Mycobacteria

REVIEW

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Antimicrobial susceptibility pattern in non-tuberculous mycobacteria in Iran: a systematic review

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Abstract

Background Non-tuberculous mycobacteria (NTM) are ubiquitous environmental bacteria that can cause a variety of infections in humans, particularly those with underlying lung diseases. These infections are increasing worldwide and their antimicrobial susceptibility has decreased even more than that of tuberculous mycobacteria. Therefore, determining the local antimicrobial susceptibility of NTM can provide appropriate treatment strategies.

Materials and methods This study, conducted based on the PRISMA statement, is a systematic review to assess non-tuberculous mycobacteria (NTM) prevalence and drug susceptibility patterns in Iran between 2012 and 2023. Data was extracted from various databases and screened for eligibility using the Rayyan app.

Results Thirteen studies were included with clinical and environmental samples. Most of the studies were tested for antimicrobial susceptibility based on the CLSI broth dilution method. NTM species varied widely in their susceptibility to common antibiotics. They were generally less susceptible to first-line antituberculosis drugs and meropenem, and predominantly sensitive to amikacin and secondly clarithromycin.

Conclusion Although NTM isolates are widespread in Iran and have increased resistance to common TB drugs, there is no evidence of this in the literature yet. Our systematic review suggests that amikacin is the most effective drug against almost all NTM species common in Iran.

Keywords Drug resistance, Antibiotic susceptibility, Antimicrobial resistance

Introduction

Non-tuberculous mycobacteria (NTM) are a diverse group of bacteria found in the environment and have received attention in recent years due to their increased antimicrobial resistance, even surpassing Mycobacterium tuberculosis. NTM causes pulmonary disease in patients with injured airways (e.g. cystic fibrosis [CF], chronic obstructive pulmonary disease [COPD]), suppressed immune system (e.g. age-related, drug-induced, congenital and acquired immunodeficiency syndromes), and gastroesophageal reflux disease (GERD) [1, 2]. The most important diagnostic challenge is the similarity of the appearance of NTM to M. tuberculosis (causative agent of TB) on a microscopic

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examination of sputum samples from patients with suspected mycobacterial pulmonary disease as a gold standard detection method. This diagnostic challenge is further complicated by the ability of NTM to adapt to and resist treatment with a variety of antibiotics, including those typically effective against tuberculosis [3]. Therefore, knowledge of the drug susceptibility profile of NTM strains is necessary for the appropriate management of NTM-infected patients.

Although several studies have investigated the prevalence and drug susceptibility patterns of NTM in Iran, there is no comprehensive synthesis of the available evidence. A systematic review is needed to obtain an overview of the prevalence and distribution of drug-resistant NTM strains in Iran. Our study builds on previous studies by synthesizing and analyzing all available data on NTM susceptibility patterns in Iran, and it also provides a comprehensive and up-to-date understanding of the current state of drug resistance in NTM strains in this country. The findings of this study will be of interest to clinicians, researchers, and policymakers involved in the diagnosis and management of NTM infections, and will also provide a basis for future research in this field.

Materials and methods

Search strategy

This study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [4].

We conducted a comprehensive literature search using PubMed, Scopus, Web of Science, Scientific Information Database (SID), and Magiran to identify relevant studies on the prevalence and drug susceptibility patterns of NTM in Iran. The search was conducted in November 2022 and updated in July 2023 to include articles published between 2012 and 2023.

Our search strategy included both MeSH terms and free-text keywords related to non-tuberculous mycobacteria, prevalence, drug resistance, antimicrobial susceptibility, and atypical mycobacteria. We also searched the reference lists of included studies and relevant systematic reviews for additional studies that might have been missed. We restricted the search to studies published in English or Persian.

The search strategy was developed in consultation with a research librarian, and we used a combination of subject headings and text words to search for relevant studies. We used the latest version of the Rayyan app [5] for screening the titles and abstracts and for the inclusion and exclusion process.

Study selection

We screened the titles and abstracts of all identified articles to determine their eligibility for inclusion. The full text of potentially eligible articles was then reviewed to determine whether they met the following inclusion criteria: being original research (e.g., no case reports, editorials, or reviews), being conducted in Iran and reported in English or Persian, containing data of the drug susceptibility patterns ± prevalence of NTM species, clearly identifying of sample isolation, detection and identification method, samples being taken from humans or environment, using a single standard drug susceptibility testing method and reporting susceptibility rates based on that method. Otherwise, the studies were excluded. Any discrepancies regarding the inclusion of a study were resolved through discussion and consensus among the review authors.

Data extraction

Two reviewers independently extracted data from the included studies using a standardized data extraction form. The following data were extracted: study design, sample size, patient comorbidities, drug susceptibility testing methods, and antimicrobial susceptibility patterns of NTMs to different drugs.

Limitations

It should be noted that this review is subject to several limitations. Firstly, we only included studies published in English and Persian, which could lead to linguistic biases. Secondly, research is limited to articles published between 2012 and 2023 and we cannot rule out the possibility of relevant studies outside that time frame. Finally, the tool used for quality assessment of included studies (ROBINS-E) is not completely fitting into characteristics of studies included and it is just the most appropriate one (e.g. questions for quality assessment asked in domains 5 and 7 of this tool are not applicable for these studies). Despite these limitations, this review provides valuable information on the prevalence and sensitivity of NTM drugs in Iran, which can inform the development of more effective strategies for preventing and treating NTM infections in this population.

Results

Thirteen articles (11 with only clinical samples, 1 with only environmental samples, and 1 with a mixture of clinical and environmental samples) were included in the systematic review, with sample sizes ranging from 8 to 198 (Fig. 1). Table 1 summarizes the characteristics of the items included in this report. The methods for measuring antimicrobial susceptibility in the 10 studies

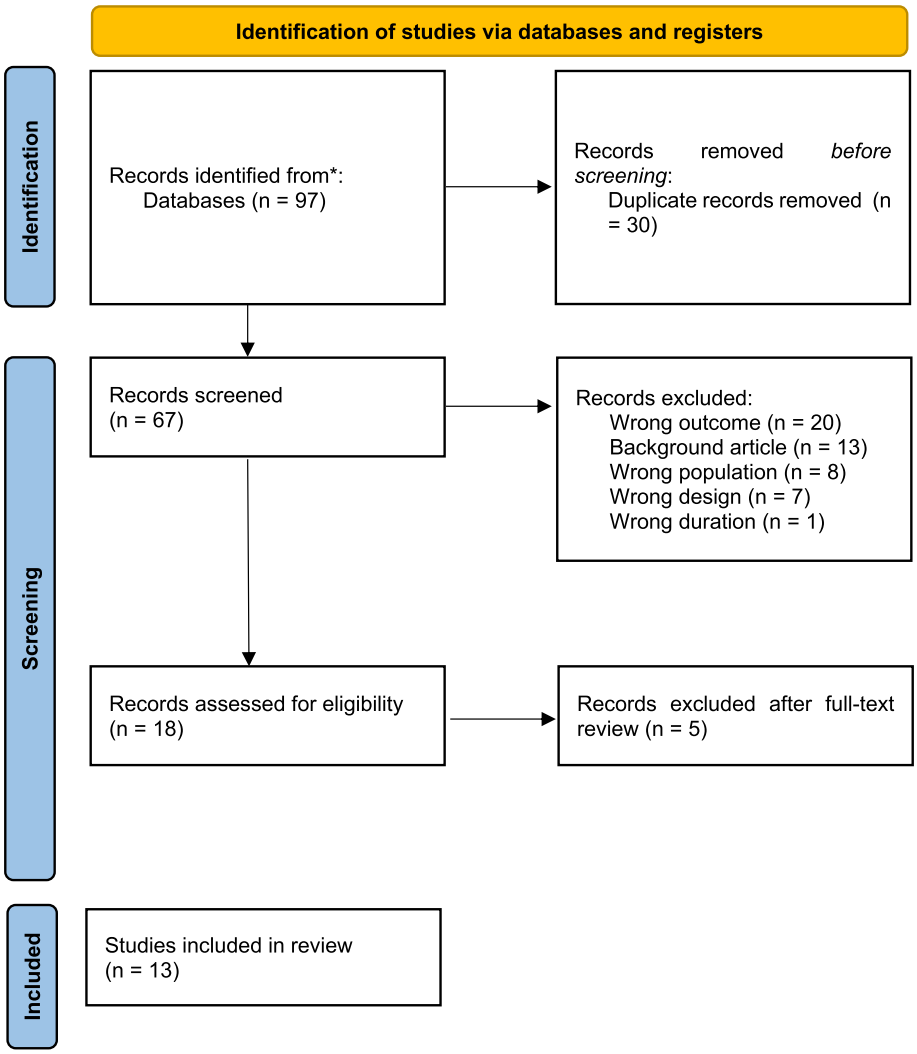

Fig. 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only [4]

were based on Clinical and Laboratory Standards Institute (CLSI) guidelines based on the broth microdilution method which is the recommended method for drug susceptibility testing of Mycobacterium tuberculosis and non-Tuberculous mycobacteria. The REMA (REsazurin Microtiter Assay) plate and E-test methods were each used in one study. The use of antimicrobial susceptibility testing methods other than CLSI in two of the thirteen studies does not impact our reported drug susceptibility results, as each standard institution establishes its own cutoff values for resistance, which were consistently applied in those articles to report resistance rates. Quality assessment done by ROBINS-E tool which was the most appropriate one. Results are produced by ROBVIS tool and depicted in Fig. 2 [6].

Table 2 summarizes an extensive report on the rate of antimicrobial susceptibility of NTM species to different drugs. Sample sources were mainly regional reference laboratories for tuberculosis, patients from major tuberculosis centers, and water sources. *M. avium* showed the lowest susceptibility to first-line anti-TB drugs, and the highest susceptibility to amikacin, ciprofloxacin, and cefoxitin. *M. abcessus* showed the lowest susceptibility to meropenem and trimethoprim-sulfamethoxazole and the highest susceptibility to amikacin. *M. fortuitum* showed the lowest susceptibility to clarithromycin, meropenem, and ciprofloxacin, and the highest susceptibility to trimethoprim-sulfamethoxazole. *M. chelonae* showed the lowest susceptibility to ciprofloxacin, doxycycline, and trimethoprim-sulfamethoxazole, and the highest

Table 1 Characteristics of studies included in the systematic review

Code	First author	Publication	Study period	Sample size	Setting	Province	Sample Origin	DST method
N01 [7]	Moghaddam S	2022	2022	198	Env	Tehran	Teaching hospital waters	CLSI 2011
N02 [8]	Daneshfar S	2022	2019 – 20	50	Cln	Khuzestan, Kermanshah, Tehran, Fars	Pulmonary isolates suspected of NTM from RTB-RLs	CLSI 2011
N03 [9]	Akrami S	2022	2017 – 20	77	Cln	–-	sputum samples of suspected TB patients from RTB-RL	CLSI 2011
N04 [10]	Dezhkhi S	2021	2019 – 20	92	Cln	Tehran	Patients with TB-like symptoms referred to Hospital	PCR
N05 [11]	Hojatpanah N	2019	–-	10	Cln	Mash'had	Patients from RTB-RL	REMA plate
N06 [12]	Feysia S. G	2020	–-	8	Cln	–-	HIV seropositive patients diagnosed with mycobacterial diseases	CLSI
N07 [13]	Karami-Zarandi	2019	2017 – 19	41	Cln	Tehran	Specimen from RTB-RL	CLSI 2011
N08 [14]	Nasiri M. J	2019	2014 – 18	25	Cln	Tehran	Patients with NTM pulmonary diseases referred to RTB-RL	CLSI 2011
N09 [15]	Khosravi A. D	2018	2016 – 18	95	Cln	Khuzestan, Kermanshah, Hormozgan	pulmonary isolates of NTM from major TB centers	CLSI 2011
N10 [16]	Esfahani B. N	2016	–-	41	Cln + Env	Isfahan	Medical university microbial collection and Water samples	CLSI
N11 [17]	Heidarieh P	2015	–-	88	Cln	Golestan, Isfahan, Kermanshah, Khuzestan, Tehran	Patients with suspected TB or NTM-related disease	CLSI 2003
N12 [18]	Saifi M	2013	2010 – 11	32	Cln	Tehran	Patients with suspected TB	–-
N13 [19]	Hashemzadeh M	2023	2019 – 22	50	Cln	Khuzestan, Tehran, Kerman, Isfahan, Fars	Specimen from RTB-RL	CLSI 2011

DST Drug Susceptibility Testing, *Cln* Clinical, *Env* Environmental, *CLSI* Clinical Laboratory Standards Institute, *RTB-RL* regional TB reference laboratory

susceptibility to amikacin. *M. simiae* showed the lowest susceptibility to first-line anti-TB drugs and the highest susceptibility to amikacin. *M. kansasii* showed the lowest susceptibility to isoniazid and the highest susceptibility to amikacin.

Discussion

This systematic review shows low susceptibility rates to first-line antituberculosis drugs and meropenem. Different susceptibility rates to ciprofloxacin and trimethoprim-sulfamethoxazole. High susceptibility rate to amikacin. Therefore, amikacin is the most effective drug in this review.

Mycobacterium Avium Complex (MAC)

Studies included in our systematic review showed a low incidence of MAC in Iran. However, this number of MAC species were susceptible to clarithromycin, amikacin, and moxifloxacin, and resistant to linezolid, rifampin, and isoniazid. This finding is consistent with the study in Hainan, China [20]. A study from eight Japanese hospitals of 154 isolates collected from patients with MAC-induced pulmonary disease from 2013 to 2014 found a low moxifloxacin susceptibility rate, which is also in agreement with our review [21]. All isolates from the largest MAC study included in our systematic review appeared to be resistant to isoniazid, rifampin, and linezolid making them MDR species [9]. A number of 43 MAC specimens in a study in Wenzhou, China showed high susceptibility to clarithromycin and amikacin, whereas low susceptibility to moxifloxacin and linezolid [22]. Similar results were obtained in a study of 98 MAC strains isolated from 2006 to 2016 at a tertiary center in central Germany [23]. Another study of 108 NTM specimens isolated from respiratory sources during two periods (2003–2007 and 2013–2017) in a major

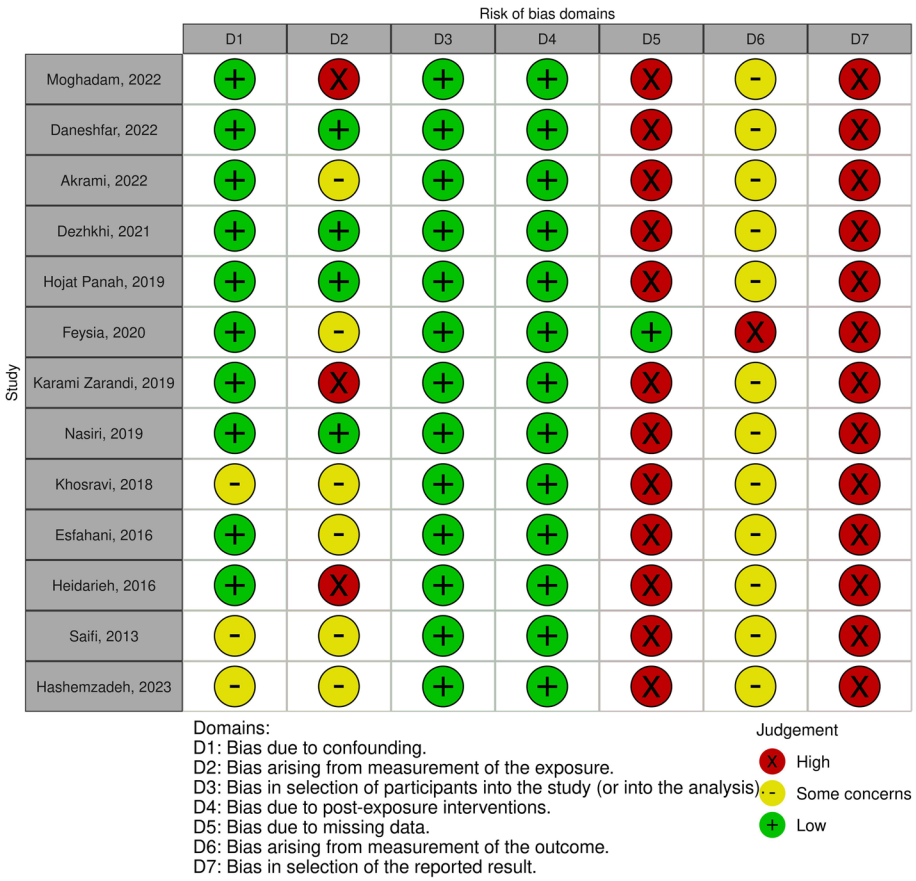

Fig. 2 Quality assessment of included studies based on ROBINS-E checklist visualized by ROBVIS tool [6]

tertiary care center in Lebanon showed high susceptibility to clarithromycin and low susceptibility to moxifloxacin [24]. The results of these studies are consistent with our systematic review, except for the high sensitivity to moxifloxacin in our review. As mentioned above, the low frequency of MAC in Iran leads to the difference between our studies and others.

The two main genetic mutations that make MAC clinically drug-resistant are the 23s rRNA gene for macrolides and the 16s rRNA gene for amikacin [25]. However, this resistance was not related to mutations in *gyrA*, *gyrB*, or *VNTR* genotypes [21]. Additionally, another study also confirmed that these mutations were not attributed to moxifloxacin resistance after assessing 105 MAC or MABC isolates, including 72 moxifloxacin-resistant strains [26].

Non-MAC mycobacteria

RGM

Mycobacterium abscessus complex (MABC) Similar to our study, a study on 373 Non-Tuberculous Mycobacteria in Patients with Suspected Pulmonary Tuberculosis in Hainan Island, China between 2014 and 2021 represented low levels of susceptibility (about 10%) of MABC to ciprofloxacin, imipenem, moxifloxacin, doxycyclin, trimethoprim-sulfamethoxazole, and tobramycin [20]. In our study, MABC showed 70–100% resistance to clarithromycin As shown in a study conducted in Korea, in which 83% of MABC subspecies were resistant to this drug [27]. Another study of 67 MABC strains isolated from patients with skin and soft tissue infections at a tertiary teaching hospital in Taiwan from 2012 to 2016 showed high susceptibility to cefoxitin, amikacin, and clarithromycin (5–30%). Studies included in our systematic review showed high susceptibility to cefoxitin and amikacin (93–97%), but low susceptibility to clarithromycin (0–30%) [28]. A study conducted on 43 MABC isolates from respiratory samples in Shanghai, China from 2014 to 2018 showed high susceptibility to amikacin and cefoxitin and low susceptibility to clarithromycin and doxycycline. This is completely consistent with the results of our review except imipenem which had a high susceptibility rate in the Shanghai study contrary to its low susceptibility rate in our review [29]. Our major included study on MABC shows similar periods and isolated sources to other studies around the world. Therefore, the differences should be

Table 2 Antimicrobial susceptibility pattern of different NTM species to various antibiotics (resistance rates in percent)

Code	Spp	N	AMK	CIP	CLR	LZD	INH	RIF	EMB	IMI	CFN	MXF	DXC	SXT	MER	SMN	TMN	KMN
N06 [12]	MAC	1	-	-	0.0	-	100.0		100.0	100.0	-	-	-	-	-	-	-	-
N07 [13]	MAC	1	0.0	0.0	0.0	100.0	-	-	-	100.0	0.0	-	-	-	-	-	-	-
N03 [9]	MAC	10	0.0	-	10.0	100.0	100.0	100.0	30.0	-	-	10.0	-	-	-	-	-	-
N07 [13]	M. abcessus	3	66.7	100.0	100.0	66.7	-	-	-	100.0	100.0	-	-	-	-	-	-	-
N09 [15]	M. abcessus	7	-	-	100.0	-	-	-	-	-	-	-	-	-	-	-	-	-
N10 [16]	M. abcessus	2	-	75.2	-	-	-	-	-	-	-	-	-	-	-	-	-	-
N11 [17]	M. abcessus	30	6.7	83.3	70.0	40.0	-	-	-	83.3	3.3	86.7	86.7	96.7	96.7	-	70.0	-
N01 [7]	M. fortuitum	12	8.3	50.0	33.3	25.0	-	-	-	50.0	58.4	41.7	83.8	0.0	33.3	-	8.3	-
N06 [12]	M. fortuitum	3	0.0	33.0	-	-	100.0	-	100.0	100.0	-	-	-	-	-	-	-	-
N07 [13]	M. fortuitum	13	7.7	15.4	92.3	61.6	-	-	-	100.0	100.0	-	-	-	-	-	-	-
N09 [15]	M. fortuitum	46	-	-	56.5	-	-	-	-	-	-	-	-	-	-	-	-	-
N10 [16]	M. fortuitum	25	-	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
N11 [17]	M. fortuitum	85	1.2	47.1	14.1	7.1	-	-	-	9.4	9.4	29.4	42.3	0.0	49.4	-	1.2	-
N13 [19]	M. fortuitum	50	-	-	64.0	18.0	-	-	-	-	-	-	-	-	-	-	-	-
N06 [12]	M. chelonae	1	0.0	0.0	-	-	100.0	0.0	100.0	100.0	-	-	-	-	-	-	-	-
N07 [13]	M. chelonae	1	0.0	0.0	100.0	100.0	-	-	-	0.0	100.0	-	-	-	-	-	-	-
N11 [17]	M. chelonae	39	28.2	100.0	33.3	43.6	-	-	-	53.8	30.8	59.0	100.0	100.0	89.7	-	30.8	-
N12 [18]	M. chelonae	3	-	-	-	-	100.0	100.0	0.0	-	-	-	-	-	-	66.7	-	33.3
N01 [7]	M. simiae	18	5.5	11.0	100.0		100.0		100.0	-	-	-	-	100.0		100.0	-	-
N02 [8]	M. simiae	53	0.0	-	15.1	75.5	100.0	100.0	64.2	-	-	34.0	-	-	-	-	-	-
N03 [9]	M. simiae	21	9.5	-	23.8	100.0	100.0	100.0	52.4	-	-	47.6	-	-	-	-	-	-
N04 [10]	M. simiae	92	6.5	8.6	-	-	100.0	100.0	100.0	-	-		-	-	-	-	-	6.5
N05 [11]	M. simiae	10	-	-	0.0	-	-	-	-	-	-	10.0		60.0		0.0	-	-
N06 [12]	M. simiae	1	-	-	-	-	100.0	-	100.0	100.0	-	-	-	-	-	-	-	-
N07 [13]	M. simiae	17	47.1	47.1	58.8	94.1	100.0	94.1	100.0	100.0	100.0	-	-	-	-	-	-	-
N08 [14]	M. simiae	25	100.0	100.0	100.0	-	100.0	100.0	100.0	-	-	-	-	-	-	100.0	-	100.0
N11 [17]	M. simiae	48	14.6	81.3	100.0	89.6	100.0	-	83.3	-	-	-	100.0	100.0		81.3	-	-
N12 [18]	M. simiae	1	-	-	-	-	100.0	0.0	0.0	0.0	-	-	-	-	-	0.0	-	0.0
N01 [7]	M. kansasii	18	-	66.7	0.0	0.0	0.0	-	0.0	-	-	0.0	-	-	-	-	-	-
N03 [9]	M. kansasii	46	0.0	-	17.4	89.1	97.8	43.5	30.4	-	-	13.0	-	-	-	-	-	-
N06 [12]	M. kansasii	2	0.0	-	50.0	-	100.0	-	50.0	100.0	-	-	-	-	-	-	-	-
N07 [13]	M. kansasii	7	42.9	14.3	14.3	42.9	100.0	71.4	85.7	100.0	-	-	-	-	-	-	-	-
N11 [17]	M. kansasii	40	5.0	50.0	0.0	0.0	0.0	-	0.0	-	-	0.0	100.0	7.5		35.0	-	-
N12 [18]	M. kansasii	9	-	-	-	-	100.0	88.9	88.9	-	-	-	-	-	-	100.0	-	88.9
N01 [7]	M. aurum	28	25.2	42.6	39.1	3.6	-	-	-	42.6	57.1	39.1	35.7	7.1	28.6	-	0.0	-
N10 [16]	M. conceptionense	1	-	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
N10 [16]	M. gordonae	10	-	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
N12 [18]	M. gordonae	9	-	-	-	-	88.9	44.4	66.7	-	-	-	-	-	-	88.9	-	77.8
N10 [16]	M. smegmatis	1	-	0.0	-	-	-	-	-	-	-	-	-	-	-	-	-	-
N01 [7]	M. mucogenicum	16	0.0	12.5	6.2	6.2	-	-	-	6.2	6.2	0.0	25.0	0.0	25.0	-	6.2	-
N01 [7]	M. phocaicum	20	5.0	80.0	10.0	10.0	-	-	-	25.0	25.0	5.0	50.0	5.0	20.0	-	50.0	-

Spp. Species, *AMK* Amikacin, *CIP* Ciprofloxacin, *CLR* Clarithromycin, *LZD* Linezolid, *INH* Isoniazid, *RIF* Rifampin, *EMB* Ethambutol, *IMI* Imipenem, *CFN* Cefoxitin, *MXF* Moxifloxacin, *DXC* Doxycyclinm, *SXT* Trimethoprim-Sulfamethoxazole, *MAC* Mycobacterium Avium Complex

due to differences in antibiotic consumption patterns in each society.

Maycobacterium fortuitum In southern and eastern China, a study of 51 M. fortuitum samples isolated from major TB-specialized hospitals from 2012 to 2014 showed high susceptibility to moxifloxacin and amikacin; Intermediate susceptibility to meropenem, cefoxitin, and imipenem; And low susceptibility to linezolid, clarithromycin, and tobramycin. Based on our study, the results are broadly consistent with our systematic review, except for

moderate susceptibility to clarithromycin and linezolid and high susceptibility to tobramycin [30]. Isolates of our included studies had been mostly obtained from TB patients which is similar to the study of China. However, a number of studies on *M. fortuitum* included in our review had been isolated from water sources. The implementation period of major studies was 2010–2014 and 2019–2022. This may be the reason for the difference in resistivity.

IGM

M. simiae In our review, *M. simiae* demonstrated high susceptibility to amikacin, intermediate susceptibility to clarithromycin and moxifloxacin, and low susceptibility to linezolid, imipenem, first-line anti-TB drugs, streptomycin, kanamycin, trimethoprim-sulfamethoxazole, and doxycycline. In a study of 108 NTM specimens isolated from respiratory sources during two periods (2003–2007 and 2013–2017) in a major tertiary care center in Lebanon, *M. simiae* showed low susceptibility to rifampin, ethambutol, ciprofloxacin, rifabutin, linezolid, moxifloxacin, and cotrimoxazole, and high susceptibility to amikacin and clarithromycin [24]. Another study on 103 *M. simiae* isolates from respiratory sources at a tertiary care center in Lebanon between 2004 and 2016 showed high susceptibility to clarithromycin and amikacin and low susceptibility to trimethoprim-sulfamethoxazole and moxifloxacin [31]. The results are similar to those of our review, except for the median susceptibility rate for clarithromycin in our systematic review. Differences in treatment regimens may explain the moderate susceptibility to clarithromycin in our review, in contrast to the low susceptibility in Lebanon, as the differences between isolates were negligible. Furthermore, these different susceptibility rates may be due to water contamination by this microorganism [15, 32, 33]. The main mutated genes that strongly influence the reduction of antimicrobial susceptibility in *M. simiae* are the *rrl* gene (clarithromycin resistance) and *gyrA* and *gyrB* (moxifloxacin resistance) [8, 9].

SGM

Mycobacterium kansasii Multidrug therapy for *M. kansasii* consists of rifampin, isoniazid, and ethambutol. Although the susceptibility of *M. kansasii* to these drugs was expected to be higher, studies included in our systematic review reported low to moderate susceptibility rates to these drugs; with the highest rate for isoniazid. Thus, second-line drugs such as amikacin, ciprofloxacin, linezolid, moxifloxacin, doxycyxline, and trimethoprim-sulfamethoxazole can be tested [34]. We noted some contradictory results. For instance, the resistance rate of *M. kansasii* to isoniazid was highest in studies N03, N06, and N07, whereas studies N01 and N11 showed no resistance to this drug. A study of 85 samples of *M. kansasii* isolated in Poland between 2000 and 2015 showed high susceptibility rates to amikacin, rifampin, trimethoprim-sulfamethoxazole, and moxifloxacin; This is similar to the results of our systematic review. In this study, susceptibility to ethambutol, ciprofloxacin, and clarithromycin was low. However, our study showed that the sensitivity to these drugs was moderate to high. [35]. Another study of 69 *M. kansasii* isolates in Brazil showed high susceptibility to clarithromycin, moxifloxacin, and amikacin, and low susceptibility to ciprofloxacin and ethambutol. This is consistent with the results of our review. The only difference was a high sensitivity rate for trimethoprim-sulfamethoxazole in the systematic review, which was low in the Brazilian study [36]. In China, a study of 60 *M. kansasii* isolates showed low susceptibility to ciprofloxacin and ethambutol, which is inconsistent with our study. However, the high susceptibility rates to amikacin, rifampin, and moxifloxacin are similar to the results of our systematic review [37]. The difference may be due to the fact that a significant number of isolates from our included studies belong to study N01, which had been performed on water isolates. Another reason could be various frequency and treatment regimens in different geographical areas. The main mutated genes that strongly influence the reduction of antimicrobial susceptibility in *M. simiae* are the *rrl* gene (clarithromycin resistance), *rpoB* (rifampin resistance), *gyrA*, and *gyrB* (moxifloxacin resistance) [9].

Conclusion

Our systematic review suggests that amikacin is the most effective drug against almost all NTM species common in Iran. Despite being a major concern, the reduced susceptibility rate to first-line anti-TB drugs in NTM species may be a clue in the clinical field to suspect NTM in patients with the diagnosis of TB when the patients are unresponsive to anti-TB treatment. The low susceptibility rates to carbapenems are a concern since they are used in cases of multi-drug resistant (MDR) and extensively drug-resistant (XDR) TB. The emergence of resistance to trimethoprim-sulfamethoxazole is a warning that we should reduce the frequency of using broad-spectrum antibiotics to treat NTM. The results of our systematic review were negatively affected by limited access to antibiotic susceptibility data (especially for MAC), particularly on the low susceptibility drugs' side. Therefore, it may be more refined in the future as more data on sensitivity becomes available.

Acknowledgements

The authors would like to thank the Clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their help and support in conducting this study.

Authors' contributions

Data curation, Ibrahim Bahrami Mianrood and Shahrzad Shahrokhi; methodology, Ilad Alavi Darazam; validation, Ilad Alavi Darazam; investigation, Ibrahim Bahrami Mianrood and Shahrzad Shahrokhi; data curation, Ibrahim Bahrami Mianrood and Shahrzad Shahrokhi; writing—original draft preparation, Ibrahim Bahrami Mianrood and Shahrzad Shahrokhi; writing—review and

editing, Farid Javandoust Gharabagh and Lida Lotfollahi; supervision, Ilad Alavi Darazam; All authors have read and agreed to the published version of the manuscript.

Funding
Not applicabale.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 12 June 2024 Accepted: 14 November 2024
Published online: 15 April 2025

References

1. Falkinham J. Ecology of Nontuberculous Mycobacteria—Where Do Human Infections Come from? Semin Respir Crit Care Med. 2013;34(01):095–102.
2. Lipman M, Kunst H, Loebinger MR, Milburn HJ, King M. Non tuberculous mycobacteria pulmonary disease: patients and clinicians working together to improve the evidence base for care. Int J Infect Dis. 2021;113(Suppl 1):S73-7.
3. Raju RM, Raju SM, Zhao Y, Rubin EJ. Leveraging Advances in Tuberculosis Diagnosis and Treatment to Address Nontuberculous Mycobacterial Disease. Emerg Infect Dis. 2016;22(3):365–9.
4. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, PRISMA, et al. explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2020;2021:372.
5. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
6. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2020;n/a(n/a). Available from: https://doi.org/10.1002/jrsm.1411. [cited 2020 May 21].
7. Moghaddam S, Nojoomi F, Dabbagh Moghaddam A, Mohammadimehr M, Sakhaee F, Masoumi M, et al. Isolation of nontuberculous mycobacteria species from different water sources: a study of six hospitals in Tehran. Iran BMC Microbiol. 2022;22(1):261.
8. Daneshfar S, Khosravi AD, Hashemzadeh M. Drug susceptibility profiling and genetic determinants of drug resistance in Mycobacterium simiae isolates obtained from regional tuberculosis reference laboratories of Iran. Dholakia YN, editor. PLoS ONE. 2022;17(8):e0267320.
9. Akrami S, Dokht khosravi A, Hashemzadeh M. Drug resistance profiles and related gene mutations in slow-growing non-tuberculous mycobacteria isolated in regional tuberculosis reference laboratories of Iran: a three year cross-sectional study. Pathog Glob Health. 2022. p. 1–11.
10. Dezhkhi H, Farnia P, Haddadi A, Farnia P, Velayati AA. Characterization of Clinical Isolates of Mycobacterium simiae Using Drug Susceptibility Tests and Molecular Analyses. Curr Microbiol. 2021;78(6):2324–31.
11. Hojatpanah N, Askarizadeh F, Jamehdar SA, Ghazvini K. Evaluation Drug Susceptibility of Clinical Isolates of Mycobacterium Simiea Using REMA Plate Method in Mashhad. J North Khorasan Univ Med Sci. 2021;13(3):51–6.
12. Feysia SG, Hasan-Nejad M, Amini S, Hamzelou G, Kazemian H, Kardan-Yamchi J, et al. Incidence, Clinical Manifestation, Treatment Outcome, and Drug Susceptibility Pattern of Nontuberculous Mycobacteria in HIV Patients in Tehran, Iran. Ethiop J Health Sci. 2020;30(1). Available from: https://www.ajol.info/index.php/ejhs/article/view/195771. [cited 2023 Jan 11].
13. Karami-Zarandi M, Bahador A, Gizaw Feysia S, Kardan-Yamchi J, Hasan-Nejad M, Mosavari N, et al. Identification of Non-Tuberculosis Mycobacteria by Line Probe Assay and Determination of Drug Resistance Patterns of Isolates in Iranian Patients. Arch Razi Inst. 2019;74(4):375–84.
14. Nasiri MJ, Amini S, Nikpor Z, Arefzadeh S, Mosavi M, Dabiri H, et al. Emergence of multidrug-resistant *Mycobacterium simiae* : An in vitro study from a regional tuberculosis reference laboratory in Iran [Internet]. Microbiology; 2019. Available from: https://doi.org/10.1101/549428. [cited 2023 Jan 11].
15. Khosravi AD, Mirsaeidi M, Farahani A, Tabandeh MR, Mohajeri P, Shoja S, et al. Prevalence of nontuberculous mycobacteria and high efficacy of D-cycloserine and its synergistic effect with clarithromycin against Mycobacterium fortuitum and Mycobacterium abscessus. IDR. 2018;11:2521–32.
16. Nasr Esfahani B, Zarkesh Esfahani FS, Bahador N, Moghim S, Radaei T, Rezaei Yazdi H, et al. Analysis of DNA gyrA Gene Mutation in Clinical and Environmental Ciprofloxacin-Resistant Isolates of Non-Tuberculous Mycobacteria Using Molecular Methods. Jundishapur J Microbiol. 2016;9(3). Available from: https://brief.land/jjm/articles/56622.html. [cited 2023 Jan 11].
17. Heidarieh P, Mirsaeidi M, Hashemzadeh M, Feizabadi MM, Bostanabad SZ, Nobar MG, et al. In Vitro Antimicrobial Susceptibility of Nontuberculous Mycobacteria in Iran. Microb Drug Resist. 2016;22(2):172–8.
18. Saifi M, Jabbarzadeh E, Bahrmand AR, Karimi A, Pourazar S, Fateh A, et al. HSP65-PRA identification of non-tuberculosis mycobacteria from 4892 samples suspicious for mycobacterial infections. Clin Microbiol Infect. 2013;19(8):723–8.
19. Hashemzadeh M, Zadegan Dezfuli AA, Khosravi AD, Ahmad Khosravi N, Hashemi SA. Frequency of mutations in erm(39) related to clarithromycin resistance and in rrl related to linezolid resistance in clinical isolates of Mycobacterium fortuitum in Iran. AMicr. 2023;70(2):167–76.
20. Wang J, Chen Z, Xu Y, Qiu W, Chen S, Pei H, et al. Screening and Drug Resistance Analysis of Non-Tuberculous Mycobacteria in Patients with Suspected Pulmonary Tuberculosis on the Hainan Island. China IDR. 2023;16:463–76.
21. Yamaba Y, Ito Y, Suzuki K, Kikuchi T, Ogawa K, Fujiuchi S, et al. Moxifloxacin resistance and genotyping of Mycobacterium avium and Mycobacterium intracellulare isolates in Japan. J Infect Chemother. 2019;25(12):995–1000.
22. He G, Wu L, Zheng Q, Jiang X. Antimicrobial susceptibility and minimum inhibitory concentration distribution of common clinically relevant non-tuberculous mycobacterial isolates from the respiratory tract. Ann Med. 2022;54(1):2500–10.
23. Wetzstein N, Kohl TA, Andres S, Schultze TG, Geil A, Kim E, et al. Comparative analysis of phenotypic and genotypic antibiotic susceptibility patterns in Mycobacterium avium complex. Int J Infect Dis. 2020;93:320–8.
24. Araj GF, Baba OZ, Itani LY, Avedissian AZ, Sobh GM. Non-tuberculous mycobacteria profiles and their anti-mycobacterial resistance at a major medical center in Lebanon. J Infect Dev Ctries. 2019;13(7):612–8.
25. Griffith DE. Treatment of Mycobacterium avium Complex (MAC). Semin Respir Crit Care Med. 2018;39(3):351–61.
26. Kim SY, Jhun BW, Moon SM, Shin SH, Jeon K, Kwon OJ, et al. Mutations in gyrA and gyrB in Moxifloxacin-Resistant Mycobacterium avium Complex and Mycobacterium abscessus Complex Clinical Isolates. Antimicrob Agents Chemother. 2018;62(9):e00527-e618.
27. Lee SH, Yoo HK, Kim SH, Koh WJ, Kim CK, Park YK, et al. The Drug Resistance Profile of *Mycobacterium abscessus* Group Strains from Korea. Ann Lab Med. 2014;34(1):31–7.
28. Lee MC, Sun PL, Wu TL, Wang LH, Yang CH, Chung WH, et al. Antimicrobial resistance in Mycobacterium abscessus complex isolated from patients with skin and soft tissue infections at a tertiary teaching hospital in Taiwan. J Antimicrob Chemother. 2017;72(10):2782–6.
29. Guo Q, Wei J, Zou W, Li Q, Qian X, Zhu Z. Antimicrobial susceptibility profiles of Mycobacterium abscessus complex isolates from respiratory specimens in Shanghai. China Journal of Global Antimicrobial Resistance. 2021;25:72–6.
30. Zheng HW, Yu PA, He GX, Song YY, Zhao YL. Antimicrobial Susceptibility Testing and Molecular Characterization of *Mycobacterium fortuitum* Isolates in China. Biomed Environ Sci. 2017;30:376.

31. Hamieh A, Tayyar R, Tabaja H, Zein S EL, Bou Khalil P, Kara N, et al. Emergence of Mycobacterium simiae: A retrospective study from a tertiary care center in Lebanon. Santin M, editor. PLoS ONE. 2018;13(4):e0195390.
32. Nasiri MJ, Amini S, Nikpor Z, Arefzadeh S, Mousavi SMJ, Goudarzi H. Drug Susceptibility Testing of Mycobacterium Simiae: An Emerging Pathogen in Iran. Infect Disord Drug Targets. 2021;21(4):619–22.
33. Azadi D, Shojaei H, Pourchangiz M, Dibaj R, Davarpanah M, Naser AD. Species diversity and molecular characterization of nontuberculous mycobacteria in hospital water system of a developing country. Iran Microb Pathog. 2016;100:62–9.
34. Brown-Elliott BA, Woods GL. Antimycobacterial Susceptibility Testing of Nontuberculous Mycobacteria. J Clin Microbiol. 2019;57(10):e00834-e919.
35. Bakuła Z, Modrzejewska M, Pennings L, Proboszcz M, Safianowska A, Bielecki J, et al. Drug Susceptibility Profiling and Genetic Determinants of Drug Resistance in Mycobacterium kansasii. Antimicrob Agents Chemother. 2018;62(4):e01788-e1817.
36. de Carvalho LD, de Queiroz Mello FC, Redner P, Campos CED, de Souza Caldas PC, da Silva Lourenço MC, et al. Drug susceptibility profile of Mycobacterium kansasii clinical isolates from Brazil. J Glob Antimicrob Resist. 2019;19:228–30.
37. Guo Y, Cao Y, Liu H, Yang J, Wang W, Wang B, et al. Clinical and Microbiological Characteristics of Mycobacterium kansasii Pulmonary Infections in China. Lamichhane G, editor. Microbiol Spectr. 2022;10(1):e01475-21.

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