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Review Article

Public Health Section

Efficacy of Short-course Weekly Isoniazid and Rifapentine Regimen as Tuberculosis Preventive Treatment among Population at Risk of Developing Disease: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Tuberculosis (TB) remains a major public health problem in India. Individuals with latent infection do not have active disease and cannot spread Tuberculosis Infection (TBI). The prevalence of latent TB in India is very high, ranging from 40-50%. About 5 to 10% of them may convert into active TB disease. The national program primarily recommends treatment for active TB, while treatment of latent TB is recommended only in special situations.

Aim: To assess the efficacy of short-course weekly Isoniazid and Rifapentine (HP) regimen as Tuberculosis Preventive Treatment (TPT) among various risk groups.

Materials and Methods: A systematic review and meta-analysis were conducted, involving of about 10 Randomised Control Trials (RCTs). Studies published between 2006 and 2023 were included. Online databases such as PubMed, Google Scholar, Clinical Trial Registry India, and grey literature were searched using keywords like Isoniazid, Rifapentine, and trial.

Results: In terms of TB incidence, the pooled risk ratio favoured the weekly HP regimen, estimated at 0.69 (0.49, 0.97, 95% CI). Regarding the incidence of hepatotoxicity, the weekly HP regimen showed neither superiority nor inferiority to comparators, with a pooled risk ratio of 0.50 (0.23, 1.05, 95% CI). The odds of completing treatment were 2.19 times greater for the weekly HP regimen than for controls, with a pooled odds ratio of 2.19 (1.64, 2.92; 95% CI).

Conclusion: The weekly HP regimen is superior to other regimens in reducing the incidence of TB. Additionally, the duration of the HP regimen is shorter compared to the commonly advised nine-month Isoniazid regimen. Compared with the daily dosage of Isoniazid, the weekly HP regimen offers better compliance. It also exhibits a significantly higher treatment completion rate. In summary, the weekly HP regimen is superior to other regimens.

Keywords: Immunity, Latent tuberculosis, *Mycobacterium tuberculosis*, National tuberculosis programme, Tuberculosis preventive treatment regimine

INTRODUCTION

TB is an airborne disease caused by *Mycobacterium tuberculosis (M. tuberculosis)*. Despite being an age-old disease, it remains a major public health problem in developing countries like India. India has the highest burden of TBI. It has been estimated that nearly 35-40 crores of people in India may have TBI, with around 25 lacs of victims developing TB disease annually. On an average, 5-10% of those infected may develop TB disease over time [1]. The risk of developing the disease is higher among populations at risk, defined as a group of individuals susceptible to an event like infection, disease, or death during the time period of interest. This group involves apparently healthy people, those with health problems, and individuals at the extremes of age, mainly newborns, children, and elderly persons [2].

Latent TBI (LTBI) is a condition characterised by a positive tuberculin skin test in patients who show no clinical or radiological features suggestive of active disease. Persons with LTBI do not have active disease and cannot spread infection to others. The prevalence of LTBI in India is very high, ranging from 40-50% in various populations, indicating that at any given time, >500 million population would have latent TB in the country. However, only 5 to 10% of these cases may convert into active disease in one's lifetime, primarily when their immunity is low. Our environment carries a heavy load of *M. tuberculosis* and is the largest source of TB in India. Therefore, despite the high prevalence of latent TB in a heavily populated country like ours, the national program recommends treatment only for active TB, reserving treatment of latent TB for special situations [3].

TB affects people of both sexes and all age groups, but the highest burden is seen in adult men, who account for 56% of all TB cases. The greatest percentage of cases is found in the age range of 25 to 54 years. However, in the Eastern Mediterranean, South-East Asia, and Western Pacific regions, the TB epidemic is most prevalent among elderly people. In these regions, the notification rate progressively increases with age, reaching its peak at 65 years or older. Most cases of TB in elderly people are associated with the reactivation of dormant lesions. The awakening of these lesions is attributed to changes in the immune system related to senescence, notably the decline in the ability to reactivate previously acquired immunity, and/or additional factors [4].

The risk of developing the disease from an infection depends on various factors, with the most important being the individual's immunity status. This risk is increased more than 25 times among contacts of confirmed TB patients, 16-21 times in the case of HIV co-infection, and 3-4 times in other immunocompromised states like diabetes, etc., [1]. Worldwide, new recommendations to expand

TPT to populations beyond those currently recommended by the WHO, such as healthcare workers, migrants, people with diabetes mellitus, and other vulnerabilities (like elderly people), are gaining augmented.

New guidelines for the Programmatic Management of TPT (PMTPT) in India were released in July 2021 under the National TB Elimination Program (NTEP) by the Central TB Division, Ministry of Health and Family Welfare (MoHFW) in New Delhi, India. The program has identified certain populations at risk and prioritised them as the target population for whom TPT is recommended. TPT interventions can also be extended to other risk groups, provided they are guided by the state TPT committee based on the differential TB epidemiology, if the risk of active TB among them is higher than that of the general population in the respective states [1].

The daily Isoniazid regimen is the most widely used TPT for high-risk groups like people living with Human Immunodeficiency Virus (HIV) infection and children aged less than five years. In recent years, evidence on the efficacy and safety of newer, shorter TPT regimens has been growing worldwide, and the WHO has recommended multiple TPT options. The national program needs to move towards shorter, safer, and more effective regimens [1].

Available evidence shows similar preventive efficacy with a shorter Rifapentine-based TPT regimen, both in HIV-positive and HIV-negative individuals, as monotherapy or in combination with Isoniazid. The short-course weekly HP regimen was also associated with a higher completion rate in all subgroups [5]. Compared to the nine-month daily Isoniazid (9H) regimen, this regimen has a better completion rate, as evident from the studies conducted in Taiwan [6,7]. A systematic review on Adverse Events (AE) of Rifapentine and Isoniazid in comparison with other treatments for latent infection (23 RCTs and 55 non-randomised studies) shows a lower rate of AEs with 3HP [8].

Initially, TPT was restricted to high-risk groups such as people living with HIV and children aged less than five years, and Isoniazid monotherapy was commonly used within a narrow scope. In recent years, TPT has been expanded to other at risk groups, including children over 5 years, adolescents, and adult Household Contacts (HHC) of pulmonary TB patients, as well as other risk groups like individuals who are on immunosuppressive therapy, have silicosis, are on anti-Tumour Necrosis Factor (TNF) treatment, are on dialysis, or are preparing for organ or haematologic transplantation. Likewise, new short courses, especially multidrug combinations, are also available in addition to INH monotherapy. Although very few reviews [8-11] are available on short course regimens, no major reviews have been conducted after the release of guidelines of the programmatic management of TPT under NTEP by the Central TB Division, MoHFW, New Delhi. This review was conducted involving available risk groups as study participants.

The systematic review was conducted with the objective to assess the efficacy of the short-course weekly HP regimen as TPT among various risk groups. Results of the current review will aid public health personnel and practitioners in making decisions about new regimens.

MATERIALS AND METHODS

A systematic review and meta-analysis were conducted, involving 10 RCTs. The studies were published between 2006 and 2023. Online databases such as PubMed and Google Scholar, the Clinical Trial Registry India, and grey literature were searched using “Isoniazid,” “Rifapentine,” and “trial” as keywords.

Registration

The current systematic review (ID-CRD42023425276) has been registered in PROSPERO. PROSPERO is an international database of prospectively registered systematic reviews in health and social care, welfare, public health, education, crime, justice, and international development, where there is a health-related outcome. It aims to provide a comprehensive listing of systematic reviews registered at inception to help avoid duplication. It is produced by the Centre for Reviews and Dissemination, University of York, York, United Kingdom, and funded by the National Institute for Health Research (NIHR).

Types of Studies Considered

RCTs and clinical trials were included for the review. Mixed methods and other types like qualitative studies, were not considered.

Study Participants

Population at risk of developing disease either from latent infection or those who are apparently healthy with no active disease in the following settings:

1. People living with HIV (+ Anti-retroviral Therapy)
   - Adults and children aged more than 12 months
   - Infants aged less than or equal to 12 months with HIV in contact with active TB
2. Household Contacts (HHC) below five years of pulmonary TB patients (TPT to all after ruling out active TB disease)
3. Household Contacts five years and above of pulmonary TB patients (TPT among TBI positive after ruling out TB disease).
4. Individuals receiving immunosuppressive therapy, suffering from silicosis, recipients of anti-TNF treatment, on dialysis, preparing for organ or haematologic transplantation [1].
5. People at the extremes of age, namely newborns, children, and elderly persons [2].

Types of Interventions

RCTs with short-course weekly regimens of HP as interventions were included. Studies with interventions of varying combinations of drugs along with HP were excluded.

Types of Outcome Measures

The reduction in the incidence of TB was the primary measurement in the review. In addition, the rate of treatment completion and the incidence of hepatotoxicity were also measured [Table/Fig-1] [12-21].

Search Methods

Online databases, such as PubMed and Google Scholar, were searched for relevant studies. In the case of PubMed, “Rifapentine” and “Isoniazid” were the keywords used. The Boolean operator “AND” and filters for clinical trials and RCTs were applied, resulting in the identification of approximately 55 studies. In the case of Google Scholar, “Rifapentine,” “Isoniazid,” and “Trial” were the keywords used. On applying “All in Title” as the search operator, around 24 studies were identified. When searching for studies in the Clinical Trials Registry India, “Rifapentine” either along with “Isoniazid” or alone was the keyword used. On applying Word Matching Criteria for Intervention and Comparator agents, about nine studies were identified [Annexure-1].

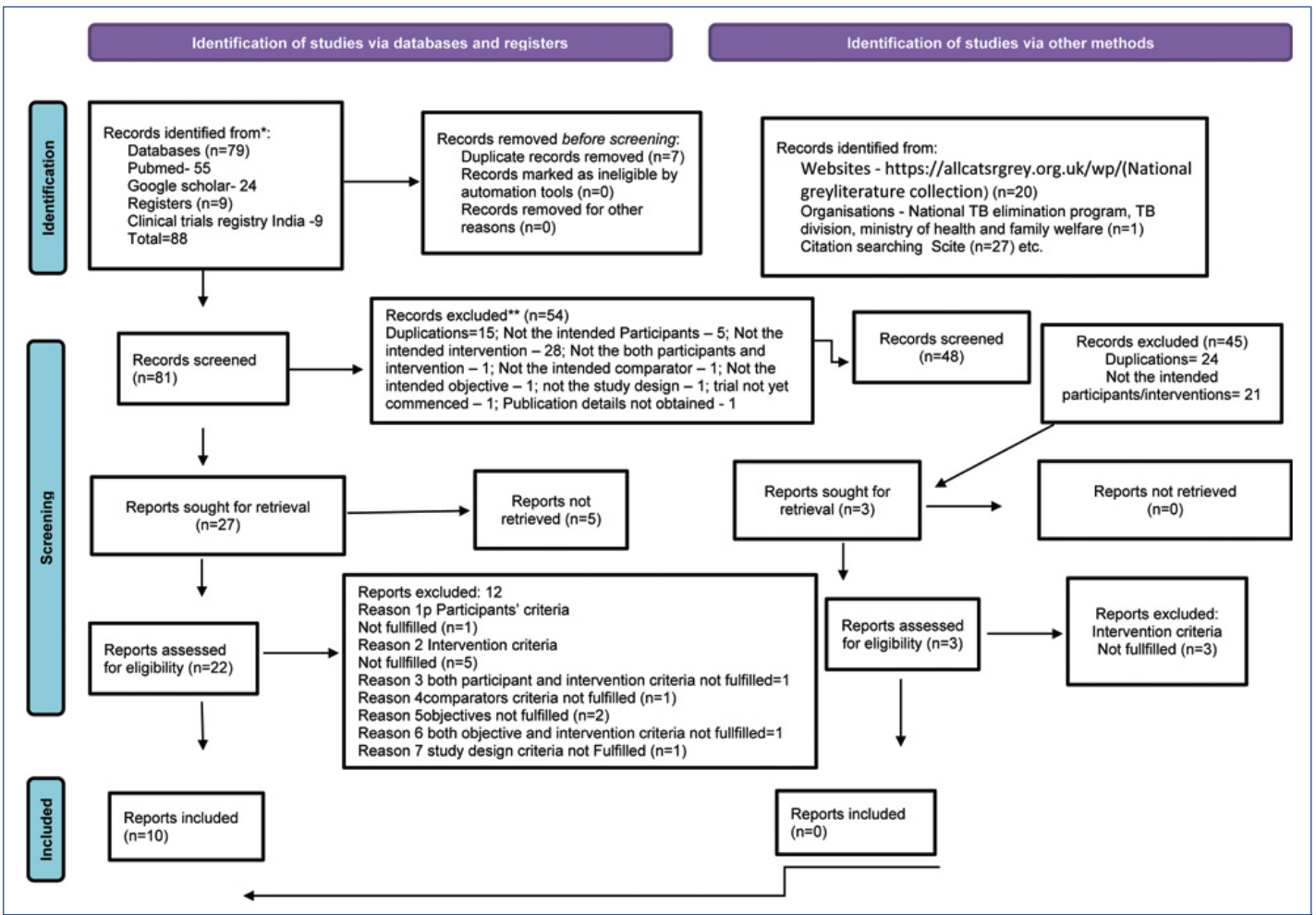
Grey literature was searched for unpublished data. The national grey literature collection’s website, https://allcatsrgrey.org.uk/wp/, was searched for suitable studies. “Rifapentine” and “Isoniazid” were the keywords used individually or in combination. At the end of the stepwise search [Annexure-1], 20 studies were identified. Guidelines for the programmatic management of TPT in India, released under NTBEP, TB division, MoHFW (https://tbcindia.gov.in/WriteReadData/l892s/Guidelines%20for%20Programmatic%20Management%20of%20TB%20Preventive%20Treatment%20in%20India.pdf), were scrutinised for operational definitions of TPT, latent infection, etc. Additionally, Scite, the citation searching page, was searched for related data. “Isoniazid,” “Rifapentine,” and “trial”

were the keywords used. On applying the filter for randomised clinical trials, approximately 27 studies were identified [Annexure-1].

After an extensive search, about 136 studies were identified as relevant. Before screening, about seven duplicate records were removed. During the screening process, about 99 studies were excluded due to various reasons, as mentioned in the PRISMA flow diagram displayed in [Table/Fig-2]. Among the remaining 30 studies, an endeavour was made to retrieve information about Rifapentine-based short course regimens. However, it was unable to retrieve the required information from approximately five studies. After the retrieval process, 25 studies remained, which were then screened for eligibility. The PICO (P- Participants, I- Intervention, C- Comparator,

S. No.	First author	Study design, type of analysis	Study period, follow-up	Study participants	Sample size-intervention	Sample size-control	Duration, frequency of HP therapy	Dose of HP therapy	Type of comparator	Number of TB cases in intervention	Number of TB cases in control
1	Gao L et al., [13]	RCT, PP and ITT	2015 to 2017, two years	Elderly people	1284	1155	Three months weekly	H-900 mg P-900 mg	H2P2, untreated	10	14
2	Martinson NA et al., [14]	RCT, PP and ITT	2002 to 2005, two years	HIV-infected adults	328	327	Three months weekly	H-900 mg P-900 mg	INH	24	22
3	Ruan QL et al., [15]	RCT, PP and ITT	2014 to 2017, three years	Silicosis patients	254	259	Three months weekly	H-900 mg P-900 mg	Untreated	9	19
4	Schechter M et al., [16]	RCT, PP and ITT	2001 to 2003, two years	Household contacts	206	193	Three months weekly	H-900 mg P-900 mg	RZ	4	1
5	Sterling TR et al., [17]	RCT, ITT	2001 to 2008, three years	Close contact with a patient with TB, Recent conversion to a positive tuberculin skin test, HIV infection	3986	3745	Three months weekly	H-900 mg P-900 mg	INH	7	15
6	Sterling TR et al., [18]	RCT, ITT	2001 to 2013, three years	HIV-infected persons, close contact	206	193	Three months weekly	H-900 mg P-900 mg	INH	2	6
7	Swindells S et al., [12]	RCT, PP and ITT	2012 to 2014, three years	HIV-infected persons, close contact	1488	1498	One month weekly	H-300 mg P-300-600 mg	INH	32	33
8	Villarino ME et al., [19]	RCT	2001 to 2010, three years	Children and adolescents	471	434	Three months weekly	H-100-300 mg P-300-900 mg	INH	0	3
9	Xin H et al., [20]	RCT, PP and ITT	2015 to 2020, five years	At risk middle aged and elderly population	1298	1151	Three months weekly	H-900 mg P-900 mg	H2P2, untreated	12	26
10	Zhang H et al., [21]	RCT, PP and ITT	2015 to 2018, two years	At risk individuals with inactive TB	345	332	1 1/2 months Bi-weekly	H-500-600 mg P-450-600 mg	Untreated	8	7

[Table/Fig-1]: Characteristic of studies - study design and type of analysis, study period and follow-up, study population, sample size, duration and frequency and dose of HP, comparator, TB cases [12-21].
RCT: Randomised control design; PP: Per protocol analysis; ITT: Intention to treat analysis; INH: Isoniazid; RZ: Rifampicin-pyrazinamide; HIV: Human immunodeficiency virus; TB: Tuberculosis



[Table/Fig-2]: PRISMA 2020 flow diagram, included searches of databases, registers and other sources.

O-Objective/Outcome) criteria were used to test eligibility. About 15 studies were found to be ineligible, and the remaining 10 studies were included in the review process [Table/Fig-2].

Data Extraction

Two reviewers independently screened the selected studies, applying eligibility criteria and extracting information about materials, methods, baseline characteristics, and measures of effects. Any disagreements were resolved independently by a third reviewer. The data extraction was performed using RevMan, a software tool.

Risk of Bias Assessment

The Cochrane risk of bias (RoB-2) tool is a recently revised instrument used to assess the risk of bias in the studies. Methods of randomisation, allocation concealment, masking, treatment allocation, deviation from intended treatment, missing outcome data, outcome measurement, and selection in reported results were assessed for risk of bias.

Meta-analysis

RevMan, the software tool, was used for meta-analysis of the data. Risk ratios for the incidence of active TB and hepatotoxicity were estimated, while the odds ratio was estimated for the treatment completion rate. Risk ratios or odds ratios of included studies were combined to produce a pooled effect using the random-effects model, and forest plots were synthesised. The Chi-square test and I^2 statistics were used to explore heterogeneity. A funnel plot was used to assess publication bias. Sensitivity analysis was performed to test the influence of any one or more of the studies on the pooled risk ratio. Subgroup analysis was conducted to compare the recently recommended weekly HP regimen with the standard daily Isoniazid regimen.

RESULTS

Characteristics of Studies

The studies were found to have been published between 2006 and 2023. All the studies were RCTs. Short-course weekly HP regimens were administered in the intervention groups, while the control groups received nine months of Isoniazid, Rifampicin-Pyrazinamide, or remained untreated [Table/Fig-1,3] [12-21].

Risk of Bias Assessment

[Table/Fig-4] provides information about the risk of bias in the studies included in the review. All of the studies had adequately minimised bias related to missing outcome data. Nearly all of the studies had appropriately measured the outcomes, and the majority of them had reported all expected results without any selection bias. In the case of the randomisation process, some concern of bias could not be ruled out in most of the studies. Some concern of deviation from the intended treatment was possible in most of the studies. Overall, about three-fourths of the studies were found to have some concern towards bias, while the remaining studies were at a potentially high-risk of bias.

Primary Outcome- Reduction in Incidence of TB

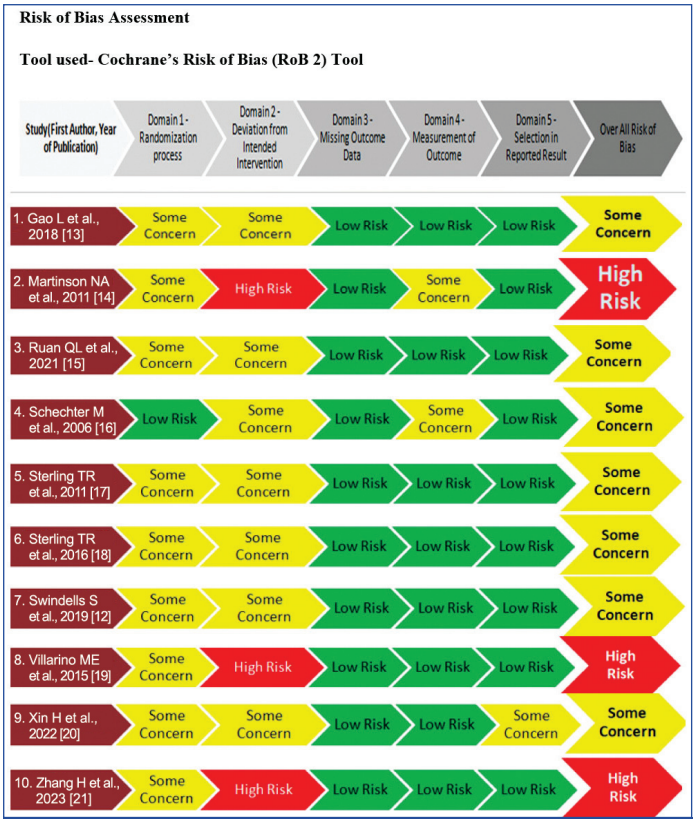
The outcomes of the studies are presented in [Table/Fig-5], while the forest plot for the reduction in the incidence of TB by the weekly HP regimen and comparators from the included studies is displayed in [Table/Fig-6]. These tables provide information about the risk ratios, along with their upper and lower limits for each study included. The pooled risk ratio for the weekly HP regimen is 0.69 (0.49, 0.97, 95% CI) when compared with other controls, indicating that the weekly HP regimen is comparable with others in reducing TB incidence. Furthermore, this difference was statistically significant, demonstrating that the weekly HP regimen is superior to any other regimen.

A sensitivity analysis was conducted to assess whether any of the studies influenced the pooled effect size. The forest plot displayed in [Table/Fig-6] shows that the study by Swindells S et al., carries more weight (19.5%) in the pooled effect size compared to other studies [9]. The sensitivity analysis was conducted after excluding this particular study.

Following the sensitivity analysis, the forest plot in [Table/Fig-7] indicates that the pooled risk ratio for the weekly HP regimen is estimated to be 0.63 (0.43, 0.93, 95% CI) when compared with other controls. This suggests that the weekly HP regimen remains comparable with others in reducing TB incidence. Furthermore, the difference is once again found to be statistically significant even after excluding the study that contributed relatively more weight. Therefore, the HP weekly regimen has been reaffirmed as superior to any other regimen.

S. No.	First author	Year of publication	Journal	Region	Study setting
1	Gao L et al., [13]	2018	European Respiratory Journal	China, Zhengzhou, Zhongmou County	Health and Epidemic Prevention Station, Zhengzhou, Henan province
2	Martinson NA et al., [14]	2011	New England Journal of Medicine	South Africa, Soweto	Community with a high prevalence of HIV infection and TB
3	Ruan QL et al., [15]	2021	Clinical Microbiology and Infection	China, Wenling	City, where the occupation of quarry worker is linked to silicosis
4	Schechter M et al., [16]	2006	American Journal of Respiratory and Critical Care Medicine	Brazil, Rio de Janeiro	Households contacts of patients with newly diagnosed pulmonary TB at public clinics
5	Sterling TR et al., [17]	2011	The New England Journal of Medicine	United States, Canada, Brazil, and Spain-countries with low to moderate TB incidence rates	Settings in which treatment of latent M.TBI is logistically feasible and a high public health priority
6	Sterling TR et al., [18]	2016	AIDS	The United States,, Brazil, Spain, Peru, Canada, and Hong Kong-countries with low to moderate TB incidence rates	Settings in which treatment of latent *Mycobacterium tuberculosis* infection is logistically feasible and a high public health priority
7	Swindells S et al., [12]	2019	New England Journal of Medicine	Africa, Asia, South America, North America, and the Caribbean	Areas of high TB prevalence or who had evidence of LTBI
8	Villarino ME et al., [19]	2015	JAMA Pediatrics	United States, Canada, Brazil, Hong Kong (China), and Spain	TB Trials Consortium (TBTC) sites and six International Maternal Paediatric and Adolescents AIDS Clinical Trials Group (IMPAACT) sites
9	Xin H et al., [20]	2022	European Respiratory Journal	China	Rural residents
10	Zhang H et al., [21]	2023	Emerging Microbes and Infections	China, Zhongmu County	Rural communities with an average TB incidence of57 per 100,000 for three consecutive years

[Table/Fig-3]: Characteristic of studies- Author information, year of publication, journal, region and study setting [12-21].
LTBI: Latent tuberculosis infection



[Table/Fig-4]: Risk of bias in studies.

with other controls, indicating that the weekly HP regimen is comparable with others in terms of hepatotoxicity incidence. However, the difference was not statistically significant, thus failing to demonstrate the superiority of the HP weekly regimen compared with other regimens.

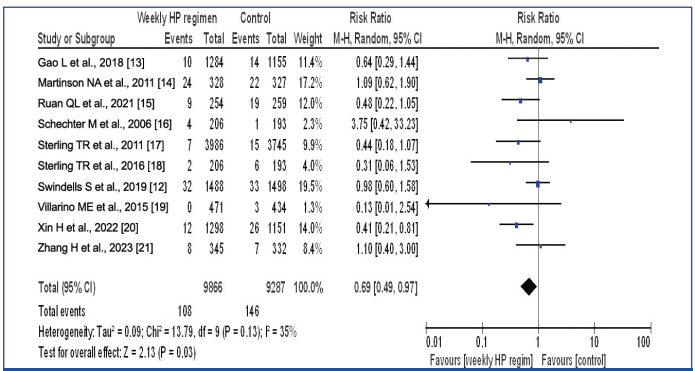
Treatment Completion Rate: [Table/Fig-9] displays the forest plot for the treatment completion rate of the weekly HP regimen and comparators. It provides information about the odds ratio with upper and lower limits for each study. The pooled odds ratio for the weekly HP regimen is 2.19 (1.64, 2.92, 95% CI) when compared with other controls, indicating that the weekly HP regimen is comparable with others in terms of treatment completion. The odds of completing treatment are 2.19 times greater for the weekly HP regimen, indicating that the treatment completion rate is significantly greater for the short-course weekly HP regimen than for the controls. Furthermore, the difference is statistically significant, demonstrating the superiority of the HP weekly regimen over any other regimen.

Subgroup Analysis- Short Course Weekly HP Regimen Versus Daily Isoniazid Regimen

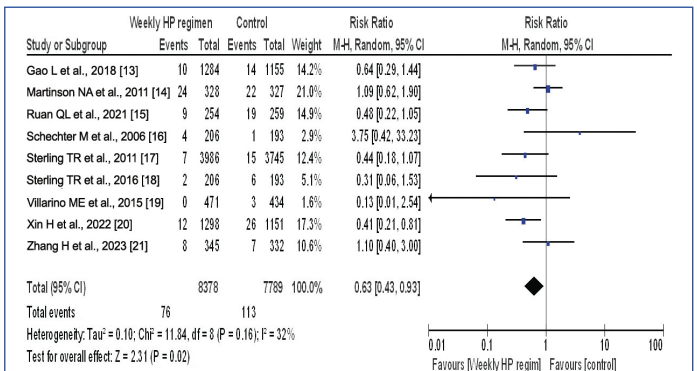
Among the comparators, the daily Isoniazid regimen is commonly practiced. A subgroup analysis was conducted to compare the weekly HP regimen with the daily Isoniazid regimen. According to the forest plot displayed in [Table/Fig-10], the pooled risk ratio for the weekly HP regimen is 0.75 (0.47, 1.22, 95% CI) when compared with the daily Isoniazid regimen, indicating that the HP weekly regimen is comparable with the daily Isoniazid regimen in terms

S. No.	Articles	Intervention (HP)		Control		Outcomes		
		Events	Total	Events	Total	Reduction in incidence of TB (Risk ratio)	Reduction in incidence of hepatotoxicity (Risk ratio)	Higher treatment completion rate (Odds ratio)
1	Gao L et al., [13]	10	1284	14	1155	0.64 (0.29, 1.44)	0.87 (0.41, 1.81)	1.62 (1.32, 1.98)
2	Martinson NA et al., [14]	24	328	22	327	1.09 (0.62, 1.90)	--	
3	Ruan QL et al., [15]	9	254	19	259	0.48 (0.22, 1.05)	5.40 (0.63, 45.85)	
4	Schechter M et al., [16]	4	206	1	193	3.75 (0.42, 33.23)	0.16 (0.04, 0.69)	0.91 (0.41, 2.02)
5	Sterling TR et al., [17]	7	3986	15	3745	0.44 (0.18, 1.07)	0.16 (0.10, 0.27)	2.06 (1.85, 2.29)
6	Sterling TR et al., [18]	2	206	6	193	0.31 (0.06, 1.53)	0.53 (0.28, 1.02)	4.53 (2.68, 7.64)
7	Swindells S et al., [12]	32	1488	33	1498	0.98 (0.60, 1.58)	0.67 (0.42, 1.08)	3.84 (2.59, 5.74)
8	Villarino ME et al., [19]	0	471	3	434	0.13 (0.01, 2.54)	--	
9	Xin H et al., [20]	12	1298	26	1151	0.41 (0.21, 0.81)	--	1.75 (1.21, 2.53)
10	Zhang H et al., [21]	8	345	7	332	1.10 (0.40, 3.00)	--	
		108	9866	146	9287	Pooled effect		
						0.63 (0.43,0.93)	0.50 (0.23,1.05)	2.19 (1.64,2.92)
	Difference between weekly HP regimen and Control					Statistically significant	Not significant	Statistically significant

[Table/Fig-5]: Outcomes of studies [12-21].



[Table/Fig-6]: Reduction in incidence of TB Infection (TBI) among participants. Receiving weekly Isoniazid-Rifapentine (HP) regimen, compared with other regimens

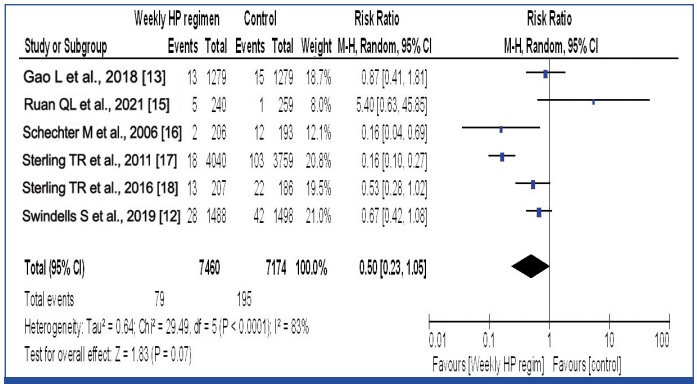


[Table/Fig-7]: Reduction in incidence of TB among participants receiving. Weekly Isoniazid - Rifapentine (HP) regimen, compared with Other regimens (exclusion of the study "Swindell S 2019" which has contributed relatively more weightage in pooled effect (sensitivity analysis))

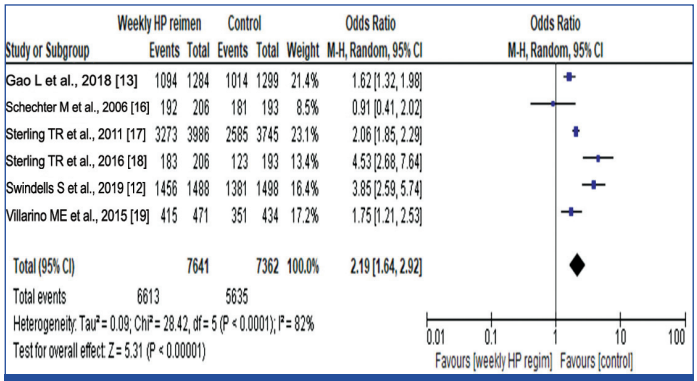
Secondary Outcomes

Hepatotoxicity Incidence: According to [Table/Fig-5] and the forest plot displayed in [Table/Fig-8], the pooled risk ratio for the weekly HP regimen is 0.50 (0.23, 1.05, 95% CI) when compared

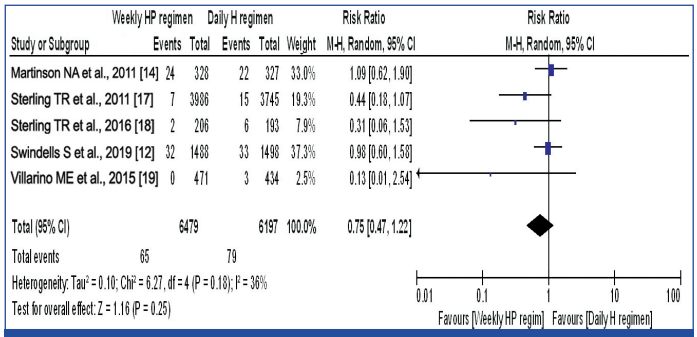
of reducing the incidence of TB. However, the difference was not statistically significant, thus failing to demonstrate the superiority of the weekly HP regimen compared with the daily Isoniazid regimen.



[Table/Fig-8]: Weekly Isoniazid - Rifapentine (HP) regimen neither superior nor inferior to other regimens in case of incidence of hepatotoxicity.



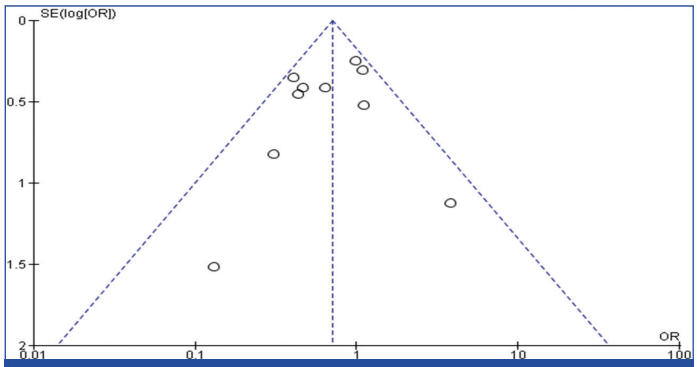
[Table/Fig-9]: Higher treatment completion rate among participants receiving weekly Isoniazid- Rifapentine (HP) regimen, compared with other regimens.



[Table/Fig-10]: Weekly Isoniazid- Rifapentine (HP) regimen neither, superior nor inferior to daily H regimen in case of reduction in incidence of TB.

Publication Bias

Based on the funnel plot displayed in [Table/Fig-11], all the studies were found to lie within the triangular region and were symmetrically scattered on both the right and left-sides of the funnel plot. This indicates the absence of noticeable publication bias.



[Table/Fig-11]: Absence of noticeable publication bias.

DISCUSSION

About 10 studies were included in the current systematic review, and a meta-analysis was conducted. The outcomes measured included the reduction in the incidence of TB, the incidence of hepatotoxicity, and the treatment completion rate.

Reduction in Incidence of TB-Weekly HP Regimen is Superior to Other Regimens

In a systematic review conducted by Njie GJ et al., the pooled odds ratio was 0.89 (0.46, 1.70, 95% CI), indicating that the weekly HP regimen was neither superior nor inferior to any other control [9]. A similar result was found in the review by Hamada Y et al., where the pooled risk ratio was 0.73 (0.23, 2.29, 95% CI) [10]. These results contrast with the review conducted by Tseng SY et al., and the current work [11]. In Tseng SY et al., review, the pooled odds ratio was 0.38 (0.18, 0.80, 95% CI), favouring the weekly HP regimen [11]. Similarly, in the current review, the pooled risk ratio (0.69 (0.49, 0.97, 95% CI)) remained in favour of the weekly HP regimen.

In Njie GJ et al., work, among the studies included, the study by Martinson NA et al., was found to carry 56.1% of the weightage, with the respective odds ratio being 1.12 (0.68, 1.84, 95% CI) [9,14]. This huge weightage of the mentioned study might have influenced the pooled effect. Likewise in the work by Hamada Y et al., only two studies were analysed to estimate the pooled effect [10]. On the other hand, in the present review, out of the 10 studies included, the study by Swindell S et al., carried a relatively larger weightage of about 19.5% [12]. Despite conducting sensitivity analysis by excluding the mentioned study, the pooled risk ratio (0.63 (0.43, 0.93, 95% CI)) continued to favour the weekly HP regimen. Therefore, this finding could be considered consistent.

Incidence of Hepatotoxicity- Weekly HP Regimen is Neither Superior Nor Inferior to Other Comparators

In the review by Tseng SY et al., the pooled odds ratio was 0.18 (0.12, 0.26, 95% CI), suggesting that the HP regimen is associated with a lower risk of hepatotoxicity [11]. A similar result was revealed in the review by Hamada Y et al., where the pooled risk ratio was 0.26 (0.12, 0.55, 95% CI) [10]. In the present review, the pooled risk ratio was 0.50 (0.23, 1.05, 95% CI), indicating that the weekly HP regimen is neither superior nor inferior to the comparators in terms of the risk of developing hepatotoxicity. The inclusion of a multitude of comparators, including regimens based on Pyrazinamide, or Isoniazid alone, and untreated controls, might be a possible explanation for the non-significant pooled effect in the present review.

Treatment Completion Rate- Weekly HP Regimen is Superior to Other Comparators

In the current review, the odds of completing treatment were 2.19 times greater for the weekly HP regimen than for the controls (pooled odds ratio-2.19 (1.64, 2.92; 95% CI)). Similar results were found in other reviews. In the work by Tseng SY et al., the pooled odds ratio was 2.30 (2.10, 2.53, 95% CI) [11]. Likewise in the reviews conducted by Njie GJ et al., and Hamada Y et al., the pooled effects were 2.97 (2.10, 4.21, 95% CI) and 1.25 (1.01, 1.55, 95% CI), respectively [9,11]. Irrespective of various settings, all the reviews discussed here explored that the treatment completion rate was significantly greater for the weekly HP regimen than for any other comparator. The probable reason for the association between the short-course weekly HP regimen and its greater treatment completion rate, when compared with other regimens, could be the shorter duration and more convenient weekly dosage.

Short Course Weekly HP Regimen Neither Superior Nor Inferior to Standard Daily Isoniazid Regimen

Subgroup analysis was done to compare the recently recommended weekly HP regimen with the standardised daily Isoniazid regimen. In the present work, the weekly HP regimen was found to be neither superior nor inferior to the daily H regimen (pooled risk ratio-0.75 (0.47, 1.22, 95% CI)). Similar results were found in the review by Njie GJ et al., for the 6-month INH with OR 1.09 (0.60, 1.99, 95% CI) and the 9-month INH with OR 0.47 (0.20, 1.12, 95% CI), as well as in the review by Hamada Y et al., for the 6/9H, with RR 0.73 (0.23,

2.29, 95% CI) [9,10]. Contrastingly, in Tseng SY et al.'s review, the pooled odds ratio favoured the weekly HP regimen over the daily H regimen, with a value of 0.38 (0.18, 0.80, 95% CI) [11]. Except for one, all the reviews discussed here suggested that the weekly HP regimen was neither superior nor inferior to the daily H regimen.

Limitation(s)

Currently, there are hardly any RCTs available for some of the risk groups. Although the results of the current review were found to be consistent on a large scale, its application to certain groups, like patients on immunosuppressive therapy, anti-TNF treatment, dialysis, and those preparing for organ or haematologic transplantation, has yet to be extensively studied.

CONCLUSION(S)

The weekly HP regimen is superior to other regimens for several reasons. Firstly, in terms of reducing the incidence of TB, the weekly HP regimen shows statistically significant comparability and was found to be superior to any other regimen. Secondly, regarding the incidence of hepatotoxicity, although there was no significant difference between the weekly HP regimen and other regimens, the HP regimen still remains comparable to others. Thirdly, although there was no statistically significant difference, the weekly HP regimen remains comparable to the daily Isoniazid regimen. The duration of the HP regimen was shorter compared to the longer duration (nine months in most cases) of the H regimen. Additionally, Isoniazid has to be taken daily, while the weekly HP regimen has a more convenient weekly dosage, resulting in better compliance than the daily H regimen. Fourthly, compared with all other regimens, the weekly HP regimen has a statistically significant higher level of treatment completion rate.

Altogether, it can be well established that the weekly HP regimen is superior to other regimens. It can be concluded that the weekly HP regimen is a better option among various regimens as TPT because of its shorter duration, more convenient weekly dosage, better treatment completion, and the resultant high level of compliance among the population at risk of developing TB disease.

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[ANNEXURE-1]

S. No.	Database/ other search engines	Keywords	Other search strategies	Filters	Records found
1.	Pubmed	Rifapentine, Isoniazid	Boolean operator – AND	Clinical trials, Randomised control trials	55
2.	Google scholar	Rifapentine, Isoniazid, Trial	Search operator – All in title	----	24
3.	Clinical Trials Registry India	Step – 1 Isoniazid, Rifapentine	----	----	0
		Step – 2 Rifapentine	Word Matching Criteria – Intervention and Comparator agents	----	9
4.	Grey literature - National grey literature collection's website (https://allcatsrgrey.org.uk/wp/)	Step – 1 Isoniazid, Rifapentine, Trial	----	----	0
		Step – 2 Isoniazid, Rifapentine	----	----	0
		Step – 3 Rifapentine	----	----	0
		Step – 4 Isoniazid	----	----	20
5.	Organisations - National TB elimination program, TB division, ministry of health and family welfare	Tuberculosis preventive treatment	----	----	1
6.	Citation searching - Scite	Isoniazid, Rifapentine, Trial	----	Randomised clinical trials	27