3-month daily rifampicin and isoniazid compared to 6- or 9-month isoniazid for treating latent tuberculosis infection in children and adolescents less than 15 years of age: an updated systematic review

To the Editor:

One-third to one-quarter of the world's population is estimated to have latent tuberculosis infection (LTBI) [1]. These infected persons are at risk for developing active disease with a lifetime risk of reactivation estimated to be 5–10% [2]. Prevention of reactivation of LTBI in population groups with higher risk of progression to active disease than the general population, is critical to end the global TB epidemic [3].

The World Health Organization (WHO) recommends 6-month isoniazid (6H) monotherapy for the treatment of LTBI in children [4]. However, the effectiveness of 6H is compromised by low rates of treatment completion and adverse events [5]. A systematic review of the literature on the options for treating LTBI in children was conducted in 2012. The review found out that 3- or 4-month rifampicin (R) and isoniazid (H) combination therapy was as effective as 6H or 9H monotherapy with higher completion rate and no evidence of increased hepatotoxicity [6].

Currently, a water-dissolvable and child-friendly fixed-dose combination of R and H is available [7]. We thus performed an updated systematic review to evaluate the effectiveness of a 3RH combination therapy compared with a 6H or 9H monotherapy for the treatment of LTBI in children and adolescents <15 years of age. The outcome measurements were: TB incidence, mortality, adverse events, treatment adherence and treatment completion and drug resistance. The literature search was conducted in PUBMED and EMBASE databases, from December 2012 to January 2017, to identify studies published after the previous review [6]. Abstract books of international conferences, and reference lists of included studies were also searched.

Literature search strategies were developed using text words: 1) "latent tuberculosis"; 2) "isoniazid"; 3) "rifampicin"; 4) "treatment" or "prophylaxis"; 5) "children", and related terms. Studies were selected based on participants (children and adolescents <15 years of age); interventions (a 3RH daily combination therapy); comparators (a 6H or 9H daily monotherapy). The review was limited to English, French and Spanish languages.

We assessed the quality of individual studies in terms of their study design and execution. Relative risks (RRs), comparing relative effects of 3RH with 6H or 9H, were calculated using Stata 14: Data Analysis and Statistical Software (StataCorp LP, College Station, TX, USA). We could not conduct a meta-analysis due to the limited number of included studies and their clinical and methodological heterogeneity. Findings were reported in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement [8].

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Treatment of latent tuberculosis infection in children with a 3-month daily rifampicin and isoniazid regimen is safe with better compliance, adherence and completion rate than a 6- or 9-month isoniazid monotherapy http://ow.ly/x28Z30jDfCE

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TABLE 1 3-month daily rifampicin and isoniazid compared to 6- or 9-month isoniazid for treating latent tuberculosis infection (LTBI) in children and adolescents <15 years of age

First author [ref.]	Study group	Study type	Outcome	Key results	Relative risk
Galli [9]	Children (aged <18 years) with LTBI Daily 9H (n=264) *versus* daily 3RH (n=220)	Retrospective study	Adverse effects	3RH 1/220 (0.45%) *versus* 9H 5/264 (1.9%); p=0.3	0.24 (0.03–2.04)
Spyridis [10]	Children (aged <15 years) with LTBI Period 1: 1995–1998 Daily 9H (n=232) *versus* daily 4RH (n=238) 7–11-year follow-up Period 2: 1999–2002 Daily 4RH (n=236) *versus* daily 3RH (n=220) 3–7-year follow-up	Prospective randomised controlled trial	Treatment compliance	Period 1: 4RH (92%) *versus* 9H (86%); p=0.011 Period 2: No significant difference in compliance for 3RH *versus* 4RH; p=0.510	1.07 (1.01–1.14)
			Drug adverse effects	GI: 6.5% 9H *versus* 0.7% 4RH; p<0.0001 Transient increase in liver enzymes: 6% 9H *versus* 1.2% RH; p<0.0001 In RH group 1.3% rash and 0.7% photosensitivity Treatment discontinuation due to adverse events was none in both groups	0.332 (0.197–0.559)
			Treatment efficacy	Proportion of compliant patients who developed chest radiograph changes suggestive of active tuberculosis: 24% 9H *versus* 11.8% 4RH; p<0.0001 13.6% 4RH *versus* 11% 3RH; p=0.079 No clinical disease observed in either group	0.492 (0.318–0.762)
van Zyl [11]	Children <5 years with adult household pulmonary tuberculosis contact (n=181) 2 TB disease; 72 infected; 105 exposed; 2 incompletely evaluated Daily 6H (n=105); 3RH (n=72)	Retrospective study	Completion rate	66.6% in 3HR; 27.6% in 6H; p<0.0001 In children aged <2 years: 43/66 (65.2%) in 3HR; 2/19 (10.5%) in 6H; p<0.0001	2.41 (1.70–3.43) 6.19 (1.65–23.23)

The search identified 281 unique hits. We excluded 17 studies due to duplication and 240 studies by title and abstract review. Full text review was conducted for 24 studies, and we found only one study that can be included in the current updated systematic review [9]. We identified two papers from the previous review [10, 11]; the other papers were not relevant for the current review due to either their population or interventions (not 3RH). Thus, three papers were finally included in the current review.

Galli *et al.* [9] "reported the results of a multicentre retrospective review, using records of children (aged <18 years) diagnosed with active and latent TB between January 2010 and December 2012, in 27 health facilities in Italy." Spyridis *et al.* [10] "published the results of a prospective, randomised, controlled study conducted in 1995–2005 among children aged <15 years of age at Department of Paediatrics in Athens University, Greece. Patients were enrolled during two time periods (period 1, from 1 January 1995 through 31 December 1998; and period 2, from 1 January 1999 through 31 December 2002)." van zyl *et al.* [11] "reported the results of a retrospective study comparing 3RH with 6H in children <5 years of age, identified as household contacts of adult pulmonary TB, conducted from January 1996 to September 2003, in Cape Town, South Africa (table 1)." A judgement on the quality of these studies indicated that there was a high risk of bias in each study.

Treatment efficacy: the proportion of compliant patients who developed chest radiograph (CXR) changes suggestive of active TB was 24% in 9H and 11.8% in 4RH ($p<0.0001$) in period 1, and 13.6% in 4RH and 11% in 3RH ($p=0.079$) in period 2. The risk of development of CXR changes was significantly lower in those given 4RH compared to 9H with RR equivalent to 0.492 (95%CI 0.318 to 0.762). However, there was no clinical disease observed in either group. Data on treatment efficacy were not available from the two observational studies [10].

Adverse events: the rate of gastro-intestinal related adverse events was 6.5% in 9H and 0.7% in 4RH ($p<0.0001$). There was a transient increase in liver enzymes in 6% of study participants in 9H compared with 1.2% in 4RH ($p<0.0001$) with a RR of adverse events equivalent to 0.332 (95% CI: 0.197 to 0.559); however, there was no treatment discontinuation due to adverse events in both groups [10]. The rate of liver function impairment was 0.45% in 3RH and 1.9% in 9H though there was no significant difference ($p= 0.3$) [9].

Treatment compliance and adherence: treatment compliance was 92% in 4RH and 86% in 9H ($p=0.011$) during period 1. There was, however, no significant difference in compliance in 3RH and 4RH ($p=0.510$) during period 2 with a RR (95%CI) equivalent to 1.07 (1.01 to 1.14) [10]. Treatment completion rate of 3RH (66.7%) was significantly higher than that of 6H (27.6%) with a RR equivalent to 2.41 (95%CI 1.70 to 3.43) [11].

Drug resistance: none of the included studies reported about development of drug resistance following preventive treatment among children and adolescents <15 years of age.

In summary, the updated systematic review found that adherence was significantly better in 3RH than in 6H or 9H. Children who received 9H monotherapy were less compliant than those who received short-course combination therapy. No serious drug-related adverse effects were detected; moreover, the risk of side effects was lower in children treated with a 3RH combination therapy compared to a 9H monotherapy. Data on preventive efficacy were limited and reported from only one study. Although the study reported no patient who developed clinical disease during the follow-up period, new radiographic findings suggestive of possible active TB disease were less common in patients who received a 3RH combination regimens than those treated with a 9H monotherapy.

There are also other studies, not included in this review due to absence of a control group, which suggested findings consistent with our review that treatment with short-course RH produced a greatly reduced proportion of paediatric notifications of tuberculosis. They were also tolerated without any toxicity [12]. Another cohort study published in 2010 reported that 3RH has very high efficacy and no significant hepatitis [13].

Even though studies included in this review did not report on the development of drug resistance following TB preventive treatment in children, systematic reviews done mostly among adults showed no evidence of a significant association between development of drug resistance and use of isoniazid or rifamycins for preventive treatment. However, exclusion and diagnosis of active TB among children is difficult. Therefore, it is important to establish a national surveillance system to monitor drug resistance among children receiving preventive treatment [14].

This review has a number of limitations. First, very few studies compared 3RH with 6H or 9H for the treatment of LTBI in children and adolescents <15 years of age. Secondly, children were classified as having TB disease based on clinical presentation and/or CXR changes that may result in false positive or

false negative diagnoses. However, data from a systematic review among adults and children suggest that 3RH has similar efficacy to 6H or 9H; therefore, it is plausible that 3RH has at least similar or better efficacy compared to 6/9H in children as well [15]. Lastly, two of the three studies are from low-TB burden countries and the findings from the studies may not be generalisable to high-TB burden countries.

In conclusion, treatment of LTBI in children with a daily 3RH regimen is safe with better compliance, adherence and completion rate than a 6H or 9H monotherapy. Hence, 3RH can be considered as a preferable option, compared to isoniazid monotherapy, for treating LTBI particularly in light of availability of child friendly formulations. Nevertheless, more and better-quality evidence is needed on the effectiveness and safety of this regimen.

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