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ORIGINAL ARTICLE

Cost-effectiveness of HIV and syphilis antenatal screening: a modelling study

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ABSTRACT

Objectives The WHO called for the elimination of maternal-to-child transmission (MTCT) of HIV and syphilis, a harmonised approach for the improvement of health outcomes for mothers and children. Testing early in pregnancy, treating seropositive pregnant women and preventing syphilis reinfection can prevent MTCT of HIV and syphilis. We assessed the health and economic outcomes of a dual testing strategy in a simulated cohort of 100 000 antenatal care patients in Malawi.

Methods We compared four screening algorithms: (1) HIV rapid test only, (2) dual HIV and syphilis rapid tests, (3) single rapid tests for HIV and syphilis and (4) HIV rapid and syphilis laboratory tests. We calculated the expected number of adverse pregnancy outcomes, the expected costs and the expected newborn disability-adjusted life years (DALYs) for each screening algorithm. The estimated costs and DALYs for each screening algorithm were assessed from a societal perspective using Markov progression models. Additionally, we conducted a Monte Carlo multiway sensitivity analysis, allowing for ranges of inputs.

Results Our cohort decision model predicted the lowest number of adverse pregnancy outcomes in the dual HIV and syphilis rapid test strategy. Additionally, from the societal perspective, the costs of prevention and care using a dual HIV and syphilis rapid testing strategy was both the least costly ($226.92 per pregnancy) and resulted in the fewest DALYs (116 639) per 100 000 pregnancies. In the Monte Carlo simulation the dual HIV and syphilis algorithm was always cost saving and almost always reduced DALYs compared with HIV testing alone.

Conclusions The results of the cost-effectiveness analysis showed that a dual HIV and syphilis test was cost saving compared with all other screening strategies. Updating existing prevention of mother-to-child HIV transmission programmes in Malawi and similar countries to include dual rapid testing for HIV and syphilis is likely to be advantageous.

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INTRODUCTION

In 2008, the global burden of active syphilis in pregnant women was estimated at 1.36 million women.[1] Africa had the highest proportion of women with seropositive syphilis tests during antenatal care, at 2.13% compared with all other regions.[1] Without screening and treatment, maternal syphilis can lead to serious adverse pregnancy outcomes, including stillbirth, prematurity, low birth weight, neonatal mortality and infant syphilis infection.[2–5] Maternal treatment, which consists of a single intramuscular injection of benzathine penicillin,[6] greatly reduces the risks of adverse pregnancy outcomes.[7 8] However, syphilis screening has been inconsistent, primarily because of challenges associated with laboratory testing and, until recently, low prioritisation by local health systems and global governing bodies.[4 9]

In contrast, maternal HIV infection, which can also be transmitted to the infant, is screened for in a significantly larger proportion of pregnant women. Antenatal HIV testing and treatment has received tremendous support from donors and governments,[4] leading to strengthened health systems and increased rates of case identification through point-of-care testing. Although antenatal HIV screening has been very successful, without syphilis screening babies continue to die from congenital syphilis.[10] Implementation of syphilis point-of-care testing in resource limited settings has been more recent.[11–17] The WHO is calling for a harmonised approach to the elimination of HIV and syphilis.[5] The similarity of interventions needed to prevent adverse pregnancy outcomes due to HIV and syphilis suggests that an integrated approach to the elimination of maternal-to-child transmission of HIV and syphilis is feasible. Dual elimination would address Millennium Development Goals 4, 5 and 6 by improving maternal and child health outcomes and by reducing the spread of HIV infection.[18]

During antenatal care, screening for HIV and syphilis is the first step toward treatment and prevention of transmission. While rapid point-of-care HIV tests are consistently used in sub-Saharan Africa, screening options for syphilis vary considerably; there are currently options for rapid point-of-care tests, laboratory-based tests and new *dual* point-of-care tests that combine HIV and syphilis testing into a single rapid test.[19] While the performance of those tests has been previously reported,[19–23] to our knowledge, the cost-effectiveness of different HIV and syphilis screening programmes, including the use of dual HIV and syphilis tests, is not available. We undertook a cost-effectiveness analysis of various HIV and syphilis screening algorithms in order to provide funders and policy-makers with additional information into the costs and benefits of each option.

METHODS

Procedures (screening algorithms and model structure)

We conducted a cost-effectiveness analysis of four HIV and syphilis screening algorithms that are currently used in antenatal care: (1) HIV rapid test

only, (2) dual HIV and syphilis rapid test, (3) single rapid tests for HIV and syphilis and (4) HIV rapid and syphilis laboratory-based tests. We assumed the laboratory tests were a combination of rapid plasma reagin and *Treponema pallidum* particle agglutination assay.[24] Using a hypothetical cohort of 100 000 antenatal patients, we calculated the expected number of adverse pregnancy outcomes, the expected costs and the expected newborn disability-adjusted life years (DALYs) for each screening algorithm.[25 26] We used disability weights of zero for losses due to stillbirth and miscarriages. The estimated costs and DALYs for each screening algorithm were assessed from a societal perspective using Markov progression models. The analytic horizon was the life expectancy of the child. Schematics of the Markov model can be seen in the online supplementary appendix Figure.[w1]

Input parameters

We estimated the number of expected adverse pregnancy outcomes (fetal death or stillbirth, neonatal death, prematurity or low birth weight, congenital syphilis infection and HIV mother-to-child transmission) through a decision tree. Each pregnancy was assumed to be singleton. The tree incorporated the epidemiology of HIV and syphilis, the reported uptake for testing, test sensitivity, the likelihood of treatment versus loss-to-follow-up and the anticipated pregnancy outcomes given the woman's disease and treatment status. All model inputs were determined from the published literature, unless otherwise stated (table 1). When available, we used data from Malawi for the setting of the analysis. Malawi was chosen as a real example of a low-income economy in sub-Saharan Africa with endemic HIV and syphilis and a response similar to other countries in the region. Malawi has approximately 638 900 births annually, so our hypothetical cohort of 100 000 women presenting for antenatal care represented approximately one-sixth of the country's annual births.[27] For the primary analysis we used an HIV prevalence at antenatal care of 10.6% with 24.8% of HIV-infected women presenting with AIDS.[28 29] Syphilis prevalence among HIV-uninfected women was 1.1% and among HIV-infected women was 2.2%.[28 29] For the single rapid syphilis test, results on sensitivity and specificity from three published studies were averaged and the range from the three was used for sensitivity analyses.[30 w2] Ranges used for sensitivity analyses were otherwise assumed using a 50% spread around the base-case estimate or the 95% CI from the literature. Each method for range estimation is displayed in table 1. Variables that have strong evidence for inputs from the literature or the Malawi government reports were not ranged. Additionally, because the prevalence of adverse pregnancy outcomes in some women (eg, those with untreated syphilis and HIV infection) totalled 100%, these outcomes were kept stable in the model without a range.

Malawi, along with other sub-Saharan African countries, is currently implementing Option B+ for the prevention of mother-to-child transmission of HIV. Under Option B+, HIV-infected mothers start combination antiretroviral therapy from 14 weeks of gestation and continue for life, regardless of CD4 t-cell count.[w3] Our model included Option B+ for HIV treatment and the WHO-recommended syphilis treatment consisting of a single intramuscular dose of benzathine penicillin 2.4 MU.[w4]

Costs for individual test materials and supplies were determined from the literature, negotiated agreements between suppliers and Unicef or WHO, or direct communication with suppliers. Costs incurred by the health system for time for each test were calculated using WHO published health worker salaries for the region[w5] and when available, published times needed for each procedure.[24] Patient costs for clinic attendance and testing were included.[24] Test procurement and distribution costs of tests were not included. Treatment costs for both syphilis and HIV infection in mothers at time of screening and lifetime for the child were included. Those costs included health system and patient cost at time of testing, and the health system throughout treatment. All costs were converted to 2012 dollars using the World Bank GDP deflator.[w6] Costs and DALYs were discounted annually by 3%.[w7]

We assumed that women with effectively treated syphilis would have the same rates of pregnancy outcomes as women without syphilis infection. The model also assumed that if syphilis relapse were to occur, it would occur during the first year.[w8] We used an uptake of HIV testing of 83% and 8% for syphilis based on reported test coverage in the country in July through September 2013.[w9] We assumed an uptake of the dual test equal to that of the HIV rapid test. For the testing algorithms that looked at two separate tests for HIV and syphilis, the model assumed that if a woman were tested for syphilis, she was also tested for HIV. We assumed that there was no loss-to-follow-up among children with congenital syphilis whose mothers were tested and received treatment for syphilis, but for whom the treatment failed.

Sensitivity analyses

We conducted several sensitivity analyses. We conducted one-way sensitivity analyses to determine the impact that key inputs had on the cost and effectiveness estimates, as shown in table 1. Additionally, we conducted three Monte Carlo multiway sensitivity analyses, allowing all the variables with ranges in table 1 to vary, assuming uniform distributions. We conducted Monte Carlo simulations to sample randomly from those distributions for 1000 model iterations and calculated the incremental cost and effectiveness compared with each other test algorithm.

This analysis was non-human subject research that did not require institutional review board oversight. All analyses were conducted using TreeAge Pro Software 2015 (Williamstown, Massachusetts, USA).

RESULTS

Health and cost outcomes

Our cohort decision model for 100 000 pregnant women attending antenatal care in Malawi predicted a total of 15 820 adverse pregnancy outcomes in the HIV rapid test only strategy, 15 779 adverse pregnancy outcomes in the HIV rapid and laboratory-based syphilis testing strategy, 15 778 adverse pregnancy outcomes in the single rapid test for HIV and syphilis strategy and 15 370 adverse pregnancy outcomes in the dual HIV and syphilis rapid test strategy (see online supplementary appendix table). Given the base-case parameters, the strategy using the dual HIV and syphilis rapid test was both the least costly ($214.79 per pregnancy) and resulted in the fewest DALYs (108 693 per 100 000 pregnancies). The results of the cost-effectiveness analysis showed that a dual HIV and syphilis test was cost saving compared with all other screening strategies indicating all other screening were both more costly and less effective (table 2).

Monte Carlo simulation (multiway sensitivity analysis)

The Monte Carlo simulation (figure 1) showed that the dual HIV and syphilis test remained the most cost-effective algorithm for nearly all iterations, was cost saving for all iterations and

Table 1 Description, point values, range and sources for all variables used in a cost-effectiveness model of different algorithms of HIV and syphilis testing in pregnancy

Variable	Base-case value	Range	Sources
Maternal characteristics			
Median age at first birth	20		w18
Disease prevalence			
HIV prevalence among pregnant women	10.6%	5.3%–15.9%*	28
AIDS prevalence among HIV-infected pregnant women	24.82%		Assumption
Syphilis prevalence among HIV-uninfected pregnant women	1.09%	0.54%–1.63%*	28
Syphilis prevalence among HIV-infected pregnant women	2.17%	1.09%–3.26%*	28
History of syphilis infection (adequately treated previous infections) in HIV-uninfected women	5%	2.5%–7.5%*	Assumption
History of syphilis infection (adequately treated previous infections) in HIV-infected women	10%	5%–15%*	Assumption
Disease progression			
Average progression time for HIV to AIDS in treated child	10 years		Assumption
Average progression time for AIDS to death in treated child	5 years		Assumption
Average progression time for HIV to AIDS in untreated child	1 year		Assumption
Average progression time for AIDS to death in treated child	1 year		Assumption
Test performance			
Syphilis test sensitivity			
Dual HIV and syphilis test	0.89	0.84–0.94	20
Syphilis rapid	0.82	0.63–0.97	30 w1 w2
Syphilis laboratory-based	1		24
Syphilis test specificity			
Dual HIV and syphilis test	0.99	0.97–1.00	20
Syphilis rapid	0.96	0.92–0.99	30 w1 w2
Syphilis laboratory-based	1		w16
Syphilis test specificity in those with previously treated syphilis infection			
Dual HIV and syphilis test	0.91		Assumption
Syphilis rapid	0.91		w1
Syphilis laboratory-based	1		
HIV test sensitivity			
Dual HIV and syphilis test	0.99	0.95–1.00	20
HIV rapid	1		w10
HIV test specificity			
Dual HIV and syphilis test	0.99	0.997–0.999	20
HIV rapid	0.96	0.85–1	w10
Loss-to-follow-up			
Syphilis loss-to-follow-up (for laboratory tests)	20%		w19
HIV loss-to-follow-up	23.9%		w20
HIV and syphilis treatment			
Infants born to women who test positive for HIV and receive treatment who receive nevirapine	77.19%		Assumption
Proportion of children known to be HIV-exposed who were enrolled in ART	67%		28
Probability of syphilis treatment success for the mother	98%		w16
Pregnancy outcomes			
Syphilis-uninfected mothers			
Stillbirth/early fetal death	4.6%	3.0%–7.1%	3
Neonatal death	3%	2.1%–4.3%	3
Prematurity or low birth weight	6.3%	3.5%–11.0%	3
MTCT of HIV in HIV-treated mothers (in utero+intrapartum/postnatal, 12 month)	4.99%		w21
MTCT of HIV in HIV-untreated mothers (in utero+intrapartum/postnatal, 12 month)	24.17%		w22
Syphilis-infected mothers (syphilis-untreated)			
Congenital syphilis	15.5%	7.5%–29.0%	3
Prematurity or low birth weight	12.1%	3.9%–31.8%	3
Neonatal death	12.3%	9.3%–16.2%	3
Stillbirth/early fetal death	25.6%	18.5%–34.2%	3
Additional effects in HIV-coinfected mothers (HIV-treated)			
MTCT of HIV in HIV-treated mothers (in utero+intrapartum/postnatal)	9.05%		29
Prematurity or low birth weight	2.74%		3
Additional effects in HIV-coinfected mothers (HIV-untreated)			
MTCT of HIV	34.5%		29
Prematurity or low birth weight and MTCT of HIV	9.36%		3 29

Continued

Table 1 Continued

Variable	Base-case value	Range	Sources
Costs (2012 US dollars)			
Labour costs			
Pretest counselling (both HIV and syphilis)	$0.44		w5†
Sample collection (single test)	$0.27		w5†
Preparing and inoculating test (single test)	$0.37		24
Reading and recording results (single test)	$0.63		24
Post-test counselling, syphilis positive	$0.62		w5†
Post-test counselling, syphilis negative	$0.18		w5†
Post-test counselling, HIV positive	$1.24		w5†
Post-test counselling, HIV negative	$0.18		w5†
Patient cost			
Travel cost	$1.49		Assumption
Testing time cost (dual test)	$0.48		24
Testing time cost (single tests)	$0.71		Assumption
Test cost			
Single syphilis rapid test	$0.55		WHO catalogue
Single HIV rapid test	$0.81		UNICEF agreement
Laboratory-based syphilis tests	$2.53		w13
Dual HIV and syphilis test	$1.30	$1.20–$2.60	Assumption
Early infant diagnosis	$32.50		w23
Treatment for syphilis (2.4 MU benzathine penicillin)	$2.38		w16
Pregnancy outcome cost			
Healthy	$72.59	36.30–108.89*	w16
Congenital syphilis	$804.54	402.27–1206.81*	w16
Premature	$1508.84	754.42–2263.26*	w16
Neonatal death	$3577.58	1788.79–5366.37*	w16
Stillbirth	$72.59	36.30–108.89*	w16
MTCT HIV	$1358.18	679.09–2037.27*	w24
Nevirapine for 12 months for infant	$16.60	8.30–24.90*	
Disability weights			
AIDS (no treatment)	0.545		25
HIV	0.053		25
Death	1		–
Congenital syphilis (3 years)	0.315		26
Low birth weight (1 year)	0.106		26
Neonatal death	1		–
Stillbirth	0		–
Miscarriage	0		–
Test uptake			
Syphilis rapid test	0.08	0.04–0.12*	w9
Syphilis laboratory test	0.08	0.04–0.12*	w9
HIV rapid test	0.83	0.415–0.95‡	w9
Dual HIV and syphilis test	0.83	0.415–0.95‡	Assumption
Early infant diagnosis	0.9		w23
Other			
Life expectancy of newborn	50 years		w25
Discount rate	3%		w26

Women are assumed to have unknown HIV and syphilis status at time of testing.
*Ranges calculated using a 50% spread.
†Labour costs were calculated using salaries published by the WHO (w5) and assumed times for length of each procedure.
‡Ranges are calculated using a 50% reduction for the lower bound and an assumption for the top.
ART, antiretroviral therapy; MTCT, maternal-to-child transmission.

had the highest number of DALYs averted for all but a few iterations compared with the HIV rapid test only algorithm.

One-way sensitivity analyses

Figure 2A, B reflect the impact of altering model parameter values from lower to upper end ranges (table 1) on incremental cost and effectiveness of HIV rapid test only versus dual HIV and syphilis testing. Parameters that had a large effect on incremental cost included HIV and syphilis prevalence, risk of prematurity or low birth weight among syphilis-uninfected and HIV-positive untreated mothers, and probability of neonatal death in syphilis-uninfected and HIV-positive untreated mothers. Variables that influenced the relative effectiveness were HIV prevalence among pregnant women, uptake of dual HIV

Table 2 Summary results from the cohort decision model comparing the expected effects (DALYs) of the pregnancy and total costs (2012 US dollars) for all four antenatal HIV and syphilis testing algorithms in the Malawi setting of a theoretical cohort of 100 000 pregnant women receiving antenatal care using the base-case value model inputs

	Total costs ($)	Incremental cost ($)	DALYs lost	Incremental DALYs lost
Dual HIV and syphilis test	21 479 390	–	108 693	–
Single rapid tests for HIV and syphilis	21 864 363	384 972	110 691	1998
HIV rapid test screening only	21 875 298	395 908	110 875	2182
HIV rapid test and laboratory-based test for syphilis	21 893 483	414 092	110 697	2004

DALYs, disability-adjusted life years.

and syphilis testing, syphilis prevalence in HIV-uninfected women and stillbirth or early fetal death among syphilis-uninfected HIV-positive untreated mothers. The higher the HIV and syphilis prevalence, the more the money that was saved and the more the DALYs that were averted using a dual HIV and syphilis test rather than an HIV rapid test only. In each one-way sensitivity analysis dual HIV and syphilis testing remained relatively less expensive and more effective compared with HIV rapid testing alone. We found that the cost of the dual test needed to be greater than $6.04 in order for the dual testing algorithm to no longer be most dominating. We conducted an additional sensitivity analysis in which we removed the patient time and labour costs from the model and found that the dual HIV and syphilis test algorithm remained the most cost-effective.

DISCUSSION

We used health services data and economic estimates to compare four testing approaches for preventing adverse pregnancy outcomes due to maternal HIV and syphilis infection. Our model of 100 000 pregnant women in Malawi found that using a dual HIV and syphilis rapid test algorithm in antenatal care would reduce the number of adverse outcomes of pregnancy. The dual HIV and syphilis rapid test algorithm was found to lead to lower overall costs and decreased newborn DALYs when compared with the other screening algorithms, given the base-case parameters, which were chosen to match the current epidemiologic state of HIV and syphilis in Malawi.

Using a Monte Carlo simulation comparing the dual HIV and syphilis rapid test algorithm to HIV rapid test only algorithm we were able to show that even when accounting for uncertainty of inputs the dual rapid HIV and syphilis test was always cost saving and almost always associated with fewer DALYs. We varied base-case estimates for a number of the variables in the model and found that the dual HIV and syphilis rapid test algorithm dominated the HIV rapid test only algorithm.

Dual HIV and syphilis tests have performed very well in the laboratory, with sensitivities and specificities over 99% for both the HIV antibody and treponemal antibody detection.[19 21 23] Additionally, a field evaluation of a dual HIV and syphilis test used in this cost-effectiveness analysis displayed excellent HIV antibody detection and very good treponemal antibody detection.[20] Those performance results are similar to evaluations of single rapid tests.[30 w1 w2 w10] Our analysis suggests that integrating the screening of syphilis into antenatal HIV prevention programmes through dual rapid point-of-care testing would positively affect case finding and the prevention of maternal-to-child transmission of syphilis. A dual rapid point-of-care test also has the potential to save costs and increase uptake by leveraging current procurement and testing systems that have already been strengthened in HIV testing programmes. However, with the implementation of any changes in a programme comes additional start-up costs, such as training, new contracts and product registration activities. Those costs were not included in our analysis, but would reflect one-time programmatic costs and would therefore likely have a minimal effect over time. Additionally, we assumed no loss-to-follow-up for rapid testing as women could be tested and treated at the same visit. In order to implement same visit testing and treatment programmes, effective logistical coordination and consistent medication supply are needed.

Other cost-effectiveness studies have looked at HIV and syphilis integration of HIV and syphilis testing; however as far as we

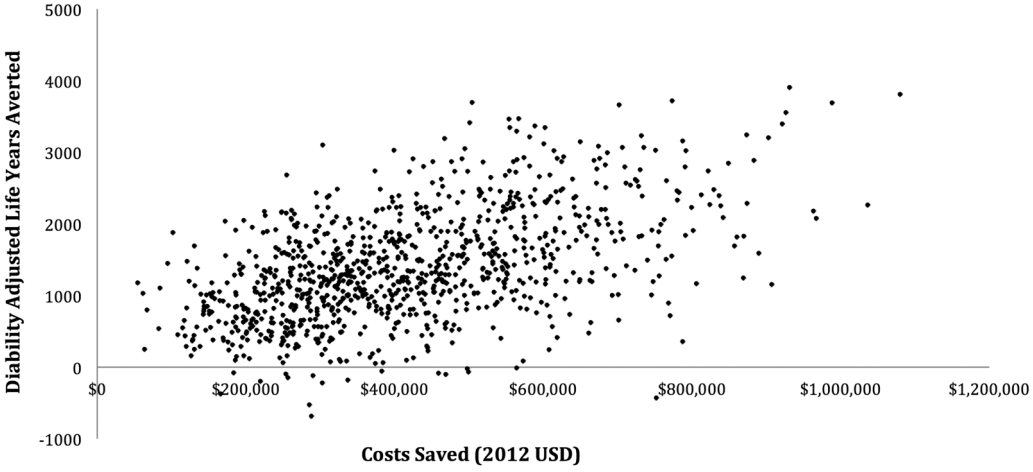

Figure 1 Distribution of costs saved versus effectiveness from Monte Carlo simulation when using the dual HIV and syphilis test algorithm compared with the rapid HIV test only algorithm. Each dot is representative of an iteration of the model run (n=1000). The dual HIV and syphilis algorithm was always cost saving and almost always reduced disability-adjusted life years compared with HIV testing alone.

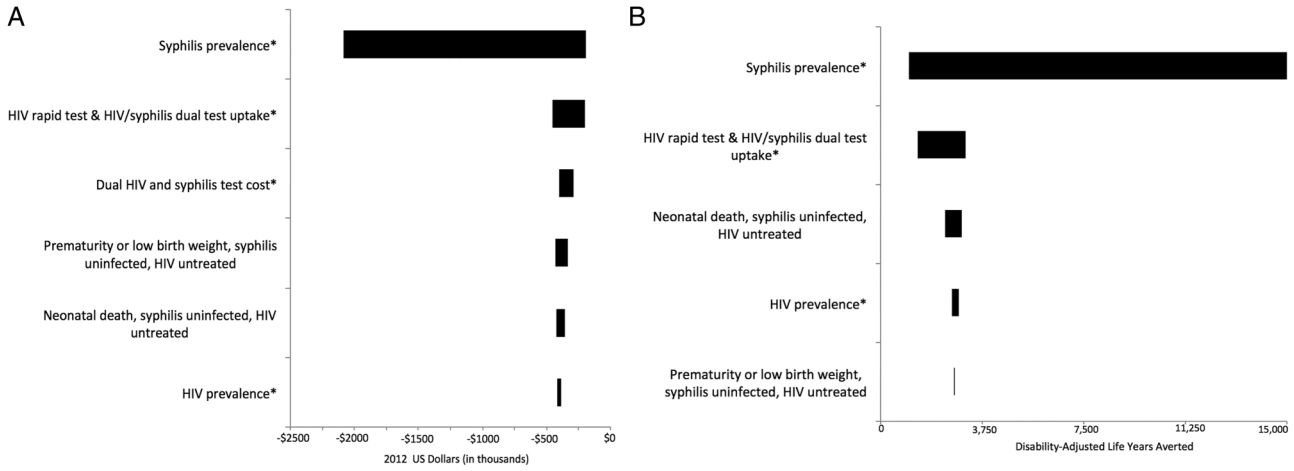

Figure 2 (A) Tornado diagram of sensitivity analysis: incremental cost of HIV rapid test only versus dual HIV and syphilis test. This tornado diagram is a graphical representation of how the relative cost is impacted by varying model parameters from lower to upper ranges. (B) Tornado diagram of sensitivity analysis: incremental effectiveness of HIV rapid test only versus dual HIV and syphilis test. This tornado diagram is a graphical representation of how the relative effectiveness is impacted by varying model parameters from lower to upper ranges. *HIV prevalence was varied between 6%–18%; syphilis prevalence was varied between 0.5%–6% in HIV uninfected (1%–12% in HIV infected); HIV test uptake was varied between 41.5%–95%; dual test cost was varied between $1.20–$2.60.

know, the current analysis was the first to include dual HIV and syphilis rapid tests.[17 w11–w15] Owusu-Edusei and colleagues found that even in a low prevalence setting in China, integrating the screening of syphilis into HIV antenatal screening programmes was considerably more cost-effective, with a cost-effectiveness ratio more than 15 times lower than screening for HIV alone.[w13] Other studies using data from sub-Saharan Africa found that syphilis screening in antenatal care was cost saving.[w14 w16] Additionally increased syphilis screening among HIV-infected men who have sex with men in North America was shown to be cost-effective.[w17]

Our analysis was subject to several limitations. It aimed to assess the health effects and costs in the infant by screening for syphilis and/or HIV in pregnancy. Therefore, we did not include health effects or costs after pregnancy for the mother. Consequently, the benefits of syphilis testing in antenatal care using a dual test may be underestimated because this intervention would have an effect on two individuals, the mother as well as the infant, at once. Additionally, we were not able to account for the costs of procurement and distribution of the tests. However, the most cost-effective algorithm in the analysis was the dual HIV and syphilis rapid test, and because this algorithm requires procurement of a single test device as opposed to two or more test devices, it is likely that if procurement and distribution costs had been included, additional cost savings would have been identified. We did not account for adverse side effects or overtreatment rates of HIV and/or syphilis. Additionally, we assumed smooth implementation of dual test strategy with uptake at the same rate as the single HIV-test algorithm. While this is likely, given that it replaces a single test with another single test, the acceptability of the new test to both patients and healthcare providers will need to be evaluated. Dual tests have shown good field performance in some settings; however, additional evaluations are required to understand how they will perform in specific settings.[20] An additional limitation of this analysis is that our model was structured such that we assumed that each test's sensitivity and specificity were independent. The strengths of our study were that we included the four most common test algorithms for HIV infection and syphilis screening, which allowed us to identify the most cost-effective algorithm of all four. Additionally, we conducted both one-way and two-way sensitivity analyses that allowed us to vary estimates to gain further insight on what factors had the largest impact on adverse pregnancy outcomes, progression of disease and cost.

The results of the current analysis help provide important cost-effectiveness information about new dual rapid testing technology when compared with existing testing strategies. As dual point-of-care rapid testing programmes are rolled out, actual costs and programmatic data, particularly testing uptake, should be evaluated. Further surveillance of syphilis infections, screening and adverse pregnancy outcomes may allow more accurate cost-effectiveness estimates. The dual HIV and syphilis rapid test algorithm was the most cost-effective strategy that we analysed. Adding dual rapid testing to the existing prevention of mother-to-child HIV transmission programmes in Malawi and similar countries is likely to be advantageous.

Key messages

- Globally syphilis affects more pregnancies than HIV and millions of pregnant women are HIV and/or syphilis infected each year.
- This article presents results from a cost-effectiveness analysis of various HIV and syphilis screening algorithms in order to provide funders and policy-makers with information into the costs and benefits of each option.
- Use of a dual HIV and syphilis test was cost saving compared with all other screening strategies.
- Updating existing prevention of mother-to-child HIV transmission programmes in Malawi and similar countries to include dual rapid testing for HIV and syphilis is likely to be advantageous.

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Contributors CCB performed the literature review, wrote the manuscript and contributed to model building and analysis. EL built the models, performed the analysis, supported literature review and provided review of the manuscript. LJA revised the models and performed sensitivity analyses. JDK conceived of the analysis and provided oversight.

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