ORIGINAL ARTICLE

Mycobacterium simiae pulmonary disease in Iran: systematic review and meta-analysis

M. J. Nasiri[1], M. Heidary[3], T. Azimi[4], H. Goudarzi[1], P. Tabarsi[2], D. Darban-Sarokhalil[3] and M. M. Feizabadi[5]

1) *Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences,* 2) *Clinical TB and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences,* 3) *Department of Microbiology, School of Medicine, Iran University of Medical Sciences,* 4) *Department of Medical Microbiology, School of Public Health and* 5) *Department of Medical Microbiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

Abstract

Mycobacterium simiae is one of the most common nontuberculous mycobacteria (NTM) microorganisms causing lung disease in many countries in the world. A reliable estimate of the extent of *M. simiae* pulmonary disease has not been well investigated in Iran. We systematically searched multiple databases to identify relative studies. Studies were excluded if they did not use the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) diagnostic criteria for NTM diseases. Data were extracted independently and in duplicate. We assessed pooled estimate by using a random model effect, and sources of heterogeneity were assessed by using Cochran's *Q* and the I^2 statistic. The potential for publication bias was explored by using Begg's and Egger's tests. All analyses were conducted with Stata 14.0 (StataCorp, College Station, TX, USA). Of 172 articles identified, seven met the inclusion criteria. Of 355 patients who were culture positive for NTM, 82 had M. *simiae* pulmonary disease according to the ATS/IDSA diagnostic criteria. The pooled frequency of *M. simiae* pulmonary disease among patients with NTM was 25.0% (95% confidence interval, 16.8–33.2). No evidence of publication bias was observed among the included studies (p >0.05 for Begg's and Egger's tests). Clinical isolates of *M. simiae* are increasingly being recognized as a cause of pulmonary disease in Iran and need further attention by health authorities.

Keywords: Iran, *Mycobacterium simiae*, systematic review
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Corresponding author: Mohammad Javad Nasiri, Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
E-mail: mj.nasiri@hotmail.com

Introduction

Infections caused by nontuberculous mycobacteria (NTM) have been recently reported as an important public health problem in many parts of the world, especially in developing countries [1–3]. Iran is a tuberculosis (TB)-endemic country with an annual incidence of 22 cases per 100 000 population [4]. On the basis of the studies from this country, 5% to 10% of mycobacterial infections are caused by NTM [5]. *Mycobacterium simiae* is among the most prevalent NTM in Iran and has been recently recognized as an emerging pathogen [6–9]. It causes pulmonary disease and disseminated infection in both immunocompromised and immunocompetent patients [6,10].

M. simiae are commonly isolated from environmental sources such as soil, tap water and the water supply, and therefore its isolation does not necessarily imply disease because positive cultures may only represent colonization [6]. On the basis of the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) guidelines, clinical, radiographic and microbiologic criteria are needed for the diagnosis of NTM diseases [11]. IDSA recommended that treatment regimens differ according to the NTM species, and management is a complicated process [11]. Pulmonary disease caused by *M. simiae* may be easily confused with *Mycobacterium tuberculosis*

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[7,12]. Most isolates of *M. simiae* are resistant to all first-line anti-TB drugs, and for patients with *M. simiae* pulmonary disease, initial therapy usually consists of a regimen containing clarithromycin or moxifloxacin [11,13,14].

Clinical *M. simiae* isolation has been reported from many places in the world [15–19]. For example in the United states, India and Oman, *M. simiae* was among the most prevalent isolates of NTM [1]. Previous studies in Iran did not use ATS/IDSA criteria to report the prevalence of *M. simiae.* Furthermore, no specific information regarding the *M. simiae* pulmonary disease is available in Iran. Thus, a reliable estimate of the *M. simiae* pulmonary disease is needed for the programmatic management of the disease within the context of national TB control programmes.

In this study, we aimed to investigate the frequency of pulmonary *M. simiae* among NTM disease using a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20].

Methods

Search strategy

To identify relevant studies, PubMed, Web of Science, Embase and Iranian databases were searched for articles published from January 2000 to December 2017. Search terms included 'mycobacterium,' 'mycobacterium simiae' and 'Iran.' Titles and abstracts of all identified articles were screened by two authors. Likewise, full text of potentially relevant articles were assessed for eligibility independently and in duplicate by two investigators. In all included studies, we attempted to contact the authors for confirmation whether they used ATS/IDSA criteria.

Inclusion and exclusion criteria

We included all cross-sectional studies that evaluated the prevalence or frequency of *M. simiae* infections in Iran. Studies were included if they used ATS/IDSA diagnostic criteria [11] to report NTM infections and used standard methods for NTM diagnosis.

Studies that did not use ATS/IDSA diagnostic criteria for NTM diseases, as well as standard methods for NTM diagnosis, were excluded. Studies were also excluded if they did not report the number of *M. simiae* cases or if they considered only environmental samples.

Data extraction

Data were extracted using an extraction form independently and in duplicate by two investigators. Information included the first author name, publication year, enrollment time, study name, location, design and population (i.e. sample size). Differences in data extraction between investigators were resolved by consensus.

Quality assessment of studies

We assessed study quality using checklist provided by the Joanna Briggs Institute [21].

Statistical analysis

Analyses were performed by using random-effects weights. The between-study heterogeneity was assessed by Cochran's *Q* and the I^2 statistic. I^2 values of 25%, 50% and 75% were considered to represent low, moderate and high heterogeneity, respectively [22]. Publication bias was assessed statistically by using Egger's and Begg's tests as well as the funnel plot ($p < 0.05$ was considered indicative of statistically significant publication bias; funnel plot asymmetry also suggests bias in meta-analysis) [23]. Analyses were conducted by STATA 14.0 (StataCorp, College Station, TX, USA).

Results

Of 172 articles identified, seven studies met the inclusion and exclusion criteria (Fig. 1). Because in Iran data on the prevalence or frequency of TB and NTM are from the TB suspected cases and not the general population, in all included studies TB suspected cases were investigated. From 355 patients who were culture positive for NTM, 82 had M. *simiae* pulmonary disease according to the ATS/IDSA diagnostic criteria (Table 1). Pooling all studies, the frequency of *M. simiae* pulmonary disease among patients with NTM was 25.0% (95% confidence interval, 16.8–33.2) (Fig. 2).

Using Cochran's *Q* and the I^2 statistic analysis, heterogeneity was evident ($I^2 = 99$, $p < 0.001$). The Begg's and Egger's tests provided no evidence for publication bias ($p > 0.05$). On visual inspection, the funnel plot did not indicate any publication bias (Fig. 3).

Discussion

This study indicated a relatively high frequency of *M. simiae* pulmonary disease among patients with NTM in Iran. These findings may have important diagnostic and therapeutic implications.

In recent years, clinical isolation of *M. simiae* has been widely reported from different regions of the world such as Europe, the United States and the Middle East [7,30–35]. *M. simiae* was also reported to be the most common NTM

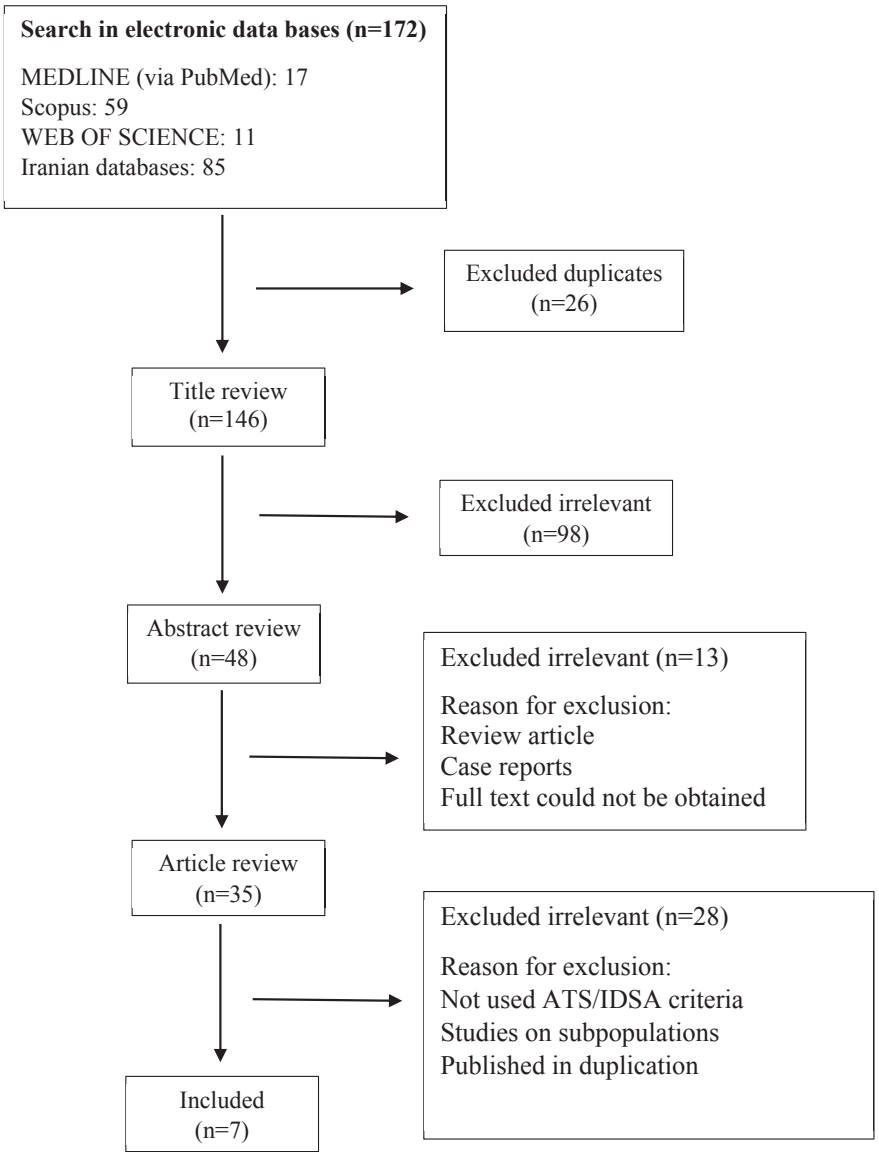

FIG. 1. Flowchart of study selection for inclusion.

species in India (22%), France (15.1%), Oman (14.3%), United States (3.0%) and Saudi Arabia (1.4%) [1,36,37]. Uses of newest laboratory diagnostic methods were assumed to be one of the reasons for increased reports of this organism. Furthermore, increasing the number of patients with underlying diseases such as prior pulmonary TB, silicosis, chronic obstructive pulmonary disease, non–cystic fibrosis bronchiectasis and other comorbidities, such as diabetes mellitus,

TABLE 1. Identified studies reporting frequency of *Mycobacterium simiae* pulmonary disease

Study	Study time	City	No. of suspected TB cases	No. of culture-positive cases	No. of patients with NTM diseases	No. of patients with *M. simiae* pulmonary disease
Tabarsi (2009) [24]	2002–2006	Tehran	NR	NR	12	2
Zaker (2012) [25]	2010–2011	Tehran	2385	270	63	12
Baghaei (2012) [26]	2002–2009	Tehran	NR	NR	120	26
Shafipour (2013) [27]	2010–2011	Gorgan	3336	319	16	6
Hashemi-Shahraki (2013) [6]	2009–2012	Ahvaz	190	117	23	8
Nour-Neamatollahie (2016) [28]	2011–2013	Tehran	10 377	380	59	4
Nasiri (2017) [29]	2014–2016	Tehran	7200	410	62	24

NR, not reported; NTM, nontuberculous mycobacteria; TB, tuberculosis.

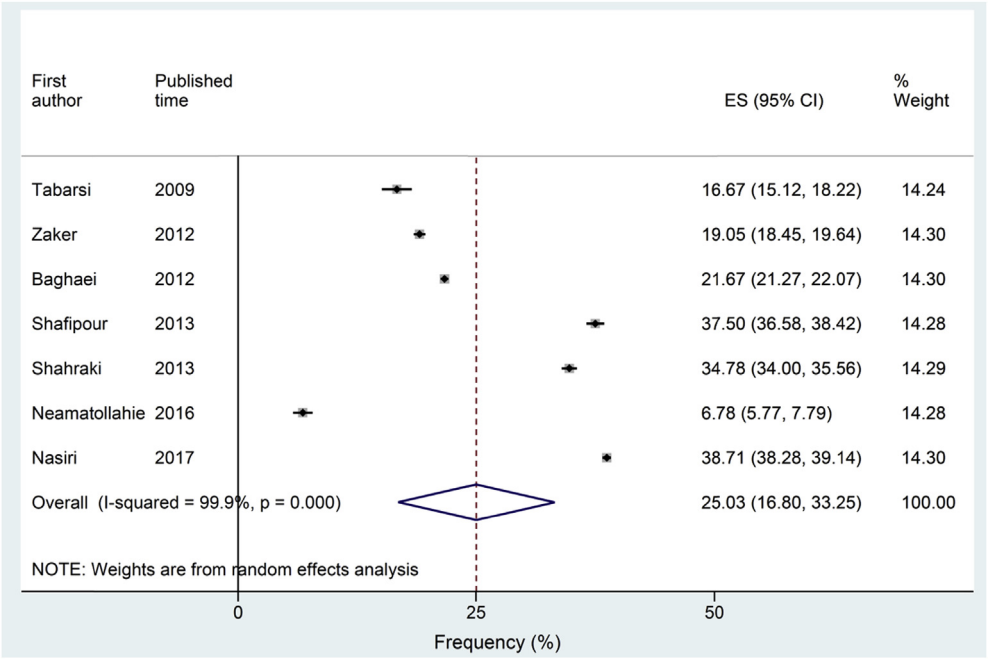

FIG. 2. Forest plots of studies investigating the frequency of *Mycobacterium simiae* pulmonary disease.

cardiovascular diseases and malignancies, could predispose people to *M. simiae* infection [38,39].

M. simiae is endemic to Iran, accounting for more than 30% of all NTM pathogens isolated in the country in 2014–2016 [29]. Previous studies emphasized that preexisting lung disease, particularly TB, is an important risk factor for pulmonary NTM infection [24,39]. In our included studies, *M. simiae* were mostly isolated from patients who had been previously diagnosed as new TB cases or who were infected with multidrug-resistant TB. Treatment of patients with definite *M. simiae* disease is an important challenge because there are no evidence-based treatment regimens [14]. *M. simiae* is poorly susceptible to first-line anti-TB drugs [14]. A treatment regimen containing a macrolide, moxifloxacin and one or two additional drugs based on drug susceptibility testing results may be advisable to treat disease caused by *M. simiae* [14].

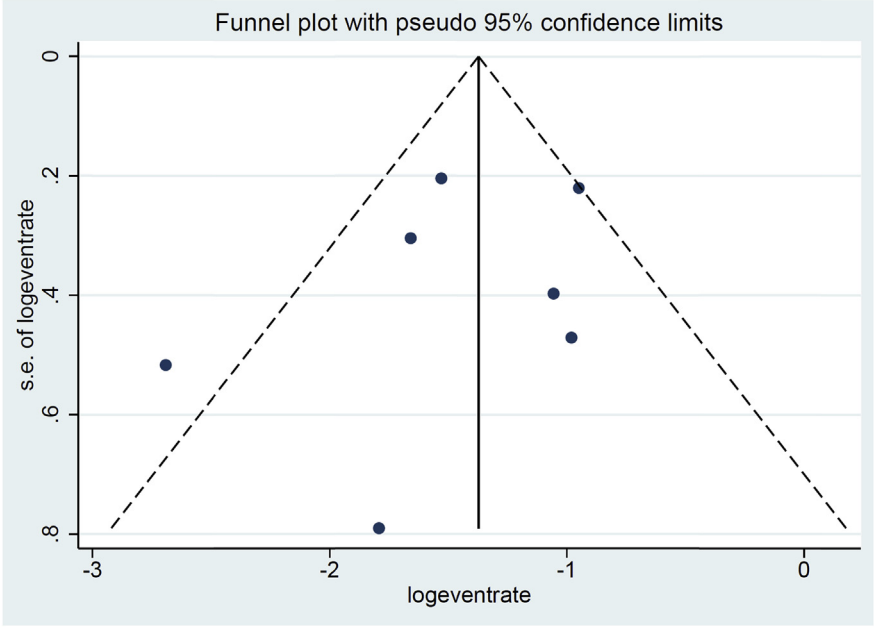

FIG. 3. Funnel plot of studies to investigate publication bias (no evidence for publication bias was observed).

Unfortunately, there is not enough infection-control impact on hospitalized patients for *M. simiae,* and its isolation from respiratory specimens may indicate colonization rather than disease in most cases. According to the reports, *M. simiae* isolates recovered from humans are estimated to be clinically relevant in 9% to 21% of specimens [30]. Therefore, the distinction of *M. simiae* respiratory infection from pulmonary TB has significant practical importance. Furthermore, when the infection is considered to be clinically significant, selection of optimal treatment regimens should be taken into account by physicians.

Strengths and limitations

To our knowledge, this is the first study of status of *M. simiae* pulmonary disease in Iran. Our findings could help the programmatic management of the disease within the context of national TB control programmes. This meta-analysis had also some limitations which should be considered. First, there was a considerable heterogeneity between studies, which should be considered when interpreting results. To explore the heterogeneity of studies, we conducted subgroup and sensitivity analyses. Subgroup analyses found that variables such as number of included patients contributed to the heterogeneity. Second, because the frequency of *M. simiae* pulmonary disease are not yet studied in many regions of Iran, it cannot fully show the frequency of pulmonary *M. simiae* disease in the country.

Conclusions

In Iran, clinical isolates of *M. simiae* are increasingly being recognized as a cause of pulmonary disease; this finding merits further attention by health authorities. Further studies will provide more insights into the understanding of the epidemiology of this infection.

Conflict of interest

None declared.

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