

A conversation with the Bill & Melinda Gates Foundation, May 11, 2018

Participants

- Dr. Jerker Liljestrand – Interim Deputy Director, Bill & Melinda Gates Foundation
- Lee Pyne-Mercier – Senior Program Officer, Bill & Melinda Gates Foundation
- Jillian Foote – Program Officer, Bill & Melinda Gates Foundation
- Stephan Guyenet – Research Consultant, GiveWell
- Josh Rosenberg – Senior Research Analyst, GiveWell

Note: These notes were compiled by GiveWell and give an overview of the major points made by Dr. Jerker Liljestrand, Mr. Lee Pyne-Mercier, and Ms. Jillian Foote.

Summary

GiveWell spoke with Dr. Liljestrand, Mr. Pyne-Mercier, and Ms. Foote of the Bill & Melinda Gates Foundation as part of its investigation into interventions to prevent congenital syphilis. Conversation topics included challenges to working on syphilis and potential opportunities for funders in this space.

Background information on congenital syphilis

Magnitude of the problem

Congenital syphilis is a significant contributor to newborn mortality and stillbirth, leading to ~350,000 adverse pregnancy outcomes per year, with stillbirths and neonatal deaths accounting for approximately half of these outcomes. The true numbers may be higher than this, since syphilis is often not recognized as the cause of stillbirths and early neonatal deaths.

Though syphilis has been treatable for ~60 years, the problem remains large in scale due to a lack of attention.¹

Global funding landscape

There is a large funding gap for work on congenital syphilis. Global efforts to control sexually transmitted infections (STIs) other than HIV are limited, so there is no large international funding stream for syphilis, and as a result most funding for antenatal care services comes from government budgets. However, governments often neglect to prioritize interventions for congenital syphilis or to purchase the necessary commodities.

¹ Lawn, J. E. *et al.* Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet (London, England)* 387, 587–603 (2016).

Wijesooriya NS *et al.* Global burden of maternal and congenital syphilis in 2008 and 2012: a health systems modelling study.

Challenges to working on syphilis

Structural challenges

There are several structural issues that make organizing around syphilis difficult, despite the large burden of disease.

Global lack of attention

Before syphilis was found to be treatable in 1947, it was acknowledged as a serious disease and received a high degree of attention in public health campaigns. This public health work significantly decreased the prevalence of syphilis in developed countries because syphilis interventions are simple, inexpensive, and effective, and can be easily managed by an organized health system.

Unfortunately, attention to syphilis as a public health issue has waned over time due to the near-disappearance of syphilis as a population-level threat in most wealthy countries. As a result, the problem remains unaddressed in many developing countries.

Stigmatization of syphilis

Syphilis is stigmatized both in individual countries and on a global level, and is neglected as a result. The stigma partly comes from the fact that those who contract syphilis in high-income countries are mostly members of marginalized groups, such as female sex workers and men who have sex with men (MSM).

Lack of community organization

During the global HIV crisis, communities of people who were disproportionately exposed to HIV organized around the disease. These communities arose because HIV was incurable and threatened lives in the developed world, but because syphilis is curable, people do not develop lifelong identities around it, so there are no comparable communities organizing for syphilis.

Global programs for sexually transmitted infections (STIs) and HIV

In the 1980s and 1990s, the World Health Organization (WHO) ran programs that included both STIs (e.g. syphilis, gonorrhea, chlamydia) and HIV. The programs diverged when HIV threatened to become a global epidemic, since syphilis and other STIs had largely been controlled in high-income countries by that point. During this time, HIV received an influx of funding that did not extend to other STIs.

Today, STI programs at global organizations remain small, and STI programs are correspondingly small, even in countries where STIs are still a significant public health issue.

Vaccination

Technical difficulties in developing a vaccine

For various reasons, it is difficult to create an effective vaccine for syphilis. This is true even in cases where there are no complications (e.g. antibiotic resistance), and even though the disease is fairly well-understood.

Timing of vaccination

Active syphilis can be transmitted from a mother to her baby at any time during the pregnancy, so delivering a syphilis vaccine during pregnancy would not prevent all adverse outcomes. Instead, the vaccine would need to be administered to the entire population of fertile women, and could be administered to fertile men as well. This is a fundamentally different type of operation than vaccinating pregnant women, and would be more logistically difficult than simply adding an extra vaccine to those already administered during pregnancy.

Shortage of treatment drugs

Since the 1950s, syphilis has been treated with benzathine penicillin G (BPG), which costs ~11 cents per dose in most low and middle income countries. Recently, BPG has stocked out in 39 countries, including Germany, the United States, Brazil, South Africa, and several countries in East Africa. This makes running syphilis programs in those countries essentially impossible, since there is no way to effectively treat the disease.

Causes

Stockouts are primarily a result of problems in the market that have arisen due to the fact that BPG has become so inexpensive. Namely, since everyone knows that the drug is very cheap, buyers are not willing to pay much for it. This makes profit margins extremely thin, so producers take extreme measures in order to maximize their profits.

One such extreme measure is running only one production cycle per year. This means that if countries or programs miss the production cycle, they must wait an entire year to obtain more BPG regardless of their need. It also means that there is no way to correct for shortages if either suppliers or buyers incorrectly forecast BPG demand.

Another reason for stockouts is that when countries are prioritizing their essential medicines budget, BPG is often last on the list. This is part of the general lack of prioritization of syphilis.

Work to mitigate the problem

The Gates Foundation is working with the Clinton Health Access Initiative (CHAI) to increase BPG availability by improving the functioning of the market. The program will increase transparency in the market, allowing producers to forecast demand more accurately and protecting countries from supply insecurity. For example, if a

country is buying from two providers that both buy their product from a single factory, the increased transparency will allow the country to be aware that its product base is not diversified.

Rapid diagnostic tests (RDTs)

One of the most significant developments in syphilis treatment in the last few decades has been the availability of single rapid test kits for syphilis, also known as point-of-care tests (POCTs). Results for these tests come back within twenty minutes, which eliminates the need for health workers to send samples of venous blood to a lab and wait several days for results.

In recent years, dual POCTs that test for both HIV and syphilis have been developed, and these are just beginning to become widely available. The Gates Foundation believes that sustainably transitioning countries to using these dual tests may dramatically increase syphilis screening rates.

Transitioning to dual POCTs

Advantages of POCTs over lab testing

Much of the antenatal care in low-income countries takes place either at health centers or via community outreach. If a health worker tests for syphilis by sending venous blood to a lab, they must wait several days for the test results, and there is a high risk that the patient will not return to the health center to receive the result. In addition, even if the patient does return, the treatment drug may not be available that day. Sending positive POCT results to a lab for confirmation results in the same problem.

The best way to ensure that patients with syphilis get treated appropriately is to act on POCT results immediately, without relying on additional confirmatory tests. This is especially important in high-syphilis environments.

Differences in interpreting lab tests vs POCTs

If a patient has had syphilis in the past, it leaves a serological scar which remains even after the syphilis is no longer active or contagious. Different tests vary in how they interpret these scars.

Because interpretation of the test results differs, training is a required part of the transition from lab tests to POCTs. Health workers need to understand that when a POCT returns positive, they should initiate treatment.

Technical implementation details

Partnership

Transitioning countries to dual RDTs would require a proactive partnership between a group willing to procure the test kits and a group equipped to figure out the technical details of implementation. It is important to develop and adapt guidelines to ensure that the test kits were used effectively.

Inputs for the intervention

In addition to the test kits themselves, the following would also be necessary:

- **Treatment drugs** – Availability of BPG is sometimes a problem.
- **Training** – The Gates Foundation sees an opportunity to collaborate with the HIV community to provide necessary training for the transition.
- **Technical work** – Some diagnostic and treatment algorithms need to be updated.

Syphilis as an antenatal care intervention

Renewed interest in antenatal care

Antenatal care has been largely neglected for ~15 years as attention has been focused on the birthing process, and as progress has been made and more women around the world are delivering in facilities, there has been a renewed focus on the importance of antenatal and post-natal care. This renewed global interest makes now a good time to work on syphilis.

The Gates Foundation's vulnerability framework

Antenatal care is a top priority in the Gates Foundation's recently refreshed maternal, newborn, and child health (MNCH) strategy, which is based on the 'growth and resilience framework.' Essentially, this framework means that the Gates Foundation is convinced on scientific grounds that improving the condition of the newborn child is the most important thing for the child's healthy development and survival through childhood. In particular, it is important to:

- Ensure that the pregnancy is healthy
- Ensure that the birth is well-attended
- Provide appropriate care and feeding in the first 28 days of the infant's life

Reframing syphilis as part of a package of interventions for antenatal care

Part of addressing syphilis is addressing the stigma that prevents more people from working on it. Global partners need to devise interventions that reframe syphilis as a general health issue, shifting focus away from the stigmatized question of how the disease is contracted. The Gates Foundation hopes that reframing syphilis testing as a standard part of antenatal care will help to reduce the stigma around syphilis.

Linking syphilis and HIV programs

Linking STI and HIV treatment together again could make syphilis less neglected. For example, while over 70% of women globally are screened for HIV during pregnancy and treated appropriately, only ~36% of women are screened for syphilis during pregnancy, so merging syphilis and HIV screening programs could

increase coverage rates for syphilis.² Dr. Liljestrand hopes that dual POCTs will serve a similar purpose.

Combining the programs would also be mutually beneficial because addressing STIs and HIV together decreases the risk of co-infection.

Challenges

Most countries with high rates of syphilis are heavily donor-dependent for their HIV testing commodities, and donors for HIV have become more limited. This makes the prospect of combining syphilis programs with HIV programs less appealing.

Potential opportunities for funders

Facilitating country-level work

There have been a number of studies showing that it is highly cost-effective for countries to invest in syphilis control at a national level. This suggests that a potentially effective approach for outside funders is to focus on programs that make countries more likely to invest in syphilis.

Global Validation of Elimination of Mother-to Child Transmission (EMTCT) of HIV and Syphilis

Global validation of EMTCT of HIV and syphilis is a certification procedure managed by the WHO. The program has been successful in increasing country-level investment in syphilis control, and the process is seeing increasing interest, with more and more countries applying and submitting data.

Data collected through this program show that while at a global level there is a lack of action, several countries are making significant progress on congenital syphilis, including China and India. As of mid-2018, ten countries – including Thailand, Belarus, Moldova, Cuba, and some Latin American countries – have eliminated congenital syphilis in their populations. However, the countries that are being certified as having eliminated congenital syphilis are not the countries that face the largest disease burdens.

Organizational opportunities

It would be valuable for someone to address the global lack of attention to syphilis. This work would involve ensuring that the community of people who care about syphilis comes together in technical discussions, does advocacy and convening, and sends people to advocate for syphilis at meetings about antenatal care or HIV.

² http://www.who.int/gho/hiv/epidemic_response/PMTCT/en/

Dadont W, Sarah Hawkes. Eliminating mother-to-child transmission of syphilis: the need for more consistent political commitment J Public Health Emerg 2016

Potential funding opportunities

WHO antenatal care guidelines

The Gates Foundation recently awarded a grant to WHO to help five countries achieve compliance with WHO's 2016 Guideline on Antenatal Care. A funder interested in syphilis control could support work in these five countries with a specific focus on the syphilis component.

UNICEF's Quality, Equity, Dignity (QED) initiative

There are ten countries that want to improve quality of care for MNCH through the UNICEF-funded QED initiative. A funder could focus on quality of care for syphilis in those countries, which would build momentum and allow other donors to come in and support syphilis without having to do so in isolation.

Human resources

In addition to direct interventions, it is also necessary to provide a small amount of strategically placed human resources. Currently, the only person in the world who works full-time on congenital syphilis prevention is Dr. Melanie Taylor, who works with WHO and the United States Centers for Disease Control and Prevention (CDC). Guaranteeing Dr. Taylor's funding would help legitimize discussion of syphilis as a public health issue, and would require only a relatively small investment.

The Gates Foundation's past work on syphilis

Investment Cases

Work that the Gates Foundation previously commissioned for syphilis resulted in three national-level investment cases in India, Nigeria, and Zambia and a global-level investment case. An investment case is "a description of the changes that a country wants to see with regard to RMNCAH and a prioritized set of investments required [to] achieve these results."

PATH grant

Several years ago, the Gates Foundation made a grant to PATH focused on dual testing for the elimination of congenital syphilis, which helped to support advocacy, tools, and data.

PATH and WHO worked together under the Gates Foundation grant. The research that came out of this collaboration contributed to the development of improved tools for estimating rates of congenital syphilis, as well as improved surveillance data. PATH also provided some resources to WHO to support Dr. Taylor and her work on syphilis.

PATH supported the development of dual RDTs by conducting both laboratory and field evaluations. It also did intense work in Zambia, Nigeria, and India. The work in India resulted in a national strategy for congenital syphilis, which led India to a significant turning point, and Zambia made some policy progress.

Other people to talk to about syphilis prevention and control

- **Dr. Elwyn Chomba** – Permanent Secretary, Zambian Ministry of Community Development, Mother and Child Health
- **Dr. Stefan Swartling Peterson** – Chief of Health, UNICEF
- **Dr. Pierre Buekens** – Dean, Tulane University School of Public Health and Tropical Medicine

All GiveWell conversations are available at <http://www.givewell.org/conversations>