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What is the use of rapid syphilis tests in the United States?

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Brief summary:

Syphilis testing is complicated. Rapid syphilis tests may change screening practices in the United States, but first more studies are needed to demonstrate the advantages and disadvantages in the field.

Keywords

Syphilis; treponemal; nontreponemal; serology; screening

Diagnosing syphilis can be a challenge because most syphilis tests detect antibodies, not *T. pallidum* or related antigens. In the absence of direct detection methods for *T. pallidum*, syphilis is usually diagnosed as a “probable case” based on a combination of a treponemal test, a nontreponemal test, clinical history, physical exam, and records of past tests. In many clinics, patient samples are sent to an off-site lab for syphilis serologic tests which may result in delays in both treatment of the patient and initiation of partner services. Ideally, tests would allow reliable diagnosis during a single visit to reduce loss-to-follow-up and increase timeliness of treatment. Several rapid tests are under development or in use internationally and one has been recently cleared for use in the United States outside of laboratory settings. This new rapid test detects antibodies to *T. pallidum* and does not include a test for nontreponemal antibodies which is part of most algorithms designed to diagnose syphilis. Is rapid diagnosis and treatment possible in an outreach setting? In what circumstances can a rapid treponemal test improve access to treatment and other services? Here we consider what the tests can do, what the settings might be, and what experience has been to date.

Syphilis testing

Treponemal tests detect antibodies to *T. pallidum*; they become reactive a few weeks after infection, and usually remain reactive thereafter even with successful treatment.¹

Nontreponemal tests detect antibody to cardiolipin (which is released from damaged host cells and/or *T. pallidum* and correlates well with the body’s reaction to infection); they

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become reactive a few weeks after infection and often (but not always) become non-reactive within months to years after successful treatment.¹

Persons with lesions of primary syphilis (and persons recently exposed to syphilis) may have treponemal tests and nontreponemal tests that are still non-reactive, so treatment is recommended when history or exam suggests syphilis even when tests are non-reactive.²⁻⁴

Screening for syphilis begins with a treponemal or a nontreponemal test, and stops if the initial test is non-reactive.⁵ If an initial nontreponemal test is reactive, and a follow-up treponemal test is non-reactive, the nontreponemal test is considered to be a false-positive.¹ However, if the initial treponemal test is reactive and the nontreponemal test is non-reactive, there is the possibility of an old untreated infection because the nontreponemal test can become non-reactive late in infection.¹ Thus, treatment is recommended if the patient also tests reactive on a second treponemal test (such as a *Treponema pallidum* particle agglutination [TP-PA] test).⁶

If both tests (treponemal and nontreponemal) are reactive, then the patient has had syphilis at some time. If there is no history of treatment for syphilis, the patient should be treated. If the patient has a history of treatment for syphilis, diagnosis is based on a comparison of the current nontreponemal titer with past nontreponemal test titers. A four-fold increase in titer is indicative of a new infection.¹

Rapid tests

The ideal syphilis rapid test would be fast, cheap, easy to use, capable of being stored at room temperature, and would require little or no resources (equipment, light, water). In international settings, WHO, PAHO, and UNICEF goals of preventing maternal-to-child transmission of HIV and syphilis by 2020 have fostered the development and use of rapid tests in resource-poor settings where laboratory capability is limited. The tests are especially useful for screening pregnant women or when patient follow-up is difficult. In these settings, treatment may be based on the treponemal test alone, especially during pregnancy because the consequences of untreated syphilis are so high.⁷

There are many rapid tests under development or in-use outside of the United States as single treponemal tests, or as treponemal tests combined with HIV or HCV rapid tests.⁸ A number of rapid tests that are targeting a global market and seeking WHO prequalification approval including: Chembio DPP HIV-Syphilis (a dual treponemal and HIV test) (Chembio, Medford NY, USA); SD DUO (a treponemal and HIV test) made by Standard Diagnostics which is now Alere (SD Bioline, Gyeonggi-do, Korea); and Multiplo (a treponemal and HIV test) (Medmira, Halifax, Nova Scotia, Canada). Furthermore, Chembio is currently seeking FDA clearance for DPP Syphilis Screen and Confirm which has both treponemal and nontreponemal tests in one cartridge (SD Bioline, Gyeonggi-do, Korea).⁹

Only one test has been FDA cleared for use in the United States, the Syphilis Health Check, which was cleared in 2011 and CLIA-waved in December, 2014 (manufactured by VEDA LAB of Alencon, France, for Diagnostics Direct, LLC, Cape May Court House, NJ. Trinity Biotech USA, Inc., of Jamestown, NY is the exclusive US distributor). This is a qualitative

rapid membrane immune-chromatographic test which can detect antibodies to *T. pallidum* by whole blood (fingerstick), serum, or plasma in about 10 minutes.¹⁰ The manufacturer recommends checking personnel for color blindness before they begin using this test because it can be subjective when the bands are very light. As with other treponemal tests, a non-reactive test cannot rule out an infection acquired within the preceding few months. Because it is an antibody test, a reactive result requires additional testing using a nontreponemal test. The manufacturers insert reports there is a 98% agreement with other treponemal tests.”

Use in the United States:

Programmatically, the utility of a rapid treponemal test remains in question. Specifically, when and where might a rapid treponemal test be useful in the United States? A number of clinical settings are possible, including emergency departments or urgent care clinics, STD clinics, HIV clinics, family planning clinics, antenatal clinics, prison/jail, drug treatment facilities, health fairs, community outreach settings (special populations of interest), mobile vans, commercial sex venues, needle exchange sites, and other areas where there is a high risk of loss to follow-up. A major benefit of a rapid test would be if it facilitated quick treatment of the infected person.

So far, data regarding the use of rapid syphilis tests in the United States is very limited. One program in Pennsylvania is doing outreach screening of persons who are at high risk but have no history of syphilis, and treating persons with reactive rapid tests while waiting for results of confirmatory standard tests. They have tested 557 men who have sex with men (MSM), 27 had reactive results, and 14 of them had reactive confirmatory treponemal and nontreponemal tests and newly diagnosed syphilis. Six small STD clinics in Texas have used rapid treponemal tests as confirmatory tests for patients who have reactive stat nontreponemal tests and no previous history of syphilis. Other programs that use the rapid test are waiting for confirmatory test results before treating. One project is screening 18-to-34-year-old men attending the emergency room at Henry Ford Hospital in Detroit, Michigan. Outreach screening has begun in Texas and New York City where persons with reactive tests are referred to a clinic for care. New York City staff can access reactor files from the field to see if someone has had syphilis in the past. Programs in Texas and Pennsylvania are beginning to use the rapid test in the field as part of partner investigations. Partners who were last exposed more than 90 days prior to testing would be considered uninfected if the rapid test is negative. Treatment is recommended regardless of test results for partners with more recent exposure,⁴ but the nature of the interview would be different for partners who have reactive rapid tests results.

Challenges faced by programs implementing rapid syphilis tests will be similar to those challenges faced when using other syphilis tests. Because treponemal tests remain reactive after treatment, they are unable to distinguish past infections from re-infections. Due to this, some programs begin the screening process by asking persons if they have ever had syphilis and not using the rapid test for persons who have a history of syphilis. Others are testing everyone, because it is unclear how often persons correctly remember having syphilis. Some offer conventional testing (which requires a blood draw) to persons who have had syphilis in

the past. Currently, syphilis in the United States is largely concentrated among MSM. In 2014, 90.8% of persons with primary and secondary syphilis were men, and among the men with information on sex of sex partner, 82.9% were MSM.¹¹ It was estimated that 4% of HIV-infected MSM in Seattle acquired syphilis in 2011.¹² This high concentration of prior treated syphilis poses two problems for screening with a single treponemal test. First, most reactive treponemal tests in the population will be found among persons who have had syphilis in the past, so most persons with a reactive treponemal test will not have current infection. Second, many who are acquiring infection will be acquiring it for the second or third time, so only testing persons with no past history of syphilis will mean missing many of the new infections. Even rapid nontreponemal tests will face challenges because nontreponemal tests often remain reactive for years, and require quantitative titers for comparison to old titers.¹ For example, following the high rates of syphilis in the 1990s, testing in correctional facilities (between 2000–2007) found about 5% had reactive treponemal and nontreponemal tests, but 95% of those persons with reactive tests had previously diagnosed infections.¹³ Similarly, a study in high-risk areas of North Carolina found 45/239 (19%) had reactive treponemal tests of which 18 out of the 45 had reactive nontreponemal tests; however 15 of the 18 had been already adequately treated.¹⁴

This is an exciting time for diagnostics. As new tools are developed, opportunities to improve practice will be identified. Rapid syphilis tests are very helpful for screening pregnant women in resource-poor settings.¹⁵ In the United States, they have been helpful for quickly confirming reactive nontreponemal tests in some settings. Screening with the rapid treponemal tests in the United States offers theoretical advantages and disadvantages. It should be emphasized that: 1) rapid syphilis tests should not replace standardized reference assays in laboratories; and 2) every reactive treponemal rapid test should be followed by a nontreponemal test to identify probable syphilis. Many questions about the use of rapid tests in the United States remain unanswered. Independent data from programs that try rapid tests are needed to help determine the net benefit and guide use in the future.

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