**TB PREVALENCE, INCIDENCE, AND SUSCEPTIBILITY IN CHILDREN WHO ARE HIV-EXPOSED-UNINFECTED**

# **Background**

1. TB infects 7.5 million children <15 years old each year,[1] and 1 million children develop TB disease.[2, 3] In 2021, 209,000 children <15 years old died from TB,[3] making TB a top-ten killer of children worldwide.[4] Children <5 years old bear the brunt of TB mortality, with 80% of child TB deaths occurring in this age group.[3] Several factors drive this disproportionate mortality burden: immune immaturity and acquired immunodeficiency (e.g. from HIV or malnutrition) impair control of TB infection;[5, 6] young children may lack the physiologic reserve to compensate for severe infections; and TB diagnosis is often delayed or never achieved, in part due to the paucibacillary nature of pediatric TB disease and suboptimal diagnostic options for this age group.[7]

Thanks to expanded antiretroviral therapy (ART) and perinatal HIV prevention services, most children born to the 1.3 million women with HIV giving birth each year do not acquire HIV.[8] Yet compared to HIV unexposed children, cHEU experience increased infectious diseases severity and mortality, primarily in the first 2 years of life.[9, 10]

To date, observational studies of TB prevalence and incidence among cHEU compared to children who are HIV-unexposed-uninfected have yielded contradictory results. In the South African Pneumonia Etiology Research for Child Health (PERCH) study, *Mycobacterium tuberculosis* (Mtb) contributed to a slightly higher etiologic fraction of childhood pneumonia in cHEU <5 years old compared to cHUU.[11] Likewise, a follow-up survey from the P1041 trial documented very high rates of TB exposure among cHEU.[12] However, others have found similar rates of IGRA positivity between cHEU and cHUU in South Africa and Botswana.[13]Immunologic studies have demonstrated decreased perinatal transfer of Mtb antibodies from mothers to HIV-exposed newborns.[14] These studies have taken place against a backdrop of changing access to potent ART and decreasing rates of perinatal HIV infection.

Whether cHEU should be considered as a priority group for TB prevention efforts (beyond efforts already devoted to young children) is not clear. Overall, there is a need to collate, summarize, and compare studies of TB in cHEU compared to cHUU.

# **Objectives:** We aim to describe the prevalence and incidence of TB exposure, infection, and disease in cHEU versus cHUU, and to summarize findings regarding immunologic susceptibility to TB in cHEU versus cHUU.

# **Review questions**

What is the risk/prevalence/odds of tuberculosis in children aged 0 to 18 years born to HIV-positive mothers who are unexposed to HIV?

What biologic characteristics have been identified that may confer increased TB risk among cHEU versus cHUU?

# **Searches**

Sources: PubMed, Embase, Web of Science, CINAHL

Screening procedures & inclusion/exclusion criteria: We will screen titles/abstracts (stage 1) and full text articles (stage 2) using the following eligibility criteria. Studies meeting eligibility in Stage 1 will be passed to Stage 2. A Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram will be generated to capture inclusion/exclusion, and reasons for exclusion.

**Inclusion criteria**

* Describes cHEU 0-18 years old
* Describes TB prevalence or incidence among cHEU

OR

* Assesses immunologic factors in cHEU with direct regard to TB susceptibility

**Exclusion criteria**

* Case reports or uncontrolled case series that do not specifically assess biologic drivers of TB susceptibility

The following PICOS table outlines inclusion/exclusion criteria:

|  |  |  |
| --- | --- | --- |
|  | **Inclusion Criteria** | **Exclusion Criteria** |
| **P -** Patient, Population or Problem | * Studies reporting TB prevalence and/or incidence in cHEU < 18 years old * Studies describing immunology of TB in cHEU | * Studies that do not describe TB prevalence/incidence/risk * Studies that do not differentiate between cHEU and cHUU |
| **I -** Intervention/  Exposure | * Maternal HIV infection without child HIV infection | * Studies that do not report perinatal HIV exposure status * Studies that report outcomes for children who are HIV infected, but not children who are HIV exposed-uninfected |
| **C -** Comparison | * Children who are not HIV exposed | N/A |
| **O -** Outcome | * TB infection/disease prevalence ratio * TB infection/disease incidence ratio * TB infection/disease prevalence * TB biological risk | * Studies that do not report TB outcomes |
| **S -** Study Type | * Observational studies * Interventional (experimental) studies | * Viewpoints, commentaries, review articles * Case reports and case series not reporting analysis of biological mechanisms underlying TB susceptibility among cHEU |
| **T -** Time Period | * All time periods | * NA |

Search terms:

**PubMed**: ("HIV exposed" OR “HIV exposure” OR "HIV positive mother" OR "hiv-exposed uninfected" OR "heu" OR "in utero hiv exposure" OR “HIV exposure”) AND ("Tuberculosis"[Mesh] OR Tuberculosis).

Results: 181.

**Embase**: ('HIV exposed' OR ‘HIV exposure’ OR ‘HIV positive mother’ OR 'hiv-exposed uninfected' OR heu OR 'in utero hiv exposure') AND (Tuberculosis/exp OR Tuberculosis).  
Results: 255.

**Web of Science**: ("HIV exposed" OR “HIV exposure” OR "HIV positive mother" OR "hiv-exposed uninfected" OR heu OR "in utero hiv exposure") AND (Tuberculosis).  
Results: 271.

**CINAHL**: ("HIV exposed" OR “HIV exposure” OR "HIV positive mother" OR "hiv-exposed uninfected" OR heu OR "in utero hiv exposure") AND ((MH Tuberculosis+) OR Tuberculosis).  
Results: 82.

Search date: November 25, 2024

Total references identified: 789

Total unique references identified after deduplication: 424

Data extraction: Covidence

Data elements to be extracted:

|  |  |  |
| --- | --- | --- |
| **Study characteristics** | **Participant characteristics** | **Outcomes** |
| * Identifying characteristics (author, journal) * Publication year * Study start and end years * Study type * Prospective vs retrospective study * Follow-up time for children * Setting (country, locality) * Inclusion/exclusion criteria * Sample size * HIV infection ascertainment (mothers, children) * TB infection and disease ascertainment   + Method   + Frequency of assessment * What TPT standard of care was used for the population * What antiretroviral therapy (ART) standard of care was used for the population * What ART prophylaxis or pre-emptive therapy was used for children * Factors adjusted for in multivariable models of prevalence or incidence * Limitations | * Maternal information   + Age, other key demographics   + CD4 (median/range)   + Viral load (median/range)   + Proportion diagnosed with HIV during index pregnancy   + TB treatment during or after pregnancy * Child information   + Age at enrollment   + HIV infection status   + Post-natal receipt of antiretroviral therapy   + Receipt of TPT   + Known TB exposure | * TB infection   + Positive TST (defined using standard cutoffs)   + Positive IGRA * TB disease   + Positive mycobacterial culture   + Positive AFB smear   + Consistent clinical presentation + treatment * TB exposure * Time to diagnosis * Biological factors identified that may affect susceptibility to TB disease * Follow-up time |

# **Types of study to be included**

Observational studies (e.g., cohort, case-control, and cross-sectional studies) and experimental studies (including randomized controlled trials) addressing the association between HIV-unexposed children and tuberculosis risk.

# **Condition or domain being studied**

This systematic review aims to study TB in children aged 0 to 18 years who are cHEU. We will seek studies that compare epidemiology and susceptibility to control groups of cHUU when possible, though uncontrolled studies will also be included.

We will seek literature on:

1) TB exposure (with exposure defined by each study, given variable definitions of what constitutes a clinically relevant TB exposure)

2) TB immune sensitization (defined as a positive tuberculin skin test or interferon gamma release assay)

3) TB disease (defined as a microbiologic and/or clinical diagnosis of pulmonary or extrapulmonary TB disease)

# **Participants/population**

The key population is cHEU 0-18 years old, compared to population-relevant control cHUU.

# **Intervention(s), exposure(s)**

Primary exposure: cHEU status

Secondary exposures:

* Maternal HIV control (CD4 count during pregnancy, Viral Load during pregnancy)
* Maternal HIV antiretroviral regimen and adherence
* Study year
* Population TB prevalence (measured at the local population level when possible, or measured at the country level when local population rates are not reported)

# **Comparator(s)/control**

We will report

When available, the comparator group will be cHUU 0-18 years old.

# **Main outcome(s)**

Primary outcome: prevalence of TB (measured as a composite of infection or disease) in cHEU compared to cHUU. These rates will be either age-matched or within the same age strata.

Secondary outcomes:

* Prevalence and incidence of TB infection and disease in cHEU.
* Incidence of TB infection and/or disease in cHEU compared to cHUU.
* Exposure to individuals with infectious TB in cHEU compared to cHUU.
* Descriptions of immune susceptibility to Mtb in cHEU.

Prevalent and incident TB infection will be defined as a positive tuberculin skin test and/or interferon gamma release assay, as specified by authors of the study.

Prevalent and incident TB disease will be defined as positive microscopy, culture, or other molecular test, or consistent clinical presentation as defined by the authors of the study. Exposure to individuals with infectious TB will be defined by each study. Immune susceptibility will be defined by the authors, and may include innate or adaptive immune system features that affect children’s risk of TB.

## **Measures of effect**

Prevalence Ratio, Relative risk (RR), odds ratio (OR), or hazard ratio (HR) of tuberculosis among cHEU children compared to cHUU.

We will also qualitatively summarize prevalence and incidence in cHEU compared to population-level estimates or historical controls.

Assessment of biologic drivers of differential risk will be summarized qualitatively.

# **Additional outcome(s)**

NA

# **Risk of bias (quality) assessment**

We will assess risk of bias and quality using the the Newcastle-Ottawa Scale for assessing quality of cohort and case-control studies.

# **Strategy for data synthesis**

We will perform a systematic review and if possible metanalysis of studies reporting prevalence of TB infection/disease in cHEU vs cHUU.

If possible using available data, we will stratify prevalence by age group:

<1 year old

1-2 years old

3-5 years old

5-10 years old

11-14 years old

15-18 years old

If possible using available data, we will assess annual incidence ratios of TB disease in cHEU vs cHUU.

# **Analysis of subgroups or subsets**

Stratification possible based on sex per above. Additional stratification based on setting (low- versus high-TB country) will also be pursued if data permit.

# **Contact details for further information**

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# **Review team members and their organisational affiliations**

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# **Type and method of review**

Systematic review with a potential meta-analysis

# **Anticipated or actual start date**

November 25, 2024

# **Anticipated completion date**

Unknown

# **Funding sources/sponsors**

No funding

# **Conflicts of interest**

None

# **Language**

English

# **Country**

United States

# **Stage of review**

# **Subject index terms status**

# **Subject index terms**

# **Date of registration in PROSPERO**

# **Date of first submission**

# **Stage of review at time of this submission**

Searches performed; study selection in progress.

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