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Resistance of *Mycobacterium tuberculosis* strains to Rifampicin: A systematic review and meta-analysis

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Abstract

Introduction: Antitubercular drug resistance strain is a horrifying barrier to effective TB treatment and prevention. The present study aimed to determine the

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prevalence and geographical distribution of rifampicin-resistance *M. tuberculosis* (MTB) strains.

Methods: We searched two electronic databases, PubMed and EMBASE, until 26 March 2017 and updated our search on 27 April 2018 and accessed all prevalence studies of MTB strain and their drug susceptibility patterns to rifampicin. The pooled prevalence estimate was determined using random effects model.

Results: We identified 23 studies satisfying the inclusion criteria. The proportion of rifampicin resistance strains was diverged depending on the type of strains, country and Regions. The pooled estimate of rifampicin-resistance strains of MTB for the included studies was 4% (95% CI: 3−5%). In subgroup analysis based on World Health Organization (WHO) Regions, the pooled estimate of rifampicin-resistance strains of MTB was 11% (95% CI: 9−13%) with the Western Pacific Region 24%, Europian Region 10%, South-East Asian Region 6%, African Region 3% and Region of American 1%. Beijing family was the most dominant strain resistance to rifampicin with pooled prevalence of 14% (95% CI: 10−18%). The pooled prevalence of other families, i.e. EAI, T, CAS, MANU, Haarlem, LAM and Ural, was $\leq$2% for each.

Conclusion: High burden of rifampicin resistance MTB strains was identified in the Western Pacific Region. Of these, Beijing family was predominantly resistance to rifampicin in Western Pacific Region and South-East Asian Region and also spread to European Region and Region of American.

Keyword: Infectious disease

1. Introduction

Tuberculosis (TB) is the universal health crisis cause of morbidity and mortality worldwide, causing 1.3 million deaths among HIV-negative and 374,000 deaths among HIV-positive people in 2016 [1]. Drug-resistant TB (DR-TB) reached alarming levels with the emergence of strains that are virtually untreatable with the existing drugs [2, 3, 4] and is a serious determinant of treatment success. Therefore, to advance a treatment achievement, the *Mycobacterium tuberculosis* (MTB) drug susceptibility patterns in community-based care should be determined [1]. DR-TB, particularly multidrug-resistant TB (MDR-TB) and extensive drug-resistant-TB, have become the most important public health problem in many countries [3, 5, 6]. Using molecular techniques such as spoligotyping, DNA fingerprinting [7] and variable number of tandem repeats together with drug susceptibility test is recommended to determine the MTB strains circulating in the community and their drug susceptibility profile [8]. Spoligotyping is used to cluster MTB strains into different lineages such as Beijing, Ural, Haarlem, East African-Indian (EAI), Latin American and Mediterranean (LAM), Central-Asian or Delhi (CAS), T and Orphan and they

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are the most known families circulating in the world [5, 9]. These studies indicated that drug resistant strains are found in all families of MTB identified by spoligotyping method, i.e. Beijing, Ural, EAI, LAM, T, CAS, Orphan, MANU, Haarlem and other new strains. However, the rate of drug resistance developed in these strains is not well studied. Rifampicin resistance MTB strains make a treatment complicated because it is the elements of both MDR and extensively drug resistance and thus it is the key indicator for MDR tuberculosis [10, 11, 12]. We aimed to identify all the published literature and to establish the best possible evidence base of strain identification and drug susceptibility test. Therefore, we performed a systematic review and meta-analysis to determine the prevalence and geographical distribution of rifampicin resistance MTB strains; which is critical in TB control program.

2. Methods

2.1. Search strategy and selection criteria

We systematically reviewed published studies, from the PubMed and EMBASE databases until 26th March 2017 and updated on the 27th of April, 2018. Studies that reported the prevalence of major *Mycobacterium tuberculosis* families and their drug susceptibility patterns were included with searching terms ((((drug susceptibility[tiab] AND "humans"[MeSH Terms]) OR "Microbial Sensitivity Tests"[MeSH]) AND "humans"[MeSH Terms]) AND ((species[tiab] OR family[tiab]) OR strain [tiab])) AND ((TB[tiab] OR tuberculosis[tiab]) OR ("Tuberculosis"[MeSH] OR "Extensively Drug-Resistant Tuberculosis"[MeSH] OR "Tuberculosis, Multidrug-Resistant"[MeSH])) AND "humans"[MeSH Terms].

2.2. Inclusion and exclusion criteria

Observational studies obtained from the literature search were checked by title and citation. References from the selected studies were also assessed to ensure that no relevant studies were omitted. Studies were required to meet the following inclusion criteria: 1, involving strain identification and drug sensitivity test for anti-TB drug (rifampicin); 2, drug test outcome resistance or susceptible for each strain (e.g. the number of Beijing strains resistance to rifampicin; 3, clearly defined molecular typing method (spoligotyping) and Antibiogram test procedure; and 4, outcomes reported according to World Health Organization (WHO) classification of drug sensitivity (including susceptible, mono-drug resistance, multidrug resistance, or extensively drug resistance. Only original studies written in English were considered for this study.

Studies were excluded from the analysis for any of the following reasons: 1, involving article with no report on strain and drug susceptibility pattern; 2, focusing on treatment with first and second line of anti-TB drugs but not strain identification;

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3, did not specify strains with drug sensitivity profile; 4, duplicate publications of the same study; 5, available only in abstract form or not in full text. The selection of articles for review was done in three stages: looking at the titles alone, then abstracts, and then full-text articles (Fig. 1).

2.3. Study quality and risk of bias assessment

The selected studies were assessed for quality with high quality studies included for analysis. National Institutes of Health (NIH) Quality assessment tool for Observational Cohort and Cross-Sectional Studies was employed to assess the risk of bias of the included studies [13]. Based on a study design, nine appropriate questions were used for assessing the included studies. The studies that acquired a score of

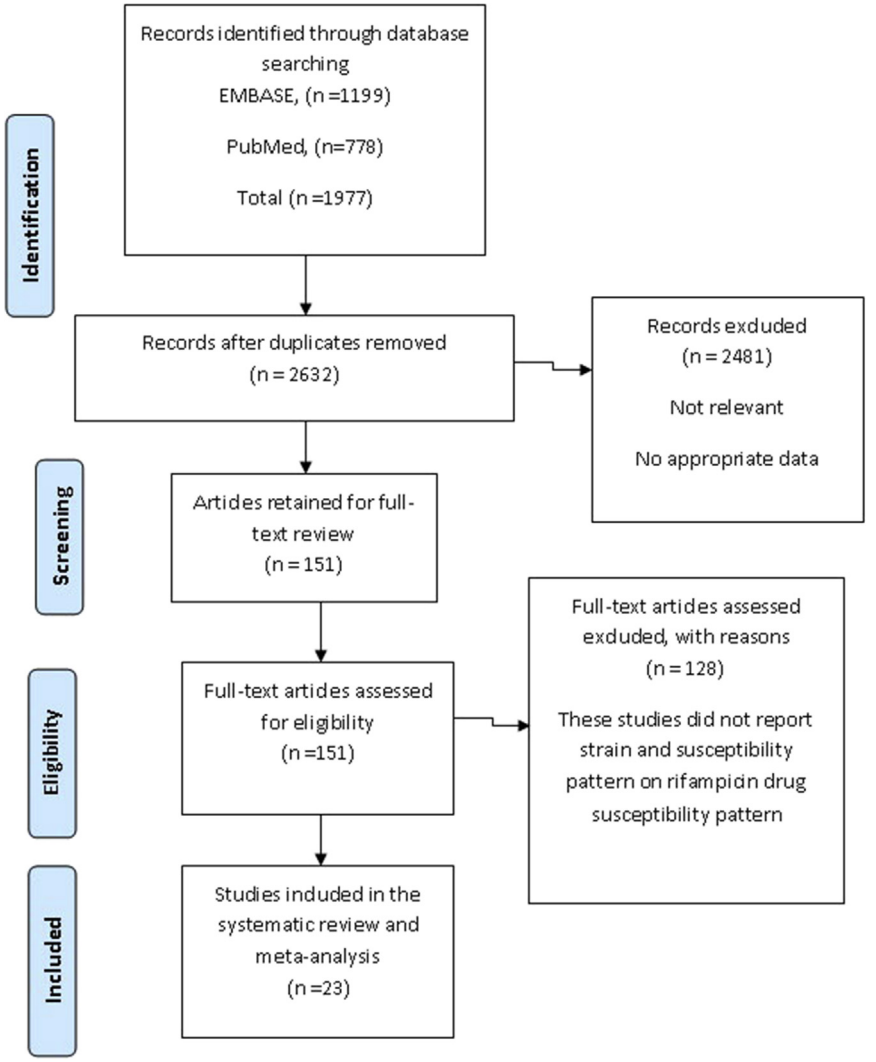

Fig. 1. PRISMA flow diagram for screening selection and evaluation of articles.

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8−9 were judged as high quality studies with less estimated risk of bias and used for sensitivity test. In the case where the study population overlapped the following measure was taken: the current and larger study population included in the analysis and on the condition, the smallest population afforded data on the result or variable not reported in the larger study results were included for that specific variable.

2.4. Data extraction and statistical analysis

Data abstraction was performed by two reviewers using a standardized abstraction form. When there was disagreement, the relevant paper was reviewed and differences were resolved by consensus. Microsoft Excel and STATA version 13 (Stata corporation, college station, Texas, USA) were used for data entry and analysis respectively. Data related to rifampicin susceptibility test outcomes for *M. tuberculosis* strains were extracted from published studies as described above. A random effects model was used to obtain the pooled effect size of the proportion of successful outcome, the strains resistance to rifampicin within the countries and Regions, across studies. Heterogeneity of the studies was estimated by calculating I^2 and Cochrane p values. I square measures the proportion true variation (heterogeneity) due to between study variation across studies and was used to identify violation in the assumption of homogeneity when $I^2 > 60$ %. The results were presented in a table as forest plot; additionally prevalence with corresponding 95% CI was obtained for the overall estimate.

2.5. Ethical considerations

All the important protocol for this systematic review and meta-analysis was registered on the PROSPERO International Prospective register of systematic reviews, managed by the University of York. The PROSPERO 60277, with ID = CRD42017060277. For more information, the following link can be accessed from: http://www.crd.york.ac.uk/PROSPERO/display_record.

3. Results

3.1. Literature searches and selection

We identified a total of 2632 citations from our initial electronic databases search. All the obtained articles were checked by title and citation then on the condition an article appeared relevant, the abstract was reviewed. Based on title and abstract reviewing, 2481 articles were excluded. Therefore, 151 articles were retained for full-text review and finally 23 studies were selected based on inclusion and exclusion criteria for this review (Fig. 1).

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3.2. Characteristics of the included studies

The included studies were from six WHO Regions, namely African Region, Region of the America, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region (Table 1). A total of 14481 collected samples from TB patients in twelve countries were analyzed. Since there was mixed reports in case of sex and age groups in most studies, we could not identify the number of male and female participants. The resistance MTB families reported in the included studies were; Beijing, Ural, Haarlem, CAS, LAM, EAI, T and MANU families. And they were identified as the causative agents of tuberculosis in the world. For each families of MTB resistance to rifampicin, the prevalence was analyzed for the selected studies as follows: Beijing nineteen studies [14, 15, 16, 17, 18, 19, 20, 21, 22, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31], LAM ten studies [15, 17, 23, 25, 28, 29, 32, 33, 34, 35], T ten studies [3, 15, 16, 17, 23, 27, 28, 32, 34, 35], EAI eight studies [18, 22, 25, 27, 28, 29, 33, 36], Ural four studies [15, 17, 30, 34] Haarlem five studies [15, 23, 25, 28, 34], CAS four studies [15, 29, 30, 35] and MANU two studies [16, 29]. The proportion of rifampicin resistance varies by the type of regions and strains. Rifampicin resistance Beijing family was the most predominant strain nearly in all the studies considered in this review.

3.3. Sensitivity analysis

The quality assessment was based on nine domains, namely: study population clearly specified and defined; inclusion/exclusion criteria; sample size justification, power description; data collection method; combined genotyping methods; Complete grouping of the isolates into their Families; drug susceptibility testing method and statistical test used to analyze the data. The most common quality benchmarks failed by the studies were: sample size justification, power description and combined genotyping methods. Eleven studies with high quality scores (greater or equal to eight out of ten) were included. The pooled estimate of rifampicin resistance strains of MTB for the high quality studies was 10% (95% CI: 7−13%) with ($I^2 = 97.08$ % and $p = 0.00$). The analysis indicates that quality score was affecting the overall pooled prevalence of rifampicin resistance strains of MTB and reduce the degree of heterogeneity between the studies with non-significant value. The low quality studies were one of the factors for study bias as shown above.

3.4. Systematic review

3.4.1. Beijing strains

A total of 1340 (9.25%) rifampicin resistance Beijing strains was identified out of 14481 evaluated MTB isolated from patients. Eigteen studies reported rifampicin resistance Beijing family. Of these studies, nine were conducted in Western Pacific Region,

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Table 1. Studies on rifampicin resistance MTB families isolated from TB patients.

Author	Publication year	Country	Region	Cases (total number)	Main outcome
Liu, H.-C., et al.	2016	China	Western Pacific Region	265	Both Beijing and non-Beijing family at least resistance to one anti-TB drug was 28.47% (41/144) and 25.62% (31/121) respectively
Pang, Y., et al.	2012	China	Western Pacific Region	3634	Beijing family was highly prevalent and also the most resistance to rifampicin
Li, Y., et al.	2016	China	Western Pacific Region	1017	About 90.5% and 6.3% were identified as Beijing and T-families respectively. Of these 347 (34.1%) was resistance to at least one of the first line drug.
Li, Q., et al.	2016	China	Western Pacific Region	510	The majority of isolates belonged to the Beijing genotype (95.3%, 486/510 isolates) and 332 isolates were rifampicin resistant strains.
Hu, Y., et al	2016	China	Western Pacific Region	1222	Of the collected isolates 298 (24.4%) were resistant to one of the 1st-line drug and 73 (5.9%) were resistant to both INH and RIF and 967 (79.1%).
Guo, Y., et al	2011	China	Western Pacific Region	158	A 123 (77.8%) isolates were identified as the Beijing genotype, and it was the most strain resistance to rifampicin.
Zhou, Y., et al.	2017	China	Western Pacific Region	3133	Beijing lineage was identified as the highest proportion of members about 14%, resistant to rifampicin.
Purwar, S., et al	2011	India	South-East Asian Region	74	The drug susceptibility patterns was shown 11 (14.86%) were MDR, significantly higher in Beijing strain than the others
Mokrousov, I., et al	2013	Russia	European Region	103	The identified families were Beijing (n = 62), T (n = 14), LAM (n = 9), Ural-2 (n = 6) and Ural-1 (n = 3) and 20 isolates were RIF-resistant.
Millet, J., et al.	2014	France	European Region	1184	Based on spoligotyp; T family 30.1%, LAM 23.7%, Haarlem 22.2%, EAI 7.2% and others about 6.5%. MDR cases have been seen in LAM genotype.
Lukoye, D., et al.	2014	Uganda	African Region	497	The identified genotype include; T2-Uganda, T2 (17.1%), CAS, LAM, and T1, Haarlem, MANU, T2T3, T3_Eth, undesignated, and EAI. About 15.1% the isolates were showed resistance to at least one of the first-line anti-TB drugs.

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Table 1. (*Continued*)

Author	Publication year	Country	Region	Cases (total number)	Main outcome
Bazira, J., et al	2011	Uganda	African Region	125	About 59.2% were Uganda genotype and 4.8% were rifampicin resistance strains.
López-Rocha, E., et al	2013	Mexico	Region of American	248	About 95.3% was Euro-American lineage and, 9.7% of the isolates were resistant to one or more drugs and only 0.8% resistance to rifampicin.
Flores-Treviño, S., et al.	2015	Mexico	Region of American	68	The majority lineages were T (38.2%), Haarlem (17.7%), LAM (17.7%) and others 16.3%. Beijing family was 1.5% with the most MDR isolates
Lisdawati, V., et al.	2015	Indonesia	South-East Asia Region	404	EAI family comprised 15.3 % but Beijing family isolates resistance to any of the first line anti-TB drugs was significantly higher than non-Beijing families.
Chaidir, L., et al.	2015	Indonesia	South-East Asia Region	198	The mainly frequent lineage found among all isolates was EAI (n = 66, 33.7%), followed by Euro-American (n = 38, 19.4%) and 15 (7.6%) of the total was rifampicin resistance strains
Kuhleis, D., et al	2015	Brazil	Region of America	392	The most prevalent lineage were; LAM family 40%, T family 22%, Haarlem family 17.5% t and 15% of the isolates were resistant to at least one of the first line drug.
Kibiki, G. S., et al.	2007	Tanzania	African Region	130	The genotype distribution was: CAS 33.8.0%, LAM 18.4%, EAI 6.2%, Beijing 5.4%, T- 8.4% and 9.2% others. The drug susceptibility pattern was showed, 12 (10.8%) of the 111 tested strains were resistant to at least one anti-TB drugs.
Haeili, M., et al	2013	Iran	Eastern Mediterranean Region	291	Ural was highly prevalent lineage about 34.3% followed by CAS 24%, T 18.2%, Manu2 7.5% and LAM 6.1%. A 5% MDR and 10% mono-resistance strains were detected.
Liu, Y., et al.	2017	China	Western Pacific Region	268	Of 268 isolates, 219 was identified as Beijing family, in which 42(19.2%) was resistance to RFM.
Cox, H. S., et al	2005	Uzbekistan and Turkmenistan	European Region	397	On the whole, 50% of the isolates were Beijing genotype while 75% of Beijing genotype was MDR-TB.

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Table 1. (*Continued*)

Author	Publication year	Country	Region	Cases (total number)	Main outcome
Bocanegra-García, V., et al.	2014	Mexico	Region of American	72	LAM (42.85%) and T (28.57) was resistance to rifampicin.
Nguyen, H. Q., et al	2017	Vietnam	Western Pacific Region	91	About 7.7% of extensively drug resistance isolates, in which, majority were Beijing family

reported 1309 (97.68%) resistance Beijing family [2, 16, 20, 21, 22, 28, 29, 30, 31], three studies were conducted in South-East Asia Region, reported 15 (1.11%) resistance Beijing family [15, 19, 25], two studies were conducted in European Region and identified 14 (1.04%) resistance Beijing family [17, 24] and two studies were conducted in Region of American but only two resistance Beijing family [18, 23]. One study which was conducted in African Region [29] and one study conducted in Eastern-Mediterranean Region did not report a rifampicin resistance Beijing family [30]. For the studies conducted in both African Region and Eastern-Mediterranean Region, all the identified Beijing strains were susceptible to rifampicin. Ben J. Marais et al (2006) reported that drug resistance Beijing genotype isolated from children with TB in peri-urban Kampala, Uganda was susceptible to rifampicin [37].

In some of the studies, the number of each family was not clearly reported in the total isolates. So we failed to calculate the ratio of each families or strains in the total collected samples and also susceptible strains to resistance strains. Many studies were using Spoligotyping with the combination of culture-based drug susceptibility test in African region and other part of the world but they failed to identify the family or the strains of *M. tuberculosis* resistance or susceptible to specific anti-tuberculosis drug [38].

3.4.2. Non-Bejing families

A number of studies reported that anti-TB drug resistance strain were found in all MTB families identified. The studies included in this review also indicating similar patterns. However, Orphan family was not reported as rifampicin resistance TB in the included studies. The prevelance of rifampicin resistance non-Beijing families were less than 6% and were found in all WHO Regions. For instance, resistance Haarlem family was reported from Region of American, South-East Asia and European Region [17, 23, 28], CAS reported from South-East Asia, European and African Region and EAI and T families were reported from Western Pacific, South-East Asia, European and African Region [25, 29, 33, 39]. Ural was the only strain reported from East Medterranian Region, in Iran as rifampicin resistance, but it was identfed in South-East Asia, India and Region of American, Brazil, with low prevelance [15]. Resistance MANU was reported from Western pacific Region only [16].

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On the other hand resistance LAM was reported from all the WHO Regions except from East Medterranian Region.

3.4.3. Meta-analysis

The pooled estimate of rifampicin resistance strains of MTB for the included studies was 11% (95% CI: 9−14%) with very high heterogeneity ($I^2 = 98.84$ % and $p = 0.00$) (data not presented). In sub group analysis, based on WHO Region the pooled estimate of the burden of rifampicin-resistance MTB strain was 11% (95% CI; 9−14%) with high heterogeneity between studies ($I^2 = 99.84\%$, $p = 0.00$). Of the six WHO Regions, the Western Pacific Region contributed 23% (95% CI; 16−30%) followed by European Region 10% (95% CI; 0−20%), South-East Asian Region 6% (95% CI; 0−13%), African Region 3% (95% CI; 2−4%) and Region of American 1% (95% CI; 0−2%) with $I^2 = 75.57$ % and $p = 0.01$, whereas Eastern Mediterranean Region it was insignificant as shown in Fig. 3.

We also performed sub group analysis based on the rifampicin-resistance MTB families. The outcome showed that the pooled estimate of the prevalence was 4% (95% CI; 3−5%) with high heterogeneity between the groups, $I^2 = 97.74\%$ and $p = 0.00$. Beijing family was the most leading strain resistance to rifampicin and its pooled prevalence was 14% (95% CI; 10−18%) and the heterogeneity between the studies $I^2 = 99.05\%$ $p = 0.00$. The prevalance of other families were EAI 2%, T, CAS and MANU each 1% and Haarlem, LAM and Ural were 0% (Fig. 2).

The heterogeneity among the studies was observed within Region and families. Also in a similar way, it was observed in studies on Beijing, T and EAI family. But for the other families (Ural, Haarlem, CAS, LAM and MANU) the heterogeneity among studies was not significant as shown in Fig. 2. One of the studies reported on MANU family was conducted in China, out of 3634 total isolates evaluated for rifampicin susceptibility test, 20 (0.55%) MANU strains were identified as resistant [16]. The studies conducted on rifampicin resistance strains were mostly from Western Pacific Region whereby China has shared the majority. In this review, eight studies were included from Western Pacific Region, of these seven were from China. According to these studies, Beijing family was the most rifampicin-resistance strains [14, 16, 20, 22]. On the other hand, there were many reports on rifampicin resistance MTB from Eastern Mediterranean Region and African Region but most of the studies relied on gen-expert method or culture based drug susceptibility test that has no ability to identify the strain or family of MTB [40]. It is may be due to lack of application of molecular epidemiology like spoligotyping with the combination of phenotypic drug susceptibility test [10], which can be due to poor laboratory infrastructures [36, 41].

A funnel plot was constructed based on effect estimate and accuracy of each study to assess for the presence of publication bias. The Begg funnel plot symmetry

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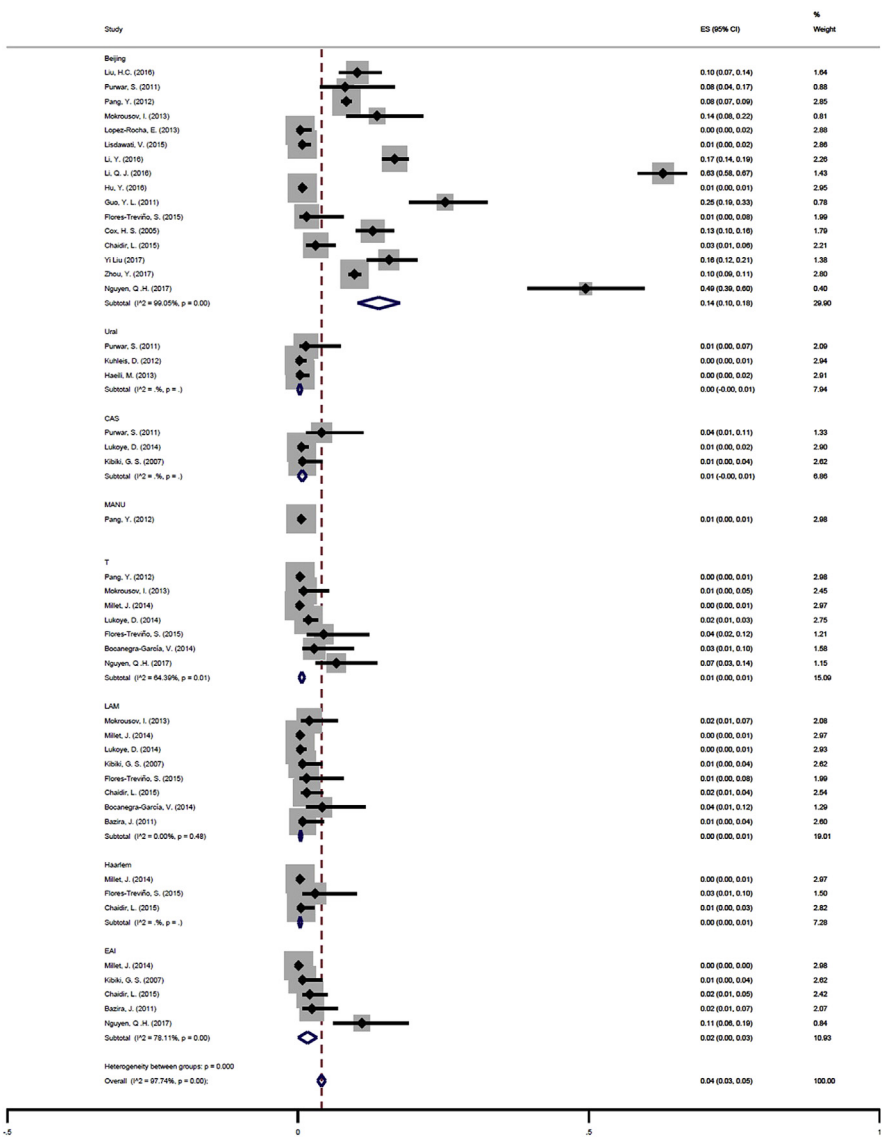

Fig. 2. Forest plot showing pooled and individual weighted prevalence of rifampicin-resistance MTB families, included 23 studies. ES: Estimate, IC: Confidence interval.

suggested potential publication bias for the overall prevalence of rifampicin resistance *M. tuberculosis* family (Fig. 4). Black dots represent actual studies included in this systematic review and the asymmetry of these dots indicates possible publication bias.

4. Discussion

The molecular methods used in typing TB such as spacer oligonucleotide typing (Spoligotyping) and mycobacterial interspersed repetitive unit- (MIRU-) variable number tandem repeats (VNTR) have crucial in understanding the epidemiology

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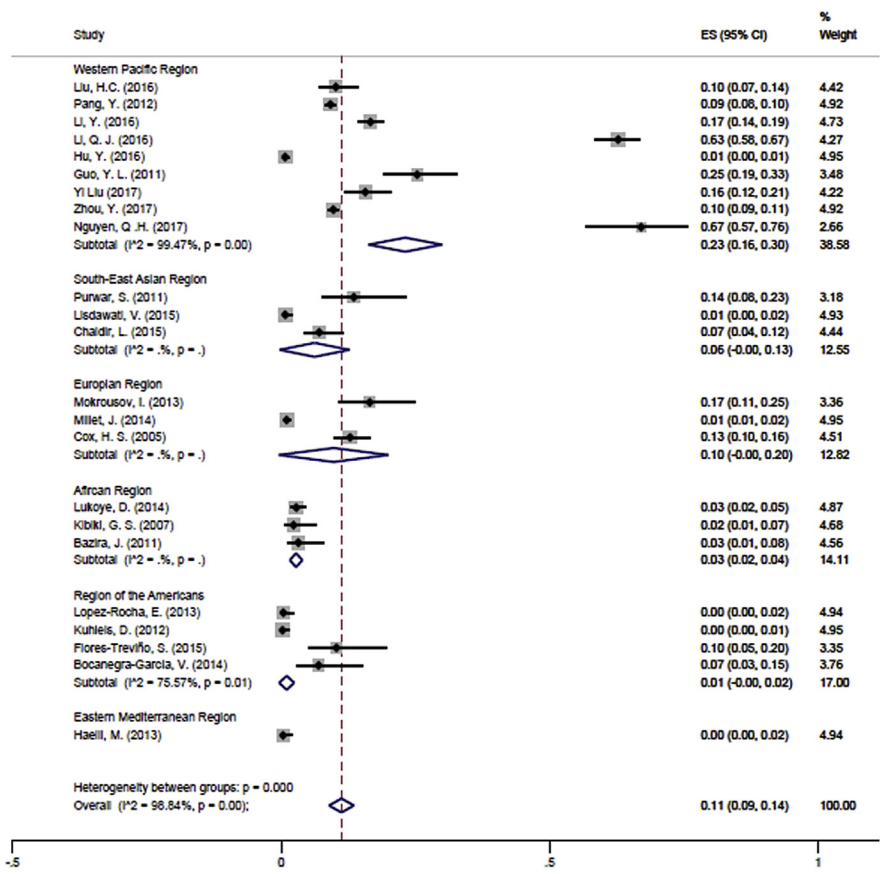

Fig. 3. Forest plot showing Sub analysis of WHO Regions of 23 studies reported on MTB strains resistance to rifampicin. ES: Estimate; CI: Confidence interval.

of TB [8, 42]. Spoligotyping is the simplest and rapid approach to determine the family of *M. tuberculosis* [9, 38, 43]. The drug susceptibility patterns of each family can be identified when it is used with the combination of phenotypic (culture-based) drug susceptibility test method [43]. Rifampicin targets RNA polymerase β-subunit coded by rpoB gene, which has been found in all bacteria with different size and nucleotide sequence vary between bacterial species, including mycobacteria [44, 45]. The mutation in *rpoB* gene in MTB is the main cause for rifampicin resistance [10, 46, 47]. Previous studies reported that about 95% [10] of rifampicin resistance strains underwent mutation in the short region of the rpoB gene and currently an important target for screening this strain [10, 46]. Using the hot spot regions such as rpoB, katG and -15 region inhA, potentially to identify 100% of rifampicin and 89% of isoniazid resistance strains and the new assay which targets the rpoB531, 516 and 526, katG315, gyrA94, 91 and 90 and rrs1401 regions have the ability to distinguish 100% for rifampicin resistance strains [46]. The methods used for detecting drug resistance *M. tuberculosis* can affect the outcome. For instance, solid medium based (Löwenstein−Jensen media) drug susceptibility test methods which relied on colony

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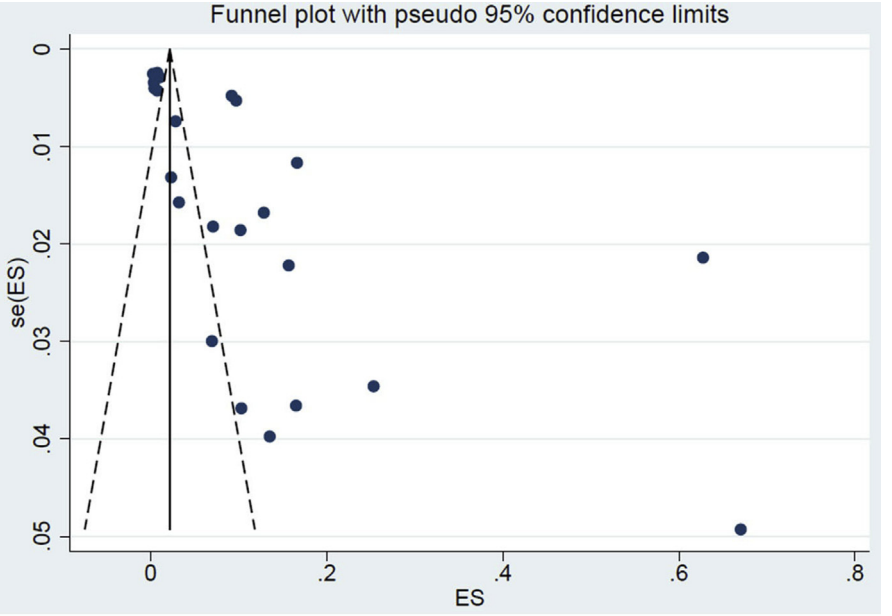

Fig. 4. - Begg funnel plot with pseudo 95% confidence limits of results of 23 studies reported on MTB strains resistance to rifampicin. ES: Estimate; CI: Confidence interval.

formation need more than one month [48], and detected by visual inspection for colonies and in such a case error may occur during reading [49]. Xie, Y.L., et al. (2017) investigated the sensitivities of the phenotypic drug susceptibility assay on isoniazid, moxifloxacin, ofloxacin, amikacin and kanamycin for identifying resistance isolates. According to this study, 83.3% for isoniazid (95% CI, 77.1 to 88.5) and except moxifloxacin at a critical concentration, the specificity of the assay for the detection of phenotypic resistance was 94.3% or greater for all drugs. But using DNA sequencing for detecting mutations associated with resistance genes were 98.1% for isoniazid (95% CI, 94.4 to 99.6), and the specificity for all drugs was 99.6% (95% CI, 97.9 to 100) or greater [50]. Of twenty three included studies, three studies used both genotyping (detecting mutation in rpoB, katG, gyrA and rrs gene) and phenotypic (proportional method) drug susceptibility methods for detecting resistance isolates [28, 29, 32] ad five studies target drug resistance mutations in rpoB, katG [17, 21, 22, 51, 52], gyrA inhA and rrs gene for identifying drug resistance strain [17, 22, 52]. The remaining 15 studies relied on medium based proportional method.

WHO recommended Gene Xpert MTB/Rifampicin assay in screening for MDR-TB in new cases, because it is easy and cost effective method [1], but it cannot identify the family or strains of MTB.

Drug resistance in Beijing strains leading MTB lineage in Eastern Asia. This may indicate that Beijing genotype strains develop mechanisms of escaping from antituberculosis drugs due to advanced frequencies of particular drug resistance-granting mutations [11]. Our study showed that Beijing family with high prevalence

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in Western Pacific Region and South-East Asia Region was the most family resistance to rifampicin. In some Regions rifampicin is used for treating other diseases like brucellosis, which might be a contributing factor in drug resistance [43], because mono-drug treatment can result in drug tolerant strains [53]. Several studies showed that most of drug resistance TB developed as a result of insufficient treatment of active pulmonary TB, poor drug selection are well-recognized contributor [54], and transmission of MDR strains in the community also play role in increasing of the infection [5, 55]. One study conducted in Uganda reported that no strain was resistance to rifampicin [38] Moreover, there was similar report from Morocco in which LAM strains have dominated the collection [56]. According to WHO report, 490,000 cases of MDR-TB emerged in 2016 and additionally there were about 110,000 cases susceptible to isoniazid but resistance to rifampicin. Three countries that contribute 47% of MDR TB cases to the world were China, India and the Russian Federation [1]. The report from Turkey ministry of health showed that the resistance proportion to isoniazid, rifampicin, ethambutol, streptomycin, and MDR were 13.8%, 6.6%, 4.3%, 7.5%, and 5.3% respectively [3]. Another study conducted in Pakistan reported that about 4.6% of the isolates were identified as rifampicin resistance TB, but the families or strains were not identified [57]. The prevalence of Beijing family in India was relatively low (3−11%). According to Purwar et al. (2011), out of 74 isolates, 10.8% was Beijing family with 87.5% resistance to at least one drug, 75% MDR and 12.5% extensive MDR [15]. This indicates that Beijing family has a considerable association with rifampicin resistance in India [58]. In a similar way, the study conducted in 2012 in China, showed that 13.2% of the Beijing isolates were rifampicin resistance strains [16]. Another study that was conducted in Zigong, China showed that 55.5% of the total isolates was Beijing family in which 18.5% was resistance to rifampicin [2]. Our study showed that, out of 1387 rifampicin resistant isolates, 1298 (93.58%) were Beijing family isolates, followed by T = 36 (2.77%), MANU = 20 (1.56%), EAI = 19 (1.46%), LAM = 17(1.30%), Haarlem = 7 (0.5%), CAS = 7 (0.5%) and Ural = 3 (0.2%). Moreover, we observed variation in weight between Regions. Accordingly, the Western Pacific Region contributed 35.87%, followed by South-East Asian Region (13.10%), European Region (13.38%), African Region (14.74%), Region of America (17.74%), and Eastern Mediterranean Region (5.17%) (Fig. 3).

Our finding of significant publication bias may be a reflection of wide heterogeneity in reported prevalence of rifampicin resistance *M. tuberculosis* strains or families and of potential gaps in data from unreported prevalence in certain subpopulations. And also using GeneXpert MTB/Rifampicin assay and culture based phenotypic drug susceptibility test has shown different accuracy. Other possible reasons for this finding include differences in study sample sizes, TB culture methods, and variation in study rigor. Our finding may also reflect temporal variability in existing risk for rifampicin resistance-TB among study populations (Fig. 4).

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Further studies should be carried out to verify the relationship between the specified mutations and *M. tuberculosis* sub-lineages among a large number of drug-resistant isolates.The demographic information was incomplete in most of the included studies, so we failed to calculate the significant prevalence of rifampicin resistance strains among gender and the distribution pattern of age groups of the population.

In conclusion, reporting the drug susceptibility pattern of each family is critical in an epidemiological study of drug resistant strains and the rate of resistant strain to each anti-tuberculosis drug. The present analysis found that Beijing family was the predominant strain resistance to rifampicin in all over the world. Spoligotyping is important in genotyping MTB to identify the most significant factors which may affect TB control program for various factors involved in the distribution of rifampicin resistance strains.

Declarations

Author contribution statement

Seifu Gizaw Feyisa, Hossein Kazemian: Conceived and designed the analysis; Analyzed and interpreted the data; Wrote the paper.

Ahmed Abdulahi Abdurahman, Eshetu Ejeta Chaka: Analyzed and interpreted the data.

Worku Jimma: Conceived and designed the analysis; Wrote the paper.

Jalil Kardan Yamchi: Contributed analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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