

Cost-effectiveness analysis of syphilis screening and treatment

Summary

Evidence Action (EA) is exploring the opportunity to support and accelerate the adoption of dual HIV/syphilis rapid testing in various geographies, with the core purpose of achieving improved health impacts for mothers and their children via increased syphilis screening and treatment rates for pregnant women. We conducted an analysis to assess the cost-effectiveness of accelerating adoption of the dual test relative to GiveDirectly's cost-effectiveness within GiveWell's CEA framework. We also calculated a cost per DALY averted outcome measure.

In this brief, we present (a) the results from the cost-effectiveness analyses; (b) a description of the intervention; (c) a discussion of the key methodological choices made in estimating the model; and, (d) a list of the assumptions made as to specific parameters where they differ from GiveWell's BOTEC.

Results

Below are the key results, which may be subject to change as additional factors may be incorporated into the analysis at a later time.

	Liberia higher prev.	Liberia lower prev.	Indonesia higher prev.	Indonesia lower prev.
Syphilis screen and treat vs cash	44.28x	14.21x	36.85x	15.73x
Cost per DALY averted	\$3.29	\$10.25	\$3.61	\$8.45

Note: This does not include a leverage calculation, which we expect to be a significant factor.

Background on Proposed Intervention

Globally, there are nearly one million pregnant women with active syphilis infections that result in over 350,000 adverse pregnancy outcomes including spontaneous abortion, stillbirth, preterm birth, low birth weight, neonatal death, and congenital syphilis. Over 200,000 fetal or neonatal lives are lost each year, another 100,000 children suffer from lifelong deformities and

disabilities due to congenital syphilis, and 40,000 children have reduced health and economic outcomes as a result of their low birth weight.

Syphilis has been an easily treatable infection for the last 50 years. A single, \$1.35 dose of benzathine penicillin-G (BPG), ideally given before the start of the 3rd trimester, can avert over 80% of the most severe adverse outcomes. Syphilis infections can be diagnosed using a rapid point-of-care fingerstick test that costs under \$1.00 and produces results in under 20 minutes.

Most recently, dual rapid tests capable of simultaneously identifying HIV and syphilis for \$1.50 or less have been developed and pre-qualified by the World Health Organization (WHO). While syphilis screening rates have stalled or languished globally, most countries have achieved high screening rates for HIV among pregnant women. With the advent of the dual HIV/syphilis rapid test, there now exists an opportunity to bridge the gap in syphilis care via introduction and scaled-up usage of the dual test. With this approach, existing HIV funding, procurement and supply chain systems, and health provider knowledge and skills in HIV screening during pregnancy can all be utilized to achieve gains in syphilis screening in short order.

In general, countries face barriers to adopting and scaling-up usage of the dual test and in subsequent syphilis treatment that could be resolved through comprehensive programmatic support. These include:

- Lack of funding to procure the dual test and related syphilis commodities like benzathine penicillin.
- Difficulty in accurately quantifying commodity volumes and managing regular distribution to the facility level to minimize stock outs.
- Lack of technical capacity needed to update guidelines.
- Slow or ineffective registration of the dual test through lengthy bureaucratic processes.
- Inability to access or lack of awareness of competitive dual test prices.
- Challenges in implementing a training cascade to ready health care providers.
- Ineffective systems for monitoring and evaluation
- Poor coordination across subunits within the Ministry of Health responsible for maternal and child health and infectious diseases.

Overall, we are assuming this will be accomplished via a relatively light-touch in-country presence as much of the system will take advantage of existing HIV PMTCT programming.

Methodology Decisions for Discussion

There are several methodological choices made in generating the cost-effectiveness model that are important to discuss and ensure alignment on before proceeding forward. These are:

Cost of Dual Testing

In the current version of the model, the price of the dual test is taken as the marginal price above the HIV single rapid test. This decision was reached with the following rationale: from a country's perspective, the true choice the government is making is whether attaining higher syphilis screening rates is worth the extra money needed to switch from the HIV single test to the dual test. The marginal difference between the HIV single rapid test and the dual test differs by country due to differences in test costs across geography, impacting the cost-effectiveness.

Other methodological alternatives for this input could be to: 1) account for the full cost of the dual test, or 2) allocate a proportion of the dual test that is the cost of syphilis testing. If the model takes on the full cost of the dual test but only includes syphilis benefits (leaving out HIV benefits), we would be grossly underestimating the cost-effectiveness for syphilis treatment. On the latter option, we do not have any further information on the relative manufacturing costs of the syphilis vs. HIV sides of the test and so do not have a basis for choosing how much of the costs are attributable to syphilis. For these reasons, as well as the initial argument in favor of this position, we felt that the most reasonable assumption would be to take the marginal price difference above the HIV single rapid test.

Consistent with this approach, we have not included marginal labor time costs for providers to administer the test. Given that we are considering costs as the marginal costs above HIV screening, we have not seen any data that suggests using the dual test is more time intensive than the HIV single test. In fact, the HIV rapid test takes the same amount of time (approx. 20 minutes) to complete as the dual HIV/syphilis rapid test.

Additional Benefits

Although it's a small proportion of overall estimated benefits, we incorporated the estimated impact of reducing cases of low birth weight in infants, as this is a proven health benefit of treating syphilis in pregnant mothers. The model assumes that 6% of infants of syphilis-infected mothers have low birth weight based on estimates taken from Gomez et al. (2013). The model has incorporated reductions in low birth weight as a health benefit but there are also education and economic benefits to averting a low birth weight that may be considered in the future.

We have also chosen to omit three additional benefits at this stage. The first is the benefit of preventing potential cases of tertiary syphilis among women who are treated. Tertiary syphilis results in cardiovascular complications, severe disfigurement, and neurological problems that can end in mortality. Tertiary syphilis develops in 15-40% of adults decades after infection if they are never treated for syphilis. The second omitted benefit is that of reducing the risk of mother-to-child transmission of HIV. According to a large prospective study in Malawi, syphilis infections in pregnant women were associated with a 2.7-fold increase in the rate of

mother-to-child transmission of HIV.¹ The final omitted benefit is the averted medical costs of treatment for those who are born with congenital syphilis and those who are born at a low birth weight.

Time Frame of Analysis

There are many potential options in deciding the appropriate time frame of analysis. We have chosen a conservative approach and modeled the costs and benefits only over the years that Evidence Action intends to provide governments direct programmatic support. We have reason to believe that this intervention would lead to sustained future gains in syphilis screening and treatment after the conclusion of the intervention, but have currently set this outside the scope of analysis, pending further conversations with GiveWell.

Key Assumptions

1. Prevalence of active maternal syphilis

a. **GiveWell:** 5%

b. **Evidence Action:** country-specific estimates ranging from 0.5% to 8.5%

There are two main sources for estimates of syphilis prevalence: a country's own reported data into the Global AIDS Monitoring System (GAMS) and modeled estimates via [Spectrum STI](#). We believe the Spectrum STI estimates, which tend to be lower than GAMS estimates, are more likely to be accurate given the modelers' decisions to weight point estimates based on the likely bias of the data and to apply smoothing to account for reasonable year-on-year changes. Where possible, we are aiming to collect more data from governments and better identify whether we are over- or under-estimating syphilis burden. As an example, we have included Liberia's own estimate obtained from a sentinel surveillance survey (much lower than what was estimated in Spectrum-STI) and evaluated the range of possible cost-effectiveness. Furthermore, Indonesia claims a higher prevalence as compared to Spectrum-STI in their Regulation on the Triple Elimination of Mother-to-Child Transmission of HIV, Syphilis, and Hepatitis B that was also included in the analysis.

2. Fraction of all syphilis infections that are latent.

a. **GiveWell:** none

b. **Evidence Action:** 35%

Women who are infected with syphilis for over two years have infections that are latent, rather than active. Our model accounts for active and latent infections separately. Latent infections have no adverse health impacts during pregnancy, nor do they have any immediate impacts on the health of the mother. Women who have latent infections require three doses of penicillin, as compared to the one dose required to cure someone with an active infection. The rapid test is unable to distinguish between

¹ Mwapasa, Victor et al. (2006) Maternal syphilis infection is associated with increased risk of mother-to-child transmission of HIV in Malawi. *AIDS*. 20(14): 1869-1877.

active and latent infections. As a result, it falls on providers to gather patient history to make determinations and on patients to return for their multiple treatments. Since identifying latent infections and treating them fully is challenging, we have assumed those with latent infections will get treated once but no health benefits are derived from this -- adding to overall costs but not benefits.

3. Sensitivity of the dual rapid test.

- a. **GiveWell:** 72.85%
- b. **Evidence Action:** 94.09%

GiveWell's estimate of sensitivity averages estimates of the sensitivity of syphilis single rapid testing as reported in [Terris-Prestholt, et al. \(2015\)](#).² Since we are estimating the impact of dual testing, we rely on a systematic review and meta-analysis conducted by Gliddon et al. (2017)³ that evaluated the performance of the dual HIV/syphilis test across 18 studies. The sensitivity estimate used in this model is the average of eleven point estimates of the sensitivity of the syphilis side of the SD Bionline dual rapid test, in particular, since that is the only one in the study that has been pre-qualified.

4. Specificity of the dual rapid test.

- a. **GiveWell:** none
- b. **Evidence Action:** 98.45%

The estimate of specificity was based on the same systematic review and meta-analysis used for estimating sensitivity (Gliddon et al., 2017). Specificity refers to the likelihood of someone testing positive who is not actually infected with syphilis. While the risk of adverse outcomes from treatment in this case is negligible, the costs of these unnecessary treatments will contribute to overall program expenses, particularly when considered at the national scale.

5. Treatment rate.

- a. **GiveWell:** 100%
- b. **Evidence Action:** country-specific estimates ranging from 76.9% to 78%.

According to data reported by countries in GAMS, many do not treat all those who test positive during screening. A less than 100% treatment rate would diminish the potential impact from screening more women, so our estimates more fully account for the state of service delivery. In the model, we take treatment rates shared by governments, apply discounts based on information shared by local stakeholders during country scoping visits. We further allow the treatment rate to improve with time as a result of Evidence Action's programmatic support and awareness of overall

² Terris-Prestholt, Fern, et al. (2015) The cost-effectiveness of 10 antenatal syphilis screening and treatment approaches in Peru, Tanzania, and Zambia. *International Journal of Gynaecology and Obstetrics*. 130(Suppl 1):S73-S80.

³ Gliddon HD., et al. (2017) A systematic review and meta-analysis of studies evaluating the performance and operational characteristics of dual point-of-care tests for HIV and syphilis. *Sex Transm Infect*. 93:S3-S15.

government efforts aimed at increasing treatment. The ultimate treatment rate applied in the benefits vs. cash analysis averages the treatment rate across the years in which Evidence Action intends to support the government.

6. **Rate of HIV screening.**

a. **GiveWell:** none

b. **Evidence Action:** country-specific estimates ranging from 85% to 90%

The adoption of the dual test assumes that syphilis screening rates will reach the level of HIV screening rates once the test is fully rolled-out. A core assumption of the model's impact, therefore, is the rate of HIV screening over time in each geography. After analyzing the available data on HIV screening rates, we forecasted screening rates using historical trends and contextual knowledge on expected government attention to HIV. We assume high HIV screening rates will be attained in Indonesia and Liberia (85% and 90%, respectively) over 5 years.

7. **Cost per person screened.**

a. **GiveWell:** \$3.70

b. **Evidence Action:** country-specific estimates ranging from \$0.58 to \$3.96

Evidence Action has accounted for costs by taking the full aggregate of what would be spent by the government and Evidence Action at a country level. Costs include commodities (syphilis single test, dual HIV/syphilis rapid test, and benzathine penicillin), the costs of training providers on using the dual test and Evidence Action's staff and operational costs. Healthcare provider time is not included because we've considered costs as the marginal costs above ongoing HIV testing; the dual test will not take longer than the existing HIV rapid test and time spent on treatment is expected to be marginal. Outside of training, it's likely that incorporating the dual test into current practices would require minimal systemic effort and cost. The cost per person screened is arrived at by totaling overall costs across the years of the program and dividing by the total number of women who would be screened in a given country across that same time period. This methodology for identifying the cost per person screened accounts for variability in country-level costs and economies of scale.

8. **Reinfection.**

a. **GiveWell:** none

b. **Evidence Action:** country-specific estimates ranging from 0.4% to 1.6%

Given low rates of male partner treatment, it is possible that women will get reinfected between when they've been treated and the delivery of their child. These reinfections will negate any benefit received from the initial screening and treatment. There is no data on reinfection rates but one possible proxy is the seroconversion rate. The seroconversion rate refers to the fraction of women who test negative during their first ANC visit but then test positive when they are retested at time of birth. In other words, it is the rate of women who become infected between their first ANC visit and their

delivery date. According to Blencowe et al. (2011)⁴, 0.4% to 2.8% of pregnant women undergo seroconversion in high-prevalence areas. This data is not available in low-prevalence areas because those countries do not screen women multiple times over the course of their pregnancies. The average value was assumed for high prevalence countries (>1%) and the minimum value was assumed for low prevalence countries (<1%). We may reduce these estimates in the future if we think we can undertake approaches to reducing reinfection risk such as improved counseling of pregnant women, behavioral interventions to increase rates of male partner treatment, etc. At that time, we will also incorporate any relevant costs to these interventions into the overall model.

9. Leverage Adjustment.

a. **GiveWell:** Unknown

b. **Evidence Action:** Overall, we expect the leverage factor to be influential in GiveWell's cost-effectiveness estimate. Over the course of Evidence Action's involvement in a country, we expect government costs to make up at least 35% of total programmatic costs in Liberia and 70% of total programmatic costs in Indonesia. The majority of these costs are driven by the cost of the dual test, which is expected to be undertaken largely by the government (or The Global Fund), but may vary depending on capacity and willingness. Furthermore, we predict that the probability is low that government costs would replace philanthropic costs in our absence. Our aim is to accelerate full-scale adoption of dual testing, which will require a commensurate increase in funding on the part of the government (or The Global Fund) for commodities and overall program management that would not occur in the absence of Evidence Action's involvement across the described program areas.

⁴ Blencowe Hannah, Cousens Simon, Kamb Mary, Berman Stuart, Lawn Joy E. (2011) Lives Saved Tool supplement detection and treatment of syphilis in pregnancy to reduce syphilis related stillbirths and neonatal mortality. *BMC Public Health*. 11(Suppl 3): S9.