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**TITLE:** Cost-effectiveness analysis of point-of-care rapid testing versus laboratory-based testing for antenatal screening of syphilis in Brazil

**Running title:** Cost-Effectiveness Antenatal Syphilis Testing

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## **Abstract**

### *Background*

Severe consequences of mother-to-child transmission of syphilis and high increasing incidence of congenital syphilis remains an important public health problem in Brazil.

### *Objectives*

To assess cost-effectiveness of a rapid point-of-care test (RT) and treatment of positive mothers immediately compared to laboratory-based standard test (ST) with treatment at next follow-up visit.

### *Methods*

Decision analytic model was developed to estimate the incremental cost effectiveness ratio (ICER) between antenatal syphilis screening strategies. Model was built with lifetime horizon from Brazilian health system perspective using 3% and 5% discount rate. A hypothetical cohort of pregnant women at reproductive age enter the model. Health outcomes: low birth weight, stillbirths, neonatal deaths and congenital syphilis were estimated in Disability-Adjusted Life Years (DALYs) lost. Micro-costing 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 US\$2.63 (RT) and US\$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 US\$298.08. After 10000 PSA model runs, incremental cost and health benefits were US\$0.15 (95%CrI -1.56- 1.92) and 0.00042 DALYs (95%CrI -0.0036-0.0044) respectively, mean ICER of

US\$357.44 per DALY. Screening with RT has a 58% chance of being the optimal strategy at a threshold of US\$3,200 per DALY.

### *Conclusions*

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

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

### **Highlights**

- Latin-American countries had been doing relevant efforts in the control of sexually transmitted diseases and particularly for elimination of mother-to-child syphilis transmission. Economic study on the cost-effectiveness of screening gestational syphilis with rapid diagnostic tests during prenatal care has absolute relevance for the country, considering the severe consequences of mother-to-child transmission of the disease and the high incidence of congenital syphilis in Brazil.
- We show that syphilis screening in pregnancy with rapid test and treatment of positives in the same day of antenatal visit is likely to be a highly cost-effective strategy in Brazil. This is significant because despite the free access to treatment by pregnant women in the Unified Health System (SUS) 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 last years.
- Economic evaluation could help the Ministry of Health decision makers in setting the future directions for the syphilis mother-to-child transmission strategy and provide a better understanding of new testing technologies. Our findings indicate that strategies including rapid

tests for syphilis should be reinforced and prioritized in local settings and could be extended to other low- and middle-income countries.

## **1. Introduction**

Latin-American countries account for up to 25% of the 2 million annual cases of gestational syphilis. Annually, an estimated 100000 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/1000 live births in 2017 (2). The benefits of preventing congenital syphilis through antenatal screening have been demonstrated 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 test (NTT), such as the Venereal Diseases Research Laboratory test (VDRL) in combination with a treponemal test (TT) such as Treponema Pallidum Hemagglutination Assay (TPHA) (5). Whilst 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 in comparison allow presumptive diagnostics and the possibility of immediate treatment. Whilst 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 programmes (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 because despite the free access to treatment by pregnant women in the Unified Health System (SUS) 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.



## **2. 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, sexual active women between 10 and older than 49 years old (reproductive age in Brazil) (18).

### ***Setting and location***

There is a Brazilian program for reducing morbidity and mortality from gestational syphilis and congenital syphilis (16) considering early diagnosis and treatment one of the most effective strategies of syphilis control at antenatal care sites for pregnant women screening.

### ***Study perspective and time horizon***

We adopted the public health system perspective. A lifetime horizon was used in order 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%CI 0.98-1.47) of women in pregnancy based on a large hospital-based cohort study considering only the births that occurred in public health care units (19).

### ***Comparators***

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.

RTs have been shown to have good sensitivity, median of 0.86 (IQR 0.75, 0.94) and high specificity, median of 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, RT is unable to distinguish between past and active syphilis.

The 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 focuses on outcomes for the baby and does not include maternal outcomes (22). The adverse birth outcomes included are stillbirth (i.e. foetal loss or miscarriage), low birth weight and prematurity, neonatal death and live born with syphilis. Live births with syphilis include both asymptomatic and symptomatic newborns. We do not include conditions associated with syphilis, such as Human immunodeficiency virus infection and acquired immune deficiency 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 i.m.) will cure a person who has primary, secondary or early latent syphilis (24,25) and three 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 5–10% of pregnant women with syphilis report a history of

penicillin allergy (25,26). According to CDC (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 DALYs (*Disability-adjusted life years*) lost, defined as the sum of years of life lost due to 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 (SSA) 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 modelling (29). Additionally, we adjusted the data to the mean expectancy life in Brazil (75 years in 2015).

### ***Modelling vertical syphilis transmission***

A literature review published by Gomez et al (30) estimated that adverse birth outcomes were observed in 66.5% (95%CI 53.4, 81.8) of the women with untreated syphilis. Similarly, Shahrook et al (31) showed 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 non-medical costs or indirect costs were not included.

A micro-costing 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), only for secondary data, they were inflated 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 (PPP) using the World Bank's conversion factor. Costing procedures were in accordance with previously published methods (33).

The total cost of testing (US\$) based on reagents and labour were estimated:

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

A; Reagents= unit cost of tests

B; Labor= cost estimated based on time used to perform the test by 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 labour to perform testing was set up on 20 min of nurse's labour (RT) and 45 min of laboratory technician's labour (ST) took from literature (32) and expert opinion.

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

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

$n$  = 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 Health Logistics Department from Ministry of Health (governmental purchasing system, <https://www.comprasgovernamentais.gov.br/>) and inpatient costs estimated from Table of Procedures, Drugs, Orthotics and Prostheses and Special Materials (OPM) of the Unified Health System – SUS (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 two 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, treatment and follow up.

All costs in 2015 US international dollars (USD), 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 1<sup>st</sup> or 2<sup>nd</sup> trimester). A second test is also performed at 3<sup>rd</sup> 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 (RT) or at the next follow-up visit, which represents the standard test (ST).

In either of the strategies, if a patient is tested positive, a nontreponemal test must be performed monthly to assess treatment outcomes and identify failures due to non-treatment, incomplete or inadequate treatment or re-infection.

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

### ***Analytic Model Overview***

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

Pregnant women enter the model by being tested for syphilis. Women have 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 is 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 is based on the test result and clinical evaluation.

Test results are modelled using the sensitivity and specificity for the appropriate test (RT vs. ST). Additional tests are performed (monthly) to confirm treatment success. Women with High Titre Active Syphilis (VDRL>1:8 and TPHA positive) receive the administration of new treatment with benzathine penicillin G.

Health outcomes depend on whether the mother fully complies with treatment and include stillbirth or miscarriage, low birth weight or prematurity, neonatal death, live born with syphilis, or an infant without congenital syphilis. Cost-effectiveness ratios were estimated in 2015 USD international dollars/ DALY.

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

### ***Key assumptions of model***

- Pregnant women with maternal syphilis were modelled 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 modelled as incident infections based on the study of Cerda et al (21).
- Single dose treatment is used for primary, secondary or early latent syphilis.
- Incomplete treatment is considered to have the same efficacy as untreated cases and costs 50% of complete treatment.
- If new infected or still-infected pregnant women are identified during the follow up of positives, they are treated.
- The foetus receives full efficacy of therapy (97%) following a single maternal treatment.
- Time for initiating the treatment with ST ranges between 1 week (test result available) and 4 weeks (next follow up visit).
- There is a probability of remission in untreated women due to antibiotic therapy with penicillin for infections other than syphilis.

- Multiple pregnancies are not included in the model.
- Probability of re-infection due to non-treated partner is not included in the model.
- Costs relating to training, consumables and equipment (Lab for ST) were not included in our model due to non-availability of data. These costs should be prorated proportionally with performing 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. Specific 5% discount rate recommended by MoH 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 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-/middle-income countries (36). Whilst their estimates relate to quality adjusted life years (QALYs) gained, they use DALYs and QALYs interchangeably in their paper as a summary measure of morbidity and mortality. The PPP-adjusted thresholds for Brazil were US\$3,210-10,122 and we have 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 epidemiological 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 in order to identify potential errors.

### ***Ethics***

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

### **3. Results**

Parameters definitions and values are presented in Tables 1 and 2. Test characteristics for RT and ST were derived from two 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 also 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. Beta distributions are used for event probabilities and gamma distributions for cost and HRQoL parameters, a full listing of parameter values is provided in Table 3.

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

The cost-effectiveness plane (Figure 2) shows the standardized cost-effectiveness plane per person based on 10000 model runs in which uncertain model parameters are varied simultaneously in a probabilistic sensitivity analysis. The mean incremental cost of RT versus ST is US\$0.15. This suggests that RT is more costly. The incremental cost is uncertain because the model parameters are uncertain. The 95% credible interval for the incremental cost ranges from US\$-1.56 to US\$1.92. The probability that RT is cost-saving compared to ST is 0.428.

The mean incremental benefit of RT versus ST is 0.00042 DALY. Again, there is some uncertainty due to model parameters, with the 95% credible interval for the incremental benefit ranging from (-0.0036 DALY, 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 US\$357.44 per DALY with 3% discount rate.. The Cost-Effectiveness Acceptability Curve presented in Figure 3 shows that at a threshold value for cost-effectiveness of US\$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 US\$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 US\$0.035 and the mean incremental effect per person is 1e-04 DALY.

The Value of Information (VOI) analysis is reported in full in the Supplementary Appendix. 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.

#### **4. 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 US\$298.08 per DALY averted for RT compared to ST is lower than both the WHO recommended once per capita GDP (38) and the Woods cost effectiveness threshold values (36), at a threshold value of US\$ 3,200 per DALY for Brazil. Probabilistic sensitivity analysis (PSA) conducted at both 3% and 5% discount rate showed no significant differences in ICER, US\$357.44 and US\$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 consider the current antenatal screening cost-effectiveness literature, it shows 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 versus VDRL/TPHA test). Some studies focused on comparing different combinations of testing and treatment. For instance, the study carried out by Larson and colleagues for Zambia considered costs per DALY averted under the assumption of full adherence to guidelines (lowest costs) as well as when all positive are treated (slightly higher costs compared to full adherence). The highest costs per DALY were observed in scenarios with fewer adherences. The variations in cost per DALY were due to the number of DALYs averted in each scenario considered (39). The economic implications of scaling up was also considered in some studies (40,41). Other studies analyzed syphilis RTs in combination with HIV testing or syphilis testing only versus other combinations with HIV tests (42,43).

One study undertaken in South Africa, a middle-income country, focused on the comparison between the combination of RTs and confirmatory TPHA off-site, the current practice at the time

versus on-site rapid testing (12). Furthermore, many of the studies are 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 and South America and Caribbean (11,12). Those studies have estimated costs ranging from US\$4 to US\$46 per DALY averted (32,41,44–47), however, these countries have a higher prevalence of maternal syphilis than Brazil.

The study performed by Owusu-Edusei and colleagues for Sub-Saharan Africa showed 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 (48).

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

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 tests and non-treponemal tests vary with the types of tests as well as the stages of syphilis infection, the mainstay of diagnosis for syphilis still depends on 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 become relevant to raise awareness among professionals of 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, enhancing the use of rapid testing, such as the congenital syphilis elimination campaigns that have been shown to be effective (49) in reducing perinatal morbidity and mortality.

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

<b>Model Parameters</b>	<b>Baseline Value</b>	<b>Range 95% CI</b>		<b>Sources</b>
Prevalence of Maternal Syphilis	0.012	0.0098	0.0147	(20)
<b>Tests</b>				
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)
<b>Treatment</b>				
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)
<b>Status of Infection</b>				
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
<b>Outcomes</b>				
Probability of stillbirth or foetal 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 new born with congenital syphilis given syphilis infected mother	0.155	0.075	0.29	(18,35)

RT= Rapid test; ST= Standard test; CI= Confidence interval.

Table 2. Model parameters: Costs (US\$ international) and QoL values

<b>Model Parameters</b>	<b>Baseline Value</b>	<b>Lower Bound</b>	<b>Upper Bound</b>	<b>Sources</b>
<b>Costs (US\$)</b>				
Rapid Test – ICS ( <i>test supplies + nurse labour</i> )	1.29	0.64	1.93	(a)
Standard Tests - VDRL/TPHA ( <i>test supplies + technician labour</i> )	1.21	0.61	1.82	(a)
VDRL – Follow up (test performed at least 3 times) ( <i>test supplies + technician labour</i> )*3	1.91	0.95	2.86	(a) Expert Opinion
Treatment - B Penicillin G per women (1 dose)	0.26	0.13	0.39	(b)
Treatment - B Penicillin G per infant with CS*	115.53	57.77	173.30	(b)
<b>QoL Values</b>				
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)
<b>Others</b>				
N° of children per birth	1			Expert Opinion

(\*)Aqueous crystalline penicillin G, every 8 h for 10 days + daily hospitalization costs

ICS= Immunochromatographic syphilis test; VDRL= Venereal disease research laboratory test; TPHA= Treponema pallidum haemagglutination test.

QoL= Quality of life; DALY= Disability-Adjusted Life Year. SB= Stillbirth; LBW= Low birth weight; ND= Neonatal death; CS= Congenital Syphilis.

(a) Department of STD, AIDS and Viral Hepatitis from Health Surveillance Secretariat of Ministry of Health. Drug Logistics Management and Strategic Inputs (Gerência de Logística de Medicamentos e Insumos Estratégicos – GLMIE).

(b) Health Logistics Department from Ministry of Health (governmental purchasing system) and Table of Procedures, Drugs, Orthotics and Prostheses and Special Materials (OPM) of the Unified Health System – SUS (management system, SIGTAP).

Costs and QoL values at discount rate of 3%. Also applied 5% discount rate in sensitivity analysis.

Table 3. General model parameters and distributions

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



RT= Rapid test; ST= Standard test; HRQoL= Health related quality of life; DALY= Disability-Adjusted Life Year. SB= Stillbirth; LBW= Low birth weight; ND= Neonatal death; CS= Congenital Syphilis. (a) Drug Logistics Management and Strategic Inputs (Gerência de Logística de Medicamentos e Insumos Estratégicos – GLMIE) MoH. (b) Health Logistics Department and Table of Procedures, Drugs, Orthotics and Protheses and Special Materials (OPM) of MoH (management system, SIGTAP). Cost and HRQoL parameters were applied at a 3% discount rate.

Figure 1

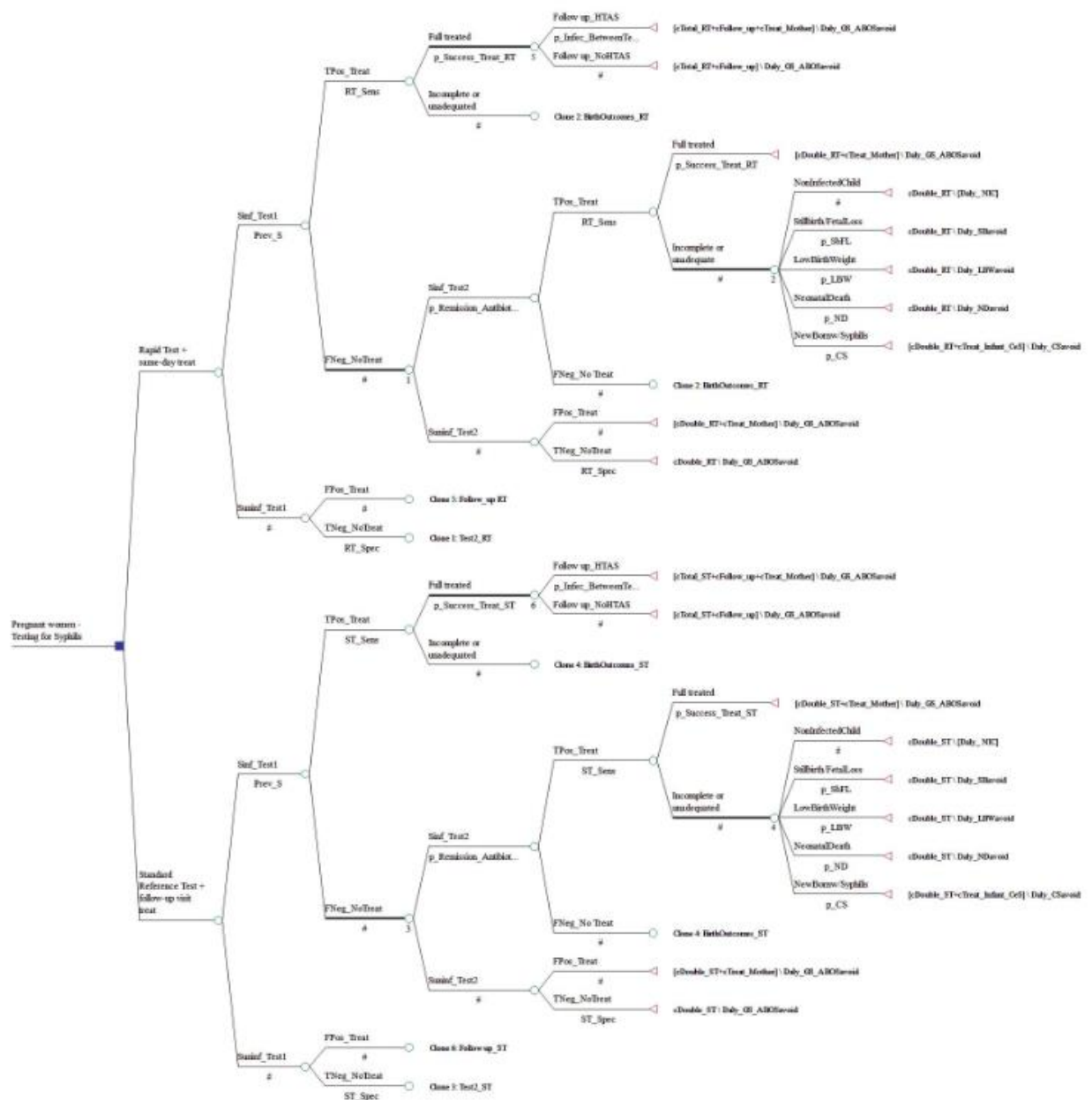


Figure 2

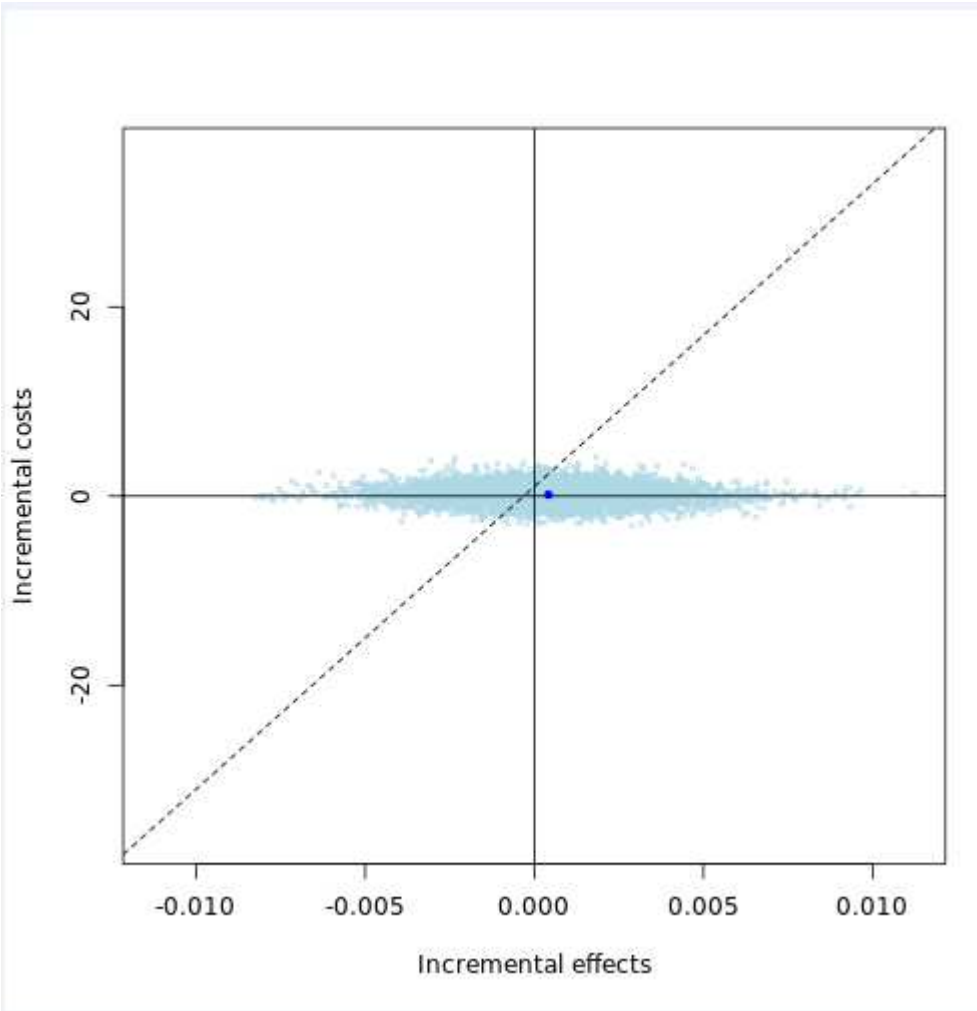


Figure 3

