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

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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 European 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 the 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).
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 (I²), (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, I² = 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.
**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).

<table>
<thead>
<tr>
<th>References</th>
<th>Country</th>
<th>Year</th>
<th>Prevalence</th>
<th>MDR</th>
<th>References</th>
<th>Country</th>
<th>Year</th>
<th>Prevalence</th>
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<td>Portugal</td>
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<td>Madagascar</td>
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<td>Mexico</td>
<td>2011</td>
<td>11.60%</td>
<td></td>
</tr>
<tr>
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<td>Pakistan</td>
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<td>0.20%</td>
<td>-</td>
<td>(62)</td>
<td>Russia</td>
<td>2011</td>
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<td>(6)</td>
<td>Turkey</td>
<td>2010</td>
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<td>-</td>
<td>(63)</td>
<td>Brazil</td>
<td>2011</td>
<td>55.30%</td>
<td></td>
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<td>(8)</td>
<td>Spain</td>
<td>2009</td>
<td>3%</td>
<td>-</td>
<td>(64)</td>
<td>Venezuela</td>
<td>2007</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>(10)</td>
<td>Spain</td>
<td>2008</td>
<td>32.10%</td>
<td>-</td>
<td>(65)</td>
<td>Brazil</td>
<td>2011</td>
<td>36.10%</td>
<td></td>
</tr>
<tr>
<td>(12)</td>
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<td>2008</td>
<td>22.5%</td>
<td>-</td>
<td>(66)</td>
<td>Russia</td>
<td>2006</td>
<td>44.8%</td>
<td></td>
</tr>
<tr>
<td>(14)</td>
<td>Germany</td>
<td>2007</td>
<td>5.8%</td>
<td>-</td>
<td>(67)</td>
<td>South Africa</td>
<td>2011</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>(16)</td>
<td>South Africa</td>
<td>2006</td>
<td>29.20%</td>
<td>Yes</td>
<td>(68)</td>
<td>China</td>
<td>2011</td>
<td>3.6%</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

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

**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, $P = 79.4$, 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.
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

![Bias assessment plot](image-url)
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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