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SYSTEMATIC REVIEW

Improving global estimates of syphilis in pregnancy by diagnostic test type: A systematic review and meta-analysis

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ABSTRACT

Background: "Probable active syphilis," is defined as seroreactivity in both non-treponemal and treponemal tests. A correction factor of 65%, namely the proportion of pregnant women reactive in one syphilis test type that were likely reactive in the second, was applied to reported syphilis seropositivity data reported to WHO for global estimates of syphilis during pregnancy. *Objectives:* To identify more accurate correction factors based on test type reported. *Search Strategy:* Medline search using: "Syphilis [Mesh] and Pregnancy [Mesh]," "Syphilis [Mesh] and Prenatal Diagnosis [Mesh]," and "Syphilis [Mesh] and Antenatal [Keyword]. *Selection Criteria:* Eligible studies must have reported results for pregnant or puerperal women for both non-treponemal and treponemal serology. *Data collection and analysis:* We manually calculated the crude percent estimates of subjects with both reactive treponemal and reactive non-treponemal tests among subjects with reactive treponemal and among subjects with reactive non-treponemal tests. We summarized the percent estimates using random effects models. *Main results:* Countries reporting both reactive non-treponemal and reactive treponemal testing required no correction factor. Countries reporting non-treponemal testing or treponemal testing alone required a correction factor of 52.2% and 53.6%, respectively. Countries not reporting test type required a correction factor of 68.6%. *Conclusions:* Future estimates should adjust reported maternal syphilis seropositivity by test type to ensure accuracy.

1. Background

In 2088, WHO estimated that, worldwide, approximately 1.4 million pregnant women had "probable active syphilis" (PAS) or syphilis infections sufficiently active to result in mother-to-child transmission (MTCT) and with the potential of subsequent adverse pregnancy outcomes [1]. Syphilis in pregnancy can be devastating and is associated with poor fetal or infant outcomes in the majority of cases, with an estimated 52% of PAS cases resulting in an adverse perinatal outcome attributable to syphilis [2]. PAS (defined as seroreactivity for both non-treponemal and treponemal tests) is used as the reporting measure by WHO since surveillance data typically do not include clinical information.

Currently, no single test or combination of tests accurately predicts the extent to which maternal syphilis infection in pregnancy will affect the fetus. However, serologic tests can be suggestive; the combination of a reactive non-treponemal test (e.g. rapid plasma regain [RPR], venereal disease research laboratory [VDRL]) and a reactive treponemal test (e.g. *Treponema pallidum* particle agglutination [TP-PA], *T. pallidum* hemagglutination assay), defined in the 2008 WHO estimates as PAS, is compelling evidence for an infection that may result in MTCT. Neither type of test is both sensitive and specific on its own. A reactive, but unconfirmed, non-treponemal test may represent a biological false-positive result, whereas a reactive treponemal test alone may represent an old or previously treated infection that poses little exposure risk for the fetus. Considered schematically (Table 1), individuals with a positive result in both test types are likely to have syphilis (Cell A). Those with a single positive result in either test type could have syphilis, but might have false-positive or past-treated infection (Cells B and C). Those with negative results in both test types are unlikely to have syphilis (Cell D).

WHO estimated that untreated syphilis in pregnancy resulted in approximately 521 000 adverse perinatal outcomes globally in 2008, including an estimated 212 000 stillbirths, 92 000 neonatal deaths, 65 000 preterm or low birth weight infants, and 152 000 syphilis-infected newborns [1]. Health outcomes were modeled based on the published literature on MTCT risk of syphilis transmission [2] and national data reported to WHO from 147 countries on antenatal clinic (ANC) attendance (at least one visit) and from 97 countries on maternal

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Table 1
Schematic of syphilis testing by test type.

		Treponemal test	
		Reactive	Non-reactive
Non-treponemal test	Reactive	A (syphilis likely)	B (biologic false positive)
	Non-reactive	C (possible past infection)	D (syphilis unlikely)

syphilis seropositivity among ANC attendees through the WHO/UNAIDS Global AIDS Response Progress Reporting System (GARPR, formerly known as HIV Universal Access Reporting: http://www.unaids.org/en/dataanalysis/knowyourresponse/globalaidsprogressreporting/). Maternal syphilis seropositivity data reported to WHO varied across countries, generally falling into four categories (Table 2). Category 1 included countries reporting the number of maternal syphilis cases reactive to both non-treponemal and treponemal syphilis tests (PAS); Category 2 included countries reporting cases reactive to non-treponemal syphilis tests only (i.e. no confirmatory treponemal testing reported); Category 3 included countries reporting cases reactive to treponemal tests only (i.e. no confirmatory non-treponemal testing reported); and Category 4 included countries for which the type of laboratory test used was not reported.

In the 2008 estimates on burden of syphilis in pregnancy, WHO applied a correction factor assuming that 65% of all reported seropositive cases among pregnant women, regardless of test type, had infections that could lead to MTCT (PAS). A correction factor was necessary since 97% (188 of 193) of countries reporting to WHO had not reported on the test type used (Category 4), and many may have included only one test type (treponemal or non-treponemal) in their case definition. The correction factor was based on data from three ANC studies in which both non-treponemal and treponemal test results were reported [3–5], allowing calculation of the proportion of seropositive women in either test type expected to be reactive for both non-treponemal and treponemal tests (i.e. A/(A + B + C), Table 1). This estimation is best suited for Category 4 countries. However, for countries in Categories 1 − 3, more precise correction factors can be calculated. In this analysis, we sought to identify more accurate correction factors for future estimates of global burden of syphilis MTCT and resultant adverse pregnancy outcomes when test type data are available. Correction factors calculated were the estimated proportion of pregnant or puerperal women with reactive non-treponemal tests that had reactive treponemal tests (correction factor for Category 2 countries), or the proportion of pregnant or puerperal women with reactive treponemal tests that had reactive non-treponemal tests (correction factor for Category 3 countries).

2. Materials and methods

For this meta-analysis, we reviewed the published literature to identify country-level studies reporting maternal syphilis seropositivity results for both treponemal and non-treponemal tests on all patients in order to estimate the likelihood that a single unconfirmed syphilis test would also be positive for the alternative test type, had it been conducted.

To identify studies, we conducted a systematic Medline search using the terms: "Syphilis [Mesh] and Pregnancy [Mesh]," "Syphilis [Mesh] and Prenatal Diagnosis [Mesh]," and "Syphilis [Mesh] and Antenatal [Keyword]", including observational studies (trials, cross-sectional serosurveys, and cohort and case-control studies) published between January 2000 and November 2013, and reporting both non-treponemal and treponemal syphilis testing results of any type in pregnant or puerperal women. We also looked at the three studies used in the original WHO correction factor estimate [3–5].

2.1. Inclusion criteria

To be included, eligible studies must have tested pregnant or puerperal women for both non-treponemal and treponemal serology and reported at least one of the following: the proportion of pregnant or puerperal women with reactive non-treponemal tests that had reactive treponemal tests (correction factor for Category 2 countries) or the proportion of pregnant or puerperal women with reactive treponemal tests that had reactive non-treponemal tests (correction factor for Category 3 countries). Studies were included regardless of type of non-treponemal (e.g. RPR, VDRL) or treponemal (e.g. fluorescent treponemal antibody absorption, TP-PA) test used, publication language, country, or age of subjects.

We used these data to estimate maternal syphilis seropositivity for countries reporting data to WHO based on a single test type (Categories 2 and 3), or that did not report the test type used (Category 4; Table 2). For Category 1 countries, we assumed that reported data should be used without correction since these are the best possible estimates for PAS cases in pregnancy when only test type (no clinical or titer) data are available. For Category 2 countries, we used the published literature to calculate estimates and 95% confidence intervals (CIs) for the proportion of pregnant women with reactive non-treponemal tests that also had reactive treponemal tests (i.e. A/(A + B) from Table 1). For Category 3 countries, we used the published literature to calculate estimates and CIs for the proportion of pregnant women with reactive treponemal tests that also had reactive non-treponemal tests (i.e. A/(A + C) from Table 1). For Category 4 countries, we assumed an equal probability of having used only non-treponemal, only treponemal, or a combined test strategy. Thus, we used the average of the estimates for the three correction factors for Categories 1 − 3 to estimate the number

Table 2
Syphilis seropositivity in antenatal women: WHO reporting categories based on syphilis test type, assumptions for new correction factors, and new correction factor estimates.

	Syphilis seropositivity			
WHO reporting categories	Category 1 (countries reporting based on both reactive non-treponemal and reactive treponemal testing)	Category 2 (countries reporting based on reactive non-treponemal testing only)	Category 3 (countries reporting based on reactive treponemal testing)	Category 4 (countries not reporting type of testing used)
Previous correction factor used for estimating probable active syphilis WHO [1]	65%	65%	65%	65%
Assumptions used for new correction factors	Additional correction factor not needed; reported data represent best estimate of probable active syphilis when only test type data are available	Proportion of pregnant women with reactive non-treponemal tests that also have reactive treponemal tests; A/(A + B) from Table 1	Proportion of pregnant women with reactive treponemal tests that also have reactive non-treponemal tests; A/(A + C) from Table 1	Non-reporting countries would be evenly distributed between Categories 1–3: average of the correction factors for Categories 1–3
New correction factor estimate (95% CI)	1.0 Actual data, no CI needed	52.2% (38.0–66.6)	53.6% (36.9–70.2)	68.6% (61.3–78.9)