At Siemens Healthineers, our purpose is to enable healthcare providers to increase value by empowering them on their journey toward expanding precision medicine, transforming care delivery, and improving patient experience, all made possible by digitalizing healthcare.

An estimated 5 million patients globally benefit every day from our innovative technologies and services in the areas of diagnostic and therapeutic imaging, laboratory diagnostics, and molecular medicine, as well as digital health and enterprise services.

We are a leading medical technology company with over 120 years of experience and 18,000 patents globally. Through the dedication of more than 50,000 colleagues in 75 countries, we will continue to innovate and shape the future of healthcare.

Product availability may vary from country to country and is subject to varying regulatory requirements. Please contact your local representative for availability.

References:

1. Singh AE, et al. Clin Microbiol Rev. 1999; 12:187-209.
2. Lafond RE, et al. Clin Microbiol Rev. 2006; 19:29-49.
3. CDC. Syphilis—CDC Fact Sheet. Atlanta, GA, U.S.: CDC; National Center for HIV AIDS, Viral Hepatitis, STD, and TB Prevention; Division of STD Prevention; [updated 2016 Jul 19]. Available from: http://www.cdc.gov/std/syphilis/STDFact-Syphilis-detailed.htm.
4. Janier M, et al. J Eur Acad Dermatol Venereol. 2014;28:1581-93.
5. Marangoni A, et al. Clin Vaccine Immunol. 2013;20:1084-8.
6. Miranda AP, et al. Braz J Infect Dis. 2008; 12:139-43.
7. Malm K, et al. J Eur Acad Dermatol Venereol. 2015;29:2369-76.
8. Ly TD, et al. Poster P618. ECCMID; 2010 Apr 10–13 Vienna, Austria.
9. Donkers A, et al. Clin Chim Acta. 2014;433:84-7.
10. Enders M, et al. Clin Vaccine Immunol. 2015; 22:17-26.
11. Park BG, et al. J Clin Microbiol. 2016;54:163-7.
12. Ratnam S. Can J Infect Dis Med Microbiol. 2005;16:45-51.
13. Larsen SA, et al. Clin Microbiol Rev. 1995; 8:1-21.
14. Se a AC, et al. Clin Infect Dis. 2010;51:700-8.
15. Soreng K. Clin Microbiol Newsl. 2014;36:157-64.
16. CDC. 2015 Sexually transmitted disease treatment guidelines: Syphilis. Atlanta, GA, U.S.: CDC; [updated 2016 July 27]. Available from: http://www.cdc.gov/std/tg2015/syphilis.htm
17. Workowski KA, et al. MMWR Recomm Rep. 2015;64:1-137.
18. Kingston M, et al. Int J STD AIDS. 2016;27: 421-46.
19. Sednaoui P, et al. Poster 1748. ECCMID; 2013 Apr 27–30; Berlin, Germany.
20. Shieh J, et al. Poster D-90. AACC; 2011 Jul 24–28; Atlanta, GA, U.S.
21. Binnicker MJ, et al. J Clin Microbiol. 2012; 50:148-50.
22. Ureda N, et al. Poster D-66. AACC; 2009 Jul 19–23 Chicago, IL, U.S.

Siemens Healthineers Headquarters
Siemens Healthcare GmbH
Henkestr. 127
91052 Erlangen, Germany
Phone: +49 9131 84-0
siemens-healthineers.com

Published by
Siemens Healthcare Diagnostics Inc.
Laboratory Diagnostics
511 Benedict Avenue
Tarrytown, NY 10591-5005
USA
Phone: +1 914-631-8000

Published by Siemens Healthcare Diagnostics Inc. · Order No. 30-21-DX-1063-76 · 09-2021 · ©Siemens Healthcare Diagnostics Inc., 2021

Syphilis Testing

Treponemal and Nontreponemal Assays

Performance Comparisons

siemens-healthineers.com

Clinical Brief

SIEMENS Healthineers

Summary

Serology testing is important to aid the rule-in or rule-out of syphilis and can include both treponemal and nontreponemal assays. Differences in performance and sensitivity among assays exist and should be considered when implementing a syphilis testing algorithm.

Introduction

Syphilis is a bacterial disease resulting from infection with Treponema pallidum (subspecies pallidum).[1,2] The course of untreated infection is shown in Figure 1.[2,3] Testing is typically done for pregnant women and those at risk for or suspected of exposure.[3,4] The bacterium cannot be cultured using routine microbiology techniques; serology assays provide the primary means of testing and diagnosis.[4]

Serology testing for syphilis

Serology testing for syphilis involves two different types of antibody-detection assays: treponemal and nontreponemal. Treponemal tests identify antibody to specific bacterial antigens such as Tp15, Tp17, and Tp47.[5-7] Studies suggest that the ability to detect Tp47 antibody does not enhance assay sensitivity beyond that achieved by assays designed to detect only Tp17 or both Tp15 and Tp17.[7-11] Approximately 85 percent of tested patients will remain seropositive for treponemal antibody even with successful treatment, so previous history must be considered when testing patients with a prior diagnosis of syphilis.[12,13]

Nontreponemal assays recognize antibody that results from exposure to lipoidal material released from damaged cells and include the RPR and VDRL assays.[4] Unlike treponemal antibodies, nontreponemal antibodies typically become nondetectable with resolution of infection.[13] Importantly, up to 30 percent of untreated late-latent infections may also become nondetectable with nontreponemal assays but remain detectable with treponemal assays.[12,13] Other causes of membrane damage such as autoimmune disease can stimulate production of nontreponemal antibody. For this reason the specificity of nontreponemal assays for syphilis is relatively low compared to that of treponemal assays.

Advantages of a reverse algorithm

An example of a reverse-testing algorithm is shown in Figure 2. The advantages can include detection of early infection,[4] automated workflow, and objective results reporting. Many countries have moved primarily to reverse testing, and some identify it as the preferred approach (specifically using an assay capable of detecting both IgM and IgG),[18] though traditional testing is still relatively common. One concern with reverse testing is the management of discordant results, where the initial treponemal assay is reactive but the nontreponemal is nonreactive. Resolution is important, as this could indicate early infection or late-latent infection in need of treatment, previously treated infection, or a false-positive result. Both the CDC and IUSTI recommend an alternate treponemal test to aid resolution of discordant results with reverse testing.[4,17]

Many of the newer automated assays offer higher sensitivity compared to some of the older, manual treponemal assays.[8,19] Some treponemal assays are designed to include detection of both IgM and IgG; others are designed to detect only IgG (with IgM-only assays available separately). Studies suggest missed infections occur when IgG-only assays are compared to those able to detect both IgG and IgM.[8,20]

Comparative performance among syphilis assays

While studies suggest most commercially available syphilis assays generally perform well, design differences inherent in the various test methodologies can lead to performance disparities. An example is differential treponemal assay sensitivity when using an alternate treponemal test to confirm a discordant result. One study showed the ADVIA Centaur® Syphilis assay (an automated treponemal assay) detecting an early (IgM-positive) infection missed by both a manual

Figure 1. Course of untreated syphilis[2,3]

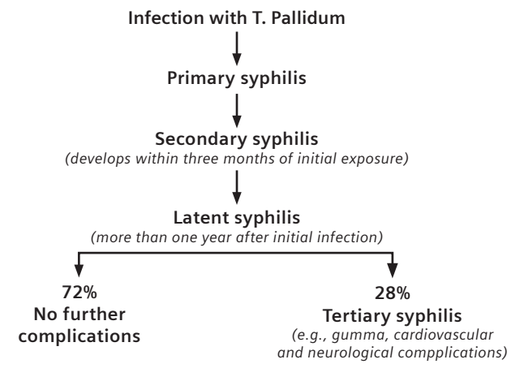
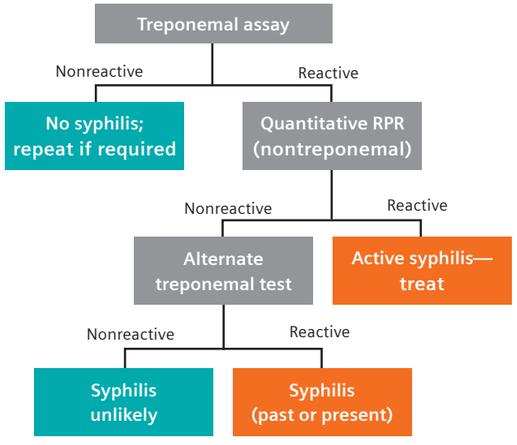


Figure 2. Example of a reverse syphilis testing algorithm[17]



*Results from third-party studies described herein are based on results that were achieved in each study's unique setting. Since there is no "typical" setting there can be no guarantee that the same results will be achieved from study to study.

treponemal assay (TPHA) and the nontreponemal test (RPR).[19] An investigation by Ly, et al. identified several patients with early syphilis, all of which were missed by the manual TPHA treponemal assay but detected by the automated treponemal assays.[8] The VDRL nontreponemal assay also missed most of these infections, consistent with other studies suggesting nontreponemal assays may not be as sensitive for early infection.[21] Sensitivity, however, can vary even among the automated assays. Whereas the four different automated treponemal assays used in the study by Ly, et al. detected all early infections, a fifth automated treponemal assay—specific for IgG—did not (Table 1).[8] Additional analysis with a separate IgM assay from the same manufacturer identified the missed samples. These and similar data[20] highlight important differences in sensitivity which can impact both testing and confirmation. Table 2 shows variability for false negatives among six different automated treponemal assays.[11]

Despite relatively good correlation among the automated treponemal assays, differences have been observed.[7,9-11,22] While sensitivity is important, specificity also matters, for example, for testing relatively low-prevalence populations such as pregnant women. Minimizing false-positive results can reduce unnecessary testing and confirmation. One recent comparison of several automated treponemal assays noted significant disparity in false-positive results but minimal differences in sensitivity (Table 3).[10]

Summary

Syphilis serology is important for testing of at-risk populations. Advantages of a reverse-testing algorithm using a sensitive, automated treponemal assay include improved clinical detection and enhanced workflow. Assay sensitivity and specificity are important, and variability has been observed among commercially available testing options.

Table 1.* Performance on early infection samples of five treponemal immunoassays: Abbott ARCHITECT Syphilis TP, Siemens Healthineers IMMULITE® 2000 Syphilis Screen, DiaSorin LIAISON Treponema Screen, Bio-Rad BioPlex 2200 Syphilis IgM, and Bio-Rad BioPlex 2200 Syphilis IgG assays.[8]

	VRDL	TPHA	ARCHITECT	IMMULITE	LIAISON	BioPlex IgM		BioPlex IgG		
			Tp15, Tp17, Tp47	Tp17	Tp17	Tp17	Tp17	Tp17	Tp17	Tp17
1	N	N	P	P	P	N	P	N	N	N
2	N	N	P	P	P	N	P	N	N	N
3	N	N	P	P	P	N	P	N	P	P
4	P	N	P	P	P	P	P	N	P	N
5	N	N	P	P	P	P	P	N	P	P
6	N	N	P	P	P	N	P	N	P	N
7	P	N	P	P	P	P	P	P	P	P

P = positive, N = negative

Table 2.* Sensitivity and missed infection: performance of six commercial assays.[11]

Assay	False Negatives (n)	Fasle Positives (n)	Sensitivity (%)	Specificity (%)	% Agreement with FTA-ABS
Siemens Healthineers ADVIA Centaur Syphilis	1	0	99.4	100	99.8
Roche COBAS Syphilis	1	0	99.4	100	99.8
Sysmex HISCL Anti-TP	2	0	98.7	100	99.7
Abbott ARCHITECT Syphilis TP	5	0	96.8	100	99.2
A & T IMMUNOTICLES AUTO	4	9	97.5	99.6	99.0
Mediace TPLA	3	2	98.1	98.0	98.0

Table 3:* Specificity and false positives for five treponemal assays.[10] Specificity was evaluated using remnant samples taken from low-risk individuals determined to be seronegative on the basis of standard treponemal and nontreponemal testing and from commercial seronegative samples.

Specificity: 8,079 samples comprising 3,500 routine samples and 4,579 remnant blood donor samples
Sensitivity: 928 remnant known syphilis-positive samples

Assay	False Negatives (n)	Fasle Positives (n)	Indeterminate (n)	Sensitivity (%)	Specificity (%)
Siemens Healthineers IMMULITE 2000 Syphilis Screen	1	0	0	99.67	100.0
Roche ELECSYS Syphilis	0	10	2	110.	99.88
Abbott ARCHITECT Syphilis TP	1	13	2	98.9	99.71
DiaSorin LIAISON Treponema Screen	0	12	0	100.0	99.66
Fujirebio Serodia-TPPA	0	2	0	100.0	99.87