ANTENATAL CLINIC-BASED SYPHILIS SCREENING AND TREATMENT TO TACKLE SYPHILIS IN PREGNANCY

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APRIL 2023
Research Report:
Large-Scale Global Health – Antenatal clinic-based syphilis screening and treatment to tackle syphilis in pregnancy

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Date of publication: 
Research period: 2022

Thanks to Kylie Abel and Urszula Zarosa for their contributions to this report. We are also grateful to the experts who took the time to offer their thoughts on this research.

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Executive summary

Syphilis is a bacterial sexually transmitted disease that still affects millions of people in low- and middle-income countries (LMICs). While it can cause health problems at any point in life, untreated syphilis in pregnancy is especially detrimental as it can result in a stillbirth or a baby born with congenital syphilis1, which may result in neonatal death or lifelong health problems. In fact, it is estimated to be among the leading causes of perinatal mortality, causing around 150,000 stillbirths and 60,000 neonatal deaths every year. Syphilis and malaria are now the leading causes of preventable stillbirths in the developing world.

All of this perinatal morbidity and mortality is preventable. With modern rapid finger-prick tests, syphilis can be detected within 20 minutes, and treatment requires as little as a single injection of penicillin. As long as treatment happens early in the pregnancy, the majority of adverse outcomes can be avoided. Antenatal clinics seem to be the ideal touchpoint for both screening and treatment, since the majority of women in LMICs nowadays attend them at least once during their pregnancy.

Despite the scale and the tractability of the problem, syphilis screening and treatment has been highly neglected, with global infection rates being flat for the past decade and very few international teams or organizations being dedicated to implementing solutions.

The intervention explored in this report is the roll-out of dual HIV/syphilis rapid diagnostic tests (RDTs) and benzathine penicillin G (BPG) for treatment of syphilis. While large historical investments in HIV and the prevention of HIV mother-to-child transmission have resulted in widespread use of HIV RDTs, syphilis is often either not screened for, or is tested by much more cumbersome laboratory blood tests. By simply replacing HIV RDTs with the dual RDTs – and ensuring that penicillin is available at antenatal clinics for immediate treatment – syphilis screening and treatment rates could quickly be brought up to match the rates for HIV.

There is very strong evidence for syphilis screening and treatment. Three companies’ dual RDTs have been pre-qualified for use by the WHO, and they have ~90% sensitivity. A meta-analysis of 18 studies found that dual RDTs are more

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1 Congenital syphilis is a disease that occurs when a mother with syphilis passes the infection on to her baby during pregnancy.
cost–effective than single rapid tests for HIV and syphilis and prevent more adverse pregnancy outcomes. Moreover, penicillin is extremely effective at treating syphilis. A meta–analysis of 24 studies, evaluating treating pregnant women with penicillin, found that this treatment is associated with:

- A 97% reduction in congenital syphilis
- An 82% reduction in the risk of stillbirth
- A 64% reduction in the risk of preterm birth
- An 80% reduction in the risk of neonatal death

Our geographical assessment indicates that this intervention could be impactful in some 5–20 countries in Sub–Saharan Africa, and South and Southeast Asia. Our expert interviews indicate that there is actually a pre–existing interest for the roll–out of dual testing in many countries, but most governments in areas with a high burden of syphilis have not had sufficient capacity or technical capability to be able to roll out these programs on their own.

**This intervention also looks very cost–effective.** We expect that the charity’s activities would consist primarily of procuring goods, providing technical and logistical support, and training antenatal–clinic staff to correctly use the rapid tests and administer treatment. Assuming that these activities would result in speeding up the roll–out of dual testing by several years, we estimate that this intervention could avert one DALY for $81 and save a life for $1,726², if both charity and government costs are considered.

**Our main concern is that, in some priority countries, this work may happen anyway in the next 5–10 years,** either through government initiatives or the work of other international organizations. However, given that the global situation looked similar five years ago and limited progress has been made since then, this concern is relatively small.

Lastly, we think that there may be a potential for a charity in this space to focus on delivering a package of interventions with antenatal clinics as the main touchpoint. These may include the prevention of mother–to–child transmission of hepatitis B, increasing the use of multiple micronutrient supplementation in pregnancy, or improving the detection and treatment rates of hypertensive disorders in pregnancy, among other interventions. This would allow the charity to cost–effectively continue to scale its impact.

² If avoiding stillbirths is treated as saving a life; if we apply a downweighting adjustment, the cost per life saved increases to $3,565.
Overall, our view is that scaling up the use of dual rapid testing for HIV and syphilis, paired with immediate syphilis treatment at antenatal clinics, is an idea worth recommending to future charity founders.
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1 Introduction

This report has been produced by Charity Entrepreneurship (CE). CE’s mission is to cause more effective charities to exist in the world by connecting talented individuals with high-impact intervention opportunities. We achieve this goal through an extensive research process and our Incubation Program. In 2022, our research process focused on the top highly scalable global health interventions.

Antenatal clinic-based syphilis screening and treatment to tackle congenital syphilis was chosen by CE research staff as a potentially promising intervention within this category. This decision was the result of a five-month process designed to identify interventions that were most likely to be high-impact avenues for future charity entrepreneurs. This process began by listing nearly 300 ideas and gradually narrowing down, examining them in more and more depth.

In order to assess how promising interventions would be for future charity entrepreneurs, we use a variety of decision tools such as group consensus decision-making, weighted factor models, cost-effectiveness analyses, quality of evidence assessments, case study analyses, and expert interviews.

This process was exploratory and rigorous, but not comprehensive – we did not research all 300 ideas in depth. As such, our decision not to take forward a charity idea to the point of writing a full report should not be seen as a view that the idea is not good.

2 Background

2.1 The scope of this report

Maternal and neonatal health continues to be among the leading sources of death and disability in developing countries.

While childhood mortality rates have fallen in recent decades, its rate in low-income countries (LICs) is still around 6.6 deaths per 100 births as of 2020, compared to 0.49 in high-income countries (see Figure 1 below).
Maternal mortality has barely decreased, with 224,000 mothers in Sub-Saharan Africa dying of pregnancy-related causes in 2006 and 202,000 in 2016 (see Figure 2 below).

Figure 1: Child mortality by countries’ level of income. Source: Roser et al. (2019)

Figure 2: Maternal mortality by region. Source: Roser and Ritchie (2013)

Antenatal clinics (ANCs) are a great touchpoint at which the health of both the mother and the unborn child can be assessed, monitored, and treated. Around 82%
of women in Sub-Saharan Africa (SSA) currently access antenatal health care at least once during their pregnancy, and coverage is continuously increasing (UNICEF Data Warehouse, n.d.). Antenatal care offers a great opportunity to deliver a suite of health interventions, from vaccinations to screening for diseases, starting a course of malaria chemoprevention, or giving women nutritional supplements to improve either their calorie intake or their levels of micronutrients.

The Copenhagen Consensus Center has assessed the cost–effectiveness of a range of interventions deliverable at antenatal clinics, and recommended the following interventions based on their high benefit–cost ratios: Tetanus toxoid vaccination, intermittent preventive treatment of malaria (IPTp), syphilis detection and treatment, iron supplementation or multiple micronutrient supplementation, balanced energy supplementation, hypertensive disorder case management, and magnesium sulfate for the management of pre-eclampsia (Friberg and Weissman, 2020). We have done a quick review and prioritization of these interventions based on their feasibility, neglectedness, and cost–effectiveness. Our assessment is summarized in the Annex to this report, available on request.

After this initial assessment, we have decided to focus on syphilis detection and treatment as the main intervention explored in this report, due to its high tractability, high cost–effectiveness, and its relative neglectedness. Specifically, our view is that a new charity in this space should focus on scaling up the roll–out of dual HIV/syphilis rapid diagnostic tests3 (RTDs), paired with ensuring robust supplies of benzathine penicillin G (BPG), as a relatively simple, highly cost–effective, yet neglected way of addressing the burden of mother–to–child transmission of syphilis.

In many countries with a high prevalence of syphilis, there are existing, well–funded programs focused on the prevention of mother–to–child transmission of HIV, which provide an opportunity for a syphilis program to be ‘attached’, instead of created from scratch. By replacing HIV–only RDTs with dual HIV/syphilis RDTs – which are only marginally more expensive – syphilis screening rates could quickly be brought up to the rate of HIV screening. Moreover, treatment is extremely simple, usually requiring only a single shot of BPG. Based on our quick geographic assessment, we think that there may be up to ~20 countries where this work could be promising.4

3 Also known as point–of–care tests
4 Note that some of these countries may have feasibility limitations that are hard to determine from desk research.
One reason why dual HIV/syphilis screening is such a strong intervention, in comparison to the other considered interventions, is that the switch to dual testing should be roughly time-neutral for ANC health workers (i.e., neither saving time nor consuming additional time), as it changes something that health workers already do – HIV testing – to another task, rather than adding tasks to health workers’ to-do lists. Since it has been difficult for us to determine ANC health workers’ capacity with desk research alone, we did not want to recommend an additional intervention to their workload without having first seen the on-the-ground reality and assessing whether they would actually have the time to do this.

However, we note that implementation is expected to be a complex task which requires coordinated efforts on multiple fronts to tackle the last-mile problems in changing standard practice (Evidence Action, n.d.; Broyles et al., 2021). Helping to roll out even a simple intervention such as this may require: (i) coordinating working between various historically siloed healthcare initiatives, (ii) development of new guidelines and screening algorithms for health workers, (iii) training health workers in following the new approaches, (iv) supporting better data collection and monitoring, and (v) enhancing supply chains for the necessary medicines.

2.2 Other promising antenatal care interventions

We also considered the other interventions recommended by The Copenhagen Consensus Center, plus a few others suggested by experts we spoke with. A new charity working in the antenatal-care space may want to decide to implement one or more of these interventions alongside syphilis screening and treatment.

The table below provides a summary of our preliminary judgment as to how promising these interventions are as possible additions to an intervention package. Interventions were given a positive rating if they were perceived as high-impact, and as either having a large degree of similarity (in terms of their theory of change) with syphilis screening and treatment, or if they are relatively simple interventions. Conversely, a low rating may be due to lower impact, dissimilarity with syphilis screening and treatment, or due to a generally high complexity. Most of the ideas were not assessed in detail in terms of cost-effectiveness; doing this in the future might change our rating. Our assessment is summarized in the Annex to this report, available on request.
### Table 1: Other interventions considered as part of this package, and their judged suitability for co-implementation with a congenital syphilis intervention.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>How promising</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiviral drugs to prevent the mother-to-child transmission of hepatitis B</td>
<td>High</td>
</tr>
<tr>
<td>Switching from iron supplementation to multiple micronutrient supplementation in pregnancy</td>
<td>Medium–High</td>
</tr>
<tr>
<td>Antihypertensive medication for women with a hypertensive disorder (including preeclampsia)</td>
<td>Medium</td>
</tr>
<tr>
<td>Low-dose aspirin for women at risk of preeclampsia</td>
<td>Medium–low</td>
</tr>
<tr>
<td>Increasing the adherence to iron/multiple-micronutrient supplementation in pregnancy</td>
<td>Medium–low</td>
</tr>
<tr>
<td>Corticosteroids for women at risk of a preterm birth</td>
<td>Medium–low</td>
</tr>
<tr>
<td>Intermittent preventive therapy for malaria in pregnancy (IPTp)</td>
<td>Low</td>
</tr>
<tr>
<td>Magnesium sulfate for preeclampsia</td>
<td>Low</td>
</tr>
</tbody>
</table>

We think that a promising strategy for a new charity in this space may be to initially focus on a single intervention in one country (or a small number of countries) and, once it has a sense of the on-the-ground reality of health workers’ capacity and has built relationships with the relevant local stakeholders,\(^5\) it can utilize these contacts in order to more quickly and effectively scale up new antenatal–care programs. Alternatively, if the early impact of the syphilis intervention looks very promising, the charity may decide to prioritize international expansion of this program over considering new interventions in the same country.

We discussed this idea with multiple experts we interviewed. Prof. Rosanna Peeling of London School of Hygiene and Tropical Medicine, and Ashley Giles from the Malaria Consortium, were supportive of the idea of focusing on a package of interventions, highlighting that there is a general push for co-implementation in

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\(^5\) Multiple actors in this and related spaces have highlighted the benefit of establishing one’s name and forming strong partnerships on the ability to deliver effective programs. For instance, Evidence Action has been relying on their pre-existing relationships from their deworming program to scale up its newer iron supplementation program, and organizations like the Global Health Impact Group have made similar observations in the HIV space.
the global health community (e.g., from the WHO) – either for organizations to find ways of implementing multifaceted interventions, or for greater collaboration between organizations that focus on single solutions. Prof. Joshua Vogel also thought that a package may be beneficial, saying that focusing on a single intervention can often lead to negative externalities on other programs in situations where staff time is limited. However, he stressed that trying to do too many things may lead to a loss of focus, so would recommend focusing on a single intervention, especially when a charity is small.

2.3 Syphilis – What is the problem?
Syphilis is a bacterial sexually-transmitted disease (STD). It can remain latent for many years and then re-emerge and damage multiple organs. If a pregnant mother has syphilis, it can be transmitted to the fetus – known as congenital syphilis – and cause a range of problems, from organ and nervous system damage to physical deformations, stillbirths, and increased neonatal mortality.

While it has become rare in high-income countries (HICs), it is still a relatively common disease in LMICs: On average, 0.9% of pregnant women in Southeast Asia and 2.2% of women in SSA test positive for the disease. The World Health Organization estimates that almost 1 million pregnant women were infected with syphilis in 2016, resulting in over 350,000 adverse birth outcomes, including 150,000 stillbirths and 60,000 neonatal deaths (WHO, 2022). That is as much as 21% of perinatal mortality in SSA (Woods, 2009). This translates to a loss of roughly 7.4 million disability-adjusted life years (DALYs) in 2019, and makes syphilis by far the deadliest STD other than HIV (Institute for Health Metrics and Evaluation, 2019).

2.4 Syphilis screening and treatment
Detecting and treating syphilis is extremely tractable. The disease can be detected within 20 minutes using a finger-prick RDT and, once diagnosed, can be treated with a single injection of benzathine penicillin G (BPG) which costs only $0.50 per dose in LMICs (or even as little as $0.11 in some countries; Nurse-Findlay et al., 2017).

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6 Note that this should be less of a concern for syphilis/HIV dual tests, which we think should be close to time-neutral, as discussed in section 2.1
7 The DALY is a metric that combines the burden of mortality and morbidity (non-fatal health problems) into a single number. One year of life lost equals 1 DALY, while one year lived with a disability equals a value between 0 and 1, depending on the severity of disability. It is the primary metric used by the World Health Organization to assess the global burden of disease.
An additional unique opportunity to speed up the rollout of syphilis testing has emerged in recent years in the form of dual HIV/syphilis testing. Dual RDTs can detect both diseases at once and, thanks to work by the Clinton Health Access Initiative (CHAI), these dual RDTs are now available in LMICs for $0.95 per test – only $0.15 more than HIV-only RDTS (Clinton Health Access Initiative, 2021; MedAccess, 2021). Three companies (SD Biosensor, Abbott, and Chembio) produce RDTs that have been pre-qualified by the WHO – meaning their quality, safety and efficacy has been verified – thus helping to streamline the process of in-country validation and procurement.

Given the historically greater focus on HIV/AIDS, HIV screening rates tend to be much higher than syphilis screening rates (43% vs 63% across SSA, with gaps varying significantly between countries, see Figure 3 below; WHO Global Health Observatory, n.d.; AIDSinfo, n.d.). As such, simply replacing HIV-only RDTs with dual RDTs would significantly contribute to closing the syphilis screening gap, and make any future improvements in HIV screening automatically translate into improvements in syphilis screening. Dual RDTs are now officially recommended by the WHO, who note that the majority of countries still rely on lab testing for syphilis (WHO, 2019).

![Syphilis screening rate and HIV screening rate](image)

**Figure 3:** Syphilis screening rates at ANCs compared with HIV screening rates in selected countries.
3 Theory of change

3.1 Barriers – why don’t countries use dual RDTs already?

Despite the simplicity of the intervention, the official WHO recommendation, availability of pre-qualified tests, and evidence of cost-effectiveness, progress in rolling out RDTs has been slow. The main predictor of a country having an effective program for the prevention of congenital syphilis is the strength of its healthcare system (based on our conversation with Rosanna Peeling and Debi Boeras). For instance, Cuba – a middle-income country well-known for its high-quality healthcare – was the first country to be validated as having eliminated mother-to-child transmission of syphilis. Most LMICs in Africa and South Asia, however, possess weaker health systems which have struggled to implement improvements to antenatal care, even when provided with clear roadmaps designed by international experts.

In their correspondence to The Lancet, Broyles et al. (2021) argue that these failures are a result of last-mile implementational challenges, including:

1. HIV and other STDs programs having been historically siloed in many countries. Coordination is needed in terms of policies and funding streams.
2. Data on HIV and syphilis testing having historically been captured in separate systems. Therefore, monitoring tools and processes need to be revised.
3. Dual testing at ANCs requires the implementation of testing algorithms for RDTs that will exist in parallel with standalone algorithms for HIV and for syphilis.
4. Separate clinical workflows and patient pathways being needed for women with known HIV infections.
5. The fact that the roll-out of RDT may come in conflict with efforts to roll out HIV self-testing and/or HIV recency testing.

The authors call for global stakeholders to “collaborate to support comprehensive and robust roll-out plans to expedite scale-up and mitigate operational hurdles.”

We may also be concerned about the stock and availability of BPG. As syphilis screening programs are scaled up we may expect there to be shortages in BPG similar to those we have seen in the period 2014–2016, where there was a worldwide shortage of BPG with some 40% of surveyed countries experiencing
issues, including in high-income countries like the USA and Canada. Shah et al. (2021) estimate that a transition to dual HIV/syphilis RDTs would lead to a short-term increase in demand for BPG of 65%, and potentially up to 160% in order to reach the WHO target of coverage of 95% screening coverage. However, we note that Anna Konstantinova of Evidence Action was not concerned about the overall availability of BPG, but she did note that by shifting syphilis diagnosis and treatment to ANCs, **BPG stocks may not be in the right places**, even if the overall country-level stocks are good (Konstantinova Interview).

Another challenge a charity may encounter is countries’ “stickiness” to existing brands and processes. While governments may be on board with the idea of dual RDTs, they may have existing contracts in place with the suppliers of HIV-only rapid tests or syphilis lab tests, and may thus need assistance with the procurement of dual RDTs. They may also be reluctant to change because of the need for additional health–worker training and for new guidelines, algorithms, and manuals to be made and printed.

On-the-ground training of health workers and their **compliance with the new guidelines** may be a challenge itself. An implementational study of syphilis RDTs in Zambia observed several issues noted by health workers switching to the new process, including (i) struggling to interpret test results (especially when they are “weakly positive”), (ii) failing to follow the correct algorithms (such as by ordering confirmatory lab tests when they weren’t needed), (iii) struggling with patient flows as a result of having to wait for 20 minutes for the RDT results, (iv) in some cases, having increased workloads as a result of now having to treat syphilis with penicillin (Ansbro et al., 2015). It should be noted, though, that the impact on patient flows and workloads is localized, and only affects specific health workers if the change means they now have extra tasks. From a system perspective, we expect that replacing laboratory tests with RDTs and bringing diagnosis and treatment together in ANCs should result in significant efficiency gains and time savings. However, the overall conclusion of health workers on the switch to dual RDTs was positive. Health workers were generally accepting of the new devices as a suitable addition to existing services, perceived the testing procedure as quick and easy to perform, and reported high patient buy-in, with patients liking the fact that they could see the test results themselves.

Conversely, there are a few barriers that we originally thought may be important but which may, in fact, be only minor, including:
• **Lack of government buy-in and/or a lack of a national policies on dual testing:** Many governments are on board with the idea of dual RDT (based on our conversation with Rosanna Peeling and Debi Boeras) and already have national policies on dual HIV/syphilis testing ([WHO, 2019](#)).

• **Dual RDTs not being registered for use:** While any test used in a healthcare system should go through a formal registration process, many governments choose to use waivers for WHO-prequalified products in order to streamline the process. As such, registration should also not be a major barrier – although this varies from country to country ([Konstantinova Interview](#)).

### 3.2 Activities – what a charity in this space could do

Given the identified barriers above, there are a range of activities a charity in this space could do. In our opinion, the key ones can be seen as the provision of technical assistance to governments and health facilities in the target countries, consisting of the following:

• **Coordinating work between government departments:** Since the rollout of dual RDTs necessitates the bringing together of HIV and syphilis programs, it will be necessary to bring together all the relevant in-country stakeholders and help them collaborate on the implementation of new processes.

• **Supply-chain strengthening:** This may involve liaising with the producers of WHO prequalified dual RDTs as well as ensuring adequate supplies of BPG via accurate demand forecasting and timely procurement.

• **In-country logistical support:** If BPG is not well stocked at ANCs, women with a positive diagnosis may go untreated. It is therefore crucial to ensure that there are appropriate BPG stocks at ANCs.

• **Updating guidelines and clinical algorithms:** This work has already been done by various international actors; however, governments may still need technical assistance with integrating international guidelines and procedures into their local healthcare systems.

• **Healthcare staff training and support:** Staff, such as nurses and doctors at ANCs, will have to be trained to correctly use the new tests and to follow the correct diagnosis and treatment procedures. They may also benefit from other kinds of support, such as provision of checklists or high-quality booklets for patient tracking (something that is used – but inconsistently – in countries like Ghana; based on a conversation with Sarah Hough, Maternal Health Initiative).

Additional activities that may be needed at the national level are **lobbying for change** in case there isn’t pre-existing government buy-in, and **supporting the**
government with the dual RDT registration process (or the application of a waiver).

Lastly, as discussed in the previous section, there exist global barriers to programs focused on syphilis, stemming from a general lack of attention and stigmatization. If these are found to be important roadblocks, the charity may choose to invest efforts in awareness raising, possibly by becoming “the face of syphilis” – a role that is currently not fulfilled by any global actors (Peeling and Boeras Interview) – or by reframing syphilis testing as a standard part of antenatal care, rather than something that only marginalized groups need (GiveWell, 2018).

3.3 Theory of change mapping

The identified barriers and suggested activities are summarized in the theory of change diagram below:

Figure 4: Theory of the change for the potential charity; editable version

The links between charity activities and outputs in the diagram rely on various assumptions, some of which are more concerning than others.

- In order to achieve better global coordination on the elimination of mother-to-child transmission of syphilis, we assume that:
○ The global health community will be willing to engage in this goal
○ The charity gains enough recognition to be able to initiate conversations and collaborations between the relevant stakeholders

- In order to achieve a **coordinated national strategy on dual testing**, we are assuming that
  ○ The charity will be able to form strong ties with the relevant in-country stakeholders
  ○ There will not be major challenges stemming from conflicts with other programs with overlapping mandates (such as community-based HIV testing)

- In order to achieve **well-supplied stocks of RDTs and BPG**, we assume that:
  ○ We can accurately forecast increased demand for BPG following dual testing
  ○ Drug manufacturers will produce enough BPG to meet global demand
  ○ We will be able to move in-country stocks of BPG to ANCs

- In order for **guidelines and algorithms for healthcare staff to be updated**, we assume that:
  ○ We can find someone to partner with who can update these medical algorithms
  ○ The long process of updating the guidelines runs smoothly, without major push backs on any level (country, state, or clinic)

- In order for **staff to be appropriately trained**, we assume that
  ○ We can design high-quality scalable training materials
  ○ We can deliver the training ourselves, or find partners who will deliver the training

**Scale:** key uncertainty, high uncertainty, some uncertainty, low uncertainty, unconcerning

### 3.4 On-the-ground vs policy focus

One aspect of the theory of change that we are somewhat uncertain about is the degree to which the charity would need to work with countries’ central/local government bodies vs focus primarily on “on-the-ground” work, such as health worker training or logistical support. While further desk research may help to answer some of these questions, we believe that much of it may depend on the reality of the specific country/countries the charity chooses to operate in. For instance, we expect greater need to work with the government if:
• The proportion of ANCs that are public is high: Publicly-run ANCs are likely to be more tightly controlled by the healthcare system; therefore, the proportion of the charity’s work that is focused on publicly-run ANCs is likely to be indicative of its level of collaboration with the government.

• Compliance with healthcare guidelines is monitored and enforced: If healthcare guidelines are closely followed and compliance is monitored, working with the healthcare system will be more important compared to a situation where current guidelines are only loosely enforced.

• Health worker training is centrally organized: If the continuing education of health care workers is centrally coordinated, then working with the government will be key. Conversely, if clinics themselves are responsible for training their staff, more of the charity’s activities will be directly ANC-focused.

This question has implications for the international scalability of the charity’s program: The more a charity’s activities are government-focused, the more bespoke its approach is likely to have to be and the more complicated it may be to replicate its work in a new country. However, such a situation may put the charity in a better place to grow its impact locally, by expanding its work to other ANC-based interventions in the countries where it has already built a good relationship with the government.

The uncertainty about the level of government involvement is also reflected in our cost-effectiveness analysis (CEA). Version A of the CEA assumes that variable costs, such as the cost of procuring RDTs and BPG and of training health workers, would be absorbed by the charity, while version B assumes that those would be absorbed by the government. Each model has its pros and cons: If these costs are covered by the charity – assuming it can attract sufficient resources from international funders – it puts less strain on low-income countries’ already resource-constrained health systems, likely making the program more appealing to the government and removing the risk of funding being discontinued if the governments’ priorities shift. Conversely, if these costs are covered by the government there will presumably be greater ownership of the program, which may contribute to better integration with other initiatives and activities. It will also increase the chances of continuity if/when the charity discontinues its operations in that country.
4 Geographic assessment

The geographic assessment is done in two stages. First, we look at where existing organizations are working and what they are doing. This information will later be used as an input in the formal geographic assessment as a measure of neglectedness (the greater the number of organizations already working in a country, the less neglected the problem is in that country and, therefore, the less promising it is to start a new organization in). Second, we conduct the formal geographic assessment with the aim of finding the top priority countries for starting a new nonprofit.

4.1 Where existing organizations work

Evidence Action is the only global organization that has a dedicated program for the scaling of dual HIV/syphilis RDT. They currently operate in Liberia, with plans to expand to Zambia and Cameroon, and to run a pilot in Indonesia.

4.2 Geographic assessment

We performed a quick geographic mapping exercise in order to (i) identify the highest-impact countries a new charity should focus on, (ii) to assess the scale of the potential impact\(^8\) in those highest-impact countries (since we assume that the charity would focus on working in one or a small number of specific countries).

We constructed a weighted-factor model, made up of a scalability score (weight 3), a tractability score (weight 1), and a neglectedness score (weight 2). These were constructed as follows:

- For the **scalability score**, we first calculated the *maximum number of additional women treated by dual testing per year* = *Total number of births per year in the country* \(\times\) *Syphilis rate in pregnant women* \(\times\) *ANC attendance rate among pregnant women* \(\times\) *(HIV screening rate – syphilis screening rate)*. Then, we calculated the z-score of the logarithm of this value.\(^9\)

- The **tractability score** was calculated\(^9\) based on the Fragile State Index (an indicator of the strength of the central government), the Corruption Perceptions Index (an indicator of the level of abuse of power by the state), the syphilis infection rate among pregnant women (arguing that higher

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\(^8\) The WHO has developed a [Syphilis Estimation Tool] to help organizations and governments predict case rates of syphilis in LMICs, and estimate the impact of interventions. While we have not used it in our geographic assessment or our cost-effectiveness analysis, other researchers may find it useful.

\(^9\) An improvement to this model could be made by adding extrapolated rates for syphilis screening – similar to what we’ve done in our cost-effectiveness analysis model (see section 7) – so that countries that have already been showing good improvements in the recent past are down-weighted.

\(^9\) Specifically, transformed the two indices and the syphilis rate into z-scores, took an average of the three values and added +0.5 if the country already has a policy on dual testing or –0.5 if it doesn’t.
concentration of cases implies greater tractability), and whether or not the country already has a policy on dual HIV/syphilis testing (The Fund for Peace, 2022; Transparency International, 2022; WHO Global Health Observatory, n.d.; WHO, 2022b).

- The Neglectedness score is a function of whether other international organizations are already working in this country on the rollout of dual RDTs, as detailed in the section above. We would ideally like this score to also incorporate the existing extent of use of dual RDTs. However, to our knowledge, this data is not currently being collated anywhere.11

Taking a weighted average of all of these factors, our geographic assessment suggests that the following countries could be promising for a new charity to work in: the Democratic Republic of the Congo, Ghana, Guinea, India, Niger, Angola, Mali, Indonesia, Tanzania, and Mozambique.

5 Quality of evidence

5.1 Evidence that a charity can make a change in this space

We have not found any studies testing the effect of introducing dual HIV/syphilis RDTs on health outcomes. However, there have been at least 4 RCTs which evaluated the impact of using point-of-care (POC) screening and treatment of syphilis, rather than using the standard laboratory tests. We summarize the findings of these studies below:

- Myer et al. (2003): A study in South Africa where the intervention group used rapid POC syphilis screening and testing and the control group continued with off-site laboratory testing and treatment at a follow-up visit. There was not a statistically significant effect between the intervention and control groups on syphilis treatment rates or infant mortality rates. The authors attribute this null result to technical and logistical difficulties around the on-site testing and treatment (in the treatment arm), and relatively high quality of the status quo laboratory–testing services (in the control arm). Note that the tests used in this trial were an older methodology requiring separation of serum from blood cells; the newer RDTs that we recommend use whole blood, thus simplifying the screening procedure.

11 One of our interviewees even told us that countries themselves often do not know the extent to which their existing syphilis screening is based on lab tests, syphilis rapid tests, and dual tests.
- **Munkhuu et al. (2009):** A study in Mongolia where, again, the intervention group used rapid POC syphilis screening and testing, and the control group continued with off-site laboratory testing and treatment at a follow-up visit. The intervention increased syphilis testing rates by 20 percentage points, treatment rates by 10 percentage points, and reduced cases of congenital syphilis by 94 percent.

- **Betrán et al. (2018):** A study in Mozambique where clinics were randomized to receive kits containing rapid POC syphilis tests, a cupboard to store these supplies, a tracking sheet to monitor stocks, and a one-day training session. The trial found statistically significant impacts on the rate of syphilis testing which increased from 66% to 96%, and the rate of syphilis treatment which increased from 61% to 86%.

- **Althabe et al. (2019):** A study in the Democratic Republic of the Congo and Zambia which showed that a provision of screening and testing supplies, paired with a behavioral intervention – consisting of training, reminders, supervision and feedback – resulted in 99.9% health worker compliance with syphilis screening and treatment. The control group, which received the supplies only, had a syphilis-treatment rate of only 43%.

Jointly, these studies demonstrate that a well-designed intervention that tackles all the major barriers to syphilis POC screening and treatment can result in near-perfect coverage of maternal syphilis treatment.

In terms of specific organizations’ experience, Evidence Action is the most obvious example of a charity working in this space. However, as it only started working in Liberia in 2020, the effectiveness of its program is still yet to be seen.

There are case studies of countries that have been very successful in this space. For example, Cuba was the first country to be validated as having eliminated mother-to-child transmission of syphilis. This demonstrates that even a middle-income country can achieve this ambitious goal; however, we do note that Cuba has an unusually well-functioning healthcare system, and so its experience may be less of a blueprint if we want to work with countries with weaker healthcare systems.

We can also look to all the great work done in reducing mortality from HIV as an example of what could also be achieved with syphilis infection and mortality. Between 1996 and 2001, more than 3 million people were infected with HIV every year. Since then the number of new infections has reduced to below 2 million. The
number of HIV and AIDS-related deaths reached a peak in 2004 and 2005, when close to 2 million people died each year. Since then, the annual number of deaths from AIDS has also declined and, since 2016, fewer than 1 million people die annually from AIDS (Roser and Ritchie, 2019).

5.2 Evidence that the change has the expected health effects

According to a meta-analysis of 18 studies, dual syphilis/HIV RDTs show acceptable sensitivity and specificity for diagnosing syphilis infection, which are comparable to laboratory-based tests (Gliddon et al., 2017). Moreover, in their modeling study, Rodriguez et al. (2021) found that dual RDTs are more cost-effective than single rapid tests for HIV and syphilis, and prevented more adverse pregnancy outcomes.

As BPG is recognised by consensus as an effective treatment for syphilis, there have been no RCTs evaluating the efficacy of this drug in treating congenital syphilis, as it would be unethical to withhold BPG. Therefore, we rely on observational studies. A meta-analysis of 24 observational studies found that 80% of adverse events of congenital syphilis could be prevented with a single injection of BPG administered up to 28 days before delivery, and that treating pregnant women with BPG was associated with:

- A 97% reduction in the risk of giving birth to an infant infected with syphilis
- An 82% reduction in the risk of stillbirth
- A 64% reduction in the risk of preterm birth
- An 80% reduction in the risk of neonatal death

(Blencowe et al., 2011; GiveWell, 2021).

6 Expert views

6.1 Anna Konstantinova (Evidence Action)

Profile: Anna Konstantinova is the senior manager of Evidence Action’s maternal syphilis program. Evidence Action provides technical assistance to governments to support the scale up of syphilis testing and treatment in pregnancy with HIV/syphilis dual RDTs.

Main takeaways: There is definitely room for a new organization working in the space. Work on maternal syphilis is highly neglected, and so the more attention that comes to this issue and the more partners working in this space, the better. There
are many governments that want to adopt the dual test and need support. There is definitely a lot of work to be done, and currently not a lot of partners to do this work.

Evidence Action has not found the procurement or validation of dual RDTs to be a barrier in their work in Liberia. However, they have found the stickiness of certain brands a challenge where governments might be reluctant to shift from one brand of RDT to another, as they have already trained their workforce on how to use one. Therefore, even if a new brand comes on board, and is cheaper and has better performance, it may be difficult to convince governments to switch to procuring these tests instead; as they would need to retrain health workers and reprint all of their guidelines.

Anna was also not concerned about the availability of BPG. Although there were real challenges in the global availability of BPG a few years ago, where global shortages compounded country shortages, these global shortages have now mostly been addressed. Evidence Action has found that it would be rare for there to be stockouts of BPG, but that it would be more likely that the stock was misaligned. For example, BPG might be available in one place, but the testing is being done in another place (e.g., at ANCs).

6.2 Prof. Rosanna Peeling (London School of Hygiene and Tropical Medicine) and Dr. Debi Boeras (Global Health Impact Group)

Profiles:

Professor Rosanna Peeling is the Chair of Diagnostics Research at the London School of Hygiene and Tropical Medicine, and Director of the International Diagnostics Centre. She was previously the Head of Diagnostics Research at the UNICEF/UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases (WHO/TDR) and the Chief of the Canadian National Laboratory for Sexually Transmitted Diseases.

Dr. Debi Boeras is the founder and CEO of the Global Health Impact Group which supports the development and implementation of WHO guidelines. Debi also has 10 years’ experience of working on HIV programs in LMICs.

Both interviewees have worked on projects in SSA aimed at introducing dual HIV/syphilis testing, and have first-hand experience with the barriers to scaling such programs.
Main takeaways: Rosanna and Debi were excited about, and supportive of, a new charity working in this space. They thought that it was important for someone to be willing to “be the face of syphilis” as there is often no in-country “champion” to actually oversee the implementation of a program. They pointed out that a lack of local stakeholders overseeing the implementation of syphilis-screening programs is often the cause of program failure. They thought that a new organization could be well suited to performing this role.

6.3 Jacob Trefethen (Open Philanthropy)
Profile: Jacob is senior program officer who oversees Open Philanthropy's science and science policy programs.

Main takeaways: In a conversation, Jacob has reaffirmed to us his view (shared publicly here and here) that syphilis is a large-scale, overlooked problem and that much of its current burden of disease would be preventable if dual HIV/syphilis RDTs were scaled up.

6.4 Summary of views
All experts were enthusiastic about a new charity working on scaling up syphilis screening and treatment. These conversations were also useful to get a sense of what barriers others have previously faced in this space – such a lack of coordination between existing stakeholders, weak local program oversight, local stockouts of BPG, and general stigma associated with syphilis – and what barriers may be less of an issue than we previously thought – including procurement and validation of dual RDTs, and potential global stockouts of BPG.

7 Cost-effectiveness analysis
The cost-effectiveness of this intervention depends on (i) the exact charity activities and their associated costs (e.g., the cost of health worker training), (ii) the chosen country and the potential for impact there, based on its current prevalence of maternal syphilis as well as its current rates of syphilis and HIV screening, (iii) the projected counterfactual – how quickly we think the country’s government or another NGO actor would scale up syphilis testing and treatment in the absence of our intervention.
Our cost–effectiveness analysis (CEA) is modeled in Ghana as it scored high in our country prioritization, and is a mid–sized country whose CEA can be seen as (very) roughly representative of that of other high–scoring countries, such as Guinea, Angola or Tanzania.

Our CEA suggests that this intervention is very cost–effective, as it estimates that a charity focused on rolling out this program in Ghana would be able to avert one DALY for roughly $81 and to save a life for $1,726.12,13,14

For comparison, GiveWell’s CEA of Evidence Action’s syphilis–screening program in Liberia estimates a cost per life saved of $1,186 which is roughly in line with our estimate.

7.1 Effects

At a high level, our cost–effectiveness analysis modeled the effects of this intervention as follows:

- First, we calculated the maximum additional number of pregnant women we could treat if HIV testing was fully replaced by dual HIV/syphilis testing today.
  - This would take the syphilis testing rate from 56.5% to 95% in Ghana, i.e., a 38.5pp increase. Later in the model, we assume that this takes four years of linear improvements to go from the baseline to the maximum rate.
- Based on the results from the empirical (observational) studies outlined in our evidence review, we estimate the numbers of averted (i) stillbirths, (ii) neonatal deaths, (iii) cases of children who are born with symptoms of congenital syphilis (and survive), and (iv) cases of low–birthweight children.
- In the model, each of these is then multiplied by the estimated associated DALY burden. It is worth noting that these are very uncertain and somewhat subjective (for instance, the DALY weight of stillbirths) and have a relatively large impact on the final estimate.

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12 We note that these estimates are highly uncertain and strongly depend on the structure, assumptions, and specific inputs into the CEA. Nevertheless, we take these results as indicative of this program having a potential to be among the most cost–effective interventions currently available in global health.
13 Averting stillbirths is also counted as saving a life in this calculation. If we downweight the value of averting stillbirths using GiveWells moral weights – in a way we already do in the DALY calculation – then the cost per life saved increases to $3,565.
14 We also created two other versions of the model, with slightly different assumptions about the counterfactual trends and how discounting is done. Those have yielded $55/DALY and $62/DALY.
15 Symptoms of congenital disease include facial and skeletal abnormalities, hearing loss, and organ problems.
- We then apply several downward adjustments on these treatment effects, such as the overall expected probability of success of a new charity working in this space, and a 4% discount rate for all future benefits and costs.

Counterfactuals

We assume that, in the absence of our intervention, syphilis screening rates would continue increasing in Ghana at a constant rate of 4.5pp per year (based on a linear regression estimate from the past decade). This implies that in the absence of our intervention, the syphilis screening rate would reach 95% in nine years. Therefore, we assume that, after nine years, the counterfactual impact of the intervention is zero.

One thing that stands out in the CEA is that the counterfactual rate of improvement in Ghana is assumed to be quite large – 4.5pp per year. How representative is this trend of the other countries? Is it the case that most countries’ syphilis screening rates are improving at a similarly fast rate?

To get a sense of this, we plotted the trends for 33 SSA countries from the WHO database – all countries that had at least five years’ worth of data in the period 2008–2019 (WHO Global Health Observatory, n.d.b).
Figure 5: Syphilis screening rates in SSA (2008–2019). Source: WHO Global Health Observatory (n.d. b)

We can see that there is quite a lot of variation in the slopes of the trend lines – some going up, some are nearly flat, and some are going down.\textsuperscript{16} The table below provides a summary of the slopes of this set of trend lines. It indicates that the trend in Ghana isn’t fully representative of SSA countries, lying roughly halfway between the median and the 3rd quartile of the distribution. The typical (median) country in this dataset only improves its syphilis screening rate by 2.0pp per year, meaning it might take decades at the current trend for it to reach the WHO target of 95% coverage (depending on its starting point, of course).

<table>
<thead>
<tr>
<th>Minimum</th>
<th>1st quartile</th>
<th>Mean</th>
<th>Median</th>
<th>3rd quartile</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>−17.6pp</td>
<td>−1.1pp</td>
<td>1.5pp</td>
<td>2.0pp</td>
<td>5.0pp</td>
<td>12.0pp</td>
</tr>
</tbody>
</table>

\textsuperscript{16} Note that a lot of this data is noisy, so individual trend lines shouldn't be over-interpreted.
7.2 Costs

We included the following cost estimates in our CEA:

- Fixed charity costs which have been held constant across all CEs conducted this research round
- Variable costs, including (i) staff costs, (ii) cost of procuring RDTs and BPG, and (iii) the cost of training health workers to diagnose and treat syphilis.

8 Implementation

This section summarizes our concerns (or lack thereof) about different aspects of a new charity putting this idea into practice.

<table>
<thead>
<tr>
<th>Factor</th>
<th>How concerning is this</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talent (difficulty of finding founders and/or key hires)</td>
<td>Low</td>
</tr>
<tr>
<td>Access to information</td>
<td>Low</td>
</tr>
<tr>
<td>Access to relevant stakeholders</td>
<td>Low</td>
</tr>
<tr>
<td>Feedback loops</td>
<td>Low</td>
</tr>
<tr>
<td>Funding</td>
<td>Low-medium</td>
</tr>
<tr>
<td>Scalability</td>
<td>Medium</td>
</tr>
<tr>
<td>Neglectedness</td>
<td>Low-medium</td>
</tr>
<tr>
<td>Execution difficulty/Tractability</td>
<td>Low-medium</td>
</tr>
<tr>
<td>Negative externalities</td>
<td>Low</td>
</tr>
<tr>
<td>Positive externalities</td>
<td>Low</td>
</tr>
</tbody>
</table>

Table 2: Summary of possible implementation challenges.

8.1 Talent

Scaling up syphilis screening and treatment is not a prohibitively complex area, so it should not be difficult to find talent capable of working on this issue. Strong generalists should be able to relatively quickly get up to speed with the issue. This is not a highly technical intervention, and thus a healthcare background is a preferred but not disqualifying requirement.
8.2 Access

Information

Antenatal care is an area where a lot of data gets routinely captured. For instance, in Ghana, many ANCs keep booklets with a page for each pregnant mother, where they record all the tests and interventions that have been delivered to her.

From an international perspective, country-level data is available on most of the relevant parts of this issue from major databases, such as the WHO Global Health Observatory or UNICEF’s Data Warehouse. The end points that we care about in this context – stillbirths, neonatal mortality, congenital syphilis and birth weight – are all regularly captured. Although, as with any health data in LMIC contexts, there may be local issues with data quality that the charity should be aware of and watch out for.

One kind of data we have not been able to find yet, is current usage of dual RDTs by country. We suspect that the data on sales may be obtainable from the three certified manufacturers of dual RDTs; however, sales may not accurately reflect usage. The team of Professor Rosanna Peeling used to keep a dashboard on this but this is no longer up to date. The team at Evidence Action have told us that they were only able to obtain this data in countries where they’ve done scoping visits. As such, in-person visits may be needed in order to understand actual usage.

Stakeholders

Many countries are already on board with the idea of using RDTs, and have policies in favor of rolling them out. Past studies also indicate support for RDTs in clinics. Therefore, we expect largely positive reception from the relevant stakeholders, and relatively easy access to them.

In terms of local stakeholders, the charity will presumably need to work with national governments (possibly multiple departments) and local governments, to get buy-in and form collaborations. We assume that it will be clear early on whether a given country’s government is interested in collaborating, so work in countries that are not interested can be terminated relatively quickly and charity resources focused elsewhere.
Another important stakeholder may be bodies that are responsible for overseeing health workers’ education. In Ghana, patient-facing ANC staff are typically qualified nurses, who are required to take quarterly refresher courses to keep their certifications (based on a conversation with Sarah Hough, Maternal Health Initiative). Such courses could be a great touchpoint for educating health workers on how to use dual RDTs. We don’t have a reason to believe that accessing the relevant bodies would be especially difficult, but equally don’t have data or experience to confidently say that it would be easy.

8.3 Feedback loops
Usage of RDTs and of BPG is easily observable. Measuring the impact on disease prevalence will be harder, but given how effective BPG is, that too should also be relatively easy to measure.

8.4 Funding
Syphilis is generally underfunded; part of what the charity may do is to try to direct more funding to it. That being said, GiveWell is keen to fund work in this space (GiveWell, 2021).

There is funding available for dual RDTs from the HIV/AIDS space, from the Global Fund and PEPFAR.

8.5 Scale of the problem
While the problem of congenital syphilis is large worldwide, the burden is spread across many countries. We expect that the cost of implementing dual testing in a single country may be in the range of $1–10 million USD over several years. Even if the charity works in multiple countries in parallel, it is unlikely that it could scale to be able to absorb tens of millions of dollars per year (as some other charities considered in this research round do).

There is also a risk of doing work that is not fully counter-factual, either because the country’s government is able to do this work themselves or because organizations like Evidence Actions may do the work. However, in our conversation with Evidence Action, they told us that there are many governments who need assistance with this work, and they themselves are currently only planning to work in a few countries.
8.6 Neglectedness

Despite the scale of the problem and the simplicity of the solution, maternal and congenital syphilis have been a highly neglected topic, with global deaths due to syphilis being stable over the past decade.

Figure 6: Deaths from syphilis by age group. Source: Our World in Data

This stands in contrast to HIV treatment, which has received a lot of attention and funding over the past two decades — to the extent that under-five mortality, attributable to HIV, is now significantly lower than mortality due to syphilis.

Figure 7: Under-5 mortality and DALY burden of HIV and syphilis. Source: Institute of Health Metrics and Evaluation (2019b)
In a conversation with GiveWell, representatives from the Bill and Melinda Gates Foundation listed multiple reasons for this, including a lack of attention resulting from the disease being so rare in developed countries; stigmatization due to the fact that it is an STD whose highest rates are among marginalized groups, such as female sex workers and men who have sex with men; and a historical divergence of HIV and other STD programs as a result of HIV becoming a global health threat (GiveWell, 2018).

There are multiple reasons why a woman with syphilis may not be treated, including not attending ANCs, not being screened, and being screened but not treated – for instance, due to unavailability of BPG or due to the fact that BPG is not available at the ANC and the woman is required to make a separate hospital visit (which she may fail to do). Based on 2016 global estimates by Korenromp et al. (2019), failure to screen was the leading reason, being responsible for 57% of syphilis–associated adverse birth outcomes. This was followed by 21% of mothers not enrolled in antenatal care, and 16% of mothers who were screened but not treated.

Lastly, use of dual RDTs for syphilis detection has itself been neglected as a strategy. Despite the fact the WHO has now officially recommended that countries use dual RDTs, and has called the intervention an “easy win” in terms of feasibility of scale–up and “one of the most cost–effective antenatal interventions”, progress remains slow (WHO, n.d.). Many countries still rely on slow and costly laboratory lab tests, instead of point–of–care RDTs.

To our knowledge, Evidence Action is the only global organization that has a dedicated program for the scaling of dual HIV/syphilis RDT. They currently operate in Liberia, with plans to expand to Zambia and Cameroon and to run a pilot in Indonesia. While these are some of the highest–burden countries, there remain many others where rolling out dual RDTs would be highly impactful, as identified in our geographic assessment.

Although there aren’t any other organizations doing direct implementation work in this space, there are a few other relevant international stakeholders to be aware of:

- CHAI who focus on market shaping for BPG and the HIV/syphilis dual RDTs, in partnership with MedAccess.
- The Global Fund (Fight AIDS, Tuberculosis and Malaria) and PEPFAR work as procurers of the HIV/syphilis dual RDTs.
Global Health Impact Group are interested in how they could support work in this area, but don’t currently have specific programs or activities in this space. They are most interested in how they can help countries learn from each other on what it takes to adopt the dual test, and help provide more of a global platform.

- Jhpiego has also recently shown some interest in working on the dual tests and helping to scale the adoption of it.

8.7 Tractability
The implementation barriers, due to which RDTs haven’t been rolled out, all seem surmountable for a highly skilled and dedicated team.

A small concern here is that an RDT-rollout program may come into conflict with some other overlapping programs, such as HIV (community-based) self-testing (Broyles et al., 2021), or programs aiming for “triple elimination” of HIV, syphilis, and hepatitis B (Cohn et al., 2021). We recommend that the charity founders explore hepatitis B in more depth, including the tractability and cost-effectiveness of preventing its mother-to-child transmission, and what plans and policies international and national organizations have for its elimination. While a conflict with hepatitis B programs presents a potential challenge for a charity that is only focused on syphilis, it also potentially creates an opportunity for greater impact if the charity itself decides to focus on improving the screening and treatment rates of hepatitis.

The implementation barriers due to BPG potentially being in the wrong place also seem surmountable for a highly skilled and dedicated team. There is a small chance that as demand for BPG increases, there is a risk of stockouts that may be difficult for a small charity to mitigate. We advise to engage early with the pharmaceutical companies producing BPG, and to be on top of countries’ procurement cycles and the companies BPG production cycles, in order to mitigate the risk of BPG being under-produced (globally) or under-supplied (locally).

8.8 Externalities

Positive externalities
Syphilis has been a somewhat neglected disease in the past two decades. By focusing on delivering a syphilis screening and treatment intervention, the charity may be
able to help raise awareness of maternal and neonatal syphilis more broadly and help inspire action even in non-target countries.

Another positive externality, from the charity’s perspective, is that working in an LMIC on rolling out this intervention will help it understand the local health care situation and build relationships with relevant government stakeholders. This would put it in a great position to potentially roll out other interventions in the ANC space later (as is discussed in the Annex).

Negative externalities

Syphilis is treated with BPG, a form of penicillin. As such, there are several potential concerns:

- **Side effects of penicillin**: These can include nausea, vomiting, diarrhea, itching, and other reactions. None of these seem too concerning.

- **Penicillin allergy**: If BPG is given to a person with penicillin allergy, it triggers life-threatening anaphylaxis. In the UK, the proportion of people with a penicillin allergy is estimated at 0.18% (Bhattacharya, 2010). All medical staff should be trained in the treatment of anaphylaxis, and given that BPG to treat syphilis is given on-site, we assume that the rate of untreated adverse outcomes is low. If the woman has prior knowledge of being allergic to penicillin, a desensitization procedure is recommended, to allow BPG treatment without triggering an allergic reaction (Rac et al., 2017).

- **The Jarisch–Herxheimer reaction (JHR)**: The JHR is an inflammatory reaction triggered by the toxins released by the destroyed syphilis bacteria. It usually begins within three hours of administering BPG, and lasts for less than 24 hours. Its prevalence is high: around 25% of syphilis patients treated with BPG experience it (Yang et al., 2010). Most cases are mild, with symptoms like muscle aches, fever, chills, and headaches. However, pregnant women may also experience reduced fetal movement, and there may be some risk of preterm birth or stillbirth (Klein et al., 1990; Macumber et al., 2022). Unfortunately, there are no good studies of the prevalence of these complications, and observational studies are difficult to interpret since preterm birth and stillbirth are also associated with untreated syphilis. In our understanding, the prevalence of severe JHR is likely very low. While we expect it to reduce the cost-effectiveness of treating maternal syphilis, we
expect this reduction to be relatively small, and essentially already absorbed in the effect-size discount that we have already applied in our CEA.17

- **Antibiotic resistance**: There is no documented risk of BPG resistance in Treponema bacteria (the causative agent of syphilis; Nieuwenburg et al., 2020) or group A Streptococci (against which it is also used; Gartlan et al., 2022). We have not found information about other concerning types of resistance to BPG, so overall this doesn't seem concerning.

9 Conclusion

Overall, our view is that a new charity scaling up syphilis screening and treatment in pregnancy is an idea worth recommending to future charity founders.

While there are already ongoing efforts to implement this idea in many LMICs, they have often encountered implementational challenges and have failed to reach their goal due to last-mile problems. A new charity dedicated to providing technical support to those countries’ healthcare systems could achieve rapid and cost-effective impact, by tackling one of the major causes of perinatal mortality.

References


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17 Specifically, we discount the effect sizes of BPG on adverse syphilis outcomes by 20%, to account for the fact that the original estimate comes from case–control observational (of mothers with vs without syphilis) and that we expect mothers who never had syphilis have better pregnancy outcomes than those who get treated with BPG.


Clinton Health Access Initiative (2021). Five things you should know about the new partnership to increase access to dual HIV/syphilis testing. Available at: https://www.clintonhealthaccess.org/blog/five-things-you-should-know-about-the-new-partnership-to-increase-access-to-dual-hiv-syphilis-testing/ (Accessed 23 February 2023).


Macumber, et al. (2022). Retrospective Cohort Study of the Incidence and Outcomes of Jarisch–Herxheimer Reactions After Treatment of Infectious Syphilis in Late


WHO Global Health Observatory (n.d.). Women accessing antenatal care (ANC) services who were tested for syphilis (%). Available at: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/women-accessing-antenatal-care-(anc)-services-who-were-tested-for-syphilis-(%) (Accessed 23 February 2023).

WHO Global Health Observatory (n.d. b). Antenatal care attendees who were positive for syphilis (%). Available at: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/antenatal-care-attendees-who-were-positive-for-syphilis-(%) (Accessed 23 February 2023).