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Early View

Review

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Global burden of non-tuberculous mycobacteria in the cystic fibrosis population: a systematic review and meta-analysis

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Take-home message: In this systematic review and meta-analysis, we investigated the burden of non-tuberculous mycobacteria in individuals with cystic fibrosis and found that the worldwide prevalence of infection is around 8%.

Abstract

Background: People living with cystic fibrosis have an increased risk of lung infection with non-tuberculous mycobacteria (NTM), which is reportedly increasing. We conducted a systematic review of the literature to estimate the burden (prevalence and incidence) of non-tuberculous mycobacteria in the cystic fibrosis population. **Methods:** Electronic databases, registries, and grey literature sources were searched for cohort and cross-sectional studies reporting epidemiological measures (incidence and prevalence) of NTM infection or NTM pulmonary disease (NTM-PD) in cystic fibrosis. The last search was conducted in September 2021; we included reports since database creation and registry reports published since 2010. The methodological quality of studies was appraised with the Joanna Briggs Institute tool. A random-effects meta-analysis was conducted to summarize the prevalence of NTM infection, and the remaining results are presented in a narrative synthesis. **Results:** Ninety-five studies were included in this review. All 95 studies reported on NTM infection, and 14 of these also reported on NTM-PD. The pooled estimate for the point prevalence of NTM infection was 7.9% (CI 95%, 5.1 – 12.0%). In meta-regression, sample size and geographical location of the study modified the estimate. Longitudinal analysis of registry reports showed an increasing trend in NTM infection prevalence between 2010 and 2019. **Conclusions:** The overall prevalence of NTM infection in CF is 7.9% and is increasing over time based on international registry reports. Future studies should report screening frequency, microbial identification methods, and incidence rates of progression from NTM infection to pulmonary disease.

Introduction

Cystic fibrosis (CF) is an autosomal recessive condition, caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene. The incidence is approximately 1 in 3,000 - 4,000 newborns in Caucasian populations, with variable estimates of incidence in other ethnicities [1, 2]. CF is characterized by chronic pulmonary symptoms and a progressive decline in lung function leading to respiratory failure or lung transplantation [1, 3]. The underlying pathology of CF favors microbial colonization and confers additional susceptibility to infections with fungi, viruses and bacteria, which in turn accelerate the respiratory compromise [4].

Non-tuberculous mycobacteria (NTM) are free-living organisms with pathogenic potential. Individuals with underlying immunosuppression or structural lung damage are at increased risk of infection with these bacteria [5, 6]. In the CF population, patients can have transient or chronic infection with NTM. The latter can be indolent or contribute to radiographic changes and concurrent symptoms referred to as NTM pulmonary disease (NTM-PD), which often warrants antimicrobial therapy [7]. However, both conditions (chronic infection and NTM-PD) can be associated with poorer respiratory outcomes and are relative contraindications for lung transplant [8, 9]. Recent reports show that the overall detection rate for NTM has been increasing in the general population. For instance, in the United States of America, the prevalence increased from 8.2 per 100,000 to 20 per 100,000 persons between 1997 and 2007 [10–12]. A similar trend has been described in cystic fibrosis populations worldwide [7, 13–15]. The recent increase in awareness about the impact of NTM on CF lung disease could account for a rise in detection rates through improved screening practices.

Despite the availability of data in CF registries, the global burden of NTM remains poorly defined. The burden of NTM infection and NTM-PD can vary according to age, environmental exposure, geographical region, and microbial identification methods used [7–9]. Particularly, estimates from geographical regions without established registries are typically underrepresented. Furthermore, divergent screening and laboratory practices (internationally and nationally) make it difficult to compare or generalize estimates from different locations. To

estimate the burden of NTM-related conditions in the CF population, we conducted a systematic review of the incidence and prevalence of NTM infection and NTM-PD among people living with CF and explored factors that contribute to heterogeneity in these estimates.

Methods

Review question

We designed our review question based on population, condition, outcome (epidemiological measure) and study design, as recommended by current guidelines [16, 17]. Briefly, we screened for cross-sectional or cohort studies reported in English including people with CF (population), and evaluating NTM infection or NTM-PD (condition). NTM infection was defined as isolation of any NTM on at least one occasion per patient; the criteria for NTM-PD were specified in each study. Reporting of at least one epidemiologic measure among incidence rate, incidence proportion, point prevalence, or period prevalence was required for inclusion. The full criteria are described in **Supplementary Table 1**. The review protocol was registered to the International Prospective Register of Systematic Reviews, PROSPERO (CRD42020200418) in July 2020. In October 2020, before the abstract screening, we updated the grey literature sources and screening procedures.

Literature search

EMBASE and MEDLINE were searched in September 2020 using the criteria specified in **Supplementary Methods 1**; an updated search was conducted in September 2021. We manually reviewed the conference proceedings from relevant research meetings between 2010 and 2020 (North American Cystic Fibrosis, European Cystic Fibrosis Society, American Thoracic Society, and the Infectious Diseases Society of America conferences). Also, we performed forward and backward searches for highly cited references in Web of Science (listed in **Supplementary Table 2)** using Google Scholar and Web of Science. Finally, the United States of America (CF Foundation), Canadian (CF Canada), European (European CF Society), Australian, and Brazilian registry reports published between 2010 and 2021 were included.

Screening and data extraction

All records were retrieved and exported in Research Information Systems format. Initial manual deduplication evaluated Author, Title, and Year of publication. Then, we performed automated deduplication using the SRA De-Duplicator software and Covidence [18, 19]. Screening of reports and full-text manuscripts, data extraction, and risk of bias assessment was conducted independently by two reviewers (M.P. and M.A.); discrepancies were solved by consensus or by a third reviewer (B.Q.). Epidemiological measures of interest reported in each study were included for analysis. Abstract screening evaluated language, study type, the inclusion of CF population, and reporting of any measures of interest. Full-text screening evaluated all eligibility criteria defined in **Supplementary Table 1**. For unretrievable reports, we requested access to unpublished full manuscripts from authors via email on at least two separate occasions. The Joana Briggs Institute tool was used to assess methodological and reporting quality [16, 17, 20–22]. Overall low risk of bias was defined as low risk in the assessments of the sampling frame, sample size, population description, and statistical methods. High risk was determined by a high-risk assessment in any of the following: sampling frame, sampling scheme, sampling size, population description, identification methods, or statistical calculation. Data extraction was based on a pre-specified data dictionary piloted with 10 studies (**Supplementary Table 2**). For period prevalence, point prevalence, and incidence proportion, we extracted proportions, the number of cases, and the sample size. We did not impute any missing data. In studies with unclear years of data collection, we assumed that data was obtained from the year before publication. The body of evidence was not evaluated for certainty given the lack of adapted tools for single proportion measures.

Data analysis

Data were analyzed with the meta and metafor packages in R studio and R version 4.1.1 [23–26]. Risk of bias plots were produced with the robvis and ggplot2 packages [27, 28], and tables with the flextable package [29]. We pre-specified the use of random-effects models based on expected heterogeneity by study region and dates. To model proportion data, we used generalized linear models with LOGIT transformation [30–32]. Point and annual prevalence of NTM infection were summarized together in the meta-analysis because they contain comparable

time frames of evaluation (a year or less). The remaining epidemiologic measures including period prevalence of NTM infection, incidence of NTM infection, prevalence (point or period) of NTM-PD, and incidence of NTM-PD are reported in supplementary tables and text only. Period prevalence of NTM infection and NTM-PD were not pooled due to varying time intervals among studies, while the rest of the epidemiologic measures had a small number of studies. To avoid the overrepresentation of registry reports in the meta-analysis, we included only the most recent report per registry with both numerator and denominator available to calculate prevalence. Secondary data analyses of registry data were also excluded from meta-analysis to reduce redundancy with the registry reports. Heterogeneity was assessed with the I^2 index and 95% confidence interval, with a significance level established at $p < 0.10$. Publication bias was explored graphically using sample size as a predictor of bias in the funnel plot [33].

We pre-specified subgroup analyses by study design, age category (pediatric vs adult), year of data collection (before 2000, 2001 to 2009, and 2010 – 2019), geographical region (grouped as North America, Europe, and others), and the most common individual NTM species reported in CF (*Mycobacterium abscessus* complex - MABs and *Mycobacterium avium* complex - MAC). The prespecified meta-regression model was optimized by maximum likelihood and used the same transformation as the meta-analysis (LOGIT). We evaluated the goodness of fit in the model using Akaike's information criteria by stepwise inclusion of pre-specified coefficients. Exploratory (unspecified) analyses include a longitudinal trend of prevalence in registries and subgroup analyses by region for MAC and MABs. Sensitivity analyses included three meta-analyses of NTM infection point (and annual) prevalence. The first excluded a study that screened patients only in the presence of increased symptoms, the second included only registry data, and the third excluded studies that did not use standardized culture media for identification of NTM. Reporting is based on the recommendations of the Joanna Briggs Institute and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [16, 34]. The final dataset, the code for analysis, the data collection form and other study forms are available at https://github.com/azmigueldario/SR_prevalence_NTM

Results

Description of studies

After removing duplicates, 1703 references were included for abstract screening, 291 were reviewed as full-text, and 95 were included in the systematic review. The PRISMA flowchart in **Figure 1** summarizes the screening process. The abstract and full-text screening processes had a Cohen's kappa of 0.899 and 0.698, respectively, and all disagreements were resolved by consensus. The majority of the publications originated from Europe (42%) or North America (33%). The most common study design was cross-sectional registry (n=44, 46%), followed by cross-sectional non-registry (n=35, 37%), and cohort (n=16, 17%). A majority of studies (n = 75; 79%) included a mixture of pediatric and adult patients. The most represented period of data capture was 2010-2019 (n=65, 68%), concordant with the availability of registry data. As expected, registry reports and studies using registry data had a larger median sample size (4278, IQR 2230 – 15048) compared to the median of non-registry studies (155, IQR 92 – 382). **Supplementary Tables 4 to 8** summarize the characteristics of included studies by the epidemiologic measure of interest. Annual or point prevalence of NTM infection was reported in 67 studies, and period prevalence of NTM infection in 43 studies. The incidence proportion of NTM infection was reported in 5 studies. NTM-PD point prevalence was reported in 2 studies and period prevalence in 13 studies, but no studies reporting incidence of NTM-PD were found.

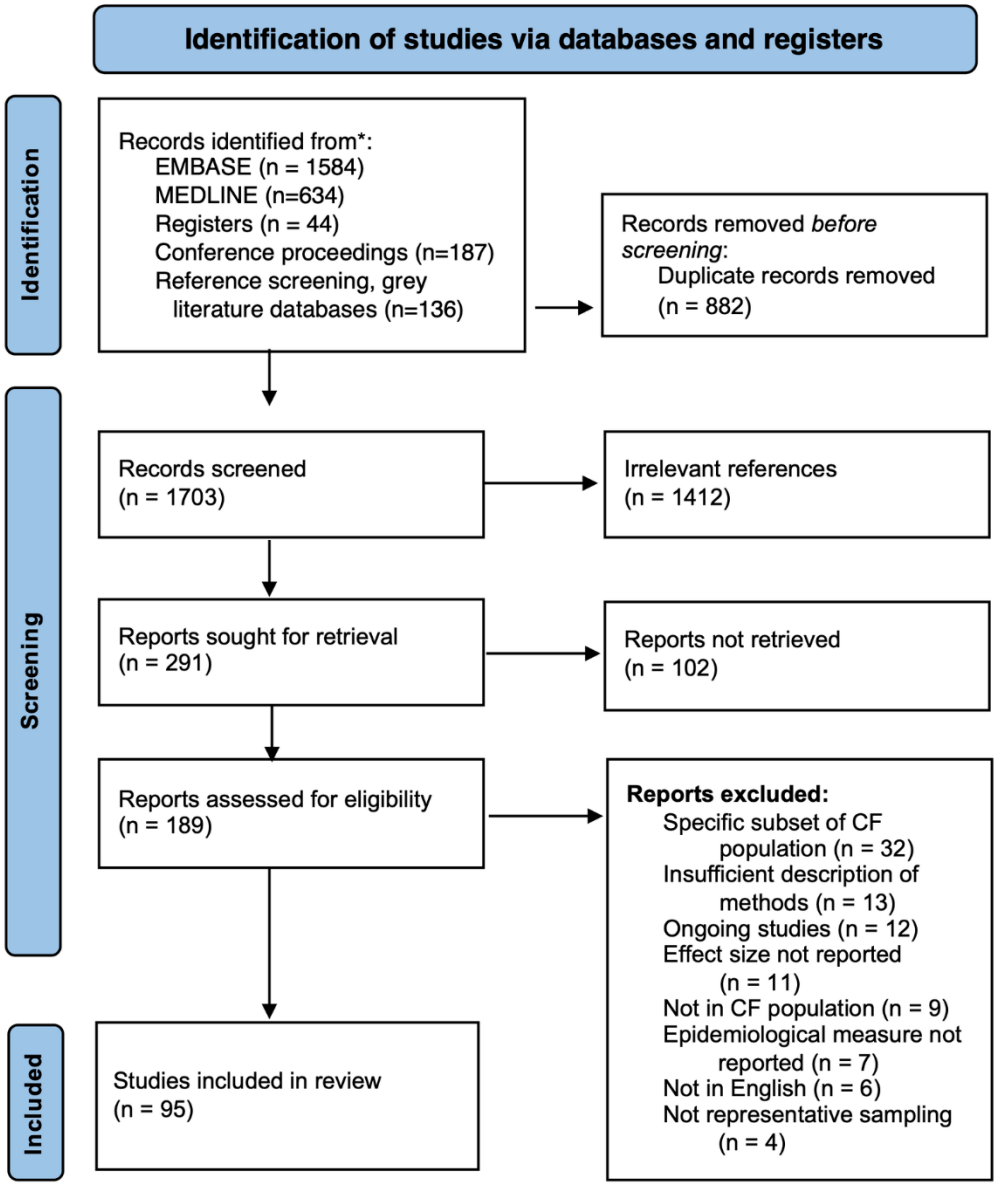

Figure 1. Prisma flowchart summarizing identification of reports, retrieval of manuscripts, and screening steps.

Figure 2. Summary plots of quality appraisal of studies included in the systematic review using the Joanna Briggs Institute tool for systematic reviews of prevalence. Domain 5 applies to survey studies and was not evaluated. a**)** Summary of all included registry reports (n=44). **b)** Summary of all included non-registry reports (n=51). **ROB overall**: overall risk of bias determined as specified in methods.

The results of the quality assessment are summarized in **Figure 2**. Registry reports had mostly low-risk scores on the domains of sampling frame, sampling approach, sample size, and population description. In contrast, registry reports had mostly unclear risk in identification methods (77%), and high or unclear risk in standardized measurement and response rate. The latter is expected as identification methods are not typically collected by registries. Non-registry studies had a higher risk of bias scores in terms of sample size and population description. Also, non-registry studies showed higher quality assessment in reporting of identification methods (Fisher test $p<0.001$) compared to registry reports. By epidemiologic measure, studies that reported the incidence of NTM infection had, in general, a low risk of bias for all questions except sample size and response rate. Studies reporting NTM-PD also had a high risk of bias for sample size and population description, and mostly low/unclear risk for the remaining domains **(Supplementary Figure 1).**

NTM infection point (annual) prevalence

Point prevalence and annual prevalence of NTM infection were summarized together in a meta-analysis of 21 studies. For registry data, we used the most recent report that included both the number of cases and sample size. Also, 4 studies that used registry data between 2010 and 2019 were excluded to avoid duplication of data. The primary random-effects model (**Figure 3**) produced an NTM infection prevalence estimate of 7.9 % (95% CI 5.1 – 12.0%), with a 95% prediction interval (interval in which a future observation is most likely to fall) of 1.0 – 41.6% and substantial heterogeneity in the estimate (I^2 = 99%). The characteristics of studies reporting point and annual prevalence of NTM infection are summarized in **Supplementary Table 4**.

The heterogeneity of results was explored through sub-group analyses (**Supplementary Figure 2**). We did not examine age because 81% (17/21) of included studies had a mix of pediatric and adult populations without individual estimates reported for each group. No significant difference was found between subgroups of registry (n = 5) and non-registry studies (n = 16); heterogeneity was large for all subgroups ($I^2 > 90$). The pre-specified subgroup meta-analyses by first year of data collection and geographical region showed no significant differences among subgroups ($p > 0.05$). Studies conducted in other regions (Latin America and

the Caribbean, Middle East, Africa, and Australia) had less precise estimates, 4 % (95% CI 0.2 – 40.1) than those conducted in Europe or North America.

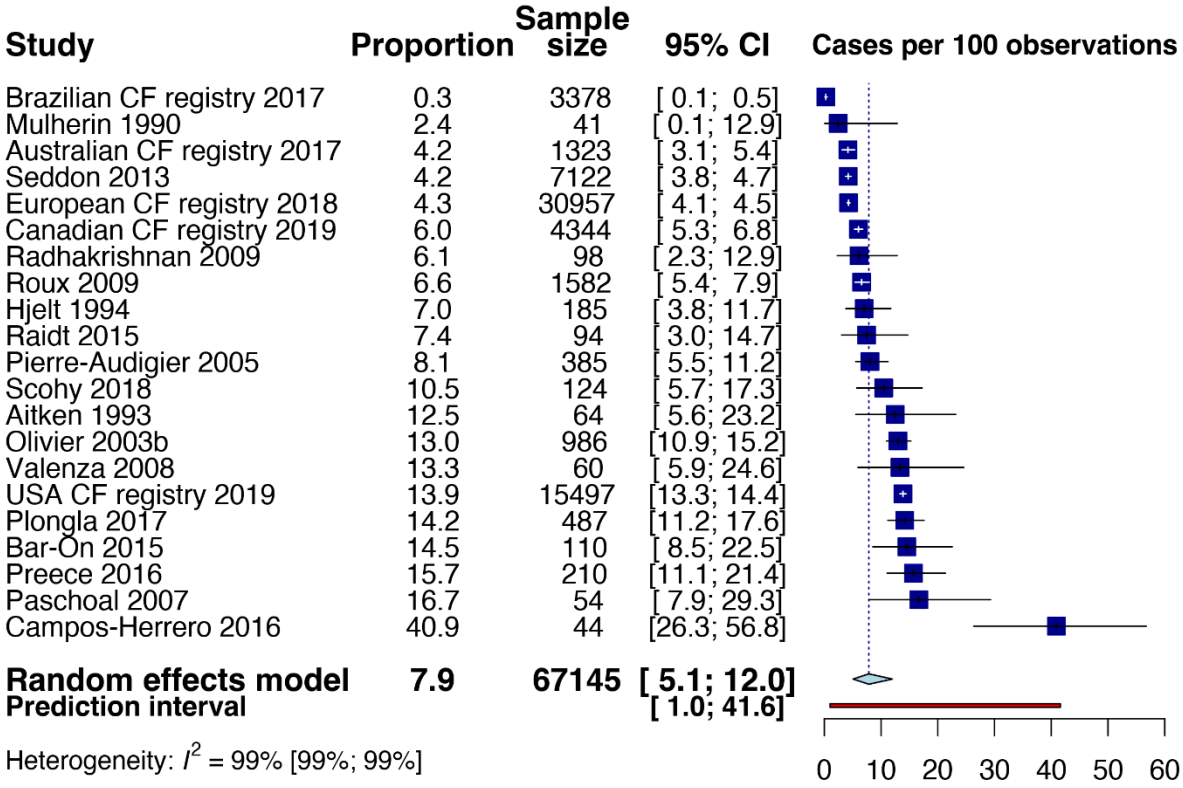

Figure 3. Random effects meta-analysis of LOGIT transformed NTM infection prevalence (annual and point) in the cystic fibrosis population (n = 21). Includes last registry year which reports raw numbers for cases and evaluated patients.

The prevalence (point and annual) of NTM infection was analyzed separately for MAC and MABs (n =11 for both) (**Figure 4**). The variability was lower for these two estimates than in the analysis including all NTM species, although heterogeneity remained greater than 80%. The MAC estimate is 3.7% (95% PI 0.7 – 17.8%) and the MABs estimate is 4.1% (95% PI 1.1 – 14.7%). In an exploratory subgroup analysis examining prevalence by geographical region, a significantly lower prevalence (annual and point) of MAC infection was seen in Europe (1.7%; 95% CI 1.2 – 2.5; I^2 = 27%) compared to North America (7.8%, 95% CI 5.3 – 11.3; I^2 = 80.7%). No differences were found in MABs infection prevalence by geographical region (**Supplementary Figure 3**). The funnel plot examining the relationship between sample size and

NTM infection prevalence showed no graphical asymmetry or statistically significant difference (Peter's test, p = 0.4) to suggest publication bias (**Supplementary Figure 4**) [35].

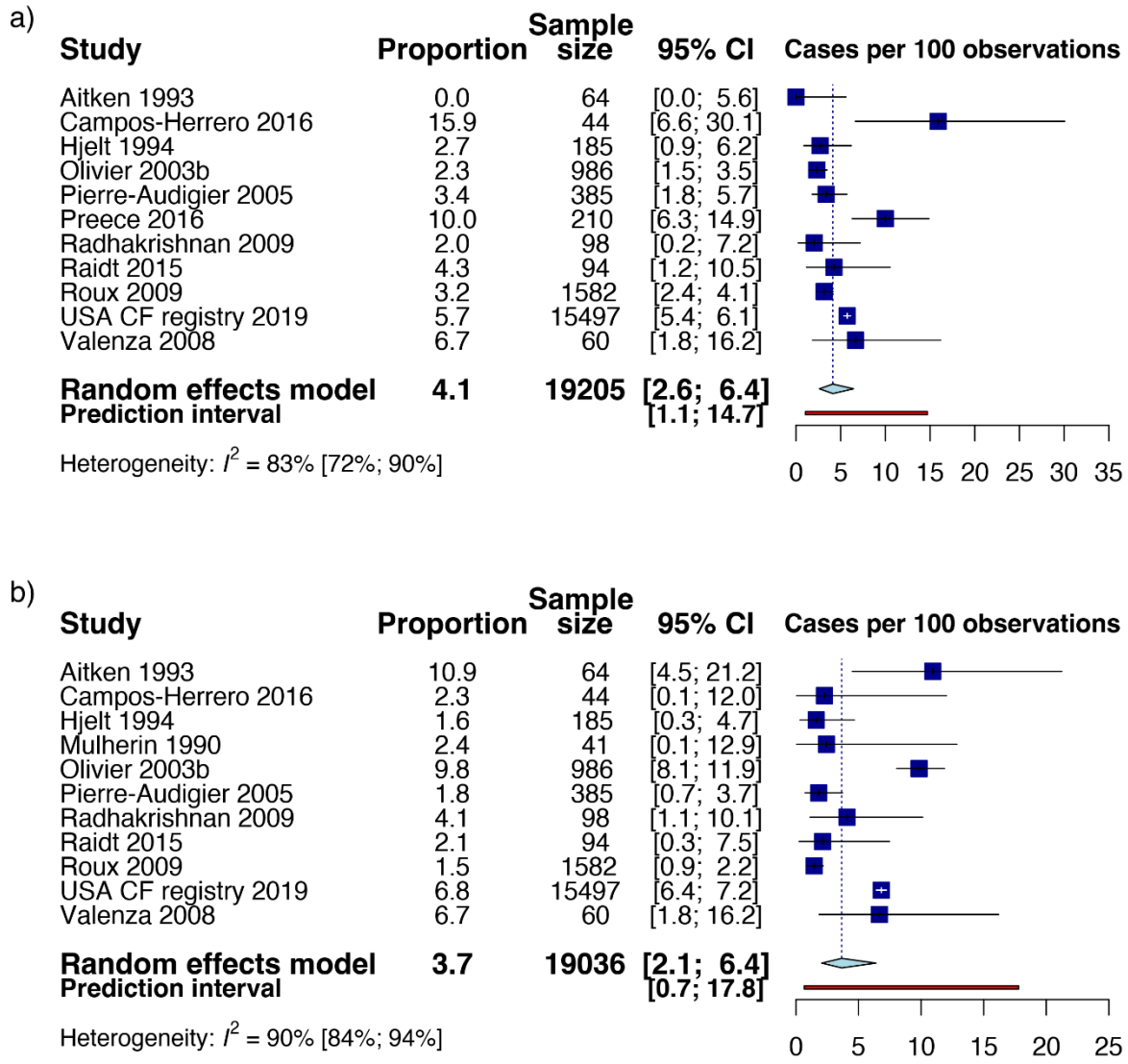

Figure 4. Meta-analyses of **(a)** *Mycobacterium abscessus* complex; and **(b)** *Mycobacterium avium* complex infection in the cystic fibrosis population including studies that reported point and annual prevalence.

We evaluated which factors were significantly affecting the NTM infection prevalence while controlling for other covariates using meta-regression. The final model included the pre-specified variables study region, sample size category, year of data collection, and study design. Age category was excluded because of the small number of studies reporting pediatric and adult estimates separately. As shown in **Table 1**, 'other' geographical region and sample size < 1000 had a significant effect on the estimated LOGIT prevalence ($p < 0.05$). Proportions are obtained by [$e^{coef} / (1 + e^{coef})$]. The calculated estimate for the intercept (5.3%) provides the NTM infection prevalence (point and annual) for studies with all reference categories: cross-sectional registry studies with sample sizes > 3,000 conducted in North America between 2010-2019. Each coefficient shows the magnitude of change in the associated category while holding all other covariates constant. On average, studies conducted in regions other than Europe and North America had a reduced estimate of NTM infection prevalence of 1.5% compared to those conducted in North America while all other factors are held constant. Also, studies with sample sizes below 1000 had a larger estimate on average (22.9%) compared to those with sample sizes above 3000 while holding all other covariates constant.

Additional potential sources of variability included differences in the study populations, NTM testing frequency, microbial identification methods, and NTM species distribution. Among the patient characteristics of the included studies, the distribution of female sex was homogeneous (median of 47.9%, range 43.3 – 56.2%, n = 15). Most studies included mixed pediatric and adult populations. Due to missing data, we could not determine whether differences in ethnicity or lung disease severity (i.e., FEV1) could have affected the estimates. The frequency of testing was also difficult to assess as a source of variability because it was only reported in 28.6% (6/21) of studies in the meta-analysis. Furthermore, a single study screened for NTM only in the presence of symptoms but a sensitivity analysis removing this study had no impact on the primary meta-analysis results (**Supplementary Figure 3c**). Out of 67 studies reporting NTM infection point prevalence or annual prevalence, only 24 described the specimen analyzed (all used sputum alone or with other samples), and 14 the culturing method. In the meta-analysis, five studies did not report the specimen and seven failed to report the culturing method. Mycobacterial growth indicator tubes (MGIT) and Lowenstein-Jensen (L-J) medium were the most frequently used methods in 12/14 studies for point/annual prevalence of NTM

infection[36]. However, the length of incubation, method of speciation, and decontamination procedures varied significantly among studies.

As most registries effectively capture the CF population in a region, we conducted a sensitivity analysis with only registry data (**Supplementary Figure 5a**). The results with only registry reports differed from those in the main meta-analysis; the estimate was 3.4% (95% CI, 0.7 – 16.1%) with significant heterogeneity (I^2=100%, n = 5). Also, to evaluate the impact of using culture media other than those recommended by clinical practice guidelines (Mycobacterial Growth Indicator Tube – MGIT and Lowenstein-Jensen), we conducted a sensitivity analysis excluding four studies (**Supplementary Figure 5b**). The estimate was close to the one in the main meta-analysis, 7.1% (95%CI, 4.2 – 12%), suggesting that the use of non-standardized culture media does not affect the overall results.

NTM infection period prevalence

Supplementary Table 5 summarizes the characteristics of studies that reported period prevalence of NTM infection in an interval longer than one year (n = 32). A majority were cross-sectional non-registry studies (n = 22, 69%) conducted in Europe (n = 20, 62%) with mixed pediatric and adult populations (n = 17, 53%). Typically, studies collected data spanning five or more years (n = 8, 56%), while the longest study period was fourteen years [37]. The variability in prevalence estimates was larger in studies with longer study periods (**Supplementary Figure 6**). In summary, most estimates of NTM infection period prevalence were between 6.6% and 19% (IQR). No meta-analysis was conducted due to diverging study periods. The median sample size was 192 (IQR, 104 - 444), and only 12 studies had sample sizes larger than 300 participants.

NTM infection incidence

Incidence was reported as incidence proportion in five studies, with no reports of incidence rate [14, 38–41] **Supplementary Table 6** summarizes **t**he characteristics and estimates of these studies. Besides secondary registry analyses (Hatziagorou 2020 and Binder 2013), studies had small sample sizes (110 or less). The annual estimates of incidence proportion per year were typically below 10%. The highest estimate (14.3% - 2002) was reported by the study with the smallest sample size (Campos-Herrero 2016, n = 44) [38]. In contrast, the estimates of

the study with the largest sample size (Hatziagorou 2020) ranged from 1.3 to 1.8% between 2011 and 2016 [40].

NTM pulmonary disease

Point prevalence of NTM-PD was only reported in 2 studies, and both had small sample sizes. Radhakrishnan 2009 [42] reported a prevalence of 1/98 (1.0%) using data collected in 2004 and based on the ATS 2007 criteria [43]. Bar-On 2015 evaluated annual prevalence in Israel between 2002 and 2011, using the ATS 2007 criteria, and reported a prevalence between 2.5% and 11.3%, see **Supplementary Table 7** [14].

NTM-PD period prevalence was reported in 13 studies, with estimates ranging between 0.8% (3-year period) and 22.7% (10-year period), see **Supplementary Table 8** [38, 44]. Most studies were conducted in Europe (7/13), with the remaining ones in Israel, Brazil, and a French territory in Africa. Most of them applied the ATS 2007 criteria (n=8), two used ATS 1997 criteria, and three studies failed to report the criteria used to define NTM-PD. Only three studies had sample sizes above 300 participants. No reports of NTM-PD incidence were identified.

Discussion

This is the most comprehensive systematic review on the prevalence and incidence of NTM infection and NTM-PD in the CF population. The estimated prevalence (annual and point) of NTM infection in CF was 7.9% based on a meta-analysis of all non-registry and registry studies. For the most common mycobacteria in CF, the prevalence of infection with MABs was estimated at 4.1% and MAC at 3.7%. NTM-PD had only two reports of point prevalence, and estimates of period prevalence were usually below 10%, despite variable interval lengths per study (n = 13). In general, all included studies had good quality in the appraisal of sampling and statistical methods, but poorer scores in reporting of microbiological methods and screening approaches.

We employed meta-regression to elucidate the contributors to heterogeneity in the meta-analysis of NTM infection prevalence (point and annual) and showed that a smaller sample size,

and geographical region outside of North America and Europe produced significantly different estimates. However, only 4 studies were represented in this 'other' geographic region group, and it included a mixture of minimally represented populations in Asia, Latin America, and the Middle East; with likely variable screening practices. In an exploratory analysis, we observed a lower prevalence of infection with MAC in European studies. Interestingly, some studies from Western Europe have reported a predominance of MABs infection in contrast to the dominance of MAC often seen in North America [45–48].

The differential estimate of NTM infection prevalence according to sample size is likely driven by differences in study design. In a subgroup analysis (**Supplementary Figure 2a**), registry studies, which tended to be larger with unclear microbial identification methods and screening practices of participating registry sites, had a lower estimate of NTM infection prevalence (point/annual) than non-registry studies. This difference was not statistically significant. In contrast, non-registry studies had good concordance in microbiological identification methods (culture and specimens) and reported screening frequency more often but the studies were generally small with the potential for selection bias. Heterogeneity due to included population characteristics could not be evaluated due to differences in primary data reporting of summary (mean, median) and distribution (median, mean, IQR, range) measures. Information related to the age range of first NTM detection could help with screening efforts as culturing frequency can be intensified during this higher risk period. Yet, the primary data reporting for age did not allow further exploration of its effect on NTM infection prevalence. To obtain comparable estimates from different countries and regions, harmonization of screening practices and identification methods is necessary [7]. We encourage adherence to published reporting guidelines for observational studies (i.e., STrengthening the Reporting of OBservational studies in Epidemiology) and standardization of registry reporting to facilitate longitudinal and global comparisons [49, 50].

In recent years, an increase in the global burden of NTM in all populations has been reported [8, 14, 51–53]. Our analyses did not show significant differences in prevalence in the subgroup by years of data collection. Given the methodological variability between studies, we explored the longitudinal report of NTM infection annual prevalence within individual registries

with comparable methods over the years. An increasing trend of prevalence was observed in all but the Brazilian registry (**Supplementary Table 4 and Supplementary Figure 7**), where an overall low prevalence of NTM infection has been consistently reported [54]. Improved screening rates, novel detection methods, and increased awareness may explain this increase [7].

Only a few studies reported NTM infection incidence measures (n=5) or NTM-PD prevalence (n = 13 for period prevalence and n = 2 for point prevalence). From a limited set of studies with small sample sizes, the incidence proportion of NTM infection seems to be less than 10% per year in European populations [38, 40], without sufficient data from North America or other regions to make meaningful conclusions. Moreover, the conversion rate to NTM-PD after initial NTM infection remains unclear as no studies have reported the incidence of NTM-PD. Hopefully, ongoing studies like the PREDICT trial (NCT02073409), which is evaluating a standardized approach to NTM-PD diagnosis in CF, will help establish an approximate risk of progression [55].

Overall, the results from this systematic review present a comprehensive view of the known burden of NTM in CF while pointing out gaps in knowledge [56]. Accurate epidemiological data about the frequency and risk of NTM infection in CF is necessary to inform clinical decision-making and health policy. Identification of high-risk groups can help facilitate prevention and surveillance strategies to improve prognosis and quality of life. There was large variability and a wide prediction interval for our NTM infection meta-analysis, which may limit its utility for decision making. Unfortunately, a lack of reported data in primary studies did not allow for further exploration of the sources of heterogeneity beyond the ones already described. Once CFTR modulators are widely implemented, their impact on infection prevalence is likely to change and our results may serve as a baseline to measure its impact on NTM and NTM-PD. However, future prevalence and incidence estimates might also be difficult to interpret and compare against historical estimates since obtaining sputum samples on demand for surveillance is becoming more challenging for patients on highly effective CFTR modulators. Finally, moving forward, we advocate for a stronger emphasis on reporting standards of microbiological identification methods and screening procedures for registry and non-registry studies [50]. A significant and relatively low-cost way to build upon this work is creating a living systematic

review of the NTM burden in CF; which could be updated annually with new registry and observational data to enhance surveillance of trends [57].

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Table 1. Results of meta-regression for NTM infection point prevalence

Coefficients	LOGIT-estimate	SE	Lower CI	Upper CI	p value
Intercept	-2.884	0.373	-3.615	-2.153	< 0.01
Design (Ref: Cross-sectional - registry)					
Cross-sectional - non-registry	-0.290	0.893	-2.040	1.461	0.746
Cohort	-0.268	0.726	-1.691	1.155	0.712
Sample size (Ref: > 3000)					
1000 - 3000	0.978	0.652	-0.299	2.256	0.133
Less than 1000	**1.671**	**0.682**	**0.335**	**3.007**	**0.014**
Region (Ref: North American)					
European region	-0.424	0.396	-1.201	0.353	0.285
Other regions	**-1.302**	**0.501**	**-2.284**	**-0.320**	**0.009**
Reporting year (Ref: 2010 - 2019)					
2000 - 2009	0.412	0.542	-0.651	1.474	0.447
Before year 2000	-0.652	0.490	-1.612	0.308	0.183

LOGIT-estimates are back-transformed to proportions through the formula $e^{coef} / (1 + e^{coef})$. **CI:** confidence interval. **SE:** standard error. **'Other'** regions include Africa, Latin America and the Caribbean, and the Middle East

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Supplementary Methods 1 – Systematic review search strategies

Database: OVID Inc. MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)
Search Strategy:

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1 exp Cystic Fibrosis/ (35441)
2 (cystic adj3 fibrosis).mp. (51651)
3 CFTR.mp. (11167)
4 or/1-3 (52236)
5 exp Nontuberculous Mycobacteria/ (11647)
6 exp Mycobacterium Infections, Nontuberculous/ (35039)
7 ((abscessus or avium or atypic* or gordonae or kansasii) adj5 mycobacteri*).mp. (16561)
8 (non*tuberculosis or non*tuberculous or NTM or "mycobacteria other than tuberculosis" or MOTT).mp. (14149)
9 or/5-8 (52341)
10 4 and 9 (576)

Database: OVID Inc. Embase
Search Strategy:

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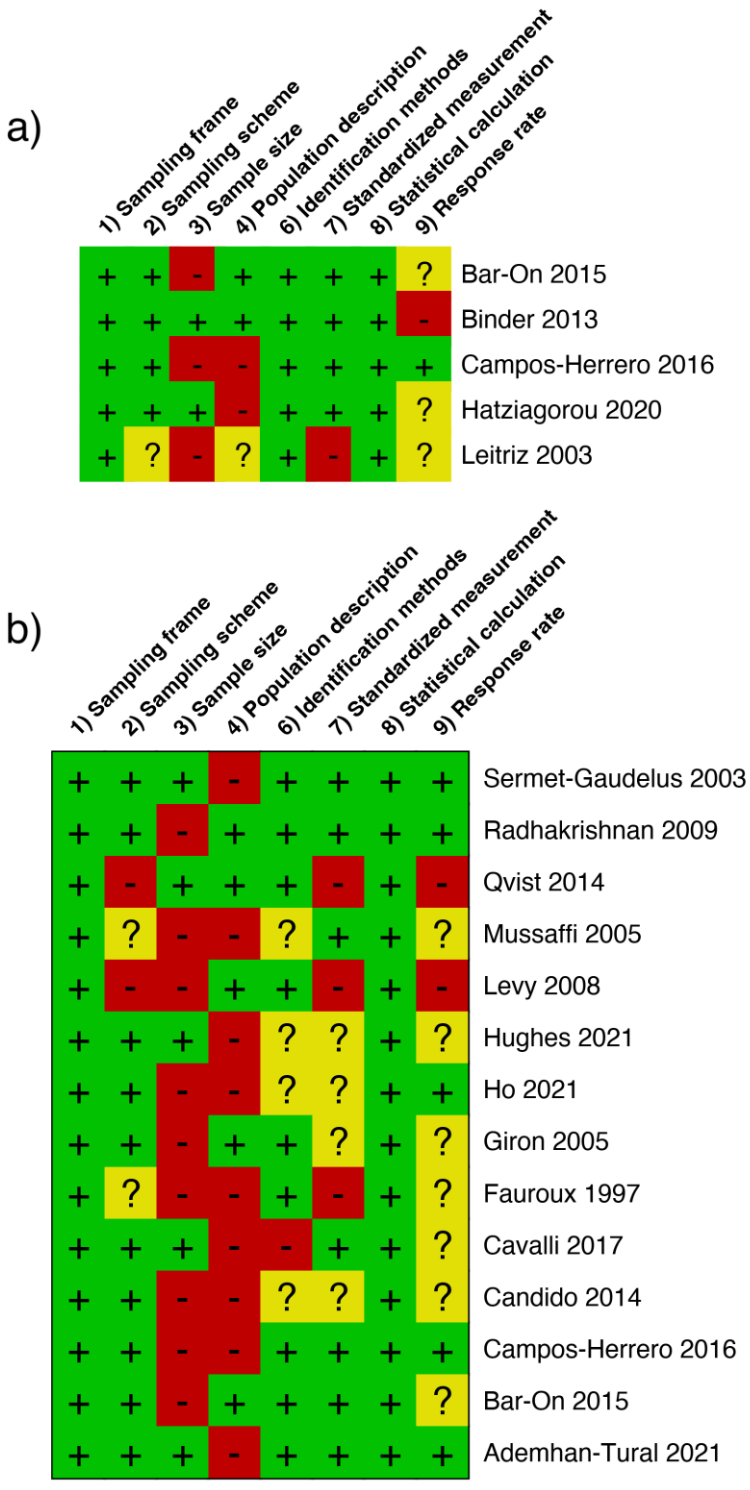
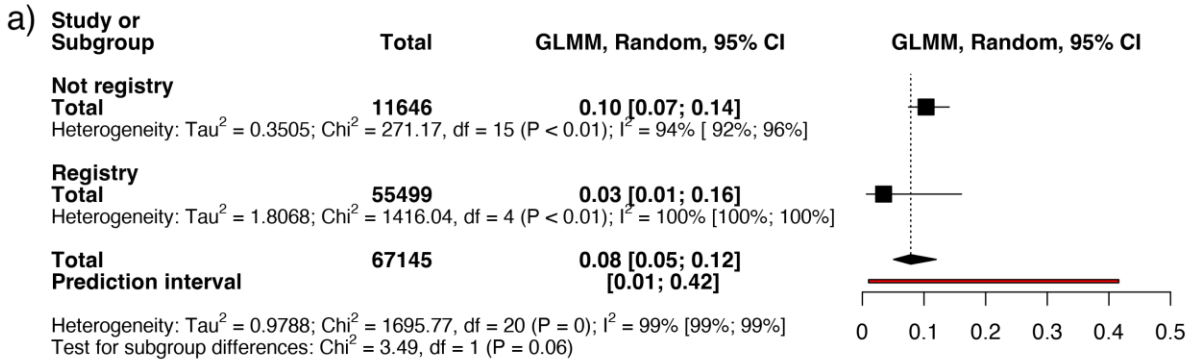
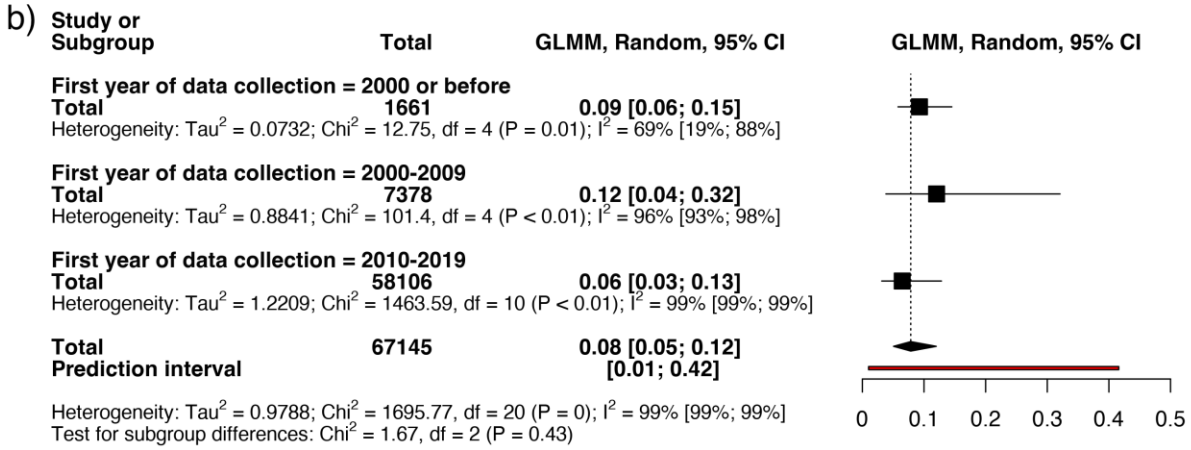
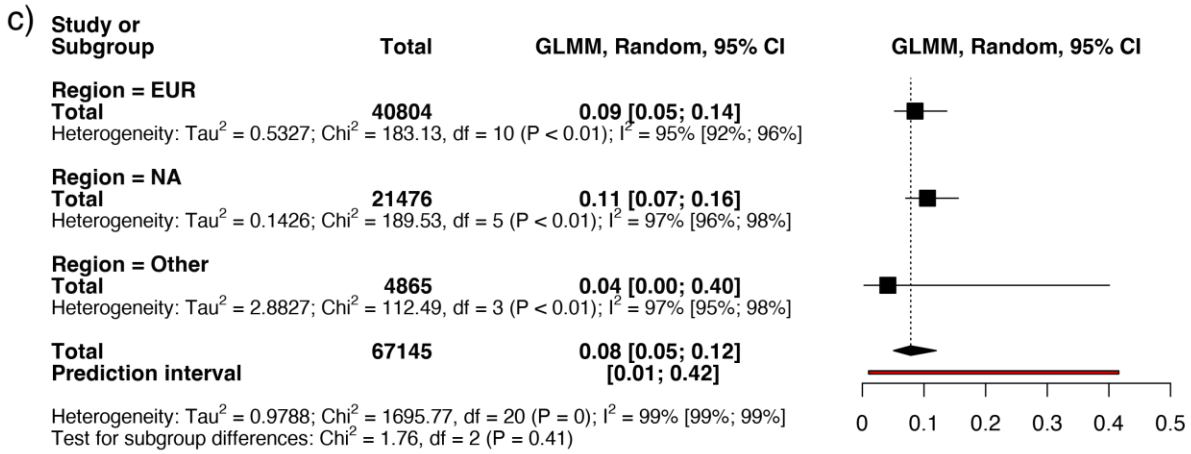
1 cystic fibrosis/ (71509)
2 (cystic adj3 fibrosis).mp. (84692)
3 CFTR.mp. (17470)
4 or/1-2 (84692)
5 atypical mycobacteria/ (4439)
6 atypical mycobacteriosis/ (5361)
7 ((abscessus or avium or atypic* or gordonae or kansasii) adj3 mycobacteri*).mp. (24844)
8 (non*tuberculosis or non*tuberculous or NTM or "mycobacteria other than tuberculosis" or MOTT).mp. (9445)
9 or/5-8 (29259)
10 4 and 9 (1427)



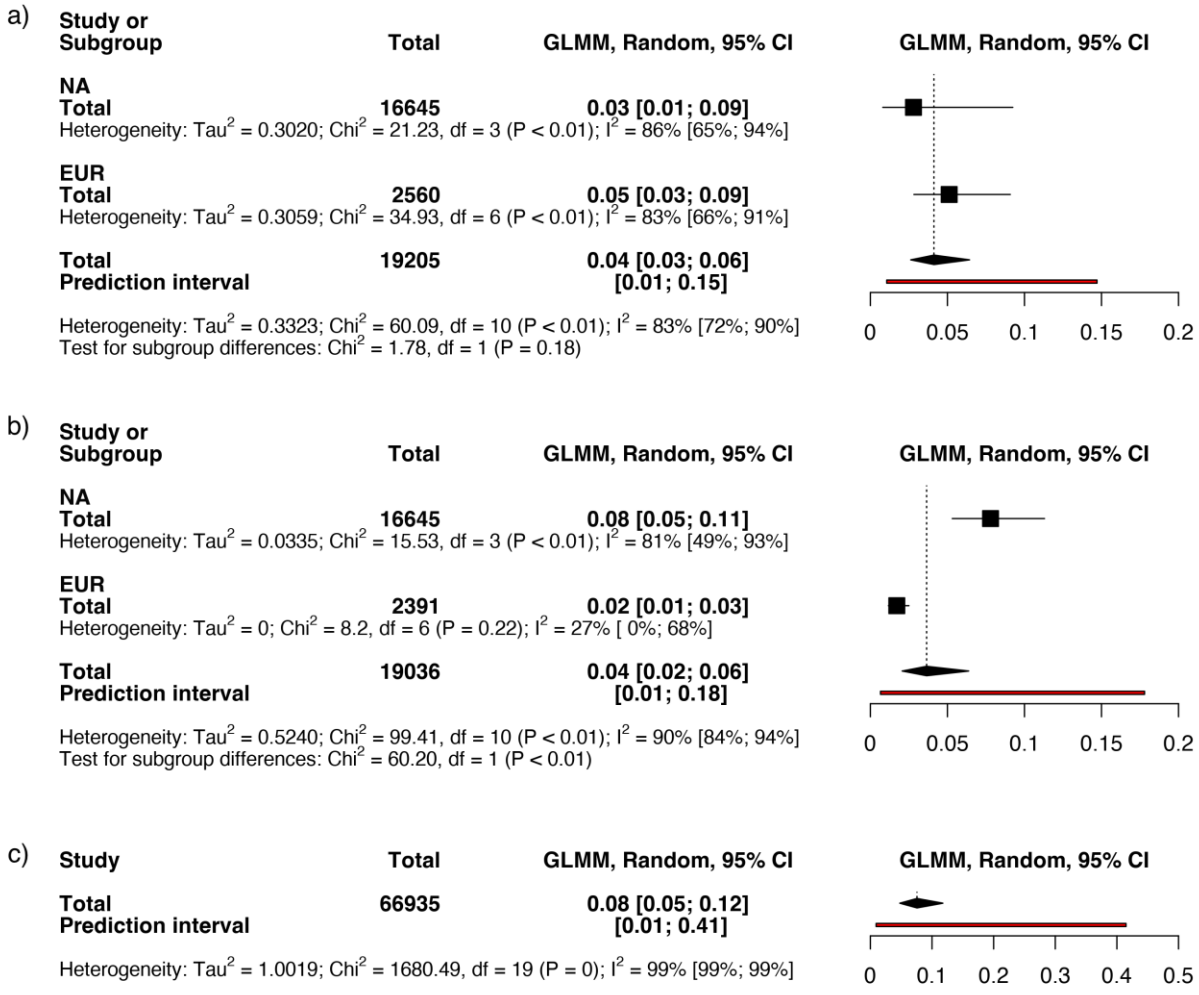
Supplementary Figure 1. Traffic light plots for quality assessment of: **(a)** studies reporting incidence of NTM infection and fourteen (n = 5); and **(b)** studies reporting prevalence of NTM-PD (n = 14).



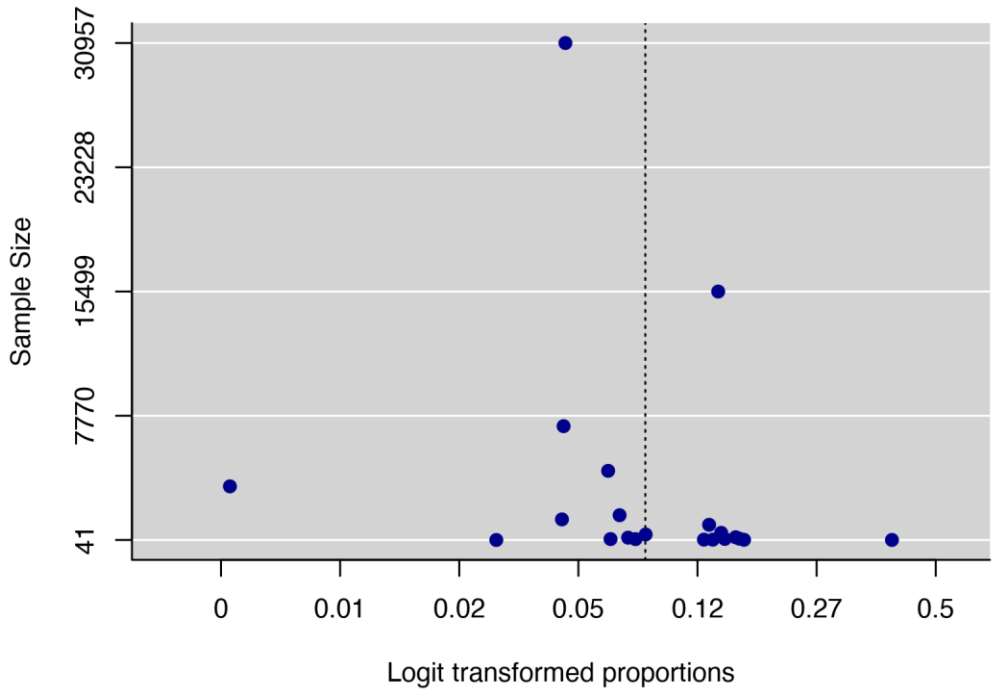




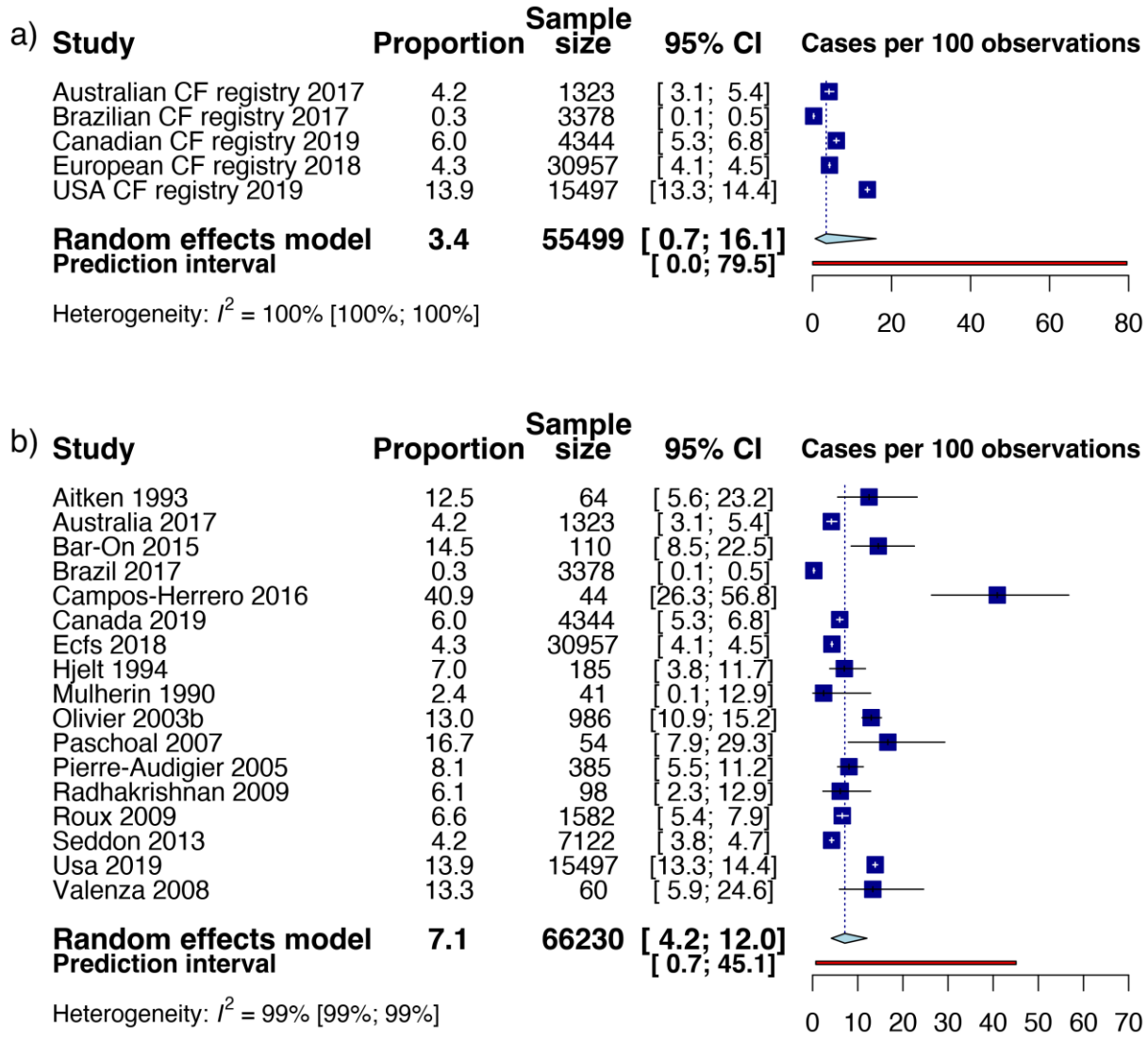
Supplementary Figure 2. Subgroup analyses of NTM infection prevalence stratified by (**a**) registry and non-registry studies; (**b**) year of data collection; and (**c**) geographical region. **NA**: North America. **EUR**: Europe. **Other** Latin America and the Caribbean, Asia, Africa and Middle-East



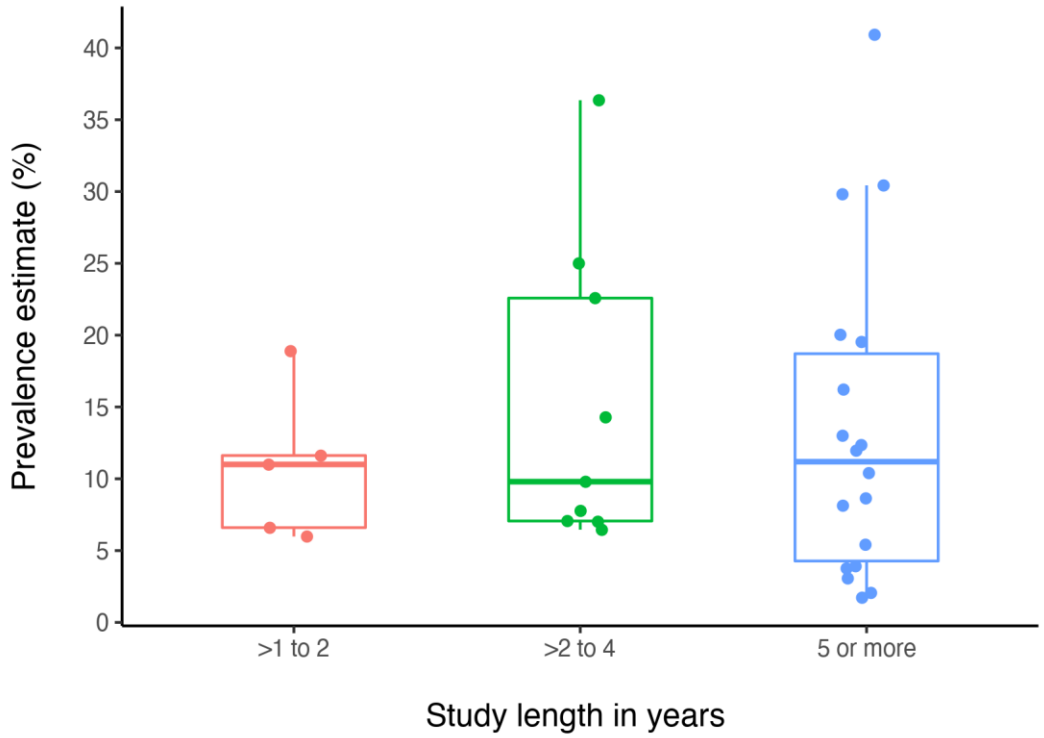
Supplementary Figure 3. Exploratory subgroup analysis by geographical region for meta-analyses of: (**a**) *Mycobacterium abscessus* complex; (**b**) Mycobacterium avium complex; All included studies came from either Europe – **EUR-** or North America -**NA-**. (**c**) Sensitivity analysis of NTM infection prevalence meta-analysis excluding the study Preece 2016, which screened only by clinical indication.



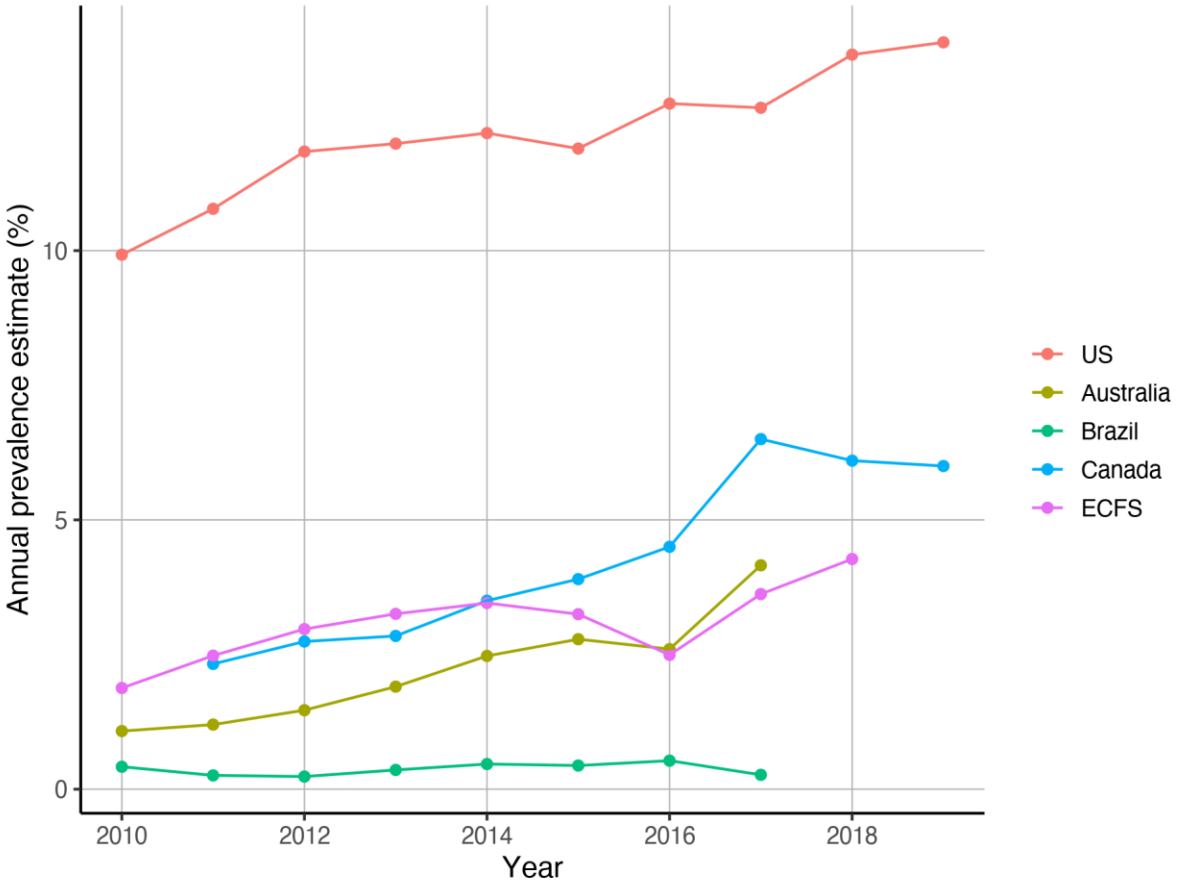
Supplementary Figure 4. Funnel plot exploring the relationship between study sample size and NTM infection prevalence/proportion (LOGIT transformed)



Supplementary Figure 5. Sensitivity analyses exploring the estimate of NTM infection point (and annual) prevalence only in registry reports (n = 5) **(a)**. Sensitivity analyses exploring the estimate of NTM infection point (and annual) prevalence after excluding four studies (Preece 2016, Raidt 2015, Plongla 2015 and Scohy 2018) that used non-standardized culture media for indentification of NTM **(b)**.



Supplementary Figure 6. Box-plots showing the estimates of period prevalence in studies (n = 32) according to the time-interval evaluated.



Supplementary Figure 7. Trend of NTM infection prevalence in five different registries between 2010 and 2019.

Supplementary Table 1. Eligibility criteria for systematic review

Population (P): People with Cystic Fibrosis	• Includes CF patients of any age • Excludes studies with a specific subgroup of CF patients (transplant recipients, Allergic broncho-pulmonary aspergillosis, macrolide exposure, chronic *Pseudomonas* spp. infection)
Condition (C): NTM infection or NTM pulmonary disease	Reporting of NTM infection • Defined by isolation of a nontuberculous mycobacteria on at least one occasion • Microbiological detection methods (culture, direct staining, PCR, MALDI-TOF, not reported) Reporting of pulmonary NTM disease • Based on accepted criteria for diagnosis (ATS 1997, ATS 2007, CFF/ECFS 2016)
Outcome (O): Prevalence or incidence	Reporting of NTM: • Point prevalence (at a given point in time) • Period prevalence (over a time period) • Incidence rate (person-time measures) • Incidence proportion (percentage of new cases/ at risk patients)
Study design (S): Prospective or cross-sectional	• Study design must be cohort, clinical trial or cross-sectional (including registry reports). • Excludes reviews, letters to the editor, commentaries and case reports.
Others	• English language reports • No restriction on date of publication • No restriction by geographic region

CFF: Cystic Fibrosis Foundation. **ATS**: American Thoracic Society. **ECFS**: European Cystic Fibrosis Society.

Supplementary Table 2 - Grey literature sources and hand searched references

Grey literature source	URL
Canadian Institute for Health Information (CIHI). Quick Stats	https://www.cihi.ca/en/quick-stats
IQVIA	https://www.iqvia.com/
Institute for Clinical Evaluative Sciences (ICES). Publications	http://www.ices.on.ca/Publications.aspx
Institute of Health Economics (IHE). Database of Online Health Statistics	http://www.ihe.ca/health-statistics-database)
New Brunswick Ministry of Health, Office of the Chief Medical Officer of Health. Epidemiology and Surveillance	http://www2.gnb.ca/content/gnb/en/departments/ocmoh/epidemiology_surveillance.html
Public Health Agency of Canada (PHAC). Public Health Infobase	http://infobase.phac-aspc.gc.ca/index-en.html
Statistics Canada. Diseases and physical health conditions.	https://www150.statcan.gc.ca/n1/en/subjects/health/diseases_and_physical_health_conditions
Center for Disease Control (USA). National center for health statistics.	https://www.cdc.gov/nchs/
The Organization for Economic Co-operation and Development	https://data.oecd.org/
World Health Organization – Global health observatory.	https://www.who.int/data/gho
BMC proceedings	https://bmcproc.biomedcentral.com/)

DOI of articles used in forward and backward reference search	
DOI: 10.1164/rccm.200207-678OC	DOI: 10.1097/MCP.0b013e328365ab33
DOI: 10.1128/CMR.00068-09	DOI: 10.1002/ppul.23825
DOI: 10.1164/ajrccm/147.5.1271	DOI: 10.1128/AAC.00861-10
DOI: 10.1136/thoraxjnl-2015-207360	DOI: 10.1164/ajrccm.185.2.231
DOI: 10.1002/ppul.24913	DOI: 10.1128/JCM.01257-09
DOI: 10.1513/AnnalsATS.201709-727OC	DOI: 10.1016/j.jcf.2007.06.006
DOI: 10.1378/chest.126.2.566	DOI: 10.3201/eid1403.061405
DOI: 10.1164/rccm.200604-571ST	DOI: 10.1378/chest.102.1.70
DOI: 10.1126/science.aaf8156	DOI: 10.1136/thoraxjnl-2017-210927
DOI: 10.1016/j.jcf.2009.12.001	

Supplementary Table 3. Data dictionary for extraction in systematic review

variable_name	Question
id	First author surname + year of publication
title	Full title of the study/report
publication_date	Annotate the year of publication of the primary report
study_design	Which study design was used? (cross-sectional, cohort study, registry, etc.)
eligibility	Which inclusion and exclusion criteria were used/reported in the study?
sample_size	How many individuals were included in each group?
reference_population	Which was the sampling frame for recruitment?
region	Continent where the study was conducted
country	Country(ies) where the study population was recruited
study_funding	What is the source of funding for the study?
study_aims	What is the explicit aim of the manuscript? As reported by the authors, even if it is not aimed at prevalence/incidence
conflicts_interest	Are there perceived or reported conflicts of interests?
cf_definition	What is the criteria for definition of cystic fibrosis used in the study?
age	What is the age distribution among included participants? (only those tested for NTM)
females	What is the distribution of females among included participants? (only those tested for NTM)
ethnicity	What is the ethnicity of included participants? (only those tested for NTM)
lung_function	What is the distribution of lung function measures in the study?
genotype	What is the distribution of CF genotype among included participants?
bmi	What is the distribution of body mass index in participants tested for NTM?
testing_freq	What is the reported testing frequency for NTM in the study?
infection_definition	How was pulmonary NTM infection defined?
disease_definition	How was pulmonary NTM disease defined?
ntm_specimen	Which sample(s) type were used to test for NTM? (sputum, saliva...)
ntm_technique	What type of decontamination technique was used prior to NTM detection?
ntm_molecular	What molecular method was used to detect NTM?
ntm_culture	What type of media and technique was used to culture the NTM?
ntm_speciation	How was the species of infecting NTM identified?
mabc_distribution	What is the distribution of Mycobacterium abscessus complex bacteria in the study population?
avium_distribution	What is the distribution of Mycobacterium avium complex bacteria in the study population?
ntm_other_distribution	What is the distribution of NTM species in the study (M. avium, M. abscessus, M. gordonae, etc.)
point_infection	What is the reported **point prevalence** for NTM infection?
point_disease	What is the reported **point prevalence** for **NTM-PD?**
year_point	In which year was the point prevalence calculated?
period_infection	What is the reported **period prevalence** of **NTM infection?**
period_disease	What is the reported **period prevalence** of **NTM-PD?**
period_years	In which years was the period prevalence calculated?
incidence_calculation	Briefly describe how the estimate of incidence was calculated.

incidence_rate	Incidence reported as a rate (longitudinal studies): number of cases over the adjusted follow-up period
incidence_proportion	Incidence reported as **new cases of NTM-PD** during a period of follow up over the at-risk patients
fac_corticosteroid	Percentage of the population at risk and those with positive NTM infection/disease that are in corticosteroid therapy
fac_aspergillus	Percentage of patients with presence of *Aspergillus spp.* in respiratory cultures at time of NTM positivity
fac_ABPA_diagnosis	Percentage of the population at risk and those with positive NTM infection/disease that have an ABPA diagnosis
fac_macrolide	Percentage of the population at risk and those with positive NTM infection/disease that are receiving macrolides

Supplementary Table 4. Characteristics of studies reporting NTM infection point (or annual) prevalence (n = 67)

Study ID	Study design	Sample size	Location	Age (y)	Females	Specimen	Culture method	Speciation	Year or interval	Prevalence estimate
Abidin 2020** [1]	Cross-sectional	4,687	United Kingdom	9 (5 - 13) [median; IQR]	51.4%	NR	NR	NR	2016 2017 2018	3.5% 3.1% 3.6%
Adjemian 2014** [2]	Cross-sectional	10,527	United States	27 (12 - 82) [mean; range]	NA	NR	NR	NR	2010 - 2011	13.2%
Adjemian 2018 [3]	Cross-sectional	16,153	United States	12 to 18 - 23% 18 to 60 - 75% ≥60 - 2%	48%	NR. Annual screening (only 77% had 2/5 years of testing)	NR	NR	2010	11.0%
Aitken 1993 [4]	Cross-sectional	64	United States	17 - 50 [range]	**NTM +** 50% **NTM -** 57.1%	Sputum. Frequency NR	Auramine and Kinyoun stains. L-J, BACTEC 12B and 7H11	NR	Dec 1990 - Dec 1991	12.5%
Australia 2010 [5]	Registry	1,946 (tested*)	Australia	median: 17.6 mean: 19 Adults: 1,500 (49%)	46.9% (n = 3,063)	Sputum, BAL. Frequency NR	NR	NR	2010	1.1%
Australia 2011 [6]	Registry	2,001 (tested*)	Australia	mean: 19.2 Adults: 1,528 (49%)	47.3% (n = 3,133)	Sputum, BAL. Frequency NR	NR	NR	2011	1.2%
Australia 2012 [7]	Registry	2,182 (tested*)	Australia	median: 17.7 Adults: 1,556 (49%)	47.1% (n = 3,156)	Sputum, BAL. Frequency NR	NR	NR	2012	1.5%
Australia 2013 [8]	Registry	2,206 (tested*)	Australia	median: 17.9 mean: 20 Adults: 1,613 (50%)	47.1% (n = 3,235)	Sputum, BAL. Frequency NR	NR	NR	2013	1.9%
Australia 2014 [9]	Registry	2,021 (tested*)	Australia	median: 18.4 mean: 20.5 Adults: 1,684 (51%)	47.0% (n = 3,294)	Sputum, BAL. Frequency NR	NR	NR	2014	2.5%
Australia 2015 [10]	Registry	2,047 (tested*)	Australia	median: 18.8 mean: 20.9 Adults: 1,756 (52%)	46.8% (n = 3,379)	Sputum, BAL. Frequency NR	NR	NR	2015	2.8%

Australia 2016 [11]	Registry	1,769 (tested*)	Australia	median: 18.4 mean: 20.5 Adults: 1,684 (51%)	46.6 (n = 3,422)	Sputum, BAL. Frequency NR	NR	NR	2016	2.6%
Australia 2017+ [12]	Registry	1,323 (tested*)	Australia	median: 19.6 mean: 21.7 Adults: 1,684 (54%)	46.3% (n = 3,156)	Sputum, BAL. Frequency NR	NR	NR	2017	4.2%
Bar-On 2015 [13]	Cohort	110 (2011)	Israel	**2008** **NTM +** 17.8 (4.3 - 55.3**)** **NTM –** 15.2 (0.2 - 59.3) [median; range**]**	2008 **NTM -** 47.9% **NTM +** 35.3%	Sputum. Screened every 3-6 months	L-J and BACTEC MGIT. Monitored for 8 weeks	Mycobacteria Genotype kits	2003 2004 2005 2006 2007 2008 2009 2010 2011	5.1% 4.5% 4.4% 6.5% 7.3% 8.8% 12.4% 13.5% 14.5%
Brazil 2010 [14]	Registry	1,440	Brazil	12.9 (10.9) [mean ± sd]	47.6% (n = 1,798)	NR	NR	NR	2010	0.4%
Brazil 2011 [15]	Registry	1,440	Brazil	13.2 (10.9) [mean ± sd]	46.5% (n = 2,182)	NR	NR	NR	2011	0.3%
Brazil 2012 [16]	Registry	2,132	Brazil	13.5 (11.0) [mean ± sd]	46.9% (n = 2,669)	NR	NR	NR	2012	0.2%
Brazil 2013 [17]	Registry	2,238	Brazil	13.9 (11.8) [mean ± sd]	47.2% (n = 2,924)	NR	NR	NR	2013	0.4%
Brazil 2014 [18]	Registry	2,571	Brazil	13.6 (11.2) [mean ± sd]	47.2% (n = 2,924)	NR	NR	NR	2014	0.5%
Brazil 2015 [19]	Registry	2,961	Brazil	14.2 (12) [mean ± sd]	47.8% (n = 3,806)	NR	NR	NR	2015	0.4%
Brazil 2016 [20]	Registry	3,212	Brazil	13.8 (11.6) [mean ± sd]	48% (n = 4,654)	NR	NR	NR	2016	0.5%
Brazil 2017+ [21]	Registry	3,378	Brazil	14.6 (11.9) [mean ± sd]	48% (n = 5,128)	NR	NR	NR	2017	0.3%

Campos-Herrero 2016 [22]	Cross-sectional	44	Spain	**NTM+** 12 (5 - 59) [median; range]	**NTM +** 38.9%	Sputum. Frequency NR	BACTEC MGIT and on L-J	Phenotypic tests and/or nucleic acid hybridization assays	2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012	33.3% 24% 19.2% 12.5% 0% 12.5% 12.9% 13.3% 9.7% 8.8% 9.1%
Canada 2011 [23]	Registry	3,913	Canada	median: 20 mean: 21.8	47.3% (n = 3,913)	NR	NR	NR	2011	2.3%
Canada 2012 [24]	Registry	3,975	Canada	median: 21 mean: 22.3	47.1% (n = 3,975)	NR	NR	NR	2012	2.7%
Canada 2013 [25]	Registry	4,077	Canada	median: 21.4 mean: 22.6	47.1% (n = 4,077)	NR	NR	NR	2013	2.8%
Canada 2014 [26]	Registry	4,128	Canada	median: 21.9	46.9% (n = 4,182)	NR	NR	NR	2014	3.5%
Canada 2015 [27]	Registry	4,192	Canada	median: 22.3	47.1% (n = 4,192)	NR	NR	NR	2015	3.9%
Canada 2016 [28]	Registry	4,246	Canada	median: 22.7	46.4% (n = 4,246)	NR	NR	NR	2016	4.5%
Canada 2017 [29]	Registry	4,309	Canada	median: 22.8	46.1% (n = 4,302)	NR	NR	NR	2017	6.5%
Canada 2018 [30]	Registry	4,371	Canada	median: 23.5	46.5% (n = 4,371)	NR	NR	NR	2018	6.1%
Canada 2019+ [31]	Registry	4,344	Canada	median: 23.7	46.6% (n = 4,344)	NR	NR	NR	2019	6%
ECFS 2010 [32]	Registry	31,932	European countries	17.8 (0 - 80.1) [median; range]	47.7% (n = 32,248)	NR	NR	NR	2010	2.3%
ECFS 2011 [33]	Registry	26,700	European countries	mean: 19.6 17.9 (9.3 - 27.5) [median; IQR]	47.5% (n = 36,340)	NR	NR	NR	2011	2.5%
ECFS 2012 [34]	Registry	27,686	European countries	mean: 19.8 18.1 (9.3 - 28) [median; IQR]	47.4% (n = 37,404)	NR	NR	NR	2012	3.0%
ECFS 2013 [35]	Registry	28,596	European countries	mean: 20.1 18.4 (9.3 - 28.5) [median; IQR]	47.3% (n = 38,985)	NR	NR	NR	2013	3.3%

ECFS 2014 [36]	Registry	28,961	European countries	mean: 20.5 18.6 (9.4 - 29.2) [median; IQR]	47.4% (n = 35,582)	NR	NR	NR	2014	3.5%
ECFS 2015 [37]	Registry	31,763	European countries	mean: 20.7 18.8 (9.4 - 29.5) [median; IQR]	47.5% (n = 42,054)	NR	NR	NR	2015	3.3%
ECFS 2016 [38]	Registry	25,464	European countries	mean: 21 19 (9.5 - 30) [median; IQR]	47.4% (n = 44,719)	NR	NR	NR	2016	2.5%
ECFS 2017 [39]	Registry	39,667	European countries	mean: 20.8 18.5 (9.1 - 30) [median; IQR]	47.4% (n = 48,204)	NR	NR	NR	2017	3.6%
ECFS 2018+ [40]	Registry	30,957	European countries	mean: 19.8 18.5 (9.2 - 30.3) [median; IQR]	47.5% (n = 49,886)	NR	NR	NR	2018	4.1%
Gardner 2019** [41]	Cross-sectional	5,333	United Kingdom	6 (2 - 12) [median; IQR]	49.1% (n = 5,333)	NR. Annual screening.	NR	NR	2010 2011 2012 2013 2014 2015	1.3% 1.7% 1.8% 2.1% 3.6% 3.8%
Hatziagorou 2020 [42]	Cohort	41,101	European countries	NA	NA	NR	NR	NR	2011 2012 2013 2014 2015 2016	2.6% 3.1% 3.4% 3.5% 3.3% 3.3%"
Hjelt 1994 [43]	Cross-sectional	185	Denmark	15.3 (2.2 - 38.5) [mean; range]	NA	Sputum. Three samples in 3 months	L-J	Nucleic-acid hybridization or biochemical tests	1987 - 1988	7%
Mulherin 1990 [44]	Cohort	41 (tested*)	Rep. of Ireland	NA	NA	Sputum. Frequency NR	L-J	NR	1990 (uncertain)	2.4%
Olivier 2003 [45]	Cross-sectional	986	United States	23 ± 9 [mean ± sd]	47% (n = 986)	Sputum. Frequency NR	L-J and BACTEC MGIT	RGM by Hsp65 sequencing. Slow growers by PCR and restriction digest	1994 (uncertain)	13.0%
Paschoal 2007 [46]	Cross-sectional	54	Brazil	41.8 ± 17.2 [mean ± sd]	50%	Sputum. Frequency NR	NR	NR	2003 - 2004	16.7%
Pierre-Audigier 2005 [47]	Cross-sectional	385	France	12.0 ± 6.1 [mean ± sd]	47.3% (n = 385)	Sputum. Three times per year.	L-J up to 10 weeks.	RGM by biochemical techniques and hsp65 sequencing. MAC by PCR probes	2000	8%

Plongla 2017 [48]	Cohort	487	United States	14.9 (<1 - 71) [median; range]	53.6% (n = 487)	Sputum/tracheal aspirates, pharyngeal swabs, bronchial wash and BAL fluids. Frequency NR	MGIT L-J, RGM medium, and BCSA.	RGM by MALDI-TOF MS IVD system. Others by 16S rRNA sequencing.	Dec 2015 - Apr 2016	14.7%
Preece 2016 [49]	Cross-sectional	210	United Kingdom	<1 - 77 [range]	NA	Sputum. Less than 10% were regularly screened	RGM medium and BCSA	Sequencing of two genes among RPO-B, HSP65 and SOD-A	Feb - Sep 2014	17.5%
Radhakrishnan 2009 [50]	Cross-sectional	98	Canada	**NTM +** 15.1 ± 2.2 **NTM –** 14.0 ± 3.0 [mean ± sd]	**NTM+** 66.7% **NTM-** 53.3%	Sputum. Tested once in the year of study.	MGIT and L-J, up to 7 weeks	AccuProbe test for MAC and *M. gordonae*. Others by HP-LC	Mar - Nov 2004	6.1%
Raidt 2015 [51]	Cross-sectional	94	Germany	mean: 24.9	47.9%	Sputum or deep pharyngeal swab. Frequency NR	BCSA	GenoType Mycobacterium CM/AS assay	2011	7.4%
Roux 2009 [52]	Cohort	1,582	France	18.9 (0.3 - 82) [mean; range]	48.6% (n = 1,582)	Sputum. Frequency NR	MGIT and/or Lowenstein Colestos slants.	Sequencing of hsp65, 16S-23S intergenic region and rpoB (only MABs)	2014	6.6%
Salsgiver 2016 [53]	Cohort	**Total** 31,915 **Tested*** unknown	United States	NA	NA	Sputum or BAL (< 12 years). Frequency NR	NR	NR	2012	12.0%
Scohy 2018 [54]	Cross-sectional	124	Belgium	24.5 (6 - 68) [median; range]	47%	Sputum. Frequency NR	BACTEC MGIT and RGM medium	MALDI-TOF MS, Geno-Type NTM-DR and genotyping for MABs	Sep 2016 - Mar 2017	16.1%
Seddon 2013 [55]	Cross-sectional	7,122	United Kingdom	**Pediatric** 46.5% **Adults** 53.4%	NA	NR. 33/42 centers tested annually, 9 only by symptoms.	NR	NR	2008 - 2009	4.2%
USA 2010 [56]	Registry	9,462	United States	17.2 (0 to 82) [median; range]	48.2%	NR	NR	NR	2010	9.9%
USA 2011 [57]	Registry	10,848	United States	mean: 19.5 17.5 (0 to 81) [median; range]	48.2%	NR	NR	NR	2011	10.8%
USA 2012 [58]	Registry	11,927	United States	mean: 19.8 17.7 (0 to 82) [median; range]	48.3%	NR	NR	NR	2012	11.8%
USA 2013 [59]	Registry	12,873	United States	mean:20.2 median:17.2	48.5%	NR	NR	NR	2013	12%

USA 2014 [60]	Registry	13,602	United States	mean:20.6 median:18.3	48.4%	NR	NR	NR	2014	12.2%
USA 2015 [61]	Registry	14,225	United States	mean:20.9 median:18.6 Adults - 51.6%	48.4%	NR	NR	NR	2015	11.9%
USA 2016 [62]	Registry	14,501	United States	mean:21.3 median:19	48.4%	NR	NR	NR	2016	12.7%
USA 2017 [63]	Registry	15,041	United States	mean:21.7 median:19.3	48.4%	NR	NR	NR	2017	12.7%
USA 2018 [64]	Registry	15,067	United States	mean:22.2 median:18.6	48.2%	NR	NR	NR	2018	13.6%
USA 2019+ [65]	Registry	15,497	United States	mean:22.7 median:20.3	48.1%	NR	NR	NR	2019	13.9%
Valenza 2008 [66]	Cross-sectional	60	Germany	18 (6 - 41y) [median; range]	43.3% (n = 60)	Sputum. Frequency NR	MGIT	Sequencing of the 16S rRNA-gene	2006	13.3%
Viviani 2016** [67]	Cross-sectional	13,593	France, Sweden and UK	17.6 (0 - 82.5) [median; range]	47.4% (n = 13,593)	NR	NR	NR	2009	2.8%

BACTEC MGIT: Mycobacterial Growth Indicator Tubes.by BACTEC. **L-J**: Lowenstein-Jensen egg-based medium. **BAL:** Bronchoalveolar lavage. **RGM:** Rapid growing mycobacteria (M. abscessus complex). **MALDI-TOF MS:** matrix-assisted laser desorption/ionization- time-of-flight mass spectrometry. **HP-LC**: High performance liquid chromatography. **BCSA**: Burkholderia cepacia selective agar. **Tested*** specifies the actual number of at-risk patients tested for NTM in respiratory samples. ****** Excluded from meta-analysis as the data was duplicated with the registry reports. **+** Included in meta-analysis as the last report with raw data available from a registry.

Supplementary Table 5. Characteristics of studies reporting period prevalence of NTM infection in an interval longer than a year (n = 32)

Study ID	Study design	Sample size	Location	Age(y)	Females	Specimen	Method culture	Speciation	Period	Prevalence estimate
Abidin 2021 [1]	Cross-sectional	4,687	United Kingdom	9 (5 - 13) [Median; IQR]	51.4%	NR	NR	NR	2016 - 2018	6.5%
Ademhan-Tural 2021 [68]	Cohort	485	Turkey	**NTM+** 19 (8 - 27) [median; range]	**NTM+** 30% (n=10)	Sputum, BAL. Annual screening.	MGIT and L-J.	Commercial reverse hybridization assays	2012 - 2020	2.1%
Ahmed 2019 [69]	Cohort	42	United Kingdom	**NTM +** 12.7 ± 3.4 **NTM -** 11.2 ± 3.7 [mean ± sd]	45.2%	Induced sputum. Annual screening.	L-J and BACTEC MGIT. Incubated up to 12 weeks	NR	Jan 2012 - Dec 2016	14.3%
Aiello 2018 [70]	Cross-sectional	117	Brazil	**NTM +** 21 (9 - 56) [mean ± sd]	**NTM+** 42.8%	Sputum or BAL. Annual screening	BACTEC MGIT, up to 42 days of incubation	PCR-restriction enzyme analysis	Jan 2014 - Dec 2015	6%
Bange 2001 [71]	Cross-sectional	214	Hannover, Germany	NR	NA	Sputum, tracheal aspirates, and BAL. Frequency NR.	BACTEC MGIT	PCR amplification of 16S rRNA gene and sequencing	Sep 1997 - Mar 1999	7%
Bar-On 2015 [13]	Cohort	180	Israel	2008 **NTM +** 17.8 (4.3 - 55.3) **NTM –** 15.2 (0.2 - 59.3) [median; range]	2008 **NTM -** 47.9% **NTM +;** 35.3%	Sputum. Screened every 3-6 months	L-J and BD BACTEC MGIT. Monitored for 8 weeks	Mycobacteria Genotype kits	Jan 2002 - Dec 2011	18.9%
Campos Herrero 2016 [22]	Cross-sectional study	44	Gran Canaria, Spain	12 (5 - 59) [median; range]	**NTM+** 38.9%	Sputum. Frequency NR	BACTEC MGIT 960 and L-J medium	Phenotypic tests and/or nucleic acid hybridization assays	2002 - 2012	40.9%
Candido 2014 [72]	Cross-sectional	129	Brazil	NR	NA	Sputum. Frequency NR	L-J	Hsp65 PCR restriction analysis and partial sequencing of the RpoB gene	Jun 2009 - Mar 2012	7.8%
Cavalli 2017 [73]	Cohort	401	France	18.9 ± 7.4 [mean ± sd]	42%	Sputum. Annual screening	NR	Hsp65 sequencing	1997 - 2002	8.6% (n = 139)

Esther 2005 [74]	Cross-sectional	431 114 (BAL)	United States	**NTM+** 7.7 ± 3.8 [mean ± sd]	47%	Sputum and BAL. Screened by symptoms.	L-J (8 wk) an BACTEC 7HB12 vial (4 wk)	NR	1993 - 2002	3.9%
Esther 2010 [75]	Cross-sectional	829	United States	NR	NA	Sputum, BAL. Frequency NR.	NR	Biochemical methods and Hsp65 sequence analysis after 2007	2000 - 2007	13.7%
Fauroux 1997 [76]	Cohort	106	France	1 - 18y [range]	57.1%	Sputum. Screened twice per year	L-J	Biochemical methods	May 2012 - Dec 2013	6.6%
Fernandez-Caso 2020 [77]	Cross-sectional	92	Madrid, Spain	29.1 ± 9.5 [mean ± sd]	48.9%	Sputum. Frequency NR	NR	MALDI-TOF MS and PCR followed by reverse hybridization	2010 - 2017	30.4%
Gardner 2019 [41]	Cross-sectional	5,333	United Kingdom	6 (2 - 12) [median; IQR]	49.1%)	NR. Annual screening.	NR	NR	2010 - 2015	5.4%
Giron 2005 [78]	Cohort	28	Spain	25.3 ± 6.7 [mean ± sd]	42.8%	Sputum. Frequency NR	Coletsos and liquid MGIT 960 with modified 7H9 broth	NR	Jan 1996 - Dec 1999	25%
Ho 2021 [79]	Cross-sectional	171	Tropical French Reunion Island, Africa	**NTM +** 16 (10 - 23) [median; range]	55%	Sputum and BAL. Annual screening.	NR	16S rRNA gene sequencing after ruling out MTBC using the AccuProbe MTB DNA probe kit	2002 - 2015	29.8%
Hughes 2021 [80]	Cross-sectional	567	United Kingdom	**MABs** 11.8 (3.2 – 17.3) **MAC** 12.7 (3.6 – 16.7) **Other NTM** 11.6 (7.4 – 15.9) [median; range]	**NTM +** 63.5% (n = 63)	Sputum and BAL. Frequency NR.	NR.	NR.	2011 - 2018	10.4%
Kilby 1992 [81]	Cross-sectional	87	United States	**NTM +** 25.8 ± 4.6 [mean ± sd]	70.6%	Sputum. Tested by clinical symptoms.	L-J and BACTEC 7H12	Biochemical techniques and DNA probes for MAC	1981 - 1990	19.5%
Kopp 2015 [82]	Cross-sectional (US registry)	30,896	United States	<18y - 55.7% ≥18y - 44.3%	48.1%	NR	NR	Biochemical methods	2007 - 2012	8.1%

Leitriz 2004 [83]	Cohort	91	Munich, Germany	17.8 ± 9.2 [mean ± sd]	58.2%	Sputum/BAL. Frequency NR	BACTEC modified 7H12, L-J. Incubated for 8 weeks.	Nucleic acid probes, 16S rRNA sequencing, and biochemical tests	Jan 1999 - Dec 2000	11%
Levy 2008 [84]	Cross-sectional	186	Israel	20.5 ± 10.4 [mean ± sd]	60.2%	Sputum. Frequency NR	MB/BacT bottle, L-J and Middlebrook 7H11 plate, up to 7 weeks.	Biochemical methods and drug susceptibility patterns. MAC confirmed by RNA/DNA probes	Jul 2001 - Jul 2003	22.6%
Mussaffi 2005 [85]	Cross-sectional	139	Israel	2 - 52 [range]	NA	Sputum. Frequency NR.	NR	NR	1997 - 2002	8.6%
Oliver 2001 [86]	Cohort	37	Spain	21 (4 - 48) [mean; range]	NA	Sputum. Sampled twice in a week for study.	Coletsos, L-J and ESP liquid medium for 56 days.	Biochemical tests, and hybridization probes for MAC	2001 (uncertain)	16.2%
Olivier 2003 [45]	Cross-sectional	986	United States	23 ± 9 [mean ± sd]	47%	Sputum. Frequency NR	L-J and BACTEC MGIT.	RGM by Hsp65 sequencing. Slow growers by PCR and restriction digest	1994 (uncertain)	13%
Phelippeau 2015 [87]	Cohort	354	France	≥18 y - 235 <18y - 119	56.2%	NR	MGIT and Coletsos slant	Partial *rpo B* sequencing	Jan 2010 - Sep 2014	7.1%
Qvist 2014 [88]	Cohort	198	Denmark	NR	NA	Sputum, laryngeal aspirates or BAL. Annual screening.	L-J and BACTEC MGIT, incubated for 8 weeks. BCSA for 14 days.	MALDITOF and 16S rRNA sequencing locally.	May 2012 - Dec 2013	11.6%
Qvist 2015 [89]	Cross-sectional	1,270	Denmark, Norway and Sweden	19(13 - 22) [median; IQR]	**NTM+** 26.7%	Sputum, BAL, laryngeal suction. Annual screening.	L-J, BACTEC MGIT or BCSA	16-23s spacer/*rpoB/hsp65* sequencing, biochemical tests, hybridization, GenoType Mycobacterium CM and/or growth on L-J	2000 - 2012	12.4%
Satana 2014 [90]	Cross-sectional	130	Turkey	12.1 ± 3.1 [mean ± sd]	47.6%	Sputum. Frequency NR	BACTEC MGIT and L-J for 10 weeks.	GenoType Mycobacterium CM/AS assay	Apr 2003 - Nov 2008	3.1%
Sermet-Gaudelus 2003 [91]	Cross-sectional	296	France	11.3 (0.2 - 32) [mean; range]	53.4%	Sputum. Annual screening	L-J with 10 wks of incubation	RGM by biochemical methods/hsp65 sequencing. MAC through PCR probes	Jan 1996 - Dec 1999	9.8% MABs - 5.1%
Smith 1984 [92]	Cross-sectional	223	United Kingdom	**NTM +** 21 (17 - 29) [mean; range]	**NTM+** 50%	Sputum. Screened by symptoms.	NR	Biochemical methods	1978 - 1984 (uncertain)	1.7%

Torrens 1998 [93]	Cross-sectional	372	United Kingdom	16.1 ± 4.5 [mean ± sd]	**NTM+** 28.6%	Sputum. Frequency NR	L-J	NR	1989 - 1997 (uncertain)	3.8%
Yan 2020 [94]	Cross-sectional	99	Melbourne, Australia	**MABS+** 13 (6 - 17) [mean; range]	40.9%	Sputum, BAL. Tested annually	NR	NR	Jan 2013 - Mar 2017	36.4% [screened 99/238]

NTM: Nontuberculous mycobacteria. **MGIT:** Mycobacterial Growth Indicator Tubes. **L-J:** Lowenstein-Jensen egg-based medium. **BAL:** Broncho-Alveolar Lavage. **RGM:** Rapid growing mycobacteria (*M. abscessus* complex). **MAB:** *M. abscessus* complex. **MAC:** Mycobacterium avium complex. **PCR:** Nucleic acid amplification by polymerase chain reaction. **MALDI-TOF MS:** matrix-assisted laser desorption/ionization- time-of-flight mass spectrometry. **NR:** Not reported. **BCSA:** *Burkholderia cepacia* selective agar. **MTBC:** *Mycobacterium tuberculosis*.

Supplementary Table 6. NTM infection incidence proportion (n = 5)

Study ID	Study design	Sample size	Location	Age(y)	Females	Specimen	Culture method	Incidence definition	Years	Incidence proportion
Bar-On 2015 [13]	Cohort (retrospective)	110	Israel	2008 **NTM +** 17.8 (4.3–55.3) **NTM –** 15.2 (0.2–59.3) [median;range]	2008 **NTM +** 35.3% **NTM -** 47.9%	Sputum. Frequency NR	L-J and BACTEC MGIT. Incubated up to 8 wks.	Percentage of patients with a new NTM positive sputum / all clinic patients at the end of that year (includes those with a different strain)	2003 2004 2005 2006 2007 2008 2009 2010 2011	1.4% 1.3% 2.2% 3.3% 4.3% 3.1% 5.5% 5.2% 8.7%
Binder 2013 [95]	US registry Cohort (retrospective)	5,403	United States	**MAC** 25 ± 13 **MABs** 23 ± 13 [mean ± sd]	49.3% (n = 5212)	NR	NR	Incident cases: patients with positive mycobacterial culture in 2011 and negative culture in 2010	2011	3.5%
Campos-Herrero 2016 [22]	Cross-sectional	44	Gran Canaria, Spain	**NTM +** 12 (5-59) [median;range]	**NTM +** 38.9%	Sputum. Frequency NR	BACTEC MGIT 960 and L-J	Percentage of patients with a NTM positive culture for the first time during each calendar-year	2002 2003 2004 2005 2006 2007 2008 2009 2010:2012	14.3% 4 % 7.7 % 4.2% 0 % 12.5% 6.5% 6.7% 0 %
Hatziagorou 2020 [42]	Cohort (prospective)	41,101	European countries	NR	NR	NR	NR	Patient with a first-time positive culture for *Mycobacterium* spp. with negative cultures in prior two years	2011 2012 2013 2014 2015 2016	1.4% (n = 15,308) 1.3% (n = 19,350) 1.3% (n = 22,173) 1.8% (n = 22,952) 1.5% (n = 23,536) 1.4% (n = 24,137)
Leitriz 2004 [83]	Cohort (prospective)	91	Munich, Germany	17.8 ± 9.2 [mean±SD]	58.2%	Sputum/Broncho-Alveolar lavage. Frequency NR.	BACTEC 460 12B and L-J. All specimens for 8 wks.	New cases over the number of study population at risk (total population minus prevalent cases)	Jan 1999 - Dec 2000	8%

MGIT: Mycobacterial growth indicator tubes. **L-J:** Lowenstein-Jensen egg-based culture medium. **NTM:** nontuberculous mycobacteria

Supplementary Table 7. Characteristics of studies reporting NTM-PD point prevalence (n = 2)

Study ID	Study design	Sample size	Location	Age(y)	Females	Specimen	Culture method	NTM-PD criteria	Years	Point prevalence
Bar-On 2015 [13]	Cohort	70 (2002) 110 (2011)	Israel	**2008** **NTM +** 17.8 (4.3–55.3) **NTM -** 15.2 (0.2–59.3) [median; range]	**2008** **NTM +** 35.3% **NTM -** 47.9%	Sputum. Screened every 3-6 months	L-J and BACTEC MGIT. Incubated at 37 °C incubator up to 8 wks	ATS 2007	2003 2004 2005 2006 2007 2008 2009 2010 2011	2.5 % 3.4 % 3.3 % 4.3 % 7.3 % 8.8 % 11.3 % 7.7 % 5.5 %
Radhakrishnan 2009 [50]	Cross-sectional	98	Canada	**NTM +** **1**5.1 ± 2.2 **NTM -** 14.0 ± 3.0 [mean ± sd]	**NTM +** 66.7% **NTM -** 53.3%	Sputum. Annual screening in study period	BACTEC MGIT and L-J. Incubated at 37°C for up to 7 wks	ATS 2007	Mar 2004 - Nov 2004	1.0 %

MGIT: Mycobacteria growth indicator tube. **L-J:** Lowenstein Jensen egg-based medium. **NTM:** nontuberculous mycobacteria. **ATS:** American Thoracic Society.

Supplementary Table 8. Characteristics of studies reporting NTM-PD period prevalence (n = 13)

Study ID	Study design	Sample size	Location	Age(y)	Females	Specimen	Culture method	NTM-PD criteria	Years	Point prevalence
Bar-On 2015 [13]	Cohort	70 (2002) 110 (2011)	Israel	**2008** **NTM +** 17.8 (4.3–55.3) **NTM -** 15.2 (0.2–59.3) [median; range]	**2008** **NTM +** 35.3% **NTM -** 47.9%	Sputum. Screened every 3-6 months	L-J and BACTEC MGIT. Incubated at 37 °C incubator up to 8 wks	ATS 2007	Jan 2002 - Dec 2011	9.4%
Ademhan-Tural 2021 [68]	Cohort	485	Turkey	**NTM+** 19 (8 - 27) [median; range]	**NTM+** 30% (n = 10)	Sputum, BAL. Annual screening.	MGIT and L-J	ATS 2007	2012 - 2020	1.0%
Campos Herrero 2016 [22]	Cross-sectional	44	Gran Canaria, Spain	12 (5 - 59) [median; range]	**NTM+** 38.9%	Sputum. Frequency NR	BACTEC MGIT and L-J	ATS 2007	2002 - 2012	22.7%
Candido 2014 [72]	Cross-sectional	129	Brazil	NA	NA	Sputum. Frequency NR	L-J	ATS 2007	Jun 2009 - Mar 2012	0.8%
Cavalli 2017 [73]	Cohort	401	France	18.85 ± 7.4 [mean ± sd]	42%	Sputum. Annual screening	Not specified	ATS 2007	1997 - 2002	3.7%
Fauroux 1997 [76]	Cohort	106	France	1 - 18y [range]	57.1%	Sputum. Screened twice per year.	L-J medium	Unknown	May 2012 - Dec 2013	1.9%
Giron 2005 [78]	Cohort	28	Spain	25.3 ± 6.7 y [mean ± sd]	42.8%	Sputum. Frequency NR	Coletsos and liquid MGIT 960 with modified 7H9 broth	Unknown	Jan 1996 - Dec 1999	8%
Ho 2021 [79]	Cross-sectional	171	Tropical French Reunion Island, Africa	**NTM +** 16 (10 - 23) [median; range]	55%	Sputum and BAL. Annual screening.	NR	Unknown	2002 - 2015	7%

Hughes 2021 [80]	Cross-sectional	567	United Kingdom	**MABs** 1.8 (3.2 – 17.3) **MAC** 12.7 (3.6 – 16.7) **Other** 11.6 (7.4 – 15.9) [median; range]	67.8% (n = 59)	Sputum and BAL. Frequency NR.	NR	ATS 2007	2011 - 2018	6.2%
Levy 2008 [84]	Cross-sectional	186	Israel	20.5 ± 10.4 [mean ± sd]	60.2%	Sputum. Frequency NR	MB/BacT, L-J, and Middlebrook 7H11. Up to 7 wks	ATS 2007 and ATS 1997	Jul 2001 - Jul 2003	6.4% and 10.8%
Mussaffi 2005 [85]	Cross-sectional	139	Israel	2 - 52 [range]	NA	Sputum. Frequency NR.	Not described	ATS 1997	1997 - 2002	4.3%
Sermet-Gaudelus 2003 [91]	Cross-sectional	296	France	11.3 (0.2 - 32) [mean - range]	53.4%	Sputum. Annual screening	L-J up to 10 wks	ATS 1997	Jan 1996 - Dec 1999	1.4%
Qvist 2014 [88]	Cohort	198	Denmark	NA	NA	Sputum, laryngeal aspirates or BAL. Annual screening	L-J slants and MGIT for 8 weeks. BCSA for 14 days	ATS 2007	May 2012 - Dec 2013	9.6%

MGIT: Mycobacteria growth indicator tube. **RGM**: Rapid-growing mycobacteria. **L-J:** Lowenstein Jensen egg-based medium. **NTM:** nontuberculous mycobacteria. **BAL:** Broncho-Alveolar Lavage. **ATS:** American Thoracic Society. Polymerase chain reaction assay. **MALDI-TOF:** matrix-assisted laser desorption/ionization- time-of-flight. **NR:** Not reported

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