

# 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.<sup>1</sup> Latent tuberculosis infection (LTBI) is a condition of immune response to stimulation by mycobacterium tuberculosis bacilli with no evidence of active TB disease.<sup>2</sup> TB has been reported to reactivate in about 5% to 10% of patients with LTBI.<sup>3</sup> Managing LTBI to prevent active disease is important to control and eliminate TB.<sup>4</sup>

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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.<sup>5-8</sup> 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.<sup>5-8</sup> 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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Conflicts of interest: Dr. Yi-Shin Huang and Dr. Yi-Hsiang Huang, editorial board members at Journal of the Chinese Medical Association, have no roles in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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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 fulltext 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 casecontrol 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.<sup>5</sup> 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

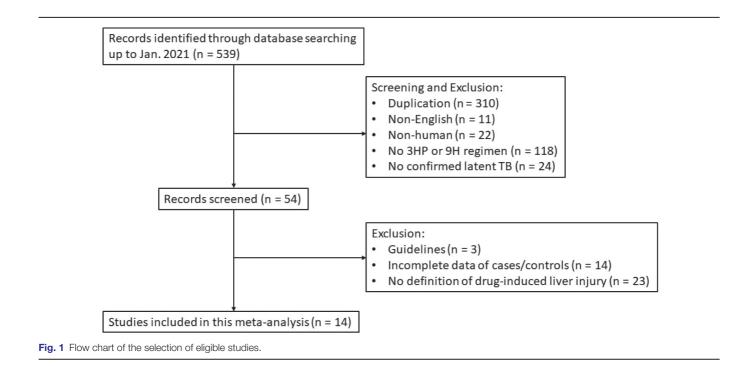
#### 2.3. Statistical analysis

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<sup>2</sup> 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 metaanalysis (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<sup>2</sup> = 0%; p = 1.00). Further subgroup analysis revealed that the patients who received the 3HP regimen



												<u>0</u>		
		_			Admin-	1	Age, mean	, u			Treatment	reactivation		
First author, year	Country Race		Enrollment years	Study design	istration mode	Numbers (3HP/9H)	or median " (3HP/9H)	Male, % (3HP/9H)	UILI (3HP/9H)	Detinition of DILI	Definition of completion rate, DILI % (3HP/9H)	rate, % (3HP/9H)	Follow-up duration	Quality°
Sterling, 2011 <sup>10</sup>	U.S.	Multiracial	2001-2008	RCT	DOT	3986/3745	36.0 <sup>b</sup> /35.0 <sup>a</sup>	55.4/53.5	18/103	AST > 3x ULN	82.1/69.0	0.2/0.4	33 months	6
Villarino, 2015 <sup>11</sup>	U.S.	Multiracial	2001-2010	RCT	DOT	471/434	10.0ª/12.0ª	53.8/47.6	0/0	AST > 3x ULN	88.1/80.9	0/0.7	33 months	8
Lines, 2015 <sup>12</sup>	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 <sup>13</sup>	U.S.	Multiracial	2001-2013	RCT	DOT	207/186	36.0ª/36.0ª	70.9/67.9	3/12	AST > 3x ULN	88.8/63.7	0.9/3.1	33 months	6
Huang, 2016 <sup>14</sup>	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 <sup>15</sup>	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 <sup>16</sup>	U.S.	Multiracial	2005-2014	case-control	SAT	55/202	35.0/35.0	52.7/53.0	2/0	ALT > 5x ULN	87.3/57.9	No data	No data	9
Simkins, 2017 <sup>17</sup>	U.S.	Multiracial	2012-2014	case-control	SAT	43/110	55.2/59.8	76.7/66.4	0/0	AST > 2x ULN	93.0/47.3	0/0	19 months	9
Sun, 2018 <sup>18</sup>	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	œ
Moro, 2018 <sup>19</sup>	U.S.	Multiracial	2001-2008	RCT	DOT/SAT	31/56	23.0ª/25.0ª	¢0/0	0/1	ALT > 3x ULN	No data	No data	33 months	œ
Chen, 2018 <sup>20</sup>	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 <sup>21</sup>	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 <sup>22</sup>	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 <sup>23</sup>	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	œ

a b b 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

quality: 7-9; medium quality: 4-6; low quality: < 4.

high

assessment scale.

<sup>b</sup>All pregnant women. <sup>c</sup>Newcastle- Ottawa quality 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.<sup>6</sup> 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 halflife of rifampin (2-3 h).<sup>24</sup> 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.<sup>24</sup> 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

	DILI		Non- I			Odds Ratio		Odds Ratio
Study or Subgroup			Events			M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl
STERLING 2011	18	121	3968	7610	66.6%	0.16 [0.10, 0.27]		-
VILLARINO 2015 LINES 2015	0 0	0 3	471 45	905 136	1.4%	Not estimable 0.29 (0.01, 5.68)	2015 2015	
YAMIN 2016	0	4	40 53	164	1.4%	0.23 [0.01, 4.38]	2015	
HUANG 2016	Ő	21	101	670	4.0%	0.13 [0.01, 2.17]		<
STERLING 2016	3	15	204	378	7.8%	0.21 [0.06, 0.77]		
ARGUELLO PEREZ 2017	0	7	55	250	2.0%	0.23 [0.01, 4.18]		
SIMKINS 2017	0	6	43	147	2.3%	0.18 [0.01, 3.35]	2017	
CHEN 2018	0	2	21	42	1.5%	0.20 [0.01, 4.42]	2018	• • • • • • • • • • • • • • • • • • • •
MORO 2018	0	1	31	86	0.7%	0.59 [0.02, 14.85]	2018	
SUN 2018	2	9 8	130	254	4.4%	0.27 [0.06, 1.34]		
WHEELER 2019 FENG 2020	1	5	111 291	196 388	4.8% 2.8%	0.11 [0.01, 0.91] 0.22 [0.04, 1.35]		
LIN 2021	Ó	Ő	50	91	2.0 /0	Not estimable		
21112021	Ŭ			0.		1101 0041114010	2021	
Total (95% CI)		202		11317	100.0%	0.18 [0.12, 0.26]		•
Total events	26		5574					
Heterogeneity: Chi <sup>2</sup> = 1.53, d			; I² = 0%					0.01 0.1 1 10 100
Test for overall effect: Z = 8.4	9 (P < 0.0	10001)						NON- DILI DILI
	DILI		Non- I	DILI		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
1.1.1 ASIAN								
HUANG 2016	0	21	101	670	4.0%	0.13 [0.01, 2.17]		
CHEN 2018	0	2	21	42	1.5%	0.20 [0.01, 4.42]	2018	
SUN 2018 FENG 2020	2	9 5	130 291	254 388	4.4% 2.8%	0.27 [0.06, 1.34] 0.22 [0.04, 1.35]	2018 2020	
LIN 2021	0	0	291	388 91	2.070	Not estimable	2020	
Subtotal (95% CI)	0	37	50	1445	12.6%	0.21 [0.07, 0.60]	2021	◆
Total events	4		593					
Heterogeneity: Chi <sup>2</sup> = 0.22, d	f= 3 (P =	0.97); l	l² = 0%					
Test for overall effect: Z = 2.8	9 (P = 0.0	104)						
1.1.2 MULTIRACIAL								
STERLING 2011	18	121	3968	7610	66.6%	0.16 [0.10, 0.27]	2011	
VILLARINO 2015	0	0	471	905		Not estimable	2015	
LINES 2015	0	3	45	136	1.4%	0.29 [0.01, 5.68]	2015	
STERLING 2016	3	15	204	378	7.8%	0.21 [0.06, 0.77]	2016	
YAMIN 2016	0	4 6	53 43	164 147	1.8%	0.23 [0.01, 4.38]	2016	
SIMKINS 2017 ARGUELLO PEREZ 2017	0	7	43 55	250	2.3% 2.0%	0.18 [0.01, 3.35] 0.23 [0.01, 4.18]	2017	
MORO 2018	0	1	31	86		0.5910.02.14.85		
MORO 2018 WHEELER 2019	0 1	1	31 111	86 196	0.7% 4.8%	0.59 [0.02, 14.85] 0.11 [0.01, 0.91]		
						0.59 [0.02, 14.85] 0.11 [0.01, 0.91] 0.17 [0.11, 0.26]	2018	•
WHEELER 2019 Subtotal (95% CI) Total events	1 22	8 165	111 4981	196	4.8%	0.11 [0.01, 0.91]		•
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 1.11, d	1 22 f= 7 (P =	8 165 0.99); I	111 4981	196	4.8%	0.11 [0.01, 0.91]		•
WHEELER 2019 Subtotal (95% CI) Total events	1 22 f= 7 (P =	8 165 0.99); I	111 4981	196	4.8%	0.11 [0.01, 0.91]		•
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 1.11, d	1 22 f= 7 (P =	8 165 0.99); I	111 4981	196 9872	4.8%	0.11 [0.01, 0.91]		•
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events	1 22 f = 7 (P = 9 (P < 0.0 26	8 165 0.99); 1 10001) 202	111 4981 F = 0%	196 9872	4.8% 87.4%	0.11 (0.01, 0.91) <b>0.17 (0.11, 0.26)</b>		•
WHEELER 2019 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>22</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% Cl) Total events Heterogeneity: Chi <sup>22</sup> = 1.53, d	1 22 f = 7 (P = 9 (P < 0.0 26 f = 11 (P =	8 165 0.99);1 0001) 202 = 1.00)	111 4981 F = 0%	196 9872	4.8% 87.4%	0.11 (0.01, 0.91) <b>0.17 (0.11, 0.26)</b>		• • • •
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events	1 22 f = 7 (P = 9 (P < 0.0 26 f = 11 (P = 9 (P < 0.0	8 165 0.99);1 00001) 202 = 1.00) 00001)	111 4981 1 <sup>2</sup> = 0% 5574 ; 1 <sup>2</sup> = 0%	196 9872 11317	4.8% 87.4% 100.0%	0.11 (0.01, 0.91) <b>0.17 (0.11, 0.26)</b>		• • • • • • • • • • • • • • • • • • •
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = 1.53, d Test for overall effect: Z = 8.4	1 22 f = 7 (P = 9 (P < 0.0 26 f = 11 (P : 9 (P < 0.0 s: Chi <sup>2</sup> = 1	8 165 0.99);1 00001) 202 = 1.00) 00001)	111 4981 P = 0% 5574 ; P = 0% f = 1 (P =	196 9872 11317 0.74), I <sup>2</sup>	4.8% 87.4% 100.0%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26]		NON- DILI DILI
WHEELER 2019 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for overall effect: Z = 8.4 Test for subgroup difference:	1 22 f = 7 (P = 9 (P < 0.0 26 f = 11 (P = 9 (P < 0.0 5: Chi <sup>2</sup> = 1 DILI	8 165 0.99); 1 00001) 202 = 1.00) 10001) 0.11, dt	111 4981 1 <sup>2</sup> = 0% 5574 ; 1 <sup>2</sup> = 0% f = 1 (P = <b>Non-I</b>	196 9872 11317 0.74), I <sup>2</sup> DILI	4.8% 87.4% 100.0% = 0%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] Odds Ratio	2019	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for overall effect: Z = 8.4 Test for subgroup difference:	1 22 f = 7 (P = 9 (P < 0.0 26 f = 11 (P : 9 (P < 0.0 s: Chi <sup>2</sup> = 1	8 165 0.99); 1 00001) 202 = 1.00) 10001) 0.11, dt	111 4981 1 <sup>2</sup> = 0% 5574 ; 1 <sup>2</sup> = 0% f = 1 (P = <b>Non-I</b>	196 9872 11317 0.74), I <sup>2</sup> DILI	4.8% 87.4% 100.0% = 0%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26]	2019	NON- DILI DILI
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for subgroup difference: Study or Subgroup	1 22 f = 7 (P = 9 (P < 0.0 26 f = 11 (P = 9 (P < 0.0 5: Chi <sup>2</sup> = 1 DILI	8 165 0.99); 1 00001) 202 = 1.00) 10001) 0.11, dt	111 4981 1 <sup>2</sup> = 0% 5574 ; 1 <sup>2</sup> = 0% f = 1 (P = <b>Non-I</b>	196 9872 11317 0.74), I <sup>2</sup> DILI	4.8% 87.4% 100.0% = 0%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] Odds Ratio	2019 Year	NON- DILI DILI Odds Ratio
WHEELER 2019           Subtotal (95% CI)           Total events           Heterogeneity: Chi² = 1.11, d           Test for overall effect: Z = 7.9           Total (95% CI)           Total events           Heterogeneity: Chi² = 1.53, d           Test for subgroup difference:           Study or Subgroup           1.1.1 PROSPECTIVE           STERLING 2011           VILLARINO 2015	1 22 f= 7 (P = 9 (P < 0.0 f= 11 (P : 9 (P < 0.0 s: Chi <sup>2</sup> = 1 <u>DILI Events</u> 18 0	8 165 0.99); 1 00001) 202 = 1.00) 00001) 0.11, dt 10001 11, dt 121 0	111 4981 F = 0% 5574 ; F = 0% f = 1 (P = <u>Non-I</u> <u>Events</u> 3968 471	196 9872 11317 0.74), I <sup>2</sup> DILI Total 7610 905	4.8% 87.4% 100.0% = 0% <u>Weight</u> 66.6%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] Odds Ratio <u>M.H. Fixed, 95% CI</u> 0.16 [0.10, 0.27] Not estimable	2019 Year 2011 2015	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for overall effect: Z = 8.4 Test for subgroup difference: Study or Subgroup 1.1.1 PROSPECTIVE STERLING 2011 VILLARING 2015 STERLING 2016	1 22 f = 7 (P = 9 (P < 0.0 26 f = 11 (P : 9 (P < 0.0 s: Chi <sup>2</sup> = 1 DILI Events 18 0 3	8 165 0.99); 1 00001) 202 = 1.00) 00001) 0.11, dt 10001 11, dt 121 0 15	111 4981 F = 0% 5574 ; F = 0% f = 1 (P = <u>Non-I</u> <u>Events</u> 3968 471 204	196 9872 11317 0.74),   <sup>2</sup> 0ILI Total 7610 905 378	4.8% 87.4% 100.0% = 0% Weight 66.6% 7.8%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77]	2019 Year 2011 2015 2016	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for overall effect: Z = 8.4 Test for subgroup Study or Subgroup 1.1.1 PROSPECTIVE STERLING 2011 VILLARINO 2015 STERLING 2016 HUANG 2016	1 22 f = 7 (P = 9 (P < 0.0 f = 11 (P : 9 (P < 0.0 s: Chi <sup>2</sup> = 1 DILI Events 18 0 3 0	8 165 0.99);   00001) 202 = 1.00) 0001) 0.11, dt 10001) 0.11, dt 121 0 15 21	111 4981 P = 0% 5574 ; P = 0% f = 1 (P = Non-1 Events 3968 471 204 101	196 9872 11317 0.74), I <sup>2</sup> 0ILI 7610 905 378 670	4.8% 87.4% 100.0% = 0% <u>Weight</u> 66.6% 7.8% 4.0%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17]	2019 Year 2011 2015 2016 2016	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for overall effect: Z = 8.4 Test for subgroup difference: Study or Subgroup 1.11 PROSPECTIVE STERLING 2011 VILLARING 2016 HUANG 2016 MORO 2018	1 22 f= 7 (P = 9 (P < 0.0 26 f= 11 (P = 9 (P < 0.0 s: Chi <sup>2</sup> = 1 DILI Events 18 0 3 0 0	8 165 0.99); I 00001) 202 = 1.00) 00001) 0.11, dt 0.11, dt 121 0 15 21 15 21 1	111 4981 P = 0% 5574 ; P = 0% f = 1 (P = Non-I Events 3968 471 204 101 31	196 9872 11317 0.74),   <sup>2</sup> 0.74),   <sup>2</sup> 0.7610 905 378 670 86	4.8% 87.4% 100.0% = 0% Weight 66.6% 7.8% 4.0% 0.7%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85]	2019 Year 2011 2015 2016 2016 2018	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for overall effect: Z = 8.4 Test for subgroup difference: Study or Subgroup 1.1.1 PROSPECTIVE STERLING 2011 VILLARING 2016 HUANG 2016 MORO 2018 SUN 2018	1 22 f= 7 (P = 9 (P < 0.0 26 f= 11 (P : 9 (P < 0.0 5: Chi <sup>2</sup> = 1 <b>DILI</b> Events 18 0 3 0 0 2	8 165 0.99); ( 00001) 202 = 1.00) 0001) 0.011, dt 121 0 15 21 1 9	111 4981 F = 0% 5574 ; F = 0% f = 1 (P = Non-I Events 3968 471 204 101 31 31	196 9872 11317 0.74),   <sup>2</sup> 0 L  7610 905 378 670 86 254	4.8% 87.4% 100.0% = 0% Weight 66.6% 7.8% 4.0% 0.7% 4.4%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.06, 1.34]	2019 Year 2011 2015 2016 2016 2018 2018 2018	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for overall effect: Z = 8.4 Test for subgroup difference: Study or Subgroup 1.11 PROSPECTIVE STERLING 2011 VILLARING 2016 HUANG 2016 MORO 2018	1 22 f= 7 (P = 9 (P < 0.0 26 f= 11 (P = 9 (P < 0.0 s: Chi <sup>2</sup> = 1 DILI Events 18 0 3 0 0	8 165 0.99); I 00001) 202 = 1.00) 0001) 0.11, dt 0.11, dt 121 0 15 21 15 21 1	111 4981 P = 0% 5574 ; P = 0% f = 1 (P = Non-I Events 3968 471 204 101 31	196 9872 11317 0.74),   <sup>2</sup> 0.74),   <sup>2</sup> 0.7610 905 378 670 86	4.8% 87.4% 100.0% = 0% Weight 66.6% 7.8% 4.0% 0.7%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.06, 1.34] 0.22 [0.04, 1.35]	2019 Year 2011 2015 2016 2018 2018 2018 2020	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>®</sup> = 1.11, d Test for overall effect: Z = 7.9 Total events Heterogeneity: Chi <sup>®</sup> = 1.53, d Test for overall effect: Z = 8.4 Test for subgroup Study or Subgroup 1.1.1 PROSPECTIVE STERLING 2011 VILLARING 2015 STERLING 2016 HUANG 2016 MORO 2018 SUN 2018 FENG 2020 LIN 2021 Subtotal (95% CI)	1 22 f=7 (P = 9 (P < 0.0 26 f=11 (P = 9 (P < 0.0 s: Chi <sup>2</sup> = 1 <b>DILLI</b> Events 18 0 3 0 2 2	8 <b>165</b> 0.99); ( 10001) <b>202</b> = 1.00) 10001) 0.11, dt 121 0 15 21 1 9 5	111 4981 F = 0% 5574 ; F = 0% f = 1 (P = Non-I Events 3968 471 204 101 31 1300 291	196 9872 11317 0.74),  * 0ILI 7610 905 378 670 86 254 388	4.8% 87.4% 100.0% = 0% Weight 66.6% 7.8% 4.0% 0.7% 4.4%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.06, 1.34]	2019 Year 2011 2015 2016 2018 2018 2018 2020	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for subgroup 1.1 PROSPECTIVE STERLING 2016 effective STERLING 2016 MORO 2018 SUN 2018 SUN 2018 SUN 2021 Subtotal (95% CI) Total events	1 22 f= 7 (P = 9 (P < 0.0 26 f= 11 (P : 9 (P < 0.0 s: Chi <sup>#</sup> =1 DILI Events 18 0 3 0 0 2 2 0 0 25	8 165 10001) 202 = 1.00) 10001) 0.011, dt 121 0 15 21 1 9 5 0 172	4981 = 0% 5574 ; P = 0% f = 1 (P = Non-I Events 3968 471 204 101 31 130 291 50 5246	196 9872 11317 0.74),  * 0.74),  * 0.7410 905 378 670 86 254 388 91	4.8% 87.4% 100.0% = 0% Weight 66.6% 7.8% 4.0% 0.7% 4.4% 2.8%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.06, 1.34] 0.22 [0.04, 1.36] Not estimable	2019 Year 2011 2015 2016 2018 2018 2018 2020	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for overall effect: Z = 8.4 Test for subgroup difference: Study or Subgroup 1.1.1 PROSPECTIVE STERLING 2011 VILLARING 2016 HUANG 2016 HUANG 2016 SUN 2018 SUN 2018 SUN 2018 SUN 2018 SUN 2018 SUN 2018 SUN 2018 SUN 2018 SUN 2018 SUN 2018 Total events Heterogeneity: Chi <sup>2</sup> = 1.15, d	1 22 f = 7 (P = 9 (P < 0.0 26 f = 11 (P : 9 (P < 0.0 s: Chi <sup>2</sup> = 1 DILLI Events 18 0 0 0 2 2 0 f = 5 (P =	8 165 00001) 202 = 1.00) 0001) 0.11, dt 121 0 15 21 1 9 5 0 172 0.95);	4981 = 0% 5574 ; P = 0% f = 1 (P = Non-I Events 3968 471 204 101 31 130 291 50 5246	196 9872 11317 0.74),  * 0.74),  * 0.7410 905 378 670 86 254 388 91	4.8% 87.4% 100.0% = 0% Weight 66.6% 7.8% 4.0% 0.7% 4.4% 2.8%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.06, 1.34] 0.22 [0.04, 1.36] Not estimable	2019 Year 2011 2015 2016 2018 2018 2018 2020	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>®</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>®</sup> = 1.53, d Test for overall effect: Z = 8.4 Test for subgroup 1.11 PROSPECTIVE STERLING 2016 HUANG 2016 MORO 2018 SUN 2018 FENG 2020 LIN 2018 FENG 2020 LIN 2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>®</sup> = 1.15, d Test for overall effect: Z = 7.9	1 22 f = 7 (P = 9 (P < 0.0 26 f = 11 (P : 9 (P < 0.0 s: Chi <sup>2</sup> = 1 DILLI Events 18 0 0 0 2 2 0 f = 5 (P =	8 165 00001) 202 = 1.00) 0001) 0.11, dt 121 0 15 21 1 9 5 0 172 0.95);	4981 = 0% 5574 ; P = 0% f = 1 (P = Non-I Events 3968 471 204 101 31 130 291 50 5246	196 9872 11317 0.74),  * 0.74),  * 0.7410 905 378 670 86 254 388 91	4.8% 87.4% 100.0% = 0% Weight 66.6% 7.8% 4.0% 0.7% 4.4% 2.8%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.06, 1.34] 0.22 [0.04, 1.36] Not estimable	2019 Year 2011 2015 2016 2018 2018 2018 2020	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for subgroup difference: Study or Subgroup 1.11 PROSPECTIVE STERLING 2011 VILLARING 2015 STERLING 2016 HUANG 2016 MORO 2018 SUN 2018 SUN 2018 FENG 2020 LIN 2021 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.15, d Test for overall effect: Z = 7.9 1.12 CASE- CONTROL	1 22 59 (P < 0.C 26 6 = 11 (P = 9 (P < 0.C 9 (P < 0.C 9 (P < 0.C 1 (P = 9 (P < 0.C 1 (P = 9 (P < 0.C 2 (P = 0))) 1 (P = 0) 9 (P < 0.C 2 (P = 0)) 2 (P = 0) 2	8 165 0.99); 00001) 202 = 1.00) 00001) 0.011, dt 121 0 15 21 1 1 9 5 0 0 172 0.95); 10001)	111 4981 F = 0% 5574 ; P = 0% (; P = 0% (; P = 0% 3968 471 204 101 31 30 281 130 294 (; P = 0% 5246 F = 0%	196 9872 11317 0.74), P DILI 7610 905 378 676 80 80 80 80 80 80 80 80 80 80 80 80 80	48% 87.4% 100.0% = 0% Weight 66.6% 7.8% 4.0% 0.0% 2.8% 86.2%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.59 [0.06, 1.34] 0.22 [0.04, 1.35] 0.27 [0.01, 1.34] 0.22 [0.04, 1.35]	2019 2011 2011 2015 2016 2018 2018 2018 2018 2018 2019	NON- DILI DILI Odds Ratio
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for subgroup difference: Study or Subgroup 1.1 PROSPECTIVE STERLING 2016 HUANG 2016 MURA 2016 MURA 2016 MURA 2016 MURA 2016 SUN 2018 SUN 2018 SUN 2018 SUN 2018 SUN 2018 Heterogeneity: Chi <sup>2</sup> = 1.15, d Test for overall effect: Z = 7.9 1.12 CASE-CONTROL LINES 2015	$\begin{array}{c} 1 \\ 22 \\ 17 \\ 7 \\ 7 \\ 19 \\ 19 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10$	8 165 0.99); (0001) 202 = 1.00) 10001) 0.011, dt 121 0 15 0 172 0 172 0.95); (0001) 3	111 4981 F = 0% 5574 F = 0% f = 1 (P = Fevents 3968 471 101 310 204 101 313 130 5246	196 9872 11317 0.74), F 005 378 670 905 378 670 805 254 388 91 10382	48%, 87.4% 100.0% = 0% Weight 666.6% 7.8% 0.7% 4.4% 2.8% 86.2%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.04, 1.34] 0.22 [0.04, 1.35] Not estimable 0.17 [0.11, 0.27]	2019 Year 2011 2015 2016 2018 2018 2020 2021 2021	NON- DILI DILI
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for overall effect: Z = 8.4 Test for subgroup 1.11 PROSPECTIVE STERLING 2016 HUANG 2016 SURV 2018 SURV 2018 Heterogeneity: Chi <sup>2</sup> = 1.15, d Test for overall effect: Z = 7.9 1.12 CASE-CONTROL LINES 2015 YAMIN 2016	1 22 27 (P = 9 9 (P < 0.0.1 9 (P < 0.0.1 9 (P < 0.0.1 0 (P < 0.0.1) 0 (P < 0.	8 165 0.99); (: 00001) 202 = 1.00) 0001) 0.011, dt 121 0 15 21 1 9 5 0 172 0.95); (: 00001) 3 4	111 4981 F = 0% 5574 4 ; F = 0% (= 1 (P = Non-1 Events 3968 471 30 471 30 291 30 5246 53 53	196 9872 11317 0.74), P DILI Total 7610 905 378 670 864 388 91 10382 1366 164	48% 87.4% 100.0% = 0% Weight 666% 7.8% 4.0% 2.8% 86.2%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.06, 1.34] 0.22 [0.02, 14.85] Not estimable 0.17 [0.11, 0.27] 0.29 [0.01, 5.68] 0.23 [0.01, 5.68] 0.23 [0.01, 5.68]	2019 Year 2011 2015 2016 2018 2020 2021 2021 2021 2021 2015 2016	NON- DILI DILI
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for subgroup difference: Study or Subgroup 1.1 PROSPECTIVE STERLING 2016 HUANG 2016 MURA 2016 MURA 2016 MURA 2016 MURA 2016 SUN 2018 SUN 2018 SUN 2018 SUN 2018 SUN 2018 Heterogeneity: Chi <sup>2</sup> = 1.15, d Test for overall effect: Z = 7.9 1.12 CASE-CONTROL LINES 2015	$\begin{array}{c} 1 \\ 22 \\ 17 \\ 7 \\ 7 \\ 19 \\ 19 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10 \\ 10$	8 165 0.99); (0001) 202 = 1.00) 10001) 0.011, dt 121 0 15 0 172 0 172 0.95); (0001) 3	111 4981 F = 0% 5574 F = 0% f = 1 (P = Fevents 3968 471 101 310 204 101 313 130 5246	196 9872 11317 0.74), F 005 378 670 905 378 670 805 254 388 91 10382	48%, 87.4% 100.0% = 0% Weight 666.6% 7.8% 0.7% 4.4% 2.8% 86.2%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.55 [0.02, 14.85] 0.27 [0.06, 1.34] 0.22 [0.04, 1.35] Not estimable 0.17 [0.11, 0.27] 0.29 [0.01, 5.68] 0.23 [0.01, 4.18]	2019 Year 2011 2015 2016 2018 2020 2021 2021 2021 2021 2021 2021	NON- DILI DILI
$\label{eq:constraints} \begin{array}{l} \label{eq:constraints} \\ \mbox{Wheteletter} 2019 \\ \mbox{Subtotal} (95\% Cl) \\ \mbox{Total events} \\ \mbox{Heterogeneity: Chi^2 = 1.11, d} \\ \mbox{Test for overall effect: $Z = 7.9$ \\ \mbox{Total events} \\ \mbox{Heterogeneity: Chi^2 = 1.53, d} \\ \mbox{Test for overall effect: $Z = 8.4$ \\ \mbox{Test Links 2010} \\ \mbox{StreRLINS 2011} \\ \mbox{VILLARINS 2015} \\ \mbox{StreRLINS 2016} \\ \mbox{HUANG 2016} \\ \mbox{SUN 2018} \\ \mbox{SUN 2018} \\ \mbox{Subtotal (95\% Cl)} \\ \mbox{Total events} \\ \mbox{Heterogeneity: Chi^2 = 1.15, d} \\ \mbox{Test for overall effect: $Z = 7.9$ \\ \mbox{L1.2 CASE-CONTROL} \\ \mbox{Link 2016} \\ \mbox{ARCUELLO PEREZ 2017} \\ \end{array}$	1 22 17 (P = 0 17 (P < 0.7 26 9 (P < 0.7 11 (P < 0.7 12 (P < 0.7	8 165 0.99); (10001) 202 = 1.00) 00001) 0.11, dt 121 0 15 21 1 9 5 0 172 0.95); (10001) 3 4 7	111 4981 ₽ = 0% 5574 4 5574 6 1 (P = 0% 1 (P = 0%) 5246 5246 5355 555 455 535 555 455 555 455 557 557	196 9872 11317 0.74),  * 7610 905 378 670 86 264 388 91 10382 136 164 250	48%, 87.4% 100.0% = 0% Weight 66.6% 7.8% 4.0% 0.4% 2.8% 86.2%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.77] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.06, 1.34] 0.22 [0.02, 14.85] Not estimable 0.17 [0.11, 0.27] 0.29 [0.01, 5.68] 0.23 [0.01, 5.68] 0.23 [0.01, 5.68]	2019 Year 2011 2015 2016 2018 2018 2020 2021 2021 2015 2016 2017 2017	NON- DILI DILI
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for subgroup difference: Study or Subgroup 1.1 PROSPECTIVE STERLING 2011 VILLARING 2015 STERLING 2016 MORO 2018 SUN 2018 SUN 2018 FENG 2020 LIN 2021 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.15, d Test for overall effect: Z = 7.9 <b>1.12 CASE: CONTROL</b> LINES 2015 YAMIN 2016 ARGUELLO PEREZ 2017 SIMKINS 2017 CHEN 2018	$\begin{array}{c} 1 \\ 22 \\ 27 \\ 7 \\ 7 \\ 7 \\ 7 \\ 7 \\ 7 \\ 7 \\$	8 165 0.99); [10001] 202 = 1.00) 0001] 001] 0.11, dt 121 0 15 0 172 0.95); [10001] 3 4 7 6 2 8	111 4981 F = 0% 5574 4 ; F = 0% (= 1 (P = Non-1 Events 3968 471 204 101 31 3068 471 309 5246 6 F = 0% 45 53 55 55 54 33 53 53 53 53 53 53 53 53 53	196 9872 11317 0.74), P DILI 7010 905 378 670 86 205 86 905 378 86 91 10382 1366 164 164 250 260 147 42 96	48%, 87.4% 100.0% = 0% 666.6% 7.8% 0.7% 4.4% 0.7% 86.2% 1.4% 2.3% 1.5%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.71] 0.59 [0.02, 14.85] 0.27 [0.04, 1.34] 0.22 [0.04, 1.35] Not estimable 0.17 [0.11, 0.27] 0.29 [0.01, 5.68] 0.23 [0.01, 4.18] 0.23 [0.01, 4.18] 0.18 [0.01, 3.35] 0.20 [0.01, 4.18] 0.18 [0.01, 3.35] 0.20 [0.01, 4.18] 0.18 [0.01, 0.91]	2019 Year 2011 2015 2016 2018 2020 2021 2015 2016 2016 2017 2017 2017	NON- DILI DILI
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WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for subgroup difference: Study or Subgroup 1.1 PROSPECTIVE STERLING 2011 VILLARING 2015 STERLING 2016 MORO 2018 SUN 2016 MORO 2018 SUN 2018 FENG 2020 LIN 2021 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.15, d Test for overall effect: Z = 7.9 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.17, d Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 0.37, d Test for overall effect: Z = 2.9	$\begin{array}{c} 1 \\ 22 \\ 1 = 7 \ (\mathbb{P} < 0.c) \\ 26 \ (\mathbb{P} < 0.c) \\ 1 = 11 \ (\mathbb{P} < 0.c) \ (P$	8 165 0.99); (10001) 202 = 1.00) 10001) 0.011, dt 121 121 121 121 121 0 15 21 172 0.95); (10001) 3 4 7 6 2 8 30 1.00); (1 100); (1 100) 1.00) 1.00) 1.00 1.0	1111 4981 P = 0% 5574 4 5574 6 (r = 1 (P = Non-1 Events 3968 4 471 204 101 31 31 30 5246 P = 0% 45 53 55 43 321 111 328	196 9872 11317 0.74), P DILI 7610 905 378 670 86 254 86 91 10382 136 164 254 10382 136 164 147 4250 147 425 935	48%, 87.4% 100.0% = 0% Weight 66.6% 7.8% 0.7% 4.0% 0.7% 4.4% 2.3% 1.4% 2.3% 1.5% 2.3% 1.5% 1.3.8%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.27] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.06, 1.34] 0.22 [0.04, 1.35] Not estimable 0.17 [0.11, 0.27] 0.29 [0.01, 5.68] 0.23 [0.01, 4.18] 0.23 [0.01, 4.18] 0.18 [0.01, 3.35] 0.20 [0.01, 4.18] 0.18 [0.01, 3.35] 0.20 [0.01, 4.42] 0.18 [0.01, 0.97] 0.18 [0.06, 0.57]	2019 Year 2011 2015 2016 2018 2020 2021 2015 2016 2016 2017 2017 2017	NON- DILI DILI
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$\label{eq:source} \begin{split} & \text{WHEELER 2019} \\ & \text{Subtotal (95% CI)} \\ & \text{Total events} \\ & \text{Heterogeneity: Chi^2 = 1.11, d} \\ & \text{Test for overall effect: } Z = 7.9 \\ \hline & \text{Total (95% CI)} \\ & \text{Total events} \\ & \text{Heterogeneity: Chi^2 = 1.53, d} \\ & \text{Test for subgroup difference:} \\ & \text{Steed or Subgroup} \\ \hline & \text{Iteror Substant (95% CI)} \\ \hline & \text{Total events} \\ \hline & \text{Heterogeneity: Chi^2 = 0.17, d} \\ \hline & \text{Subtotal (95% CI)} \\ \hline & \text{Total events} \\ \hline & \text{Heterogeneity: Chi^2 = 0.37, d} \\ \hline & \text{Test for overall effect: } Z = 2.9 \\ \hline \\ \hline & \text{Total (95% CI)} \\ \hline \hline \end{array}$	$\begin{array}{c} 1\\ 22\\ f=7 \ (P < 0.c\\ 0 \ (P < 0.c\ (P < 0.c$	8 165 0.99); (0001) 202 = 1.00) 0001) 0.11, dr 121 0 15 21 1 9 5 0 0 172 0.95); () 00001) 3 4 7 6 2 8 30 1.00); 1 003 202 = 1.00) 202 = 1.00) 202 = 1.00 202 = 1.00 = 1.00 = 1.0	111 4981 F = 0% 5574 (F = 0% (= 1 (P = Frents 3968 471 204 101 31 30 291 30 5246 (F = 0% 45 53 55 43 321 111 328 (F = 0% 5574	196 9872 11317 0.74), P DILI 7610 905 378 670 86 254 86 91 10382 136 164 254 10382 136 164 147 4250 147 425 935	48%, 87.4% 100.0% = 0% Weight 66.6% 7.8% 0.7% 4.0% 0.7% 4.4% 2.3% 1.4% 2.3% 1.5% 2.3% 1.5% 1.3.8%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.27] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.06, 1.34] 0.22 [0.04, 1.35] Not estimable 0.17 [0.11, 0.27] 0.29 [0.01, 5.68] 0.23 [0.01, 4.18] 0.23 [0.01, 4.18] 0.18 [0.01, 3.35] 0.20 [0.01, 4.18] 0.18 [0.01, 3.35] 0.20 [0.01, 4.42] 0.18 [0.01, 0.97] 0.18 [0.06, 0.57]	2019 Year 2011 2015 2016 2018 2020 2021 2015 2016 2016 2017 2017 2017	NON- DILI DILI Odds Ratio M-H, Fixed, 95% CI 
WHEELER 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.11, d Test for overall effect: Z = 7.9 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1.53, d Test for subgroup difference: Study or Subgroup 1.1 PROSPECTIVE STERLING 2011 VILLARING 2015 STERLING 2016 MORO 2018 SUN 2018 SUN 2018 FENG 2010 LINA 2016 MORO 2018 SUN 2018 FENG 2010 LINA 2016 HEARO 2010 LINA 2017 Total events Heterogeneity: Chi <sup>2</sup> = 1.15, d Total events Heterogeneity: Chi <sup>2</sup> = 0.37, d Test for overall effect: Z = 2.9 Total events Heterogeneity: Chi <sup>2</sup> = 0.37, d Test for overall effect: Z = 2.9 Total events Heterogeneity: Chi <sup>2</sup> = 0.37, d Test for overall effect: Z = 2.9 Total events Heterogeneity: Chi <sup>2</sup> = 0.37, d Test for overall effect: Z = 2.9	$\begin{array}{c} 1 \\ 22 \\ 1 \\ 7 \\ 7 \\ 7 \\ 7 \\ 7 \\ 7 \\ 7 \\ 7 \\ 7$	8 165 0.99); (:0001) 202 = 1.00) 0001) 202 = 1.00) 10001) 121 1 1 1 1 1 1 9 5 0 172 0.95); (: 0.95);	1111 4981 F = 0% 5574 4 (F = 0% f = 1 (P = Freents 3968 4 471 204 101 310 291 300 291 100 5246 6 53 55 43 21 111 328 F = 0% 5574 4 5574 4 5577 4 577 577 577 57 577	196 9872 11317 0.74), P 0LL Total 905 378 670 86 254 86 254 87 10382 136 164 250 147 42 1965 147 42 1935	48%, 87.4% 100.0% = 0% Weight 66.6% 4.0% 0.7% 4.4% 2.8% 86.2% 1.4% 1.8% 2.0% 2.0% 1.3.8% 13.8%	0.11 [0.01, 0.91] 0.17 [0.11, 0.26] 0.18 [0.12, 0.26] 0.18 [0.12, 0.26] 0.16 [0.10, 0.27] Not estimable 0.21 [0.06, 0.27] 0.13 [0.01, 2.17] 0.59 [0.02, 14.85] 0.27 [0.06, 1.34] 0.22 [0.04, 1.35] Not estimable 0.17 [0.11, 0.27] 0.29 [0.01, 5.68] 0.23 [0.01, 4.18] 0.23 [0.01, 4.18] 0.18 [0.01, 3.35] 0.20 [0.01, 4.18] 0.18 [0.01, 3.35] 0.20 [0.01, 4.42] 0.18 [0.01, 0.97] 0.18 [0.06, 0.57]	2019 Year 2011 2015 2016 2018 2020 2021 2015 2016 2016 2017 2017 2017	NON- DILI DILI

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.<sup>25–29</sup> 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,

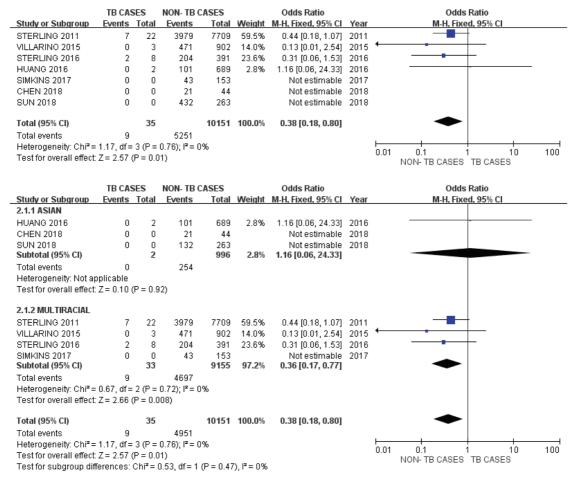


Fig. 3 Forest plot of efficacy to prevent tuberculosis infection among patients receiving 3HP compared with 9H regiment in seven studies and subgroup analysis of different ethnic populations. Events denote patients received 3HP regimen.

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.<sup>10,13,16,18,20,23</sup> 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.<sup>10</sup> Another randomized control study also demonstrated a high rate of systemic drug reactions in patients receiving the 3HP regimen.<sup>18</sup> 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,<sup>30</sup> 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 rifampicinresistant 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.

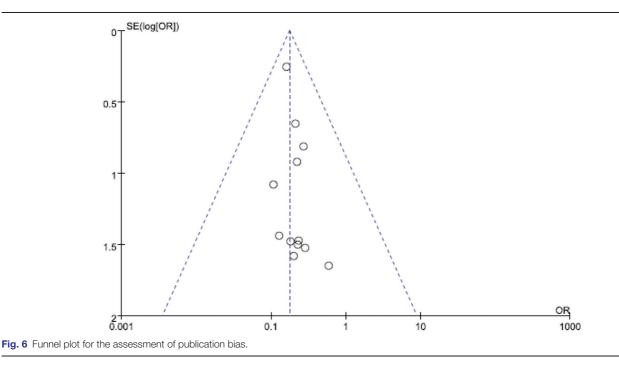
There are some limitations to this meta-analysis. First, we only compared the 3HP and 9H regimens, so that our results cannot be extrapolated to 3HP with other diverse regimens. Second, although children, patients with human immunodeficiency virus infection, pregnant women, renal transplant candidates, 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 selfadministered 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.

Study or Subgroup	Events	Total	Events	rotal	vveidnī	M-H, Fixed, 95% Cl	rear	M-H. Fixed, 95% CI
STERLING 2011	3273	5858	713	1873	79.3%	2.06 [1.85, 2.29]		
LINES 2015	35	84	10	55	1.2%	3.21 [1.43, 7.23]		
/ILLARINO 2015	415	766	56	139	7.2%	1.75 [1.21, 2.53]		
HUANG 2016	98	613	3	78	0.7%	4.76 [1.47, 15.39]	2016	
STERLING 2016	183	306	23	93	2.4%	4.53 [2.68, 7.64]	2016	
(AMIN 2016	42	117	11	51	1.6%	2.04 [0.95, 4.38]	2016	
ARGUELLO PEREZ 2017	48	165	7	92	1.1%	4.98 [2.15, 11.55]	2017	
SIMKINS 2017	40	92	3	61	0.3%	14.87 [4.34, 50.96]	2017	
CHEN 2018	19	37	2	7	0.3%	2.64 [0.45, 15.37]		
5UN 2018	118	220	14	43	1.8%	2.40 [1.20, 4.78]		
WHEELER 2019	110	149	12	65		12.46 [6.03, 25.73]		
ENG 2020	250	321	43	72	2.6%	2.37 [1.38, 4.07]		
LIN 2021	41	66	45	25	0.8%	2.92 [1.12, 7.59]		
JIN 2021	41	00	9	25	0.0 %	2.92 [1.12, 7.59]	2021	
fotal (95% CI)		8794		2654	100.0%	2.30 [2.10, 2.53]		•
Fotal events	4672		906					
Heterogeneity: Chi <sup>2</sup> = 48.08,			5					0.01 0.1 1 10 10
Fest for overall effect: Z = 17	.62 (P < 0.00001)							NON- COMPLETE TREATMENT COMPLETE TREATMENT
	COMPLETE TRE	ATMENT I	NON- COMPLETE TR	EATMENT		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events		Weight	M-H, Fixed, 95% CI	Year	
3.1.1 ASIAN								
	98	613	3	78	0.7%	4.76 [1.47, 15.39]	2016	
CHEN 2018	19	37	2	7	0.3%	2.64 [0.45, 15.37]		
SUN 2018	118	220	14	43	1.8%	2.40 [1.20, 4.78]		
	250	321	43					
ENG 2020				72	2.6%	2.37 [1.38, 4.07]		
LIN 2021 Subtotal (95% CI)	41	66 1257	9	25 225	0.8% 6.2%	2.92 [1.12, 7.59] 2.75 [1.92, 3.94]	2021	•
Fotal events	526	1257	71	225	0.270	2.75 [ 1.52, 3.54]		-
Heterogeneity: Chi² = 1.29, c Fest for overall effect: Z = 5.5	df = 4 (P = 0.86); I <sup>2</sup>	= 0%	~ ~					
3.1.2 MULTIRACIAL								
STERLING 2011	3273	5858	713	1873	79.3%	2.06 [1.85, 2.29]	2011	
INES 2015	35	84	10	55	1.2%	3.21 [1.43, 7.23]		
/ILLARINO 2015	415	766	56	139	7.2%	1.75 [1.21, 2.53]		
STERLING 2016	183	306	23	93	2.4%	4.53 [2.68, 7.64]		
(AMIN 2016	42	117	11	51	1.6%	2.04 [0.95, 4.38]		
ARGUELLO PEREZ 2017	48	165	7	92	1.1%			
SIMKINS 2017	40	92	3	61		14.87 [4.34, 50.96]		
AVHEELER 2019	110	149	12	65		12.46 [6.03, 25.73]		
Subtotal (95% Cl)	110	7537	12	2429	93.8%	2.27 [2.06, 2.50]	2019	•
Fotal events	4146		835					
Heterogeneity: Chi² = 46.05, Fest for overall effect: Z = 16								
fotal (95% CI)		8794		2654	100.0%	2.30 [2.10, 2.53]		•
Fotal events	4672		906					
Heterogeneity: Chi <sup>2</sup> = 48.08,		001): I <sup>2</sup> = 759						ter t t
								0.01 0.1 1 10 10

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.

Study or Subgroup								
Study of Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
STERLING 2016	2	2	205	391	3.1%	4.54 [0.22, 95.13]	2016	
ARGUELLO PEREZ 2017	3	3	52	254	1.2%	27.00 [1.37, 530.88]	2017	
CHEN 2018	2	2	19	42	2.5%	6.03 [0.27, 133.11]	2018	
SUN 2018	54	76	78	187	76.9%	3.43 [1.93, 6.09]	2018	<b>-</b> ∎-
LIN 2021	7	10	41	79	16.3%	2.16 [0.52, 8.97]	2021	
Total (95% CI)		93		953	100.0%	3.60 [2.18, 5.97]		◆
Total events	68		395					
Heterogeneity: Chi <sup>2</sup> = 2.41,	df = 4 (P = 0.66);	<sup>2</sup> = 0%						
Test for overall effect: Z = 4.	98 (P < 0.00001	)						0.001 0.1 1 10 1000 NON- FLU LIKE SYNDROME FLU LIKE SYNDROME
								NOTATED EIKE STINDKOME TEO EIKE STINDKOME
	FLU LIKE SYN	DROME	NON- FLU LIKE SY	NDROME		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
4.1.1 ASIAN								
CHEN 2018	2	2	19	42	2.5%	6.03 [0.27, 133.11]	2018	
SUN 2018	54	76	78	187	76.9%	3.43 [1.93, 6.09]		
LIN 2021	7	10	41	79	16.3%	2.16 [0.52, 8.97]		
Subtotal (95% CI)		88		308	95.7%	3.28 [1.94, 5.55]		•
Total events	63		138					
Heterogeneity: Chi <sup>2</sup> = 0.50,								
Test for overall effect: Z = 4.	44 (P < 0.00001)	)						
4.1.2 MULTIRACIAL								
STERLING 2016	2	2	205	391	3.1%	4.54 [0.22, 95.13]	2016	
ARGUELLO PEREZ 2017	3	3	52	254		27.00 [1.37, 530.88]	2017	
Subtotal (95% CI)		5		645	4.3%	10.84 [1.29, 90.72]		
Total events	5		257					
Heterogeneity: Chi <sup>2</sup> = 0.68,		<sup>2</sup> = 0%						
Test for overall effect: Z = 2.	20 (P = 0.03)							
Total (95% CI)		93		953	100.0%	3.60 [2.18, 5.97]		◆
Total events	68		395					
Heterogeneity: Chi <sup>2</sup> = 2.41,	df = 4 /P = 0.66\	17 - 0.04						0.001 0.1 1 10 1000

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.



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.

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