An Update on Prevalence of Non tuberculosis Mycobacteria in Clinical Samples from 2000 – 2022; A Retrospective Systematic Review and Meta - Analysis

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ABSTRACT

BACKGROUND
This study aimed to investigate the prevalence of non - tuberculosis mycobacteria in clinical samples from 2000 - 2022 through systematic review and Meta - analysis.

METHODS
This literature search conducted by reviewing published studies addressing the prevalence of NTMs from clinical samples in Iran according to PRISMA (Preferred Reporting Items for Meta - Analyses and Systematic Reviews) protocol. Search strategy was performed for original articles in Persian and English published between 1th January 2000 - 2022 in databases such as Scopus, PubMed, Web of Science, Google Scholar, and Iranian databases. Analysis was conducted for calculating the prevalence of NTM and its 95 % confidence interval (95 % CI) by Comprehensive Meta - Analysis (CMA).

RESULTS
Our study showed that the combined prevalence of NTMs in positive mycobacterial cultures was 4.5 %(95 % Cl: 3.1 - 6.5). *M. simiae* (35.8 % [95 % CI 16.4 - 44.4]), *M. intracellulare* (19 % [95 % CI 8.7 - 28.3]), and *M. kansasii* (13.4 % [95 % CI 7.3 - 24.3]) were the most common NTM species among SGM, while *M. fortuitum* (24.6 % [95 % CI 12.9 - 46.7]), *M. terrae* (18.5 % [95 % CI 11.5 - 29.2), and *M. gastri* (15.9 % [95 % C I6.0 - 41.2]) were the most prevalent NTM species among Rapidly Growing Mycobacteria (RGM)

CONCLUSION
Regarding the prevalence of NTMs in clinical samples, which some of them such as *M. simiae* could have clinical manifestations similar to tuberculosis. Therefore, the use of molecular methods for the identification of NTM is necessary.

KEYWORDS
Non - tuberculosis mycobacteria, Atypical mycobacterium, Rapid growing mycobacterium

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INTRODUCTION

Non - Tuberculosis Mycobacteria (NTM) are described as mycobacterial pathogens other than Mycobacterium Tuberculosis (MOTT) and Mycobacterium leprae strains. NTMs are a heterogeneous group of bacteria that together cause a fundamental but frequently unvalued global burden of disease.[1,2] NTMs are ubiquitous bacteria with a high prevalence in the environment. There is ample evidence that these microorganisms originate from the environment, of note, for the first time in the 1980's, NTM was identified as a human pathogen.[3,4] Though most NTM are saprophytes but it is reported that one - third of them are related to human diseases.[5] generally, most NTMs are aerobic, immotile bacteria with a firm and dense cell Wall.[6] The thickness of NTM cell wall functions as a natural protective shield against disinfectants and antibiotics.[7] Therefore, NTMs grow in most environments around humans. Since NTMs retrieved from domestic and animal products, and also man - made systems such as medical devices, and drinking water systems, water tanks and shower streams, this may explain the increasing rate of infections mediated by NTMs.[8,9] Infections caused by NTMs are relatively uncommon and often reported in immunocompromised persons.[10]

NTMs have certain features similar to M tuberculosis and may cause diseases like M tuberculosis that make the NTMs difficult to differentiate from tuberculosis.[11] Nevertheless, NTMs usually do not respond to common Tuberculosis (TB) drug regimens, causing misdiagnosis and poor treatment, especially in low - resource settings.[12] Current evidence advice that diseases resulting from NTMs are much more prevalent globally than previously believed, and possibly rising in frequency worldwide.[13]

A report from Canada showed that the incidence of the estimated diseases of non - tuberculosis mycobacteria was 150000 cases per year and also according to USA experts opinion, the NTM prevalence is much higher in some cases than tuberculosis.[14] NTMs were classified by Ernest Runyon based on growth rates, colony morphology, and pigmentation in 1959, accordingly, NTMs categorized into 4 groups, rapid growers (I to III groups), and IV group, which are slow growers (SGM).[15-17]

These organisms cause 4 distinct clinical diseases, including progressive pulmonary disease, superficial lymphadenitis, disseminated diseases, of the skin and soft tissue infections.[18]

The subject of NTM is in particular troubling in developing countries owing to limited published information and unsuitable identification. Meta - analysis studies on the prevalence of non - tuberculosis mycobacteria in Iran have been conducted in previous years.

Given that the last meta - analysis in this field conducted in 2016, and that the topic is of great importance and updating the prevalence of NTMs is necessary, we decided to conduct this study from 2000 - 2022. Therefore, this study aimed to investigate the prevalence of non - tuberculosis mycobacteria in clinical samples during 2000 - 2022.[19]

LITERATURE REVIEW

Literature Search Strategy

This literature search has conducted by reviewing published studies addressing non - tuberculosis mycobacteria prevalence from clinical samples in Iran according to PRISMA (Preferred reporting items for meta - analyses and systematic reviews) protocol. The search strategy was performed for only the original cross sectional studies in Persian and English published between 1th January 2000 to 2022 in international electronic databases such as Scopus, PubMed, Web of Science, Google Scholar, and also Iranian electronic databases including Scientific Information Database. The search process was according to the combination of Medical Subject Headings (Mesh) text words such as " Non - Tuberculosis Mycobacteria ", " NTM ", " MOTT ", " a typical mycobacterium ", " RGM ", " SGM " and " Iran ". As an example among the different databases, the search strategy strings in PubMed is summarized as follows, Non - tuberculosis Mycobacteria or a typical mycobacterium. It is important to note that all searches have performed in Persian databases with Persian equivalent words with the same strategy. As well, the reference section of the original and review studies was reviewed to find further articles for including in present systematic review and Meta - analysis. All of these searches have completed by two researchers individually.

Inclusion and Exclusion Criteria

We included studies that met the following eligible inclusion criteria: (1) original data have addressed, (2) studies presented the prevalence of NTMs, (3) accepted standard methods (e.g. growth in Lowensteine Jensen (LJ) media containing P – Nitro Benzoate (PNB) or Thiophene - Carboxylic Acid Hydrazide (TCH), growth rate, pigment production, growth at 42°C and 44°C, tellurite reduction, arylsulfatase activity, tween hydrolysis, nitrate reduction, catalase, urease and tolerance to the NaCl 5 %), or molecular methods such as PCR - RFLP (PRA hsp 65), sequencing of hsp, PCR and sequencing of 16s rRNA, multiplex allele - specific polymerase chain reaction (MAS - PCR), Line Probe Assay (LPA), PCR and sequencing rpoB gene, sequencing germ gen, multilocus sequence analysis of 16S rRNA, rpoB, and ITS genes were used. Reviews, case reports, and conference abstracts, studies have been described in languages other than English or Persian, studies not performed according to the accepted standard methods. Studies published before 2000 and studies did not address the prevalence of NTMs were excluded.

Quality Assessment

The studies quality has assessed using the criteria specified in Critical Appraisal Skills Programmed checklists.[20] this assessment has based on the answers to ten questions designed for each study. If any query data was available, the answer scored as 'yes'. In case of doubt or lack of appropriate answer, it was categorized, as no or cannot tell. Based on the number of questions answered "Yes" the studies were classified into three categories: strong (8 - 10), medium (6 - 8) and weak (< 6).[21] finally, weak studies did not obtain approval for this study.

Data Extraction

In this review, two researchers extracted the data independently, shared the extracted data, and then included in the data extraction form. They would seek help from another researcher if there were differences in data extraction. Extracted data included first author, study's time, publication time, geographic location, NTM, methods, and Mean age of patients.

Statistical Analysis

Meta - analysis was conducted for calculating the prevalence of NTM and its 95 % confidence interval (95 % CI) by Comprehensive Meta - analysis Random effect models was used and tested with Cochran's Q test, and I_2 to determine the possibility of heterogeneity between studies. As well as Egger weighted regression test was applied to a statistical assessment of publication bias and $p < 0.05$ was considered statistically significant. In addition to this method, funnel plot was also used to evaluate publication bias in the studies.

RESULTS

According to the flow diagram of Figure 1, 1078 articles were recognized through searching databases, then, 452 duplicate articles were excluded, 626 studies were assessed, 201 articles were removed because their title or abstract were not relevant. Then, 425 full texts evaluated, and 399 studies with justified reasons (studies with the lack of sufficient data, missed data, unclear data, defect in reporting data, and non - use of suitable statistical analysis for data analysis, studies with no standard methods, reference standard not met, studies with the lack of outcomes).

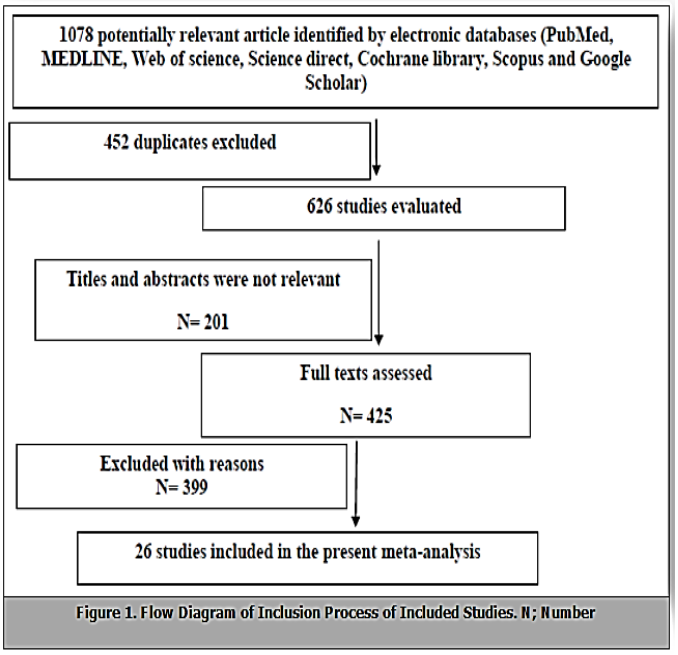

Figure 1. Flow Diagram of Inclusion Process of Included Studies. N; Number

The remaining 26 eligible studies systematically reviewed and analyzed. The characteristics of the included studies summarized in Table 1. The mean age of positive patients for NTMs was between 11 - 80 year. Geographic location included Tehran, Kashan, Khuzestan, Tabriz, Yazd, Golestan, Kermanshah, Mashhad, and Hormozgan (Table 1).

First Author	Study time	Publication	Location	Sample size	NTM n (%)	Methods Used for identification	Mean Age Patient
Derakhshani Nejad	2003 - 11	2014	Tehran	8322	124	Conventional tests, PCR - RFLP	57 ±18.9
Heidari	2007 - 8	2009	Tehran	371	43	Conventional tests, PCR - RFLP	14 - 80
Nasiri	2010 - 12	2014	Tehran	6426	9	Conventional tests, sequencing	Nov - 80
Javid	2007 – 8	2009	Golestan	104	17	Conventional tests, sequencing	14 ≤ 65
Shafipour	2010 - 11	2013	Golestan	336	16	Conventional tests	44 ± 23.3
Moghtaderi	2000 - 10	2011	Tabriz	235	15	Conventional tests	-
Heidar Nejad	2001	2001	Tabriz	165	10	Conventional tests	44.01 ± 18.23
Naserpour, Farivar	2002 – 4	2006	Sistan - Baluchestan	210	59	Conventional tests	20 ≤ 60
Naderi	2003 – 4	2006	Sistan - Baluchestan	150	20	Conventional tests	-
Namaei	2002	2003	R Khorasan	1700	8	Conventional tests	-
Hashemi - Shahraki	2008 - 12	2014	Khuzestan	2313	92	Conventional tests, sequencing	-
Hashemi – Shahraki	2009 - 12	2013	khuzestan	190	23	Conventional tests, sequencing	48.3 - 57.1
Khosravi	2007 - 8	2009	Khuzestan	150	8	Conventional tests,	24 - 36
Yazdi	2009 - 10	2012	Yazd	32	1	Conventional tests	
Zilaee	2012 - 15	2016	Kashan	106	4	PRA hsp 65	-
Nour – Neamatollahie	2011 - 13	2017	Tehran	10,377	59	PCR - RFLP (PRA hsp 65	50.9 ± 7.6
Nasiri	2014 - 16	2018	Tehran	410	56	PCR - RFLP (PRA hsp 65)	50.9 ± 7.6
Nasiri	2016 - 17	2018	Tehran	230	12	hsp 65- PRA, sequencing of 16S rRNA, rpoB, and ITS genes	51.4
Irandoost	2014 - 16	2018	Tehran	6800	64	PRA and sequencing of hsp 65	-
Aghajani	2011 - 19	2019	Tehran	15829	591	hsp 65 - PRA, sequencing of 16S rRNA, rpoB, and ITS genes	50.7 ± 1 8.4
Mortazavi	2015 - 17	2019	Tehran	478	53	Hsp 65 - PRA, sequencing 16S rRNA, rpoB	43.4 ± 15.7
Davari	2013 - 15	2018	Tehran	520	61	Multilocus sequence, analysis of 16S rRNA, 2rpoB, and ITS genes	49.6 ± 16.6
Karami –Zarandi	2017 - 19	2019	Tehran	5061	60	LPA, PCR and sequencing 16s Rrna	58.3 ± 18.3
Khosravi	2016 - 18	2018	Khuzestan, Kermanshah, Hormozgan	55	40	PCR and sequencing rpoB gene, sequencing erm gene	47.4 ± 19.9

Ayoubi	2011 – 18	2021	Tehran	15771	658	(RFLP) - PCR of a hsp65 fragment, Nested - PCR	-
Shafipour	2016 - 18	2021	Gorgan	2994	12	Conventional tests, PCR (16S rRNA gene)	59.9 ± 16.9

Table 1. Characteristics of Included Studies in the Present Review.

All included studies used conventional methods for the detection of mycobacteria. These methods including (e.g. growth in Lowensteine Jensen (LJ) media containing P - Nitrobenzoate (Pnb) or Thiophene - Carboxylic Acid Hydrazide (TCH), growth rate, pigment production, growth at 42 ˚C and 44 ˚C, tellurite reduction, arylsulfatase activity, tween hydrolysis, nitrate reduction, catalase, urease and tolerance to the NaCl 5 %). The majority of NTM were isolated from respiratory and BAL samples.

Overall Effects

Combined prevalence of non - tuberculosis mycobacteria in clinical samples our review showed that the prevalence of NTMs in positive mycobacterial cultures varied from 0.1 - 72.7 % in included studies. As shown in Figure 2 and Table 2, the combined prevalence of NTMs in clinical samples was 4.5 %(95 % CI: 3.1 - 6.5), Q = 1562.7 and Z = 15.2, I_2 = 98.4, and p = 0.00.

Subgroups	**No. studies**	**Heterogeneity test**			**Egger's test**			**Random model**	
		Prevalence (95 % CI)	Z	p	Q	p	I	t	p
Combined NTMs	26	4.5(3.1 - 6.5)	15	0	1563	0	98	1	1
		Slowly Growing Mycobacteria (SGM)							
M. simiae	25	35.8(16.4 - 44.4)	2.5	0	102	0	93	3	0
M. kansasii	22	13.4(7.3 - 24.3)	5.1	0	64	0	88	1	1
M. gordonae	13	6.6(0.6 - 17.5)	3.6	0	32	0	90	1	0
M. intracellulare	13	19 (8.7 - 28.3)	17	0	2.7	0	0	2	0
M. avium complex	12	10.3 (1.6 - 18.1)	15	0	1.7	0	0	1	1
M. szulgai	23	9.1 (3.2 - 28.1)	2.1	0	1.1	0	0	0	0
		Rapid Growing Mycobacteria (RGM)							
M. fortuitum	24	24.6 (12.9 - 46.7)	2.2	0	152	0	94	2	0
M. abscessus	12	10.6 (4.3 - 11.8)	9.1	0	2.1	0	0	1	0
M. chelonae	11	6.8 (3.8 - 11.7)	11	0	2.2	0	12	1	0
M. thermoresistibile	10	2.95 (1.4 - 8.1)	7.2	0	0.8	0	0	0	0
M. terrae	19	18.5 (11.5 - 29.2)	8.1	0	0	0	0	0	0
M. gastri	23	15.9 (6.0 - 41.2)	6.4	0	1.4	0	0	0	0

Table 2. Overall Effects and Combined Prevalence of NTMs.

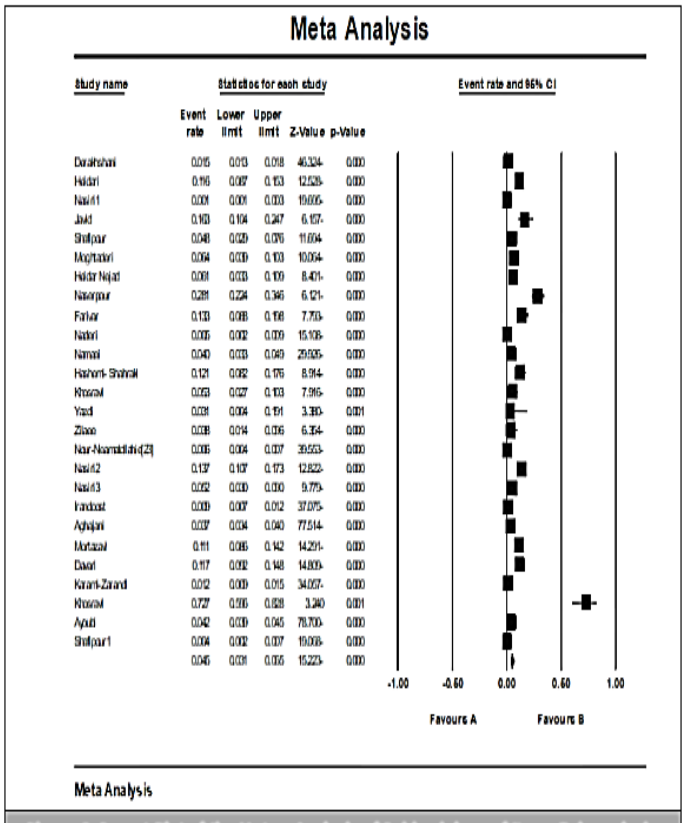

Figure 2. Forest Plot of the Meta - Analysis of Epidemiology of Non - Tuberculosis Mycobacteria in Clinical Samples From Iran

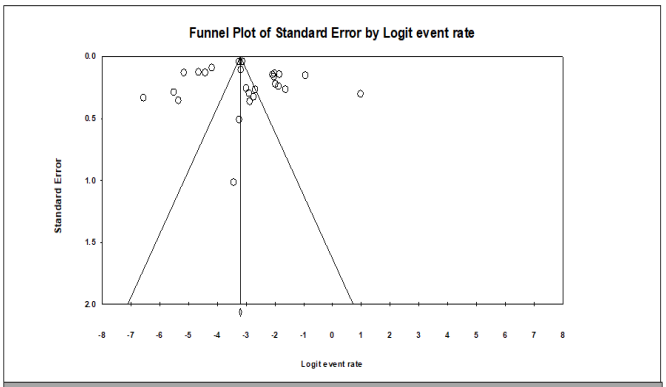

Figure 3. Funnel Plot of the Meta - Analysis of Epidemiology of Non - Tuberculosis Mycobacteria in Clinical Samples from Iran.

Sources of Heterogeneity

A funnel plot is a plot used for effect size against sample size or some other indicator related to precision of the estimate. According to Funnel plot publication bias was visually found amongst included studies (Figure 3), because 95 % of studies didn't lie within the two limit lines (inside funnel). If no bias was observe, it was symmetrical about the correct population effect size and got narrower as the sample size enlarged. Egger's weighted regression test can recognize small - study effects and not tell if publication bias occurs. When we used, similarly, the findings suggesting the presence of bias in the studies (p = 0.6). Therefore, there is a probably publication bias in studies included due to small studies.

Sub Group Analysis For Slow Growing Mycobacteria and Rapid Growing Mycobacteria Species: As reported in Table 2, *M. simiae* (35.8 % [95 % CI 16.4 - 44.4]), *M. intracellulare* (19 % [95 % CI 8.7 - 28.3]), and *M. kansasii* (13.4 % [95 % CI 7.3 - 2 4.3]) were the most common NTM species among SGM, while *M. fortuitum* (24.6 % [95 % CI 12.9 - 46.7]), M. terrae (18.5 % [95 % CI 11.5 - 29.2), and *M. gastri* (15.9 % [95 % CI 6.0 - 41.2]) were the most prevalent NTM species among Rapidly Growing Mycobacteria (RGM).

DISCUSSION

For our knowledge, many studies do not address non - tuberculosis mycobacteria as a public health problem, and physicians and microbiologists do not know much about their infection. Therefore, there is not much data about these microorganisms and their frequency distribution at least in Middle Eastern and third world countries and this has created a particular challenge to infection control Strategies.[22] Our review showed that the prevalence of NTMs in clinical samples varied from 0.1 - 72.7 % in included studies. As mentioned in the results, the majority of NTM were isolated from respiratory and BAL samples. These findings emphasize the importance of identifying NTM from suspected pulmonary TB patients.[23] In line with our findings, a study from Saudi Arabia reported that pulmonary specimens were predominant sputum 52 (54.7 %) and bronchial lavage / wash - 21 (22.1 %).[24] The difference in the prevalence of non - tuberculosis mycobacteria in the studies included in this review is probably due to the molecular techniques used in each study, geographic region, types of clinical specimens, trained TB laboratory personnel, sanitation, and living conditions. We showed that the combined prevalence of NTMs isolated from clinical samples in Iran during 2000 - 2022 was 4.5 %. Because the manifestations of NTM and tuberculosis are similar and all non - tuberculosis mycobacteria are acid - fast and cannot be segregated by phenotypic methods, NTM may be mistaken for tuberculosis, also diseases resulted from NTM, typically does not respond to anti - tuberculosis drugs.[25-28]In addition, in some cases, it found that patients considered having Multi - Drug Resistance (MDR) - TB had NTMs. Of course, studies and reports should be interpreted with caution, because it is frequently challenging to differentiate if the NTMs are a real source of infection or a contaminant in clinical samples.[29-36] Reports from Saudi Arabia reported the same prevalence of NTMs 1.4 %. In agreement with our study, Pokka both from Nigeria reported NTM prevalence of 16.5 %, and 15 %, respectively. Similarly, studies from Canada and the Netherlands reported a higher NTM prevalence of 33 %, and 25 %, respectively. A systematic review and Meta - analysis conducted from Iran showed that the pooled prevalence of NTMs about 10.2 % that is higher than our current study, where the combined prevalence of NTMs was reported 11.2 %.[37-42] This difference in prevalence of NTMs from the identical place (Iran), probably referred to sources of NTMs, because we reported them from clinical samples, but they reported from Suspected TB patients. In recent years, there are increased reports of NTM, the reasons for this are, active searching for NTM,

improvements in culture methods, and most importantly, the use of molecular sensitive techniques. Here, we presented the combined prevalence of 4.5 % in clinical specimens that it agreement with previous study conducted in Iran in 2016. Subgroup analysis in our review showed that the combined prevalence of *M. simiae* (35.8 % [95 % CI 16.4 - 44.4]), M intracellular (19 % [95 % CI 8.7 - 28.3]), and *M. kansasii* (13.4 % [95 % CI 7.3 - 24.3]) were the most common NTM species among SGM, while *M. fortuitum* (24.6 % [95 % CI 12.9 - 46.7]), *M. terrae* (18.5 % [95 % CI 11.5 - 29.2), and *M. gastri* (15.9 % [95 % CI 6.0 - 41.2]) were the most prevalent NTM species among rapidly growing mycobacteria (RGM). RGM species are among the most predominant NTM associated with nosocomial infections.[43-49] As described by previous reports, tap water, dialysis water provided from tap water, drinking water, and shower water, piped water systems in clinical settings such as hospitals are the common sources of NTM nosocomial infections. Another point is that RGMs are somewhat resistant to standard disinfectants such as chlorine, alkaline glutaraldehydes, and antimicrobial agents compared to TB, thus, their eradication is difficult. Therefore, they will make major problems for programs of hospital control strategies. In line with our study, a previous review that has studied the distribution of NTM species from environmental and clinical samples in the Middle East, from NTM isolated from clinical specimens in the Middle East, 58.7 % were SGM and 41.2 % were RGM, also, they reported the similar prevalence of SGM / RGM (56.4 % / 44.6 %) in Iran. Besides, comparable with our findings, they reported M fortuitum (60.1 %) as the most prevalent RGM retrieved from the clinical specimens in Middle East. As well, they reported M fortuitum in 71.9 %, 54.4 %, 46.6 %, and 48.9 % of RGM isolates recovered from Iran, Saudi Arabia, Turkey, and Pakistan, respectively. Other reports from neighboring countries (Saudi Arabia and Kuwait) found M fortuitum as the prevalent isolate, too The proportions of RGM in pulmonary diseases from Iran and other Asian countries are much higher than in other European and American countries for example, studies from Netherlands and the United States, this rate was about 3 % and 5 %, respectively simian was the most predominant SGM from studied NTM isolates in this meta - analysis. This finding is in accordant with previous reviews from Iran. On contrary, in developed countries, avium complex has been described as the most common NTM species.[50-59] It is worth to mention that *M. simiae* is an endemic SGM in Iran. It often is not distinguishable from TB complex due to its similar clinical and radiologic manifestations also with no response to ant - TB drugs. Therefore, it should be strongly sought for simian in cases where anti - TB treatment does not respond.

The main point of this comprehensive review is that missing NTM infection particularly pulmonary diseases lead to unsuitable treatment, imposing health costs on patients and health systems, increasing mortality, and economic consequences. Nevertheless, most of the laboratories do not yet have a diagnosis of non - tuberculosis in their program owing to the lack of appropriate equipment and qualified experts. In most recent studies, improved molecular methods led to more and better diagnosis of NTM. National TB Reference Laboratories necessitate to standardizing existing protocols for the identification of NTM in Middle Eastern countries. Thus, owing to the rising importance of NTM, quick and trustworthy identification is significant as an active management strategy against NTM Infections. The main limitation of the current study is that studies published other English and Persian languages have been missed of our review.[60-66]

CONCLUSION

In summary, our study reported a relatively high combined prevalence of NTMs in clinical samples, which some of them such as *M. simiae* can have clinical and radiologic manifestations similar to TB and because they do not respond to anti - TB drugs, they are considered Multi - Drug Resistance (MDR) - TB. Therefore, standardizing laboratories and the use of molecular methods for the detection of NTM is necessary.

CONFLICTS OF INTEREST

None declared.

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None, we declare that we do not have any competing interests.

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