DOI: 10.51745/najfnr.10.21.35-45

REVIEW ARTICLE

Human and Clinical Nutrition

Impact of Micronutrient Supplementation on Sputum Conversion Kinetics in Pulmonary Tuberculosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Tuberculosis (TB) remains a global health challenge, accounting for over 10 million incident cases and 1.6 million deaths annually as of 2021. The kinetics of sputum smear or culture conversion are critical determinants of patient infectiousness and long-term clinical prognosis. Although micronutrients—including vitamins *A* and *D*, and zinc—are known to modulate host immune responses, their specific efficacy in accelerating mycobacterial clearance remains a subject of academic debate.

Aims: This study aimed to systematically evaluate whether the adjunctive administration of micronutrient supplements alongside standard anti-tuberculosis therapy (ATT) significantly reduces the duration required for sputum smear or culture conversion in patients infected with *Mycobacterium tuberculosis*.

Methods: Following the PRISMA 2020 guidelines, a comprehensive search of PubMed, ScienceDirect, and the Cochrane library was executed for studies published through March 2025. Only randomized controlled trials (RCTs) comparing ATT micronutrient supplementation versus ATT alone were eligible for inclusion. The primary endpoint was the time to sputum smear or culture conversion. Data synthesis was performed using Review Manager (v 5.4.1), with outcomes expressed as mean differences (*MD*) and odds ratio (*OR*). Heterogeneity was addressed through fixed or random-effects modeling as appropriate.

Results: Twelve RCTs involving 3,377 participants met the inclusion criteria. Meta-analysis revealed that micronutrient supplementation significantly abbreviated the time to sputum conversion (*MD* = -4.48 days; 95% CI: –7.54 to –1.41; p = 0.004). Furthermore, the odds of achieving negative sputum status were significantly elevated by the second month of treatment (*OR* = 1.59; 95% CI: 1.03 – 2.46), although this effect was not observed at the one-month or three-month intervals. While vitamin *D* was the most frequently studied intervention, vitamin *A*, zinc, and multi-micronutrient formulations were also represented. Risk of bias was rigorously assessed using the Cochrane tool.

Conclusion: Adjunctive micronutrient therapy appears to modestly but significantly accelerate sputum conversion in TB patients. These findings suggest that nutritional fortification may serve as a viable auxiliary strategy to enhance standard treatment regimens. However, further investigation is warranted to outline the efficacy of specific nutrient combinations and their impact across diverse demographic populations.

Keywords: Tuberculosis; Micronutrient; Dietary supplements; Adjunctive Therapy; Sputum Conversion Kinetics.

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Received: July 04, 2025
Revised: July 26, 2025
Accepted: January 21, 2026
Published: February 23, 2026

Article edited by:
Prof. Khaled Méghit Boumèdiene
Article reviewed by:
Dr. Alfian Nur Rosyid
Dr. Imen Benchikh

Cite this article as: Soetedjo, F.A., Kristijanto, J.A.F., Khamidah, N. (2026). Impact of Micronutrient Supplementation on Sputum Conversion Kinetics in Pulmonary Tuberculosis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *The North African Journal of Food and Nutrition Research, 10* (21): 35 – 45. https://doi.org/10.51745/najfnr.10.21.35-45

1 INTRODUCTION

Nutritional status is a fundamental determinant of human physiological resilience and immunological competence, directly influencing both the susceptibility to pathogens and the trajectory of clinical recovery. Among communicable diseases, tuberculosis (TB) persists as a preeminent global health challenge. In 2021 alone, an estimated 10.6 million individuals contracted TB, resulting in 1.6 million fatalities and cementing its status as a leading cause of infectious mortality worldwide (Bagcchi, 2023). Beyond the immediate clinical ramifications, TB imposes a substantial socioeconomic burden, particularly within low- and middle-income countries. In these regions, patients frequently endure protracted periods of economic instability and social isolation due to delayed microbiological clearance (Iskandar *et al.*, 2023; Roxas *et al.*, 2025).

A critical prognostic milestone in the management of TB is sputum smear or culture conversion, which signifies a substantial reduction in bacillary load and a concomitant decrease in transmission potential. Current international guidelines dictate that standardized antitubercular therapy be administered in two distinct stages: an initial two-month intensive phase (2HRZE), followed by a four-month continuation phase (4HR) (Pooranagangadevi &

Padmapriyadarsini, 2022). Achieving timely sputum conversion within the first two months serves not only as a primary indicator of therapeutic efficacy but also as a vital public health benchmark for effective disease containment.

Micronutrients—most notably vitamins *A* and *D*, zinc, and selenium—are essential modulators of immune regulation. Their capacity to enhance macrophage polarization, fortify T-cell-mediated responses, and reduce oxidative stress is well-documented in the literature (Shi & Yan, 2020). However, despite compelling mechanistic plausibility and supportive *in vitro* findings, evidence from randomized controlled trials (RCTs) regarding the efficacy of adjunctive micronutrient supplementation in accelerating sputum conversion remains equivocal (Verrall *et al.,* 2025; Xiong *et al.,* 2020). This lack of consensus highlights a significant knowledge gap that necessitates a rigorous synthesis of the existing literature.

Consequently, this systematic review and meta-analysis seek to evaluate whether adjunctive micronutrient supplementation significantly reduces the duration required for sputum smear or culture conversion in patients receiving standard anti-tuberculosis treatment. By integrating data from multiple RCTs, this study aimed to provide definitive clarity on a question of clinical and public health relevance.

2 Material and Methods

2.1 Study Design and Reporting Standards

This systematic review and meta-analysis were executed in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page *et al.,* 2021). The research architecture was reinforced by the PICO framework defined as follows:

- Population (P): Patients with confirmed *Mycobacterium tuberculosis* infection receiving standardized antitubercular therapy.
- Intervention (I): adjunctive micronutrient supplementation (e.g., Vitamin *D*, Vitamin *A*, zinc, or multi-micronutrient formulations).
- Comparator (C): Standardized antitubercular therapy administered alone or in conjunction with a placebo.
- Outcomes (O): Primary outcomes included the duration required for sputum smear or culture conversion and the conversion status at designated follow-up intervals.

2.2 Search Strategy and Evidence Selection

A systematic search was conducted across PubMed, ScienceDirect, and the Cochrane Library to identify relevant literature published through March 2025. The search strategy employed a synergistic combination of Medical Subject Headings (MeSH) and free-text keywords related to "tuberculosis", "micronutrients", and "dietary supplementation" (refer to Table 1. for the exhaustive search strategy).

Retrieved citations were exported to EndNote™ (Clarivate, Philadelphia, PA, USA) for reference management and the systematic removal of duplicates. Initial de-duplication involved automated matching of bibliographic metadata (titles, authors, publication year, and DOIs/PMID), followed by a rigorous manual verification. To prevent the inclusion of overlapping datasets, multiple publications originating from the same trial were cross-referenced by evaluating study settings, recruitment periods, sample sizes, intervention regimen and doses, and reported outcomes. In instances of redundant reporting, the most comprehensive dataset was prioritized for primary extraction, with ancillary reports utilized solely for methodological clarification.

Table 1. Search Strategy for the Identification of Eligible Studies Across Electronic Databases

Connected by OR		Connected by OR
Tuberculosis[mh] OR Tuberculosis[tiab] OR Tuberculoses[tiab] OR Kochs Disease[tiab] OR Koch's Disease[tiab] OR Koch Disease[tiab] OR Mycobacterium tuberculosis infection[tiab] OR Infection, Mycobacterium tuberculosis[tiab] OR Infections, Mycobacterium tuberculosis[tiab] OR Mycobacterium tuberculosis Infections[tiab]	AND	Vitamin A[mh] OR Vitamin B Complex OR Ascorbic Acid[mh] OR Vitamin E[mh] OR Vitamin D[mh] OR Zinc[mh] OR Selenium[mh] OR Dietary Supplements[mh] Vitamin A[tiab] OR Vitamin B Complex[tiab] OR Ascorbic Acid[tiab] OR Vitamin C[tiab] OR Vitamin E[tiab] OR Tocopherols[tiab] OR Vitamin D[tiab] OR Zinc[tiab] OR Selenium[tiab] OR Dietary Supplements[tiab]

2.3 Eligibility Criteria

Studies were eligible for inclusion if they met the following criteria: (i) RCTs involving human subjects with confirmed TB; (ii) comparative evaluation of standard therapy with versus without adjunctive micronutrients; (iii) reporting of sputum conversion kinetics as an outcome; (iv) publication in English language; and (v) availability of sufficient quantitative data to calculate mean differences (*MD*), or odds ratio (*OR*), with 95% confidence intervals (CI).

Exclusion criteria comprised non-randomized designs, *in vitro* or animal models, and studies lacking an appropriate control group; if sputum smear/culture conversion outcomes were not reported. Furthermore, conference abstracts, editorials, and review articles were excluded to ensure the synthesis was based on peer-reviewed, original experimental data

2.4 Data Extraction and Management

Two authors (FAS and JAFK) independently extracted data from eligible studies using a standardized data collection form. Extracted variables included primary author, publication year, geographical setting, demographic characteristics, intervention specifics (type and dose), anti-tuberculosis treatment regimen, sputum conversion outcome (smear and/or culture), and follow-up duration. Following extraction, datasets were subjected to item-by-item cross-verification. Discrepancies were resolved through consensus or, where necessary, adjudicated by a third investigator (NK). When numerical outcome data were presented in formats inappropriate for direct pooling, they were transformed using validated statistical methods to ensure consistency across the meta-analysis.

2.5 Risk of bias assessment

The methodological quality of the included trials was independently assessed using the Cochrane Risk of Bias tool (RoB 1.0) (Higgins *et al.,* 2011). This tool evaluates seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Any discrepancies were resolved through discussion; where consensus could not be reached, a third reviewer (NK) adjudicated.

Although RoB 2 is currently the recommended tool for randomized trials (Sterne *et al.,* 2019), we utilized RoB 1.0 for this review because several included RCTs were conducted and reported in periods when trial registration, published protocols, and detailed reporting of analysis plans were not consistently available. In this context, applying RoB 2 would have required outcome-specific judgments heavily driven by unavailable reporting elements (e.g., prespecified analysis intentions and deviations from intended interventions), which risks producing largely non-discriminative ratings across studies. We therefore employed RoB 1.0 to provide a transparent, domain-based appraisal that could be applied consistently across all included trials. To avoid overinterpretation, we applied conservative judgments (rating domains as "unclear risk" when information was insufficient) and interpreted within the context of the overall risk-of-bias profile.

2.6 Data Synthesis and Statistical Analysis

Statistical analyses were performed using Review Manager (RevMan) version 5.4.1. For continuous outcomes (duration of conversion in days), *MD*s were pooled via the inverse-variance method. For dichotomous outcomes (conversion status), pooled effect sizes were expressed as ORs utilizing the Mantel–Haenszel method (Seputra *et al.,* 2021).

Moreover, we reported *OR* (rather than risk ratios) for dichotomous outcomes to ensure consistency across studies and because *OR* is a standard effect measure for pooling binary outcomes in RevMan using the Mantel–Haenszel approach. *OR* was interpeted as odds (not risks), noting that *OR* may diverge from risk ratios when event rates are high.

In instances, when continuous outcomes were presented as the median (m) and interquartile range (IQR; q1 - q3), the sample mean and standard deviation were estimated using the method described by Wan *et al.* (2014). Specifically, the mean was approximated using the following formula:

$$\bar{x} \approx \frac{(q1 + m + q3)}{3}$$

The standard deviation (s) was derived from the IQR as

$$s \approx \frac{(q3 - q1)}{\eta(n)}$$

where $\eta(n) = 2E[Z_{(3q+1)}]$. For practical implementation, Wan *et al.* (2014) provided a large-sample approximation for the standard deviation:

$$s \approx (q_3 - q_1)/[2\Phi^{-1}(\frac{0.75n - 0.125}{n + 0.25})]$$

It should be noted that for sufficiently large sample sizes (n), this expression converges to the widely recognized approximation:

$$s \approx \frac{(q3 - q1)}{1.35}$$

Statistical significance was defined as $p < 0.05$. Inter-study heterogeneity was assessed via the Chi-square (Q) test and quantified using the I^2 statistic. For both continuous and dichotomous outcomes, a random-effects model was applied when heterogeneity was substantial ($I^2 > 50\%$); otherwise, a fixed-effect model was used, as reflected in the corresponding forest plots. Sensitivity analyses were performed to assess the robustness of pooled estimates and to identify potential sources of variance (Seputra *et al.,* 2021).

3 Results

3.1 Eligible Studies

The systematic literature search yielded an initial pool of 1,273. Upon the removal of 105 duplicates, 1,168 unique citations underwent title and abstract screening. Following

this preliminary assessment, 1,109 records were excluded due to irrelevance to the pre-defined research objectives. The remaining 59 full-text articles were rigorously assessed for eligibility. Subsequent to the full-text review, 47 studies were excluded for failing to satisfy the inclusion criteria—primarily due to the absence of pertinent outcome data, nonrandomized designs, or the utilization of non-standard interventions.

Ultimately, 12 studies met all eligibility criteria and were incorporated into the final meta-analysis. The systematic study selection process is detailed in the PRISMA 2020 flow diagram (Figure 1) and the baseline characteristics of the included trials are synthesized in Table 2. Notably, Ralph *et al.* (2013) employed a 2×2 factorial design, which permitted the simultaneous evaluation of vitamin *D* and *L*-arginine as adjunctive therapeutic agents.

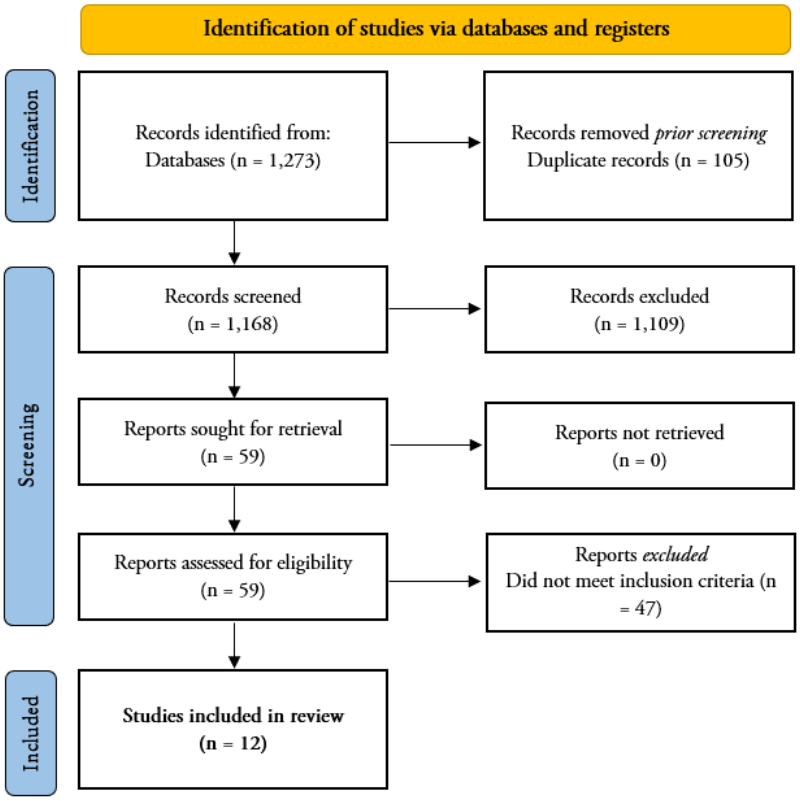

Figure 1. PRISMA 2020 Flow Diagram

3.2 Data Synthesis and Meta Analysis

A cumulative cohort of 3,377 participants across 12 RCTs was analyzed to evaluate the efficacy of adjunctive micronutrient supplementation on sputum smear or culture conversion kinetics. In five of the included trials, conversion time was reported as the median with an IQR. To facilitate meta-analytical pooling, these summary statistics were converted into estimated mean and standard deviation employing the approach described above by Wan *et al.* (2014).

Aggregate analysis demonstrated that micronutrient supplementation significantly reduced the time required for sputum conversion compared to standard antitubercular therapy alone (*MD* = -4.48 days; 95% CI: -7.54 to -1.41; p = 0.004; Figure 2).

Regarding dichotomous outcomes, the odds of achieving sputum conversion during the first month of treatment did not reach statistical significance (*OR* = 0.85; 95% CI: 0.65 – 1.11; p = 0.24; Figure 3A). However, a statistically significant improvement in conversion rates was observed by the second month (*OR* = 1.59; 95% CI: 1.03 – 2.46; p = 0.04; Figure 3B). By the third month, although the pooled odds ratio remained high (*OR* = 2.20) the results were not statistically significant (95% CI: 0.32 – 15.07; p = 0.42; Figure 3C), likely due to substantial variance and wide confidence intervals reflecting limited data availability at this time point.

Table 2. Characteristics of Included Studies

Study ID	First Author, Year	Country	Age Range (years)	Interventions	Anti-TB Regimen	Primary Outcome	Duration of Follow Up
1	Pakasi *et al.* (2010)	Indonesia	15 – 55	Vitamin A (5000 IU) and Zinc (15 mg) once daily for 6 months, oral	2HRZE then 4HR	Sputum smear conversion	6 months
2	Wen *et al.* (2022)	China	18 – 70	Calcitriol 0.25 µg two times daily for 24 weeks, oral	2HRZE then 4HR or $2HR_tLE$ then $4HR_t$	Sputum culture conversion	24 weeks
3	Ganmaa *et al.* (2017)	Mongolia	17 – 84	Vitamin D3 3.5 mg (140,000 IU) at 0/2/4/6 weeks, oral	2HRZE	Sputum culture conversion	8 weeks
4	Tukvadze *et al.* (2015)	Republic of Georgia	18 – 63	Vitamin D3 1.25 mg (50,000 IU) 3 times weekly for 8 weeks, then every 2 weeks for 8 weeks, oral	2HRZE then 4HR	Sputum culture conversion	16 weeks
5	Daley *et al.* (2015)	India	18 – 72	Vitamin D3 2.5 mg (100,000 IU) at 0/2/4/6 weeks, oral	2HRZE	Sputum culture conversion	8 weeks
6	Martineau *et al.* (2011)	United Kingdom	18 – 75	Vitamin D3 2.5 mg at 0/2/4/6 weeks, oral	2HRZE	Sputum culture conversion	8 weeks
7	Wang *et al.* (2020)	China	N/A; median = 44	Vitamin D 400 IU and Vitamin A 2,000 IU once daily for 2 months, oral	2HRZE then 4HR	Sputum smear conversion	6 months
8	Salahuddin *et al.* (2013)	Pakistan	16 – 86	Vitamin D3 (cholecalciferol) 600,000 IU at 0/2 weeks, intramuscular	2HRZE then 6HE	Weight gain and chest radiograph improvement	12 weeks
9	Range *et al.* (2005)	Tanzania	N/A; mean = 35	Multi-micronutrients (Vitamin A 5000 IU, vitamin B1 20 mg, vitamin B2 20 mg, vitamin B6 25 mg, vitamin B12 50 µg, folic acid 0.8 mg, niacin 40 mg, vitamin C 200 mg, vitamin E 60 mg, vitamin D3 200 IU, selenium 0.2 mg, and copper 5 mg) once daily for 8 weeks, oral	2HRZE then 4HE or 4HR	Sputum culture conversion	8 weeks
	Range *et al.* (2005)	Tanzania	N/A; mean = 35	Zinc 45 mg once daily for 8 weeks, oral	2HRZE then 4HE or 4HR	Sputum culture conversion	8 weeks
10	Ralph *et al.* (2013[#])	Indonesia	15 – 65	Vitamin D3 50,000 IU (1.25 mg) orally at weeks 0 and 4 (4-weekly for 8 weeks); 2×2 factorial trial also evaluating L-arginine 6.0 g/day for 8 weeks	2HRZE then 4HR	Sputum culture conversion and clinical score	24 weeks
11	Afzal *et al.* (2018)	Pakistan	N/A; mean = 39.02	Vitamin D 100,000 IU at 0/2/4/6 weeks, intramuscular	3HRZE then 6HR	Sputum smear conversion	12 weeks
12	Hasanain *et al.* (2019)	Egypt	N/A; mean = 33.2	Cholecalciferol 600 IU once daily for 6 months, oral	2HRZE then 4HR	Sputum culture conversion	4 months

[#]Ralph *et al.* (2013) used a 2×2 factorial design (vitamin D and L-arginine). For this review, data were extracted for the vitamin D main comparison (active vitamin D vs placebo vitamin D) to avoid double-counting participants.
N/A: Non-available data

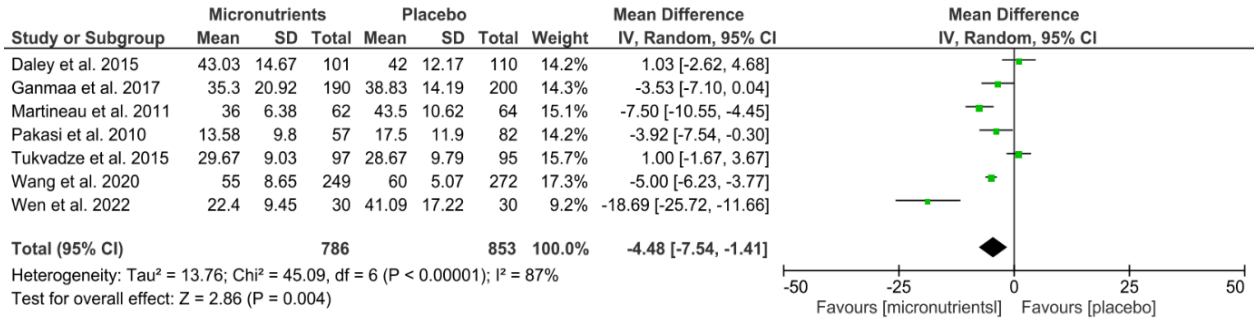

Figure 2. Mean Difference of Time to Sputum Smear/Culture Conversion (in days)

3.3 Heterogeneity Assessment

Significant inter-study heterogeneity was detected within the continuous outcome data, warranting the implementation of a random-effects model for the analysis of mean differences. In contrast, the analysis of sputum conversion at the one-month interval exhibited low heterogeneity (I^2 = 11%), justifying the use of a fixed-effect model (Figure 3A). For the two- and three-month intervals, moderate to high levels of heterogeneity were observed; therefore, random-effects models were applied to accommodate this variance (Figures 3B and 3C).

3.4 Risk of Bias Assessment

The methodological quality of the included trials was appraised using the Cochrane Risk of Bias tool (Higgins *et al.*, 2011), with domain-level evaluations summarized in Figure 4. Across the 12 trials, random sequence generation was

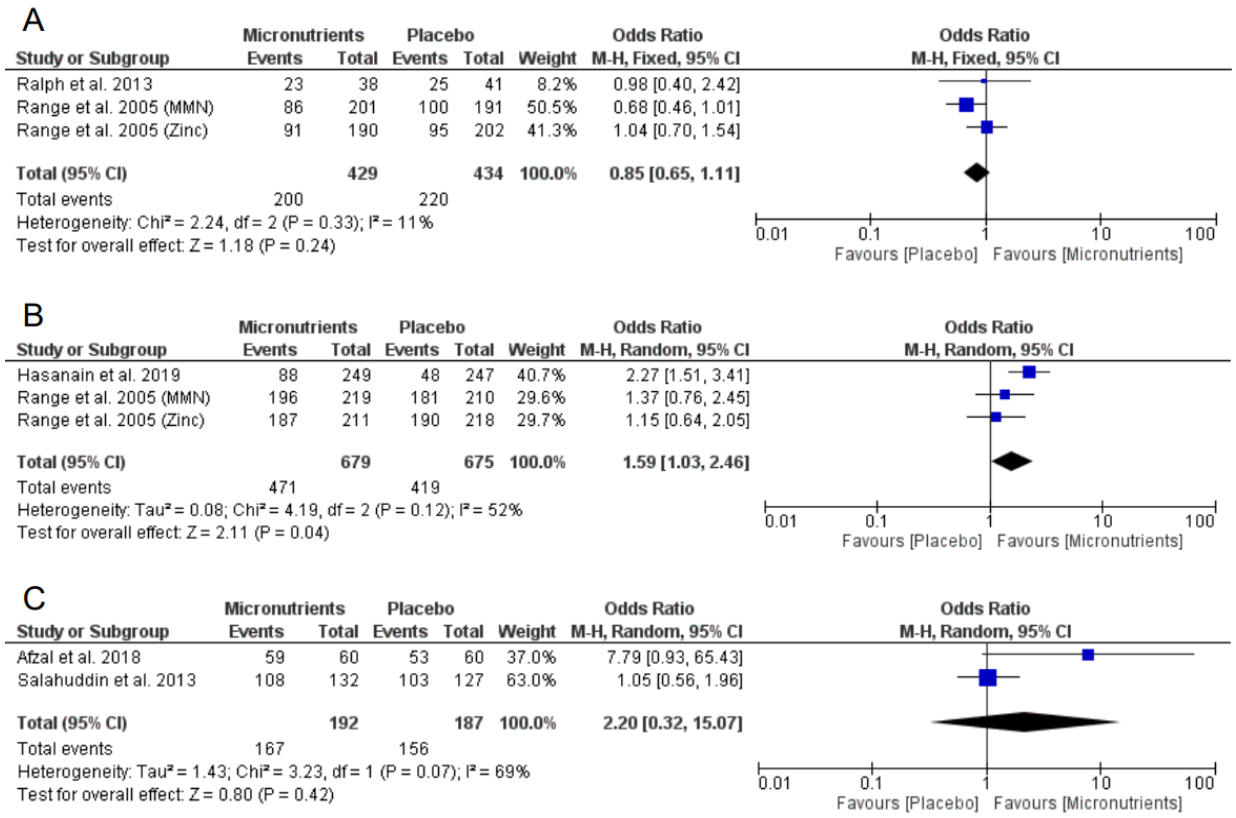

Figure 3. Odds Ratio of Negative Result of Sputum Smear/Culture in the First Month of Therapy (A), Second Month of Therapy (B), and Third Month of Therapy (C)

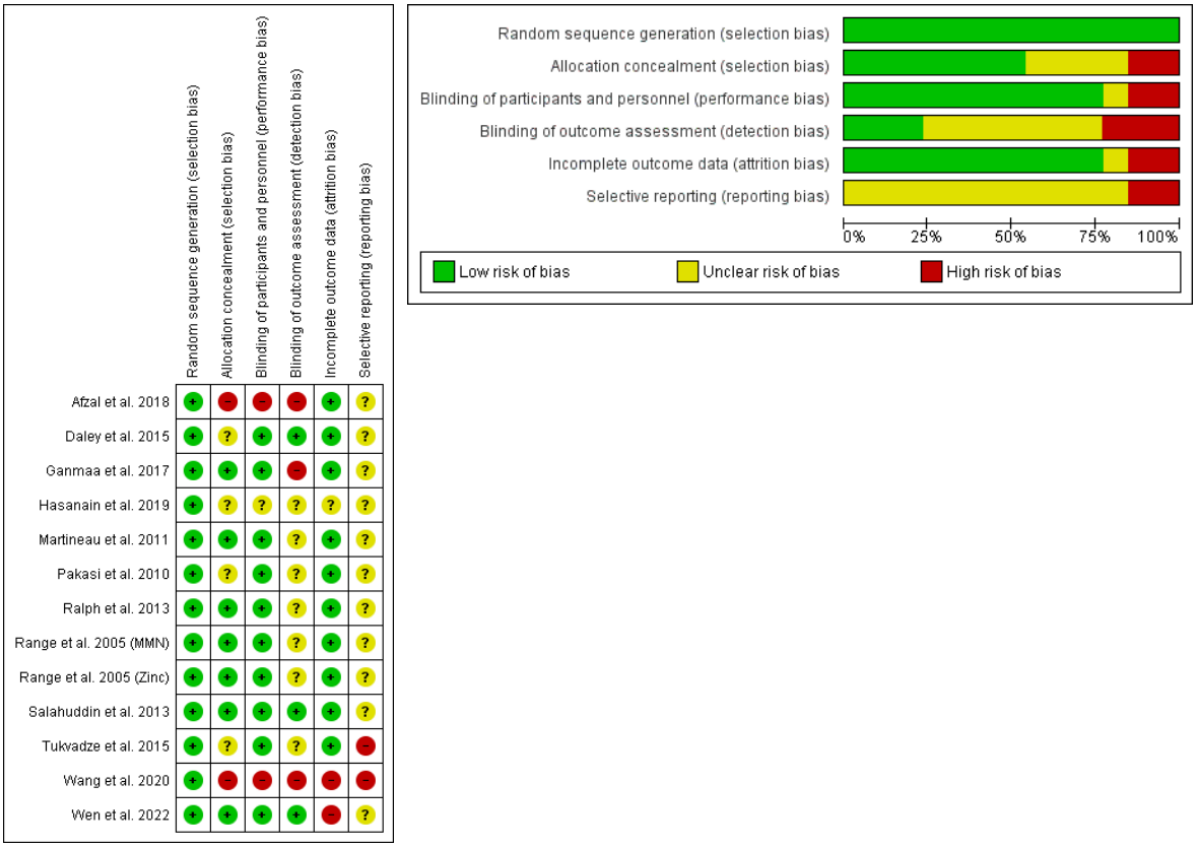

Figure 4. Risk of Bias Across all Included Studies

uniformly characterized as a low risk of bias. In contrast, allocation concealment and blinding—specifically the blinding of outcome assessment— exhibited considerable variability. This led to a preponderance of "unclear" ratings and a marginal number of "high risk" designations in these domains.

While the majority of studies demonstrated a low risk of bias concerning incomplete outcome data, a minority raised concerns regarding attrition rates. Selective reporting was frequently classified as an unclear risk, with high-risk judgments appearing in only a reduced number of trials. Overall, the risk of bias assessment indicates that the primary sources of uncertainty within the evidence base stem from suboptimal reporting of concealment and blinding protocols, as well as selective outcome reporting; these factors were meticulously considered during the interpretation of the pooled estimates.

4 Discussion

The present systematic review and meta-analysis synthesized evidence from 12 randomized controlled trials evaluating the efficacy of micronutrient supplementation in accelerating sputum smear or culture conversion among patients undergoing treatment for pulmonary tuberculosis (TB) (Afzal *et al.,* 2018; Daley *et al.,* 2015; Ganmaa *et al.,* 2017; Hasanain *et al.,* 2019; Martineau *et al.,* 2011; Pakasi *et al.,* 2010; Ralph *et al.,* 2013; Range *et al.,* 2005; Salahuddin *et al.,* 2013; Tukvadze *et al.,* 2015; Wang *et al.,* 2020; Wen *et al.,* 2022). The pooled findings indicate that adjunctive micronutrient supplementation significantly attenuates the duration required for sputum conversion—which constitutes a critical surrogate marker for therapeutic success and reduced community transmission. These findings support the hypothesis that targeted nutritional interventions may enhance immune response and complement standard anti-tubercular therapy (Shi & Yan, 2020; Verrall *et al.,* 2025; Xiong *et al.,* 2020).

The observed clinical benefit aligns with established biological plausibility, as micronutrients are indispensable modulators of both innate and adaptive immunological pathways (Gombart *et al.,* 2020; Lai *et al.,* 2021). Within the identified literature, a preponderance of trials focused on vitamin *D* supplementation, while research into multi-micronutrient formulations, vitamin *A*, and zinc remained comparatively sparse. Vitamin *D*, in particular, has been demonstrated to catalyze the intracellular eradication of

Mycobacterium tuberculosis by macrophages (Papagni *et al.,* 2022; Wahyunitisari *et al.,* 2017). Mechanistically, 1,25-dihydroxyvitamin D_3 enhances the expression of complement receptor immunoglobulins on macrophages, thereby optimizing phagocytic activity and bacillary clearance (Small *et al.*, 2021). Such mechanisms provide a robust theoretical framework for the clinical observation of rapid sputum conversion in vitamin *D*-supplemented cohorts (Afzal *et al.,* 2018; Daley *et al.,* 2015; Ganmaa *et al.,* 2017; Martineau *et al.,* 2011; Ralph *et al.,* 2013; Salahuddin *et al.,* 2013; Wang *et al.,* 2020; Wen *et al.,* 2022).

Vitamin *A* also occupies a critical role in TB immunity; metabolites such as all-trans retinoic acid have activate potent antimicrobial pathways within dendritic cells and macrophages (Kim *et al.,* 2019; Wheelwright *et al.,* 2014). Nevertheless, clinical evidence regarding its efficacy remains inconclusive. Notably, RCTs by (Pakasi *et al.,* 2010) and (Wang *et al.,* 2020) reported no significant effect of vitamin *A* on conversion kinetics. This lack of consensus suggests that therapeutic outcomes may be heavily influenced by confounding variables, including baseline nutritional status, specific dosing protocols, and the presence of concurrent micronutrient deficiencies.

Furthermore, despite its recognized antioxidant and antimicrobial properties, ascorbic acid (vitamin *C*) was not investigated in any RCTs identified by our search. This is noteworthy, given *in vitro* studies indicating that vitamin *C* exerts bactericidal effects on both drug-sensitive and drug-resistant strains of *Mycobacterium tuberculosis* via pro-oxidant mechanisms such as the Fenton reaction (Vilchèze *et al.,* 2018). The current absence of clinical data regarding vitamin *C* underscores a significant knowledge gap that warrants prioritized investigation in future trials.

While the current meta-analysis demonstrates the potential of micronutrient supplementation to reduce sputum conversion time, several limitations merit consideration. First, the majority of the included studies failed to account for baseline micronutrient levels, HIV co-infection, ethnic variation, or pre-existing comorbidities, all of which may significantly modulate treatment response. Second, the heavy emphasis on vitamin *D* in the current literature limits the generalizability of these findings to further micronutrients. Finally, substantial heterogeneity in dosing regimens, formulations, and intervention durations likely contributed to the observed variability in outcomes.

Future research should prioritize high-powered RCTs that stratify participants by baseline nutritional status, co-infections, and demographic factors. Moreover, head-to-head trials comparing individual micronutrients or synergistic combinations are necessary to clarify their respective contributions to TB recovery. Such evidence will be vital for the integration of evidence-based nutritional strategies into national TB control programs.

5 Conclusions

This meta-analysis provides evidence that adjunctive micronutrient supplementation, when utilized as a complement to standardized anti-tubercular therapy, is associated with a statistically significant reduction in the time to sputum smear or culture conversion. These findings highlight the potential of micronutrients as immunomodulatory agents capable of enhancing therapeutic efficacy. Incorporating targeted nutritional support into tuberculosis management strategies may not only improve clinical outcomes but also accelerate the control of infectiousness at the population level. Further high-quality, stratified trials are essential to determine the optimal type, dose, and timing of micronutrient interventions across diverse global populations.

Source of funding: No funding was received for this study.

Acknowledgment: The authors gratefully acknowledge the staff of the Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, for their support in the preparation of this manuscript.

Previous presentations: The content of this manuscript has not been presented elsewhere in any form.

Authors' Contribution: FAS: Conceptualization, Methodology, Supervision, Project Administration, Validation, Writing – Original Draft, Writing – Review & Editing. **JAFK**: Data Curation, Formal Analysis, Investigation, Visualization, Writing – Original Draft, Writing – Review & Editing. **NK**: Formal Analysis, Visualization, Validation, Writing – Review & Editing.

Conflicts of Interest: All authors declare that they have no competing interests.

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