INPLASY

The impact and safety of vitamin D supplementation in enhancing tuberculosis treatment in the Middle East: a protocol for a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 April 2026 and was last updated on 21 April 2026.

INTRODUCTION

Review question / Objective The aim of this systematic review and meta-analysis is to examine the impact and safety of vitamin D supplementation, administered as an adjunct to standard anti-tuberculosis therapy (ATT), on treatment outcomes in patients with active pulmonary tuberculosis in the Middle East region.
The review addresses the following PICO-structured question:
• Population (P): Patients diagnosed with active pulmonary tuberculosis residing in Middle Eastern countries (including Egypt).
• Intervention (I): Vitamin D supplementation (any form — cholecalciferol, calcitriol, ergocalciferol, 25-hydroxyvitamin D — any dose, any route, any duration) administered in addition to standard anti-tuberculosis therapy.
• Comparison (C): Standard anti-tuberculosis therapy alone, or standard anti-tuberculosis therapy combined with placebo.
• Outcome (O): Sputum smear/culture conversion rate; time to sputum smear/culture conversion; TB symptom score; adverse events including mortality; serum vitamin D level; and additional biological and patient-centred outcomes.
Primary question: Does adjunctive vitamin D supplementation, compared with standard anti-tuberculosis therapy alone or with placebo, improve microbiological and clinical treatment outcomes in adults with active pulmonary tuberculosis in the Middle East?

Rationale Tuberculosis (TB) remains a major public-health burden worldwide, with 10.8 million incident cases reported globally in 2023 and approximately 8.6% of these occurring in the World Health Organization Eastern Mediterranean Region. Country-level TB incidence in the Middle East ranges from 1 per 100,000 per year in some jurisdictions to over 250 per 100,000 in others, and approximately 86,000 TB deaths were reported in the region in 2023.
The active metabolite of vitamin D, 1,25-dihydroxyvitamin D, modulates innate immunity — including induction of antimicrobial peptides such as cathelicidin — and cellular defence mechanisms

relevant to the containment of Mycobacterium tuberculosis, providing biological plausibility for adjunctive vitamin D during TB therapy. Randomised controlled trials (RCTs) and individual-participant-data meta-analyses at the global level have produced heterogeneous results, with an overall non-significant effect on broad clinical endpoints but possible benefits in selected subgroups (e.g., by vitamin D receptor genotype or by baseline deficiency status) and on some microbiological endpoints (e.g., time to sputum culture conversion).

Existing global systematic reviews pool heterogeneous populations with wide variability in baseline vitamin D status, genetics, nutritional environment, and clinical context. The Middle East is documented to have paradoxically high rates of vitamin D deficiency despite abundant sunlight, together with distinctive TB epidemiology. A region-specific synthesis is therefore warranted to generate evidence applicable to Middle Eastern health systems and to estimate the effect of vitamin D supplementation in a population most likely to benefit from deficiency correction. A preliminary search of PROSPERO, INPLASY, MEDLINE, and the Cochrane Database of Systematic Reviews did not identify a completed or ongoing systematic review focused specifically on vitamin D supplementation during TB treatment restricted to the Middle East region.

Condition being studied Active pulmonary tuberculosis — an infectious disease caused by Mycobacterium tuberculosis and transmitted by inhalation of airborne droplet nuclei produced by individuals with active pulmonary TB. Standard treatment for drug-sensitive TB comprises an initial intensive phase with four first-line agents (isoniazid, rifampicin, pyrazinamide, and ethambutol) followed by a continuation phase with isoniazid and rifampicin, with a typical total duration of six months. Outcomes are influenced by nutritional status, drug susceptibility, HIV co-infection, and comorbidities such as diabetes mellitus. The factor of interest in this review is adjunctive vitamin D supplementation as a modifier of microbiological, clinical, and biological treatment outcomes.

METHODS

Search strategy The search will combine free-text terms and controlled vocabulary (MeSH in PubMed/MEDLINE; Emtree-equivalent and database-native indexing for Scopus and Cochrane CENTRAL). Keywords include: tuberculosis, TB, "Mycobacterium tuberculosis", "Vitamin D", cholecalciferol, calcitriol, ergocalciferol, "25-hydroxyvitamin D", "Vitamin D supplementation", "sputum smear", "sputum culture", "sputum conversion", "culture conversion", "treatment success", "immune response", "adverse events", mortality, and relapse, combined using the Boolean operators AND and OR.

No date restrictions will be applied at the search stage. Search filters used (where applied) and the exact number of records retrieved from each database will be reported in the final PRISMA 2020 flow diagram.

Participant or population Patients of any age and either sex with a confirmed diagnosis of active pulmonary tuberculosis, recruited and treated in a Middle Eastern country. The Middle East will be operationalised according to World Health Organization Eastern Mediterranean Region definitions and standard geopolitical usage, and includes (but is not limited to) Egypt, Iran, Saudi Arabia, Iraq, Jordan, Lebanon, Syria, Palestine, Israel, the Gulf Cooperation Council states, Yemen, Sudan, Afghanistan, and Pakistan.

Studies containing mixed populations (e.g., a mix of pulmonary and extrapulmonary TB, or a mix of Middle-Eastern and non-Middle-Eastern participants) will be included only if outcome data for eligible participants are reported separately; otherwise such studies will be excluded. Patients with multi-drug-resistant or extensively drug-resistant TB will not be excluded a priori, but will be flagged during data extraction to allow subgroup consideration.

Intervention Vitamin D supplementation of any form (cholecalciferol [D3], ergocalciferol [D2], calcitriol, or 25-hydroxyvitamin D), any dose (e.g., 600 IU/day, 800 IU/day, 50,000 IU/week, single high-dose bolus up to 450,000 IU), any route (oral or intramuscular), and any duration, administered in addition to a standard anti-tuberculosis therapy regimen. Co-interventions (e.g., nutritional support, DOTS programme enrolment) are permitted provided that they are applied equally to intervention and comparison groups within each included study.

Comparator Standard anti-tuberculosis therapy alone, or standard anti-tuberculosis therapy plus matched placebo (oral placebo, or intramuscular normal saline injection). Studies in which the comparator group also received vitamin D (at a different dose or schedule) will be excluded unless a truly unsupplemented or placebo-only arm is available.

Study designs to be included Randomised controlled trials (RCTs) are the primary study design of interest. Comparative non-randomised interventional studies and case-control studies with a clearly defined intervention and comparator group will also be eligible, in order to broaden the evidence base given the small number of trials expected in the region.Excluded designs: single-arm studies; non-comparative observational studies; case reports and case series; conference abstracts without full-text availability; narrative reviews; systematic reviews and meta-analyses; and other secondary research.

Eligibility criteria Inclusion criteria:
• Patients diagnosed with active pulmonary tuberculosis.
• Study conducted in a Middle Eastern country (as defined in Item 12).
• Intervention group received vitamin D supplementation in addition to standard anti-tuberculosis therapy.
• Comparison group received standard anti-tuberculosis therapy alone or standard anti-tuberculosis therapy plus placebo.
• At least one of the pre-specified primary or secondary outcomes reported.
• Comparative study design (intervention and comparison groups reported separately).
• Full-text article available.
Exclusion criteria:
• Non-journal articles, case reports, conference abstracts, and other non-full-text publications.
• Non-comparative studies (single-arm studies).
• Systematic reviews, meta-analyses, narrative reviews, and other secondary research.
• Studies conducted wholly outside the Middle East region.
• Studies in which the intervention was not vitamin D supplementation, or in which the comparator also received vitamin D without a placebo or no-supplement arm.
Additional restrictions (with justification):
• Publication status: full-text peer-reviewed journal articles only, to ensure adequate methodological information is available for quality appraisal and data extraction.
• Language: see Item 25.
No additional arbitrary restrictions (e.g., publication year, sample size) will be applied.

Information sources Bibliographic databases:
• PubMed / MEDLINE
• Scopus
• Cochrane Library (Cochrane Central Register of Controlled Trials, CENTRAL)
Additional source-tracing: reference lists of all included studies and of topic-relevant systematic reviews will be screened manually for further eligible studies (snowball search). Grey literature, dissertations/theses, conference proceedings, and hand searches of specific journals are not planned, reflecting the decision to limit eligibility to full-text peer-reviewed journal publications.

Main outcome(s) • Sputum smear or sputum culture negative conversion rate (dichotomous; proportion of patients achieving negative smear/culture at the end of the reported follow-up).
• Time to sputum smear / culture conversion (continuous, measured in weeks or months from treatment initiation).
Timing of measurement: at each reported follow-up time point (typically the end of the intensive phase at 2 months, and the end of treatment at 6 months, or as reported by included studies). Measurement scale: microbiological assessment by sputum smear microscopy or sputum culture as defined in each primary study.

Additional outcome(s) • TB symptom score (continuous; TB Score, Symptom Count Ratio, or equivalent standardised instrument).
• Adverse events, including all-cause mortality (dichotomous; incidence of any reported adverse event and of death during the study period).
• Health-related quality of life (continuous; e.g., SF-12 or other validated instruments).
• Serum inflammatory markers (continuous; C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]).
• Change in body weight and/or body-mass index (continuous).
• Serum vitamin D level — 25-hydroxyvitamin D (continuous; ng/mL or nmol/L, with unit conversion where necessary).
These outcomes are included to provide supporting biological and patient-centred evidence around the primary microbiological endpoints.

Data management Selection process: records retrieved from the three databases will be exported and deduplicated. Two reviewers will independently screen titles and abstracts against the eligibility criteria, followed by independent full-text screening of records passing the first stage. Disagreements at either stage will be resolved by discussion; unresolved disagreements will be adjudicated by a third reviewer.
Data extraction: a standardised data-extraction form will be built in Microsoft Excel. Extracted items will include: first author; year of publication; country/region; study design; total sample size and group sample sizes; participant demographics (age, sex); details of the vitamin D intervention (formulation, dose, route, frequency, duration);

details of the comparator; follow-up duration; and each outcome measure reported (including timing and unit of measurement). Two reviewers will extract data independently; disagreements will be resolved by discussion with a third reviewer.
Software: Microsoft Excel (data extraction and management), Review Manager (RevMan) version 5.4 (meta-analysis and forest plots), and Robvis (risk-of-bias visualisation).

Quality assessment / Risk of bias analysis Randomised controlled trials will be appraised using the Cochrane Risk of Bias 2 (RoB 2) tool, which assesses bias arising from the randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Traffic-light plots and summary plots will be generated with the Robvis online tool.
Case-control studies will be appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case-Control Studies (10 items). Overall study quality will be categorised based on the number of "Yes" responses: 0–4 = poor quality; 5–7 = moderate quality; 8–10 = good quality.
Risk-of-bias assessment will be performed independently by two reviewers, with disagreements resolved through discussion and, if necessary, adjudication by a third reviewer. The certainty of evidence for each primary outcome will be considered using the GRADE framework where feasible, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Strategy of data synthesis Quantitative synthesis will be conducted using Review Manager (RevMan) 5.4. For dichotomous outcomes (e.g., sputum smear/culture-negative conversion rate, mortality, adverse events), the odds ratio (OR) with 95% confidence intervals will be used as the effect measure, computed using the Mantel–Haenszel method. For continuous outcomes (e.g., TB symptom score, time to conversion, serum CRP/ESR, serum vitamin D, body weight/BMI), the mean difference (MD) with 95% confidence intervals will be used, computed using the inverse-variance method; standardised mean differences will be used if the same construct is reported on different scales.
Between-study heterogeneity will be assessed using the I^2 statistic, interpreted with the thresholds $I^2 \approx 25\%$ (low), 50% (moderate), and 75% (high). A random-effects model will be used as the primary model, given anticipated clinical and methodological heterogeneity across trials (different vitamin D formulations, doses, dosing schedules, and follow-up durations). A two-sided p-value < 0.05 will be considered statistically significant.
If an outcome is reported in too few studies (< 2 studies) or the studies are clinically too heterogeneous to combine, results will be summarised narratively rather than pooled.
Publication bias will be evaluated using funnel plots and Egger's test if ≥ 10 studies are available for a given outcome; otherwise, limitations of such assessment will be noted.

Subgroup analysis Where sufficient data are available, the following pre-specified subgroup analyses will be conducted for the primary microbiological outcome:
• By country / sub-region within the Middle East (e.g., Egypt versus Iran).
• By vitamin D formulation and dosing schedule (daily low-dose regimens versus high-dose bolus regimens).
• By baseline vitamin D status (deficient versus sufficient, where reported).
• By study design (randomised controlled trial versus case-control study).
The number of subgroup analyses has been kept small to limit the risk of spurious findings.

Sensitivity analysis Pre-specified sensitivity analyses will include:
• Restricting the pooled analysis to randomised controlled trials only (excluding the case-control study).
• Restricting to studies judged to be at low risk of bias.
• Using a fixed-effect model instead of a random-effects model to assess the robustness of the pooled estimate.
Consistency of pooled effect estimates across these analyses will be interpreted as supportive of the robustness of the main findings.

Language restriction No language restriction will be applied at the search stage. Records published in languages other than English or Arabic will be considered for inclusion where translation is feasible; if translation.

Country(ies) involved Saudi Arabia.

Keywords tuberculosis; vitamin D; cholecalciferol; sputum conversion; Middle East; adjunctive therapy; systematic review; meta-analysis.

Dissemination plans The results of this systematic review and meta-analysis will be disseminated through publication in a peer-reviewed international journal in the field of infectious diseases, respiratory medicine, or

nutrition. Findings will additionally be presented at relevant national and regional scientific conferences. A plain-language summary will be prepared to facilitate communication with clinicians, policymakers, and the public in the Middle East region. The INPLASY registration number and DOI will be cited in the final publication.

Contributions of each author

Author 1 - Hana Abdalla - Author 1 conceptualized the idea and performed the methodology, data analysis, and manuscript writing.
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