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**Review Article**

# Trends in the Antibiotic Resistance of Non-Tuberculous Mycobacteria in Iran: A Systematic Review and Meta-Analysis

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**Abstract**

**Background:** Non-tuberculous mycobacteria (NTM) infections have been continuously increasing as major concerns of public health in Iran. Because innate resistance of NTM species, the treatment of these infections is difficult task, but until now resistance pattern of NTM and suitable regimens are not determined.

**Methods:** We systematically searched the relevant studies in PubMed, Scopus, and Embase (Until Dec 2022). All statistical analyses were carried out using the statistical package R.

**Results:** Eleven studies included in the analysis were performed in 6 provinces and investigated 1223 NTM clinical species. The majority of the studies originated in Tehran. Among the first-line anti-TB drugs, almost all NTM species were highly resistant to first-line anti-TB drugs. No significant difference in the isoniazid resistance rate was found in the slow or rapid-growing species and Runyon's classification of NTM isolates. A decreased in the prevalence of ciprofloxacin, clarithromycin, and moxifloxacin resistance were showed in during 2013-2022 years.

**Conclusion:** Most investigated antibiotics have a minor effect on NTM species and a steady increase of resistance has been seen in last few years then, need more-effective alternative regimens is clear.

**Keywords:** Non-tuberculous mycobacteria (NTM); Antibiotic; Resistance; Systematic review; Meta-analysis

## Introduction

Non-tuberculous mycobacteria (NTM) infections have been continuously increasing as major concerns of public health in various parts of worldwide, especially in developing countries (1, 2). In other hand, the potentially opportunistic/pathogenic NTM are emerging nowadays

which result in pulmonary and non-pulmonary infections like; nosocomial infections, hypersensitivity, pneumonitis, asthma, gang ionic infection, and infection of skin/soft tissue in human specially in patients with impaired immunity as a result of malignancies, organ transplantation, and HIV infection, those with chronic pulmonary diseases, and the elderly (1-3). Moreover, they can cause tuberculosis-like infections, therefore, correct identification of these
*Mycobacteria* and also drug susceptibly testing is necessary to avoid faulty treatment. However, in compared with tuberculosis, the data on NTM infections remains inadequate. Infectious Diseases Society of America (IDSA) recommended that treatment regimens vary according to the NTM species/subspecies, extent of disease, drug susceptibility results, and underlying comorbidities species (4). Unlike tuberculosis, distribution and scattering resistance pattern of NTM are not necessitated to be stated to public health authorities in Iran, and so, accurate emergence and epidemiological data is limited (5).
Thus, we performed a metadata analysis of antimicrobial resistance on NTM species in Iran could help to formulate NTM species eradication strategies in Iran.

## Methods

### *Guidelines*

This review was reported accordant with the Preferred Reporting Items for Systematic Reviews and Meta Analyses guidelines (PRISMA).

### *Data Sources and Search strategy*

Three bibliographic databases, including international databases (MEDLINE [PubMed], Scopus, Embase) for relevant articles were searched (Dec 2022) by using the following keywords: ("non-tuberculosis" OR "non-tuberculous mycobacterium" OR "non-tuberculosis mycobacterial" OR "NTM" OR "mycobacteria other than tuberculosis" OR "MOTT" "atypical mycobacterium") AND ("drug resistance" OR "drug susceptibility") AND ("Iran") in the Title/Abstract/Keywords fields. No limitation was used while searching databases. The search was restricted to all cross-sectional studies that have been published in English and present the prevalence resistance of NTM isolates in Iran. The records found through database searching were merged and the duplicates were removed using EndNote X7 (Thomson Reuters, New York, NY, USA). The reviewers screened all titles and abstracts independently and excluded duplicates, irrelevant data, then they independently assessed the remaining articles for inclusion.

### *Inclusion and Exclusion criteria*

The following items were abstracted from each included study: first author, study dates, publication year, provinces, patient characteristics (age, gender), sample source, identification methods, numbers of NTM isolates, NTM species, slow or rapid-growing of NTM isolates, Runyon's classification of NTM isolates, methods of drug sensitivity testing (DST), and number of NTM resistant isolates. The exclusion criteria were as follows: 1) studies that contained duplicate data or were overlapping articles; 2) animal research, reviews, meta-analysis and/or systematic review, and conference abstracts; 3); no clear methods of isolation/identification and DST and 4) resistance rates were not presented or clearly reported.

### *Data Abstraction*

One of the team researchers randomly evaluated the search results and confirmed that no relevant study had been ignored. All these steps were done by the three authors and any disagreements about article selection were resolved through discussion, and a fourth author acted as arbiter. Three reviewers screened all titles and abstracts separately and excluded irrelevant or duplicate articles first. Three reviewers then separately evaluated the remaining articles for inclusion. Discrepancies were resolved by discussion.

### *Quality Assessment*

The quality of the included studies was assessed using an adapted version of the tool proposed by

the Newcastle-Ottawa assessment scale adapted for cross-sectional studies. A score ranging from 0 to 7 points was attributed to each study (≥ 6 points: high quality, ≤ 5 points: low quality).

### Study outcomes

The main outcome of interest was the weighted pooled resistance rates (WPR) of NTM isolates in Iran. A subgroup analysis was performed by publication date (2013-2018, and 2019-2022), slow or rapid-growing of NTM isolates, and Runyon's classification of NTM isolates.

### Statistical analysis

Iranian cross-sectional studies presenting raw data on antibiotic susceptibility in NTM isolates were included in the meta-analysis using the meta-prop (6) command in R statistical software all prevalence statistics by species, publication year, slow or rapid-growing of NTM isolates, and Runyon's classification of NTM isolates. All statistical interpretations were reported on a 95% confidence interval (CI) basis. All statistical analyses were carried out using the statistical package R 3.6.0 (R Foundation for Statistical Computing: Vienna, Austria) (7).

### Publication bias

Publication bias was analysed using Egger's linear regression test.

### Ethical approval

The study protocol was approved by the Health Research Ethics Committee of the Ilam university of medical sciences (reference no. IR.MEDILAM.REC.1400.183).

## Results

### Systematic literature search

Overall, 230 records were identified in the initial search. From these, 190 articles were excluded after an initial screening of the title and abstract due to their irrelevance and duplication. The full texts of the remaining 40 articles were reviewed (Fig. 1). From the 40 articles, 29 were excluded for the following reasons: animal research, reviews, meta-analysis and/or systematic review, conference abstracts, no clear methods of isolation/identification/DST and resistance rates were not presented or clearly reported. Finally, 11 cross-sectional studies (8-18) were included in this meta-analysis. The studies included in this meta-analysis evaluated antibiotic resistance to imipenem, amikacin, clarithromycin, doxycycline, azithromycin, ciprofloxacin, linezolid, meropenem, moxifloxacin, trimethoprim/sulfamethoxazole (TMP-SMZ), isoniazid, rifampin, cefoxitin, kanamycin, ethambutol, streptomycin, and ethionamide (Supplementary File- Not published- Readers may contact the corresponding author I if needed).

### Characteristics of included studies

Eleven studies included in the analysis were performed in 6 provinces and investigated 1223 NTM clinical species [*M. simiae* (n:474), *M. abscessus* (n:186), *M. fortuitum* (n:166), *M. kansasi* (n:155), *M. intracellular* (n:90), *M. chelonae* (n:56), *M. avium* (n:24), *M. gordonae* (n:14), *M. chimaera* (n:10), *M. thermoresistibile* (n:6), *M. elephantis* (n:5), *M. genavense* (n:5), *M. parascrofulaceum* (n:5), *M. farcinogenes* (n:3), *M. marinum* (n:3), *M. porcinum* (n:3), *M. scrofulaceum* (n:3), *M. terrae* (n:3), *M. gastri* (n:2), *M. parafortuitum* (n:2), *M. peregrinum* (n:2), *M. flavescens* (n:1), *M. fragae* (n:1), *M. lentiflavium* (n:1), *M. montefiorense* (n:1), *M. trivale* (n:1), and *M. virginiense* (n:1).] using a total of 17 different drugs. The majority of the studies originated in Tehran. MIC-based methods were the most common DST method, followed by a proportional method. All 11 studies had a cross-sectional design. While NTM species are mostly resistant to first-line anti-TB drugs, they are generally included in NTM DST.

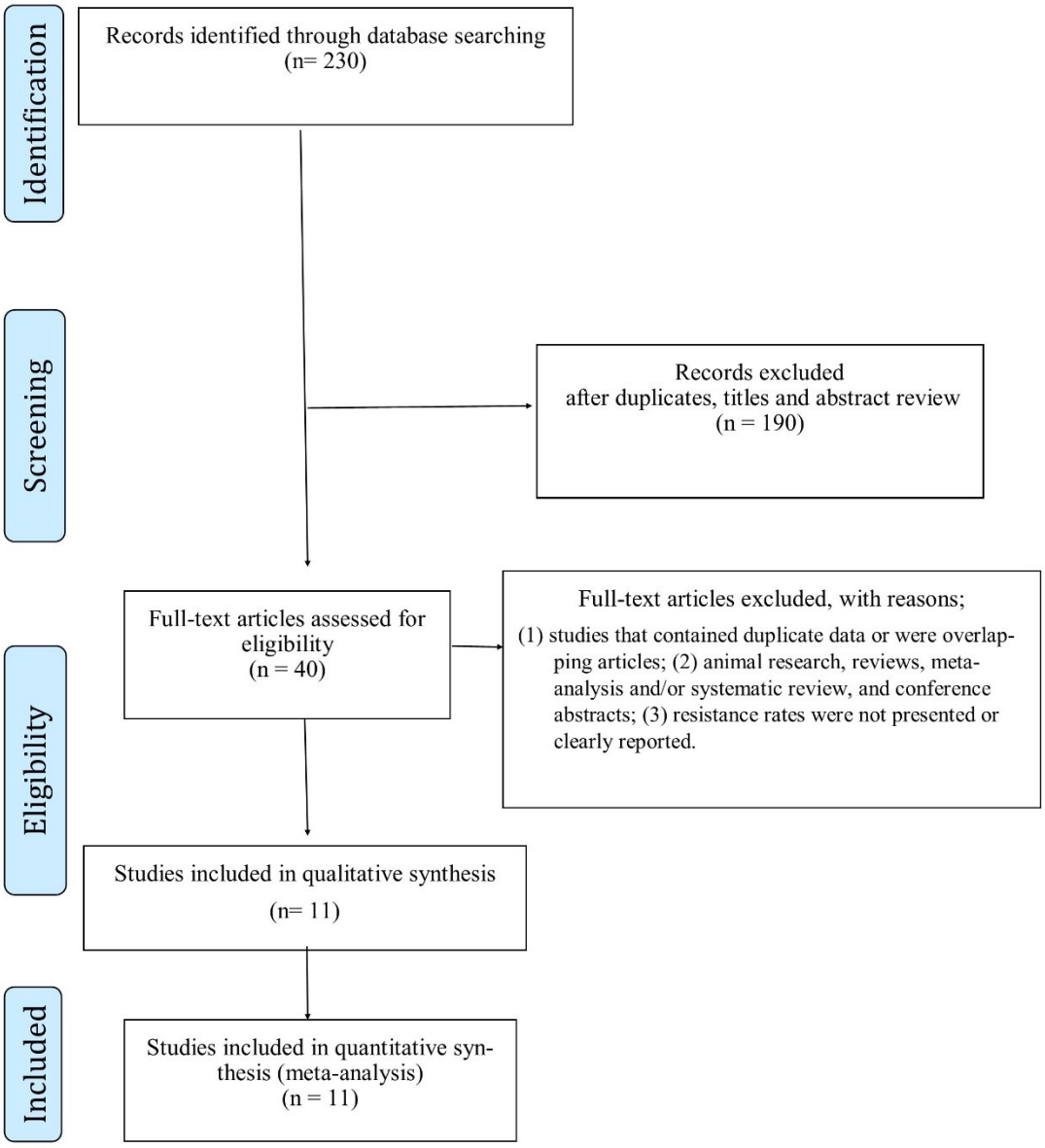


**Fig. 1:** The PRISMA flowchart of included studies

### *Meta-analysis results*

The WPR rates for each antibiotic are shown in Fig. 2 and Table 1. The pooled prevalence (2013-2022) of resistance to individual antibiotics are shown in Fig. 3. An analysis of antibiotic resistance rates among the slow or rapid growing of NTM displayed that there were too few antibiotics to which the slow or rapid growing of NTM isolates showed a high sensitivity rate (Table 2). Data on the resistance of each antibiotic and the subgroup analyses by species, publication year, slow or rapid-growing, and Runyon's classification of NTM isolates are shown in the Supplementary File, Fig. 2, Fig. 3, Tables 1 and 2.

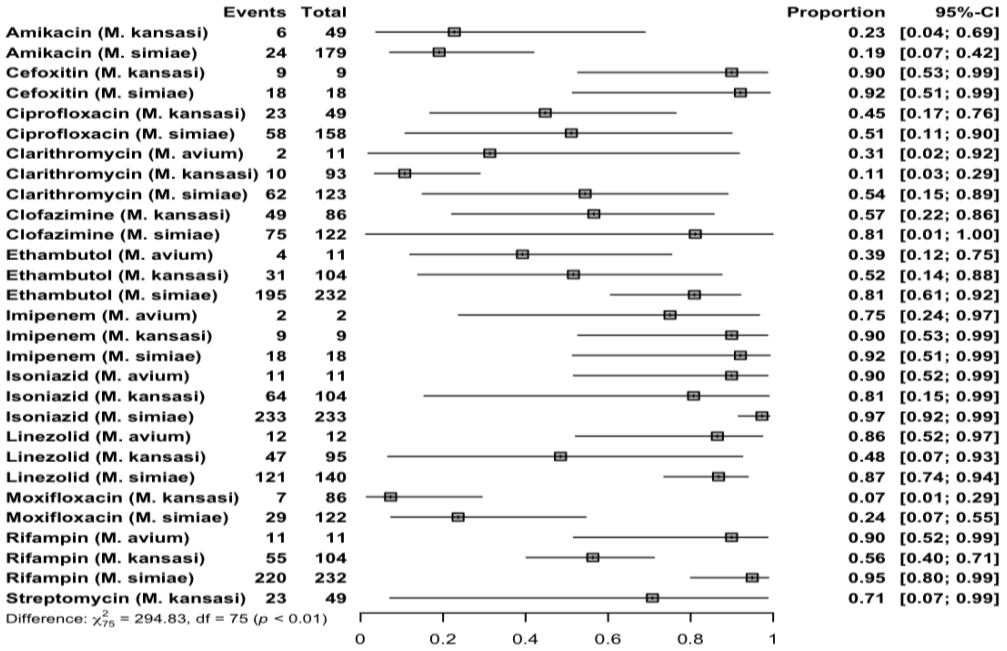


**Fig. 2:** The pooled antibiotics resistance prevalence in NTM species

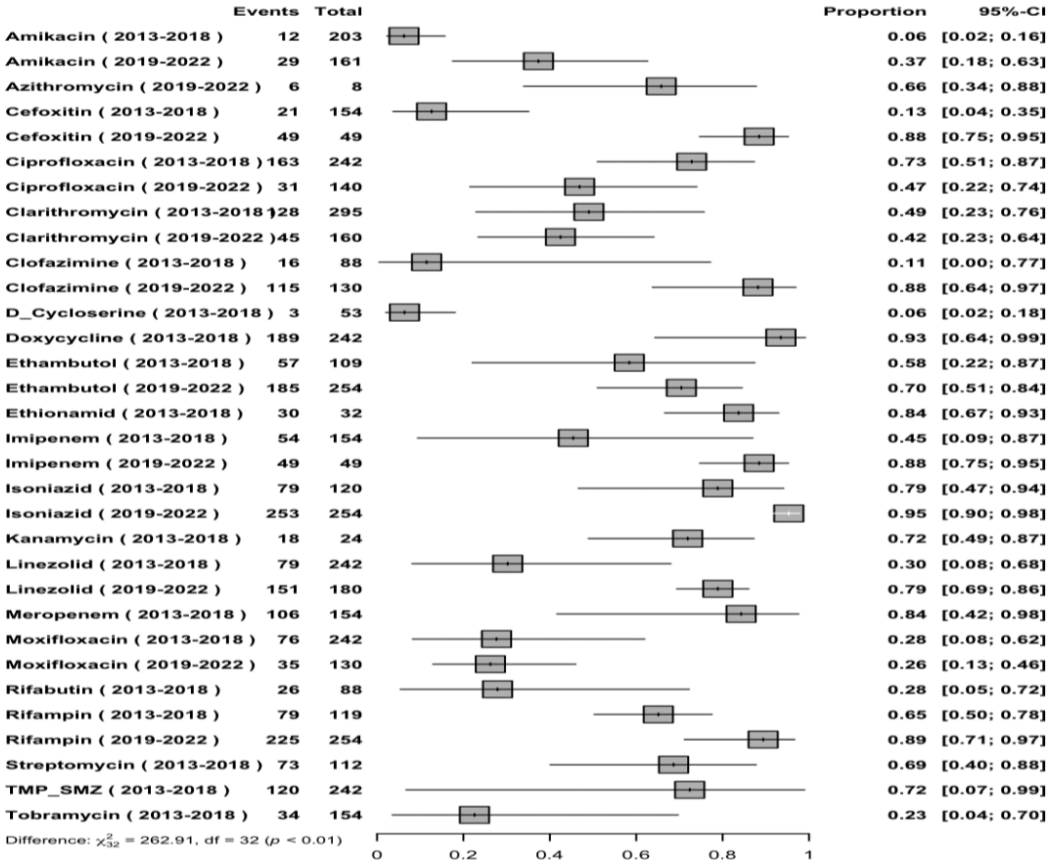


**Fig. 3:** The prevalence of antibiotic in NTM species stratified by published year

**Table 1:** Prevalence of antibiotic resistance of NTM species in Iran

| *Antibiotics* | *(n, N)* | *Proportion (%) (95% CI)* | *Heterogeneity (%) ($I^2$)* | *Egger Test* |
|---|---|---|---|---|
| Amikacin | (41, 364) | 22 (11, 38) | 73 | 0.0129 |
| Kanamycin | (24, 116) | 52 (13, 89) | 85 | 0.2421 |
| Cefoxitin | (70, 203) | 67 (38, 87) | 80 | 0.0008 |
| Ciprofloxacin | (194, 382) | 59 (39, 76) | 84 | 0.1222 |
| Clarithromycin | (173, 455) | 46 (29, 63) | 82 | 0.1222 |
| Moxifloxacin | (111, 372) | 28 (15, 47) | 87 | 0.1689 |
| Doxycycline | (189, 242) | 93 (64, 99) | 90 | < .0001 |
| Clofazimine | (131, 218) | 67 (31, 90) | 89 | 0.1689 |
| Imipenem | (103, 203) | 78 (52, 92) | 83 | 0.0587 |
| Azithromycin | (6, 8) | 66 (34, 88) | 0 | 0.2120 |
| Linezolid | (203, 422) | 67 (48, 82) | 85 | 0.1538 |
| Meropenem | (106, 154) | 84 (42, 98) | 92 | 0.0012 |
| TMP-SMZ | (120, 242) | 72 (7, 99) | 94 | 0.0818 |
| Tobramycin | (34, 154) | 23 (4, 70) | 93 | 0.0298 |
| Isoniazid | (332, 374) | 89 (75, 95) | 59 | 0.5651 |
| Rifabutin | (26, 88) | 28 (5, 72) | 92 | - |
| Rifampin | (304, 373) | 79 (66, 87) | 61 | 0.0030 |
| Ethambutol | (242, 363) | 68 (51, 81) | 75 | 0.0835 |
| Streptomycin | (73, 112) | 69 (40, 88) | 75 | 0.5958 |
| D-cycloserine | (3, 53) | 6 (2, 18) | 0 | - |
| Ethionamide | (30, 32) | 84 (67, 93) | 0 | 0.6189 |

I-squared; $I^2$, Confidence Interval; CI, Trimethoprim/sulfamethoxazole; TMP-SMZ, n; number of resistance isolates, N; number of included isolates

### *Resistance to first-line anti-TB drugs*

Among the first-line anti-TB drugs, almost all NTM species were highly resistant to first-line anti-TB drugs (Table 1). The susceptibility to isoniazid was determined in 374 NTM species; the WPR was 89% (95% CI 77%-95%) (Table 1). The subgroup analysis that compared the data from 2013-2018 (WPR 79%; 95% CI 47%-94%), and 2019-2022 (WPR 95%; 95% CI 90%-98%) indicated an increase in the resistance rate (Fig. 3). No significant difference in the isoniazid resistance rate was found in the slow or rapid-growing species and Runyon's classification of NTM isolates (Supplementary File). The susceptibility to rifampin was determined in 373 NTM species; the WPR was 79% (95% CI 66%-87%) (Table 1). The subgroup analysis that compared the data from 2013-2018 (WPR 65%; 95% CI 50%-78%), and 2019-2022 (WPR 89%; 95% CI 71%-97%) indicated an increase in the rifampin resistance rate (Fig. 3). A high rifampin resistance rate was found in the slow or rapid-growing species (Table 2).

**Table 2:** The pooled prevalence of resistance to individual antibiotics stratified by slow or rapid growing of NTM species

| *Antibiotics* | *Groups* | *(n, N)* | *Proportion (%)(95% CI)* | *Heterogeneity (%) ($I^2$)* | *P. value* |
|---|---|---|---|---|---|
| Amikacin | Slow | (31, 229) | 22 (10, 41) | 73 | 0.97 |
| | Rapid | (10, 135) | 23 (4, 66) | 77 | |
| Linezolid | Slow | (180, 247) | 78 (58, 90) | 73 | 0.04 |
| | Rapid | (50, 157) | 46 (24, 70) | 79 | |
| Kanamycin | Slow | (23, 113) | 56 (11, 93) | 88 | - |
| | Rapid | - | - | - | |
| Cefoxitin | Slow | (28, 28) | 56 (11, 93) | 81 | 0.02 |
| | Rapid | (42, 28175 | 48 (19, 78) | 0 | |
| Ciprofloxacin | Slow | (82, 208) | 50 23, 78) | 88 | 0.36 |
| | Rapid | (112, 174) | 70 (41, 88) | 78 | |
| Clarithromycin | Slow | (74, 227) | 26 (12, 48) | 73 | 0.02 |
| | Rapid | (99, 228) | 64 (40, 82) | 83 | |
| Clofazimine | Slow | (131, 218) | 67 (31, 90) | 89 | |
| | Rapid | - | - | - | - |
| Doxycycline | Slow | (88, 88) | 99 (93, 100) | 0 | 0.06 |
| | Rapid | (101, 154) | 83 (36, 98) | 91 | |
| Imipenem | Slow | (29, 29) | 88 (67, 96) | 0 | 0.27 |
| | Rapid | (74, 174) | 70 (33, 92) | 89 | |
| Azithromycin | Slow | (31, 229) | 22 (10, 41) | 73 | 0.97 |
| | Rapid | (10, 135) | 23 (4, 66) | 77 | |
| Linezolid | Slow | (180, 247) | 78 (58, 90) | 79 | 0.04 |
| | Rapid | (50, 175) | 46 (24, 70) | 73 | |
| Meropenem | Slow | - | - | - | - |
| | Rapid | (106, 154) | 84 (42, 98) | 92 | |
| TMP-SMZ | Slow | (51, 88) | 71 (0, 100) | 95 | 0.97 |
| | Rapid | (69, 154) | 74 (1, 100) | 95 | |
| Tobramycin | Slow | - | - | - | - |
| | Rapid | (34, 154) | 23 (4, 70) | 93 | |
| Isoniazid | Slow | (325, 367) | 90 (76, 96) | 64 | 0.64 |
| | Rapid | (7,7) | 84 (48, 97) | 0 | |
| Rifampin | Slow | (297, 366) | 78 (65, 88) | 66 | 0.67 |
| | Rapid | (7, 7) | 84 (48, 97) | 0 | |
| Ethambutol | Slow | (238, 359) | 67 (48, 81) | 77 | 0.46 |
| | Rapid | (4,4) | 83 (35, 98) | 0 | |
| Streptomycin | Slow | (73, 112) | 69 (40, 88) | 75 | - |
| | Rapid | - | - | - | |
| | Slow | (27, 29) | 83 (65, 93) | 0 | - |
| Ethionamide | Rapid | - | - | - | |

I-squared; $I^2$, Confidence Interval; CI, Trimethoprim/sulfamethoxazole; TMP-SMZ, n; number of resistance isolates, N; number of included isolates

The highest and lowest in the rifampin resistance rate were showed in rapid (84%) and photochromogenic (46%) species. The susceptibility to ethambutol was determined in 363 NTM species; the WPR was 61% (95% CI 51%-81%) (Table 1). The subgroup analysis that compared the data from 2013-2018 (WPR 58%; 95% CI 22%-87%), and 2019-2022 (WPR 71%; 95% CI 51%-84%) indicated a significant increase in the resistance rate (Fig. 3). An increase in the ethambutol resistance rate was found in the slow or rapid-growing species. The highest and lowest in the ethambutol resistance rate were showed in rapid (83%) and non-chromogenic (66.67%) species (Supplementary File). The susceptibility to streptomycin was determined in 112 NTM species; the WPR was 69% (95% CI 40%-88%) (Table 1). An increase in the streptomycin resistance rate indicated from 2013-2018 (WPR 76%; 95% CI 44%-99%), to 2019-2022 (WPR 100%; 95% CI 100%-100%) (Fig. 3). The highest in the streptomycin resistance rate was showed in photochromogenic (72%) species (Supplementary File). The susceptibility to ethionamide was determined in 32 NTM species; the WPR was 84% (95% CI 67%-93%) (Table 1). The highest ethionamide resistance rate was showed in photochromogenic (89%) species (Supplementary File). Among the most common clinical NTM species, *M. avium, M. simiae* and *M. kansasii* showed the high resistance to rifampin or isoniazid (Fig. 2).

### Resistance to beta-lactams

Among beta-lactam drugs (imipenem, meropenem, and cefoxitin), almost all NTM species were highly resistant (67% to 84%) to beta-lactam drugs. The WPRs to imipenem, meropenem, and cefoxitin were 78% (95% CI 52%-92%), 84% (95% CI 42%-98%), and 67% (95% CI 38%-87%) (Table 1). A significant increase in the imipenem and cefoxitin resistance rates indicated from 2013-2018 (WPR 45%; 95% CI 9%-87% and WPR 13%; 95% CI 4%-35%), to 2019-2022 (WPR 88%; 95% CI 75%-95% and WPR 88%; 95% CI 75%-95%) (Fig. 3). Thus, the frequency of imipenem and cefoxitin resistance in NTM species during the years 2018-2022 represents a > 2-fold and > 6-fold increase over the years 2013–2018. The highest imipenem and cefoxitin resistance rates were showed in slow-growth species (Table 2). Among the most common clinical NTM species, *M. avium, M. simiae,* and *M. kansasii* showed the high resistance to beta-lactams (Fig. 2).

### Resistance to aminoglycosides

Among aminoglycosides drugs (amikacin, tobramycin and kanamycin), almost all NTM species were highly resistant to aminoglycosides drugs. The WPRs to amikacin, kanamycin, and tobramycin were 22% (95% CI 11%-38%), 52% (95% CI 13%-89%), and 23% (95% CI 4%-70%) (Table 1). An increase in the amikacin resistance rate indicated from 2013-2018 (WPR 6%; 95% CI 2%-16%), to 2019-2022 (WPR 37%; 95% CI 18%-63%) (Fig. 3). The amikacin resistance rate was showed same in slow and rapid growth species (Supplementary File).

### Resistance to fluoroquinolones

Among fluoroquinolones drugs (ciprofloxacin and moxifloxacin), almost all NTM species were moderately resistant to fluoroquinolones drugs. The WPRs to ciprofloxacin and moxifloxacin were 59% (95% CI 39%-76%), and 28% (95% CI 15%-47%). A decrease in the ciprofloxacin and moxifloxacin resistance rates indicated from 2013 to 2022 years (Fig. 3). An increase of ciprofloxacin resistance rates was showed in rapid-growing NTM species than slow-growing. Among the most common clinical NTM species, *M. simiae* showed the highly resistance to ciprofloxacin (Fig. 2).

### Resistance to macrolides

Among macrolide drugs (clarithromycin and azithromycin), almost all NTM species were highly resistant to macrolide drugs. The WPRs to clarithromycin and azithromycin were 46% (95% CI 29%-63%) and 66% (95% CI 34%-88%). The clarithromycin resistance rate was from 2013-2018 (WPR 49%; 95% CI 23%-76%) to 2019-2022 (WPR 49%; 95% CI 23%-76%) (Fig. 3). A significant increase in clarithromycin resistance

rate was showed in rapid -growing species than slow -growing NTM species ($P$= 0.02) (Table 2). Among the most common clinical NTM species, *M. abscessus*, *M. fortuitum,* and *M. simiae* showed the highly resistance to clarithromycin (Supplementary File).

### Resistance to other drugs

Among other drugs (doxycycline, linezolid, TMP-SMZ), almost all NTM species were highly resistant (Table 1). A significant increase in the linezolid rate indicated from 2013-2018 to 2019-2022 (Fig. 3). An increase in the doxycycline and linezolid resistance rates were showed in slow-growing species than rapid-growing NTM species (Table 2).

### Publication bias

Egger's regression test was performed to assess publication bias. However, the $P$-value of Egger's test confirmed the existence of publication bias for the amikacin, doxycycline, meropenem, tobramycin, rifampin, and cefoxitin groups ($P\leq$ 0.05) (Table 1).

## Discussion

NTM species are becoming a new world health concern and infections, morbidity, and mortality rate due to NTM species are increasing across the globe especially, to the immunocompromised population (19). Several infections are related to NTM, which dived into pulmonary infections and extrapulmonary infections such as skin and wound infections and catheter-associated infections (20). However, our knowledge of NTM and their infections is rare weak financial support and poor diagnostic tools are the main reasons for limited data on NTM (21, 22). This limitation and high-level innate resistance can worsen treatment outcomes (23). Because, based on different species, applying regimens is different (24). Moreover, these regimens are time-consuming, toxic, and costly (25). On the other hand, available drugs for NTM-associated infection are limited, and acquired resistance to most commonly used antibiotics makes a big concern. A matter of concern in our analysis is the increase in resistance rate in recent years.

The first-line anti-TB drugs consist of isoniazid, rifamycin (rifampin, rifapentine, or rifabutin), ethambutol, and streptomycin are used for the treatment of NTM infections, especially against slow-growing mycobacteria (26). Isoniazid (INH) is the most famous anti-mycobacterial drug which doesn't affect other bacteria. INH is a prodrug that is activated by the enzyme KatG (encoded by kat gene) produced by mycobacterium. In addition, INH is capable to inhibition of mycolic acid synthesis by the effect on InhA (encoded by inhA gene) a carrier protein to transfer lipid precursors. Therefore, the mutation in kat and inhA genes is associated with isoniazid resistance (27). In our study, a high resistance rate to INH was reported, which is following previous studies (28, 29). However, in a previous study, M. kansasii isolated from Taiwan showed a less resistance rate (27%) to INH (30). Rifampin is another important drug for the treatment of NTM infections (31). Rifampin is capable of binding to DNA-dependent RNA polymerase (encoded by rpoB) and inhibits the RNA chain elongation (31).

Our analysis extracted data from 2013-2018 and 2019-2022 indicated an increase in the resistance rate and this steady increase in the resistance to rifampin is a new concern. In concordance with previous studies (28, 29, 32) the highest resistance rate to rifampin was demonstrated in rapid growth mycobacteria. In contrast, slow-growth species, especially scotochromogenic species showed better sensitivity to rifampin (31). Ethambutol is competent to inhibit the mycobacterial cell wall synthesis by interfering in the biosynthesis of arabinogalactan a key part of the mycobacterial cell wall (33). Resistance to ethambutol is associated with mutations in the embCAB operon (33). Like other first-line anti-TB drugs, the highest and lowest ethambutol resistance was reported in rapid growth species. But in another study ethambutol among first-line anti-TB drugs, demonstrated the highest resistance (72%) against M. kansasii (30). Based on our analysis, in

accordance with other studies (34) among first-line anti-TB drugs, streptomycin was the most active antibiotic against NTM species.

Our analysis indicated a steady increase in the resistance rate of isoniazid, rifampin, ethambutol and streptomycin. This steady increase resistance of NTM to first line anti-TB drugs is growing problem, particularly because of increasing prevalence of infection in many parts of the world. Probably, increase in the infection frequency and exposure to drugs are the most reason for changing trends of antimicrobial susceptibility and increase in the resistance rate.

In this meta-analysis, NTM species demonstrated a highly resistant to beta-lactam drugs. Generally, due to beta-lactamase production by NTM, beta-lactam drugs are not a suitable choice for the treatment of NTM infections (35). However, cefoxitin and imipenem along with beta-lactamase inhibitor (avibactam) have been applied for the treatment of M. abscessus (36, 37). The analysis shows cefoxitin and imipenem are more effective against the rapid growth of mycobacteria. Meanwhile, the highest resistance is illustrated in slow-growth species.

Aminoglycosides especially amikacin is one of the key drugs for the treatment of mycobacterium avium complex pulmonary disease (MAC-PD), in particular in macrolide-resistant species (34). Aminoglycosides (amikacin and kanamycin) are capable to inhibit of bacterial protein synthesis by binding to bacterial 30S ribosomal subunit (38). However, owing to the presence of a mutation at the 16S rRNA gene (*rrs*) resistant isolates were emerged which responsible to decrease treatment success rates (33, 39). Our results showed that most NTM species are moderate resistant to amikacin and kanamycin.

Along with amikacin, Fluoroquinolones are other recommended drugs for macrolide-resistant MAC-PD species (40). Fluoroquinolones inhibit bacterial DNA replication and synthesis. In fact, both critical bacterial enzymes to DNA replication including DNA gyrase and topoisomerase IV are the main targets of Fluoroquinolones antimicrobials (David). Therefore, mutations in the quinolone resistance-determining region (QRDR) of gyrA and gyrB are the most significant reason to emerging of resistance (41, 42). Moreover, efflux pumps are defined as another resistance mechanism (43).

In accordance with a previous study, owing to high-level resistance, the prescription of moxifloxacin for rapid growth species is not recommended (44). Our analysis demonstrated a significant difference in antimicrobial susceptibility patterns between ciprofloxacin and moxifloxacin. A comparison of results in two time periods showed a decrease in resistance to ciprofloxacin and moxifloxacin. Probably, the rate of drug consumption in these years is the major reason for defining this phenomenon. Probably prescription and consumption of moxifloxacin in the treatment of NTM are more than ciprofloxacin and we know selective pressure (the rate of drug consumption) is associated with the development of resistance (26).

In this meta-analysis, resistance to macrolides was ≥ 46%. On the other hand, macrolides are the mainstay for the treatment of NTM (34, 40). Macrolides antibiotics (clarithromycin and azithromycin) inhibit the bacterial protein synthesis by binding to bacterial large (50S) ribosomal subunit (33) and mutation in encoding genes (in the 23SrRNA) is a considerable reason for resistance (45).

In addition to the above-mentioned mechanisms, other resistance mechanisms such as target change, antibiotic-destructive enzymes, and change in uptake or efflux pumps will allow for resistance development.

## Conclusion

Treatment of NTM infections with the available drugs is a difficult task. Because most evaluated antibiotics have a minor effect on NTM species. On the one hand, a steady increase of resistance in the last few years in comparison to years ago showed that to combat NTM infections we need more-effective regimens. For example, bedaquiline and delamanid after complete evaluation can be suitable candidates in the future. Besides, in-

vestment and effort in the development of new antibiotics to improve the diagnosis of NTM species are required. Until introducing new options continuous surveillance with regard to antibiotic resistance is essential. Finally, to control antibiotic resistance development, rapid and proper identification of NTM and restriction on unprofessional antibiotic consumption are crucial.

## Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

## Acknowledgements

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## Competing Interests

The authors declare that they have no competing interests.

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