Review Article

Prevalence and occurrence rate of *Mycobacterium tuberculosis* Haarlem family multi-drug resistant in the worldwide population: A systematic review and meta-analysis

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Background: Transmission of *Mycobacterium tuberculosis* (*M. tuberculosis*) can occur in different ways. Furthermore, drug resistant in *M. tuberculosis* family is a major problem that creates obstacles in treatment and control of tuberculosis (TB) in the world. One of the most prevalent families of *M. tuberculosis* is Haarlem, and it is associated with drug resistant. Our objectives of this study were to determine the prevalence and occurrence rate of *M. tuberculosis* Haarlem family multi-drug resistant (MDR) in the worldwide using meta-analysis based on a systematic review that performed on published articles. **Materials and Methods:** Data sources of this study were 78 original articles (2002-2012) that were published in the literatures in several databases including PubMed, Science Direct, Google Scholar, Biological abstracts, ISI web of knowledge and IranMedex. The articles were systematically reviewed for prevalence and rate of MDR. Data were analyzed using meta-analysis and random effects models with the software package Meta R, Version 2.13 ($P < 0.10$). **Results:** Final analysis included 28601 persons in 78 articles. The highest and lowest occurrence rate of Haarlem family in *M. tuberculosis* was in Hungary in 2006 (66.20%) with negative MDR-TB and in China in 2010 (0.8%), respectively. From 2002 to 2012, the lowest rate of prevalence was in 2010, and the highest prevalence rate was in 2012. Also 1.076% were positive for MDR and 9.22% were negative (confidence interval: 95%).0020. **Conclusion:** Many articles and studies are performed in this field globally, and we only chose some of them. Further studies are needed to be done in this field. Our study showed that *M. tuberculosis* Haarlem family is prevalent in European countries. According to the presence of MDR that was seen in our results, effective control programs are needed to control the spread of drug-resistant strains, especially Haarlem family.

Key words: Haarlem family, multi-drug resistant, *Mycobacterium tuberculosis*, prevalence

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INTRODUCTION

Mycobacterium tuberculosis (*M. tuberculosis*) is a primarily human pathogen that causes tuberculosis (TB) disease.[1] This disease damages the lungs, central nervous system, lymphatic system and circulatory system.[2] Rate of infection with *M. tuberculosis* is associated with host's inherited susceptibility, environmental risk factors and genetic variations.[3] There are approximately 8 million new TB cases each year and over 2 million deaths because of this disease.[4] Different studies showed that the one-third of the worldwide population is infected with *M. tuberculosis* and new cases occur at a rate of 1/s.[5] Transmission of TB can occur through different ways such as: Human-to-human and human-to-animal, poor hygienic conditions, blood and fecal contamination (transmission) and inhalation of contaminated droplets that are released from the lungs of an infected individual (coughing and inhalation). Prevention and control of TB infection can be achieved through the prompt detection and treatment of infectious patients, air related precautions, and treatment of people who are suspected or confirmed to have TB disease and vaccination with the TB vaccine (Bacillus Calmette — Guerin [BCG]). There are several kinds of tests that are used to detect TB bacteria: The tuberculin skin test and TB blood tests (Centers for Disease Control or test). The typing method is based on DNA presence of polymorphism at one particular chromosomal locus, the "Direct Repeat" (DR) region, which is in *M. tuberculosis* complex bacteria.[6] This locus was first described in *Mycobacterium bovis* BCG. The DR region in *M. bovis* BCG consists of directly repeated sequences of 36 base pairs, which are interspersed by nonrepetitive DNA spacers, each 35-41 base pairs in

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length.[7] The main genotype families of *M. tuberculosis* include Beijing, Haarlem, Africa, East-African-Indian, Latin American and Mediterranean strains. The Haarlem genotype is associated with widespread epidemics and drug resistance.[4,8] Several meta-analyses are conducted on different aspects of *M. tuberculosis* around the world: Trunz *et al*. showed by a meta-analysis that BCG vaccination was effective against childhood TB, meningitis and TB in the military and the number of cases that were prevented was highest in South East Asia (46%), sub-Saharan Africa (27%) and in the western Pacific region (15%).[9] Ling *et al*. (2008) in Canada by a meta-analysis investigated on the multi-drug resistant (MDR) TB based on genotype MTBDR assays and they showed that the sensitivity and specificity were 98.1% and 98.7% for rifampicin resistance, respectively.[10] Yang *et al*. (2011) in China using a systematic review and Meta-Analysis showed that the prevalence of drug-resistant TB in new cases was 27.9% and in previously treated cases was 60.3%.[11] Nowadays, this MDR quality is a major problem in TB treatment and control. Also, drug resistance in TB patients will increase in cases of improper use of antibiotics. Drug resistance is raising in areas with weak TB control programs. Also, transmission of TB to other individuals by drug-resistant patients is easily possible. Determining the *M. tuberculosis* prevalence and occurrence rate of MDR-TB can help to control and plan therapies. So it is important to know specific families that are over represented among drug-resistant cases, and in particular if these resistant strains are successfully transmitted within the community. Haarlem family is associated with drug resistance and rapid clonal expansion; this genotype has epidemic potential.[12] The aim of this study was to determine the prevalence and distribution rate of the Haarlem family MDR in worldwide using a meta-analysis based on a systematic review that performed on published articles.

MATERIALS AND METHODS

Search strategy

The different literature databases and original articles that were published in the time span of 2002-2012 in English language for determination of *M. tuberculosis* Haarlem family prevalence and occurrence rate of MDR in this family in worldwide population were obtained from valid and credible web sites: PubMed) http://www.ncbi.nlm.nih.gov/pubmed), Science Direct (http://www.sciencedirect.com), Google Scholar (http://www.scholar.google.co.uk), Biological Abstracts (http://www.science.thomsonreuters.com) and ISI web of knowledge (http://www.pcs.webofknowledge.com) in Thomsonreuters, the years of coverage of these web sites are 1955, 1977, 2006, 2009 and 1958, respectively. Also, some article was found in IranMedex (http://www.www.iranmedex.com). We contacted several study authors in the cellular and molecular research center and microbiology department of Kurdistan University of medical sciences, located in Sanandaj, Iran to identify some additional studies. The last search was performed in the winter of 2012. For the means of searching in different websites, several key words were entered. For example TB Haarlem, molecular epidemiology, MDR and spoligotyping were entered in PubMed (Advanced search part). In some cases, search process got limited because in order to reach to some of the papers' full text, we should have had a specific username and password and hence we only used their abstracts which were available or free.

Data extraction and assessment of studies quality

Process for selecting the studies

All the information in different articles and papers used in this study were surveyed by authors. Two reviewers did the searching independently. When there was any disagreement between them for selecting specific articles, they discoursed about selecting it. Also, eligibility for each paper was determined in Excel data sheets (CEB603, Chino-Excel Technology). The following data were extracted from original publications: Number of cases, websites, Author, Study place (country), Year of the research, Sample size, and prevalence of Haarlem and MDR association.

Inclusion and exclusion criteria

Inclusion criteria

1. Research articles with full text,
2. Articles with abstract in English.

Excluded studies

1. Review articles,
2. Congress abstracts,
3. Studies that reported in languages other than English and
4. Studies that were not available for us in abstract or full text,
5. Studies that their sampling location was uncertain,
6. Studies that locations of sampling was performed at the same time,
7. Studies that their data were not clear.

Data synthesis and meta-analysis

Variables of our study were prevalence of TB infection and Haarlem family MDR in different countries (2002-2012). According to different studies performed in various countries, it was concluded that high levels of prevalence of TB infection and Haarlem family MDR can exist in different countries. Hence, the prevalence of Haarlem family of TB in 78 studies was the main outcome. The variance of the prevalence was computed using the binomial distribution (confidence interval [CI]: 95%). Meta-analysis with the random effect model was applied to combine the prevalence among studies. There was sensitivity (how the uncertainty in the output of a mathematical model or system can be apportioned to different sources of uncertainty in its

inputs) and heterogeneity among studies. I^2 and Q ($P < 0.10$) statistical tests were used to check out this heterogeneity (I^2 static is percentage of observed total variation across studies that are due to heterogeneity rather than chance. It is calculated as $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df degrees of freedom. Negative values of I^2 are put equal to zero so that I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Q is the weighted of squares on a standardized scale. It is reported with a *P* value with low *P* values indicating the presence of heterogeneity. This test however is known to have low power to detect heterogeneity, and it is suggested to use a value of 0.01 as a cut of for significance. Conversely, Q has too much power as a test of heterogeneity if the number of studies is large. Subgroup analyses were assessed using Chi-square tests, and it was done for continents). Stratified analyses were subsequently performed with respect to geographical locations and MDR-TB among the Haarlem family isolates.[13] Meta-analysis was carried out using the software package Meta R (Version 2.13.2, Copyright 2011, The R Foundation for Statistical Computing).

$$\text{Sensitivity} = \frac{\text{Number of true positives}}{\text{Number of true positives} + \text{number of false negatives}}$$

Publication bias

There was some evidence of publication bias in the subsample of studies. Some of these studies did not find a positive association between antibiotic consumption and antibiotic resistance. Also, excluded studies that were introduced above are publication Bias.

RESULTS

Description of included and excluded studies

According to our investigation in PubMed, Science Direct, Google Scholar, Biological Abstracts, ISI web of knowledge and IranMedex we had 78 inclusions (research articles with full text and abstracts in English) and in end 26 exclusions (Review articles, congress abstracts, studies that reported in languages other than English, studies that were not available for us in abstract or full text, studies that their sampling location was uncertain, studies that locations of sampling was performed at the same time, studies that their data were not clear) for this meta-analysis [Figure 1].

Samples information

In our study, 78 articles were reviewed from 33 different countries. The names of these countries are mentioned in Table 1.

The total population for prevalence of Haarlem family of *M. tuberculosis* that was included in this meta-analysis was 28,601. The major risk factors for *M. tuberculosis* infection were geographical areas and MDR-TB among Haarlem family. The typing method described in these studies was based on DNA polymorphism that exists at one particular chromosomal locus, the DR region, which is uniquely present in *M. tuberculosis* complex bacteria.

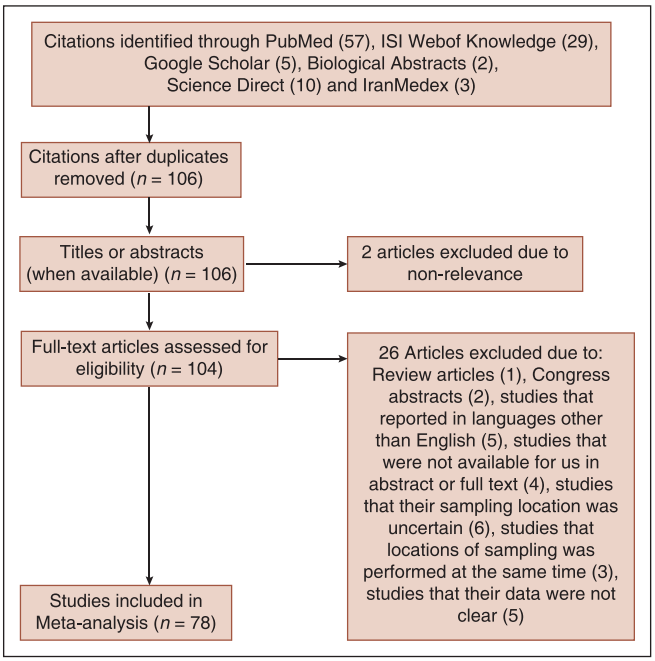

Figure 1: Flow diagram for study selection

Prevalence of *Mycobacterium tuberculosis* Haarlem family in the worldwide population

In this study, 78 different studies with a total number of 28,601 persons from 2002 to 2012 were subjected. For this meta-Analysis, prevalence of *M. tuberculosis* Haarlem Family in worldwide population was analyzed according to the year of occurrence and MDR-TB. The highest rate of prevalence was in Hungary in 2006 (66.20%) with negative MDR-TB and the lowest rate was in China in 2010 (0.8%), also MDR-TB was observed in these studies (CI: 95%) [Table 1].

Year

The data for 11 groups were analyzed for the period of 2002-2012. The lowest rate of prevalence was in 2010, and stood at 6.42% (95% CI: 5.91-6.95%). But the highest prevalence was attained in 2012, and stood at 20.62% (95% CI: 17.48-24.05%). The heterogeneity, I^2 = 97.7, heterogeneity Chi-squared = 383. 86 (d.f = 9) $P < 0.00$, estimate of between-study variance tau-squared = 0.01 and $P = 0.00$. Also results of publication bias presented in Figures 2-4 and Table 2.

Multi-drug resistant tuberculosis

Multi-drug resistant tuberculosis prevalence analysis in our 78 previously mentioned studies, showed that 1.076% (95%

Table 1: Data that were extracted from published documents about country, year, sample size, prevalence and *M. tuberculosis* Haarlem family MDR

Site	References	Study place (country)	Year	Sample size	Prevalence Haarlem (%)	MDR association
PubMed	[14]	China	2010	131	0.80	Yes
ISI	[15]	UK	2010	2261	0.90	Yes
PubMed	[16]	China	2011	195	1.03	
PubMed	[17]	Sudan	2011	235	1.30	
ISI	[18]	Malawi	2010	760	1.40	
ISI	[19]	Trinidad and Tobago	2009	132	1.50	
PubMed	[20]	Pakistan	2010	926	1.60	
Google Scholar	[21]	China	2011	223	2.20	Yes
PubMed	[22]	Taiwan	2010	39	2.56	Yes
PubMed	[23]	Venezuela	2006	873	3	
Biological abstracts	[23]	Venezuela	2006	670	3	
ISI	[24]	India	2011	101	3	
PubMed	[25]	Mexico	2011	267	3.00	
PubMed	[8]	South Africa	2006	391	3.00	Yes
PubMed	[26]	Mozambique	2010	445	3.10	
PubMed	[27]	Italy	2005	248	3.20	
ISI	[28]	Japan	2005	101	4	No
PubMed	[29]	Iran	2010	1074	4.10	
PubMed	[30]	China	2010	2346	4.48	
PubMed	[31]	Ireland	2010	171	4.70	
PubMed	[29]	Afghani Immmigrant	2010	668	4.90	
PubMed	[32]	Georgia	2010	183	5	Yes
PubMed	[33]	Venezuela	2009	1298	5	Yes
PubMed	[34]	Turkey	2007	114	5.30	
PubMed	[35]	Brazil	2011	1991	5.40	
Google Scholar	[36]	Russia	2006	87	5.80	
ISI	[37]	Brazil	2011	114	7	
PubMed	[37]	Brazil	2011	114	7	
PubMed	[38]	Saudi Arabia	2007	1505	7.50	
PubMed	[39]	Mexico	2011	118	7.70	
PubMed	[40]	Russia	2009	90	7.80	Yes
Google Scholar	[23]	Venezuela	2007	36	8	
PubMed	[41]	Iran	2008	258	8.60	Yes
PubMed	[42]	Portugal	2004	219	8.70	
PubMed	[43]	Guinea-Bissau	2011	414	8.85	
ISI	[44]	Indonesia	2009	336	9.30	
PubMed	[45]	Russia	2007	217	10	No
ScienceDirect	[46]	Portugal	2007	665	10	
ISI	[45]	Russia	2007	217	10	Yes
PubMed	[29]	Turkey	2010	381	10.20	
PubMed	[47]	Bulgaria	2008	113	10.60	No
ISI	[48]	Turkey	2009	220	10.90	Yes
PubMed	[49]	Taiwan	2008	138	10.90	
PubMed	[50]	Ghana	2011	162	11.53	
PubMed	[51]	Turkey	2008	94	12.40	
ISI	[52]	Turkey	2007	56	12.50	No
PubMed	[53]	Spain	2009	31	13	
ScienceDirect	[54]	Madagascar	2005	298	13.10	
PubMed	[55]	Taiwan	2008	356	13.50	Yes
PubMed	[56]	Russia	2002	122	13.90	
ScienceDirect	[57]	Taiwan	2008	208	13.90	
PubMed	[58]	Sierra Leone	2008	97	14.40	Yes
ScienceDirect	[49]	Taiwan	2008	138	14.50	
PubMed	[59]	Iran	2009	34	14.70	
PubMed	[60]	Turkey	2007	145	15.90	

Table 1: Continued

Site	References	Study place (country)	Year	Sample size	Prevalence Haarlem (%)	MDR association
PubMed	[61]	Honduras	2010	206	16	No
PubMed	[62]	Poland	2010	27	17.40	Yes
PubMed	[63]	Paraguay	2007	220	18.20	
GoogleScholar	[64]	Taiwan	2011	494	18.20	Yes
IranMedex	[65]	Iran	2006	439	19.40	No
PubMed	[66]	Italy	2007	829	19.90	
PubMed	[67]	Taiwan	2012	516	20	
PubMed	[68]	Italy	2010	1080	21.30	
ISI	[69]	Italy	2009	1009	21.40	
PubMed	[70]	Guadeloupe, Martinique, and French Guiana	2006	744	21.70	
PubMed	[71]	Sweden	2004	220	23.20	No
IranMedex	[72]	Iran	2008	30	23.30	Yes
PubMed	[73]	Turkey	2012	95	24.20	Yes
PubMed	[74]	Colombia	2011	152	25.00	
ScienceDirect	[74]	Colombia	2011	152	25.00	
IranMedex	[75]	Iran	2009	238	27.70	Yes
PubMed	[76]	Spain	2008	134	28.40	
PubMed	[77]	Germany	2011	277	31	
ISI	[78]	Iran	2006	263	33.50	
Biological abstracts	[79]	Iran	2009	220	34.10	Yes
PubMed	[80]	Germany	2007	216	37	
PubMed	[81]	Iran	2009	146	39.10	Yes
PubMed	[82]	Hungary	2006	68	66.20	

*No = Study number; MDR = Multi-drug resistant; *M. tuberculosis* = *Mycobacterium tuberculosis*

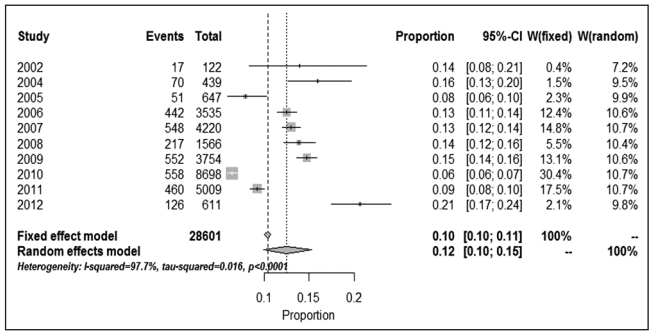

Figure 2: Pooled sensitivity (confidence interval: 95%) and heterogeneity for *Mycobacterium tuberculosis* Haarlem family in worldwide population based on year (Method: Inverse variance method [Freeman Turkey double arcsine transformation])

CI: 10.30-11.23%) were positive MDR. But, prevalence for negative MDR was 9.22% (95% CI: 8.3-10.2%). Heterogeneity, I-squared = 79.4, heterogeneity Chi-squared = 9.69 (d.f = 2) $P < 0.001$, Estimate of between-study variance Tau-squared = 0.00 and $P = 0.00$. Also there is no publication bias [Figures 5 and 6, Table 3].

DISCUSSION

Mycobacterium tuberculosis causes TB disease and possibly death.[3] The aim of our study was to determine the prevalence and rate of occurrence of MDR Haarlem family of *M. tuberculosis* in the worldwide using meta-analysis and a systematic review based on published articles in the period of 2002-2012. Molecular epidemiology fulfills to establish a dynamic transmission of disease. Results in our study showed that the lowest and highest rates of prevalence were in 2010 and 2013, respectively. 1.076% of samples were positive for MDR and 9.22% were negative for MDR. TB cases have decreased since 2005 and new cases since 2002. For example China has a % 80 decline in its TB mortality rate. 80% of the population in Asian and African countries has positive tuberculin test, but 5-10% of the USA population has positive tuberculin test. In 2007, Swaziland with 1200 cases per 100,000 people had the highest incidence rate of TB. India with 2.0 million new cases had the largest total incidence.[5,83,84] In our study the lowest rate of Haarlem family prevalence was 6.42% in 2010 and the highest prevalence rate was 20.62% in 2012. TB morbidity has decreased worldwide but an increase in the incidence and prevalence of MDR-TB can be observed.[85] Also in our results the highest and lowest rates of occurrence of Haarlem family of *M. tuberculosis* in worldwide population were in Hungary in 2006 (66.20%) and in China in 2010 (0.8%), respectively. Risk factors that are important for considering when we talk about *M. tuberculosis* occurrence rate are poor living conditions, unhealthy work environments, crowded places, poverty, and lack of access to proper medical care, and factors that impair the host's defense against TB infection such as HIV infection, malnutrition, smoking, diabetes, alcohol abuse, and indoor air pollution. These factors can be effective on prevalence of *M. tuberculosis* family in different

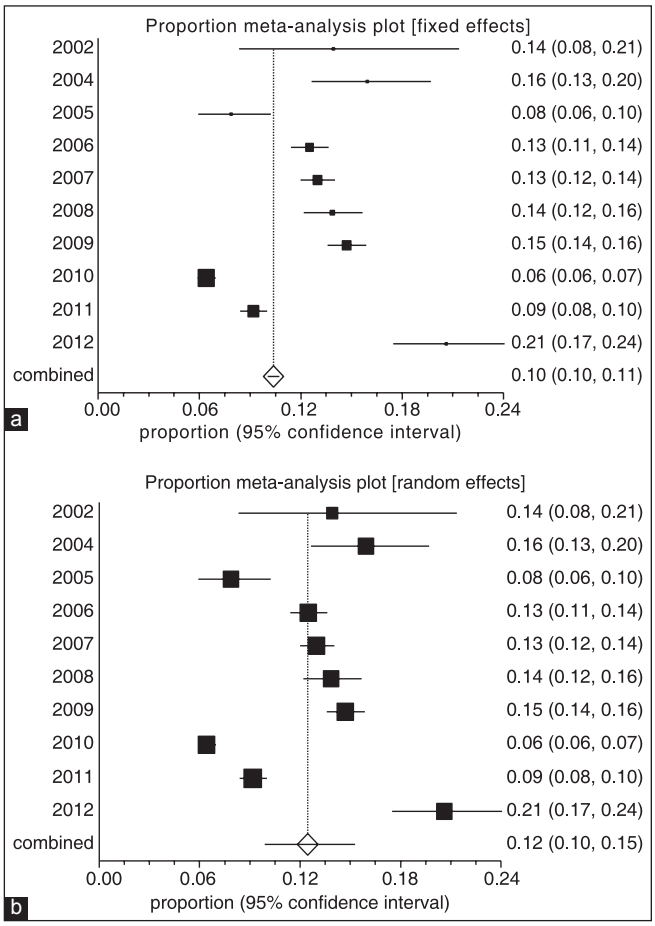

Figure 3: Forest plot of fixed (a) and random (b) effect estimates for pooled sensitivity and heterogeneity estimates for prevalence of Haarlem family of *Mycobacterium tuberculosis* in worldwide population based on year (confidence interval: 95%)

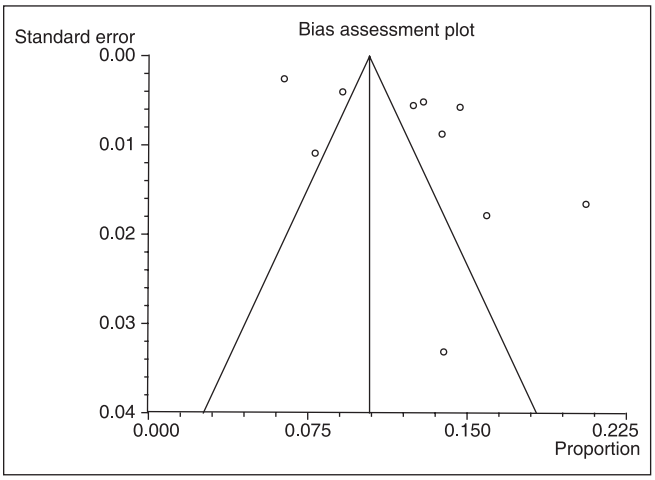

Figure 4: Results of publication bias in for *Mycobacterium tuberculosis* Haarlem family in worldwide population based on year (confidence interval: 95%)

Table 2: Pooled sensitivity (CI: 95%) and heterogeneity for *M. tuberculosis* Haarlem family in worldwide population based on year

n	Proportion	95% CI (exact)	% W (fixed; random)	Year
1	0.13	0.08; 0.21	0.42; 7.16	2002
2	0.15	0.12; 0.19	1.53; 9.46	2004
3	0.07	0.05; 0.10	2.26; 9.85	2005
4	0.12	0.11; 0.13	12.35; 10.62	2006
5	0.12	0.11; 0.14	14.75; 10.65	2007
6	0.13	0.12; 0.15	5.47; 10.39	2008
7	0.14	0.13; 0.15	13.12; 10.63	2009
8	0.06	0.05; 0.06	30.40; 10.73	2010
9	0.09	0.08; 0.10	17.51; 10.67	2011
10	0.20	0.17; 0.24	2.13; 9.80	2012

Fixed effects (inverse variance)
Pooled proportion=0.10 (95% CI=0.10-0.10)
Noncombinability of studies
Cochran *Q*=383.85 (df=9) *P*<0.00
Moment-based estimate of between studies variance=0.01
I^2 (inconsistency)=97.7% (95% CI=97.1-98.1%)
Random effects (DerSimonian – Laird)
Pooled proportion=0.12 (95% CI=0.09-0.15)
Bias indicators
Begg-Mazumdar: Kendall's tau=0.02, *P*>0.99 (low power)
Egger: Bias=7.37 (95% CI=0.64-14.10) *P*=0.03
Harbord: Bias=6.91 (92.5% CI=−1.18-15.01) *P*=0.1

*Number of trials combined = 10; CI = Confidence interval (95%); W = Weights; df = Degrees of freedom; *P* = Probability value; *M. tuberculosis* = *Mycobacterium tuberculosis*

regions according to our study as compared to other studies.[86,87] These data suggest that different factors such as spread of strains of MDR-TB (primary drug resistance) or the development of drug resistance in the drug-susceptible *M. tuberculosis* strains due to treatment default or failure (acquired resistance) in patients are important factors for MDR-TB existence. Durmaz *et al*. in Turkey showed that genetic diversity and major spoligotype families of drug-resistant *M. tuberculosis* from different regions of Turkey in clinical isolates was for T super-family (29%), Latin-American and Mediterranean (33.5%), Haarlem (14%), and the S lineage (3%).[88] Thus, genetic variation in TB plays an important role in the prevalence of the disease.[3] Based on these results genotyping of *M. tuberculosis* is an important factor for TB control. Several molecular techniques exist to identity *M. tuberculosis* such as variable-number tandem repeats of different families of genetic elements that are called mycobacterial interspersed repetitive units and polymerase chain reaction-based spoligotyping.[89,90] In another study Marais *et al*. in South Africa by spoligotyping that they performed for drug susceptibility testing on 391 isolates; 12.5% were resistant to isoniazid, and 20% were resistant to both isoniazid and rifampin. In Marais study, Haarlem genotype family with 53.1% was significantly associated with drug resistance, so association between antibiotic resistance and prevalence of Haarlem family can be confirmed by spoligotyping.[8] The most common method that is used in clinical molecular epidemiology of TB is spoligotyping that is used extensively.[91,92] This technique showed various profiles of Haarlem family of *M. tuberculosis* that were obtained from different populations.[93] Bazira

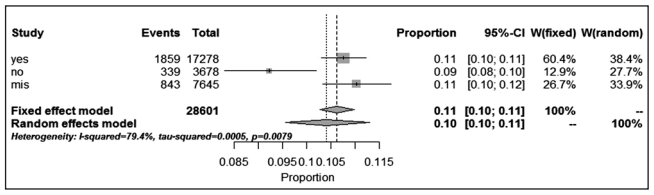

Figure 5: Pooled sensitivity (confidence interval: 95%) and heterogeneity estimates for prevalence of Haarlem family of *Mycobacterium tuberculosis* in worldwide population based on multi-drug resistant tuberculosis (Method: Inverse variance method [Freeman Turkey double arcsine transformation])

Table 3: Pooled sensitivity (CI: 95%) and heterogeneity estimates for prevalence of Haarlem family of *M. tuberculosis* in worldwide population based on MDR-TB

n	Proportion	95% CI (exact)	Percentage weights (fixed; random)	MDR
1	0.10	0.10; 0.11	60.40; 38.42	Yes
2	0.09	0.08; 0.10	12.86; 27.65	No
3	0.11	0.10; 0.11	26.73; 33.92	Miss

Fixed effects (inverse variance)

Pooled proportion=0.10 (95% CI=0.10-0.10)

Noncombinability of studies

Cochran Q=9.68 (df=2) P=0.00

Moment-based estimate of between studies variance=0.00

I^2 (inconsistency)=79.4% (95% CI=0-91.6)

Random effects (DerSimonian – Laird)

Pooled proportion=0.10 (95% CI=0.09-0.11)

Quantifying heterogeneity: Tau 2=0.0005, H=2.2 (1.23; 3.93); I_2=79.4% (34.3%; 93.5%). Test of heterogeneity: Q=9.69; df: 2; P<0.0079

Bias indicators

Begg-Mazumdar: Kendall's <too few strata>*

Egger: Bias=<too few strata> (95% CI=*to*) P=*

Harbord: bias=−4.199132 (92.5% CI=−39.10-30.70) P=0.49

*Number of trials combined = 3; CI = Confidence interval (95%); W = Weights; df = Degrees of freedom; P = Probability value; *There's probably no CI and real value. *M. tuberculosis* = *Mycobacterium tuberculosis*; MDR = Multi-drug resistant; TB = Tuberculosis; CI = Confidence interval

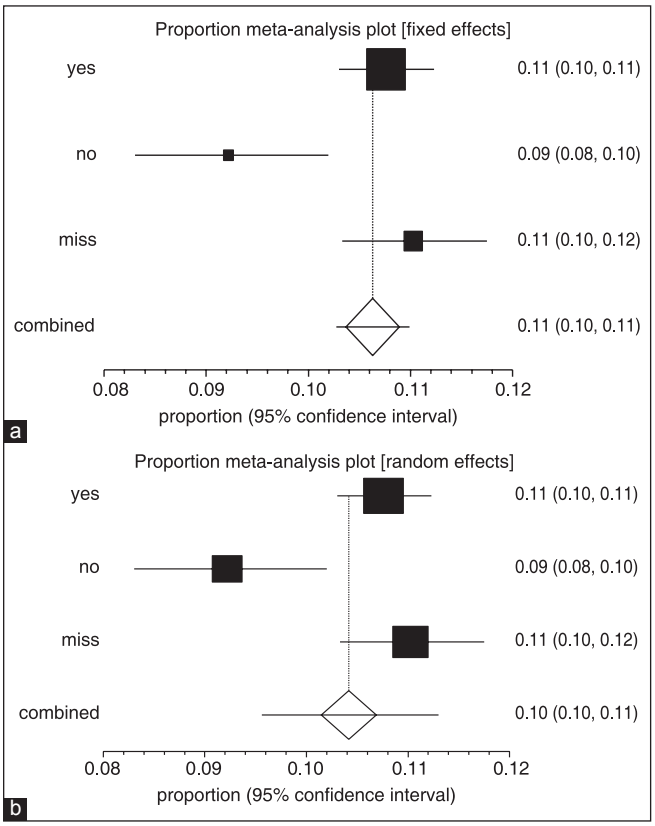

Figure 6: Forest plot of fixed (a) and random (b) effect estimates for pooled sensitivity (confidence interval [CI]) and heterogeneity estimates for prevalence of Haarlem family of *Mycobacterium tuberculosis* in worldwide population based on multi-drug resistant tuberculosis (CI: 95%)

et al. in Uganda by spoligotyping on 125 isolates revealed that 79 spoligotype patterns, with an overall diversity of 63.2%. Resistance mutations to either rifampicin or isoniazid were detected in 6.4% of the isolates. Multidrug resistance was seen in 1.6% of the cases.[94] Mutation in bacterium and diversion of the genotypes are largely in *M. tuberculosis* families and their resistance to drugs may be different among various families.[95] Research articles of our study were gathered for meta-analysis from different websites, including newest researches in PubMed, Science Direct, Google Scholar, Biological Abstracts and ISI web of knowledge in Thomsonreuters in regard to prevalence of TB in world health population. The difference in percentages in databases is logical based on published medical journals. Also we used the Endnote software for our search and deleted overlap studies. In this review, 78 studies were selected for analysis; therefore power of statistical analysis is great and association with drug resistance document in total published reports. Since Haarlem strains are largely transmitted in cities of different countries, causing health problems and outbreak of MDR-TB in populations. This family isolated from patients in different locations in Europe, Asia and USA, so its detection and prevention is necessary.[3,96] We hope results of this study can be effective on control and prevention of Haarlem Family of *M. tuberculosis* in world populations.

CONCLUSION

This study's results indicate the dynamics of transmission of Haarlem family and its association in drug resistance and they can improve our vision about TB in worldwide populations. Tracking and designing programs for controlling TB infection and MDR is necessary for public health because *M. tuberculosis* families can be transmitted between different populations in the world. TB infection has been decreasing in recent years, but our results showed that the prevalence rate in 2010 was more than other years that we surveyed about. Therefore, control of its transmission and drug-resistant patients are required. This meta-analysis provides comprehensive and reliable data on the prevalence and occurrence rate of *M. tuberculosis* Haarlem family MDR among different countries and may be helpful in prevention of its occurrence.

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AUTHOR'S CONTRIBUTION

RR contributed in original idea and protocol, conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. DR was statistical consulting. PS contributed in wrote and editing of this manuscript. SR contributed in wrote and editing of this manuscript conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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