International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Clinical and perinatal outcomes of congenital syphilis in high-income settings during the post-2015 resurgence: a retrospectively registered protocol for an availability-restricted evidence review with exploratory meta-analysis

INPLASY202690031
doi: 10.37766/inplasy2026.9.0031
Received: 7 September 2026
Published: 7 September 2026

Hung, MC; Wei, HH.

Corresponding author:
Hsihsien Wei

alira123@gmail.com

Author Affiliation:
1. Division of Infectious Diseases, Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan; 2. Department of Pediatrics, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; 3. Department of Pediatrics, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan; 4. Institute of Emergency and Critical Care Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan.

ADMINISTRATIVE INFORMATION

Support - This research received no external funding.

Review Stage at time of this submission - Retrospective registration. The authors began the review before they had time to complete registration. Screening, extraction and exploratory meta-analysis preceded registration. Manuscript revision, targeted risk-of-bias adjudication and final author verification remain ongoing. The analyses are not prospectively prespecified.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202690031

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 September 2026 and was last updated on 7 September 2026.

INTRODUCTION

Review question / Objective To characterize clinical and perinatal outcomes of congenital syphilis in high-income settings using reports containing data from 2015 onward, and to assess outcome-specific feasibility for exploratory meta-analysis. Outcomes considered are stillbirth, preterm birth, low birthweight, neonatal death and early clinical manifestations. Maternal-syphilis pregnancies, exposed infants and source-classified congenital syphilis cases are distinguished. The retained evidence set is restricted by adequate full-text availability through Elicit and is not a comprehensive assessment of all identified candidates. The quantitative synthesis estimates stillbirth composition among source-classified congenital syphilis case records in two Canadian reporting settings; it does not estimate risk among all infected pregnancies or a representative high-income-country prognosis.

Rationale Reported congenital syphilis outcomes vary with case classification, ascertainment, clinical-event period and denominator. A source-defined proportion among classified cases is distinct from pregnancy-level risk. This review examines those compatibility limitations before synthesis. Its rationale is transparent description of the available evidence and the limits of pooling, not a claim that every eligible report has been assessed or that no related review exists.

Condition being studied Congenital syphilis and associated fetal, perinatal and early childhood outcomes. Surveillance-defined congenital syphilis, clinically supported infection and exposure-only populations are distinguished.

Stillbirth, prematurity, low birthweight, neonatal death and early manifestations are considered separately. Prevention pathways and classification-framework comparisons provide narrative context rather than interchangeable clinical endpoints.

METHODS

Search strategy Executed on 25 August 2026; publication window 1 January 2015-30 July 2026. Queries recovered from native digital records; line breaks are formatting only. No country or outcome terms restricted retrieval.

PubMed submitted query:

```
(
(
"Syphilis, Congenital"[Mesh]
OR "congenital syphilis"[tiab]
OR "congenital lues"[tiab:~0]
OR "lues congenita"[tiab:~0]
OR (congenital[tiab] AND syphili*[tiab])
OR ((fetal[tiab] OR foetal[tiab] OR fetus*[tiab] OR foetus*[tiab]
OR newborn*[tiab] OR neonat*[tiab] OR infant*[tiab])
AND syphili*[tiab])
)
OR
(
(
"Syphilis"[Mesh]
OR "Treponema pallidum"[Mesh]
OR syphili*[tiab]
OR "Treponema pallidum"[tiab]
)
AND
(
"Pregnancy"[Mesh]
OR "Pregnancy Complications, Infectious"[Mesh]
OR pregnan*[tiab]
OR maternal[tiab]
OR gestation*[tiab]
OR antenatal[tiab]
OR prenatal[tiab]
OR perinatal[tiab]
OR obstetric*[tiab]
OR "mother-to-child"[tiab]
OR "mother to child"[tiab]
OR "vertical transmission"[tiab]
)
)
)
AND 2015/01/01:2026/07/30[dp]
```

Web of Science Core Collection submitted query (Topic field):

```
"congenital syphilis"
OR "congenital lues"
OR "lues congenita"
OR "syphilis congenita"
OR "lues connata"
OR (congenital AND (syphili* OR "Treponema pallidum" OR "T pallidum"))
OR (
(fetal* OR foetal* OR fetus* OR foetus* OR newborn* OR neonat* OR infant*)
AND (syphili* OR "Treponema pallidum" OR "T pallidum")
)
OR (
(syphili* OR "Treponema pallidum" OR "T pallidum")
AND (
pregnan* OR matern* OR gestation* OR antenatal* OR prenatal*
OR perinatal* OR obstetr* OR gravid* OR parturient*
OR "mother-to-child" OR "mother to child"
OR "vertical transmission" OR transplacent*
OR "in utero" OR MTCT OR PMTCT
)
)
```

The Web of Science date setting and Exact Search OFF are supported by historical workflow documentation, not a recovered native filter display. Complete citation-index selection remains unavailable. PubMed automatic query translation was not recovered. No unsupported language-filter setting is inferred.

Participant or population Main-review contributions require outcome data from 1 January 2015 onward, or separately extractable data from that period, in high-income settings. The recovered eligibility record specifies World Bank FY2027 high-income categories and distinguishes pregnancies or fetuses classified by the source and affected infants or children younger than 24 months. The original dated country-list snapshot is unavailable. Maternal-infection and exposure-only cohorts are kept separate from congenital-syphilis case populations. For the exploratory stillbirth synthesis, the denominator comprises source-classified liveborn and stillborn congenital syphilis case records from Alberta (2017-2020) and Winnipeg (2019-2020).

Intervention Not applicable as an intervention review. The condition of interest is congenital syphilis; maternal infection, treatment timing and prevention pathways are contextual variables. No intervention-effect estimate is claimed.

Comparator No external comparator is required for the selected single-arm, source-defined stillbirth proportion. Exposed infants, uninfected infants, maternal-syphilis pregnancies and alternate case classifications are not treated as interchangeable comparator groups. No causal treatment comparison or pooled adjusted association is estimated.

Study designs to be included Observational cohort and surveillance analyses, cross-sectional reports, claims-based studies and clinical series within the retained roster. Design, population and outcome compatibility determine permitted use; narrative-only reports are not automatically eligible for pooling.

Eligibility criteria Eligibility and analytical use follow the retained, author-adjudicated report roster. Main-review data must meet the clinical-period and high-income-setting requirements and provide interpretable outcome-specific definitions and denominators. Publication year alone does not establish clinical-period eligibility. Mixed-era, phenotype-selected and contextual reports retain their assigned supplementary narrative roles. Assessment was restricted to adequate original text accessible through Elicit within the available time. At the 7 September 2026 analysis cutoff, 648 candidates had no obtained full text and did not undergo full-text eligibility assessment; nonretrieval is not an eligibility exclusion. Twenty additional reports awaiting information remain outside the fixed analysis. This availability restriction and selection of the quantitative subset are post hoc, not prospectively specified.

Information sources PubMed and Web of Science Core Collection were searched on 25 August 2026 for publications from 1 January 2015 to 30 July 2026. Native query and export provenance was recovered. Elicit supported record processing and text access. Embase, CENTRAL, CINAHL and WHO Global Index Medicus appeared in the earlier proposed abstract, but completed searches of those sources are not established and are not claimed. Contextual surveillance reports are used within the fixed roster; no separately executed comprehensive gray-literature search is claimed.

Main outcome(s) Originally considered clinical outcomes were stillbirth, preterm birth, low birthweight, neonatal death and early clinical manifestations. The post hoc quantitative estimand is the proportion stillborn after 20 weeks among source-classified congenital syphilis case records, including liveborn and stillborn records, in the selected Canadian settings. Alberta contributes 2017-2020; Winnipeg contributes 2019-2020. Possible early-2019 under-ascertainment is retained as a limitation. The summary is case composition, not risk among all infected pregnancies, an attributable risk or a high-income-country-wide prognosis. Case frameworks are not harmonized using unavailable individual data.

Additional outcome(s) Preterm birth requires a compatible definition below 37 completed weeks. Low birthweight requires less than 2500 g; small-for-gestational-age and categories including 2500 g are not substituted. Neonatal death requires death on days 0-27 after live birth with a corresponding liveborn denominator. Manifestations require an explicit observation window and assessment denominator. No compatible multi-source set supported pooling these outcomes in the retained roster. Missing values are not zero events. Prevention-cascade nodes retain their own analysis units and denominators; case-classification comparisons remain framework crosswalks, not diagnostic-accuracy analyses.

Data management Stable report identifiers, source locations, event counts, denominators, case definitions, clinical periods and verification status are preserved in structured records. Raw inputs are retained separately from processed data, executable code and generated outputs. Jurisdiction-by-year and data-source-by-year grids identify overlap. One contribution per source cohort is used; annual rows and companion reports are not independent studies. The record documents AI-assisted decisions adopted by the lead author, but does not establish independent dual-human screening or extraction throughout. AI assistance is not counted as a human reviewer. Original appraisal entries, author decisions, analysis locks and change logs are retained. Final human verification and author responsibility remain required.

Quality assessment / Risk of bias analysis The appraisal register contains outcome-specific JBI assessments and a conditional ROBINS-E pathway. For the descriptive stillbirth fractions, use of the JBI prevalence checklist is proposed for targeted author adjudication; the underlying studies remain retrospective surveillance analyses. This is not an appraisal of Alberta's maternal risk-factor regression. At the current analysis lock, both pooled sources retain Seek further information. Their continued exploratory use does not convert them to low risk of bias. Unadopted tool and item-level proposals remain distinct from original human

entries. Independent duplicate full-text appraisal and a completed GRADE assessment are not claimed. Formal tool selection and final targeted judgments must be confirmed before any corresponding status is changed.

Strategy of data synthesis The analysis has already been executed and is retrospectively documented. Source-specific proportions use exact Clopper-Pearson confidence intervals. The principal post hoc exploratory random-effects synthesis uses the Freeman-Tukey double-arcsine transformation, restricted maximum likelihood and modified Knapp-Hartung inference, with the residual variance multiplier floored at one and Student t quantiles with k-1 degrees of freedom. Miller inversion uses harmonic mean source size; out-of-range transformed limits are bounded to the probability domain and flagged. Only two geographically distinct Canadian sources contribute. Annual rows, companion reports and alternate classifications are not treated as independent evidence. Multiple births and repeated maternal episodes cannot be explicitly modeled using the available aggregate data. Other outcomes remain unpooled where population, definition, denominator or permitted-use compatibility is not established. All numerical outputs are generated by executable Python analysis with archived software versions and an analysis lock. No imputation, continuity correction, adjusted-effect pooling, prediction interval, meta-regression or funnel-asymmetry test was performed.

Subgroup analysis No formal subgroup hypothesis tests or meta-regression were performed because only two sources contribute to the selected synthesis. Narrative comparisons do not establish subgroup effects. The Winnipeg 2020-only restriction is a post hoc sensitivity analysis, not an independent subgroup meta-analysis.

Sensitivity analysis Completed post hoc checks compare Freeman-Tukey normal versus modified Knapp-Hartung intervals, a binomial-normal generalized linear mixed model with normal and t intervals, and a logit REML/modified Knapp-Hartung model. Freeman-Tukey inversion is checked using minimum, harmonic, arithmetic and maximum source sizes. Analyst-selected variance-inflation scenarios use Alberta multipliers of 1.25, 1.5 and 2, and double both sources' variances; these are stress tests, not estimated design effects. Source-exclusion checks leave no meta-analysis when fewer than two sources remain. A Winnipeg 2020-only sensitivity, with Alberta unchanged, examines the impact of avoiding possible early-2019 under-ascertainment. It does not establish complete ascertainment in 2020. The overlapping baseline and restricted datasets are not independent evidence. These choices followed inspection of source findings and/or earlier models and are not prospectively prespecified.

Language restriction The submitted queries contain no language restriction; a complete record of native interface language-filter settings and screening-level language eligibility remains unverified.

Country(ies) involved Taiwan.

Other relevant information Retrospective registration is being prepared after screening, extraction and exploratory analysis. The authors began the review before they had time to complete registration. Screening, data extraction and exploratory analyses were undertaken before registration. The present record must not be described as a prospectively registered protocol. The availability restriction, selected Canadian case-composition estimand, modified Knapp-Hartung emphasis and Winnipeg 2020-only sensitivity are post hoc decisions. Original locked analyses and decisions will remain identifiable. Some formal appraisals, historical eligibility evidence and author verifications remain unresolved; registration does not close those gaps. AI-assisted candidate processing, extraction proposals, code generation, consistency checking and drafting are disclosed, without treating AI as an independent human reviewer. This draft has not been submitted, assigned a registration number or paid for.

Author-affiliation mapping (in author order): Miao-Chiu Hung, affiliations 1 and 2; Hsihsien Wei, affiliations 3 and 4. The four numbered affiliations are listed in the organisational affiliation field. Corresponding author: Hsihsien Wei (alira123@gmail.com). The lead author identified Miao-Chiu Hung as the second human reviewer and confirmed the contribution allocation reported for both authors. This does not establish independent duplicate full-text review throughout the review; the procedures and verification limitations remain as described. Final approval of the submission version by all authors remains to be confirmed.

Keywords ongenital syphilis; stillbirth; perinatal outcomes; high-income settings; evidence synthesis; meta-analysis.

Dissemination plans The findings are intended for a peer-reviewed manuscript submitted to Life. Registration timing, availability restrictions, post hoc analyses and remaining evidence limitations will be disclosed. A verified registration number and date will be added only after INPLASY registration is confirmed. The final public route for the reproducibility materials requires author confirmation.

Contributions of each author

Author 1 - Miao-Chiu Hung - Methodology; investigation; writing – review and editing.
Author 2 - Hsihsien Wei - Conceptualization; methodology; formal analysis; investigation; writing – original draft; writing – review and editing; visualization; supervision.
Email: alira123@gmail.com