International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Ethambutol induced optic neuropathy

INPLASY202660086

doi: 10.37766/inplasy2026.6.0086

Received: 17 June 2026

Published: 18 June 2026

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202660086

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 June 2026 and was last updated on 18 June 2026.

INTRODUCTION

Review question / Objective Review question (PICOS).
• Population (P): Adults (≥18 years) receiving ethambutol for tuberculosis or non-tuberculous mycobacterial disease.
• Intervention/Exposure (I): Ethambutol exposure, characterized where possible by dose (mg/kg/day), cumulative dose, and duration.
• Comparators (C): Ethambutol-exposed patients without optic neuropathy, lower-dose/shorter-duration exposure, or non-exposed controls, where reported (not required for descriptive incidence/phenotype outcomes).
• Outcomes (O): (i) incidence/prevalence; (ii) risk factors; (iii) clinical features (visual acuity, color vision, fields, disc appearance) and structural/electrophysiological findings (OCT pRNFL, GCIPL; VEP); (iv) visual outcomes after cessation and predictors; (v) screening/monitoring approaches and performance.
• Study designs (S): Cohort, case–control, and cross-sectional studies, and case series; prior systematic reviews used for cross-checking and reference screening but not double-counted.

Rationale Despite a large descriptive literature, key questions remain incompletely resolved: the true dose-stratified incidence under contemporary (including extended NTM) regimens; which risk factors are robustly supported versus inconsistently reported; the diagnostic and prognostic value of structural imaging (OCT) and electrophysiology; and what monitoring strategy best balances early detection against feasibility in high-burden settings. Several prior systematic reviews have addressed components of this question, incidence during active TB treatment, outcomes under extended regimens, comparative risk factors, and longitudinal OCT changes but a consolidated synthesis spanning incidence, risk, phenotype, prognosis, and monitoring is lacking. This review aims to aggregate and critically appraise the available evidence across these domains to inform clinical monitoring, patient counseling, and future research priorities.

Condition being studied Ethambutol-induced optic neuropathy.

METHODS

Search strategy The following databases were searched from inception to May 2026. PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science Core Collection, and Scopus. Reference lists of included studies and of relevant prior reviews were hand-searched, and grey literature (conference proceedings, theses, and trial/pharmacovigilance registries) was screened. Non-English records without an available English full text or professional translation were excluded, and this is acknowledged as a limitation. Any information obtainable solely through author correspondence was not used.
The search combined controlled vocabulary (MeSH/Emtree) and free-text terms for the exposure and the outcome. A representative MEDLINE (PubMed) strategy is shown below; full strategies for all databases appear in Supplementary Appendix S1.
#1 "Ethambutol"[Mesh] OR ethambutol[tiab] OR myambutol[tiab] OR EMB[tiab]
#2 "Optic Nerve Diseases"[Mesh] OR "Optic Neuropathy, Ischemic"[Mesh]
OR "optic neuropath*"[tiab] OR "optic neuritis"[tiab]
OR "toxic optic*"[tiab] OR "optic atroph*"[tiab]
OR "visual loss"[tiab] OR "visual impairment"[tiab]
OR "ocular toxicit*"[tiab] OR "visual toxicit*"[tiab]
OR dyschromatopsia[tiab] OR "colour vision"[tiab] OR "color vision"[tiab]
#3 #1 AND #2.

Participant or population Eligible participants were adults (≥18 years) who received ethambutol for mycobacterial disease (TB or NTM). Studies confined to pediatric populations were recorded separately and not combined with adult data. Studies in which ethambutol exposure could not be isolated from other plausibly neurotoxic agents were eligible only if EON was diagnosed using explicit criteria attributing the neuropathy to ethambutol.

Intervention The exposure of interest was ethambutol, ideally characterized by daily dose (mg/kg/day), regimen (intensive vs continuation; standard vs extended NTM), cumulative dose, and treatment duration at symptom onset.

Comparator Ethambutol-exposed patients without optic neuropathy, lower-dose/shorter-duration exposure, or non-exposed controls, where reported (not required for descriptive incidence/phenotype outcomes).

Study designs to be included Cohort, case–control, and cross-sectional studies, and case series; prior systematic reviews used for cross-checking and reference screening but not double-counted.

Eligibility criteria Inclusion criteria: adult ethambutol recipients reporting ≥1 prespecified outcome (incidence, risk factor, clinical/structural/electrophysiological finding, or visual outcome), in a Tier 1 or Tier 2 design as defined above.
Exclusion criteria: reviews, meta-analyses, editorials, commentaries, and conference correspondence (their reference lists were hand-searched for primary studies but they were not included as studies); animal, in-vitro, and other preclinical studies (used only as narrative mechanistic context in the Introduction and Discussion); studies in which ethambutol could not be implicated as the cause by explicit diagnostic criteria; non-English reports without an available English full text or translation; and duplicate cohorts (the most complete or most recent report retained).

Information sources The following databases were searched from inception to May 2026. PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science Core Collection, and Scopus.

Main outcome(s) (i) incidence/prevalence; (ii) risk factors; (iii) clinical features (visual acuity, color vision, fields, disc appearance) and structural/electrophysiological findings (OCT pRNFL, GCIPL; VEP); (iv) visual outcomes after cessation and predictors; (v) screening/monitoring approaches and performance.

Data management Records were exported to a reference manager and de-duplicated. Two reviewers independently screened records and assessed eligibility; disagreements were resolved by consensus, with a third reviewer available for unresolved conflicts. Inter-reviewer agreement was quantified using Cohen's κ (κ = 0.87). Reasons for exclusion at the full-text stage were recorded and are reported in the PRISMA flow diagram.
A tiered eligibility framework was applied. Tier 1 comprised cohort, case-control, and cross-sectional studies, as well as case series of ≥5 patients; these constituted the primary evidence base for incidence, risk factors, and visual outcomes. Tier 2 comprised case reports and series of <5 patients, included only where they documented a feature not captured by Tier 1

evidence (an atypical presentation, an unusual dose or time-course, a genetic/mechanistic precipitation, or a novel imaging/electrophysiology finding); Tier 2 reports were summarized descriptively and were not combined with Tier 1 data.

Quality assessment / Risk of bias analysis Risk of bias was appraised at the study level using design-appropriate tools — the Newcastle–Ottawa Scale for cohort and case-control studies and JBI critical-appraisal checklists for cross-sectional studies and for Tier 2 case reports/series — and the certainty of the body of evidence for each outcome domain was considered using a GRADE-informed narrative judgment.

Strategy of data synthesis Evidence was synthesized narratively (SWiM), grouped by outcome domain (incidence, risk factors, clinical and structural phenotype, and visual outcomes) and supported by structured summary tables.

Subgroup analysis Subgroup analysis, if appropriate, would be performed based on Ethambutol dosage, age groups, co-morbidities, visual outcome, and prognostic analysis.

Sensitivity analysis Sensitivity analyses will be performed by:
a. excluding studies without explicit diagnostic criteria for ethambutol optic neuropathy;
b. excluding studies reporting only subclinical toxicity (e.g., isolated color vision, contrast sensitivity, or electrophysiological abnormalities without clinically manifest EON);
c. excluding studies judged at high risk of bias;
d. conducting leave-one-out analyses where meta-analysis is feasible.

Language restriction Non-English records without an available English full text or professional translation were excluded.

Country(ies) involved United States of America.

Keywords Ethambutol; optic neuropathy; toxic optic neuropathy; tuberculosis; mitochondrial optic neuropathy; optical coherence tomography; drug safety; systematic review.

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