

INPLASY

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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.

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

Hung, MC; Wei, HH.

ADMINISTRATIVE INFORMATION

Support - This research received no external funding.

Review Stage at time of this submission - Retrospective. Reported analyses have been executed. Manuscript revision, review-wide eligibility assessment and appraisal remain ongoing. This amendment documents completed post hoc extensions and does not indicate a new prospective review.

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 10 September 2026.

INTRODUCTION

Review question / Objective To characterize clinical and perinatal outcomes of congenital syphilis in high-income settings using reports with data from 2015 onward, and assess outcome-specific feasibility for exploratory meta-analysis. The availability-restricted evidence review retains the original Canadian stillbirth composition estimand and adds a broader stillbirth sensitivity and restricted preterm-birth and low-birthweight models. The resulting quantities are source-specific descriptive proportions, not representative high-income-country risks.

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 Main-review contributions require outcome data from 1 January 2015 onward, or separately extractable data from that period, in the specified high-income settings, with interpretable outcome definitions and denominators. Publication year alone does not establish clinical-period eligibility. Mixed-era, phenotype-selected and contextual reports retain restricted narrative roles. The original availability-restricted release contained a 648-record layer without completed full-text eligibility assessment and a separate 20-record awaiting-information layer. Those statuses are not eligibility exclusions. On 8 September, 105 matching original texts were identified within the 648 records: 69 existing public originals, 22 newly obtained public originals and 14 prior local originals. The remaining 543 records lacked verified matching original texts. This recovery neither changed the publication window nor added a database-search yield. It did not demonstrate completed independent duplicate-human assessment of the 105 records. Subsequent source verification covered the four reports contributing to the analytical extension.

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. The exact submitted queries and documented interface-setting limitations are unchanged. Elicit supported record processing and full-text access. The 8 September targeted public/local recovery occurred within the original 648-record layer and publication window; it was not a new database or comprehensive gray-literature search. No completed searches of Embase, CENTRAL, CINAHL or WHO Global Index Medicus are added to the account.

Main outcome(s) The retained Canadian stillbirth composition estimand (S1) is the proportion stillborn after 20 weeks among source-classified congenital syphilis case records, including liveborn and stillborn records. Alberta contributes 2017-2020 (27/117), and Winnipeg contributes 2019-2020 (12/52). The Winnipeg 2020-only sensitivity replaces its baseline contribution with

8/30 while retaining Alberta. The estimand is source-specific case composition, not risk among all infected pregnancies or a representative high-income-country prognosis. Possible early-2019 under-ascertainment and source classification differences remain limitations.

Additional outcome(s) S2 broader stillbirth sensitivity. US surveillance from the 50 states and District of Columbia, 2016-2022 (848/13,344), is added to Alberta and Winnipeg. US stillbirth uses at least 20 weeks or birthweight above 500 g and requires known vital status and gestational age. This three-source analysis is a nonharmonized sensitivity; case frameworks are not made equivalent using unavailable individual data.

P1 preterm birth. Birth before 37 completed weeks is evaluated among source-classified clinical/laboratory congenital syphilis liveborn cases with known gestational age. Contributions are SET-NET in six states, 2018-2021 (confirmed/highly probable scenario; 81/179), and New Zealand births in 2017-2020 (confirmed/probable cases; 7/11). The full syphilis-exposed cohort is not substituted for the selected SET-NET population.

L1 low birthweight. Birthweight below 2500 g is evaluated among corresponding source-classified liveborn cases with recorded birthweight: New Zealand births in 2017-2020 (3/11) and Budapest, 2015-2025 (2/7). Missing birthweights are omitted from the evaluable denominator without imputation. Small-for-gestational-age classifications and categories including 2500 g are not substitutes for this endpoint.

Other outcomes. Neonatal death requires death during days 0-27 after live birth and a corresponding liveborn denominator. Manifestations require a defined observation window and assessment denominator. No pooled neonatal-death or manifestation model is claimed. Prevention-cascade units and classification-framework comparisons retain narrative roles.

Data management Stable report identifiers, source locations, source classifications, clinical periods, counts, denominators and missingness are retained. Historical screening candidate entries, dated author adoption, original inputs, processed data and executable code remain distinguishable. A complete subsequent independent two-author rescreen of all 3213 citations is not documented in the evidence reported here. Retrieval of a text does not establish eligibility. Prior scoped approvals are retained; later AI-assisted source checks and appraisal proposals

are distinguished from subsequent author adoption. No missing outcome is recoded as an absent event.

Quality assessment / Risk of bias analysis The JBI prevalence checklist is applied to descriptive outcome fractions without reclassifying surveillance or claims studies as clinical cohorts. Prior adopted appraisals cover Alberta and Winnipeg stillbirths, US 2018 stillbirths, Arizona stillbirths and deaths after live birth, and Korean jaundice claims. They apply only to the specified results. The Canadian sources are retained for their specified exploratory role with item-level limitations; their historical at-lock Seek further information statuses remain in the original record and historical source-exclusion scenario, rather than being presented as the current adopted disposition. On 9 September 2026, both authors adopted the nine-item judgments and source-specific rationales for the five added report-outcome contributions after source checks. Earlier adoption dates are not retrospectively reassigned to 9 September. AI-assisted proposals and subsequent author adoption are separately documented. Candidate layers labelled Reviewer 1 or Reviewer 2 and their Agreement or Consensus fields do not establish independent human inter-reviewer agreement. No, Unclear and Yes judgments are retained without a score-derived low-risk category. Review-wide appraisal remains incomplete; no formal certainty grading or missing-results bias assessment was completed.

Strategy of data synthesis Source-specific proportions use two-sided exact Clopper-Pearson 95% confidence intervals. Exploratory random-effects models use the half-scaled Freeman-Tukey double-arcsine transformation with variance $1/(4n + 2)$, restricted maximum likelihood, and modified Knapp-Hartung inference. The residual variance multiplier is floored at one, and intervals use Student t quantiles with $k - 1$ degrees of freedom. Miller inversion uses the harmonic mean denominator, mapping transformed limits beyond the feasible domain to probability boundaries. S1 and its Winnipeg replacement sensitivity each use two Canadian sources; S2 uses three sources; P1 and L1 each use two sources. One contribution per source cohort is included within each model. Annual rows, companion reports and alternative classifications are not independent studies. US national surveillance and SET-NET may overlap across models, and New Zealand contributes to two outcomes; no cross-model total of unique infants is calculated. Aggregate data do not permit explicit modeling of multiple births or repeated maternal episodes. All numerical outputs are

generated by executable code with retained input and code provenance. These analyses and the emphasis on modified Knapp-Hartung inference are post hoc.

Subgroup analysis The existing methodological sensitivities are retained: uncorrected logit-REML/modified Knapp-Hartung, binomial-normal GLMMs with normal and t-based intervals, and alternative Miller inverse sizes using minimum, harmonic mean, arithmetic mean and maximum denominators. GLMM t-based intervals are sensitivity approximations, not modified Knapp-Hartung intervals; the inverse-logit random-intercept estimate is not a marginal population risk. These approaches are applied to the expanded models. Leave-one-source-out analyses are added for S2. The original Canadian variance-inflation stress tests and Winnipeg 2020-only replacement sensitivity remain identifiable. Removing one source from a two-source model leaves a single-source estimate. No formal subgroup tests, meta-regression, prediction interval, funnel-asymmetry test, adjusted-effect pooling, continuity correction or imputation is claimed.

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 The review was registered retrospectively as INPLASY202690031

on 7 September 2026. The initial availability restriction, Canadian case-composition estimand, modified Knapp-Hartung emphasis and Winnipeg sensitivity were post hoc. The 8-9 September extensions followed inspection of source findings and earlier results; they do not become prospective specifications through this amendment. The original registered PDF, candidate layers, code, analysis locks and dated author decisions remain identifiable. Elicit supported record processing and full-text access. AI tools also supported candidate assessment, source checks, extraction and appraisal proposals, code generation and execution, figures, numerical checks and drafting; Claude provided adversarial discussion. Elicit, ChatGPT, Claude and OpenAI Codex are identified in the manuscript. The original manuscript reported the Claude interface label Fable 5.1 Extra; historical model versions were not uniformly recoverable. AI is not counted as a human reviewer or author. Authors retain responsibility for verification, interpretation and final content. Their retrospective report of personal review does not establish a complete new independent two-author rescreen of all 3213 citations or independently developed replacement code. On 10 September, both authors adopted four historical source-setting checks; these scoped decisions do not establish contemporaneous duplicate review. Registration does not close unresolved eligibility, appraisal or historical-record gaps.

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 Congenital syphilis; stillbirth; preterm birth; low birthweight; high-income settings; evidence synthesis; exploratory meta-analysis; retrospective registration.

Dissemination plans The findings are intended for submission to Life with the manuscript, Supplementary File S1 and accompanying data and code materials. Registration timing, availability restrictions, post hoc changes and remaining

limitations will be disclosed. The original registration number and DOI are retained. The official amendment date will be cited after publication is confirmed; an amendment-submission date will be reported only when supported by a receipt.

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

Amendments field

Registration and purpose. This amendment concerns INPLASY202690031, registered retrospectively on 7 September 2026 (doi:10.37766/inplasy2026.9.0031). It records administrative corrections, clarifies the provenance of assessments, and documents post-registration, post hoc extensions of the same review. Screening, extraction and the original Canadian stillbirth analysis preceded registration. The original registered version and its historical analytical scope remain identifiable.

Administrative correction. The published first version retained pre-submission wording stating that registration was being prepared, that the draft had not been submitted or assigned a number, and that registration details would be added after confirmation. These statements conflict with its published registration metadata and are corrected. The old payment and pending-author-approval wording is not used to infer a payment date or a date of approval of the original submission. The keyword is corrected from ongenital syphilis to congenital syphilis.

Recovery and analytical extension. On 8 September 2026, targeted recovery within the original 648-record unassessed layer identified 105 matching original texts. This did not constitute a new database search or a complete duplicate-human eligibility assessment. Four additional reports supported expanded analyses: US national surveillance, SET-NET, New Zealand and Budapest. Quantitative use of the first three was approved on 8 September; Budapest low birthweight was added on 9 September after an earlier decision against low-birthweight

pooling. The rationale was outcome-specific synthesis of interpretable source counts using restricted evaluable denominators.

Added models. The expanded analyses comprise a broader, nonharmonized stillbirth sensitivity (S2; US surveillance plus the two Canadian sources), preterm birth (P1; SET-NET and New Zealand), and low birthweight (L1; New Zealand and Budapest). Specifications and counts were frozen before the respective new pooled outputs, after source findings and earlier analyses were known. The original Canadian stillbirth estimand (S1) and the Winnipeg 2020-only replacement sensitivity remain unchanged. The added models are exploratory post hoc analyses.

Appraisal and provenance. Prior adopted appraisals cover the two Canadian stillbirth results and four restricted, unpooled results. Separately, on 9 September 2026 both authors adopted all five added report-outcome JBI appraisals after source checks. This amendment does not assign that date to every prior appraisal. AI-assisted candidate judgments, later author decisions and historical workflow fields remain separately identified. Author adoption does not establish blinded de novo assessment, complete independent duplicate screening, or a review-wide low-risk designation. No formal GRADE assessment is claimed.