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Economic Evaluation

Cost-Effectiveness Analysis of Point-of-Care Rapid Testing Versus Laboratory-Based Testing for Antenatal Screening of Syphilis in Brazil

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ABSTRACT

Objectives: Severe consequences of mother-to-child transmission of syphilis and high increasing incidence of congenital syphilis remains an important public health problem in Brazil. Our objective was to assess the cost-effectiveness of a rapid point-of-care test (RT) and treatment of positive mothers immediately compared with a laboratory-based standard test (ST) with treatment at next follow-up visit.

Methods: A decision analytic model was developed to estimate the incremental cost-effectiveness ratio (ICER) between antenatal syphilis screening strategies. The model was built with lifetime horizon from Brazilian health system perspective using 3% and 5% discount rates. A hypothetical cohort of pregnant women at reproductive age were used in the model. Health outcomes: low birth weight, stillbirths, neonatal deaths and congenital syphilis were estimated in disability-adjusted life-years (DALYs) lost. Microcosting study and secondary data provided parameters of direct medical costs. Probabilistic sensitivity analysis was undertaken.

Results: For base case, the mean cost per pregnant woman screened was $2.63 (RT) and $2.48 (ST), respectively. Maternal syphilis was associated with a loss of 0.0043 DALYs (RT) and 0.0048 DALYs (ST) per mother screened. Expected value of incremental cost per DALY averted was $298.08. After 10 000 probabilistic sensitivity analysis model runs, incremental cost and health benefits were $0.15 (95% credible interval −1.56 to 1.92) and 0.00042 DALYs (95% credible interval −0.0036 to 0.0044), respectively, with a mean ICER of $357.44 per DALY. Screening with RT has a 58% chance of being the optimal strategy at a threshold of $3,200 per DALY.

Conclusions: In Brazil, antenatal screening with syphilis RT and immediate treatment is likely to be cost-effective compared with standard screening and must be prioritized in local settings.

Keywords: cost-effectiveness, maternal syphilis, pregnant women, rapid test, syphilis screening.

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Introduction

Latin American countries account for up to 25% of the 2 million annual cases of gestational syphilis. Annually, an estimated 100 000 stillbirths in the region are attributable to congenital syphilis. The prevalence of gestational syphilis in Latin American countries varies from 0.08% to 7.0% by country.[1] In Brazil, the rate of detection of gestational syphilis and incidence rate of congenital syphilis has increased since 2010, reaching 8.6 reported cases per 1000 live births in 2017.[2] The benefits of preventing congenital syphilis through antenatal screening have been reported in the literature.[3,4] The advent of rapid testing has brought the possibility of faster treatment with improved compliance. However, it is still paramount to establish the cost-effectiveness of different screening strategies within country-specific contexts.

To date, the conventional approach to testing recommended by the World Health Organization (WHO) has been an algorithm of nontreponemal tests (NTTs), such as the Venereal Disease Research Laboratory test (VDRL) in combination with a

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treponemal test (TT) such as *Treponema pallidum* hemagglutination assay (TPHA).[5] Although VDRL+TPHA testing provides high sensitivity and specificity, the necessary delay in generating results means that women identified as positive are treated only in the next visit, with some consequent loss to follow-up. Rapid tests (RTs), in comparison, allow presumptive diagnostics and the possibility of immediate treatment. Although there is some evidence that RT may have a similar sensitivity and higher specificity than conventional testing, it may not differentiate between past and current infection.[6-10]

Despite the existing evidence of the cost-effectiveness of rapid syphilis tests in antenatal screening programs,[11,12] most studies were undertaken in African countries with few in South America or the Caribbean region. Studies conducted in Brazil focus on assessing the diagnostic performance, usefulness, and costs of a rapid treponemal antibody assay to detect syphilis in high-risk populations,[13-15] with no evidence concerning cost-effectiveness. The Brazilian program for reducing morbidity and mortality from gestational and congenital syphilis[16] has gradually been adopting tracking techniques through rapid tests for early detection of cases and abandoning the conventional reference test.[17] The aim of this change is to bring about increased uptake of syphilis testing, increased treatment rates, and reduction in adverse pregnancy outcomes such as low birth weight or prematurity, stillbirths or miscarriage, neonatal deaths, and congenital syphilis.

This study was nested in the Project Evaluation of Strategies for Tracking Dengue and Syphilis in Primary Care sponsored by the Department of Science and Technology of Brazilian Ministry of Health developed in 2015, with the objective to bring responses about the gradual implementation of rapid testing in the program of antenatal screening in public health units along the country. The relevance of this issue for health policy is that, despite the free access to treatment by pregnant women in the Unified Health System and the increased diagnosis and improved access to prenatal care, the number of new cases of syphilis in pregnancy and childbirth have been increasing in recent years.

The goal of this study was to build a decision analytic model to compare the cost-effectiveness of rapid versus conventional syphilis screening strategies at antenatal care sites to prevent mother-to-child syphilis transmission and to avert adverse birth outcomes in Brazil. Two antenatal syphilis screening strategies were compared, performing a rapid test (immunochromatographic syphilis [ICS]) on site with same-day treatment versus the standard reference test (VDRL+TPHA) performed off site with treatment at follow-up visit.

Materials and Methods

Population

The population is a hypothetical cohort of all pregnant women who receive antenatal care and are at risk of sexual transmitted infection, specifically syphilis. This includes, in Brazil, sexually active women between 10 and 49 years old (reproductive age in Brazil).[18]

Setting and Location

In Brazil, there is a national plan for reducing morbidity and mortality from gestational syphilis and congenital syphilis,[16] which considers early diagnosis and treatment one of the most effective strategies of syphilis control at antenatal care sites for screening pregnant women.

Study Perspective and Time Horizon

We adopted the public health system perspective. A lifetime horizon was used to capture the full potential health impact of antenatal syphilis screening and to enable budgetary consequences in primary care sites to be estimated. Effects and costs were discounted at 3% and 5%.

Prevalence

Prevalence of syphilis was estimated at 1.2% (95% confidence interval [CI] 0.98-1.47) of women in pregnancy according to a large hospital-based cohort study that considered only births that occurred in public healthcare units.[19]

Comparators

Antenatal syphilis screening strategies were compared, using a rapid test (ICS) on site with same-day treatment versus the standard reference test (VDRL+TPHA) performed off site with treatment at follow-up visit.

RTs have been found to have good sensitivity (median 0.86; interquartile range [IQR] 0.75, 0.94) and high specificity (median 0.99; IQR 0.98, 0.99), according to the systematic review by Tucker et al.[9]

Recently another study found pooled sensitivity and specificity of 0.85 (95% CI 0.73, 0.92) and 0.98 (95% CI 0.95, 0.99), respectively.[10] These values were used in the model. Despite its high specificity, RTs are unable to distinguish between past and active syphilis.

The standard test (ST) comprising NTT (VDRL) and TT (TPHA) provides a sensitivity of 0.88% (0.78, 1.00) and specificity of 0.98 (0.98, 1.00).[6,20,21]

Health Outcomes

The focus of antenatal syphilis screening is on eliminating mother-to-child syphilis transmission; therefore the model focused on outcomes for the baby and did not include maternal outcomes.[22] The adverse birth outcomes included were stillbirth (ie, fetal loss or miscarriage), low birth weight and prematurity, neonatal death, and live birth with syphilis. Live births with syphilis included both asymptomatic and symptomatic newborns. We did not include conditions associated with syphilis, such as human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS).

Efficacy of Treatment

Penicillin G has been found to be effective in eradicating syphilis of all clinical stages as well as congenital infection.[23] A single dose of long-acting benzathine penicillin G (2.4 million units intramuscularly) will cure a person who has primary, secondary, or early latent syphilis,[24,25] and 3 doses at weekly intervals is recommended for individuals with late latent syphilis or latent syphilis of unknown duration.[24]

Benzathine penicillin is associated with a very low risk of adverse complications. Literature suggests approximately 6% or 5% to 10% of pregnant women with syphilis report a history of penicillin allergy.[25,26] According to the Centers for Disease Control and Prevention[24] and adopted in Brazil,[17] pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin. Penicillin allergy was not included separately in the model.

Measurement of Effectiveness

Utility values were estimated in terms of disability-adjusted life-years (DALYs) lost, defined as the sum of years of life lost

because of premature mortality and years lived with disability adjusted for severity.[27] The DALYs for adverse outcomes averted were estimated from a single study[28] that presented data for 43 countries in sub-Saharan Africa adjusted for undiscounted local life expectancy, the neonatal standard loss function, and relevant disability weights. A full systematic review was not undertaken to identify this evidence; however, the study was identified using published principles for searching and choosing the best available evidence for modeling.[29] Additionally, we adjusted the data to the mean expectancy life in Brazil (75 years in 2015).

Modeling vertical syphilis transmission

A literature review published by Gomez et al[30] estimated that adverse birth outcomes were identified in 66.5% of the women with untreated syphilis (95% CI 53.4-81.8). Similarly, Shahrook et al[31] found that about 69% of pregnant women with active infection might experience adverse birth outcomes. The probabilities related to status of infection associated with model health outcomes, low birth weight, stillbirths, neonatal deaths, and congenital syphilis are listed in Table 1.

Measurement of Costs

Direct medical costs were captured for costs of tests (RT, ST), value of personnel time, treatments (mother and child), and inpatient care (congenital syphilis). Direct nonmedical costs and indirect costs were not included.

A microcosting study was conducted to estimate the resource utilization associated with each screening strategy (RT, ST) and follow-up of women treated, treatment of maternal syphilis, and inpatient costs of congenital syphilis based on national data available. Costs were expressed in Brazilian real (BRL), and they were inflated, for secondary data only, to 2015 BRL using the Brazilian Central Bank's cumulative inflation rate for the period between the date of each cost's source and 2015. Finally, all costs were converted to dollars with purchasing power parity using the World Bank's conversion factor. Costing procedures were in accordance with previously published methods.[32]

The total cost of testing (in USD) based on reagents and labor were estimated:

$$C_{testing} = C_A + C_B$$

where C is the cost, A is reagents unit cost of tests and B is the labor cost estimated based on time used to perform the test by a professional or technician.

Unit costs of tests were provided by the Drug Logistics Management and Strategic Inputs of DST Diseases, AIDS and Viral Hepatitis from Health Surveillance Secretariat of Ministry of Health. Salaries for nurses and laboratory technicians were national mean values. Time of labor to perform testing was set as 20 minutes of a nurse's labor (RT) and 45 minutes of a laboratory technician's labor (ST), which was based on the literature[33] and expert opinion.

The follow-up to assess treatment outcomes and potential reinfection involves a nontreponemal qualitative and quantitative test (VDRL) every month after starting the treatment. This cost was also accounted for pregnant women with a positive RT at the first visit. The costs ($C_{follow\text{-}up}$) are estimated by

$$C_{follow-up} = (C_{testing} \times n)$$

where n is the number of visits that pregnant women have the opportunity to take a monitoring test.

An expert opinion was consulted to estimate the mean number of visits pregnant women accomplish to monitor treatment, seeking to bring us closer to real-life data; n = 3 was included in the model.

The cost of treating gestational syphilis to avoid disease progression and/or vertical transmission is estimated by

$$[C_{GestationalS}] = C_{testing} + C_{treat} + C_{follow-up}$$

Unit costs of penicillin to treat maternal and congenital syphilis were provided by the Health Logistics Department of the Ministry of Health (governmental purchasing system, https://www.

Table 1. Parameter values: tests, treatment, status of infection, and outcomes.

Model parameters	Baseline value	Range	95% CI	Sources
Prevalence of maternal syphilis	0.012	0.0098	0.0147	20
Tests				
Sensitivity of rapid test	0.85	0.73	0.92	10
Specificity of rapid test	0.98	0.95	0.99	10
Sensitivity of standard test	0.95	0.78	1	6,23
Specificity of standard test	0.98	0.98	1	6
Treatment				
Probability of treatment efficacy if administered adequately (early or late syphilis)	0.97	0.94	0.99	12
Probability of compliance full treatment with RT	0.89	0.81	0.95	12
Probability of compliance full treatment with ST	0.61	0.47	0.73	12
Status of infection				
Probability of remission due to antibiotic therapy with penicillin due to other infection different to syphilis	0.001	0	0.005	Expert opinion
Probability of new infection between tests (incidence)	0.002	0.001	0.004	23
Probability of remain infected after inadequate treatment	0.99	0.99	1	Expert opinion
Outcomes				
Probability of stillbirth or fetal loss given syphilis-infected mother	0.256	0.185	0.342	18
Probability of low birth weight or prematurity given syphilis-infected mother	0.131	0.039	0.318	18
Probability of neonatal death given syphilis-infected mother	0.123	0.093	0.162	18
Probability of newborn with congenital syphilis given syphilis-infected mother	0.155	0.075	0.29	18,35

CI indicates confidence interval; RT, rapid test; ST, standard test.

comprasgovernamentais.gov.br/), and inpatient costs were estimated from "Table of Procedures, Drugs, Orthotics and Prostheses and Special Materials (OPM)" of the Unified Health System (SIGTAP Management System, http://sigtap.datasus.gov.br/tabela-unificada/app/sec/inicio.jsp).

The unit treatment and follow-up costs are the same for both testing strategies (RT, ST), but the total cost depends on the probabilities of treatment compliance, which differ for the 2 strategies.

Total cost of a congenital syphilis case does not take into account the appointment cost because it is part of routine neonatal care, either for testing or treatment and follow-up.

All costs in 2015 US international dollars (USD) in the year when the study was carried on are listed in Table 2.

General Model

Pregnant women with access to prenatal care are evaluated for syphilis at the first antenatal visit (usually during the first or second trimester). A second test is also performed in the third trimester in those with a negative result at first testing.[5]

Depending on the syphilis screening strategy, women are informed of the result and initiate treatment either immediately, which we term the rapid test, or at the next follow-up visit, which represents the standard test.

In either of the strategies, if a patient tests positive, an NTT must be performed monthly to assess treatment outcomes and identify failures as a result of nontreatment, incomplete or inadequate treatment, or reinfection.

The comparative strategies are in accordance with the norms of the Brazilian Low Risk Prenatal Care Program.[17]

Analytic Model Overview

The model incorporated three steps of antenatal care: syphilis testing, treatment prescription, and treatment adherence.

Pregnant women entered the model by being tested for syphilis. Women had two possible starting states: infected or uninfected. The proportion of infected women was represented by national data on syphilis prevalence.[34] For uninfected women, the probability of acquiring syphilis during pregnancy was represented by the primary and secondary syphilis incidence rates.[34] They could either be tested with RT and receive same-day treatment if indicated or receive the ST and be treated during the follow-up visit. Screening was performed in all pregnant women at least once, at first antenatal care visit and at third trimester of pregnancy for women negative at first testing. Prescription of benzathine penicillin G was based on the test result and clinical evaluation.

Test results were modeled using the sensitivity and specificity for the appropriate test (RT vs ST). Additional tests were performed (monthly) to confirm treatment success. Women with high-titer active syphilis (VDRL > 1:8 and TPHA positive) received the administration of new treatment with benzathine penicillin G.

Health outcomes depended on whether the mother fully complied with treatment and included stillbirth or miscarriage, low birth weight or prematurity, neonatal death, live birth with syphilis, or live birth without congenital syphilis. Cost-effectiveness ratios were estimated in 2015 USD international dollars per DALY.

The decision analytic model was built and programmed using DATA Pro Healthcare (TreeAge Software, http://www.treeage.com) (Fig. 1). Monte Carlo methods with 10 000 replicates were used to estimate economic outcomes.

Key Assumptions of Model

The key assumptions of the model were as follows:

- Pregnant women with maternal syphilis were modeled at primary, secondary, or early latent syphilis stage of disease (44.1%) based on national data reported and high probability of congenital transmission 94.0% (47.0-1.00).[12]
- New infections occurring between the first and second test were modeled as incident infections based on the study of Cerda et al.[21]
- Single-dose treatment was used for primary, secondary, or early latent syphilis.

Table 2. Model parameters: costs (USD international) and QoL values.

Model Parameters	Baseline value	Lower bound	Upper bound	Sources
Costs (USD)				
Rapid test: ICS *(test supplies + nurse labor)*	1.29	0.64	1.93	49
Standard tests: VDRL/TPHA *(test supplies + technician labour)*	1.21	0.61	1.82	49
VDRL: Follow-up (test performed at least 3 times) *(test supplies + technician labor) × 3*	1.91	0.95	2.86	49 Expert opinion
Treatment: benzathine penicillin G per women (1 dose)	0.26	0.13	0.39	50
Treatment: benzathine penicillin G per infant with CS*	115.53	57.77	173.30	50
QoL Values				
DALY per SB case	10.32	7.10	14.21	28
DALY per LBW case	0.67	0	2.93	28
DALY per ND case	10.32	6.88	14.78	28
DALY per CS case	1.98	0.96	3.71	28
Others				
No. of children per birth	1			Expert opinion

Note. Costs and QoL values at discount rate of 3%. Also applied 5% discount rate in sensitivity analysis.
CS indicates congenital syphilis; DALY, disability-adjusted life-year; ICS, immunochromatographic syphilis test; LBW, low birth weight; ND, neonatal death; SB, stillbirth; VDRL, Venereal Disease Research Laboratory test; qoL, Quality of life; TPHA, *Treponema pallidum* hemagglutination test.
*Aqueous crystalline penicillin G, every 8 hours for 10 days + daily hospitalization costs.

- Incomplete treatment was considered to have the same efficacy as untreated cases and cost 50% of complete treatment.
- If new infected or still-infected pregnant women were identified during the follow up of positives, they were treated.
- The fetus received full efficacy of therapy (97%) after a single maternal treatment.
- Time for initiating the treatment with ST ranged between 1 week (test result available) and 4 weeks (next follow-up visit).
- There was a probability of remission in untreated women because of antibiotic therapy with penicillin for infections other than syphilis.
- Multiple pregnancies were not included in the model.
- Probability of reinfection because of a nontreated partner was not included in the model.
- Costs relating to training, consumables, and equipment (laboratory for ST) were not included in our model because of nonavailability of data. These costs should be prorated proportionally with performance of other laboratory testing.

Uncertainty

Probabilistic sensitivity analysis (PSA) was conducted, and summary statistics and graphical illustrations are provided to illustrate the uncertainty in model outcomes. The specific 5% discount rate recommended by the Ministry of Health was applied in the sensitivity analysis. Value of information (VOI) analysis allows identification of those parameters that cause most decision uncertainty and estimates the potential value of reducing uncertainty by further data collection.

Interpretation of Results

In Brazil, a cost-effectiveness threshold has not been published by the government. Consequently, many studies have adopted WHO recommendations on the cost-effectiveness of interventions.[35]

Recently, cost-effectiveness thresholds based on opportunity cost were estimated for a wide range of low- and middle-income countries.[36] Although their estimates related to quality-adjusted life-years (QALYs) gained, they used DALYs and QALYs interchangeably in their article as a summary measure of morbidity and mortality. The purchasing power parity–adjusted thresholds for Brazil were US$3210 to US$10 122, and we used the lowest estimated value within the analysis.

Validation

Validation of the conceptual model was undertaken by discussing the decision problem with Brazilian advisers who highlighted clinical and epidemiologic aspects to be considered. A draft model incorporated all comments and suggestions, and a second cycle of review improved the development of the model. Model parameters were identified in accordance with the criteria for recommended minimum search requirements,[29] and implementation within the model was verified. The model was double programmed with a parallel build in Excel to identify potential errors.

Ethics

Institutional and national review bodies approved the research, including the Committee of Ethics in Research from Oswaldo Cruz Institute from Oswaldo Cruz Foundation and the Brazilian National Committee of Ethics in Research.

Results

Parameters definitions and values are presented in Tables 1 and 2. Test characteristics for RT and ST were derived from 2 recent systematic reviews.[9,10] Literature reviews provided the probabilities of adverse outcomes, compliance, and successful treatment.[12,30,37] Brazilian data were used in the model for the parameters describing prevalence of maternal syphilis,[19] probability of new infection between tests, [21] and costs of testing and treatments. Additionally, the expert opinion of Brazilian advisers was used to generate values where no published sources were available. Statistical distributions were used to describe uncertainty in model parameters. β distributions are used for event probabilities and γ distributions for cost and health-related quality-of-life parameters. A full listing of parameter values is provided in Table 3.

The mean cost of the rapid testing strategy was estimated at $2.63 per pregnant woman screened compared with a cost of $2.48 for the standard strategy. Rapid testing was associated with a loss of 0.0043 DALYs compared with 0.0048 DALYs lost with standard testing. Expected value of incremental cost per DALY averted was $298.08.

The cost-effectiveness plane (Fig. 2) indicates the standardized cost-effectiveness plane per person based on 10 000 model runs in which uncertain model parameters were varied simultaneously in a PSA. The mean incremental cost of RT versus ST is $0.15. This suggests that RT is more costly. The incremental cost is uncertain because the model parameters are uncertain. The 95% CrI for the incremental cost ranges from –$1.56 to $1.92 (USD). The probability that RT is cost-saving compared with ST is 0.428.

The mean incremental benefit of RT versus ST is 0.00042 DALY. Again, there is some uncertainty because of model parameters, with the 95% CrI for the incremental benefit ranging from –0.0036 to 0.0044 DALY. The probability that RT is more beneficial than ST is 0.595.

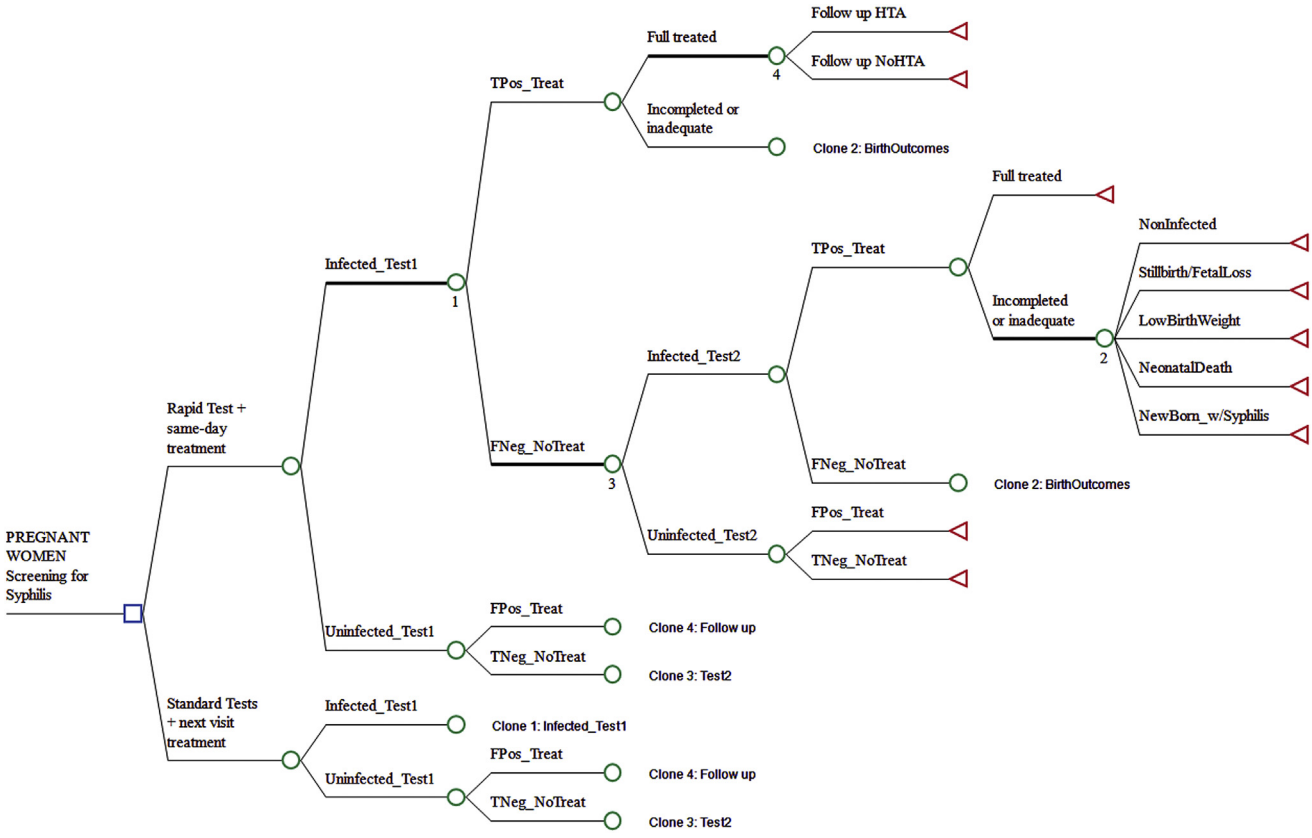
The incremental expected cost per unit of benefit is estimated at $357.44 per DALY with a 3% discount rate. The cost-effectiveness acceptability curve presented in Figure 3 shows that at a threshold value for cost-effectiveness of $3200 per DALY, the strategy with the highest probability of being most cost-effective is RT, 58.42%. Sensitivity analysis of 5% discount rate estimates the ICER of $342.29 per DALY with the highest probability of RT strategy being most cost-effective is 58.41%. The mean incremental cost per person is $0.035 and the mean incremental effect per person is 0.0001 DALY.

The VOI analysis is reported in full in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2020.03.004. The VOI analysis identifies that the parameters causing the greatest decision uncertainty are the sensitivity of both tests RT and ST, treatment compliance with ST, the probability of treatment success with ST, the probability of infection between tests, and treatment compliance with RT. The analysis also reports the potential value of reducing uncertainty by data collection within further research or through implementation evaluation.

Discussion

This analysis suggests that antenatal syphilis screening with RT incorporating treatment of positive women in the same day is a potentially cost-effective strategy. The expected ICER of $298.08 per DALY averted for RT compared with ST is lower than both the WHO-recommended once per capita gross domestic product[35] and the Woods cost-effectiveness threshold values,[36] at a threshold value of $3,200 per DALY for Brazil. PSA conducted at

Figure 1. Decision tree model on antenatal syphilis screening strategies. Pregnant women's access to prenatal care to be screened for syphilis was entered in the model by two alternative strategies: (A) rapid testing (RT; immunochromatographic syphilis [ICS] test) where a woman who is positive is treated immediately on site, same day, same visit; or (B) standard testing (ST; VDRL + *Treponema pallidum* hemagglutination assay [TPHA]) where a woman who tests positive is treated only in the next follow-up visit, if she returns, or when the test result is available. Additionally, in all positive women (TPos, FPos) a nontreponemal test must be performed monthly to follow up the cure or identify failures due to re-infection. Women have to be screened for syphilis at the first antenatal visit; and a second test is performed at 30 weeks of gestation in all women who test negative (TNeg, FNeg) at the first testing, when women with false negatives have the chance to be treated. Incomplete or inadequate treatment can lead to adverse birth outcomes: stillbirth or fetal loss, low birthweight and prematurity, neonatal death, or live birth with syphilis. All costs of testing and treatments are also included in the outcomes.



both 3% and 5% discount rates found no significant differences in ICER, with $357.44 and $342.29 per DALY, respectively. However, the uncertainty, principally in comparative screening test sensitivities and treatment compliance rates, is such that RT screening may still be more costly and less effective than ST.

When we considered the current antenatal screening cost-effectiveness literature, we found variation in the cost-effectiveness estimates; however, those estimates are not directly comparable with our findings for a variety of reasons. First, the types of comparators differ from our choice of investigation (RT vs VDRL/TPHA test). Some studies focused on comparing different combinations of testing and treatment. For instance, the study carried out by Larson et al[38] for Zambia considered costs per DALY averted under the assumption of full adherence to guidelines (lowest costs) in addition to when all positive are treated (slightly higher costs compared with full adherence). The highest costs per DALY were identified in scenarios with fewer adherences. The variations in cost per DALY were due to the number of DALYs averted in each scenario considered.[38] The economic implications of scaling up were also considered in some studies.[39,40] Other studies analyzed syphilis RTs in combination with HIV testing or syphilis testing only versus other combinations with HIV tests.[41,42]

One study undertaken in South Africa, a middle-income country, focused on the comparison between the combination of RTs and confirmatory TPHA off-site testing, the current practice at the time, versus on-site rapid testing.[12] Furthermore, many of the studies were undertaken in countries with very different income patterns and congenital syphilis prevalence. Brazil is a middle-income country, and the majority of studies about the cost-effectiveness of rapid tests for syphilis screening were carried out in resource-limited countries in sub-Saharan Africa, South America, and the Caribbean.[11,12] Those studies have estimated costs ranging from US$4 to US$46 per DALY averted[33,40,43-46]; however, those countries have a higher prevalence of maternal syphilis than Brazil.

The study performed by Owusu-Edusei et al[47] in sub-Saharan Africa found that the dual point-of-care test (laboratory-based rapid plasma reagin combined with TPHA) was the most promising option in a resource-poor setting, considering a prevalence of 10% infected, with the potential to decrease losses to follow-up and reduce overtreatment.

The main limitation of our work is essentially the absence of Brazilian data for some parameters needed to populate the model

Table 3. General model parameters and distributions.

Variable description	Deterministic mean	Distribution type	α, β, λ	Rounded	Sources
Event probabilities					
Sensitivity of RT	0.85	β	45.28	7.99	10
Specificity of RT	0.98	β	183.49	3.74	10
Probability of compliance treatment with RT	0.89	β	67.42	8.33	12
Sensitivity of ST	0.95	β	47.20	2.48	6,21
Specificity of ST	0.98	β	736.89	15.04	6
Probability of compliance treatment with ST	0.61	β	32.38	20.70	12
Prevalence of disease	0.012	β	91.04	7495.52	19
Probability of efficacy of treatment	0.97	β	172.52	5.34	12
Probability of remission due to antibiotic therapy	0.001	β	0.61	612.41	Expert opinion
Probability of infection between tests (incidence)	0.002	β	6.81	3399.99	21
Probability of remain infected due to inadequate treatment	0.99	β	1505.02	15.20	Expert opinion
Probability of stillbirth	0.256	β	30.14	87.59	30
Probability of low birth weight	0.131	β	2.81	18.66	30
Probability of neonatal death	0.123	β	42.70	304.45	30
Probability of congenital syphilis	0.155	β	6.59	35.94	30,37
Cost parameters					
Cost of RT	1.29	λ	15.36	11.91	49
Cost of ST	1.21	λ	15.36	12.67	49
Cost of follow-up with nontreponemal test	1.91	λ	15.35	8.04	49 Assumed
Cost of treat the mother	0.26	λ	15.36	59.54	50
Cost of treat the infant with congenital syphilis	115.53	λ	15.36	0.13	50
HRQoL parameters					
Daly_SBavoid	10.32	λ	32.39	0.35	28
Daly_LBWavoid	0.67	λ	0.79	0.13	28
Daly_NDavoid	10.32	λ	26.25	0.28	28
Daly_CSavoid	1.98	λ	7.98	0.45	28

CS indicates congenital syphilis; DALY, disability-adjusted life-year; HRQoL, health-related quality of life; LBW, low birth weight; ND, neonatal death; RT, rapid test; SB, stillbirth; ST, standard test.

and the assumptions made that could introduce uncertainties. Data collection to assess the impact of treatment compliance with ST in Brazil would improve the accuracy of estimates. In addition, the prevalence of past infection must be included in more elaborated analytical model considering that woman with past infection can trigger treatment and follow-up. Parameters causing most of the decision uncertainty, such as the sensitivity of RT and ST tests, must deserve special attention for further research considering the shortage of good-quality diagnostic accuracy studies. Our analysis uses parameter estimates from a study in a rural area, yet higher compliance rates may be expected in urban areas with better access to assistance, health education, and awareness on prevention. The implication of this is that RT will have better cost-effectiveness in rural setting, whereas in an urban setting ST may still be the better economic option.

Other limitations are related to including only the costs to outpatient activity, thus excluding any scenario in which hospitalization would be necessary (other adverse pregnancy events different from congenital syphilis). In addition, the model does not include partner tracing and treatment. This is due to a lack of evidence concerning the impact of partner tracing on the probability of reinfection. Laboratory costs for the standard test (consumables, equipment) also must be estimated to include in the total cost of testing. Data collection in further research or implementation evaluation should focus on these remaining uncertainties.

Conclusions

The present work is an important evaluation of ongoing implementation of testing strategies to detect and promptly treat maternal syphilis and to prevent syphilis-related birth outcomes in Brazil and other low- and middle-income countries. Although the sensitivity and specificity of treponemal and nontreponemal tests vary with the types of tests as well as the stages of syphilis

Figure 2. Cost-effectiveness plane for rapid testing (RT) compared with standard testing (ST) syphilis screening strategies.

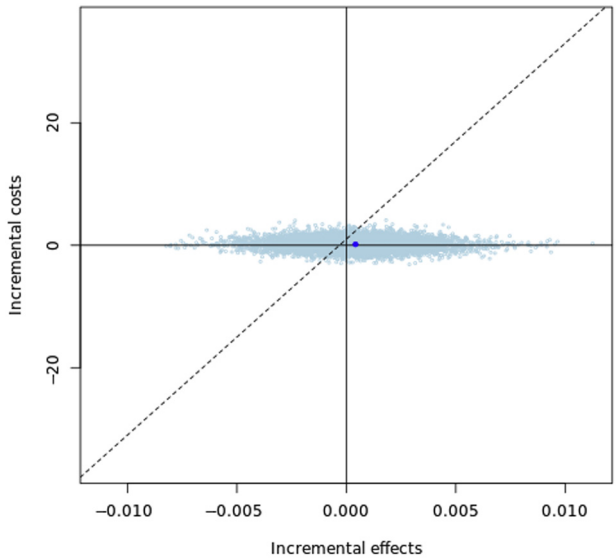
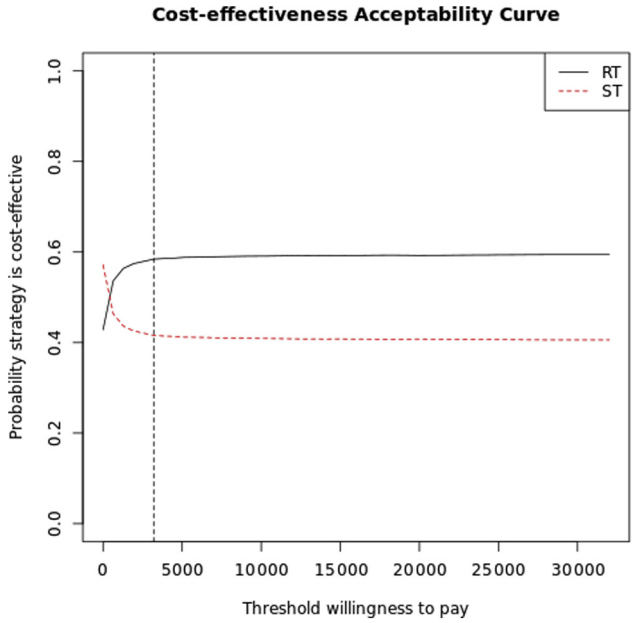


Figure 3. Cost-effectiveness acceptability curve of syphilis rapid testing (RT) versus standard testing (ST).



infection, the mainstay of diagnosis for syphilis is still serologic testing.

The results from this economic evaluation could help the Brazilian Ministry of Health decision makers in setting future directions for the syphilis mother-to-child transmission strategy and provide a better understanding of new testing technologies. It has become relevant to raise awareness among professionals regarding the benefit of testing by RT in preventing adverse events for the baby and improving the training of nurses and technicians in their best use. Furthermore, our findings indicate that strategies including RTs for syphilis screening should be reinforced and prioritized in local settings and could potentially be extended to other low- and middle-income countries. Even other strategies can act in synergy to enhance the use of rapid testing, such as the congenital syphilis elimination campaigns that have been found to be effective[48] in reducing perinatal morbidity and mortality.

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Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2020.03.004.

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