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Syphilis in pregnancy and associated adverse outcomes:
Global estimates and analysis of multinational antenatal surveillance data

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By

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B.A., Lewis and Clark College, 2003

Thesis Committee Chair: Roger W. Rochat, MD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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Introduction The World Health Organization (WHO) first estimated global syphilis infections based on national antenatal data in 2008. The WHO aims to validate congenital syphilis elimination for countries with low incidence rates and high performing antenatal care (ANC) systems. Our objective was to estimate for 2011 the global, regional and national number of pregnant women with probable active syphilis and associated adverse pregnancy outcomes, and ANC coverage for syphilitic women.

Methods We used WHO data on syphilis seropositivity for ANC attendees from 121, ANC coverage from 167, and live births from 193 of 194 WHO member-states. WHO regional advisors and peer-reviewed literature sources provided proportions describing relationships between variables for our calculations. We estimated the number of probable active maternal syphilis infections and conducted a sensitivity analysis for three testing and treatment scenarios to estimate associated adverse outcomes.

Results In 2011, we estimated that globally 882,851 pregnant women had syphilis infections leading to 346,983 congenital syphilis outcomes including 141,307 stillbirths or early fetal deaths, 61,021 neonatal deaths, 43,139 preterm or low birth weight newborns, and 101,517 clinical infections in infants. Among the 691,972 (78.4%) syphilitic women who attended ANC, those who were not tested or not treated had 226,678 (65.3%) adverse outcomes. From 2008 to 2011 global numbers of maternal and congenital syphilis decreased by 525,960 and 197,274 infections respectively, and 25 more countries reported syphilis seropositivity.

Discussion There continue to be, in 2011, a large number of maternal and congenital syphilis infections. There appear to be global decreases and there may be a true change in the global burden of disease along with changes in completeness of reporting between 2011 and 2008. Limitations of these estimates include missing syphilis seropositivity including over 50% of countries in Europe and the Mediterranean, and using estimates for the proportion of “probable active” syphilis and for regional testing and treatment coverage.

Conclusions Syphilis infections in pregnancy continue to cause perinatal morbidity and mortality. Improving the completeness and quality of reporting, and access to quality antenatal care, syphilis testing, and treatment are critical to eliminating congenital syphilis as a public health problem.

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DEDICATION AND ACKNOWLEDGEMENTS

Dedication

This research is dedicated, with respect, to people who needlessly suffer and die from preventable health afflictions such as syphilis and to those committed to reaching them.

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This research would not have been possible without the support of many people. The author would like to acknowledge the valuable contributions of many colleagues towards the development of this thesis.

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To colleagues at the Centers for Disease Control and Prevention, the World Health Organization, collaborating countries, and local government for efforts dedication to eliminating congenital syphilis, for efforts to improve surveillance and to government and private health practitioners, who screen, diagnose correctly and correctly treat women and their partners.

The author would also like to give special thanks to her family and friends for their love and support, and especially to her husband and best friend Todd Bruce for his encouragement, patience, and perspective.

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CHAPTER 1: Introduction

Background of the Problem

Syphilis. Syphilis is a severe and preventable sexually transmitted bacterial infection caused by the spirochete *Treponema pallidum*, which if untreated leads to severe chronic illnesses in men and women that damages internal organs such as the heart, brain, and liver and can result in death.[1] Condoms may reduce the risk of syphilis transmission if it prevents contact by the uninfected with chancres or lesions that may be present in primary, secondary, and early latent stages of syphilis in the infected.[1-3]

Congenital syphilis and its prevention. Untreated in pregnancy, syphilis is transmitted from mother-to-child in over fifty percent of cases expressing itself as early fetal or neonatal death, preterm or low birth weight newborns, or clinical disease in infants.[4-8] Maternal syphilis screening followed by prompt treatment of seropositive women and their partners with at least 2.4 million units of benzathine penicillin is sufficient to cure congenital syphilis in infants and prevent most adverse pregnancy outcomes.[9]

Global Elimination of Congenital Syphilis (ECS) Initiative, 2007. The World Health Organization (WHO) garnered international support and recognized that congenital syphilis could be eliminated as a public health problem through universal antenatal syphilis screening and treatment of infected pregnant women and their partners with the establishment of the ECS Initiative in 2007. Subsequent efforts made towards congenital syphilis elimination would contribute to three Millennium Development Goals (MDGs): reducing childhood mortality (MDG 4); improving maternal health (MDG 5); and combatting HIV/AIDS, malaria, and other diseases (MDG 6).[10]

The ECS Initiative is supported by four pillars: 1) ensure sustained political commitment and advocacy; 2) increase access to, and quality of, maternal and newborn health services; 3) screen and treat pregnant women and their partners; and 4) establish surveillance, monitoring and evaluation systems.[11]

Four guiding principles for country-level action to control congenital syphilis are: 1) a country-driven process; 2) an integrated approach; 3) a rights based approach; and 4) partnership and collaboration.[11]

Antenatal care screening and treatment interventions. The WHO recommends several preventive interventions to eliminate congenital syphilis including promoting and ensuring universal access to high quality antenatal care services for pregnant women.[8] Antenatal syphilis screening and treatment of infected pregnant women and their partners are direct and cost-effective interventions to prevent neonatal infection and associated morbidity and mortality even where prevalence in pregnant women is low.[5] Syphilis screening in the general population is an indirect intervention and is not necessarily cost-effective in all settings because it is not clear how many people would need testing and treatment to prevent one adverse pregnancy outcome. Pregnant women are used as a proxy for the general population because they routinely seek medical care and are routinely screened. WHO recommends universal syphilis screening for pregnant women as a basic part of antenatal care.[11,12]

Global surveillance, monitoring, and evaluation of the ECS. The three core indicators for monitoring and evaluating progress were defined as, 1) testing antenatal care attendees for syphilis at first visit, 2) positive syphilis serology in pregnant women, and 3) treatment of syphilis-seropositive pregnant women.[13]

In 2008, Ministries of Health of WHO member-states began reporting aggregated country data, where possible, for these indicators to WHO, Joint United Nations Programme on HIV and AIDS (UNAIDS), and United Nations Children's Fund (UNICEF) Joint Online Tool, formerly known as the Universal Access (UA) Surveillance Reporting, or more recently as the Global AIDS Progress Reporting (GARPR) System.[14]

The guidelines and processes for the evaluation of the country elimination of congenital syphilis are currently underway.[15] The validation target for the elimination of mother-to-child transmission of syphilis is an incidence of congenital syphilis ≤ 50 cases per 100,000 live births.[15] Countries must also attain the following process indicators and targets: 1) ≥ 95% antenatal coverage, 2) ≥ 95% syphilis screening, and 3) ≥ 95% treatment of syphilis seropositive pregnant women. Countries meeting these criteria will be assessed using these minimum global standards for the validation of congenital syphilis elimination that year.[15]

Using multinational surveillance data to establish a baseline. Most recent global estimates for 2008 indicate there were 1,408,811 pregnant women with syphilis infections and 544,257 related congenital syphilis outcomes including 221,777 stillbirths or early fetal deaths, 95,821 neonatal deaths, 68,010 preterm or low births weight newborns, and 158,649 clinical infections in infants globally.[16a]

Regionally, the highest to lowest burden of maternal syphilis infections were 603,293 in Asia (42.8%), 583,529 in Africa (41.4%), 106,500 in the Americas (7.5%),

[a] The reported estimates reflect a correction in the number of live births for Ethiopia, which are not currently updated in the published manuscript by Newman et al, 2013. This thesis will cite this reference utilizing corrected estimates throughout the thesis.

53,825 in the Pacific (3.8%), 40,062 in the Mediterranean (2.8%), and 21,602 in Europe (1.5%). Closely corresponding with maternal syphilis numbers, the regional burden of congenital syphilis infections were 230,763 in Asia, 246,982 in Africa, 29,061 in the Americas, 15,231 in the Pacific, 17,435 in the Mediterranean, and 4,786 in Europe.[16]

Around 1,099,168 (78.0%) pregnant women with syphilis infections attended antenatal care and 347,883 (63.9%) of adverse outcomes occurred in untested or untreated antenatal care attendees.[16]

Statement of the Problem

Untreated syphilis in pregnancy is transmitted from mother-to-child in over fifty percent of cases expressing itself as early fetal or neonatal death, preterm or low birth weight newborns, or clinical disease in infants.[4-7] Syphilis is most common among subgroups of the population within countries and more broadly on the global level with limited resources, or live on the margins of society such as the poor, those lacking access to healthcare, and those with many sexual partners.[3] While the incidence of congenital syphilis can be significantly reduced with a relatively simple set of interventions, as long as syphilis is prevalent among adults in the population transmission from mother-to-child will remain high.[11]

Efforts to eliminate congenital syphilis requires interventions through high performing antenatal care systems defined by a minimum global standard: it is accessed by at least 95% of pregnant women at least once early in pregnancy, with the basic antenatal package provided to at least 95% of attendees, and timely treatment of at least 95% of infected pregnant women and their sexual partners.[15] This will not eliminate

transmission from mother-to-child completely due to the limited effectiveness of penicillin in crossing the placental barrier, but will markedly reduce adverse outcomes.[9]

Numerous barriers also impede achieving high performing antenatal care systems resulting in challenges to controlling and eliminating congenital syphilis. Pregnant women with lower socioeconomic status and those living in rural settings, in particular, face challenges to accessing care. While four antenatal visits are recommended throughout pregnancy, many women only attend once, and then not early enough to prevent congenital syphilis.[11,12] The women who attend antenatal care are too often not provided the basic antenatal services.[12] Providing syphilis screening in facilities without the proper testing kits, technical expertise, equipment, and an energy source to run the equipment poses challenges.[17] Timely diagnosis can be an issue depending on the timing of the first visit and the existence or distance to laboratory facilities.[17] Treating maternal infections requires appropriate follow-up, with test results and the availability of the appropriate treatment for the infected. Information on treatment of their sexual partners is currently not being monitored. Barriers to treating their partners such as cultural variations, stigma, and behaviors are contributing challenges in control and elimination efforts.

Frequent reporting and estimation of syphilis in pregnancy and associated adverse outcomes can more rapidly reflect changes in the quality of surveillance data, inform sexually transmitted infection prevention programs, and measure the overall burden of disease which may serve as an early warning sign for changes in transmission of other sexually transmitted infections such as HIV.[13]

Purpose of the Study

The purpose of this study is to estimate for 2011, 1) the number of pregnant women with syphilis infections nationally, regionally, and globally; 2) the number of related adverse outcomes including early fetal death, neonatal death, preterm or low birth weight newborns, and clinical disease in infants regionally and globally; and 3) antenatal care coverage for women with syphilis. These numbers will update those recently estimated for 2008, which provides a baseline for comparison.[16]

Additional estimation for the ten countries with the highest number of live births provides analysis of countries with the potential to have the highest burden of maternal and congenital syphilis globally.

Research Questions and Hypothesis

Three main questions guide this research and analysis:

1) What are the global and regional estimated number of pregnant women with syphilis and associated adverse outcomes for 2011?

2) How do 2011 estimates differ from 2008 estimates globally and regionally?

3) What are the estimates for ten countries with the greatest number of live births? How have they changed since 2008?

We hypothesized that this analysis will demonstrate changes in maternal and congenital syphilis infections from 2008 to 2011.

Importance of the Study/Significance Statement

This study provides updated estimates for 2011, evidence to support efforts made towards the Global Elimination of Congenital Syphilis that aim to achieve congenital

syphilis elimination targets defined by a minimum global standard by WHO. WHO will assess and validate the elimination of mother-to-child transmission of syphilis for countries that have an incidence of congenital syphilis ≤ 50 cases per 100,000 live births.[15] Countries with high performance antenatal care systems are characterized by process indicators defining the minimum standard of ≥ 95% antenatal coverage, ≥ 95% screening, and ≥ 95% treatment of seropositive pregnant women for the elimination of mother-to-child transmission of syphilis.[15]

Scope of the Study

This study is limited to data reported by the Ministries of Health for member-states of WHO. This convenience sample includes 121 of 194 countries and 79.3% of global births.

Limitations include four key assumptions that inform our estimates:

1) WHO regional expert advisors estimate that the proportion of syphilis seropositive women with probable "active syphilis" and transplacental transmission is 65%. They use 0.65 as a correction factor accounting for the type of test used to determine seropositivity and the proportion of pregnant women in which syphilis is likely transmitted from mother to child.
2) WHO regional expert advisors provided their expert opinions with regard to proportions for the worst, middle, and best case regional scenario for testing and treatment due to the limited availability of data on the proportions of antenatal attendees tested and treated for syphilis.

3) A systematic review by Blencowe et al provided the assumptions of penicillin effectiveness for each adverse outcome associated with syphilis.[9]
4) A systematic review and meta-analysis by Gomez et al provided the expected proportion of women that have any syphilis related adverse outcome.[5]

Definition of Terms

Probable active syphilis infections. A seropositive treponemal and/or non-treponemal test results.

Adverse outcomes. Early fetal death, neonatal death, prematurity or low birth weight, and clinical disease associated with maternal syphilis.

Early fetal death. Death occurring at 22 through 28 weeks gestation, which does not include losses, or miscarriages, in the first trimester.

Stillbirth. Fetal death in the third trimester (≥ 1000 g birth weight or ≥28 completed weeks of gestation).

Preterm birth. Born alive before 37 weeks gestation.

Low birth weight. Weighing less than 2500 g, up to and including 2499 g, at birth.

Neonatal death. Death in the first 28 days of life.

Clinical disease in infants. Syphilis in infants < 2 years with microbiological evidence of syphilis infection.[15]

Antenatal coverage (at least one visit). The percentage of women aged 15-49 with a live birth in a given time period that received antenatal care provided by a skilled health personnel (doctors, nurses, or midwives) at least once during pregnancy, as a percentage of women age 15-49 years with a live birth in a given time period.[18]

Elimination. Reduction to zero of the incidence of disease or infection in a defined geographical area.[19] The target for validating the elimination of mother-to-child transmission of syphilis is an incidence of congenital syphilis ≤ 50 cases per 100,000 live births.[15] Process indicators include a minimum standard of ≥ 95% antenatal coverage, ≥ 95% screening, and ≥ 95% treatment of seropositive pregnant women.[15]

CHAPTER 2: Comprehensive Review of Literature

Introduction

This chapter reviews and cites the work of those who paved the way and guided this study and in the process provided the rationale for carrying out this research. It is arranged in sections, covering topics relevant to this study.

The origins of syphilis

Syphilis is a sexually transmitted bacterial infection caused by the spirochete *Treponema pallidum*.[1,3] It is related to three other non-venereal human treponematoses known as endemic syphilis – yaws (*Treponema pertenue*), pinta (*Treponema pallidum carateum*), and bejel (*Treponema endemicum*, confusingly also referred to as endemic syphilis) – found in geographically different parts of the world.[3,20]

Which geographically bound endemic syphilis strain mutated into venereal syphilis and initially spread across the globe has long fueled the debate and controversy about the origins of syphilis. Hackett, Crosby, and Rothschild argue their perspectives and give a sense of the debate.[20-22]

Hackett postulates that while there has been no treponeme known outside of humans except in rabbits, the human treponematoses arose long ago from animal infection.[20] He hypothesizes that endemic syphilis spirochetes developed about 7000 B.C giving rise to venereal syphilis in growing cities in south-west Asia about 3000 B.C.[20] Towards the end of the fifteenth century, around the time venereal syphilis was recognized as a disorder, he argues there was likely further mutation into a more severe

venereal syphilis infecting Europe and was spread throughout the world by European exploration.[20]

Crosby pours through texts, "Galen and Avicenna and other medical writers knew nothing of germ theory or antibiotics, but they were accomplished clinicians and could describe the surface symptoms of a disease as well as any modern physician."[21] He hypothesizes that treponematoses were originally one disease that mutated into related but distinct disorders including venereal syphilis, which developed in the Americas and was brought to Europe by Columbus and his crew.[21]

Rothschild took to reading the bones osseous signature or destruction caused by treponemal disease on the tibia of skeletons.[22] He found the origins of treponemal disease, yaws, in Africa, which subsequently spread to Asia and into North America.[22] Bejel mutated somewhere along the way.[22] Syphilis arose about 8,000 years later.[22] The presence of bone evidence in the Dominican Republic at the time Columbus landed provides the confidence that syphilis originated in the new world and was brought back to Europe.[22]

As Crosby writes, "it would take months of labor merely to assemble a full bibliography of the subject" however these sources provide a foundation for further exploration of published works on the topic.[21] As there has been no clear conclusion, the body of knowledge surrounding these questions will continue to grow and the debate rages on.

Stages, symptoms, and transmission

Syphilis presents itself clinically with great diversity earning its name as the 'Great Mimicker or Imitator'.[1,3] Manifestations of syphilis include primary, secondary, and tertiary stages, interspersed by inactive, or latent, infection.[1-3]

In the primary stage there may be the presence of a single or multiple painless chancre in sites exposed to sexual activity including in and around the genitals, anus, and mouth persisting from three to six weeks which may go unnoticed if hidden from view or may not present any systemic symptoms.[1] Chancres may persist into the secondary phase with a faint skin rash often found on the palms and soles, which are typically not pruritic.[1] Early neurosyphilis begins in the secondary stage affecting the nervous system. Without treatment, the skin rash will disappear in tertiary, or late, syphilis and progress into lesions of the skin, bones, or organs, dementia, and cardiovascular disorders.[1-3]

Sexual transmission of syphilis is possible during primary, secondary, and early latent stages requiring exposure to spirochetes concentrated in chancres and lesions. Condoms may reduce the risk of contracting syphilis if it prevents contact with the spirochetes for the uninfected.[2]

Syphilis crosses the placenta in over fifty percent of cases infecting the fetus as early as nine to 10 weeks of gestation.[4-7,23] Syphilis transmission in pregnancy can happen at any stage of infection.[24] The longer a woman has syphilis prior to pregnancy the greater are the chances of fetal survival.[3,25] Pregnant women with syphilis infections tested and treated in the third trimester are 2.24 times as likely to have an associated adverse outcome compared with those tested and treated in the first and second trimester.[8] Congenital syphilis may be asymptomatic or express itself as early fetal or

neonatal death, preterm or low weight birth, or skin rash or inflammation of the brain in the newborn, which may be due to the intense inflammatory response.[3] If these symptoms are not apparent at birth there may be later signs such as dental deformations, hearing loss, or inflammation of the cornea.[1]

Syphilis diagnosis

The ability to diagnose syphilis has been available for a century but it is difficult. *Treponema pallidum* is closely related antigenically and is structurally identical to non-venereal, or endemic human treponematoses: yaws (*Treponema pertenue*), pinta (*Treponema pallidum carateum*), and bejel (*Treponema endemicum*); laboratory analysis is unable to distinguish between the human treponematoses and all human treponemoses appear to look the same under a microscope.[3,21,22] Due to the inability of laboratory tests and more modern DNA technologies to distinguish between the human treponematoses, the endemic syphilis treponematoses (yaws, pinta, and bejel) could potentially be misclassified as venereal syphilis.[21,22]

Because *Treponema pallidum* cannot be cultured and there is no single diagnostic test, direct and indirect laboratory methods are used in combination to diagnose syphilis.[9,26]

Direct detection of *Treponema pallidum* by darkfield microscopy requires the examination of fluid or smears from chancres or lesions, examination of the tissues, or nucleic acid amplification methods such as polymerase chain reaction tests.[26] These methods are not typically available outside of research settings and follow-up serology is recommended to confirm diagnosis.[9,26]

Indirect tests through serological detection of antibodies supporting a syphilis diagnosis are most commonly used.[26] Serological tests fall into two categories: non-treponemal and treponemal.[26] Non-treponemal tests require a microscope or rotator for processing to detect antibody to reaginic antigen found in both *T. pallidum*, especially in early in infection, and some human tissues.[11] The first serologic test was developed in 1906 by Wasserman but was not sensitive enough for syphilis so more sensitive non-treponemal tests used today Venereal Disease Research Laboratory (VDRL) and Rapid plasma reagin (RPR) were developed.[27] Although non-treponemal tests are quick and inexpensive, which is useful for screening, they are not specific to *T. pallidum* and misinterpretation is common by inexperienced laboratory technicians.[11] These tests are non-reactive in 13% to 41% of adults with primary syphilis and almost always reactive in the secondary phase.[28] Confirmation by treponemal tests is recommended.[26]

Treponemal tests specifically detect the T. pallidum antibody and therefore cannot differentiate between a past or current infection.[26] They are more expensive and can be technically more difficult to perform.[27] Examples of treponemal tests include Treponema Pallidum Haemaglutination Assay (TPHA) and Fluorescent Treponemal Antibody absorption (FTA-Abs).[26]

Rapid tests were more recently developed to address the needs of more remote areas where results can take weeks to receive and the tested may not return for results.[17] Rapid tests do not require trained personnel, refrigeration to store reagents, and electricity or gas to run the refrigerator, centrifuge, and shaker allowing for diagnosis outside of a laboratory setting at the point of care.[17] Most rapid tests today are treponemal but a combination non-treponemal and treponemal rapid tests are underway.[17]

Treatment of syphilis in pregnancy

Penicillin was discovered in 1928 by Alexander Fleming and found to be an effective treatment for syphilis in 1943 during World War II.[29] Penicillin was used shortly thereafter to treat pregnant women with syphilis replacing arsenic therapy which involved a series of injections typically of neoarsphenamine plus bismuth discussed by Paley in 1937.[27]

Walker discusses the various guidelines and debate on the appropriate treatment of syphilis during pregnancy including the Centers for Disease Control and Prevention reaffirmed by the U.S. Preventive Services Task Force, the International Union against Sexually Transmitted Infections, and the WHO views.[27]

Maternal syphilis screening followed by prompt treatment of seropositive women and their partners with the appropriate dose of benzathine penicillin is sufficient to cure infants and prevent most adverse pregnancy outcomes.[9] Blencowe found "a reduction in the incidence of clinical congenital syphilis of 97% (95% c.i. 93 - 98%) with detection and treatment of women with active syphilis in pregnancy with at least 2.4MU penicillin."[9] Penicillin treatment is associated with the reduction of early fetal death by 82%, neonatal death by 80%, preterm delivery by 64%, and congenital syphilis by 97%.[9]

Cost-effectiveness of syphilis screening in antenatal care

Walker provides a background on the costs of treating and not treating syphilis in pregnancy.[27] He identifies studies for 1997 by Bateman on hospital cost of congenital syphilis in addition to Stray-Pedersen (1983) and Williams (1985) on the cost-benefit of

screening pregnant women in developed countries, which laid the foundation for routine syphilis screening programs in the United States and the United Kingdom.[27]

Antenatal syphilis screening and treatment of infected pregnant women and their partners are direct and cost-effective interventions to prevent neonatal infection and associated morbidity and mortality, even where prevalence in pregnant women is low.[5,17,30,31] Syphilis screening in the general population is an indirect intervention and may not be cost-effective in all settings because it is unclear how many people would need testing and treatment to prevent one adverse outcome. Investing in interventions to improve screening in antenatal care is worthwhile given the required resources because they could reduce the incidence of stillbirth and perinatal death associated with syphilis by 50%.[8]

Global Elimination of Congenital Syphilis Initiative rationale and estimation

In 2007, Schmid published the first global and regional estimates of congenital syphilis using literature from published and unpublished reports which used serologically confirmed tests among antenatal care attendees between 1997 and 2003.[32] Schmid estimated about 2,036,753 maternal syphilis cases occurred with related adverse outcomes; the lower and upper estimate bound ranged between 728,547 and 1,527,565 depending on the data source.[32] He addressed the important economic and social implications of congenital syphilis.[32]

The 2007 Initiative for the ECS mobilized active surveillance of maternal syphilis by the WHO in 2008 through the collection of antenatal care data reported by Ministries of Health in the WHO, UNAIDS, and UNICEF Joint Online Tool.

Using national antenatal care data, instead of literature, Newman produced maternal and congenital syphilis estimates for 2008.[16] Global estimates for 2008 indicate that about 1,408,811 pregnant women had syphilis infections and 544,257 pregnancies were associated with congenital syphilis outcomes including 221,777 stillbirths or early fetal deaths, 95,821 neonatal deaths, 68,010 preterm or low births weight newborns, and 158,649 clinical infections in infants globally.[16]

Summary of Current Problem

Syphilis has been recognized as a distinct disorder since the fifteenth century. Distinction between its non-venereal strains using darkfield microscopy and laboratory analyses poses challenges and with the inability to culture the bacteria makes diagnosis difficult.[26] Serological non-treponemal and treponemal tests are most commonly used in combination to support diagnosis.[26] With the development of rapid syphilis tests, the ability to perform point of care testing is possible with fewer resources and technical ability, which addresses the needs of many facilities in low-resource settings.[17] Maternal syphilis screening followed by prompt treatment of seropositive women and their partners with 2.4MU benzathine penicillin is sufficient to cure infants and prevent most adverse pregnancy outcomes.[9]

Studies indicating that antenatal syphilis screening and treatment of infected pregnant women and their partners are direct and cost-effective interventions to prevent

neonatal infection and associated morbidity and mortality lead to the support and recommendation of routine syphilis screening programs by the WHO.[27]

Estimation of syphilis in pregnancy and associated adverse outcomes can more rapidly reflect changes in the quality of surveillance data, inform sexually transmitted infection prevention programs, and measure the overall burden of disease which may serve as an early warning sign for changes in transmission of other sexually transmitted infections such as HIV.[13] This study will further investigate changes in syphilis in pregnancy and associated adverse outcomes for 2011 to inform global programs and identify regions that need attention.

CHAPTER 3: Manuscript (for submission to The Lancet)

Syphilis in pregnancy and associated adverse outcomes:
Global estimates and analysis of multinational antenatal surveillance data

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Contribution of Student

For this manuscript, the student compiled data sources, calculated estimates, analyzed data, adapted and developed figures and tables, and wrote the manuscript with editorial assistance from Lori M. Newman and Roger W. Rochat.

Summary

Introduction The World Health Organization (WHO) first estimated global syphilis infections based on national antenatal data in 2008. The WHO aims to validate congenital syphilis elimination for countries with low incidence rates and high performing antenatal care (ANC) systems. Our objective was to estimate for 2011 the global, regional and national number of pregnant women with probable active syphilis and associated adverse pregnancy outcomes, and ANC coverage for syphilitic women.

Methods We used WHO data on syphilis seropositivity for ANC attendees from 121, ANC coverage from 167, and live births from 193 of 194 WHO member-states. WHO regional advisors and peer-reviewed literature sources provided proportions describing relationships between variables for our calculations. We estimated the number of probable active maternal syphilis infections and conducted a sensitivity analysis for three testing and treatment scenarios to estimate associated adverse outcomes.

Results In 2011, we estimated that globally 882,851 pregnant women had syphilis infections leading to 346,983 congenital syphilis outcomes including 141,307 stillbirths or early fetal deaths, 61,021 neonatal deaths, 43,139 preterm or low birth weight newborns, and 101,517 clinical infections in infants. Among the 691,972 (78.4%) syphilitic women who attended ANC, those who were not tested or not treated had 226,678 (65.3%) adverse outcomes. From 2008 to 2011 global numbers of maternal and congenital syphilis decreased by 525,960 and 197,274 infections respectively, and 25 more countries reported syphilis seropositivity.

Discussion There continue to be, in 2011, a large number of maternal and congenital syphilis infections. There appear to be global decreases and there may be a true change in the global burden of disease along with changes in completeness of reporting between 2011 and 2008. Limitations of these estimates include missing syphilis seropositivity including over 50% of countries in Europe and the Mediterranean, and using estimates for the proportion of “probable active” syphilis and for regional testing and treatment coverage.

Conclusions Syphilis infections in pregnancy continue to cause perinatal morbidity and mortality. Improving the completeness and quality of reporting, and access to quality antenatal care, syphilis testing, and treatment are critical to eliminating congenital syphilis as a public health problem.

Introduction

Syphilis is a sexually transmitted bacterial infection which if untreated leads to severe chronic illnesses in men and women that damages internal organs such as the heart, brain, and liver and can result in death. Untreated in pregnancy, the disease is transmitted from mother-to-child in over fifty percent of cases expressing itself as early fetal or neonatal death, preterm or low weight birth, or clinical disease in the newborn.[4-7] Maternal syphilis screening followed by prompt treatment of seropositive women and their partners with at least 2·4 million units of benzathine penicillin is sufficient to cure congenital syphilis in infants and prevent most adverse pregnancy outcomes.[9]

Antenatal syphilis screening and treatment of infected pregnant women and their partners are direct and cost-effective interventions to prevent neonatal infection and associated morbidity and mortality even where prevalence in pregnant women is low.[5,17] Syphilis screening in the general population is an indirect intervention and is not necessarily cost-effective in all settings because it is not clear how many people would need testing and treatment to prevent one adverse pregnancy outcome. The World Health Organization (WHO) has recommended universal syphilis screening for pregnant women as a basic part of antenatal care.[12,13] Pregnant women are used as a proxy for the general population because they routinely seek medical care and are routinely screened.

The 2007 Initiative for the Global Elimination of Congenital Syphilis (ECS) mobilized active surveillance of syphilis in pregnancy through the

collection of routine data by existing national antenatal care systems. The three core indicators for monitoring and evaluating progress were defined as, 1) testing antenatal care attendees for syphilis at first visit, 2) positive syphilis serology in pregnant women, and 3) treatment of syphilis-seropositive pregnant women.[13] The ECS Initiative aims to improve maternal and newborn health and contribute to three Millennium Development Goals (MDGs): reducing childhood mortality (MDG 4); improving maternal health (MDG 5); and combatting HIV/AIDS, malaria, and other diseases (MDG 6).[10]

Ministries of Health began reporting to the WHO, Joint United Nations Programme on HIV and AIDS (UNAIDS), and United Nations Children's Fund (UNICEF) Joint Online Tool in 2008. Baseline estimates for 2008 monitoring progress towards the elimination of mother-to-child transmission of syphilis indicate that about 1,408,811 maternal and 544,257 congenital syphilis infections occurred worldwide.[16b]

WHO will validate the elimination of congenital syphilis in countries that have achieved targets defined by a minimum global standard by the WHO: countries that have an incidence of congenital syphilis ≤ 50 cases per 100,000 live births and that have attained the ≥ 95% antenatal coverage, ≥ 95% syphilis screening for attendees, and ≥ 95% treatment of seropositive pregnant women.[15]

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[b] The reported estimates reflect a correction in the number of live births for Ethiopia, which are not currently updated in this manuscript. This thesis will cite this reference utilizing these corrected estimates throughout the work.

Frequent reporting and estimation of syphilis in pregnancy and associated adverse outcomes can more rapidly reflect changes in the quality of surveillance data, inform sexually transmitted infection prevention programs, and measure the overall burden of disease which may serve as an early warning sign for changes in transmission of other sexually transmitted infections such as HIV.[13]

This paper serves as an update to the 2008 estimates. The objective of this analysis was to estimate for 2011 the global, regional and national number of women with probable active syphilis infections and the number of adverse outcomes associated with syphilis in pregnancy overall and for regions and populous countries, as well as antenatal care (ANC) coverage for women with syphilis.

Methods

We did not conduct human subjects research and submission to an institutional review board (IRB) was not appropriate. The population included 194 WHO member states.[14] Ministries of Health reported aggregated antenatal surveillance data where available. Analysis was performed on this convenience sample.

We followed the methodology used to estimate the number of syphilis in pregnancy infections and their associated adverse outcomes for 2008.[16] The four estimation steps include:

Step A and B: We estimated the number of pregnant women with probable active syphilis infections who attended or did not attend antenatal care at

the country level for all WHO member countries and summed according to WHO designated regions and overall for the global total.

Step C and D: We used sensitivity analysis to estimate the number of adverse outcomes associated with syphilis in pregnancy. The sensitivity analysis included three testing and treatment scenarios. We did the analysis separately for women who attended or did not attend antenatal care. We made worst, middle, best estimates separately for attendees who were tested and treated, untested and untreated and for pregnant women not attending antenatal care for each WHO designated region and summed for the global total. Additionally, we estimated these outcomes for the ten countries with the highest number of live births.

Probable active syphilis infections (PASI) are defined by seropositive treponemal and/or non-treponemal test results. Adverse outcomes include early fetal death, neonatal death, prematurity or low birth weight, and clinical disease associated with maternal syphilis. We used routine service delivery data reported by Ministries of Health wherever possible.

Data Sources

We used data from four sources for our estimates:

1) The WHO, UNAIDS, and UNICEF Joint Online Tool, formerly known as the Universal Access (UA) Surveillance Reporting, or more recently as the

Global AIDS Progress Reporting (GARPR) System provided the most recent percentage of syphilis seropositivity data (notation: A_1);

2) The United Nations Development Programme World Population Prospects provided national numbers of live births for 2011 (notation: LB);
3) Cousens et al estimated national numbers of stillbirths for 2009 (notation: SB);[33]
4) WHO Global Health Observatory reports the percentage of women with at least one antenatal care visit (notation: A_4).[34]

To address aggregated data submitted by Sudan prior to the separation and creation of the nation of South Sudan, we collected from the Republic of South Sudan Ministry of Health their live birth counts projected for 2013 and antenatal coverage for at least one visit from the Sudan Household Health Survey 2010.

The four-step estimation process

In this section, we detail how we estimated for 2011 the global, regional and national number of women with probable active syphilis infections and the number of adverse outcomes associated with syphilis in pregnancy overall and for regions and ten countries with the highest number of live births.

We estimated numbers for 194 WHO member countries, six WHO regional designations, and overall global totals.[14,35]

Step A and B:

First, we estimated the number of pregnant women with probable active syphilis infections in each country and then summed the data for each region and overall for global totals.

$$\sum_{i=1}^{r,g} PASI^{c} = (A_1) * (A_2) * (P_1)$$

c: Country indicates calculations for each 149 WHO member state.[14]

r: Region indicates calculations for six WHO regional designations.[35]

g: Global indicates a calculation for all 149 WHO member states.[14]

$PASI^{c}$: The estimated number of probable active syphilis infections per country.

$\sum_{i=1}^{r,g} PASI^{c}$: The estimated number of probable active syphilis infections per country summed for each region and overall for the global total.

A_1: The percentage of syphilis seropositivity in antenatal care attendees is the most recently reported syphilis seropositivity for antenatal care attendees. We imputed the regional median where data was unavailable. See Table 1.

A_2 : The estimated number of pregnant women is the sum of the number of live births (LB), stillbirths (SB), and early fetal deaths (EFD).

$$A_2 = LB + SB + EFD$$

EFD: Since estimates of early fetal death are not available for many countries we estimated these to be approximately 20% of stillbirths based on the relationship of early to late fetal death from a limited number of studies conducted primarily in high-income countries.[36,37]

$$EFD = 0.2 * SB$$

P_1: The proportion of syphilis seropositive women with probable "active syphilis" transmitting syphilis to their fetus is 0.65. WHO regional expert advisors estimated 0.65 as the correction factor accounting for the type of test used to determine seropositivity and the proportion of pregnant women in which syphilis is likely transmitted from mother to child.

Second, we estimated the number of pregnant women with probable active syphilis infections attending antenatal care.

$$\sum_{i=1}^{r,g} PASI_{ANC}^{c} = (A_1) * (A_2) * (P_1) * (A_4)$$

$$B_1 = \sum_{i=1}^{r} PASI_{ANC}^{c}$$

ANC: Representing pregnant women attending antenatal care.

B_1: The number of pregnant women with probable active syphilis attending antenatal care summed for each region.

A_4: The percentage of pregnant women attending antenatal care is the most recently reported percentage of pregnant women attending antenatal care for each country. We imputed the regional median where data was unavailable.

Finally, we estimated the number of pregnant women with probable active syphilis infections NOT attending antenatal care.

$$\sum_{i=1}^{r,g} PASI_{NoANC}^{c} = (A_1) * (A_2) * (P_1) * (1 - A_4)$$

$$B_2 = \sum_{i=1}^{r} PASI^{c}_{NoANC}$$

NoANC: Representing pregnant women not attending antenatal care.

B_2: The number of pregnant women with probable active syphilis infections not attending antenatal care for regions.

Step C and D:

First, we estimated the regional number of pregnant women with probable active syphilis not attending antenatal care with an adverse outcome.

$$AO^{r}_{NoANC} = (B_1) * (P_{AO})$$

AO: Adverse outcomes.

P_{AO}: The expected proportion of women that have any syphilis related adverse outcome without treatment. See Table 1.

Second, we estimated the regional number of pregnant women with probable active syphilis attending antenatal care under the worst, middle, and best case testing and treatment regional scenarios for the proportion of inadequately treated attendees with an adverse outcome.

$$AO^{r}_{ANC,TT} = (B_2) * ({}_rT_{w,m,b}) * (P_{AO})(1 - E_{AO})$$

${}_rT_{w,m,b}$: The estimated proportions for the worst, middle, and best case testing and treatment scenario for each region. See Table 2.

E_{AO}: The assumptions of penicillin effectiveness for each adverse outcome associated with syphilis. See Table 1 above.

Third, we estimated the regional number of pregnant women with probable active syphilis attending antenatal care under the worst, middle, and best case testing and treatment regional scenarios for the proportion of untested or untreated attendees with an adverse outcome.

$$AO^{r}_{ANC,NTT} = B_2 * \left(1 - {}_{r}T_{w,m,b}\right) * \left(P_{AO}\right)$$

Fourth, the regional estimated number of adverse outcomes associated with syphilis in pregnancy:

$$AO^{r} = AO^{r}_{ANC,TT} + AO^{r}_{ANC,NTT} + AO^{r}_{NoANC,NTT}$$

Finally, we summed the regional number of adverse outcomes associated with syphilis in pregnancy for the worst, middle, and best case scenarios for a range of global totals:

$$\sum_{i=1}^{g} AO^{r}$$

We report the middle case testing and treatment scenario numbers for adverse outcomes associated with syphilis in pregnancy.

Results

We estimated that during 2011 about 882,851 pregnant women had active syphilis infections and 346,983 associated congenital syphilis outcomes including 141,307 stillbirths or early fetal deaths, 61,021 neonatal deaths, 43,139 preterm or low birth weight newborns, and 101,517 clinical infections in infants globally. Around 691,972 (78·4%) pregnant women with syphilis infections attended antenatal care

with 21,047 (6·1%) adverse outcomes with testing and treatment and 226,678 (65·3%) adverse outcomes without testing or treatment in antenatal care. See Table 3.

The regional burden of maternal syphilis infections was 520,415 in Africa (59·0%), 104,305 in Asia (11·8%), 116,270 in the Mediterranean (13·2%), 82,508 in the Americas (9·6%), 47,412 in the Pacific (5·4%), and 11,941 in Europe (1·4%). Figure 1 shows the regional distribution of maternal syphilis for women attending and not attending antenatal care. Of note, an estimated 111,958 African (21·5%) and 44,919 Mediterranean (38·8%) pregnant women with probable active syphilis infections did not attend antenatal care.

Figure 2 shows the regional distribution of congenital syphilis outcomes for worst, middle, and best case testing and treatment scenarios. Considering the middle testing and treatment scenario for associated adverse outcomes, about 216,969 occurred in Africa (62·5%), 39,922 in Asia (11·5%), 51,089 in the Mediterranean (14·7%), 22,452 in the Americas (6·5%), 13,901 in the Pacific (4·0%), and 2,649 in Europe (0·8%).

Table 4 shows global and regional differences in the number of countries reporting syphilis seropositivity and the median prevalence of maternal syphilis seropositivity reported by Ministries of Health. The global median prevalence of syphilis in pregnancy declined 27·5%from 1·09% seroprevalence in 2008 to 0·79% seroprevalence in 2011. Within this period, the number of countries that ever reported seropositivity increased by 25·8% from 97 (50·3%) to 122 (63·2%).

Among the regions, Europe had the greatest median positivity decrease with a change of 67·9% from 0·16% to 0·05% and the greatest increase in the number of reporting countries by 53·8% from 13 (25·0%) to 20 (38·5%). In Asia, the change in median prevalence of positivity decreased by 53·0% from 0·62% to 0·29% with a 28·6% increase in reporting from 7 (70·0%) to 9 (90·0%). In contrast, the Mediterranean increased in seropositive prevalence by 1583·5% from 0·06% to 0·96% with an increase in reporting by 42·9% from 7 (33·3%) to 10 (47·6%).

Table 5 shows maternal and congenital syphilis decreased globally with variations by region. Global estimates of probable maternal syphilis infections decreased by 37·3% from 1,408,811 in 2008 to 882,851 in 2011 and congenital syphilis outcomes decreased by 36·2% from 544,257 to 346,983 over the same period. Asia and the Mediterranean had the greatest regional differences. In Asia, maternal syphilis decreased by 82·7% from 603,293 to 104,305 and associated adverse outcomes decreased by 82·7% from 230,763 to 39,922. In the Mediterranean, the number of maternal syphilis infections increased by 190·2% from 40,062 to 116,270 and associated adverse outcomes by 193·0% from 17,435 to 51,089 infections.

Table 6 shows the regional numbers of adverse outcomes for the middle case testing and treatment scenario and numbers of adverse outcomes if at least 95% of pregnant women attended antenatal care and at least 95% of antenatal attendees were screened, and 95% of those infected were treated. Europe is

nearing the elimination of congenital syphilis target (1,642) with 2,649 congenital infections. Africa is furthest from achieving elimination targets (74,741) with 216,969 congenital infections.

Table 7 highlights the ten countries with the highest number of live births and their global proportion for 2011 and 2008. In 2011 these nations delivered 55·5% of live births worldwide compared with 57·0% in 2008.

Table 8 shows the difference between the prevalence of syphilis seropositivity in pregnant women attending antenatal care and the estimated number of maternal and congenital syphilis infections for 2011 compared with 2008 for the countries with the highest number of live births. In these ten countries, the global burden of maternal and congenital syphilis is 40·6% and 39·8%, which is slightly lower than the 60·5% and 40·6% in 2008 respectively.

Among these populous countries, seropositivity increased in Pakistan, the Democratic Republic of the Congo, and Bangladesh. Using the regional median of the Mediterranean for both 2008 and 2011 estimates, Pakistan had the most notable increases in syphilis seroprevalence with 1583·5% change from 0·06% to 0·96% and increases in maternal and congenital syphilis by a difference of 29,459 (2,317·6% change) and 7,670 (1298·9% change) infections respectively. Syphilis seroprevalence in ANC in the Democratic Republic of Congo increased by a difference of 1·3%, a 65·0% change, and maternal syphilis increased by a difference of 25,430 (164·5% change) and congenital syphilis 10,191 (158·1% change).

Notable decreases occurred from 2008 to 2011. India had (or experienced) an estimated 87·0% decline in the number of probable active maternal syphilis infections from 406,550 to 52,918 noting an 87·1% decrease in seropositivity from 2·26% to 0·29% with a steady live birth count around 27 million from 2008 to 2011. With about four million live births, Indonesia had an estimated 79·9% change in maternal syphilis counts from 162, 676 to 33,542 with seropositivity dropping from 5·83% to 1·17%.

Table 8 shows the numbers of adverse outcomes for the middle case testing and treatment scenario and numbers of adverse outcomes if at least 95% of pregnant women attended antenatal care and at least 95% of antenatal attendees were screened, and 95% of those infected were treated for the ten countries with the highest number of live births. The United States is nearing the minimum global standard for the elimination of congenital syphilis target (2,243) with 4,154 congenital infections followed by China with a validation target of 3,130 adverse outcomes with a middle case number of 5,911 infections. Nigeria is furthest from achieving the elimination of congenital syphilis validation target of 9,555 with 29,752 adverse outcomes associated with syphilis in pregnancy.

Discussion/Limitations/Conclusion

This study provides the third global measurement of syphilis in pregnancy and associated adverse outcomes. Our analysis demonstrates changes in global and regional numbers of maternal and congenital syphilis infections for 2011

compared with 2008 estimates, which use the same methodology rooted in national antenatal service delivery data effectively addressing publication bias in initial estimates for 1997-2003.

In 2011 about 882,851 pregnant women had active syphilis infections and 346,983 associated congenital syphilis infections occurred worldwide. This is lower than the 1·4 million maternal and 544,257 infections reported for 2008 suggesting progress may have been made over the past three years in syphilis prevention and control.[16]

Ensuring access to antenatal care and providing quality antenatal services continues to be a challenge. About 691,972 (78·4%) infected pregnant women attended antenatal care and due to the absence of screening or treatment of infected women 226,678 (65·3%) related adverse outcomes occurred during 2011. Access to antenatal care by syphilitic pregnant women appears to have marginally increased by 0·4% while the overall quality of care provided diminished by 6·1% from 2008 to 2011. Considering our sample is from pregnant women attending antenatal care and syphilis is most common among subgroups of the population such as those lacking access to healthcare, these estimates likely overestimate coverage of syphilis in pregnancy due to selection bias.[3] Still, the aim to enable access to antenatal care for every woman, stocking the appropriate screening resources for each facility, and ensuring every women attending care gets tested and follow-up treatment for her and her sexual partners is critical not only to

congenital syphilis elimination efforts but fundamental to providing the human right to health care.

Completeness in syphilis seroprevalence in antenatal care has improved since 2008 although estimates could be greatly improved with annual updates from more countries. Syphilis seroprevalence of pregnant women reporting for 121 of 194 (63·2%) WHO member-states is a 25·8% increase from the 97 of 193 (50·3%) in 2008 shown in Table 6. Imputing median values for the countries where data was unavailable assumes that the syphilis prevalence in reporting countries is the same as non-reporting countries although differences are likely. The extent of these differences varies depending on the composition of countries with a region.

Largely, estimates indicate declines in maternal and congenital syphilis for all regions except for the Mediterranean shown in Table 5. Less than 50% of Mediterranean countries report seropositivity (42·9%) in 2011. The 28·6% increase in reporting by countries, such as Syria and Somalia, and updates from Djibouti, Sudan, South Sudan, Oman, and Yemen increased in the median seropositivity from 0·06% to 0·95%, a 957·7% increase, which gives rise to infection numbers for non-reporting and high population countries, such as Pakistan.

Rapid declines in Asia by 82·7% from 2008 to 2011 affected the regional distribution of the burden of maternal and congenital syphilis; maternal infections dropped from 603,293 (42·8%) to 104,305 (11·9%) and congenital infections

declined from 230,763 (42·4%) to 39,922 (11·6%) congenital infections. In Africa, the numbers of maternal and congenital infections decreased but their global burden rose from 583,529 (41·4%) to 520,415 (59·6%) maternal and 246,982 (45·4%) to 216,69 (63·3%).

The countries with the highest number of live births provide insight about the fall of infections observed in Asia shown in Table 7. India and Indonesia account for 94·6% of the decline observed in Asia due their high numbers of live births. This change uses the middle case testing and treatment assumption, which may not accurately reflect testing and treatment proportions for each country because it was developed to characterize regions more generally. Coupled with changes in seropositivity in antenatal care attendees from 2·26% to 0·29% in India and from 5·83% to 1·17% in Indonesia we can better understand the drop in the estimated number of infections in Asia.

A major limitation of the data is the lack of localized information from within countries. Disease patterns within countries may vary substantially more than what is observed between regions and countries. Validation of our estimates is needed and encouraged at a national level at minimum but should have community level data to identify and control outbreaks.

In summary, this analysis demonstrates that despite global decreases in maternal and congenital syphilis infections, syphilis continues to be a substantial cause of preventable perinatal morbidity and mortality varying greatly between and within regions and countries. Improving access to quality antenatal care early

in pregnancy, syphilis testing of pregnant women at first antenatal care visit, and treatment of infected pregnant women and their partners must be a prioritized to control and eliminate congenital syphilis. Frequently reported nationally representative data on the three main indicators – testing of antenatal care attendees for syphilis at first visit, positive syphilis serology in pregnant women, and treatment of syphilis-seropositive pregnant women – is needed to improve explanations of global, regional, and country-level trends.

Figures and Tables

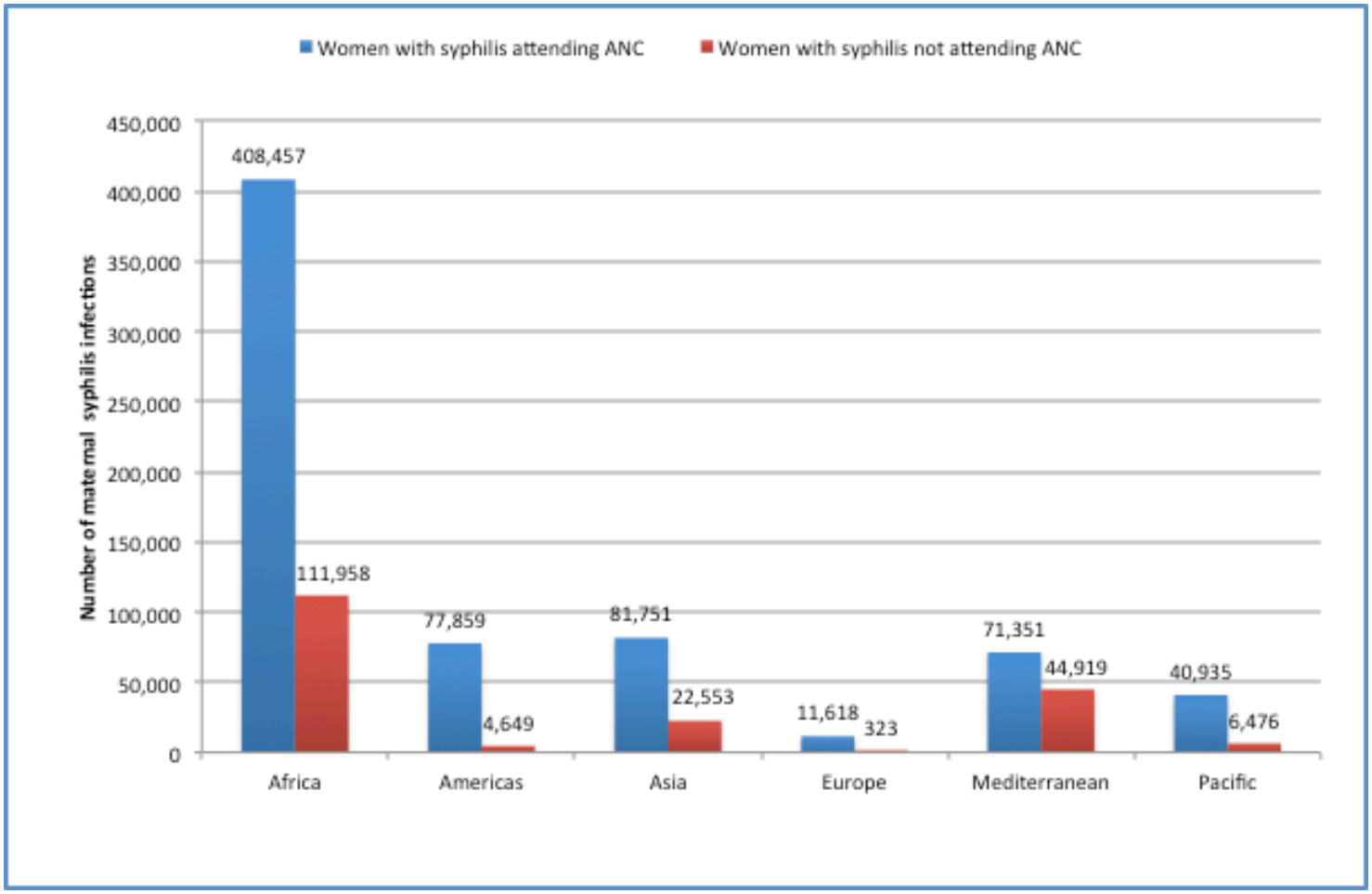

Figure 1. The estimated number of pregnant women with clinical syphilis infections attending antenatal care at least once or not attending antenatal care for each World Health Organization designated region in 2011.

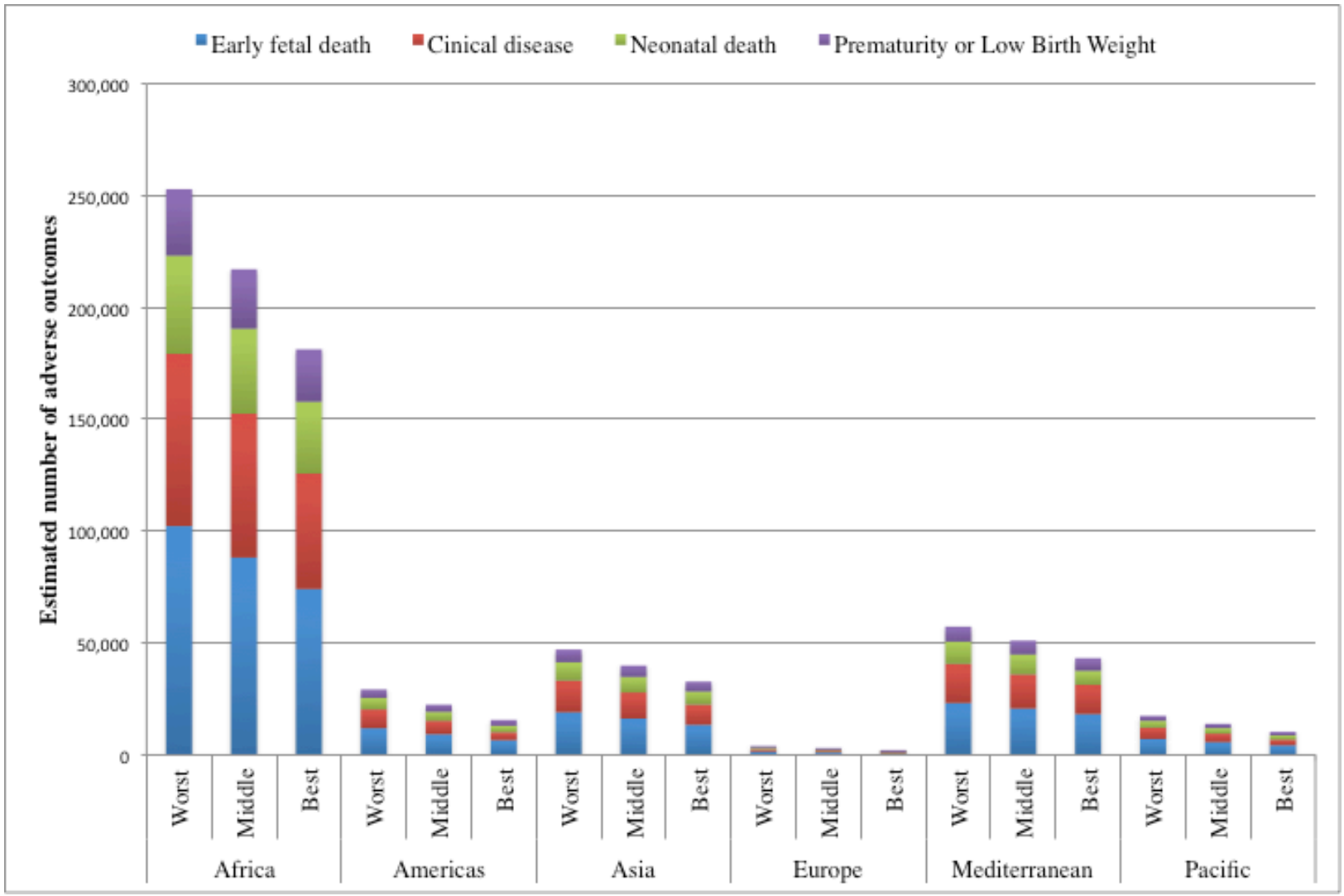

Figure 2. The estimated global number of adverse pregnancy outcomes in 2011 associated with maternal syphilis by region for the worst, middle, and best case testing and treatment scenarios.

Table 1. The expected proportion of adverse outcomes associated with syphilis in pregnancy without treatment and the assumed effectiveness of penicillin treatment in reducing a given adverse outcome.

Adverse Outcome	Expected Outcomes Proportion	Effectiveness of Penicillin
Any adverse outcome	52%	84%*
Early fetal death	21%	82%
Neonatal death	9%	80%
Prematurity or low birth weight	6%	64%
Clinical disease	16%	97%

* This is the weighted average using the expected outcomes proportions as the weights.

Table 2. Estimated proportions for the worst, middle, and best case testing and treatment scenario for each region for 2011.

Region	Worst Case 2011	Middle Case 2011	Best Case 2011
Africa	10%	30%	50%
Americas	40%	60%	80%
Asia	20%	40%	60%
Europe	50%	70%	90%
Mediterranean	10%	30%	50%
Pacific	40%	60%	80%

Table 3. Estimated numbers of adverse outcomes for pregnant women attending antenatal care under tested and treated, untested or untreated, or not attending antenatal care proportions and calculated for based on the worst, middle, and best case testing and treatment scenarios globally, 2011.

Adverse Outcomes	One or more antenatal care visit						No Antenatal Care Visit No services provided	Totals		
	Tested and treated			Not tested or treated						
	Worst	Middle	Best	Worst	Middle	Best	Any case	Worst	Middle	Best
Early fetal death	4,447	**9,679**	14,910	120,606	**91,543**	62,480	**40,085**	165,138	**141,307**	117,475
Neonatal death	2,118	**4,609**	7,100	51,688	**39,233**	26,777	**17,179**	70,985	**61,021**	51,056
Preterm or low birth weight	2,541	**5,531**	8,520	34,459	**26,155**	17,852	**11,453**	48,453	**43,139**	37,824
Clinical disease	565	**1,229**	1,893	91,890	**69,747**	47,604	**30,541**	122,996	**101,517**	80,038
Totals	9,671	**21,047**	32,424	298,643	**226,678**	154,713	**99,257**	407,572	**346,983**	286,394

Table 4. Global and regional differences of the prevalence and reporting of maternal syphilis seropositivity between 2008 and 2011 estimates.

Region	2008 Positivity Data			2011 Positivity Data			Difference between 2008 and 2011			
	Number Reporting (%)	Regional Reporting (%)	Median Positivity (%)	Number reporting	Regional Reporting (%)	Median Positivity (%)	Reporting Difference	% Change in Reporting	Median Difference	% Change in Median Positivity
Africa	38	84.4%	2.13%	40	88.9%	1.57%	2	5.3%	-0.56%	-26.4%
Americas	21	61.8%	0.84%	28	82.4%	0.55%	7	33.3%	-0.29%	-34.8%
Asia	7	70.0%	0.62%	9	90.0%	0.29%	2	28.6%	-0.33%	-53.0%
Europe	13	25.0%	0.16%	20	38.5%	0.05%	7	53.8%	-0.11%	-67.9%
Mediterranean	7	33.3%	0.06%	10	47.6%	0.96%	3	42.9%	0.90%	1583.5%
Pacific	11	42.3%	0.33%	15	57.7%	0.76%	4	36.4%	0.44%	132.8%
Global Total	**97**	**50.3%**	**1.09%**	**122**	**63.2%**	**0.79%**	**25**	**25.8%**	**-0.30%**	**-27.4%**

Table 5. The difference between maternal and congenital syphilis numbers and the proportion of the global burden in 2011 compared with 2008.

Region	2008				2011				Difference between 2008 and 2011			
	Maternal	Global Burden (%)	Congenital	Global Burden (%)	Maternal	Global Burden (%)	Congenital	Global Burden (%)	Maternal	% Change	Congenital	% Change
Africa	583,529	41.42%	246,982	45.38%	520,415	58.95%	216,969	62.53%	-63,114	-10.8%	-30,013	-12.2%
Americas	106,500	7.56%	29,061	5.34%	82,508	9.35%	22,452	6.47%	**-23,992**	**-22.5%**	-6,609	**-22.7%**
Asia	603,293	42.82%	230,763	42.40%	104,305	11.81%	39,922	11.51%	-498,989	-82.7%	-190,841	-82.7%
Europe	21,602	**1.53%**	4,786	**0.88%**	11,941	**1.35%**	2,649	**0.76%**	**-9,661**	**-44.7%**	-2,137	**-44.6%**
Mediterranean	40,062	2.84%	17,435	3.20%	116,270	13.17%	51,089	14.72%	76,208	190.2%	33,654	193.0%
Pacific	53,825	**3.82%**	15,231	**2.80%**	47,412	**5.37%**	13,901	**4.01%**	**-6,413**	**-11.9%**	-1,329	**-8.7%**
Global Total	**1,408,811**	100.00%	**544,257**	100.00%	**882,851**	100.00%	**346,983**	100.00%	-525,960	-37.3%	**-197,274**	-36.2%

Table 6. Estimated number of adverse outcomes associated with syphilis in pregnancy in the middle case testing and treatment scenario and the minimum targets for the validation of the elimination of congenital syphilis by the World Health Organization based on ≥ 95% antenatal coverage, ≥ 95% testing, and ≥ 95% treatment of syphilis seropositive pregnant women aggregated for each region.

Region	Stillbirth or Early Fetal Death		Neonatal Death		Prematurity or Low Birth Weight		Infected Infant		Any Adverse Outcome	
	Middle	ECS Validation	Middle	ECS Validation	Middle	ECS Validation	Middle	ECS Validation	Middle	ECS Validation
Africa	88,186	32,244	38,015	14,624	26,519	14,044	64,249	13,829	**216,969**	**74,741**
Americas	9,282	5,033	4,062	2,285	3,157	2,209	5,951	2,121	**22,452**	**11,648**
Mediterranean	20,731	8,094	8,923	3,672	6,154	3,528	15,281	3,466	**51,089**	**18,760**
Europe	1,107	711	489	324	404	316	648	292	**2,649**	**1,642**
Asia	16,273	6,499	7,033	2,946	5,003	2,823	11,614	2,805	**39,922**	**15,073**
Pacific	5,727	2,918	2,499	1,324	1,902	1,275	3,774	1,242	**13,901**	**6,759**
Global Total	**141,307**	**55,499**	**61,021**	**25,175**	**43,139**	**24,196**	**101,517**	**23,754**	**346,983**	**128,624**

Table 7. The live birth counts for ten countries with the highest number of live births in 2008 and 2011.

	Live births count, 2008	Global Total (%)	Live births count, 2011	Global Total (%)
India	26,912,842	19.8%	27,098,275	20.1%
China	18,133,735	13.3%	16,431,611	12.2%
Nigeria	6,027,913	4.4%	6,457,908	4.8%
Pakistan[a]	5,336,931	3.9%	4,763,694	3.5%
Indonesia	4,219,718	3.1%	4,331,100	3.2%
United States[a]	4,398,904	3.2%	4,322,394	3.2%
Bangladesh	3,429,541	2.5%	3,016,199	2.2%
Brazil	3,104,862	2.3%	2,995,976	2.2%
Congo, Democratic Republic	2,886,065	2.1%	2,911,849	2.2%
Ethiopia	3,090,390	2.3%	2,613,323	1.9%
10 Countries Sub-Total	**77,540,901**	**57.0%**	**74,942,329**	**55.5%**
Sub-Total of Countries Reporting	**104,166,522**	**76.5%**	**107,074,100**	**79.3%**
Global Total	**136,088,145**	1	**134,997,386**	1

[a]Values are based on regional medians because country data was unavailable.

Table 8. The difference in syphilis seropositivity prevalence in antenatal care (ANC) attendees and the estimated number of maternal and congenital syphilis infections between 2011 and 2008 for the ten countries with the highest live births with respect to reporting countries and globally for all World Health Organization member-states.

Countries with highest number of live births	Prevalence of syphilis seropositivity in ANC attendees		Maternal Syphilis Infections				Congenital Syphilis Infections				Differences and percent change between 2008 and 2011					
	2008	2011	2008	Global burden	2011	Global burden	2008	Global Burden	2011	Global Burden	Seropositivity	% Change	Maternal	% Change	Congenital	% Change
India	2.26%	0.29%	406,550	28.9%	52,918	6.0%	158,722	29.2%	20,567	5.9%	-2.0%	-87.1%	-353,632	-79.2%	-138,155	-79.7%
China	0.33%	0.20%	39,072	2.8%	21,645	2.5%	10,978	2.0%	5,911	1.7%	**-0.1%**	**-39.0%**	**-17,427**	**-11.6%**	**-5,067**	**-15.5%**
Nigeria	1.50%	1.50%	61,881	4.4%	66,058	7.5%	27,464	5.0%	29,752	8.6%	0.0%	0.0%	4,177	70.3%	2,288	69.9%
Pakistan[a]	0.06%	0.96%	2,082	0.1%	31,541	3.6%	969	0.2%	8,639	2.5%	**0.9%**	**1583.5%**	**29,459**	**2317.6%**	**7,670**	**1298.9%**
Indonesia	5.83%	1.17%	162,676	11.5%	33,542	3.8%	58,098	10.7%	11,979	3.5%	-4.7%	-79.9%	-129,134	-67.1%	-46,119	-67.7%
United States[a]	0.84%	0.55%	24,188	1.7%	15,509	1.8%	6,610	1.2%	5,551	1.6%	**-0.3%**	**-34.8%**	**-8,680**	**2.3%**	**-1,059**	**31.7%**
Bangladesh	0.62%	0.62%	29,042	2.1%	12,834	1.5%	6,254	1.1%	5,460	1.6%	0.0%	0.0%	-16,208	-29.5%	-794	36.9%
Brazil	1.60%	1.10%	32,616	2.3%	21,671	2.5%	8,564	1.6%	5,747	1.7%	**-0.5%**	**-31.1%**	**-10,945**	**6.0%**	**-2,817**	**5.3%**
Congo, Democratic Republic	1.98%	3.27%	38,675	2.7%	64,105	7.3%	15,793	2.9%	25,984	7.5%	1.3%	65.0%	25,430	164.5%	10,191	158.1%
Ethiopia	2.67%	2.20%	55,411	3.9%	38,784	4.4%	26,776	4.9%	18,436	5.3%	**-0.5%**	**-17.7%**	**-16,627**	**11.7%**	**-8,340**	**8.0%**
10 Countries Sub-Total	-	-	**852,193**	**60.5%**	**358,606**	**40.6%**	**320,227**	**58.8%**	**138,026**	**39.8%**	-	-	**-493,586**	**-32.9%**	**-182,201**	**-32.4%**
Sub-Total of Countries Reporting	-	-	**1,309,018**	**92.9%**	**743,196**	**84.2%**	-	-	-	-	-	-	**-565,822**	**-9.4%**	-	-
Global Total	-	-	**1,408,811**	**1**	**882,851**	**1**	**544,257**	**1**	**346,983**	**1**	-	-	**-525,960**	**0.0%**	**-197,274**	**0.0%**

[a]Values are based on regional medians because country data was unavailable.

[b]Missing values for aggregate prevalence of syphilis seropositivity and congenital syphilis are currently unavailable.

Table 9. Estimated number of adverse outcomes associated with syphilis in pregnancy under the assumptions of the middle case testing and treatment scenario and minimum numbers for the validation of the Elimination of Congenital Syphilis (ECS) with universal coverage (≥ 95%) of antenatal care with universal syphilis testing and treatment for the ten highest live birth countries.

Region	Stillbirth or Early Fetal Death		Neonatal Death		Prematurity or Low Birth Weight		Infected Infant		Any Adverse Outcome	
	Middle	ECS Validation	Middle	ECS Validation	Middle	ECS Validation	Middle	ECS Validation	Middle	ECS Validation
India	8,379	3,300	3,620	1,496	2,565	1,433	6,003	1,425	**20,567**	**7,654**
China	2,443	1,350	1,069	612	830	586	1,569	583	**5,911**	**3,131**
Nigeria	12,064	4,119	5,189	1,867	3,560	1,789	8,939	1,779	**29,752**	**9,555**
Pakistan[a]	5,581	1,967	2,403	892	1,660	854	4,107	850	**13,750**	**4,562**
Indonesia	4,895	2,092	2,120	948	1,533	908	3,430	903	**11,979**	**4,852**
United States of America[a]	1,719	967	753	438	587	420	1,095	418	**4,154**	**2,243**
Bangladesh	2,218	800	955	363	664	347	1,623	346	**5,460**	**1,856**
Brazil	2,379	1,284	1,042	584	816	572	1,510	523	**5,747**	**2,963**
Democratic Republic of Congo	10,571	3,998	4,561	1,812	3,202	1,736	7,651	1,727	**25,984**	**9,272**
Ethiopia	7,463	2,419	3,206	1,096	2,175	1,050	5,591	1,045	**18,436**	**5,610**
Global Total	**57,712**	**22,295**	**24,917**	**10,109**	**17,593**	**9,695**	**41,518**	**9,598**	**141,740**	**51,698**

[a]Values are based on regional medians because country data was unavailable.

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