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

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INTRODUCTION

Tuberculosis (TB), an infectious and chronic disease caused by Mycobacterium tuberculosis, is one of the leading causes of death worldwide. 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]. We aimed to synthesize the available 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 following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA NMA) and Cochrane Collaboration recommendations and registered at PROSPERO (CRD142933) [3]. Searches were conducted in Pubmed and Scopus (May-2021). Randomized controlled trials comparing treatments for LTBI in patients up to 15 years, and reporting data on the incidence of the disease, death or adverse events were included. 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

After excluding duplicates, we identified 946 records in databases that entered the screening process, with considered irrelevant. During the full-text appraisal, 10 studies were excluded, resulting in five trials. Other two studies were added by manual search, finally resulting in n=7 randomized controlled trials for analysis (Figure 1).

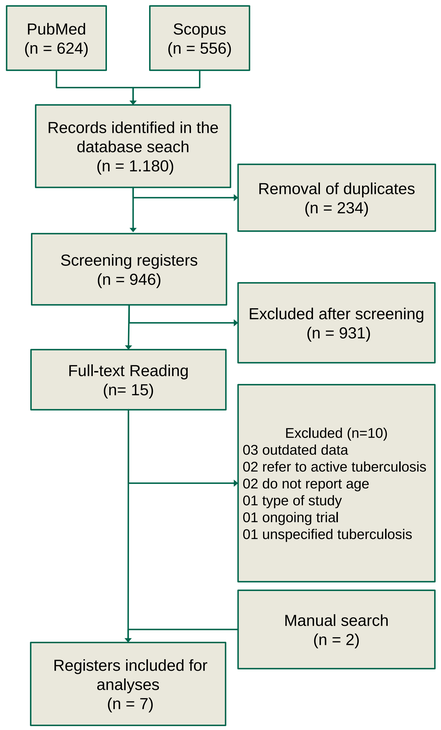

Figure 1. Flowchart

RESULTS

A network were built for the outcome of tuberculosis incidence (Figure 2). All networks were considered robust and no inconsistencies were found between direct and indirect results. Placebo was significantly associated with a higher incidence of tuberculosis 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 8 (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]).

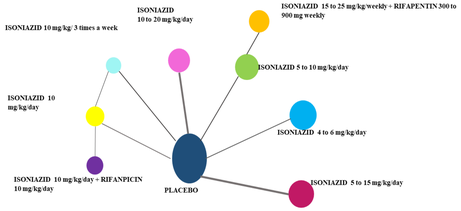

Figure 2. Network of incidence of tuberculosis

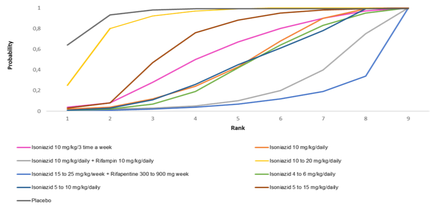

Figure 3.SUCRA for incidence of tuberculosis

The combination INH 15-25 mg/kg/week + RIP 300-900 mg/week presented higher efficacy, significantly preventing tuberculosis, when compared to INH monotherapy 10-20 mg/kg/day (OR 95% ICr 35.70 [1.49, 171.87]).
Figure 3 shows the SUCRA results. The combinations INH + RIP followed by INH + RIF were the best alternatives considering efficacy, with lower rates of incidence of tuberculosis (10% and 19,5%, respectively). Lower doses of INH monotherapy presented around 40% probability for the incidence of tuberculosis. 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%).

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.

REFERENCES

1. Guidelines on tuberculosis infection prevention and control - World Health Organization. [Internet]. 2019. [updated 2020 Mar 24].
2. Basu RR, Whittaker E, Seddon JA, Kampmann B. Tuberculosis susceptibility and protection in children. Lancet Infect Dis 2019; 19:96–108.
3. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions [Internet]. 2011. [updated March 2020].