Cost utility of penicillin use in primary care for the prevention of complications associated with syphilis

Custo-utilidade do uso da penicilina na atenção primária para a prevenção de complicações associadas à sífilis congênita

Roberto Carlos Lyra da Silva[1], Antonio Augusto de Freitas Peregrino[2], Regina Rocco[3], Lilian Reinaldi Ribeiro[4], Daniel Aragão Machado[4], Carlos Roberto Lyra da Silva[4]

ABSTRACT

Introduction: Despite penicillin being the drug of choice for the treatment of syphilis, many pregnant women who test positive for syphilis do not receive the drug as recommended by the Ministry of Health, contributing to the increase in costs associated with congenital syphilis. **Objective:** This study aims to estimate the incremental cost-effectiveness ratio of administering at least one dose of 2.4 million IU of benzathine penicillin in the first trimester of pregnancy as soon as the result of a positive rapid treponemal test performed during antenatal care in primary care units of the Brazilian National Health System. **Methods:** An analytical model was proposed based on a decision tree. The perspective of the analysis was the one used in The Brazilian National Health System. The clinical outcomes were abortion, prematurity, neonatal death, stillbirth, and congenital syphilis, estimated in terms of disability-adjusted life-years. Only direct costs were considered. Deterministic and probabilistic sensitivity analyses were performed. **Results:** The model predicted that the most efficient strategy is the one that includes the administration of penicillin in primary care for cases of gestational syphilis. This strategy is more effective, although more costly. The cost per disability-adjusted life-years averted with the use of this strategy was estimated at R$49.79 (US$ 10.67). **Conclusion:** The prenatal strategy in primary care units that includes the administration of penicillin to pregnant women with syphilis during the first trimester of pregnancy has the greatest potential to be cost-effective.

Keywords: Syphilis, congenital. Prenatal care. Primary health care. Penicillins. Cost-benefit analysis.

RESUMO

Introdução: A despeito de a penicilina ser o medicamento de escolha para o tratamento da sífilis, muitas gestantes com teste positivo para sífilis não recebem o medicamento como recomendado pelo Ministério da Saúde, concorrendo para o aumento dos custos associados à sífilis congênita. **Objetivo:** Estimar a razão de custo-efetividade incremental da administração de pelo menos uma dose de 2,4 milhões de Unidades Internacionais de penicilina benzatina no primeiro trimestre de gravidez, tão logo se tenha o resultado de um teste rápido treponêmico positivo realizado na consulta pré-natal em unidades de atenção primária do Sistema Único de Saúde. **Métodos:** Um modelo analítico foi proposto a partir de uma árvore de decisão. A perspectiva da análise foi a do Sistema Único de Saúde. Os desfechos em saúde foram aborto, prematuridade, morte neonatal, natimorto e sífilis congênita, estimados em termos de anos de vida ajustados a incapacidades (*disability-adjusted life-years*). Apenas os custos diretos foram considerados. Análises de sensibilidade determinística e probabilística foram realizadas. **Resultados:** O modelo previu que a estratégia mais eficiente é aquela que inclui a administração da penicilina na atenção primária aos casos de sífilis gestacional. Embora essa estratégia possa representar maior custo, apresenta maior efetividade. O custo por *disability-adjusted life-years* evitado com o uso dessa estratégia foi estimado em R$49,79. **Conclusão:** A estratégia de pré-natal nas unidades de atenção primária que inclui a administração da penicilina em gestantes com sífilis ainda no primeiro trimestre de gestação é a que apresenta o maior potencial para ser custo-efetiva.

Palavras-chave: Sífilis congênita. Pré-natal. Atenção primária. Penicilinas. Custo-efetividade.

INTRODUCTION

Although the reduction of maternal–infant mortality had been indicated as one of the main objectives of the Pact for Health launched by the Ministry of Health (MH) in 2006, and even if the reduction of vertical syphilis transmission rates had been one of the priorities, congenital syphilis is still a huge problem in Brazil[1].

Syphilis during pregnancy, although carrying a significant public health and economic burden, is still a problem with less debate. In 2016, when the disease was declared a serious public health problem in Brazil, more than half a million (~661,000) cases of congenital syphilis were reported worldwide, resulting in more than 200,000 stillbirths and neonatal deaths[2].

It is estimated that annually almost 1.5 million pregnant women worldwide are probably infected with active syphilis. A significant number of untreated syphilis-affected pregnancies result in a clinical outcome of vertical transmission, termed *congenital syphilis*[3].

Fetal infection is severe, especially when it occurs in the first year of infection. The outcomes of infection in the first year include low birth weight, premature birth, abortion, stillbirth, and early and late clinical manifestations[4].

The benefits of preventing and treating congenital syphilis early by prenatal screening and antibiotic therapy have been reported in the medical literature. Apart from penicillin, no other drugs have proved effective against syphilis in pregnancy and prevention of congenital syphilis[5-7].

The United Nations Children's Fund (UNICEF) recommends that penicillin be dispensed and administered in primary health care units, since it considers that referring patients to hospital units and emergency departments, due to fear of anaphylactic reactions with the administration of this antibiotic, hinders the implementation of immediate and effective treatment[8].

Therefore, the health system needs to ensure that all women diagnosed with syphilis are effectively treated. It is essential that these women are cared for during clinical and laboratory follow-up

[1]Universidade Federal do Estado do Rio de Janeiro, Alfredo Pinto School of Nursing, Postgraduate Coordination – Rio de Janeiro (RJ), Brazil.
[2]Universidade do Estado do Rio de Janeiro, Faculty of Nursing, Department of Social Medicine Studies – Rio de Janeiro (RJ), Brazil.
[3]Universidade Federal do Estado do Rio de Janeiro, School of Medicine and Surgery – Rio de Janeiro (RJ), Brazil.
[4]Universidade Federal do Estado do Rio de Janeiro, Alfredo Pinto School of Nursing – Rio de Janeiro (RJ), Brazil.

in the health services. Their infants and their infected sexual partners should also be assisted by health programs to break the chain of transmission.

The use of rapid treponemal tests in the first prenatal visit and the use of penicillin represent the most important strategy in interrupting this chain. However, it is still crucial to establish the cost-effectiveness of different screening strategies within the context of each country.

This study was funded by the Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) and by the pharmaceutical company Roche do Brasil, with the aim of bringing answers about the need to expand the supply and administration of penicillin in pregnant women, in the prenatal screening program in primary care units in the country.

The relevance of this issue for health policy is that, despite access to treatment by pregnant women in the The Brazilian National Health System (SUS), increased diagnosis, and better access to prenatal care, the number of new cases of congenital syphilis has increased in the country in recent years.

OBJECTIVE

The aim of this study was to construct a decision analytic model to evaluate the efficiency of administering at least one dose of 2.4 million international units (IU) of benzathine penicillin in pregnant women with syphilis. The dose should be administered soon after the test result is positive for syphilis. Benzathine penicillin is preferably used before the first month of pregnancy. If the required dosage is not used or the start of treatment is delayed, vertical transmission may occur.

METHODS

The method used in this study was Health Technology Assessment (HTA), which can be understood as a comprehensive way of researching the technical (almost always clinical), economic, and social consequences, in the short and long term, of the use of health technologies, as well as their direct and indirect effects, both desirable and undesirable, with the following objectives: to ensure that technologies are safe and avoid harm; to ensure that they are effective and bring benefits; and to ensure that they are used appropriately[9].

Population

The study population consists of a hypothetical cohort of pregnant women assisted in primary care units during prenatal care by the SUS, with no age limit, who present a potential risk of contracting syphilis during pregnancy.

Situation and location

In Brazil, there is a national plan to reduce morbidity and mortality due to gestational syphilis and congenital syphilis, which considers early diagnosis and treatment until the first trimester of pregnancy, more effective strategies for syphilis control in prenatal care settings for screening pregnant women[10].

Study perspective and time horizon

We adopted the SUS perspective. Life expectancy was adopted as the time horizon to capture the potential health impacts of prenatal screening strategies for gestational syphilis in primary care units, as well as congenital syphilis and adverse effects related to the disease. Effectiveness and costs were discounted by 5%.

Prevalence

The prevalence of syphilis during pregnancy in Brazil was estimated at 1.02% (95%CI 0.84–1.25), and the incidence of congenital syphilis at 8.6 cases per 1000 live births, considering only women whose deliveries were performed in public hospitals[11,12].

Comparators

The strategy for early screening and treatment of pregnant women with syphilis recommends that, until the third month of pregnancy, at least one dose of 2.4 million IU benzathine penicillin should be administered in the primary care unit. Another adjusted dose of benzathine penicillin should be given to the newborn (NB) as soon as possible for all cases of syphilis identified by rapid treponemal test or VDRL (Venereal Disease Research Laboratory) test.

The comparator is the strategy to postpone the start of treatment for pregnant women with syphilis, by negligence, due to ignorance of the recommendations of the MH, or out of caution due to the possibility of occurrence of allergic reactions associated with the administration of penicillin, which causes the health professional to refer the woman to a medium complexity unit to start treatment.

Clinical outcomes

One of the goals of prenatal screening for gestational syphilis is the elimination or mitigation of vertical transmission of syphilis. However, in the proposed model for cost-utility analysis, the outcome of interest is focused on the NB and not on the pregnant woman.

Thus, the complications and sequelae for the NB considered in the model were as follows: fetal loss or miscarriage, prematurity or low birth weight, neonatal death, and live birth of NB with congenital syphilis, symptomatic or not. No other infection or health condition associated with syphilis was considered.

Treatment effectiveness

Penicillin is already incorporated and available for treatment in the SUS since 2015, for use, including in care units for the treatment of primary syphilis, including pregnant women, secondary and recent latent syphilis[13,14].

The MH recommends the administration of penicillin G benzathine, at a dose of 2.4 million IU, intramuscular (IM), single dose (1.2 million IU in each gluteus). In cases of late latent or latent syphilis with unknown duration and tertiary syphilis, penicillin G benzathine, 2.4 million IU, IM, should be administered weekly for 3 weeks, for a total dose of 7.2 million IU[14].

Evidence suggests that no other treatment has proven to be as safe and effective in treating syphilis in pregnancy and preventing

congenital syphilis as penicillin-containing regimens. Although possible, the occurrence of adverse events associated with drug use is estimated at 2% per course of treatment, and anaphylactic reactions occur in only 0.01–0.05% of patients, with approximately 2 deaths per 100,000 treatments[8,5,15].

Effectiveness measures

Since these are intervention strategies whose outcomes are focused on the NB, effectiveness was measured in terms of health utility value and was estimated by disability-adjusted life-years (DALYs), which are defined by the sum of the years of life lost due to premature mortality and the years of life lived with some disability or handicap due to the severity of the disease.

The DALYs for each of the outcomes imputed in the model and associated with syphilis in pregnancy and congenital syphilis were taken from a single study, which evaluated the cost-effectiveness of rapid tests for screening cases of syphilis among pregnant women attending the SUS. Although the aforementioned study extrapolated utility measures estimated in African countries, the authors were careful to make the necessary adjustments considering life expectancy in Brazil[16].

The study design followed the recommendations of the Methodological Guideline of Economic Evaluation and the Methodological Guideline of Budgetary Impact Analysis, of the Brazilian Network of Health Technology Assessment[9].

Vertical transmission probabilities

Pregnant women diagnosed and treated early have reduced risk of vertical transmission of syphilis and less chance of presenting unfavorable outcomes to the child compared to those who received late drug intervention. However, we know that inadequate prenatal care, in turn, is a crucial factor for the increase in cases of congenital syphilis, given that the opportunity for diagnosis and treatment mostly occurs during this period[17-19].

The probability of unfavorable NB outcomes associated with gestational syphilis is estimated to be 66.5% (95%CI 53.4–81.8) when the pregnant woman is not diagnosed and treated early for syphilis. The probabilities of cure with or without treatment and imputed outcomes in the model are presented in **Table 1**.

Cost estimates

Only direct medical costs were considered and expressed in real (BRL) The micro-costing technique was adopted to estimate the associated costs in each of the strategies compared in the analysis. Public domain information sources from the MH and the Ministry of Economy of Brazil were consulted on the Internet from November 5 to 15, 2021, including SUS Table of Procedures, Medicines and Orthoses, Prostheses and Special Materials (OPM) Management System (SIGTAP); Price Panel and Federal Government Purchasing System (COMPRASNET); and Tabnet System – DATASUS, in the period from November 5 to 16, 2021.

All costs were calculated considering non-twin pregnancy. The total cost of the test for syphilis detection refers to the performance of three tests, of which at least one is a rapid treponemal test performed in the pregnant woman and another is a VDRL performed in the NB.

The cost of the treatment of syphilis in NBs considered the need to hospitalize them to receive the doses of penicillin and the maximum length of stay of 10 days in pediatric beds, added to the costs of acquisition of penicillin. The costs with the treatment of syphilis in pregnant women considered only the costs with the acquisition and administration of the antibiotic and prenatal consultations.

Costs with desensitization for administration of penicillin and clinical management of outcomes associated with allergic and anaphylactic reactions were not considered in the model.

The costs of penicillin acquisition were estimated separately from the treatment costs, considering only the price of a 2.4 million IU vial of benzathine penicillin in purchases made by the federal government.

The delivery costs considered the average of the values paid by the SUS for normal delivery and cesarean delivery without dystocia. The costs of curettage were considered in cases of miscarriage or fetal loss.

Newborn care considered the costs with the first care at the time of delivery. Considering the need for hospitalization of premature NB in intensive care units, the costs were estimated considering the average stay of the NB for 6 days in a neonatal intensive care unit.

The cost and health-related quality-of-life parameters are shown in **Table 2**.

General structure of the analytical model

The proposed model basically incorporates three moments: prenatal care, which includes, among other things, testing of the pregnant woman for syphilis using the rapid treponemal test, treatment of positive cases for syphilis, and care of the NB, which includes, among other things, in addition to testing with the VDRL test immediately after birth, the treatment of cases of congenital syphilis according to the MS protocols.

Pregnant women who are seen in primary care units for prenatal care in the SUS, and who enter the model, are subject to two approach strategies:

Table 1. Estimates of probabilities of outcomes.

Outcomes	Base value	Lower value	Highest value	Reference
Probability of cure without treatment	0.01	0	0.01	Romero[16]
Probability of cure with treatment	0.97	0.94	0.99	Romero[16]
Stillbirth probability	0.046	0.03	0.071	Gomez[3]
Probability of neonatal death	0.021	0.03	0.043	Gomez[3]
Probability of abortion	0.046	0.03	0.071	Gomez[3]
Probability of newborn with congenital syphilis	0.155	0.075	0.29	Romero[16]

Table 2. Parameters imputed in the model.

Parameters	Base value	Lower value	Highest value	Reference
Newborn costs at birth[a]	55.20	27.60	82.80	03.10.01.002-0
Syphilis treatment cost[a]	258.77	129.38	388.15	03.03.01.012-6
Testing costs for syphilis[b]	8.49	4.23	12.75	02.02.03.111-0 02.14.01.007-4
Curettage cost[a]	179.62	89.81	268.80	04.11.02.001-3
Delivery cost[a]	494.56	443.40	545.73	03.10.01.003-9 04.11.01.003-4
Cost of hospitalization in neonatal ICU[a]	3051.78	1525.86	4573.74	08.02.01.013-0
Cost of hospitalization in neonatal ICU[c]	10.39	5.20	15.58	Price Panel[c]
Cost with NB penicillin + hospitalization[d]	2496.24	1248.12	3744.36	Tabnet and Pricing Panel[d]
DALY for stillbirth	10.32	7.1	14.21	Romero[16]
DALY for miscarriage	10.32	7.1	14.21	Romero[16]
DALY for prematurity	0.67	0	2.93	Romero[16]
DALY for case of congenital syphilis	1.98	0.96	3.71	Romero[16]
DALY por in case of neonatal death	10.32	7.1	14.21	Romero[16]

NB: newborn; ICU: intensive care unit; DALY: disability-adjusted life-years. [a]http://sigtap.datasus.gov.br.; [b]http://tabnet.datasus.gov.br.; [c]Available from: https://paineldeprecos.planejamento.gov.br/analise-materiais (cited on Nov 02, 2021). [d]Cost of acquiring penicillin plus 10 days of hospitalization at the average price of the Hospitalization Authorization (AIH) for 6 days of average length of stay. Costs are in reais (R$).

1. The pregnant woman performs the first rapid test for syphilis in the first prenatal consultation, in the first trimester of pregnancy, and negative cases are tested again in the third trimester. Positive cases are treated immediately after the test result is known, with at least one dose of 2.4 million IU benzathine penicillin (appropriate treatment). At delivery, the NB is tested with VDRL, regardless of the result of the non-treponemal rapid test performed in the mother, and, if the result is positive, it will receive treatment with penicillin, and the hospitalization of the NB is required according to the MH protocol.
2. The pregnant woman may or may not be tested for syphilis until the first trimester of pregnancy. Tested and positive pregnant women do not receive immediate treatment and are referred to a medium complexity unit, delaying the start of treatment (inadequate treatment).

The probabilities of cure of syphilis with and without adequate treatment, regardless of the form of infection, were represented by the efficacy of penicillin treatment using at least one dose of 2.4 million IU of benzathine penicillin[16].

Clinical outcomes are associated with the likelihood of the pregnant woman and her child having received adequate or inadequate treatment for syphilis, or of developing outcomes associated with the infection.

The incremental cost-effectiveness ratio (ICER) in 2021 was estimated in BRL per DALY averted. The decision analytic model (**Figure 1**) was built and analyzed using TreeAge Pro Healthcare software, considering the following assumptions:

- Multiple gestation was not considered in the model.
- The average birth weight of the NB is 3.5 kg (Tabnet).
- Syphilis infections in pregnant women are detected between the first and second test[17].
- A single dose of benzathine penicillin of 2.4 million IU was used for the treatment of any form of syphilis in pregnancy.
- The mother–child binomial is considered cured at the end of treatment if they are adequately treated with the protocol recommended by the MH and complete the treatment.
- Incomplete treatment of syphilis was considered to have the same efficacy as no treatment, and cases of reinfection were not considered in the model.
- The model did not separately incorporate the risks of adverse events associated with cases of allergic reactions to penicillin.

Sensitivity analysis

Model uncertainties were treated by means of multivariate deterministic and probabilistic sensitivity analyses (Monte Carlo simulation). The summary statistics provided in the sensitivity analyses were plotted on Tornado diagrams, acceptability curves, and incremental cost-effectiveness scatter plots for better visualization and interpretation of the uncertainties in the model results.

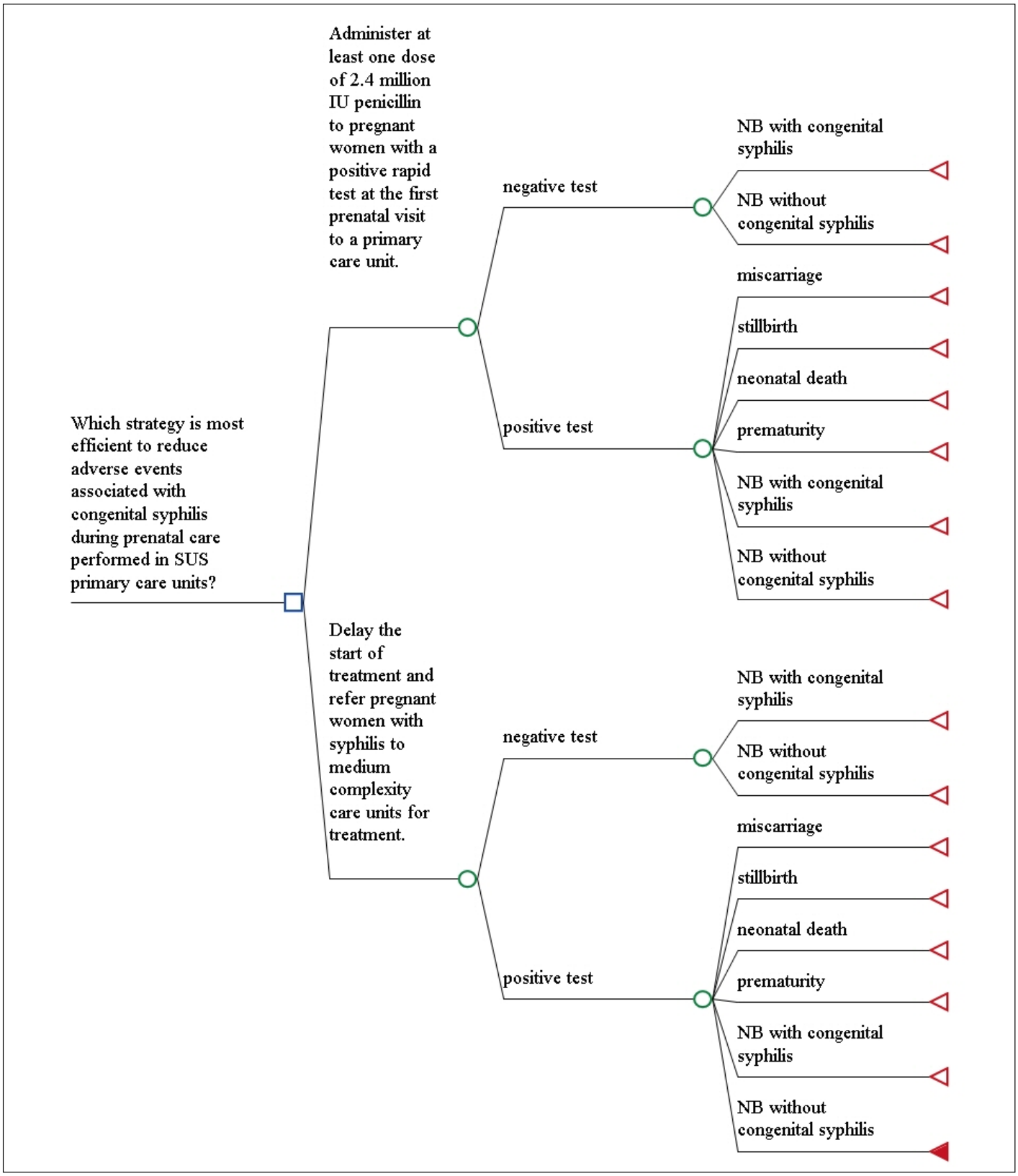
For the sensitivity analyses, costs were varied by more or less 50% and a specific discount rate of 5%, recommended by the MH, was applied for costs and effectiveness. The results of the sensitivity analyses made it possible to evaluate the robustness of the model and to identify the parameters that contribute to increased uncertainty.

Interpretation of results

In the present study, no specific willingness-to-pay threshold was defined for all analyses, considering that the Brazilian government has not yet officially indicated a threshold for defining cost-effective technologies in the SUS[20]. However, for the sensitivity analyses, a willingness-to-pay threshold of R$1,000 was considered for the acceptability curve analysis, and R$100 for the Monte Carlo simulations analysis, all arbitrarily and considering the ICER estimated by the model in the cost-effectiveness analysis.

RESULTS

The average cost associated with the strategy that uses appropriate treatment for cases of congenital syphilis was estimated at R$1,075.67. The cost of inadequate treatment was estimated at



The entry of pregnant women into the model can be based on two strategies for the prevention of congenital syphilis. In the first strategy, the pregnant woman is tested for syphilis with a rapid treponemal test in the first and third trimesters of pregnancy. Positive cases are treated with penicillin and, likewise, the newborn is treated. In the other strategy, this does not happen and treatment of the pregnant woman is delayed. Inadequate treatment can result in: stillbirth or fetal loss, low birth weight and prematurity, neonatal death, or live birth with syphilis. All testing and treatment costs are also included in the results.

SUS: The Brazilian National Health System; NB: newborn.

Figure 1. Decision tree model on strategies to reduce cases and complications associated with gestational and congenital syphilis.

R$729.39. The graph of the cost-effectiveness analysis shown in **Figure 2** suggests that the administration of at least one dose of 2.4 million IU of penicillin for cases of pregnant women whose test was positive for syphilis may be the most efficient strategy for reducing complications and sequelae associated with congenital syphilis.

The model predicted that administering at least one dose of 2.4 million IU of penicillin to pregnant women with syphilis in the first prenatal visit following prenatal care performed in a primary care unit after knowledge of the test result and until the first trimester of pregnancy can prevent on average 6.80 DALYs more than the strategy with which it was compared, despite the fact that it represents an incremental cost of R$346.27.

The expected value per DALY (ICER) avoided among NBs by administering penicillin to pregnant women in the first trimester of pregnancy was estimated at R$50.95, resulting in a net monetary benefit (BLM) of R$3,017,65.12, higher than the estimated BLM for its comparator of R$2,300,827.00.

The multivariate deterministic sensitivity analysis demonstrated that the model results are robust and are unlikely to be impacted by variations in the parameters adopted in the variables imputed in the model.

The Tornado diagram presented in **Figure 3** shows that, for an expected value of ICER of R$49.79, the variable that could impact the model the most is the cost of treating the NB with penicillin.

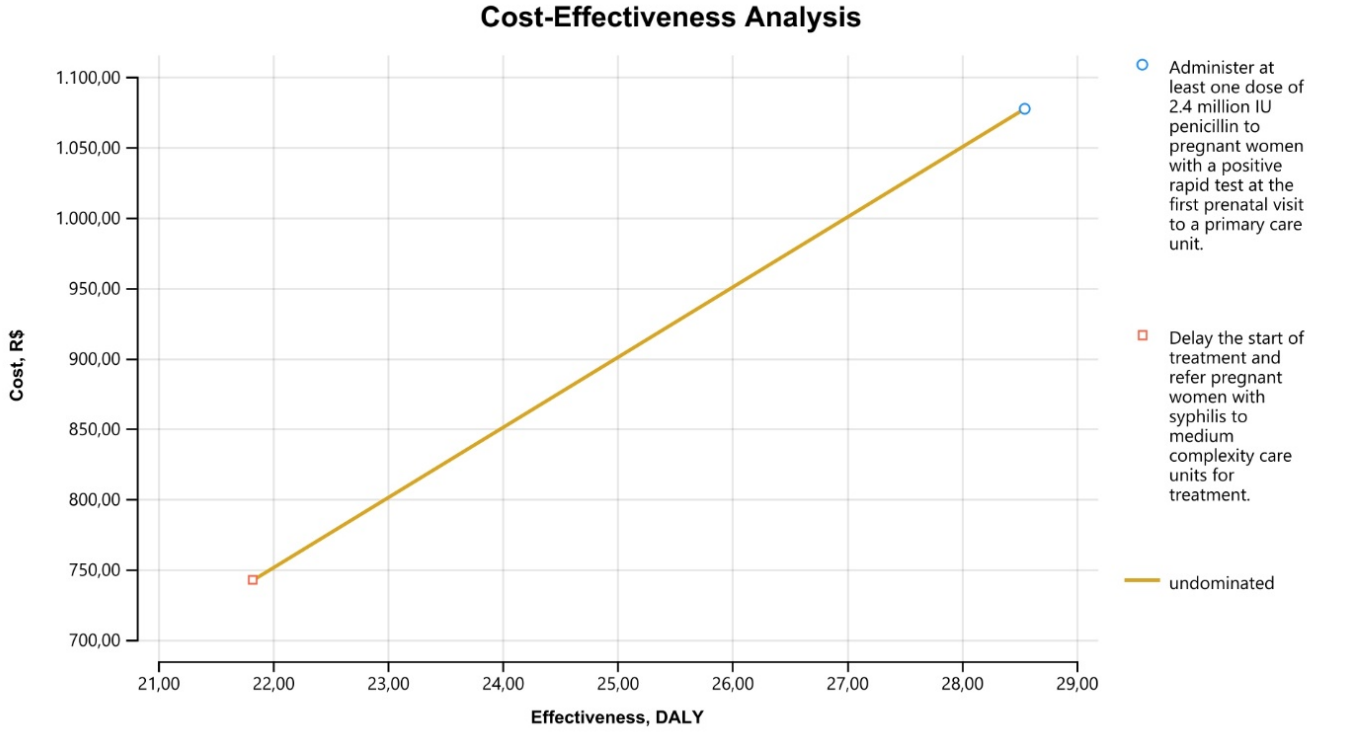
Considering the BLM in the Tornado diagram presented in **Figure 4**, it is observed that it is the avoided DALYs that would impact the model the most, considering R$3,011,577.51 as the expected value with the administration of penicillin, in terms of BLM.

The cost-effectiveness acceptability curve (**Figure 5**) shows that, if the willingness to pay per averted DALY was R$32, the two strategies would have the same probability of being cost-effective. From this value, administering penicillin in primary care becomes more likely to be cost-effective, and, from R$700, the probability of being cost-effective would have already reached 100%, and, therefore, investment above this value is unnecessary, as the probability of the strategy being cost-effective would not change

The cost-effectiveness plot plotted as an incremental cost-effectiveness scatter plot (**Figure 6**) represents the 10,000 Monte Carlo simulations. The plot shows a higher concentration of interactions considered cost-effective (green stars) compared to those considered non-cost-effective (red diamonds), considering a willingness-to-pay threshold of R$100 per DALY averted (represented by the bold dotted line). The confidence interval of the analysis was 95% (represented by the ellipse).

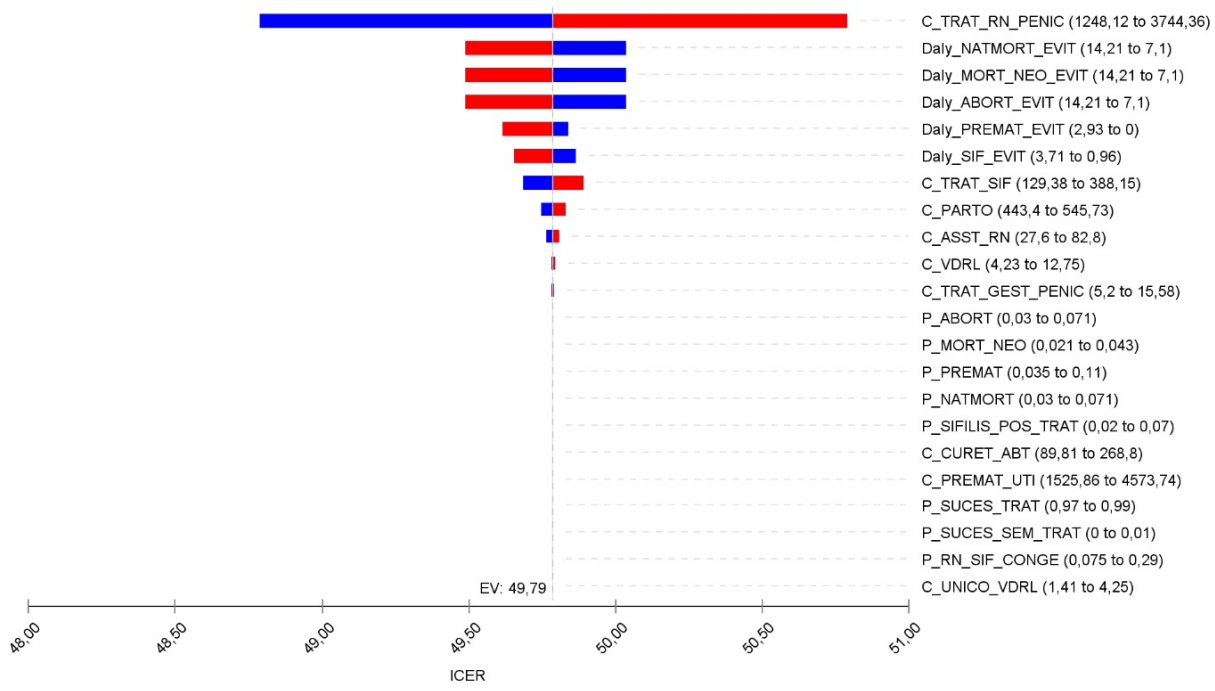
From this graph, it can be seen that none of the 10,000 iterations in the Monte Carlo simulation, considering a willingness-to-pay threshold of R$100 per additional DALY averted, places the strategy that administers penicillin in primary care to pregnant women with syphilis in the upper left quadrant of the graph (quadrant II), which represents the most costly and least effective alternative.

One also notices a higher concentration of iterations located between quadrants I (to the right and above) and IV (to the right



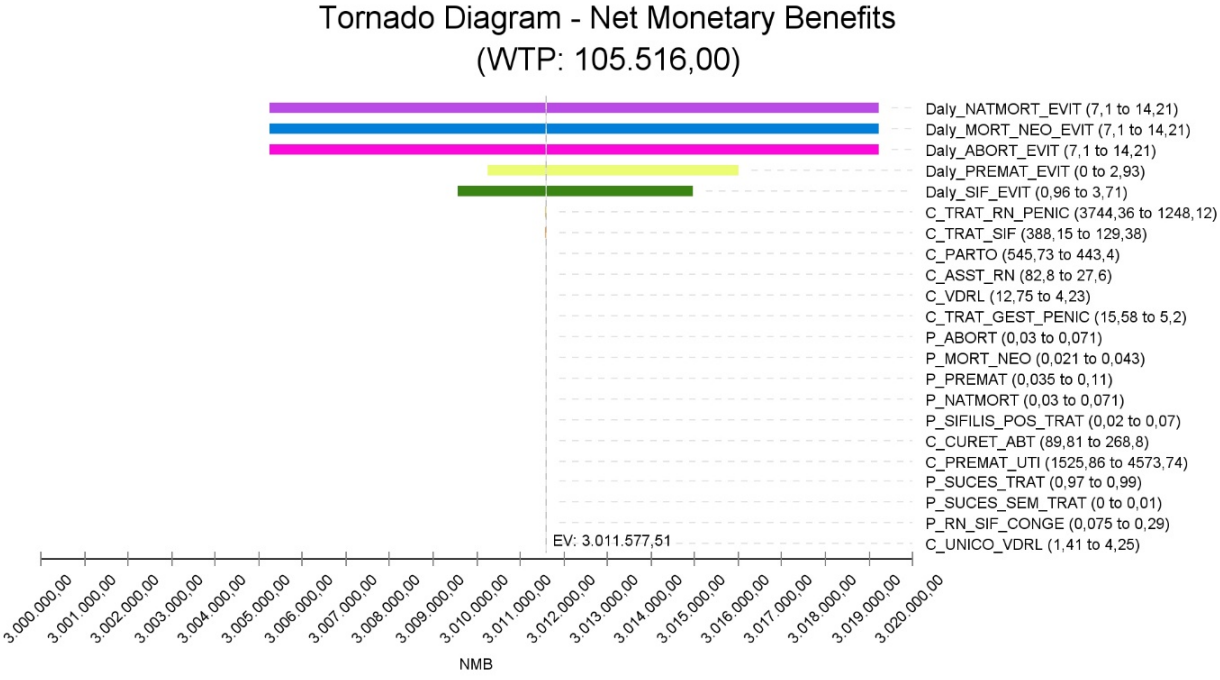
The blue circle represents the strategy that adopts penicillin administration in primary care for pregnant women with a positive rapid syphilis test identified and treated in the first trimester of pregnancy. The red square represents the comparator. The yellow sloping line connecting the two strategies represented in the graph shows the cost-effectiveness threshold and indicates that either of the two alternatives may be cost-effective, depending on willingness to pay.

Figure 2. Cost-effectiveness plan graph.



O custo do tratamento do recém-nascido com penicilina pode impactar muito mais do que o número de anos de vida ajustados a incapacidades evitados.
NB: newborn; DALY: disability-adjusted life-years; VDRL: venereal disease research laboratory; SIGTAP: procedures, medicines and orthotics, prosthetics table management system.

Figure 3. Tornado diagram plot of the expected value of the incremental cost-effectiveness ratio per disability-adjusted life-years averted for the newborn associated with the use of penicillin in primary care, in the first trimester of pregnancy, to treat women with syphilis.



The expected value of net monetary benefit associated with the use of penicillin in primary care, even in the first trimester of pregnancy, to treat women with VDRL+ for syphilis. In this case, it is the number of disability-adjusted life-years averted, rather than the cost of treating the newborn with penicillin, that may most impact the outcomes estimated by the model.
NB: newborn; DALY: disability-adjusted life-years; VDRL: venereal disease research laboratory; SIGTAP: procedures, medicines and orthotics, prosthetics table management system.

Figure 4. Tornado diagram graph.

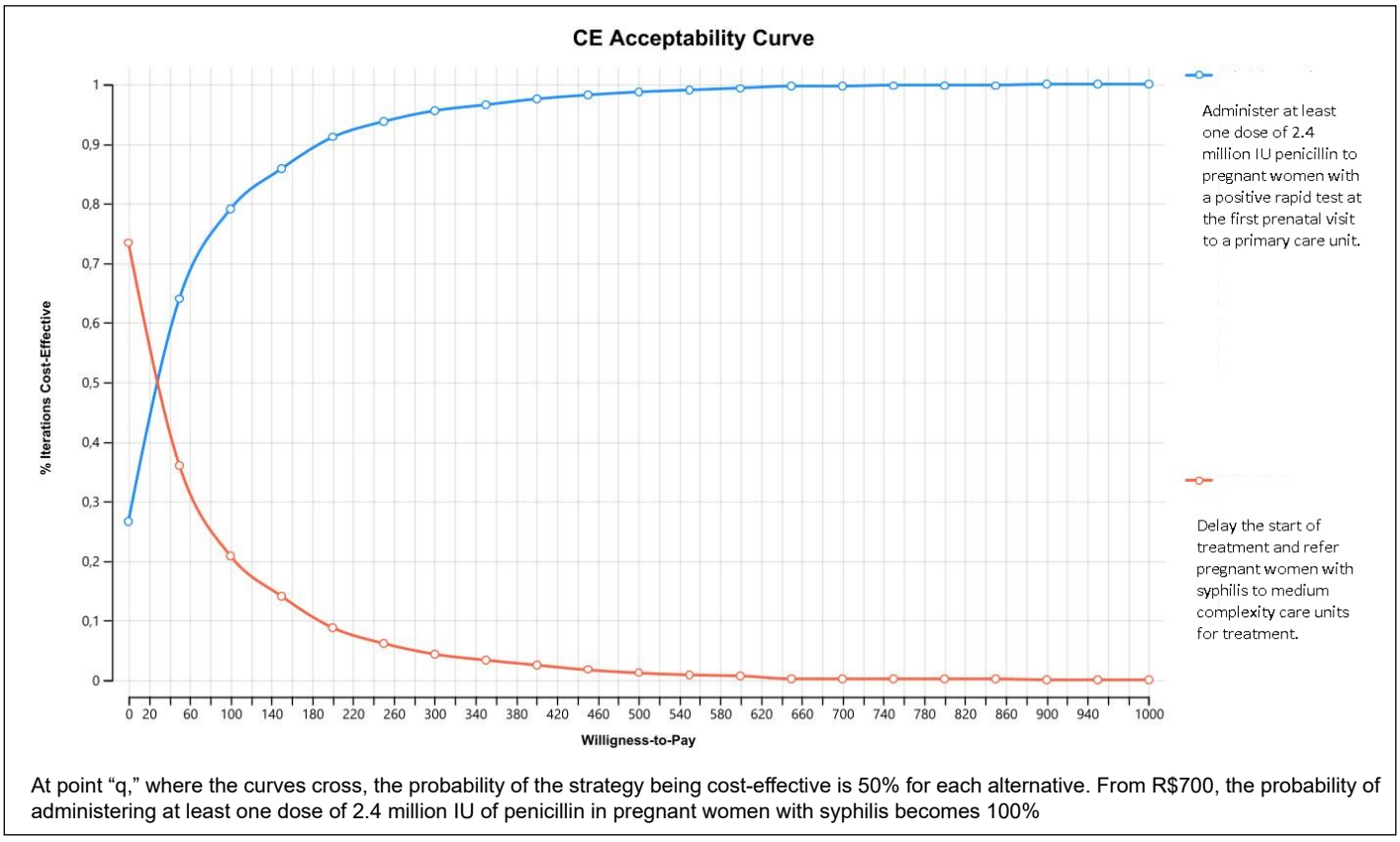


Figure 5. Acceptability curve.

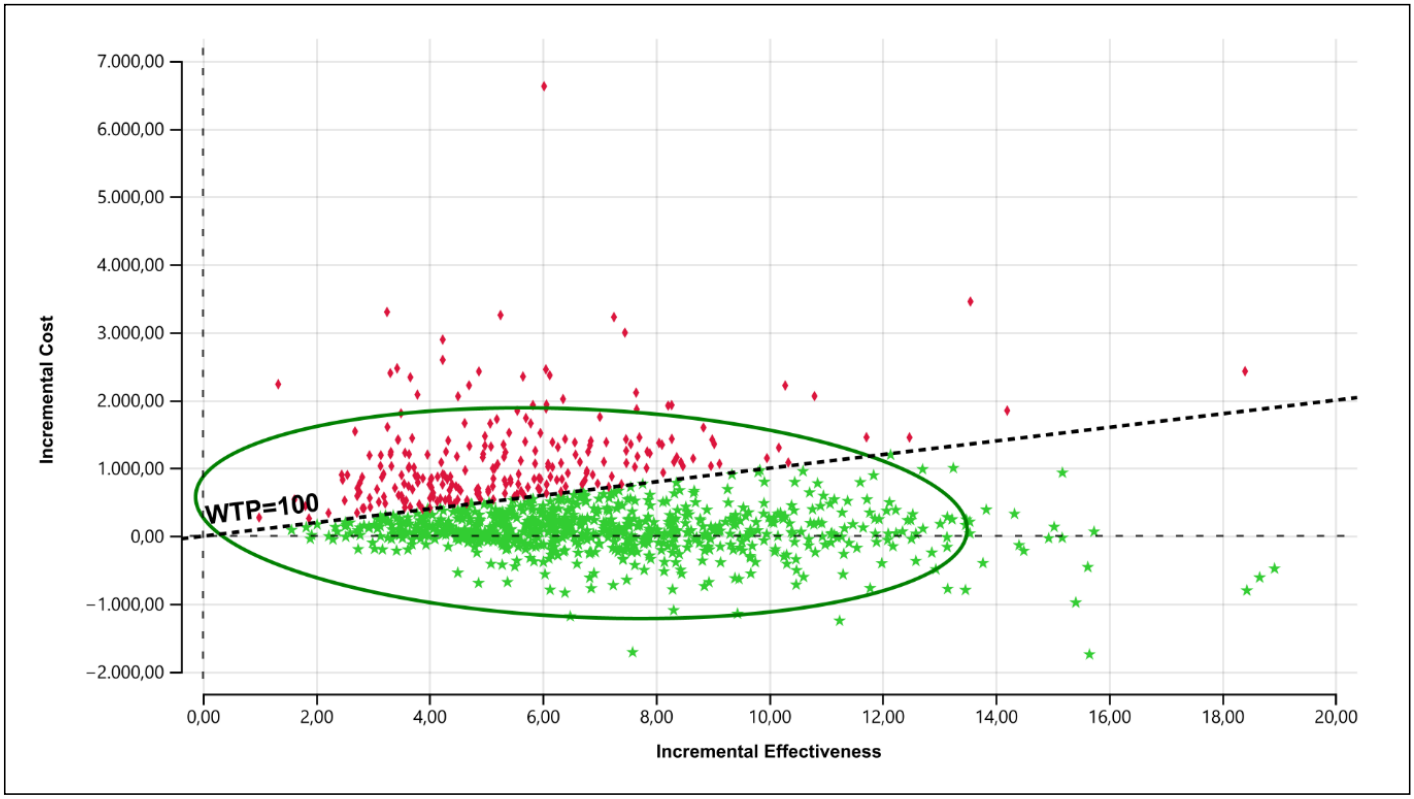


Figure 6. The strategy that adopts the appropriate treatment (represented by the green stars in the graph) in relation to its purchaser (represented by the red diamonds) was the one that resulted in the most cost-effective iterations in the 10,000 simulations performed, considering a threshold of R$100.00 per disability-adjusted life year avoided.

and below), all (76.1%) located in the graph, in components below the dotted line that represents the threshold for willingness to pay. Only 23.9% of the iterations suggest that the administration of penicillin in primary care is not cost-effective, as they would result in an ICER above the considered threshold of the analysis (R$100.00).

DISCUSSION

Since 2017, as an access measure, benzathine benzylpenicillin has become a strategic component in the RENAME (National List of Essential Medicines) with centralized procurement by the MH[21].

As benzathine benzylpenicillin is considered by the MH the only safe and effective option for the proper treatment of pregnant women, any other treatment performed during pregnancy should be considered inadequate treatment of the mother, and the NB should be notified as congenital syphilis and submitted to clinical and laboratory evaluation for diagnostic definition and therapeutic management. Therefore, given the possibility of congenital syphilis and the complications and sequelae associated with the infection, the costs of treating the disease tend to be higher when the treatment of pregnant women is not adequate.

Although the MH supports actions to combat syphilis by offering to states and municipalities benzathine penicillin for the treatment of the entire population diagnosed with the disease and, due to the current epidemiological scenario, it is recommended immediate treatment with benzathine benzylpenicillin after only one reagent test for syphilis (treponemal or non-treponemal test), at least 5.9% of pregnant women did not undergo proper treatment in the country[22].

An observational study conducted in Brazil suggests that the incidence of congenital syphilis may be lower in municipalities with greater availability of penicillin treatment in primary care. In these municipalities, the incidence rate of the disease is 2.67 cases per thousand live births, compared to 2.80 in municipalities with less supply. The study also showed that the percentage of municipalities where more than half of the health teams administer penicillin in pregnant women in primary care is only 41.90%, and the Southeast region presents the lowest percentage with only 22.71%. The highest percentage was observed in the North, with 73.12%[23].

The analysis of the model suggests that the administration of at least one dose of 2.4 million IU of penicillin for the treatment of pregnant women diagnosed with syphilis, still in the first trimester of pregnancy, during the first prenatal consultations performed in the SUS primary care units, is potentially the most efficient, and therefore cost-effective, strategy for reducing cases of congenital syphilis and the complications and sequelae associated with this disease during pregnancy.

The model results suggest an expected value for the ICER of R$47.52; therefore, for each additional DALY that is intended to be avoided by administering penicillin in primary care in pregnant women with syphilis, this is the amount of resources to be invested, much lower than the threshold of willingness to pay suggested by the WHO for Brazil, of approximately twice the national per capita gross domestic product, which in 2019 was estimated at R$35,161.70 by the Brazilian Institute of Geography and Statistics[24].

The results of the model, from the economic point of view, corroborated by data from the WHO, arrives at a cost of treatment of a pregnant woman with syphilis is US$29.00[14], or R$153.99 if we consider the average exchange rate of the American currency in the last 6 months in Brazil (R$5.31). It is not acceptable that gestational syphilis and other sexually transmitted infections (STIs) result in an expenditure of 28 million reais due to the need to perform medium and high complexity procedures in the SUS, when the disease could have been treated in primary care. It is reasonable to attribute this high cost of treating the disease to the low percentage of penicillin offered to pregnant women in primary care in Brazil.

Studies that evaluated the use of penicillin in the treatment of pregnant women and NB with syphilis from the perspective of cost-effectiveness are scarce. In Brazil, the National Commission for the Incorporation of Technologies in the Unified Health System (Conitec) unanimously recommended the incorporation of benzathine penicillin for the prevention of congenital syphilis during pregnancy, indicating its use in primary care units, even without having developed economic analysis or budget impact studies, but only based on robust clinical evidence on the efficacy and safety of the drug[13].

In the scientific literature consulted, variations in cost-effectiveness estimates were observed, probably due to the different methodologies and designs used, as well as the different technologies or strategies compared and outcomes considered in the analytical models proposed. Therefore, these estimates should not be directly compared to those found in this study.

Although the SUS should be considered a particular system, with peculiar characteristics when it comes to funding, coverage, and access to health services, and despite the fact that the studies identified in the literature have very different characteristics from this one, it seems evident that, regardless of the strategy used for the screening of cases of syphilis in pregnancy and the characteristics of the health services in each country, the use of penicillin is part of the strategies considered more cost-effective in the different studies identified in the literature.

A study conducted in Zambia, for example, estimated lower costs per averted DALY associated with gestational and congenital syphilis if there was full adherence to the guidelines established in the country for diagnosis and treatment of the disease. Higher costs per averted DALY were identified in scenarios of low adherence to guidelines that recommend, among other measures, the immediate administration of benzathine penicillin in pregnant women with positive results[25].

A study developed in China estimated the cost per DALY (RCEI) associated with congenital syphilis avoided in the country at US$215.00, or R$1,141.65. However, the study considered, in addition to institutional costs (e.g., costs of screening and diagnosis of gestational and congenital syphilis and human resources, transportation, monitoring, and supervision of the program), the individual costs paid by the patients and families associated with the treatment of the mother and child binomial, travel expenses, and loss of productivity and income due to the disease, which may explain a ICER so different from that found in our study[16].

In Brazil, a recent study published in 2020 assessed the cost-effectiveness of using rapid tests at the point of care and immediate initiation of treatment with penicillin in cases of pregnant women with positive test for syphilis. The comparator was the screening strategy with standard VDRL-type test and initiation of treatment

at the next prenatal visit. The authors estimated an avoided cost per DALY of US$298.00, or R$1,582.80, associated with the use of the strategy that uses rapid tests and initiates treatment immediately with penicillin for syphilis positive cases, concluding that this is the most cost-effective strategy[16].

It is possible that the high ICER (cost per averted DALY) estimated in this Brazilian study in relation to what we found can be explained basically by differences in the structures and assumptions assumed in the analytical models proposed. The model proposed by Romero (2020) considered, for example, the possibility of reinfection between tests and the possibility of treatment failure, as well as the estimates of accuracy of the tests compared in the model and the possibility of false-positive and false-negative results, which would imply, for example, the need for unnecessary treatment, therefore increasing the final costs of each strategy analyzed.

Study strengths

Strengths of the study are its potential to reaffirm the MH's protocol for the treatment of pregnant women with syphilis and the prevention of congenital syphilis as the most cost-effective alternative for the management of the disease, as well as its potential for the dissemination of economic and health analysis designs as a tool to guide clinical and managerial decision-making, with a view to the maximization and allocative efficiency of financial resources in the SUS.

Study limitations

The main limitation of our study is essentially the lack of Brazilian data for some parameters imputed in the analytical model, such as the utility associated with complications and sequelae associated with syphilis.

The very structure of the model, based on a decision tree, did not allow us to further reduce the uncertainties regarding the costs and consequences associated with the disease, as well as the strategies for screening and long-term treatment (life expectancy of the NB), in addition to not having considered the partners of pregnant women regarding the screening and treatment of cases positive for syphilis.

CONCLUSION

This study allowed reaffirming that the strategy of treating gestational syphilis cases with the administration of at least one dose of 2.4 million IU of penicillin, preferably during the prenatal visit, performed in the SUS primary care units, for pregnant women with syphilis tested by the rapid treponemal test, is the most efficient for reducing cases of congenital syphilis and reducing the impact of the disease on the quality of life of NBs in the SUS.

Approval by the Human Research Ethics Committee

The study is based on an economic modeling whose data imputed in the model were extracted from the scientific literature, the research protocol was not submitted to ethical appreciation.

Participation of each author

RCLS: Conceptualization, Methodology, elaboration, Formal Analysis. AAFP: Methodology, Writing – review & editing. RR: Writing – review & editing. LRR: Writing – review & editing. DAM: Writing – review & editing. CRLS: Writing – review & editing

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Conflict of interest

The authors declare no conflicts of interest.

REFERENCES

1. Ministério da Saúde (BR). Transmissão vertical do HIV e sífilis: estratégias para redução e eliminação. 2014 [cited on Jan 02, 2021]. Available from: http://www.aids.gov.br/sites/default/files/anexos/publicacao/2014/56610/folder_transmissao_vertical_hiv_sifilis_web_pd_60085.pdf
2. Korenromp EL, Rowley J, Alonso M, Mello MB, Wijesooriya NS, Mahiané SG, et al. Global burden of maternal and congenital syphilis and associated adverse birth outcomes-Estimates for 2016 and progress since 2012. PLoS One. 2019;14(2):e0211720. https://doi.org/10.1371/journal.pone.0219613
3. Gomez GB, Kamb ML, Newman LM, Mark J, Broutet N, Hawkes SJ. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. Bull World Health Organ. 2013;91(3):217-26. https://doi.org/10.2471/BLT.12.107623
4. Organização Mundial da Saúde (OMS). Diagnóstico laboratorial de doenças sexualmente transmissíveis, incluindo o vírus da imunodeficiência humana. Brasília: Ministério da Saúde, 2015.
5. Tan NX, Rydzak C, Yang LG, Vickerman P, Yang B, Peeling RW, et al. Prioritizing congenital syphilis control in south China: a decision analytic model to inform policy implementation. PLoS Med. 2013;10(1):e1001375. https://doi.org/10.1371/journal.pmed.1001375
6. toner BP. Rapid tests for maternal syphilis screening: effective and cost-effective. Sex Transm Dis. 2008;35(9):785-6. https://doi.org/10.1097/OLQ.0b013e31818638ee
7. Pan American Health Organization (PAHO) (2017). Elimination of mother-to-child transmission of HIV and syphilis in the Americas. Washington: PAHO; 2016
8. United Nations International Children's Emergency Fund (Unicef). Como prevenir a transmissão vertical do HIV e da sífilis no seu município [Internet]. Nova Iorque: Unicef; 2016 [cited on Dez 02, 2021]. Available from: http://www.unicef.org/brazil/pt/br_hivsifilis_edu.pdf
9. Ministério da Saúde (BR). Diretrizes metodológicas: estudos de avaliação econômica de tecnologias em saúde. Brasília: Ministério da Saúde; 2014; 145p.
10. Ministério da Saúde (BR). Plano operacional para a redução da transmissão vertical do HIV e da sífilis no Brasil. Brasília: Ministério da Saúde; 2007.
11. Domingues RMSM, Szwarcwald CL, Souza, PRB, Leal MDC. (2014). Rev Saúde Pública. 2014; 48(5): 766-74. https://doi.org/10.1590/S0034-8910.2014048005114
12. Ministério da Saúde (BR). Boletim Epidemiológico. Brasília: Ministério da Saúde; 2018.
13. Ministério da Saúde (BR). Penicilina Benzatina para prevenção da Sífilis congênita durante a gravidez [Internet]. Relatório de Recomendação N.150 da Comissão Nacional de Incorporação de Tecnologias no SUS – CONITEC, 2015 [cited on Dez 02, 2021]. Available from: http://conitec.gov.br/images/Relatorios/2015/Relatorio_Penicilina_SifilisCongenita_final.pdf

14. Ministério da Saúde (BR). Protocolo clínico e diretrizes terapêuticas para prevenção da transmissão vertical de HIV, Sífilis e Hepatites virais [Internet]. Brasília: Ministério da Saúde. 2020 [cited on Dez 02, 2021]. Available from: http://conitec.gov.br/images/Consultas/Relatorios/2020/PCDT_PTV_HIV_CP_42_2020.pdf
15. Felix MMR, Kuschnir FC. Alergia à penicilina: aspectos atuais. Adolesc Saúde (Online). 2011;8(3):43-53. https://doi.org/10.31744/einstein_journal/2021MD5703
16. Romero CP, Marinho DS, Castro R, Aguiar Pereira CC, Silva E, Caetano R, et al. Cost-effectiveness analysis of point-of-care rapid testing versus laboratory-based testing for antenatal screening of Syphilis in Brazil. Value Health Reg Issues. 2020;23:61-9. https://doi.org/10.1016/j.vhri.2020.03.004
17. Hawkes SJ, Gomez GB, Broutet N. Early antenatal care: does it make a difference to outcomes of pregnancy associated with syphilis? A systematic review and meta-analysis. PLoS One. 2013;8(2):e56713. https://doi.org/10.1371/journal.pone.0056713
18. Mesquita KO, Lima GK, Filgueira AA, Flôr SMC, Freitas CASL, Linhares MSC, et al. Análise dos casos de Sífilis congênita em Sobral, Ceará: contribuições para assistência pré-natal. DST – J Bras Doenças Sex Transm. 2012;24(1):20-7. https://doi.org/10.5533/2177-8264-201224107
19. Cardoso ARP, Araújo MAL, Cavalcante MS, Frota MA, Melo SP. Análise dos casos de sífilis gestacional e congênita nos anos de 2008 a 2010 em Fortaleza, Ceará, Brasil. Ciênc Saúde Colet. 2018;23(2):563-74. https://doi.org/10.1590/1413-81232018232.01772016
20. Bertram MY, Lauer JA, Joncheere K, Edejer T, Hutubessy R, Kieny MP, et al. Cost-effectiveness thresholds: pros and cons. Bull World Health Organ. 2016;94(12):925-30. https://doi.org/10.2471/BLT.15.164418
21. Ministério da Saúde (BR). Relação Nacional de Medicamentos Essenciais: RENAME 2017. Brasília: Ministério da Saúde; 2017 [cited on Dez 02, 2021]. 210 p. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2017/prt2436_22_09_2017.html
22. Ministério da Saúde (BR). Programa Nacional de DST e AIDS. Boletim Epidemiológico Sífilis 2016. Brasília: Ministério da Saúde; 2017 [cited on Jan 02, 2022]. Available from: http://www.aids.gov.br/pt-br/pub/2016/boletim-epidemiologico-de-sifilis-2016
23. Figueiredo DCMM, Figueiredo AM, Souza TKB, Tavares G, Vianna RPT. Relação entre oferta de diagnóstico e tratamento da sífilis na atenção básica sobre a incidência de sífilis gestacional e congênita. Cad Saúde Pública. 2020;36(3):e00074519. https://doi.org/10.1590/0102-311X00074519
24. Instituto Brasileiro de Geografia e Estatística (IBGE). Produto interno bruto Ano de 2019. [cited on Nov 28, 2021]. Available from: https://www.ibge.gov.br/explica/pib.php
25. Larson BA, Lembela-Bwalya D, Bonawitz R, Hammond EE, Thea DM, Herlihy J. Finding a needle in the haystack: the costs and cost-effectiveness of syphilis diagnosis and treatment during pregnancy to prevent congenital syphilis in Kalomo District of Zambia. PLoS One. 2014;9(12):e113868. https://doi.org/10.1371/journal.pone.0113868

Address for correspondence
LILIAN REINALDI RIBEIRO
Rua Irineu Correa, 291 – Irajá
Rio de Janeiro (RJ), Brazil.
CEP: 21235-540.
E mail: lilianreinaldi@hotmail.com

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