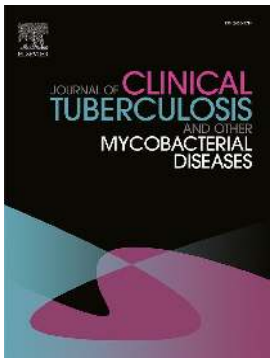


Evolution of evidence on vitamin D supplementation in tuberculosis: A comprehensive umbrella review of nine systematic reviews

Jhosmer Ballena-Caicedo, Lupita Ana Maria Valladolid-Sandoval, Fiorella E. Zuzunaga-Montoya, Víctor Juan Vera-Ponce

PII: S2405-5794(26)00047-1

DOI: https://doi.org/10.1016/j.jctube.2026.100625

Reference: JCTUBE 100625

To appear in:

Please cite this article as: J. Ballena-Caicedo, L.A.M. Valladolid-Sandoval, F.E. Zuzunaga-Montoya, et al., Evolution of evidence on vitamin D supplementation in tuberculosis: A comprehensive umbrella review of nine systematic reviews, (2024), https://doi.org/10.1016/j.jctube.2026.100625

Evolution of evidence on vitamin D supplementation in tuberculosis: A comprehensive umbrella review of nine systematic reviews

Jhosmer Ballena-Caicedo[1], Lupita Ana Maria Valladolid-Sandoval[1], Fiorella E. Zuzunaga-Montoya[1], Víctor Juan Vera-Ponce[1*]

[1] Facultad de Medicina (FAMED), Universidad Nacional Toribio Rodríguez de Mendoza de Amazonas (UNTRM), Amazonas, Perú
*Correspondence

Jhosmer Ballena-Caicedo, https://orcid.org/0009-0002-7070-7434
7330178022@untrm.edu.pe
Lupita Ana Maria Valladolid-Sandoval, https://orcid.org/0009-0000-0165-5963
luamavasa1911@gmail.com
Fiorella E. Zuzunaga-Montoya, https://orcid.org/0000-0002-2354-273X
fiorellazuzunaga@gmail.com
Víctor Juan Vera-Ponce, https://orcid.org/0000-0003-4075-9049
vicvepo@gmail.com

Abstract

Background: Vitamin D supplementation as adjunctive therapy in tuberculosis has generated multiple systematic reviews with variable conclusions. The proliferation of syntheses in this field requires comprehensive evaluation to determine the temporal evolution of evidence and its translation into clinical recommendations.

Objective: To synthesize systematic reviews on vitamin D supplementation in tuberculosis, evaluate the temporal evolution of conclusions, examine heterogeneity in clinical outcomes, and determine the quality of available evidence for clinical practice.

Methods: An umbrella review was conducted in accordance with PRIOR guidance for overviews of reviews, searching MEDLINE, Embase, Web of Science, and Scopus. Systematic reviews examining vitamin D as adjunctive therapy in tuberculosis were included. Methodological quality was assessed using AMSTAR-2 and ROBIS, and evidence certainty was evaluated with GRADE adapted for umbrella reviews. Overlap among primary randomized trials was quantified using a citation matrix and the corrected covered area (CCA).

Results: Nine systematic reviews (2009-2022) were identified, encompassing 300-2,991 participants. A citation matrix identified 16 unique primary RCTs and 64 trial occurrences across nine reviews, corresponding to very high overlap (CCA = 37.5%). Meta-analytic findings consistently demonstrated null effects for primary outcomes: culture conversion RR 1.04-1.05, time to conversion HR 1.04-1.15, and mortality without significant differences. Subgroup analyses revealed potential effects in VDR TaqI tt genotype (HR 8.09, 95% CI 1.36-48.01) and multidrug-resistant tuberculosis (RR 2.40, 95% CI 1.11-5.18), although these findings were based on small sample sizes. Safety profiles were favorable with hypercalcemia <2%.

Conclusions: Current evidence from overlapping systematic reviews does not support routine vitamin D supplementation as adjunctive therapy to improve tuberculosis treatment outcomes in unselected populations. Signals in VDR TaqI tt genotype carriers and multidrug-resistant tuberculosis remain hypothesis-generating and require prospective validation before clinical translation.

Keywords (MeSH Terms): Vitamin D; Tuberculosis, Pulmonary; Systematic Review; Meta-Analysis; Cholecalciferol; Dietary Supplements; Antitubercular Agents; Evidence-Based Medicine; Clinical Trials as Topic; Treatment Outcome.

Introduction

Tuberculosis remains one of the leading causes of mortality from infectious diseases worldwide, with approximately 10.6 million new cases and 1.6 million deaths reported in 2021 [1]. Despite advances in the development of effective antituberculosis treatments, the emergence of multidrug-resistant strains and the prolonged duration of conventional treatment have driven the search for adjunctive therapies that may improve clinical outcomes [2]. Among the proposed interventions, vitamin D supplementation

has generated considerable interest due to its established role in modulating innate and adaptive immune responses [3].

Interest in vitamin D as adjunctive therapy in tuberculosis is based on robust mechanistic evidence demonstrating its capacity to regulate the expression of antimicrobial peptides, particularly cathelicidin LL-37, which exhibits direct bactericidal activity against Mycobacterium tuberculosis [4,5]. In vitro studies have demonstrated that vitamin D activates human macrophages to eliminate intracellular mycobacteria by inducing autophagy and nitric oxide production [6]. Additionally, observational studies have established consistent associations between vitamin D deficiency and increased susceptibility to tuberculosis, with recent meta-analyses documenting relative risks of 1.4 to 2.9 for the development of active tuberculosis in individuals with severe deficiency [7].

The translation of these mechanistic and observational findings into clinical benefits has motivated multiple randomized controlled trials since 2006, followed by a proliferation of systematic reviews that have attempted to synthesize this growing evidence [8,9]. However, the results of these studies have been inconsistent, with some reporting modest benefits in bacteriological conversion and others demonstrating no significant effects [10,11]. Currently, World Health Organization (WHO) guidelines for tuberculosis treatment do not include specific recommendations on vitamin D supplementation [12].

Nevertheless, recent narrative reviews continue to suggest a potential role for vitamin D in tuberculosis based on mechanistic evidence, creating a discrepancy between translational plausibility and evidence-based clinical recommendations [13,14]. However, the specific evidence gap is not merely whether vitamin D has been studied, but whether the apparent evolution of conclusions across systematic reviews reflects independent accumulation of evidence, repeated synthesis of overlapping randomized trials, differences in outcome definitions, or selective emphasis on statistically significant subgroup findings. Therefore, this umbrella review aimed to synthesize systematic reviews on vitamin D supplementation in tuberculosis, evaluate the temporal evolution and redundancy of the evidence base, examine heterogeneity across clinical outcomes and subgroups, and determine the certainty of available evidence for clinical practice.

Methods

Design

This UR was developed following the PRIOR (Preferred Reporting Items for Overviews of Reviews) guidelines for umbrella reviews [15], as well as the methodological framework proposed by Aromataris et al. [16] for UR.

Eligibility criteria

Systematic reviews (SR) and meta-analyses examining vitamin D supplementation as adjunctive therapy in the treatment or prevention of tuberculosis were included. Reviews were eligible if they included at least three randomized controlled trials that specifically evaluated vitamin D (cholecalciferol, ergocalciferol, or active metabolites) versus placebo or standard care in patients with active tuberculosis or individuals at risk of developing tuberculosis. Narrative reviews, individual patient data meta-analyses, and reviews focusing exclusively on observational studies were excluded. There were no language restrictions. The detailed search strategy is presented in Supplementary Material 1.

Reviews evaluating multi-micronutrient interventions were excluded only when the effect of vitamin D could not be disentangled from other co-administered nutrients. This criterion was applied to preserve causal attribution to vitamin D supplementation, because pooled effects from combined nutritional interventions may reflect the influence of other micronutrients, nutrient-nutrient interactions, correction of general malnutrition, or background nutritional status rather than vitamin D itself. Reviews were considered eligible when they provided a separate vitamin D arm or extractable vitamin D-specific analysis.

Overlap among systematic reviews was anticipated and was not used as an exclusion criterion, because the unit of inclusion in this umbrella review was the systematic review rather than the primary randomized trial. Reviews with identical or highly overlapping primary studies were retained when they met eligibility criteria, as they contributed to the assessment of redundancy, methodological quality, and temporal evolution of conclusions. However, their pooled estimates were not interpreted as independent

confirmation of efficacy. Accordingly, Wang et al. and Cabrera Andrade et al. were both retained, while their partially overlapping primary-study sets were explicitly considered during interpretation.

Search Strategy

Comprehensive research was conducted in MEDLINE (PubMed), Embase, Web of Science, and SCOPUS from 2000 to July 4, 2025. The search strategy combined Medical Subject Headings (MeSH) terms and free-text words related to "Vitamin D," "cholecalciferol," "tuberculosis," "systematic review," and "meta-analysis." Reference lists of reviews included were also manually screened. Search strategies were developed with the assistance of an experienced medical librarian and adapted for each database, while maintaining sensitivity and specificity. The temporal limitation from 2000 was applied because controlled research on vitamin D and tuberculosis emerged in the late 1990s.

Study selection and data extraction

Three reviewers (VJVP, JJBC, and LAMV) independently screened titles and abstracts using the Rayyan QCRI platform for systematic screening. Disagreements were resolved through discussion or consultation with a fourth reviewer (FEZM). Eligibility data were exported from Rayyan to Microsoft Excel for subsequent management and analysis. Full-text articles of potentially eligible studies were retrieved and assessed for inclusion using predefined criteria by the same three independent reviewers.

Data extraction was performed independently by three reviewers (VJVP, JJBC, and LAMV) using standardized forms piloted in Microsoft Excel that captured review characteristics (first author, publication year, search dates, databases consulted, number of included studies, total participants), methodological characteristics (study design, inclusion criteria, quality assessment methods, statistical approaches), included primary studies with publication years, outcome measures, effect estimates with confidence intervals, subgroup analyses, and safety data. Information on search strategies, inclusion criteria, quality assessment methods, statistical approaches, and conflict of interest declarations was extracted. Discrepancies in data extraction were resolved through consensus among extractors and review by the senior investigator (FEZM).

Assessment of overlap across systematic reviews

To quantify the degree of overlap in primary randomized controlled trials across the included systematic reviews, we constructed a citation matrix in which rows represented unique primary RCTs and columns represented systematic reviews. A trial was counted when vitamin D was an explicit intervention arm, either alone or as part of a factorial/co-intervention design. Broader micronutrient trials without a vitamin D-specific arm or extractable vitamin D-specific contribution were not counted for this overlap assessment. Overall overlap was quantified using the corrected covered area (CCA) [36], calculated as (N - r)/(r x c - r), where N represents the total number of trial occurrences across reviews, r the number of unique primary RCTs, and c the number of systematic reviews. Pairwise overlap was also assessed using shared trial counts, Jaccard similarity, and overlap coefficients. The citation matrix and coding decisions are provided in Supplementary Material 5.

Methodological quality assessment

The methodological quality of the included systematic reviews was assessed using two complementary tools, applied independently by three reviewers (VJVP, JJBC, and LAMV). AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews-2) [17] evaluated 16 domains of systematic review methodology including formulation of a research question with adequate PICO elements, prospective protocol registration, justification of included study designs, comprehensiveness of literature search strategy, duplicate study selection and data extraction, presentation of excluded studies list with justification, detailed description of included studies, assessment of risk of bias in primary studies, reporting of funding sources for studies, use of appropriate statistical methods for quantitative synthesis, evaluation of risk of bias impact on meta-analysis results, consideration of such bias in interpretation of findings, explanation of observed heterogeneity, assessment of publication bias, and declaration of review authors' conflicts of interest. Each domain was rated as "Yes," "Partial Yes," or "No," with overall confidence ratings categorized as "High," "Moderate," "Low," or "Critically Low."

ROBIS (Risk of Bias in Systematic Reviews) [18] was applied to assess risk of bias specifically in four domains: study eligibility criteria, identification and selection of studies, data collection and study

appraisal, and synthesis and findings. Each domain was rated as having a "Low," "High," or "Unclear" risk of bias, with an overall risk of bias judgment. ROBIS complemented AMSTAR-2 by focusing specifically on bias rather than broader methodological quality, providing an assessment of whether systematic review conclusions were supported by evidence. Disagreements in both tools were resolved through discussion between assessors or consultation with a fourth reviewer (FEZM).

Evidence Grading

Evidence quality for primary outcomes was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach adapted for UR [19]. Evidence quality was initially rated as "High" for outcomes from systematic reviews of randomized controlled trials, but was subsequently downgraded due to concerns about risk of bias, inconsistency, indirectness, imprecision, and publication bias. Additional downgrading was applied for excessive overlap between reviews without methodological justification and for credibility concerns in subgroup analyses. The final evidence quality was categorized as "High," "Moderate," "Low," or "Very Low," with explicit justification provided for each domain assessment. GRADE grading was performed independently by two investigators (VJVP and JJBC) with discrepancy resolution through structured discussion.

Publication bias judgments were based on the assessments reported within the included systematic reviews. We did not perform de novo funnel plots or statistical tests for funnel plot asymmetry at the umbrella-review level, because outcome-specific evidence sets generally included few primary trials and several reviews shared overlapping primary studies, limiting the validity and power of such analyses. Therefore, absence of a reported publication-bias signal was interpreted as no major concern reported by included reviews, not as definitive evidence that publication bias was absent.

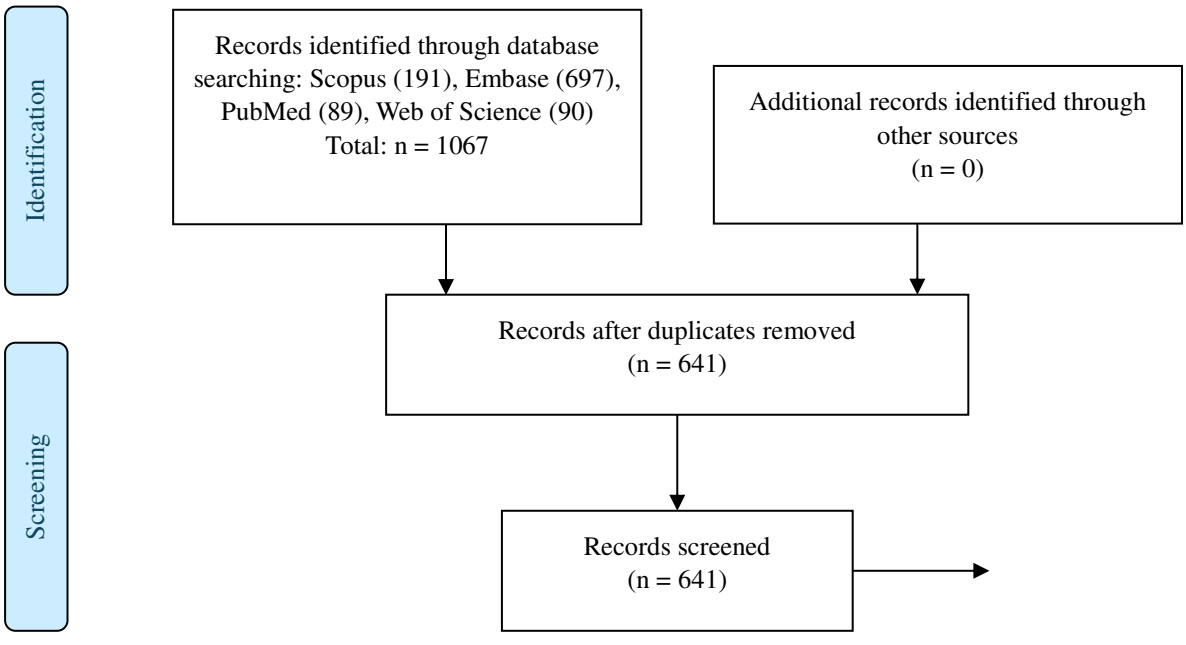
Ethics approval and consent to participate

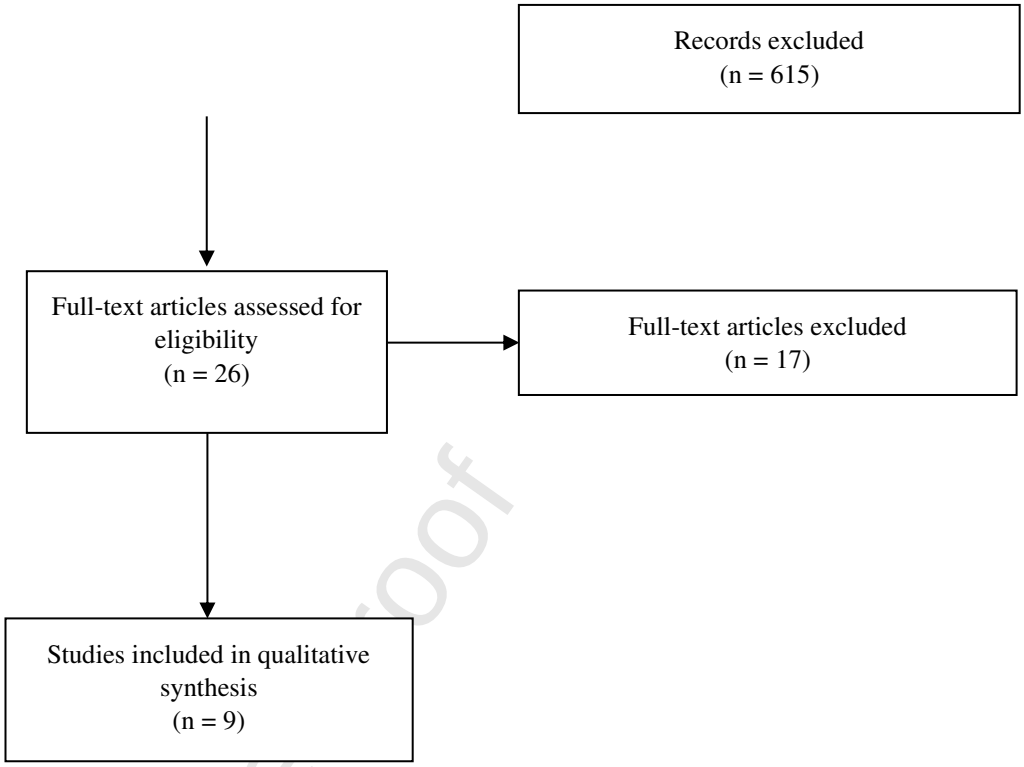
This umbrella review analyzed previously published systematic reviews and did not involve the collection of primary data from human participants. Therefore, ethics committee approval and informed consent were not required for this study. All included systematic reviews reported appropriate ethical approvals for their respective primary studies.

Results

Article selection process

The systematic search across four databases (Scopus, Embase, PubMed, and Web of Science) identified a total of 1,067 records, with no additional records identified through other sources. After duplicate removal, 641 unique records were obtained for assessment. During the initial screening phase, 615 records that did not meet basic eligibility criteria were excluded, resulting in 26 articles selected for full-text evaluation. Detailed review of these articles led to the exclusion of 17 additional studies that did not meet specific inclusion criteria. Finally, 9 systematic reviews were included in the qualitative synthesis between 2009 and 2022 [20–28] (Figure 1).





Supplementary Material 2. Flowchart of Study Selection

Characteristics of included systematic reviews

The selected reviews showed variation in scope and methodology, with study numbers ranging from 4 tuberculosis-specific trials in Yamshchikov et al. [20] to 12 trials in Goyal et al. [28], and participant numbers spanning from 300 to 2,991 individuals. The temporal evolution revealed progressive methodological development, beginning with Yamshchikov et al.'s exploratory narrative review examining vitamin D in infectious diseases [20], progressing through Xia's (2014) first formal meta-analysis [21] of 841 participants, to Wu Hong-Xia et al.'s analysis of 1,787 participants [25] (Table 1).

Search strategies varied in comprehensiveness. Wallis et al. [23] used only PubMed with basic terms ("Tuberculosis", "Clinical trial," "Vitamin D"), while Wu Hong-Xia et al. [25] and Zhang et al. [26] employed multi-database approaches with synonym lists including "cholecalciferol", "calcidiol", "calcitriol", "ergocalciferol", "25-hydroxyvitamin D", "vitamin D2", and "vitamin D3". The geographical distribution of the included populations was global, encompassing studies from Africa, Asia, Europe, and North America, with a concentration in countries with a high tuberculosis burden.

Intervention characteristics demonstrated heterogeneity in dosing regimens. Doses ranged from Morcos (1998) [29]administering 1,000 IU daily for 8 weeks (total 56,000 IU) to Ralph et al. [30] providing 50,000 IU daily for 8 weeks (total 2,800,000 IU). Most studies utilized cholecalciferol, with administration routes including daily oral dosing, intermittent oral boluses, and intramuscular injections. Variation in dosing standardization represented a challenge in interpreting pooled effects across studies.

Population characteristics varied among included studies. Mean ages ranged from 26.7 to 43.7 years across the review populations, with 60-67% of participants being male in most reviews. HIV coinfection rates varied from complete exclusion in some studies to over 50% in African populations included in Grobler et al. [22]. Baseline vitamin D deficiency was prevalent across populations, with levels of 6.0 to 79.1 nmol/L across studies. Wu Hong-Xia et al. [25] reported baseline 25(OH)D concentrations of 7.8-77.5 nmol/L in intervention groups versus 6.0-79.1 nmol/L in control groups. The geographical distribution showed a correlation with latitude, with Wallis et al. [23] observing higher deficiency rates in United Kingdom studies compared to equatorial regions.

Table 1: Characteristics of Included Systematic Reviews

First Author, Year	Type	Primary Objective	Search Until	Databases (n)	RCTs (n)	Participants (n)	Population	Intervention	Primary Outcome	Funding
Yamshchikov 2009	SR	Review vitamin D as adjuvant therapy in infections	2009	2 (PubMed, Ovid)	4 TB-specific of 13 total	300 (estimated)	Adults and children with active TB	Vitamin D2/D3 (40 IU-100,000 IU)	Sputum conversion (descriptive)	NR
Xia 2014	SR+MA	Evaluate impact of vitamin D on TB treatment	December 2013	8	5	841	Newly diagnosed TB	2.5-30 mg total in 8 weeks	Sputum conversion 6 weeks	NR
Wallis 2016	SR	Vitamin D as host-	2015	1 (PubMed)	8	1,206	Smear/ culture	2.5-30 mg (8 weeks)	Sputum convers	None

		directed therapy in TB					positive TB		ion 8 weeks	
Wang 2018	SR+MA	Efficacy and safety of vitamin D in pulmonary TB	October 2016	6	5	661	Pulmonary TB	50,000 - 60,000 IU high dose	Negative smear conversion	NR
Wu Hong-Xia 2018	SR+MA	Evaluate vitamin D efficacy in pulmonary TB	November 2017	4	8	1,787	Pulmonary TB ≥16 years	Oral/IM boluses, daily	Smear/ culture conversion	None
Zhang 2019	SR+MA	Improve anti-TB therapy effects in adults	February 2019	3	5	1,126	Adult pulmonary TB ≥18 years	7.5-35 mg oral	Time to culture conversion	None
Cabrera Andrade 2020	SR+MA	Effectiveness of micronutrients in pulmonary TB	November 2017	6	5	661	Active pulmonary TB	Vitamin D subset *	Negative smear conversion	NR
Grobler 2016	SR (Cochrane)	Nutritional supplements in active TB	February 2015	5	8 VitD of 35 total	2,649 VitD of 8,285	Active TB ± HIV	Variable (includes VitD)	Mortality, cure	Cochrane
Goyal 2022	SR+MA	Role of vitamin D vs placebo in TB management	June 2021	2	12	2,991	Adult TB	Wide range	Time to culture conversion	NR

Abbreviations: SR=Systematic Review; MA=Meta-analysis; TB=Tuberculosis; RCTs=Randomized Controlled Trials; IU=International Units; IM=Intramuscular; NR=Not Reported

Note: RCT counts in Table 1 reflect the review-level descriptions reported by each systematic review. Supplementary Material 5 reports the vitamin D-coded primary RCTs used for overlap assessment; for broader nutritional reviews, only trials with an explicit vitamin D arm were counted in the citation matrix.

Overlap of primary randomized trials across systematic reviews

The citation matrix identified 16 unique primary RCTs contributing to 64 trial occurrences across the nine included systematic reviews. The overall CCA was 37.5%, indicating very high overlap among the review

evidence base. Goyal et al. covered the complete RCT sets included by Wallis et al., Wu Hong-Xia et al., and Zhang et al., and covered 80% of the RCTs included by Wang et al. and Xia et al. Grobler et al. covered the complete vitamin D-coded RCT set included by Cabrera Andrade et al. and 80% of the RCTs included by Wang et al. and Xia et al.

Formal overlap assessment also showed that Wang et al. and Cabrera Andrade et al. were overlapping but not completely duplicative: they shared three primary trials among nine unique trials identified across both reviews, corresponding to an overlap coefficient of 60.0%. Therefore, overlapping reviews were retained to characterize redundancy, methodological variation, and temporal evolution of the evidence base, but their pooled estimates were not interpreted as independent confirmation of efficacy.

Methodological quality and risk of bias assessment

Methodological quality was assessed using two complementary tools: AMSTAR-2 to evaluate the overall quality of systematic review conduct, and ROBIS to specifically assess risk of bias in synthesis and interpretation of results.

The AMSTAR-2 assessment revealed considerable variation in methodological quality (Supplementary Material 2). One review achieved high quality rating: Grobler et al. [22], characterized by complete compliance with all AMSTAR-2 items. Five reviews [21,25–28] received moderate quality ratings, with minor limitations in non-critical domains such as protocol registration, reporting of funding sources, or declaration of conflicts of interest. Three reviews [20,23,24] received critically low ratings due to multiple limitations in critical domains.

Notably, Yamshchikov et al. [20] presented significant limitations, including failure to register a protocol, omission of duplicate selection and extraction processes, and inadequate assessment of the risk of bias in individual studies, as well as neglect of this risk in result interpretation. Wallis et al. [23] reported similar deficiencies, including a restricted literature search (limited to PubMed only), the absence of protocol registration, inadequate documentation of duplicate processes, and the omission of a formal bias assessment of the included studies. Finally, Wang et al. [24] lacked protocol registration, did not adequately report individual risk of bias or its impact on interpretation, and did not consider publication bias, which collectively compromised its overall rating.

The ROBIS assessment (Supplementary Material 3) showed that most reviews had a low risk of bias for the study identification and selection processes. However, several reviews showed moderate to high risk in the specification of eligibility criteria, particularly Wang et al. [24] and Cabrera Andrade et al. [27], which exhibited evidence restriction in their methodological approaches. The synthesis and interpretation domain showed variable quality, with narrative reviews, such as those by Wallis et al. [23], appropriately avoiding meta-analysis. In contrast, quantitative syntheses employed statistical methods consistent with the study design and the nature of the available data.

Primary clinical outcomes and effect estimates

Meta-analytic findings consistently demonstrated null effects for primary tuberculosis outcomes in general populations (Figure 2 and Supplementary Material 4). Sputum culture conversion, evaluated in six reviews-four with meta-analyses-showed effect estimates clustering around the null value. Wu Hong-Xia et al. [25] reported a statistically significant positive finding with OR 1.22 (95% CI 1.04-1.43, p=0.02), while other later or broader syntheses found non-significant effects: Zhang et al. [26] RR 1.05 (95% CI 0.99-1.10, p=0.08), Goyal et al. [28] RR 1.04 (95% CI 0.98-1.11, p=0.21), and Grobler et al. [22] RR 0.94 (95% CI 0.84-1.06) at 2 months.

Sputum smear conversion, evaluated in eight studies, six with meta-analyses, showed similar patterns, with most effect estimates near unity. Wang et al. [24] and Cabrera Andrade et al. [27], two overlapping but not identical reviews, reported the same pooled estimate of RR = 0.99 (95% CI: 0.91-1.07; p = 0.77). Their concordance was therefore interpreted as consistency between partially overlapping syntheses rather than as independent replication. Meanwhile, Wu Hong-Xia et al. [25] found a statistically significant effect with OR = 1.21 (95% CI: 1.05-1.39; p = 0.007). Other results included: Xia et al. [21],

with RR = 0.61 (95% CI: 0.24-1.56; p = 0.30); and Goyal (2022), with RR = 1.07 (95% CI: 0.94-1.21; p = 0.31).

The statistically significant estimates reported by Wu Hong-Xia et al. should be interpreted as potential efficacy signals rather than dismissed as spurious findings. A genuine pharmacological effect in selected populations, dosing contexts, or baseline vitamin D strata remains biologically plausible. However, these findings were modest in magnitude, were not consistently reproduced in later or broader syntheses, and were counterbalanced by null estimates for time-to-conversion outcomes. Therefore, they were considered hypothesis-generating signals within a predominantly null evidence base, rather than definitive evidence supporting routine supplementation.

Time to conversion outcomes, evaluated in five studies, three with meta-analyses, and analyzed using hazard ratios, consistently showed that vitamin D supplementation did not accelerate conversion. Zhang et al. [26] reported HR = 1.04 (95% CI: 0.89–1.23; p = 0.60) for culture conversion and HR = 1.15 (95% CI: 0.93–1.41; p = 0.20) for smear conversion. Wu Hong-Xia et al. [25] found HR = 0.97 (95% CI: 0.76–1.23; p = 0.77), while Goyal [28] reported HR = 1.06 (95% CI: 0.92–1.23; p = 0.43).

Mortality outcomes consistently showed no significant benefits, although wide confidence intervals indicated limited statistical power. Wu Hong-Xia et al. [25] reported OR = 1.22 (95% CI: 0.74–2.04; p = 0.43), Zhang et al. [26] RR = 0.86 (95% CI: 0.20–3.74; p = 0.83), Grobler et al. [22] RR = 0.86 (95% CI: 0.46–1.60), and Goyal et al. [28] RR = 1.16 (95% CI: 0.41–3.27; p = 0.78). The consistency of null findings across different analytical approaches reinforced confidence in the absence of clinically relevant benefits in unselected populations.

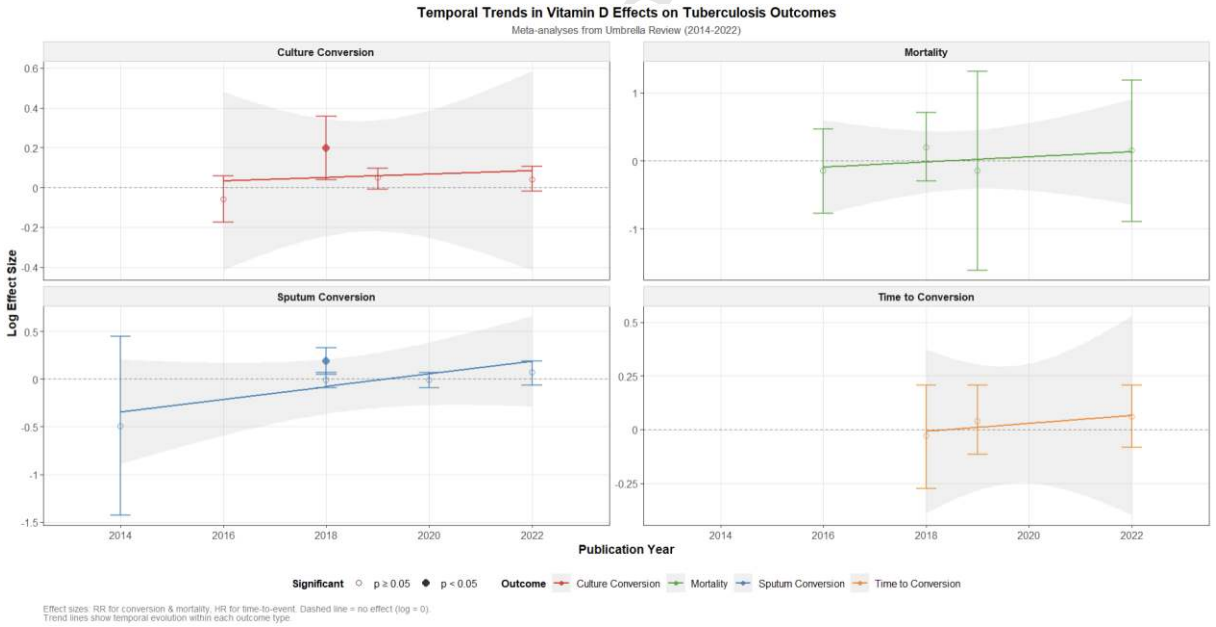


Figure 2. Temporal trends in effect sizes for vitamin D supplementation outcomes in tuberculosis treatment by meta-analysis publication year (2014-2022)

Subgroup analyses, statistical heterogeneity, and sensitivity analyses

Several reviews reported subgroup analyses with statistically significant effects. Wallis (2016) [23] and Zhang et al. [26] reported effects in patients with VDR TaqI tt genotype: HR 8.09 (95% CI 1.36-48.01, p=0.02) for sputum conversion, based on approximately 30 patients. Zhang et al. [26] reported effects in multidrug-resistant tuberculosis: RR 2.40 (95% CI 1.11-5.18, p=0.03) for culture conversion. Other subgroup analyses showed variable results. Stratification by baseline vitamin D deficiency showed inconsistent patterns across reviews. Analyses by HIV status yielded non-significant results: Grobler et al. [22] found RR 0.86 (95% CI 0.46-1.60) in HIV-negative patients versus RR 0.92 (95% CI 0.69-1.23) in HIV-positive patients. Dose-response relationships did not demonstrate consistent patterns across reviews. Interpretation of these subgroup findings requires consideration of limited sample sizes, the

exploratory nature of analyses, and the absence of correction for multiple comparisons in the original reviews.

Heterogeneity between studies varied across outcomes and reviews. Sputum conversion outcomes showed low to moderate heterogeneity, with Zhang et al. [26] reporting I^2 = 14% for time to culture conversion and I^2 = 42% for time to smear conversion. Wu Hong-Xia et al. [25] found variable heterogeneity by outcome, with conversion rates showing I^2 = 0% while biochemical outcomes such as serum 25(OH)D levels demonstrated I^2 = 99%, reflecting diverse dosing regimens and measurement approaches. Goyal et al. [28] reported moderate heterogeneity for most outcomes: I^2 = 43% for time to culture conversion, I^2 = 40% for culture conversion rate, and I^2 = 50% for smear conversion rate. Authors attributed this heterogeneity to differences in diagnostic criteria, population characteristics, and intervention protocols. Wang et al. [24] and Cabrera Andrade et al. [27] reported low heterogeneity (I^2 = 0%) for smear conversion.

Sensitivity analyses were variably reported across reviews. Wu Hong-Xia et al. [25] demonstrated consistency between intention-to-treat and per-protocol analyses, with stable results when excluding studies with heterogeneity (I^2 > 50%). Zhang et al. [26] found stability when restricting analyses to high-quality studies and when comparing ITT versus per-protocol populations. Xia et al. [21] performed a sensitivity analysis by study quality using the Jadad scale, finding similar results when excluding studies that scored less than 3.

Safety profile and adverse events

The safety profile was consistent across all reviews. Hypercalcemia, the primary theoretical concern, occurred rarely, with no significant differences between treatment groups. Xia et al. [21] reported 1.67% hypercalcemia in vitamin D groups versus 1.23% in placebo groups (p=0.69), while Zhang [26] found RR 1.28 (95% CI 0.34-4.79, p=0.72). Wu Hong-Xia et al. [25] and Goyal et al. [28] confirmed these findings through comprehensive safety analyses, which showed no significant differences in hypercalcemia rates.

Serious adverse events remained consistently low across reviews. Wu Hong-Xia et al. [25] reported OR 1.02 (95% CI 0.48-2.20, p=0.95), while Goyal et al. [28] found RR 0.83 (95% CI 0.26-2.60, p=0.74). Xia et al. [21] documented serious adverse events in 1.24% of vitamin D recipients with no significant difference from placebo. Non-serious adverse events showed similar patterns, with Wu Hong-Xia et al. [25] reporting OR 1.06 (95% CI 0.65-1.74, p=0.80).

Notable safety events included two paradoxical reactions documented by Wallis et al. [23] in the Martineau study, where patients developed psoas and paraspinal abscesses requiring therapeutic drainage despite microbiological improvement. One potentially treatment-related death was reported by Salahuddin et al. [31] (due to rapidly progressive respiratory failure within two weeks of randomization, although causality remained uncertain. The overall safety profile, based on data from nearly 3,000 participants, supported vitamin D supplementation as a low-risk intervention with rare serious complications.

Dosing Strategies and Pharmacological Considerations

Dosing strategies employed in primary studies showed heterogeneity. Total cumulative doses ranged from 56,000 IU (1.4 mg) in Morcos et al. [29] administering 1,000 IU daily for 8 weeks, to 2,800,000 IU (70 mg) in Ralph et al. [30] providing 50,000 IU daily for 8 weeks. Most studies employed high-dose intermittent regimens rather than daily supplementation, with popular approaches including 100,000 IU (2.5 mg) every two weeks for 4 doses [32,33] or 600,000 IU (15 mg) intramuscularly in two divided doses [31].

The pharmacological rationale for these diverse approaches remained poorly established, with no clear dose-response relationships emerging from meta-analyses. Reviews attempting stratified analyses by dose, including Xia et al. [21] with categorization into low (2.5 mg), intermediate (7.5-10.5 mg), and high (30 mg) total doses over 8 weeks, failed to demonstrate clear efficacy patterns. This lack of dose optimization represented a fundamental limitation in field development.

Evidence quality and GRADE assessment

Our GRADE assessment revealed generally low to moderate quality evidence across major outcomes (Table 2). Sputum smear conversion achieved moderate quality evidence, downgraded one level for serious study design limitations, but maintaining reasonable precision and consistency. Sputum culture conversion and time to conversion both received low-quality ratings, downgraded due to serious limitations and imprecision resulting from wide confidence intervals.

Mortality outcomes received low-quality evidence due to very serious imprecision reflecting low event rates and inadequate statistical power across studies. Safety outcomes achieved moderate quality evidence, with consistent findings across multiple large studies but downgraded for some imprecision in estimating rare events.

Subgroup analyses received very low-quality evidence ratings. VDR genotype effects, despite statistical significance, were downgraded due to very serious limitations (small sample size and post-hoc analysis) and very serious imprecision (wide confidence intervals). Similarly, multidrug-resistant tuberculosis effects received very low quality ratings due to serious limitations and very serious imprecision from small patient numbers.

Table 2. Evidence Quality and GRADE Assessment

Outcome	Studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Final Quality
Culture Conversion	6	Serious (-1)	Not serious	Not serious	Serious (-1)	No major concern*	⊕⊕⊖⊖ LOW
Smear Conversion	8	Serious (-1)	Not serious	Not serious	Not serious	No major concern*	⊕⊕⊕⊖ MODERATE
Time to Conversion	5	Not serious	Serious (-1)	Not serious	Serious (-1)	No major concern*	⊕⊕⊖⊖ LOW
Mortality	9	Not serious	Not serious	Not serious	Very serious (-2)	No major concern*	⊕⊕⊖⊖ LOW
Adverse Events	8	Not serious	Not serious	Not serious	Serious (-1)	No major concern*	⊕⊕⊕⊖ MODERATE
VDR tt Subgroup	2	Very serious (-2)	Not assessable	Not serious	Very serious (-2)	Not assessable	⊕⊖⊖⊖ VERY LOW
Multidrug-resistant TB	2	Serious (-1)	Not assessable	Not serious	Very serious (-2)	Not assessable	⊕⊖⊖⊖ VERY LOW

*Publication bias was not formally reassessed at the umbrella-review level. Judgments were based on assessments reported by the included systematic reviews and should not be interpreted as definitive absence of missing evidence.

GRADE Quality: ⊕⊕⊕⊕ HIGH; ⊕⊕⊕⊖ MODERATE; ⊕⊕⊖⊖ LOW; ⊕⊖⊖⊖ VERY LOW

Discussion

Main findings

The present umbrella review synthesized nine systematic reviews published between 2009 and 2022 that examined vitamin D supplementation in tuberculosis treatment. In unselected populations, the accumulated evidence did not support a consistent clinical benefit for bacteriological conversion, time to conversion, mortality, or adverse-event outcomes. The main positive findings were confined to selected analyses, including Wu Hong-Xia et al. for smear and culture conversion, the VDR TaqI tt

subgroup, and multidrug-resistant tuberculosis. These findings were interpreted as potential efficacy signals rather than proof of routine benefit, because they were modest or based on small subgroup datasets and were not consistently reproduced across later syntheses.

Overlap of primary evidence and added value of this umbrella review

The high degree of overlap among primary RCTs is central to the interpretation of this umbrella review. The overall CCA of 37.5% indicates that the review-level evidence base is highly redundant, particularly because recent reviews repeatedly synthesized the same core trials. Therefore, convergence across systematic reviews should not be interpreted as independent replication across distinct bodies of primary evidence. Rather, the added value of this umbrella review lies in explicitly mapping redundancy, comparing methodological quality and risk of bias across reviews, documenting the temporal evolution of conclusions, and distinguishing robust population-level null findings from hypothesis-generating subgroup signals. This interpretation directly addresses the risk that repeated systematic reviews may create an inflated impression of cumulative certainty when they rely on substantially overlapping primary data.

Interpretation of statistically significant and subgroup findings

The statistically significant findings reported by Wu Hong-Xia et al. may represent genuine pharmacological effects in selected populations, and they should not be dismissed simply because later syntheses were predominantly null. Nevertheless, the magnitude of these effects was modest, the findings were not consistently reproduced across broader reviews, and time-to-conversion analyses remained null. The most defensible interpretation is therefore that these results are potential efficacy signals requiring contextual explanation, not definitive evidence for routine adjunctive vitamin D in unselected tuberculosis populations.

The VDR TaqI tt finding should be interpreted as a biologically plausible but clinically immature signal. Its very low certainty rating reflects the small sample size, post-hoc nature of the analysis, wide confidence interval, and lack of independent prospective validation. Therefore, this subgroup should not influence routine clinical practice, although it may justify prespecified evaluation in individual-patient-data meta-analyses or future genotype-stratified trials.

In contrast, the multidrug-resistant tuberculosis signal may have greater clinical relevance because it concerns a high-need population and showed a potentially meaningful effect estimate. Nevertheless, the very low certainty rating remains appropriate because the estimate was derived from limited subgroup data with imprecision and insufficient independent replication. This finding should therefore be interpreted as a priority for targeted prospective research, not as evidence for routine implementation.

Dose heterogeneity and residual uncertainty

Dose heterogeneity should be interpreted primarily as a source of uncertainty rather than as definitive proof of inefficacy. The evaluated regimens covered a broad pharmacological range, from low daily dosing to high-dose intermittent or intramuscular strategies, which makes a large uniform benefit in unselected tuberculosis populations less likely. However, the absence of a formal dose-response analysis prevents exclusion of alternative explanations, including inadequate timing, insufficient target 25(OH)D attainment, population-specific pharmacokinetics, or an untested optimal regimen. Therefore, dosing heterogeneity supports the narrower conclusion that currently evaluated regimens have not shown consistent clinical benefit, but it does not definitively exclude benefit under optimized or subgroup-specific dosing strategies.

Clinical and research implications

From a clinical perspective, the current evidence does not support prescribing vitamin D solely to improve tuberculosis treatment outcomes in unselected patients. However, correction of vitamin D deficiency remains appropriate for established general health indications, independent of tuberculosis-specific efficacy. This distinction is important because a lack of tuberculosis-specific benefit should not be interpreted as a general contraindication to vitamin D supplementation when deficiency correction is clinically indicated.

Future research should be restricted to clearly justified populations or mechanisms, such as drug-resistant tuberculosis, severe vitamin D deficiency, pediatric tuberculosis with malnutrition, extrapulmonary disease, or genetically defined subgroups. Such studies should be adequately powered to test prespecified effect modification rather than repeating underpowered analyses in broad adult populations. Individual-patient-data meta-analyses of existing trials may also clarify treatment-effect heterogeneity without requiring immediate duplication of new randomized trials.

Limitations

Several limitations should be considered. First, this umbrella review depended on data and methodological judgments reported by included systematic reviews rather than de novo extraction from every primary trial for every outcome. Second, publication bias was not formally reassessed at the umbrella-review level because the outcome-specific evidence sets included few trials and several reviews shared overlapping primary studies. Third, we did not formally assess whether funding sources of the underlying randomized trials influenced trial design, dosing strategies, outcome selection, or direction of effects. Although review-level funding and conflict-of-interest declarations were extracted, these data are insufficient to support causal inferences about sponsor influence on null or positive findings.

The discordance between mechanistic plausibility and absence of consistent clinical benefit remains informative for translational research. In vitro studies demonstrating macrophage activation, cathelicidin LL-37 induction, and intracellular mycobacterial elimination provide a credible biological rationale [4,5]. However, translation to patient-important outcomes may be limited by tissue bioavailability, local concentrations in pulmonary lesions, interactions with systemic inflammation, background nutritional status, and host genetic variability. The present evidence therefore favors targeted mechanistic and subgroup-focused research over repetition of broad, unselected supplementation trials.

Conclusions and recommendations

Current evidence from nine systematic reviews does not support routine vitamin D supplementation as adjunctive therapy to improve tuberculosis treatment outcomes in unselected populations. This conclusion is strongest for bacteriological conversion and safety outcomes, and more limited for mortality, dose-response patterns, and subgroup effects because of imprecision, overlap among primary trials, and heterogeneous dosing strategies.

Signals observed in VDR TaqI tt genotype carriers and patients with multidrug-resistant tuberculosis remain hypothesis-generating and require prospective validation or individual-patient-data analyses before clinical translation. Correction of vitamin D deficiency remains appropriate for established general health indications, independent of tuberculosis-specific efficacy.

DECLARATIONS

Ethics approval and consent to participate

Since this manuscript is a secondary data-based study, it was not required.

- **Informed consent:** Since this is a secondary data analysis, informed consent was not required.
- **Clinical trial number:** not applicable.

Consent for publication

Not applicable

Data availability

All data extraction tables, quality assessment scores, and search strategies are available in the supplementary materials. Additional data are available from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

The authors declare that generative artificial intelligence (AI) and large language models (LLMs) were not used in the conception, data analysis, or initial drafting of this manuscript.

Conflict of interest

The authors declare no conflict of interest

Funding
This study was funded by the Vicerectorado de Investigación of the Universidad Nacional Toribio Rodríguez de Mendoza de Amazonas.

Acknowledgments
Special thanks to the members of Universidad Nacional Toribio Rodríguez de Mendoza de Amazonas (UNTRM), Amazonas, Peru, for their support and contributions throughout the completion of this research.

Authors' contribution
Víctor Juan Vera-Ponce: Conceptualization, Investigation, Formal analysis, Methodology, Funding acquisition, Resources, Writing - Original Draft, Writing - Review & Editing
Jhosmer Ballena-Caicedo: Conceptualization, Investigation, Methodology, Writing - Original Draft, Writing - Review & Editing
Lupita Ana Maria Valladolid-Sandoval: Methodology, Data Curation, Writing - Original Draft, Writing - Review & Editing
Fiorella E. Zuzunaga-Montoya: Software, Formal analysis, Investigation, Data Curation, Methodology, Writing - Original Draft, Writing - Review & Editing

Bibliographic references
[1] Global Tuberculosis Report 2024 n.d. https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2024 (accessed August 10, 2025).
[2] Dheda K, Gumbo T, Maartens G, Dooley KE, McNerney R, Murray M, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. Lancet Respir Med 2017:S2213-2600(17)30079-6. https://doi.org/10.1016/S2213-2600(17)30079-6.
[3] Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311:1770–3. https://doi.org/10.1126/science.1123933.
[4] Adams JS, Ren S, Liu PT, Chun RF, Lagishetty V, Gombart AF, et al. Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. J Immunol Baltim Md 1950 2009;182:4289–95. https://doi.org/10.4049/jimmunol.0803736.
[5] Gombart AF. The vitamin D–antimicrobial peptide pathway and its role in protection against infection. Future Microbiol 2009;4:1151. https://doi.org/10.2217/fmb.09.87.
[6] Yuk J-M, Shin D-M, Lee H-M, Yang C-S, Jin HS, Kim K-K, et al. Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. Cell Host Microbe 2009;6:231–43. https://doi.org/10.1016/j.chom.2009.08.004.
[7] Huang S-J, Wang X-H, Liu Z-D, Cao W-L, Han Y, Ma A-G, et al. Vitamin D deficiency and the risk of tuberculosis: a meta-analysis. Drug Des Devel Ther 2016;11:91–102. https://doi.org/10.2147/DDDT.S79870.
[8] Nursyam EW, Amin Z, Rumende CM. The effect of vitamin D as supplementary treatment in patients with moderately advanced pulmonary tuberculous lesion. Acta Medica Indones 2006;38:3–5.
[9] Martineau AR, Timms PM, Bothamley GH, Hanifa Y, Islam K, Claxton AP, et al. High-dose vitamin D(3) during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-blind randomised controlled trial. Lancet Lond Engl 2011;377:242–50. https://doi.org/10.1016/S0140-6736(10)61889-2.
[10] Ganmaa D, Munkhzul B, Fawzi W, Spiegelman D, Willett WC, Bayasgalan P, et al. High-Dose Vitamin D3 during Tuberculosis Treatment in Mongolia. A Randomized Controlled Trial. Am J Respir Crit Care Med 2017;196:628–37. https://doi.org/10.1164/rccm.201705-0936OC.
[11] Mily A, Rekha RS, Kamal SMM, Arifuzzaman ASM, Rahim Z, Khan L, et al. Significant Effects of Oral Phenylbutyrate and Vitamin D3 Adjunctive Therapy in Pulmonary Tuberculosis: A Randomized Controlled Trial. PloS One 2015;10:e0138340. https://doi.org/10.1371/journal.pone.0138340.
[12] WHO consolidated guidelines on tuberculosis: module 4: treatment and care n.d. https://www.who.int/publications/i/item/9789240107243 (accessed August 10, 2025).

[13] Tabsh N, Bilezikian JP. Vitamin D Status as a Risk Factor for Tuberculosis Infection. Adv Nutr Bethesda Md 2025;16:100394. https://doi.org/10.1016/j.advnut.2025.100394.
[14] Santos-Mena A, González-Muñiz OE, Jacobo-Delgado YM, Rivas-Santiago B. Shedding light on vitamin D in tuberculosis: A comprehensive review of clinical trials and discrepancies. Pulm Pharmacol Ther 2024;85:102300. https://doi.org/10.1016/j.pupt.2024.102300.
[15] Gates M, Gates A, Pieper D, Fernandes RM, Tricco AC, Moher D, et al. Reporting guideline for overviews of reviews of healthcare interventions: development of the PRIOR statement. The BMJ 2022;378:e070849. https://doi.org/10.1136/bmj-2022-070849.
[16] Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid Based Healthc 2015;13:132–40. https://doi.org/10.1097/XEB.0000000000000055.
[17] Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009;62:1013–20. https://doi.org/10.1016/j.jclinepi.2008.10.009.
[18] Whiting P, Savović J, Higgins JPT, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol 2016;69:225–34. https://doi.org/10.1016/j.jclinepi.2015.06.005.
[19] Prasad M. Introduction to the GRADE tool for rating certainty in evidence and recommendations. Clin Epidemiol Glob Health 2024;25:101484. https://doi.org/10.1016/j.cegh.2023.101484.
[20] Yamshchikov AV, Desai NS, Blumberg HM, Ziegler TR, Tangpricha V. Vitamin D for treatment and prevention of infectious diseases: a systematic review of randomized controlled trials. Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol 2009;15:438–49. https://doi.org/10.4158/EP09101.ORR.
[21] Xia J, Shi L, Zhao L, Xu F. Impact of vitamin D supplementation on the outcome of tuberculosis treatment: a systematic review and meta-analysis of randomized controlled trials. Chin Med J (Engl) 2014;127:3127–34.
[22] Grobler L, Nagpal S, Sudarsanam TD, Sinclair D. Nutritional supplements for people being treated for active tuberculosis. Cochrane Database Syst Rev 2016;2016:CD006086. https://doi.org/10.1002/14651858.CD006086.pub4.
[23] Wallis RS, Zumla A. Vitamin D as Adjunctive Host-Directed Therapy in Tuberculosis: A Systematic Review. Open Forum Infect Dis 2016;3:ofw151. https://doi.org/10.1093/ofid/ofw151.
[24] WANG J, FENG M, YING S, ZHOU J, LI X. Efficacy and Safety of Vitamin D Supplementation for Pulmonary Tuberculosis: A Systematic Review and Meta-analysis. Iran J Public Health 2018;47:466–72.
[25] Wu H-X, Xiong X-F, Zhu M, Wei J, Zhuo K-Q, Cheng D-Y. Effects of vitamin D supplementation on the outcomes of patients with pulmonary tuberculosis: a systematic review and meta-analysis. BMC Pulm Med 2018;18:108. https://doi.org/10.1186/s12890-018-0677-6.
[26] Zhang J, Chen C, Yang J. Effectiveness of vitamin D supplementation on the outcome of pulmonary tuberculosis treatment in adults: a meta-analysis of randomized controlled trials. Chin Med J (Engl) 2019;132:2950–9. https://doi.org/10.1097/CM9.0000000000000554.
[27] Cabrera Andrade BK, Garcia-Perdomo HA. Effectiveness of micronutrients supplement in patients with active tuberculosis on treatment: Systematic review/Meta-analysis. Complement Ther Med 2020;48:102268. https://doi.org/10.1016/j.ctim.2019.102268.
[28] Goyal JP, Singh S, Bishnoi R, Bhardwaj P, Kaur RJ, Dhingra S, et al. Efficacy and safety of vitamin D in tuberculosis patients: a systematic review and meta-analysis. Expert Rev Anti Infect Ther 2022;20:1049–59. https://doi.org/10.1080/14787210.2022.2071702.
[29] Morcos MM, Gabr AA, Samuel S, Kamel M, el Baz M, el Beshry M, et al. Vitamin D administration to tuberculous children and its value. Boll Chim Farm 1998;137:157–64.
[30] Ralph AP, Waramori G, Pontororing GJ, Kenangalem E, Wiguna A, Tjitra E, et al. L-arginine and vitamin D adjunctive therapies in pulmonary tuberculosis: a randomised, double-blind, placebo-controlled trial. PloS One 2013;8:e70032. https://doi.org/10.1371/journal.pone.0070032.
[31] Salahuddin N, Ali F, Hasan Z, Rao N, Aqeel M, Mahmood F. Vitamin D accelerates clinical recovery from tuberculosis: results of the SUCCINCT Study [Supplementary Cholecalciferol in recovery from tuberculosis]. A randomized, placebo-controlled, clinical trial of vitamin D supplementation in patients with pulmonary tuberculosis'. BMC Infect Dis 2013;13:22. https://doi.org/10.1186/1471-2334-13-22.
[32] Martineau AR, Timms PM, Bothamley GH, Hanifa Y, Islam K, Claxton AP, et al. High-dose vitamin D3 during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-

blind randomised controlled trial. The Lancet 2011;377:242–50. https://doi.org/10.1016/S0140-6736(10)61889-2.
[33] Daley P, Jagannathan V, John KR, Sarojini J, Latha A, Vieth R, et al. Adjunctive vitamin D for treatment of active tuberculosis in India: a randomised, double-blind, placebo-controlled trial. Lancet Infect Dis 2015;15:528–34. https://doi.org/10.1016/S1473-3099(15)70053-8.
[34] Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr Rev 2019;40:1109–51. https://doi.org/10.1210/er.2018-00126.
[35] Mangaonkar AA, Ferrer A, e Vairo FP, Cousin MA, Kuisle RJ, Gangat N, et al. Clinical applications and utility of a precision medicine approach for patients with unexplained cytopenias. Mayo Clin Proc 2019;94:1753–68. https://doi.org/10.1016/j.mayocp.2019.04.007.
[36] Pieper D, Antoine S-L, Mathes T, Neugebauer EAM, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol 2014;67:368-75. https://doi.org/10.1016/j.jclinepi.2013.11.007.

Supplementary material 1. Search strategy

Search strategy in PUBMED	
#1	"Vitamin D"[Mesh] OR "vitamin D"[tiab] OR "25-hydroxyvitamin D"[tiab] OR "25(OH)D"[tiab] OR "cholecalciferol"[tiab] OR "ergocalciferol"[tiab] OR "calcitriol"[tiab] OR "calcidiol"[tiab] OR "vitamin D2"[tiab] OR "vitamin D3"[tiab] OR "1,25-dihydroxyvitamin D"[tiab] OR "1α,25-dihydroxyvitamin D3"[tiab] OR "hydroxyvitamin D"[tiab] OR "25-hydroxyvitamin D3"[tiab] OR "1,25(OH)2D3"[tiab] OR "25(OH)D3"[tiab] OR "colecalciferol"[tiab] OR "vitamina D"[tiab]
#2	"Tuberculosis"[Mesh] OR "tuberculosis"[tiab] OR "TB"[tiab] OR "mycobacterium tuberculosis"[tiab] OR "pulmonary tuberculosis"[tiab] OR "extrapulmonary tuberculosis"[tiab] OR "MDR-TB"[tiab] OR "XDR-TB"[tiab] OR "multidrug-resistant tuberculosis"[tiab] OR "drug-resistant tuberculosis"[tiab] OR "mycobacterial infection"[tiab] OR "tubercular"[tiab] OR "anti-tuberculosis"[tiab] OR "antituberculosis"[tiab] OR "tuberculosis treatment"[tiab]
#3	"systematic review"[tiab] OR "systematic reviews"[tiab] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta analysis"[tiab] OR "metaanalysis"[tiab] OR "revisión sistemática"[tiab] OR "revisiones sistemáticas"[tiab] OR "metaanálisis"[tiab] OR "meta análisis"[tiab] OR "overview of reviews"[tiab] OR "umbrella review"[tiab] OR "umbrella reviews"[tiab] OR "review of reviews"[tiab] OR "scoping review"[tiab] OR "narrative review"[tiab] OR "pooled analysis"[tiab]
#4	#1 AND #2 AND #3
Search strategy in SCOPUS	
#1	TITLE-ABS-KEY ("vitamin D" OR "25-hydroxyvitamin D" OR "25(OH)D" OR cholecalciferol OR ergocalciferol OR calcitriol OR calcidiol OR "vitamin D2" OR "vitamin D3" OR "1,25-dihydroxyvitamin D" OR "1α,25-dihydroxyvitamin D3" OR "hydroxyvitamin D" OR "25-hydroxyvitamin D3" OR "1,25(OH)2D3" OR "25(OH)D3" OR colecalciferol OR "vitamina D")
#2	TITLE-ABS-KEY (tuberculosis OR "TB" OR "mycobacterium tuberculosis" OR "pulmonary tuberculosis" OR "extrapulmonary tuberculosis" OR "MDR-TB" OR "XDR-TB" OR "multidrug-resistant tuberculosis" OR "drug-resistant tuberculosis" OR "mycobacterial infection" OR tubercular OR "anti-tuberculosis" OR antituberculosis OR "tuberculosis treatment")
#3	TITLE-ABS-KEY ("systematic review" OR "systematic reviews" OR "meta-analysis" OR "meta analysis" OR "metaanalysis" OR "umbrella review" OR "overview of reviews" OR "review of reviews" OR "scoping review" OR "narrative review" OR "pooled analysis")
#4	#1 AND #2 AND #3
Search strategy in Web of Science	
#1	TS=("vitamin D" OR "25-hydroxyvitamin D" OR "25(OH)D" OR cholecalciferol OR ergocalciferol OR calcitriol OR calcidiol OR "vitamin D2" OR "vitamin D3" OR "1,25-dihydroxyvitamin D" OR "hydroxyvitamin D" OR "25-hydroxyvitamin D3" OR "1,25(OH)2D3" OR "25(OH)D3" OR colecalciferol OR "vitamina D")
#2	TS=(tuberculosis OR "TB" OR "mycobacterium tuberculosis" OR "pulmonary tuberculosis" OR "extrapulmonary tuberculosis" OR "MDR-TB" OR "XDR-TB" OR "multidrug-resistant tuberculosis" OR "drug-resistant tuberculosis" OR "mycobacterial infection" OR tubercular OR "anti-tuberculosis" OR antituberculosis)
#3	TS=("systematic review" OR "systematic reviews" OR "meta-analysis" OR "meta analysis" OR "umbrella review" OR "overview of reviews" OR "review of reviews" OR "scoping review" OR "narrative review")
#4	#1 AND #2 AND #3
Search strategy in EMBASE	
#1	'cholecalciferol'/exp OR 'ergocalciferol'/exp OR 'calcitriol'/exp OR 'calcidiol'/exp OR 'vitamin d'/exp OR 'vitamin d':ti,ab,kw OR '25-hydroxyvitamin d':ti,ab,kw OR '25(oh)d':ti,ab,kw OR 'cholecalciferol':ti,ab,kw OR 'ergocalciferol':ti,ab,kw OR 'calcitriol':ti,ab,kw OR 'calcidiol':ti,ab,kw OR 'vitamin d2':ti,ab,kw OR 'vitamin d3':ti,ab,kw OR '1,25-dihydroxyvitamin d':ti,ab,kw OR '1α,25-dihydroxyvitamin d3':ti,ab,kw OR 'hydroxyvitamin d':ti,ab,kw OR '25-hydroxyvitamin d3':ti,ab,kw OR '1,25(oh)2d3':ti,ab,kw OR '25(oh)d3':ti,ab,kw OR 'colecalciferol':ti,ab,kw OR 'vitamina d':ti,ab,kw
#2	'tuberculosis'/exp OR 'lung tuberculosis'/exp OR 'extrapulmonary tuberculosis'/exp OR 'mycobacterium tuberculosis'/exp OR 'multidrug resistant tuberculosis'/exp OR 'tuberculosis':ti,ab,kw OR 'tb':ti,ab,kw OR 'mycobacterium tuberculosis':ti,ab,kw OR 'pulmonary tuberculosis':ti,ab,kw OR 'extrapulmonary tuberculosis':ti,ab,kw OR 'mdr-

	tb':ti,ab,kw OR 'xdr-tb':ti,ab,kw OR 'multidrug-resistant tuberculosis':ti,ab,kw OR 'drug-resistant tuberculosis':ti,ab,kw OR 'mycobacterial infection':ti,ab,kw OR 'tubercular':ti,ab,kw OR 'anti-tuberculosis':ti,ab,kw OR 'antituberculosis':ti,ab,kw OR 'tuberculosis treatment':ti,ab,kw
#3	'systematic review'/exp OR 'meta analysis'/exp OR 'review'/exp OR 'systematic review':ti,ab,kw OR 'systematic reviews':ti,ab,kw OR 'meta-analysis':ti,ab,kw OR 'meta analysis':ti,ab,kw OR 'metaanalysis':ti,ab,kw OR 'umbrella review':ti,ab,kw OR 'overview of reviews':ti,ab,kw OR 'review of reviews':ti,ab,kw OR 'scoping review':ti,ab,kw OR 'narrative review':ti,ab,kw OR 'pooled analysis':ti,ab,kw
#4	#1 AND #2 AND #3

Supplementary Material 2: Methodological Quality Assessment (AMSTAR-2)

Study	Item 1: PICO	Item 2: Protocol	Item 3: Adequate Search	Item 4: Selection Criteria	Item 5: Duplicate Selection	Item 6: Duplicate Extraction	Item 7: Exclusions Listed	Item 8: Detailed Description	Item 9: Individual RoB	Item 10: Funding	Item 11: MA Methods	Item 12: RoB in MA	Item 13: RoB in Interpretation	Item 14: Heterogeneity	Item 15: Publication Bias	Item 16: CoI	Overall Rating
	Yes	No	Partial	Partial	No	No	No	Yes	No	No	N/A	N/A	No	No	No	Yes	**Critically Low**
	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Not reported	Yes	Not reported	Partial	Yes	Yes	Yes	**Moderate**
	Yes	No	Partial	Yes	Not reported	Not reported	Not reported	Yes	Not reported	Not reported	N/A	N/A	Yes	Yes	Not reported	Yes	**Critically Low**
	Yes	Not reported	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Not reported	Yes	Not reported	Not reported	Yes	No	Not reported	**Critically Low**
	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not reported	Yes	Not reported	Yes	Yes	No	Not reported	**Moderate**
	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Not reported	Yes	Yes	Yes	Not reported	**Moderate**
	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Not reported	Yes	**Moderate**
	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**High**
	Yes	Yes	Yes	Yes	Yes	Yes	Not reported	Yes	Yes	Not reported	Yes	Not reported	Yes	Yes	Not reported	Yes	**Moderate**

Critical Items:

- **Item 2**: Protocol registration before review initiation
- **Item 7**: Comprehensive list of excluded studies with justifications

- **Item 9**: Adequate assessment of risk of bias in individual studies
- **Item 11**: Use of appropriate methods for statistical combination of results
- **Item 13**: Consideration of risk of bias in interpretation/discussion of results
- **Item 15**: Adequate assessment of publication bias

Non-Critical Items:

- **Item 1**: Research question includes adequate PICO elements
- **Item 3**: Explanation of study design selection for inclusion
- **Item 4**: Use of comprehensive literature search strategy
- **Item 5**: Study selection performed in duplicate
- **Item 6**: Data extraction performed in duplicate
- **Item 8**: Adequate description of included studies with sufficient detail
- **Item 10**: Reporting of funding sources for included studies
- **Item 12**: Assessment of potential impact of risk of bias on meta-analysis results
- **Item 14**: Adequate explanation of observed heterogeneity in results
- **Item 16**: Reporting of potential conflicts of interest

Overall Rating Criteria:

- **High**: No critical weaknesses or up to one non-critical weakness
- **Moderate**: More than one non-critical weakness; the review provides an accurate and comprehensive summary of available study results
- **Low**: One critical weakness with or without non-critical weaknesses
- **Critically Low**: More than one critical weakness with or without other weaknesses

Scoring: Yes = Fully complies; Partial = Partially complies; No = Does not comply; N/A = Not applicable (for narrative reviews without meta-analysis); Not reported = Information not available

Supplementary Material 3: ROBIS Assessment (Risk of Bias in Systematic Reviews)

Study	Domain 1: Eligibility	Domain 2: Identification	Domain 3: Selection	Domain 4: Synthesis	Overall Risk
Yamshchikov 2009	High	High	Low	High	High
Xia 2014	Low	Low	Low	Low	Low
Wallis 2016	Low	Unclear	Low	N/A	Low
Wang 2018	Unclear	Low	Low	Low	Low
Wu Hong-Xia 2018	Low	Low	Low	Low	Low
Zhang 2019	Low	Low	Low	Low	Low
Cabrera 2020	Unclear	Low	Unclear	Low	Unclear
Grobler 2016	Low	Low	Low	Low	Low
Goyal 2022	Low	Low	Low	Low	Low

Supplementary Material 4: Main Effects on Primary Outcomes

Study	Culture Conversion	Smear Conversion	Time to Conversion	Mortality	Heterogeneity (I^2)
Yamshchikov 2009	Not quantified	Not quantified	Not quantified	Not quantified	N/A
Xia 2014	NR	RR 0.61 (0.24-1.56), p=0.30	NR	RD -0.01 (-0.04 to 0.03)	61%
Wallis 2016	Qualitative analysis	Qualitative analysis	Qualitative analysis	Qualitative analysis	N/A
Wang 2018	NR	RR 0.99 (0.91-1.07), p=0.77	NR	RD -0.01 (-0.04 to 0.03)	0%
Wu Hong-Xia 2018	OR 1.22 (1.04-1.43), p=0.02	OR 1.21 (1.05-1.39), p=0.007	HR 0.97 (0.76-1.23), p=0.77	OR 1.22 (0.74-2.04), p=0.43	Variable by outcome
Zhang 2019	RR 1.05 (0.99-1.10), p=0.08	HR 1.15 (0.93-1.41), p=0.20	HR 1.04 (0.89-1.23), p=0.60	RR 0.86 (0.20-3.74), p=0.83	0-42%
Cabrera 2020	NR	RR 0.99 (0.91-1.07), p=0.77	NR	RD -0.01 (-0.04 to 0.03)	0%
Grobler 2016	RR 0.94 (0.84-1.06), 2 months	NR	NR	RR 0.86 (0.46-1.60), HIV-	Variable
Goyal 2022	RR 1.04 (0.98-1.11), p=0.21	RR 1.07 (0.94-1.21), p=0.31	HR 1.06 (0.92-1.23), p=0.43	RR 1.16 (0.41-3.27), p=0.78	27-50%

Abbreviations: NR = Not Reported; RR = Relative Risk; OR = Odds Ratio; HR = Hazard Ratio; RD = Risk Difference

Supplementary Material 5: Citation Matrix and Corrected Covered Area Assessment

Table S5.1. Coding rules used to construct the citation matrix

Item	Specification
Unit of analysis	Unique primary RCT.
Reviews included	Yamshchikov 2009; Xia 2014; Wallis 2016; Wang 2018; Wu Hong-Xia 2018; Zhang 2019; Cabrera Andrade 2020; Grobler 2016; Goyal 2022.
Trials counted	Primary randomized trials in active tuberculosis in which vitamin D was an explicit active intervention, either alone or as part of a factorial/co-intervention arm.
Trials not counted	Broader micronutrient trials without an explicit vitamin D arm or an extractable vitamin D-specific contribution.
Cell coding	1 = the primary RCT was included in the systematic review; blank = not included or not coded for that review.
Purpose	To quantify review-level overlap; no treatment effects were re-estimated.

Table S5.2. Corrected covered area calculation

Parameter	Value	Definition or calculation
N	64	Total number of primary RCT occurrences across the nine systematic reviews.
r	16	Number of unique primary RCTs in the citation matrix.
c	9	Number of included systematic reviews.
Formula	CCA = (N - r) / (r x c - r)	Corrected covered area formula.
CCA	0.375	(64 - 16) / (16 x 9 - 16).
CCA (%)	37.5%	Very high overlap according to conventional CCA thresholds: slight 0-5%, moderate 6-10%, high 11-15%, and very high >15% [S1].

Table S5.3. Review-level primary RCT counts used in the CCA calculation

Systematic review	Primary RCTs counted	Share of total occurrences
Yamshchikov 2009	4	6.2%
Xia 2014	5	7.8%
Wallis 2016	8	12.5%
Wang 2018	5	7.8%
Wu Hong-Xia 2018	8	12.5%
Zhang 2019	5	7.8%
Cabrera Andrade 2020	7	10.9%
Grobler 2016	10	15.6%
Goyal 2022	12	18.8%

Table S5.4. Citation matrix of primary RCTs across systematic reviews

Primary RCT	Country/setting	Yamshchikov 2009	Xia 2014	Wallis 2016	Wang 2018	Wu Hong-Xia 2018	Zhang 2019	Cabrera Andrade 2020	Grobler 2016	Goyal 2022	Total
Morcos 1998	Egypt; children	1	1						1		3
Martineau 2007	UK; immunologic study	1									1
Nursyam 2006	Indonesia	1	1	1		1		1	1	1	7
Wejse 2009	Guinea-Bissau	1	1	1		1		1	1	1	7
Salahuddin 2013	Pakistan		1	1	1	1				1	5
Martineau 2011	United Kingdom		1	1	1	1	1	1	1	1	8
Kota 2011/2012	India; TB plus diabetes				1			1	1		3
Singh 2013	India							1	1		2
Ralph 2013	Indonesia			1	1				1	1	4
Daley 2015	India			1		1	1	1	1	1	6
Tukvadze 2015	Georgia			1	1	1	1	1	1	1	7
Mily 2015	Bangladesh			1		1	1		1	1	5
Ganmaa 2017	Mongolia					1	1			1	3
Farazi 2017	Iran									1	1
Afzal 2018	Pakistan									1	1
Hasanain 2019	Egypt									1	1
Column total		4	5	8	5	8	5	7	10	12	64

Note: RCT = randomized controlled trial.

Table S5.5. Pairwise overlap between systematic reviews

Review A	Review B	A trials	B trials	Shared	Jaccard (%)	Overlap coefficient (%)	A covered by B (%)
Wallis 2016	Goyal 2022	8	12	8	66.7%	100.0%	100.0%
Wu Hong-Xia 2018	Goyal 2022	8	12	8	66.7%	100.0%	100.0%
Cabrera Andrade 2020	Grobler 2016	7	10	7	70.0%	100.0%	100.0%
Wu Hong-Xia 2018	Zhang 2019	8	5	5	62.5%	100.0%	62.5%
Zhang 2019	Goyal 2022	5	12	5	41.7%	100.0%	100.0%
Wallis 2016	Grobler 2016	8	10	7	63.6%	87.5%	87.5%
Wallis 2016	Wu Hong-Xia 2018	8	8	7	77.8%	87.5%	87.5%
Wallis 2016	Wang 2018	8	5	4	44.4%	80.0%	50.0%
Wallis 2016	Zhang 2019	8	5	4	44.4%	80.0%	50.0%
Wang 2018	Goyal 2022	5	12	4	30.8%	80.0%	80.0%
Wang 2018	Grobler 2016	5	10	4	36.4%	80.0%	80.0%
Xia 2014	Goyal 2022	5	12	4	30.8%	80.0%	80.0%
Xia 2014	Grobler 2016	5	10	4	36.4%	80.0%	80.0%
Xia 2014	Wallis 2016	5	8	4	44.4%	80.0%	80.0%
Xia 2014	Wu Hong-Xia 2018	5	8	4	44.4%	80.0%	80.0%
Zhang 2019	Grobler 2016	5	10	4	36.4%	80.0%	80.0%
Wu Hong-Xia 2018	Grobler 2016	8	10	6	50.0%	75.0%	75.0%
Yamshchikov 2009	Grobler 2016	4	10	3	27.3%	75.0%	75.0%
Yamshchikov 2009	Xia 2014	4	5	3	50.0%	75.0%	75.0%
Cabrera Andrade 2020	Goyal 2022	7	12	5	35.7%	71.4%	71.4%
Wallis 2016	Cabrera Andrade 2020	8	7	5	50.0%	71.4%	62.5%
Wu Hong-Xia 2018	Cabrera Andrade 2020	8	7	5	50.0%	71.4%	62.5%

Grobler 2016	Goyal 2022	10	12	7	46.7%	70.0%	70.0%
Wang 2018	Cabrera Andrade 2020	5	7	3	33.3%	60.0%	60.0%
Wang 2018	Wu Hong-Xia 2018	5	8	3	30.0%	60.0%	60.0%
Xia 2014	Cabrera Andrade 2020	5	7	3	33.3%	60.0%	60.0%
Zhang 2019	Cabrera Andrade 2020	5	7	3	33.3%	60.0%	60.0%
Yamshchikov 2009	Cabrera Andrade 2020	4	7	2	22.2%	50.0%	50.0%
Yamshchikov 2009	Goyal 2022	4	12	2	14.3%	50.0%	50.0%
Yamshchikov 2009	Wallis 2016	4	8	2	20.0%	50.0%	50.0%
Yamshchikov 2009	Wu Hong-Xia 2018	4	8	2	20.0%	50.0%	50.0%
Wang 2018	Zhang 2019	5	5	2	25.0%	40.0%	40.0%
Xia 2014	Wang 2018	5	5	2	25.0%	40.0%	40.0%
Xia 2014	Zhang 2019	5	5	1	11.1%	20.0%	20.0%
Yamshchikov 2009	Wang 2018	4	5	0	0.0%	0.0%	0.0%
Yamshchikov 2009	Zhang 2019	4	5	0	0.0%	0.0%	0.0%

Table S5.6. Coding notes for primary RCT classification

Primary RCT	Country/setting	Coding note	Systematic reviews including the trial
Morcos 1998	Egypt; children	Targeted vitamin D intervention; older pediatric RCT.	Yamshchikov 2009; Xia 2014; Grobler 2016
Martineau 2007	UK; immunologic study	Coded because Yamshchikov included it; not a clinical adjunctive-treatment outcome trial.	Yamshchikov 2009
Nursyam 2006	Indonesia	Targeted vitamin D adjunctive-treatment RCT.	Yamshchikov 2009; Xia 2014; Wallis 2016; Wu Hong-Xia 2018; Cabrera Andrade 2020; Grobler 2016; Goyal 2022
Wejse 2009	Guinea-Bissau	Targeted vitamin D adjunctive-treatment RCT; Grobler labels it Wejse 2008 GNB.	Yamshchikov 2009; Xia 2014; Wallis 2016; Wu Hong-Xia 2018; Cabrera Andrade 2020; Grobler 2016; Goyal 2022
Salahuddin 2013	Pakistan	Targeted vitamin D adjunctive-treatment RCT.	Xia 2014; Wallis 2016; Wang 2018; Wu Hong-Xia 2018; Goyal 2022
Martineau 2011	United Kingdom	Targeted high-dose vitamin D3 adjunctive-treatment RCT.	Xia 2014; Wallis 2016; Wang 2018; Wu Hong-Xia 2018; Zhang 2019; Cabrera Andrade 2020; Grobler 2016; Goyal 2022
Kota 2011/2012	India; TB plus diabetes	Vitamin D plus calcium/no-placebo design; coded where included by the SR.	Wang 2018; Cabrera Andrade 2020; Grobler 2016
Singh 2013	India	Vitamin D plus calcium arm; coded only in broader nutrition/micronutrient reviews.	Cabrera Andrade 2020; Grobler 2016
Ralph 2013	Indonesia	Factorial/co-intervention RCT with vitamin D arms.	Wallis 2016; Wang 2018; Grobler 2016; Goyal 2022
Daley 2015	India	Targeted vitamin D adjunctive-treatment RCT.	Wallis 2016; Wu Hong-Xia 2018; Zhang 2019; Cabrera Andrade 2020; Grobler 2016; Goyal 2022
Tukvadze 2015	Georgia	Targeted high-dose vitamin D3 adjunctive-treatment RCT.	Wallis 2016; Wang 2018; Wu Hong-Xia 2018; Zhang 2019; Cabrera Andrade 2020; Grobler 2016; Goyal 2022
Mily 2015	Bangladesh	Factorial/co-intervention RCT with vitamin D arms.	Wallis 2016; Wu Hong-Xia 2018; Zhang 2019; Grobler 2016; Goyal 2022

Primary RCT	Country/setting	Coding note	Systematic reviews including the trial
Ganmaa 2017	Mongolia	Targeted vitamin D adjunctive-treatment RCT; appeared after Grobler 2016.	Wu Hong-Xia 2018; Zhang 2019; Goyal 2022
Farazi 2017	Iran	Targeted vitamin D RCT included in Goyal 2022 only among these SRs.	Goyal 2022
Afzal 2018	Pakistan	Targeted vitamin D RCT included in Goyal 2022 only among these SRs.	Goyal 2022
Hasanain 2019	Egypt	Targeted vitamin D RCT included in Goyal 2022 only among these SRs.	Goyal 2022

Supplementary reference

[S1] Pieper D, Antoine SL, Mathes T, Neugebauer EAM, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. Journal of Clinical Epidemiology. 2014;67(4):368-375. doi:10.1016/j.jclinepi.2013.11.007.