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ORIGINAL ARTICLE

# Hepatotoxicity, efficacy and completion rate between 3 months of isoniazid plus rifapentine and 9 months of isoniazid in treating latent tuberculosis infection: A systematic review and meta-analysis

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## Abstract

**Background:** The mainstay therapy for latent tuberculosis infection is a 9-month regimen of daily isoniazid (9H) and a 3-month regimen of 12 once-weekly doses of isoniazid and rifapentine (3HP). We performed this updated meta-analysis to compare hepatotoxicity, efficacy and completion rate between these two regimens.

**Methods:** We searched all literature in the major medical databases using the subject search terms "isoniazid" and "rifapentine", and performed a systemic review and meta-analysis.

**Results:** A total of 14 studies were eligible for the meta-analysis, which included 5600 (49%) patients who received the 3HP regimen and 5919 (51%) patients who received the 9H regimen. A total of 202 (2%) patients had a drug-induced liver injury (DILI) and 11317 (98%) did not. The pooled odds ratio (OR) of DILI in the 3HP regimen was 0.18 (95% confidence interval [CI], 0.12-0.26; $p < 0.0001$), compared with the 9H regimen. This result remained consistent in subgroup analyses of ethnicity and study design. The 3HP regimen was superior to the 9H regimen in the prevention of active tuberculosis (OR, 0.38, 95% CI, 0.18-0.80, $p = 0.01$). Furthermore, the 3HP regimen was associated with a better completion rate than the 9H regimen (OR: 2.30, 95% CI, 2.10-2.53, $p < 0.0001$).

**Conclusion:** The 3HP regimen is superior to the 9H regimen, with less hepatotoxicity, and better efficacy and completion rate in treating latent tuberculosis infection.

**Keywords:** Drug-induced liver injury; Isoniazid; Latent tuberculosis infection; Meta-analysis; Rifapentine

## 1. INTRODUCTION

Tuberculosis (TB) is a major health issue worldwide, and an estimated 1.4 million people died from TB in 2019.[1] Latent tuberculosis infection (LTBI) is a condition of immune response to stimulation by mycobacterium tuberculosis bacilli with no evidence of active TB disease.[2] TB has been reported to reactivate in about 5% to 10% of patients with LTBI.[3] Managing LTBI to prevent active disease is important to control and eliminate TB.[4]

Various treatment strategies have been proposed to prevent active TB in patients with LTBI. Among them, a 9-month regimen of daily isoniazid (9H) is the most commonly used regimen. However, a 3-month regimen of 12 once-weekly doses of isoniazid and rifapentine (3HP) has recently been demonstrated to decrease anti-TB drug-induced liver injury (DILI) and shorten the treatment course.[5–8] A few studies have suggested that the 3HP regimen is comparable to the 9H regimen in terms of safety, efficacy, and completeness of treatment. However, most previous studies have been conducted in the US and enrolled Caucasian patients.[5–8] DILI is a potential adverse drug reaction associated with all anti-TB drugs. Several new studies have been published since the last meta-analysis in this field. Consequently, the safety and efficacy between these two regimens need to be re-evaluated, especially in populations other than Caucasians. Therefore, we performed this updated meta-analysis to compare the occurrence of DILI, the effectiveness of preventing TB reactivation, and treatment completion rate between the 3HP and 9H regimens, with a particular focus on ethnic differences.

## 2. METHODS

### 2.1. Identification and retrieval of studies

We conducted a literature search for articles on the 3HP and 9H regimens published up to January 2021 in PubMed,

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Medline, Embase, and the Cochrane Database of Systemic Reviews using the medical subject heading search terms "isoniazid" and "rifapentine". Articles were selected for full-text review based on the title and abstract. In addition, we manually searched the reference lists of the retrieved articles to increase the number of potentially relevant articles. Only articles relevant to the 3HP and 9H regimens were selected for this systematic review and meta-analysis. Two researchers independently examined all articles and assessed their eligibility for this study. Discordant opinions were resolved by consensus with the other co-authors.

### 2.2. Inclusion and exclusion criteria

We included both prospective studies and retrospective case-control studies in the meta-analysis. The inclusion criteria were: (1) patients receiving standard latent TB treatment including the 3HP or 9H regimen; (2) having data on patients with or without DILI; and (3) studies with a clear definition of DILI, including the upper normal limit of serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST), used to define DILI. The exclusion criteria were: (1) incomplete data on the number of cases and controls with or without DILI; (2) use of the same patient/control group in a second article; and (3) animal studies. The studies included in the analysis were reviewed for the following characteristics: authors and year of publication; ethnicity of the enrolled patients; prospective or retrospective case-control study; administration mode; and definition of DILI.

TB reactivation was defined as sputum culture-confirmed TB or clinically diagnosed active TB from a chest X-ray. Treatment completion was defined as a patient taking >80% of his/her total doses.[5] Due to the various follow-up periods in different studies, a minimal follow-up duration of 19 months was required in this study.

The Newcastle-Ottawa quality assessment scale was used to evaluate the quality of each included study as follows: high quality 7-9, medium quality 4-6, and low quality <4.[9]

### 2.3. Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) for the incidence of DILI and other parameters between the 3HP and 9H regimens were calculated. Fixed model forest plot meta-analysis for all eligible studies was performed first. Heterogeneity was assessed using between-study variance using $I^2$ statistics with a cutoff value of 50%, or the chi-square test for Cochran Q statistics with $p < 0.10$. If significant heterogeneity was found, a random-effects model was used to analyze the pooled data. Funnel plots were used to assess publication bias. All statistical analyses were performed using Review Manager Version 5.4 (RevMan for Windows, 2020; The Cochrane Collaboration, Oxford, UK).

## 3. RESULTS

A total of 539 articles were retrieved from the initial search, of which 14 were determined to be eligible for the meta-analysis (Fig. 1). The baseline characteristics of the included studies are listed in Table 1.[10–23] Of the patients who underwent treatment for LTBI, 5600 (49%) received the 3HP regimen and 5919 (51%) received the 9H regimen. A total of 202 (2%) patients had DILI and 11 317 (98%) did not. Five studies were based on Asian patients, one on Caucasian patients, and one on African American patients, and the other seven studies included patients of various ethnicities (Table 1). Eight studies were prospective randomized clinical trials, and six studies were retrospective case-control studies. Only one study used a strict definition of DILI as serum alanine ALT more than five times the upper limit of normal value (ULN), while the other studies used a loose definition of DILI (ALT or AST >2 or 3 ULN).

The pooled OR of all studies for the occurrence of DILI with the 3HP regimen was 0.18 (95% CI, 0.12-0.26; $p < 0.0001$, Fig. 2) compared with the 9H regimen. No heterogeneity was noted among the studies ($I^2 = 0\%$; $p = 1.00$). Further subgroup analysis revealed that the patients who received the 3HP regimen

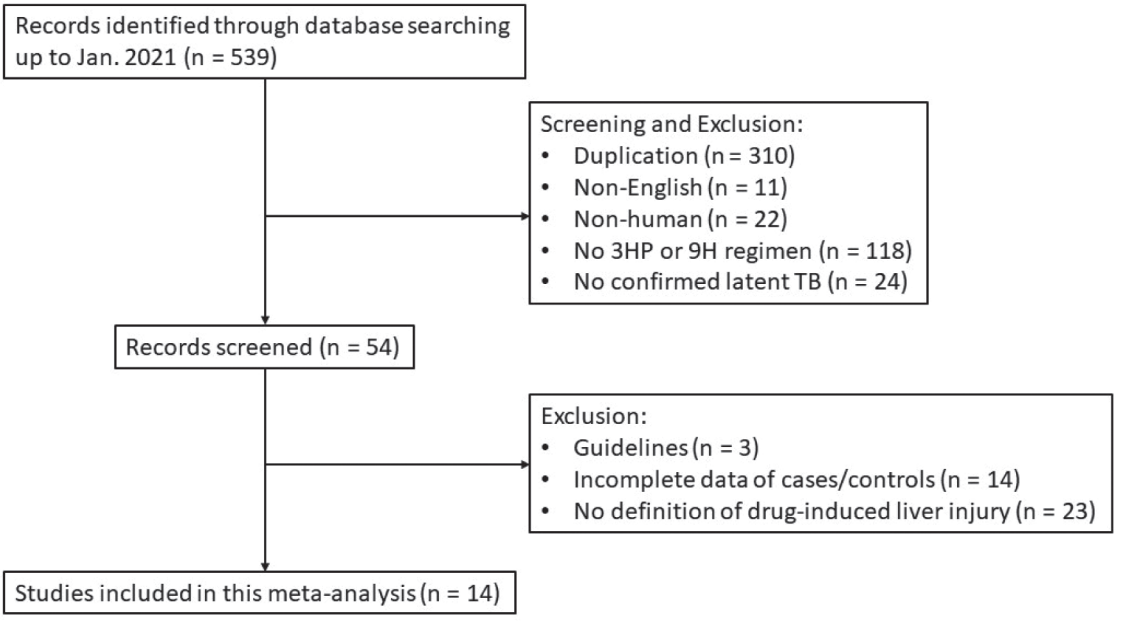


**Fig. 1** Flow chart of the selection of eligible studies.

**Table 1**

**Main characteristics of included studies in order of publication year**

| First author, year | Country | Race | Enrollment years | Study design | Administration mode | Numbers (3HP/9H) | Age, mean or median [a] (3HP/9H) | Male, % (3HP/9H) | DILI (3HP/9H) | Definition of DILI | Treatment completion rate, % (3HP/9H) | TB reactivation rate, % (3HP/9H) | Follow-up duration | Quality[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sterling, 2011[10] | U.S. | Multiracial | 2001-2008 | RCT | DOT | 3986/3745 | 36.0[b]/35.0[a] | 55.4/53.5 | 18/103 | AST > 3x ULN | 82.1/69.0 | 0.2/0.4 | 33 months | 9 |
| Villarino, 2015[11] | U.S. | Multiracial | 2001-2010 | RCT | DOT | 471/434 | 10.0[a]/12.0[a] | 53.8/47.6 | 0/0 | AST > 3x ULN | 88.1/80.9 | 0/0.7 | 33 months | 8 |
| Lines, 2015[12] | U.S. | Caucasian | 2012-2013 | case-control | DOT | 45/94 | 40.1/38.0 | 42.2/42.5 | 0/3 | AST > 3x ULN | 77.8/52.1 | No data | 19 months | 7 |
| Sterling, 2016[13] | U.S. | Multiracial | 2001-2013 | RCT | DOT | 207/186 | 36.0[b]/36.0[a] | 70.9/67.9 | 3/12 | AST > 3x ULN | 88.8/63.7 | 0.9/3.1 | 33 months | 9 |
| Huang, 2016[14] | Taiwan | Asian | 2014 | case-control | DOT | 101/590 | 34.9/34.5 | 43.6/52.9 | 0/21 | AST > 3x ULN | 97.0/87.3 | 0/0.3 | 60 months | 7 |
| Yamin, 2016[15] | U.S. | African American | 2012-2013 | case-control | DOT | 53/115 | 41.2/38.3 | 49.1/71.3 | 0/4 | AST > 3x ULN | 79.2/65.2 | No data | 24 months | 7 |
| Arguello Perez, 2017[16] | U.S. | Multiracial | 2005-2014 | case-control | SAT | 55/202 | 35.0/35.0 | 52.7/53.0 | 0/7 | ALT > 5x ULN | 87.3/57.9 | No data | No data | 6 |
| Simkins, 2017[17] | U.S. | Multiracial | 2012-2014 | case-control | SAT | 43/110 | 55.2/59.8 | 76.7/66.4 | 0/6 | AST > 2x ULN | 93.0/47.3 | 0/0 | 19 months | 6 |
| Sun, 2018[18] | Taiwan | Asian | 2014-2016 | RCT | DOT | 132/131 | 31.7/32.0 | 61.4/54.2 | 2/7 | AST > 3x ULN | 89.4/77.9 | 0/0 | 24 months | 8 |
| Moro, 2018[19] | U.S. | Multiracial | 2001-2008 | RCT | DOT/SAT | 31/56 | 23.0[a]/25.0[a] | 0/0[b] | 0/1 | ALT > 3x ULN | No data | No data | 33 months | 8 |
| Chen, 2018[20] | Taiwan | Asian | 2015-2017 | case-control | DOT | 21/23 | 62.1/62.0 | 28.6/34.8 | 0/2 | ALT > 3x ULN | 90.5/78.3 | 0/0 | 24 months | 5 |
| Wheeler, 2019[21] | U.S. | Multiracial | 2013-2014 | case-control | DOT | 112/92 | No data | No data | 1/7 | AST > 3x ULN | 90.2/42.4 | No data | 16 months | 7 |
| Feng, 2020[22] | Taiwan | Asian | 2017-2019 | case-control | DOT/SAT | 293/100 | No data | No data | 2/3 | ALT > 3x ULN | 85.3/71.0 | No data | 24 months | 7 |
| Lin, 2021[23] | Taiwan | Asian | 2014-2020 | case-control | DOT/SAT | 50/41 | 58.0/54.8 | 72.0/65.9 | 0/0 | ALT > 3x ULN | 82.0/61.0 | No data | 24 months | 8 |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = a drug-induced liver injury; DOT = directly observed therapy; RCT = randomized controlled trial; SAT = self-administered therapy; TB = tuberculosis; ULN = upper limit of normal value.
[a]Median age.
[b]All pregnant women.
[c]Newcastle- Ottawa quality assessment scale, high quality: 7-9; medium quality: 4-6; low quality: < 4.

had a lower risk of DILI than those who received the 9HP regimen in both the Asian patient (OR = 0.21; 95% CI, 0.07-0.60; $p = 0.004$) and other ethnicity (OR = 0.17; 95% CI,0.11-0.26; $p < 0.0001$) subgroups, and the prospective (OR = 0.17; 95% CI, 0.11-0.27; $p < 0.0001$) and case-control (OR = 0.18; 95% CI, 0.06-0.57; $p = 0.003$) study subgroups.

Seven studies had available data on treatment efficacy, and the analysis showed that the 3HP regimen was superior to the 9H regimen in the prevention of active TB (OR = 0.38; 95% CI, 0.18-0.80; $p = 0.01$, Fig. 3). Subgroup analysis revealed that this better TB prevention effect also existed in multiracial studies. However, only two cases had a reactivation of TB in three Asian studies, and the number was too small to achieve statistical significance.

One study did not have data on treatment completion rate. Therefore, the treatment completion rate was analyzed in the other 13 studies, with an OR of 2.30 (95% CI, 2.10-2.53,; $p < 0.0001$, Fig. 4) for the 3HP regimen, suggesting that the completion rate was about 2 times higher with the 3HP regimen than the 9H regimen. Subgroup analysis of the Asian and multiracial studies also showed a better complete rate with the 3HP regimen than the 9H regimen.

Fig. 5 depicts the occurrence of flu-like syndrome between the 3HP and 9H regimens. Flu-like syndrome occurred more frequently with the 3HP regimen than the 9H regimen in all patients in the studies with these data (OR = 3.60; 95% CI, 2.18-5.97; $p < 0.001$), and also in the Asian and multiracial groups.

The funnel plot in Fig. 6 shows that there were few studies in the left lower quadrant, suggesting that studies with small study size and effect size were not enrolled in this meta-analysis. Publication bias may have existed in this study.

## 4. DISCUSSION

LTBI is an important health threat which should be managed carefully. 3HP and 9H are the two most commonly used regimens to treat LTBI. Our meta-analysis included 14 studies with relatively high quality and focused on DILI, treatment efficacy and completion rate of these two regimens. We found that the 3HP regimen was superior to the 9H regimen in terms of DILI, efficacy and completion rate.

A recent meta-analysis reported that the 3HP regimen had similar efficacy to the 6H and 9H regimens, with a significantly lower risk of DILI and higher treatment completion rate.[6] However, this review only included four studies. Another three meta-analyses compared the 3HP regimen with many other regimens and found that it was as safe as the other regimens. Our meta-analysis focused on the 3HP and 9H regimens and included five updated high-quality articles from Taiwan, and we found that the 3HP regimen was superior to and not just equivalent to the 9H regimen in safety and efficacy. This may be a recommendation for health authorities and healthcare providers globally to implement the 3HP regimen for LTBI.

The superior efficacy of the 3HP regimen may be due to a low rate of DILI, short treatment duration, and high completion rate. In addition, the mean rifapentine elimination half-life is 13.3 to 24.3 h, which is much longer than the elimination half-life of rifampin (2-3 h).[24] The maximum plasma concentrations of rifapentine are well above the minimum inhibitory concentrations for mycobacterium tuberculosis after administering the standard 600-mg dose. Ingestion of this dose with a high-fat meal increases the peak concentration and the area under the curve by 43% to 50% over fasting values.[24] Whether the pharmacokinetic characteristics of rifapentine achieve better efficacy is open to debate. Of note, there was a publication bias in this meta-analysis as shown in the funnel plot analysis (Fig. 6). This

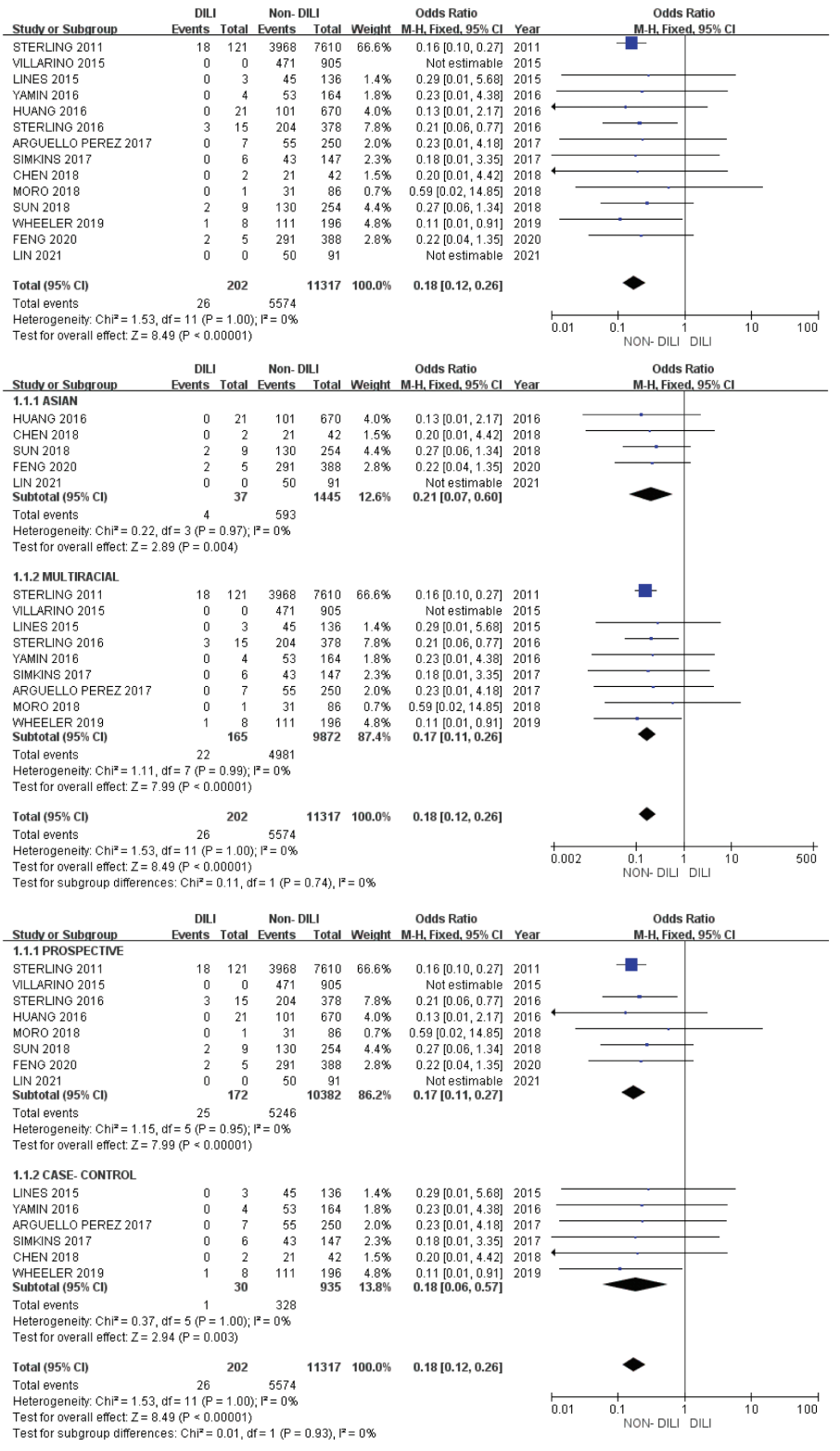


**Fig. 2** Forest plot of association between 3HP regimen and the risk of drug-induced liver injury (DILI) compared with 9H regimen in all eligible 14 studies and subgroup analysis of different ethnic populations and study designs. Events denote patients received 3HP regimen.

suggested that the meta-analysis tended to enroll studies wi th a large sample size and effect size, which may have helped to show the better efficacy of the 3HP regimen. Further studies with a smaller sample size and effect size are needed to consolidate the superior role of the 3HP regimen in the prevention of TB.

Diverse ethnicity and genetic polymorphisms may influence the susceptibility to DILI.[25–29] Nine of the included studies in this meta-analysis were from the US, and five were from Asia (all from Taiwan). Seven of the studies from the US included patients of various ethnicities, of whom Caucasians were the majority,

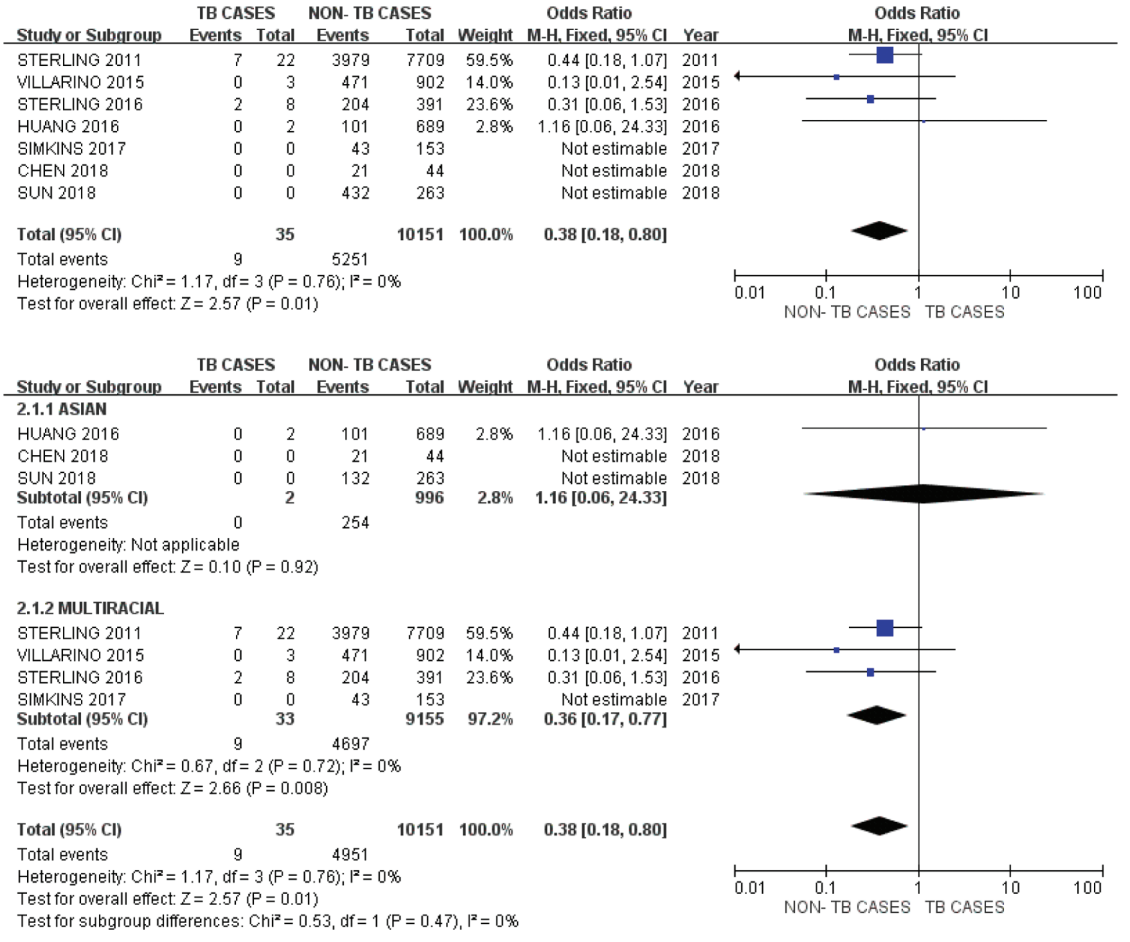


**Fig. 3** Forest plot of efficacy to prevent tuberculosis infection among patients receiving 3HP compared with 9H regiment in seven studies and subgroup analysis of different ethnic populations. Events denote patients received 3HP regimen.

and one study recruited all African Americans. Therefore, we specifically analyzed the Taiwanese patients as one subgroup and found that the results remained the same across Taiwanese and other ethnic populations. However, further studies are warranted to investigate whether this result can be extrapolated to other Asian populations.

Interestingly, although a lower DILI rate was noted among the patient receiving the 3HP regimen than the 9H regimen, those who received the 3HP regimen seemed to have more other adverse drug reactions such as skin rash, flu-like syndrome, dizziness, headache, nausea/vomiting, fever, and fatigue.[10,13,16,18,20,23] A randomized control trial reported that possible hypersensitivity reactions occurred in 152/4040 (3.8%) patients receiving the 3HP regimen and 17/3759 (0.5%) patients receiving the 9H regimen.[10] Another randomized control study also demonstrated a high rate of systemic drug reactions in patients receiving the 3HP regimen.[18] We analyzed flu-like syndrome in this meta-analysis and found that it was more frequent in patients receiving the 3HP regimen than the 9H regimen (Fig. 5), both in the Asian and multiracial studies. Because most of the adverse reactions were not serious and resolved easily, the benefit of the 3HP regimen over the 9H regimen is still justified.

Base on the US CDC guidelines,[30] the 3HP regimen is not recommended for: (1) pregnant women or women expecting to become pregnant in 3 months; (2) children younger than 2 years of age; (3) people with human immunodeficiency virus infection who are taking antiretroviral medications with clinically significant or unknown drug interactions with once-weekly 3HP; or (4) people presumed to be infected with isoniazid- or rifampicin-resistant strains. For these specific populations, further meta-analyses are needed after more relevant reports have been published.

Since the definition of DILI may influence the study results, we considered this issue in our analysis. A serum ALT level of more than 3 times the ULN was defined as indicating DILI in 12 of the 14 included studies. One study defined DILI as an elevation in ALT level of more than five times the ULN, and another as an ALT level more than two times the ULN. As the definition of DILI used in the studies seemed to similar across the studies, we did not analyze it further.

There are some limitations to this meta-analysis. First, we only compared the 3HP and 9H regimens, so that our results cannot be extrapolated to 3HP with other diverse regimens. Second, although children, patients with human immunodeficiency virus infection, pregnant women, renal transplant candidates, and uremic patients with dialysis were enrolled into some of their studies, further studies on these special populations are needed to validate the consistency of the results. Third, two different drug administration policies, directly observed therapy, and self-administered therapy (SAT), may have affected the results of this study. However, only two studies used SAT alone, which was too few to perform further subgroup analysis. Fourth, although 14 studies were included in this study, around 70% of the cases came from the PREVENT TB trial, which may have affected the results of this meta-analysis. However, the published articles from this trial enrolled different patient groups.

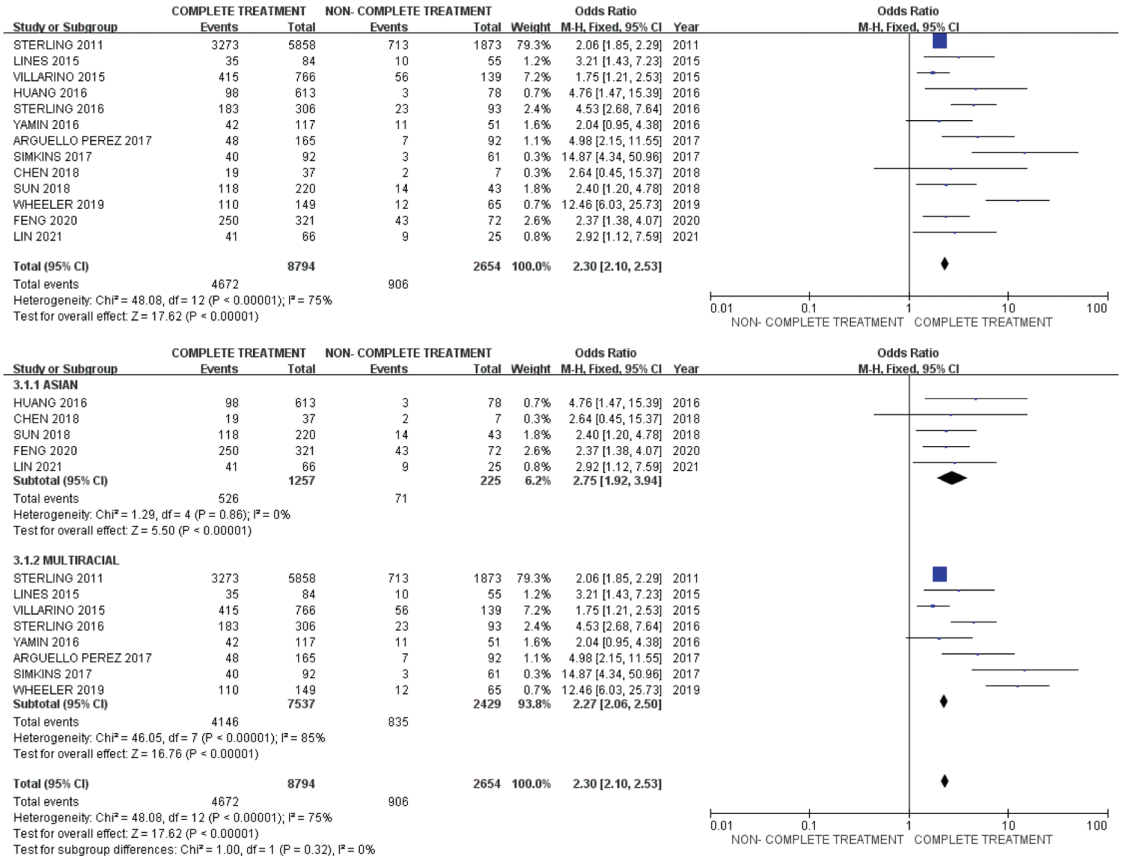


**Fig. 4** Forest plot of treatment completion rate among patients receiving 3HP compared with 9H regimen in 13 studies and subgroup analysis of different ethnic populations. Events denote patients received 3HP regimen.

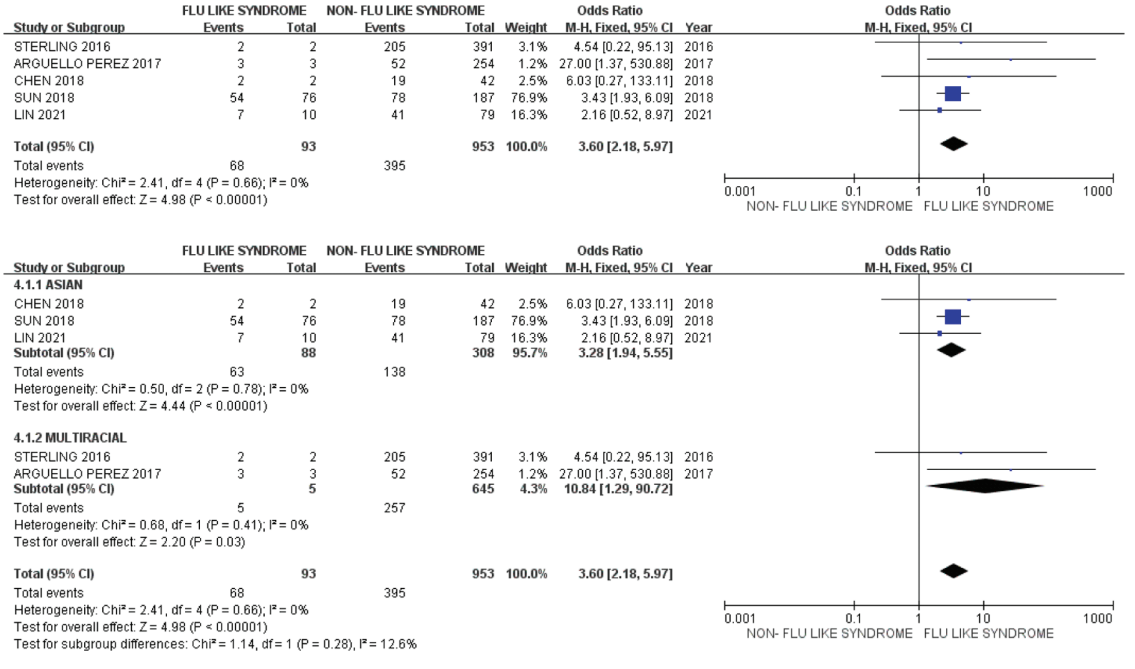


**Fig. 5** Forest plot of flu-like syndrome among patients receiving 3HP compared with 9H regimen in 5 studies and subgroup analysis of different ethnic populations. Events denote patients received 3HP regimen.

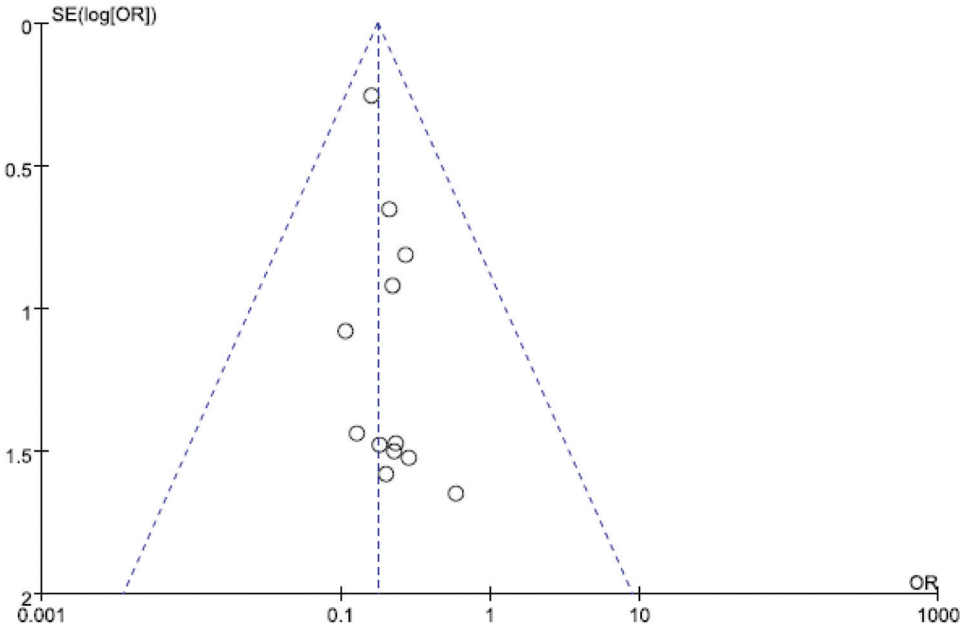


**Fig. 6** Funnel plot for the assessment of publication bias.

In conclusion, in this meta-analysis, we found that the 3HP regimen was safer in terms of DILI, better effective and completion rate comparing with the 9H regimen in the treatment of patients with LTBI. In addition, there were no ethnic differences in the results. Compared to the 9H regimen, the 3HP regimen is a better treatment choice for LTBI.

## ACKNOWLEDGMENTS

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