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Estimating Syphilis Seroprevalence Among Patients in a Sexually Transmitted Infections Clinic in Lilongwe, Malawi

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Abstract

The syndromic management of genital ulcer disease (GUD) misses asymptomatic syphilis cases but is widely utilized in limited resource settings without diagnostic capabilities, to ensure treatment for the most common etiologies of GUD. We used rapid serology tests for syphilis screening at a Malawian sexually transmitted infections clinic. The estimated seroprevalence was 9% and was highest among patients with genital ulcers (26%) and newly diagnosed HIV infection (19%). Rapid syphilis screening has the potential to increase syphilis detection, but accurate patient histories regarding syphilis diagnosis and prior treatment are needed.

Keywords

Syphilis (Treponema pallidum); Africa; Screening; Diagnosis

Introduction:

Countries with limited resources, such as Malawi, rely heavily on the syndromic diagnosis of genital ulcer disease (GUD) to treat syphilis cases.[1, 2] Although this strategy ensures the treatment of all early symptomatic syphilis, it results in overtreatment. GUD has other common etiologies, including herpes and chancroid, and the proportion of syphilis-associated GUD cases in Malawi has decreased from 17% in 1992–1993 to 5% in 2004–2006.[3–5]

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Conversely, the syndromic approach can also lead to the underdiagnosis of syphilis. Syndromic management of syphilis relies entirely on symptomatic patients seeking treatment before their clinical manifestations resolve. However, syphilitic chancres can be transient, non-painful intravaginal and anal lesions may go undetected, and the stages after secondary syphilis are often asymptomatic. Consequently, when patients with syphilis wait for the early symptoms to resolve without seeking medical care, or self-treat with alternative therapies until the symptoms subside, the infection goes undetected and untreated. With a reported 1% of Malawian women testing seropositive for syphilis during antenatal care visits in 2018, underdiagnosis of syphilis as well as overtreatment, is probable.[6]

Traditional etiologic syphilis diagnosis includes a non-treponemal antibody test and a treponemal antibody assay as the screening and confirmatory tests, respectively.[7] These methods however, are not yet feasible in many settings that lack laboratory resources and integrated systems for patient follow-up.

In 2006, the WHO recommended the use of rapid syphilis tests for targeted syphilis screening in countries with limited access to other screening tests.[8] The most commonly available rapid tests are treponemal antibody tests, which have high sensitivities, high specificities, and provide results within 10–15 minutes at low cost (~$1-$3 per test).[7, 8] Rapid treponemal antibody tests cannot distinguish between active and previously treated infections, but they have been widely implemented in antenatal clinics across Malawi to prevent the irreparable outcomes of congenital syphilis.[9, 10] Similar syphilis screening programs may also be feasible in Malawian sexually transmitted infections (STI) clinics, though universal rapid testing in such venues where medical charts are non-existent, may lead to repeated overtreatment among patients with multiple visits.

The diagnostic gap left by syndromic management renders the high-risk patient population at STI clinics vulnerable to significant underdiagnosis of syphilis, while the utility of an expanded syphilis screening program to catch untreated cases remains unknown. To assess the syphilis burden in an STI clinic, we implemented a rapid syphilis test screening program in a high-risk, high-volume STI clinic in Lilongwe, Malawi. We used rapid syphilis tests to estimate the seroprevalence of syphilis and to assess the feasibility of additional diagnostic testing.

Methods:

Between August 7 - September 1, 2017, we conducted a cross-sectional study in the STI clinic at Bwaila District Hospital in Lilongwe, Malawi. Bwaila is the primary public hospital in Lilongwe District, with a catchment population of 1.4 million people. In addition to providing general STI care, the STI clinic serves as a referral center for complicated STI cases and has approximately 13,000 patient visits each year. Rapid syphilis testing was offered to all STI clinic patients during our study period, in conjunction with the standard HIV rapid test screening during the HIV Testing Services (HTS) portion of each patient's visit. This strategy, based on patient convenience and the optimization of clinic flow, required the exclusion of known HIV-infected patients from syphilis testing. Per routine

protocol, all clinic patients underwent a genital examination by a nurse, where GUD diagnosis was based on the presence of one or more genital ulcers.

Patients receiving HTS who agreed to the syphilis screening provided the standard fingerstick blood sample for both HIV rapid testing and rapid treponemal antibody testing. HIV testing was conducted according to Malawian standard of care with the Alere Determine™ HIV-1/2 test (Alere Medical Co., Ltd., Japan; sensitivity: 100.0%; specificity: 99.8%) and Uni-Gold™ HIV test (Trinity Biotech, Ireland; sensitivity: 100.0%; specificity: 99.5%).[11–13] Syphilis rapid testing was done with either the Alere Determine™ Syphilis TP test (Alere Ltd., United Kingdom; sensitivity: 100.0%; specificity: 100.0%) or SD Bioline 3.0 Syphilis test (Standard Diagnostics, South Korea; sensitivity: 99.3%; specificity: 99.5%), which were provided by the Malawi Ministry of Health.[14, 15] All positive treponemal tests were treated as a syphilis case regardless of GUD status. These definitions were adopted from the WHO guidelines for the use of syphilis rapid tests in settings without non-treponemal tests, as well as the WHO guidelines for pregnant women, which are the most globally standardized guidelines for syphilis testing with single rapid tests.[8, 10] Due to the unreliability of self-reported clinical history and prior syphilis treatment information among the clinic population, anyone who tested positive was treated with three weekly doses of benzathine penicillin 2.4 MU by intramuscular injection per Malawi STI standard of care.[1] Patients who screened positive were encouraged to notify his or her sexual partners for subsequent testing and treatment, but no follow-up visits were scheduled per standard of care.

We estimated the prevalence of syphilis seropositivity across the patient population, stratified by gender, age, HIV status and GUD diagnosis. We calculated exact confidence intervals and used Fisher's exact test to assess differences in proportions (α=0.05). Finally, we also compared the diagnostic capabilities of the two management strategies by using the rapid syphilis tests as a reference to assess the sensitivity of GUD for detecting syphilis cases. Data collection for this study was approved by the Institutional Review Board (IRB) at the University of North Carolina [IRB# 08–1123] and the Malawian National Health Science Research Committee (NHSRC) [NHSRC#: 551]. Requirements for written informed consent were waived by both regulatory committees.

Results:

Syphilis seropositivity prevalence:

A total of 848 patients had a rapid syphilis test, HIV test, and genital exam over the 4-week study period (Table 1); 371 patients (44%) were male, 679 (80%) were between 20 and 39 years old, and 89 (10%) tested HIV positive. Ten percent of patients (82) were diagnosed with GUD.

In total, 73 (9%) patients (95% CI: 7%−11%) had a positive rapid syphilis test (10% among males, 8% among females) (Table 1). Among the 82 patients diagnosed with GUD, 26% (95% CI: 17%−36%) had a positive rapid test, compared to 7% (95% CI: 5%−9%) of patients without GUD ($p<0.0001$). Of the 89 patients who tested positive for HIV, 19% (95% CI: 12%−29%) had a positive syphilis test, compared to 7% (95% CI: 6%−9%) among those

who were HIV negative ($p<0.001$). Furthermore, among patients with a positive rapid syphilis test, 23% tested newly positive for HIV.

Concordance of GUD diagnosis and syphilis rapid tests:

While 9% (73/848) of the study population had a positive rapid syphilis test, only 2% had a positive test result and GUD, leaving more than 6% of the population syphilis seropositive with no observed genital ulcers. Specifically, among the 73 patients with a positive syphilis test, 71% (95% CI: 59%−81%) did not have GUD (HIV-uninfected: 70%; HIV-infected: 76%) (Table 2). Thus, if all positive rapid tests indicated an active case of syphilis, GUD would have had a sensitivity of 29% for detecting syphilis. Conversely, 74% (95% CI: 64% −83%) of participants with GUD tested syphilis seronegative, but were treated syndromically for primary syphilis as standard of care.

Discussion:

Among STI patients in Malawi, we found an overall syphilis seroprevalence of 9% using rapid treponemal antibody testing, and the prevalence was highest among patients with a new HIV diagnosis and those with GUD. The prevalence estimates did not account for the imperfect sensitivity and specificity of the rapid tests; however, our estimates far exceeded the 3% prevalence reported among a ‘low-risk’ cross-section of Malawian blood donors in 2015, the 1% prevalence reported nationally among Malawian antenatal care in 2018, and the 6% reported in the neighboring antenatal clinic at Bwaila District Hospital.[6, 16, 17]

Our findings demonstrate that the syndromic diagnosis of GUD is not sufficient to identify patients who may need syphilis treatment, and that the addition of rapid treponemal antibody tests in resource limited STI clinics would significantly increase detection. While we were unable to determine the number of active infections with traditional syphilis testing within our study population, a 2015 study from an Argentinian STI clinic estimated that 26% of patients who tested syphilis seropositive via rapid test had a negative non-treponemal serology test, due mainly to previous treatment or false positive results.[18] Assuming that 26% of those in our study with a positive rapid test had been previously treated and therefore had no active genital ulcers, syndromic diagnosis of GUD still only had an overall sensitivity of 39% for detecting active syphilis in our clinic population. Thus, by relying on syndromic diagnosis alone, less than half of the patients with syphilis would have been identified and received treatment.

Syndromic diagnosis, which was integrated into care before the introduction of rapid tests, is effective in treating symptomatic STIs and can reduce the chance of forward transmission.[4] However, due to the myriad of poor health outcomes from untreated syphilis including neurosyphilis and ocular syphilis, use of rapid syphilis tests to detect latent infections among high-risk populations in STI clinics would be prudent.

All patients with a positive serology were treated with three weekly doses of benzathine penicillin, per Malawian protocol. We could not implement non-treponemal tests in our clinic due to the inability to return test results on the same day and to track patients and their labs across a multi-day follow-up. While use of a rapid treponemal test alone is insufficient

for most syphilis screening algorithms, it is an acceptable practice recognized by the WHO in many resource-limited health care settings.[19] Additional medical histories to determine prior treatment for syphilis are crucial to avoid repeat treatment; however, limited electronic and paper medical records to track patient histories make it difficult to find documentation of prior therapies. Rapid antibody tests offer a better diagnostic alternative than forgoing screening entirely but concerns regarding overtreatment are valid and should be further evaluated.

Our results also highlight the well-known interaction between syphilis and HIV. Both Malawian and WHO guidelines recommend HIV screening among persons with STIs.[8, 11, 20] Our findings validate these recommendations, since nearly one quarter of patients newly diagnosed with HIV tested seropositive for syphilis. We integrated syphilis testing with HIV testing as it was the most efficient point in the care trajectory, and feasible for both patients and staff. However, all persons with a known HIV-infection, who may have been at increased risk for syphilis co-infection, were excluded from testing (approximately 15% of patients).

Rapid tests have become increasingly important diagnostic tools, and are widely available, cost-effective, and have acceptable sensitivity and specificity. Chembio Diagnostic Systems (Medford NY, USA) recently developed the DPP Syphilis Screen and Confirm rapid test that includes both treponemal and NTT for syphilis diagnosis.[21] In addition, other rapid tests have been developed that offer combined treponemal antibody and HIV antibody testing.[22, 23] Although these types of rapid tests are not yet available in Malawi due to cost, the integration of both types of rapid test into one, promises more accurate syphilis (and HIV) diagnosis in resource-limited settings.

Rapid treponemal antibody tests offer an inexpensive way to expand the diagnosis of syphilis in limited resource countries. Based on our results, we recommend implementing rapid treponemal antibody testing in STI clinics with high-risk populations in Malawi and integrating syphilis screening along with HIV testing, particularly among those that test newly HIV-positive. Accurate staging of syphilis is critical to providing appropriate treatment. Therefore, the collection of routine patient histories to determine timing of exposure, syphilis symptoms, and prior therapy is important to guide therapy for persons with positive rapid tests in the absence of an NTT. However, unless the clinical presentation is consistent with primary or secondary syphilis, clinics in resource-limited areas using rapid treponemal antibody tests alone will need to continue providing treatment for syphilis of unknown duration.

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Table 1.

Prevalence of syphilis seropositivity at Bwaila District Hospital STI Clinic, by category

Characteristic	N	Positive RT (n)	Prevalence % (95% CI)	P-Value
Total	**848**	**73**	**8.6 (6.8–10.7)**	
By Sex:				
Female	477	36	7.5 (5.3–10.3)	0.22
Male	371	37	10.0 (7.1–13.5)	
By Age Group:				
0–19 Years	59	2	3.4 (0.4–11.7)	0.13
20–29 Years	412	42	10.2 (7.4–13.5)	
30–39 Years	267	24	9.0 (5.8–13.1)	
40+ Years	110	5	4.5 (1.5–10.3)	
By HIV Status:				
HIV Negative	759	56	7.4 (5.6–9.5)	<0.001
HIV Positive	89	17	19.1 (11.5–28.8)	
By GUD Dx				
No GUD Dx	766	52	6.8 (5.1–8.8)	<0.0001
GUD Dx	82	21	25.6 (16.6–36.4)	

Abbreviations: RT= Rapid Test; GUD= Genital Ulcer Disease; Dx= Diagnosis

Table 2.

Syphilis seropositivity without symptomatic GUD at presentation

Characteristic	Positive RT (n)	Positive RT without GUD (n)	Untreated by Syndromic Dx* % (95 CI)
Total	**73**	**52**	**71.2 (59.4–81.2)**
By Sex:			
Female	36	25	69.4 (51.9–83.7)
Male	37	27	73.0 (55.9–86.2)
By HIV Status:			
HIV Negative	56	39	69.6 (55.9–81.2)
HIV Positive	17	13	76.5 (50.1–93.2)

Abbreviations: RT= Rapid Test; GUD= Genital Ulcer Disease; Dx= Diagnosis

*Hypothetically untreated for syphilis relying solely on syndromic diagnosis of GUD; all patients with a positive rapid test were treated with 3 weekly doses of 2.4 MU benzathine penicillin