CADTH Horizon Scan

Rapid Syphilis Testing
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Key Messages

• This Horizon Scan summarizes available information regarding rapid point-of-care testing for the detection of *Treponema pallidum*, the bacteria that causes syphilis.

• Rapid point-of-care testing to screen people for a possible case of syphilis allows health care providers to screen people where they are, rather than relying on people’s access to traditional health care settings. The rapid provision of test results can also help to guide treatment in the moment, rather than requiring additional appointments that could increase the number of people with active syphilis infections lost to follow-up.

• There are currently no point-of-care syphilis tests licensed for use by Health Canada; however, at least 1 multiplex syphilis and HIV-1/HIV-2 detection test could be licensed for use in Canada by the end of 2022.

• Based on the evidence reviewed, rapid tests for the detection of syphilis appear to be adequately sensitive and specific for screening. The use of point-of-care testing, at-home self-testing, at-home sample collection methods, and telemedicine and virtual care options may be interventions to consider as health care systems move forward and work to catch up on the screening backlog and missed tests related to the COVID-19 pandemic, and also find ways to connect with people who have previously been harder to reach.

Point-of-Care Tests Can Facilitate a Faster Syphilis Diagnosis Than Standard Lab Tests

Traditional lab tests used to diagnose syphilis can take weeks to provide a result. Point-of-care tests can provide the user with a result in less than 20 minutes, and may help to improve uptake because they can be administered in locations outside of traditional health care settings.

How It Works

Syphilis infection is confirmed by the detection of antibodies. The presence of treponemal antigens can indicate a current or past infection, so tests for treponemal antigens alone cannot confirm a current infection. A positive treponemal test is usually confirmed with a non-treponemal test.

Point-of-care tests for syphilis are visually interpreted, rapid vertical flow immunoassays that can be performed by health care providers using a fingerstick or IV blood sample. They can test for syphilis alone, or may include multiplex testing for both syphilis and HIV-1 and HIV-2 antibodies. Some rapid tests can return results in as little as 1 minute. Recently, in Canadian trials, rapid multiplex tests have been used to help curb the spread of outbreaks and provide immediate access to treatment. Currently available point-of-care tests for syphilis are only able to test for the presence of treponemal antigens and do not have the ability to detect non-treponemal antigens. Therefore, these tests are designed to be used to screen a person for a potential current syphilis infection, but additional non-treponemal testing is required to confirm the diagnosis. In harder to reach populations, the initial screening test may be
the only time a health care provider gets to see the person being tested and, in some cases, treatment may be initiated before the diagnosis is confirmed if there are concerns that a person might not return to receive the results of the confirmatory diagnostic test.

Who Might Benefit?

Syphilis is a curable sexually transmitted infection (STI) caused by the bacteria Treponema pallidum. Syphilis is the third most reported notifiable STI in Canada, following chlamydia and gonorrhea. In 2020, the rate of infectious syphilis in Canada was 24.7 per 100,000 population, up from 5.1 per 100,000 in 2011. Infection rates increased in almost all provinces, but the relative increase in the Prairie provinces was particularly large, increasing by more than 400%. Infection rates are consistently higher for those who are male, but the female infection rate in Canada increased by 773% between 2016 and 2020. Some have attributed the rise to changes in behaviour, such as increased substance use and the increasing use of dating apps, and the corresponding increased accessibility to multiple sexual partners.

Persistent syphilis infection can cause long-term issues like heart, brain, and nerve damage in adults. Syphilis can be passed from a pregnant parent to their unborn child and cause complications like stillbirth, premature delivery, and disability in infants. Early syphilis infection can be treated with antibiotics. Syphilis can also increase a person's risk of becoming infected with HIV. Syphilis has a long latent phase of infection before symptoms begin to show, which makes it difficult to screen for and inhibits efforts to prevent transmission and reduce infection rates. People who tend to be the most likely to become infected with syphilis are also more likely to face barriers to seeking preventive health care and attending regular health screenings. National and international efforts are under way to reduce the global incidence of syphilis by up to 90% by 2030.

People face many barriers to accessing STI screening, including syphilis testing. These barriers may include access to reliable transportation, access to a phone or the internet to make an appointment, access to a primary care provider or sexual health clinic, or other pre-existing health issues like substance use disorders. Traditional lab-based diagnostic testing for syphilis can take a week or longer to provide results to guide patient care. This delay can lead to further spread of syphilis by those with unknown infection and can also result in loss to follow-up for people who do not return to receive their test results or obtain treatment. Point-of-care tests allow providers to test people where they are, whether that is at a usual medical appointment, sexual health clinic, emergency department, or outreach site, and provide a preliminary test result and treatment plan immediately.

Availability in Canada

The tests used in recent Canadian clinical studies, the Medmira Multiplo TP/HIV and bioLytical INSTI multiplex tests (refer to Figure 1), have not received Health Canada regulatory approval. bioLytical anticipates the INSTI® Multiplex HIV-1/2 Syphilis Antibody Test will receive a class IV medical device licence from Health Canada before the end of 2022. The Medmira Multiplo TP/HIV test and the Medmira Multiplo complete syphilis (TP/nTP) antibody
test tests have received a CE mark in Europe, but are not FDA approved. The bioLytical INSTI multiplex test has received the CE mark for the HIV component (CE mark for syphilis by self-declaration), but is not currently FDA approved.

There is 1 standalone point-of-care syphilis test available in the US, the Syphilis Health Check assay, and 1 multiplex assay, the DPP HIV Syphilis System, authorized for use by the FDA; however, these are not available for use in Canada.

What Does It Cost?

The cost of the bioLytical INSTI Multiplex HIV-1/2 Syphilis Antibody Test is anticipated to be C$24.99. There is potential for these point-of-care tests to reduce costs within the Canadian health care system by removing the need for lab-based tests for screening purposes. Lab tests could be reserved for confirmation of a positive point-of-care screening test, thereby reducing the costs of lab materials and human resources required for syphilis testing.

In an economic analysis, dual screening for HIV and syphilis was shown to be more cost-effective than single rapid tests for each when examining the costs of prevention and care related to pregnancy.

Figure 1: bioLytical INSTI Multiplex HIV-1/2 Syphilis Antibody Test

Source: Reprinted with permission from Stephanie Ritchie, bioLytical Laboratories Inc.
Current Practice

In Canada, there are 2 blood test screening algorithms used to diagnose syphilis. Most provinces use the reverse algorithm, which uses a treponemal test to screen for infection by detecting treponemal antibodies in the blood sample; and a quantitative non-treponemal test, typically a rapid plasma reagin (RPR) test, to detect non-treponemal antibodies and confirm positive treponemal test results.\textsuperscript{10,11} Treponemal tests will typically show a positive result for life once a person has had syphilis, regardless of treatment, which can lead to false-positive test results and means a positive treponemal test result should be confirmed with a non-treponemal test to accurately diagnose an active, untreated case of syphilis.\textsuperscript{11} These tests require time to complete and a patient will be tested, diagnosed, and treated across a number of appointments.\textsuperscript{1}

Although there may be circumstances in which the benefit of treponemal tests alone for diagnosis (instead of screening) may outweigh the risk of overtreatment, WHO recommends that all positive point-of-care tests for syphilis be confirmed using a standard laboratory test.\textsuperscript{1}

What Is the Evidence?

As demonstrated in a variety of controlled lab evaluation studies\textsuperscript{12-14} field evaluations,\textsuperscript{15,16} and systematic reviews and meta-analyses,\textsuperscript{9,17,18} rapid tests for the detection of syphilis appear to be adequately sensitive and specific for screening. A summary of diagnostic accuracy for a variety of point-of-care syphilis and syphilis/HIV multiplex tests is provided in Table 1. The current commercially available tests are only able to detect treponemal antibodies and cannot distinguish between an active and a prior treated syphilis infection. Positive results therefore require confirmation with a non-treponemal lab test to diagnose a current case of syphilis.

Safety

No information was identified regarding safety issues related to the use of rapid, point-of-care syphilis testing.

Issues to Consider

People with a suspected case of syphilis through point-of-care testing will still require follow-up with a health care provider to receive their confirmatory diagnostic tests results and complete treatment. The implementation of point-of-care testing for syphilis can help to reduce the time to diagnosis and also reduce the number of patients lost to follow-up by allowing health care providers to initiate treatment based on the person’s screening test result rather than waiting weeks to receive the confirmation of diagnosis to begin treatment.
Table 1: Evaluation of Point-of-Care Diagnostic Test Accuracy for the Detection of Syphilis

<table>
<thead>
<tr>
<th>Test name</th>
<th>Study setting</th>
<th>Number of samples or participants</th>
<th>Overall sensitivity (95% CI)</th>
<th>Overall specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tsang et al. (2022)(^2) (lab study)</strong></td>
<td></td>
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</tr>
<tr>
<td>Reveal Rapid TP Antibody Test</td>
<td>Controlled lab and samples with known serological status</td>
<td>Sensitivity = 40 samples Specificity = 100 samples</td>
<td>95.0%</td>
<td>83.3%</td>
</tr>
<tr>
<td>DPP Syphilis Screen and Confirm Test</td>
<td>Controlled lab and samples with known serological status</td>
<td>Sensitivity = 40 samples Specificity = 100 samples</td>
<td>87.5%</td>
<td>98.3%</td>
</tr>
<tr>
<td><strong>Angel-Miller et al. (2021)(^1) (SR and MA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACON Syphilis Test</td>
<td>Field conditions (1 study)</td>
<td>1,439 participants</td>
<td>1.00 (0.74 to 1.00)</td>
<td>0.99 (0.98 to 0.99)</td>
</tr>
<tr>
<td>SD Bioline HIV/Syphilis DuoTest</td>
<td>Field conditions (1 study)</td>
<td>401 participants</td>
<td>0.92 (0.78 to 0.98)</td>
<td>0.93 (0.90 to 0.96)</td>
</tr>
<tr>
<td>Determine Test</td>
<td>Field conditions (1 study)</td>
<td>198 participants</td>
<td>0.97 (0.83 to 1.00)</td>
<td>1.00 (0.98 to 1.00)</td>
</tr>
<tr>
<td>ICS Test</td>
<td>Field conditions (1 study)</td>
<td>684 participants</td>
<td>0.94 (0.89 to 0.98)</td>
<td>0.93 (0.90 to 0.95)</td>
</tr>
<tr>
<td>Qualpro Syphicheck-WB</td>
<td>Field conditions (1 study)</td>
<td>1,617 participants</td>
<td>0.71 (0.62 to 0.79)</td>
<td>0.98 (0.97 to 0.98)</td>
</tr>
<tr>
<td>Syphilis Health Check</td>
<td>Field conditions (3 studies)</td>
<td>3,008 participants</td>
<td>0.87 (0.80 to 0.92)</td>
<td>0.75 (0.59 to 0.87) 0.77 (0.46 to 0.95)</td>
</tr>
<tr>
<td>SD Bioline Test</td>
<td>Field conditions (2 studies)</td>
<td>1,649 participants</td>
<td>0.67 (0.52 to 0.79)</td>
<td>0.92 (0.62 to 100.0)</td>
</tr>
<tr>
<td>Serodia</td>
<td>Field conditions (1 study)</td>
<td>198 participants</td>
<td>0.87 (0.70 to 0.96)</td>
<td>1.00 (0.98 to 1.00)</td>
</tr>
<tr>
<td>Visitect Syphilis Test</td>
<td>Field conditions (1 study)</td>
<td>506 participants</td>
<td>0.79 (0.63 to 0.90)</td>
<td>1.00 (0.99 to 1.00)</td>
</tr>
<tr>
<td><strong>Bristow et al. (2020)(^1) (SR and MA)</strong></td>
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<td></td>
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</tr>
<tr>
<td>Syphilis Health Check</td>
<td>Controlled lab studies (5 studies)</td>
<td>NR</td>
<td>98.5% (92.1 to 100)</td>
<td>95.9% (81.5 to 100)</td>
</tr>
<tr>
<td>Syphilis Health Check</td>
<td>Prospective studies (10 studies)</td>
<td>NR</td>
<td>87.7% (71.8 to 97.2)</td>
<td>96.7% (91.9 to 99.2)</td>
</tr>
<tr>
<td>Test name</td>
<td>Study setting</td>
<td>Number of samples or participants</td>
<td>Overall sensitivity (95% CI)</td>
<td>Overall specificity (95% CI)</td>
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<td>-----------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
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<tr>
<td><strong>Stafylis et al. (2019)^15 (field evaluation)</strong></td>
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</tr>
<tr>
<td>INSTI Multiplex HIV-1/ HIV-1/Syphilis Antibody Test</td>
<td>4 outpatient clinics of the AIDS Health Foundation</td>
<td>274 participants</td>
<td>56.8 (44.7 to 68.2)</td>
<td>98.5 (95.7 to 99.7)</td>
</tr>
<tr>
<td><strong>Van Den Heuvel et al. (2019)^13 (lab evaluation)</strong></td>
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<tr>
<td>SD Bioline HIV/Syphilis Duo</td>
<td>Controlled lab and WHO specimen reference panel</td>
<td>400 specimens</td>
<td>100 (98.2 to 100)</td>
<td>99.5 (97.2 to 100)</td>
</tr>
<tr>
<td>DPP HIV/Syphilis Assay</td>
<td>Controlled lab and WHO specimen reference panel</td>
<td>400 specimens</td>
<td>100 (98.2 to 100)</td>
<td>96.0 (92.3 to 98.3)</td>
</tr>
<tr>
<td>Mulipro Rapid TP/HIV Antibody Test</td>
<td>Controlled lab and WHO specimen reference panel</td>
<td>400 specimens</td>
<td>99.5 (97.2 to 100)</td>
<td>99.5 (97.2 to 100)</td>
</tr>
<tr>
<td>INSTI Multiplex HIV-1/ HIV-1/Syphilis Antibody Test</td>
<td>Controlled lab and WHO specimen reference panel</td>
<td>400 specimens</td>
<td>99.5 (97.2 to 100)</td>
<td>88.0 (89.1 to 96.5)</td>
</tr>
<tr>
<td><strong>Obafemi et al. (2019)^16 (field evaluation)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Syphilis Health Check</td>
<td>6 outreach sites</td>
<td>690 MSM with no prior history of syphilis</td>
<td>90.0 (55.5 to 99.5)</td>
<td>98.5 (97.3 to 99.3)</td>
</tr>
<tr>
<td><strong>Pereira et al. (2018)^14 (lab evaluation)</strong></td>
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<td></td>
</tr>
<tr>
<td>Syphilis Health Check</td>
<td>Controlled lab and samples with known serological status compared with treponemal tests alone</td>
<td>1,406 archived human serum samples</td>
<td>88.7 (86.2 to 90.0)</td>
<td>93.1 (90.0 to 94.9)</td>
</tr>
<tr>
<td>Syphilis Health Check</td>
<td>Controlled lab and samples with known serological status compared with lab test panel consensus</td>
<td>1,406 archived human serum samples</td>
<td>95.7 (93.6 to 97.2)</td>
<td>93.2 (91.0 to 95.1)</td>
</tr>
<tr>
<td><strong>Gliddon et al. (2017)^8 (SR and MA)</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD BIOLINE HIV/ Syphilis Duo Test</td>
<td>Manufacturer’s studies (syphilis component only)</td>
<td>NR</td>
<td>89% to 100%</td>
<td>91% to 100%</td>
</tr>
<tr>
<td>MedMira Multiplo Rapid TP/HIV Antibody Test</td>
<td>Manufacturer’s studies (syphilis component only)</td>
<td>NR</td>
<td>81% to 95%</td>
<td>93% to 100%</td>
</tr>
<tr>
<td>Chembio DPP HIV/ Syphilis Assay</td>
<td>Manufacturer’s studies (syphilis component only)</td>
<td>NR</td>
<td>46% to 97%</td>
<td>100%</td>
</tr>
</tbody>
</table>
User Perspectives

Qualitative evaluations of the use of rapid tests for the detection of syphilis, and particularly dual tests with HIV detection, found that users were generally positive about their experience with the tests. The short time to receive the results and the need for a single finger prick sample to run both tests were important characteristics that users liked. Rapid tests used in settings outside of traditional medical care settings, like mobile outreach programs, provided a discrete, easy to access, and effective way for people to be screened. Users in 1 study indicated that they would be more likely to be tested regularly if a mobile clinic continued to be offered.

Related Developments

Following the most recent Canadian trials of the combined syphilis and HIV-1/HIV-2 tests, further trials are ongoing in Saskatchewan. The trial will start at clinics and pharmacies in Regina, and will potentially expand to include Indigenous communities. bioLytical is working toward introducing a self-test version of the INSTI Multiplex HIV-1/2 Syphilis Antibody Test in the first quarter of 2023. The Stopping Syphilis Transmission in Arctic Communities Through Rapid Diagnostic Testing (STAR) study began in January 2020 and will continue through the end of 2022. Its aim is to evaluate the clinical and epidemiological impact of using the Chembio DPP Syphilis Screen and Confirm Test, a rapid test that can detect both treponemal and non-treponemal antibodies and provide a confirmed diagnosis at the point of care, in the context of ongoing transmission in Nunavut and Nunavik. The test is not currently available for use in Canada and was obtained for use in the study through Health Canada’s Special Access Program.

In the US, individuals can purchase kits for syphilis testing with at-home sample collection. The tests do not provide the user with rapid results, but facilitate the user to collect their own fingerprint blood sample that is then sent by mail to a lab for processing. The results are usually returned within 7 business days. Some, but not all, of these at-home test kits include follow-up advice from a medical professional upon receipt of the results. The use of these sorts of tests may increase access for some, but their use requires the ability to pay out of pocket for the point-of-care kits, and internet access to be able to order them. Despite the availability of these tests to the individual, none of these tests have FDA authorization for at-home use. These tests cost between US$29 and US$78.

Clinical trials are ongoing in China evaluating the use of a rapid saliva-based molecular detection test for syphilis. Researchers have identified high levels of \( T. pallidum \) DNA in

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<table>
<thead>
<tr>
<th>Test name</th>
<th>Study setting</th>
<th>Number of samples or participants</th>
<th>Overall sensitivity (95% CI)</th>
<th>Overall specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chembio DPP HIV/Syphilis Assay</td>
<td>Lab setting</td>
<td>NR</td>
<td>93% to 100%</td>
<td>NR</td>
</tr>
<tr>
<td>Chembio DPP HIV/Syphilis Assay</td>
<td>Field settings</td>
<td>NR</td>
<td>91% to 100%</td>
<td>NR</td>
</tr>
</tbody>
</table>

CI = confidence interval; DPP = dual path platform; ICS = immunochromatographic strip; MA = meta-analysis; MSM = men who have sex with men; NR = not reported; SR = systematic review; TP = treponemal.
saliva samples of people diagnosed with laboratory-confirmed syphilis. Saliva samples are collected in convenient and non-invasive ways and their use in testing could help to increase acceptability and ease of use.

Looking Ahead

The service restrictions related to the COVID-19 pandemic resulted in a decrease in routine screening procedures and uptake of voluntary STI testing and screening. This decreased uptake has highlighted the potential for increasing testing and screening outside of traditional clinical settings and using alternative testing and sample collection methods. The use of point-of-care testing, at-home self-testing, at-home sample collection methods, and telemedicine and virtual care options may be interventions to consider as health care systems move forward and work to catch up on the screening backlog and missed tests, and also find ways to connect with people who have previously been harder to reach.
References


