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Cost Effectiveness of the Reverse Sequence Algorithm Compared With the Traditional Algorithm for Syphilis Screening Among Pregnant Women

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Abstract

Background. The traditional syphilis screening algorithm, which involves a nontreponemal assay followed by confirmatory treponemal testing, has been challenged by an alternative approach known as the reverse sequence algorithm. The latter reverses the order of the tests and incorporates a second treponemal test for discordant results. While the reverse sequence may offer operational advantages, there is a need for formal cost-effectiveness analyses (CEA) to compare these two syphilis screening alternatives.

Methods. We conducted a CEA from the healthcare sector perspective to compare the reverse sequence with the traditional algorithm. We employed a decision-tree for pregnant women in prenatal care (PNC), which included the possibility of congenital syphilis outcomes. A simulated cohort of 10,000 people was screened over one year to estimate total costs and quality-adjusted-life-years (QALYs) under each algorithm. We estimated incremental cost-effectiveness ratios (ICER). Sensitivity analyses were performed to identify influential parameters affecting the ICERs and to conduct scenario analyses.

Results. During PNC, the reverse sequence detected four more cases, overtreated 185 more individuals, and prevented 0.42 more congenital syphilis cases (ICER=\$463,735 per QALY gained), compared to the traditional algorithm. Sensitivity analyses revealed that syphilis prevalence had the greatest impact on ICER. To achieve ICERs below \$50,000 per QALY gained, syphilis prevalence would need to exceed 6% during PNC.

Conclusions. Our analysis indicates that under likely parameter values, the reverse sequence algorithm is equally effective but more costly than the traditional algorithm, and therefore not cost-effective. Although treponemal test automation may offer potential savings in laboratory costs, these are outweighed by overtreatment costs.

Precis:

The reverse sequence algorithm for syphilis screening is not cost-effective compared to the traditional algorithm among pregnant women

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Keywords

Syphilis Prevention; Congenital Syphilis Prevention; Syphilis Screening; prenatal care; pregnant women

Introduction

Untreated syphilis in pregnant women poses a significant risk of perinatal transmission to the fetus, potentially leading stillbirth or severe fetal and neonatal outcomes.¹ Pregnant women are therefore a key population for syphilis prevention and control efforts.² CDC guidelines recommend syphilis screening at the first prenatal visit, with repeat testing at 28 weeks of gestation and at delivery for individuals at increased risk.² Pregnant women should receive penicillin treatment according to their stage of syphilitic infection.²

One screening approach is known as the traditional algorithm,² which begins with a nontreponemal assay such as the rapid plasma reagin (RPR) or the Venereal Disease Research Laboratory (VDRL) tests, followed by treponemal confirmatory test, such as chemiluminescence or enzyme immunoassay.³ In contrast, the reverse sequence algorithm (henceforth, reverse sequence) starts with a treponemal immunoassay test (a step that can be automated), followed by a confirmatory non-treponemal test, and a second—different from the first one—treponemal test for discordant samples, e.g., *Treponema pallidum* particle agglutination (TP-PA) test.^{2,4} The reverse sequence may improve case detection rates, especially in primary and late latent stages, but can also yield more false positives, increasing overtreatment and overall costs.⁵

Given the rising burden of syphilis in the United States and growing interest in improving the efficiency of screening programs, we conducted a cost-effectiveness analysis of these two algorithms from the healthcare sector perspective. Our objective was to estimate the health and economic consequences of syphilis screening among pregnant women in prenatal care (PNC) and examine how results vary across different scenarios.

Methods

We compared the screening algorithms in terms of their ability to accurately identify those with and without syphilis. The decision-model was designed following the testing sequence for each algorithm (Figure 1). The traditional algorithm begins with an RPR test, followed by an immunoassay (IA) test for confirmation. We used the RPR test based on its superior performance compared to the VDRL test and similar cost;⁶ performing the RPR is \$1.5 more expensive per test than the VDRL.⁷ Additionally, all IA tests are found to have similar testing performance; therefore we did not specify a particular IA test for this analysis.⁶ On the other hand, the reverse sequence begins with an IA test, reactive samples undergo confirmation using an RPR test, and discordant samples are further evaluated using a TP-PA test. Furthermore, we also considered the potential for vertical syphilis transmission and included cost and health outcomes related to congenital syphilis (CS). After a CS infection, the pregnancy could result in either a stillbirth, a live fetus with symptoms, or a live fetus without symptoms (Appendix 1).⁸

Costs and outcomes in our analysis were estimated from a healthcare sector perspective.⁹ Outcomes were measured using quality-adjusted life-years (QALYs), allowing us to capture both mortality and morbidity consequences. Thus, the analytical time horizon for case identification was 1 year but since health consequences are not immediately observed, we used a lifetime perspective to estimate the costs and QALYs associated with the identified and unidentified cases. We used the average lifetime number of QALYs lost per untreated syphilitic infection, as well as per congenital syphilis case for both the parent and infant to estimate the total number of QALYs lost under each algorithm. Utility values were extracted from Lee et al., 2022,¹⁰ which used Markov models and decision trees to quantify the average lifetime number of QALYs lost per syphilis and congenital syphilis infection in the United States. Utility losses per untreated syphilitic infection included the possibility of long-term sequelae, such as ocular and neurological complications. Further, among fetuses born with symptoms due to CS, the utility losses included the possibility of having low birth weight, condyloma lata, snuffles, syphilitic rash, and hepatosplenomegaly.^{10,11} We chose Lee et al., 2022,¹⁰ due to the rigor and recency of the estimates, and the fact that they were conducted specifically for the U.S. population. Regarding costs, our analysis considered the costs of testing and treatment in each stage of syphilis (i.e., primary, secondary, early latent, and late latent or unknown duration), as well as the possibility of long-term multiple sequelae among undetected infections. Costs were updated to 2024 USD using the price index for Personal Consumption Expenditure specific for health care and based on third quarter for 2024.¹²

Analytical framework

We built a decision tree for pregnant women in PNC that followed a simulated cohort of 10,000 people, which were categorized as infected or not infected based on the prevalence of syphilis (Appendix 1). Given the historic increases in syphilis, we assumed a high prevalence of syphilitic infection of 1% among pregnant women. Nonetheless, we also considered both lower and higher values in our sensitivity analyses described further below. Infections were further divided into the four infection stages based on the prevalence of each stage. Thus, the decision model incorporates different levels of test sensitivity by infection-stage,^{6,13} as well as differential treatment costs. Infected cases were further categorized as true positives or false negatives depending on how each algorithm classified these cases. True positive cases received treatment according to their infection's state, per CDC guidelines.² Primary, secondary, and early latent cases received a single dose of benzathine penicillin G (commercialized as Bicillin® L-A) at 2.4 million units administered intra-muscularly; late latent or unknown duration cases were administered three 2.4 million doses at 1-week intervals.² Because the decision tree only observed results until initial treatment, estimates did not consider treatment failure, the need for repeated treatment, or the possibility of reinfection.

We assumed all false negative, i.e., pregnant individuals whose infections were missed at screening, remained untreated. Thus, this was the only group from which vertical syphilis transmission could occur (Appendix 1). These cases had a probability of infecting the newborn, leading to CS cases.¹⁴ When a CS transmission occurred there were three possible outcomes: stillbirth, a newborn with symptoms, and a newborn without symptoms.⁸ We did

not include miscarriages as these are often reported without a cause and are not listed as CS infant outcomes.⁸ Symptomatic newborn infections triggered a treatment for syphilis in the birthing parent and the newborn, whereas in the case of stillbirth, only for the parent received treatment. If the newborn was asymptomatic, both the parent and the newborn remain untreated.

Uninfected people were divided into two groups: with and without a history of previous syphilitic infection. Previously infected people might remain reactive to serologic tests leading to a higher likelihood of being misclassified as positive cases and resulting in lower test specificity.¹⁵ Each screening algorithm then classified negative cases as true negatives or false positives. The false positive group received unnecessary treatment (i.e., overtreatment) corresponding to late latent or unknown duration syphilis (Appendix 1).

All modeling parameters, including the prevalence of syphilis and its distribution across disease stages, test sensitivity and specificity by stage, the number of QALYs lost per missed infection and per case of CS, and costs, were obtained through a comprehensive literature review. The estimation of treatment costs required further analysis which we detailed in Appendix 2. We collected base values and their corresponding uncertainty ranges (henceforth, feasible range). In addition, for most influential parameters we determined an extended range, comprised of possible but unlikely values, for further analysis. Table 1 presents all the parameters used in the model.

Statistical analysis

We estimated baseline results using the point-estimate of each parameter. We also conducted a probabilistic sensitivity analysis (PSA) by drawing 1,000 samples from the parameters' probability distributions, based on their feasible range, to obtain 95% credible intervals (95%CI).¹⁶ This approach allowed us to assess the robustness of our results against parameter uncertainty. Further, we calculated the positive and negative predictive values (PPV and NPV, respectively) for each screening algorithm.

To identify possible situations where the reverse sequence might be cost-effective compared to the traditional algorithm, we employed two approaches: univariate and multi-way sensitivity analyses, and both the feasible and extended ranges, for a total of four complementary sensitivity analyses. From the univariate analysis using feasible ranges, we identified influential parameters and summarized these findings using tornado plots. The four most influential parameters were further examined through additional univariate sensitivity analysis using their extended range distributions.

For the multi-way analysis, we considered all parameters within their feasible ranges, as applied in the PSA. For parameters with higher expected variability, such as prevalence of syphilis, proportion of people with known previous infections, and costs of testing and treatment, we also explored their extended range distributions. We drew 10,000 deviates from these extended ranges using a uniform distribution and a Latin Hypercube sampling technique to ensure a well-balanced representation.¹⁶ We used classification trees to identify the parameter combinations that resulted in the reverse sequence being cost-effective. While there are no officially recognized cost-effectiveness threshold for public health interventions

in the U.S., we employed the most frequently used cost-effectiveness thresholds for illustrative purposes in this sub-analysis: cost-effective (ICER <\$50,000 per QALY gained), borderline cost-effective (ICER between \$50,000 and \$150,000) or not cost-effective (ICER >\$150,000 per QALY gained).¹⁷ To determine the optimal tree depth for classification accuracy, we employed a 1,000-fold cross-validation approach.

We conducted two additional analyses. First, based on baseline results we estimated the economic burden to perform contact tracing on all identified cases (Appendix 3). Second, we performed a threshold analysis to estimating at what cost of the RPR test the reverse sequence is cost-effective (Appendix 4).

All statistical analysis were conducted in R statistical software version 4.3.0 (R Core Development Team) with the libraries Open Tree¹⁸ and Caret¹⁹.

Results

Compared to the traditional algorithm for syphilis screening, the reverse sequence had an ICER of \$463,735 (95%CI \$53,688, \$28,577,378) per QALY gained among pregnant women in PNC. From the PSA, we found that in 98% of the simulations, the reverse sequence had an ICER above \$50,000 per QALY gained (Appendix 5). Furthermore, the reverse sequence identified four more true cases per 10,000 people at a cost of \$132,165 per additional case identified and prevented 0.42 additional case of CS at a cost of \$558,017 (Table 2). Further, the reverse sequence led to 185 additional false positives. The overall PPVs of the reverse sequence were lower than the traditional algorithm: 22% vs. 38%. Overall, the reverse sequence incurred an additional total cost of \$0.56 million (95%CI 0.23, 4.04) and generated 1.20 total additional QALYs (95%CI 0.06, 9.73) compared to the traditional algorithm (Table 2). Thus, the reverse sequence generated slightly higher number of QALYs but was importantly more expensive than the traditional algorithm.

The reverse sequence generated higher costs in testing, treating true positives, and treating false positives than the traditional algorithm (Figure 2). The largest cost difference was in overtreatment due to the large number of false positives generated by the reverse sequence. The cost of testing was more than twice as high in the reverse sequence. This was primarily due to the reverse sequence applying a treponemal test to all screened individuals, which is more expensive than the RPR test used in the traditional algorithm. Additionally, the reverse sequence required one extra test in certain circumstances (treponemal testing applied to discordant samples), compared to the traditional algorithm. On the other hand, the smallest cost difference was observed in treating true positives, due to the slightly higher number of cases identified by the reverse sequence, most of which were in the late latent or unknown duration stage (Appendix 6).

Based on the univariate sensitivity analysis, the prevalence of syphilis and the sensitivity of the RPR test among late latent or unknown duration cases were identified as the two most influential parameters (Figure 3). However, considering the feasible uncertainty ranges for all parameters, no single parameter's range could generate a scenario where the reverse sequence was cost-effective compared to the traditional algorithm. When exploring the

parameters' extended range, a syphilis prevalence $>9\%$ and $\leq 81\%$, generated a scenario where the reverse sequence cost less than \$50,000 per QALY gained. If the prevalence exceeded 81%, the reverse sequence became cost-saving, meaning it was not only cheaper but also more effective than the traditional algorithm (Appendix 7).

From the multi-way sensitivity analysis, considering feasible uncertainty ranges, we were unable to identify a specific scenario where the reverse sequence was cost-effective. When exploring the extended ranges, the reverse sequence had a probability of 95% of being cost-effective if the prevalence of syphilis exceeded 6.2% (base values: 1%, 95%CI 0.06, 3.3; Table 1) and the cost of treating a late latent or unknown duration case less than \$1,486 (\$2,820, 95%CI 1,732, 6,002) (Appendix 8). These necessary conditions for cost-effectiveness are unrealistic considering the current prevalence levels of syphilis.

From the scenario-analyses, we found that following up cases identified by the reverse sequence algorithm would cost twice as much compared to the traditional algorithm, \$47,094 vs. \$26,247 (Appendix 3). Further, for the reverse sequence to generate an ICER below \$50,000 per QALY gained the cost per test will need to be at least \$60 among pregnant women (Appendix 4).

Discussion

We conducted a cost-effectiveness analysis to quantify the incremental value of the reverse sequence compared to the traditional algorithm at screening for syphilis, engaging in treatment, and preventing CS cases among pregnant women undergoing PNC. Our findings indicate that the reverse sequence is not cost-effective. While it identified slightly more cases than the traditional algorithm, it also resulted in a higher overtreatment rate. The reverse sequence generated almost the same number of QALYs as the traditional algorithm but at a much higher cost, resulting in ICER values well above \$50,000 per QALY gained, \$463,735 per QALY gained among pregnant women (Table 2). In a previous study based on a simulated cohort, Owusu-Edusei et al, concluded, similarly to our analysis, that the reverse sequence was more expensive than the traditional algorithm due to higher overtreatment.²⁰ Furthermore, Buono et al found that the reverse sequence costs more from a healthcare perspective but resulted in lower laboratory costs.²¹ Both studies concluded the reverse sequence was preferable based on the cost-per-case-detected, however, this is not directly comparable to the cost-per-QALY we used. In our analysis, the reverse sequence costs less than \$50,000 per QALY gained only under an unrealistically high syphilis prevalence of $>6\%$, among other conditions.

We estimated that implementing the reverse sequence would result in an additional cost of \$0.56 million per 10,000 pregnant women (Table 2). The main reason for this increased expenditure lies in the level of overtreatment associated with the reverse sequence (Figure 2). The secondary treponemal test performed on discordant samples contributes to both identifying additional true cases but also increasing false positives.²² A previous study found no difference in the number of identified cases or overtreatment rate when excluding the second treponemal test from the reverse sequence.²³ Therefore, the trade-off proposed by the reverse sequence involves balancing the benefits of identifying and treating more cases (and

the downstream consequences that might bring such as reducing infectivity rates) and the additional costs associated with overtreatment.

Our findings clearly demonstrate that the reverse sequence is a significantly more expensive alternative to the traditional algorithm once treatment costs are considered in addition to testing, without offering any significant effectiveness gains. However, there are economic factors that may influence the preference for the reverse sequence among laboratories and public health departments. Based on survey data 15.9% of clinical laboratories and 20.5% of public health laboratories in the U.S. reported using the reverse sequence syphilis screening algorithm.^{24,25} One potential reason is the reduction in manually performed nontreponemal tests. Implementing the reverse sequence reduces operator interaction and can be particularly beneficial in settings facing staff shortages or challenges in retaining trained technologists, which increases labor costs.^{5,26} Thus, it is possible that the cost of performing RPR testing is higher than the value applied in this analysis. Our findings suggest that for the reverse sequence to be cost-effective, the cost per test will need to be at least \$60 (Appendix 4). While this price is several times higher than the baseline value, further research is necessary to gain a better understanding of operational costs associated with each serologic test for syphilis screening, enabling a more accurate characterization of the resource demands imposed by each algorithm on laboratories and local health departments.

Limitations

Our analysis assumed that treatment was provided exclusively based on testing, and other factors such as presence of clinical signs or symptoms or behavioral elements that could lead to presumptive treatment were not included.² These elements could improve the number of true cases identified by the reverse sequence, but not the amount of overtreatment, leaving the cost-effectiveness assessment largely unchanged. Additionally, we assumed the cost of overtreatment was the same as the treatment, ignoring the consequences of the time lost for the patient and provider. Further, the analysis did not consider potential severe side effects associated with Bicillin® L-A, the negative social consequences of receiving a wrongful positive diagnosis, or the need for penicillin desensitization among pregnant women with reported penicillin allergy.² Including these treatment and overtreatment cost elements would likely negatively affect the reverse sequence, increasing the ICERs even further. Our assumed 1% prevalence is higher than typically observed, but sensitivity analyses show this favors the reverse sequence algorithm. At lower, more realistic prevalence levels, its performance worsens relative to the traditional algorithm, making our assumption conservative with respect to the conclusion that the reverse sequence is not cost-effective.

On the other hand, according to the STI Treatment Guidelines,² if the second treponemal test applied to discordant samples is positive, persons with a history of previous treatment might not require additional treatment. In practice, clinicians might investigate patients' history before initiating re-treatment and those with adequately documented history of successful prior treatment would not be treated again. Therefore, our model likely overestimates the cost of overtreatment under the reverse algorithm as well as the ICER values. Nonetheless, this assumption also reflects a real-world operational limitation of the reverse algorithm,

which necessitates careful clinical judgment, access to prior records, and clinician time, requirements that may not always be feasible in all practice settings.

Strengths

We assessed incremental health and economic value of the reverse sequence compared to the traditional algorithm in a priority population for which very limited evidence existed prior to this study. We achieved this by using the best scientific evidence available to parameterize our models realistically and specifically to our population of interest. Our analysis included CS outcomes which allowed us to have a comprehensive assessment of the performance of each algorithm, including the consequences for both the parent and the fetus or newborn. We conducted several sensitivity analyses to assess the performance of the reverse sequence under a multitude of conditions.^{27,28}

Conclusions

Our study found that the reverse sequence algorithm is an equally effective but more costly than the traditional algorithm for syphilis screening and congenital syphilis prevention among pregnant women, when accounting for testing and treatment costs and lifetime QALYs. The reverse sequence only demonstrated an economic advantage when syphilis prevalence levels exceeded 6%, which is substantially higher than those typically observed in this population. While the traditional algorithm remains more economically efficient in low-prevalence settings, our analysis supports a context-specific screening strategy where the choice of algorithm is informed by local epidemiology. Furthermore, the prices included in this study may not include all operational or administrative costs associated with using each algorithm. Future research could further investigate these aspects to improve the understanding of their advantages and disadvantages from an operational standpoint. By shedding light on the cost-effectiveness considerations associated with different screening algorithms, our study aims to support decision-making processes in public health settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

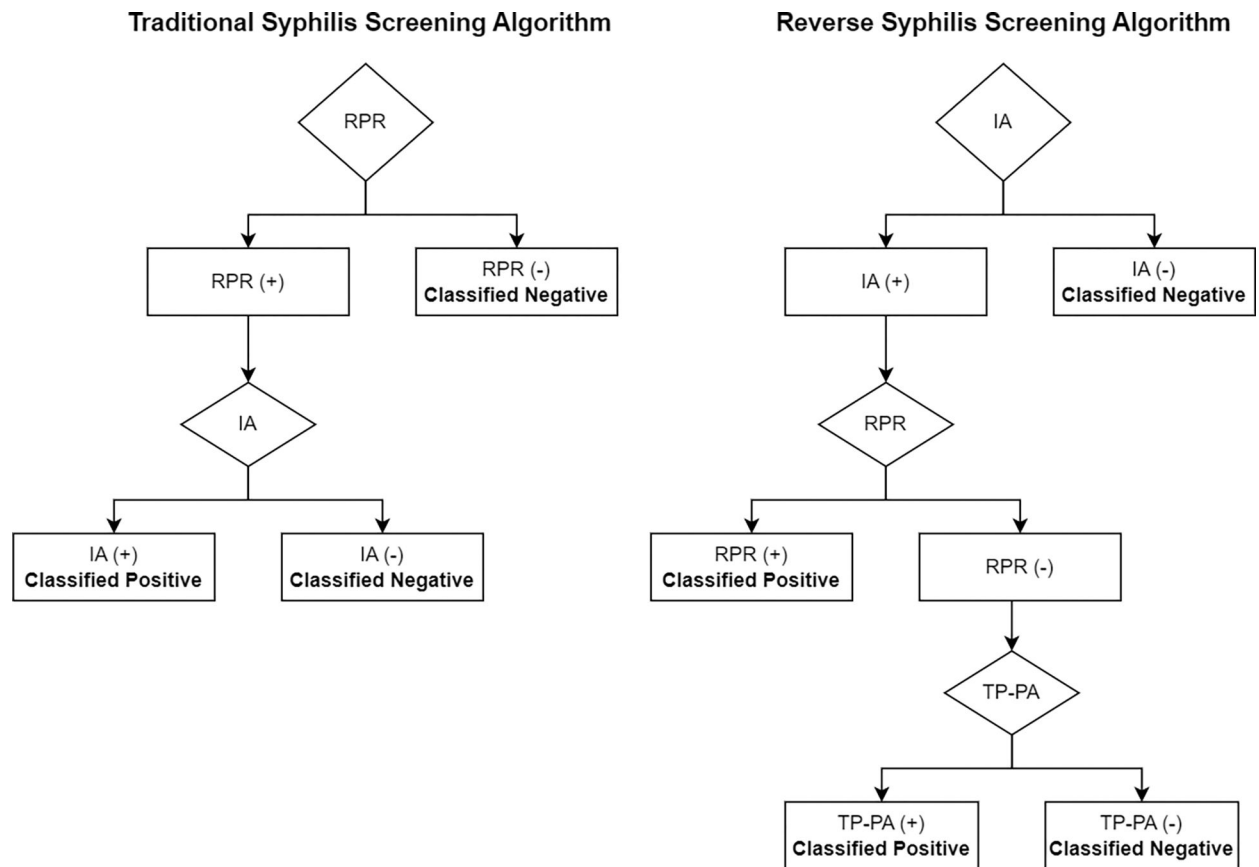
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**Figure 1.**

Schematic Representation of Syphilis Screening Algorithms. The reverse sequence algorithm changes the order of the tests included in the traditional algorithm, such that it performs an initial screening with an immunoassay (IA) test (treponemal) which is then confirmed by the rapid plasma reagin (RPR) (nontreponemal). Further, the reverse sequence algorithm adds a second treponemal test, the *Treponema pallidum* particle agglutination (TP-PA; treponemal test), for samples with discordant results.

Source: Based on Soreng et al,⁵ and Papp et al.⁴

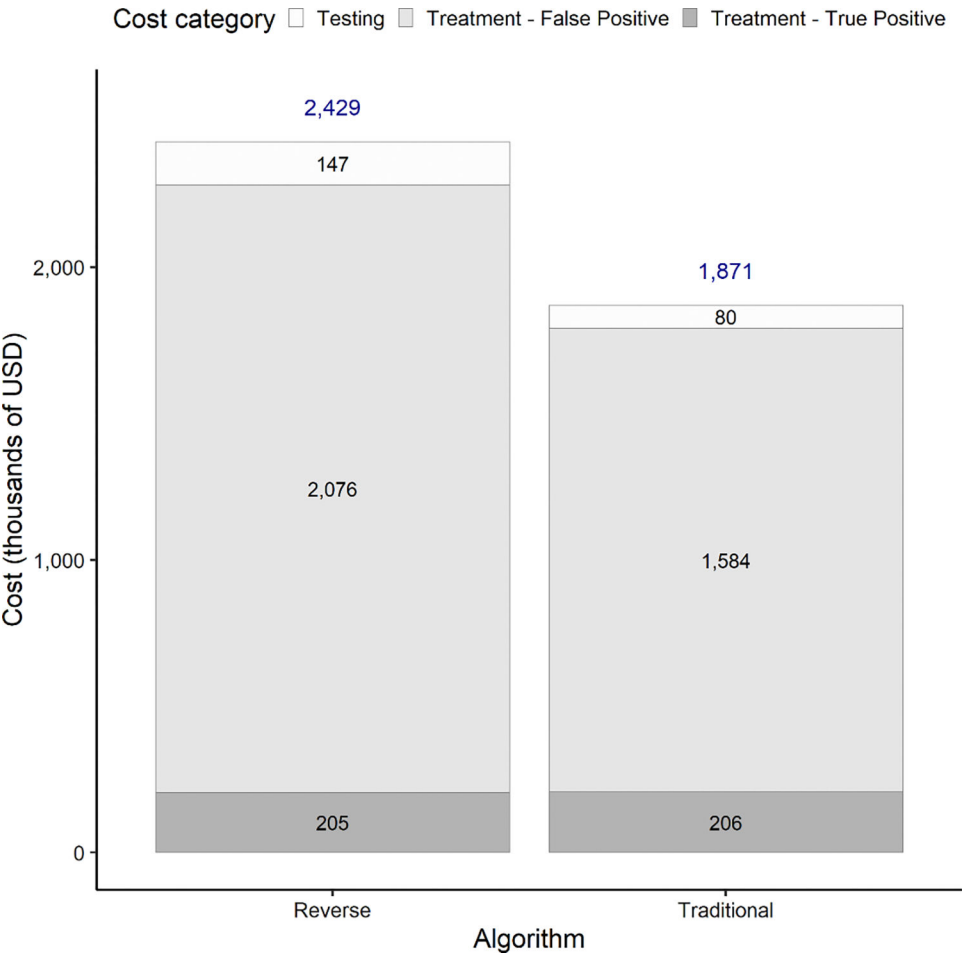


Figure 2. Costs accrued by the reverse sequence and traditional algorithms for syphilis screening, broken down into testing and treatment for true positive and false positive cases, among pregnant women in prenatal care (PNC). Costs are expressed in 1 2024 U.S. Dollars. Values are rounded to the nearest integer.

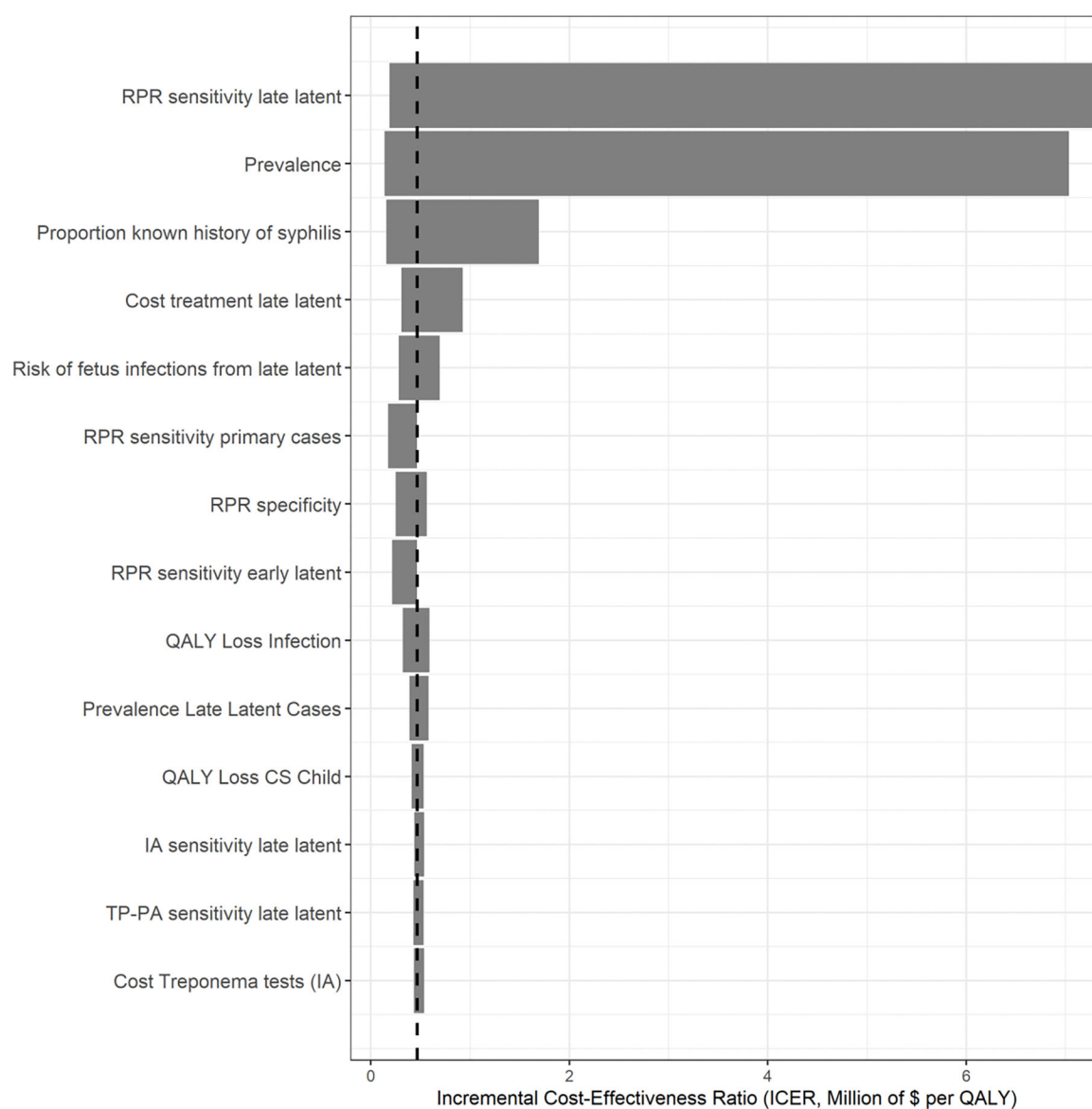


Figure 3.

Univariate sensitivity analysis for the cost-effectiveness of the reverse sequence algorithm for syphilis screening compared to the traditional algorithm among pregnant women undergoing prenatal care (PNC). Tornado plots show the parameters that modified the baseline Incremental Cost-Effectiveness Ratio (ICER) by at least 10%.

The vertical, dashed line within the plot represents the baseline ICER. The width of each bar is determined by the ICER value under the lower and higher values of the parameter's feasible range. In this analysis, the ICER is estimated by modifying one parameter at a time to better understand each parameter's influence in the ICER, and consequently the cost-effectiveness of the reverse sequence algorithm, compared to the traditional algorithm. Negative values (ICER<0) indicate, in this analysis, that the traditional algorithm is cost-

saving. I.e. it produces a higher number of quality-adjusted life-years (QALYs) at a cheaper cost than the reserve sequence algorithm.

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Table 1.

Parameters used in the cost-effectiveness analysis of the reverse sequence syphilis screening algorithm compared to the traditional algorithm among pregnant women undergoing prenatal care (PNC).

Parameter	Base value	Feasible uncertainty range	Probability distribution	Extended uncertainty range	Reference
<i>Epidemiologic parameters</i>					
Prevalence of syphilis (%)	1	3.3 – 3.3	Beta (1.31, 105.42)	0 – 100	Assumed
Prevalence of early latent cases (%)	26.6	21.3 – 31.9	Beta (59.48, 161.63)		6,29
Prevalence of late latent cases (%)	47	37.6 – 56.4	Beta (43.16, 47.18)	27 – 80	6,29
Prevalence of primary cases (%)	9.2	7.4 – 11.1	Beta (73.18, 712.53)		6,29
Prevalence of secondary cases (%)	17.2	13.7 – 20.6	Beta (66.88, 318.66)		6,29
Proportion known history of syphilis (%)	2.5	0.6 – 10	Beta (2.17, 47.1)	0 – 100	Assumed half of among GBMSM ³⁰
<i>Test performance parameters</i>					
IA persistent reactivity among those with syphilis history (%)	97.3	-	Fixed		6
IA sensitivity early latent (%)	98.5	83.8 – 100	Beta (14.66, 0.51)		6
IA sensitivity late latent (%)	94.1	81.7 – 99.9	Beta (15.54, 0.74)		6
IA sensitivity primary (%)	95.6	84.9 – 98.9	Beta (34.37, 2.08)		6
IA sensitivity secondary (%)	100	96.2 – 100	Beta (79.61, 0.72)		6
IA specificity (%)	93.6	78.4 – 99.5	Beta (16.38, 1.15)		6
RPR reactivity for reasons unrelated to syphilis infection (%)	16	0 – 45	Beta (0, 0.45)		Assumed 5% higher than among GBMSM ³¹
RPR sensitivity early latent (%)	100	95 – 100	Beta (54.62, 0.6)		13
RPR sensitivity late latent (%)	89	73 – 100	Beta (8.31, 0.51)		13
RPR sensitivity primary cases (%)	100	77 – 100	Beta (9.73, 0.49)		13
RPR sensitivity secondary (%)	100	-	Fixed		13
RPR specificity (%)	83	48 – 99	Beta (5.03, 1)		13
TP-PA persistent reactivity among those with syphilis history (%)	92.5	-	Fixed		6
TP-PA sensitivity early latent (%)	100	90.7 – 100	Beta (29.63, 0.64)		6
TP-PA sensitivity late latent (%)	86.8	76 – 93.8	Beta (41.72, 6.34)		6
TP-PA sensitivity primary (%)	94.5	84.9 – 98.9	Beta (34.37, 2.08)		6
TP-PA sensitivity secondary (%)	100	96.2 – 100	Beta (79.61, 0.72)		6
TP-PA specificity (%)	100	99 – 100	Beta (473.58, 1.55)		6
<i>Risk of congenital syphilis</i>					
Probability of symptoms given fetal syphilis infection (%)	33.2	15 – 50	Beta (6.95, 14.31)		8,10
Probability stillbirth (%)	6.5	4 – 10	Beta (15.31, 204.27)		8,10

Parameter	Base value	Feasible uncertainty range	Probability distribution	Extended uncertainty range	Reference
Risk of fetal infections from all stages except late latent (%)	50	30 – 60	Beta (15.89, 18.59)		14
Risk of fetal infections from late latent (%)	10	5 – 20	Beta (6.72, 48.64)		14
<i>Costs per outcome</i>					
Cost Office visit (\$)	121	35 – 181	Gamma (5.53, 0.05)		32
Cost RPR (\$)	6	3 – 7	Gamma (19, 3.81)	1 – 30	21
Cost Treponema tests (IA, TP-PA) (\$)	14	9 – 25	Gamma (13.27, 0.79)	5 – 50	32
Cost of treating congenital syphilis (\$)	44,963	26,978 – 62,948	Gamma (19.01, 0)		33
Cost stillbirth (\$)	2,496	1,872 – 2,871	Gamma (72.43, 0.03)		34
Cost treatment late latent (\$) [‡]	2,782	1,775 – 5,723	Gamma (10.26, 0)	200 – 5,100	32,35
Cost treatment, except late latent (\$) [‡]	1,265	609 – 3,305	Gamma (5.2, 0)	100 – 2,900	32,35
Cost undetected and untreated (\$) [‡]	1,470	789 – 3,513	Gamma (6.53, 0)	400 – 3000	32,35
<i>Lifetime QALYs lost [‡]</i>					
QALYs lost per missed infection	0.1	0.04 – 0.23	Beta (4.41, 30.26)		10
QALYs lost per congenital syphilis case for the parent	0.06	0.01 – 0.14	Beta (2.32, 34.22)		10
QALYs lost per congenital syphilis case for the infant	1.79	1.43 – 2.16	Lognormal (0.58, 0.11)		10

IA: chemiluminescence or enzyme immunoassay; RPR: rapid plasma regain; TP-PA: Treponema pallidum particle agglutination; CS: congenital syphilis; QALY: Quality-Adjusted Life-Year; GBMSM: gay, bisexual, and other men who have sex with men.

Costs are expressed in 2024 U.S. Dollars.

[‡] Treatment costs for primary, secondary, early syphilis, and latent or unknown duration take into account the probability of developing neurological or ocular syphilis manifestations³² and benzathine penicillin G 2.4 million units costs from the Federal Supply Schedule.³⁵ The cost of undetected and untreated reflects the costs of treating sequelae after 30 years of initial infection, i.e., false negative cases. The treatment costs includes the probability of being treated inadvertently and health outcomes associated with untreated syphilis.³² Appendix 2 provides further detail in the calculations.

[‡] Lifetime QALYs lost expressed the discounted, average number of QALYs lost due to syphilis per infection and, by population and outcome.

The “Probability distribution” column corresponds to the feasible uncertainty range for each parameter parameterized to its probability distribution, to be used in the probabilistic sensitivity analysis (PSA).

Values in the “Extended uncertainty range” column are available for the four most influential parameters for each population identified from the one-way sensitivity analysis (i.e., syphilis prevalence, proportion of people with history of past syphilitic infection, cost of treating a late latent case, and utility loss among untreated), and parameters with expected significant setting variability (i.e., prevalence of late latent cases, cost of syphilis treatment in all stages, cost of screening tests, in addition to syphilis prevalence and proportion of people with history of infection). The bounds in the extended range correspond to the natural bounds of the parameter (i.e., prevalence, history of past syphilis, and utility loss among untreated), symmetric with respect to the base value given an assumed upper or lower bound in the logarithm scale (i.e., prevalence of late latent cases, costs of screening tests) or in the natural scale (i.e., treatment costs in all syphilis stages). These values were assumed to explore the parameters’ values space and therefore do not have a reference.

Table 2.
Cost-effective assessment of the reverse sequence algorithm for syphilis screening compared to the traditional algorithm among pregnant women in prenatal care (PNC). Baseline results are presented accompanied by 95% credible intervals in parentheses, obtained from probabilistic sensitivity analysis.

	Reverse Sequence Algorithm	Traditional Algorithm	Difference
	<i>Cost-Effectiveness: Baseline results (95% credible interval)</i>		
Costs (Millions of USD)	2.43 (1.51 – 7.54)	1.87 (0.89 – 5.21)	0.56 (0.23 – 4.04)
Number of QALYs lost	–1.79 (–16.36 – –0.15)	–2.99 (–25.15 – –0.30)	1.20 (0.06 – 9.73)
ICER (Millions of USD per QALY)			0.46 (0.054 – 28.58)
	<i>Case Identification: Baseline results (95% credible interval)</i>		
True Cases	96 (10 – 466)	92 (10 – 454)	4 (0.1 – 21)
False Positive (Overtreated)	332 (102 – 1,215)	147 (4 – 726)	185 (42 – 884)
True Negatives	9,568 (8,433 – 9,719)	9,753 (8,978 – 9,856)	–185 (–884 – –42)
False Negatives (Missed)	4 (1 – 26)	8 (1 – 41)	–4 (–21 – –1)
PPV (%)	22.41 (1.83 – 67.25)	38.44 (4.67 – 96.69)	–16.03 (–72.21 – –1.06)
NPV (%)	99.96 (99.71 – 100)	99.91 (99.56 – 100)	0.04 (0.00 – 0.22)
CS Cases	0.74 (0.06 – 6.40)	1.16 (0.12 – 9.78)	–0.42 (–3.9 – –0.03)

CS: congenital syphilis. QALY: Quality-Adjusted Life-Year; PPV: Predicted Positive Value; NPV: Negative Predicted Value; USD: U.S. Dollars.
Costs are expressed in 2024 U.S. Dollars.