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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.

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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 microorganisms, 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
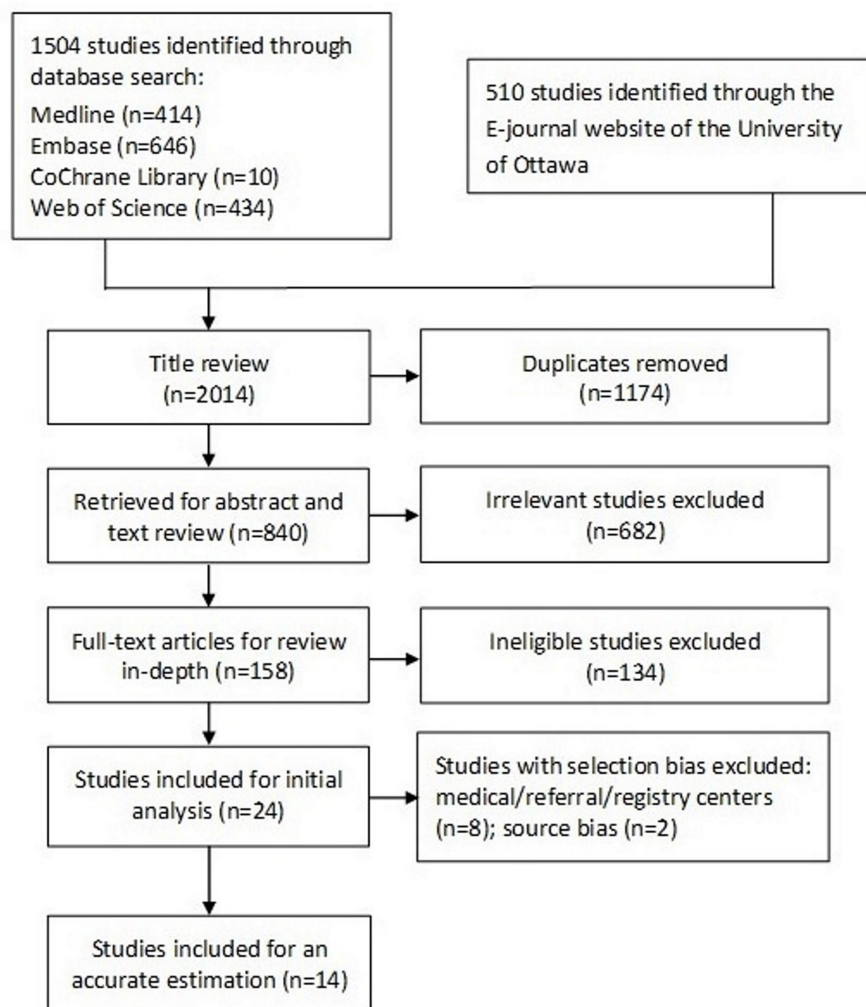

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.
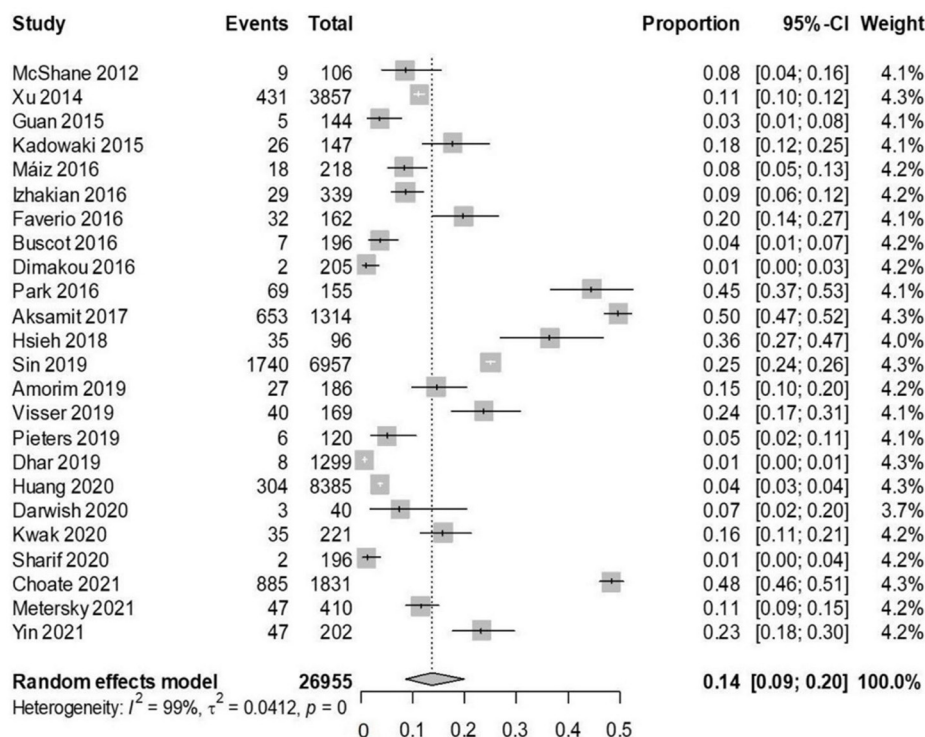
Figure 2 Forest plot of all included 24 studies from the systematic review.

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
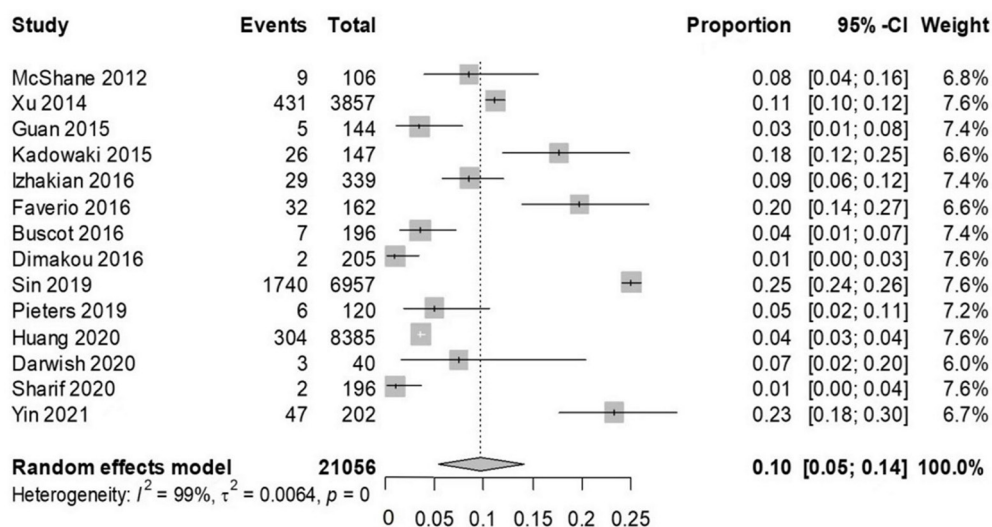

Study	Events	Total	Proportion	95% -CI	Weight
McShane 2012	9	106	0.08	[0.04; 0.16]	6.8%
Xu 2014	431	3857	0.11	[0.10; 0.12]	7.6%
Guan 2015	5	144	0.03	[0.01; 0.08]	7.4%
Kadowaki 2015	26	147	0.18	[0.12; 0.25]	6.6%
Izhakian 2016	29	339	0.09	[0.06; 0.12]	7.4%
Faverio 2016	32	162	0.20	[0.14; 0.27]	6.6%
Buscot 2016	7	196	0.04	[0.01; 0.07]	7.4%
Dimakou 2016	2	205	0.01	[0.00; 0.03]	7.6%
Sin 2019	1740	6957	0.25	[0.24; 0.26]	7.6%
Pieters 2019	6	120	0.05	[0.02; 0.11]	7.2%
Huang 2020	304	8385	0.04	[0.03; 0.04]	7.6%
Darwish 2020	3	40	0.07	[0.02; 0.20]	6.0%
Sharif 2020	2	196	0.01	[0.00; 0.04]	7.6%
Yin 2021	47	202	0.23	[0.18; 0.30]	6.7%
Random effects model		**21056**	**0.10**	**[0.05; 0.14]**	**100.0%**

Heterogeneity: I^2 = 99%, τ^2 = 0.0064, p = 0

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
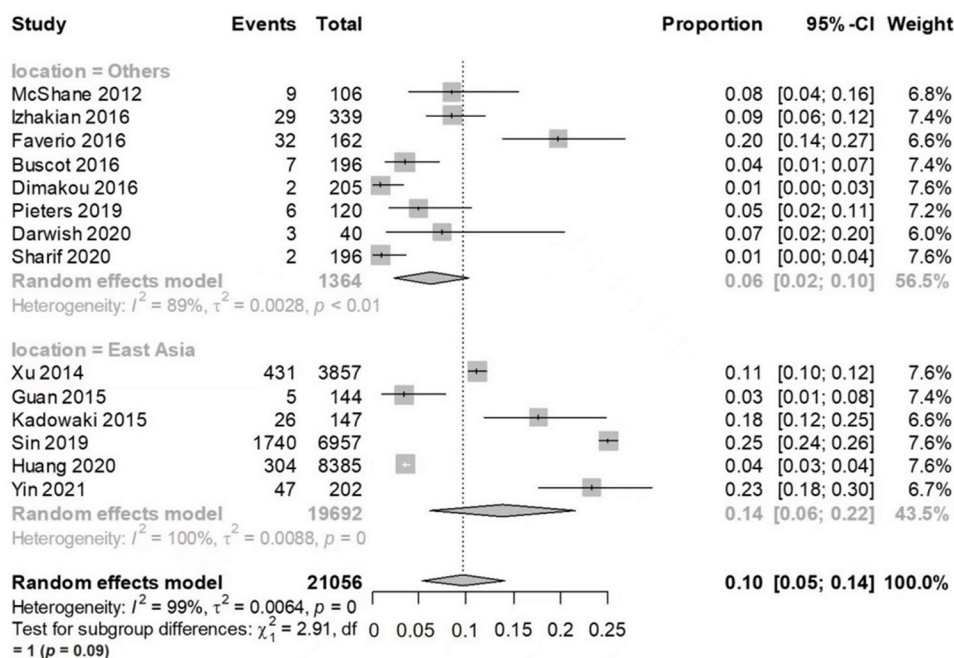

Figure 4 Forest plot for subgroup analysis by geographical location.

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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REFERENCES

1 Weycker D, Hansen GL, Seifer FD. Prevalence and incidence of noncystic fibrosis bronchiectasis among US adults in 2013. *Chron Respir Dis* 2017;14:377–84.
2 Quint JK, Millett ERC, Joshi M, *et al*. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *Eur Respir J* 2016;47:186–93.
3 Martinez-Garcia MA, Polverino E, Aksamit T. Bronchiectasis and Chronic Airway Disease: It Is Not Just About Asthma and COPD. *Chest* 2018;154:737–9.
4 Nicotra MB, Rivera M, Dale AM, *et al*. Clinical, pathophysiologic, and microbiologic characterization of bronchiectasis in an aging cohort. *Chest* 1995;108:955–61.
5 Griffith DE, Aksamit TR. Bronchiectasis and nontuberculous mycobacterial disease. *Clin Chest Med* 2012;33:283–95.
6 Lopeman RC, Harrison J, Desai M, *et al*. *Mycobacterium abscessus*: environmental bacterium turned clinical nightmare. *Microorganisms* 2019;7:90.
7 Cowman S, Wilson R, Loebinger MR. Opportunistic mycobacterial diseases. *Medicine* 2016;44:390–2.
8 Falkinham JO. Mycobacterial aerosols and respiratory disease. *Emerg Infect Dis* 2003;9:763–7.
9 Lapinel NC, Jolley SE, Ali J, *et al*. Prevalence of non-tuberculous mycobacteria in HIV-infected patients admitted to hospital with pneumonia. *Int J Tuberc Lung Dis* 2019;23:491–7.
10 Weiss CH, Glassroth J. Pulmonary disease caused by nontuberculous mycobacteria. *Expert Rev Respir Med* 2012;6:597–613.
11 Shteinberg M, Stein N, Adir Y, *et al*. Prevalence, risk factors and prognosis of nontuberculous mycobacterial infection among people with bronchiectasis: a population survey. *Eur Respir J* 2018;51:1702469.
12 Park Y, Kim CY, Park MS, *et al*. Age- and sex-related characteristics of the increasing trend of nontuberculous mycobacteria pulmonary disease in a tertiary hospital in South Korea from 2006 to 2016. *Korean J Intern Med* 2020;35:1424–31.
13 Chang AB, Fortescue R, Grimwood K, *et al*. European respiratory Society guidelines for the management of children and adolescents with bronchiectasis. *Eur Respir J* 2021;58:2002990.
14 Pierre-Audigier C, Ferroni A, Sermet-Gaudelus I, *et al*. Age-related prevalence and distribution of nontuberculous mycobacterial species among patients with cystic fibrosis. *J Clin Microbiol* 2005;43:3467–70.
15 Andréjak C, Nielsen R, Thomsen Vibeke Ø, *et al*. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. *Thorax* 2013;68:256–62.
16 Lee G, Lee KS, Moon JW, *et al*. Nodular bronchiectatic Mycobacterium avium complex pulmonary disease. Natural course on serial computed tomographic scans. *Ann Am Thorac Soc* 2013;10:299–306.
17 Aksamit TR, O'Donnell AE, Barker A, *et al*. Adult patients with bronchiectasis: a first look at the US bronchiectasis research registry. *Chest* 2017;151:982–92.
18 Máiz L, Girón R, Olveira C, *et al*. Prevalence and factors associated with nontuberculous mycobacteria in non-cystic fibrosis bronchiectasis: a multicenter observational study. *BMC Infect Dis* 2016;16:1–7.
19 Sin S, Yun SY, Kim JM, *et al*. Mortality risk and causes of death in patients with non-cystic fibrosis bronchiectasis. *Respir Res* 2019;20:271.
20 Hoefsloot W, van Ingen J, Andrejak C, *et al*. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. *Eur Respir J* 2013;42:1604–13.
21 Chandrasekaran R, Mac Aogáin M, Chalmers JD, *et al*. Geographic variation in the aetiology, epidemiology and microbiology of bronchiectasis. *BMC Pulm Med* 2018;18:83.
22 Kamada K, Yoshida A, Iguchi S, *et al*. Geographical distribution and regional differences in 532 clinical isolates of rapidly growing mycobacterial species in Japan. *Sci Rep* 2021;11:4960.
23 Chu H, Zhao L, Xiao H, *et al*. Prevalence of nontuberculous mycobacteria in patients with bronchiectasis: a meta-analysis. *Arch Med Sci* 2014;10:661–8.
24 Stephenson D, Perry A, Appleby MR, *et al*. An evaluation of methods for the isolation of nontuberculous mycobacteria from patients with cystic fibrosis, bronchiectasis and patients assessed for lung transplantation. *BMC Pulm Med* 2019;19:2.
25 Ranganathan P, Aggarwal R. Study designs: part 1-an overview and classification. *Perspect Clin Res* 2018;9:184–6.
26 Stout JE, Koh W-J, Yew WW. Update on pulmonary disease due to non-tuberculous mycobacteria. *Int J Infect Dis* 2016;45:123–34.
27 van Ingen J. Microbiological diagnosis of nontuberculous mycobacterial pulmonary disease. *Clin Chest Med* 2015;36:43–54.
28 Faverio P, Stainer A, Bonaiti G. Characterizing non-tuberculous mycobacteria infection in bronchiectasis. Int J Mol Sci 1913;2016:17.
29 Visser SK, Bye PTP, Fox GJ, *et al*. Australian adults with bronchiectasis: the first report from the Australian bronchiectasis registry. *Respir Med* 2019;155:97–103.
30 Bonaiti G, Pesci A, Marruchella A, *et al*. Nontuberculous mycobacteria in noncystic fibrosis bronchiectasis. *Biomed Res Int* 2015;2015:197950
31 Horne D, Skerrett S. Recent advances in nontuberculous mycobacterial lung infections. *F1000Res* 2019;8:1710–8.
32 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928–9.

33 Park J, Kim S, Lee YJ, *et al*. Factors associated with radiologic progression of non-cystic fibrosis bronchiectasis during long-term follow-up. *Respirology* 2016;21:1049–54.

34 Hsieh M-H, Lin C-Y, Wang C-Y, *et al*. Impact of concomitant nontuberculous mycobacteria and *Pseudomonas aeruginosa* isolates in non-cystic fibrosis bronchiectasis. *Infect Drug Resist* 2018;11:1137–43.

35 Choate R, Aksamit TR, Mannino D, *et al*. Pseudomonas aeruginosa associated with severity of non-cystic fibrosis bronchiectasis measured by the modified bronchiectasis severity score (BSI) and the FACED: the US bronchiectasis and NTM research registry (BRR) study. *Respir Med* 2021;177:106285.

36 Amorim A, Meira L, Redondo M, *et al*. Chronic bacterial infection prevalence, risk factors, and characteristics: a bronchiectasis population-based prospective study. *J Clin Med* 2019;8:315.

37 Dhar R, Singh S, Talwar D, *et al*. Bronchiectasis in India: results from the European multicentre bronchiectasis audit and research collaboration (EMBARC) and respiratory research network of India registry. *Lancet Glob Health* 2019;7:e1269–79.

38 Metersky ML, Choate R, Addrizzo-Harris D, Bronchiectasis and NTM Research Registry Investigators. The association of long-term macrolide therapy and nontuberculous mycobacterial culture positivity in patients with bronchiectasis. *Chest* 2021;160:466–9.

39 Aksamit TR, Choate R, O'Donnell AE. United States bronchiectasis registry longitudinal follow up at two years. *Am J Respir Crit care Med Conf Am Thorac Soc Int Conf ATS* 2017;195.

40 Shteinberg M, Nassrallah N, Jrbashyan J, *et al*. Upper airway involvement in bronchiectasis is marked by early onset and allergic features. *ERJ Open Res* 2018;4:00115-2017 doi:10.1183/23120541.00115-2017

41 Kwak N, Lee JH, Kim H-J, *et al*. New-onset nontuberculous mycobacterial pulmonary disease in bronchiectasis: tracking the clinical and radiographic changes. *BMC Pulm Med* 2020;20:293.

42 Falkinham 3rd JO. nontuberculous mycobacteria in the environment. *Clin Chest Med* 2002;23:529–51.

43 Fowler SJ, French J, Screaton NJ, *et al*. Nontuberculous mycobacteria in bronchiectasis: prevalence and patient characteristics. *Eur Respir J* 2006;28:1204–10.

44 Koh W-J, Lee KS, Kwon OJ, *et al*. Bilateral bronchiectasis and bronchiolitis at thin-section CT: diagnostic implications in nontuberculous mycobacterial pulmonary infection. *Radiology* 2005;235:282–8.

45 Tabarsi P, Baghaei P, Farnia P, *et al*. Nontuberculous mycobacteria among patients who are suspected for multidrug-resistant tuberculosis—need for earlier identification of nontuberculosis mycobacteria. *Am J Med Sci* 2009;337:182–4.

46 Tabarsi P, Baghaei P, Farnia P, *et al*. Nontuberculous mycobacteria among patients who are suspected for multidrug-resistant tuberculosis-need for earlier identification of nontuberculosis mycobacteria. *Am J Med Sci* 2009;337:182–4.

47 Faverio P, Stainer A, Bonaiti G, *et al*. Characterizing non-tuberculous mycobacteria infection in bronchiectasis. *Int J Mol Sci* 2016;17:16.

48 Mirsaeidi M, Hadid W, Ericsoussi B, *et al*. Non-tuberculous mycobacterial disease is common in patients with non-cystic fibrosis bronchiectasis. *Int J Infect Dis* 2013;17:e1000–4.

49 Wickremasinghe M, Ozerovitch LJ, Davies G, *et al*. Non-tuberculous mycobacteria in patients with bronchiectasis. *Thorax* 2005;60:1045–51.

50 Bicmen C, Gunduz AT, Coskun M, *et al*. Molecular detection and identification of Mycobacterium tuberculosis complex and four clinically important nontuberculous mycobacterial species in smear-negative clinical samples by the genotype mycobacteria direct test. *J Clin Microbiol* 2011;49:2874–8.

51 Griffith DE, Aksamit T, Brown-Elliott BA, *et al*. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007;175:367–416.

52 McShane PJ, Naureckas ET, Strek ME. Bronchiectasis in a diverse US population. *Chest* 2012;142:159–67.

53 J-F Xu, X-B Ji, Fan L-C. Nontuberculous mycobacteria lung infection in bronchiectasis in China: prevalence and clinical characteristics. *Am J Respir Crit Care Med* 2014:D109.

54 Guan W-J, Gao Y-H, Xu G, *et al*. Aetiology of bronchiectasis in Guangzhou, southern China. *Respirology* 2015;20:739–48.

55 Kadowaki T, Yano S, Wakabayashi K, *et al*. An analysis of etiology, causal pathogens, imaging patterns, and treatment of Japanese patients with bronchiectasis. *Respir Investig* 2015;53:37–44.

56 Izhakian S, Wasser WG, Fuks L, *et al*. Lobar distribution in non-cystic fibrosis bronchiectasis predicts bacteriologic pathogen treatment. *Eur J Clin Microbiol Infect Dis* 2016;35:791–6.

57 Buscot M, Pottier H, Marquette C-H, *et al*. Phenotyping adults with non-cystic fibrosis bronchiectasis: a 10-year cohort study in a French regional university hospital center. *Respiration* 2016;92:1–8.

58 Dimakou K, Triantafillidou C, Toumbis M, *et al*. Non CF-bronchiectasis: Aetiologic approach, clinical, radiological, microbiological and functional profile in 277 patients. *Respir Med* 2016;116:1–7.

59 Pieters A, Bakker M, Hoek RAS, *et al*. Predicting factors for chronic colonization of Pseudomonas aeruginosa in bronchiectasis. *Eur J Clin Microbiol Infect Dis* 2019;38:2299–304.

60 Huang H-Y, Chung F-T, Lo C-Y, *et al*. Etiology and characteristics of patients with bronchiectasis in Taiwan: a cohort study from 2002 to 2016. *BMC Pulm Med* 2020;20:45.

61 Darwish A, Mahalawy E I, El Dahdouh S. Nontuberculous Mycobacterium as a hidden cause of noncystic fibrosis bronchiectasis. *Egypt J Chest Dis Tuberc* 2020;69:46.

62 Sharif N, Baig MS, Sharif S, *et al*. Etiology, clinical, radiological, and microbiological profile of patients with non-cystic fibrosis bronchiectasis at a tertiary care hospital of Pakistan. *Cureus* 2020;12.

63 Yin H, Gu X, Wang Y, *et al*. Clinical characteristics of patients with bronchiectasis with nontuberculous mycobacterial disease in mainland China: a single center cross-sectional study. *BMC Infect Dis* 2021;21:1216.