Prevalence of nontuberculous mycobacteria in patients with bronchiectasis: a meta-analysis

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Abstract

Introduction: Nontuberculous mycobacteria (NTM) have emerged as critical opportunistic pathogens of lung diseases recently. Patients with preexisting bronchiectasis are susceptible to NTM. Nevertheless, patients with preexisting bronchiectasis are susceptible to NTM but the prevalence of NTM pulmonary infection in different species and geographical areas is still not fully understood.

Material and methods: The relevant data of the prevalence of NTM in patients with bronchiectasis were retrieved by searching the main databases such as PubMed, MEDLINE, Cochrane Library, and EMBASE. This meta-analysis was performed using Rev. Man 5.1 and Stata 11.0 software. The collected information of NTM prevalence was chosen as the effect size.

Results: The results of the meta-analysis showed that the overall prevalence of NTM was 9.3% in patients with bronchiectasis. The further stratification of subgroup analysis indicated that the combined prevalence of NTM was higher in studies whose "sample size" was more than or equal to 100 ($p = 0.002$), in studies in which "time of study" was after or equal to 2002 ($p < 0.001$), in studies in which "participants' geographic location" was Asian ($p < 0.001$) and in studies whose "method of study" was retrospective ($p = 0.002$) as well, compared with corresponding groups.

Conclusions: Our findings suggested that the prevalence NTM infection is high in patients with bronchiectasis. A larger number of definitive randomized trials are still required to assess this research issue.

Key words: bronchiectasis, nontuberculous mycobacteria, prevalence, meta-analysis.

Introduction

Bronchiectasis is defined pathologically as abnormal and irreversible dilatation of the bronchi, with the potential to cause devastating illness including chronic productive cough, airway obstruction, shortness of breath and recurrent infections [1]. There is usually an initial event which causes impairment of mucociliary clearance of the bronchial tree. The respiratory tract becomes colonized by bacteria that inhibit ciliary function and promote further lung damage by the host's immune system [2]. Non-

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tuberculous mycobacteria (NTM) are ubiquitous environmental organisms that sometimes cause respiratory disease [3, 4]. Because person-to-person transmission has been less reported, it has been proposed that the environment is the major source of NTM infection [5]. Representatives of many species, such as *Mycobacterium avium*, *M. fortuitum* and *M. chelonae*, have been recovered from environmental samples (e.g., water and soil) [6]. Moreover, DNA fingerprints have been shown to be identical between patient and environmental isolates [7]. Of the NTM species, mycobacterium avium complex (MAC) is one of the most common pathogens of NTM pulmonary infection [8]. Levin has suggested that the combination of bronchiectasis and parenchymal nodules had an overall sensitivity of 80% and a specificity of 87% for positive MAC culture and patients with bronchiectasis are predisposed to infection with NTM [9].

As several studies have reported an increasing incidence of NTM in patients with bronchiectasis, recently [10–12], it is therefore important to investigate whether differences of NTM species and geographical area influence NTM prevalence in patients with bronchiectasis. Environmental habitats occupied by nontuberculous mycobacteria are also shared by humans, and the number of individuals with heightened susceptibility to mycobacterial disease is growing (e.g., through immunosuppression) [13]. It is therefore important to investigate whether a geographical difference is associated with NTM prevalence. To date, no systematic reviews regarding these patients are available.

In the present study, we conducted a systematic review of published findings and used meta-analysis techniques to quantitatively combine results of NTM prevalence in patients with bronchiectasis.

Material and methods

Source of materials

This meta-analysis was performed based on the Quality of Reporting of Meta-analyses guidelines [14].

We searched multiple electronic bibliographic databases without language restriction, including PubMed, MEDLINE and EMBASE, Springer, Elsevier Science Direct, Cochrane Library and Google Scholar (literature was published up to December 2012). The key words of "bronchiectasis", "bronchiectasis", "nontuberculous mycobacterium", "NTM", "non-tuberculosis mycobacterial", "mycobacterium", "study" and "trial" were used for searching. Meanwhile, references from retrieved papers were checked for any additional study. We only recruited full-published papers, not any meeting or conference abstracts.

Inclusion and exclusion criteria of studies

Inclusion criteria of studies mainly comprised: 1) an investigation for patients with bronchiectasis (prospective studies, retrospective studies or cross-sectional studies, etc.); 2) the definition of bronchiectasis; 3) the effect size of the prevalence of NTM; 4) sample size ≥ 50; 5) papers that were published before 2012. In addition, we excluded studies if they only described NTM data unassociated with bronchiectasis, were reduplicated studies or records, or did not calculate the prevalence of NTM in the patients of bronchiectasis.

Search methods

Two investigators independently searched the electronic databases. An independent PubMed and MEDLINE search was done (by LZ and HX) with the same method. An independent Springer and Elsevier Science Direct search was done (by ZZ and JZ) with the same method. An independent Cochrane Library and Google Scholar search was done (by TG and SG) with the same method. The abstracts were reviewed independently by two investigators (by LZ and ZZ) to determine if they met eligibility criteria for inclusion. References in the studies were reviewed (by HX and JZ) to identify additional studies. Where discrepancies occurred, a third investigator (TG) did additional assessment.

Evaluation of quality and extraction of data

Evaluation of quality mainly included methods of studies, sample size, and recruitment of respondents. Initial screening was done by reading the document title and abstract, then reading the full text of papers for secondary screening, to determine whether studies were included according to inclusion criteria finally. Two investigators independently completed this course, if there were any discrepancies, by means of discussion in order to reach an agreement.

We developed and modified a data abstraction form after a training exercise for investigators. Data items were study details (e.g., the first author's name, year of study, year of publication, location of participants, method of studies), characteristics of participants (e.g., age, sample size), and the prevalence of NTM in the patients of bronchiectasis. Two investigators (LZ and JZ) extracted the data independently using the standard protocol and the result was reviewed by a third investigator (HX). We contacted the authors of the studies included to obtain further information for data items that needed clarification. Discrepancies were resolved by discussion with our research team or contract with original investigators, who were all sent data extraction sheets with requests

for correction. We recorded the first author's name, time of study, time of publication, country, geographic location, sample size, age, study method and the prevalence of NTM.

Meta-analysis methods

The meta-analysis combined the prevalence of NTM in the patients of bronchiectasis, and then studies stratified by sample size, time of study, participants' geographic location and method of study, using subgroup analysis.

The meta-analysis was performed in fixed and random effect models. The point estimates of effect size, the prevalence of NTM, and its 95% confidence interval (95% CI) were estimated for each study. We assessed the within- and between-study variation or heterogeneity by testing Cochran's Q-statistic [15]. This heterogeneity test assessed the null hypothesis that all studies were evaluating the same effect. A significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies, and then the random effect model was used for meta-analysis as well as to take into account the possibility of heterogeneity between studies. Otherwise, the fixed effect model was used. The fixed effect model assumes that all of the studies estimate the same underlying effect and considers only within-study variation. We also quantified the effect of heterogeneity using $I^2 = 100\% \times (Q - df)/Q$ [16]. The I^2-statistic measures the degree of inconsistency in the studies by calculating what percentage of the total variation across studies results from heterogeneity rather than by chance.

The overall or pooled estimate of effect size (the prevalence of NTM) was obtained using the Mantel and Haenszel method in the fixed effect model [17] and using the DerSimonian and Laird method in the random effect model [18]. The calculation of the pooled effect size in the meta-analysis was performed weighting individual effect sizes by the inverse of their variance. The significance of the pooled effect size was determined by the Z-test.

Evaluation of publication bias

Egger's linear regression test was used to measure the asymmetry of the funnel plot. If there is asymmetry, with smaller studies showing effects that differ systematically from larger studies, the regression line will not run through the origin. The intercept α provides a measure of asymmetry – the larger its deviation from zero, the more pronounced the asymmetry. Funnel plots were used to detect publication bias, but they required a range of studies of varying sizes and subjective judgment, and thus we evaluated publication bias using Egger's linear regression test [19], which measures funnel plot asymmetry on the natural logarithm scale of the effect size.

Analyses were performed using the software Review Manager 5.1 (Cochrane Collaboration, http://ims.cochrane.org/revman) and the STATA software package v. 11.0 (Stata Corporation, College Station, TX, USA). All the p values were two sided. A p value less than 0.05 was considered statistically significant. In order to test the reliability of the results, we also performed the sensitivity analysis after removal of the biggest [20] or smallest [21] sample size of studies or the study with the biggest prevalence of NTM [22] to repeat the meta-analysis.

Results

Characteristics of eligible studies

The study selection process is shown in Figure 1. Initially, the electronic searches yielded 6012 items (PubMed: 2057; MEDLINE: 1505; Springer: 968; Elsevier Science Direct: 782; Cochrane Library: 68; Google Scholar: 632), of which 662 studies were removed because of duplication. In addition, 640 of these articles were excluded on the basis of the title and abstract (88 were review articles; 132 not bronchiectasis; 420 did not report NTM prevalence data). Fourteen of the remaining 22 studies were excluded upon a full text search (11 for only NTM data reported but not for bronchiectasis; 3 due to data not available).

Eight eligible studies [20–27] were recruited in the meta-analysis, and the characteristics of included studies are summarized in Table I. Trial participants were aged 13–88 years. Geographic location included Europe, Asia and Australia and
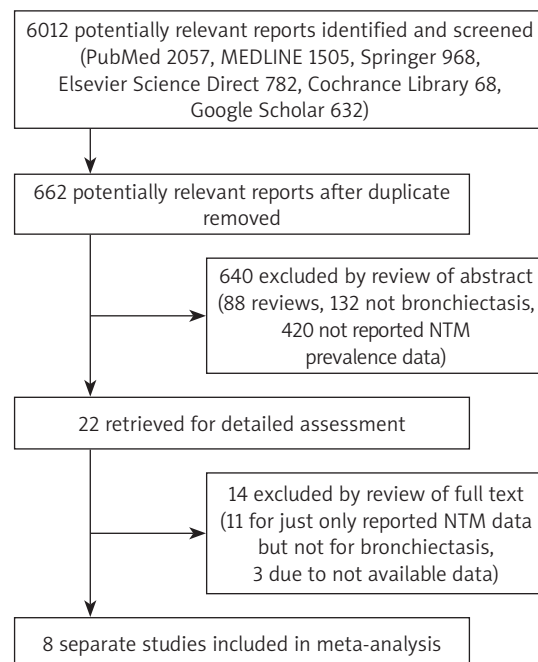

Figure 1. Flow diagram for selecting a study for meta-analysis

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Table I. Characteristics of studies included in the meta-analysis

Study	Time of study	Publication [years]	Country	Sample size	Age [years]	Method of study	Definition of NTM growth rate	NTM [%]
Wickremasinghe, et al. [21]	1991–2001	2005	United Kingdom	100	26–85	RS	MAC culture positive	2.0
Wang, et al. [20]	2001–2006	2008	China	105	13–76	RS	NTM other species positive	6.7
Lee, et al. [16]	2002	2004	South Korea	866	59*	RS	NTM other species positive	8.1
King, et al. [23]	1990–2004	2007	Australia	89	57*	PS	MAC culture positive	2.0
Koh, et al. [18]	2000–2002	2005	South Korea	105	17–88	RS	NTM other species positive	30
Palwatwichai, et al. [17]	1998–1999	2002	Thailand	50	30–85	PS	NTM other species positive	6.0
Fowler, et al. [19]	2002–2003	2006	United Kingdom	98	59*	PS	NTM other species positive	10.2
Tabarsi, et al. [22]	2002–2006	2009	Iran	79	22–70	Undescribed	NTM other species positive	15.2

*Mean age; NTM – nontuberculous mycobacteria, RS – retrospective study, PS – prospective study

the majority of participants were of east Asian (75.4%). The prevalence of NTM was detected from 2.0% to 34.3% among patients with bronchiectasis. We performed subgroup analysis on the basis of simple size, time of study, participants' geographic location, method of study and different species of NTM. In addition, diagnostic methods for NTM mainly included sputum examination, *Haemophilus influenza* examination and chest CT scan. NTM growing rate was defined as positive MAC isolates as well as positive sputum cultures for NTM species.

Overall effects

A total of 8 separate studies, consisting of 1492 bronchiectasis patients, were included in this meta-analysis. The heterogeneity test showed that there were heterogeneities between studies ($Q^2 = 64.62$, $I^2 = 89.2\%$, $p < 0.01$), so we used the random effect model to combine the prevalence of NTM. The overall meta-analysis indicated that the combined prevalence of NTM was 9.3% (95% CI 5.0–13.6%) in patients with bronchiectasis (Figure 2). Publication bias was assessed by inspection of the funnel plot. For NTM prevalence, the distribution of studies was asymmetrical, explaining that publication bias may exist in this meta-analysis (Figure 3). However, the results of Egger's linear regression test did not show there was publication bias in this study ($t = 1.27$, $p > 0.05$) (Table II).

Subgroup analyses for NTM prevalence in bronchiectasis

We performed a subgroup analysis that was stratified by sample size, time of study, participants' geographic location and method of study. The further stratification of subgroup analysis indicated that the pooled prevalence of NTM was higher when sample size ≥ 100 compared to sample size < 100 (1.1%, 95% CI (4.1–18.2%) vs. 7.7% 95% CI (1.8–13.6%)). The analysis of study time indicated that the combined prevalence was lower before 2002 (2.8%, 95% CI (0.4–0.6%) vs. 9.6%, 95% CI (6.2–13.1%)). The geographical difference of NTM illustrated that participants in Asia were more likely to be infected by NTM than those in Europe (13.1%, 95% CI (6.3–19.9%) vs. 5.6%, 95% CI (2.3–13.6%)). Furthermore, prevalence of NTM was higher when the method of study was retrospective compared to prospective (5.5%, 95% CI (0.4–10.7%) vs. 11.1%, 95% CI (4.1–18.2%)) (Table III).

Subgroup analyses for different species of NTM

Subgroup analysis of different NTM species is illustrated in Table III. The two most prevalent
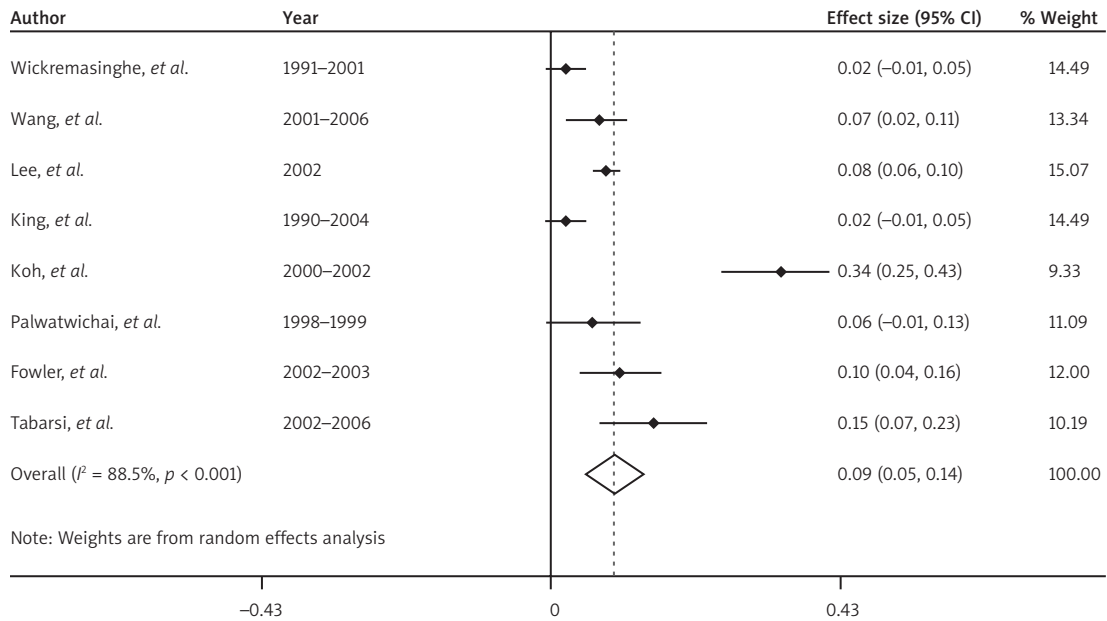
Author	Year		Effect size (95% CI)	% Weight
Wickremasinghe, *et al.*	1991–2001		0.02 (–0.01, 0.05)	14.49
Wang, *et al.*	2001–2006		0.07 (0.02, 0.11)	13.34
Lee, *et al.*	2002		0.08 (0.06, 0.10)	15.07
King, *et al.*	1990–2004		0.02 (–0.01, 0.05)	14.49
Koh, *et al.*	2000–2002		0.34 (0.25, 0.43)	9.33
Palwatwichai, *et al.*	1998–1999		0.06 (–0.01, 0.13)	11.09
Fowler, *et al.*	2002–2003		0.10 (0.04, 0.16)	12.00
Tabarsi, *et al.*	2002–2006		0.15 (0.07, 0.23)	10.19
Overall (I^2 = 88.5%, p < 0.001)			0.09 (0.05, 0.14)	100.00
Note: Weights are from random effects analysis				

−0.43   0   0.43

Figure 2. Forest plot for meta-analysis of the prevalence of NTM in patients with bronchiectasis

NTM species were MAC (25.7, 95% CI (12.6, 38.8)) and *M. abscessus* (43.2, 95% CI (26.6, 60.9)) compared to others. Although pooled prevalence of *M. chelonae* was lower (3.5, 95% CI (0.9, 6.2)), it has been widely investigated in 5 studies [21, 23–26]. In addition, the heterogeneity has been identified in the group of MAC (p < 0.001, I^2 = 96.9).

Evaluation of sensitivity analysis

The sensitivity analysis showed that the meta-analysis estimates were unchanged after removal of the study that had the biggest [20] or smallest sample size or the highest prevalence of NTM [22].

Discussion

To date, this is the first meta-analysis investigating the prevalence of NTM in patients with bronchiectasis. Many previous studies have reported the prevalence of NTM in patients with bronchiectasis. However, those studies were limited by small size of samples and weak statistical power. In this study, 8 eligible studies that included 1492 patients with bronchiectasis were collected. The overall meta-analysis showed that the combined prevalence of NTM was 9.3% (95% CI 5.0–13.6%) in patients with bronchiectasis, indicating that NTM infection was common in patients with bronchiectasis.

The subgroup analysis also showed that the combined prevalence of NTM was higher when the sample size was ≥ 100, time of study was after 2002, geographic location was in Asia, and method of study was retrospective, compared with prospective groups. The reason that NTM was
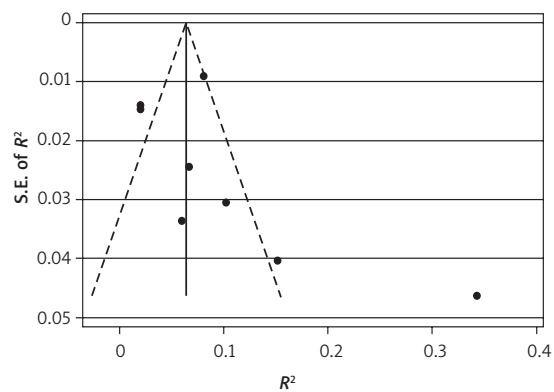

Figure 3. Funnel plot for meta-analysis of the prevalence of NTM in patients with bronchiectasis

more prevalent in the larger sample size (≥ 100) is unclear. A possibility is that substantial random errors may confound the results when the sample size is small. In general, a small sample may have a higher rate of random errors compared to a large sample [28]. Additionally, reasons for the increased reports (research year ≥ 2002) of NTM patients with bronchiectasis may be related to: i) active searching for NTM; ii) improvements in culture technique that reduce bacterial overgrowth; iii) factors that favor transmission such as contaminated air and water supplies; and iv) a more susceptible host reflecting increasing NTM infection in the general population [29]. Furthermore, our finding confirmed that the difference of participants' geographic location is highly associated with the prevalence of NTM. It is speculated that the prevalence of NTM infection is higher in Asia because of inadequate safe water supply, poor sanitation and living conditions.

Table II. Sub-group meta-analysis of NTM prevalence in bronchiectasis

Subgroups	No. of studies	Random model			Test of heterogeneity			Egger's test for publication bias	
		NTM prevalence (95% CI) [%]	Z	Value of p	Q	Value of p	I² (%)	t	Value of p
Overall effects	8	9.3 (5.0, 13.6)	4.24	< 0.001	64.62	< 0.001	89.2	1.27	0.25
Sample size ≥ 100	4	11.1 (4.1, 18.2)	3.11	0.002	48.9	< 0.001	93.9	4.24	0.076
Sample size < 100	4	7.7 (1.8, 13.6)	2.58	0.01	13.43	0.004	77.7	3.82	0.481
Research year ≥ 2002	3	9.6 (6.2, 13.1)	5.51	< 0.001	3.23	0.198	38.2	9.36	0.164
Research year < 2002	2	2.8 (–0.4, 0.6)	1.74	0.081	1.21	0.272	17.2	–	–
Asian	5	13.1 (6.3, 19.9)	3.77	< 0.001	34.80	< 0.001	88.5	2.6	0.312
European	2	5.6 (–2.3, 13.6)	1.39	0.166	5.95	0.015	83.2	–	–
Prospective study	3	5.5 (0.4, 10.7)	2.10	0.036	6.28	0.043	68.1	3.49	0.307
Retrospective study	4	11.1 (4.1, 18.2)	3.11	0.002	48.9	< 0.001	93.9	3.82	0.481

Table III. Sub-group meta-analysis of species distribution among definite cases

Subgroups	No. of studies	Random or fixed model			Test of heterogeneity			Egger's test for publication bias	
		NTM prevalence (95% CI) [%]	Z	Value of p	Q	Value of p	I² (%)	t	Value of p
MAC	4	25.7 (12.6, 38.8)	3.85	< 0.001	95.46	< 0.001	96.9	5.70	0.03
M. kansasii	3	3.7 (0.1, 7.3)	2.03	0.043	0.05	0.97	0.0	0.09	0.95
M. chelonae	5	3.5 (0.9, 6.2)	2.59	0.01	8.30	0.08	51.8	2.73	0.07
M. fortuitum	4	1.6 (0, 3.2)	1.93	0.054	2.56	0.28	22.0	3.84	0.16
M. malmoense	2	1.3 (–0.7, 3.2)	1.26	0.21	1.60	0.21	37.5	–	–
M. xenopi	2	3.1 (–0.3, 6.5)	1.76	0.08	1.30	0.26	39.0	–	–
Slow growth mycobacteria	1	0.01 (–0.9, 2.8)	1.00	0.32	–	–	–	–	–
M. abscessus	1	43.2 (26.6, 60.9)	4.99	< 0.001	–	–	–	–	–
Scotochromogen	1	2.0 (–0.8, 4.8)	1.43	0.15	–	–	–	–	–
M. avium intracellulare	1	3.1 (–0.3, 6.5)	1.76	0.08	–	–	–	–	–
M. simiae	2	1.3 (–0.2, 2.9)	1.66	0.09	0.28	0.60	0.0	–	–
Mycobacterium spp.	1	2.0 (–0.8, 4.8)	1.43	0.15	–	–	–	–	–
M. terrae	1	1.0 (–0.01, 0.03)	1.01	0.32	–	–	–	–	–
Aloei	1	1.0 (–0.9, 2.8)	1.00	0.32	–	–	–	–	–

Moreover, the stratification of NTM species indicates that patients with bronchiectasis are susceptible to be infected with MAC, *M. chelonae*, *M. fortuitum* and *M. abscessus*, and long-term bacteria colonization is established. Our study supports the previous report that MAC bacteria were most frequently isolated (13–81%) and were the most common cause of pulmonary NTM disease (43–81%) [30]. Also, rapidly growing mycobacteria (RGM) (e.g. *M. fortuitum* complex, *M. abscessus*, *M. chelonae*) were frequently identified in pulmonary samples from Taiwan, China and Singapore [31–36]. Conversely, the species profile of NTM in patients without bronchiectasis is extremely different, with *M. kansasii* and *M. xenopi* predominating but MAC present in less than 10% of cases [37, 38]. The mode of transmission of NTM is not well defined, but environmental exposure may be the major factor [39]. NTM existed in the outside environment, and were conditional pathogenic bacteria. Treatment of pulmonary NTM infection is complex, requiring multiple antibiotics and a prolonged treatment course [40]. With the application of antibiotics, genetic diseases such as cystic fibrosis of the lung, immunodeficiency disease and disorders of cilia movement were becoming the general causes of bronchiectasis [41]. NTM infections and α_1-antitrypsin deficiency syndrome were all predisposing factors [42] which led to bronchiectasis becoming one of the potential factors in AIDS.

Some limitations of this study should be discussed. First of all, only published studies were included in the present meta-analysis. Thus, publication bias may exist, although the statistical test did not detect it. Secondly, significant heterogeneity was detected in the current meta-analysis. However, it was not a major problem because we did subgroup analysis to reduce the heterogeneity. Third, different populations may result in significant heterogeneity across the 8 eligible studies. Fourth, the symptoms or complications of NTM infected patients with bronchiectasis were not clearly reported. Fifth, the accuracy of TNM prevalence can be overestimated if the definite case only indicates patients with more severe symptoms which require a clinic visit. Finally, the present study was restricted to non-RCT trials, and a small number of selected trials. Thus, a larger number and higher quality of RCT studies are still warranted.

In conclusion, the present meta-analysis confirms the concept that the prevalence of NTM infection is high in patients with bronchiectasis. Additionally, it has identified that patients with bronchiectasis are susceptible to infection with long-term bacteria such as MAC, *M. chelonae*, *M. fortuitum* and *M. abscessus*. However, the surveillance of NTM species is relatively inaccurate for estimating the incidence of pulmonary disease and disease caused by MAC. Future studies should evaluate outcomes including the impacts of new tests on clinical decision making and the cost-effectiveness of new tests for NTM-infected patients.

Acknowledgments

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