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Treatment completion and safety profile of once-weekly 3HP regimen for tuberculosis preventive treatment in children and adolescents: a systematic review

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Abstract

Background Children and adolescents are at increased risk of progressing from latent to active tuberculosis (TB). The 3-month, once-weekly isoniazid and rifapentine (3HP) regimen offers a shorter tuberculosis preventive treatment (TPT) option. However, evidence regarding its completion rates and safety in these populations remains limited.

Objective To evaluate treatment completion rates and adverse events associated with the 3HP regimen in children and adolescents.

Methods A systematic review of studies evaluated the 3HP regimen in children and adolescents with LTBI was conducted. Databases including PubMed, Embase, Cochrane Library, and CINAHL were searched to identify relevant studies. Data on treatment completion rates and adverse events were extracted and analyzed descriptively.

Results Ten studies involving children and adolescents aged 0–20 years were reviewed. Treatment completion rates were higher with 3HP regimen ranged from 70.9 to 100%, with a favorable safety profile. Mild adverse events, including nausea, vomiting, and abdominal pain, were reported, with no serious adverse events or hepatotoxicity observed.

Conclusions The 3HP regimen demonstrates high completion rates and safety profile in children and adolescents with LTBI, highlighting its suitability for this population. Expanding its implementation in programmatic settings is crucial to advancing global TB elimination.

Keywords Latent tuberculosis infection, Tuberculosis preventive treatment, Rifapentine and Isoniazid, 3HP, Children and adolescents

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Introduction

Despite being a preventable disease, tuberculosis (TB) remains a significant global public health challenge and a leading cause of morbidity and mortality among children and adolescents [1]. According to the World Health Organization (WHO), approximately 1.3 million children and adolescents were newly diagnosed with TB in 2023, representing 12% of the global TB burden [2]. It is estimated that nearly one-quarter of the world's population has latent tuberculosis infection (LTBI), including 7.5 million children and adolescents annually [3, 4]. This can be defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of disease [5]. Around 5–10% of those with LTBI will progress to active TB disease later in life. Without tuberculosis preventive treatment (TPT), 5–10% of individuals with LTBI will progress to active TB during their lifetime [6, 7].

Children and adolescents are particularly vulnerable to developing severe TB following infection compared to adults [8, 9]. TPT is a cornerstone of TB control and elimination strategies [10, 11]. Among the various TPT regimens recommended by WHO [5], the 9-month daily isoniazid regimen (9H) remains the most widely implemented due to its long history of use, favorable tolerance, and robust evidence of efficacy [12, 13]. However, children's adherence to the 9H regimen is consistently poor across high- and low-burden settings [14]. Key barriers include the regimen's long duration and challenges caregivers face in administering daily isoniazid. For example, some caregivers may not see their children daily or may forget to provide the medication, impacting adherence [15]. One of the shorter TPT regimens is a 3-month, once-weekly isoniazid and rifapentine (3HP), which has demonstrated higher treatment completion and an improved safety profile in adults [16–20]. Despite its potential benefits, evidence regarding the use of 3HP in children and adolescents remains limited [21]. Hence, this systematic review aims to address the knowledge gap by evaluating the current evidence on treatment completion and adverse events associated with the 3HP regimen for LTBI in children and adolescents, with a focus on considerations for implementation.

Methods

Study design

The protocol for this systematic review was registered with PROSPERO (Registration ID: CRD42023474898). The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, which were followed for both study design and reporting [22] The primary objective of this review was to evaluate the treatment completion rates and safety profile of the 3HP regimen for LTBI in children and adolescents. Due to the limited number of eligible studies and their substantial clinical and methodological heterogeneity, a meta-analysis was not feasible.

Ethical consideration

This study was approved exemption from ethical review by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University (CMU) [Exemption Number: 0541/2566].

Search strategy and selection criteria

Online databases, including PubMed, Embase, Cochrane Library and Cumulative Index to Nursing and Allied Health Literature (CINAHL), were searched for relevant studies up to February 3, 2025. Briefly, the search strategy using combinations of the terms: ((child* OR pediatric* OR adolescent* OR youth*) AND ((latent tuberculosis [MeSH Terms]) OR (tuberculosis OR "tuberculosis infection" OR "latent tuberculosis infection" OR LTBI OR TBI))) AND (3HP OR "isoniazid and rifapentine" OR "rifapentine and isoniazid"). A faculty librarian at the Faculty of Medicine, CMU was consulted for search terms and publications with inaccessible full texts. Authors corresponding to the study were contacted for further information as needed. There was no language restrictions imposed. The full search terms are illustrated in supplementary file 1.

The inclusion criteria for this systematic review were as follows: (i) studies involving children and adolescents under 20 years of age; (ii) participants diagnosed with LTBI; (iii) those who received 3HP as TPT; and (iv) studies reporting data on treatment completion and/or the safety profile of 3HP, with or without a comparator. Studies were excluded if they consisted of case reports, conference proceedings, or meeting abstracts, or if they lacked sufficient information on the primary outcomes of interest. Additionally, studies were excluded if data specific to children and adolescents could not be extracted separately from adult data.

The screening process involved two authors (SP and NB) independently reviewing titles and abstracts of the identified studies, followed by a full-text evaluation to determine eligibility. Discrepancies between the two reviewers were resolved through consensus discussion with a third author (CA).

Data extraction

The primary outcome was treatment completion of 3HP which was defined as a documented receipt of 11 or 12 doses of 3HP regimen within 16 weeks of treatment initiation, according to original randomized controlled trial (RCT) definition [16]. The secondary outcome was adverse events (AEs), graded from 1 to 4.

Data were extracted from the eligible studies based on the following variables: study characteristics (first author, publication year, country, study design, sample size, number of participants receiving the 3HP regimen and any comparators, if applicable), participant characteristics (median age, age range, race and HIV status), intervention details (type and duration of TPT regimens), and treatment outcomes (completion rates for 3HP and comparators, if applicable and adverse events associated with TPT). Outcome measurements were reported across all relevant metrics, such as numbers and percentages.

Risk of bias assessment

The risk of bias was evaluated based on the type of study included in the review. For RCT, the Cochrane Risk of Bias Tool (version 2) was used to classify the risk of bias as low, high, or unclear [23]. This tool assesses bias across five domains: (1) the randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) outcome measurement, and (5) selection of reported results.

For non-randomized studies of interventions, the risk of bias was assessed using the Risk of bias in non-randomized studies of intervention (ROBINS-I) tool, which evaluates bias in the following domains: confounding factors, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of reported results [24]. The risk of bias was categorized as critical, serious, moderate or low.

The risk of bias assessment was conducted independently by two authors (SP and NB). Any discrepancies were resolved through discussion with all authors (KP, WJ, and CA) to reach the consensus.

Data analysis

Data were analyzed using descriptive statistics. Treatment completion rates and adverse events were reported as frequencies and percentages, generated in Microsoft Excel.

Results

We identified 361 records from searching the four databases during initial search (last search February 3, 2025). After removing duplicates and exclusion for other reasons (irrelevance and clinical trial for registration), we screened the titles and abstracts of 180 records, from which we reviewed 55 full-text articles. Consequently, 10 articles (9 articles contain outcome of treatment completion and 5 articles contain outcome of AEs) met the inclusion criteria and were included in the systematic review (Fig. 1).

Characteristics of included studies

This review included 10 studies published between 2015 and 2024, comprising 1 RCT and 9 non-RCT studies. These studies were conducted across diverse TB burden settings. Low TB burden settings included the United States [25–30], Canada [25], and Spain [25], while high TB burden settings included China [31], Pakistan [32–33] and India [34]. Only two studies directly compared the 3HP regimen with either the daily 9 H or the daily 4R regimens. An implementation study from Pakistan [32] evaluated clinical outcomes, TPT uptake, and completion rates during the 6 H period versus the 3HP period. The age of study participants ranged from 2 to 20 years. Few studies provided data on comorbidities, such as HIV and malnutrition. Table 1 provides a detailed summary of the characteristics of the included studies.

Treatment completion of 3HP regimen

The systematic review included data from 10 studies reporting treatment outcomes for children and adolescents with LTBI who initiated the 3HP regimen. Treatment completion rates ranged from 70.9 to 100% across these studies (Table 2), with variations influenced by the method of administration, either directly observed therapy (DOT) or self-administered therapy (SAT).

High completion rates were observed in studies employing DOT, with Villarino et al. (2015) reporting an 88.1% completion rate and Yang et al. (2021) achieving 100%. Similarly, Hatzenbuehler et al. (2016) and Sandul et al. (2017) reported completion rates of 100% and 94.5%, respectively, in DOT-based implementations.

Studies utilizing SAT also demonstrated favorable outcomes. Jaswal et al. (2022) and Hussain et al. (2023), conducted in high-burden settings, reported completion rates of 70.9% and 76.9%, respectively, underscoring the feasibility of scaling up 3HP in programmatic contexts.

The 3HP regimen consistently outperformed traditional LTBI regimens, such as 9 months of isoniazid (9 H) or 4 months of rifampin (4R). Cruz et al. (2018) reported higher completion rates for 3HP (96.8%) compared to 9 H (79.8%) and 4R (87.9%). In a similar comparative study by Jaswal et al. (2022), 3HP demonstrated a significantly higher completion rate (70.9%) than 6 H (48.6%).

Adverse events (AEs)

The 3HP regimen demonstrated a favorable safety profile, with a low incidence of adverse events (AEs) among children and adolescents across the included studies. The majority of reported AEs were mild to moderate in severity (Grade 1–2). Gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and decreased appetite, were the most frequently observed AEs. Other commonly reported events included flu-like symptoms, rash,

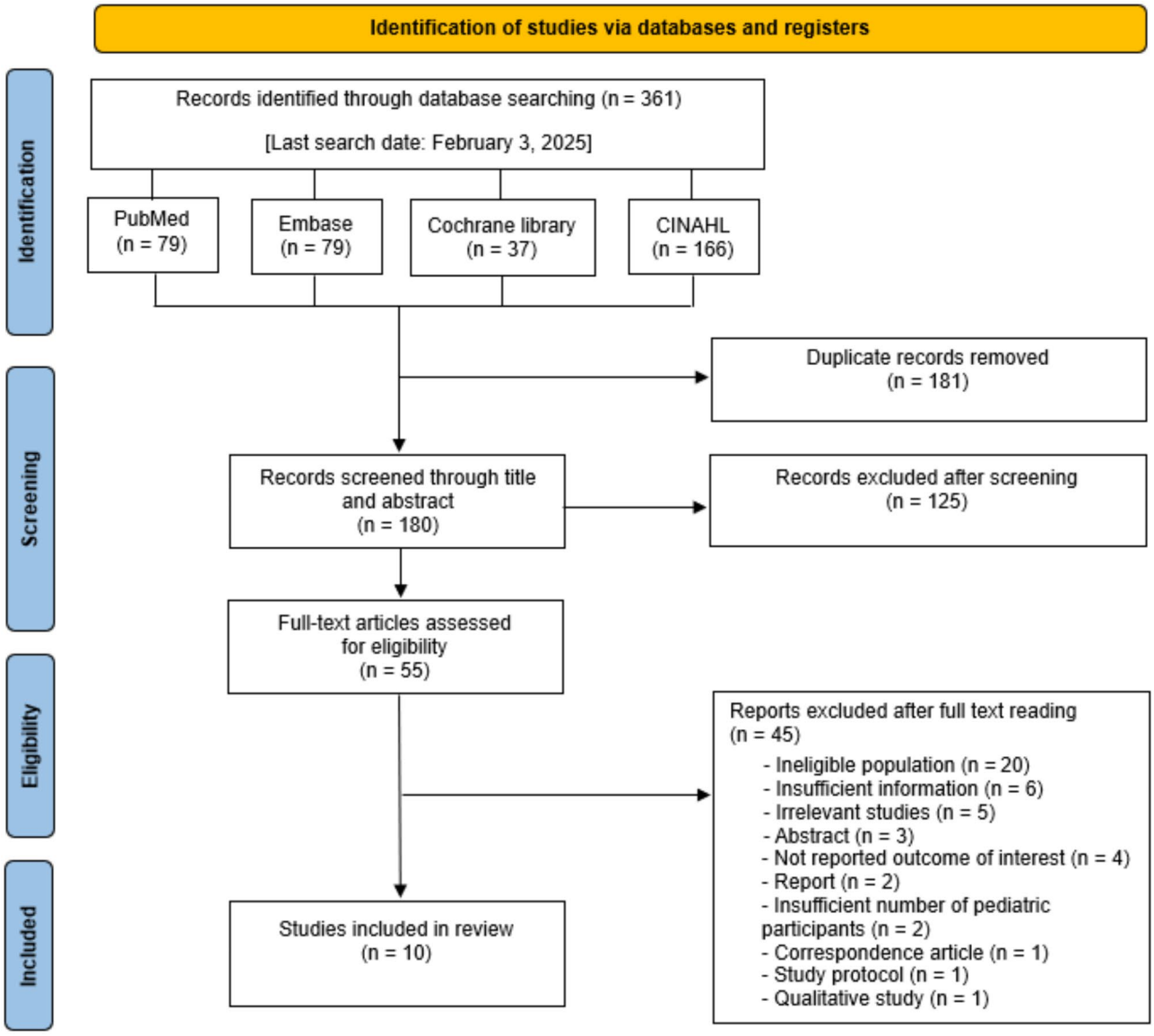


Fig. 1 PRISMA flow diagram of screening and selection processes

and mild neurological symptoms such as headache and dizziness.

Severe AEs (Grade 3–4) were rare. Isolated cases of Grade 3 events, such as anaphylaxis and significant nausea leading to inadequate caloric intake and weight loss, were reported in one study. Importantly, no cases of Grade 4 events, serious adverse events (SAEs), or hepatotoxicity were documented across the reviewed studies (Table 3). These findings highlight the tolerability of the 3HP regimen in pediatric populations.

Risk of bias assessment

The risk of bias in RCT (Table 4) judged this to be at low risk of bias. For other non-randomized studies, one had low risk of bias, six studies had some concern, and two studies had serious risk of bias (Table 5).

Discussion

This systematic review highlights the high treatment completion rates and favorable safety profile of the 3HP regimen for LTBI in children and adolescents. Completion rates ranged from 70.9 to 100% across diverse settings, indicating its potential to improve adherence. The 3HP regimen, which is shorter in duration than the 9 H or 4R treatments, appears to be a key factor contributing to these higher adherence rates. Structured programs utilizing DOT consistently resulted in higher completion rates, while SAT, supported by effective programmatic strategies, also yielded satisfactory results, especially

Table 1 Characteristics of the included studies

Study	Design	Year conducted	Country,	Sample size (*N*)	Age range (years)	Intervention (*n*)	Control (*n*)	Method of administering
Villarino ME [25], 2015	RCT	2001–2010	US, Canada, Brazil, Hongkong, and Spain	1,058	2–17	3HP (471)	9 H (434)	SAT or DOT
Cruz AT [26], 2016	A prospective cohort study	2014–2015	US	80	2–19	3HP (80)	N/A	N/A
Hatzenbuehler LA [27], 2016	A prospective cohort study	(N/A)	US	16	N/A, ninth and tenth grade classes	3HP (16)	N/A	DOT
Sandul AL [28], 2017	An obervational cohort study	2011–2013	US	164	2–17	3HP (164)	N/A	N/A
Cruz AT [29], 2018	A retrospective cohort study	2014–2017	US, Latin America, Asia, Africa, and Middle East	667	0–18	3HP (283)	9 H (252) 4R (132)	SAT or DOT
Peck GM [30], 2021	A retrospective chart review	2017–2019	US	22	2–20	3HP (22)	N/A	DOT
Yang H [31], 2021	A prospective cohort	2019–2020	China	26	1–14	3HP (26)	N/A	N/A
Jaswal M [32], 2022	Implementations study	2017	Pakistan	824	2–14	3HP (454)	6 H (370)	SAT
Hussain H [33], 2023	Implementations study	2018–2021	Pakistan	9,599	2–19	3HP (8,974)	N/A	SAT
Kinikar A [34], 2024	Implementation study	2021–2023	India	91	2–18	3HP (91)	N/A	N/A

Abbreviations: RCT, randomized controlled trial; US, United states; N/A, not available; DOT, directly observed therapy; SAT, self-administered therapy; 3HP, once-weekly isoniazid and rifapentine; 9 H, 9-month of isoniazid; 4R, 4-month of rifampicin; N, number

in resource-limited settings. These findings suggest that 3HP offers flexibility in treatment administration, which could enhance its appeal and feasibility in diverse settings.

Although the safety profile of 3HP further supports its potential as a feasible treatment option for pediatric LTBI, but the AEs varies across studies. AEs observed were predominantly mild to moderate, with no reports of serious adverse events such as hepatotoxicity or fatalities. A review of the included studies identifies gastrointestinal (GI) events, influenza-like symptoms, and cutaneous reactions as the most commonly reported side effects. These outcomes align with findings from adult studies [18, 35–38] and provide additional evidence for the regimen's tolerability in children and adolescents. Moreover, the safety profile of the 3HP regimen may differ between children and adults due to variations in drug metabolism, immune system development, and body weight. In India, concerns arise from the absence of RCTs and limited safety data. Key issues include the potential for isoniazid doses to exceed safe levels for individual subjects, the need to account for acetylator status, and the lack of pyridoxine recommendations as an adjunct [39]. In adults, comorbidities in older age can contribute to more frequent and severe AEs [40]. While a study in India found low incidences of AEs in children, continued monitoring is recommended [34]. Dosing recommendations, based on normal weight children, may not be applicable to overweight or obese children due to a lack of pharmacokinetic data in this group. Given the rise of childhood obesity, further studies are necessary to ensure appropriate dosing [41].

Despite these promising results, there remain critical knowledge gaps, particularly regarding the use of 3HP in children under 2 years of age and in children and adolescents living with HIV. Pharmacokinetic variability in younger children, influenced by factors such as tablet integrity and food intake [42], warrants further investigation. Additionally, data on the co-administration of 3HP with antiretroviral therapies, such as dolutegravir, is lacking, making it difficult to establish safety and efficacy in this vulnerable group. Addressing these gaps is essential for extending the benefits of 3HP to these high-risk populations.

Moreover, while 3HP has demonstrated efficacy and well-tolerated among children and adolescents, primarily in non-HIV-infected, in clinical trials [25]. It has also proven safe and well-adhered to in vulnerable populations, including children and adolescents living with HIV and young household contacts (aged 2–5 years) of pulmonary TB patients [34]. Furthermore, recent studies have established weight-based dosing for children, enhancing precision and safety compared to age-based methods [41]. However, the current tablet formulation,

Table 2 Treatment completion of the included studies

Study	Controls	Method of administering	Treatment completion outcome		Interpretation
			3HP (%)	Controls (%)	
Villarino ME [25], 2015	9 H	SAT or DOT	88.1	80.9 (9 H)	The 3HP regimen was as effective as 9 H for preventing TB in children aged 2–17 years, with high completion rates and comparable safety.
Cruz AT [26], 2016	N/A	N/A	99	N/A	The 3HP regimen showed high completion rates and minimal adverse events in children.
Hatzenbuehler LA [27], 2016	N/A	DOT	100	N/A	School-based TB education, screening, IGRA testing, and 3HP treatment effectively identify and treat at-risk adolescents.
Sandul AL [28], 2017	N/A	N/A	94.5	N/A	3HP completion rates in routine care exceeded those in trials and other regimens, supporting its potential to accelerate US TB elimination.
Cruz AT [29], 2018	9 H 4R	SAT or DOT	96.8	79.8 (9H) 87.9 (4R)	Shorter regimens increased completion rates.
Peck GM [30], 2021	N/A	DOT	N/A	N/A	Data suggest the short-course regimen for pediatric LTBI may have higher adverse event rates than expected.
Yang H [31], 2021	N/A	N/A	100	N/A	The 3HP regimen shows high completion and good tolerance in this population.
Jaswal M [32], 2022	6 H	SAT	70.9	48.6 (6 H)	In high-burden settings, household contacts had increase TPT completion with shorter regimens, despite similar uptake rates.
Hussain H [33], 2023	N/A	SAT	76.9	N/A	High acceptance and completion of 3HP in two Pakistani cities highlight its potential for effective scale-up in urban settings to enhance TPT reach and impact.
Kinikar A [34], 2024	N/A	N/A	95.6	N/A	The study demonstrates the feasibility and uptake of the planned nationwide 3HP rollout.

Abbreviations: N/A, not available; 3HP, once-weekly isoniazid and rifapentine; 9 H, 9-month of isoniazid; 4R, 4-month of rifampicin; TB, tuberculosis; IGRA, interferon gamma release assay; US, United states; AEs, adverse events; LTBI, latent tuberculosis infection; TPT, tuberculosis preventive treatment

Table 3 Adverse events (AEs) of 3HP regimen for LTBI treatment among children and adolescents

Study	Adverse events (AEs)						
	Grade 1–2 (events/total, %)	**Grade 3–4 (events/total, %)**	**GI events**	**Influenza-like event**	**Cutaneous events**	**Others**	**Serious AEs[a]**
Villarino ME [25], 2015	11/539, 2%	- Grade 3 (3/539, 0.6%)	N/A	Influenza-like events accounted for three treatment discontinuations	- Pruritic rash - Oral blisters and fever	None	None
Cruz AT [26], 2016		5/80, 6.3%[b]	– 2 transient nausea/vomiting with normal LFT – 2 abdominal pain (1 with normal and 1 with abnormal LFT)	None	– 1 transient, nonurticarial rash	None	
Cruz AT [29], 2018	Grade 1[c] (24/281, 8.5%)	None	– 5 decreased appetite – 5 abdominal pain, 5 nausea and/or vomiting	None	– 4 rash – 1 pruritus	– 6 headache – 3 dizziness – 1 myalgias	None
Peck GM [30], 2021	10/22, 45%	- Grade 3 (2/22, 9%): anaphylaxis, nausea leading to inadequate caloric intake and weight loss	Nausea, abdominal pain, vomiting, weight loss, diarrhea	Influenza syndrome	Dermatologic	Headache, anorexia, fever, neurotoxicity	None
Yang H [31], 2021	Grade 1 (10/26, 38.5%)	None	Abdominal pain and vomiting (the most frequently reported)	Flu-like symptoms	Cutaneous reactions	None	None

Abbreviations: N/A, not available; GI, gastrointestinal; LFT, liver function test

[a] Serious AEs included death during therapy or within 60 days of the last dose, life-threatening events, hospitalization, disability or permanent damage, and congenital anomaly

[b] Any AE

[c] Grading system used by the US Department of Health and Human Services for AEs. Grade 1: mild; asymptomatic or mild symptoms only requiring clinical or diagnostic observations, but no intervention

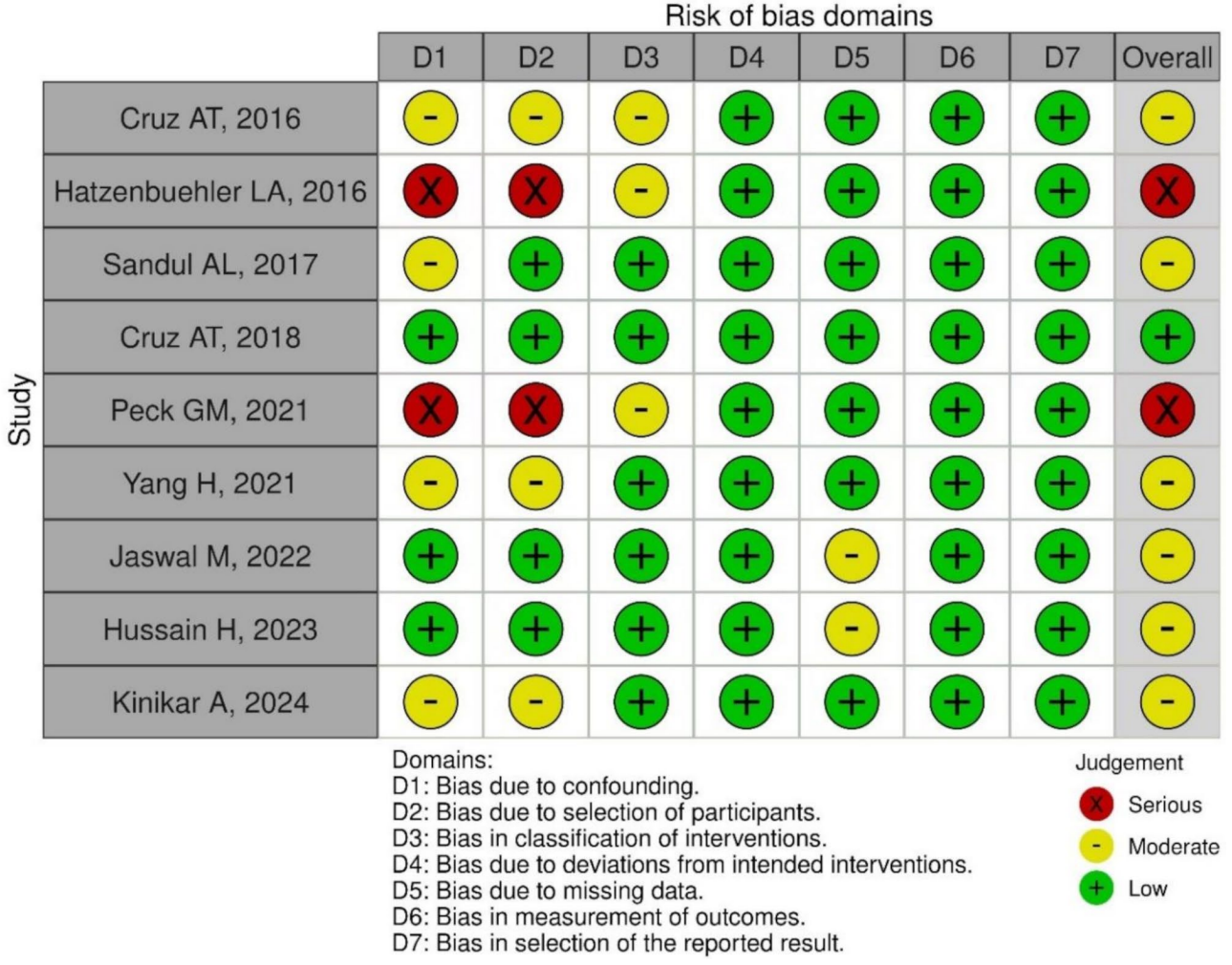
Table 4 Risk of bias of one randomized controlled trial using the Risk of Bias 2 assessment tool (RoB 2; The Cochrane Collaboration)

Studies	Domains	Bias arising from the randomization process			Risk of material bias	Bias due to deviations from intended interventions							Risk of material bias	Bias due to missing outcome data				Risk of material bias	Bias in measurement of the outcome					Risk of material bias	Bias in selection of the reported result			Risk of material bias	Risk of bias
	Signaling question	1.2	1.1	1.3		2.1	2.2	2.3	2.4	2.5	2.6	2.7		3.1	3.2	3.3	3.4		4.1	4.2	4.3	4.4	4.5		5.2	5.3	5.1		
Villarino ME [25], 2015	Response options	Y	Y	N	Low	Y	Y	N		N			Low	Y				Low	N	N	Y	N		Low	N	N	N	Low	Low
	Interpretation																												

with its large pill burden, remains a challenge for younger children. Ongoing studies, such as the TBTC Study 35 and DOLPHIN KIDS (estimated study completion on December 2025), aim to address these challenges by developing child-friendly formulations and exploring alternative administration strategies [43]. Recently, TBTC Study 35, which assessed the safety and dosing of the 3HP regimen in children with LTBI. The study confirms the safety of 3HP in children aged 0–12 years, providing critical data on appropriate dosing based on weight, rather than age ranges, and contributing to improved TB management in pediatric populations [44]. This research, alongside the availability of a child-friendly rifapentine formulation, supports the WHO's updated TB preventive treatment guidelines and brings the global goal of ending TB in children closer to reality.

The potential challenges in the practical application of the 3HP regimen among children and adolescents include limited drug access, high costs, and adherence issues. Younger patients may struggle with the 12-week treatment duration, leading to discontinuation. Directly observed therapy (DOT) also presents logistical difficulties, requiring coordination between healthcare providers, families, and schools [45]. A key determinant of 3HP adherence in children is the availability of pediatric-friendly formulations, which can improve medication acceptance and compliance [46]. Addressing these issues involves improving drug availability, providing

Table 5 Risk of bias in non-randomized studies of interventions (ROBINS-I) tool assessment



family education, and using community health workers to support adherence, while integrating the regimen into school-based programs to ensure better reach and compliance. Additionally, the previous literatures on the cost-effectiveness of short-course regimens in children, which have shown that household contact investigations combined with TPT can be highly cost-effective [47–50].

This review also highlights several limitations. Many of the included studies had small sample sizes, lacked comparator groups, and were predominantly conducted in low TB-burden settings. This limits the generalizability of the findings, especially to high TB-burden regions where the disease burden and risk profiles may differ. Additionally, variability in drug administration strategies, such as the use of DOT versus SAT, introduces potential biases that need further exploration. Another ongoing challenge in the global fight against TB is the slow uptake of tuberculosis preventive therapy (TPT) in children and adolescents [51–53]. Future research should prioritize randomized controlled trials among various pediatric populations with comparator groups and larger sample sizes to strengthen evidence for 3HP. Studies on cost-effectiveness, long-term outcomes, and implementation in high-TB burden regions are particularly critical. Innovations in adherence support, such as digital tools and community-based approaches, may further enhance 3HP's impact and accelerate progress toward global TB elimination targets.

Conclusion

The 3HP regimen demonstrates high completion rates, well-tolerability, and safety for TPT among children and adolescents, making it a preferable option for this population. Its shorter duration and favorable profile position it as a practical alternative to traditional regimens, with the potential to enhance adherence and reduce the global TB burden. Accelerated and widespread implementation of 3HP, particularly in programmatic settings, is urgently needed to achieve global TB elimination targets.

Abbreviations

AEs	Adverse events
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DOT	Directly observed therapy
GI	Gastrointestinal
IGRA	Interferon gamma release assay
LFT	Liver function test
LTBI	Latent tuberculosis infection
N	Number
N/A	Not available
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
ROBINS-I	Non-randomized studies of intervention
SAT	Self-administered therapy
TB	Tuberculosis
TPT	Tuberculosis preventive treatment
US	United states
WHO	World Health Organization
3HP	3-month, once-weekly isoniazid and rifapentine
4R	4-month of rifampicin
9 H	9-month daily isoniazid regimen

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10832-7.

Supplementary file 1

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Author contributions

Study conception and design were done by SP, NB, KP, WJ and CA. Data collection, analysis, interpretation and drafted the manuscript was performed by SP and NB. KP, WJ and CA supervised for edited the manuscript. All authors reviewed the results, revised the manuscript, and approved the final version of the manuscript for publication.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethic approval and consent to participate

Not applicable. This systematic review involves no direct human or animal subjects, and only involves the analysis of published data.

Clinical trial

Not applicable.

Consent for publication

Not applicable. This article does not contain any individual person's data in any form.

Conflict of interest

None declared.

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