has some limitations. Few studies were included in the systematic review. Given the high heterogeneity among trials, low-moderate methodological quality and lack of a core outcome set (i.e., standard report of outcomes), few outcomes could be statistically analyzed and no subgroup analyses (e.g., according to the diagnostic approaches, year of publication, region/country) were feasible. The included trials differ in terms of size, risk of bias, external validity. We tried to avoid systematic errors by performing transitivity and sensitivity analyses (results were similar to the original analyses). Yet, these studies represent the available evidence on the effect of TB treatments for this population; our findings may foster the conduction of further trials targeting the most promising drugs in the field. As any other method NMA is not free of limitations. The validity of this approach depends on the distribution of relative treatment effect modifiers across comparisons. Treatment rankings should not be interpreted in isolation from the relative treatment effects.

Finally, given the available evidence, we primarily recommend the combined therapy INH 15–25 mg/kg/week + RIP 300–900 mg/week for short-term periods to be used as the first-line approach for pediatric LTBI. INH 10 mg/kg/day + RIF 10 mg/kg/day can also be a promising alternative for these patients. The use of long-term INH monotherapy at higher doses should be avoided.

Authorship statement

All authors meet the ICMJE authorship criteria. JMS, FFL, FST and RP designed the study and were responsible for its organization and coordination. JMS, PI, FBM and ELD performed studies' eligibility and data extraction. Methodological risk of bias assessment and GRADE approach were conducted by JMS, BB and AMJ with contributions from all the authors. Statistical analyses were performed by MMF and FST. All authors contributed to the writing of the final manuscript.

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The funding had no role in the study design, data collection and analysis, writing of the report nor in the decision to submit the article for publication.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.08.023.

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