



# Gestational syphilis and stillbirth in the Americas: a systematic review and meta-analysis

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## Suggested citation

Arnesen L, Serruya S, Durán P. Gestational syphilis and stillbirth in the Americas: a systematic review and meta-analysis. *Rev Panam Salud Publica*. 2015;37(6):422–9.

## ABSTRACT

**Objective.** To perform a systematic review and meta-analysis of reported estimates of the association between gestational syphilis (GS) and stillbirth in the Americas region.

**Methods.** Cochrane Library, Embase, LILACS, MEDLINE/PubMed, PLOS, and ScienceDirect were searched for original research studies quantifying the relationship between GS and stillbirth in the region. A final sample of eight studies was selected. A cumulative meta-analysis plus four subgroup meta-analyses of study data on the association between maternal syphilis during pregnancy and stillbirth were conducted. The four meta-analyses were based on 1) definition of cases and the control; 2) syphilis treatment (presence or absence, effective or ineffective); 3) definition of stillbirth as “showing no signs of life at birth”; and 4) definition of stillbirth based on low birth weight and gestational age. Random-effects meta-analyses were used to calculate pooled estimates of stillbirth with exposure to GS, and each subgroup analysis was tested for heterogeneity.

**Results.** Women with GS had increased odds of stillbirth (pooled odds ratio (OR): 6.87; 95% confidence interval: 2.93, 16.08). There was considerable heterogeneity across the eight studies (percentage of variance ( $I^2$ ) = 95). The funnel plot was not statistically significant, pointing to a lack of publication bias. Increased odds of stillbirth among pregnant women with syphilis were also seen in all four subgroup meta-analyses.

**Conclusions.** GS is a major contributing factor for stillbirths in the Americas. Interventions targeting GS are highly cost-effective and, along with high-quality point-of-care testing, should be implemented across the region to help reach the goal of eliminating congenital syphilis.

## Key words

Stillbirth; syphilis; Americas; Latin America; West Indies.

The World Health Organization (WHO) estimates that 1.36–2.0 million pregnancies are affected by syphilis each year, making congenital syphilis more common than perinatal HIV infection (1–4). Among pregnancies affected by syphilis, 50%–80% will result in adverse birth outcomes without proper treatment (1, 4–6). Prominent among these

outcomes is stillbirth, which occurs in 30%–40% of cases (4–6). Globally, syphilis is the main cause for more than 460 000 stillbirths annually (1, 2, 7). In areas of high syphilis prevalence as many as half of all stillbirths may be attributed to that infection (5, 8).

Globally, the Americas region has the highest incidence rate of syphilis and accounts for up to 25% of the 2 million annual cases of gestational syphilis (GS) (3, 9). Prevalence of GS in the Americas

(Canada, Latin America and the Caribbean, and the United States) varies by country from 0.0%–7.0% (1, 2, 9–11). Each year, an estimated 100 000+ stillbirths in the Americas are attributable to congenital syphilis, defined as an infant born to a mother who was untreated or inadequately treated for syphilis during pregnancy, or an infant with a positive syphilis test (3, 10, 12).

In 1995, the Pan American Health Organization (PAHO) approved the Re-

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gional Plan of Action for the Elimination of Congenital Syphilis, defining elimination as incidence of  $\leq 0.5$  cases of congenital syphilis, including stillbirths, per 1 000 births (13). In 2010, PAHO Member States approved a strategy and plan of action<sup>2</sup> that affirmed these elimination goals and set a target date of 2015 (3, 10, 15). Elimination is possible with proper treatment—a single dose of 2.4 million units of benzathine penicillin G (BPG), in most cases, which is almost 100% effective at preventing syphilis-associated adverse outcomes in pregnancy when given in a timely manner (1, 5, 7, 15, 16). Moreover, the cost-effectiveness of antenatal syphilis screening and treatment has been shown repeatedly (5, 6, 16). The World Bank and WHO both cite antenatal syphilis screening and treatment as one of the “most cost-effective interventions available” (1, 10).

While stillbirth and other adverse birth outcomes due to syphilis are preventable through cost-effective interventions, syphilis-attributable stillbirths are still occurring in the Americas. Past research in the region showed an increased risk of stillbirth with exposure to GS (17–24). Overall, research in the region has focused on GS prevalence, the persistence of inequalities in health outcomes related to GS, calls to action (to test and treat pregnant women), and small geographic areas within a given country, and has not included examination of GS and stillbirth at the regional level (17–25). To the best of the authors' knowledge, no previous meta-analysis has examined the relationship between GS and stillbirth in the Americas. The systematic review and meta-analyses reported here identified and analyzed reported estimates of the association between GS and stillbirth in the region.

## MATERIALS AND METHODS

A systematic review and five meta-analyses (one cumulative analysis and four subgroup analyses) were carried out in accordance with Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) requirements for systematic reviews and meta-analyses (26, 27).

<sup>2</sup> Strategy and Plan of Action for the Elimination of Mother-to-Child Transmission of HIV and Congenital Syphilis (14).

## Search strategy and inclusion criteria

Using text search strings, a search was conducted for studies that examined the association between GS and stillbirth for all years covered in the following databases up to 6 October 2013: Cochrane Library, Embase, LILACS, MEDLINE/PubMed, PLOS (all journals), and ScienceDirect (journals only). Publications found in the search were included in the analysis if they contained at least one term from each of the five categories (“syphilis,” “mother-to-child transmission,” “pregnancy,” “stillbirth,” and “Americas region”) shown in Table 1. Studies in English, French, Portuguese, and Spanish were considered. Reports published only as abstracts were excluded if all necessary data were not available in the abstract. Reference lists were then manually searched for other potential studies of relevance to the analysis.

The five meta-analyses covered original observational, case-control, cohort, or randomized trial studies conducted in the Americas that reported 1) counts of syphilis-positive pregnant women (all stages of infection), 2) counts of syphilis-negative pregnant women, and 3) the number of stillbirths associated with each group (Figure 1). Animal research, systematic reviews, and other meta-analyses were excluded. When studies reported outcomes from more than one year, the

most recent data were used. For overlapping studies, the most relevant analysis was considered. Because there is no international consensus on the definition of stillbirth, the criteria for use of this term vary in the literature (5, 8, 16, 17, 20). In this analysis, the definitions used by the authors of the original study were used as the classification criterion for two subgroup meta-analyses.

Two independent researchers extracted data on the number of stillbirths among mothers with GS, and among mothers without GS, and the totals in each group, from the eight studies selected for the final sample. The data were then discussed to rationalize any differences in extracted values, resulting in agreed-upon values presented in each study.

## Statistical analysis

The unadjusted odds ratio (OR) estimates and corresponding 95% confidence intervals (CIs) were calculated from the data extracted from each study. A cumulative meta-analysis was used to assess the overall relationship between GS and stillbirth. Random-effects models were used to estimate the pooled ORs and the respective 95% CIs. The  $I^2$  statistic was used to test for heterogeneity (percentage of variance) due to differences in the studies beyond random chance. Publication bias was addressed with visual inspection of a funnel plot.

**TABLE 1. Search terms used to identify reference pool of selected articles on stillbirth in syphilis-positive and syphilis-negative women ( $n = 8$ ), Americas region, 1945–2015**

Category	Search terms
Syphilis	<i>Syphilis, congenital syphilis, gestational syphilis, great pox, lues, chancre, treponemal infection, treponemal, maternal syphilis, T. palladium</i>
Mother-to-child transmission (MTCT)	<i>Mother to child transmitted infection, mother to child, MTCT, transplacental, vertical transmission, vertical perinatal transmission</i>
Pregnancy	<i>Pregnancy, pregnant women, women, pregnant, woman, pregnancies, gestation</i>
Stillbirth	<i>Stillbirth, stillborn, fetal death, mortality, death, perinatal mortality</i>
Americas region	<i>Latin America, America, Caribbean, Americas, US, USA, United States, United States of America, Anguilla, Antigua and Barbuda, Antigua &amp; Barbuda, Antigua, Barbuda, Netherlands Antilles, Argentina, Aruba, Bahamas, Barbados, Belize, Bermuda, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Dominica, Ecuador, El Salvador, Grenada, Guadeloupe, Guatemala, French Guiana, Guyana, Haiti, Honduras, Cayman Islands, Turks and Caicos Islands, Turks &amp; Caicos Islands, Turks, Caicos, British Virgin Islands, Virgin Islands, Jamaica, Martinique, Mexico, Montserrat, Nicaragua, Panama, Paraguay, Peru, Puerto Rico, Venezuela, Dominican Republic, Saint Kitts and Nevis, St. Kitts and Nevis, Saint Kitts &amp; Nevis, St. Kitts &amp; Nevis, Saint Kitts, St. Kitts, Nevis, St. Vincent and the Grenadines, Saint Vincent &amp; the Grenadines, Saint Vincent and the Grenadines, St. Vincent &amp; the Grenadines, St. Vincent, Saint Vincent, Grenadines, Saint Lucia, Surinam, Trinidad and Tobago, Trinidad &amp; Tobago, Trinidad, Tobago, Uruguay</i>

Four subgroup meta-analyses were carried out to examine potential sources of heterogeneity. Two of the analyses were based on whether treatment was a factor in dividing the study comparison groups. The first of those analyses included studies that compared untreated and/or ineffectively treated syphilis-positive mothers with those treated effectively for syphilis and/or syphilis-negative mothers. The second compared syphilis-positive mothers to syphilis-negative mothers. Two additional meta-analyses were carried out based on definitions of stillbirth. The first included studies that defined stillbirth as the fetus showing no signs of life at birth. The second included studies that defined stillbirth by lower bounds on birth weight and/or gestational age. The  $I^2$  statistic was used to test for heterogeneity in each subgroup after controlling for the respective identifying covariate. All pooled analyses were done in Review Manager (RevMan) version 5.2 (The Nor-

dic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

## RESULTS

A total of 1 021 potential references were identified for the study, of which 19 were eligible for review by two independent researchers (Figure 1). Eleven studies were excluded because they were based on modeled estimates, did not link gestational syphilis and stillbirth cases, analyzed the same study population as another included reference, lacked a non-syphilis comparison group, or did not indicate the number of stillbirths observed in the non-syphilis group. The eight studies remaining after the two independent researchers' reviews were included in the meta-analysis (17, 20, 24, 25, 28–31). Citations for excluded papers are available from the authors.

The studies that were included were conducted from 1945 to 2015 in the

Americas. The biggest proportion of selected studies were carried out in the United States, followed by Argentina and Bolivia. Studies varied in terms of focus (which included efficacy of syphilis treatment and the effect of syphilis on stillbirth) and by whether syphilis treatment was given to all mothers, some mothers, or no mothers. Table 2 shows the characteristics of the eight studies included in the analysis ( $n = 414\ 020$ ).

The selected studies used three different definitions of stillbirth: 1) fetus weighing  $\geq 500$  g (17) at  $> 20$  weeks gestation (28), 2) fetus showing no signs of life at full term (31), and 3) fetus showing no signs of life at delivery (24, 25). One study reported ranges for gestational age and birth weight (24–42 weeks and 400–3 950 g, respectively) (20). Two studies did not define stillbirth or present ranges for gestational age or birth weight (29, 30).

## Selected comparison groups

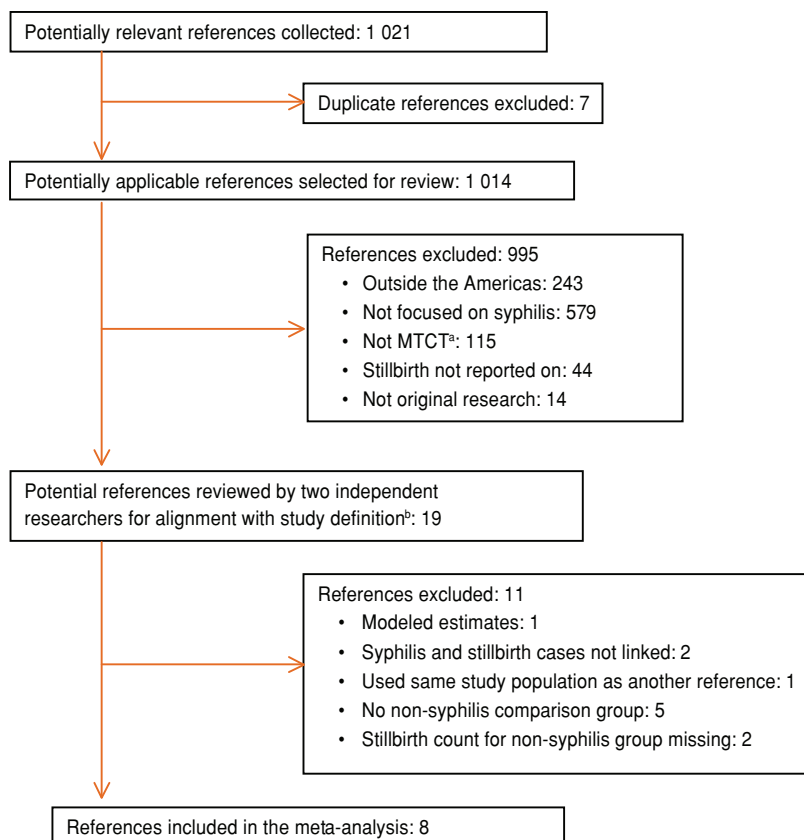
One subgroup meta-analysis examined treatment as a contributor to heterogeneity and included studies comparing untreated and ineffectively treated GS to successfully treated cases and those without syphilis (25, 29, 30). The subgroup had a pooled OR of 13.23 (95% CI: 0.99, 177.66). While still showing some heterogeneity ( $I^2 = 75\%$ ), the studies included in this subgroup were more homogeneous than the cumulative meta-analysis (Table 3).

Another subgroup meta-analysis investigated specific treatment but excluded treatment as a grouping factor, including only those studies comparing syphilis cases with non-syphilitic controls, divided without regard to treatment (17, 20, 24, 28, 31). The subgroup had a pooled OR of 6.21 (95% CI: 2.23, 17.34) and a heterogeneity similar to the cumulative meta-analysis, with  $I^2 = 97\%$  (Table 3).

## Selected definitions of stillbirth

Two meta-analyses were conducted based on the study's definition of stillbirth. One subgroup defined stillbirth as a fetus born without signs of life (24, 25) and had a pooled OR of 2.46 (95% CI: 1.36, 4.46). This subgroup was more homogeneous than those included in the first two meta-analyses, with an  $I^2 = 64\%$  (Table 3). The second subgroup included studies that defined stillbirth based on

**FIGURE 1. Flow chart of process and criteria used in literature review selection of eight studies on stillbirth in syphilis-positive and syphilis-negative women, Americas region, 1945–2015**



<sup>a</sup> Mother-to-child transmission.

<sup>b</sup> Studies were included if they fulfilled the following criteria: assessed syphilis as the main exposure; the outcome of interest was stillbirth, or stillbirth was included in the outcome (e.g., adverse birth outcomes); reported count of stillbirths for both syphilitic women and non-syphilitic women; conducted in the Americas.

**TABLE 2. Characteristics of eight studies included in a review and analysis to determine the odds of stillbirth in syphilis-positive and syphilis-negative women, Americas region, 1945–2015**

Lead author, date, and reference	Location	Study period	Sample size	Population	Comparison (exposure)	Mother treated before delivery	Treatment given	Comments
Alexander 1999 (30)	United States (Dallas, Texas)	1 Sep 1987–31 Aug 1989	340	Pregnant women with untreated syphilis	Gestational syphilis treatment failures versus successful treatment	Yes (all)	Penicillin	All serologic testing done at the same lab. Four of six treatment failures delivered within two weeks of treatment (possible Jarisch-Herxheimer reactions)
Arnesen 2015 (24)	Argentina, Bolivia, Colombia, Ecuador, El Salvador, Guyana, Haiti, Honduras, Nicaragua, Paraguay, Uruguay,	Jan 2009–Dec 2012	356 168	All live or stillborn deliveries	Gestational syphilis versus women without syphilis	Not reported	— <sup>a</sup>	No data on postpartum syphilis test
CDC <sup>b</sup> 1998 (29)	United States (Baltimore, Maryland)	1 Jan 1996–30 Mar 1997	90	Pregnant women with syphilis	Untreated gestational syphilis or ineffectively treated versus successful treatment	Yes (controls only)	Penicillin	Maternal demographics similar between cases and controls
Greenwood 1994 (17)	Jamaica	1 Sep 1986–31 Aug 1987	10 477	Singleton fetal deaths	Gestational syphilis versus women without syphilis	Not reported	—	Dates of study for cases and controls overlapped but were not equal periods of time (longer for cases)
Ingraham 1950 (31)	United States (Philadelphia, Pennsylvania)	1945–1949	10 625	Pregnant women	Women with early or late syphilis versus women without syphilis	No	—	Dates of study for cases and controls overlapped but were not all the same dates
Lumbiganon 2002 (25)	Argentina (Rosario), Cuba (Havana), Saudi Arabia (Jeddah), Thailand (Kohn Kaen Province)	Not stated	20 063	Pregnant women	Untreated gestational syphilis versus successful treatment or women without syphilis	Yes (controls only)	Decision made at the institutional level	Those negative for syphilis and those treated were in the control group. Adjusted for non-randomized nature of the syphilitic status variable
McFarlin 1994 (28)	United States (Detroit, Michigan)	Sep 1991–Oct 1992	8 128	Pregnant women with syphilis	Gestational syphilis versus women without syphilis	Some	Penicillin or erythromycin	Charts reviewed retrospectively, so not recorded by uniformly trained staff. Eight women desensitized to penicillin allergy
Southwick 2001 (20)	Bolivia (Cochabamba, El Alto, La Paz)	Jun–Nov 1996	1 513	All live or stillborn deliveries	Gestational syphilis versus women without syphilis	Some	Penicillin	Treatment frequently given at delivery or before discharge

<sup>a</sup> Not applicable.<sup>b</sup> U.S. Centers for Disease Control and Prevention.

lower bounds for birth weight (500 and 400 g) and/or gestational age (20 and 24 weeks) (17, 20, 28) and had a pooled OR of 4.94 (95% CI: 3.77, 6.48). Statistically, this was the most homogeneous subgroup in the analysis, with an  $I^2 = 14\%$  (Table 3).

### Cumulative estimates and heterogeneity

Cumulative analysis of the 414 020 births showed a statistically significant increase in the odds of stillbirth among mothers with syphilis during pregnancy

(pooled OR: 6.87; 95% CI: 2.93, 16.08; Table 4). The random-effects model was used for this analysis because the study populations had not been treated for syphilis homogeneously. There was considerable heterogeneity among the studies in the meta-analysis ( $I^2 = 95\%$ ). The funnel plot was not statistically significant, pointing to a lack of publication bias.

### DISCUSSION

The analysis shows a positive relationship between GS and stillbirth, as

other articles from the Americas have reported previously (3, 18, 19, 21–23, 32). Previous research around the world has also shown GS to be associated with a relative risk (RR) of 2–5 for stillbirth, with some studies showing a noticeably higher risk, such as research conducted in Tanzania that found syphilis-positive women had an RR of 18 for stillbirth (5, 33–35). Past studies have also reported an increased likelihood of stillbirth among syphilis-positive women; one study conducted in Mozambique reported an OR of 5.3 for stillbirth among syphilis-positive women, and a recent

**TABLE 3. Estimated odds of stillbirth in syphilis-positive and syphilis-negative women based on review and analysis of eight selected studies, by subgroup, Americas region, 1945–2015**

Lead author, date, and reference	Exposed to syphilis		Not exposed to syphilis		Weight (%)	Odds ratio	
	Events	Total	Events	Total		M-H, random <sup>a</sup> (95% CI) <sup>b</sup>	M-H, random, 95% CI
<b>Subgroup 1: No treatment and ineffective treatment for syphilis vs. effective treatment for syphilis and no syphilis</b>							
Alexander 1999 (30)	2	6	0	334	27.1	371.67 (15.52, 8898.43)	
CDC <sup>c</sup> 1998 (29)	4	62	0	28	28.6	4.38 (0.23, 84.26)	
Lumbiganon 2002 (25)	11	285	223	19 778	44.3	3.52 (1.90, 6.52)	
Total (95% CI)	— <sup>d</sup>	353	—	20 140	100.0	13.23 (0.99, 177.66)	
Total events	17	—	223	—	—	—	
Heterogeneity: Tau <sup>2</sup> = 3.86, Chi <sup>2</sup> = 7.98, df = 2 (P = 0.02); I <sup>2</sup> = 75% <sup>e</sup> Test for overall effect: Z <sup>f</sup> = 1.95 (P = 0.05)							
<b>Subgroup 2: Syphilis vs. no syphilis</b>							
Arnesen 2015 (24)	29	3 875	1 432	364 276	20.5	1.91 (1.32, 2.76)	
Greenwood 1994 (17)	100	524	458	9 953	20.8	4.89 (3.86, 6.20)	
Ingraham 1950 (31)	50	302	57	10 323	20.4	35.74 (23.96, 53.30)	
McFarlin 1994 (28)	10	253	90	7 929	19.3	3.58 (1.84, 6.97)	
Southwick 2001 (20)	11	72	—	1 399	19.0	7.70 (3.71, 16.01)	
Total (95% CI)	—	5 026	32	393 880	100.0	6.21 (2.23, 17.34)	
Total events	200	—	2 069	—	—	—	
Heterogeneity: Tau <sup>2</sup> = 1.30, Chi <sup>2</sup> = 122.95, df = 4 (P < 0.00001); I <sup>2</sup> = 97% Test for overall effect: Z = 3.49 (P = 0.0005)							
<b>Subgroup 3: Stillbirth defined as “no signs of life at delivery”</b>							
Arnesen 2015 (24)	29	3 875	1 432	364 276	58.4	1.91 (1.32, 2.76)	
Lumbiganon 2002 (25)	11	285	223	19 778	41.6	3.52 (1.90, 6.52)	
Total (95% CI)	—	4 160	—	384 054	100.0	2.46 (1.36, 4.46)	
Total events	40	—	1 655	—	—	—	
Heterogeneity: Tau <sup>2</sup> = 0.12, Chi <sup>2</sup> = 2.81, df = 1 (P = 0.09); I <sup>2</sup> = 64% Test for overall effect: Z = 2.98 (P = 0.003)							
<b>Subgroup 4: Stillbirth defined by lower bounds on birth weight and/or gestational age</b>							
Greenwood 1994 (17)	100	524	458	9 953	72.4	4.89 (3.86, 6.20)	
McFarlin 1994 (28)	10	253	90	7 929	15.0	3.58 (1.84, 6.97)	
Southwick 2001 (20)	11	72	32	1 399	12.6	7.70 (3.71, 16.01)	
Total (95% CI)	—	849	—	19 281	100.0	4.94 (3.77, 6.48)	
Total events	121	—	580	—	—	—	
Heterogeneity: Tau <sup>2</sup> = 0.01, Chi <sup>2</sup> = 2.32, df = 2 (P = 0.31); I <sup>2</sup> = 14% Test for overall effect: Z = 11.58 (P < 0.00001)							

<sup>a</sup> Random Mantel–Haenszel odds ratio.

<sup>b</sup> Confidence interval.

<sup>c</sup> U.S. Centers for Disease Control and Prevention.

<sup>d</sup> Not applicable.

<sup>e</sup> Tau<sup>2</sup>: tau-squared test statistic; Chi<sup>2</sup>: chi-squared test statistic; df: degrees of freedom; I<sup>2</sup>: % of variance.

<sup>f</sup> Z: z-test statistic.

meta-analysis shows that fetal loss and stillbirth are 21% more frequent among syphilis-positive women (36, 37).

Overall, the cumulative meta-analysis showed that syphilis-positive women in the Americas have a 6.87 times higher odds of stillbirth compared to women that do not have syphilis; no evidence of publication bias was found (Table 4). The subgroup meta-analyses also showed increased odds of stillbirth among women with GS (Table 5). All of the analyses were presented in random-effects models because all but one of the four sub-

groups had high heterogeneity (i.e., they were not homogeneous populations). These study sample characteristics also allowed the authors to generalize the results to populations in the Americas region—the focus of this analysis.

All relevant data that were found were used in the cumulative meta-analysis in order to convey the most comprehensive overview of the current relationship between GS and stillbirth in the Americas. Studies that either did not investigate the relationship between GS and stillbirth or were conducted with a study population

outside the Americas were excluded. Of the eight studies included in the cumulative meta-analysis, one included combined data from Saudi Arabia and Thailand as well as Argentina and Cuba (25). This study was included in the analysis nonetheless because it stated a low prevalence of syphilis for Saudi Arabia and Thailand and thus appeared to be mainly representative of the situation in the Americas.

Syphilis treatment is nearly 100% effective and prevents adverse birth outcomes attributable to syphilis (1, 5, 7, 15,

**TABLE 4. Estimated odds of stillbirth in syphilis-positive and syphilis-negative women based on review and analysis of eight selected studies, Americas region, 1945–2015**

Lead author, date, and reference	Exposed to syphilis		Not exposed to syphilis		Weight (%)	Odds ratio	
	Events	Total	Events	Total		M-H, random <sup>a</sup> (95% CI <sup>b</sup> )	M-H, random (95% CI)
Alexander 1999 (30)	2	6	0	334	4.9	371.67 (15.52, 8898.43)	
Arnesen 2015 (24)	29	3 875	1 432	364 276	15.4	1.91 (1.32, 2.76)	
CDC <sup>c</sup> 1998 (29)	4	62	0	28	5.4	4.38 (0.23, 84.26)	
Greenwood 1994 (17)	100	524	458	9 953	15.7	4.89 (3.86, 6.20)	
Ingraham 1950 (31)	50	302	57	10 323	15.3	35.74 (23.96, 53.30)	
Lumbiganon 2002 (25)	11	285	223	19 778	14.6	3.52 (1.90, 6.52)	
McFarlin 1994 (28)	10	253	90	7 929	14.4	3.58 (1.84, 6.97)	
Southwick 2001 (20)	11	72	32	1 399	14.2	7.70 (3.71, 16.01)	
Total (95% CI)	— <sup>d</sup>	5 379	—	414 020	100.0	6.87 (2.93, 16.08)	
Total events	217	—	2 292	—	—	—	

Heterogeneity: Tau<sup>2</sup> = 1.19, Chi<sup>2</sup> = 131.52, df = 7 (P < 0.00001); I<sup>2</sup> = 95%<sup>e</sup>  
 Test for overall effect: Z<sup>f</sup> = 4.44 (P < 0.00001)  
<sup>a</sup> Random Mantel–Haenszel odds ratio.  
<sup>b</sup> Confidence interval.  
<sup>c</sup> U.S. Centers for Disease Control and Prevention.  
<sup>d</sup> Not applicable.  
<sup>e</sup> Tau<sup>2</sup>: tau-squared test statistic; Chi<sup>2</sup>: chi-squared test statistic; df: degrees of freedom; I<sup>2</sup>: % of variance.  
<sup>f</sup> Z: z-test statistic.

**TABLE 5. Summary of meta-analyses of eight selected studies on stillbirth in syphilis-positive and syphilis-negative women, by subgroup, Americas region, 1945–2015**

Meta-analysis	Number of studies	Pooled OR <sup>a</sup>	95% CI <sup>b</sup>	% of variance <sup>c</sup>
Cumulative meta-analysis	8	6.87	(2.93, 16.08)	95
Subgroup 1: No treatment and ineffective treatment for syphilis vs. effective treatment for syphilis and no syphilis	3	13.23	(0.99, 177.66)	75
Subgroup 2: Syphilis vs. no syphilis	5	6.21	(2.23, 17.34)	97
Subgroup 3: Stillbirth defined as “no signs of life at delivery”	2	2.46	(1.36, 4.46)	64
Subgroup 4: Stillbirth defined by lower bounds on birth weight and/or gestational age	3	4.94	(3.77, 6.48)	14

<sup>a</sup> OR: odds ratio.  
<sup>b</sup> CI: confidence interval.  
<sup>c</sup> Heterogeneity (I<sup>2</sup>).

16, 32). Therefore, the subgroup meta-analysis of the association between GS and stillbirth only included studies that compared “no syphilis treatment” or ineffective syphilis treatment with successful syphilis treatment or syphilis-negative mothers. The association between GS and stillbirth in this meta-analysis was stronger than in any other subgroup meta-analysis (pooled OR: 13.23; 95% CI: 0.99, 177.66).

Syphilis reinfection of pregnant women treated for syphilis during pregnancy is fairly common and results in GS exposure for the neonate for the duration of the pregnancy and delivery (1, 2, 6, 15). Therefore, one subgroup meta-analysis compared the relationship between GS and stillbirth among cases clearly identified as syphilis-positive

to controls unmistakably classified as syphilis-negative. The pooled OR for this meta-analysis comparison was 6.21 (95% CI: 2.23, 17.34)—the closest to that of the cumulative meta-analysis (pooled OR: 6.87; 95% CI: 2.93, 16.08) versus all other subgroups.

The results (Table 3) clearly show that syphilis is an important factor that needs to be further addressed in the region in order to combat stillbirth. The ability to test and treat women the same day has been cited as a cost-effective, timely, and successful way to prevent adverse birth outcomes associated with untreated GS (2, 7, 16, 19, 32) and would help increase the number of GS cases that get treatment, resulting in fewer cases of congenital syphilis, including stillbirth attributable to syphilis.

In countries with a higher prevalence of syphilis, the infection is responsible for a greater proportion of stillbirths (5, 8). Combatting stillbirth and other adverse birth outcomes attributable to syphilis is easier in these high-prevalence settings because testing and treating for syphilis during pregnancy can be made the norm. This is especially true in settings using the new point-of-care syphilis tests, which also help mitigate the number of women who test positive for syphilis but are lost to follow-up, compared to traditional syphilis testing that requires a return visit to the health care facility for the results. Regardless of the level of syphilis prevalence, syphilis testing and treatment programs are among the most cost-effective interventions available (1, 5, 6, 10, 16, 32) and need to be implemented across the Americas in order for the region to attain the goal of eliminating congenital syphilis.

**Limitations**

This analysis had some limitations. First, it included studies that did not specify if GS cases had been treated or not, and some that did not specify if successfully treated GS cases were included in the case or control group. This could have led to bias in either direction, depending on how cases and controls were—and if they were—misclassified.

Second, internationally, a reactive non-treponemal test confirmed by a trepone-

mal test is considered confirmatory for syphilis (6, 19, 32). In this analysis, the determination as to whether or not a mother was a GS case or not was left to the authors of the original study. This could have led to classification bias, as some settings do not have the resources to perform nontreponemal testing, and classification standards differ by institution. Finally, the definition of stillbirth remains ambiguous in the international research community (16). As a result, the definition of stillbirth was not uniform across the eight studies analyzed in the cumulative meta-analysis. To address this discrepancy, the studies were divided into two different subgroup meta-analyses depending on how they defined stillbirth. Two studies defined all fetuses showing no signs of life at delivery as stillborn (pooled OR: 2.46; 95% CI: 1.36, 4.46) and three studies used lower birth weight and/or gestational age bounds as criteria for the stillborn classification (pooled OR: 4.94; 95% CI: 3.77, 6.48).

## Recommendations

Future research on the association between GS and stillbirth in the Americas should control for maternal syphilis treatment, definition of stillbirth, partner syphilis treatment, and definition of testing considered confirmatory for syphilis. Uniform definitions and well-documented treatment would show the association in question with the least possible classification bias. Future interventions addressing loss to follow-up among women who receive point-of-care syphilis testing and treatment should ensure third-trimester syphilis testing and applicable treatment (6), using sustainable programs, to help eliminate congenital syphilis in the Americas region and beyond.

## Conclusions

These meta-analyses provide a snapshot of the current situation regarding

GS and stillbirth in the Americas region. Although the studies included in the analysis used different definitions for stillbirth as well as case and control selection, they all showed a consistent relationship between GS and stillbirth. One strength of the analysis was the fact that all included studies examined adverse birth outcomes—specifically, stillbirth—in pregnancies with GS exposure compared to those without GS exposure, and thus allowed for assessment of the increased odds of stillbirth in the presence of untreated GS during pregnancy. Based on the results of both the cumulative and subgroup meta-analyses, GS is a major contributing factor for stillbirths in the Americas. Interventions targeting GS are highly cost-effective and, along with high-quality point-of-care testing, should be implemented across the region to help reach the goal of eliminating congenital syphilis.

**Conflicts of interest.** None.

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Manuscript received on 15 October 2014. Revised version accepted for publication on 26 February 2015.

## RESUMEN

### Sífilis gestacional y mortinatalidad en la Región de las Américas: una revisión sistemática y metanálisis

**Objetivo.** Llevar a cabo una revisión sistemática y metanálisis de los cálculos notificados de la asociación entre sífilis gestacional (SG) y mortinatalidad en la Región de las Américas.

**Métodos.** Se realizó una búsqueda en Cochrane Library, Embase, LILACS, MEDLINE/PubMed, PLOS y ScienceDirect de estudios de investigación originales que cuantificaran la relación entre la SG y la mortinatalidad en la Región de las Américas. Se seleccionó una muestra final de ocho estudios. Se efectuaron un metanálisis acumulativo y cuatro metanálisis de subgrupo de los datos de estudio sobre la asociación entre sífilis materna durante el embarazo y mortinatalidad. Los cuatro metanálisis se basaron en 1) la definición de casos y del control; 2) el tratamiento de la sífilis (presencia o ausencia, eficaz o ineficaz); 3) la definición de mortinatalidad como “ausencia de signos de vida al nacer”; y 4) la definición de mortinatalidad basada en el bajo peso al nacer y la edad gestacional. Se emplearon metanálisis de efectos aleatorios para calcular las estimaciones acumuladas de mortinatalidad con exposición a la SG, y se comprobó la heterogeneidad de cada uno de los análisis de subgrupo.

**Resultados.** Las mujeres con SG presentaron mayores probabilidades de mortinatalidad (razón de posibilidades [OR] acumulada: 6,87; IC de 95%: 2,93–16,08). Se observó una heterogeneidad considerable en los ocho estudios (porcentaje de variación [I<sup>2</sup>] = 95). El gráfico en embudo no fue estadísticamente significativo, lo que indica una ausencia de sesgo de publicación. En los cuatro metanálisis de subgrupo, también se observaron mayores probabilidades de mortinatalidad en las mujeres embarazadas con sífilis.

**Conclusiones.** La SG es un importante factor contribuyente a la mortinatalidad en la Región de las Américas. Las intervenciones dirigidas a la SG son altamente eficaces en función de los costos y deben ejecutarse en toda la región, junto con las pruebas diagnósticas de alta calidad en el lugar de asistencia, para ayudar a alcanzar la meta de eliminación de la sífilis congénita.

## Palabras clave

Mortinato; sífilis; Américas; América Latina; Indias Occidentales.