Global & Regional Estimates of Preterm and/or Low Birthweight Infants attributable to Gestational Syphilis, 2015 & 2020

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Abstract

Global & Regional Estimates of Preterm and/or Low Birthweight Outcomes attributable to Gestational Syphilis, 2015 & 2020

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Introduction: Premature birth and low birthweight are adverse outcomes of gestational syphilis. Preterm or low birthweight infants often experience health issues such as respiratory infections, diarrheal diseases, encephalopathy due to birth asphyxia, hemolytic disease, and other neonatal disorders. In addition to these immediate human consequences, their management also translates to financial distress on both the family and healthcare system. It is necessary for estimates of preterm and low birthweight infants to be included in conversations about the burden of syphilis during pregnancy. This analysis focuses on estimating the number of preterm and/or low birthweight infants attributable to gestational syphilis on a global and regional level. It also compares estimates generated within this study to those estimated in a previous study.

Methods: Data from a systematic review including studies on preterm/low birthweight infants exposed to gestational syphilis were reviewed for inclusion. Measurements of the rate of preterm/low birthweight among women with syphilis during pregnancy and among women without syphilis during pregnancy were extracted. An excess rate and relative risk approach were used to estimate the outcome. Meta-analyses were conducted with covariates on maternal treatment status. Results of the excess rate and relative risk meta-analyses were applied separately to estimate the number of preterm/low birthweight infants attributable to syphilis during pregnancy by each approach.

Results: The excess rate approach estimated 503,799 (95% UI 496,787 – 510,810) preterm/low birthweight infants attributable to syphilis globally in 2020. The relative risk approach estimated 116,124 (95% UI 109,107 – 123,140) preterm/low birthweight infants attributable to syphilis globally in 2020. For both approaches, estimates of the outcome were highest in the African region and lowest in the European & Eastern Mediterranean regions. Comparing the results of this analysis and previous estimates of preterm/low birthweight attributable to syphilis, estimates from each approach used in this analysis exceed previous estimates of the outcome on a global and regional level.

Discussion: Considering the excess rate and relative risk approaches, the relative risk approach is the more rigorous, and thus preferred estimation methodology, as it requires an additional indicator to estimate the outcome. Further investigation is needed to assess other aspects of each methodology that contribute to differences in final values. Between the excess rate approach used for this study and the excess rate approach used in a previous study, differences in the treatment-specific excess rate values utilized for each lend themselves to differences in final values. Disparity in the excess rate values between untreated women are due to a disparate number of data sources between each study, and between partially or fully treated women, variation in the analysis techniques. Alignment of data sources and innovation in data processing are a vital starting point for aligning estimates at a regional and global level across research groups. Comprehensive treatment of pregnant women with syphilis is beneficial for the reduction of preterm and/or low birthweight infants,and must be preceded by early screening of syphilis during antenatal visits.

Study Motivation & Objective

This study is an estimation & comparative analysis of the number of premature and/or low birthweight infants attributable to syphilis during pregnancy. Currently, global and regional projections of adverse pregnancy outcomes (APOs) due to gestational syphilis are estimated as part of the Global Burden of Disease (GBD) study[1] and in a study published by Korenromp et. al in 2019[2]. It's highly useful to compare estimates across research groups to encourage discussion around the data sources, modeling tools, and methodological choices that have led to final values - however, a comprehensive comparison of APOs attributable to syphilis has not yet occurred. In part, this is because Korenromp et. al has estimated the burden of stillbirth, neonatal death, congenital syphilis, and preterm/low birthweight outcomes attributable to syphilis[2], while GBD estimates have been created for each listed APO attributable to gestational syphilis[1] except for preterm/low birthweight outcomes.

This study was motivated by the opportunity to estimate the number of preterm/low birthweight infants attributable to syphilis using resources from the GBD project, and thus contribute towards a comprehensive comparison of adverse pregnancy outcomes due to gestational syphilis across research groups. To assess the robustness of final values[3], GBD resources will be leveraged in two different approaches to estimate the same outcome. It is the hope that this project will encourage a discussion of the methodological choices and data sources that have led to alignment or disparity between final estimates & communication about the next best steps.

The following activities were conducted for this study:

1. Utilized an excess rate approach in conjunction with GBD resources to estimate the number of preterm/low birthweight infants attributable to gestational syphilis at a global and regional level.
2. Utilized a relative risk approach in conjunction with GBD resources to estimate the number of preterm/low birthweight infants attributable to gestational syphilis at a global and regional level.
3. Compared estimates of the outcome enumerated with the GBD excess rate approach, GBD relative risk approach, and Korenromp study. Compared aggregated estimates of GBD APOs attributable to syphilis with estimates of APOs attributable to syphilis published by Korenromp et. al[2].

[1] (GBD Disease & Injuries Collaborators, 2020)
[2] (Korenromp, 2019)
[3] (Thabane, 2013)

Background & Significance

Syphilis is a sexually transmitted infection (STI) caused by the bacteria *Treponema Pallidum*. In adults, syphilis primarily exhibits as small sores at the site of infection, followed by the second stage of disease which is characterized by a widespread rash, sores, or systemic signs and symptoms of infectious disease. If untreated, the infection progresses to a stage of latency that can last for many years. Finally, the tertiary stage arises and is characterized by complications to major organ systems and eventually death[4].

Cases of syphilis during pregnancy have the heightened burden of potentially resulting in an adverse pregnancy outcome[5]. These outcomes include stillbirth or miscarriage, premature birth, low birthweight, neonatal death, and mother-to-child transmission (MTCT) of syphilis[6].

Preterm birth is defined as an infant born before 37 weeks of gestation[7]. Infants born prematurely may experience health issues such as respiratory distress, sensory problems, difficulty feeding, diarrheal diseases, encephalopathy due to birth asphyxia, hemolytic disease, and other neonatal disorders[7]. Infants born prematurely may also be born at a lower birth weight, although low birth weight can occur independently of preterm birth[8]. Low birthweight is used to describe infants who weigh less than 2500 grams at birth. Infants that are low birth weight also experience complications, some of which align with those of infants born prematurely, and others distinct, such as struggling to maintain body temperature independently[8]. Beyond the impact on the infant, families experience significant emotional distress and financial burden, not to mention the impact to the health insurance system[9]. As health issues persist, premature or low birthweight infants must often spend the period immediately following birth in a Neonatal Intensive Care Unit, which can be highly expensive[8].

For these reasons, it is vital for estimates of preterm/low birthweight infants attributable to syphilis to be available when discussing the burden of syphilis during pregnancy on populations. This study will contribute up-to-date estimates of the outcome to the discussion. Other estimates of preterm/low birthweight infants attributable to syphilis currently exist as a component of a study by Korenromp et al, in which an excess rate approach similar to the one used in this analysis was employed[2]. Use of the same approach across studies – albeit with different excess rate values – make a numerical comparison of the treatment-specific excess rates from each study possible, in addition to the comparison between the relative risk and excess rate approach used to estimate the outcome for this analysis.

[4] (Mayo Clinic Staff, 2019)
[5] (J.M. de Souza, 2019)
[6] (Stoltey, 2015)
[7] (GBD Risk Factor Collaborators, 2020)
[8] (CHOP, 2021)
[9] (Hodek, 2011)

Methods

This analysis consisted of two main steps. The first step was to utilize the available data to estimate the excess rate and relative risk of preterm/low birthweight infants by maternal treatment status. To be fully treated, individuals with primary, secondary or early latent syphilis infection require one dose of penicillin, and individuals with late latent or tertiary syphilis infection require three doses of penicillin[11]. Estimation of the excess rate & relative risk of the outcome were made specific to maternal treatment status to quantify the notion that the occurrence of an adverse pregnancy outcome decreases with treatment of syphilis[12]. The second step was to apply results of the meta-analyses to estimate the number of preterm/low birthweight infants attributable to syphilis for each approach.

DATA SUMMARY

Sources

Data on numerous aspects of congenital syphilis (CS) and gestational syphilis (GS) were previously collected in a systematic review conducted in the Global Burden of Disease (GBD) 2019 study. This review was aimed at identifying studies that reported birth outcomes among [syphilis] seropositive pregnant women. During full-text screening and extraction for this systematic review, each study was tagged to one or multiple categories describing which aspect of gestational or congenital syphilis the data within the study described. There are seven categories, comprised of the prevalence of gestational syphilis, stillbirth, miscarriage, preterm birth, low birthweight, the transmission of congenital syphilis, and the sequela of congenital syphilis[1]. For this study, previously collected studies containing data about preterm/low birthweight infants were reviewed against the eligibility criteria for this project and re-extracted where necessary. Each study was checked for the outcome(s) of interest, the population(s) that the outcome was reported in, the presence of information on maternal treatment status, and other metadata.

Eligibility Criteria

For inclusion, studies must report the rate of preterm/low birthweight outcomes among a cohort of pregnant women positive for syphilis. Studies were excluded if they reported the rate of preterm/low birthweight infants in a sample other than seropositive pregnant women, such as a population of symptomatic infants born to pregnant women with syphilis or livebirths to seropositive pregnancies. The latter was deemed to be an exclusion criterion because the overwhelmingly majority of studies were reported among seropositive pregnant women, and there were not enough studies reporting the rate of the outcome among a liveborn subset of seropositive pregnancies for input to a meta-analysis of the excess rate or relative risk of preterm/low birthweight infants. Lastly, studies were excluded if the rate of preterm/low

[11] (CDC STDs, 2021)
[12] (Blencowe, 2011)

birthweight infants was estimated rather than collected as raw data. Forty studies were reviewed, with 22 included for analysis.

DATA PROCESSING

Alignment of Case Definition

Many studies used for this analysis report "preterm birth" and "low birthweight" infants separately. Other studies in this analysis report the two entities together as "preterm or low birthweight" infants. These studies do not report the number of infants that experience both outcomes versus the number that only experience each one. To avoid using a rate that double counts the infants that are born with both outcomes, data extracted from each study was adjusted to reflect the mutually exclusive rate of the outcome, in which the numerator is comprised of the infants that are only born preterm, the infants that are only born at a low birthweight, and the infants that are born preterm and at a low birthweight. The adjusted, mutually exclusive rate for each study reflects the number of infants that experience these outcomes, rather than the number of outcomes that are experienced. While there was enough data in the preterm birth category and in the low birthweight category to estimate each outcome separately, the two outcomes were combined in order to align more closely with the case definition utilized in previous estimates of preterm/low birthweight attributable to syphilis.

For each scenario in which data needed to be adjusted to the mutually exclusive rate of the outcome, the prevalence of infants born preterm only, low birth weight only, and both preterm and low birthweight among all pregnancies were leveraged to create ratios between the prevalence of each category. These ratios were utilized to adjust the rate of the outcome extracted from the studies to a mutually exclusive rate. The prevalence of each listed outcome in the general population of pregnancies comes from estimates of the prevalence of gestational age and weight at birth estimated within the GBD 2020 Study[1].

Processing for MR-BRT

After data from each study were adjusted to a mutually exclusive rate, the data points were processed for each methodological approach. To estimate the excess rate of the outcome in the exposed group, for each study, the rate of the outcome in the pregnancy cohort without syphilis was subtracted from the rate of the outcome in the pregnancy cohort with syphilis. To estimate the relative risk of the outcome in the exposed group, for each study, the rate of the outcome in the pregnancy cohort with syphilis was divided by the rate of the outcome in the pregnancy cohort without syphilis.

$$excess\ rate\ of\ PTLBW = ratePTLBW_{seropositive\ pregnancies} - ratePTLBW_{pregnancies\ without\ syphilis}$$

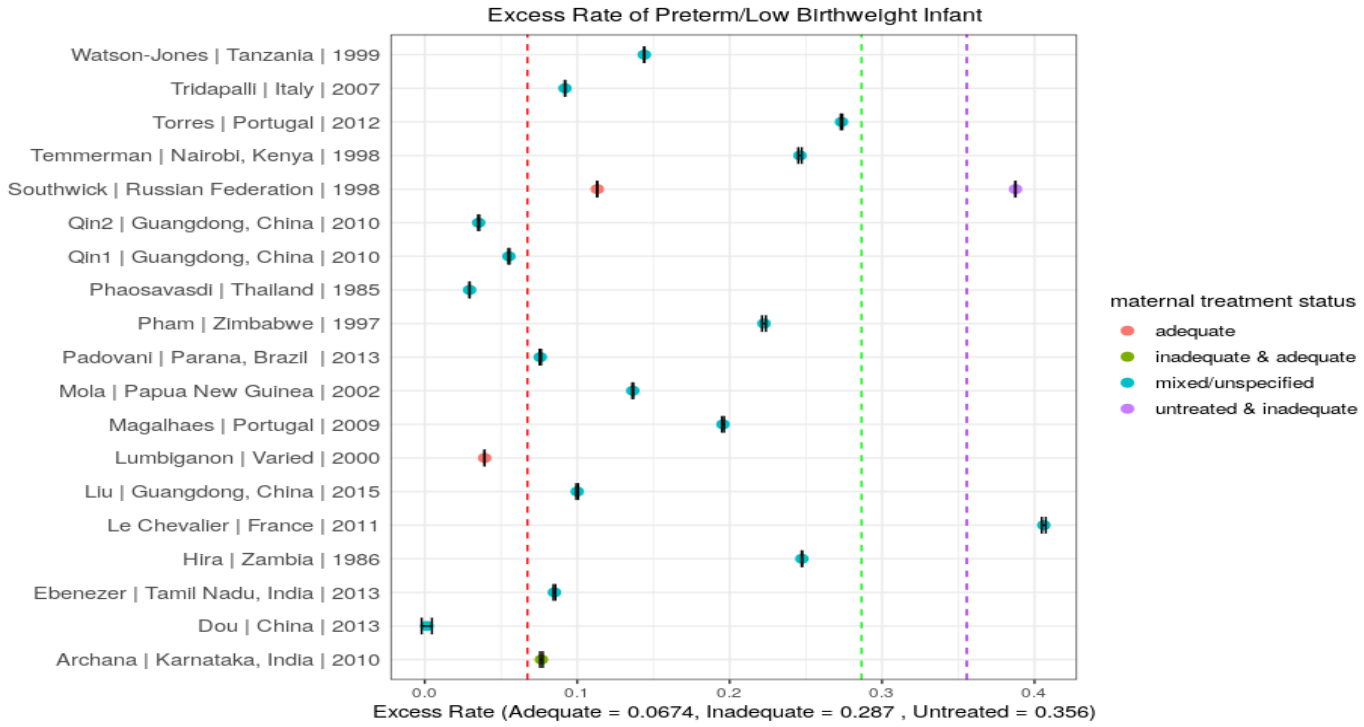
$$relative\ risk\ of\ PTLBW = \frac{ratePTLBW_{seropositive\ pregnancies}}{rate\ PTLBW_{pregnancies\ without\ syphilis}}$$

Many studies did not report the preterm/low birth weight rate among pregnant women without syphilis. For these studies, the mutually exclusive rate of preterm/low birthweight infants among all pregnancies in the location and year matching the study of interest was pulled from GBD estimates of gestational age and birthweight[1], and used as a proxy.

MODELING STRATEGY

Two meta-analyses were run; one for the excess rate approach and one for the relative risk approach. A mixed effects model was run for each approach, with fixed effects on treatment status of the mother and random effects on study type. Studies that did not specify the treatment status of the mothers were tagged as "mixed/unspecified" and leveraged to inform the coefficients on maternal treatment status. The excess rate datapoints were transformed into log-space for analysis. The relative risk datapoints were transformed into logit-space for analysis. Ten percent of outliers were trimmed from each model. These models were run using the Meta-Regression, Bayesian, Regularized, Trimmed (MR-BRT) tool, developed by researchers on the GBD study[13].

Figure 1: Excess rate of preterm/low birthweight infants among women with syphilis during pregnancy



[13] (Zheng et. al, 2020)

Table 1. Excess rate of preterm/low birthweight infants by maternal treatment status

Maternal Treatment Status	Excess Rate of Preterm/Low Birthweight Infants
Untreated	0.356 (0.084, 0.783)
Inadequate	0.287 (0.083, 0.638)
Adequate	0.067 (0.014, 0.252)

Figure 2: Relative risk of preterm/low birthweight infants among women with syphilis during pregnancy

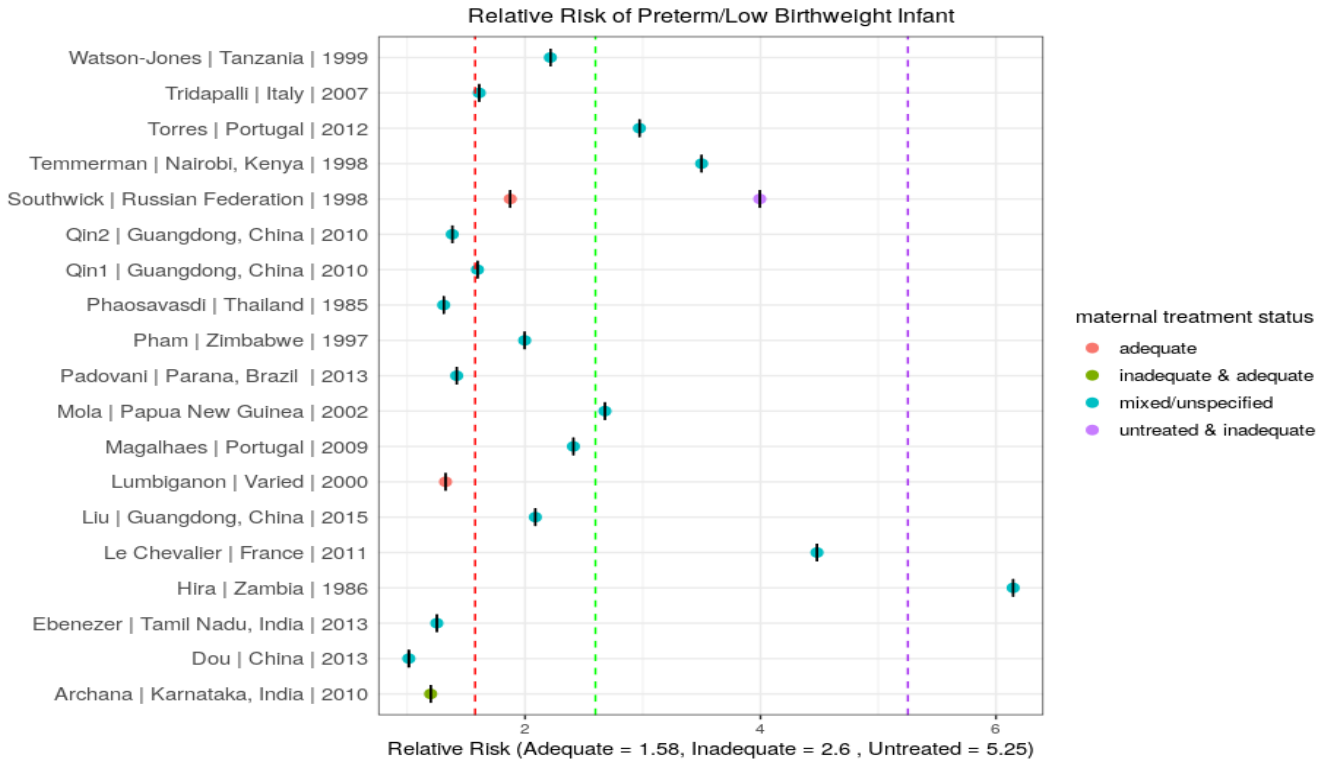


Table 2. Relative risk of preterm/low birthweight infants by maternal treatment status

Maternal Treatment Status	Relative Risk of Preterm/Low Birthweight Infants
Untreated	5.25 (2.31, 12.52)
Inadequate	2.59 (1.35, 5.09)
Adequate	1.58 (1.25, 2.03)

APPLICATION OF MRBRT RESULTS

Excess Rate

The excess rate of preterm/low birthweight infants among pregnancies with syphilis of each treatment status was multiplied by the number of pregnancies with syphilis of each treatment status, to estimate the number of preterm/low birthweight infants attributable to syphilis. The number of syphilis seropositive pregnancies by maternal treatment status was estimated as an intermediate output of the GBD 2020 estimation processes for mortality and morbidity due to congenital syphilis, and leveraged for this study[1]. Estimates of the preterm and/or low birth weight infants attributable to syphilis were estimated for every country in 2015 and in 2020, then aggregated up to regional and global levels.

$$\#PTLBW\ attr.to\ syphilis_{treatment,year,location} = excess\ rate_{treatment} * seropositive\ pregnancies_{treatment,year,location}$$

Relative Risk

The relative risk of preterm/low birthweight for pregnancies with syphilis of each treatment status were used in combination with estimates of the number of pregnancies with syphilis of each treatment status, to estimate the population attributable fraction (PAF) of the outcome for each treatment status. The PAFs were multiplied by all preterm/low birthweight infants to estimate the number of preterm/low birthweight infants attributable to syphilis. These estimates were produced for every country in 2015 and 2020, then aggregated up to a regional and global level. The number of all preterm/low birthweight infants come from GBD 2020 estimates of this outcome in the general population and were leveraged for this analysis.

$$Population\ Attributable\ Fraction = \frac{prev.seropositive\ pregnancy_{treatment,year,location} * (relative\ risk_{treatment} - 1)}{prev.seropositive\ pregnancy_{treatment,year,location} * (relative\ risk_{treatment} - 1) + 1}$$

$$\#PTLBW\ attr.to\ syphilis_{treatment,year,location} = PAF_{treatment,location} * \#PTLBW_{year,location}$$

Results

This study generated estimates for 2015 and 2020. Estimates for 2015 were generated only for comparison to Korenromp et. al estimates, which were generated for 2016. Estimates for 2020 were generated for a relevant & up-to-date estimation and comparison of each methodology carried out in this study.

Excess Rate vs. Relative Risk

Globally in 2020, this study estimated 503,799 (95% UI 496,787 – 510,810) preterm/low birth weight infants attributable to syphilis using the excess rate approach, and 116,124 (95% UI 109,107 – 123,140) preterm/low birth weight infants attributable to syphilis using the relative risk approach. Figures 3 & 4 present the geographic distributions of the number of preterm/low birth weight infants attributable to syphilis per 100,000 pregnancies in 2020, for each approach. Figure 5 presents a direct comparison of the rate of the attributable outcome estimated by the excess rate approach to the rate estimated by the relative risk approach for each country. Across countries, the excess rate estimates are consistently higher than the relative risk estimates. However, the geographic pattern of the estimates is similar across each approach, with the estimated outcome lowest in the European & Eastern Mediterranean regions, and highest using both approaches in the African Region.

Figure 3. Geographic distribution of preterm/low birthweight infants attributable to syphilis per 100,000 pregnancies, excess rate approach

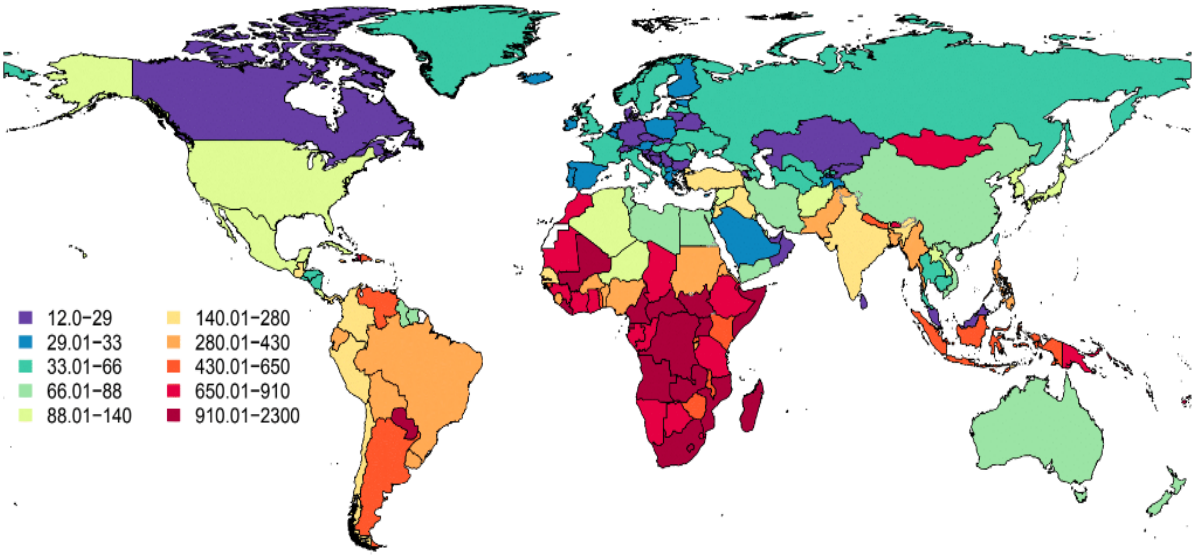


Figure 4. Geographic distribution of preterm/low birthweight infants attributable to syphilis per 100,000 pregnancies in 2020, relative risk approach

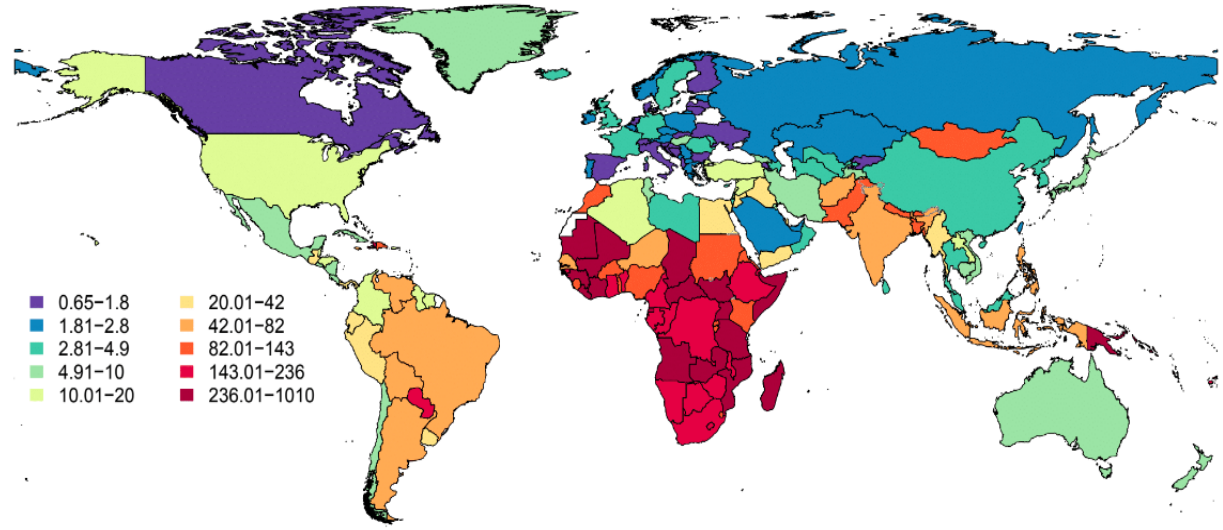
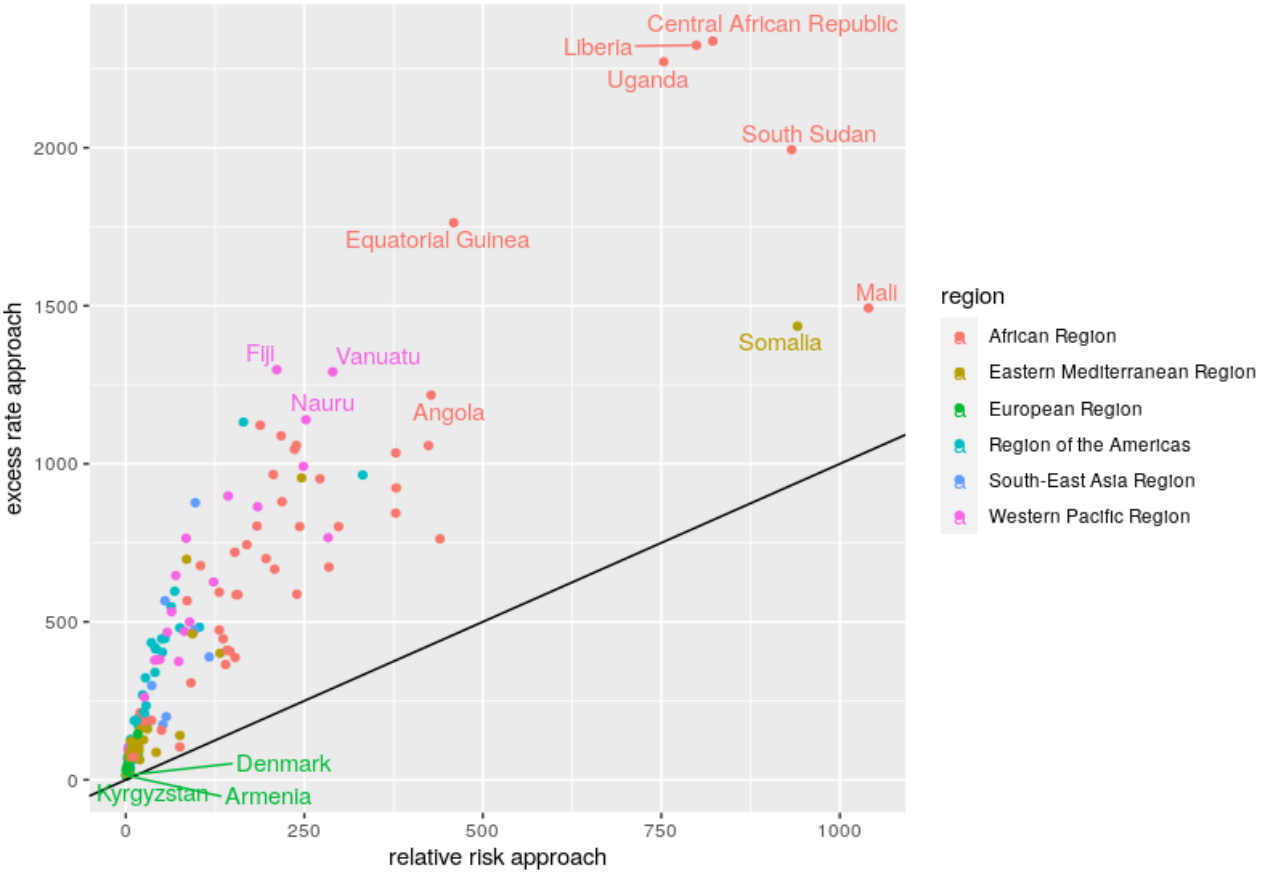


Figure 5. Excess rate versus relative risk comparison of preterm/low birthweight infants attributable to syphilis per 100,000 pregnancies in 2020



Thesis Estimates vs. Korenromp Estimates

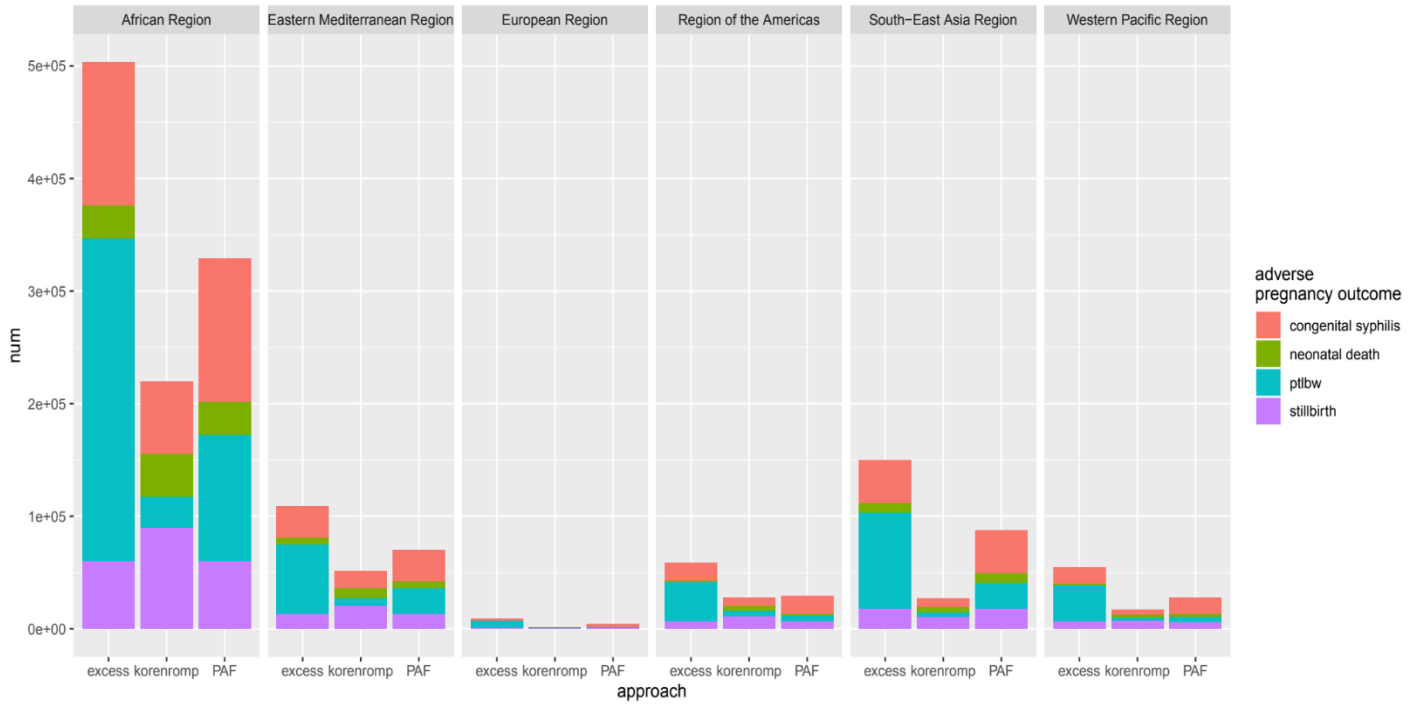
Values for the number of preterm/low birthweight infants attributable to syphilis at a regional and global level are shown in Table 3 for all approaches. Both approaches used in this study estimate higher values of the outcome in every geographic location as compared to the estimates from the Korenromp study.

Figure 6 compares all aggregated adverse pregnancy outcomes from Korenromp estimates and GBD estimates supplemented by numbers from this study. The excess rate and relative risk bars utilize the same values for stillbirth, neonatal death, and congenital syphilis, but utilize their respective values estimated within this thesis for the preterm/low birth weight portion. Korenromp estimates of APOs attributable to syphilis are lower than each of the estimates related to the GBD project, in every region of the world. However, the differences in aggregated APOs between the estimates garnered using GBD approaches and the estimates from the Korenromp study largely stem from the preterm/low birth weight estimates, while the other APOs estimated within the GBD enterprise have greater alignment to Korenromp estimates.

Table 3. Number of preterm/low birthweight infants attributable to syphilis across approaches

Location	**Excess Rate Approach (95% UI)**	**Relative Risk Approach (95% UI)**	**Korenromp et. al Study[2]**
African Region	286,020 (282,611 – 289,429)	111,420 (108,118 – 114,721)	27,318
Region of the Americas	34,535 (31,530 – 37,539)	5,116 (2,107 – 8,124)	4,284
Eastern Mediterranean Region	61,638 (59,346 – 63,929)	22,646 (20,331 – 24,960)	6,481
European Region	5,527 (1,769 – 9,285)	539 (359 - 718)	292
South-East Asia Region	84,851 (83,263 – 86,438)	22,240 (20,627 – 23,852)	3,458
Western Pacific Region	31,227 (28,312 – 34,141)	4,160 (1,481 – 6,838)	2,391
Global	503,799 (496,787 – 510,810)	116,124 (109,107 – 123,140)	44,225

Figure 6. Comparison of the number of adverse pregnancy outcomes attributable to syphilis by world region in 2015/2016



Discussion

This study introduces estimates of preterm/low birth weight attributable to syphilis into the Global Burden of Disease project and provides two different methods for estimating the outcome. It also incorporates a focus on the impact of treatment with penicillin on the occurrence of preterm/low birthweight outcomes by estimating at excess rates and relative risks by maternal treatment status. Lastly, it sets the stage for discussion between research groups on the best methodological choices and data inclusions for estimating the number of preterm/low birthweight infants attributable to syphilis during pregnancy.

Comparison of Approaches

Estimates from the Korenromp² study were created using an excess rate approach. For untreated pregnancies, in comparison to pregnancies without syphilis, a 5.8% more frequent occurrence of preterm or low birthweight outcomes was utilized in the estimation process. This excess rate came from a study published in 2013 by Gomez et. al[14]. The meta-analysis in the Gomez study included four studies on the excess rate of the outcome among women with untreated syphilis during pregnancy[14]. For treated pregnancies, in comparison to pregnancies without syphilis, a 2.1% more frequent occurrence of preterm or low birthweight outcomes was utilized in the estimation process. This value was based on expert opinion of the reduction of excess

[14] (Gomez, 2013)

preterm/low birthweight outcomes when women are treated for syphilis during pregnancy[2]. Considering the excess rate values utilized in this analysis (Table 1), all excess rates used for this study exceed those used for the Korenromp study. Moving forward, discussions between multiple research groups regarding data sharing, model fit & trimming, and other considerations will be important for determining closer alignment of excess rate values and thus, final estimates of the outcome.

Both the excess rate and relative risk approaches utilized in this study consider the number of pregnancies with syphilis in a given location and year when applying results of the meta-analysis. However, the relative risk approach is preferred because it requires that the rate of the outcome in the entire population is considered in conjunction with the risk factor - syphilis during pregnancy. The requirement of an additional indicator ensures that the relative risk approach is more rigorous than the excess rate, although the need for said additional indicator makes the relative risk estimation less accessible to groups without resources to procure such data. Beyond the indicator, future iterations of this study will need an in-depth investigation to assess the components of each methodology that lend themselves to undercounting, overcounting, or general differences in final counts between each approach.

Limitations & Future Directions

This study had a few limitations. First, the purpose of including covariates on maternal treatment status in the meta-analyses was to provide quantitative evidence that more comprehensive treatment reduces the occurrence of adverse pregnancy outcomes, specifically an outcome of preterm birth and/or low birth weight. While the meta-analyses estimated the excess rates and relative risks decreasing as the level of maternal treatment status increased, many of the data points from each study did not record treatment of the mothers and were tagged as "mixed/unspecified" in the analysis. These data points of unspecified status informed the final coefficient for each maternal treatment status, but led to wider confidence intervals on the coefficients. Still, the results of the meta-analyses conducted in this study imply that comprehensive treatment of syphilis in pregnant women is beneficial for the reduction of preterm and/or low birthweight infants, and must be preceded by early screening of syphilis during antenatal visits.

Second, most studies reviewed for this analysis reported the number of preterm/low birthweight infants born to syphilis seropositive pregnant women. Studies reporting the outcome(s) among a population of liveborn infants to seropositive pregnant women were excluded from analysis due to a lack of data about the outcome in this population. Thus, the studies included in this analysis represent the occurrence of the outcome among all seropositive pregnancies, including those that ended in stillbirth. Policymakers and health intervention programs may be most interested in the number of preterm/low birthweight infants estimated using data among a population of liveborn infants to mothers with syphilis, as this is more aligned to the creation of initiatives that prevent

the downstream outcomes of being born prematurely or at a low birth weight. Incorporating methods to estimate the outcome among populations of infants liveborn to women with syphilis during pregnancy is of utility to the field.

Third, this study employed the distribution of preterm and/or low birthweight infants in the general population to adjust data points to their mutually exclusive rates encompassing preterm, low birthweight, and infants experiencing both. This introduces a limitation because the distribution of preterm only, low birthweight only, and infants experiencing both outcomes may be different in the general population than it is in the population of infants exposed to gestational syphilis. Now considering the adjustment of data, on one hand, the estimates from this study reflect the number of infants whom experience preterm and/or low birthweight, rather than the number of outcomes experienced. However, infants that are born prematurely and/or at a low birthweight are also at risk for other APOs attributable to syphilis, such as neonatal death or vertical transmission of syphilis. This overlap is not currently accounted for in aggregated estimates of the adverse pregnancy outcomes attributable to syphilis. To report an aggregated value across all adverse pregnancy outcomes that reflects the number of infants experiencing any outcome, rather than the number of outcomes that are experienced, several indicators would be needed: the joint distribution of preterm/low birthweight and neonatal death, the joint distribution of preterm/low birthweight and congenital syphilis, and the joint distribution of congenital syphilis and neonatal death. These indicators would be helpful to avoid estimating a misrepresentative value that inflates the number of infants with an APO attributable to gestational syphilis.

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