South African National Essential Medicine List
Primary Level Medication Review Process
Component: Respiratory conditions

MEDICINE REVIEW

Question: What is the efficacy and safety of TB preventive therapy for reducing the incidence of TB amongst TB household contacts?

Date: 21 June 2022

Key findings

- Tuberculosis (TB) is a communicable disease and one of the top ten causes of death worldwide. Providing TB preventive therapy (TPT) to those at highest risk of developing active TB disease may decrease TB related morbidity and mortality.
- We conducted a review of clinical studies to assess the efficacy and safety of different TB preventive therapy options for reducing the incidence of TB in household contacts of people diagnosed with drug-susceptible TB.
- We searched for WHO guidelines, systematic reviews and randomized controlled trials related to TB preventive therapy up to 19 May 2021. We included three TB preventive regimens: daily isoniazid (INH) for six or more months, weekly rifapentine plus isoniazid for three months (3HP) and daily rifapentine plus isoniazid for one month (1HP). We looked for comparisons of the regimens compared to placebo/no treatment, and for comparisons between INH and either 3HP or 1HP.
- We included one recent WHO guideline, three systematic reviews of randomised controlled trials and three primary randomised controlled trials.
- Compared to placebo, INH probably reduces active TB by 60%, risk ratio (RR) 0.40 (95% CI 0.31 to 0.52), 11 trials, n = 73375, moderate certainty evidence (rated down for indirectness). The absolute risk of developing active TB within at least two years of follow-up was 1.7% in the placebo arms vs 0.6% in the INH arms overall. The number needed to prevent one case of active TB (NNT) was therefore 91 (95% CI 82 to 109). Assuming that the relative effect of the intervention remains constant, the anticipated NNT for a low (1%), moderate (2%) and high (5%) proportion with active TB in the comparison group are 167 (95% CI 143 to 200), 83 (95% CI 71 to 100) and 33 (95% CI 29 to 42) respectively.
- There is probably little or no difference between 3HP vs INH, or 1HP vs INH on the outcome incidence of active TB (moderate to low certainty evidence).
- TB drug induced liver injury (DILI) is the most commonly reported adverse effect.
  - *INH vs placebo:* There may be 5 more cases of DILI per 1000 patients treated with INH (95% CI 2-11) compared to placebo (moderate certainty evidence). NNH 221 (95%CI 168 to 323) - one in every 221 treated with INH preventive therapy will develop DILI.
  - *3HP vs INH:* DILI was 84% lower the 3HP group compared to INH group RR 0.163 (95% CI 0.099 to 0.268]), 1 trial, n = 7799, moderate certainty evidence), that is 23 fewer cases of hepatotoxicity per 1000 people who receive 3HP (ranging from 20 fewer to 25 fewer).
- INH resistance is important, however the data regarding this outcome is uncertain, for all comparison groups.
- Overall, INH probably reduces incidence of active TB and 3HP and 1HP may perform similarly for this outcome. DILI is increased when using INH compared to placebo but may be less when 3HP or 1HP is used. Impact on INH resistance needs further research evidence.
- The estimated total health care cost of expanding TPT to household contacts of all ages is very uncertain due to significant uncertainty in budget impact model parameters – especially primary healthcare utilization rates and clinic visit costs. The estimated *pharmaceutical acquisition costs* are less uncertain, with incremental costs (compared to current standard of care) calculated as R18.3 million for INH monotherapy for all ages, R72.9 million for the 3HP regimen (children <2y assumed to receive INH monotherapy), and R111.7 million for the 1HP regimen

(children <13y assumed to receive INH monotherapy). Estimations of total health care costs (per annum) are estimated as R19 million for current standard of care (INH monotherapy for children <5y), R167.6 million for INH monotherapy for all ages, R155.4 million for the 3HP regimen (with children <2y assumed to receive INH monotherapy), and R184.7 million for 1HP regimen (children <13y assumed to receive INH monotherapy). Refer to budget impact analysis report for detailed information.

- Feasibility is an important factor. As noted by in the WHO guideline, capacity of the health care provider to assess the intensity of exposure, risk of infection and reinfection, the risk for development of active TB, and to detect latent TB infection (LTBI) by testing, as well as capacity to weigh harm versus benefit of treatment and ability to exclude active TB disease before initiation of treatment are important considerations. Of concern, TPT coverage in under 5's to date is poor -56% and 51% in 2019 and 2020 respectively.
- Acceptability of introducing TPT for those who will be affected was considered and views may differ. There are several proponents in favour of introducing TPT, and although we did not conduct primary research on this, indirect evidence from patient perspectives from those who have HIV suggest that there may be several barriers to taking TPT in reality including economic hardship of attending clinic when well.
- The committee considered that on balance introducing TPT for all household contacts was not the preferred option. More may be achieved through improved TB treatment coverage, improved provision of TPT to children <5 years, ART coverage, infection prevention and control in healthcare settings, and multisectoral interventions towards socio-economic improvement of high-risk communities.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Based on this review, the PHC/Adult Hospital Level Committee suggests not to use TB preventive therapy for household contacts (beyond the current National policy that recommends TPT for uninfected children <5 years, exposed to a close contact of infectious pulmonary TB or LTBI confirmed on TST).

Rationale: The absolute reduction in active TB cases with TB preventive therapy to household contacts is small. TB preventive therapy may cause serious adverse reactions such as drug-induced liver injury. There are substantial logistical challenges to implementation, and this may divert resources from other aspects of the TB control programme. In addition, it is unclear whether TPT implementation for all household contacts would be acceptable and there may be substantial barriers to acceptability for patients and healthcare providers. The cost of offering TPT to household contacts of all ages will be much higher than current costs incurred due to a larger eligible patient population (more than eight-fold increase). There are concerns regarding implementation and uncertainties on the overall impact of scaling up TPT to all household contacts on the health system.

Level of Evidence: Moderate certainty clinical evidence, low certainty costing information

Review indicators: New high-quality evidence of a clinical and community-wide relevant benefit. Reduction in cost of short course TPT regimens

NEMLC RECOMMENDATION (23 JUNE 2022):

The NEMLC accepted the recommendation proposed by the PHC/Adult Hospital Level Committee. NEMLC suggested that TB preventive therapy not be used for household contacts (beyond the current National policy that recommends TPT for uninfected children <5 years, exposed to a close contact of infectious pulmonary TB or LTBI confirmed on TST).

Some members indicated that while they did not question the quality of the review, they did not support the recommendation against the use of TPT for all household contacts, and preferred the following recommendation, "*We suggest using either the option or the alternative*".

Monitoring and evaluation considerations:

Research priorities: Local AST resistance evaluations for various TB preventive therapies; Impact of TB responses to measure the effect for each action

EXECUTIVE SUMMARY

Date: 21 June 2022
Medicine (INN): Isoniazid, rifapentine
Medicine (ATC): J04AC01, J04AB05
Indication (ICD10 code): Z29.2
Patient population: Paediatric, adults
Prevalence of condition: 1 044 000 household contacts of people diagnosed with drug-susceptible TB in one year (estimated incidence of TB: n = 360 000)
Level of Care: Primary Healthcare
Prescriber Level: Nurse prescriber
Current standard of care:

- Isoniazid TB prophylaxis to all HIV-infected children, and all uninfected children <5 years, exposed to a close contact with an infectious pulmonary TB case, or confirmed LTBI on TST (Paediatric Hospital STGS and EML, 2017).
- 12H for adult PLHIV starting antiretroviral therapy (Primary Healthcare STGs and EML, 2020).

Efficacy estimates: (preferably NNT) The number needed to prevent one case of active TB with isoniazid (6H/12H) was 91 (Smieja 1999). Most of the trials provided 12H. Based on one trial (Thompson 1982), there is probably little or no difference in the incidence of active TB between 6H and 12H, RR 1.41 (95% CI 0.84 to 2.37). Note that these studies were done pre-ART. There is probably little or no difference between 3HP vs INH, or 1HP vs INH on the outcome incidence of active TB (moderate to low certainty evidence).
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PTC affiliation: WC PTC - Karen Cohen

Name of author(s)/motivator(s)

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INTRODUCTION/ BACKGROUND

Description of the condition

Tuberculosis (TB) is one of the top ten causes of death worldwide. It is estimated that globally 10 million people developed TB disease and approximately 1.5 million died of TB in 2019. (1) SA is one of eight countries accounting for two thirds of the global TB burden, with an estimated incidence of 615/100 000 population (n=360 000) in 2019. (1)

TB disease is caused by the bacillis *Mycobaterium tuberculosis* and mainly affects the lungs. *M. tuberculosis* is spread through the air by people with active TB, e.g. when they cough. People in close proximity to an active TB case have a high risk of contracting infection. Once infected with *M. tuberuculosis* a person can develop TB disease or remain infected with latent TB infection (LTBI) for life. (2) It is estimated that one third of the world's population have LTBI. LTBI can progress to disease at any stage, but the risk to disease progression is higher with recent infection and in immunocompromised individuals. (2)

Integrated person-centred TB care and prevention is one of three pillars of the WHO's 'End TB Strategy' and comprises early diagnosis of TB, treatment of all people with TB, collaborative TB/HIV care, and TB preventive treatment (TPT) of people at high risk. (1) For TB diagnosis, treatment, and prevention to be effective, the WHO emphasises the need for progress towards universal health coverage and multisectoral action on social determinants of TB including poverty, housing quality, social protection, undernutrition, and economic growth.

In 2020 in SA, the estimated incidence of TB was 554/ 100 000 population, with a treatment coverage of 58%. (3) The decline in incidence compared to 2019 is consistent with a declining trend since 2015, and treatment coverage was similar to that in 2019. In 2020 TPT was provided to 93% of HIV positive people newly enrolled on anti-retroviral therapy but to only 51% of children < 5 years who were household contacts. (3) The COVID-19 pandemic may have negatively affected preventive care of child household contacts as coverage, although still poor, was slightly higher in 2019 at 56%. (1)

Description of the interventions

Several TPT options are available. The most widely used antimicrobial for TB prevention is isoniazid. Isoniazid is a daily regimen for at least 6 months (6H). Adverse reactions include asymptomatic elevation of serum liver enzyme concentrations, peripheral neuropathy and hepatotoxicity. (4) In 2014 the Food and Drug Administration (FDA) approved a combination regimen of isoniazid and rifapentine for TB prevention. (5) This combination regimen was recently added as a recommended option for TPT by WHO in 2020. (6) The isoniazid and rifapentine combination is prescribed weekly for 3 months (3HP) or daily for 1 month (1HP). Adverse reactions to rifapentine include cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance and hepatotoxicity (4). The shorter duration of treatment and longer intervals between doses compared to isoniazid alone, makes the combination regimen potentially more acceptable and easier to implement.

How the intervention might work

TB preventive treatment has been shown to reduce the risk of disease progression in people with LTBI. (7) Household contacts of an infectious TB case are at high risk of TB infection and by excluding TB disease and providing TPT to these contacts, active disease can be prevented. However, uptake and adherence to isoniazid preventive treatment is generally reported to be poor. (8) The new combination regimens with shorter treatment duration has potential for improved uptake and adherence to TPT.

Why it is important to do this review

One of the global TB targets set by the UN high-level meeting on TB in 2018 is to provide at least 30 million people with TPT from 2018 to 2022. (1) This target is far from reached and scaled up provision of TPT is one of 10 priority recommendations of the UN Secretary-General's 2020 progress report on TB for actions needed to accelerate progress towards global TB targets.

South Africa (SA) is in the process of updating national TPT guidelines. The current SA Standard Treatment Guidelines and Essential Medicine List recommends 6 months of daily isoniazid for drug susceptible TB contacts under the age of 5 and 12 months of isoniazid for adult PLHIV starting antiretroviral therapy. To inform the updated recommended options for TPT in household contacts of infectious drug susceptible TB cases, this review assesses the efficacy and safety profile of 6H, 3HP and 1HP.

Local prevalence of drug-resistant TB
Of note is that a national cross-sectional survey (June 2012 to June 2014) of newly diagnosed and retreated TB adult patients (≥18 years old; n=101 422) showed that the prevalence of rifampicin-resistant TB was 4.6% (95% CI 3.5 to 5.7) and isoniazid-resistant TB was 9.3% (95% CI 7.9 to 10.7), higher than that of MDR tuberculosis (2.8%, 95% CI 2.0–3.6). (20)

Feasibility and acceptability considerations
The feasibility and acceptability of an expanded TPT program needs consideration before it is implemented. Although TPT initiation in HIV positive people commenced on ART was 93% in 2020 (3), commencing TPT relies on the HIV positive person returning to the clinic for ART, and ART coverage of people living with HIV was only 72% in 2020. (21) As TPT is envisaged for all household contacts, TPT coverage of children < 5years household contacts is probably a better indicator of feasibility. Of note, TPT coverage of children was only 56% in 2019 (1) and 51% in 2020. (3) While the reasons for poor coverage require exploration, possibilities include poor tracing of household contacts (particularly where healthcare providers are scarce), high transport costs for patients to get to clinics for treatment, and low acceptability among caregivers of these children. Poor TB treatment coverage (58% in 2019 and 2020) is also a concern, as it is not known if household contacts will be reached if the index case is not on treatment.

A further concern is whether TPT would be effective amidst high levels of poverty, household crowding, and undernutrition. The WHO is clear that, to be effective, TB diagnosis, treatment and prevention should occur within the context of socio-economic improvement. In Europe, approximately 50% of between country variation in TB incidence and prevalence is attributable to socio-economic disadvantage. (22) In Brazil, unemployment and household crowding have been identified as important variables associated with TB incidence which need attention. (23) Household crowding was also found to be associated with TB transmission and clustering of TB infections in Cape Town, SA. (24) The duration of effect and population level impact of TPT in a high prevalence, poor socio-economic setting with household crowding is questionable. (25)

High density patient queues in primary healthcare clinics in SA have also been identified as a risk factor for TB transmission. (26) In KwaZulu-Natal, simple infection prevention and control measures such as queue management systems, ventilation, and masks could possibly reduce incident TB cases in the community in 2021-2030 by 3.4%-8.0%.

It is possible that spending on TPT may give rise to a false sense of security, detracting from spending on social interventions and other measures of infection prevention and control. More may be achieved through improved TB treatment coverage, TPT of children <5 years, ART coverage, infection prevention and control in healthcare settings, and multisectoral interventions towards socio-economic improvement of high-risk communities.

PURPOSE/OBJECTIVE

In household contacts of people diagnosed with drug susceptible TB, what is the efficacy and safety of different TB preventive therapy options for reducing the incidence of TB?

Population:
Household contacts of patients with drug susceptible pulmonary TB with no restriction on age; regardless of TST/ IGRA testing and regardless of HIV status.
We excluded studies that assessed TPT in patients from specific risk groups only, e.g., transplant patients; therefore, in which contacts were not identified via a TB index case.

Intervention(s) and comparisons:
1. INH vs placebo/ no Rx
2. a) Rifapentine and INH for 3 months (3HP) vs INH

b) Rifapentine and INH for 3 months (3HP) vs placebo/ no Rx

3. a) Rifapentine and INH for 1 month (1HP) vs INH
   b) Rifapentine and INH for 1 month (1HP) vs placebo/ no Rx

Outcomes:

- Incidence of TB disease (Xpert or TB culture or specific case definition)
- Death
- Adverse events
- Isoniazid resistance (Xpert)
- Incidence of TB infection (TST or IGRA conversion to positive)

Study designs:

- Systematic review of randomised controlled trials
- WHO guidelines
- Randomized controlled trials

METHODS

Data sources

On 6 April 2021 we searched for WHO guidelines related to TB preventive therapy. Thereafter, we also searched for systematic reviews and randomized controlled trials in the following databases respectively:

- Epistemonikos (https://www.epistemonikos.org/en/)
- Cochrane library
- PubMed

Search strategy details are available in appendix 1.

Selecting studies for inclusion

Title and abstract and full-text screening were done in duplicate using COVIDENCE software (SvW and NB).

Data extraction

Data extraction was done by a single reviewer and checked by a second reviewer. For guidelines we extracted the relevant recommendations and evidence tables. For systematic reviews and trials, we extracted data on the methods; participants including population n, age, risk and setting; interventions including type of intervention, comparator and delivery; and primary and secondary outcomes.

Appraisal of study quality

Quality assessment was done in duplicate and conflicts were resolved with discussion (SvW and NB).

Guidelines:

We appraised the quality of guidelines using AGREE II https://www.agreetrust.org/agree-ii/

Systematic reviews:

We appraised the quality of systematic reviews using AMSTAR. Online checklist found here: https://amstar.ca/Amstar_Checklist.php

Trials:

We appraised randomised controlled trials using the standard Cochrane risk of bias assessment tool 2.0 which considers: random sequence generation, allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective outcome reporting and other sources of bias (https://training.cochrane.org/handbook/current/chapter-08).

For trials included in systematic reviews we extracted and used the risk of bias assessment from the review.

Data synthesis

Data synthesis was descriptive. The relevant measures of effect with 95% CIs were reported for all outcomes under each comparison. For the comparison of INH with placebo, we used available data to conduct GRADE assessments of the overall certainty of the evidence (9).

Budget impact analysis

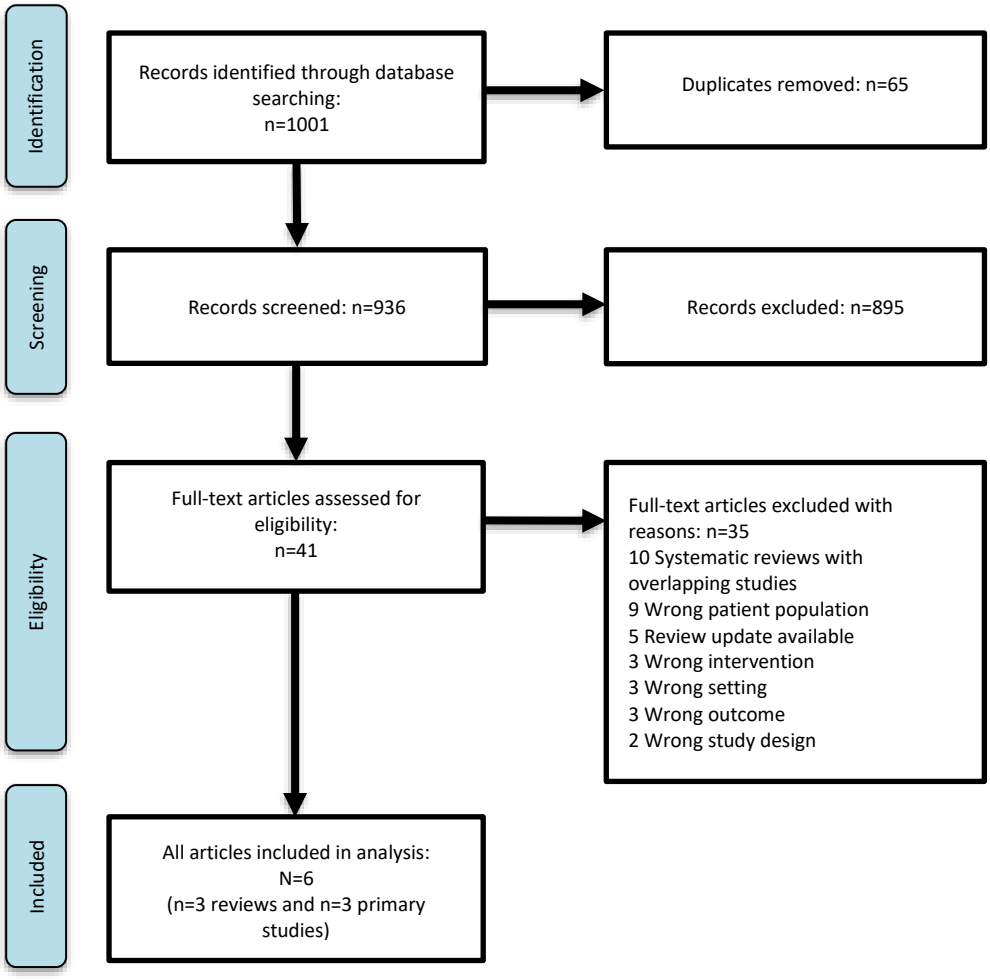
A budget impact analysis was conducted from a national public sector payer perspective. Pharmaceutical and other health care costs (and costs averted) was calculated for four TPT regimens: (1) Daily INH for 6 months for children aged <5years (standard of care), (2) Daily INH for 6 months for all ages, (3) 3HP for contacts aged >2years, daily INH for 6 months for children aged <2years , and (4) 1HP for contacts aged >13years, daily INH for 6 months for children aged <13years. The eligible population likely to receive TPT was estimated using incidence, average household size and mortality data, plus assumptions made regarding the likely uptake and discontinuation rates amongst the eligible population. Refer to budget impact analysis report for more detail and findings.

Findings

<u>Identification of studies</u>

We identified one guideline, three systematic reviews and three primary studies (see Figure 1).

Figure 1: PRISMA flow diagram



EVIDENCE SYNTHESIS

Description of guidelines and studies

Guidelines

The WHO guideline for tuberculosis preventive treatment was recently updated in 2020 and recommendations relevant to our review are provided in Table 1.

A prognostic review to inform the guideline, recommendation 6, reported that household contacts have higher risk of active TB compared to the general population regardless of age (see PICO 1: http://apps.who.int/iris/bitstream/handle/10665/260234/WHO-CDS-TB-2018.8-eng.pdf?sequence=1). However, the quality of this evidence was low. TB cases in the general population were detected passively, while TB cases in contacts were detected actively. The review also confirmed that older household contacts have lower risk of the development of active TB compared to children < 5 years. The following conditions to recommendation 6 were therefore noted:

"In this group (5 years and older) the confirmation of LTBI using either IGRA or TST would be desirable. Based on evidence of moderate to high quality, the 2015 LTBI guidelines strongly recommended the systematic LTBI testing and TB preventive treatment for contacts regardless of age in countries with a TB incidence lower than 100/100,000 population. In the current update, the guideline development group (GDG) considered that **this recommendation could be applied to any country regardless of TB burden if tests for LTBI and to rule out active TB were available and reliable.** Treatment may be justifiable without a LTBI test based on an assessment of the individual's risk of exposure and for the development of active TB in a given setting. **The GDG noted that the capacity of the health caregiver to assess the intensity of exposure, risk of infection and reinfection, the risk for development of active TB, and the ascertainment of LTBI by testing, as well as capacity to weigh harm versus benefit of treatment and ability to exclude active TB disease before initiation of treatment are important considerations in the implementation of these recommendations."**

Table 1: Characteristics of guideline(s)		
Citation (date published)	**Recommendation (pg)**	**AGREE II appraisal**
WHO consolidated guidelines on tuberculosis. Module 1: prevention - tuberculosis preventive treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.	5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable. ***(Strong recommendation, high certainty in the estimates of effect)*** 6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. ***(Conditional recommendation, low certainty in the estimates of effect)*** 17. The following options are recommended for the treatment of LTBI regardless of HIV status: **6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid**, or a 3 month regimen of daily isoniazid plus rifampicin. ***(Strong recommendation, moderate to high certainty in the estimates of effect)***. **A 1-month regimen of daily rifapentine plus isoniazid** or 4 months of daily rifampicin alone may also be offered as alternatives. ***(Conditional recommendation, low to moderate certainty in the estimates of effect)***.	**6/7**

Studies

- ***Comparison 1: INH vs placebo/no treatment***

GRADE summary of evidence tables for this comparison in household contacts were not provided in the updated 2020 WHO guideline (Table 1). In previous WHO guidelines, the decision of six or nine months of daily INH for TB household contacts was based on the prevalence of LTBI in household contacts, risk of progression of LTBI to active disease and the effect of TPT for LTBI in preventing active TB in general. (10) GRADE summary of evidence tables for this comparison, in

household contacts specifically, were therefore not provided in previous guidelines either. We identified two systematic reviews relevant to this comparison: Smieja 1999 (11) and Balcells 2006 (12).

Smieja 1999 (11) included 11 RCTs that compared INH for 6 months or more with placebo in people with an increased risk of TB (Table 2). Participants were mainly household contacts of TB index cases, but also included whole populations from high burden villages, institutions and silicosis- and transplant patients. Most study participants were enrolled regardless of PPD status. Isoniazid compared to placebo was administered at varying doses for periods ranging from 6 to 24 months. Follow-up was at least 2 years. Trials reported on outcomes of active TB, extra-pulmonary TB, hepatotoxicity and deaths. The search for Smieja 1999 (11) was updated in 2003, but as the search did not identify any new studies since 1998, it was decided that the review findings were final and would not be updated in the future. The characteristics of the individual studies included in Smieja et al. are detailed in table 2.

Balcells 2006 (12) assessed the risk for INH resistance in people exposed to primary isoniazid preventive therapy. Thirteen studies that tested INH resistance were included, of which seven were in non-HIV infected people. These seven studies included participants who were TB case contacts, patients living at mental health hospitals, X-ray scanning attendees and silicosis patients with inactive TB (Table 3). Isoniazid compared to placebo, or no treatment was administered at varying doses for periods ranging from 12 weeks to 2 years, with or without observation. Different definitions for INH resistance were used. Only two of the seven studies (Ferebee 1962, Comstock 1967) were also included in Smieja 1999 (11), but the other five were not included, due to wrong comparator (Katz 1965, Horwitz 1966, Ferebee 1970, British MRC 1992) and incomplete follow-up (Pamra 1971). Details of the individual studies included in the Balcells review are laid out in table 3.

Table 2: Characteristics of studies included in Smieja 1999 (11)

Study	**Methods**	**Participants**	**Interventions** *(all placebo controlled)*	**Outcomes reported**
Comstock 1962	Randomization by family unit	7333 Alaskan villagers in 28 villages and 2 boarding schools Enrolled regardless of PPD status Infants 2 months and older were included	Isoniazid 300mg dly for 1 yr	Active TB
Del Castillo 1965	Randomization by family unit	400 HH contacts of index cases treated at Quezon Institute, Manila, Philippines	Isoniazid 5-10mg/kg for 1 yr	Active TB
Egsmose 1965	Randomization by household	626 Kenyan rural villagers, contacts of index cases	Isoniazid 300-500mg dly for 12-24 months	Pulmonary TB (sputum microscopy or culture) Deaths
Falk 1978	Individual randomization	7036 men in US VA hospitals; abnormal CXR 98% Men Mostly 30-50 years old 77% white. Majority of this group had previous TB treatment and were excluded from analysis. N=2389 participants included	Isoniazid 300mg dly 1-2 years	Active TB
Ferebee 1962	Randomization by family unit	25033 household contacts of newly diagnosed reported tuberculosis 2/3 under 20 years old	Isoniazid 300mg/kg or 5mg/kg for one year	Active TB Extrapulmonary TB Death
Ferebee 1963	Randomization by ward or building	24838 patients in 37 country institutions for chronic psychiatric or mentally retarded in Wisconsin, Georgia, and Massachusetts, USA PPD>5mm in 50% Age 2-100 >85% white Mean age 48 (men); 54 (women) 91% had normal CXR, 9% abnormal at baseline	Isoniazid 300mg dly for 12 months	Active TB Death
Girling 1992	Individual randomization	679 Chinese men with silicosis in Hong Kong Most 45-64 63% current smokers 94% > 10mm Criteria: silicosis diagnosis, no history TB, no evidence TB, negative sputum microscopy and culture	INH 300mg dly 6 months Rifampin 600mg dly 12 wks INH+Rif 12 weeks Placebo *Only the INH and placebo arms included in the reivew (N=199)	Active TB

John 1994	Individual randomization	184 transplant or dialysis patients in India	Isoniazid 300mg or placebo for one year. Low compliance	Active TB Hepatitis Death
Mount 1962	Randomization by family unit	2824 household contacts of known TB cases in USA 1/3 children 55% PPD<5mm 60% black	Isoniazid 300mg dly for one year	Active TB Extrapulmonary TB Deaths
Thompson 1982	Individual randomization	28000 adults in Eastern Europe: 115 clinics Czechoslovakia, Finland, German Democratic Republic, Hungary, Poland, Romania, Yugoslavia Mean age 50 (20-65), attending chest clinic, abnormal chest x-ray, no previous treatment, no previous positive bacteriology 1/3 were age 55-65 PPD>6mm	Isoniazid for 3, 6 or 12 months or placebo Only placebo, 6 and 12 month arms included in analysis (N=20828)	Active TB Hepatitis
Veening 1968	Individual randomization	261 PPD positive contacts of active cases in Royal Netherlands Navy barracks	Isoniazid 600mg for 4 months then 400mg dly for total of 1 yr	Active TB
Note: **Risk of bias** not reported for each study. "Studies were assigned quality scores of 6 to 10, with a median score of 8. Agreement between observers was good (kappa=0.6). The studies which met the selection criteria were of high methodologic quality." (11)				

Table 3: Characteristics of studies included in Balcells 2006 (12)

Study	Methods	Participants	Intervention	Comparison	Randomization and treatment concealment**
Ferebee 1962	Double blinded*	Household contacts of TB patients	12 months INH, 4-7 mg/kg/day	Placebo	Unclear randomization
Katz 1965	Not blinded	Mental hospital patients with inactive lesions	2 years of INH, 300mg daily	No treatment	Assigned by odd or even hospital number
Horwitz 1966	Village/group randomization, Double blinded*	76 villagers, adults of Western Greenland	2x 13-week INH, 400 mg twice weekly	0.1 mg INH	Random number tables
Comstock 1967	Community/group randomization; Double blinded*	Residents of 28 villages and 2 boarding schools	12 months INH, 300 mg	Daily, placebo	Random number tables
Ferebee 1970	Not blinded	Household contacts with inactive lesions	INH		Unclear randomization
Pamra 1971	Group randomization Blinding not reported	424 X-ray screening attendees with inactive TB	12 months INH, 5 mg/kg/day observed for 6 years	Placebo	Unclear randomization
British MRC 1992 (Hong Kong Chest Service)	Double-blinded* placebo controlled clinical trial with matching placebos Individual randomization	679 Silicotic men subjects in Hong Kong	Group A: Rifampin for 12 weeks (R3) Group B: INH and Rifampin for 12 weeks (HR3) 24 weeks INH, 300mg/daily 2 and 5 years time points	Group C: INH alone for 24 weeks (H6) or placebo	Unclear randomization Treatment concealment – numbered packages containing isoniazid or matching placebo

Risk of bias:
A formal risk of bias assessment for each trial was not reported, but method of assigning treatment allocation, allocation concealment, blinding and publication bias were assessed
**Three studies reported a method of assigning treatment allocation (Katz 1965, Horwitz 1966, Comstock 1967); Only one study reported treatment concealment (British MRC 1992)
*Four studies were double-blinded (Ferebee 1962, Horwitz 1966, Comstock 1967, British MRC 1992)
"Funnel plots suggested little evidence of publication bias" (12)

- ***Comparison 2a: 3HP vs INH***

We identified 1 review (Hamada 2018 (13)) and 1 trial (Sun 2018 (14)) relevant to this comparison. The Hamada 2018 (13) review informed the identified WHO guideline. Hamada 2018 (13) compared 3HP with INH and included four trials. Two trials in HIV infected people were excluded as these were not household contact studies; one trial was in adults with LTBI (Sterling 2011 (15)) and one in children and adolescents with LTBI (Villarino 2015 (16)). We identified one trial which was published after the search for Hamada 2018 (13) was completed: Sun 2018 (14). Sun 2018 (14) compared 3HP with INH in a similar population of adults as Sterling 2011 (15). Characteristics of included trials are reported in Table 4a.

- ***Comparison 2b: 3HP vs no treatment***

We identified one trial relevant to this comparison: Gao 2018 (17). Gao 2018 (17) compared 3HP and 2HP to no treatment in an elderly population with LTBI. Due to a high frequency of adverse events, the treatment arms were adjusted to HP weekly for 8 weeks and HP twice weekly for 6 weeks. Characteristics are reported in Table 4b.

Table 4: Characteristics of trials comparing 3HP vs INH/no treatment

a) 3HP vs INH

Trials	RCT method	Participants	Interventions	Comparator	Outcomes reported	Risk of Bias
Sterling 2011 (15)	Open-label	US, Canada, Brazil, Spain Participants were at least 12 years of age at high risk for progression to active TB disease, which included: close contacts of a culture positive patient and positive TST; PLHIV with a positive TST or close contact with a TB patient; fibrotic changes on CXR with pos TST. Follow-up: 33 months post randomization	Observed 3 months weekly Rifapentine + INH	Self-administered 9 months of daily INH	Culture confirmed TB in children <18 years Clinical TB	β -High for performance and detection bias Unclear for 'other' bias Low for other domains
Villarino 2015 (16)	Open-label	US, Canada, Brazil, Hong Kong (China) and Spain Children (aged 2-17 years) at risk of active TB disease according to age, TST results and history of TB exposure. Proportion of participants with HIV was 2.3%. Follow-up: 3 years	12 once-weekly doses Rifapentine and INH for 3 months With supervision	270 daily doses of INH Without supervision for 9 months	Treatment discontinuation (due to AEs) Toxicity grades 1-4 Death of any cause	β -High for performance and detection bias Low for other domains
Sun 2018 (14)	Multicentre Randomized Controlled Trial	Asia, Taiwan LTBI contacts of index patients with a new diagnosis of pulmonary TB (Acid Fast Test) Aged >= 12 years with positive TST in four hospitals, within one month of unprotected exposure Follow-up: 2 years	3HP	9H Delivery: Direct observation and telephonic inquiries	Treatment completion (270-day treatment within 12 months in the 9H group and 12-dose treatment within 3 months in the 3HP group) Incidence of Adverse Drug Reactions (Hepatotoxicity)	High for performance and detection bias – RoB2 Low for other domains

b) 3HP vs no treatment

Gao 2018 (17)	Open label pragmatic Randomized Controlled Trial	China, Beijing. Rural residents aged 50-69 years with LTBI. Inclusion: 50–70-year-olds, local resident, IGRA positivity. Follow-up: 2 years	Arm A: Rifapentine plus INH (3 month once weekly) at a dose of up to 900mg, with incremental adjustments for subjects' weight <= 50 kg **(Adjusted to 8 weeks due to high frequency of AEs)** Arm B: Rifapentine (2 month twice weekly) at a dose of 600mg, with incremental adjustments for subjects' weight <= 50 kg **(Adjusted to 6 weeks due to high frequency of AEs)** Delivery: After meals with direct observation	Arm C: Untreated controls	Microbiologically confirmed active pulmonary TB or clinically determined pulmonary TB Completion of study therapy, permanent discontinuation of therapy and discontinuation due to AEs, death from any cause, grade 3 or 4 drug-related toxic effects	High for performance and detection bias – RoB2 Low for other domains
β – Cochrane Risk of Bias tool across 6 domains. "All studies were at risk of performance and detection bias for ascertaining adverse events due to lack of blinding. Three studies were at unclear risk of other bias, as the studies used a combination of individual and cluster randomization in which household members were assigned to the same group as the first enrolled member of their household. For other domains, we judged these to be at low risk of bias." (13)						

- ***Comparison 3a: 1HP vs INH***

Only one trial (Swindells 2019 (18)) reported this comparison and this trial was not in TB household contacts identified via a TB index case. Swindells 2019 (18) was an open-label trial in HIV-infected patients with LTBI, in which 1 month of daily rifapentine plus isoniazid was compared to 9 months of isoniazid alone. The outcomes reported were incident TB and death from TB or unknown cause. Details are available in table 5.

Table 5: Characteristics of trials comparing 1HP vs INH					
Trials	**Methods**	**Participants**	**Interventions**	**Comparator**	**Outcomes reported**
Swindells (18)	Open-label RCT, phase 3 noninferiority trial	HIV-infected patients living in areas with high TB prevalence Evidence of LTBI N=3000 Followed-up for median of 3.3 years 54% women Med age: 35 years Half of the patients were receiving ART	1-month regimen of daily rifapentine plus isoniazid	9 months of isoniazid alone	Diagnosis of TB Death from TB or unknown cause

- ***Comparison 3b: 1HP vs placebo/ no treatment***

We did not identify any reviews or trials relevant to this comparison.

Risk of bias of guidelines and included studies

Guidelines

The WHO consolidated guideline on TB was of high quality and scored 6/7 overall according to AGREE II appraisal (Table 1). The guideline was rated down because the search methods were not clearly reported.

Studies

- ***Comparison 1: INH vs placebo/no treatment***

For the two reviews relevant to this comparison, one was of low quality (Smieja 1999 (11)) and one of critically low quality (Balcells 2006 (12)).

- The Smieja 1999 (11) review was rated down based on unclear use of a comprehensive literature search strategy and failure to report on the funding sources of individual trials, using the AMSTAR checklist. However, due to the strict selection criteria, all the trials included in Smieja 1999 (11) were of high methodological quality and low risk of bias (Table 2).
- The Balcells 2006 (12) review was rated down for not stating publication restrictions and not presenting a list/flow diagram of excluded studies with reasons for exclusion. From the seven trials included in Balcells 2006 (12), three reported a method of assigning treatment allocation, only one reported treatment concealment and four studies were double-blinded (Table 3).

- ***Comparison 2a: 3HP vs INH***

The Hamada 2018 (13) review, relevant to this comparison was of low quality. It was rated down, because it was unclear if review methods were established before the conduct of the review and if data extraction was done in duplicate, no list of excluded studies was provided, sources of funding for included studies were not reported and the review authors did not account for risk of bias when they interpreted the results of the review.

The two studies included from the Hamada review (Sterling 2011 (15) and Villarino 2015 (16)) were at risk of performance and detection bias for ascertaining adverse events, due to lack of blinding. They also had unclear risk of 'other bias' as the studies used a combination of individual and cluster randomisation in which household members were assigned to the same group as the first enrolled member of their household. The other domains were judged at low risk of bias.

We assessed the newly identified trial, relevant to this comparison, with the Cochrane risk of bias tool. Sun 2018 (14) was an open label trial and also at risk of performance and detection bias for ascertaining adverse events as with Sterling 2011 (15) and Villarino 2015 (16).

- ***Comparison 2b: 3HP vs no treatment***

We assessed the one identified trial, relevant to this comparison, with the Cochrane risk of bias tool. In the Gao trial (17) outcome assessors were blinded to treatment allocation; however, it was an open label trial, controls did not receive any

treatment and patients could have reported symptoms (of clinically diagnosed TB) and treatment side effects differently between the arms.

- ***Comparison 3a: 1HP vs INH***

As we did not identify any reviews or new trials relevant to this comparison, we refer to the GRADE summary of evidence tables from the recent WHO guideline (see Comparison 3a under Effects of the intervention below).

Effects of the intervention

- ***Comparison 1: INH vs placebo/no treatment* (Table 6)**

1. **Incidence of TB disease:**
   The incidence of active TB is probably reduced by 60%, risk ratio (RR) 0.40 (95% CI 0.31 to 0.52), 11 trials, n = 73375, moderate certainty evidence. There are 10 fewer cases of active TB per 1,000 people who receive TPT compared to those who do not (ranging from 12 fewer to 8 fewer) within at least two years of follow-up. This translates to an overall number needed to treat (NNT) of 91 (95% CI 82 to 109).
   Given that the data included in the review spans both high and low prevalence settings, we are able to explore the likely NNT for different baseline risk of TB. Based on the relative effect of the intervention, the anticipated NNT for a low (1%), moderate (2%) and high (5%) proportion with active TB in the comparison group are 167 (95% CI 143 to 200), 83 (95% CI 71 to 100) and 33 (95% CI 29 to 42) respectively (Table 7) We also report the RR and NNT for each trial separately (see Table 6, Appendix 2).
   Most of the trials provided 12 months of INH. Based on one trial (Thompson 1982), there is probably little or no difference in the incidence of active TB between 6 months and 12 months of INH, RR 1.41 (95% CI 0.84 to 2.37).
   Incidence of extra-pulmonary TB may be reduced, RR 0.34 (95% CI 0.16 to 0.71), 4 trials, n = 44636, low certainty evidence.

2. **All-cause mortality:**
   There is probably little or no difference in all-cause mortality between those who receive TPT and those who do not, RR 1.10 (95% CI 0.94 to 1.28), n = 5, 33716, moderate certainty evidence.

3. **Adverse events:**
   No general report, here we report TPT related liver injury: there is probably an increase in TPT-related liver injury, RR 5.54 (95% CI 2.56 to 12.00), 5 more per 1,000 (from 2 more to 11 more), 1 trial (Thompson 1982), n = 20874, moderate certainty evidence. Based on this trial (Thompson 1982), there may be no difference in TPT related liver injury between 6 months and 12 months of INH, RR 0.75 (95% CI 0.48 to 1.17).

4. **Isoniazid resistance:**
   We are uncertain about the effect of TPT on development of INH resistance, RR 1.5 (95% CI 0.82 to 2.73). The studies are small and number of cases of resistance low. This remains a research gap.

5. **Incidence of TB infection:** not reported

Table 6. GRADE summary of evidence table for comparison 1: INH vs placebo

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INH	Placebo	Relative (95% CI)	Absolute (95% CI)	
Incidence of active TB											
11	RCTs	not serious*	not serious	serious[a]	not serious	none	239/40262 (0.6%)	557/33113 (1.7%)	**RR 0.40** (0.31 to 0.52)	**10 fewer per 1,000** (from 12 fewer to 8 fewer)	⊕⊕⊕◯ Moderate
Incidence of extrapulmonary TB											
4	RCTs	not serious*	not serious	serious[b]	not serious	none	9/22379 (0.0%)	28/22257 (0.1%)	**RR 0.34** (0.16 to 0.71)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕⊕⊕◯ Moderate
TB related death											
2	RCTs	not serious*	not serious	not serious	serious[c]	none	3/16318 (0.0%)	10/9396 (0.1%)	**RR 0.29** (0.07 to 1.18)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕⊕⊕◯ Moderate
TPT related hepatitis											
1	RCTs	not serious*	not serious	serious[d]	not serious	none	77/13884 (0.6%)	7/6990 (0.1%)	**RR 5.54** (2.56 to 12.00)	**5 more per 1,000** (from 2 more to 11 more)	⊕⊕⊕◯ Moderate
Hepatitis related deaths											
2	RCTs	not serious*	not serious	not serious	very serious[e]	none	5/16318 (0.0%)	0/9396 (0.0%)	**RR 4.13** (0.50 to 34.39)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low
Deaths all cause											
5	RCTs	not serious*	not serious	serious[f]	not serious	none	854/17243 (5.0%)	719/16473 (4.4%)	**RR 1.10** (0.94 to 1.28)	**4 more per 1,000** (from 3 fewer to 12 more)	⊕⊕⊕◯ Moderate
INH resistance [1]											
7	RCTs	serious[g]	not serious	serious[h]	serious[i]	none	19/110 (17.3%)	18/257 (7.0%)	**RR 1.50** (0.82 to 2.73)	**35 more per 1,000** (from 13 fewer to 121 more)	⊕◯◯◯ Very low

CI: confidence interval; **RR:** risk ratio

Explanations

*All individual trials were of high methodological quality.

a. Rated down by 1 level for indirectness. Studies ranged from 1962 to 1994. The participants were from many countries, duration of therapy was at least 1 year in the majority of studies. TB prevalence may differ from the current setting in SA.

b. Rated down by 1 level for indirectness. Most participants were contacts, but one study (Girling 1992) included silicosis patients. Duration of therapy was at least 1 year in the majority of studies. TB prevalence may differ from the current setting in SA.

c. Rated down by 1 level for imprecision due to low event numbers and wide 95% CI.

d. Rated down by 1 level for indirectness. No monitoring of serum liver enzymes or discontinuation of medication for biochemical or clinical signs of hepatotoxicity was done in this study.
e. Rated down by 2 levels for imprecision due to low event numbers and very wide 95% CIs.
f. Rated down by 1 level for indirectness. Treatment duration was 1 year or more in most of the studies. One study (John 1994) included dialysis patients, but the others were mostly contacts regardless of PPD status.
g. Rated down by 1 level. Only one study reported treatment concealment and three studies were not blinded.
h. Rated down by 1 level for indirectness. Eligible studies included participants who were TB case contacts, mental hospital patients, x-ray scanning attendees and silicosis patients with inactive TB. Isoniazid compared to placebo, or no treatment was administered at varying doses for periods ranging from 12 weeks to 2 years.
i. Rated down by 1 level for imprecision due to wide 95% CIs.

1.INH resistance from Balcells 2006; all other outcomes from Smieja 1999

Table 7. Anticipated absolute effects and NNT based on low (1%), moderate (2%) and high (5%) risk of TB in the comparison group, assuming constant relative effect of the intervention

Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Placebo	**Risk with INH**	**NNT (95% CI)**			
Incidence of active TB	**Low (1% TB prevalence)**			**RR 0.40** (0.31 to 0.52)	73375 (11 RCTs)	⊕⊕⊕◯ Moderate[a]
	10 per 1,000	**4 per 1,000** (3 to 5)	**167** (143 to 200)			
	Moderate (2% TB prevalence)					
	20 per 1,000	**8 per 1,000** (6 to 10)	**83** (71 to 100)			
	High (5% TB prevalence)					
	50 per 1,000	**20 per 1,000** (16 to 26)	**33** (29 to 42)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **NNT:** number needed to treat; **NNH:** number needed to harm

Explanations

a. Rated down by 1 level for indirectness. Studies ranged from 1962 to 1994. The participants were from many countries, duration of therapy was at least 1 year in the majority of studies.

- ***Comparison 2a: 3HP vs INH (Table 8)***

By age group:

Children and Adolescents (2 – 17 years)

1. **Incidence of TB disease:**
   There is probably little or no difference in incidence of active TB between those who receive 3HP and those who receive INH monotherapy, RR 0.132 (95% CI 0.007 to 2.542), 1 trial, n = 905, moderate certainty evidence. That is ranging from 7 fewer to 11 more cases of active TB per 1000 people who receive 3HP compared to those who receive INH monotherapy.
2. **All-cause mortality:**
   There is probably little or no difference in all-cause mortality between those who receive 3HP and those who receive INH monotherapy, RR 0.183 (95% CI 0.009 to 3.802), 1 trial, n = 1032, moderate certainty evidence.
3. **Adverse events:**
   a) **Grade III or IV**
      There may be little or no difference in grade III or IV adverse events between those who receive 3HP and those who receive INH monotherapy, RR 0.875 (95% CI 0.320 to 2.396), 1 trial, n = 1032, low certainty evidence.
   b) **Hepatotoxicity**
      There is probably little or no difference in hepatotoxicity between those who receive 3HP and those who receive INH monotherapy, RR could not be estimated (no events), 1 trial, n = 1032, moderate certainty evidence.
4. **Isoniazid resistance:**
   Could not be estimated
5. **Incidence of TB infection:**
   Not reported

Table 8. GRADE summary of evidence table for comparison 2a (children and adolescent) – 3HP vs INH WHO TB Guidelines, 2020 (19)

3-month weekly rifapentine plus isoniazid or daily isoniazid monotherapy for treatment of LTBI in children and adolescents

Population: Children and adolescents
Comparison: 6 or 9 months isoniazid
Overall quality: moderate

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
ACTIVE TB												
1 *(61)*	RCT	Not serious	Not serious	Serious[1]	Not serious[2]	None	0/471 (0.0%)	3/434 (0.7%)	RR 0.132 (0.007;2.542)	6 fewer per 1000 (from 7 fewer to 11 more)	⨁⨁⨁◯ Moderate	Critical
ALL-CAUSE MORTALITY												
1 *(61)*	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	None	0/539 (0.0%)	2/493 (0.4%)	RR 0.183 (0.009;3.802)	3 fewer per 1000 (from 4 fewer to 11 more)	⨁⨁⨁◯ Moderate	Important
ANY ADVERSE EVENTS (GRADE III OR IV)												
1 *(61)*	RCT	Serious[4]	Not serious	Serious[1]	Not serious[3]	None	7/539 (1.3%)	8/493 (1.6%)	RR 0.875 (0.320;2.396)	2 fewer per 1000 (from 11 fewer to 23 more)	⨁⨁◯◯ Low	Critical
HEPATOTOXICITY												
1 *(61)*	RCT	Not serious[5]	Not serious	Serious[1]	Not serious	None	0/539 (0.0%)	0/493 (0.0%)	Cannot be estimated	0 fewer per 1000 (from 4 fewer to 4 more)	⨁⨁⨁◯ Moderate	Critical
DRUG-RESISTANT TUBERCULOSIS												
0									Cannot be estimated		-	Important
COMPLETION RATE												
1 *(61)*	RCT	Not serious	Not serious	Serious[1]	Not serious	None	415/471 (88.1%)	351/434 (80.9%)	RR 1.089 (1.030;1.153)	72 more per 1000 (from 24 more to 124 more)	⨁⨁⨁◯ Moderate	Critical

[1] No comparison against 6 months of isoniazid. Although the trial was conducted in low TB incidence countries, this is unlikely to affect relative effect of rifapentine + isoniazid compared with isoniazid monotherapy. Downgraded by one level.
[2] Although the 95% CI of the RR is wide, the number of events was small and the CI of absolute effect is narrow. The result also met pre-stated non-inferiority margin. Not downgraded.
[3] Although the 95% CI of the RR is wide, the number of events was small and the CI of absolute effect is narrow. Not downgraded.
[4] An open-label design of the trial may have introduced ascertainment bias.
[5] Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

Adults (25 – 50 years*) (Table 9)

*In Sterling 2011 (15) the median age was 36 years (IQR 25-47) in the 3HP arm and 35 years (IQR 25-46) in the INH arm.

1. **Incidence of TB disease:**
   There is probably little or no difference in incidence of active TB between those who receive 3HP and those who receive INH monotherapy, RR 0.438 (95% CI 0.179 to 1.074), 1 trial, n = 7731, moderate certainty evidence. That is ranging from 0 fewer to 3 fewer cases of active TB per 1000 people who receive 3HP compared to those who receive INH monotherapy.
2. **All-cause mortality:**
   There is probably little or no difference in all-cause mortality between those who receive 3HP and those who receive INH monotherapy, RR 0.740 (95% CI 0.462 to 1.183), 1 trial, n = 7745, moderate certainty evidence.
3. **Adverse events:**
   a) **Grade III or IV**
      There may be little or no difference in grade III or IV adverse events between those who receive 3HP and those who receive INH monotherapy, RR 0.873 (95% CI 0.733 to 1.040), 1 trial, n = 7799, low certainty evidence.
   b) **Hepatotoxicity**
      The incidence of hepatotoxicity is probably 84% lower in those who receive 3HP than in those who receive INH monotherapy, RR 0.163 (95% CI 0.099 to 0.268), 1 trial, n = 7799, moderate certainty evidence. That is 23 fewer cases of hepatotoxicity per 1000 people who receive 3HP compared to those who receive INH monotherapy (ranging from 20 fewer to 25 fewer).
4. **Isoniazid resistance:**
   Isoniazid resistance not reported, here we report drug-resistant TB: there is probably little or no difference in drug-resistant TB between those who receive 3HP and those who receive INH monotherapy, RR 0.470 (95% CI 0.043 to 5.179), 1 trial, n = 7731, moderate certainty evidence.
5. **Incidence of TB infection:**
   Not reported

Note: Sun 2018 (14) reported on Grade III/IV adverse events (3/132 and 0/131 events in 3HP and 9H arms respectively) and hepatotoxicity (2/132 and 7/131 events in 3HP and 9H arms respectively), but the number of events was small and would not change the results from the Sterling 2011 (15) trial. We therefore did not include this trial in the GRADE summary of evidence table.

Table 9. GRADE summary of evidence table for comparison 2a (adults) – 3HP vs INH - WHO TB Guidelines, 2020 (19)

3-month weekly rifapentine plus isoniazid or daily isoniazid monotherapy for treatment of LTBI in adults without HIV

Population: Adults without HIV
Comparison: 6 or 9 months of isoniazid monotherapy
Overall quality: moderate

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
ACTIVE TB												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious[2]	None	7/3986 (0.2%)	15/3745 (0.4%)	RR 0.438 (0.179;1.074)	2 fewer per 1000 (from 0 fewer to 3 fewer)	⨁⨁⨁◯ Moderate	Critical
ALL-CAUSE MORTALITY												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	None	31/3986 (0.8%)	39/3759 (1.0%)	RR 0.740 (0.462;1.183)	3 fewer per 1000 (from 2 more to 6 fewer)	⨁⨁⨁◯ Moderate	Important
ANY ADVERSE EVENTS (GRADE III OR IV)												
1 *(60)*	RCT	Serious[4]	Not serious	Serious[1]	Not serious	None	229/4040 (5.7%)	244/3759 (6.5%)	RR 0.873 (0.733;1.040)	8 fewer per 1000 (from 3 more to 17 fewer)	⨁⨁◯◯ Low	Critical
HEPATOTOXICITY												
1 *(60)*	RCT	Not serious[5]	Not serious	Serious[1]	Not serious	None	18/4040 (0.4%)	103/3759 (2.7%)	RR 0.163 (0.099;0.268)	23 fewer per 1000 (from 20 fewer to 25 fewer)	⨁⨁⨁◯ Moderate	Critical
DRUG-RESISTANT TB												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	None	1/3986 (0.0%)	2/3745 (0.1%)	RR 0.470 (0.043;5.179)	0 fewer per 1000 (from 1 fewer to 2 more)	⨁⨁⨁◯ Moderate	Important
COMPLETION RATE												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious	None	3273/3985 (82.1%)	2585/3745 (69.0%)	RR 1.190 (1.159;1.221)	131 more per 1000 (from 110 more to 153 more)	⨁⨁⨁◯ Moderate	Critical

[1] No comparison with 6 months of isoniazid. The study included 2.7% HIV-positive participants. Although the trial was conducted in low TB incidence countries, this is unlikely to affect relative effect of rifapentine + isoniazid compared with isoniazid monotherapy. Downgraded by one level.
[2] Although the 95% CI of RR is wide, the number of events was small and the CI of absolute effect is narrow. The result also met pre-stated non-inferiority margin. Not downgraded.
[3] Although the 95% CI of RR is wide, the number of events was small and the CI of absolute effect is narrow. Not downgraded.
[4] An open-label design of the trial may have introduced ascertainment bias.
[5] Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

- ***Comparison 2b: 3HP vs no treatment***

Elderly (50 – 69 years)

Gao 2018 (17) compared 3HP and 2HP to no treatment in an elderly population. Due to a high frequency of adverse events, the treatment arms were adjusted to HP weekly for 8 weeks and HP twice weekly for 6 weeks. Results are reported in Table 10.

Table 10: Results from Gao 2018 (17)

Outcome	Regimen A HP weekly for 8 weeks *	Regimen B HP twice weekly for 6 weeks *	No treatment	Statistical method	Effect size	GRADE
Active pulmonary TB	Cumulative incidence during 2 years of follow-up 10/1284 0.78% (95% CI 0.30–1.26%)	Cumulative incidence during 2 years of follow-up 6/1299 0.46% (95% CI 0.17–1.00%)	Cumulative incidence during 2 years of follow-up 14/1155 1.21% (95% CI 0.58-1.84%)	Adjusted HR	Regimen A: 0.63, 95%CI 0.27-1.43 Regimen B: 0.41, 95%CI 0.15-1.09 (Reg B)	⊕◯◯◯ Very low**
Death (adverse effects)	1/1279	0/1279		Chi square	p = 0.999	Not reported
Grade 3 drug-related toxic effects	30/1279	32/1279		Chi square	p = 0.797	Not reported
Grade 4/5 drug-related toxic effects	3/1279	1/1279		Chi square	p = 0.625	Not reported
Hepatotoxicity	13/1279	15/1279		Chi square	p = 0.704	Not reported

* Duration of treatment was reduced from 3 months to 8 weeks for regimen A and from 2 months to 6 weeks for regimen B due to high frequency of adverse events

**Downgraded for indirectness by one level: elderly population in China (50 – 69 years); Downgraded for risk of bias by one level: trial intervention amended due to high adverse event rate; Downgraded for imprecision: very low number of events and wide confidence interval

- ***Comparison 3a: 1HP vs INH***

1. **Incidence of TB disease:**
   There may be little or no difference in incidence of active TB between those who receive 1HP and those who receive INH monotherapy, Incidence Rate Difference per 100 person-years 0.058 (95% CI -0.240 to 0.350), 1 trial, n = 2986, low certainty evidence.
2. **All-cause mortality:**
   All-cause mortality was not reported. Here we report on incidence of active TB or death from any cause: there may be little or no difference in incidence of active TB or death from any cause between those who receive 1HP and those who receive INH monotherapy, Incidence Rate Difference per 100 person-years -0.13 (95% CI -0.52 to 0.27), 1 trial, n = 2986, low certainty evidence.
3. **Adverse events:**
   a) **Grade 3 or higher (nausea, vomiting, rash, drug-associated fever, elevated liver-enzymes and peripheral neuropathy)**
      There may be little or no difference in grade III or higher adverse events between those who receive 1HP and those who receive INH monotherapy, RR 0.86 (95% CI 0.58 to 1.27), 1 trial, n = 2986, low certainty evidence.
   b) **Serious adverse events**
      There may be little or no difference in serious adverse events between those who receive 1HP and those who receive INH monotherapy, RR 0.79 (95% CI 0.59 to 1.04), 1 trial, n = 2986, low certainty evidence.
4. **Isoniazid resistance:**
   We are uncertain about the effect of TPT on development of INH resistance, RR 1.63 (95% CI 0.17 to 15.99), 1 Trial, n = 26, very low certainty evidence.
5. **Incidence of TB infection:**
   Not reported

The GRADE summary of evidence table for this comparison is available in appendix 3.

BUDGET IMPACT ANALYSIS

Refer to the Budget Impact Analysis report, 21 June 2022.

Cost effectiveness analysis

No cost-effectiveness analysis was conducted specifically to inform this review. In response to the stakeholder consultation, one of the stakeholders submitted preliminary modeling estimates of the costs and cost-effectiveness of 3HP as delivered through IMPAACT4TB, an initiative to promote the scale-up of 3HP among people living with HIV and household contacts of people with detected TB disease. Their results indicate that 3HP is likely to be a cost-effective intervention for household contacts compared to current standard of care in South Africa (incremental cost-effectiveness ratio [ICER]: R10 412).

While this is a useful indicative analysis, the scope of their analysis does not completely align with the EML review question. In addition, there is considerable uncertainty regarding the ICER calculation and model parameters and structure. A full review of the analytical model (only a report was submitted) and more comprehensive examination of clinical and cost assumptions will be required to provide detailed feedback on the applicability and potential to adapt the IMPAACT4TB cost-effectiveness analysis to this medicine review decision. It should however be noted that It is not possible to use a single ICER output of a cost-effectiveness analysis to determine if an intervention is cost effective in the South African setting in absolute terms given the absence of an established cost effectiveness threshold to guide decision making.

EXTERNAL STAKEHOLDER ENGAGEMENT

On receipt of eternal comments, engagement was held with TB advocacy groups (TB proof and TB thinktank), including a collaborative meeting on 21 April 2022. Concerns raised and data presented in these discussions have been considered in updating this review.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** **INH vs placebo** High ☐ Moderate ☒ Low ☐ Very low ☐ **3HP vs INH** High ☐ Moderate ☒ Low ☐ Very low ☐ **1HP vs INH** High ☐ Moderate ☐ Low ☒ Very low ☐ **3HP vs no treatment** High ☐ Moderate ☐ Low ☐ Very low ☒ *High quality: confident in the evidence* *Moderate quality: mostly confident, but further research may change the effect* *Low quality: some confidence, further research likely to change the effect* *Very low quality: findings indicate uncertain effect*	INH vs placebo (See GRADE summary of evidence table for comparison 1) • Incidence of active TB: moderate certainty • All-cause mortality: moderate certainty 3HP vs INH (See GRADE summary of evidence table for comparison 2) • Incidence of active TB: moderate certainty • All-cause mortality: moderate certainty 1HP vs INH (See GRADE summary of evidence table for comparison 3) • Incidence of active TB: low certainty • Incidence of active TB or death: low certainty 3HP vs no treatment (See Table 7) • Incidence of active TB: very low certainty
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** *Outcome: Reduced incidence of TB disease* • ***Compared to placebo:*** **INH vs placebo** Large ☐ Moderate ☐ Small ☒ None ☐ **3HP vs no treatment** Large ☐ Moderate ☐ Small ☐ None ☐ Uncertain ☒ • ***Compared to INH:*** **3HP vs INH** Large ☐ Moderate ☐ Small ☐ None ☒ **1HP vs INH** Large ☐ Moderate ☐ Small ☐ None ☒	INH vs placebo (See GRADE summary of evidence table for comparison 1) • Reduced incidence of active TB: RR 0.4 (95% CI 0.31 to 0.52); 0.6% (INH) vs 1.7% (placebo); NNT=91 (95% CI 82 to 109). Assuming that the relative risk reduction remains constant, the anticipated NNT for a low (1%), moderate (2%) and high (5%) proportion with active TB in the comparison group are 167 (95% CI 143 to 200), 83 (95% CI 71 to 100) and 33 (95% CI 29 to 42) respectively. • No difference in all-cause mortality: RR 1.10 (95% CI 0.94 to 1.28) 3HP vs INH (See GRADE summary of evidence table for comparison 2) • No difference in incidence of active TB: RR 0.132 (95% CI 0.007 to 2.542) in children and adolescents; RR 0.438 (95% CI 0.179 to 1.074) in adults • No difference in all-cause mortality: RR 0.183 (95% CI 0.009 to 3.802) in children and adolescents; RR 0.740 (95% CI 0.462 to 1.183) in adults 1HP vs INH (See GRADE summary of evidence table for comparison 3) • No difference in incidence of active TB: Incidence Rate Difference per 100 person-years 0.058 (95% CI -0.240 to 0.350) • Incidence of active TB or death: Incidence Rate Difference per 100 person-years -0.13 (95% CI -0.52 to 0.27) 3HP vs no treatment (See table 7) • Uncertain impact on incidence of active TB: Adjusted HR 0.63 (95% CI 0.27 to 1.43) for once weekly HP for 8 weeks – add other effect sizes Specific subgroups, such as HIV-positive household contacts, may benefit more, but the current evidence doesn't permit robust assessments of this.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** **INH vs placebo** High ☐ Moderate ☒ Low ☐ Very low ☐ **3HP vs INH** High Moderate Low x Very low **1HP vs INH**	INH vs placebo (See GRADE summary of evidence table for comparison 1) • TPT related hepatitis: moderate certainty • Grade III/IV adverse events: not reported 3HP vs INH (See GRADE summary of evidence table for comparison 2) • TPT related hepatitis: moderate certainty • Grade III/IV adverse events: low certainty of evidence 1HP vs INH (See GRADE summary of evidence table for comparison 3)

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
	High Moderate Low x Very low *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	• TPT related hepatitis: not reported • Grade III/IV adverse events: low certainty of evidence • Serious adverse events: low certainty of evidence 3HP vs no treatment • Not reported
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** *Outcome: TPT related hepatitis* **INH vs placebo** Large Moderate x Small None **3HP vs INH** Large Moderate X Small None **1HP vs INH** Large Moderate Small X None	INH vs placebo (See GRADE summary of evidence table for comparison 1) • Increased TPT related hepatitis: RR 5.54 (95% CI 2.56 to 12.00); 5 more per 1,000 (from 2 more to 11 more) 3HP vs INH (See GRADE summary of evidence table for comparison 2) • TPT related hepatitis reduced in 3HP compared to INH RR 0.163 (95% CI 0.099 to 0.268) 23 fewer cases of hepatotoxicity per 1000 people who receive 3HP compared to those who receive INH monotherapy (ranging from 20 fewer to 25 fewer). No events in children and adolescents. • No difference in Grade III/IV adverse events: RR 0.875 (95% CI 0.320 to 2.396) in children and adolescents; RR 0.873 (95% CI 0.733 to 1.040) in adults 1HP vs INH (See GRADE summary of evidence table for comparison 3) • TPT related hepatitis: Not reported - Extrapolated from 1 RCT in PLHIV • No difference in Grade III/IV adverse events: RR 0.86 (95% CI 0.58 to 1.27) • No difference in serious adverse events: RR 0.79 (95% CI 0.59 to 1.04) 3HP vs no treatment • Not reported
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention Favours control Intervention = Control *or* Uncertain X	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a	Should expanding TPT to all household contacts be recommended, consideration could be given to potential option of 3HP rather than INH as it performs similarly to INH but has different requirements that may improve feasibility/ acceptability.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes No Uncertain X	Capacity of current resources possibly insufficient and service delivery platform would need to be capacitated/ funded. Concerns of uptake of this parallel programme. To consider LTBI testing: To consider capacity to exclude TB disease before initiation of TPT, noting that in the 2018 National TB prevalence survey, 58% of culture confirmed TB cases were asymptomatic. From the WHO 2020 TPT guideline, ***"The GDG noted that the capacity of the health caregiver to assess the intensity of exposure, risk of infection and reinfection, the risk for development of active TB, and the ascertainment of LTBI by testing, as well as capacity to weigh harm versus benefit of treatment and ability to exclude active TB disease before initiation of treatment are important considerations in the implementation of these recommendations."*** The committee with insights from the programme considered that there are substantial barriers to introducing TPT. There were concerns about impact of implementation of this

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
		intervention on treatment of active TB. TPT coverage of children < 5years in SA was low 56% in 2019 (1) and 51% in 2020. Possible reasons include poor tracing of household contacts (particularly where healthcare providers are scarce), high transport costs for patients to get to clinics for treatment, and low acceptability among caregivers of these children. These barriers may apply to expanding household contact TPT beyond under 5s
RESOURCE USE	**How large are the resource requirements?** More intensive: X Less intensive: Uncertain:	**Refer to the Budget Impact analysis report, 21 June 2022.** Net cost of providing TPT for all ages for one year (total costs – pharmaceutical, healthcare, adverse effects, costs averted): INH monotherapy for all ages: R148,577,833 3HP for >2y, INH monotherapy for <2y: R136,418,923 1HP for >13y, INH monotherapy for <13y: R165,638,824 *Estimation of total health care costs very uncertain due to significant uncertainty in budget impact model parameters.* Net pharmaceutical acquisition cost of providing TPT for all ages for one year : INH monotherapy for all ages: R18,265,490 3HP for >2y, INH monotherapy for <2y: R72,886,084 1HP for >13y, INH monotherapy for <13y: R111,735,429
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: Major: Uncertain: x **Is the option acceptable to key stakeholders?** Yes: No: Uncertain: x	There is no available local survey or qualitative data as this has not yet been introduced. Indirect evidence from a study conducted in South Africa, in KwaZulu-Nata in people living with HIV suggested several barriers to acceptability of TPT such as economic hardship, potential for stigma and cultural perceptions of TPT as introducing 'dirt' / toxins (Boffa 2019). Overall, we uncertain whether healthy individuals would find it acceptable to take a course of TPT, and what the implication may be in terms of access, social stigma and costs to visit clinics. We are uncertain of the impact and acceptability of additional workload for healthcare workers, and uncertain of community healthcare workers' involvement in the Programme. The committee considered that it is possible that focus on expanding TPT may give rise to a false sense of security, detracting from spending on social interventions and other measures of infection prevention and control.
EQUITY	**Would there be an impact on health inequity?** Yes: No: Uncertain: x	Other socio-economic factors need to be considered and TPT may possibly provide a false sense of security amongst contacts and providers. Access to TPT close to where people need it may be challenging in less urban settings.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	18 November 2021	JN, KC, SVW, TK, NB, MW, TL	TB preventive therapy for household contacts (beyond the current National policy that recommends TPT for uninfected children <5 years, exposed to a close contact of infectious pulmonary TB or LTBI confirmed on TST) not be recommended. Risk-benefit assessment, logistic and budget requirements does not favour expansion of the current TPT programme.

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Appendix 1 – Search Strategy

Epistemonikos (19 May 2021)

Search strategy: (title:((tuberculosis OR TB) AND isoniazid) OR abstract:((tuberculosis OR TB) AND isoniazid))
Filtered by: Publication type: Systematic review; Systematic review question: Interventions
Records retrieved**:** 21 studies
Found no RCTs from 2018 onwards

Cochrane Central Register of Controlled Trials (CENTRAL), Issue 4 of 12, April 2021 (19 May 2021)

ID	Search	Hits
#1	[mh tuberculosis] or tuberculosis:ti,ab,kw or TB:ti,ab,kw	7903
#2	[mh isoniazid] or isoniazid:ti,ab,kw	1746
#3	#1 and #2 with Publication Year from 2018 to 2021, in Trials	230

Cochrane Library, Issue 5 of 12, May 2021 (19 May 2021)

ID	Search	Hits
#1	[mh tuberculosis] or tuberculosis:ti,ab,kw or TB:ti,ab,kw	7903
#2	[mh isoniazid] or isoniazid:ti,ab,kw	1746
#3	#1 and #2 in Cochrane Reviews	16

Pubmed (19 May 2021)

Search	Query	Results
#8	Search: (#3 AND #4 AND #5) NOT (animals[mh] NOT humans[mh]) Filters: from 2018/1/1 - 2021/5/19 Sort by: Most Recent	**837**
#7	Search: (#3 AND #4 AND #5) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	**8,472**
#6	Search: #3 AND #4 AND #5 Sort by: Most Recent	**9,081**
#5	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] Sort by: Most Recent	**5,073,720**
#4	Search: isoniazid[mh] OR isoniazid[tiab] Sort by: Most Recent	**25,384**
#3	Search: #1 OR #2 Sort by: Most Recent	**249,576**
#2	Search: tuberculosis[tiab] OR TB[tiab] Sort by: Most Recent	**240,480**
#1	Search: "Tuberculosis/drug therapy"[mh] OR "Tuberculosis/prevention and control"[mh] Sort by: Most Recent	**52,684**

Search	Query	Results
#7	Search: (#3 AND #4) NOT (animals[mh] NOT humans[mh]) Filters: Systematic Review Sort by: Most Recent	127
#6	Search: (#3 AND #4) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	16,948
#5	Search: #3 AND #4 Sort by: Most Recent	18,220
#4	Search: isoniazid[mh] OR isoniazid[tiab] Sort by: Most Recent	25,384
#3	Search: #1 OR #2 Sort by: Most Recent	249,576
#2	Search: tuberculosis[tiab] OR TB[tiab] Sort by: Most Recent	240,480
#1	Search: "Tuberculosis/drug therapy"[mh] OR "Tuberculosis/prevention and control"[mh] Sort by: Most Recent	52,684

Appendix 2

Table 6: Breakdown of Smieja trials – INH vs placebo						
Study	**Participants**		**Total events (%) Treatment**	**Total events (%) Control**	**RR (95% CI)**	**NNT (95% CI)**
Egsmose 1965	Contacts	**Kenyan** Contacts of active TB cases **Excluded previous TB**	7/325 (2%)	18/301 (6%)	0.36 (0.15; 0.85)	26 (14; 130)
Ferebee 1962		**US:** Household contacts of newly diagnosed reported tuberculosis **52% skin test negative** 2/3 under 20 years old	8/8478 (0,1%)	36/8311 (0,4%)	0.22 (0.1; 0.47)	297 (204; 547)
Mount 1962		**US:** Household contacts of known TB cases – exposure had taken place months to years earlier, **previous TB excluded** **55% PPD<5mm** 1/3 children 60% black	6/1462 (0,4%)	12/1348 (0,9%)	0.46 (0.17; 1.22)	208 (906 harm; 93 benefit)
Del Castillo 1965		**Phillippines:** HH contacts of recently diagnosed index cases treated at Quezon Institute **83% skin test positive**	16/126 (13%) [8/16 (50%) initially skin test positive)	22/167 (13%) [18/22 (82%) initially skin test positive)	0.96 (0.53;1.76)	210 (14 harm; 12 benefit)
Ferebee 1963	Patients from institutions	**US:** Patients in 37 country institutions for chronic psychiatric or mentally retarded in Wisconsin, Georgia, and Massachusetts, USA **PPD>5mm in 50%** **91% had normal CXR**, 9% abnormal at baseline Age 2-100 Mean age 48 (men); 54 (women) >85% white	61/12339 (0,5%)	173/12499 (1,3%)	0.36 (0.27;0.48)	112 (89;154)
Comstock 1962	Villagers	**Alaskan** villagers in 28 villages and 2 boarding schools **45% Previous TB exposure, as judged by CXR and skin testing** Infants 2 months and older were included	50/2480 (2%)	128/2406 (5%)	0.38 (0.27;0.52)	30 (23;44)
Veening 1968	Recent skin test converters	Royal Netherlands Navy barracks **PPD positive contacts of active cases; recent, over 3 month period skin test converters** Aged 18-20 years	1/133 (0.8%)	12/128 (9%)	0.8 (0.01;0.61)	12 (7;29)
Falk 1978	Clinical risk groups	US: VA hospitals; **abnormal CXR, no previous TB treatment** 98% Men Mostly 30-50 years old 77% white	5/889 (0.6%)	15/772 (2%)	0.3 (0.11;0.81)	74 (42;329)
Girling 1992		**Chinese** men with **silicosis** in Hong Kong Most 45-64 **63% current smokers** **94% > 10mm** All had abnormal CXRs; no history TB, negative sputum microscopy and culture	20/100 (20%)	34/99 (34%)	0.58 (0.36;0.94)	7 (4;47)
John 1994		**India: Transplant or dialysis patients**	7/92 (8%)	10/92 (11%)	0.7 (0.28;1.76)	31 (20 harm;9 benefit)

Thompson 1982		**Eastern Europe:** 115 clinics Czechoslovakia, Finland, German Democratic Republic, Hungary, Poland, Romania, Yugoslavia **Attending chest clinic, abnormal CXR:** evidence of previous TB – fibrotic changes, no previous treatment, no previous positive bacteriology **PPD>6mm** Mean age 50 (20-65) 1/3 were age 55-65	58/13838 (0.4%)	97/6990 (1.4%)	0.3 (0.22;0.42)	103 (82;139)

Appendix 3 - GRADE summary of evidence table for comparison 3a – WHO TB Guidelines, 2020 (19)

PICO 7: In people of all ages at risk of active TB, does a 1-month daily rifapentine plus isoniazid regimen safely prevent TB disease compared to other recommended TB preventive treatment regimens?

Population: PLHIV at increased risk of active TB
Overall quality: low
Bibliography: (see reference 57)
Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, et.al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis, N Engl J Med. 2019 Mar 14;380(11):1001-1011. doi: 10.1056/NEJMoa1806808.[a]

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious[b,c]	not serious	serious[d]	not serious	none	29/1488 (1.9%)	26/1498 (1.7%)	Incidence Rate Difference per 100 person-years 0.058 (-0.240 to 0.350)	-	⨁⨁◯◯ LOW	CRITICAL
INCIDENCE OF ACTIVE TB AMONG ART-NAIVE PARTICIPANTS AT ENTRY (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious[b,c]	not serious	serious[d]	not serious	none	17/740 (2.3%)	15/746 (2.0%)	Incidence Rate Difference per 100 person-years 0.07 (-0.37 to 0.51)	-	⨁⨁◯◯ LOW	CRITICAL
INCIDENCE OF ACTIVE TB AMONG TST OR IGRA POSITIVE PARTICIPANTS AT ENTRY (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious[b,c]	not serious	serious[d]	not serious	none	9/337 (2.7%)	10/349 (2.9%)	Incidence Rate Difference per 100 person-years -0.069 (-0.830 to 0.690)	-	⨁⨁◯◯	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF BACTERIOLOGICALLY CONFIRMED TB (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious[c,e]	not serious	serious[d]	not serious	none	18/1488 (1.2%)	14/1498 (0.9%)	Incidence Rate Difference per 100 person-years 0.08 (-0.15 to 0.31)	-	⨁⨁◯◯ LOW	CRITICAL
TIME TO TB DIAGNOSIS OR DEATH RELATED TO TB, WITH OTHER DEATHS TREATED AS COMPETING RISK (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION))												
1	randomised trials	serious[f]	not serious	serious[d]	not serious	none	1488 participants	1498 participants	HR 1.10 (0.65 to 1.87) [Time to TB diagnosis or death related to TB, with other deaths treated as competing risk]	2 more per 1,000 (from 6 fewer to 15 more)	⨁⨁◯◯ LOW	CRITICAL
							-	1.7% g		2 more per 1,000 (from 6 fewer to 15 more)		
INCIDENCE OF ACTIVE TB OR DEATH DUE TO UNKNOWN CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION))H												
1	randomised trials	serious[i]	not serious	serious[d]	not serious	none	32/1488 (2.2%)	33/1498 (2.2%)	Incidence Rate Difference per 100 person-years -0.023 (-0.350 to 0.300)	-	⨁⨁◯◯ LOW	CRITICAL
INCIDENCE OF ACTIVE TB OR DEATH DUE TO UNKNOWN CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (PER-PROTOCOL POPULATION))												
1	randomised trials	serious[i]	not serious	serious[d]	not serious	none	31/1456 (2.1%)	29/1381 (2.1%)	Incidence Rate Difference per 100 person-years 0.021 (-0.300 to 0.340)	-	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB OR DEATH FROM ANY CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION))												
1	randomised trials	serious [c]	not serious	serious [d]	not serious	none	45/1488 (3.0%)	51/1498 (3.4%)	Incidence Rate Difference per 100 person-years -0.13 (-0.52 to 0.27)	-	⨁⨁◯◯ LOW	CRITICAL
TIME TO DEATH FROM ANY CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c,l]	not serious	serious [d]	not serious	none	1488 participants	1498 participants	HR 0.75 (0.42 to 1.31) [Time to death from any cause]	5 fewer per 1,000 (from 11 fewer to 6 more)	⨁⨁◯◯ LOW	CRITICAL
							-	1.9% [g,l]		5 fewer per 1,000 (from 11 fewer to 6 more)		
TIME TO DEATH FROM TUBERCULOSIS (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	serious [d]	serious [k]	none	3/1488 (0.2%)	3/1498 (0.2%)	HR 1.00 (0.20 to 4.93)	0 fewer per 1,000 (from 2 fewer to 8 more) l	⨁⨁◯◯ VERY LOW	CRITICAL
ADVERSE EVENTS (GRADE 3 OR HIGHER OF NAUSEA, VOMITING, RASH, DRUG-ASSOCIATED FEVER, ELEVATED LIVER-ENZYMES AND PERIPHERAL NEUROPATHY) (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	serious [d]	not serious	none	44/1488 (3.0%)	52/1498 (3.5%)	RR 0.86 (0.58 to 1.27)	5 fewer per 1,000 (from 15 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
SERIOUS ADVERSE EVENTS (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	serious [d]	not serious	none	83/1488 (5.6%)	108/1498 (7.2%)	RR 0.79 (0.59 to 1.04)	15 fewer per 1,000 (from 30 fewer to 3 more)	⨁⨁◯◯ LOW	CRITICAL
TREATMENT COMPLETION (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c,m]	not serious	serious [d]	not serious	none	1444/1488 (97.0%)	1341/1498 (89.5%)	RR 1.04 (0.99 to 1.10)	36 more per 1,000 (from 9 fewer to 90 more)	⨁⨁◯◯ LOW	CRITICAL
TREATMENT COMPLETION AMONG ART-NAIVE PARTICIPANTS AT ENTRY (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c,m]	not serious	serious [d]	not serious	none	720/740 (97.3%)	656/743 (88.3%)	RR 1.05 (0.97 to 1.14)	44 more per 1,000 (from 26 fewer to 124 more)	⨁⨁◯◯ LOW	CRITICAL
EMERGENCE OF DRUG RESISTANCE TO ISONIAZID AMONG THOSE WITH CONFIRMED TB AND WITH DST (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	2/14 (14.3%)	1/12 (8.3%)	RR 1.63 (0.17 to 15.99)	52 more per 1,000 (from 69 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
EMERGENCE OF DRUG RESISTANCE TO RIFAMPICIN AMONG THOSE WITH CONFIRMED TB AND WITH DST (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	1/15 (6.7%)	1/12 (8.3%)	RR 0.81 (0.06 to 11.77)	16 fewer per 1,000 (from 78 fewer to 898 more)	⨁◯◯◯ VERY LOW	IMPORTANT
EMERGENCE OF DRUG RESISTANCE TO ETHAMBUTOL AMONG THOSE WITH CONFIRMED TB AND WITH DST												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	0/7 (0.0%)	1/7 (14.3%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
EMERGENCE OF DRUG RESISTANCE TO PYRAZINAMIDE AMONG THOSE WITH CONFIRMED TB AND WITH DST (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	0/6 (0.0%)	0/6 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

[a] Randomized, open-label, phase 3 noninferiority trial comparing the efficacy and safety of a 1-month regimen of daily rifapentine plus isoniazid (1-month group) with 9 months of isoniazid alone (9-month group) in HIV-infected patients who were living in areas of high tuberculosis prevalence or who had evidence of latent tuberculosis infection. Primary end point was the first diagnosis of TB or death from TB or an unknown cause. Noninferiority would be shown if the upper limit of the 95% confidence interval for the between-group difference in the number of events per 100 person-years was less than 1.25. LTBI was not confirmed in about 80% of participants. Enrolment restricted to individuals ≥13 years old who were not pregnant or breastfeeding. Overall TB incidence observed in the trial was lower than expected. The number of patients with a CD4+ <250 cells per cu mm was small, and neither inferiority nor noninferiority of the 1-month regimen was shown in this stratum.

[b] Unknown cause of death censored in this analysis, which may cause bias in incidence rate difference if some of these deaths were related to TB (dependent censoring)

[c] The GDG decided to downgrade by one level because of the open label design possibly leading to performance bias. The quality was not downgraded for Indirectness, but the GDG noted that the trial compared 1HP with 9H and therefore did not cover all other comparisons of the PICO, especially 6H, the most widespread standard of care in TB preventive treatment. The GDG noted that Inconsistency could not be judged given that there was only a single trial; results from more trials would be desirable.

[d] Trial conducted only in PLHIV and not in all people at risk of active TB.

[e] Probable TB diagnoses and deaths with non-bacteriologically confirmed TB censored at the time of event

[f] When cause of death was determined to be unknown or not related to TB by blinded external reviewers, these were treated as a competing risk rather than endpoint. Some of these may have actually been due to TB, which may bias estimate.

[g] The proportion of events among controls

[h] Per-protocol population consisted of all participants who completed treatment, or who had died or received a TB diagnosis while they were receiving treatment.

[i] Deaths were reviewed by blinded external reviewers. Unknown causes of death were included as an endpoint, but misclassification of cause of death may bias estimate

[j] There were 21 deaths in the one-month arm, 3 related to TB. There were 28 deaths in the nine-month arm, 3 related to TB.

[k] Small number of events

[l] Incidence Rate Difference per 100 person-years of 0.00 (-0.10 to 0.10)

[m] Assessed via participant self-report at clinic visits

[n] Resistance may be non-emergent and coming from infecting strain

[o] Small sample of bacteriologically confirmed TB who had drug susceptibility test results