INPLASY

Antigen-Specific Th1 Cytokine Markers and Protection Against Tuberculosis: A Systematic Review and Meta-analysis Stratified by Progression to Active Disease and Sustained IGRA Conversion

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Lin, TY; Liu, S; Pan, YY.

Corresponding author:
Yanyu Pan

yanyupan900@126.com

Author Affiliation:
Second Department of Infection, the 900th Hospital of PLA Joint Logistic Support Force.

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INTRODUCTION

Review question / Objective PICOS Framework:Population: Human participants, including those vaccinated with BCG or those exposed to Mycobacterium tuberculosis, with a focus on different age groups and geographical locations (e.g., infants, HIV-infected adults, adolescents, and healthy individuals).

Intervention: Measurement of antigen-specific Th1 cytokine responses (e.g., IFN-γ, IL-2, TNF-α) to TB-related antigens such as PPD, Ag85A, ESAT-6, or other vaccine antigens (BCG, M72/AS01E, MVA85A).

Comparison: Studies comparing the presence or magnitude of these cytokine markers between those who progress to active TB disease and those who do not, as well as comparisons between those with sustained IGRA conversion (immune response markers) and non-converters.

Outcome: The primary outcome is progression to active TB disease, while the secondary outcome includes sustained IGRA conversion, a surrogate for exposure to TB. These outcomes assess the relationship between Th1 cytokine markers and disease risk or immune activation.

Study design: Randomized controlled trials (RCTs), prospective cohort studies, and observational studies with longitudinal follow-up, focusing on immune correlates in the context of vaccine trials or natural TB exposure.

Condition being studied TB spreads through the air when an infected person coughs, sneezes, or talks. It is classified into two forms:
Latent TB: In this form, the person is infected with M. tuberculosis but does not have active disease.

The immune system controls the infection, and the individual does not show symptoms. However, latent TB can reactivate and develop into active TB, especially if the immune system becomes weakened.

Active TB Disease: This is when the bacteria multiply and cause symptoms such as chronic cough, fever, weight loss, night sweats, and fatigue. Without treatment, active TB can be fatal.

The disease disproportionately affects low- and middle-income countries, especially in regions with high rates of HIV/AIDS, malnutrition, and poor healthcare access. While the Bacillus Calmette–Guérin (BCG) vaccine has been used for TB prevention, its efficacy is variable, particularly in adults. Hence, developing more effective TB vaccines is a priority.

The immune response plays a critical role in both controlling the infection and determining the risk of progression from latent TB to active disease. Key immune markers, especially Th1 cytokines such as IFN-γ, IL-2, and TNF-α, are involved in controlling M. tuberculosis and are being studied for their potential as correlates of protection (CoPs) against TB. These cytokines help activate immune cells, such as macrophages and CD4 T cells, to fight off infection.

Understanding the relationship between these cytokine markers and TB progression could help in identifying biomarkers for vaccine efficacy, infection risk, and TB disease progression, contributing to the development of more effective TB interventions and vaccines.

METHODS

Participant or population The participants in this review are human individuals, specifically those who have been exposed to Mycobacterium tuberculosis or have received the Bacillus Calmette–Guérin (BCG) vaccine, as well as those enrolled in clinical trials or cohort studies related to tuberculosis (TB) and its prevention. The review will address participants from a variety of groups, including:

Healthy Adults and Children:

Individuals who are either naturally exposed to M. tuberculosis or vaccinated with BCG.

Healthy participants from different geographic regions with varying TB prevalence, including those from high-incidence areas.

Infants and Children:

Neonates or young children who have received the BCG vaccine as part of routine immunization programs, with a focus on their immune responses and the long-term impact of vaccination on TB susceptibility.

HIV-Infected Individuals:

Adults or children living with HIV, who may be at higher risk of developing active TB due to compromised immune function. This group is critical in understanding how immune responses to TB differ in the context of HIV infection.

Vaccine Trial Participants:

Individuals enrolled in randomized controlled trials (RCTs) testing new TB vaccines or TB vaccine boosters, such as MVA85A or M72/AS01E. These participants may be either healthy or those with prior BCG vaccination or TB exposure.

Participants in trials that assess the immune responses elicited by new TB vaccines, including the measurement of Th1 cytokine markers like IFN-γ, IL-2, and TNF-α.

TB Exposed Individuals:

People who have been in close contact with TB patients, as they may be at higher risk of TB infection and progression from latent to active disease.

Individuals from endemic regions where TB exposure is more common, allowing researchers to study immune responses related to infection risk and immune activation.

Individuals with Latent TB Infection:

Participants who have a latent TB infection but are not yet exhibiting symptoms of active TB disease. These individuals are of particular interest for understanding immune responses that may prevent progression to active disease.

Intervention The intervention(s) being evaluated in this systematic review primarily focus on immune responses to tuberculosis (TB), specifically the measurement of antigen-specific Th1 cytokine markers. These markers include:

IFN-γ (Interferon-gamma)

IL-2 (Interleukin-2)

TNF-α (Tumor Necrosis Factor-alpha)

These cytokines are produced by CD4+ T cells in response to infection with Mycobacterium tuberculosis or vaccination (e.g., BCG) and are central to the immune system's ability to control the infection. The review aims to evaluate how the magnitude of these cytokine responses can serve as correlates of protection (CoP) against progression to active TB disease or as markers of immune activation in individuals who have been exposed to TB or vaccinated.

Specific Interventions:

BCG Vaccination: The Bacillus Calmette–Guérin (BCG) vaccine, which is commonly used to vaccinate infants against TB. The review will assess how antigen-specific Th1 cytokine responses, such as those measured post-BCG vaccination, correlate with the immune response to TB.

New TB Vaccines: Investigational vaccines like MVA85A and M72/AS01E, which aim to enhance protection against TB beyond the BCG vaccine. The review will evaluate how these vaccines induce Th1 cytokine responses and whether these markers are associated with protection against TB progression or sustained IGRA conversion.

Exposure to Mycobacterium tuberculosis: For individuals who have been naturally exposed to TB (e.g., through close contact with an active TB case), the review will assess how the immune response (measured by Th1 cytokines) reflects the risk of disease progression or ongoing infection, particularly in populations with latent TB infection.

Outcome Measures:

The cytokine markers (IFN-γ, IL-2, TNF-α) will be analyzed as potential biomarkers of protection or risk, with the review focusing on:

Primary Outcome: Progression from latent TB infection to active TB disease.

Secondary Outcome: Sustained IGRA conversion, as a marker of immune response and exposure to TB.
By assessing the relationship between these Th1 cytokine responses and TB outcomes, the review aims to understand their role in TB immunity, vaccine efficacy, and disease prevention.

Comparator In this systematic review, the comparators will be individuals with lower or absent Th1 cytokine responses or no vaccination/exposure to Mycobacterium tuberculosis. Specifically, the review will compare the following:

Individuals with no or low Th1 cytokine responses (i.e., low levels of IFN-γ, IL-2, TNF-α):
These individuals may either be:

Unvaccinated or not exposed to TB.

Individuals from populations with a weak or absent immune response to TB infection or vaccination (e.g., those with immunocompromised conditions such as HIV).

No vaccination/exposure to Mycobacterium tuberculosis:

Individuals who have not received the BCG vaccine or any new TB vaccine (e.g., MVA85A, M72/AS01E).

Participants who have not been naturally exposed to M. tuberculosis and therefore have no previous immune activation against the pathogen.

The comparison will focus on evaluating how higher levels of Th1 cytokines (such as IFN-γ, IL-2, and TNF-α) in the intervention groups (e.g., BCG-vaccinated or exposed individuals) correlate with protection against progression to active TB disease or sustained IGRA conversion, compared to those with lower or absent immune responses.
By using these comparators, the review seeks to determine whether higher Th1 cytokine responses can be reliably associated with protection against TB or infection risk, and whether these markers could serve as useful correlates of protection or risk.

Study designs to be included The study designs to be included in this review are:Randomized Controlled Trials (RCTs): Evaluating TB vaccine efficacy (e.g., BCG, MVA85A, M72/AS01E) and immune responses.Prospective Cohort Studies: Following individuals exposed to TB or vaccinated, measuring Th1 cytokine responses and monitoring for progression to active TB or sustained IGRA conversion.Nested Case-Control Studies: Assessing immune responses in relation to TB progression or infection risk.Cross-Sectional Studies: Observing Th1 cytokine levels in TB-exposed populations.

Eligibility criteria The study designs to be included in this review are:

Randomized Controlled Trials (RCTs): Specifically those assessing the efficacy of TB vaccines (e.g., BCG, MVA85A, M72/AS01E) and their impact on immune responses, including Th1 cytokines.

Prospective Cohort Studies: Studies tracking individuals exposed to TB or vaccinated, measuring Th1 cytokine responses and monitoring for progression to active TB disease or sustained IGRA conversion.

Nested Case-Control Studies: Studies within larger cohorts evaluating the relationship between immune responses (Th1 cytokines) and TB progression.
Cross-Sectional Studies: Observational studies measuring immune responses in TB-exposed populations.

Information sources The following information sources will be used to identify relevant studies for this systematic review:
Electronic Databases:
PubMed/MEDLINE: For peer-reviewed articles related to TB, vaccines, and immune responses, focusing on Th1 cytokines.

Embase: A comprehensive database for biomedical literature, including studies on TB vaccine trials and immune response biomarkers.

Web of Science: For a broad collection of scientific literature, including research on immune correlates and TB vaccine efficacy.

Cochrane Central Register of Controlled Trials (CENTRAL): For randomized controlled trials (RCTs) on TB vaccines and immune responses.

CINAHL: For studies related to nursing and health research, particularly those involving TB management and vaccine trials.

Clinical Trial Registers:

ClinicalTrials.gov: For identifying ongoing or unpublished clinical trials involving TB vaccine efficacy and cytokine marker measurements.

WHO International Clinical Trials Registry Platform (ICTRP): To locate additional trials on TB vaccines and immune responses.

Grey Literature:

Conference Proceedings: Searching for abstracts and presentations from major conferences on immunology, tuberculosis, and vaccine development.

Dissertations and Theses: Relevant unpublished research related to TB and cytokine studies, available through institutional repositories and databases like ProQuest.

Reference Lists:

Reviewing reference lists of relevant systematic reviews and primary studies to identify additional studies not found through database searches.

Contact with Authors:

Reaching out to authors of relevant studies for unpublished data or clarifications on methodologies and results.

This combination of electronic databases, clinical trial registries, grey literature, and author contact will ensure comprehensive identification of relevant studies to address the review's objectives.

Main outcome(s) The main outcomes of this review are:
Progression to Active TB Disease:
Timing: Assessed over the duration of follow-up, ranging from several months to years, depending on the study.

Effect Measure: Odds ratios (ORs) for the association between antigen-specific Th1 cytokine responses (IFN-γ, IL-2, TNF-α) and the risk of progression from latent TB to active TB disease.

Sustained IGRA Conversion:

Timing: Typically assessed at multiple time points (e.g., baseline, 6 months, 12 months, etc.) to evaluate the persistence of immune activation.

Effect Measure: Mean differences (MDs) for continuous Th1 cytokine levels (IFN-γ, IL-2, TNF-α) between IGRA converters (those with a sustained positive response) and non-converters.

These outcomes will be measured using random-effects meta-analysis, with effect sizes (ORs for binary outcomes, MDs for continuous cytokine measures) to assess the strength of the association between cytokine responses and TB progression or exposure.

Quality assessment / Risk of bias analysis Quality assessment and risk of bias analysis in the

primary studies will be conducted using established tools tailored to the study design:
Randomized Controlled Trials (RCTs):
Cochrane Risk of Bias (RoB 2) Tool: This tool will be used to assess the risk of bias across key domains, including:
Randomization process (e.g., sequence generation and allocation concealment)
Deviations from intended interventions (e.g., blinding of participants and personnel)
Missing outcome data (e.g., attrition rates and reasons)
Measurement of outcomes (e.g., blinding of outcome assessors)
Selective reporting (e.g., consistency of reported outcomes with pre-specified outcomes)
Prospective Cohort Studies:
Newcastle-Ottawa Scale (NOS): This scale will be used for cohort studies, assessing:
Selection of participants (e.g., representativeness of the cohort)
Comparability of cohorts (e.g., control for confounding factors)
Outcome assessment (e.g., follow-up duration and consistency of outcome measurement)
Case-Control Studies:
Newcastle-Ottawa Scale (NOS) (adapted for case-control studies): Evaluating:
Selection of cases and controls
Comparability of groups (adjustment for confounding)
Exposure measurement (e.g., accurate and consistent measurement of immune markers and TB status)
Cross-Sectional Studies:
ROBINS-I (Risk of Bias in Non-Randomized Studies - of Interventions): This tool will be used for cross-sectional studies, assessing bias in:
Confounding (e.g., whether potential confounders were controlled for)
Selection of participants (e.g., representativeness)
Classification of interventions/exposure (e.g., accurate measurement of cytokine markers)
Missing data and reporting
In all study types, potential sources of bias such as publication bias (using funnel plots when appropriate) and small-study effects will be evaluated. We will perform sensitivity analyses to assess the robustness of findings when studies of high or uncertain risk of bias are excluded.

Strategy of data synthesis The data synthesis for this systematic review will follow a structured, step-by-step approach to ensure rigorous analysis and meaningful interpretation of the results. The strategy of data synthesis will involve both qualitative and quantitative methods, with a primary focus on meta-analysis for applicable studies. The approach will include:

1. Data Extraction:

Study Characteristics: Information will be extracted for each study, including author, year, study design, population characteristics, interventions (e.g., TB vaccines, BCG, or exposure to Mycobacterium tuberculosis), and outcome measures.

Outcome Data: The primary outcome (progression to active TB disease) and secondary outcome (sustained IGRA conversion) data will be extracted. This includes effect sizes such as odds ratios (ORs) for binary outcomes and mean differences (MDs) for continuous outcomes (e.g., Th1 cytokine levels).

Risk of Bias: Data regarding the risk of bias for each study will also be recorded to evaluate the potential influence on the results.

2. Statistical Analysis:

Meta-analysis:

For binary outcomes (e.g., progression to active TB disease), the odds ratios (ORs) will be pooled across studies using random-effects models, as the included studies may be heterogeneous in design and population.

For continuous outcomes (e.g., cytokine levels), mean differences (MDs) will be pooled. If studies report the same cytokine data on different scales, standardization will be applied, and sensitivity analysis will be used to assess robustness.

Random-effects Models: Given the anticipated heterogeneity in study designs, populations, and interventions, we will use random-effects meta-analysis, which accounts for between-study variability. We will calculate pooled estimates with 95% confidence intervals (CIs) for each effect measure.

Heterogeneity Assessment: The I^2 statistic will be used to quantify the degree of heterogeneity across studies. High heterogeneity ($I^2 > 50\%$) will be flagged for further exploration, including subgroup analyses and sensitivity analyses. We will explore sources of heterogeneity through:

Subgroup analyses: Based on study design, population (e.g., HIV-positive vs. HIV-negative), type of intervention (e.g., BCG vs. new vaccine),

and outcome measure (e.g., progression vs. IGRA conversion).

Sensitivity analyses: To assess the influence of studies with high risk of bias or significant methodological differences on the pooled results.

3. Exploration of Publication Bias:

Funnel Plots: These will be generated to assess for small-study effects and publication bias, particularly in cases where a sufficient number of studies are available for meta-analysis.

Egger's Test: For more formal testing of publication bias, especially in the case of continuous outcomes, Egger's regression test will be applied.

4. Narrative Synthesis:

If meta-analysis is not feasible due to insufficient homogeneity between studies or a lack of comparable effect measures, we will conduct a narrative synthesis of the findings. This will involve summarizing the direction and strength of associations between Th1 cytokine markers and TB outcomes, highlighting key trends and inconsistencies.

5. Qualitative Summary:

For studies with non-quantifiable data or differing outcome measures, we will summarize findings qualitatively, describing patterns of cytokine responses and their relationship with TB progression and infection risk across different populations and vaccine strategies.

6. Risk of Bias Consideration in Synthesis:

The findings will be interpreted in light of.

Subgroup analysis Subgroup analysis will be conducted to explore potential sources of heterogeneity and to examine whether specific factors influence the association between Th1 cytokine responses and TB outcomes. The subgroups will be based on the following characteristics:

1. Study Design:

Randomized Controlled Trials (RCTs) vs. Observational Studies: To determine if differences in study design affect the strength or consistency of the findings.

Prospective Cohort Studies vs. Cross-Sectional Studies: This will help assess whether long-term follow-up and continuous data on cytokine responses provide more reliable results compared to studies with a snapshot of immune responses.

2. Population Characteristics:

HIV-Positive vs. HIV-Negative Individuals: HIV infection can significantly affect immune responses, so we will assess whether Th1 cytokine responses are stronger or weaker in HIV-infected individuals and if they correlate differently with TB progression.

Infants/Children vs. Adults: Considering that the immune system behaves differently in children and adults, we will examine if age influences the association between Th1 cytokine responses and TB outcomes.

Healthy vs. TB-Exposed/Latent TB Populations: We will explore whether the immune response in individuals with latent TB or those at high risk of exposure to Mycobacterium tuberculosis differs from healthy individuals, in terms of cytokine profiles and their association with progression or exposure.

3. Type of Intervention:

BCG Vaccine vs. New Vaccine Candidates (e.g., MVA85A, M72/AS01E): As different vaccines may induce varying levels of immune responses, we will assess whether the type of vaccine influences the association between Th1 cytokine markers and TB protection.

Vaccinated vs. Non-Vaccinated Individuals: This comparison will help determine whether cytokine responses are more strongly associated with protection in vaccinated individuals.

4. Outcome Measures:

Progression to Active TB Disease vs. Sustained IGRA Conversion: We will assess whether the strength of the association between Th1 cytokine responses and TB outcomes differs between individuals who progress to active disease and those with sustained IGRA conversion (indicating recent exposure).

5. Cytokine Type:

IFN-γ, IL-2, TNF-α: Since different cytokines may have varying roles in TB immunity, we will analyze whether one cytokine or a combination (e.g.,

polyfunctional responses) is more predictive of TB protection.

By performing these subgroup analyses, we aim to identify specific factors that may influence the strength or direction of the association between Th1 cytokine responses and TB outcomes, providing more tailored insights into the immunological markers for TB protection and risk.

Sensitivity analysis Sensitivity analysis will be performed to assess the robustness of the findings and the impact of certain study characteristics or methodological factors on the overall results. This will help determine whether the conclusions of the systematic review are influenced by specific study designs, biases, or quality issues. The following sensitivity analyses will be conducted:

1. Exclusion of Studies with High Risk of Bias:

Purpose: To evaluate whether studies with a high risk of bias (e.g., issues with randomization, blinding, or incomplete reporting) significantly influence the pooled results.

Method: Studies rated as high risk or with unclear risk of bias across key domains (e.g., randomization, missing data, and outcome measurement) will be excluded, and the meta-analysis will be rerun to see if the overall effect size changes.

2. Exclusion of Outlier Studies:

Purpose: To determine whether any single study has an outsized influence on the pooled results, especially in cases of high heterogeneity.

Method: Individual studies identified as outliers in Baujat plots (which assess influence on both effect size and heterogeneity) will be excluded one at a time, and the meta-analysis will be recalculated to assess whether the effect size shifts.

3. Analysis of Study Design Variability:

Purpose: To assess whether differences in study design (e.g., randomized trials vs. cohort studies) lead to varying results.

Method: Separate meta-analyses will be performed for RCTs, cohort studies, and observational studies. Sensitivity analysis will determine whether study design significantly impacts the overall conclusions.

4. Exclusion of Small Studies:

Purpose: To examine the influence of small studies, which may be more prone to bias, on the overall effect size.

Method: Studies with a small sample size (e.g., fewer than 50 participants) will be excluded, and the analysis will be rerun to see if the results are more consistent when larger studies are prioritized.

5. Assessment of Imputation of Missing Data:

Purpose: To evaluate how missing or imputed data might affect the overall results.

Method: If missing data are handled via imputation, the analysis will be performed both with and without imputed data to assess whether imputation methods affect the findings.

6. Impact of Publication Bias:

Purpose: To check if the results are influenced by publication bias, where positive or significant findings are more likely to be published.

Method: Funnel plots will be visually inspected for asymmetry, and Egger's test will be performed to statistically assess publication bias. Sensitivity analysis will exclude studies contributing to funnel plot asymmetry to check for the impact on pooled results.

7. Heterogeneity Exploration:

Purpose: To determine if high levels of heterogeneity ($I^2 > 50\%$) are driven by specific study characteristics.

Method: Sensitivity analysis will be used to explore whether variations in study characteristics (e.g., population, assay platforms, type of TB.

Country(ies) involved The study involves authors and affiliations from China, specifically from Fujian Medical University and the 900th Hospital of PLA Joint Logistic Support Force, both located in Fuzhou, China.

Keywords tuberculosis; correlate of protection; correlate of risk; IFN-γ; IL-2; TNF-α; polyfunctional T cells; IGRA conversion; vaccine trials; systematic review.

Contributions of each author
Author 1 - Tianyu Lin.
Author 2 - Sheng Liu.
Author 3 - Yanyu Pan.