A 10 -year survey on prevalence and occurrence rate of multi-drug resistant *Mycobacterium tuberculosis* in Latin American and Mediterranean Families: A Systematic review and meta-analysis

Samaneh Rouhi[1, 2], Daem Roshani[3], Pegah Shakib[1, 2], Fatemeh AhangarKani[4], Rashid Ramazanzadeh[2, 5*]

1. Student Research Committee, Kurdistan University of Medical Sciences, Sanandaj, Iran
2. Cellular and Molecular Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran
3. Social Determinants of Health Research Center, Kurdistan University of Medical Sciences, Sanandaj, Iran
4. Antimicrobial Resistance Research Center, Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran
5. Department of Microbiology, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran

***Corresponding author:**Tel: +98 9143104424Fax: +98 8716664674
Address: Cellular & Molecular Research Center and Microbiology Department, Faculty of Medicine, Kurdistan University of Medical Science, Pasdaran Street, Post cod. 66177-13446, Sanandaj, Iran
E-mail:atrop_t51@yahoo.com
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Abstract

Introduction: Latin American and Mediterranean (LAM) is a family of *Mycobacterium tuberculosis* (*M. tuberculosis*). Drug resistant in *M. tuberculosis* LAM family is a major problem in the world population. Our objective of this study was to determine the prevalence of *M. tuberculosis* LAM family with multi-drug resistant (MDR) in the worldwide by a meta-analysis and systematic review.

Materials and methods: Data sources of this study were 68 original articles (2001-2012) which were published in different databases. Research articles with full text in English were selected. Review articles, congress abstracts, studies that were reported in languages other than English and also studies that were not available for us in abstract or full text were excluded. Data that were obtained from prevalence and occurrence rate of MDR *M. tuberculosis* LAM family were analyzed using meta-analysis random effects models with software package Meta R, Version 2.13 ($P < 0.10$).

Results: During 10 years, lowest rate of prevalence was observed in 2010 and 2006 (95% CI: 5.91%-6.95%) and highest prevalence rate was in 2006 (95% CI: 17.48%- 24.05%). prevalence of MDR- *M. tuberculosis* analysis showed positive MDR between them (95% CI: 10.30%-11.23%). Prevalence for negative MDR was 9.22% (95% CI: 8.3%- 10.2%).

Conclusion: Our study showed that *M. tuberculosis* LAM family is prevalent in Europian countries. LAM sub lineage was a major focus of studies that carried out in different countries. The proper technique for prevention of transmission of *M. tuberculosis* is necessary.

Keywords: Prevalence, *Mycobacterium tuberculosis*, Latin American and Mediterranean Family, Multi-Drug Resistant

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Introduction

Tuberculosis (TB) is a bacterial infectious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*).It is still an important cause of morbidity and mortality (1, 2). TB can be seen in various forms including pulmonary and extra pulmonary (3). Epidemiological estimates in 2011 showed 1.4 million deaths and 8.7 million new cases of TB in world (4). For example, reports in Moscow showed *M. tuberculosis* morbidity about 50 cases per 100,000 people in 2008 (5). The best way to treat TB is antibiotic treatment. Antibiotics used to treat including first-line drugs (isoniazid, rifampin, ethambutol, and streptomycin) and second-line drugs (aminoglycosides, kanamycin, amikacin, and fluoroquinolones) (6-9). The dramatic rise and the increasing emergence of drug-resistant *M. tuberculosis* isolates are causes for concern attention to this disease (10-13). Many reports presented multi-drug resistance (MDR) -*M. tuberculosis* that resistant to at least both isoniazid and rifampin. This problem cause TB, increasing treatment period, rising health care costs, and mortality rates (14-16). Also studies showed that transmission of different *M. tuberculosis* families are associated with drug resistance in worldwide populations. The main genotype families of *M. tuberculosis* are beijing, haarlem, east-african-indian(EAI), latinamerican and mediterranean(LAM), U and T strains (9, 10). LAM is one of *M. tuberculosis* phylogenetic family and its name is derived from the geographical area which was isolated. LAM sub lineage was a major focus of studies in different area of Americas, Europe, Africa and Russia (11). Different studies reported MDR-*M. tuberculosis* among *M. tuberculosis* LAM family; Ignatova et al. in Russia reported that members of the LAM families were MDR in the populations that were studied (17). In other study,Valcheva et al. in Bulgaria showed that a higher MDR rate among LAM families (18). Dymova et al. in Russian using variable number tandem repeat (VNTR) and restriction fragment length polymorphism (RFLP) - insertion sequence (IS) 6110-typing showed that, in *M. tuberculosis*isolates that were isolated from 98 TB patients, 75 different genetic profiles were detected. Also an association was observed between the LAM strain family and MDR (19, 20). Therefore, control and MDR patient's detection are required for TB treatment. The aim of our study is a survey on prevalence and occurrence rate of *M. tuberculosis* LAM family with MDR during 10 years among different countries, based on a systematic review and meta-analysis. It may be helpful in prevention and control of *M. tuberculosis* LAM family with MDR in the world population.

Materials and methods

Data Sources: For prevalence determination of *M. tuberculosis* LAM family with MDR and occurrence rate in the worldwide population, literature databases (PubMed, Science Direct, Google Scholar, ISI Web of Science, and Biological Abstracts) and original articles were considered between 2001-2012 years in English language. Key words for search in databases were *M. tuberculosis*, TB, LAM family and MDR.

Study Selection: Process for selecting the studies: the data includes number of cases, websites, author, study place, year of the research, sample size, and prevalence of LAM and MDR association. Inclusion criteria were: (1) research articles with full text, (2) articles with abstract in English. Excluded studies were: (1) review articles, (2) congress abstracts, (3) studies that reported in languages other than English, (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, and (7) studies that their data were not clear (see Flowchart 1).

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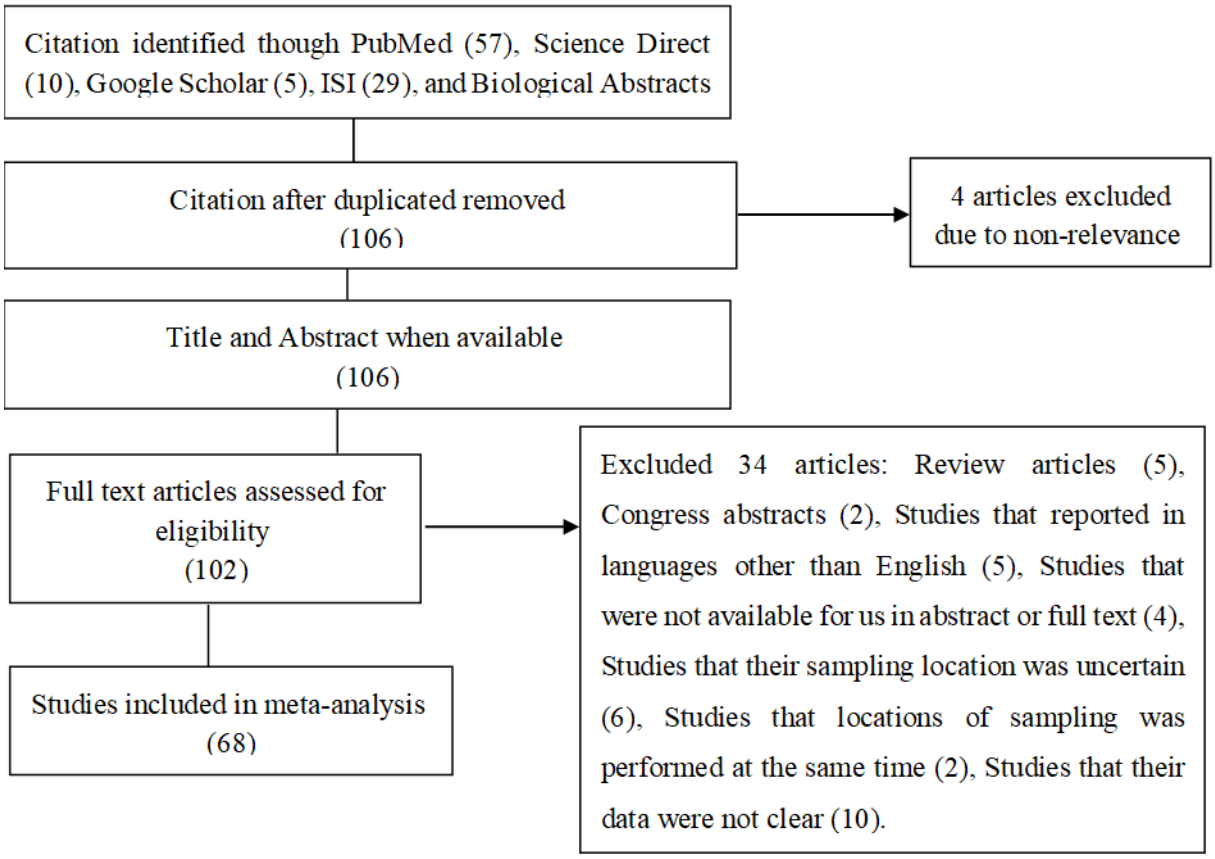
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Data Extraction: In our study 106 articles were selected. The variance of prevalence was computed using binomial distribution and meta-analysis with the random effect model which was applied to combine the prevalence among the studies. There was sensitivity and heterogeneity among the studies. Inconsistency (I^2), (95% confidence interval, CI) and Cochran Q ($P<0.10$) statistical tests were used to check out this heterogeneity. Meta R Version 2.13 software package for Meta-analysis was applied.

Results

68 original articles (published 2001 to 2012) were reviewed from 106 original articles. The total population that was obtained from articles in this meta-analysis was 25501 (Table 1). According to the countries and the years, the highest prevalence rate of *M. tuberculosis* LAM family was in Venezuela in 2006 and the lowest rate was in Pakistan and Iran in 2010 and 2006 (both 0.2 %), respectively Also patients with MDR -TB were observed in these studies (Table 1)

Prevalence of *M. tuberculosis* LAM family in Worldwide Population Based on Years of Study: The data for 10 groups were analyzed during 2001-2012. The lowest rate of prevalence was observed in 2010 and 2006 [6.42% (95% CI: 5.91%-6.95%)]. Highest prevalence rate was in 2012 [20.62% (95% CI: 17.48%- 24.05%)]. In this heterogeneity, $I^2= 97.7$, Chi-squared = 383. 86, degrees of freedom (df) = 9 with $P < 0.00$ and between-study variance (tau-squared) = 0.01 with P= 0.00 were obtained. Also, publication bias result is presented in Figure 1 (also, Table 2).



Flowchart 1. Flow diagram for study selection.

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Table 1. Data that were extracted from published documents about country, year, and prevalence of *M. tuberculosis* Latin American and Mediterranean (LAM) family and multi-drug resistant (MDR).

References	Country	Year	Prevalence	MDR	References	Country	Year	Prevalence	MDR
(1)	Georgia	2010	18%	Yes	(18)	Tanzania	2006	22%	-
(3)	Ghana	2011	1.54%	-	(36)	Turkey	2007	28.60%	No
(5)	Guinea	2011	18.12%	-	(37)	Russia	2007	46%	No
(7)	Brazil	2011	10.30%	-	(38)	UK	2010	0.80%	Yes
(9)	Colombia	2011	49.34%	-	(39)	Italy	2007	11.20%	-
(11)	Mozambique	2010	37%	-	(40)	Brazil	2011	55.3%	-
(13)	Honduras	2010	55%	-	(41)	Turkey	2007	7.90%	-
(15)	Ireland	2010	4.10%	-	(42)	Malawi	2010	51.70%	-
(17)	Malawi	2010	44.30%	-	(43)	Turkey	2007	29%	-
(19)	Taiwan	2010	2.56%	Yes	(44)	Italy	2009	12.80%	-
(20)	Guadeloupe	2006	19.70%	-	(45)	Paraguay	2007	52.3%	-
(21)	Poland	2010	13.00%	Yes	(46)	Saudi Arabia	2007	7.2%	-
(22)	Iran	2006	0.2%	No	(47)	China	2011	1.1%	Yes
(23)	China	2010	0.80%	Yes	(48)	Venezuela	2006	74%	-
(24)	Indonesia	2009	6.3%	-	(49)	Colombia	2011	49.34%	-
(25)	South Africa	2010	28.80%	-	(50)	Italy	2005	5.2%	-
(26)	Myanmar	2009	4.50%	Yes	(51)	Taiwan	2008	5.80%	-
(27)	Italy	2010	12.80%	-	(52)	Russia	2004	23.8%	-
(28)	Turkey	2009	15%	Yes	(53)	Portugal	2007	51%	-
(29)	Russia	2009	17.8%	Yes	(54)	Russia	2004	49.6%	-
(30)	South Africa	2000	29.50%	No	(55)	Taiwan	2008	3.80%	-
(31)	Venezuela	2009	53%	Yes	(56)	Sweden	2004	8%	No
(32)	Japan	2005	2%	No	(57)	Madagascar	2005	6%	-
(33)	sough	2008	29.20%	No	(58)	Turkey	2012	5.30%	Yes
(34)	Trinidad	2009	11.40%	-	(59)	Sudan	2011	2.60%	-
(35)	Sierra Leone	2008	15.5%	Yes	(60)	Iran	2009	0.45%	Yes
(2)	Mexico	2011	14.40%	-	(61)	Mexico	2011	11.60%	-
(4)	Pakistan	2010	0.20%	-	(62)	Russia	2011	10.4%	-
(6)	Turkey	2010	18.40%	-	(63)	Brazil	2011	55.30%	-
(8)	Spain	2009	3%	-	(64)	Venezuela	2007	64%	-
(10)	Spain	2008	32.10%	-	(65)	Brazil	2011	36.10%	-
(12)	Turkey	2008	22.5	-	(66)	Russia	2006	44.8%	-
(14)	Germany	2007	5.8%	-	(67)	South Africa	2011	33%	-
(16)	South Africa	2006	29.20%	Yes	(68)	China	2011	3.6%	Yes

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

Stratum	Proportion	95% CI	% Weights (fixed, random)	Year
1	0.29	0.24; 0.34	1.53; 9.80	2000
2	0.31	0.28; 0.35	3.05; 10.05	2004
3	0.05	0.03; 0.07	2.81; 10.03	2005
4	0.44	0.42; 0.45	14.55; 10.26	2006
5	0.44	0.21; 0.23	18.32; 10.27	2007
6	0.16	0.13; 0.19	3.40; 10.08	2008
7	0.25	0.23; 0.26	15.84; 10.27	2009
8	0.23	0.22; 0.24	22.35; 10.28	2010
9	0.16	0.15; 0.17	17.68; 10.27	2011
10	0.05	0.01; 0.11	0.41; 8.64	2012

MDR-TB: MDR -TB prevalence analysis showed positive MDR between *M. tuberculosis* LAM family (95% CI: 10.30%-11.23%). Prevalence for negative MDR was 9.22% (95% CI: 8.3%- 10.2%). In this heterogeneity, I^2= 79.4, Chi squared = 9.69, df = 2 with P< 0.00, tau squared = 0.00 with P= 0.00 were observed. Also, no publication bias was observed.

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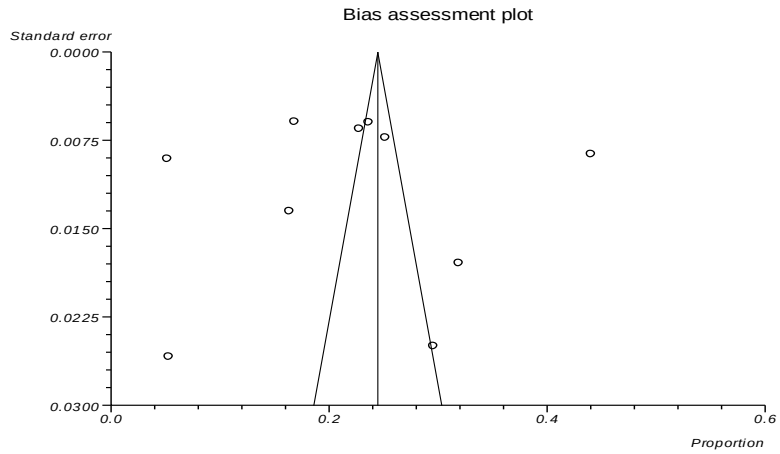


Figure 1. Results of publication bias for *M. tuberculosis* LAM family in worldwide population based on year (CI: 95%).

Discussion

Studies proved that MDR in patients with TB is related with high mortality (1). In this study we survey prevalence and occurrence rate of MDR-*M. tuberculosis* LAM family during 10 years between world population according to a systematic review and meta-analysis. Results in this study showed that lowest and highest rates of *M. tuberculosis* LAM family prevalence were in 2010 (0.2 %) and 2006 (0.2 %), and 2006 (74%), respectively. Also a transmission of this family was observed in our study during 10 years among 36 countries. Dye et al. in 2009 in Switzerland reported that estimated global TB incidence was 63% during 1997–2006 between 211 countries (68). Different factors can affect TB occurrence rate in countries. These factors including poor living conditions, cigarette smoking, diabetes, chronic peritoneal dialysis, MDR-TB, imprisonment, HIV infection, alcohol abuse, and air pollution (69).Jagielski et al. in 2009 in France reported that MDR strains (13%) were detected in 27 patients with TB (70). Also Durmaz et al. in Turkey in 2007 showed MDR in clinical isolates of *M. tuberculosis* of T super-family (29%), LAM (33.5%), Haarlem (14%), and S lineage (3%) (71). MDR positive in different countries in our study was observed. Also negative MDR was 9.22%. Different factors such as spread of MDR-TB strains, acquired resistance during resistance gene transmission in patients and geographical distribution among neighboring countries are important factors for MDR-TB different rates in studies. Also genetic variation is related to prevalence and spread of drug-resistant strains. So genotyping is an important tool for detection of origin and transmission patterns of drug-resistant strains (72). There are several methods for molecular typing of *M. tuberculosis* such as: Spoligotyping, RFLP typing based on the IS6110 and VNTR (6 -8). Spoligotyping is a major technical for molecular typing of *M. tuberculosis* (70). This 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 (7). The DR locus consists of conserved direct repeatations interspersed with unique spacer sequences (8). Therefore we study LAM family prevalence and occurrence rate by spoligotyping method. Association between LAM family and MDR in articles that obtained in different countries was observed. In a study in 2014 in Iraq, Ahmed et al. with spoligotyping yielded 39 patterns among 270 isolates from 134 patients. In Ahmed's study, 70 isolates were found as MDR (73). Imperiale et al. in 2013 in Argentina by spoligotyping showed that Haarlem, LAM and T family were the main

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spoligotyping families and katG315 gene mutation was mainly associated with LAM family (74). Resistance to drugs in *M. tuberculosis* families may be associated with MDR and different among various families (69). In our meta-analysis different original article obtained from PubMed, Science Direct, Google Scholar, Biological Abstracts, and ISI web of knowledge in Thomson Reuters with regard to prevalence of LAM family in world population. In this review, we use statistical analysis and proved association drug resistance in total published reports. MDR -*M. tuberculosis* families can be found in different countries, so an outbreak of MDR-TB in populations can be occurred. A program for detection and prevention of MDR-*M. tuberculosis* family's transmission is necessary (69, 75). It is hoped this systematic review and meta-analysis can be effective on control, prevention of transmission, origin detection of LAM Family and its control.

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