Heliyon 9 (2023) e19554

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Prevalence of rifampicin resistant pulmonary tuberculosis using geneXpert assay in Ethiopia, a systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Xpert MTB/RIF assay
Pulmonary tuberculosis
Rifampicin resistance
Meta-analysis
Ethiopia

ABSTRACT

Background: Drug-resistant tuberculosis continues to be a global public health threat. Ethiopia is one of the high-burden countries for tuberculosis and multi-drug resistant tuberculosis. The estimated annual incidents of tuberculosis were 119 per 100,000 populations in 2021 and the prevalence of multi-drug resistance tuberculosis is about 0.7% among newly diagnosed cases in Ethiopia. On time detection of rifampicin resistance is essential for the management of the disease and earlier treatment initiation. Among the different diagnostic tests; Xpert is widely used for the rapid detection of *Mycobacterium tuberculosis* and rifampicin resistant in the country. The prevalence of rifampicin resistance-pulmonary tuberculosis varied from locality to locality and the estimated national prevalence of rifampicin resistance pulmonary tuberculosis is not available in the country. Therefore, the aim of this meta-analysis was to summarize the results of available studies and generate pooled prevalence estimate of rifampicin resistance pulmonary tuberculosis in Ethiopia.

Methods: Literature search was carried out using PubMed and Scopus public databases. Original articles conducted in Ethiopia and those containing a prevalence report of rifampicin resistance pulmonary tuberculosis diagnosed by Xpert *Mycobacterium tuberculosis*/rifampicin resistance assay were included in the meta-analysis. All retrospective and prospective studies published until May 2022 were screened in the study. The methodological qualities of included article were assessed using Joanna Briggs Institute quality assessment tool for cross-sectional studies. Random effect model was used to determine the pooled prevalence of rifampicin resistance pulmonary tuberculosis. Subgroup analysis and regression were carried out across regional states and study designs. Heterogeneity across studies was assessed using I^2 test. The data were analyzed using STATA version 14.

Result: A total of 1570 titles were identified and 34 studies met the inclusion criteria. Of the total 17,292 pulmonary tuberculosis patients who were identified from the included articles, 1669 were rifampicin resistance pulmonary tuberculosis. The pooled prevalence of rifampicin resistant among pulmonary tuberculosis patients diagnosed with Xpert *Mycobacterium tuberculosis*/rifampicin resistance assay was 9.67% (95% CI: 8.11–11.24). The highest pooled prevalence was from Oromia11.84% (95% CI: 4.49–19.2%) and the lowest rifampicin resistance was identified in

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https://doi.org/10.1016/j.heliyon.2023.e19554
Received 23 November 2022; Received in revised form 8 August 2023; Accepted 25 August 2023
Available online 28 August 2023

Amhara Regional State, 8.51% (95% CI: 5.96–11.06%). The pooled prevalence rates of rifampicin resistant among pulmonary tuberculosis patients were 10.18% (95% CI: 6.85–13.51) and 9.57% (95% CI: 7.68–11.47) in prospective and retrospective types of cross-sectional studies.
Conclusion: Our study showed that the pooled prevalence of rifampicin resistance among pulmonary tuberculosis patients was 9.67%. This showed that the occurrence of rifampicin resistance pulmonary tuberculosis among Mycobacterium tuberculosis patients remains high in Ethiopia. Regional state wise, rifampicin resistance variation was small. Further meta-analysis of factors associated with rifampicin resistance among pulmonary tuberculosis patients as well as among extrapulmonary *Mycobacterium tuberculosis* cases should be carried out.

1. Background

Tuberculosis (TB) is a complex and chronic infectious disease caused by *Mycobacterium tuberculosis* (MTB). It affects the lung parenchyma as pulmonary TB but TB can also affect other body parts and is known as extra-pulmonary TB (EPTB) [1,2]. TB is one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent and ranks second next to COVID-19. Approximately 9.9 million people fell ill with TB (127 cases per 100,000 population) and 1.3 million deaths among HIV-negative people with an additional 214,000 deaths among HIV-positive people in 2020 [3].

The first line drug for TB consists of rifampicin, isoniazid and pyrazinamide and ethambutol [4]. Drug-resistant TB continues to be a public health threat. The bacteria develop resistance to a single drug or combination of drugs at a time. Multidrug-resistant TB is caused by bacteria that develop resistance to at least isoniazid and rifampicin. Close to half a million people developed rifampicin-resistant TB (RR-TB), of which 78% had multidrug-resistant TB (MDR-TB) in 2019 [5]. Under WHO guidelines, the detection of MDR/RR-TB requires the use of WHO recommended tests such as Xpert MTB/RIF as initial diagnosis [2]. The Xpert MTB/RIF assay is an automated, real-time nucleic acid amplification technology run on the multi-disease platform GeneXpert [6]. GeneXpert MTB/RIF assay detects MTB and RR-conferring mutations simultaneously in a closed system. It is also suitable for use outside conventional laboratory settings in less than 2 h, directly from sputum samples. The test is currently recommended as a first-line diagnostic test in endemic countries [7].

Ethiopia is one among the high-burden countries for TB and multi-drug resistant TB (MDR-TB). The estimated annual incidents of TB was 119 per 100,000 population, in 2021 [8] and an estimated 5800 MDR-TB cases each year in Ethiopia [9]. The prevalence of MDR-TB was 2.7% and 14% among new cases and re-treatment cases, respectively [9]. GeneXpert is one of the rapid and sensitive molecular assays used for the initial diagnosis of MTB as well as for rifampicin resistance in Ethiopia. Although several studies have investigated rifampicin resistance among PTB patients using Xpert MTB/RIF assay in different regions of Ethiopia, a meta-analysis showing a pooled prevalence of rifampicin resistance has not yet been reported. Hence, this study aimed to estimate the pooled prevalence of rifampicin resistance which was reported by geneXpert assay in Ethiopia.

2. Materials and methods

2.1. Eligibility criteria

Original articles published in Ethiopia and those containing a prevalence report of RR-PTB as diagnosed by Xpert MTB/RIF assay were included. Both retrospective and prospective studies were included. Publication year and sample size were not used as exclusion crtiteria. Studies with insufficient information about patients' characteristics were excluded.

2.2. Information sources and search strategy

Eligible articles were retrieved from PubMed/MEDLINE and Scopus electronic databases. The search was carried out using appropriate MeSH terms, keywords and boolean operators. The following keywords and combinations were used during the search: "Tuberculosis" OR "*Mycobacterium tuberculosis*" OR "Pulmonary Tuberculosis" OR "drug resistance MTB" OR "RR MTB" AND "Xpert MTB/RIF assay" AND "Ethiopia". In addition, locally available references or grey literatures were included in the meta-analysis. Finally, a total of 34 articles published from 2015 to May 2022 were included in this review.

2.3. Study selection

All of the identified articles were exported to EndNote 9 reference manager software. After removing the duplicates, screening was done by reading the title followed by reading the abstract and then by reviewing the full article. Articles that did not fulfill the inclusion criteria were excluded. Article selection was done by two authors (MD and ZM) independently. Any differences in the process were resolved by discussion. Article selection was carried out using PRISMA flowchart.

2.4. Data collection process and data items

Data from the included articles were extracted using piloted data extraction Excel sheet. The data collection were carried out by two authors (MD and ZM) in duplicate and independently. Disagreements on the extracted data were resolved by discussion. The data items included name of first author, year of publication, study period, region, study design, sample size (number of PTB cases), population type and number of rifampicin resistant cases.

2.5. Study risk of bias assessment

To evaluate the risk of bias among included studies, we used the Joanna Briggs Institute quality assessment tool for cross-sectional studies [10] (see Table S1). The risk of bias assessment was carried out by two reviewers (MD and ZM). The risk of bias tool contains eight domains and each domain contains questions with alternative answers such as "yes", "no", "unclear" or "not applicable" independently.

2.6. Effect measures and synthesis methods

Pooled prevalence and 95% confidence intervals (95% CI) of RIF-resistance among patients with confirmed PTB were the effect measure. Random-effects model based on the DerSimonian and Laird method [11] was used. Publication bias was assessed qualitatively using funnel plot symmetry and quantitatively using Egger's regression tests ($p < 0.05$). To minimize study hetrogenecity, subgroup meta-analysis and meta-regression were carried. To evaluate the influence of each on the overall pooled data and assess robustness of the synthesized results, sensitivity analysis was carried out. Further, I^2 test and *P*-values were used to assess heterogeneity across studies [12]. The analysis outputs were summarized using tables, forest plot and funnel plot.

2.7. Certainty assessment

To display the accuracy of each meta-analysis output, each analysis was accompanied with 95% CI. The interpretation of results was done by incorporating 95% CI, weight and quality of each study. The analyses were performed using STATA version 14 (IC; Stata Corporation, College Station, TX, USA).

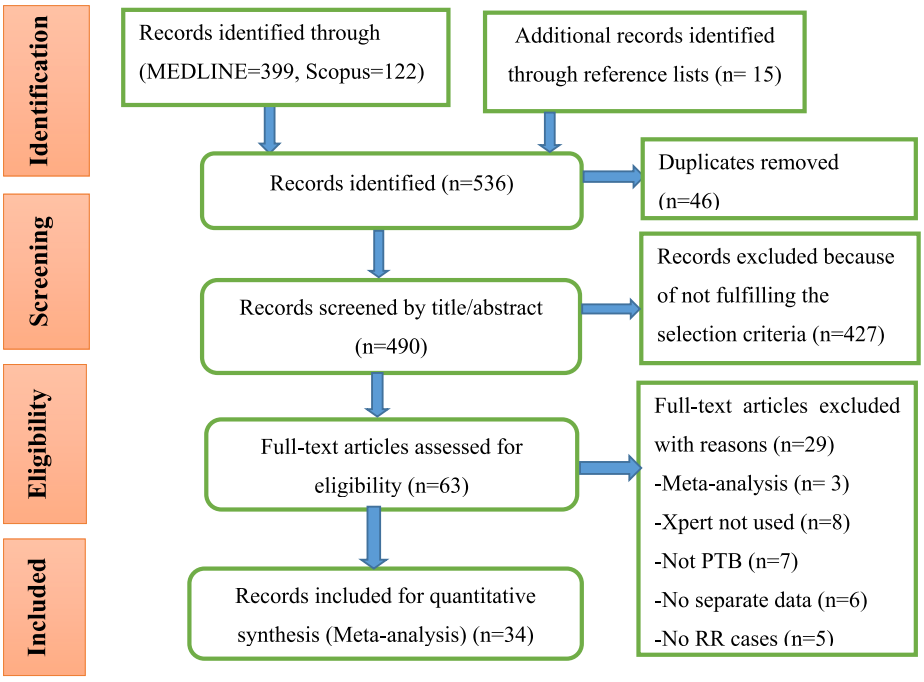

Fig. 1. PRISMA flow diagram depicting the selection process of articles.

3. Results

3.1. Study selection

A total of 536 articles were retrieved from PubMed, Scopus and reference lists of published articles. After removing 46 duplicate articles, 490 articles were further screened by title and abstract. Of those articles, 427 articles were removed by title and abstract. The remaining 63 articles were subjected to full-text screening. Finally, 34 articles fulfilled the eligibility criteria and were enrolled in the meta-analysis [13–46]. The article selection was carried out following the PRISMA flow diagram (Fig. 1).

3.2. Characteristics of included articles

From the total 34 articles, 17,292 bacteriologically confirmed PTB patients were identified. The period of articles published vary between 2012 and 2020. The studies included in this meta-analysis were derived from nine regional states of Ethiopia. The majority (~35%) of the articles were from the Amhara Regional State [13–24]. In all included articles, Xpert MTB/RIF assay was performed according to the WHO guidelines. The sample size ranged from nine to 2941 participants enrolled per study. The prevalence of rifampicin resistance ranged from 2.3% to 34.33% among PTB patients included in the review. The 20 included articles were prospective cross-sectional studies and the remaining 14 articles were retrospective cross-sectional studies. Of the total PTB patients included in the articles, 1669 PTB cases were RR (Table 1).

4. Results of synthesis

The overall prevalence of RR among all PTB patients was 9.67% (95% CI 8.11–11.24%) as indicated in Fig. 2. The pooled prevalence of RR among PTB patients was almost comparable among regions, the highest being in the Oromia region (11.84%, 95% CI: 4.49–19.2%) and the lowest in the Amhara region (8.51%, 95%CI: 5.96–11.06%). Although a higher prevalence of RR was reported

Table 1
Characteristics of the included studies investigating the pooled prevalence of rifampicin resistance among PTB patients.

Author name	Year of publication	Region	Study design	Study subject	Total PTB cases (N)	RIF-resistant patients (N)	OQS
Gebreyes et al., [13]	2021	Amhara	RC	26,656	2941	245	6
Derbie et al. [14]	2016	Amhara	RC	1922	258	24	6
Gelaw et al. [15]	2021	Amhara	PC	424	14	1	6
Gebretsadik et al. [16]	2020	Amhara	PC	423	38	2	8
Habtie et al. [17]	2016	Amhara	PC	353	14	1	7
Mekonnen et al. [18]	2015	Amhara	PC	124*	124	7	6
Jaleta et al. [19]	2017	Amhara	RC	12,685	448	71	7
Gizachew et al. [20]	2017	Amhara	PC	265	9	1	8
Liyew et al. [21]	2020	Amhara	PC	384	22	2	7
Selfegna and Alelign [22]	2022	Amhara	PC	170	19	3	6
Andualem and Belayneh [23]	2021	Amhara	RC	4109	323	13	6
Mulu*et al.* [24]	2017	Amhara	PC	505	64	6	7
Haile et al. [25]	2021	SNNP	RC	5944	899	137	5
Gadissa et al. [26]	2017	Orromia	PC	562	50	2	7
Gebreyesus et al. [27]	2020	Tigray	RC	30,935	2387	215	6
Arega et al. [28]	2019	Addis Ababa	RC	12,685	1876	186	7
Belachew et al. [29]	2021	SNNP	PC	321	98	4	5
Assefa et al. [30]	2015	Somali	PC	227	44	4	7
Tsegaye et al. [31]	2019	Addis Ababa	PC	13,803	19	3	6
Ejeta et al. [32]	2018	Gambella	RC	995	193	9	8
Bizayen et al. [33]	2019	Afar	PC	384	94	4	8
Kahsu and Hailay [34]	2020	Tigray	RC	5944	1414	131	6
Negash [35]	2020	Tigray	RC	7793	756	66	6
Diriba et al. [36]	2021	Orromia	RC	17,745	2090	107	6
Negash et al. [37],	2020	Tigray	PC	6322	300	42	8
Worku and Befikadu [38]	2015	SNNP	PC	236	39	8	7
Worku et al. [39]	2019	Sidama	PC	1828	217	45	5
Tadesse et al. [40]	2016	Orromia	PC	67*	67	23	8
Zewdie et al. [41]	2020	Orromia	RC	2300	491	127	8
Araya et al. [42]	2020	Addis Ababa	RC	12,685	1714	169	8
Sinshaw et al. [43]	2019	Addis Ababa	PC	418	27	3	7
Taye et al. [44]	2021	Orromia	PC	301	40	2	8
Admassu et al. [45]	2022	Orromia	RC	2220	171	4	8
Merid et al. [46]	2019	SNNP	PC	544	32	2	8

Key: RIF= Rifampicin, PTB= Pulmonary tuberculosis, RC= Retrospective, PC= Prospective, OQS = Overall quality score, * = all study subjects included in the study are PTB patients.

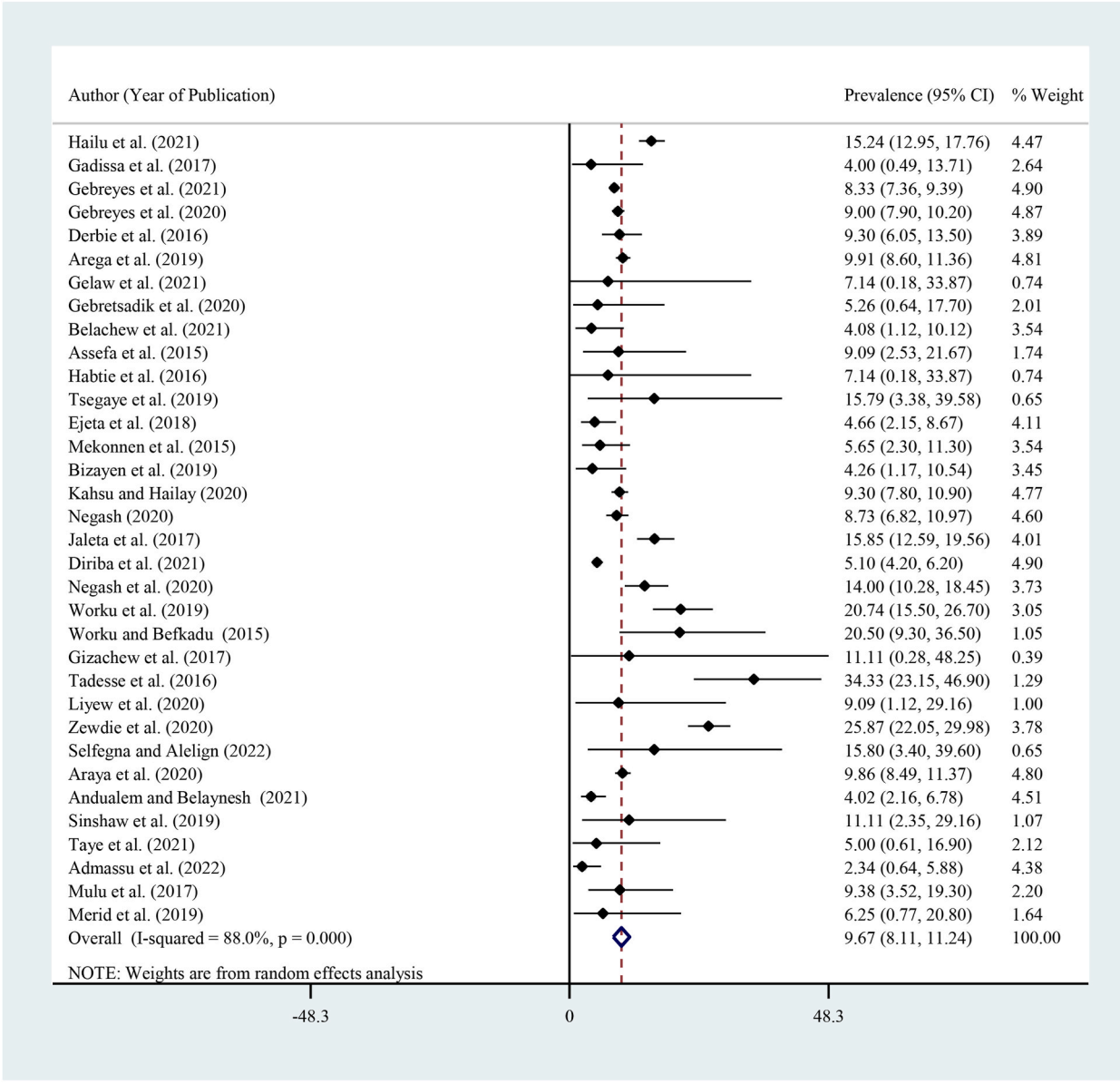

Fig. 2. Forest plot showing the prevalence of RIF-resistance among PTB patients.

from Afar, Gambella, and Sidama, we were not able to compare it with other regions as a result of a single report from each region (Fig. 3). The pooled prevalence of RR among PTB patients was 9.57% (95% CI 7.68–11.47) in retrospective studies while it was 10.18% (95% CI 6.85–13.51) in prospective studies (Fig. 4).

4.1. Risk of bias in studies

The risk of bias for each individual article was measured as "no risk of bias", "yes" and "no information", and "no applicable". Each domain has either one or zero scores. A score of no risk of bias and no information got a score of one, yes and no information scored zero. Thus, each study has a total score of zero to eight, with a higher score indicating higher quality of data. Of the total 34 articles assessed 11 and 9 articles obtained a score of eight and seven points, respectively, indicating high quality of the articles (Table 1). The quality assessment tools used in the study was attached as supplementary material 1 (S1 Table). Overall, the included articles were judged as good quality.

Further, to visually inspect publication bias, funnel plot and egger's regression analyses were carried out. The results showed that the funnel plot symmetry showed the absence of publication bias across studies (Fig. 5). The funnel plot graphic asymmetry was further assessed by Egger's linear regression test for the presence of publication bias ($p < 0.05$). The test showed there was no evidence of

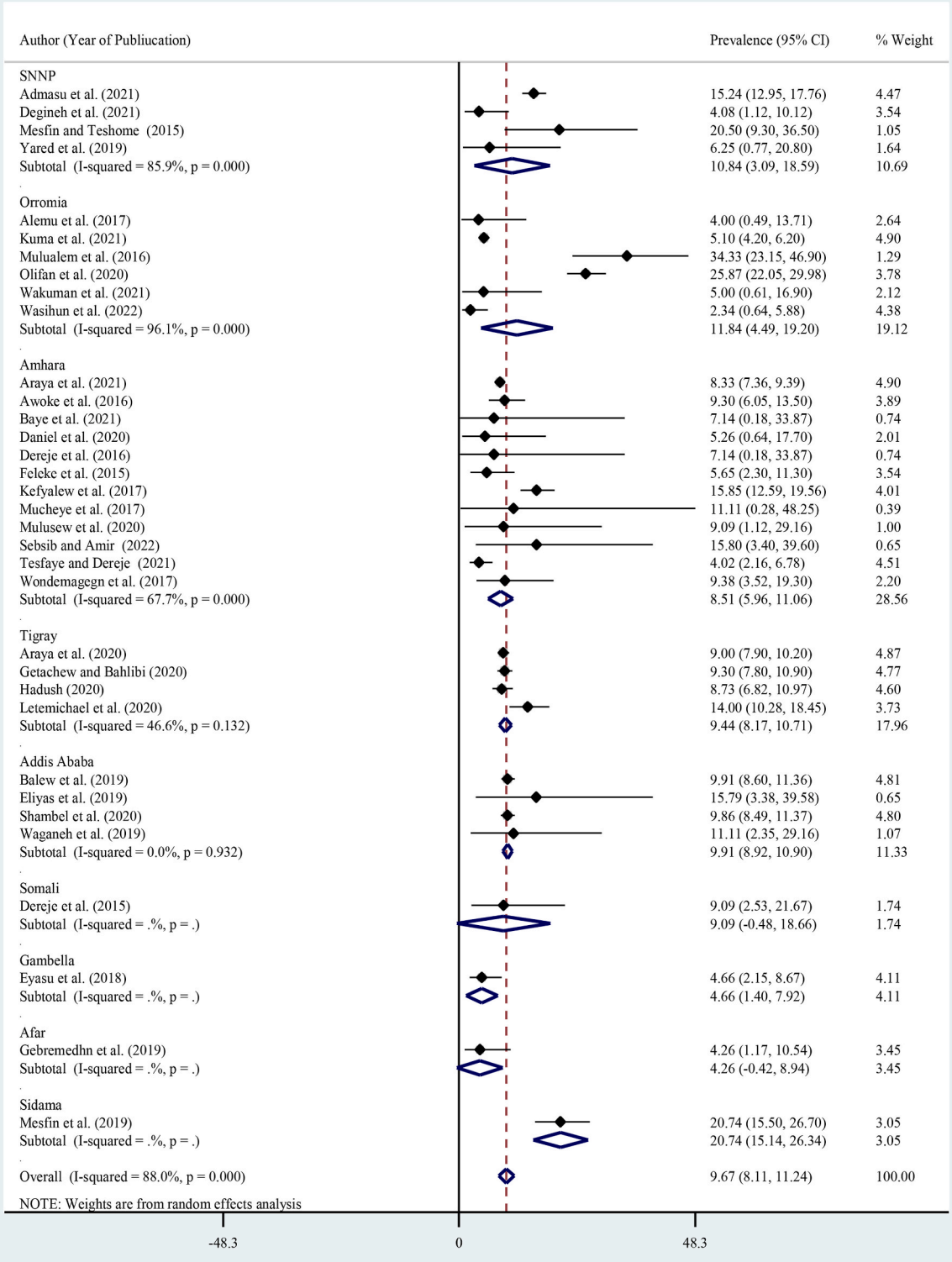

Fig. 3. Forest plot for the pooled prevalence of RIF-resistance among PTB patients by region.

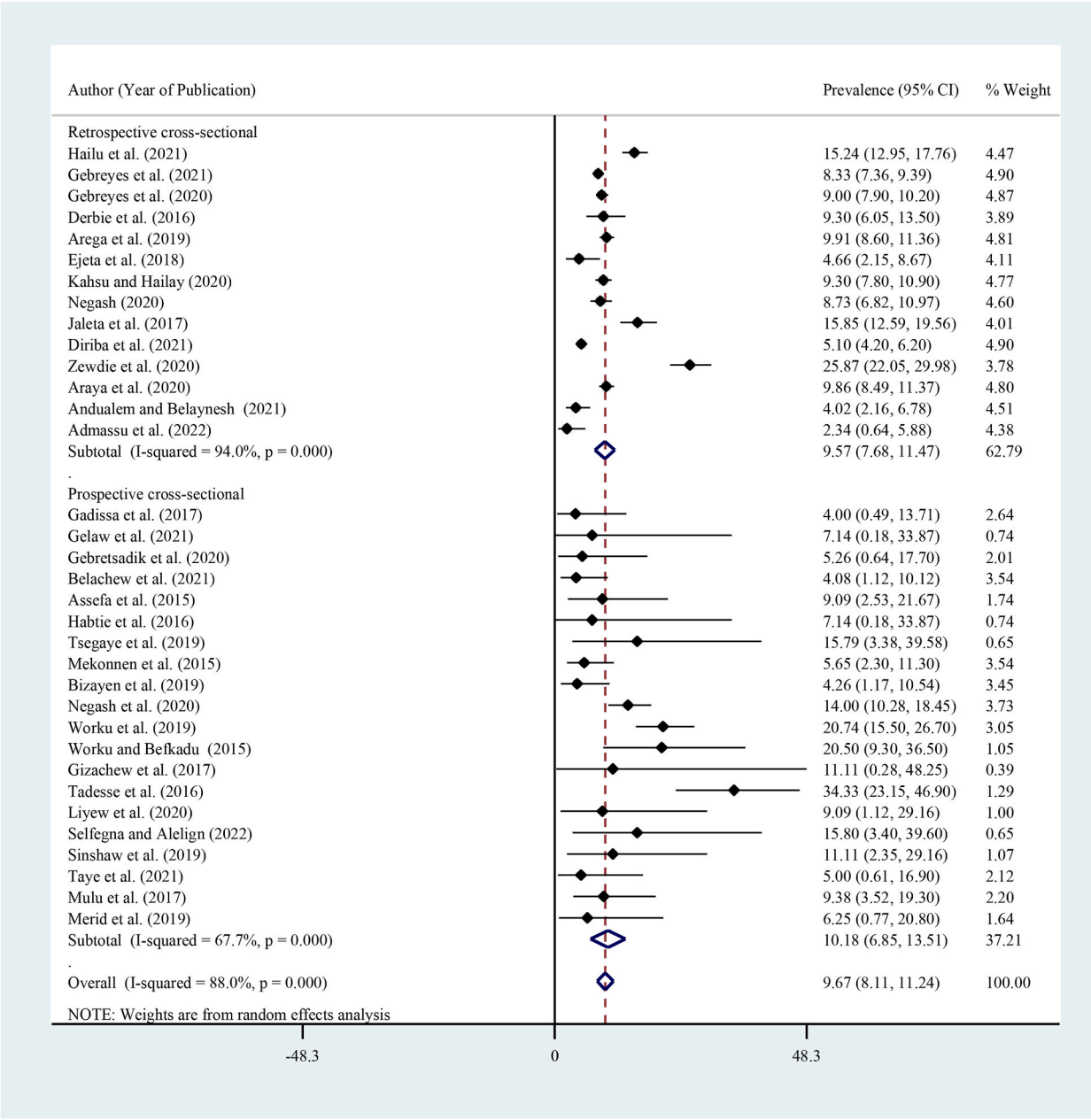

Fig. 4. Forest plot for the pooled prevalence of rifampicin resistance among PTB patients by study design.

publication bias for the prevalence of RR among PTB patients at p = 0.620 (Table 2).

5. Results of individual studies

The meta-analysis of all included articles are presented below (Fig. 2). A closer look at the 95%CI and weight of each study revealed that included articles varied widely. Articles with small weight and small sample size showed very wide 95%CI and imprecision of their associated data. For instance, Gelaw et al. (2020), Habtie et al. (2016), Tsegayeet al. (2019), Gizachew et al. (2017), Liyew et al. (2020) and Sinshaw et al. (2019) were articles with lower accuracy of individual results [15,17,20,21,31,43].

To further assess heterogeneity, a subgroup analysis was carried out. Nevertheless, single articles reported from Gambella, Somali, Afara and Sidama were not used for comparison purposes against pooled results. The subgroup analysis showed variation in terms of heterogeneity across regions (Fig. 3). Furthermore, the type of study design (e.g., prospective vs retrospective cross-sectional) reported in each article was carried out for subgroup analysis and the results of the two groups showed a slight difference in terms of pooled

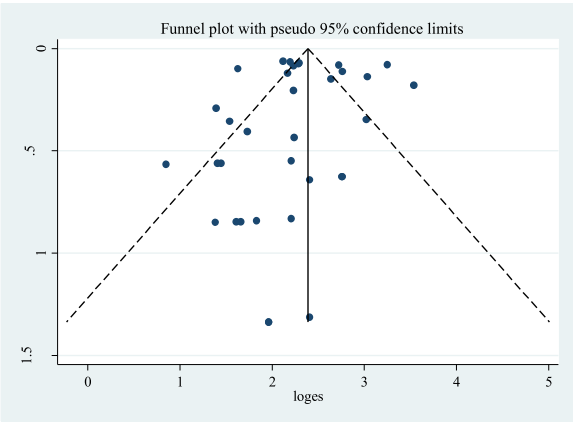

Fig. 5. Funnel plot symmetry for assessing publication bias where; loges: logarithmic of the effect size while s. e loges: standard errors of loges.

Table 2
Results from the Egger's meta-regression test assessing the absence of small-study effects.

Egger's test for small-study effects:
Regress standard normal deviate of intervention effect estimate against its standard error.

Number of studies = 34				Root MSE = 3.308		
Std_Eff	Coef.	Std.Err	t	P > |t|	(95% Confidence interval)	
Slope	2.431061	0.1149582	21.15	0.000	2.196899	2.665223
bias	−0.4179873	0.8353234	−0.50	0.620	−2.119485	1.283511

Test of HO: no small-study effects P = 0.620.

prevalence of RR (Fig. 4).

Meta-regression analysis was carried out to assess the effect of study region and design to the observed heterogeneity. The meta-regression analysis showed that region of study (regression coefficient: 1.031; 95% CI: 0.9430–1.1265; *p-value* = 0.493) and study design (regression coefficient: 0.8128; 95% CI: 0.5133–1.2871; *p-value* = 0.365) did not contribute to the observed heterogeneity in this study. The source of heterogeneity might be associated with the nature of study participants and socio-economic factors.

5.1. Certainty of evidence

The funnel plot, 95% CI of each article and overall data, and meta-regression showed that the pooled prevalence data can be rated as good quality data.

6. Discussion

Global TB control and prevention are challenging due to the emergence of drug-resistant bacilli [47]. The use of molecular-based diagnostic methods, with the detection of mutations in specific genes associated with anti-TB drug resistance, is more efficient and effective. Utilization of these methods in clinical microbiology laboratories could reduce the turnaround time required to diagnose cases from weeks to hours [48]. Early detection of drug-resistant MTB should be strengthened for the management of TB patients and this eventually minimizes the spread of rifampicin-resistant tuberculosis strains in the community [28,29,47].

The present systematic review and meta-analysis was conducted to determine the pooled prevalence of rifampicin resistance among PTB patients as diagnosed by Xpert MTB/RIF assay in different regions of Ethiopia. The pooled prevalence of RIF-resistance among 17,292 PTB patients was 9.67% in Ethiopia. The observed pooled prevalence of RIF-resistance among PTB patients is higher than among extra-PTB patients reported in a systematic review and meta-analysis in the country [49]. The finding of this result was nearly similar to a primary study conducted in the Democratic Republic of Congo [50] and a systematic review and meta-analysis from Iran [51]. In contrast to our finding, higher rifampicin resistance was reported in a systematic review and meta-analysis from Sudan [52]. These variations might be associated with the differences in the level of mutation of genes of the bacterium associated with rifampicin resistance across countries.

The prevalence of rifampicin resistant PTB among the included studies in Ethiopia varied from 2.3% to 34.3% across studies in the country [13–46]. The pooled prevalence of rifampicin resistance among regions ranged from 8.5% to 11.8%. Low prevalence of rifampicin resistance was reported in Afar and Gambela regions. The variation of rifampicin resistant PTB across the regions might be related to the number of studies on rifampicin resistant, geographical variation, differences in patient selection, sample size and PTB

control practice.

The pooled prevalence of RIF-resistance among PTB patients conducted using prospective (10.18%) and retrospective (9.57%) cross-sectional study designs were almost comparable in the present study. The result might suggest that prospective cross-sectional studies were better to manage data effectively than retrospective cross-sectional studies. However, there is no statistically significant difference between the two methods. The study design may not have an impact on the pooled results.

Many countries in the world have adopted an algorithm placing Xpert MTB/RIF assay as the initial diagnostic test for rifampicin resistance [53–57]. The results from the early programmatic implementation of Xpert MTB/RIF testing in nine countries indicated that testing with Xpert MTB/RIF assay could detect a large number of people with TB that could be missed by traditional routine health services being provided in low-income countries like Ethiopia [58]. As more number of cases are rapidly detected and treated, there will be a reduction in the transmission of primary drug resistant MTB in the community. Even though there is a limited resource in Ethiopia, the number of TB laboratories that use Xpert MTB/RIF for rapid diagnosis of TB and detection of rifampicin resistance is increasing steadily.

6.1. Limitations of the study

This meta-analysis has certain limitations. Included studies were cross-sectional, providing only snapshots of the situation at a particular moment in time and fail to capture the dynamic nature of the study population. The lack of an adequate number of studies, particularly those recording the diagnostic performance of Xpert for rifampicin resistance made it impossible to evaluate the diagnostic accuracy of Xpert MTB/RIF assay for the diagnosis of rifampicin resistance among PTB patients. In addition, the lack of sufficient information and data from some regions such as Benshangul Gumuz, Somali, Afar, Gambella and Sidama did not make our pooled prevalence of RR fully representative of the entire country. Moreover, this meta-analysis was based only on published studies and important data might be missed from unpublished studies. Furthermore, due to the lack of published meta-analysis regarding rifampicin resistance PTB using Xpert assay only, we did not discuss it by comparing it with other studies. Finally, we did not conduct sensitivity test to assess the effect of individual study on the overall effect.

7. Conclusions

Our study showed that the pooled prevalence of RR among PTB patients was 9.67%. This implies that the occurrence of RR-PTB among TB patients remains high in Ethiopia. Region-wise, RR variation was small. Implementation of a rapid diagnostic test using Xpert MTB/RIF assay as an initial diagnostic test for persons suspected of having a RIF-resistant PTB would be helpful for the control of the drug resistance. Further meta-analysis of factors associated with RR-PTB as well as with RR extra-pulmonary TB cases must carried out.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Consent for publication

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank all authors used for this systematic review and meta-analysis.

Acronyms/abbreviations

CDC Center for Disease Control and Prevention
HIV/AIDS Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
MDR/RR-TB Multi-Drug Resistant/Rifampicin-Resistant Tuberculosis
MDR-TB Multi-Drug Resistant Tuberculosis
MTB/RIF *Mycobacterium tuberculosis*/Rifampicin

PTB Pulmonary Tuberculosis
RR-PTB Rifampicin-Resistant Pulmonary Tuberculosis
RR Rifampicin resistance
TB Tuberculosis
WHO World Health Organization

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e19554.

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