PERCEPTION, EFFICACY, AND TREATMENT OUTCOMES OF POINT-OF-CARE SYPHILIS TESTING IN CANADA AND THE UNITED STATES: A LITERATURE REVIEW

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Abstract

Introduction: Syphilis is a preventable sexually transmitted infection that causes systemic manifestations in the absence of appropriate treatment. The rise in infectious syphilis cases across Canada over the past several years has brought forth accessibility concerns for traditional serological laboratory testing. Despite the recent approval of rapid syphilis testing for use in professional settings by Health Canada, point-of-care syphilis testing remains underutilized.

Objectives: This study investigates current literature on rapid point-of-care testing as an initial screening measure for infectious syphilis. The aim of this review is to explore the perception, field performance, and treatment outcomes of rapid syphilis testing in Canada and the United States to determine the utility of shifting toward point-of-care screening in Canada.

Methods: A literature search using Google Scholar and PubMed databases identified articles examining the field performance of rapid syphilis testing in Canada and the United States in the last 24 years (2000-2024). Five primary research articles satisfied the inclusion criteria and were included in this review.

Results: Five observational studies found rapid syphilis testing was generally well-accepted, highly specific with few false positives and negatives, and significantly reduced time to treatment compared to serological laboratory standards. Sensitivity and predictive value were variable; however, sensitivity improved with rising RPR titers.

Conclusion: This review suggests that point-of-care testing is adequate as an initial screening measure for infectious syphilis but should be supplemented by traditional serological laboratory testing. The inability of treponemal tests to discern infectious syphilis from a previously treated infection is a key limitation of currently available rapid tests. Given the ease of test administration and the low burden of overtreatment with benzathine penicillin G, future studies should investigate the utility of point-of-care syphilis screening in resource-limited communities in rural and northern Canada.

Introduction

Background

Syphilis is a preventable sexually transmitted infection (STI) caused by the bacterium *Treponema pallidum* (1). The infection can be transmitted sexually by direct contact with an active lesion on the genitals, breasts, oral cavity, or lips or vertically during pregnancy (2). In the former, *T. pallidum* is spread to the uninfected partner via microscopic skin abrasions, infiltrating their subcutaneous tissues (2). At the time of presentation, symptoms of syphilis vary depending on the stage of the infection. Early syphilis infection appears weeks to months following an initial infection and is divided into primary and secondary syphilis (2). Primary syphilis is characterized by the eruption of a lesion at the site of inoculation approximately three weeks after the initial infection, most commonly on the genitalia (2). Primary syphilis infection often goes undiagnosed because the chancre is typically painless and will self-resolve within three to six weeks without intervention (2).

Without appropriate detection and treatment of primary syphilis, some individuals will develop systemic manifestations known as secondary syphilis (2). Individuals with secondary syphilis may complain of constitutional symptoms, including fever, malaise, myalgias, anorexia, weight loss, or widespread adenopathy (2). Common dermatological manifestations include a diffuse, symmetrical, erythematous maculopapular rash spanning the trunk and extremities, characteristic lesions on the palms and soles, and alopecia (2). Gastrointestinal complaints, neurological symptoms, and visual or auditory disturbances may also occur (2). Those with secondary syphilis who fail to seek treatment typically have spontaneous resolution of symptoms (2). The term early latent syphilis is used for asymptomatic individuals who have acquired a syphilis infection within the last twelve months (2). Early latent syphilis infection can progress to

asymptomatic late latent syphilis or tertiary syphilis if the patient develops significant cardiac complications or gummatous disease from the infection (2). Of note, an individual is only at risk of infecting others if they have primary, secondary, or early latent syphilis (1).

Congenital syphilis

Antenatal transplacental transmission is the most common means of vertical transmission of infectious syphilis and can occur as early as nine weeks gestation (3). Once placental infection occurs, mobile spirochete bacteria pass from maternal blood into the amniotic fluid, entering fetal circulation (4). Although the infection can spread at any stage of maternal disease, the risk of transmission in pregnancy increases with gestational age (5). Marked fetal abnormalities are more common after 20 weeks' gestation, owing to the heightened immunologic response of the fetus in the latter half of pregnancy (5). The viability of the fetus is a major concern, as stillbirth is a well-documented consequence of syphilis in pregnancy (6). If syphilis is acquired near term, vertical transmission may also occur during delivery if the neonate contacts maternal secretions or an active genital lesion (5).

Without treatment, the probability of fetal transmission of primary or secondary syphilis exceeds 70% (7), with 90-100% infectivity seen in clinical practice (8). The risk of vertical transmission in latent syphilis is less but still significant at 40% and 10% for early latent and late latent syphilis, respectively (8). Antenatal syphilis exposure causes spontaneous abortion, stillbirth, or hydrops fetalis in 40% of affected pregnancies, with infection acquired during the first trimester posing the greatest risk (8). In 2020, 11% of stillbirths recorded in Winnipeg, Manitoba, were to mothers with confirmed maternal syphilis, underlining the significant association between antenatal syphilis and pregnancy non-viability (6). At birth, neonates with previous high-risk antenatal syphilis exposure are typically asymptomatic (8). When present,

manifestations of congenital syphilis include hematological abnormalities such as anemia and thrombocytopenia, rhinitis, rash, generalized lymphadenopathy, jaundice, hepatomegaly, skeletal abnormalities, and neurosyphilis (8,9).

Epidemiology

Despite the goal of near eradication announced by the Canadian government in 1998, the rates of infectious syphilis have been increasing steadily since the early 2000s, with unprecedented numbers reported after 2017 (1). From 2017 to 2021, the national rate of infectious syphilis increased by 166% and disproportionately affected Canadians aged 25-39 (1). During this period, the province of Manitoba saw the rate of infectious syphilis increase by an astonishing 422%, and as of 2021, 98.1 per 100,000 Manitobans were given a syphilis diagnosis (1). In 2022, 13,953 cases of infectious syphilis were reported across Canada, 27% of which self-identified as gay, bisexual, or a man that has sexual relations with another man (10). Moreover, provinces and territories with previously low rates of infectious syphilis saw unprecedented rises in 2022, with 53 new cases identified in the Yukon, leading to a 643% increase from 2021 (10). Data showing the number of infectious syphilis cases by Canadian province and territory in 2022 can be seen in Figure 1.

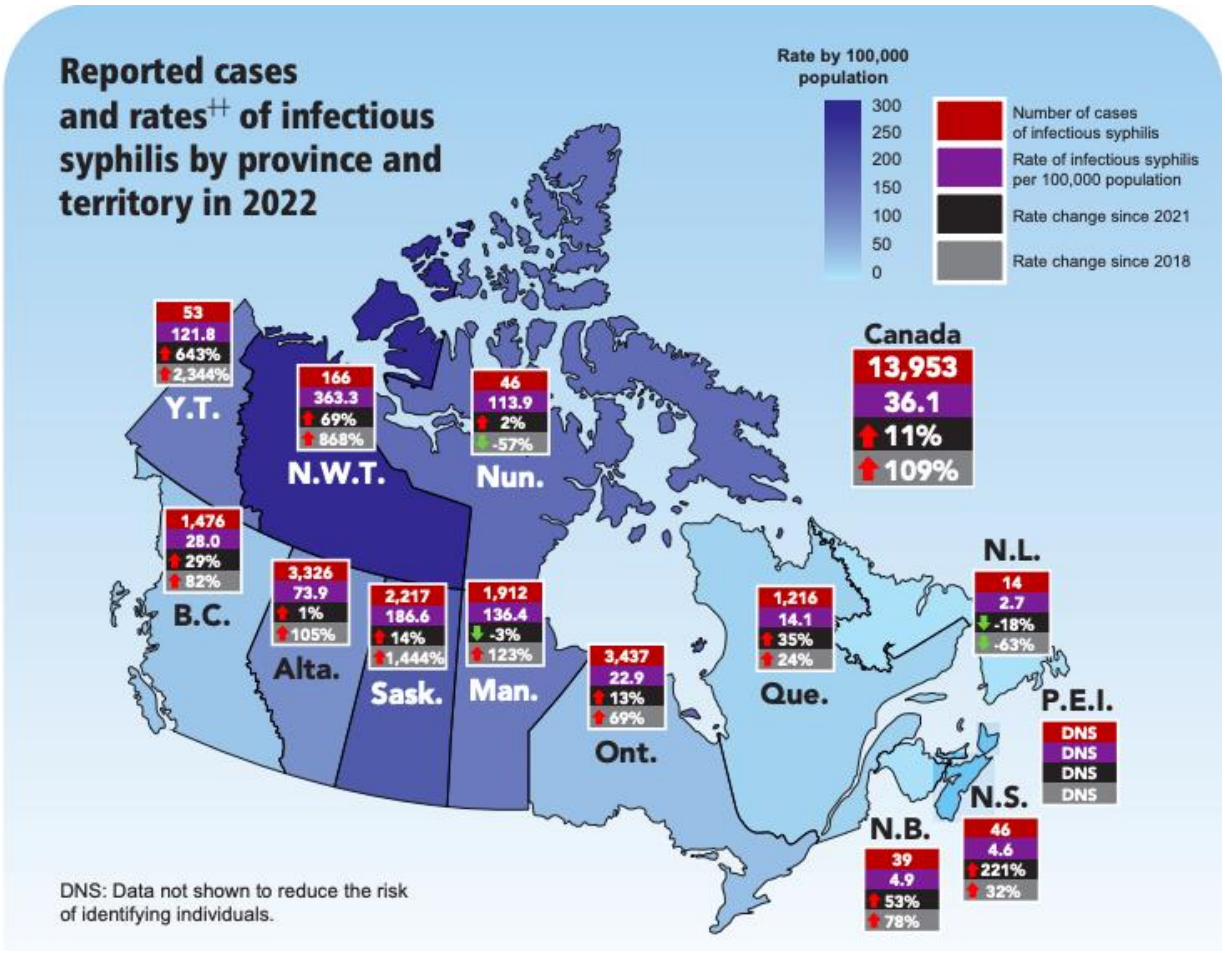


Figure 1. Reported infectious syphilis cases across Canada in 2022 (10).

In Canada, the increasing prevalence of infectious syphilis among heterosexual couples of childbearing age explains the sharp increase in congenital syphilis seen over the last several years (1). Between 2017 and 2021, recorded cases of early congenital syphilis increased by a staggering 1271% (1). In 2022, there were 246 reported cases of congenital syphilis across Canada, 117 of which were confirmed early congenital syphilis cases (10). Again, provinces with historically low prevalence saw significant increases, with Ontario reporting a 143% rise in congenital syphilis cases from 2021 to 2022 (10). Data showing the confirmed cases of early congenital syphilis across Canada in 2022 can be found in Figure 2.

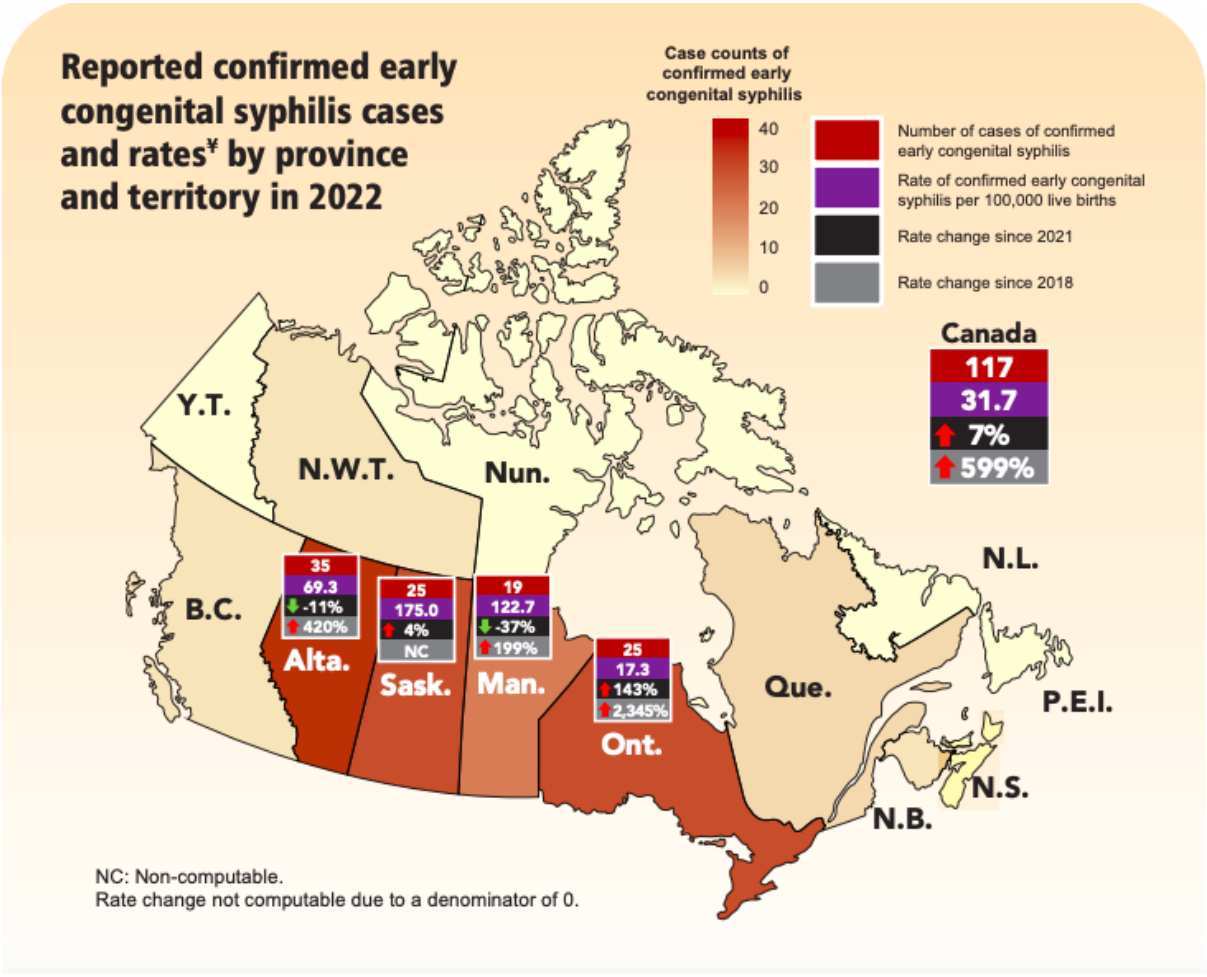


Figure 2. Reported cases of confirmed early congenital syphilis across Canada in 2022 (10).

Laboratory diagnosis and treatment of infectious syphilis

The spread of infectious syphilis is preventable with timely diagnosis, patient counseling, and initiation of appropriate antibiotic therapy with benzathine penicillin G (BPG). In Manitoba, routine syphilis testing is done at the Cadham Provincial Laboratory (CPL) using the reverse algorithm (11). The reverse algorithm consists of an initial assay for treponemal antibodies specific to syphilis, followed by confirmatory non-treponemal antibody testing, including Rapid Plasma Reagin (RPR) or Venereal Disease Research Laboratory (VDRL) testing (11). New

positive cases are also subject to a final *T. pallidum* particle agglutination (TTPA) test to confirm the diagnosis (11). Although treponemal tests are sensitive in early syphilis infection, once positive, they remain positive for life and are, therefore, unreliable in diagnosing reinfection or confirming treatment efficacy (12). Unlike treponemal tests, a positive result on a non-treponemal test will typically become negative following successful treatment (12). This makes non-treponemal tests useful in monitoring disease activity, as falling titers infer a positive response to treatment (12). Despite this, non-treponemal tests are less specific.

Both treponemal and non-treponemal tests are serological and require a blood sample to be delivered and processed in a laboratory setting. This necessitates a delay between the initial point of contact and the release of results. In resource-capable centers across Canada, it can take 8 days to receive serological test results for syphilis (13). Accordingly, it is reasonable to infer that turnaround time may increase when serological specimens are collected in rural communities and transported to larger centers. A delay in receiving test results may increase non-compliance to follow-up, especially when additional barriers are present, such as systematic discrimination and stigmatization in healthcare settings. For patients who live high-risk lifestyles or have multiple sexual partners, the risk of infecting others while waiting for test results may be significant. This solidifies the need for more rapid and accessible syphilis testing, particularly in remote communities across Canada. On March 27th, 2023, the first rapid point-of-care (POC) syphilis test was approved by Health Canada (14). The NSTI® Multiplex HIV-1/2 Syphilis Antibody Test is now available nationwide for professional use in field settings (14). However, despite recent approval in Canada, POC syphilis testing remains underutilized.

Study objectives

Given the novelty of rapid syphilis testing in Canada, there is insufficient literature discussing the use of POC testing as an initial screening measure for infectious syphilis in the non-laboratory setting. As such, this study aims to investigate the potential utility of offering rapid syphilis screening in Canadian communities. To achieve this, this literature review will investigate patient perception of POC syphilis testing, diagnostic field performance, and time to treatment following a reactive rapid test.

Given the exceptional increase in infectious syphilis nationwide over the last several years, this research is important to determine whether rapid testing can improve syphilis screening and expedite treatment, particularly in marginalized communities. If sufficient evidence exists supporting the use of POC testing, this will give Canadian healthcare providers the option to screen for infectious syphilis at the initial point of contact, which may be significant in resource-limited settings. Accordingly, the findings of this literature review have the potential to increase access to sexual healthcare for underserved Canadians.

Methods

Inclusion criteria

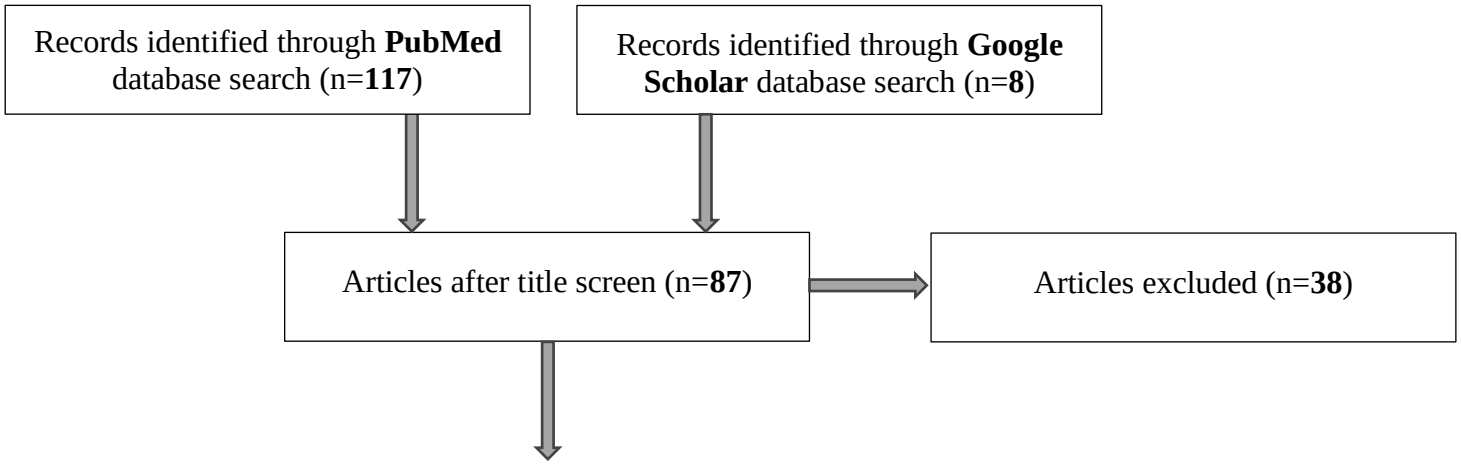
Several inclusion criteria were established to ensure suitability for this literature review. These included studies relevant to the research question published in English and conducted in developed countries within the last 24 years (2000-2024). To be deemed relevant to the research question, studies needed to discuss the uptake, efficacy, and treatment outcomes of rapid POC testing for infectious syphilis in Canada or the United States. Five articles were chosen for a full review as they fulfilled the above criteria.

Search strategy

A literature search was conducted using Google Scholar and PubMed from November 10th, 2023 to February 1st, 2024. The time frame for the search was adjusted to 2000-present using the key terms syphilis AND “point of care testing” OR POCT or RPOCT, and the mesh terms syphilis OR “syphilis, congenital” AND “point-of-care testing” on PubMed. Construction of the searches performed was as follows: ((syphilis) AND ("point of care testing" OR POCT OR RPOCT)) OR (("Syphilis"[Mesh] OR "Syphilis, Congenital"[Mesh]) AND "Point-of-Care Testing"[Mesh]).

Study selection

The employed search strategy generated 8 results in Google Scholar and 117 results in PubMed, for a total of 127 articles. These articles were screened by title for relevance to the research question. Only complete articles published in English with unrestricted access were included. This left 87 articles to be screened using title and abstract to ensure a focus on the uptake, efficacy, and treatment outcomes of rapid syphilis testing. Articles failing to meet two or more of the inclusion criteria were excluded. Additionally, studies not conducted in Canada or the United States were omitted. This yielded 8 articles, which were reviewed in full and narrowed to include 5 articles to be analyzed in this literature review. The study selection process is outlined in Figure 3.



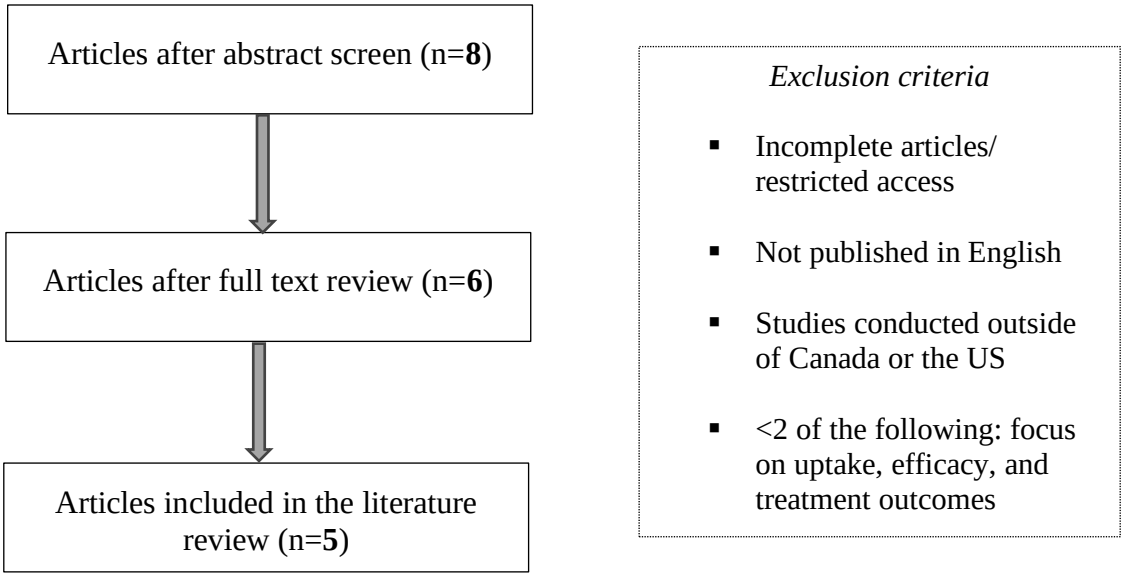


Figure 3. PRISMA flow diagram outlining the study selection process.

Results

The literature search revealed five articles that met the study objectives and discussed the field use of rapid syphilis testing in Canada and the United States. All studies were observational and compared the efficacy of POC syphilis testing to the current laboratory standard. Each study received ethics approval from their respective jurisdiction. The study sample sizes ranged from 274 to 1364 patients, with significantly more males included and a median age of 29.5 years old. Notable themes across studies included willingness to be screened for infectious syphilis with rapid tests, diagnostic field performance of POC tests compared to laboratory standards, and time to treatment following a positive rapid test. Table 1 (Appendix) summarizes the studies in this literature review and discusses study conditions, patient demographics, methods, objectives, results, treatment outcomes, conclusions, and limitations.

Acceptability of rapid point-of-care syphilis testing in Canada and the United States

In 2011, Bergman et al. (15) investigated the field performance of POC syphilis testing in non-clinical settings in Edmonton, AB, Canada. Of the 1265 participants offered concomitant syphilis and HIV POC testing, 81.5% consented (15). Only two participants declined rapid syphilis testing, and in five visits, POC testing kits were unavailable (13). Median age and gender did not predict who consented to rapid testing (15). Testing sites for men who have sex with men (MSM) had the highest rate of acceptance of POC testing, owing to the potential benefit of having rapid tests readily available in these settings (15). In contrast, testing was more likely to be declined by participants attending community-based organizations, such as inner-city drop-in centers (15).

In 2015, Fakile et al. (16) offered POC syphilis testing to 999 men seeking services in an urban emergency department (ED) in Detroit, MI, USA, who had no prior history of syphilis. 965 men met inclusion criteria and consented to rapid testing (16). The following year, Obafemi et al. (17) offered POC syphilis testing to men who self-identified as gay, bisexual, or MSM, with no prior history of syphilis at six non-clinical sites in the Denver Metropolitan Area of CO, USA (17). Of the 1081 eligible clients, 64% consented to POC testing, while the remaining clients declined rapid syphilis testing but accepted traditional screening with rapid plasma reagin (RPR) alone (17). Oluyomi et al. (17) found that POC testing was more likely to be declined by individuals with a self-reported history of anonymous sexual partners, chlamydia, and gonorrhea (17).

In 2016, Stafylis et al. (18) evaluated the performance of a dual rapid POC test for HIV and syphilis at four outpatient clinics of the AIDS Healthcare Foundation (AHF) in Los Angeles, CA, USA, and New York City, NY, USA. All 274 eligible participants consented to syphilis screening with rapid testing in exchange for a $25 gift card. More recently, between August 2020

and February 2022, Singh et al. (14) offered concurrent HIV and syphilis POC testing to individuals at five sites in Alberta, Canada. Participants were recruited with a $20 gift card, except those tested in a correctional facility (14). A previous diagnosis of syphilis did not exclude individuals from participating in the study (14). Of the 1526 eligible participants, all consented to rapid syphilis screening (14).

Field performance of rapid point-of-care syphilis testing

In 2011, Bergman et al. (15) investigated the field performance of the SD Bioline Syphilis 3.0 point-of-care test to screen at-risk populations in Edmonton, AB, Canada. The test performed well, with perfect specificity, 85.3% sensitivity, 100% positive predictive value (PPV), and 99.5% negative predictive value (NPV) (15). Of the 1,031 tests performed, only five provided a false negative result compared to standard laboratory testing (15). There were no false positives (15). Almost a decade later, Singh et al. (14) evaluated the efficacy of two rapid dual POC syphilis and HIV tests in the same Canadian province using a similar patient population (14). Both the INSTI Multiplex HIV-1/HIV-2/Syphilis point-of-care test and the MedMira Multiplo Rapid TP/HIV point-of-care test were highly specific and had sensitivities of 76.7% and 86.1%, respectively (14). Both tests had increased sensitivity in those individuals with an RPR of ≥1:8 dilutions (14). Only 4 of 1,364 participants tested falsely positive for syphilis, and there were no false negatives (14).

In 2015, Fakile et al. (16) assessed the utility of the Syphilis Health Check point-of-care test in an urban ED in the midwestern state of Michigan, USA. The rapid test was more specific than sensitive, with statistics of 99.0% and 76.9%, respectively (16). Men who self-reported MSM were over seven times more likely to have a reactive POC test compared to men with no history of MSM (16). In this study, the Syphilis Health Check had a PPV of only 50%, which is

explained by the low prevalence of infectious syphilis found in the sample population (16). 10 of 965 rapid tests produced a false positive result, whereas 3 tests gave a false negative result (16). Interestingly, two of the individuals with a reactive rapid test and a negative RPR were found to have a primary syphilis chancre on physical examination (16). Moreover, all individuals receiving a false negative result had an RPR titer of 1:1, whereas those testing positive on both rapid test and RPR had a median titer of 1:16 (16). The following year, Obafemi et al. (15) also evaluated the field performance of the Syphilis Health Check at six outreach sites in Denver, CO, USA. Unlike the Fakile et al (16) study, rapid syphilis tests were only performed on men who self-identified as gay, bisexual, or MSM, without a self-reported history of syphilis infection (17). Obafemi et al. (17) found higher test sensitivity at 90.0% but comparable specificity and PPV at 98.5% and 47.4%, respectively (17). Again, the low PPV reflects a low prevalence of infectious syphilis amongst study participants. Of the 690 participants who received rapid syphilis testing, there were 10 false positives and a single false negative (17). A third study by Stafylis et al. (18) was conducted in the same time frame and assessed the efficacy of Syphilis Health Check as well as the INSTI Multiplex HIV-1/HIV-2/ Syphilis. This study included men and women presenting to outpatient clinics of the AIDS Healthcare Foundation (AHF) on the west and east coast of the United States (18). They found the Syphilis Health Check to have a specificity of 97.0% and a sensitivity of 73.0%, and the INSTI Multiplex HIV-1/HIV-2/Syphilis to have a specificity of 98.5% and a sensitivity of 56.8%. Interestingly, neither brand of rapid test produced an inaccurate result, which is discordant with previous studies that found the Syphilis Health Check to have a relatively high false positive rate (16,17).

Linking clients to treatment following a reactive point-of-care syphilis test

Over a decade ago, Bergman et al. (15) accurately diagnosed four new cases of infectious syphilis using rapid POC testing. Two individuals received same-day treatment with intramuscular BPG (15). The other two individuals were incarcerated and had their treatment delayed by 5 and 19 days (15). Ten years later, in the same Canadian province, Singh et al. (14) used two rapid POC tests to identify 202 cases of infectious syphilis, 87.4% of which received same-day treatment. For the remaining 34 individuals, the median time to treatment was 4 days (14). Additionally, one individual with a false positive result and three participants with previously treated syphilis received treatment that was not required (14). Two individuals were lost to follow-up and did not receive appropriate treatment (14).

Between 2015 and 2016, Fakile et al. (16) used rapid POC testing to diagnose 11 new cases of infectious syphilis, providing same-day treatment to all patients. Six individuals with a reactive point-of-care test were advised to follow up with a clinical care provider for treatment, none of which attended their appointment (16). Obafemi et al. (17) used rapid syphilis testing to screen for infectious syphilis in clients seeking services at several outreach settings. POC testing accurately diagnosed 9 new syphilis cases, achieving a median treatment time of 1 day (17). Those individuals screened using traditional RPR had a median treatment time of 9 days, highlighting how laboratory testing delays timely access to the appropriate therapy (17). Stafylis et al. (18) assessed the field performance of two rapid POC syphilis tests at several AIDS Healthcare Foundation clinics. Unfortunately, the researchers failed to discuss the diagnostic capabilities of each test and chose to omit treatment outcomes, making their findings less robust for this review (18).

Discussion

This study aims to determine whether rapid syphilis testing is suitable as an initial screening measure for infectious syphilis in Canada. Factors influencing the suitability of rapid syphilis testing include patient perception and acceptability, diagnostic field performance, and time to treatment. The five studies included in this literature review suggest rapid syphilis testing is well-accepted by patients, adequately efficacious, and expedites time to treatment. Still, variable test sensitivities and the risk of falsely positive or negative results must be considered.

Perception of rapid vs. traditional laboratory testing for infectious syphilis

Most studies included in this literature review found POC syphilis testing to be well received by individuals seeking sexual healthcare and STI screening (14,16,18). An interesting discovery was that rapid syphilis screening was deemed acceptable by 80.1% of patients presenting to an urban ED for reasons unrelated to STIs (16). This finding suggests that patients appreciate having options when it comes to screening for sexually transmissible infections. Moreover, the ease of test administration likely makes POC testing a more attractive means for screening, particularly for individuals without imminent sexual health concerns. The ability to be screened for infectious syphilis at the first point of contact may also empower patients to be aware of their STI status, which may promote improved accountability. This further supports the potential public health benefit of offering rapid STI screening to patients seeking any means of healthcare. Obafemi et al. (17) investigated the suitability of rapid syphilis screening in vulnerable populations and found POC testing was less accepted by the male population self-identifying as gay, bisexual, or MSM. Notably, of the 2,963 clients presenting to outreach sites during this study, 434 individuals declined all syphilis screening (17). This suggests that the stigma of being tested for syphilis with or without a subsequent diagnosis continues to be a

barrier to receiving appropriate sexual healthcare regardless of test modality (17). Of the 1,081 individuals specifically offered POC syphilis screening in this study, 391 declined or were ineligible but accepted traditional screening with RPR (17). Although this number seems significant, the authors failed to distinguish between those clients who found rapid testing unacceptable and those who were ineligible, making this comparison less robust (17). Moreover, a more recent study conducted by Singh et al. (14) found that testing sites for MSM had the highest rates of acceptance for POC syphilis testing. This may be explained by the recent strides made across Canada to acknowledge and validate gender identity discordance and non-traditional sexual orientation. Moreover, given that stigmatization remains a key barrier to accessing sexual healthcare, if this population is willing to take the initial step and seek STI services, it is reasonable to infer that they would accept rapid syphilis screening, especially if confirmatory serological testing is also offered concurrently.

Variable sensitivities and the risk of inaccurate point-of-care test results

A consistent finding in the literature is the relatively high specificity but variable sensitivity of POC syphilis tests (14,15,18). Since highly specific tests give few false positive results, most individuals with a positive rapid test will have infectious syphilis, lowering the risk of overtreatment (19). In contrast, relatively poor POC test sensitivity remains a key concern. A test with lower sensitivity is more likely to produce a false negative and miss a syphilis infection when present (19). Despite test sensitivity as low as 56.8% in this review (18), the rate of false negatives study-wide did not exceed 0.5% (15). Although this seems promising, this finding may be due to the low prevalence of infectious syphilis in the study populations. Moreover, false negatives could be mitigated if confirmatory serological testing was offered alongside POC testing (14,17).

A consistent finding between studies was that the sensitivity of treponemal antibody detection by POC tests increased with increasing RPR titers (14,16,18). Remarkably, the rapid syphilis test used by Fakile et al. (16) correctly identified all cases of infectious syphilis in individuals with an RPR titer ≥1:2 dilutions that also had a positive TTPA. Similarly, both POC tests used by Singh et al. (14) were more sensitive in individuals with an RPR titer of ≥1:8 dilutions, with sensitivities increasing to >97.9%. These findings are significant as higher RPR titers have been associated with greater transmission risk and thus may require more imminent treatment (18). Obafemi et al. (17) found that those with a reactive result on a rapid POC test had a medium RPR titer of 1:32, with a 1:1 to 1:64 dilutions range. Although less impressive, the authors failed to provide a further breakdown of their results, making the relationship between sensitivity and increasing RPR titers less clear. Lastly, regardless of reported test performance, the role of clinical judgment when interpreting test results cannot be overlooked. Fakile et al. (16) revealed that two patients with a positive POC test but a negative RPR result had primary syphilis chancres on physical examination. This is consistent with the finding that treponemal tests can detect cases of early primary syphilis approximately three weeks before an individual becomes reactive with non-treponemal RPR assay (16,20).

Limitations of treponemal point-of-care syphilis tests

An overarching theme in the literature is the inability of treponemal tests to discern between current and previously treated syphilis infections. Given that all available POC syphilis tests across Canada and the United States are treponemal and detect antibodies to *T. pallidum* proteins (14,15-18), the efficiency of rapid syphilis testing has been questioned. To complicate this further, the overwhelming rise in infectious syphilis across Canada over the past several years (1,10) implies that instances of reinfection will become more common, making treponemal

testing futile on its own (15). If an individual is not a reliable historian, access to provincial health databases is imperative to confirm the diagnosis and clearance of a previous syphilis infection to avoid unnecessary retreatment (15,16). Although this is a foreseeable barrier in developing countries, timely access to patient records in Canada is generally attainable. In their study, Bergman et al. (13) avoided the unnecessary treatment of all individuals previously diagnosed and treated for syphilis by accessing the provincial database. Similarly, Fakile et al. (14) were able to identify 17 study participants with known syphilis infection via patient interviews, medical chart reviews, and state surveillance data. An obvious alternative to this is obtaining quantitative, nontreponemal testing to identify previously treated individuals (15). However, this may be less feasible in resource-limited settings.

Benefits of immediate treatment may outweigh overtreatment

The use of POC tests for the initial screening of infectious syphilis has been shown to significantly reduce the time between diagnosis and treatment in individuals with an active syphilis infection (14,15-17). Fakile et al. (16) provided same-day treatment to all 11 individuals with a reactive rapid test and history or clinical findings consistent with an active syphilis infection. Obafemi et al. (17) directly compared the median treatment time of those screened using rapid syphilis testing and those screened with the traditional syphilis algorithm used in the United States. The average treatment time for those testing positive on a POC test was 1 day, compared to 9 days for those waiting for a laboratory result (17). Moreover, two of the individuals found to have infectious syphilis in the study were subsequently diagnosed with neurosyphilis and received inpatient treatment with intravenous BPG within 24 hours of the positive POC test result (17). In Canada, Singh et al. (14) provided same-day treatment to 167 of 202 individuals found to have infectious syphilis via a positive POC test. Of the four infectious

syphilis cases identified via rapid testing by Bergman et al. (15), 2 individuals received same-day treatment, whereas the remaining 2 were treated several days later. The author's rationale for this is certainly controversial. Since these individuals were incarcerated, they argued that delaying treatment was acceptable to confirm the diagnosis with serological laboratory testing, as the risk of transmission was essentially removed (15). A recent report published by the government of Canada looked at the prevalence of sexually transmitted infectious diseases among incarcerated individuals in federal custody (21). Of the 837 individuals included in the survey, 8.3% of female inmates and 4.3% of male inmates were determined to have infectious syphilis (21). Moreover, given that the study findings were based on a survey completed by the inmates themselves, it is likely that cases were underreported (21). Accordingly, the prevalence of syphilis among incarcerated individuals and the risk of transmission between inmates should not be overlooked.

Finally, although confirmatory testing remains the gold standard for the diagnosis and treatment of STIs, the idea of empirically treating patients for infectious syphilis in the appropriate clinical context is not unreasonable. One can argue that given the safety profile of intramuscular BPG, the benefits of timely treatment outweigh the risks of overtreatment (22). This suggestion particularly applies to patients at an increased risk of being lost to follow-up. In the Fakile et al. (16) study, 6 individuals with a reactive rapid syphilis test were scheduled to follow up for treatment, yet all failed to attend their appointments. Given the high specificity of rapid syphilis tests, the probability that these individuals had a true syphilis infection is highly likely (16). Accordingly, providing treatment at the initial point of contact would have benefited the patient and may have also helped protect future sexual partners from acquiring a syphilis infection. In these instances, prevention appears to outweigh the risk of unnecessary treatment.

Limitations and future directions

This literature review was conducted to determine the suitability of POC testing as an initial screening measure for infectious syphilis in Canada. A limitation of this review is that only two studies assessed the field performance of rapid syphilis testing in Canada. Although a reasonable comparison can be made between Canada and the United States, Canada now largely uses the reverse algorithm for the laboratory diagnosis of syphilis rather than the traditional algorithm (11). Accordingly, the POC test results used in Canadian versus American studies were compared to differently ordered laboratory standards, which may have played a role in the reported performance of the rapid tests.

Another limitation of this review is that no studies assessed the performance of rapid syphilis tests in northern or remote communities. Although participants across studies were often marginalized or stigmatized by society, POC testing was offered in resource-rich settings, such as emergency departments and STI clinics. As such, these sites could simultaneously perform POC tests and phlebotomy for confirmatory testing. This makes the findings of this review less generalizable to resource-limited communities in Canada, which may benefit most from rapid syphilis testing. Factors that may limit the uptake of rapid testing in small community settings, including privacy and confidentiality concerns, must also be addressed. A study conducted in rural Appalachia found that a primary barrier deterring individuals from rapid HIV testing was fear of being recognized at a testing site (23). As syphilis faces similar stigmatization, this is a valid concern. Interestingly, a recent Canadian study investigated the acceptability of pharmacist-mediated POC HIV testing in rural communities and reported that participants found the process convenient and discreet, suggesting that privacy can be maintained in small

communities with limited infrastructure (24). Additional limitations of the included studies can be found in Table 1 (Appendix).

Ideally, POC syphilis testing would be able to discern active infectious syphilis from a previously treated infection. Although not discussed in this review, rapid tests with treponemal and nontreponemal components have been suggested to reduce the likelihood of over-treatment when a patient's infectious status is unknown. Albeit sparse, current research suggests dual treponemal and nontreponemal POC tests perform well in a controlled laboratory setting (25) and when used in sexual health clinics and outreach settings (26). Additional research in North America is required to determine whether these findings are generalizable to Canada and the United States.

Conclusions

Despite the limited body of research assessing the field performance of rapid syphilis testing in Canada and the United States, the findings of this review support the use of POC testing as an initial screening measure for infectious syphilis in Canada, given that concurrent phlebotomy is performed for confirmatory laboratory testing. Those individuals receiving a positive result can be linked to same-day treatment, removing the risk of being lost to follow-up. Non-clinicians' ability to facilitate testing poses a significant advantage (15,17,18), especially for rural and remote communities, since physicians and physician assistants (PAs) may not be stationed on site. Still, implementation will be challenging. The adoption of rapid syphilis testing will require systematic changes to current healthcare practices. One consideration is how rapid test results will be integrated into public health data. If de-centralized results are poorly represented, this may lead to underreporting of infectious syphilis across Canada. Accordingly, the support of public health leaders is imperative in bringing this testing modality to fruition.

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Appendix

Table 1. Summary of five articles examined in this literature review.

Study	Bergman et al[15]	Fakile et al[16]	Obafemi et al[17]	Stafylis et al[18]	Singh et al[14]
Location	Edmonton, AB, CAN	Detroit, MI, USA	Denver, CO, USA	Los Angeles, CA, USA and New York, NY, USA	Alberta, CAN
Time frame	2011-2012	2015-2016	2016-2018	2016-2017	2020-2022
Total sample size **Consented/ criteria met**	*n* = 1183 *n* = 1031	*n* = 999 *n* = 965	*n* = 2963 *n* = 690	*n* = 274 *n* = 274	*n* = 1526 *n* = 1364
Participant demographics	♀*n*=272 ♂*n*=759 Median age=30	♀*n*=910 ♂msm *n*=55 Median age=25	♂msm *n*=690 Median age=31	♀*n*=30 ♂*n*=244 Age= ≥18	♀*n*=604 ♂*n*=755 Other *n*=5 Median age=32
Testing site	Correctional facilities, inpatient addictions facilities, health centre, community-based organizations (e.g., inner city drop-in centers, organizations serving sex trade workers, gay bars, bathhouses)	Henry Ford Hospital ED	Six outreach sites in the Denver Metropolitan Area	Four outpatient clinics of the AIDS Healthcare Foundation (AHF) in LA and NYC	STI clinic, inner city ED, UC centre, correctional facility, First Nation's community
Test administrator	RN, outreach support workers	RN with additional training in POC tests	Public health outreach workers	Trainer counsellor	RN

Study objectives	1. Evaluate the feasibility and diagnostic performance of a POC syphilis test in outreach (non-clinical) settings 2. Document new syphilis cases identified in the study population	1. Evaluate the performance of POC syphilis tests in an ED setting 2. Assess implementation of rapid syphilis testing in the ED 3. Compare test results in self-reported MSM to non-MSM	1. Compare performance of POC test algorithm to the traditional RPR-based algorithm to diagnose previously untreated syphilis 2. Determine whether time to treatment is shortened for new cases of syphilis identified by POC testing	1. Evaluate the field performance of the INSTI Multiplex in a community clinical setting using laboratory-based reference tests 2. Compare performance of the INSTI Multiplex to Syphilis Health Check; the currently used standard of care rapid screening assay		1. Evaluate the performance and treatment outcomes of two dual syphilis/HIV point-of- care tests	
POC test	SD Bioline Syphilis 3.0	Syphilis Health Check	Syphilis Health Check	INSTI Multiplex HIV-1/HIV-2/ Syphilis	Syphilis Health Check	INSTI Multiplex HIV-1/HIV-2/ Syphilis	MedMira Multiplo Rapid TP/ HIV
Result time	5-20 min	10-15 min	10-15 min	1 min	10-15 min	<5 min	
Standard laboratory test	Treponemal-specific EIA → quantitative RPR titre → line immunoassay	Quantitative RPR titre → TPPA assay → Trep-Sure EIA	Quantitative RPR titre → TPPA assay → fluorescent treponemal antibody test	LA: TPPA → quantitative RPR titre NY: TPEIA → quantitative RPR titre		Treponemal-specific EIA → quantitative RPR titre → TPPA assay	
	Sen=85.3% (CI 68.9–95.0) Spec=100.0% (CI 99.6–100.0)	Sen=76.9% (CI 95%) Spec=99.0% (CI 95%) PPV=50% (CI 95%)	Sen=90% (CI 55.5-99.8%) Spec=98.5% (CI 97.2-99.3) PPV=47.4% (CI 99.2-100%)	Sen=56.8% (CI 44.7-68.2) Spec=98.5% (CI	Sen=73.0% (CI 61.4-82.6) Spec=97.0% (CI	Sen=76.7% (CI 72.7-80.2) Spec=99.8% (CI 99.2-99.9)	Sen=86.1% (CI 82.8-88.9) Spec=99.5% (CI 98.8-99.8)

Results	PPV=100.0% (CI 88.1–100.0) NPV=99.5% (CI 98.9–99.8) Positivity rate=2.8% FN=0.5% FP =nil	NPV=99.7% (CI 95%) Positivity rate=2.1% FN= 0.3% FP=1.0% Reactive POC msm=10.9% Reactive POC non-msm=1.5%	NPV= 98.5% (CI 24.5-71.1%) Positivity rate=2.8% FN=0.1% FP=1.5%	95.7-99.5) Positivity rate=15.3% FN=N/A FP=N/A	93.6-98.9%) Positivity rate=19.7% FN=N/A FP=N/A	PPV=99.5% (CI 98.1-99.1) NPV=88.4% (CI 86.3-90.3) Positivity rate=27.6% FN=0.4% FP=0.5%	PPV=99.1% (CI 97.6-99.5) NPV=92.8% (CI 90.9-94.3) Positivity rate=31.2% FN=0.4% FP=0.2%
Treatment outcomes	New syphilis diagnosis = 4 (13.8%) Previously treated infection = 25 (86.2%) Same day treatment = 2 (50.0%)	New syphilis diagnosis = 11 (1.1%) Previously treated infection = 3 (0.3%) ***Follow up required to confirm active infection = 6 (1.6%)*** Same day treatment = 11 (64.7%)	New syphilis diagnosis = 9 (1.3%) Previously treated infection = 0 (by design) POC: median time to treatment = 1 day (range 0-6 days) RPR: median time to treatment = 9 days (range 7-13 days)	N/A		New syphilis diagnosis = 191 (50.7%) Non-infectious syphilis diagnosis = 16 (2.2%) Previously treated infection = 168 (44.6%) Same day treatment = 167 (86.5%)	New syphilis diagnosis = 193 (24.0%) Non-infectious syphilis diagnosis = 20 (4.7%) Previously treated infection = 208 (48.9%)

Conclusions	1. At-risk populations seeking STI testing found POC syphilis tests to be acceptable 2. POC sypilis tests performed well in outreach settings 3. New cases of syphilis were identified and linked to treatment	1. POC syphilis tests detected a high proportion of participants with active syphilis in an urban ED 2. POC syphilis tests can be a useful to screen for syphilis infection where access to laboratory testing is not feasible or immediate result is necessary 3. POC syphilis tests can detect patients with early primary syphilis whose RPR is not yet positive	1. POC syphilis testing is a viable initial screening measure and may be useful in outreach settings where the ability to perform phlebotomy may be limited, or loss to follow up is a concern 2. When POC syphilis testing was negative, the diagnosis of syphilis was highly unlikely 3. POC syphilis testing significantly decreased time to treatment, and resulted in the prompt admission of patients with neurosyphilis to hospital for IV treatment	1. The specificity for treponemal antibodies was very high but sensitivity was significantly lower that that reported by the manufacturers 3. POC syphilis testing can be performed by non-medical professionals	1. This study confirmed the ability to offer single-visit testing and treatment for syphilis in diverse clinical settings 2. Majority of infectious syphilis cases were treated immediately following the positive POC syphilis test result, saving costs associated with additional clinic visits, reducing number of cases lost to follow-up, and preventing ongoing disease transmission
Limitations	1. Treponemal POC syphilis tests do not differentiate between new and old syphilis infections 2. Small sample size, high prevalence of previously treated syphilis, low prevalence of new cases of infectious syphilis	1. Few positives on POC syphilis tests lead to a precise estimate of specificity, but wide CI on the estimated sensitivity 2. Young population, males only, low prevalence of previous syphilis infection	1. This study excluded those with a previously documented or self-reported syphilis infection, therefore POC syphilis tests may have falsely identified those with prior history as new cases 2. Determination of sensitivity of the POC syphilis test compared to the RPR-based algorithm was limited by the low incidence of syphilis in the study	1. This study did not discuss time to treatment or treatment outcomes 2. Moderate sample size limits the precision of estimates 3. The INSTI Multiplex was not evaluated for cases of	1. There were a significant number of invalid test results early in the study secondary to test administrators' lack of experience, and ongoing issues with small blood clots on the Multiplo test membrane 2. This study was conducted in populations with a high syphilis prevalence, therefore findings may not be generalizable to lower prevalence settings

	3. Non-random sample from high-risk outreach settings, possible selection bias	3. No longitudinal data on POC syphilis test results over time in previously treated patients and whose RPR titer declines to non-reactive	population resulting in wide CI and low PPV 3. While time to treatment was significantly shorter in the POC syphilis test group, this comparison was between small numbers of patients	primary syphilis infection, therefore it is not possible to make estimates on its performance in those groups of patients	3. Unlike in this study, many jurisdictions do not have real-time access to prior syphilis history, therefore findings may not be generalizable to settings that need to base treatment decisions on patient-reported history

***All lost to follow up*

Legend: ED=emergency department, UC=urgent care, RN=registered nurse, POC=point-of-care, MSM=men that have sex with men, RPR=rapid plasma regain, EIA=enzyme immunoassay, TPPA=treponema pallidum particle agglutination, TPEIA=treponema pallidum enzyme immunoassay, Sen=sensitivity, Spec=specificity, CI=confidence interval, PPV=positive predictive value, NPV=negative predictive value, FP=false positive, FN=false negative, STI=sexually transmitted infection