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Global prevalence of non-tuberculous mycobacteria in adults with non-cystic fibrosis bronchiectasis 2006–2021: a systematic review and meta-analysis

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ABSTRACT

Objective To accurately estimate the global prevalence of non-tuberculous mycobacteria (NTM) in adults with non-cystic fibrosis (non-CF) bronchiectasis and to determine the proportion of NTM species and subspecies in clinical patients from 2006 to 2021.

Design Systematic review and meta-analysis using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Data sources Medline, Embase, Cochrane Library and Web of Science were searched for articles published between 2006 and 2021.

Eligibility criteria for selecting studies We included all the prospective or retrospective studies without language restrictions and all patients were adults (≥18 years of age) with non-CF bronchiectasis. The studies estimated the effect size of the prevalence of NTM with a sample size ≥40, and patients were registered in and after 2006.

Data extraction and synthesis Two reviewers screened the titles, abstracts and full texts independently. Relevant information was extracted and curated into tables. Risk of bias was evaluated following the Cochrane Collaboration's tool. Meta-analysis was performed with software R Statistics V.3.6.3 using random effect model with 95% CI. I^2 index and Q statistics were calculated to assess the heterogeneity, and mixed-effects meta-regression analyses were performed to identify the sources of heterogeneity. The proportions of NTM subspecies were examined using Shapiro-Wilk normality test in R.

Results Of all the 2014 studies yielded, 24 met the inclusion criteria. Of these, 14 were identified to be randomised controlled studies and included for an accurate estimation. The global prevalence of NTM in adults with non-CF bronchiectasis from 2006 to 2021 was estimated to be approximately 10%, with great variations primarily due to geographical location. *Mycobacterium avium* complex was the most common subspecies, followed by *Mycobacterium simiae* and *Mycobacterium gordonae*.

Conclusions The prevalence of NTM in adults with non-CF bronchiectasis has been on the rise and the most common subspecies changed greatly in recent years. More cohort studies should be done in many countries and regions for future estimates.

PROSPERO registration number CRD42020168473.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study systematically reviewed the data over the past 16 years according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and employed the Cochrane Collaboration's tool to evaluate risk of bias.
⇒ Factors causing overestimation, such as clinical data from bronchiectasis medical/referral/registry centres, were considered during the meta-analysis.
⇒ The significance of non-tuberculous mycobacteria subspecies in clinical practice was examined.
⇒ Due to strict selection criteria, much data had to be excluded in this study, resulting in limited data from Africa and America.
⇒ For molecular method (PCR), only one study was eligible with limited sample size, making a comparison of detection methods impossible.

INTRODUCTION

The prevalence of non-cystic fibrosis (non-CF) bronchiectasis increased dramatically in recent years, and it is the third most common respiratory disease after asthma and chronic obstructive pulmonary disease (COPD).[1–3] The airways of patients with non-CF bronchiectasis are chronically colonised by a variety of pathological micro-organisms, such as yeasts, filamentous fungi and non-tuberculous mycobacteria (NTM).[4] Currently, it is widely believed that non-CF bronchiectasis and NTM infection are inter-related,[5] and NTM causes human disease as opportunistic pathogens within a complex clinical context,[6 7] such as COPD or CF.[8] Several factors, including age, sex, cigarette smoking, HIV infection and underlying health conditions, are associated with the susceptibility to NTM infection.[9–11] People living with HIV is particularly vulnerable to NTM infection due to immunodeficiency conditions.[9] Host factors, such as smoking, are believed to be important determinants

of the susceptibility to NTM infection.[10] The age for the highest prevalence of NTM pulmonary disease was in the 50s for women and in the 70s for men, except for those over 80 years of age[12]; whereas NTM is rarely isolated in children and adolescence with non-CF bronchiectasis,[13] especially in those under 15 years old.[14] Thus, this study focused exclusively on the prevalence of NTM in adults. Among these factors, concomitant bronchiectasis may be the strongest factor associated with NTM infection.[15] As a result, although the mechanism of NTM infection, as well as its impact on clinical outcomes, is not well understood,[16] it is hypothesised that NTM infection may lead to bronchiectasis.[5]

The reported prevalence of NTM in the population with non-CF bronchiectasis varied widely among studies,[11 17–19] and the NTM prevalence in adults with non-CF bronchiectasis from some studies might be overestimated as the data originated from bronchiectasis medical/referral/registry centres, where NTM in respiratory secretions were routinely screened.[11] Meanwhile, studies worldwide have discovered great geographical variation among species of NTM,[20 21] which may also account for the variability in the prevalence of NTM pulmonary disease. Geographical factors, such as climate, geological distribution and regional differences, may affect NTM activity, but the underlying mechanism remains elusive.[22] Moreover, sample size,[23] detection methods[24] and study design[25] may also contribute to the variations. In addition, *Mycobacterium kansasii, Mycobacterium szulgai* and *Mycobacterium malmoense* have been recognised as causative agents in most patients, whereas *Mycobacterium gordonae, Mycobacterium terrae* and *Mycobacterium fortuitum* were less virulent and they were usually believed to be contaminants rather than causative agents.[26 27] Therefore, determining the prevalence of NTM subspecies in patients with non-CF bronchiectasis is important to understand the role of NTM in the disease, and may guide clinical treatments by dealing with the microbes in an earlier stage and improving patient outcomes.

Multiple studies have found that NTM isolation rates are increasing in recent years, which may be attributable to the advancement of detection methods.[28–30] Chu *et al* reported that the prevalence of NTM was 9.3% in 2014,[23] and *Mycobacterium abscessus* and *Mycobacterium avium* complex (MAC) were the two most prevalent NTM subspecies. However, all the clinical data in this study were collected prior to 2006, which could not reflect the recent trends. It is therefore necessary to update the estimate of the global prevalence of NTM after 2006 for better understanding of the pathogenesis of non-CF bronchiectasis. Herein, we aim to determine the global prevalence of NTM in adults with non-CF bronchiectasis from 2006 to 2021, explore the possible source of heterogeneity in the prevalence of NTM pulmonary disease and identify the significance of NTM subspecies in clinical practice.

METHODS

We conducted a systematic review on NTM airway colonisation in adults with non-CF bronchiectasis from 2006 to 2021 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA-P checklist 2020; online supplemental file 1),[31] and performed a meta-analysis on the global prevalence of NTM, as well as the proportion of their subspecies.

Search strategy and selection criteria

We searched the databases on Medline, Embase, Cochrane Library and Web of Science for articles published from 2006 to December 2021, using keywords 'nontuberculous mycobacter*', 'NTM', 'non-tuberculous mycobacter*', 'nontuberculous mycobacter*', 'atypical Mycobacter*', 'bronchiectasis', 'sputum', 'microbiome', 'bronchiectas*' and 'Kartagener*'. Databases were searched without language restrictions (online supplemental file 2 table S1). We also reviewed the references cited by selected articles to identify additional studies meeting the inclusion criteria. Two researchers (YZ and WM) searched titles and abstracts and selected articles based on the inclusion criteria; any discrepancies were solved by consensus with the help of a third reviewer (SWW).

We included all observational studies fulfilling the following criteria: (1) prospective or retrospective studies; (2) studies in adults (≥18 years of age) with non-CF bronchiectasis as defined by the authors; (3) studies estimating the effect size of the prevalence of NTM; (4) sample size ≥40; (5) clinical patients or the vast majority of clinical patients in and after 2006; and (6) publications before 2021. We excluded studies if: (1) it only described NTM data unassociated with bronchiectasis; (2) duplicate studies or records or did not calculate the prevalence of NTM in the patients with bronchiectasis; (3) participants included CF; (4) cultures included both NTM and tuberculous mycobacteria simultaneously; or (5) case reports, commentary or review articles.

Data extraction

Data were extracted by two reviewers (YZ and WM) independently using the standard protocol, and discrepancies were resolved through consultation with the third researcher (SWW). The following information of included studies were extracted: (1) last name of the first author, year of publication, country of the population studied; (2) time of study; (3) sample size; (4) mean age of patients; (5) data source; (6) cohort study design, whether retrospective or prospective; (7) specimen source such as sputum or bronchoscopy specimen; (8) laboratory method of NTM tested; (9) definition of NTM positive; and (10) infection rate of NTM in adults with non-CF bronchiectasis with the classification of NTM. For missing information, we communicated with the authors; if the information was unavailable after communications, this study was excluded. Two reviewers (YZ and WM) evaluated the risk of bias in individual studies following the Cochrane Collaboration's tool.[32]

Quantitative analysis

Software R Statistics V.3.6.3 was used for statistical analysis. The random effect model with a 95% CI was adopted as we included observational studies and presumed high study heterogeneity. The I^2 index and Q statistic were calculated to assess study heterogeneity. The original prevalence of patients positive for NTM was tested for normality using the Shapiro-Wilk normality test in R. The results of the test determine if the original prevalence needs transformation before being pooled, and risk of bias assessment determines if a study should be excluded for sensitivity analysis. Mixed-effects meta-regression analyses were performed to identify possible sources of heterogeneity. Proposed moderator variables include the method of NTM specimen examination (MBC vs PCR), study design (prospective vs retrospective), sample size (both as a categorical variable and a continuous variable) and geographical location of the participants. A p value less than 0.1 was defined as statistically significant. Subgroup analyses were conducted by stratifying studies by proved moderator variable based on the results of meta-regression analyses. Lastly, the prevalence of each NTM subspecies reported in the finally included studies was examined.

Patient and public involvement

There was no direct patient or public involvement in this review.

RESULTS

Characteristics of eligible studies

The systematic review yielded 2014 articles. After eliminating duplicates and articles that did not match the inclusion criteria, a total of 24 independent studies including 26 944 patients with non-CF bronchiectasis were included in this systematic review and meta-analysis (figure 1). The characteristics of the 24 studies were summarised (online supplemental file 2 table S2).

Overall effects

Initial analysis of all the selected studies

The results of the Shapiro-Wilk normality test showed that the prevalence requires transformation before

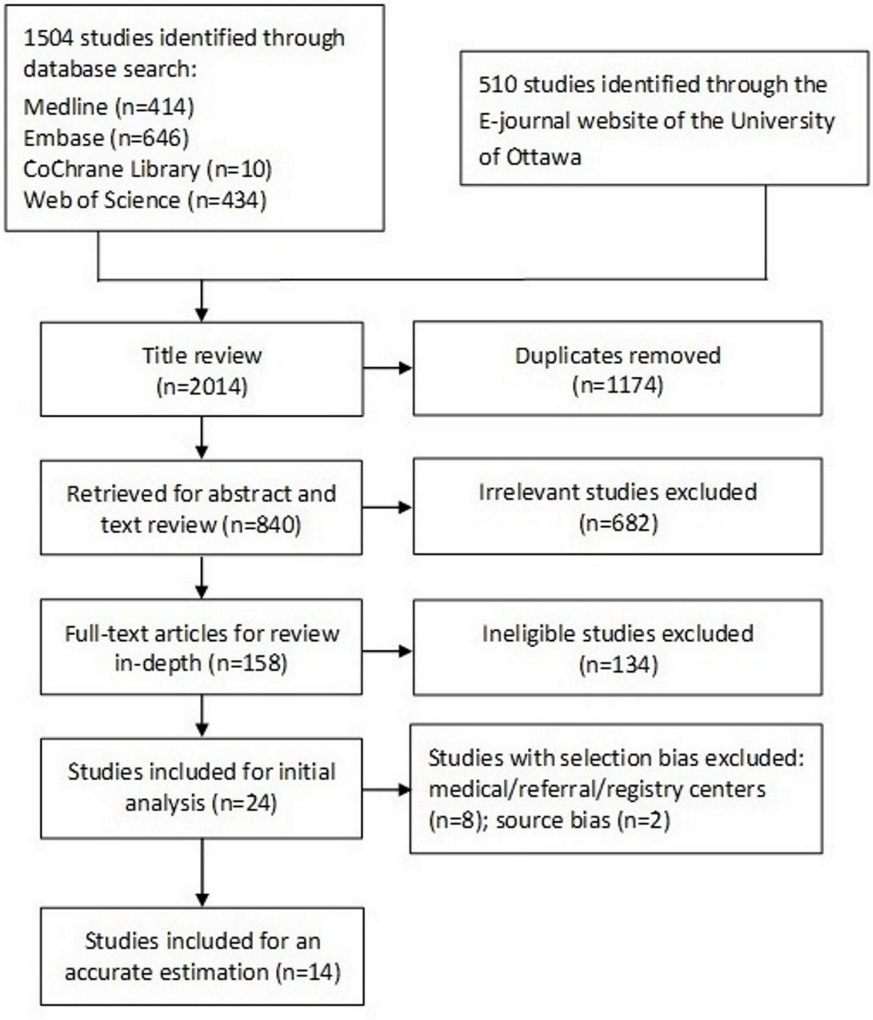

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

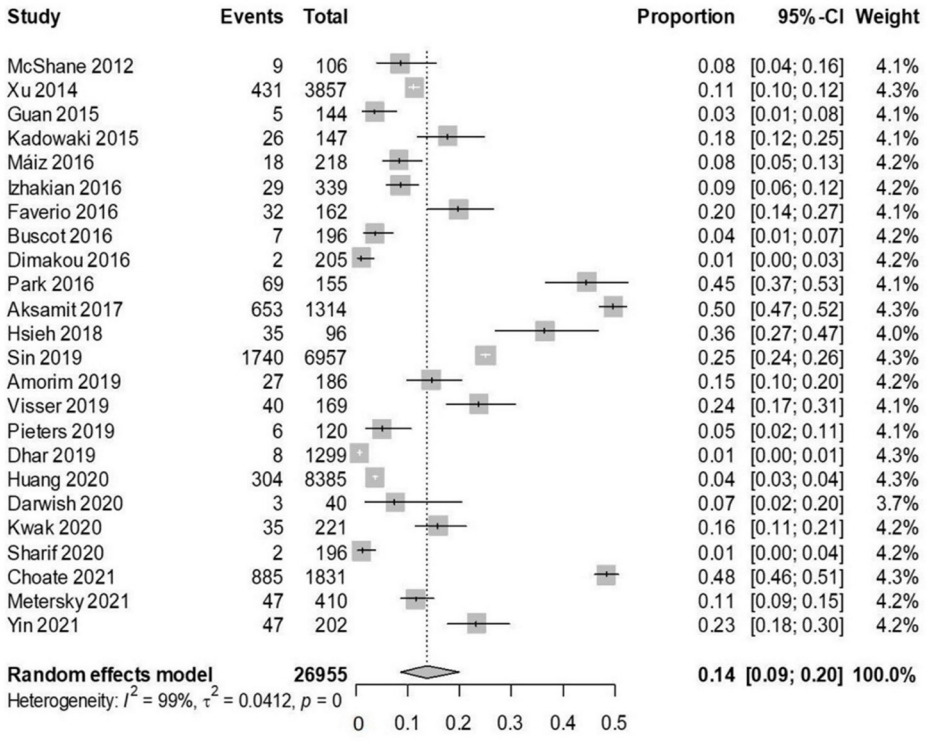

Figure 2 Forest plot of all included 24 studies from the systematic review.

pooling because they do not follow a normal distribution (W=0.857, p value=0.003). The Freeman-Tukey double arcsine transformation of the original prevalence was then made and pooled. Pooled analysis of the 24 included studies shows that the prevalence of NTM in adults with non-CF bronchiectasis was estimated at 13.76% (95% CI 8.53% to 19.97%) (figure 2). Result of the χ^2 test for heterogeneity was 99.5% for the 24 studies, indicating a great degree of variations among these studies.

Overestimation existed in the selected studies

Figure 2 indicates that the clinical data from four studies (Park *et al*,[33] Aksamit *et al*,[17] Hsieh *et al*[34] and Choate *et al*[35]) were visually identified as outliers from the forest plot, whose prevalence (50%, 36%, 24% and 48%) was substantially higher and the CIs had no or little overlaps with the CIs of other studies or the total effect size, indicating studies from bronchiectasis medical/registry/referral centres tremendously increased the estimated prevalence of NTM. Similarly, the clinical data from the other four studies (Amorim *et al*,[36] Visser *et al*,[29] Dhar *et al*[37] and Metersky *et al*[38]) were also from bronchiectasis referral centres. Shteinberg and Aksamit believed that the estimates of NTM prevalence from bronchiectasis referral centres were exaggerated,[39 40] suggesting that including these eight studies would inevitably overestimate the prevalence of NTM in adults with non-CF bronchiectasis and therefore should be excluded. In another study, only the patients who had been followed up for at least 5 years were included in analysis.[18] Additionally, Kwak *et al*'s study in 2020 only included the patients who had participated in a non-NTM bronchiectasis cohort and then studied the NTM infection afterwards.[41] The patients in both studies were not randomly selected, and that may also result in inaccurate estimates. Thus, our risk of bias assessment (online supplemental file 2 table S3) suggested that, out of all the 24 studies selected, 10 studies should be excluded from the sensitivity analysis to avoid an overestimation of the prevalence of NTM.

An accurate estimate of the prevalence of NTM infection from 2006 to 2021

Based on the analysis above, 14 independent studies were included in the meta-analysis for an accurate estimate of the prevalence of NTM in adults with non-CF bronchiectasis (table 1). These studies encompassed 21 056 patients with non-CF bronchiectasis and NTM has been isolated from 2643 patients. All the patients were ≥18 years old. The prevalence of NTM in adults with non-CF bronchiectasis ranged from 1.0% to 25%. The results of the Shapiro-Wilk normality test showed that the prevalence follows a normal distribution (W=0.877, p value=0.053) and needs no transformation. Our sensitivity analysis showed that the prevalence of NTM infection in adults with non-CF bronchiectasis from 2006 to 2021 was 9.75% (95% CI 5.41% to 14.09%) (figure 3). Results of the χ^2 test for heterogeneity were 99.3%, suggesting a great degree of variations among the 14 included studies. Notably, this was an overall estimate of the prevalence of NTM infection in adults with non-CF bronchiectasis, regardless of

Table 1 Characteristics of studies included in the systematic review and meta-analysis

Author and year	Country	Time of sampling	Mean age (years)	Sample size	Patients with NTM	Study design	Method of detection	NTM (%)
McShane *et al* 2012[52]	USA	2009–2011	≥18	106	9	RS	Sputum culture	8.5
Xu *et al* 2014[53]	China	2009–2012	47.4	3857	431	RS	Sputum culture	11.2
Guan *et al* 2015[54]	China	2012–2013	44.6	144	5	PS	Sputum culture	3.5
Kadowaki *et al* 2015[55]	Japan	2008–2012	73	147	26	RS	Sputum culture	17.7
Izhakian *et al* 2016[56]	Israel	2006–2014	64	339	29	RS	Bronchoalveolar/lavage cultures	8.6
Faverio *et al* 2016[47]	Italy	2006–2014	65	162	32	PS	Bronchoalveolar/sputum culture	19.8
Buscot *et al* 2016[57]	France	2002–2012	61.0	196	7	RS	Sputum/bronchoalveolar lavage culture	3.6
Dimakou *et al* 2016[58]	Greece	2009–2014	60.5	205	2	PS	Sputum culture	1.0
Sin *et al* 2019[19]	Korea	2005–2016	59.6	6957	1740	RS	Sputum culture	25
Pieters *et al* 2019[59]	Netherland	2012–2016	60	120	6	RS	Sputum culture	5.0
Huang *et al* 2020[60]	China	2002–2016	65.5	8385	304	RS	Sputum culture	3.6
Darwish *et al* 2020[61]	Egypt;	2017–2018	55.2	40	3	PS	Sputum PCR	7.5
Sharif *et al* 2020[62]	Pakistan	2017–2019	NA	196	2	PS	Sputum culture	1.0
Yin *et al* 2021[63]	China	2018–2020	62	202	47	RS	Sputum/BAL culture	23.3

AFB, acid fast bacillus smear; BAL, bronchoalveolar lavage; MBC, mycobacteria culture; NA, not available; NTM, non-tuberculous mycobacteria; PS, prospective study; RS, retrospective study.

the underlying health condition such as HIV, age, sex and smoking.

Meta-regression and subgroup analysis

To understand the mechanisms of variations, we subgrouped the included 14 studies based on four characteristics (table 2). We performed mixed-methods meta-regression analyses using Metafor package in R. Moderating variables including the method of NTM specimen examination (R^2 analogue=0.00%, test of moderators p=0.802), sample size (as continuous variable, R^2 analogue=0.00%, test of moderators p=0.479; as categorical variable, R^2 analogue=0.00%, test of moderators p=0.390) and study design (R^2 analogue=4.82%, test of moderators p=0.222) failed to explain the heterogeneity among studies. The moderator geographical location of the participants explained 14.2% of the between-study variance (test of moderators p=0.083).

Subsequently, we conducted a subgroup analysis by stratifying studies into reports from East Asian (including China, Korea and Japan) and other geographical

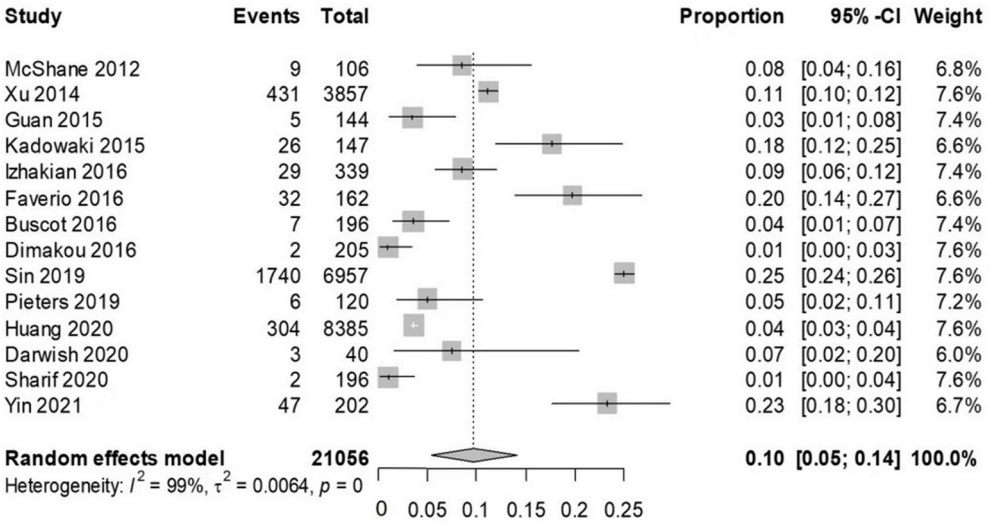

Figure 3 Forest plot of a sensitivity analysis of 14 studies for an accurate estimate of global prevalence of NTM in adults with non-CF bronchiectasis in 2006–2021. CF, cystic fibrosis; NTM, non-tuberculous mycobacteria.

Table 2 Subgroup classification for data analysis

Study	Time of clinical data	NTM positive (n)	Patients (n)	Sample size	Study location	Study type	Culture method
McShane *et al*[52]	2009–2011	10	106	<200	Others	RS	MBC
Xu *et al*[53]	2009–2012	431	3857	≥200	East Asia	RS	MBC
Guan *et al*[54]	2012–2013	5	144	<200	East Asia	PS	MBC
Kadowaki *et al*[55]	2008–2012	26	147	<200	East Asia	RS	MBC
Izhakian *et al*[56]	2006–2014	29	339	≥200	Others	RS	MBC
Faverio *et al*[47]	2006–2014	32	162	<200	Others	PS	MBC
Buscot *et al*[57]	2002–2012	7	196	<200	Others	RS	MBC
Dimakou *et al*[58]	2009–2014	2	205	≥200	Others	PS	MBC
Sin *et al*[19]	2005–2016	1740	6957	≥200	East Asia	RS	MBC
Pieters *et al*[59]	2012–2016	6	120	<200	Others	RS	MBC
Huang *et al*[60]	2002–2016	304	8385	≥200	East Asia	RS	MBC
Darwish *et al*[61]	2017–2018	3	40	<200	Others	PS	PCR
Sharif *et al*[62]	2017–2019	2	196	<200	Others	PS	MBC
Yin *et al* [63]	2018–2020	47	202	≥200	East Asia	RS	MBC
Sum		2644	21 056				

AFB, acid-fast bacillus smear; MBC, mycobacteria culture; PS, prospective study; RS, retrospective study.

locations. The pooled NTM prevalence of the six East Asian studies was 7.50% higher than that of the eight studies from other countries (13.87%, 95% CI 6.23% to 21.52% vs 6.37%, 95% CI 2.38 to 10.36%) (figure 4). The χ^2 test found better homogeneity among studies from other countries. These analyses suggested that the variations among the 14 included studies were not due to sample sizes, study types and specimen examination methods, but geographical locations. Further studies on regional differences, such as climate, soil, water, culture, may help to understand the epidemiology of NTM infection in adults with non-CF bronchiectasis.

Subspecies analysis

Lastly, we estimated the prevalence of NTM subspecies in patients with non-CF adult bronchiectasis reported in the included 14 studies. Because more than one NTM subspecies might be identified in a specimen, we used the times

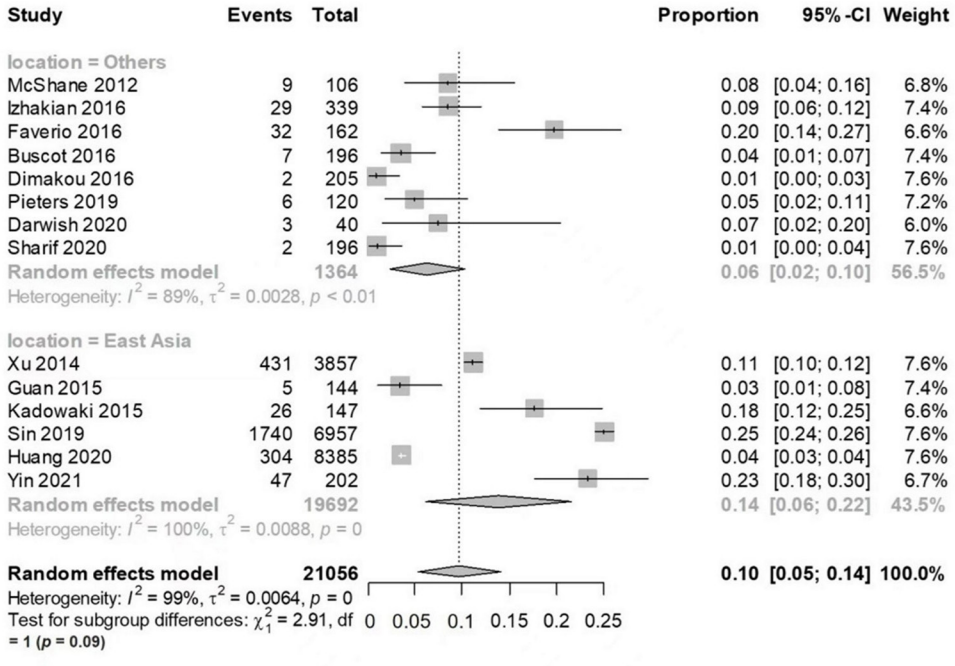

Figure 4 Forest plot for subgroup analysis by geographical location.

Table 3 The proportion of subspecies in NTM positive specimens

NTM type	Studies (n)	Proportion (95% CI (%))	Effect model	Method of data transformation	Test of heterogeneity		
					Q	P value	I^2 (%)
MAC	9	77.6 (64.0 to 91.1)	Random	PRAW	66.0	<0.001	87.9
M. abscessus	4	7.83 (0.00 to 15.8)	Random	PRAW	10.47	0.015	71.4
M. chelonae	5	5.70 (2.21 to 9.18)	Fixed	PRAW	0.42	0.981	0
M. gordonae	2	10.5 (1.65 to 19.3)	Fixed	PRAW	0.23	0.635	0
M. fortuitum	3	5.27 (0.64 to 9.91)	Fixed	PRAW	0.35	0.841	0
M. simiae	2	17.28 (0.00 to 36.80)	Random	PRAW	3.20	0.073	68.8
M. kansasii	3	4.70 (0.41 to 8.98)	Fixed	PRAW	0.70	0.705	0
Undetermined	2	2.31 (0.00 to 6.43)	Fixed	PRAW	1.31	0.253	23.5
M. xenopi	1	7.69 (1/13)	–	–	–	–	–
M. shimoidei	1	3.03 (1/33)	–	–	–	–	–
M. terrae	1	2.1% (1/47)	–	–	–	–	–

Proportion in each study=number of specimens tested positive for a specific subspecies/total NTM-positive specimen in the study; the proportions of NTM subspecies identified in only one study were calculated, rather than pooled.
M. abscessus, *Mycobacterium abscessus*; MAC, *Mycobacterium avium* complex; *M. chelonae*, *Mycobacterium chelonae*; *M. fortuitum*, *Mycobacterium fortuitum*; *M. gordonae*, *Mycobacterium gordonae*; *M. kansasii*, *Mycobacterium kansasii*; *M. shimoidei*, *Mycobacterium shimoidei*; *M. simiae*, *Mycobacterium simiae*; *M. terrae*, *Mycobacterium terrae*; *M. xenopi*, *Mycobacterium xenopi*; PRAW, raw data.

of a subspecies being identified for pooling or calculating the proportion (online supplemental file 2 table S4). The method of data transformation was determined considering the characteristics of the raw proportions. Out of all 14 studies, 9 reported the number of confirmed cases or specimens of each NTM subspecies (table 3). Our results showed that the most widely identified NTM species in our review is MAC, reported in nine studies with a pooled proportion of 77.6% (95% CI 64.0% to 91.1%), followed by *M. simiae* (17.28%, 95% CI 0.00% to 36.80%) and *M. gordonae* (10.50%, 95% CI 1.65% to 19.3%).

DISCUSSION

Main findings

Our systematic review including 24 studies from multiple geographical locations in the initial meta-analysis found that the global prevalence of NTM in adults with non-CF bronchiectasis from 2006 to 2021 was 14%. However, when the 10 studies with source bias in the clinical data were excluded from meta-analysis, this percentage decreased to 10%. An updated, accurate estimate of global prevalence of NTM is of clinical significance, and data with source of bias should be excluded in such an estimation.[5 16] As a result, with available data, the most accurate estimation of global prevalence of NTM infection in adults with non-CF bronchiectasis should be 10%.

Our subgroup analyses found that of all the four factors we investigated, the great variation of the prevalence of NTM among studies was primarily due to geographical difference, whereas sample size, study type and detection method only slightly affected the estimates. The pooled NTM prevalence of East Asia (13.87%, 95% CI 6.23% to 21.52%) was 7.50% higher than that of other continents on the Earth (6.37%, 95% CI 2.38% to 10.36%) (figure 4). Interestingly, the prevalence of NTM among countries or within the same continent, or even among regions within the same country also varied greatly (figure 3). The mechanisms for this geographical variation remain elusive, and unknown factors may contribute to the high prevalence of NTM in some countries or regions. It was speculated that environment factor such as climate, soil and water,[6–8 42] and regional differences in techniques[43] may account for the geographical variations of NTM prevalence. Further studies on the geographical variations may contribute to the prevention of NTM in adults with non-CF bronchiectasis.

Comparison with literature

Compared to Chu *et al*'s study in 2014, of which all the clinical data were between 1990 and 2006,[23] the clinical data in this study were primarily from 2006 to 2021. Thus, this study provided an updated estimate of the NTM prevalence in adults with non-CF bronchiectasis. Moreover, within the same amount of time, the number of studies tripled from 8 to 24, indicating an increasing interest in the prevalence of NTM in patients with non-CF bronchiectasis during the past 15 years.[30] Without taking the source bias into consideration, Chu *et al*'s study in 2014 estimated that the prevalence of NTM from 1990 to 2006 was 9.3%. In contrast, our initial analysis estimated that the prevalence of NTM from 1990 to 2006 was 13.76%, suggesting an increasing trend of NTM infections in patients with non-CF bronchiectasis.

After an in-depth analysis of the report in 2014 by Chu *et al*,[23] we found that the prevalence of NTM from 1990 to 2006 might have been overestimated, primarily because out of all eight studies included in this study, two were

from bronchiectasis medical/referral centres (Koh *et al*, 2005; Tabarsi *et al*, 2009).[44 45] Koh *et al* reported a prevalence of NTM as high as 30.0%. However, many patients in this study were not bronchiectasis but bronchiolitis.[44] Tabarsi *et al* reported that the prevalence of NTM was 15.2%, but the cases might have included multidrug-resistant tuberculosis.[46] Thus, we believe that in this study, only six studies were valid for the estimate of the prevalence of NTM in patients with bronchiectasis. Accordingly, we recalculated the prevalence of NTM in patients with bronchiectasis of the six valid studies, finding that the real prevalence of NTM from 1990 to 2006 was not 9.3%, but 5% (online supplemental file 2 figure S1). This systematic review and meta-analysis estimated that the global prevalence of NTM from 2006 to 2021 was approximately 10% (9.75%, 95% CI 5.41% to 14.09%), implicating the increasing trend in the prevalence of NTM infections in adults with non-CF bronchiectasis over the past 15 years.

Moreover, Chu *et al* reported that from 1990 to 2006, the three most prevalent NTM subspecies were *M. abscessus* (43.2%, 95% CI 26.6% to 60.9%), MAC (25.7%, 95% CI 12.6% to 38.8%) and *M. kansasii* (3.7%, 95% CI 0.1% to 7.3%). This analysis discovered that from 2006 to 2021, the three most prevalent NTM subspecies turned to be MAC (77.6%, 95% CI 64.0% to 91.1%), *M. simiae* (17.28%, 95% CI 0.00% to 36.80%) and *M. gordonae* (10.50%, 95% CI 1.65% to 19.30%). Evidently, MAC has turned to be the most common subspecies in the past 15 years. Studying the underlying mechanism may help to understand the role of NTM infection in the pathogenesis of non-CF bronchiectasis.

Implications for research and practice

The increasing interest in NTM infection in non-CF bronchiectasis worldwide in recent years indicates the microbes may play an important role in the pathogenesis of the disease.[47] In general, of all patients with a positive culture, only 25%~60% meet the criteria for NTM pulmonary disease.[26] Our data showed that up to 65%, or even up to 90% of the total NTM infections in bronchiectasis patients were subspecies MAC, similar to the data previously estimated.[44 48 49] Some subspecies, such as *M. kansasii*, *M szulgai* and *M. malmoense*, were considered causative agents, whereas the others, such as *M. gordonae*, *M. terrae* and *M. fortuitum* were believed to be less virulent contaminants.[26 27] Therefore, the three most prevalent NTM species converted from *M. abscessus*, MAC and *M. kansasii* into MAC, *M. simiae* and *M. gordonae*. This conversion might be clinically significant to reveal the role of NTM in the disease, thereby guiding clinical treatments and making an accurate prognosis.[27 50] However, a diagnosis of infection in lung disease does not dictate the initiation of antibiotic therapy against NTM species. Instead, the healthcare team should consider the potential risks and benefits for individual patients of a prolonged course of treatment with multiple antibiotics.[51]

Strengths and limitations

In the study by Chu *et al* in 2014, all the clinical data were prior to 2006. In contrast, the clinical data in this paper were between 2006 and 2021. There were no data and time overlaps between the two studies and thus, results from this study may represent the current trend of NTM prevalence in adults with non-CF bronchiectasis. Moreover, this study took source bias into consideration, thereby providing an updated and more accurate estimate of the prevalence of NTM in adults with non-CF bronchiectasis, which may be significant to direct clinical treatments.

This study has several limitations as well. First, only one study from Africa and one study from North America met the inclusion criteria, indicating that the data for these continents were less representative. Second, sample size is limited so in the analysis of determinants of NTM infections we have used $p<0.1$ instead of conventional cut-off $p<0.05$ to define statistical significance. Third, the inspection methods may significantly affect detection rates.[28–30] After the inclusion criteria were applied, only one study used PCR to detect NTM species was available in the literature with limited sample size, making a comparison of different detection methods for species analysis impossible. Fourth, the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) Statement (2007) recommended that NTM positive culture results should be from at least two separate expectorated sputum samples.[51] Of the 14 studies included in this study, NTM detection method was described in detail in 9 studies (including 1 using PCR), only 6 studies met the ATS/IDSA standard criteria, 5 did not report the number of specimens of NTM subspecies. The laboratory differences may partially account for the geographical variations of the NTM prevalence.

It is noteworthy to mention that the percentage presented herein (approximately 10%) is an overall estimate for the global prevalence of NTM in adults with non-CF bronchiectasis from 2006 to 2021. As per the prevalence of NTM in a specific country or region, retrospective and prospective studies are still needed for a customised and accurate estimate. Based on the analysis and issues presented in this study, other researchers may replenish the data and provide a more accurate and up-to-date estimation in the future.

CONCLUSIONS

Our systematic review and meta-analysis suggest that the global prevalence of NTM in adults with non-CF bronchiectasis from 2006 to 2021 is estimated to be approximately 10%, with major variations in the estimated prevalence primarily driven by geographical locations. MAC is the most common organism in non-CF bronchiectasis, followed by *M. simiae* and *M. gordonae*.

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Online Supplemental File 1: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2-3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	2-3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	2
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	2-3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	2-3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	3
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	2-3

Online Supplemental File 1: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	3
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	4
Study characteristics	17	Cite each included study and present its characteristics.	3-4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	3-7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	3-7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	3-7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	3-7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	3-7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7-8
	23b	Discuss any limitations of the evidence included in the review.	8
	23c	Discuss any limitations of the review processes used.	8
	23d	Discuss implications of the results for practice, policy, and future research.	8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	1
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	9
Competing interests	26	Declare any competing interests of review authors.	9
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	9

Online Supplemental File 1: PRISMA 2020 Abstract Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review. (***At the end of the article***)	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Online Supplemental File 2: Tables and Figure

Online Supplemental File 2 for 'Global prevalence of nontuberculous mycobacteria in adults with non-cystic fibrosis bronchiectasis 2006-2021: a systematic review and meta-analysis'.

Table of Contents

Table S1: Search strings

Database and date	Yield	Duplicates	Search String used
Medline Jan 31, 2022	414	0	"Bronchiectasis" [Mesh]) AND ("Nontuberculous Mycobacteria" OR "non tuberculous mycobacter" [Mesh]) AND ("Atypical Mycobacter" [Mesh] OR ("Mycobacter abscessus" [Mesh]) OR "Mycobacter avium complex" [Mesh] OR "Mycobacter chelonae" [Mesh] OR "Mycobacter fortuitum" [Mesh] OR "Mycobacter kansasii" [Mesh] OR "Mycobacter marinum" [Mesh] OR "Mycobacter scrofulaceum" [Mesh] OR "Mycobacter smegmatis" [Mesh] OR "Mycobacter ulcerans" [Mesh] OR "Mycobacter xenopi" [Mesh])
Embase Jan 31, 2022	678	32	"Bronchiectasis" [Mesh]) AND ("Nontuberculous Mycobacteria" OR "non tuberculous mycobacter" [Mesh]) AND ("Atypical Mycobacter" [Mesh] OR ("Mycobacter abscessus" [Mesh]) OR "Mycobacter avium complex" [Mesh] OR "Mycobacter chelonae" [Mesh] OR "Mycobacter fortuitum" [Mesh] OR "Mycobacter kansasii" [Mesh] OR "Mycobacter marinum" [Mesh] OR "Mycobacter scrofulaceum" [Mesh] OR "Mycobacter smegmatis" [Mesh] OR "Mycobacter ulcerans" [Mesh] OR "Mycobacter xenopi" [Mesh])
Cochrane Library Jan 31, 2022	19	9	Bronchiectasis AND Nontuberculous Mycobacteria" OR "non tuberculous mycobacter
Web of Science Jan 31, 2022	504	70	"nontuberculous mycobacter" OR TOPIC: "non tuberculous mycobacter") OR TOPIC: "Atypical Mycobacter") OR TOPIC: (("Mycobacter abscessus" or "Mycobacter avium complex" OR "Mycobacter chelonae" OR "Mycobacter fortuitum" OR "Mycobacter* kansasii OR "Mycobacter marinum" OR "Mycobacter scrofulaceum" OR "Mycobacter smegmatis" OR "Mycobacter ulcerans" OR "Mycobacter xenopi")) OR TOPIC: "ntm"
Total	1615	111	
Other sources Jan 31, 2022	514		'Nontuberculous Mycobacteria' OR 'non-cystic fibrosis bronchiectasis'; publication date from 2006 to 2021, including citations
111 duplicates were removed to give a total of 2014 studies			

Table S2: Characteristics of studies included in the initial analysis of selected studies

Author; year	Country	Data Source	Time of sampling	Mean age (Y)	Sample size	Patients with NTM	Study design	Method of detection	NTM [%]
1. McShane, et al. 2012 [1]	USA	University Referral Center	2009-2011	≥18	106	9	RS	Sputum culture	8.5
2. Xu, et al. 2014 [2]	China	Pulmonary Hospital	2009-2012	47.4	3857	431	RS	Sputum culture	11.2
3. Guan, et al. 2015 [3]	China	Outpatient Respiratory Clinics	2012-2013	44.6	144	5	PS	Sputum culture	3.5
4. Kadowaki, et al. 2015 [4]	Japan	Medical Center	2008-2012	73	147	26	RS	Sputum culture	17.7
5. Máiz, et al. 2016 [5]	**Spain**	**Teaching hospitals**	**2012-2015**	**55.7**	**218**	**18**	**PS**	**Sputum culture**	**8.3**
6. Izhakian, et al. [6] 2016	Israel	Rabin Medical Center	2006-2014	64	339	29	RS	Bronchoalveolar lavage cultures	8.6
7. Faverio, et al. 2016 [7]	Italy	San Gerardo Hospital	2006-2014	65	162	32	PS	Bronchoalveolar /sputum culture	19.8
8. Buscot, et al. 2016 [8]	France	University Hospital	2002-2012	61.0	196	7	RS	Sputum/ bronchoalveolar lavage culture	3.6
9. Dimakou, et al. 2016 [9]	Greece	Hospital of Chest Diseases	2009-2014	60.5	205	2	PS	Sputum culture	0.9
10.* Park, et al. 2016 [10]	**Korea**	**University Hospital >5 years**	**2003-2013**	**59.6**	**155**	**69**	**RS**	**Sputum/BAL culture**	**44.5**
11.* Aksamit, et al. 2017 [11]	**USA**	**Bronchiectasis Research Registry**	**2008-2014**	**66**	**1,314**	**653**	**RS**	**Sputum culture**	**49.7**
12.* Hsieh, et al. 2018 [12]	**China**	**Bronchiectasis Medical Center**	**2005-2014**	**65.3**	**96**	**35**	**RS**	**Sputum culture**	**36.5**
13. Sin, et al. 2019 [13]	Korea	National University Hospital	2005-2016	59.6	6957	1740	RS	Sputum culture	25
14.* Amorim, et al. 2019 [14]	**Portugal**	**Bronchiectasis Referral Center**	**2011-2017**	**54.7**	**186**	**27**	**PS**	**Sputum culture**	**14.5**
15.* Visser, et al. 2019 [15]	**Australia**	**Australian Bronchiectasis Registry**	**2016-2018**	**71**	**169**	**40**	**PS**	**Sputum culture**	**23.6**
16. Pieters, et al. 2019 [16]	Netherland	University Medical Center	2012-2016	60	120	6	RS	Sputum culture	5.0
17.* Dhar, et al. 2019 [17]	**India**	**bronchiectasis registry**	**2015-2017**	**56**	**1299**	**8**	**PS**	**Sputum culture**	**0.6**

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Author; year	Country	Data Source	Time of sampling	Mean age (Y)	Sample size	Patients with NTM	Study design	Method of detection	NTM [%]
18. Huang, et al. 2020 [18]	China	Medical Record Database	2002-2016	65.5	8385	304	RS	Sputum culture	3.6
19. Darwish, et al. 2020 [19]	Egypt;	University Hospital	2017-2018	55.2	40	3	PS	Sputum PCR	7.5
20.* Kwak, et al. 2020 [20]	**Korea**	**Hospital**	**2011-2019**	**62**	**221**	**35**	**PS**	**Sputum culture**	**15.8**
21. Sharif, et al. 2020 [21]	Pakistan	Hospital	2017-2019	NA	196	2	PS	Sputum culture	1.0
22.* Choate, et al. 2021 [22]	**USA**	**Bronchiectasis & NTM Research Registry**	**2008-2018**	**63.7**	**1831**	**885**	**RS**	**Sputum culture**	**48.3**
23.* Metersky, et al. 2021 [23]	**USA**	**Bronchiectasis & NTM Research Registry**	**NA-2020**	**61.1**	**410**	**47**	**PS**	**Sputum culture**	**11.5**
24.Yin, et al. 2021 [24]	China	Hospital	2018-2020	62	202	47	RS	Sputum/BAL culture	23.3

Abbreviations: NA: Not Available; NTM: Nontuberculous Mycobacteria; MBC: mycobacteria culture; AFB: acid fast bacillus smear; BAL: bronchoalveolar lavage; RS: Retrospective Study; PS: prospective Study; UK: United Kingdom; US: United States. PCR: Polymerase Chain Reaction.

Note: Bold type with an asterisk * indicate the studies with source/selection bias. Please refer to the supplementary Table S3.

Table S3: Ratings of the quality of the evidence and Risk of Bias assessment

Study	Study Design	Domain	Source of bias	Support for Judgement	Review Author's Judgement	Risk of Bias
1. McShane, et al. 2012; US [1]	Retrospective cohort study	Attrition bias	Patient follow-up	Of all 114 patients. Two declined consent, and six patients did not follow up with the evaluation.	Eight patients were not available for the complete analysis.	Low
2. Xu, et al. 2014; Shanghai, China [2]	Retrospective cohort study	Detection bias	Detection bias	Diagnosis criterium was at least one positive culture result of NTM.	Only one positive culture result of NTM may be due to false positive or wrong operation.	Low
3. Guan, et al. 2015; Guangzhou, China [3]	Prospective randomized control cohort study	Selection bias	Patient population	Consecutively recruited from outpatient respiratory clinics.	Mild and severe symptom patients were excluded	Medium
4. Kadowaki, et al. 2015; Japan [4]	Retrospective cohort study	Selection bias	Patient selection	1. Could not perform a full screening for immunodeficiency. 2. Could not eliminate the possibility of cystic fibrosis	1. Patients with immunodeficiency were more vulnerable to NTM infection. 2. CF patients might not be completely excluded.	Low
5.* Máiz, et al. 2016; Spain [5]	**Prospective cohort study**	**Source bias**	**Population selection**	**An observational study of historical cohorts from 4 Spanish teaching hospitals with multidisciplinary and standardized non-CF bronchiectasis outpatient clinics.**	**1. Patients were outpatients, causing severe patients excluded.** **2. No unified standard for patient selection.**	**High**
6. Izhakian，et al. 2016; Israel [6]	Retrospective cohort study	Performance bias; Selection bias	Population selection	1.The study precluded patients not under medical care 2.The study is not generalizable to patients treated by other hospital staff members.	1. Patients were in hospital with severe symptoms, causing outpatients excluded. 2. Patients at the same location but from other hospital were not included.	Medium
7. Faverio, et al. 2016; Italy [7]	Prospective cohort study	Selection bias	Population selection	Data were from outpatient clinic and only patients in a stable state were recruited.	Severe patients were excluded for data analysis.	Medium
8. Buscot, et al. 2016; France [8]	Retrospective cohort study	Attrition bias	Follow-up	Functional follow-up was available in 30% of patients with a median duration of 2.7 years.	Only 30% of patients could be followed up, cause attrition bias.	Low
9. Dimakou, et al. 2016; Greece [9]	Prospective cohort study	Detection bias	Detection methods	CF screening, sweat test, saccharin test, and electron microscopy and etc. were employed for patients with different symptoms.	A standard detection method is better for diagnosis and study.	Low

Study	Design	Bias Domain	Source of bias	Support for Judgement	Review Author's Judgement	Risk of Bias
10.* Park et al. 2016; Korean [10]	**Retrospective cohort study**	**Source bias**	**Patient selection**	**The author only included the Non-CF bronchiectasis patients with followed- up for a minimum of 5 years with CT.**	**The patients were not selected randomly, but have been sick for more than 5 years, causing an overestimate of the prevalence of NTM.**	**High**
11.* Aksamit, *et al.* 2017; US [11]	**Retrospective cohort study**	**Source bias**	**Data source**	**Data was from Bronchiectasis Research Registry (BRR).**	**The cohort of patients enrolled from tertiary referral institutions with interest in NTM lung disease, the demographic information described is potentially biased, including overrepresentation of patients with NTM.**	**High**
12.* Hsieh, et al. 2018; Taiwan, China [12]	**Retrospective cohort study**	**Source bias; Selection bias**	**Data source and sample size**	**1. All 96 patients were from Linkou Medical Center. Patients with previous pulmonary tuberculosis and those who had received anti-NTM therapy were excluded. 2. Small sample population (<100).**	**Cases from medical center have source bias; Exclusion of some patients causes selection bias.**	**High**
13. Sin, et al. 2019; South Korea [13]	Retrospective controlled cohort study	Detection bias	False positive	They diagnosed by the isolation of NTM from a respiratory specimen at least once.	Isolation of NTM only once may increase the prevalence due to false positive, causing higher infection rates.	Medium
14.* Amorim, et al. 2019; Portugal [14]	**Prospective cohort study**	**Source bias; performance bias**	**Patient selection and sample size**	**1. The data was from a bronchiectasis referral center. 2. The sample size is lower than 200.**	**Cases from a bronchiectasis referral center have source bias; lower sample size increased the prevalence of NTM.**	**High**
15.* Visser, et al. 2019; Australia [15]	**Prospective cohort study**	**Selection bias; Attrition bias**	**Patient selection Incomplete and missing data**	**1. Potentially selects patients with prominent symptoms, more severe disease, and/or a higher prevalence of NTM. 2. predominantly represents non-indigenous patients 3. Patients with missing variable data were removed.**	**1. Severe patients with prominent symptoms may cause a higher prevalence of NTM. 2. Non-indigenous patients did not represent the whole population 3. Data completeness limits the number of participants.**	**High**
16. Pieters et al. 2019; Netherland [16]	Retrospective cohort study	Performance bias	Incomplete data	The majority of patients were seen every 3 months at the outpatient clinic.	Not all the patients were seen every 3 months at the outpatient clinic.	Low

Study	Design	Bias Domain	Source of bias	Support for Judgement	Review Author's Judgement	Risk of Bias
17.* Dhar, et al. 2019; India [17]	**Prospective cohort study**	**Source Bias**	**Patient selection**	**All the patients were from Indian bronchiectasis registry centers.**	**Patients from registry centers would inevitably cause an overestimation of the prevalence of NTM infections.**	**High**
18. Huang, et al. 2020; Taiwan, China [18]	Retrospective cohort study	Source bias; Detection bias	Patient Selection	1. Inability to completely confirm the bronchiectasis diagnosis. 2. A portion of bronchiectasis diagnoses based on clinical symptoms and chest radiographs, not a reliable diagnostic tool. 3. underestimated the prevalence of immunodeficiency in our cohort.	Some patients might not be bronchiectasis; immunodeficiency may cause high prevalence due to vulnerability.	Medium
19. Darwish, et al. 2020; Egypt [19]	Prospective cohort study	Detection bias Performance bias	NTM were detected by PCR Too small sample size	1. The sputum samples were assessed by PCR, and positive cases did another PCR after 2 months. 2. Sample size 40 < 200	PCR may cause false positive. The only study (of all 13 studies) NTM was not diagnosed by MBC; Small sample size increased prevalence	Medium
20.* Kwak, et al. 2020; South Korea [20]	**Prospective cohort study**	**Source Bias**	**Patient selection**	**Only the patients without NTM infection were included, and then studied their NTM infection afterwards.**	**The patients are not random cases.**	**High**
21. Sharif, et al. 2020; Pakistan [21]	Prospective cohort study	Source bias	Patient selection	This observational cohort study was conducted in the inpatient department only.	Inpatients were usually with severe symptoms, and that may cause overestimation.	Low
22.* Choate, et al. 2021; US [22]	**Retrospective cohort study**	**Source Bias**	**Patient selection**	**All the patients were from the bronchiectasis and NTM Research Registry (BRR).**	**Patients from registry centers would cause an overestimation of the prevalence of NTM infections.**	**High**
23.* Metersky et al. 2021; US [23]	**Prospective cohort study**	**Source Bias**	**Patient selection**	**All the patients were from the bronchiectasis and NTM Research Registry (BRR).**	**Patients from registry centers would cause an overestimation of the prevalence of NTM infections.**	**High**
24. Yin, et al. 2021; China [24]	Retrospective cohort study	Performance bias	Patient information collection	Much patient information was self-reported and recorded.	The self-reported information might be inaccurate and hidden.	low

Note: Bold type with an asterisk * indicate the studies with source/selection bias.

Table S4: Statistics and calculation of NTM subspecies

Subspecies of NTM	Number of Studies	All NTM Isolated Patient*	Patients with NTM subspecies	% of NTM Subspecies **	McShane	Kadowaki	Máiz	Izhakian	Faverio	Kwak	Darwish	Buscot	Dimakou	Metersky	Yin	% of NTM Isolated patients
MAC	11	255	193	**75.687**	7	28	9	14	24	29	2	7	2	40	31	
M. simiae	3	56	10	**17.857**	1		1	8								
M. gordonae	3	59	7	**11.864**	1		2		4							
M. xenopi	1	9	1	**11.111**	1											
M. fortuitum	4	103	7	**6.796**	1		2	2						2		
M. abscessus	6	208	21	**10.096**			3	3	1	3				1	10	
M. chelonae	6	182	11	**6.044**	1		1	2	2					2	3	
M. lentiflavum	1	18	1	**5.556**			1									
M. kansasii	3	88	5	**4.88**	1				1						3	
M. terrae	1	47	1	**2.128**										1		
M. shimoidei	1	32	1	**3.125**					1							
Undetermined	3	82	6	**7.317**						4	1			1		
Sum (person)	**7**	**1139**			**9**	**26**	**18**	**29**	**32**	**35**	**3**	**7**	**2**	**47**	**47**	
sum (time)					**13**	**28**	**19**	**29**	**33**	**36**	**3**	**7**	**2**	**47**	**47**	
Bronchiectasis Patients					**106**	**147**	**218**	**339**	**162**	**221**	**40**	**196**	**205**	**410**	**202**	**50.712**

Note: Of all 14 included studies, only 9 provided detection methods of NTM subspecies. *The number of all NTM is the sum of all the patients in the studies with the subspecies. **The percentage (%) of NTM infected patients is the sum of all patients with NTM infection divided by the sum of all bronchiectasis patients in all the 9 studies.

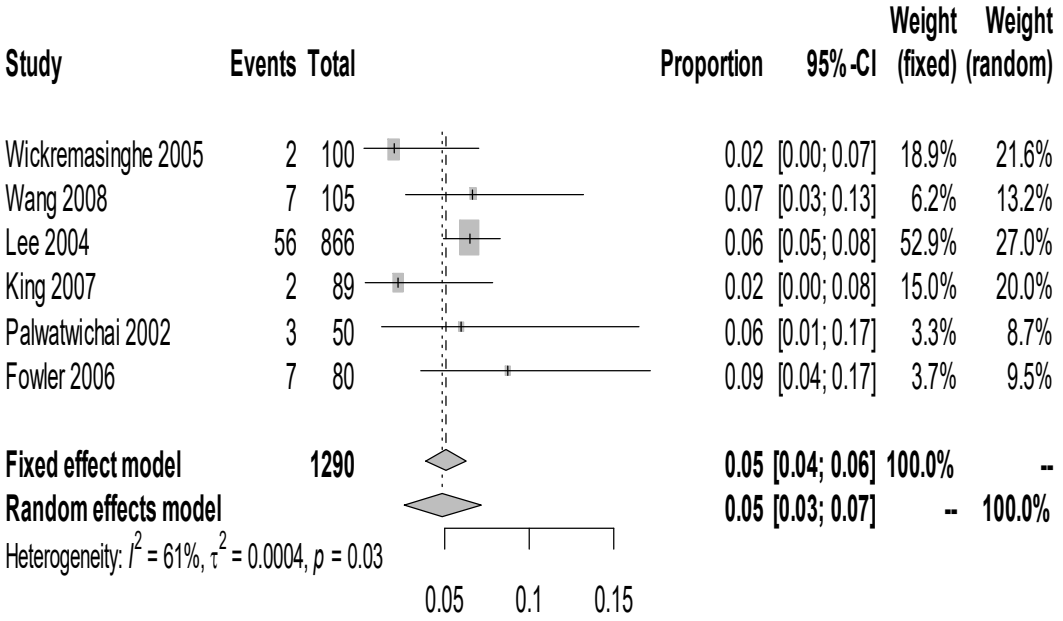

Figure S1: Re-calculating the prevalence of NTM in adults with non-cystic fibrosis bronchiectasis from 1990 to 2006 in Chu's paper "Prevalence of nontuberculous mycobacteria in patients with bronchiectasis: A meta-analysis" published in 2014 [25].

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