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Respiratory Non-Tuberculous Mycobacterial Detection in Southeast Asia: Systematic Review and Meta-analysis

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25 ● Erlina Burhan: Supervision, Writing - Review & Editing

26 **Abstract**

27 Background: Respiratory NTM detection is increasingly recognized in Southeast Asia, but its
28 frequency and reported species distribution remain incompletely characterized. Because detection
29 in respiratory specimens does not by itself establish infection or NTM pulmonary disease (NTM-
30 PD), evidence should be interpreted within the diagnostic populations studied.

31 Methods: We searched PubMed, Scopus, ProQuest, Embase, medRxiv, and
32 additional sources from August 27 to September 4, 2025. Eligible
33 studies enrolled persons aged ≥ 15 years in Southeast Asia and reported
34 laboratory-detected respiratory NTM positivity or species
35 distribution from clinical respiratory specimens. We excluded non-
36 human or environmental studies, exclusively extrapulmonary NTM,
37 case reports or series, reviews, and non-analytic reports. Risk of bias
38 was classified according to the number of low-risk items across a 10-
39 domain prevalence-study tool. Logit-transformed proportions were
40 synthesized using DerSimonian-Laird random-effects models, with
41 Paule-Mandel estimation and modified Hartung-Knapp inference as a
42 robustness analysis. We assessed heterogeneity, prediction intervals,
43 subgroup and sensitivity analyses, exploratory univariable meta-
44 regression, and funnel-plot asymmetry using Egger's test.

45 Results: Sixteen studies from seven Southeast Asian countries contributed a combined reported
46 denominator of 67,236 participants or respiratory specimens, including 4,226 NTM-positive
47 results. Seven studies were at low, eight at moderate, and one at high risk of bias. The pooled
48 proportion with respiratory NTM detection was 3.87% (95% CI 2.25%–6.57%), with
49 $I^2=99.57\%$ and a 95% prediction interval of 0.36%–31.04%. The Paule-Mandel-Hartung-

Knapp estimate was similar at 3.88% (95% CI 2.17%–6.83%). Culture-based studies yielded 4.05% (95% CI 2.22%–7.30%), and exclusion of the high-risk study yielded 4.07% (95% CI 2.35%–6.96%). Species-level information was available from only five studies; *M. intracellulare*, *M. fortuitum*, and *M. abscessus* were the most frequently reported named species, although identification completeness varied. Maritime location was associated with lower odds of detection than continental location in exploratory meta-regression ($\beta=-1.09$, $p=0.042$). Egger's test was not statistically significant ($p=0.119$).

Conclusions: Respiratory NTM was detected across diverse diagnostic settings in Southeast Asia, but the wide prediction interval precludes interpreting the pooled proportion as a uniform regional estimate or as disease prevalence. Laboratory pathways that distinguish NTM from the *M. tuberculosis* complex and support species identification may improve interpretation of NTM-positive respiratory results.

PROSPERO registration: <https://www.crd.york.ac.uk/PROSPERO/view/CRD420251138890>

Keywords: nontuberculous mycobacteria, Southeast Asia, respiratory specimens, culture

Background

Non-tuberculous mycobacteria (NTM) are also referred to as environmental mycobacteria, atypical mycobacteria, anonymous mycobacteria, or mycobacteria other than *Mycobacterium tuberculosis* (MOTT). This group excludes *M. tuberculosis* and its close relatives (*M. africanum*, *M. bovis*, *M. canetti*, *M. caprae*, *M. pinnipedii*, and *M. leprae*). The genus *Mycobacterium* now comprises nearly 200 species and 13 subspecies, broadly divided into rapidly growing forms (<7 days) and slowly growing forms (>7 days), with their distribution strongly influenced by geographical and climatic factors.[1] NTM can enter the body through inhalation, ingestion, or direct inoculation, but unlike *M. tuberculosis*, they are generally not transmitted person-to-person, with the notable exception of *M. abscessus* among individuals with cystic fibrosis. Although considered less virulent, NTM infections frequently affect people with pre-existing lung disease such as bronchiectasis. Clinically, they often resemble tuberculosis, creating significant diagnostic challenges, especially in countries with a high TB burden where NTM is frequently underrecognized due to limited awareness and inadequate laboratory facilities.[2] Importantly, detection of NTM in a respiratory specimen is not equivalent to clinically confirmed NTM pulmonary disease (NTM-PD). According to the clinical practice guideline, diagnosis of NTM pulmonary disease requires integration of compatible clinical and radiographic findings with microbiological evidence; detection from a single respiratory specimen may instead represent contamination, transient presence, or colonization.[3] Currently, no single biochemical test can reliably detect all NTM species, drug susceptibility testing is not routinely performed unless treatment fails, and therapeutic outcomes vary widely across species and subspecies.[4,5]

Globally, studies suggest that the prevalence of NTM infection and disease has been rising in recent decades.[6] The most frequently implicated pathogens include the *Mycobacterium avium* complex, followed by *M. simiae* and *M. gordonae*. Higher prevalence is observed in regions with warm, humid climates, where water quality, soil exposure, and aerosolized water increase infection risk, particularly in high-risk populations. In North America, prevalence has risen from 6.8 to 11.7 per 100,000 persons in recent years. European prevalence ranges from 6.1 to 6.6 per 100,000, while Japan reports significantly higher rates. Certain regions, such as parts of the UK and Mississippi, have documented marked increases linked to environmental and climate factors. In India, prevalence estimates vary widely (0.7% to 34%), with notable regional differences in dominant species.[7,8]

In Southeast Asia, the epidemiology of NTM shows a distinct profile compared to other regions. For instance, studies in Singapore report *M. abscessus* as the most frequently isolated species. Across the region, NTM epidemiology is shaped by the predominance of rapid-growing species such as *M. abscessus*, the influence of prior tuberculosis, and the effects of immunosuppression. Prevalence varies by country but is consistently notable in high-risk populations. However, comprehensive epidemiological data remain limited, with significant gaps in population-based and standardized surveillance, making it difficult to estimate the true burden of disease.[7–9]

Regional evidence on respiratory NTM remains fragmented across countries, clinical populations, and laboratory pathways. A synthesis that distinguishes laboratory detection from clinically confirmed NTM pulmonary disease is therefore needed to avoid overstating the available evidence. This review aimed to estimate the pooled proportion of respiratory NTM detection in the

diagnostic populations represented by Southeast Asian studies, summarize the available species-level information, and explore variation according to geographic division, population type, and detection approach. The findings are intended to help contextualize NTM-positive respiratory results and identify priorities for laboratory capacity, surveillance, and future standardized epidemiological studies.

Methods

- Review Objective and Eligibility Criteria

This systematic review and meta-analysis aimed to estimate the proportion of NTM positivity by laboratory detection in Southeast Asia and to describe the distribution of pulmonary NTM species across the region. The review question was structured using the Domain, Determinants, and Outcome (DDO) framework, which is the recommended framing for prevalence reviews in place of the intervention-oriented PICO structure. The Domain was human populations aged ≥ 15 years residing in Southeast Asia (Brunei, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, the Philippines, Singapore, Thailand, Timor-Leste, and Vietnam) investigated for suspected pulmonary NTM infection or pulmonary tuberculosis. The determinant was pulmonary NTM positivity established by laboratory detection. The Outcome was the proportion of respiratory NTM positivity by laboratory detection and/or the distribution of NTM species in clinical respiratory specimens. The full eligibility criteria mapped to the DDO framework are presented in Table 1.

Studies were eligible if NTM was investigated through microbiological confirmation using culture, PCR, sequencing, or another validated detection method and if the study reported the proportion of respiratory NTM positivity and/or the distribution of NTM species in clinical respiratory specimens, such as sputum, bronchoalveolar lavage, or lung biopsy. Eligible designs included cross-sectional studies, prospective or retrospective cohort studies, surveillance studies, and retrospective analyses providing study-level proportions of respiratory NTM detection. Publication status was not used as an eligibility restriction; records from peer-reviewed and non-peer-reviewed sources were evaluated against the same substantive eligibility criteria. No publication-date restriction was applied.

Studies were excluded if they: (i) did not report the proportion of respiratory NTM detection in humans; (ii) reported exclusively environmental or animal isolates without human pulmonary clinical data; (iii) were conducted outside Southeast Asia; (iv) were case reports, case series, narrative reviews, expert commentaries, protocols, or editorials; (v) were in vitro or experimental studies without human respiratory NTM detection data; or (vi) concerned only extrapulmonary NTM infection (e.g., skin, lymph node, disseminated disease). Where two or more reports described overlapping populations, the most complete or most recent report was retained.

- Study Design

A systematic review and meta-analysis were conducted to synthesize respiratory NTM detection in Southeast Asia. It does not, by itself, indicate NTM infection or clinically confirmed NTM-PD. The pooled estimate should also not be interpreted as general-population prevalence, because the included studies sampled heterogeneous populations, including national TB survey participants,

persons with presumed TB or other mycobacterial disease, patients with confirmed TB, and referral-center cohorts. The review was conducted and reported according to PRISMA 2020 (Supplementary File 1).

The final report adhered to the PRISMA guidelines to ensure transparent and comprehensive reporting. This protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews, CRD420251138890).[10]

- Information Resources

We searched PubMed/MEDLINE, Scopus, Embase, ProQuest, and medRxiv. ProQuest and medRxiv were included to broaden coverage beyond conventional peer-reviewed bibliographic databases by identifying potentially eligible dissertations, preprints, and other non-peer-reviewed records. Both databases were not specified in the registered protocol. Records identified through these sources were assessed using the same eligibility criteria as peer-reviewed publications. We also manually screened the reference lists of included studies and relevant reviews to identify additional potentially eligible reports. No publication-date restriction was applied.

- Search Strategy

The search strategy incorporated a combination of keywords and controlled vocabulary terms (MeSH and Emtree) related to non-tuberculous mycobacteria, NTM infections or diseases, and prevalence or epidemiology in Southeast Asia (Supplementary File 2). The retrieval date was not limited; however, the date of searching was recorded and reported for transparency. The search was conducted independently by three reviewers, and discrepancies were resolved through

consensus or arbitration by an additional reviewer. Forward and backward citation searches were performed for all included studies and relevant previous systematic reviews. The literature search was conducted from August 27, 2025, to September 4, 2025

In addition to the systematic database search, we conducted a hand search by manually screening the reference lists of all studies meeting the eligibility criteria to identify any additional relevant studies not retrieved through the database search. Records identified through this process were assessed against the same eligibility criteria as those identified via the database search.

- Data Management

All identified references were managed using Rayyan (rayyan.ai, MA, USA). Records retrieved from the database search were imported into Rayyan, where duplicate records were identified using its automated duplicate detection function. All flagged duplicates were manually reviewed by the study team to confirm accuracy prior to removal, and the remaining records were stored securely for title and abstract screening.

- Selection Process

Duplicate records were identified and removed using Rayyan. Three reviewers (ZA, ACH, IAM), working in pairs, independently screened the titles and abstracts of retrieved studies to assess eligibility. Rayyan's blind mode was activated during screening, meaning each reviewer's inclusion or exclusion decision for a given record was concealed from their screening partner until both had submitted their independent assessment, preventing one reviewer's decision from influencing the other's. In cases of disagreement, an additional reviewer (MPW) provided an independent

assessment. Discrepancies were resolved through discussion until consensus was achieved. Studies deemed potentially eligible underwent full-text assessment, and those meeting the inclusion criteria were included in the final review. A similar review process was applied during full-text assessment.

● Data Collection Process

Data were extracted using a structured form built in Google Sheets, with data items pre-specified by consensus among the review team before extraction began. The form was not formally pilot-tested prior to full extraction. Consistency was maintained through independent duplicate extraction of every included study by two reviewers, followed by item-level comparison of the two extraction records. Discordant items were rechecked against the source report and resolved by consensus; unresolved discrepancies were adjudicated by a third reviewer (MPW).

For extraction of the numerator and denominator, both values were required to refer to the same reported study population, analytic unit, and observation period. We retained the analytic unit reported by the original study, which could represent participants or respiratory specimens, and did not convert specimen- or test-level denominators into participant-level denominators when the required information was unavailable. When more than one eligible estimate was reported, we selected the estimate representing the broadest eligible study population with a clearly corresponding numerator and denominator and the most clearly defined NTM detection method. The denominator unit retained for each study is reported in the study-characteristics table. The use of heterogeneous denominator units is considered in the interpretation of the pooled estimate and acknowledged as a limitation. No automation tools were used during data extraction.

227

228 • Data Items

229 Using the DDO framework, the following data were extracted:

230 ○ Domain: Persons aged ≥ 15 years in Southeast Asia (Brunei,
231 Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, the
232 Philippines, Singapore, Thailand, Timor-Leste, Vietnam)
233 evaluated for possible pulmonary NTM disease or presumed
234 pulmonary TB. The registered PROSPERO protocol specified
235 an adult age threshold of ≥ 18 years. During full-text
236 assessment, several otherwise eligible studies were
237 identified that enrolled participants aged ≥ 15 years but did
238 not report results separately for those aged ≥ 18 years.
239 Strict application of the registered threshold would
240 therefore have required exclusion of these studies despite
241 otherwise meeting the review eligibility criteria. The
242 minimum age threshold was consequently amended to ≥ 15
243 years during the review process. This constituted a
244 deviation from the registered protocol. To evaluate
245 whether this amendment materially affected the pooled
246 estimate, we conducted a post hoc sensitivity analysis
247 restricted to studies whose eligible population was aged
248 ≥ 18 years.

249 ○ Determinants: Respiratory NTM detection

250 ○ Outcome: Study-reported proportion with respiratory NTM detection and/or
251 distribution of NTM species in clinical respiratory specimens

252 ○ Study design

- Laboratory methods: Culture media, PCR assays, sequencing techniques, and other validated detection tests. The detection approach was classified according to the method used for initial NTM isolation or detection. Studies in which NTM was initially isolated using solid culture, liquid culture, or a combination of solid and liquid culture were classified as culture-based, irrespective of whether downstream identification subsequently used antigen-based, biochemical, or molecular methods. Studies using molecular detection without preceding culture were classified as molecular-only. Studies for which the initial detection approach was insufficiently reported were classified as other/unclear.
- Geographical location: Classified a priori into two geographic divisions maritime Southeast Asia (Indonesia, Malaysia, Philippines, Brunei Darussalam, Singapore, Timor Leste) and continental Southeast Asia (Cambodia, Vietnam, Lao PDR, Thailand, Myanmar).
- NTM species: Detected species were recorded, including common NTM such as *Mycobacterium avium*, *M. intracellulare*, *M. abscessus*, and *M. kansasii*. Less frequently detected species were grouped as “other NTM.”

- Outcomes and prioritization

The primary outcome assessed was the study-reported proportion with respiratory NTM detection.

- Risk of Bias in Individual Studies

Risk of bias was assessed independently by two reviewers using the Risk of Bias Tool for prevalence studies by Hoy et al.[11] Each of the ten items in the Hoy scale was rated as low or

high risk of bias, with “unclear” assigned when insufficient information was available. Since no formal risk of bias classification was found in the article publishing the risk of bias tool, for this review, an overall risk-of-bias judgment was assigned based on the number of low-risk items (8–10=low risk; 6–7=moderate risk; ≤5=high risk). Disagreements between reviewers were resolved through discussion or consultation with a third reviewer when necessary. Risk-of-bias findings were summarized in both tabular and narrative formats and were used to guide subgroup analyses during data synthesis. Certainty of evidence was not formally assessed given the observational prevalence designs and substantial heterogeneity.

- Data Synthesis and Statistical Analysis

We synthesized study findings in two stages: (1) qualitative synthesis of study characteristics and species reporting and (2) quantitative meta-analysis of respiratory NTM detection. For each included study, the primary effect estimate was calculated as the number of NTM detected events divided by the eligible tested denominator reported by the study. When a study reported multiple estimates, we extracted the estimate corresponding to the broadest eligible population and the most clearly defined NTM identification method.

Eligible study designs were combined because each contributed the same cross-sectional effect measure: the number of respiratory NTM-positive results divided by the corresponding eligible tested denominator. Longitudinal incidence rates, time-to-event estimates, and repeated measurements were not pooled with these proportions. Differences in study design, setting,

population selection, and laboratory approach were retained in the study-characteristics table and considered potential sources of heterogeneity.

Study-level proportions were pooled with a random-effects model to account for anticipated clinical and methodological heterogeneity. Proportions were logit-transformed to stabilize variances. For studies reporting a proportion of 0 or 1, a continuity-type correction constrained the proportion to $[0.5/n, 1 - 0.5/n]$, where n was the study denominator. The within-study variance on the logit scale was calculated as $1/x + 1/(n - x)$, where x was the number of NTM-positive events. Random-effects pooling was conducted using the DerSimonian-Laird estimator for between-study variance. We also applied Paule-Mandel estimation with modified Hartung-Knapp inference as a robustness analysis of the overall pooled estimate. Pooled estimates were back-transformed to the proportion scale using the inverse logit function and presented with 95% confidence intervals and 95% prediction intervals.

Statistical heterogeneity was quantified using Cochran's Q with the p -value, I^2 statistic with 95% confidence interval (CI), τ^2 , and prediction intervals calculated using a t distribution with $k-2$ degrees of freedom. Prespecified subgroup analyses were performed to explore heterogeneity by geographic division, population type, and detection approach, and were conducted only when at least two studies were available per subgroup. Exploratory univariable meta-regression analyses were conducted to investigate potential sources of heterogeneity. Covariates included geographic division (continental versus maritime), study

quality, and study setting. Study quality was entered into meta-regression as a binary moderator comparing moderate/high-risk studies with low-risk studies because only one study was classified as high risk. Geographic division was modelled as maritime versus continental Southeast Asia, and study setting was modelled using multi-center facility-based studies as the reference category. Meta-regression results were reported as coefficients with standard errors and 95% confidence intervals, moderator-test statistics, p-values, residual τ^2 , and proportional reduction in τ^2 . The proportional reduction in between-study variance was calculated by comparing residual τ^2 from each moderator model with τ^2 from the intercept-only model. Negative values were interpreted as no heterogeneity explained and reported as 0%. Multivariable meta-regression was not performed because the small number of included studies and sparse moderator categories would have resulted in overfitted and unstable adjusted estimates.

Sensitivity analyses were conducted to assess the robustness of the pooled respiratory NTM detection estimate to study inclusion, methodological differences, and potentially influential observations. Sensitivity analyses included leave-one-out analysis, influence diagnostics, exclusion of the high-risk study, restriction to culture-based studies, and exclusion of the potentially influential study from the continental subgroup. In response to the protocol deviation in the minimum age criterion, we additionally conducted a post hoc sensitivity analysis restricted to studies whose eligible populations were aged ≥ 18 years. Small-study effects/publication bias were assessed visually using funnel plots and statistically using Egger's procedure.

All analyses were conducted in Python 3.12.13 within Google Colab. Data processing and effect-size transformations were performed using pandas (version 2.2.2) and numpy (version 2.0.2). Random-effects meta-analyses, including overall and subgroup analyses, were conducted using the DerSimonian–Laird method implemented through the `combine_effects` function in `statsmodels` (version 0.14.6). The Paule–Mandel–Hartung–Knapp robustness analysis, prediction intervals, heterogeneity confidence intervals, exploratory univariable random-effects meta-regression analyses, and sensitivity analyses were performed using custom Python routines, with `patsy` (version 1.0.2) and `scipy` (version 1.16.3) used for model specification and statistical inference. Figures were generated using `matplotlib` (version 3.10.0).

Results

- Study selection

A total of 286 records were identified from databases and registers (PubMed, Scopus, ProQuest, medRxiv, and Embase), and 17 additional records were identified through hand searching. After removal of 48 duplicates, 238 records were screened by title and abstract. Seventeen full-text reports were sought from the database/register arm, of which 14 were retrieved and assessed for eligibility; seven were excluded due to different populations ($n=3$) or different outcomes ($n=4$). From other methods, 17 full-text reports were sought, 15 were retrieved and assessed for eligibility, and six were excluded due to different populations ($n=4$) or different outcomes ($n=2$). One national government report,[12] identified through manual reference-list searching, was included because it met the substantive eligibility criteria. In total, 16 studies were included in the systematic review and meta-analysis (Figure 1).

369 • Study characteristics

370 The 16 included studies were conducted in seven Southeast Asian countries: Indonesia (n=8),
371 Malaysia (n=2), Vietnam (n=2), and Cambodia, Lao PDR, the Philippines, and Thailand (n=1
372 each). Eleven studies were conducted in maritime Southeast Asia and five in continental Southeast
373 Asia. Most studies enrolled persons evaluated for presumed TB or other mycobacterial
374 infection,[12–23] while a smaller number included patients with confirmed TB.[24–27]
375 Respiratory specimens were predominantly sputum, with some including bronchoalveolar lavage.
376 Laboratory approaches varied and included solid and/or liquid culture followed by identification
377 tests[12–15,17–25,27]. Detailed study characteristics, detection approaches, and extracted
378 numerators/denominators are summarized in Table 2.

380 • Sample-size Distribution

381 Study size varied by more than two orders of magnitude. Across the 16 studies, the study-reported
382 denominators totalled 67,236 participants or respiratory specimens, with 4,226 NTM-positive
383 results. The mean study-reported denominator was 4,202, while the median was 1,812
384 (interquartile range 288–6,755), reflecting a strongly right-skewed distribution. Denominators
385 ranged from 94 [25] to 15,776 [15]. Six studies had eligible denominators below 500, five had
386 between 500 and 4,999, and five had 5,000 or more. The four national TB prevalence surveys
387 together contributed a combined reported denominator of 41,409 participants, or 61.6% of the total
388 pooled denominator, meaning that 61.6% of the combined reported denominator came from only
389 four studies. The logit transformation and random-effects weighting used in the meta-analysis limit
390 but do not eliminate the influence of these large surveys on the pooled estimate. Study-level
391 respiratory NTM detection ranged from 0.83% [17] to 22.96% [21].

392

393 All studies enrolled predominantly adult populations, usually with
394 inclusion thresholds of ≥ 15 or ≥ 18 years. Cohort age was reported in
395 only a minority of studies, with central estimates from a median of 36
396 years (Interquartile range (IQR) 24–50) [21] to a mean of 50.9 ± 15.8 years [23].
397 Several studies reported older ages among NTM-positive participants than in their source cohorts
398 or among participants with confirmed TB, contrasting with the younger peak typical of active
399 tuberculosis. Sex distributions varied by study design: community-based national surveys were
400 female-predominant (53.4% [12]; 56.0% [17]), with higher participation among women in the
401 Philippines (82.2% versus 69.5%) [15] and Lao PDR (87.8% versus 82.1%) [21], whereas facility-
402 based studies recruiting symptomatic patients were male-predominant (54.8%–63.0% men)
403 [13,14,20,23,24]. Among NTM-positive participants this reversed, with females accounting for
404 54.5% of NTM disease and 59.5% of colonisation cases [22], 61.8% (19/32) of speciated cases
405 [18], and the single case in one cohort [20]. No study formally tested age or sex as a predictor of
406 respiratory NTM detection.

407

408 human immunodeficiency virus infection (HIV) status was reported in only five facility-based
409 studies [14,18,20,22,24] and was unavailable in the national surveys. Reported HIV frequency in
410 source cohorts ranged from 1.7% [24] to 9.0% [20]; 5.2% in a multi-center drug-resistant TB
411 cohort [14] and 2.9% among speciated NTM cases [18]. One study reported HIV as an independent
412 determinant of NTM detection (adjusted OR 4.63, 95% CI 1.68–12.77), with 36.4% of NTM lung
413 disease patients HIV-positive versus 2.4% with colonisation and 1.1% with confirmed tuberculosis
414 [22]. As HIV status was unavailable for the large surveys dominating the pooled denominator, its
415 contribution to variation in respiratory NTM detection could not be assessed.

416

417 • Species-level Reporting and Distribution

418 Species-level identification was reported in 5 of the 16 included studies (31.3%) [16,18,22–24].
419 These studies accounted for 252 of the 4,226 NTM-positive results in the review (6.0%). Reporting
420 completeness differed between studies. Ali et al. identified one of three NTM-positive isolates to
421 species level; Biyang et al. identified all three; Pham et al. and Pascapurnama et al. identified all
422 86 and 32 NTM-positive results, respectively; and Bonnet et al. presented species data for 123 of
423 128 NTM-positive participants, including 22 reported as not identified. In addition, some
424 participants in Bonnet et al. had more than one species reported. Consequently, no single common
425 denominator was used to calculate an aggregate species distribution, and the findings were
426 summarized descriptively using study-specific counts.

427

428 Across the available named-species assignments, *M. intracellulare* was reported most frequently
429 (n=52), followed by *M. fortuitum* (n=39) and *M. abscessus* (n=37), with one additional mixed *M.*
430 *abscessus*–*M. asiaticum* assignment. These counts are not mutually exclusive and were not
431 weighted by study size. The species distribution varied by study. *M. abscessus* predominated in
432 the Indonesian series [18], whereas *M. fortuitum* and *M. intracellulare* led in Cambodia [22] and
433 *M. intracellulare* in Vietnam [16]. Study-specific species data are presented in Table 3.

434

435 • Risk of bias within studies

436 Overall risk of bias, assessed using the Hoy et al.[11] tool for prevalence studies, varied across the
437 included studies (Table 4). Seven studies were categorized as low risk of bias, eight as moderate

risk of bias, and one as high risk of bias. Common limitations included incomplete reporting of sampling strategy and uncertainty regarding the representativeness of the target population.

- Pooled proportion of respiratory NTM detection

Across all included studies, the pooled proportion with respiratory NTM detection was 3.87% (95% CI: 2.25% to 6.57%) using a random-effects model (Figure 2). Study level estimates varied widely, ranging from 0.83% to 22.96%, with substantial heterogeneity across settings and detection approaches. Statistical heterogeneity was extreme ($I^2=99.57\%$, 95% CI 99.15%–99.82%; $Q(15)=3516.96$, $p<0.001$; $\tau^2=1.1853$), and the 95% prediction interval ranged from 0.36% to 31.04%. The wide prediction interval indicates that respiratory NTM detection in a comparable setting could plausibly differ substantially from the pooled mean and is therefore important for interpretation alongside the confidence interval. The Paule–Mandel analysis with modified Hartung–Knapp inference produced a pooled proportion of 3.88% (95% CI 2.17%–6.83%), with $\tau^2=1.1479$ and a 95% prediction interval of 0.37%–30.26%. Accordingly, the pooled proportion should be interpreted as an average of heterogeneous study-level detection proportions rather than as a uniform regional prevalence estimate.

- Subgroup analyses

Subgroup pooling produced descriptive estimates across geographic division, population type, detection approach, and culture medium. Formal between-category comparisons were conducted separately through univariable meta-regression for geographic division, study quality, and study setting. Population, detection-approach, and culture-medium subgroups were not subjected to formal between-subgroup tests and were interpreted descriptively. The pooled proportion was

7.75% (95% CI 2.92%–19.01%; k=5) in continental Southeast Asia and 2.77% (95% CI 1.57%–4.85%; k=11) in maritime Southeast Asia. Among persons evaluated for presumed mycobacterial infection or tuberculosis, the pooled proportion was 4.10% (95% CI 2.19%–7.54%; k=12), compared with 2.94% (95% CI 0.47%–16.26%; k=3) among patients with confirmed tuberculosis.

When classified according to the initial detection approach, the pooled proportion was 4.05% (95% CI 2.22%–7.30%; k=13) among culture-based studies and 5.52% (95% CI 1.80%–15.75%; k=2) among molecular-only studies. The single other/unclear study reported 3 NTM-positive results among 326 tested specimens (0.92%) and was not pooled. In the secondary analysis by culture medium, seven solid-culture-only studies yielded a pooled proportion of 4.22% (95% CI 1.53%–11.10%), while the two liquid-culture-only studies yielded an exploratory pooled proportion of 0.98% (95% CI 0.54%–1.78%). The individual liquid-culture estimates reported proportions of 1.73% [24] and 0.83% [17]. Heterogeneity remained substantial in most subgroups, and all subgroup findings should be regarded as descriptive and exploratory. Complete heterogeneity statistics are presented in Table 6.

- Meta-regression

Exploratory univariable meta-regression showed that maritime location was associated with lower odds of respiratory NTM detection than continental location ($\beta=-1.09$, SE 0.54, 95% CI -2.14 to -0.04; $p=0.042$). Inclusion of geographic division reduced estimated between-study variance from $\tau^2=1.1853$ in the intercept-only model to residual $\tau^2=0.9266$, corresponding to a 21.8% reduction. Moderate/high risk of bias was not significantly associated with

respiratory NTM detection compared with low risk ($\beta=-0.73$, SE 0.65, 95% CI -2.01 to 0.54; $p=0.261$). Study quality did not reduce between-study heterogeneity; residual τ^2 was 1.5687 and explained heterogeneity was therefore reported as 0%. Study setting was also not significantly associated with the outcome. These analyses were univariable, based on only 16 studies, and potentially affected by ecological confounding and multiple exploratory comparisons; they should therefore be interpreted as hypothesis-generating. Complete results are presented in Table 5.

- Sensitivity analyses

Leave-one-out analysis showed that the overall pooled proportion with respiratory NTM positivity was not materially altered by exclusion of any single study. Across the 16 leave-one-out analyses, pooled estimates ranged from 3.43% to 4.33%, compared with 3.87% (95% CI 2.25–6.57%) in the primary analysis. Exclusion of Nguyen et al.[17] produced the highest pooled estimate (4.33%; 95% CI 2.51–7.37%), whereas exclusion of Law et al.[21] from Lao PDR produced the lowest estimate (3.43%; 95% CI 2.14–5.46%). Heterogeneity remained very high in all leave-one-out analyses (I^2 99.15%–99.60%). Influence diagnostics identified Law et al. [21], which reported respiratory NTM positivity of 22.96%, as the only potentially influential study (studentized residual=2.15; Cook's distance=0.274; DFBETA=0.583); however, its exclusion did not materially alter the overall pooled estimate. Exclusion of Kusumaningrum et al. [20], the only study classified as high risk of bias, produced a pooled respiratory NTM positivity proportion of 4.07% (95% CI 2.35%–6.96%; $k=15$), with $I^2=99.60\%$, $\tau^2=1.1844$, and a 95% prediction interval of 0.37%–32.58%. This result was similar to the primary analysis, indicating that the high-risk study did not materially influence the pooled estimate.

Sensitivity analysis restricted to the 13 culture-based studies yielded a pooled respiratory NTM positivity of 4.05% (95% CI 2.22–7.30%), similar to the primary estimate, although heterogeneity remained substantial ($I^2=99.66\%$) and the 95% prediction interval was wide (0.34%–34.65%). In the continental Southeast Asia subgroup, exclusion of the potentially influential Lao PDR study reduced the pooled estimate from 7.75% (95% CI 2.92–19.01%; five studies) to 5.72% (95% CI 1.91–15.92%; four studies). Nevertheless, heterogeneity remained very high after exclusion ($I^2=98.51\%$), indicating that the Lao PDR study contributed to, but did not fully account for, the variability observed within the continental subgroup.

Eight of the 16 included studies met the originally registered eligibility threshold of ≥ 18 years. When the meta-analysis was restricted to these studies, the pooled proportion of respiratory NTM detection was 3.56% (95% CI 1.88%–6.64%), compared with 3.87% (95% CI 2.25%–6.57%) in the primary analysis. The corresponding 95% prediction interval was 0.35%–27.85%. Thus, restricting the analysis to studies meeting the originally registered age threshold produced a similar pooled point estimate, although substantial between-study variability remained.

- Publication bias

Visual inspection of the funnel plot (Figure 3) showed asymmetry, raising possible publication bias. However, with only 16 studies and substantial clinical and methodological heterogeneity, funnel-plot asymmetry is not specific for selective publication and may also reflect genuine differences in populations, settings, and diagnostic methods. Egger's regression test

531 did not identify statistically significant evidence of funnel-plot
532 asymmetry (intercept -8.89, SE 5.36, 95% CI -20.37 to 2.60; $t=-1.66$,
533 $df=14$, $p=0.119$). However, the test had limited power with 16 studies and
534 its interpretation was complicated by substantial heterogeneity.

536 Discussion

537 • Summarizing Results

538 The pooled analysis indicates that respiratory NTM was detected in approximately 4% of the
539 diagnostic observations represented by the included studies. This estimate describes the frequency
540 with which NTM was encountered within heterogeneous respiratory diagnostic pathways. It does
541 not represent general-population prevalence or the prevalence of clinically confirmed NTM
542 pulmonary disease. Interpretation of this pooled estimate is limited by substantial between-study
543 heterogeneity and the wide prediction interval. Although sensitivity analyses and alternative
544 heterogeneity estimators produced similar average estimates, they did not eliminate the
545 considerable variation between studies. The wide prediction interval suggests that respiratory
546 NTM detection may differ markedly across diagnostic populations and healthcare settings.

548 Study populations ranged from participants in national TB prevalence surveys to patients attending
549 tertiary referral centres and programmatic drug-resistant TB cohorts, representing markedly
550 different diagnostic settings and underlying probabilities of respiratory NTM detection.
551 Denominators were variably reported as participants or respiratory specimens. Laboratory
552 procedures also differed in specimen type, decontamination, culture media, incubation conditions,
553 and downstream identification methods, all of which may influence NTM recovery and
554 classification [28–32]. Variation in study period may have contributed further because

mycobacterial culture and molecular-identification practices changed over time. The pooled estimate should therefore be regarded as an average across diverse diagnostic contexts rather than a regional parameter applicable uniformly throughout Southeast Asia.

Exploratory univariable meta-regression provided some evidence that geographic division was associated with study-level respiratory NTM detection, whereas study quality and study setting were not statistically associated with the outcome. This finding should be interpreted cautiously, however, because the analysis was based on only 16 studies, used aggregate study-level characteristics, and did not simultaneously account for differences in population composition, diagnostic methods, study period, or other potentially related factors. Geographic division may capture several unmeasured differences across studies rather than represent an independent geographic effect. The meta-regression findings should be interpreted as exploratory and cannot determine whether geographic or environmental factors account for the observed heterogeneity.

Funnel-plot asymmetry raised the possibility of small-study effects or publication bias. However, Egger's regression test did not provide statistically significant evidence of funnel-plot asymmetry. This non-significant result should not be interpreted as evidence that publication bias is absent, particularly given the relatively small number of included studies and the substantial clinical and methodological heterogeneity.

The pooled point estimate remained relatively stable across different analytical decisions, although this stability does not resolve the extreme heterogeneity. The Paule–Mandel analysis with modified Hartung–Knapp inference produced an estimate similar to the primary DerSimonian–Laird

analysis. Likewise, the overall estimate was not materially altered by leave-one-out analysis, exclusion of the single high-risk study, or restriction to culture-based studies. Although the Lao PDR study was identified as potentially influential, its exclusion did not eliminate the substantial heterogeneity within continental Southeast Asia. These findings suggest that the observed variability was not attributable to one study or analytical assumption, but more likely reflected broader differences in study populations, diagnostic pathways, settings, and laboratory methods. Consequently, the wide prediction interval is more informative than the pooled confidence interval alone when considering how respiratory NTM detection may vary across comparable settings, and the pooled estimate should not be interpreted as a uniform regional prevalence estimate.

Differences in laboratory methods represent an important potential source of heterogeneity in this review. The apparently higher pooled respiratory NTM detection among solid-culture-only studies than among liquid-culture-only studies should not be interpreted as evidence that solid media are intrinsically more sensitive. These were ecological comparisons across different study populations, and only two studies used liquid culture alone. NTM recovery may be influenced by multiple components of the laboratory pathway, including specimen processing and decontamination procedures, inoculum volume, culture medium, incubation conditions and duration, criteria for defining culture positivity, and subsequent species-identification methods. The use of solid versus liquid culture media can affect detection sensitivity, while differences in specimen decontamination procedures may influence mycobacterial recovery.[3] Variations in culture conditions and species identification methods may also affect the reported detection rates and species distributions.[33] These factors were not sufficiently standardized across the included studies to isolate the effect of any single laboratory method. Indeed, within the same Cambodian

cohort, Bonnet et al. [22] reported greater NTM recovery with liquid MGIT than with solid Löwenstein–Jensen medium (8.0% versus 2.7%, $p<0.001$). The pooled cross-study differences by culture method should therefore be interpreted descriptively rather than as comparative evidence of diagnostic performance.

Unmeasured HIV-related confounding may have contributed to the observed heterogeneity. HIV status was unavailable in the extracted NTM data from the four national tuberculosis prevalence surveys, which contributed 61.6% of the combined reported denominator [12,15,17,21]. In contrast, Bonnet et al. [22] identified HIV infection as an independent factor associated with NTM isolation (adjusted OR 4.63, 95% CI 1.68–12.77). However, this association arose from one study population and cannot be assumed to apply to the other included studies. Because HIV prevalence was inconsistently reported and individual-level data were unavailable, neither the direction nor the magnitude of HIV-related confounding could be quantified. We therefore cannot determine to what extent differences in HIV prevalence contributed to the observed between-study or geographic variation in respiratory NTM detection.

The clinical relevance of respiratory NTM detection in this review is primarily diagnostic. Many of the included cohorts comprised persons being evaluated for presumed TB, in whom NTM and *M. tuberculosis* may produce overlapping clinical, radiographic, and smear findings. Detection of NTM in a respiratory specimen alone does not establish NTM-PD and should be followed by appropriate clinical and radiographic assessment and, when indicated, repeat microbiological confirmation. Nevertheless, diagnostic pathways that promptly distinguish *M. tuberculosis* complex from NTM and, when clinically relevant, identify NTM to the species or subspecies level

may reduce inappropriate anti-TB treatment, prompt appropriate reassessment and repeat sampling, and support species-informed management. Expanding access to validated molecular identification and routine species-level testing where feasible may therefore improve both TB diagnostic specificity and NTM management in Southeast Asia.

- Species Distribution Synthesis

Species-level evidence in this review was limited and methodologically heterogeneous. Only five of the 16 included studies (31.3%) reported species-level information, representing 252 of the 4,226 NTM-positive results identified across the review. The reasons for incomplete species reporting could not be established consistently from the source studies but may reflect differences in study objectives, laboratory workflows, identification methods, and reporting practices. Accordingly, the available data cannot establish the regional predominance of any NTM species. This limited reporting introduces potential selection and reporting biases, restricting the representativeness of the observed species distribution and precluding firm conclusions about regional species predominance.

Among the species that were reported, *M. intracellulare* was the most frequent named species, followed by *M. fortuitum* and *M. abscessus*, but these descriptive counts arose from a small and non-representative subset of studies with differing populations and identification methods. Comparisons with other regions should therefore be interpreted cautiously. Nevertheless, the observed species diversity reinforces the clinical importance of species- and, where relevant, subspecies-level identification, because pathogenicity, antimicrobial susceptibility, and treatment approaches differ considerably across NTM groups.[3]

647

648 • Respiratory NTM Detection in people with presumed TB and Confirmed TB Patients

649 Respiratory NTM detection was higher among people evaluated for presumed tuberculosis than
650 among those with confirmed tuberculosis, although this difference should be interpreted cautiously
651 because no formal test of subgroup differences was performed. The observed pattern may partly
652 reflect differences in case selection. Persons evaluated for presumed tuberculosis represent a
653 diagnostically heterogeneous population, and previous studies have shown that NTM may be
654 identified among patients initially diagnosed or treated as having tuberculosis, particularly in high-
655 TB-burden settings.[31]

656

657 This distinction is relevant because NTM pulmonary disease can resemble tuberculosis in its
658 symptoms, radiological findings, and smear results, particularly in high-burden settings where
659 access to species-level identification is limited. Previous tuberculosis and structural lung disease
660 may also increase susceptibility to NTM through bronchiectasis and impaired mucociliary
661 clearance.[31,34–36] These findings support consideration of NTM as part of the differential
662 diagnosis in people with presumed tuberculosis, especially when the clinical course or
663 microbiological findings are not consistent with tuberculosis. At the same time, detection of NTM
664 in a respiratory specimen should not be taken as evidence of NTM pulmonary disease without
665 further clinical and microbiological assessment.[3]

666

667 • Comparison with Previous Study

668 The frequency of respiratory NTM detection observed in this review differed from estimates
669 reported in meta-analyses from other regions, including China and Taiwan, Iran, and

Zambia.[30,37,38] Direct comparisons across regions should be interpreted cautiously because included populations and diagnostic workflows differ substantially between meta-analyses (e.g., general respiratory cohorts versus presumptive TB populations or culture-based versus molecular detection), which can strongly influence observed NTM detection. The absence of a standardized global surveillance framework for NTM-PD further limits direct comparison of disease burden across regions.

- Geographical Variation in Respiratory NTM Detection

Studies from continental Southeast Asia showed higher study-level respiratory NTM detection than those from maritime Southeast Asia, and geographic division was the only examined moderator statistically associated with detection in the exploratory meta-regression. However, this finding should be regarded as hypothesis-generating rather than evidence of a causal geographic effect. Only five studies contributed to the continental subgroup, confidence intervals were wide, heterogeneity remained substantial, and one potentially influential study from Lao PDR contributed a particularly high estimate. Moreover, because the meta-regression used aggregate study-level characteristics, this association cannot be interpreted as evidence that individuals living in continental Southeast Asia have a higher probability of NTM detection than comparable individuals living in maritime Southeast Asia.

Environmental conditions including temperature, humidity, soil characteristics, and water exposure have been associated with NTM ecology in previous studies and provide biologically plausible hypotheses for geographic variation.[39–42] However, these environmental characteristics were not directly measured in the studies included in this review and were not

evaluated as moderators in the meta-regression. Differences between maritime and continental studies may also reflect variation in study populations, diagnostic methods, healthcare settings, study periods, and other unmeasured factors. The observed geographic association cannot establish that climatic or environmental differences are responsible for the variation in respiratory NTM detection, and further studies using standardized methods and direct measurement of relevant environmental and individual-level factors are needed.

- Strengths and Limitations

This review provides a region-focused quantitative synthesis of respiratory NTM positivity across diverse Southeast Asian settings and complements the pooled analysis with descriptive species data, risk-of-bias assessment, subgroup analyses, and exploratory meta-regression. Inclusion of national surveys and facility-based cohorts broadens the range of diagnostic contexts represented. Subgroup analyses were performed to provide context-specific descriptive estimates and to generate hypotheses about heterogeneity.

Several limitations are important. First, most primary studies reported laboratory detection from respiratory specimens rather than clinically confirmed NTM pulmonary disease; the pooled result therefore represents respiratory NTM detection rather than disease prevalence. Second, the included populations were heterogeneous and are not representative of the general Southeast Asian population. Third, source studies variably reported denominators as participants or respiratory specimens. These analytic units are not strictly interchangeable and limit comparability across studies. Fourth, statistical heterogeneity remained substantial despite sensitivity and subgroup analyses, and residual between-study variation could not be fully attributed because potentially

important individual-level and methodological characteristics were inconsistently reported across studies. Formal between-category testing was limited to moderators entered into the univariable meta-regression models. Other subgroup estimates were descriptive, and all moderator analyses remained vulnerable to ecological confounding and multiple testing because only 16 studies were available. Fifth, although the funnel plot appeared asymmetric, Egger's test was not statistically significant; publication bias or small-study effects nevertheless cannot be excluded because only 16 studies were available and substantial heterogeneity complicates interpretation. Finally, species-level identification was available in only five studies and was summarized descriptively rather than statistically pooled, limiting inference regarding regional species distribution.

● Future Direction

Future research should prioritize standardized diagnostic algorithms (including molecular methods where feasible) and improved surveillance to better characterize NTM epidemiology and species distribution across Southeast Asia. Future studies should also incorporate clinical and radiological criteria to distinguish NTM pulmonary disease from transient colonization or incidental detection. Country-specific studies using standardized population definitions, sampling approaches, and diagnostic methods are needed to characterize variation within Southeast Asia.

Conclusions

This meta-analysis highlights considerable variability in respiratory NTM detection across Southeast Asia and the need for context-specific diagnostic strategies and standardized surveillance. The observed regional differences should be considered hypothesis-generating

findings rather than evidence of causality. Further research incorporating molecular identification and clinical criteria is needed to characterize the distribution and clinical significance of respiratory NTM detection in the region.

Declarations

List of Abbreviations

Abbreviation	Definition
NTM	Non-tuberculous mycobacteria
NTM-PD	Non-tuberculous mycobacterial pulmonary disease
TB	Tuberculosis
MDR-TB	Multidrug-resistant tuberculosis
RGM	Rapidly growing mycobacteria
MAC	Mycobacterium avium complex
PCR	Polymerase chain reaction
BAL	Bronchoalveolar lavage
CI	Confidence interval
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO	International Prospective Register of Systematic Reviews
MGIT	Mycobacteria Growth Indicator Tube
DNA	Deoxyribonucleic acid

745

746 **Ethics approval and consent to participate**

747 Not applicable. This study is a systematic review and meta-analysis of aggregate-level data from
748 previously published studies available in the public domain. It did not involve primary data
749 collection, access to individual participant data, or any direct interaction with human
750 participants, and ethics committee approval was therefore not required.

751

752 **Consent for publication**

753 Not applicable. This manuscript does not contain data relating to any identifiable individual.

754

755 **Availability of data and materials**

756 All data supporting the conclusions of this article are included within the article and its
757 supplementary files. The full database-specific search strategies and completed PRISMA 2020
758 checklist are provided in the supplementary files. The extracted dataset and the Python code used
759 for the meta-analysis and meta-regression are available from the corresponding author (MPW)
760 on reasonable request. The review protocol is publicly available in the PROSPERO register
761 (CRD420251138890) at <https://www.crd.york.ac.uk/PROSPERO/view/CRD420251138890>.

762

763 **Competing interests**

All authors declare no conflict of interest related to study conduct and manuscript development

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Authors' contributions

MPW conceived the study and designed the review methodology. ACH, IAM, and ZA developed the search strategy and conducted the literature search, screening, and full-text assessment. ACH, IAM, and ZA performed data extraction and risk-of-bias assessment, with MPW acting as third reviewer for discordant items. IAM and MPW developed the statistical analysis code and conducted the meta-analysis and meta-regression. IAM produced the figures. ZA managed project administration. ACH, IAM, and ZA drafted the original manuscript. MPW and EB critically reviewed and revised the manuscript. MPW supervised the analysis and EB supervised the study overall. All authors read and approved the final manuscript.

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- 907

908 **Tables**

909 **Table 1.** Eligibility criteria based on the Domain, Determinants, and Outcome framework

Element	Criteria
Domain	Human populations (≥15 years old) in Southeast Asia (Brunei, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor–Leste, Vietnam) with suspected pulmonary NTM infection or pulmonary tuberculosis
Determinant	Respiratory NTM positivity by laboratory detection
Outcome	Proportion of respiratory NTM detection by laboratory detection and/or distribution of NTM species in clinical respiratory samples

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911

Table 2. Characteristics of Included Studies

Authors, Year of Publication	Country	Geographi c Division	Study Settings	Populatio n	Age (years)	Sampl e type	Assay	NTM Identificati on	Numb er of Events	Deno minat or (unit)	Respirat ory NTM Detection	Median/ Mean Age of Cohort	Respirat ory NTM Detection (Events, %) [95% Exact Binomial CI]
Ali et al 2015[24]	Malaysia	Maritime	Facility- based study, single center	Confirmed TB	≥15	Sputu m	Liquid media- based culture	DNA probe	3	173 partici pants	1.73%	N/A	3 (1.73%) [0.36%– 4.11%]
Atiya et al 2025[13]	Malaysia	Maritime	Facility- based study, single	Presumed mycobacte rial infection/T	≥18	Sputu m	Solid or Liquid media- based	PCR	1089	8,151 sputu m sampl	13.36%	N/A(69. 6% of cultur e–	1,089 (13.36%) [12.63%

			center	B			culture			es		positives ≥40 yrs)	– 14.11%]
Biyang et al 2024[23]	Indonesia	Maritime	Facility- based study, multi- center	Presumed mycobacte rial infection/T B	≥18	Sputu m	Molecular only	PCR	3	111 sputu m sampl es (1/pati ent)	2.70%	Mean: 50.86 ± 15.79 yrs (NTM cases median: 62 yrs)	3 (2.70%) [0.56%– 6.36%]
Bonnet et al 2017[22]	Cambodi a	Continental	Facility- based study, single center	Presumed mycobacte rial infection/T B	≥15	Sputu m	Solid or Liquid media- based culture	MPT64, DNA probe	128	1,183 patient s	10.82%	Median: 54 (IQR 40–65) yrs	128 (10.82%) [9.11%– 12.64%]
Burhan et al	Indonesia	Maritime	Facility-	Presumed	≥18	Sputu	Solid or	MPT64,	8	490	1.63%	Mean:	8

2022[14]			based study, multi-center	mycobacterial infection/TB		m	Liquid media-based culture	Para-nitrobenzoic acid		participants		41.3 ± 14.1 yrs	(1.63%) [0.71%–2.92%]
Hung Viet Pham et al 2023[16]	Vietnam	Continental	Facility-based study, multi-center	Presumed mycobacterial infection/TB	≥18	Sputum	Molecular only	PCR	86	1,003 sputum samples	8.57%	Mean: 58 yrs (among NTM-positives)	86 (8.57%) [6.92%–10.37%]
Kusumaningrum et al 2024[20]	Indonesia	Maritime	Facility-based study, single center	Presumed mycobacterial infection/TB	≥15	Sputum	Solid media-based culture	MPT64	1	96 patients (≥15 years)	1.04%	NTM case: female in 16–25 age group	1 (1.04%) [0.03%–3.77%]
Lansang et al 2021[15]	Philippines	Maritime	National survey	Presumed mycobacterial	≥15	Sputum	Solid media-	MPT64	502	15,776	3.18%	N/A	502 (3.18%)

				rial infection/T B			based culture			partici pants			[2.91%– 3.46%]
Law et al 2015[21]	Lao PDR	Continental	National survey	Presumed mycobacte rial infection/T B	≥15	Sputu m	Solid media- based culture	Genotype MTBDRplu s	1444	6,290 partici pants	22.96%	Median: 36 (IQR: 24, 50) yrs	1,444 (22.96%) [21.92% – 24.00%]
Mertaniasih et al 2017[19]	Indonesia	Maritime	Facility- based study, single center	Presumed mycobacte rial infection/T B	≥18	Sputu m and BAL	Solid or Liquid media- based culture	Niacin accumulatio n test, MPT64	141	2,440 respira tory speci mens	5.78%	N/A	141 (5.78%) [4.89%– 6.74%]
Ministry of Health Republic of Indonesia	Indonesia	Maritime	National survey	Presumed mycobacte rial infection/T	≥15	Sputu m	Solid media- based culture	Niacin accumulatio n test, MPT64	405	15,12 7 partici pants	2.68%	N/A	405 (2.68%) [2.43%– 2.94%]

2015[12]				B									
Nguyen et al 2020[17]	Vietnam	Continental	National survey	Presumed mycobacte rial infection/T B	≥ 15	Sputu m	Liquid media- based culture	TBC-ID, Para- nitrobenzoi c acid	35	4,216 partici pants	0.83%	N/A	35 (0.83%) [0.58%– 1.13%]
Pascapurnama et al 2023[18]	Indonesia	Maritime	Facility- based study, single center	Presumed mycobacte rial infection/T B	≥ 18	Sputu m	Solid media- based culture	MPT64	32	2,476 patient s	1.29%	Median: 43.4 yrs (for 32 NTM cases)	32 (1.29%) [0.89%– 1.77%]
Sangsayunh and Chuchothawo n 2014[25]	Thailand	Continental	Facility- based study, single center	Confirmed TB	≥ 15	Sputu m	Solid media- based culture	Not mentioned	12	94 patient s	12.77%	N/A	12 (12.77%) [6.77%– 19.97%]

Saptawati et al, 2019[27]	Indonesia	Maritime	Facility-based study, single center	Confirmed TB and Presumed mycobacterial infection/TB	≥18	Sputum	Solid media-based culture	Para-nitrobenzoic acid	334	9,284 sputum samples	3.60%	72% of NTM cases were >35 yrs old	334 (3.60%) [3.23%–3.99%]
Ziaulhaq et al 2025[26]	Indonesia	Maritime	Facility-based study, single center	Confirmed TB	≥18	Sputum	Not mentioned	Not mentioned	3	326 patients	0.92%	NTM cases: 1 aged 18 years; 2 aged 19–59 years	3 (0.92%) [0.19%–2.20%]

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Table 3. NTM Species Distribution.

Study	NTM-positive results	Completeness of species reporting	Study-reported named species
Ali 2015 [24]	3	1 identified; 2 not speciated	<i>M. fortuitum</i> 1
Biyang 2024 [23]	3	All 3 identified	<i>M. intracellulare</i> 3
Bonnet 2017 [22]	128	Species table n=123; 22 not identified; 5 not represented	Species table available for 123 of 128 NTM-positive participants: <i>M. fortuitum</i> 28; <i>M. intracellulare</i> 23; <i>M. scrofulaceum</i> 13; <i>M. gordonae</i> 13; <i>M. abscessus</i> 14; <i>M. simiae</i> 3; <i>M. avium</i> 2; <i>M. asiaticum</i> 2; <i>M. kansasii</i> 1; <i>M. interjectum</i> 1; mixed <i>M. abscessus</i> – <i>M. asiaticum</i> 1; not identified 22. Five of the 128 NTM-positive participants were not represented in the species table. Three <i>M. intracellulare</i> reports involved another concomitant NTM species.

Pham 2023 [16]	86	All 86 identified	M. intracellulare 25; M. abscessus 10; M. fortuitum 8; M. massiliense 8; M. simiae 7; M. colombiense 5; M. parascrofulaceum 3; M. conceptionense 2; M. senegalense 2; M. parmense 2; M. gordonae 2; M. paragordonae 2; M. scrofulaceum 2; M. avium 1; M. timonense 1; M. paraense 1; M. gastri 1; M. kansasii 1; M. lentiflavum 1; M. seoulense 2. Total: 86.
Pascapurnama 2023 [18]	32	All 32 identified	M. abscessus 13; M. chelonae 6; M. fortuitum 2; M. avium 2; M. kansasii 2; M. celatum 2; M. vanbaalenii 2; M. arcueilense 1; M. conceptionense 1; M. intracellulare 1. Total: 32.

Table 4. Risk of Bias assessment Results

NO	Authors, Year of Publication	External Validity				Internal Validity						Final Risk Assessment	Remarks
		Representativeness of the national population	Representativeness of the sampling frame	Random sampling or census	Low risk of non-response bias	Direct data collection from participants	Appropriate case definition	Valid and reliable measurement instrument	Consistent data collection method	Appropriate prevalence period	Appropriate numerator and denominator		
1	Ali et al 2015	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk	Clinic-based smear-positive PTB patients; limited representativeness and potential nonresponse/selection filtering, but NTM identification via culture and DNA-based methods supports

													internal validity.
2	Atiya et al 2025	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk	Single tertiary center retrospective laboratory dataset; not population- representative and not randomly sampled, but patient data/specimens are direct and lab methods applied consistently with clear numerators/denominator s.
3	Biyang et al 2024	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Moderate Risk	The study relied on convenience sampling in a local clinical setting, which increases selection bias and limits

													representativeness, while the laboratory identification procedures were applied consistently and the numerator/denominator reporting was sufficiently clear for estimating NTM positivity (with uncertainty if the data-collection period was not explicitly stated).
4	Bonnet et al 2017	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk	Consecutive presumptive TB patients at a provincial reference hospital; external validity limited but strong internal validity

													with clear culture/speciation methods and clear numerator/denominator within defined period.
5	Burhan et al 2022	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk	Multicenter DR-TB referral hospitals; not population- representative and not random sampling. However, culture/identification workflow appears consistent and counts/denominators are clear for NTM positivity among those tested.
6	Hung Viet Pham et al	No	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Moderate Risk	This was a facility-based cross-sectional study

	2023												from northern Vietnam, so it may not represent the national population and the sampling process was not clearly random or census-based, but the study reported a defined study period and applied consistent laboratory identification for NTM positivity across participants.
7	Kusumaningrum et al 2024	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	High Risk	Single referral hospital; inclusion depends on specimen availability and sputum quality, increasing selection/nonresponse bias. Denominator

													reporting is potentially inconsistent (100 vs 155), so numerator/denominator clarity is limited.
8	Lansang et al 2021	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk	National TB prevalence survey; strong sampling framework. Some concern for nonresponse, but lab methods and denominators are clear and consistent.
9	Law et al 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk	National multistage cluster TB prevalence survey; strong external validity with defined sampling and period; lab methods and denominators support

													reliable NTM positivity estimates.
10	Mertaniasih et al 2017	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk	This was a single tertiary-hospital, laboratory-based dataset so external validity is limited, but the study used a clear respiratory-sample testing workflow with consistent methods and clearly reported counts/denominators, making the NTM positivity estimate internally reliable.
11	Ministry of Health Republic of Indonesia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Low Risk	National, PPS cluster-sampled prevalence survey with high participation and near-

	2015												complete sputum/lab results; clear NTM definition via culture with MTB exclusion and clear denominators. Culture collection not uniform across clusters (spot+morning vs morning-only)
12	Nguyen et al 2020	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk	National TB prevalence survey with multistage cluster sampling; nonparticipation around 30% suggests potential nonresponse bias, but otherwise sampling and lab methods support low overall RoB.

13	Pascapurnama et al 2023	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate Risk	Retrospective study using stored isolates and screening criteria (not random/census). External validity limited; internal validity acceptable with consistent lab identification and clear denominators for the tested subset.
14	Sangsayunh and Chuchothawon 2014	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low Risk	Single-center suspected MDR-TB patients; limited representativeness and non-random sampling, but standardized culture-based workflow and clear denominators yield

													acceptable internal validity (ensure culture-confirmed NTM counts used).
15	Saptawati et al 2019	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Moderate Risk	This was a single-center retrospective laboratory review that is not nationally representative, but it used a clearly described operational definition for NTM positivity (culture-based differentiation) with consistent testing across samples and a defined multi-year timeframe, supporting internal validity for an respiratory NTM

													detection proportion.
16	Ziaulhaq et al 2025	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Moderate Risk	This study was conducted in a referral hospital retreatment cohort so the results are not generalizable to the broader population, and although the denominator and timeframe were reported, the paper did not clearly specify the laboratory criteria used to classify NTM versus MTB, which increases uncertainty in the case definition for NTM

													positivity.
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920 For individual Hoy et al. tool domains, “Yes” indicates that the low-risk criterion was met and
921 “No” indicates that it was not met. The original Hoy et al. tool does not prescribe thresholds for
922 an overall risk-of-bias classification. For this review, an overall risk-of-bias judgment was
923 assigned based on the number of low-risk items (8–10=low risk; 6–7=moderate risk; ≤5=high risk)

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Table 5. Exploratory Univariable Meta-regression Analysis.

Moderator	Comparison	β (95% CI)	p-value	QM (df)	QM p-value	SE	Residual τ^2	Reduction in τ^2
Geographic division	Maritime vs continental	-1.09 (-2.14 to -0.04)	0.042	4.12 (1)	0.042	0.537	0.927	21.8%
Study quality	Moderate-high vs low risk	-0.73 (-2.01 to 0.54)	0.261	1.26 (1)	0.261	0.651	1.569	0%
Study setting	Overall	—	—	0.02 (2)	0.990	—	1.628	0%
↳ Single-center facility-based	vs multi-center facility-based	0.13 (-1.62 to 1.87)	0.887	—	—	0.890	—	—

↳ National survey	vs multi-center facility-based	0.07 (-1.89 to 2.04)	0.941	—	—	1.001	—	—
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928 The intercept-only model had $\tau^2=1.1853$. Negative proportional reductions in τ^2 were interpreted as no heterogeneity explained and
929 reported as 0%. Regression coefficients are differences on the logit-proportion scale; exponentiated coefficients would represent ratios
930 of the odds of respiratory NTM detection.

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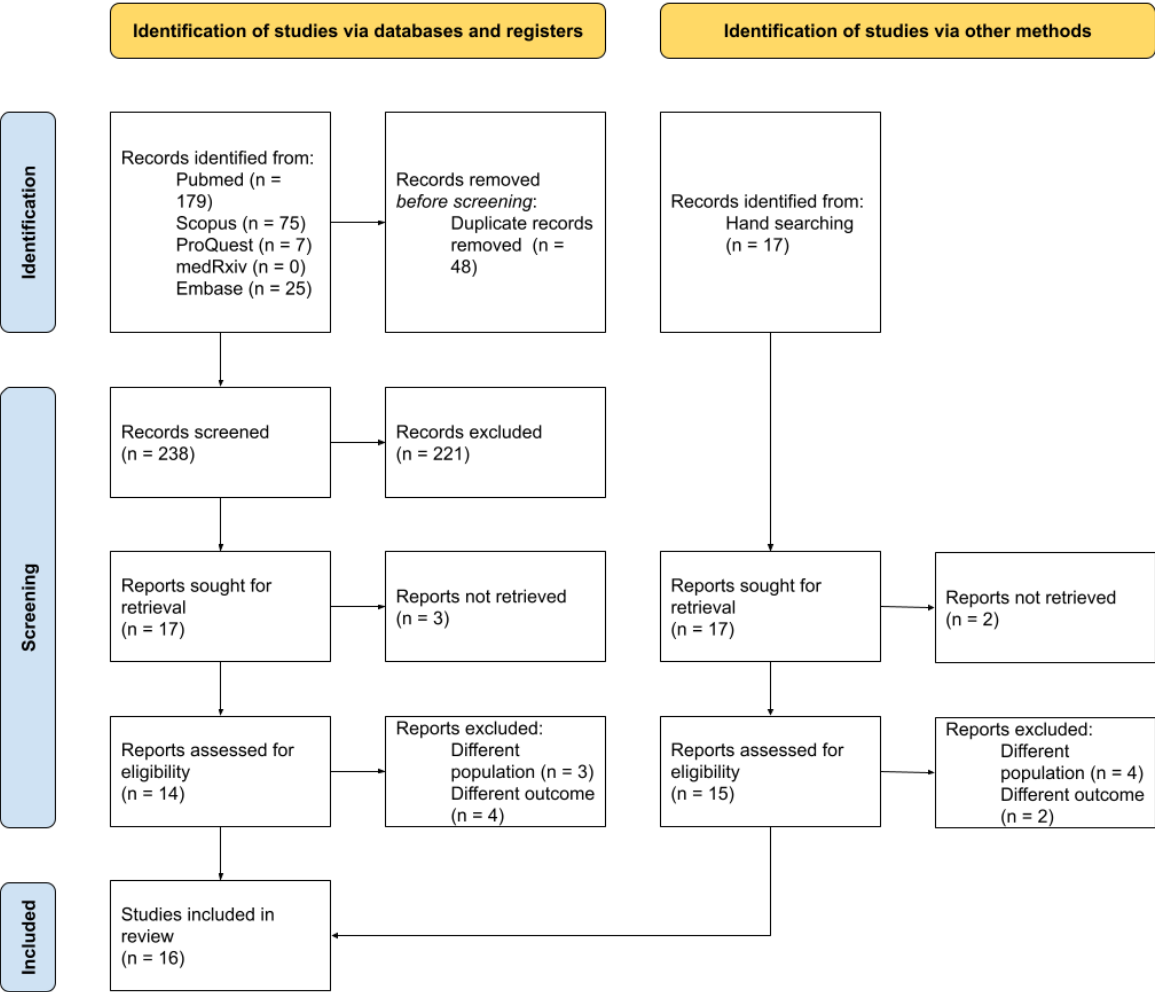
Table 6. Random-effects subgroup and sensitivity analyses

Analysis	k	Pooled proportion (95% CI)	95% PI	I ² (95% CI)	Q(df), p	τ^2
Overall	16	3.87% (2.25–6.57)	0.36–31.04	99.57% (99.15–99.82)	3516.96 (15), <0.001	1.1853
Continental	5	7.75% (2.92–19.01)	0.15–82.83	99.29% (98.52–99.94)	567.28 (4), <0.001	1.3451
Maritime	11	2.77% (1.57–4.85)	0.33–19.84	99.30% (97.65–99.70)	1432.73 (10), <0.001	0.8250
Presumed mycobacterial infection/TB	12	4.10% (2.19–7.54)	0.33–35.68	99.65% (99.28–99.88)	3139.36 (11), <0.001	1.2155
Confirmed TB	3	2.94% (0.47–16.26)	0.00–100.00	91.33% (62.25–99.72)	23.08 (2), <0.001	2.4419

Culture-based	13	4.05% (2.22–7.30)	0.34–34.65	99.66% (99.31–99.88)	3494.72 (12), <0.001	1.2200
Molecular-only	2	5.52% (1.80–15.75)	0.89–27.58	76.00% (0– 99.98)	4.17 (1), 0.041	0.5626
Solid-culture-only	7	4.22% (1.53–11.10)	0.10–65.38	99.80% (99.27–99.95)	3014.95 (6), <0.001	1.8548
Liquid-culture-only	2	0.98% (0.54–1.78)	0.42–2.27	33.83% (0– 99.94)	1.51 (1), 0.219	0.0941
Excluding high-risk study	15	4.07% (2.35–6.96)	0.37–32.58	99.60% (99.21–99.84)	3511.90 (14), <0.001	1.1844
Continental, excluding Lao PDR outlier	4	5.72% (1.91–15.92)	0.02–93.83	98.51% (96.46–99.92)	201.85 (3), <0.001	1.3109

934 CI, confidence interval; PI, prediction interval; I^2 , percentage of variability attributable to between-study heterogeneity; τ

935 ², between-study variance. Prediction intervals and heterogeneity statistics were not estimated for one-study categories. Subgroup
936 estimates are descriptive unless the corresponding characteristic was evaluated through meta-regression. Formal moderator tests for
937 geographic division, study quality, and study setting are reported in Table 5.



939

940 **Figure 1.** PRISMA 2020 flow diagram of study selection.

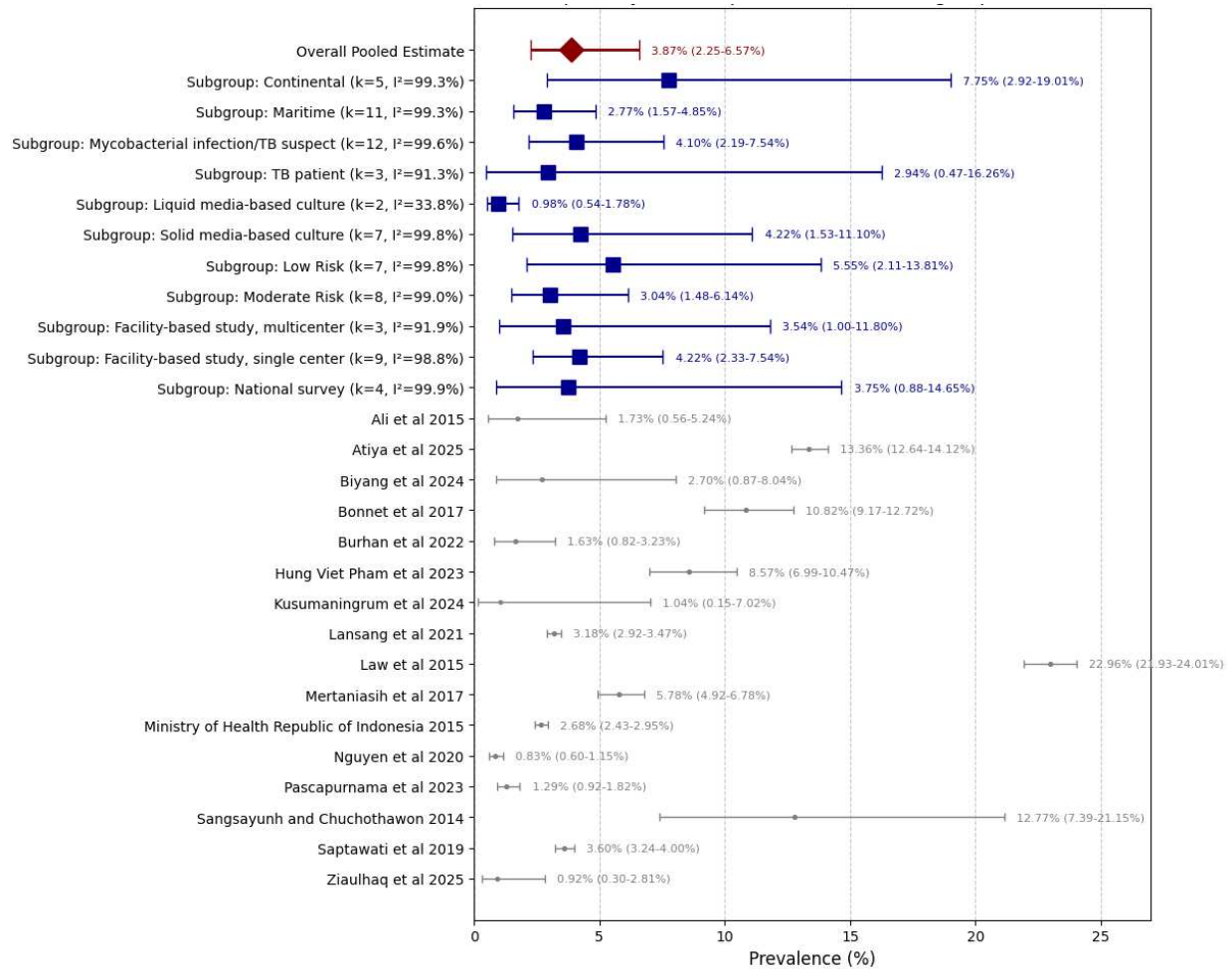


Figure 2. Forest plot showing the proportion of respiratory NTM positivity among included studies and the pooled estimate using a random-effects model.

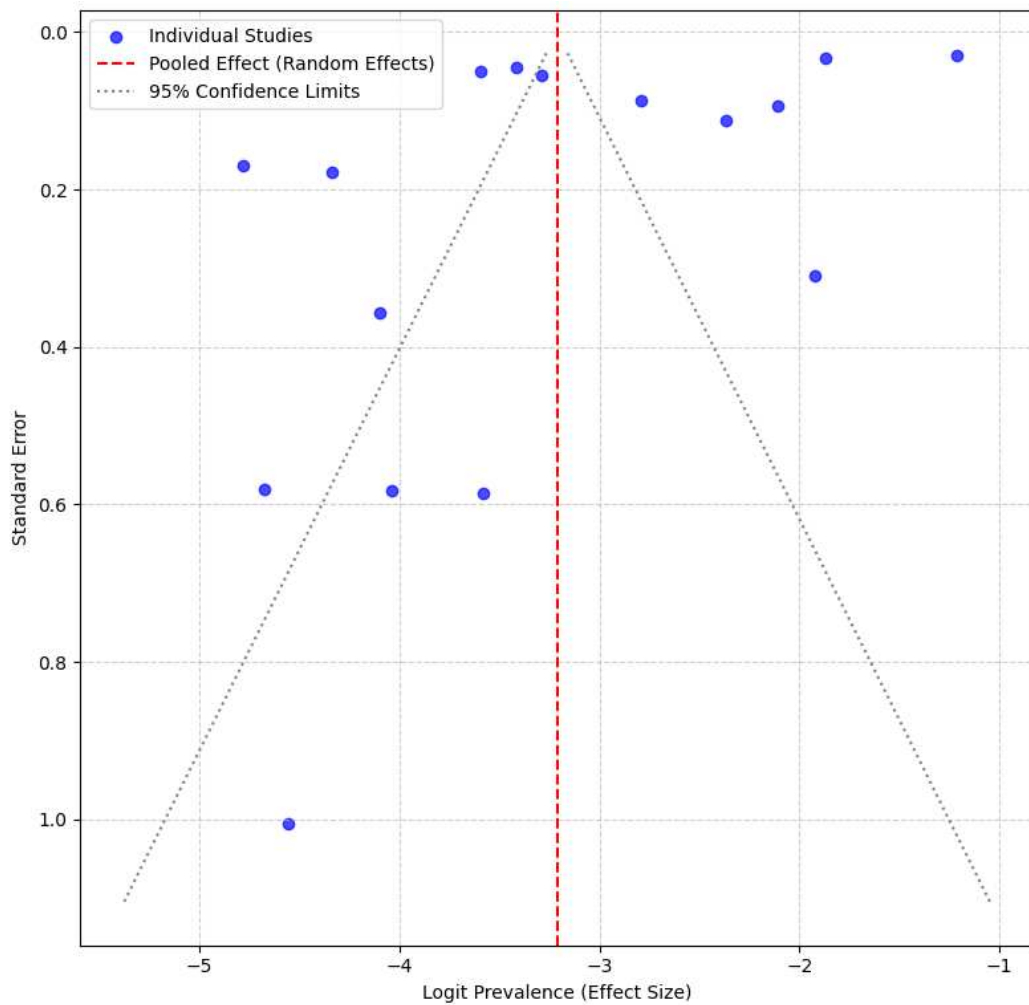


Figure 3. Funnel plot of included studies

949 **Figure Captions**

950

951 **Figure 1.** PRISMA 2020 flow diagram of study selection.

952 **Figure 2.** Forest plot showing the proportion of respiratory NTM positivity among included
953 studies and the pooled estimate using a random-effects model.

954 **Figure 3.** Funnel plot of included studies

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