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

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ABSTRACT

Background: Genotyping and drug susceptibility test of *Mycobacterium tuberculosis* (MTB) is recommended to understand the prevalence of Isoniazid resistance to facilitate early treatment initiation and controlling the spread of the resistant strain in the community. Although several primary studies reported from different parts of the world, there are few review studies that attempt to summarize the available information to support tuberculosis (TB) control program. Thus, this review aimed to determine the prevalence of isoniazid resistance MTB family and identify the high-risk WHO regions.

Methods: Medline/PubMed and EMBASE databases were searched until 22 November 2022 to access all original studies that published in English. The random effects model was used to estimate pooled prevalence of isoniazid (INH) resistance. Sub-groups analyses were done to investigate sources of heterogeneity by the type of MTB genotype and WHO regions. Random effects model was used to pool the prevalence of isoniazid resistance. Publication bias was assessed by Funnel plot, Egger's test and Begg's test statistic. Heterogeneity across studies was measured by I^2 and data was analyzed by STATA version 14.

Results: The pooled prevalence of INH resistance MTB strains was 18% (95%CI: 15–22) with high heterogeneity (I^2 = 97.70%). The subgroup analysis by WHO regions showed that the prevalence of INH resistance MTB was: 18% (95%CI: 14–23%) in Western pacific region, 25% (95%CI: 13–38%) in South-East Asian region, 34% (95%CI; 17– 52%) in European region, 8% (95%CI: 5–11%) in African region, 19% (95%CI: 10–27%) in region of America and 10% (95%CI: 9–12%) in Eastern Mediterranean region. Sub-group analysis by MTB genotype showed that 22% (95%CI: 18–26%) Beijing INH resistance, 19% (95%CI: 16–22%) unclassified strains, 27% (95%CI:10–54%) Ural, 15% (95%CI: 1–20%) CAS, 19% (95%CI: 14–24%) LAM, 15% (95%CI:11–19%) EAI 38% (95%CI: 24–51%), MANU, 22% (95%CI: 16–27%) T, 24% (95%CI: 18–31%) Haarlem, 7% (95%CI: 5–10%) Euro-American, and 41% (95%CI: 34–49%) Orphan.

Conclusion: The INH resistance was considerable in different regions of the world. The highest prevalence was observed in European, South-East Asia and America WHO regions. Beijing family is the most prevalent of INH resistance in these regions. Intervention is required to reduce INH resistance to achieve end TB strategy.

Keywords: Tuberculosis, Drug resistance, Infectious diseases, Bacterial diseases, Molecular biology

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BACKGROUND

The emergence of drug resistance MTB strains is the most obstacle in TB treatment and controlling efforts [1, 2]. Naturally, MTB can develop resistance to antibiotic in addition to acquired mutations that recently reported additional resistance. Most reports indicated that MTB acquires resistance to ant-tuberculosis mainly on chromosomal mutation under selected stress, including mistreatment [3].

Deoxyribonucleic Acid (DNA) sequencing and various drug susceptibility testing methods, including line probe assays, hybridization on DNA chips, single-strand-conformation-polymorphisms, pyrosequencing, and real-time polymerase chain reaction (PCR) focus on the detection of mutations that causes resistance has been identified and is yet in use. On the other hand, the method that can identify all resistant MTB strains accurately must be known and included in the diagnostic test. However, the occurrence and geographic distribution of INH resistance MTB mutations is not well quantified in the pathogen population [4].

In nine of the 30 high multidrug resistance TB (MDR-TB) burden countries (Democratic People's Republic of Korea, Democratic Republic of Congo, Mozambique, Nigeria, Papua New Guinea, the Philippines, the Russian Federation, Somalia and Thailand) the number of MDR-TB has increased by more than 30% between 2015 and 2016 [5]. These all prove that, drug resistance TB burden is considerable and public health concern worldwide [6].

Molecular characterization of MTB is important to understand the epidemiology of TB and to detect the suspected outbreaks and identifying the habitual patterns of an infection. Spacer oligonucleotide typing (Spoligotyping), one of the easy methods recently used for typing MTB is important to identify MTB resistance strain. This method groups MTB strains in to diverse family/lineage including: Beijing, Ural, Haarlem, East African-Indian (EAI), Latin American and Mediterranean (LAM), Central-Asian or Delhi lineage (CAS), T and Orphan which are the most common families circulating in a community [7, 8]. Using culture based drug susceptibility test or targeting resistance genes, with the combination of Spoligotying method on clinical isolates of MTB is critical in understanding the drug susceptibility profile of each family [6]. Although several primary studies reported from different parts of the world, there are few review studies that attempt to summarize the available information to support tuberculosis (TB) control program. Thus, this review aimed to determine the prevalence of isoniazid resistance MTB family and identify the high-risk WHO regions.

METHODS

Study search strategy

Search strategies were conducted in April 2019 and updated in November 2020 in Medline/PubMed and EMBASE database using the keywords: ((((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]. Primary studies published in English were searched without limitation on the year of publication.

Inclusion and exclusion criteria

Searching of studies and data extraction were conducted independently by SGF and WJ to reduce the risk of errors. A third reviewer (EE) solved any discrepancies between data extractions. The screening process was done in three stages: initially by title then, abstract and finally by full text articles. Studies (1), described and reported MTB families and drug sensitivity test for anti - TB drug (isoniazid); (2), isoniazid sensitivity test outcome: resistance or susceptible for each strains (e.g. the number of Beijing strains resistance/susceptible to isoniazid) ; (3), clearly defined molecular typing method (Spoligotyping) and isoniazid test procedure; and (4), outcomes reported according to the WHO classification of drug sensitivity (including susceptible, mono-drug resistance, multidrug resistance, or extensively drug resistance were included to this review. Studies were excluded because of not identifying strain or family of MTB and drug susceptibility pattern for each isolate; focusing on treatment with first line anti-TB drugs but not strain identification; reports that was not specify strains sensitive/resistance to a tested drug (isoniazid); duplicate publications of the same study; available only in abstract form or not in full text and the author(s) requested for full text but not responded. Screening of articles for review was depicted in Figure 1.

Study quality and risk of bias assessment

The quality and risk of bias assessment of included studies were performed by two authors (SGF and EEC) based on National Institutes of Health (NIH) Quality assessment tool for Observational Cohort and Cross-Sectional Studies [9]. Nine appropriate questions were designed to grade the included studies focusing on the following aspects: clarity and definition of study population; justification of sample size and power description; data collection methods; inclusion and exclusion criteria; the state of duration of data collection; methods of drug susceptibility testing methods; statistical test used for data analysis; molecular techniques used for strain discrimination (whether combined or single methods) and complete grouping of the isolates into their families. Studies scored ≥8 points out of 10 were considered as high quality.

Data extraction and statistical analysis

Thirty-six studies were included to this review study. Information on first authors name, publication year, families of MTB, country, sample size and WHO regions were extracted from the selected studies. Moreover, data on isoniazid susceptibility test outcomes for MTB strains was extracted from the selected studies. Data was entered to Microsoft Excel and analyzed by STATA version 14. A random effects model was used to pool the proportion of MTB strain resistance to INH. The presence of heterogeneity on the prevalence of INH resistance between primary study was assessed by Egger or I2statistic. Source of heterogeneity was assessed by sub-group analyses. Egger's test and funnel plots were used for publication bias assessment. Significance level was set at p-value < 0.05 for Begg's and Egger's tests to assess publication bias.

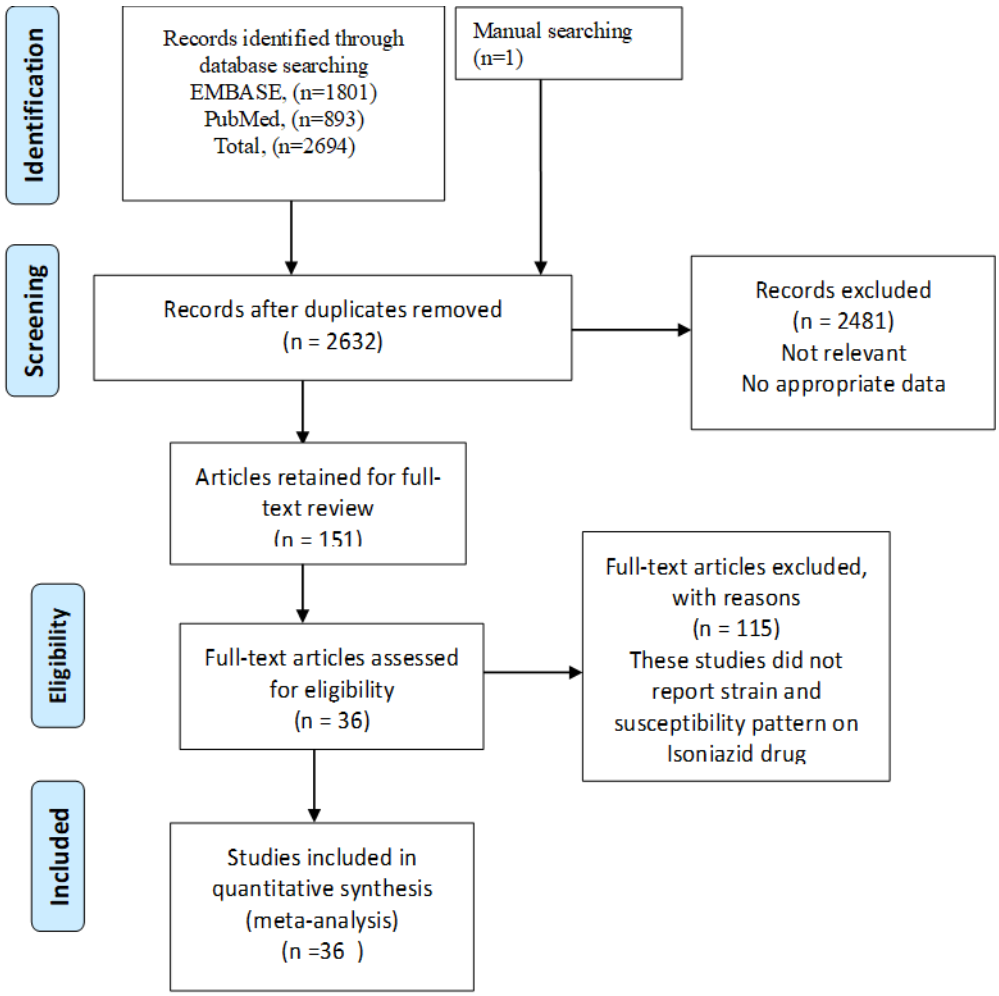

Figure 1: PRISMA flow diagram to show study selection process

RESULTS

Study searches and selection strategy

Figure 1 depicts study selection process. A total of 2632 records were retrieved after duplication removed (Table 1). A total of 2481 studies were excluded based on title and abstract, while 115 studies were excluded because of irrelevant data. Finally, 36 studies were included to meta-analysis [8, 10-44] with a total of 18877 participates. The included studies were reported from 17 countries in the six WHO regions.

Characteristics of the included studies

Table 1 describes the main characteristics of included studies. Of the 36 included studies, nine were reported from Africa region on 2358 (12.49%) MTB isolates, of which 285 (7.99%) were INH resistance. The most prevalent INH resistance families in Africa region were T=35 (15.8%), Beijing=34 (15.3%), LAM=34 (15.8%), CAS=18 (8.1%) and EAI=8 (3.6%) [14, 30, 32, 36, 37, 39, 45-48]. Two studies reported from Eastern Mediterranean region on 1278/18877 (6.8%) MTB isolates. Of the isolates reported from Eastern Mediterranean region 139/1278 (10.87%) were resistant to INH. Of 139 INH resistant strains, 72 (51.8%) belong to CAS family, which were followed by EAI=10 (7.2%), Ural=8 (5.8%) and Beijing family=5 (3.6%) [21, 34]. Six studies were reported from European region on 2123/18877 (11.2%) isolates and for 425/2123 (20.0%) isolates were showed resistance to INH. In this region the commonest INH resistance lineages include: Beijing 160/425 (36.64%), T=35 (8.23%), Haarlem=20 (4.70%), and LAM=15 (3.52%) [12, 13, 24, 35, 40, 43]. Six studies were from region of America which reported on 1689/18877 (8.94%) isolates. Of these isolates, 239/1689 (14.15%) were resistant to INH. The common INH resistance MTB lineages circulating in this region were LAM=71/239 (29.70%), T=50 (20.92%), Haarlem=23 (9.62%) and Beijing=5 (2.09%) [15, 18, 23, 41, 44, 49]. Five studies were included in this review from South East region in 1401/18877 (7.42%) isolated and 278/1401 (19.84%) isolates were resistant to INH. *Mycobacterium tuberculosis* lineages resistance to INH in this region were Beijing 104 (37.41%), CAS=76

(27.33%), EAI=26 (9.35%) and T=14 (5.03%) [16, 25, 33, 42, 50]. Eight studies were included to this review from Western Pacific region on 10028/18877 (53.12%) MTB isolates. From this, 1836/10028 (18.8%) isolates were resistant to INH which shared between the six known MTB lineages. About 1384/1836 (75.38%) INH resistant strains belonged to Beijing lineage, followed by T=46 (2.5%) and MANU 40 (2.17%) in Western Pacific region [8, 11, 17, 22, 29, 31, 38, 51]. Out of 3139 INH resistant isolates, identified from the studies across the six WHO regions, the distribution of MTB genotype was as follows: Beijing family accounted for 1692 (53.9%), T for 189 (6.0%), LAM for 126 (4.0%), MANU for 49 (1.6%), EAI for 48 (1.5%), CAS for 167 (5.3%), Haarlem for 63 (2.0%), Ural for 12 (0.38%), Orphan for 2 (0.19%), unclassified strains for 740 (23.6%), and 51 (1.6%) strains were reported as belonging to the Euro-American lineage.

Characteristics of INH resistant MTB isolates with genes mutation

Table 1 depicts the characteristics of included studies. Molecular epidemiology is a key method for controlling the transmission of drug resistant TB and understanding rate of drug resistance [52]. Therefore, assessing the degree of anti-TB drug susceptibility patterns of MTB family is helpful in identifying rate of mutations at drug target sites in the genome. Moreover, determining its relationship with the geographical locations should be assessed to clarify any significance in resistance mechanism of MTB genotypes. Studies have shown that Beijing genotype exhibits significantly higher resistance to anti-TB drugs compared to non-Beijing strains, however, no correlation has been found between this resistance and its geographical distribution. More strains were also found to be resistant to INH than rifampicin [53]. Drug resistance in MTB arises due to mutation or errors occurring during chromosomal replication in genes that encode drug targets or influence drug metabolism mechanisms, reducing the effectiveness of anti-TB therapies. Approximately 64% of all phenotypic INH resistant strains globally are associated with mutations in the *kat*G315 gene, while 19% of phenotypic INH resistant strains are linked to mutations in the *inh*A promoter and the *ahp*C-oxyR intergenic region [4]. Another study reported that out of 50 phenotypic INH resistant MTB isolates, 32 (64%) showed mutation in the *kat*G315 gene with the AGC nucleotide changed to ACC. In addition, 9 (18%) isolates had the AGC nucleotide changed to AAC and 9 (18%) isolates exhibited mutations in the *inh*A-15 gene, where the cytosine (C) nitrogenous base was replaced by thymine (T). Thus about 80% of the INH resistant isolates harboured mutations at either AGC to ACC at codon 315 in *kat*G or a substitution of C nitrogen base with T at position 15 in the *inh*A locus. Moreover, mutations in other genes, such as *ahp*C, *oxy*R and *kas*A are also likely contributing to the susceptibility to INH [54]. Another study reported that, out of 206 INH resistant MTB strains, 68.0% had a *katG* mutation and 35.0% had an *inh*A mutation. In most cases mutation in *katG* gene causes high level of INH resistance up to 94.8% and *inh*A mutation also showed about 51.5% resistance [55].

Table 1 Characteristics of included studies to determine INH resistant *Mycobacterium tuberculosis*

Author	Publication year	Method for drug susceptibility test	Country	Region	Sample Size	Main outcome
Asiimwe, B. B., et al.	2008	Proportion on *Lowenstein-Jensen* (LJ)	Uganda	African Region	344	About 28 isolates were INH resistance. Of these, 20 and 3 isolates belonged to T and LAM respectively, while the remaining belonged to another genotype.
Kamudumuli, P. S., et al.	2015	Proportion on Mycobacteria Growth Indicator Tube (MGIT)	South Africa	African Region	500	Of 77 INH resistance isolates, 20 and 57 were Beijing and non-Beijing isolates respectively.
Marais, B. J., et al.	2006	Proportion on MGIT	South Africa	Africa Region	399	Of a total of 16 isolates, 13 were INH resistant strains from the while 3 isolates were from LAM family.
Lukoye, D., et al.	2014	Proportion on LJ	Uganda	African Region	497	A 40 (8.1%) isolates were resistant to INH. LAM CAS and T families were the most dominant lineages.
Kibiki, G. S., et al.	2007	Proportion and mutation on katG and rpoB gene	Tanzania	African Region	130	Of the total tested isolates, 11 were resistant to INH in which 5 isolates belonged to LAM genotype.
Bazira, J., et al.	2011	Proportion on LJ	Uganda	African Region	125	Only 4 isolates were INH resistant strains. Of these, two isolates belonged to CAS genotype.
Getahun, M., et al.	2015	Proportion on LJ	Ethiopia	African Region	92	Five INH resistant strains were identified. Of these, three belonged to EAI and one to Euro-American lineage.
Gafirita, J., et al.	2012	Proportion on LJ	Uganda	African Region	151	Five INH resistant strains were identified of which 4 were classified as T genotype and 1 was unclassified.
Abebe, G., et al.	2018	Not mentioned	Ethiopia	African Region	177	About 34.6% and 18.5% isolates were CAS and others 1 lineage resistance to INH respectively.
López-Rocha, E., et al	2013	Myco-TB testing kit	Mexico	Region of American	248	Of the total isolate, 9 (3.8%) were INH resistant: from the Euro-American lineage 8 (3.4%) and 1 (0.4%) from the Indo-Oceanic.
Flores-Treviño, S., et al.	2015	Proportion on MGIT	Mexico	Region of American	68	A 25 INH resistant isolates were identified, in which 9(36%) was T lineage and only one strain from the Beijing lineage.
Bocanegra-García, V., et al.	2014	Proportion and mutation in inhA, katG, rpoB and ahpC genes	Mexico	Region of American	**72**	Twelve INH resistant strains were identified from; LAM 4, T 3, and 5 isolates from other families.
Kuhleis, D., et al	2012	Proportion on LJ	Brazil	Region of America	392	This study identified 7 INH resistant isolates, which belong to LAM, T, Haarlem and X genotypes.
Luiz Silva S. R., et al.	2013	Proportion on LJ	Brazil	Region of America	115	Of the total isolates 51 (43.5%) were non-Beijing INH resistance strains. LAM family was the most predominant INH resistance.
Sheen, P., et al.	2013	Not mentioned	Peru	Region of American	794	About 135 (17%) isolates were INH resistance, of this 82 (10.32%) and 53 (6.67%) were

							isolated from HIV-positive and HIV-negative patients respectively.
Liu Hai-C., et al.	2016	Proportion on LJ	China	Western Region	Pacific	265	The drug susceptibility result showed 48 isolates resistance to INH, in which 28 and 20 bisloates belonged to Beijing and non-Beijing lineage respectively.
Pang, Y., et al.	2012	Proportion on LJ	China	Western Region	Pacific	3634	Of the total isolates, 744 (20.7%) were isoniazid resistance strains, of these 497 (66.8%) and 247(31.2%) Beijing and non-Beijing strains were resistant to isoniazid respectively.
Li, Y., et al.	2016	Proportional on LJ	China	Western Region	Pacific	1017	A 210 (91%) Beijing and 19 (9%) non-Beijing strains were identified as INH resistant strains
Hu, Y., et al	2015	Mutation in katG, inhA, rpoB, embB, gyrA and rr5 genes	China	Western Region	Pacific	1222	About 96 isolates were INH resistance of which 72 isolates belonged to Beijing genotype.
Guo, Y., et al	2011	Proportion on LJ	China	Western Region	Pacific	158	Of the total 44 (27.9%) INH resistant isolates 37 (30.1%) and 7(20%) belonged to Beijing and non-Beijing genotypes respectively.
Zhou, Y., et al.	2017	Proportional on LJ	China	Western Region	Pacific	3133	Beijing lineage was identified as the most resistant to INH. About 476 Beijing and 117 Euro-American lineages were INH resistant strains
Liu, Y., et al.	2017	Proportion on LJ	China	Western Region	Pacific	268	A total of 66 INH resistant isolates were identified, of which 57 and 9 belonged to Beijing and non-Beijing lineages respectively.
Jing, A. M., et al.	2018	Proportion on LJ and MGIT	China	Western Region	Pacific	331	Of the total INH resistant strains, 26 (14.21%) and 9 (6.08%) were Beijing and non-Beijing genotypes respectively.
Arora, J. , et al.	2014	Proportion on MGIT	India	South-East Region	Asian	97	Of the total tested isolates, 57 were resistant to INH in which 23 were Beijing, while 20 CAS and 14 other lineages.
Singh, J., et al.	2015	Proportion on MGIT™ 960	India	South-East Region	Asian	628	Beijing family was the most predominant family resistant to INH. Of the total 151 INH resistant strains Beijing 59, CAS 46, EAI 14, T 11, MANU 6 and other 15 were identified.
Purwar, S., et al.	2011	Proportion on LJ	India	South-East Region	Asian	74	Out of the total, 24 (32%) were isoniazid resistant, comprising 7 Beijing isolates, 10 CAS isolates and 7 isolates from other families.
Lisdawati, V., et al.	2015	Proportion on LJ	Indonesia	South-East Region	Asia	404	INH resistant strains were identified in Beijing and non-Beijing family, 11 and 16 respectively.
Chaidir, L., et al.	2015	Mutation in rpoB, katG and inhA genes	Indonesia	South-East Region	Asia	198	EAI genotype was the most dominant INH resistant strains, 9/19, Beijing 4/19 and Euro-American and LAM each were 2/19.
Cox, S. H., et al	2005	Proportional on LJ	Uzbekistan and Turkmenistan	European Region		397	On the whole, 99 (52%) of the isolates were of the Beijing genotype resistance to INH and 56 (29%) of the non-Beijing were also resistance to INH.

Mokrousov, I., et al.	2013	Mutation in (rpoB, katG, inhA) gene	Russia	European Region	103	A total of 28 isoniazid resistant isolates were identified. Of these 14 isolates belonged to Beijing and non-Beijing family each.
Millet, J., et al.	2014	Proportional and mutation in (rpoB and katG) gene	France	European Region	1184	About 93 isoniazid resistant isolates were identified in LAM and T family and other families but not in Beijing family.
Kisa, O., et al	2012	Proportional on (LJ/BACTEC 460-TB	Turkey	European Region	95	About 73 (76.8%) isolates were resistant to INH. Haarlem genotype was the most INH resistant.
Cannas, A., et al.	2018	Proportional on LJ	Italy	European Region	230	About 23 INH resistant isolates were identified in which 23 and 2 belonged to Euro-American and Beijing lineages respectively.
Toungoussova, S. O., et al.	2003	Mutation on rpoB gene	Russia	European Region	114	About 41 and 12 W-Beijing and non-Beijing lineages were resistant isoniazid respectively.
Ayaz, A.,et al.	2012	Proportional on (Agar BACTEC 7H12)	Pakistan	Eastern Mediterranean Region	987	Among 120 INH resistant isolates, 71 and 10 belonged to CAS and EAI families respectively. T and Haarlem each 9 isolates were resistant to INH too.
Haeili, M., et al.	2013	Proportional on LJ	Iran	Eastern Mediterranean Region	291	Of 19 INH resistant strains 8 Ural, 3 Beijing and 8 other genotypes were identified.

[a] LJ: *Lowenstein-Jensen*; [b] MGIT: Mycobacteria Growth Indicator Tube

Prevalence of INH resistant MTB

The pooled analysis of 36 included studies showed that the prevalence of INH resistant was 18% (95% CI; 15–22%) with significant heterogeneity between the included studies ($p < 0.001$; $I^2 = 97.7\%$) (Fig. 2).

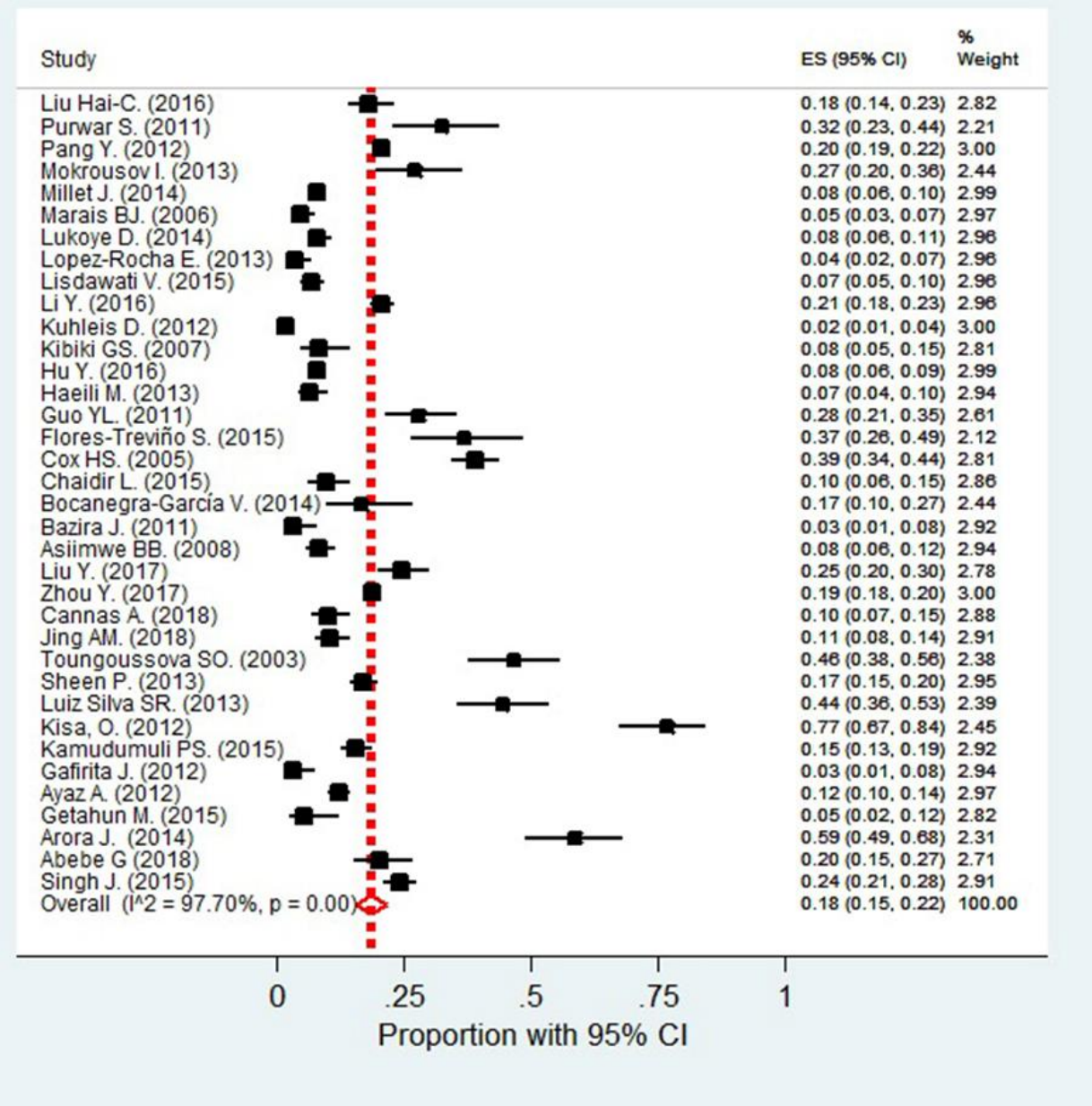

Figure 2: Forest plot on pooled prevalence of isoniazid resistance based on random-effects model *(EC-confidence interval, ES-effect size)*

Sub-group analysis showed that the prevalence of INH resistant MTB strains was 18% (95%CI; 14–23%) in Western pacific region, 25% (95%CI; 13–38%) in South-East Asian region, 34% (95%CI; 17–52%) European region, 8% (95%CI; 5–11%) in African region 19% (95%CI; 10–27%) in region of America and 10% (95%CI; 9–12% in Eastern Mediterranean region. The sub-group analysis based on the lineages of MTB showed that 22% (95% CI; 18–26%) were Beijing family, 19% (95%CI;16–22%) unclassified strains, 27% (95%CI;10–54%) Ural, 15% (95%CI; 11–20%) CAS, 19% (95%CI; 14–24%) LAM, 15% (95%CI; 11–19%) EAI, 38% (95%CI; 24–51%) MANU, 22% (95%CI; 16–27%) T, 24% (95%CI; 18–31%) Haarlem, 7% (95%CI; 5–10%) Euro-American, and 41% (95%CI; 34–49%) Orphan. This ascertain that WHO regions and lineages of MTB were the sources of heterogeneity between the included studies on the prevalence of INH resistant strains (Table 2).

According to National Institutes of Health (NIH) Quality assessment tool for Observational Cohort and Cross-

Sectional Studies, 16 studies scored greater or equal to 8 out of 10 points, and others 20 studies scored 4 to 7 points. The most frequent quality criteria failed by the studies were: sample size justification, power description and combined genotyping methods. The pooled analysis for 16 high quality studies to estimate the prevalence of INH resistance MTB strains was 21% (95% CI: 16-26%) with I^2 = 97.5% and p < 0.001 (Table 2). The analysis showed that the heterogeneity between the studies was significant by the quality of the studies. Thus, quality of included studies was the source of heterogeneity between the studies.

Table 2: Subgroup analysis by WHO regions, MTB lineage/family and study quality

Sub-group	Number of studies	ES (95% CI)	P-value	I^2 (%)
WHO region				
All studies reported from WHO regions	56	0.18(0.15–0.22)	<0.001	97.7
Western Pacific region	8	0.18(0.14–0.23)	<0.001	96.7
South-East Asia region	5	0.25(0.13–0.38)	<0.001	97.5
European region	6	0.34(0.17–0.52)	<0.001	98.8
African region	9	0.08(0.05–0.11)	<0.001	87.6
Region of America region	6	0.19(0.10–0.27)	<0.001	97.6
Eastern Mediterranean region	2	0.10(0.09–0.12)	–	–
Lineages of MTB/Family				
Beijing	25	0.22(018–0.26)	<0.001	97.4
Unclassified	34	0.19(0.16–0.22)	<0.001	97.7
Ural	3	0.27(0.01–0.54)	–	–
CAS	11	0.15(0.11–0.20)	<0.001	95.8
LAM	16	0.19(0.14–0.24)	<0.001	97.3
EAI	11	0.15(0.11–0.19)	<0.001	95.8
MANU	5	0.38(0.24–0.51)	<0.001	97.7
T	17	0.22(0.16–0.27)	<0.001	98.2
Haarlem	11	0.24(0.24–0.31)	<0.001	98.3
Euro-American	5	0.07(0.05–0.10)	<0.001	70.5
Orphan	2	0.41(0.34–0.49)	–	–
Quality of the study				
High quality	16	0.21(0.16–0.26)	<0.001	97.5
Low quality	21	0.16(0.13–0.20)	<0.001	97.8

The p-value is heterogeneity within each sub-group; WHO-World Health Organization; ES-effect size; CI-confidence interval; MTB-Mycobacterium tuberculosis; –-the result not obtained

Publication bias and heterogeneity

The funnel plot appeared asymmetry, which shows the presence of publication bias (Figure 3). Begg's and Egger's tests also revealed the presence of publication bias (p < 0.001).

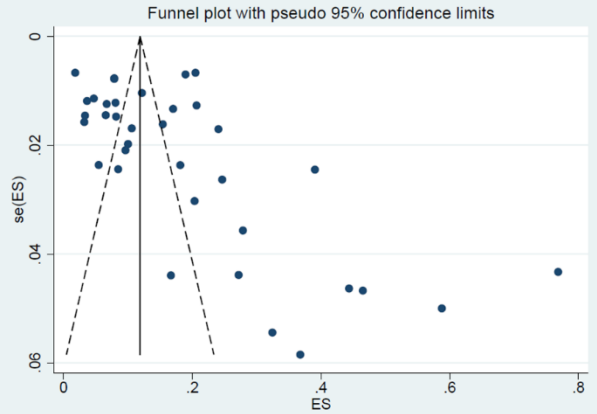

Figure 3: Funnel plot to assess publication bias

DISCUSSION

Effective treatment and prevention of MTB disease require understanding of its epidemiology and drug susceptibility patterns. Genotyping of MTB is crucial for understanding its evolutionary relationships, and the rate of transmission within the community. Spoligotyping is a widely used genotyping techniques for typing MTB, and classifying it into various lineages such as Beijing, Ural, Haarlem, EAI, LAM, CAS, T and Orphan, which are among the most recognized genotype [16]. This systematic review and meta-analysis aimed to estimate the overall pooled prevalence of INH resistance, and determine the prevalence of INH resistance by WHO regions and MTB families.

The pooled prevalence of INH resistant strain of *Mycobacterium tuberculosis* was 18% (95% CI: 15-22%) with a substantial heterogeneity among studies. The sub-group analysis based on WHO regions showed that the burden of INH resistant MTB strains were different. The prevalence of INH resistance was high in three WHO regions (European, Western Pacific and South-East Asian regions). WHO estimate indicates the incidence of both isoniazid and rifampicin resistant MTB was 3.5% (95% CI: 2.5–4.7%) in new cases and 18% (95% CI: 6.3–34%) in previously treated cases globally in 2017 [5]. The averages INH resistance devoid rifampicin resistance was 7.1% (95% CI: 6.2–8.0%) in new cases and 7.9% (95% CI: 5.9–10%) in previously treated cases globally.

These results show the absence of significant difference between previously treated and new TB cases on INH resistance [5]. The frequencies of the katG315 gene single mutation were strongly associated with the development of INH resistance in MTB strains across various WHO regions. This mutation is a key marker for INH resistance and has been reported at varying levels in different geographic areas, reflecting the regional burden of drug-resistant tuberculosis. According to the previous report, the frequency of INH resistance with single mutation katG315 was 73.5% in Africa, 61.6% in region of America, 64.1% in Eastern Mediterranean, 69.4% in European, 78.4% in South East Asia and 55.5% in Western Pacific region. On average, the contributions of the three genes responsible for INH resistance in Mycobacterium tuberculosis are distributed as follows: the *kat*G gene account for 66.3%, the *inh*A gene for 20.6% and the *ahp*C-oxyR gene for 5.4%. These genes play a significant role in the development of single mutation-mediated INH resistance [4].

Our sub-group analysis based on MTB genotype/family revealed that INH resistant MTB genotype vary across all WHO regions, and there was significant heterogeneity between the studies analyzed. The analysis showed that INH-resistant Beijing and T family strains were widespread across the globe, appearing in nearly all WHO regions. The analysis showed that INH resistant Beijing and T family strains were widespread across the globe, appearing in nearly all WHO regions. The prevalence of INH resistant Beijing strains was found to be relatively high in the Western Pacific and in South East Asia regions. The national TB surveillance conducted in the European Region identified INH-resistant Beijing strains, particularly in Uzbekistan and Turkmenistan. Out of 397 MTB isolates, 99 (24.93%) were isoniazid-resistant, all of which belonged to the Beijing lineage. The national TB surveillance conducted in the European region identified INH resistant Beijing strains, particularly in Uzbekistan and Turkmenistan [24]. Out of 397 MTB isolates, 99 (24.93%) were INH resistant, all of which belonged to the Beijing lineage [24].A drug resistance survey conducted in Uganda, based on the three studies conducted in different parts of the country across various years, analyzed a total of 966 samples collected from TB patients [27, 28, 56]. Of these, 48 (5.0%) were resistant to INH [27, 28, 56]. Among the resistant strains, 27 (56.3%) belong to the T-genotype, followed by 10 (20.8%) in the LAM genotype, and 9 (18.8%) in the CAS genotype [27, 28, 56].Similarly, three studies conducted in Mexico evaluated a total of 388 samples isolated from TB patients for INH susceptibility. Of these, approximately 27 (7.0%) were resistant to INH. Among the resistant strains, the T-genotype was the most prevalent, which accounting for 15 (55.6%) of the cases followed by the LAM genotype with 8 (29.6%). The remaining 4 (14.8%) strains belonged to other genotypes [15, 23, 26]. Two research studies conducted in Indonesia revealed that, out of 603 clinical isolates 27 (4.5%) were resistant to INH. Among these resistant strains, Beijing lineage was the most dominant, accounting for 55.6%, followed by the EAI lineage, which constituted 33.3% [16, 25]. The data found from each WHO region not only reveal the differences in the prevalence of INH resistance but also highlight significant genotypic diversity in MTB resistance across regions. The Beijing and T lineage were the most prevalent INH resistant across WHO regions. The T-genotype associated with INH resistance was also widespread globally, though at varying rates across the WHO regions. The LAM lineage's resistance INH has been documented in various studies. The Latin-American Mediterranean lineage's resistance to INH has been documented from Africa (15.8%), region of America (29.7%), and European region (3.5%). The orphan genotype resistance to INH was reported only in the Western pacific region, with very low prevalence (0.19%). A study reported from China (Western Pacific region) revealed that among 1189 MTB isolates (83.3%) belonged to Beijing family, and the occurrence of INH resistance among Beijing family strains was considerably lower compared to that among non-Beijing family strains [57]. On the other hand, Liu, Jiang et al. reported that there was no significance association between Beijing and non-Beijing genotypes regarding drug resistance incidence. New TB cases showed considerably lower resistance to isoniazid compared to retreatment cases, and the levels of mono-resistance and MDR were similar between the two groups. New TB cases showed considerably lower resistance to INH compared to retreatment cases and the levels of mono-resistance and MDR were similar between the groups. Moreover, no significant association was found between the Beijing genotype strain and resistance to the four first line anti-TB drugs [31]. The study published in 2017 revealed that the prevalence of INH resistant MTB was 13.3% in Nigeria (Africa region) [58].

In the present review there was a significant heterogeneity between the prevalence of INH resistance between studies. A significant publication bias was also observed in the current review. The heterogeneity observed in the present study may be due to the lack of large, geographically diverse studies on INH resistance patterns among strains, which could be influenced by variation within WHO regions and MTB families. A few or no study reported on INH susceptibility test in high TB burden countries. This could be attributable to the lack of laboratory facilities or experts for drug susceptibility test. It might also be difference in specificity and sensitivity of drug susceptibility testing methods for instant use of phenotypic and genotypic assays. Observational error during culture-media reading and the overall difference between culture media in recovery rate of the isolate may be another source of disparity in studies distribution.

The limitation of this study was the absence of all-necessary information such as sociodemographic variables. Therefore, relevant stratified analyses could not be performed to reveal more detailed characteristics

of the development of INH resistant TB and its associated risk factors. Few studies were reported from high burden countries. For instant, there were no studies included in this study from Bangladesh, Afghanistan, and Nigeria which have high TB burden. This absence was a significant obstacle to obtaining comprehensive outcome in the present review study. Some studies lacked comprehensive reports on data on MTB lineages identified by spoligotyping and did not provide clear data on the drug susceptibility patterns for each lineage type. The correlation between MTB genotypic diversity and drug resistance is complex and require further research supported by reliable molecular typing and drug susceptibility testing methods to better understand the prevalence of MTB genotypes and their drug susceptibility patterns.

CONCLUSION

The pooled prevalence of INH resistant TB was 18.0% (95% CI: 15.0-22.0%) in the present review study. High INH resistant TB burden was observed in Western Pacific, European and South East Asia WHO regions. The prevalence of INH resistant Beijing strains is also high in Western Pacific, South East and, European regions. Isoniazid resistant T-strains are relatively higher in American, African, and European regions. LAM strains resistant to INH is high in region of America and Orphan resistant strains was only reported from Western pacific region with lowest prevalence. Interventions are required to prevent INH resistant MTB across the world, along with studies from different parts of the world to generate compressive evidence to understand INH resistant patters.

List of abbreviations

CAS-Central-Asian or Delhi lineage; DNA-Deoxyribonucleic Acid; EAI-East African-Indian; INH-isoniazid; LAM-Latin American and Mediterranean; MDR-multidrug resistance; NIH-National Institutes of Health; MTB-Mycobacterium tuberculosis; TB-Tuberculosis; WHO-World Health Organization

Declarations

Ethical considerations

The protocol of this study was registered on Prospero international Prospective registration of systematic reviews and meta-analysis, and obtained registration number; CRD42019121360 (http://www.crd.york.ac.uk/PROSPERO/display_record).

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Competing interests

The authors declared that there is no conflict of interest

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Authors' contribution

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