January, 2020

# Increasing Screening and Treatment of Syphilis in Pregnant Women:

Evaluation of the Evidence Base and Recommendations for Evidence Action

Acronyms

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|---|---|
| AIDS | Acquired immunodeficiency syndromme |
| ANC | Antenatal care |
| API | Active pharmaceutical ingredient |
| BPG | Benzathine penicillin-G |
| CDC | Centers for Disease Control |
| CS | Congenital syphilis |
| EMTCT | Elimination of mother-to-child transmission |
| FDF | Final dose formulator |
| GAMS | Global AIDS Monitoring System |
| GHO | Global Health Observatory |
| ICS | Immunochromatographic strip |
| IDC | International Diagnostics Center |
| HIV | Human immunodeficiency virus |
| LBW | Low birth weight |
| LFA | Lateral flow assay |
| LSHTM | London School of Hygiene and Tropical Medicine |
| MoH | Ministry of Health |
| PMTCT | Prevention of mother-to-child transmission |
| POC | Point-of-care |
| POCT | Point-of-care test |
| RDT | Rapid diagnostic test |
| RHT | Rapid HIV test |
| RPR | Rapid plasma reagin |
| RST | Rapid syphilis test |
| SSA | Sub-Saharan Africa |
| STAT | Same day testing and treatment |
| STI | Sexually transmitted infection |
| TPHA | *Treponema pallidum* hemagglutination assay |
| VDRL | Venereal disease research laboratory test |
| WHO | World Health Organization |

## I. Executive Summary

*The Opportunity*

Globally, there are approximately 900,000 pregnant women with active syphilis infections that result in over 350,000 adverse outcomes, including spontaneous abortion, stillbirth, preterm birth, low birth weight, neonatal death, and congenital syphilis. While benzathine penicillin-G (BPG) has been recognized as an effective treatment for the last 50 years, new syphilis rapid tests have been recently developed and represent a unique opportunity to increase screening and treatment of syphilis among pregnant women. In particular, a new dual HIV/syphilis rapid diagnostic test allows providers to diagnose women for both syphilis and HIV with a single fingerstick, in under 20 minutes, and at a cost of around $1.50. With this dual test, countries can leverage their HIV funding and delivery systems to substantially address maternal syphilis.

*Key Barriers for Countries to Seize this Opportunity*

1. **National Strategy and Guidelines:** The country must approve the dual HIV/syphilis rapid test and integrate the new test into its guidelines for syphilis *and HIV*. This process is limited by government awareness of the syphilis problem, lack of clear ownership within a single agency, hesitation to alter the HIV diagnostic algorithm, and reticence to accept the WHO-prequalified test without further in-country testing.
2. **Financing and Procurement:** The country must secure funding and procure the dual test, which is more expensive than the HIV-only rapid test that most countries currently procure. Procurement for BPG can also be challenging due to periodic disruptions in the global supply chain. Many countries can leverage PEPFAR and Global Fund HIV funding to pay for dual tests, and may benefit from guidance to successfully navigate this process.
3. **Data and Stock Management:** The country needs data and systems to monitor and manage both syphilis prevalence and treatment outcomes, and supply of commodities. Although variable across countries, accurately collecting this data, communicating efficiently between providers and Ministries of Health, and ensuring effective stock management systems will often require additional support beyond existing resources. There may also need to be work around updating, printing, and disseminating order forms and M&E tools.
4. **Facility-Level Care:** The government must update its training curriculum and tools and train healthcare providers on the new tests and treatment protocol via a training cascade. The provider must use the rapid test to screen patients, accurately interpret the test results, and treat women who test positive with BPG. Country data tends to show very high screening rates as soon as a syphilis rapid test is available, with fairly high levels of treatment with BPG. However, false negatives are possible due to providers misreading the syphilis portion of the dual test, and some providers are hesitant to prescribe BPG.

5. **Maternal Behavior:** To get treated, pregnant women must attend antenatal care in the first place, with earlier attendance leading to better treatment outcomes. This presents a barrier for some women to get tested and effectively treated on time.

## II. The Opportunity

Globally, there are approximately 900,000 pregnant women with active syphilis infections that result in over 350,000 adverse pregnancy outcomes each year.[1] These adverse outcomes include spontaneous abortion, stillbirth, preterm birth, low birth weight, neonatal death, and congenital syphilis; over 200,000 fetal or neonatal lives are lost each year and another 100,000 children suffer from lifelong deformities and disabilities due to congenital syphilis.[1] The majority of pregnant women with active syphilis infections reside in Sub-Saharan Africa, followed by Southeast Asia.[1] Across Sub-Saharan Africa, many countries have a high syphilis prevalence of above 1%.[2]

Ongoing syphilis infections in pregnant women are a public health failure. 65% of the adverse outcomes occur in women who attend antenatal care (ANC) but are never screened for the disease and 6%[3] occur in women who are screened but never treated for syphilis.[1] All of this is despite the fact that syphilis has been an easily *identifiable* infection for the last decade and an easily *treatable* infection for the last 50 years. 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.[4] Most recently, two dual rapid tests capable of simultaneously identifying HIV and syphilis for approximately $1.50 or less have been developed and pre-qualified[5] by the World Health Organization (WHO).[6] If positive, a single, $0.77-$1.92 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.[7]

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. By providing comprehensive programmatic support to

[1] Based on 2012 estimates reported in Wijesooriya et al. (2016). More recent estimates are not available.
[2] Based on WHO report, "Global Elimination of Congenital Syphilis: Rationale and Strategy for Action".
[3] Currently, the gap in treatment is smaller than the gap in screening because most women are never being tested for the disease and so are lost in this first step of the care cascade. Once more women are tested for syphilis, gaps in treatment are likely to emerge and will need to be addressed as part of a comprehensive intervention around syphilis screening and treatment.
[4] Based on Kleutsch, Harvey and Rennie (2009); Bristow et al. (2015).
[5] When a diagnostic test is WHO pre-qualified, it means the WHO and other parties have validated that the test adheres to the ASSURED (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users) criteria.
[6] See WHO prequalification of the Abbott SD Bioline Duo and the Premier First Response Combo Test.
[7] Estimated cost of benzathine penicillin-G is taken from Kuznik et al. (2013). Treatment effectiveness is based on Blencowe et al. (2011).

countries in this process, Evidence Action may be able to play a key role in a global push to cost-effectively eliminate much of the burden of maternal syphilis.

## III. Background of Maternal Syphilis

### *A. What is Syphilis?*

Syphilis is a sexually transmitted infection caused by the *Treponemal pallidum* bacteria. The literature uses the term "maternal syphilis" to refer to syphilis in pregnant women whereas "congenital syphilis" refers to infection in the fetus if the infection is transmitted from mother to child. Often, these terms are used interchangeably to refer to the condition of syphilis in pregnant women and the risks that it can pose to the fetus.

### *B. How Does Syphilis Affect the Fetus?*

Syphilis can affect the fetus *indirectly* by impacting the blood supply to the fetus, or *directly* by transmitting from mother to child. Through the indirect pathway, syphilis causes reduced blood flow through the placenta, which restricts fetal growth. In severe circumstances, this can lead to early fetal death but more often results in a low-birth weight child. Through the direct pathway of mother-to-child transmission, the fetus has its own systemic inflammatory response to the infection that can lead to early fetal death. This can only occur after the fetus's own immune system has developed sometime between the 18th and 22nd gestational week. If the fetus survives to delivery, there is still a risk of neonatal death due to syphilis. Infants with syphilis who are able to survive the first days of life must then often contend with physical and mental disabilities caused by the infection.[8]

The distribution of the main primary adverse outcomes caused by maternal syphilis, disaggregated by region, is shown in Figure 1. It illustrates that the most severe types of outcomes are also the most common and that the burden is concentrated in Sub-Saharan Africa, followed by Southeast Asia. Among pregnant women with active syphilis, 21.4% will result in an early fetal death[9], 9% will result in neonatal death, 6% will result in a low birth weight[10] infant, and 16% will result in an infant with congenital syphilis. Beyond these primary outcomes, syphilis in pregnant women also increases the likelihood of mother-to-child transmission of HIV.[11] For this reason, syphilis has been increasingly considered a part of holistic HIV management and programming.

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[8] Having congenital syphilis as an infant can lead to deformed bones, severe anemia, enlarged liver and spleen, jaundice, blindness, deafness, meningitis, cerebral palsy, other brain and nerve problems, and skin rashes (CDC; Arnold & Ford-Jones, 2000; Blencowe et al., 2011).

[9] Early fetal deaths include miscarriages (otherwise called spontaneous abortions), which occur before the 20th gestational week, and stillbirths, which occur after this period.

[10] Infants of low birth weight are usually a result of preterm delivery. In the literature around maternal syphilis, preterm delivery and low birth weight infants are used interchangeably to refer to a single adverse outcome.

[11] Based on 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 (Mwapasa et al., 2006).

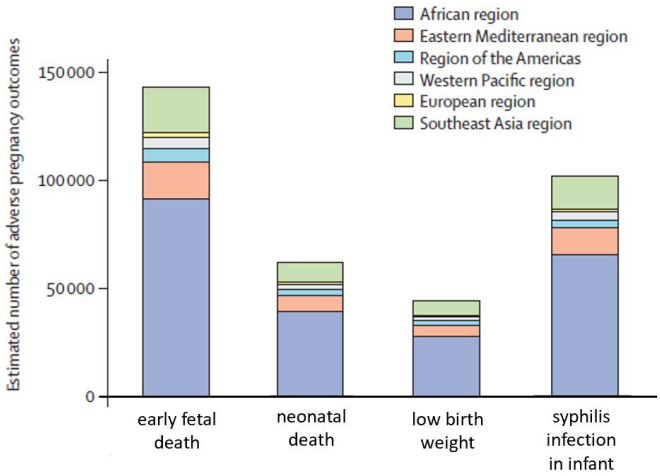


*Figure 1. Annual total number of adverse outcomes resulting from syphilis, globally.*[12]

There are two factors that alter the risk to the fetus that are important to understand when considering strategies to increase screening and treatment.

1. **Stage of the mother's syphilis infection.** The five possible stages of a syphilis infection, and the associated risk of mother-to-child transmission, are described below in Figure 2.

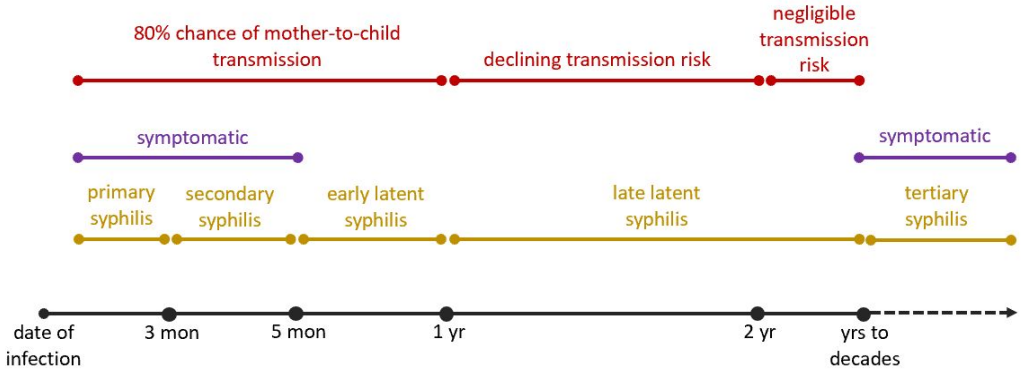


*Figure 2. Description of the stages of syphilis infection, when they occur, whether symptoms are present, and how risk of mother-to-child transmission varies depending on the stage of the infection.*[13]

In general, the risk of mother-to-child transmission is proportional to the number of *Treponemal* antibodies circulating in the mother's blood supply. The risk is highest during the "active" stage of the infection, which includes the primary, secondary, and

[12] Based on 2012 estimates reported in Wijesooriya et al. (2016). More recent estimates are not available.
[13] Based on background provided in Blencowe et al. (2011) and the WHO report, "Global Elimination of Congenital Syphilis: Rationale and Strategy for Action". There are no available estimates of the distribution of syphilis infections across the five stages.

early latent stages, lasting to approximately one year after the date of infection. The risk of mother-to-child transmission begins declining after the first year of infection and falls to near zero when the mother is two years post-infection. If syphilis remains untreated, the mother[14] faces a 15-40% chance of developing tertiary syphilis, which can pose severe risks to her long-term health and survival; however, tertiary syphilis is more likely to occur after one's childbearing years so the risk to the fetus during this stage of infection is not known.

2. **Stage of the pregnancy when the mother is treated.** The scientific consensus around maternal syphilis is that the earlier syphilis treatment occurs during pregnancy, the more likely adverse outcomes can be avoided.[15] **Early fetal death, which is the *most severe* adverse pregnancy outcome and also the one that accounts for the *largest share* of adverse outcomes (21.4% as noted above in Figure 1), often occurs during the latter part of the second trimester into the first weeks of the third trimester, meaning early treatment is the only way to prevent the majority of fetal deaths from occurring.**[16] Therefore, timing of the first ANC visit matters: effective treatment requires not simply contact with the ANC system at *any* point during pregnancy, but optimally, earlier in pregnancy. Global or regional syntheses do not exist to illustrate the distribution of women's gestational age at their first ANC visit, though country-specific data is available. We illustrate this distribution for one country - Tanzania - in Figure 3, which shows that over 20% of pregnant women in Tanzania who attend ANC would attend their first ANC visit *after* their fetus is already at risk of death.

[14] Beyond the risk of tertiary syphilis for the mother, her syphilis infection also increases the likelihood that she contracts HIV from a sexual partner and increases the seriousness of HIV/AIDS if she already has the disease (Bolan, 2012). There is no data available to determine whether this increased risk of contracting HIV varies based on the stage of syphilis infection.

[15] Researchers rely on Blencowe et al. (2011) for an understanding of treatment timing and efficacy. In support of the consensus around earlier treatment, a large prospective cohort study in China found that women who began treatment before 20 weeks gestation had a lower rate of congenital syphilis (risk ratio 0.50; 95% CI 0.38-0.64) compared to those who started treatment after 20 weeks (Zhu et al., 2010). In addition, Hawkes, Gomez, and Broutet (2013) found that, comparing those treated in the third trimester to those treated in the first or second trimesters, the odds ratio of any adverse outcome was 2.24 (95% CI 1.28-3.93).

[16] Wijesooriya et al. (2016); Blencowe et al. (2011); WHO (2010).

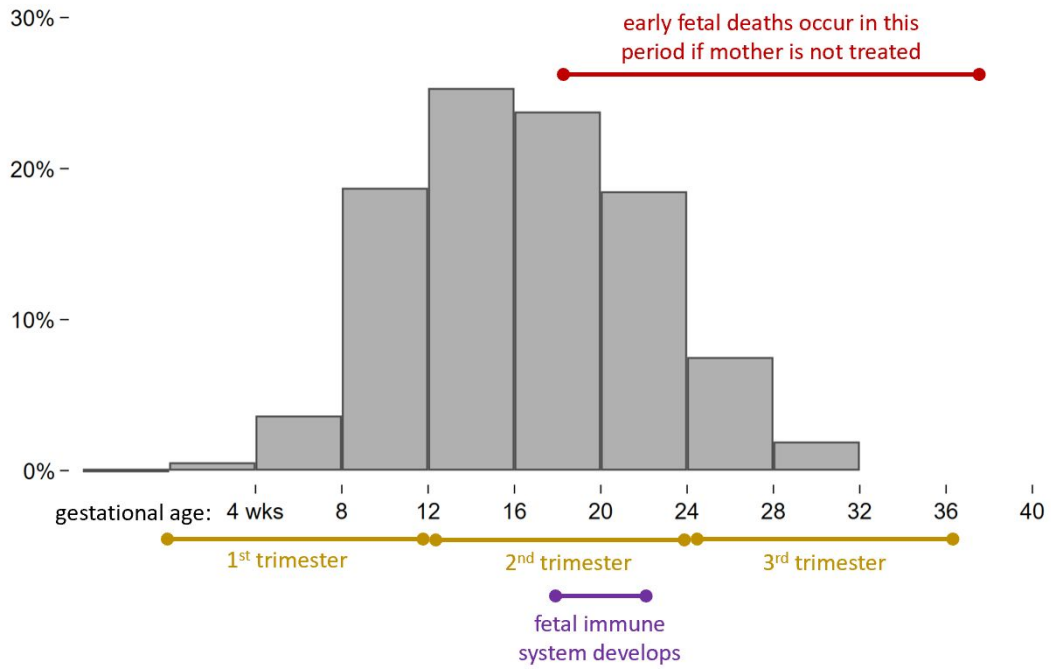


*Figure 3. Adverse outcomes due to syphilis are depicted on top of the distribution of women's gestational age at their first ANC visit. Data for the distribution of ANC visits was taken from Tanzania's 2015/2016 DHS survey.*

There is limited data available to determine the exact window of fetal death due to maternal syphilis, so it is impossible to precisely estimate the fetal deaths that are not averted because of late ANC attendance. While Tanzania's distribution of ANC attendance is an example of women attending later in their pregnancies, there are other countries, such as Indonesia, where 90% of women who attend ANC do so before the critical period depicted in Figure 3, so cross-country variation on this important factor seems to be considerable (see examples from other countries here). The WHO recommends treating women before their 24th gestational week, or at worst, at least 4 weeks before their delivery.[17]

### *C. How is Syphilis Identified?*

There are four main ways that a pregnant woman can be diagnosed with syphilis. Approximate unit cost and details on each are described below.

1. **Symptomatic Presentation** (free): The woman presents with symptoms of the infection, which usually include sores or skin rashes. As Figure 2 depicts, symptoms are only present during discrete points in the first five months after infection, although the risk to the fetus remains high beyond this period.

[17] Based on conversation with Melanie Taylor (WHO).

2. **Laboratory-Based Tests:** There are two kinds of laboratory-based tests
    a. **Treponemal** (approx. $3.00[18]): Treponemal tests identify the treponemal (syphilis) antibody if it is present in the woman's blood. Once a person has a syphilis infection, she will have treponemal antibodies in her blood for the remainder of her life, whether or not she has successfully treated the infection. Thus, these tests cannot distinguish between a current infection and one that has been clinically resolved. There are many types of lab-based treponemal tests, all of which are expensive and only available in central laboratories.
    b. **Non-treponemal** (approx. $0.15-0.23[18]): The non-treponemal test is non-specific to syphilis because it identifies a protein that is excreted when a person has one of several different infections; however, it can detect whether a syphilis infection is active. The most common non-treponemal test is the rapid plasma reagin (RPR) test. Initially, this test required extensive laboratory equipment and blood needed to be sent to central laboratories, but in the 1990s, a more portable version was developed that could be used in smaller labs because it only required a centrifuge and produced results within 30 minutes to 1 hour.

    Typical country guidelines instructed laboratories to screen patients with the non-treponemal test and then confirm positive cases using the more expensive treponemal tests to minimize overtreatment. In some cases, countries released guidelines that instructed providers to treat based on the point-of-care RPR lab tests in order to reduce loss to follow-up when pregnant women were asked to return to obtain their treponemal test results.

3. **Rapid syphilis(-only) tests** (approx. $0.47-1.00[19]): Introduced in the early 2000s, rapid syphilis tests are treponemal tests that can be used at the point-of-care by a healthcare provider. Patients receive a fingerstick and are told within 20 minutes if they are positive for syphilis. These tests do not require any laboratory equipment and can be used in or outside a healthcare facility. There are no WHO-prequalified rapid syphilis-only tests.[20] Several countries have successfully scaled-up usage of the single syphilis rapid tests. Therefore, although we see significant value in focusing our engagement on the rapid *dual* test (described below), we are also open to supporting the adoption and use of the *single* rapid syphilis test if there are conditions that make that a more feasible option for certain countries.

[18] Based on WHO report, "Global Elimination of Congenital Syphilis: Rationale and Strategy for Action".
[19] Based on Kleutsch, Harvey and Rennie (2009).
[20] Historically, the WHO has only prequalified rapid tests for key disease areas like HIV and malaria. Melanie Taylor (WHO) has indicated a single syphilis RDT was likely to be prequalified sometime in late 2019, though has not taken place thus far.

4. **Rapid dual HIV/syphilis tests**[21] (approx. $1.50 or less[22]): Introduced in the early 2010s, a dual rapid test was developed and brought to market. With a single fingerstick, a patient is diagnosed for HIV and syphilis simultaneously within 20 minutes. Like the syphilis-only rapid test, these tests do not require laboratory equipment and can be used by a healthcare provider. There are two WHO-prequalified rapid dual HIV/syphilis tests currently on the market. We expect that our work will largely focus on promoting these rapid dual tests because they are already pre-qualified and dual testing will allow countries to leverage their significantly larger streams of HIV funding for procurement.

### *D. How is Syphilis Treated?*

Syphilis infections in the *fetus* can be treated with a single, sterile injection of benzathine penicillin-G[23] (BPG) given to the mother. If the mother has either primary or secondary syphilis (i.e., 0-5 months from infection as noted in Figure 2 above), the single injection will cure *her* of the infection as well. However, if the mother has either early latent or late latent syphilis (i.e., 5 months to years post-infection), she must be treated with two additional injections of BPG beyond the one given to treat her fetus for *her* infection to be cleared. These injections must be given one week apart. Often, attempts to increase screening and treatment have documented drop-off among pregnant women who struggle to attend antenatal care for three consecutive weeks.[24] In cases where women do not complete the three-dose course of BPG required to clear the infection in her, there is *no evidence* to suggest that the fetus becomes reinfected by the mother later in the pregnancy after the first dose of BPG is given.

Most of the push for maternal syphilis treatment is focused on ensuring that a woman is diagnosed within the first or second trimester, and then treated *once* with BPG on the same day she is diagnosed. Where possible, women are encouraged to return for the full three doses, but this is not an area of focus in many countries, given the efficacy of one dose in treating infection in the fetus and given the drop-off rates after the first visit. According to a meta-analysis conducted by Blencowe et al. (2011), treating with at least one dose of BPG anytime within the first 32 weeks of pregnancy resulted in an 82% reduction in stillbirths, a 64% reduction in preterm births (a proxy for low birth weight), an 80% reduction in neonatal deaths, and a 97% reduction in congenital syphilis incidence.

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[21] In lab evaluations conducted by the WHO in Nigeria and China, the tests were evaluated for specificity (rate at which negative individuals are identified as negative) and sensitivity (rate at which positive individuals are identified as positive). The performance of the HIV side of the dual test was comparable to the performance of HIV-only rapid tests currently available on the market across all of the diagnostics evaluated. For syphilis, the WHO prequalified SD Bioline had a sensitivity of 99.1% and a specificity of 99.6%. The results for the two tests that were not approved are: ChemBio - 97% sensitivity and 99.6% specificity; MedMira - 94.2% sensitivity and 99.1% specificity.

[22] Based on International Diagnostics Center report. However, a second dual HIV/syphilis test was prequalified in June 2019 which will likely bring down the price of the dual test overall.

[23] Based on estimates from various cost-effectiveness analyses, the cost of a single dose of BPG ranges from $0.63 to $2.38 (Kuznik et al., 2015; Bristow et al., 2015). Of note, BPG is only used for treating either syphilis or rheumatic heart failure.

[24] Dinh et al. (2013); Ansbro et al. (2015); Bristow et al. (2015).

### *E. What Does the Evidence Say About Increasing Screening and Treatment?*

Three RCTs and numerous observational studies show that screening and treatment rates for syphilis among pregnant women in ANC clinics increase dramatically when rapid tests are supplied to those clinics.[25] A literature review of evidence from three countries by Terris-Prestholt et al. (2015)[26] finds that introduction of a rapid diagnostic test for syphilis at ANC increased average screening rates from between 17.8% and 91.1% to between 86.1% and 97.3%. Furthermore, Terris-Prestholt et al. (2015) finds that treatment rates[27] increased from between 56.7% and 76.8% of diagnosed cases, to between 77.4% and 93.9%. Taking this literature as a whole, it appears that, once healthcare providers have access to rapid syphilis tests, they will nearly always use them, and will usually provide treatment to those who test positive. However, the rapid increase in coverage does not necessarily equate to consistent, high-quality coverage -- in implementation studies where a syphilis single or dual rapid test is introduced, authors find challenges in stock-outs and sustained provider competency.[28] This remains an area to be explored further within countries as they introduce and scale-up usage of either the dual or single rapid tests.

For screening *and treatment* rates to reach and exceed the WHO's goal of 95%[29], the evidence suggests it may be necessary to focus on provider-level implementation and behavioral components. In the RCT conducted by Betrán et al. (2018), the intervention was a kit that contained rapid tests for syphilis, HIV, anemia, and protein in the urine, as well as whatever drugs are needed to treat all of the above conditions except HIV. It is possible some of the effectiveness of the intervention was driven by the packaging of all the supplies together. In addition, Althabe et al. (2019) recently showed that providing diagnostic tests and BPG increased screening to above 90% *but* same-day treatment only increased[30] when additional

[25] The three RCTs are Munkhuu et al. (2009), Betrán et al. (2018), and Althabe et al. (2019). Observational studies include Fleming et al. (2013), Nnko et al. (2016), Bronzan et al. (2007), Wang et al. (2015), Strasser et al. (2012), Young et al. (2018), and García et al. (2013).

[26] Terris-Prestholt et al. (2015) estimates the cost-effectiveness of different screening approaches for identifying maternal syphilis. In order to estimate the cost-effectiveness of the rapid test, the authors use the results from three non-randomized experiments (in Peru, Tanzania, and Zambia) in which the single syphilis rapid test was introduced into healthcare facilities to estimate the screening and treatment rates that would result.

[27] In these studies, researchers ensured a stable supply of BPG in addition to the stable supply of the rapid tests.

[28] PATH (2016); Mabey et al. (2012).

[29] In 2014, the WHO created a process for countries to validate that they have eliminated mother-to-child transmission of HIV and syphilis. For syphilis, countries can achieve "validation for elimination" status if their ANC attendance rate (at least one visit) is above 95%, their screening rate is above 95%, their treatment rate is above 95%, and the incidence of congenital syphilis is less than 50 per 100,000 live births. Countries that have been "validated for elimination" are listed here. In late 2017, the WHO released a separate framework for "validation for path to elimination" status, which has three tiers reserved for countries whose rate of syphilis prevalence is high enough that the country cannot meet the "validation for elimination" criteria, described here.

[30] Same-day treatment was 43.2% in the control group, which only received the supplies, and 100% in the treatment group, which received the supplies and behavioral interventions.

behavioral[31] interventions were added. These are areas we may explore further as we consider the design of a future intervention package.

One possible concern around introducing the syphilis rapid tests is that doing so may crowd out attention on HIV. However, the evidence suggests the opposite is true. When either the dual rapid test or the single syphilis rapid test is introduced, HIV screening and treatment rates either remain the same or increase[32], suggesting the rapid test may act as a means of strengthening the health system and improving overall healthcare delivery.

## IV. Methodology

To assess whether investing in efforts to increase screening and treatment of syphilis among pregnant women is potentially highly cost-effective, and what role Evidence Action might consider playing in these efforts, we have worked on three main fronts:

1. **Literature review:** We reviewed all literature cited in GiveWell's interim intervention report, in addition to numerous other resources. These included all available meta-analyses, systematic reviews, and randomized controlled trials. In addition, we reviewed many non-randomized studies documenting efforts to increase screening and treatment of syphilis among pregnant women; the studies were of various methodological types, including observational studies, case control experiments, and case studies. While these are less rigorous methodologically, they contributed to our broader understanding of context around specific interventions and/or implementation in specific geographies. Through this process, we examined the biology of maternal and congenital syphilis, effectiveness of treatment, government and financing context, usability of the new diagnostic tools, and gaps in service delivery that prevent countries from achieving high screening and treatment rates. Throughout the research, we looked for promising intervention examples that could inform our potential efforts to prototype and pilot a model for boosting screening and treatment.

2. **Expert interviews:** We spoke to a wide range of experts to clarify our learnings from the literature review, including experts interviewed by GiveWell and numerous others. These included individuals at the WHO, CHAI, the London School of Hygiene and Tropical Medicine, the Gates Foundation, and the U.S. Centers for Disease Control and Prevention (CDC), among others. We also spoke to authors who had published on the topic and some local country experts who could clarify the on-the-ground situation. A full list of experts interviewed is available in the appendix, excluding those we met during in-country scoping visits.

[31] The behavioral interventions included opinion leader selection, academic detailing visits, reminders, audits and feedback, and supportive supervision.
[32] Swartzendruber et al. (2015); Strasser et al. (2012); Fleming et al. (2013).

3. **In-country scoping visits:** We completed initial scoping visits in Indonesia, Liberia, and Ghana to fulfill several key learning objectives: (a) identify the key constraints on syphilis screening and treatment; (b) validate estimates of syphilis prevalence; (c) assess the government's existing plans for scaling up dual testing; (d) evaluate whether other stakeholders are providing the government support in this area, and; (e) determine whether the government would be open to partnering with Evidence Action. These scoping visits informed our view of the intervention model components that would be considered for each country and what assumptions should be included in our cost-effectiveness model.

## V. Systems Map and Theory of Change

Multiple decisions and actions on the part of a country's national government, its healthcare providers, and pregnant women are needed to ensure that pregnant women are effectively screened and treated for syphilis. We describe these in greater depth in this section.

Before doing so, however, it is important to highlight that countries operate within a global ecosystem that can present obstacles for even well-designed country-level efforts. Specifically, countries must contend with two global challenges related to the primary diagnostic and treatment commodities needed for addressing this issue:

1. **The benzathine penicillin-G supply chain is unstable and at risk of resulting in a global shortage of BPG.**[33] There are a limited number of active pharmaceutical ingredient (API)[34] manufacturers and final dose formulators[35] (FDFs); six API manufacturers and over 40 FDFs have left the market since the early 2000s.[26] Because of these difficulties, the WHO has been unable to pre-qualify a manufacturer of BPG and is instead working closely with several manufacturers to improve their operations for hopeful approval in the coming year.[36]

2. **The dual HIV/syphilis rapid test costs more per unit (on average) than if one were to purchase the single HIV rapid tests**.[37] The single HIV rapid tests cost between $0.43-$1.00 whereas the dual rapid test has cost approximately $1.50 in the

[33] Based on market analysis conducted by Nurse-Findlay et al. (2017).
[34] The active pharmaceutical ingredient refers to the ingredient in a pharmaceutical drug that is biologically active (in other words, it is the ingredient responsible for having the curative effect on the patient who ultimately receives the drug).
[35] The final dose formulator is the manufacturer who converts the active pharmaceutical ingredient (API) into its usable form and then packages and labels the drug. In the case of BPG, the API powder is bottled and sterilized so that a healthcare provider can resuspend it before treating a patient.
[36] Based on discussion with Melanie Taylor (WHO).
[37] The dual test is also more expensive than if a country were to purchase the single HIV test and the single syphilis test separately.

past.[38,39] Countries likely recognize that there is value to testing for syphilis among pregnant women, even though they may not value this highly. Thus, countries (or their main donors of HIV commodities, Global Fund and PEPFAR) may be willing to pay a bit more on top of the HIV-only test cost to screen for syphilis.

Global actors with experience and influence in global market dynamics, including the WHO and CHAI, are working on dual test pricing and are poised to make progress; given Evidence Action's capabilities vis-a-vis theirs, we do not recommend our involvement with these global market dynamics.

Setting aside global constraints on screening and treatment efforts, the within-country steps along the pathway toward preventing adverse outcomes due to maternal syphilis are diagrammed below in Figure 4 and explained in more detail subsequently.

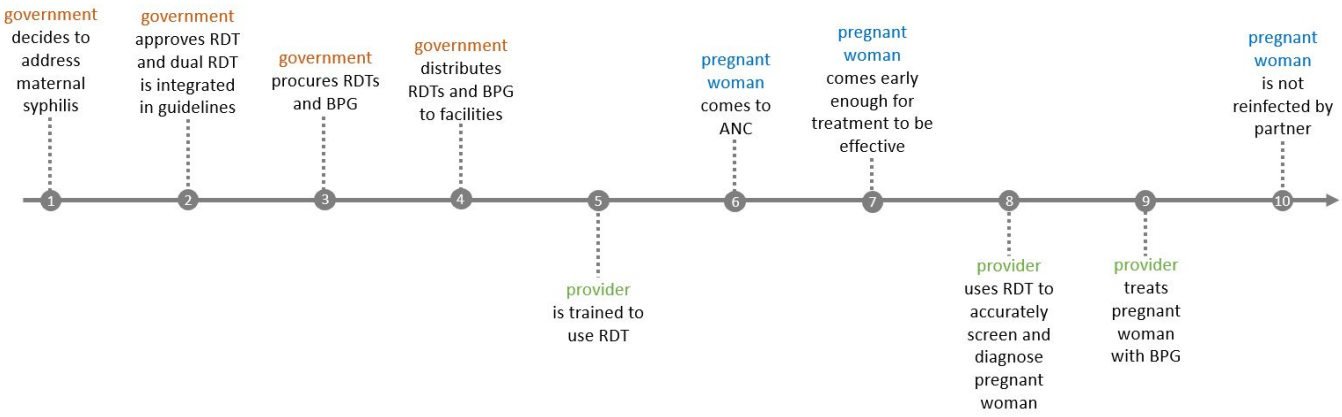


*Figure 4: Steps needed to successfully screen and treat pregnant women for syphilis.*

Step 1

**Government Buy-In:** The Ministry of Health (MoH) must ultimately decide whether or not to invest resources into addressing maternal syphilis. Documentation of a high syphilis prevalence within the country, as well as development of a clear and actionable scale up plan, acts to motivate governments to develop programs to increase screening and treatment.

[38] Cost of the syphilis rapid test is based on Kleutsch, Harvey and Rennie (2009). Cost of the HIV rapid test is based on Bristowe et al. (2015). Cost of the dual test is based on an International Diagnostics Center report.

[39] With the newly pre-qualified First Response dual test, there will likely be market competition between the two manufacturers of pre-qualified devices that may drive down prices in the near future. This would increase the willingness of countries and donors to switch from HIV single testing to HIV and syphilis dual testing.

Step 2

**Approval and Guidelines:** The syphilis rapid test and the dual HIV/syphilis rapid tests are new technologies that cannot be purchased until the country's relevant regulatory agency approves the test. Among all rapid tests capable of identifying syphilis, there are only two dual HIV/syphilis tests that are currently prequalified by the WHO.[40] Even for prequalified tests, some countries insist on conducting validation studies within their own borders before approving the test, which can introduce a lengthy validation process that is at-risk of producing contradictory results if the validation is not run correctly in-country.[41] Engagement with bott government and manufacturers can help to expedite this process and ensure quality in-country testing, if required. To roll-out the dual test, countries must also modify their diagnostic algorithms[42] for both syphilis[43] *and HIV*[44], not just syphilis, a process which requires technical assistance around HIV diagnostics as well to ensure guidelines are updated correctly.[45]

Step 3

**Financing and Procurement:** The government must secure the financial resources needed to procure rapid tests and BPG. In some countries, partner support for an initial procurement of the dual test may be crucial to catalyze uptake. In addition, many countries struggle with BPG availability, and partner procurement may be valuable here.

Step 4

**National Supply Chain:** Governments need to manage their supply chains to minimize stock-outs and expired goods at the facility level. Rapid tests have a shelf-life of 18-24

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[40] The SD Bioline HIV/syphilis duo was prequalified in 2015 and the Premier First Response combo test was prequalified in 2019.

[41] Rosanna Peeling (LSHTM) and staff at the CDC have both described how countries insist on having their own validation data. This is a lengthy process prone to errors because many countries do not have clear protocols on how to validate new diagnostic tests. If countries do not use the correct blood sample panels, or do not train their staff sufficiently ahead of time, the test may "fail" the in-country validation even though it has already passed the WHO evaluation.

[42] A diagnostic algorithm maps the tests a clinician needs to run to diagnose someone for a particular infection and the order in which those tests should be run. Usually, the first step involves a screening test given to the entire target population while the second (confirmatory) test is only run on those who test positive during screening.

[43] The WHO recommended algorithm for incorporating any type of syphilis rapid test (syphilis-only or dual) can be found here on pages 23-24.

[44] In the case of HIV, women are screened with one test. If they test positive, a second confirmatory test is used. If the screening test and confirmatory test do not match, a third test must be used. Given the complexity involved in this diagnostic algorithm, changing it to accommodate the dual test is a lengthy process. Countries are concerned about updating their HIV diagnostic guidelines because there are more stakeholders, their HIV programs are tied to large sources of money, and countries are held accountable for backslides in their HIV efforts.

[45] Melanie Taylor (WHO) has said the WHO is currently working on publishing a new, approved algorithm for use and interpretation of the dual HIV/syphilis test that countries will be able to implement directly once the guideline is released. Melanie currently estimates the new algorithm will be made available August of 2019.

months,[46] requiring diligent management of supplies. Work may also be required around forecasting, updating of logistics management information systems, and updating and printing of order forms.

Step 5

**Training:** The government must update its training curriculum and then cascade a training program that equips providers with the skills needed to use the diagnostic tool effectively. Often, providers need a refresher training on the health consequences of syphilis and how to treat the infection as well. Due to high staff turnover at ANC clinics, it may also be necessary to plan for ongoing mentorship, likely integrated into existing HIV training and mentorship systems, of staff at periodic intervals.

Step 6

**ANC Attendance:** Even if all of the infrastructure (e.g., adequate supplies, well-trained providers) are in place to facilitate screening and treatment of maternal syphilis, pregnant women must still come to antenatal care in the first place. Antenatal care attendance rates vary across countries, though many in Sub-Saharan Africa have rates above 90%. According to available data, 78% of the adverse outcomes resulting from maternal syphilis occur in women who already *do* attend antenatal care, suggesting there is significant scope for impact with an initial focus exclusively on women already having contact with the ANC system.[47]

Step 7

***Early* ANC Attendance:** Due to the biological nature of mother-to-child syphilis transmission described above, adverse outcomes are likelier to be averted if women are screened and treated earlier in their pregnancy. Among women who attend ANC at least once during their pregnancy, some attend for the first time sometime during their third trimester (24-36 weeks gestation) when the pregnancy is visible[48] although scientific consensus[49] recommends treatment before the 24th gestational week. The distribution of women's gestational age at their first ANC visit vary by country (see examples above and in the appendix), and the extent to which this presents a problem will vary by context.

Step 8

**Accurate Screening:** The provider must use the available resources to test the pregnant woman for syphilis. The provider must also interpret the test results correctly. In particular, it is important that the provider is able to accurately identify those who are infected so that women who are positive do not leave believing they are healthy.[50] This should be achievable

[46] Based on case study by Kleutsch, Harvey and Rennie (2009).
[47] Based on 2012 estimates reported in Wijesooriya et al. (2016). More recent estimates are not available.
[48] Based on Blencowe et al. (2011) and conversations with Melanie Taylor (WHO).
[49] Based on Blencowe et al. (2011).
[50] In field studies of the dual rapid test, the ability of providers to accurately identify those who are infected with syphilis ranges widely from 67% to 97% (Gliddon et al., 2017). As Mabey et al. (2006) summarizes, this is often because the test is difficult to read and providers cannot tell whether what they are seeing is a positive or a negative test. Given that some studies have found higher rates of accurately

with basic training, since these health workers are already conducting and interpreting HIV rapid tests.

Step 9

**Treatment:** The provider must act on the information received from the test. If a woman is positive for syphilis, she must be treated with a single injection of BPG, ideally during that same interaction. In some instances, healthcare providers opt for alternative treatment paths that are not medically-backed because they are concerned the woman may have an allergic reaction to penicillin, they do not feel comfortable giving a large injection, or the injection itself resuspends poorly.[51] Training on treatment and the desensitization protocol can mitigate this.

Step 10

**Reinfection:** Even if a pregnant woman is effectively treated, she can get reinfected by her male partner if that partner is not tested and treated.[52] A new infection is more likely to transmit to the fetus, putting the current or a future pregnancy at the same risk as though the woman was never screened and treated in the first place.[53] Further investigation is needed to explore both the extent of this issue and - should it be a sizeable risk - strategies to address this issue.

As the diagram above shows, a coordinated set of actions is needed to avert the adverse outcomes resulting from maternal syphilis, and many countries face challenges throughout the chain. Evidence Action plans to cost-effectively engage with national governments on particular aspects of this system to achieve better outcomes. These are discussed in greater detail within the country scoping reports.

identifying positive patients, it suggests that providers *can* be taught to better interpret the diagnostic tests.

[51] Based on conversation with Melanie Taylor (WHO) and survey responses documented in Nurse-Findlay et al. (2017).

[52] Melanie Taylor (WHO) has confirmed that little data is available on current partner treatment rates or rates of reinfection among pregnant women. One possible proxy for the reinfection rate 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), 0.4% to 2.8% of pregnant women undergo seroconversion in high-prevalence areas.

[53] In many cases, women have a latent infection. If they are treated for this infection but then become reinfected, they now have active syphilis. The above section explains the increased transmission risk between mother and child with active versus latent syphilis.

# VI. Appendix A: Distribution of First ANC Attendance Across Several Countries.

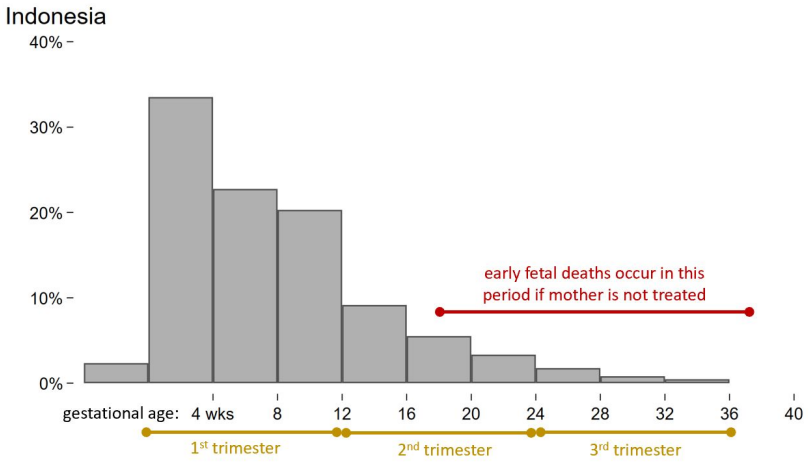


*Figure 7. Date of ANC visit was taken from Indonesia's 2012 DHS survey.*

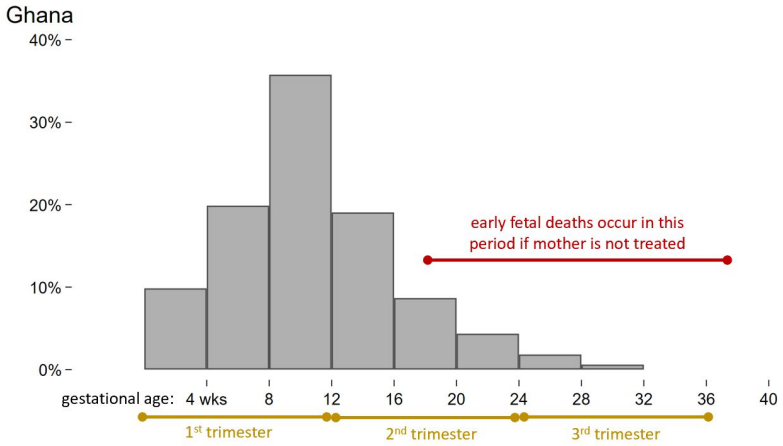


*Figure 8. Date of ANC visit was taken from Ghana's 2014 DHS survey.*

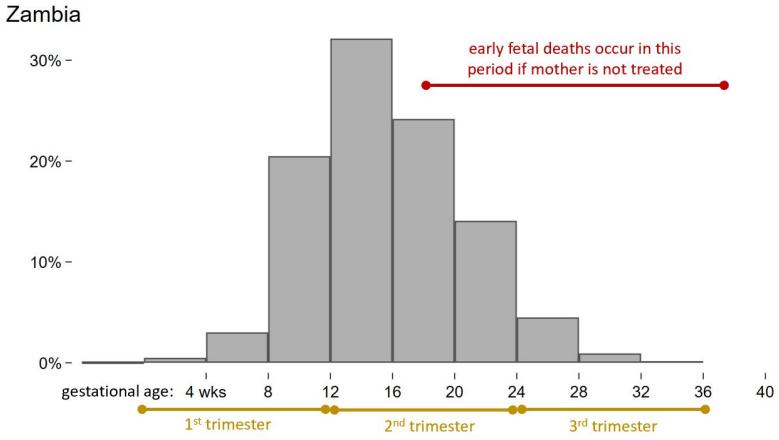


*Figure 9. Date of ANC visit was taken from Zambia's 2013/2014 DHS survey.*

## VII. Appendix B: List of Expert Interviews

| Name | Organization | Role |
|---|---|---|
| Melanie Taylor | WHO | WHO focal person for maternal syphilis; in Department of Reproductive Health and Research |
| Ana Pilar Betrán | WHO | Medical Officer, Department of Reproductive Health and Research |
| Andrew Storey | CHAI | Senior Director, New Initiatives |
| Trevor Peter | CHAI | Senior Scientific Director for Diagnostics Services |
| Nicholas Furtado | The Global Fund to Fight AIDS, TB and Malaria | Reproductive, Maternal, Newborn, Child and Adolescent Health and Health Systems Strengthening, Technical Advice & Partnerships Department |
| Seble Abebe | The Global Fund to Fight AIDS, TB and Malaria | Senior Program Officer; Liberia Portfolio Manager |
| Mo Madiba | Abbott | HIV Product Manager |
| Michele Montandon | CDC | Maternal and Child Health Branch |
| Nicholas Gaffga | CDC | Maternal and Infant HIV Team Lead |
| Amy Medley | CDC | HIV Testing Services Team |
| Keisha Jackson | CDC | International Laboratory Branch |
| Lee Pyne-Mercier | Gates Foundation | Senior Program Officer for Maternal, Newborn & Child Health |
| Tanya Shewchuk | Gates Foundation | Senior Program Officer, Integrated Delivery |
| Siobhan Malone | Gates Foundation | Senior Program Officer, HIV |
| Debbie Armbruster | USAID | Senior Maternal and Newborn Health Advisor |
| Helen Petach | USAID | Senior Science Advisor, Office of Maternal, Child Health, and Nutrition |
| Pierre Buekens | Tulane University | Former Dean, School of Public Health and Tropical Medicine |

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|---|---|---|
| Fernando Althabe | Institute for Clinical Effectiveness and Health Policy | Researcher |
| Alison Drake | University of Washington | Epidemiologist; Director of the Global Center for IntegratedHealth of Women, Adolescents, and Children |
| Eline Korenromp | Avenir Health | Senior Modeler, Spectrum-STI |
| Rosanna Peeling | London School of Hygiene and Tropical Medicine | Professor and Chair of Diagnostics Research and Director of the International Diagnostics Center |
| Debi Boeras | Global Health Impact Group | Former Lead for Molecular Diagnostics at the CDC International Laboratory Branch |
| Laura Broyles | Global Health Impact Group | Consultant; leading maternal syphilis advocacy efforts |
| Andreas Kuznik | Regeneron Pharmaceuticals | Conducted cost-effectiveness analysis of maternal syphilis screening and treatment |
| Jamilu Tukur | University of Kano, Nigeria | Professor of Obstetrics and Gynecology |
| Ima Chima | Evidence Action, Nigeria | Lead Representative for DtWI |
| James Kachingwe | Ministry of Health, Malawi | STIs Program Officer Department of HIV/AIDS |
| Prince Kasinja | Evidence Action, Malawi | Country Lead, Dispensers for Safe Water |
| Priya Pandey | Evidence Action, India | Country Director |
| Supriyatiningsih Upi | Presidium of Maternal and Neonatal Health Movement, Indonesia | Former Chairwoman |
| Bobby Syahrizal | UNICEF, Indonesia | Health Officer |
| Artha Camellia | UNICEF, Indonesia | Health Specialist, HIV and PMTCT |
| Blandina Mmbaga | Kilimanjaro Clinical Research Institute, Tanzania | Director |
| Yoriko Nakamura | R4D, Ghana | Senior Program Officer |
| Miaro-Zo Hanoa Adrianoelina | UNICEF, Madagascar | Former Head of Coordination at the Madagascar National AIDS Committee |