Prenatal Transmission of Syphilis and Human Immunodeficiency Virus in Brazil: Achieving Regional Targets for Elimination

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Background.   The Pan-American Health Organization has called for reducing (1) human immunodeficiency virus (HIV) mother-to-child transmission (MTCT) to ≤0.30 infections/1000 live births (LB), (2) HIV MTCT risk to ≤2.0%, and (3) congenital syphilis (CS) incidence to ≤0.50/1000 LB in the Americas by 2015.

Methods.   Using published Brazilian data in a mathematical model, we simulated a cohort of pregnant women from antenatal care (ANC) through birth. We investigated 2 scenarios: "current access" (89.1% receive one ANC syphilis test and 41.1% receive 2; 81.7% receive one ANC HIV test and 18.9% receive birth testing; if diagnosed, 81.0% are treated for syphilis and 87.5% are treated for HIV) and "ideal access" (95% of women undergo 2 HIV and syphilis screenings; 95% receive appropriate treatment). We conducted univariate and multivariate sensitivity analyses on key inputs.

Results.   With current access, we projected 2.95 CS cases/1000 LB, 0.29 HIV infections/1000 LB, 7.1% HIV MTCT risk, and 11.11 intrauterine fetal demises (IUFD)/1000 pregnancies, with significant regional variation. With ideal access, we projected improved outcomes: 1.00 CS cases/1000 LB, 0.10 HIV infections/1000 LB, HIV MTCT risk of 2.4%, and 10.65 IUFD/1000 pregnancies. Increased testing drove the greatest improvements. Even with ideal access, only HIV infections/1000 LB met elimination goals. Achieving all targets required testing and treatment >95% and reductions in prevalence and incidence of HIV and syphilis.

Conclusions.   Increasing access to care and HIV and syphilis antenatal testing will substantially reduce HIV and syphilis MTCT in Brazil. In addition, regionally tailored interventions reducing syphilis incidence and prevalence and supporting HIV treatment adherence are necessary to completely meet elimination goals.

Keywords.   congenital syphilis; disease elimination; human immunodeficiency virus; infectious disease transmission; mathematical models; vertical transmission.

Mother-to-child transmission (MTCT) of syphilis and human immunodeficiency virus (HIV) remains a significant public health concern in Latin America and the Caribbean (LAC). Despite effective interventions to prevent vertical transmission, each year an estimated 250 000 children are born in LAC with congenital syphilis (CS) and another 4700 are born with HIV [1, 2]. It has been shown that investments in preventing MTCT (PMTCT) of syphilis and HIV are very cost-effective and will avert morbidity and mortality among children [3, 4].

In 2013, an estimated 74% of pregnant women in LAC received HIV testing, with similar syphilis testing rates [5]. There are many steps along a "cascade" of antenatal services at which patients are lost from care, including access to antenatal care (ANC), HIV and syphilis testing and test result return, access to medications for PMTCT, infant diagnosis, and retention in treatment [6].

Among the countries of LAC, Brazil carries a significant proportion of the HIV and syphilis burden, yet it also has highly developed systems of PMTCT services and clinical data collection [7, 8]. The provision of free HIV care since 1996 has helped to develop HIV and syphilis ANC services [9], which, coupled with Brazil's geographical and economic diversity, positions the country and its regions to serve as a model for many other LAC countries [10]. Although HIV control has improved over time, CS remains a substantial problem in Brazil [11, 12].

National ministries of health in the LAC region and the Pan American Health Organization (PAHO) have declared a goal to eliminate HIV and syphilis MTCT by 2015, with a plan to integrate antenatal HIV and syphilis care [13]. In particular, these goals include the following: reducing MTCT of HIV incidence to ≤0.30 cases/1000 live births (LB), reducing risk of HIV MTCT to ≤2.0%, and reducing the incidence of CS to ≤0.50 cases/1000 LB [14].

The operational requirements needed to achieve these goals are generally understood, but more insight is needed to investigate the impact they may have on PMTCT at the regional and national level. We expanded a computer simulation model of PMTCT in HIV [15–17] to include syphilis MTCT, and we populated the model with input data specific to Brazil. We used this model (1) to project the number of neonatal HIV and syphilis cases associated with current antenatal services in Brazil and (2) to project the impact of expanding syphilis- and HIV-related services in ANC.

METHODS

Analytic Overview

We added syphilis infection and MTCT to a validated computer model of HIV MTCT [15–17]. The model incorporates each step of the cascade of ANC, including presentation to care, syphilis and HIV testing, result return, treatment availability, and treatment adherence (Supplementary Figure 1 and Appendix 1). We next simulated the cohort of women becoming pregnant each year in Brazil, and we examined scenarios that represented both "current" and expanded (or "ideal") levels of ANC services (discussed later in the Methods). Our primary outcomes were CS and pediatric HIV infection rates per 1000 LB, and risk of HIV MTCT. Because CS is tied closely to intrauterine fetal demise (IUFD) [18], we also simulated this outcome. To reflect a range of access to care and HIV and syphilis prevalence and incidence values, we projected outcomes at national and regional levels within Brazil.

Cohort Characteristics and Treatment Strategies

We simulated a representative cohort of pregnant women, first for the entire country and then separately for Brazil's 5 administrative regions (Table 1). Among pregnant women in the national cohort, the initial syphilis prevalence was 1.0% (ranging by region from 0.8% to 1.1%) [21], with a syphilis incidence of 0.2% during pregnancy [22] (see Supplementary Appendix 1 for incidence derivation). The national prevalence of HIV was 0.4%, ranging by region from 0.3% to 0.9% [19]. Among pregnant women with chronic HIV infection, 30.2% had CD4 counts ≤350/μL [20]. Human immunodeficiency virus MTCT risks were stratified by CD4 count and antiretroviral therapy (ART) receipt, based upon rates in recent literature [35–45].

Pregnant women identified with syphilis or HIV were eligible for treatment according to Brazilian and PAHO guidelines [48]. This includes penicillin treatment after syphilis diagnosis and treatment with 3-drug ART after HIV diagnosis, irrespective of CD4 count [14, 48]. Treatment and transmission were only considered until birth; due to rare postnatal syphilis transmission and wide acceptance of and government funding for formula feeding among HIV-infected Brazilian women, postnatal transmission and treatment were not considered [49].

Model Structure

The MTCT model is a decision-analytic simulation of a cohort of pregnant women from conception through delivery (TreeAge Pro, Williamstown, MA), described in detail in Supplementary Figure 1 and Appendix 1 [15–17]. The model uses a decision-tree (deterministic) structure, including probabilities of the following key events in the cascade of antenatal and perinatal care: presentation to ANC; acceptance of HIV and syphilis testing; offer of and adherence to ART for PMTCT of HIV; syphilis treatment (defined as receipt of 1 or more doses of penicillin); prevalence and incidence of syphilis and HIV; repeat syphilis testing and treatment; maternal mortality during pregnancy; HIV testing in labor for women with unknown or negative HIV status; live birth; infant HIV and syphilis infection by the time of delivery; and linkage to postnatal care and ART for mothers (further details in Supplementary Appendix).

Data

We used published Brazilian data to simulate (1) levels of uptake at each step in the ANC cascade as well as (2) clinical probabilities of HIV and CS transmission, IUFD, maternal HIV suppression, maternal syphilis cure, and maternal and neonatal mortality (Table 1). Probabilities of HIV and syphilis MTCT were based on published literature and were dependent on maternal status with regard to each disease: for syphilis, early versus late infection; for HIV, CD4 ≤350/μL versus CD4 >350/μL; as well as treatment status for both infections. We assumed that maternal infection with HIV did not affect syphilis transmission, and syphilis infection did not affect HIV transmission, given conflicting clinical evidence [50–53].

Outcomes

We projected outcomes (1) on the national level for mothers and (2) both regionally and nationally for newborns. We did

Table 1. Key Data Parameters Used in a Computer Model of Congenital Syphilis and Mother-to-Child HIV Transmission in Brazil

Parameter	Value	Range	Reference
National Parameters			
Maternal Cohort Characteristics			
Prevalence of HIV	0.004	0.0032–0.0051	[19]
Proportion of HIV+ with CD4 ≤350/μL	0.302		[20]
Prevalence of maternal syphilis at first ANC visit	0.010	0.008–0.013	[21]
Incidence of maternal syphilis (rate/pregnancy)	0.002	0.001–0.004	[22, 23]
Proportion of maternal syphilis that is early syphilis	0.250	0.100–0.400	[24]
ANC Cascade (Proportions)			
Access to ANC (of pregnant women)	0.982		[12]
Test for HIV (of women in ANC)	0.817	0.684–0.928	[19]
Test for HIV in labor (of women delivering at healthcare facility without prior positive HIV result)	0.189	0.100–0.300	[25]
On antiretroviral regimen (ART) at presentation to ANC (of diagnosed, HIV-infected women)	0.330		[8]
Start ART if diagnosed as HIV-positive	0.875	0.794–0.936	[19, 26, 27]
Adhere to ART (of all women on ART)	0.735	0.650–0.850	[28, 29]
Test for syphilis at 1st visit (of women in ANC)	0.891	0.795–0.949	[21]
Receive syphilis treatment if positive test (penicillin)	0.810	0.650–0.950	[30]
Deliver at a healthcare facility (of all pregnant women)	0.990		[12]
Test Characteristics			
Sensitivity of HIV test	0.996		[31]
Specificity of HIV test	0.997		[31]
Sensitivity of syphilis test (VDRL)	0.880	0.78–1.00	[32]
Specificity of syphilis test (VDRL)	0.980		[32]
Syphilis probabilities			
Maternal syphilis cure after treatment	0.990		[33]
Transmit syphilis to baby			
Early syphilis, untreated	0.940	0.750–0.990	[24]
Late syphilis, untreated	0.370	0.190–0.560	[24]
After treatment (any stage)	0.030	0.020–0.070	[34]
HIV probabilities[a]			
Transmit HIV to baby			
When mother's CD4 ≤350/μL, no ART	0.207	0.150–0.273	[35–38]
When mother's CD4 >350/μL, no ART	0.132	0.110–0.175	[35–38]
When mother's CD4 ≤350/μL, on ART	0.036	0.011–0.036	[39–41]
When mother's CD4 >350/μL, on ART	0.011	0.004–0.011	[41, 42]
When mother's CD4 ≤350/μL, AZT in labor only	0.134	0.100–0.300	[40, 43, 44]
When mother's CD4 >350/μL, AZT in labor only	0.055	0.050–0.080	[43–45]
Mortality of fetus in antenatal period (by maternal status)			
Delivery at a healthcare facility			
No HIV or syphilis	0.009	0.007–0.012	[14][b]
With HIV, not on ART	0.019	0.009–0.030	[14][c]
With HIV, on ART	0.009		[14]
With syphilis, not treated	0.250	0.250–0.438	[18]
With syphilis, treated	0.045		[18, 34]
With syphilis and HIV, on ART	0.250	0.250–0.438	[18]
With syphilis and HIV not on ART	0.260	0.260–0.448	[18]
Delivery at home (additional risk)	0.010	0.000–0.020	Assumption
Mortality of mother from ANC period to 6 wks post delivery	0.0006		[14]

Table 1   continued.

Parameters varied by region	National	North	Northeast	Southeast	South	Midwest	References
Regional Parameters							
Maternal HIV prevalence	0.004	0.004	0.003	0.003	0.009	0.003	[19]
Maternal syphilis prevalence	0.010	0.008	0.011	0.010	0.011	0.010	[21]
Test for HIV in ANC	0.817	0.699	0.684	0.882	0.928	0.832	[19]
Test for HIV in labor	0.189	0.169	0.285	0.162	0.095	0.141	[25]
Start antiretroviral regimen if HIV-positive	0.875	0.794	0.800	0.942	0.904	0.817	[7, 8, 26, 27, 46, 47]
Test for syphilis at 1st ANC visit	0.891	0.795	0.848	0.918	0.949	0.861	[21]
Test for syphilis on return visit	0.411	0.292	0.310	0.445	0.567	0.428	[21]

Abbreviations: ANC, antenatal care; ART, antiretroviral treatment; AZT, zidovudine; HIV, human immunodeficiency virus; VDRL, Venereal Disease Research Laboratory.

[a] Assumes reduced transmission given higher cesarean-section prevalence (Supplementary Appendix 1).

[b] Subtracting mortality from HIV, syphilis, and home delivery.

[c] Assumption of 0.010 increased mortality with untreated HIV.

not examine maternal outcomes at the regional level due to a desire to maintain focus on infant transmission and their outcomes. Modeled neonatal outcomes included the expected number of neonatal HIV and CS cases/1000 LB among the general population as well as cases of IUFD/1000 pregnancies and the HIV MTCT risk (defined as the proportion of HIV-infected women transmitting HIV to their infants during pregnancy or delivery). The absolute number of neonatal HIV and syphilis cases in each region were estimated by multiplying the projected HIV and syphilis cases/1000 LB by the number of births nationally, as well as in each region [12, 54]. All national-level projections were based on aggregate national data (Table 1), whereas regional-level analyses used data collected within each region

(Table 2). Modeled maternal outcomes included the proportion of syphilis-infected women achieving syphilis cure and the proportion of HIV-infected women receiving and adhering to ART until delivery.

Scenarios

We compared a "current access" scenario using the best available estimates of current access to PMTCT services (Table 1) to an "ideal access" scenario (95% of women in ANC tested for HIV and syphilis; 95% treated with positive result). In cases where ideal access was insufficient to meet elimination goals for the LAC region, we modeled (1) further expansion of PMTCT services as well as (2) changes in HIV and syphilis

Table 2.   Projected Outcomes in a Model-Based Study of HIV and Syphilis PMTCT in Brazil

Infant Outcomes[a]	"Current Access"	Test 95% of Women in ANC	Treat 95% of Women Diagnosed With HIV and Syphilis	Both Test and Treat 95%: "Ideal Access"[b]
Cases per 1000 Live Births				
Congenital syphilis[c]	2.95	1.51	2.42	1.00
HIV	0.29	0.14	0.20	0.10
IUFD	11.10	10.80	10.90	10.70
% Transmission				
HIV MTCT	7.1%	3.4%	4.8%	2.4%
Maternal Outcomes	At Birth, Current Access		At Birth, Ideal Access[b]	% Change With Scale-up
Maternal syphilis prevalence	0.3%		0.1%	−75.2%
% HIV+ mothers on ART and in care	51.7%		83.6%	+61.7%

Abbreviations: ANC, antenatal care; ART, antiretroviral therapy; HIV, human immunodeficiency virus; IUFD, intrauterine fetal demise; MTCT, mother-to-child transmission; PAHO, Pan American Health Organization; PMTCT, preventing MTCT.

[a] PAHO elimination targets are reducing HIV MTCT to ≤0.3 cases/1000 live births (LB), reducing HIV MTCT risk to ≤2.0%, and reducing syphilis MTCT to ≤0.50/1000 LB by 2015.

[b] "Ideal" access: 95% of women in ANC are tested for HIV and syphilis, 95% of women diagnosed with either condition are treated.

[c] Congenital syphilis is clinically defined as the sum of live-born infants with clinical evidence of syphilis infection and cases of IUFDs attributable to syphilis (Supplementary Appendix 1).

incidence and prevalence, to identify conditions necessary to meet elimination goals.

Model Validation and Sensitivity Analyses

In previous work, we validated model-derived outcomes of HIV MTCT risk against published data [15–17]. For this analysis, we also validated the expanded model for syphilis transmission outcomes, both nationally and in selected published regions of Brazil (Supplementary Appendix 1).

We conducted sensitivity analyses on key clinical and access-to-care parameters related to HIV and syphilis (ranges in Table 1). These included one-way and multiway sensitivity analyses in which we varied HIV and syphilis test sensitivity and specificity, testing rates, treatment rates, prevalence of HIV, and prevalence and incidence of syphilis (incorporating the impact of sexual behavior as well as test characteristics; Supplementary Appendix). Values for sensitivity analyses were chosen based on ranges of published data. Results of sensitivity analyses were shown (1) if they led to >10% change in an output parameter or (2) where they were anticipated to inform decisions in prioritizing PMTCT interventions despite having a <10% impact. For parameters that are well established in literature or judged to have limited implications on policy, base case parameters were not varied (ranges omitted in Table 1). The incidence of HIV during pregnancy was not included in the model because it had minimal

impact over a reasonable range consistent with a prevalence of 0.4% and lifelong disease duration. We also varied the effectiveness of penicillin in preventing CS and of ART in preventing HIV MTCT; higher effectiveness serves as a proxy measure for earlier testing, earlier treatment, higher medication availability, and greater medication adherence.

RESULTS

Current Access to Care
Infant Outcomes

At the national level for Brazil, using current access, CS and neonatal HIV rates were projected to be 2.95 and 0.29 cases/1000 LB, respectively (Table 2), with 11.11 IUFD/1000 LB. This meets the PAHO goals for cases of HIV/1000 LB, but it does not reach the other 2 HIV and CS goals. Among pregnant women with HIV, the projected HIV MTCT risk was 7.1% (Table 2, Figure 1, Current access). These results were consistent with published figures, with the exception of syphilis, which we projected to be slightly lower than the 3.3 cases/1000 LB estimated by the Brazilian Ministry of Health (MOH) [11]. Although we defined an incident case clinically, Brazilian MOH estimates define a case as any exposure without appropriate treatment (Supplementary Appendix). Projected infant outcomes varied widely between the 5 administrative regions of
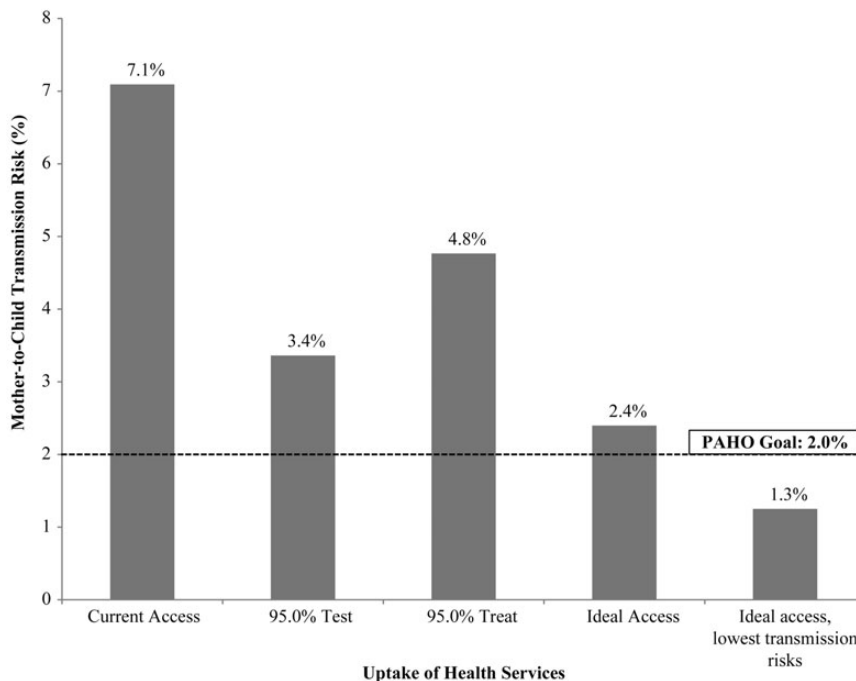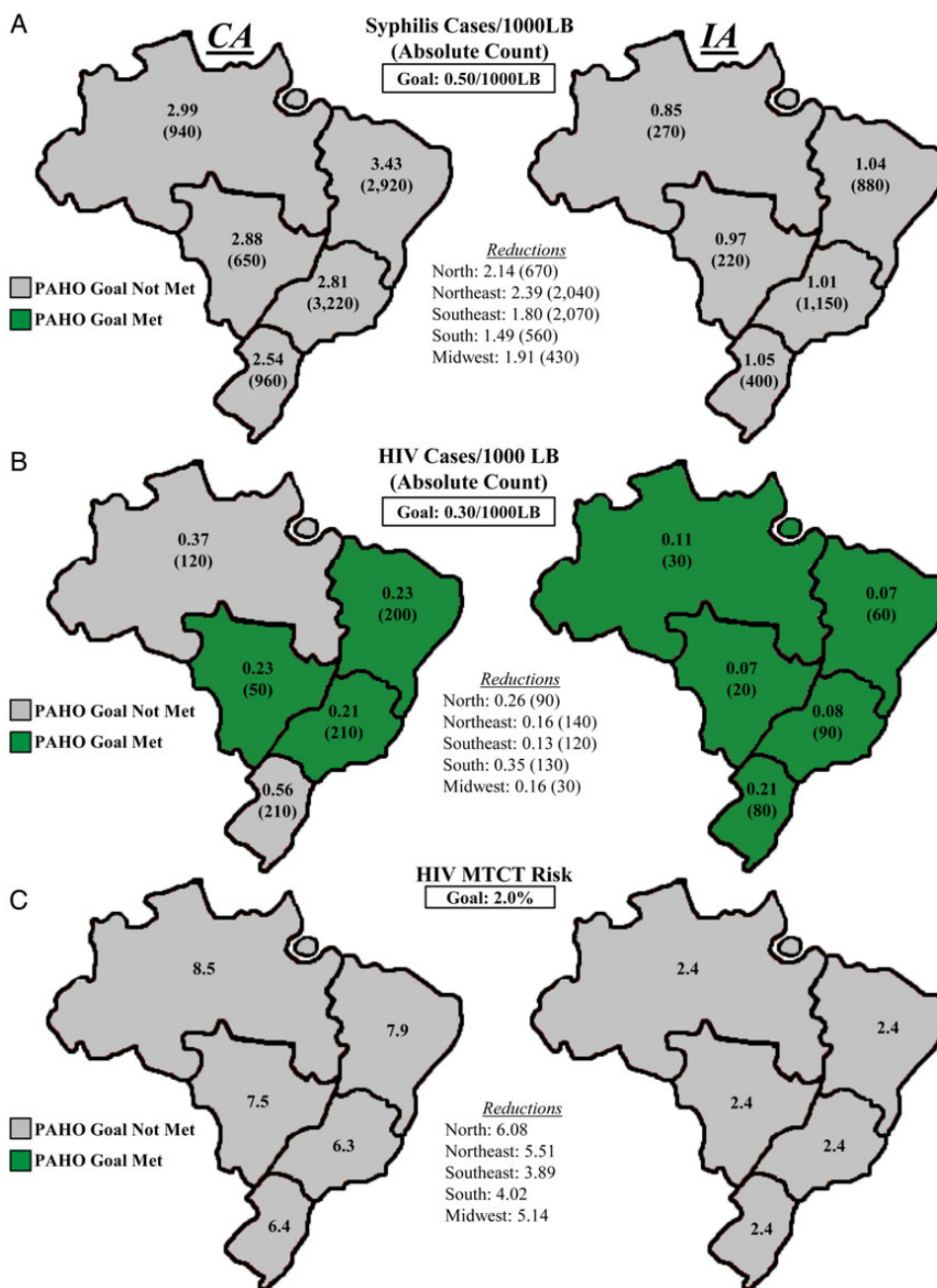

Figure 1. Mother-to-child transmission (MTCT) risk among human immunodeficiency virus (HIV)-positive women. The vertical axis shows the risk of HIV transmission from mother to child, with the horizontal axis demonstrating each modeled scenario. The MTCT risk is not below 2.0% for the "current access," the condition where 95% of mothers are tested, the condition where 95% of mothers are treated, or even for the "ideal access" scenario (95% test and 95% treat). The MTCT risk among HIV-positive women is below 2.0% only under ideal access with lowest assumed transmission risk. Abbreviation: PAHO, Pan American Health Organization.

Brazil (Figure 2). Congenital syphilis occurred with greatest frequency in the North (2.99 cases/1000 LB) and Northeastern (3.43 cases/1000 LB) regions. Cases of neonatal HIV and HIV MTCT rates varied according to HIV prevalence and PMTCT uptake: the South region had the highest rates of projected neonatal HIV cases, with 0.56 cases/1000 LB, but the North and Northeastern regions had the highest projected MTCT risks, at 8.5% and 7.9%, respectively.

Figure 2. Birth outcomes by region. (A) Projected mother-to-child transmission (MTCT) of syphilis per 1000 live births (LB) is highest in the Northeast region, which together with the Southeast makes up over 70% of all neonatal syphilis cases in Brazil. The "ideal access" scenario significantly reduces syphilis MTCT in all regions of the country, with 4110 syphilis cases avoided in the Northeast and Southeast alone. (B) Human immunodeficiency virus (HIV) cases/1000 LB are highest in the South and North, but by absolute number of cases the highest rates of pediatric HIV cases are seen in the South and Southeast. The South and Southeast alone account for over 50% of all pediatric HIV cases. Ideal access could result in a reduction of 250 pediatric HIV cases each year. (C) The risk of MTCT among HIV-infected mothers is highest in the North and Northeast region of Brazil. Achieving ideal access uptake will result in 2.4% risk of MTCT across each region. This represents a significant risk reduction in even the South and Southeast, which have the lowest MTCT risk. Abbreviations: CA, current access; IA, ideal access; PAHO, Pan American Health Organization.

Maternal Outcomes

In the current access analysis at the national level, maternal syphilis prevalence was 0.3% at the time of delivery (Table 2). The percentage of HIV-infected women on ART and in care was 51.7% at delivery.

Ideal Access to Care
Infant Outcomes

At the national level, the rates of neonatal HIV and CS in the ideal access scenario were substantially lower than in the current access scenario, driven largely by improvements in maternal testing for HIV and syphilis. Achievement of ideal access was projected to reduce CS to 1.00 cases/1000 LB and neonatal HIV to 0.10 cases/1000 LB, with 10.7 IUFD/1000 LB and a projected MTCT risk of 2.4% (Table 2; Figure 1). These results continue to meet PAHO goals for HIV cases/1000 LB (already met in the current access scenario) and approach the PAHO goals for HIV MTCT risk, but a significant gap remains for CS.

The impact of current and ideal access on infant outcomes at the regional level is shown in Figure 2. At current access, PAHO goals were met only for cases of HIV/1000 LB, and only in the Northeast and Midwest regions (both with rates of 0.23 cases/1000 LB) and the Southeast region (0.21 cases/1000 LB). Achieving ideal access was projected to meet PAHO elimination targets for number of cases of neonatal HIV/1000 LB in all regions, but even ideal access conditions would not reach elimination targets for cases of CS/1000 LB or for HIV MTCT risk in any of the regions.

Maternal Outcomes

Achieving ideal access was also projected to improve postpartum maternal outcomes at birth (Table 2). Among postpartum women, syphilis prevalence at birth decreased from 0.3% in the current access scenario to 0.1% with ideal access, and the proportion of HIV-infected women on ART and in care at birth increased from 51.7% in the current access scenario to 83.6% in the ideal access scenario.
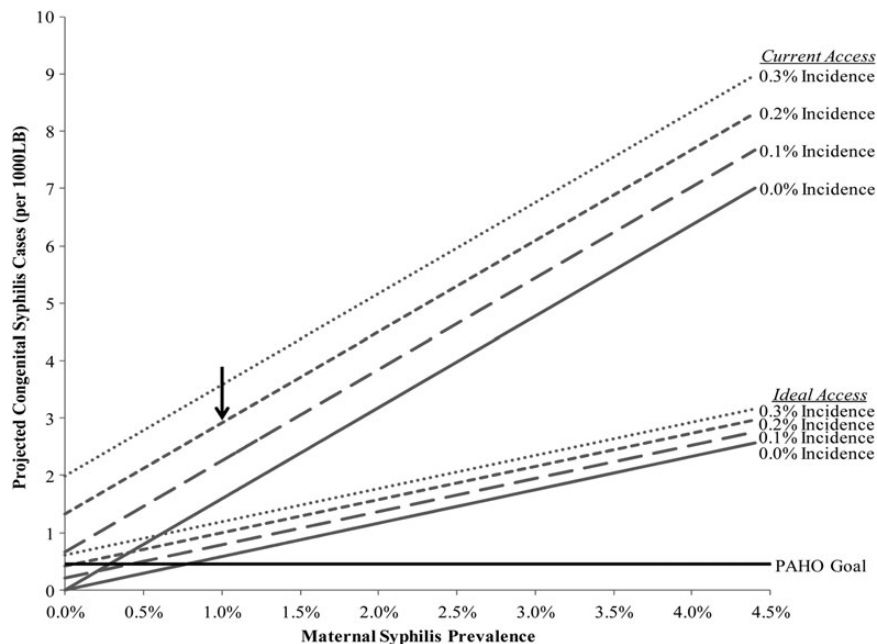
Sensitivity Analyses

In all one-way sensitivity analyses in which single parameters were varied through the ranges shown in Table 1, elimination targets for cases of CS/1000 LB and HIV MTCT were not met (Supplementary Figures S2 and S3). Simultaneous variations in multiple parameters were required to meet elimination targets. For example, HIV MTCT was ≤2.0% only when assuming both ideal access and the lowest published HIV transmission risks (Table 1), reaching rates as low as 1.3% under these conditions (Figure 1). When we examined the individual contributions of the 2 key improvements of ideal access, we found that improvements in testing (with no change in the proportion of tested women who were then treated) had a greater impact on both CS and HIV outcomes than improvements in treatment of those tested at the current access testing rate (Figure 1; Table 2).

The number of cases of CS was highly sensitive to maternal syphilis prevalence and incidence. The CS goal was only reached in the current access scenario when maternal syphilis incidence was set at zero and maternal syphilis prevalence was 0.3%; this led to a CS rate of 0.48 cases/1000 LB (Figure 3). When maternal syphilis incidence was assumed to be 0.1%, it was not possible to reach elimination goals with current access. Even with ideal access and maternal syphilis incidence of zero, a syphilis prevalence of ≤0.5% was needed to reach PAHO goals. The base-case maternal syphilis incidence of 0.2% required a prevalence of <0.2% to reach the regional goals at ideal access. If we simultaneously assumed ideal access, improved syphilis test sensitivity (99.0%), greater efficacy of syphilis treatment on transmission risk (1.0% syphilis transmission risk after treatment, compared with 3.0% in the base case), and a lower maternal syphilis incidence of 0.1%, projected syphilis "elimination" was possible at the current syphilis prevalence (projected CS rate 0.36 cases/1000 LB). Figures 1–3 and the Supplementary Appendix report additional sensitivity analyses; all other sensitivity analyses for which ranges are shown in Table 1 did not have a substantial effect on model results.

DISCUSSION

We used a validated computer model to examine the feasibility of achieving elimination targets for neonatal HIV and CS in Brazil and generated 4 key findings. First, we found that the current levels of ANC uptake in Brazil lead to HIV and syphilis transmission risks that do not yet meet most regional elimination goals. Increases in maternal testing would lead to the greatest improvements in transmission rates for both HIV and syphilis, and achievement of ideal testing and treatment levels together would have a significant impact on both diseases (Figure 1; Table 2). However, improved testing and treatment in isolation will be insufficient to completely achieve the elimination targets for either disease. This is particularly a challenge for syphilis elimination: current syphilis prevalence levels and incidence rates during pregnancy, together with imperfect test sensitivity, attenuate the effects of increasing access to ANC.

Second, to build upon this finding, we simulated the conditions necessary to achieve CS elimination goals. With the 2015 deadline now upon us, cases of CS (projected at 2.95/1000 LB) are still far from the target of ≤0.50/1000 LB. Our results show that elimination of syphilis could be reached with a combination of increased access to testing and treatment services, together with improvements in syphilis test sensitivity, reduction of maternal syphilis prevalence, and reduction of maternal syphilis incidence during pregnancy. Each of these parameters suggests specific interventions that policymakers might choose to approach elimination goals. For example, test sensitivity may be improved by new point-of-care syphilis tests [55], which may also improve linkage between a positive test and receipt of

Figure 3. Three-way sensitivity analysis, showing impact of maternal syphilis prevalence, maternal syphilis incidence, and uptake prevention of mother-to-child transmission (PMTCT) services. The vertical axis shows cases of congenital syphilis (CS)/1000 live births (LB). The horizontal axis shows the prevalence of maternal syphilis in Brazil. The black arrow indicates the base case input of 0.2% incidence with a prevalence of 1.0%. Projected results at base-case and "ideal" uptakes are shown. It is not possible to meet the Pan American Health Organization (PAHO) goals for elimination (defined as ≤0.50 cases of CS/1000 LB) unless syphilis incidence drops to 0.0% and prevalence drops below 0.5% for current levels of uptake. If uptake increases to 95%, incidence and prevalence still need to drop to at least 0.1% and 0.5%, respectively, to meet elimination targets. Transmission of syphilis still occurs at "ideal access" rates due to remaining gaps in testing and treatment, 88% sensitivity of syphilis testing (Venereal Disease Research Laboratory), and imperfect treatment efficacy (97%). Although incidence and prevalence are varied independently in the figure, in reality they will increase or decrease together.

penicillin treatment. The PMTCT services targeted before conception may reduce the prevalence and incidence of syphilis among women who may become pregnant, as well as their partners. Such services might include, for example, expanding counseling, testing, and treatment programs for syphilis in the general population and for partners of pregnant women, as well as counseling regarding behavioral risk reduction [56]. Identifying and treating syphilis in women and their partners would likely reduce transmission of the disease in addition to the prevalence. In addition, increasing uptake of third-trimester repeat testing for syphilis (per Brazilian MOH recommendations) would be valuable to reduce the impact of incident maternal infection on CS [48, 57]. It is noteworthy that CS projections were partly limited by available Brazilian data. We used national incidence estimates based on non-treponemal tests, and we downwardly adjusted these rates to account for both false-negative results in the first test and false-positive results in the second test (Supplementary Appendix 1) [58].

Third, we identified the conditions necessary to achieve HIV MTCT goals. On a national level, Brazil is currently meeting one important goal for HIV elimination (projected rate of 0.29 HIV cases/1000 LB, below the PAHO goal of ≤0.30 cases/1000 LB) and could significantly surpass the goal with reasonable improvements in HIV testing and treatment. This success reflects many years of developing excellent infrastructure for HIV care [59], particularly in the areas of Brazil that were traditionally the epicenters of the disease [8]. However, Brazil is much further from meeting the second HIV-related goal, defined as ≤2.0% MTCT, with a projected current access MTCT risk of 7.1%. To reach the ≤2.0% MTCT goal, programs will need to support not only increased testing and treatment (reflected in our ideal access scenario; Figure 1) but also interventions to support adherence throughout pregnancy (reflected in the "lowest transmission risks") [28, 29].

Fourth, the results for each of Brazil's diverse regions highlight the need to tailor HIV- and syphilis-related interventions to specific contexts, both regionally and nationally. Considering regional differences in CS, projected CS cases/1000 LB exceed PAHO goals throughout all of Brazil's regions (Figure 2), and CS cases/1000 LB are highest in the North and Northeast. These findings differ from Brazilian CS surveillance data, which describe the highest CS rates in the Southeast region. We hypothesize that these differences are due to a more robust CS surveillance system in the Southeast compared with other regions [11]. The higher CS incidence in the Northeast brings the absolute number of CS cases on par with the Southeast

despite a smaller population, underscoring the importance of focusing resources on syphilis in the Northeast region.

Considering regional differences in HIV outcomes, it is noteworthy that over half of annual infant infections with current access in Brazil are projected to be in the South and Southeast (420 of 790; Figure 2). This occurs despite relatively better ANC services there than in other regions, due to both high HIV prevalence and the large population in these regions. However, the North and Northeast regions have much higher projected HIV MTCT risks, defined as the risk of an HIV-infected woman transmitting HIV to her infant, than the South and Southeast. Combined with a stable or even increasing HIV prevalence in those regions [60], this suggests that there is significant potential to improve HIV outcomes in the North and Northeast as well. Efforts to plan CS- and HIV-related programmatic modifications throughout Latin America should incorporate the specific differences in disease prevalence and access to care between settings, as exemplified by the regions of Brazil, to ensure that interventions have the greatest impact. The effectiveness of specific interventions toward these goals in each region is an important area of future implementation science investigation.

Model-based analyses have several limitations. Model outcomes are based upon best available data at the time of analysis, which were incomplete for several parameters. In some cases, we made assumptions of the relationship between 2 events; for example, the repeat tests were independent given the lack of data on the false-negative and false-positive rate after a first false-negative or false-positive test. We conducted extensive sensitivity analyses around key uncertain parameters, varying them through wide plausible ranges, and our main conclusions were unchanged except as noted (Supplementary Appendix 1). In addition, models necessarily simplify complex biologic and behavioral processes. For example, the behavior of pregnant women's partners is only indirectly addressed through the issue of incident cases of syphilis in pregnancy [22, 23]. Despite these limitations, model-based analysis can help estimate the current status of PMTCT efforts and predict the measures necessary to achieve elimination goals [16].

CONCLUSIONS

In conclusion, increasing access to ANC services to ideal levels will have a substantial impact on vertical transmission of HIV and syphilis, preventing lifelong disease among thousands of newborns and reducing maternal morbidity and mortality from HIV and syphilis. Interventions targeted to both diseases can benefit from the same infrastructure, personnel, and information campaigns [61]. Achieving ideal access would result in HIV transmission risks approaching regional goals, while syphilis transmission rates would not reach these targets. In order to achieve elimination, policies will need to address not only individual pregnant women, but also their partners and the nonpregnant

general population, to improve prevention through reduction of disease prevalence and incidence.

Supplementary Material

Acknowledgments

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