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PERSPECTIVE



The introduction of syphilis point of care tests in resource limited settings

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ABSTRACT

Introduction: Syphilis remains an important and preventable cause of stillbirth and neonatal mortality. About 1 million women with active syphilis become pregnant each year. Without treatment, 25% of them will deliver a stillborn baby and 33% a low birth weight baby with an increased chance of dying in the first month of life. Adverse pregnancy outcomes due to syphilis can be prevented by screening pregnant women, and treating those who test positive with a single dose of penicillin before 28 weeks' gestation.

Areas covered: This manuscript covers the impact of syphilis on pregnancy outcome, the diagnosis of syphilis, with a special focus on point of care (POC) tests, and challenges to the introduction of POC tests, and their potential impact on the control and prevention of syphilis in resource limited settings.

Expert commentary: POC tests for syphilis are available which meet the ASSURED criteria, and could make syphilis screening accessible to all women anywhere in the world who attend an antenatal clinic. High quality dual POC tests for HIV and syphilis could ensure that well-funded programmes for the prevention of mother to child transmission of HIV can contribute towards increased coverage of antenatal syphilis screening, and prevent more than 300,000 adverse pregnancy outcomes due to syphilis annually. Alongside investment to increase availability of syphilis POC tests, operational research is needed to understand how best to improve screening of pregnant women and to translate test availability into improved pregnancy outcomes.

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Syphilis; point of care tests; stillbirths; prenatal screening

1. Introduction

Syphilis is caused by the bacterium *Treponema pallidum* and can be cured with a single dose of long-acting penicillin. It is transmitted between partners during sexual intercourse, and from infected pregnant women across the placenta to the developing fetus.

The clinical manifestations of syphilis are classically divided into three stages. The primary chancre is an ulcer, usually painless, and at the site of inoculation. It heals after a few weeks even in the absence of treatment. Some weeks later, the secondary stage occurs, usually with a generalized rash and symptoms involving many body systems. This also resolves, usually over weeks or months, in the absence of treatment, and is followed by the latent stage, in which the patient has no symptoms or clinical signs. Most women who transmit syphilis to their infant have latent syphilis and can only be identified by screening programs. The tertiary stage may occur many years later, affecting the skin, central nervous, or cardiovascular systems [1,2].

The World Health Organization (WHO) estimates that there are about 6 million new cases of syphilis per year. Amongst women of child-bearing age, the highest burden is in sub-Saharan Africa [3]. In 2012, about 1 million pregnant women globally were estimated to have active syphilis but, in sub-Saharan Africa, less than 50% of pregnant women attending antenatal clinic were screened for syphilis [4]. A study in Tanzania showed that, among women with syphilis who

were not treated, 25% delivered a stillborn baby, and 33% a low birth weight baby [5]. These adverse pregnancy outcomes can be prevented by a single dose of long-acting benzathine penicillin given before 28 weeks gestation [6].

Appropriate diagnostics and early treatment are crucial in preventing long-term complications of syphilis and mother-to-child transmission (MTCT). Screening pregnant women for syphilis is one of the most cost-effective health interventions. Terris-Prestholt et al. found that in Mwanza, Tanzania, where the prevalence of active syphilis in pregnant women was 6%, the cost per disability-adjusted life year (DALY) saved was \$10.56, if the impact on stillbirths averted is included [7]. Screening remains highly cost-effective at a prevalence of 2% among antenatal patients, at \$33 per DALY saved. Congenital syphilis and adverse pregnancy outcomes due to untreated syphilis represent a missed opportunity for disease prevention.

2. The diagnosis of syphilis

Appropriate diagnostic techniques are vital for the control of syphilis, which requires screening and case-finding, since most people with syphilis have no symptoms. Latent syphilis is diagnosed in individuals with reactive serological tests but no clinical features of early or late syphilis. There are two types of antibody test: treponemal and non-treponemal. Treponemal tests are specific and detect antibodies to

T. pallidum. They include the *T. pallidum* hemagglutination assay, *T. pallidum* particle agglutination assay (TPPA), fluorescent treponemal antibody absorption, treponemal enzyme immunoassay, and a number of point-of-care (POC) tests. Once positive, treponemal tests remain positive for life.

2.1. Laboratory-based tests

Non-treponemal tests include the venereal diseases research laboratory test, and the rapid plasma reagin (RPR) test, which has the advantage of not requiring a microscope. Non-treponemal tests are less specific than treponemal tests, and false-positive results are more common in pregnant women. Unlike the treponemal tests, non-treponemal tests usually revert to negative some months after successful treatment, and falling titers can be used to monitor the response to treatment. Neither treponemal nor non-treponemal tests can distinguish between syphilis and the non-venereal treponematoses (yaws, pinta, and endemic syphilis).

2.2. POC tests

Until recently, diagnostic tests for syphilis have been inaccessible in many resource limited settings, as the older tests require technical expertise, equipment, and electricity. POC tests are now available which do not require equipment, can be stored at room temperature, and can give a result in 15 min, enabling syphilis to be diagnosed at the POC, without the need for a laboratory. A diagnosis can be made at the first visit so that patients do not have to return for their results, and treatment can be given immediately: 'Same-day Testing and Treatment' (STAT). Almost every country has a policy for antenatal syphilis screening and, now that these tests are available, all pregnant women who attend antenatal clinic can be screened and treated.

A number of syphilis POC tests are available, many of which fulfill the ASSURED criteria [8] (Tables 1 and 2).

These are mostly treponemal tests, which remain positive for life, but POC tests have recently become available which identify both treponemal and non-treponemal antibodies. They are mostly immuno-chromatographic strip (ICS)-based assays, which can be used with whole blood, serum, or plasma. Antigen-antibody reactions appear as a colored line or spot on the membrane. The majority of the tests on the market fulfill the ASSURED criteria, though they vary in their sensitivity, and sensitivity is reduced when using whole blood rather than plasma or serum [11]. A systematic review by Tucker et al. identified 15

studies evaluating syphilis POC tests, representing 23,055 individual test results [12]. Thirteen of the studies were from low- or middle-income countries, and all were performed in an ANC or STI clinic setting. The median ICS syphilis test sensitivity was 86% (interquartile range 75–94%). The specificity of syphilis ICS tests ranged from 90.9% to 100.0% with a median of 99%.

Jafari et al. carried out a systematic review of POC tests for syphilis using serum and whole blood samples [13]. Only POC tests that met the ASSURED criteria were included, of which 18 were identified. The majority were ICS-based assays. The meta-analysis showed that the Determine rapid test, using a serum sample, had the best estimate for sensitivity (92.03%, 95% CI 87.22–95.77) and Syphichek had the best specificity (99.44%, 95% CI 98.96–99.81), compared to a laboratory-based treponemal test. In all comparisons, the estimated sensitivity was higher using serum than using whole blood.

Combined treponemal and non-treponemal dual ICS POC tests have recently become available which enable health-care workers to distinguish between active syphilis and past, treated infection (Table 2). The Dual Path Platform test was the first of these and has been shown to have good sensitivity and specificity in a variety of settings, although the sensitivity is decreased at low RPR titers [9]. In theory, these tests could be used to monitor the response to treatment, since the non-treponemal test should revert to negative, but they have not yet been evaluated as a test of cure.

3. The impact of POC testing for syphilis

POC tests have been shown to increase the uptake of screening for syphilis in a variety of resource-limited settings. Treponemal POC tests have been rolled out, and their impact evaluated in rural antenatal care clinics in Tanzania, Uganda, and China; both rural and urban clinics in Peru and Zambia; and in remote indigenous communities in Brazil [14]. The introduction of POC tests increased the proportion of antenatal care attenders screened for syphilis to 90%, and the proportion of pregnant women with syphilis who were treated the same day exceeded 90% in all countries. Modeling from this study has shown that POC tests are more cost-effective in screening and treating syphilis than laboratory-based testing methods such as the RPR [15]. POC tests for syphilis were rolled out nationally in China in 2010, after these studies were completed. Between 2012 and 2014, the number of people reported to the National Centre for STD Control as having been tested for syphilis increased from 4.2 million to 29.6 million per year (Chen X, personal communication).

Strasser et al. conducted a field acceptability and feasibility study of including treponemal POC syphilis testing within PMTCT HIV programs in Uganda and Zambia [16]. Significant increases in syphilis testing and treatment using a POC test were demonstrated, especially in Uganda, where access to syphilis testing was previously limited, with only 4% of women who attended ANC being tested for syphilis in rural Jinja District. Post intervention, a huge increase was seen, 99.7% of women were tested ($p < 0.0001$), and 97.8% received STAT. There was no deterioration in HIV services with the

Table 1. The ASSURED criteria.

ASSURED
A ffordable by those at risk of infection
S ensitive (few false negatives)
S pecific (few false positives)
U ser-friendly (simple to perform and requiring minimal training)
R apid (to enable treatment at first visit) and R obust (does not require refrigerated storage)
E quipment free
D elivered to those who need it

Table 2. Point-of-care tests currently on the market with available sensitivities and specificities [8–10]^a.

Test	Sample type	Test type	Target	Sensitivity (%)	Specificity (%)
Alere Determine Syphilis TP	Whole blood/serum/plasma	Treponemal POC	Treponemal antibody	59.6–100	95.7–100
Omega VisiTest Syphilis	Whole blood/serum/plasma	Treponemal POC	Treponemal antibody	72.7–98.2	98.1–100
Qualpro Syphicheck-WB	Whole blood/serum/plasma	Treponemal POC	Treponemal antibody	64–97.6	98.4–99.7
SD Bioline Syphilis 3.0	Whole blood/serum/plasma	Treponemal POC	Treponemal antibody	85.7–100	95.5–99.4
Dual Path Platform (DDP®) Syphilis Test (Chemio Diagnostic Systems, Inc.)	Whole blood/serum/plasma	Dual Treponemal and Non-Treponemal Syphilis POC	Treponemal antibody Non-treponemal antibody	90.1–98.2 80.6–98.2	91.2–98.0 89.4
SD Bioline HIV/Syphilis Duo Rapid Test (Alere/Standard Diagnostics, Inc.)	Whole blood/serum/plasma	Combined Syphilis and HIV POC	HIV antibody Treponemal antibody	97.9–99.0 93.0–99.6	99.0–100 99.1–100
DPP® HIV-Syphilis Assay (Chembio Diagnostic Systems, Inc.)	Whole blood/serum/plasma	Combined syphilis and HIV POC	HIV antibody Treponemal antibody	98.9 95.3	97.9–99.6 97.0–99.6
Multiplo Rapid TP/HIV Antibody Test (MedMira, Inc.)	Whole blood/serum/plasma	Combined syphilis and HIV POC	HIV antibody Treponemal antibody	97.9 94.1	94.2–99.5 94.2–99.1

^aA number of other POC kits are commercially available, including kits not yet licensed by the FDA, for which there is not published sensitivity and specificity data within the public domain.

addition of the rapid syphilis test. Bronzan et al. had similar results in rural antenatal clinics in South Africa, where the on site POC test resulted in the 89% of pregnant women being correctly diagnosed and treated for syphilis, compared with 61% at standard practice clinics [17].

The WHO has acknowledged the value of POC testing for syphilis, and the opportunity it provides for universal screening of pregnant women. In 2007, it launched the Initiative for the Global Elimination of Mother to Child Transmission (MTCT) of both HIV and Syphilis [18]. Their goal is for 90% of pregnant women to be tested for HIV and syphilis, and for at least 90% of seropositive pregnant women to receive treatment. The major investment in HIV PMTCT programs in many low- and middle-income countries in recent years offers an important opportunity to increase the uptake of syphilis screening. The London School of Hygiene and Tropical Medicine provides a toolkit, available on line, on how two such programs can be integrated [19]. Considerable progress has been made since 2007, with five countries so far validated as having achieved the dual elimination targets [20]. The new, dual syphilis and HIV POC tests have the potential to accelerate this process [21].

POC tests have also been used to screen hard-to-reach populations. In Brazil, health-care workers in remote communities succeeded in screening 55% of the sexually active population (defined as ≥ 10 years of age) for syphilis, exceeding the 30–40% target originally set [14]. Modeling studies have estimated the impact of using rapid tests to screen female sex workers for syphilis and shown that screening with POC tests could dramatically reduce syphilis prevalence amongst this hard-to-reach group, but strategies to reduce reinfection from regular non-commercial partners are needed to maximize impact [22].

4. Challenges in the implementation of POC testing

4.1. Training and logistics

Introducing POC tests can be challenging in resource limited settings, where a small cadre of often overworked health-care workers needs to be trained and provided with incentives to undertake additional work. Ensuring a regular supply of POC tests can also be challenging. The roll out of POC testing for syphilis in antenatal clinics in Ghana made it possible to screen women in clinics where screening had not previously been

available but, paradoxically, coverage actually decreased in larger clinics that had previously had access to laboratory testing. This was attributed to frequent stockouts of POC tests in the region [23]. A second study in Ghana found that pregnant women seeking antenatal care in the private sector were not screened for syphilis, since the rollout of POC tests had only included public sector health facilities [24].

4.2. Quality assurance

As countries begin to implement POC testing, adequate external quality assurance (QA) programs must be developed in parallel. These are routinely implemented in most laboratories but have been largely neglected in the case of POC tests. Montoya et al. noted that the accuracy of the POC testing was greater when used by laboratory staff with higher levels of training and in a setting with better infrastructure and supervision than when carried out by staff at health facilities [25]. It is clearly important that health workers using the test are properly trained and well supervised, but it is also important to monitor their performance regularly and offer remedial training to those who do not meet the required standard.

Two approaches to external QA have been piloted in the case of syphilis POC tests: the use of a proficiency panel consisting of dried positive and negative serum samples that can be reconstituted in the clinic has been evaluated in the Amazonas region of Brazil [26]; and the collection of dry blood spots at the POC, which can be retested in the laboratory, has been piloted in rural Tanzania [27]. In Brazil, 268 health-care workers tested 5 samples each, 9.3% of all samples tested were diagnosed incorrectly, and 4.1% of health-care workers reported difficulties with the POC tests. This method enabled remedial action to be taken when an incorrect result was obtained. The Tanzanian study was based in six villages in northern Tanzania. The conclusion was that DBS samples can be recommended for use with TPPA and may be of value for external QA of POC syphilis tests.

5. Expert commentary

A number of POC tests for syphilis are available which fulfill the ASSURED criteria. While the sensitivity of some of these tests is slightly lower than that of laboratory-based tests, the cases that

are missed are those with low RPR titers, which are unlikely to lead to adverse pregnancy outcomes [5]. The fact that these tests can be performed anywhere makes them far more accessible than laboratory-based tests so that in theory, it should be possible to test all women attending antenatal clinics for syphilis and treat those who test positive, at their first visit. Unfortunately, although syphilis causes more stillbirths and neonatal deaths than HIV [28], it has not been considered a high priority by national governments or international funding agencies, which have concentrated their efforts on screening pregnant women for HIV. The availability of dual HIV/syphilis POC tests, some of which have been shown to fulfill the ASSURED criteria and are available through the WHO bulk procurement program, should make it possible to ensure that all women who are screened for HIV are also screened for syphilis. This would have the potential to save at least 300,000 adverse pregnancy outcomes per year. Alongside investment to increase availability of POC syphilis tests, operational research is needed to understand how best to improve screening of pregnant women and to translate test availability into improved pregnancy outcomes.

6. Five-year view

POC tests make it possible to screen all pregnant women who attend ANC for syphilis, and to treat them immediately. What is needed now is advocacy to convince governments, funding agencies, and health program managers that this is an important and worthwhile objective, and that syphilis screening should be a political and health-care priority. The proposal for the creation of a WHO Essential Diagnostics List may provide a platform to further raise the profile of syphilis POC test kits. Alongside advocacy, operational research is needed to identify the best strategies to increase access to ANC syphilis screening and to translate availability of POC tests into improved pregnancy outcomes. The tools are available; the next step is to understand how to effectively make them available to all.

A recent study in Peru has shown that the roll out of POC tests offers an opportunity to improve other aspects of health systems as well as increasing coverage of syphilis screening [29]. Widespread adoption and use of POC tests depend on engaging the authorities; dissipating tensions between providers and identifying champions; training according to the needs of health care workers; providing monitoring, supervision, support, and recognition; sharing results and discussing actions together; consulting and obtaining feedback from clients and from those tasked with performing POC tests; and integrating syphilis screening with other services such as with rapid HIV testing.

There are limited published data on nationwide scale-up of syphilis POC tests in low-income settings. In a small pilot study in Mozambique, increased access to POC tests did not result in an increase in the proportion of women receiving syphilis screening [30]. In studies conducted alongside the scale of syphilis POC tests in Zambia, health-care acceptability of testing was high, but potential barriers to implementation, including stockouts of both POC tests and penicillin, were identified [31]. A health system-based approach will be of value in supporting all elements of the scale-up of syphilis POC tests worldwide.

Given the limited data from low-income settings, it may be valuable to draw parallels with the roll out of POC tests for

other infectious diseases such as malaria. Whilst a number of accurate malaria POC test kits are available, this has not always translated into improved targeting of antimalarials in patients presenting with fever. Ethnographic studies have demonstrated that both health-care worker and patient beliefs, as well as structural factors, affect how test results are translated into clinical actions [32]. Appropriately tailored training programs are required to translate effective tests into improved outcomes [33]. Similar implementation research is urgently required to support the scale-up of POC syphilis tests.

POC tests can be used for self-testing outside of a clinical setting through community-based organizations, in pharmacies or at home. Home-based testing for HIV has been shown to reach wide sections of communities in a diverse range of contexts and settings, providing early access to treatment [34]. Decentralizing testing for curable STIs may increase access to testing and awareness of STIs, but linkage to clinical care will be essential for diagnostic confirmation, treatment, counseling, and follow-up [35]. As with facility-based testing, further implementation research is required to guide improved access to home-based syphilis testing.

Key issues

- WHO estimates that there are 6 million new cases of syphilis per year
- 25% of pregnant women with syphilis deliver a stillborn baby
- 33% of pregnant women with syphilis deliver a low birth weight baby
- Adverse pregnancy outcomes due to syphilis can be prevented with a single dose of penicillin delivered before 28 weeks' gestation
- Most countries in the world have a policy to screen all pregnant women for syphilis
- Less than 50% of pregnant women are screened for syphilis in sub-Saharan Africa
- Point of Care tests for syphilis are available which require only one drop of blood, give a result in 15 min, are sensitive, specific, require no equipment and cost less than \$1
- Studies in low and middle income countries have shown that these POC tests can greatly increase coverage of syphilis screening in pregnancy
- Challenges in rolling out POC tests more widely include a shortage of trained health care workers, difficulties in maintaining the supply chain, and difficulties in quality assurance at the point of care

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