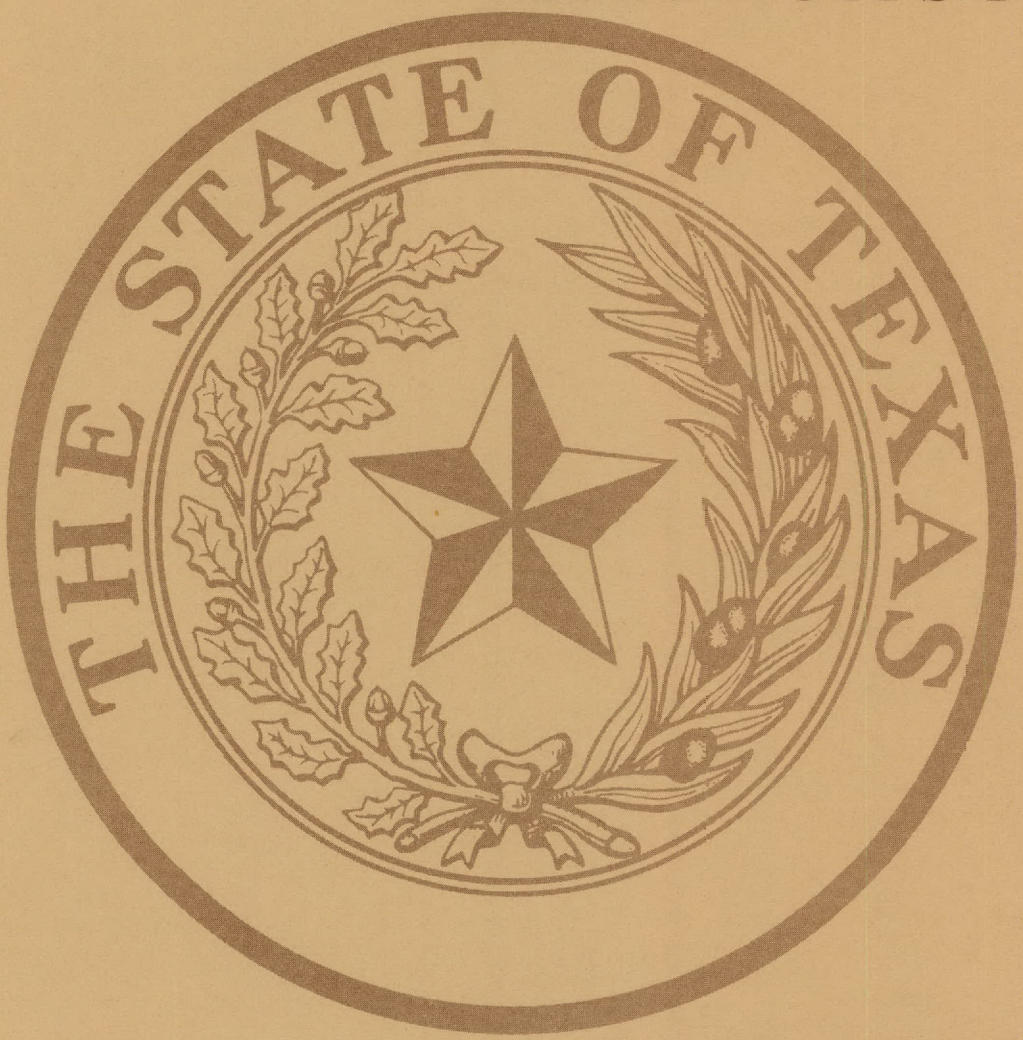
INTERPRETATION OF SEROLOGIC TESTS FOR SYPHILIS



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INTERPRETATION OF SEROLOGIC TESTS FOR SYPHILIS

Proper evaluation of serologic tests for syphilis (STS) is often a confusing matter. Many physicians are confronted only rarely with problems in this regard. The following comments are provided as a matter of review. Several tests are in use. Most common of these are the RAPID PLASMA REAGIN CIRCLE CARD (RPR) test, the VENEREAL DISEASE RESEARCH LABORATORY (VDRL) QUANTITATIVE test, the MICRO-HEMAGGLUTINATION for TREPONEMA PALLIDUM (MHA-TP) test, and the FLOURESCENT TREPONEMAL ANTIBODY ABSORPTION (FTA-Abs) test.

The RPR test is quick, inexpensive, and easy to use; it is exceptionally useful in screening, as performed in physician offices and small laboratories. This test is very sensitive; i.e., there are few false negatives. Sera that test "nonreactive" may be so regarded. Reactive tests warrant confirmation with laboratory-based testing; in most Texas laboratories, the VDRL Quantitative test is used.

VDRL Quantitative tests are reported as "nonreactive"and as "weakly reactive"(undiluted) or "reactive" at dilutions of 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, etc. "Weakly reactive" results warrant retesting after 1-2 weeks, as do all tests with more strongly reactive results. While considerable confidence may be placed in the VDRL Quantitative test, it must be remembered that *patients with active infectious primary syphilis frequently have nonreactive VDRL Quantitative and RPR tests.* This is a result of the patient's immune system lagging behind the disease process. At the time of the appearance of the primary lesion, the chancre, only about 25% of the cases will have a reactive VDRL Quantitative or RPR test. After the chancre has been present for one week, some 50% will have a reactive test; after two weeks, the ratio rises 75%. Virtually 100% of the cases will have a reactive serology by the time secondary syphilis develops. Almost all will have reactive serologies 3-4 weeks after appearance of the primary lesion. Although the development of secondary syphilis may take as long as six months, the rash or other signs may appear even before the primary lesion has "healed." Of course, treatment with penicillin and other antibiotics will interrupt the development of these stages of the disease if the dosage is adequate. If the dosage is NOT adequate, the development of clinical signs is disrupted to some extent or delayed temporarily; the development of seroreactivity to the VDRL Quantitative test may also be masked or delayed by faulty treatment.

Prior to treatment of any patient for syphilis, a VDRL Quantitative test should be performed. This test should be repeated one week after therapy and on several occasions over the next two years — see table.

Individuals who are recent (within 90 days) contacts of patients with infectious syphilis (primary and secondary stages) and who have negative RPR or VDRL tests still must receive prophylactic treatment for syphilis as an epidemiologic control measure.

In untreated primary syphilis, the seroreactivity usually reaches a titer of at least 1:4. Following treatment of the syphilis infection during the primary stage, the reactivity may be expected to continue to rise for a few weeks but should revert to nonreactivity within 6-12 months following treatment. Ninety-seven percent will be nonreactive within two or more years.

In secondary-stage syphilis, the VDRL Quantitative test is invariably reactive, usually with a titer of 1:32 or higher. While the titer may continue to rise immediately after successful treatment, the reactivity should gradually revert to nonreactivity within 18 months following the completion of successful treatment. After 2 years, over 75% will be nonreactive. If the patient with secondary syphilis develops a VERY strong reactivity, the VDRL test could be read spuriously as nonreactive, due to the prozone phenomenon. The laboratory should, therefore, be asked to dilute the "nonreactive" serum and continue the titration in all cases wherein suspicious lesions are present.

Late syphilis may be symptomatic or asymptomatic. Persons with untreated or inadequately treated diseases, of which only the history is suggestive of primary or secondary syphilis, are candidates for treatment — even if a VDRL test is negative. A patient may have SYMPTOMATIC late syphilis, either acquired or congenital, and have a nonreactive VDRL test. Evaluation by means of a test such as the MHA-TP would be necessary in such a patient. Late syphilis must be adequately treated.

Treatment of late syphilis may have no effect on the titer of reactive VDRL Quantitative tests, but after successful treatment, the titer usually decreases "four-fold" (by two "tubes"; e.g., from 1:32 to 1:8).

A stable or rising titer during the two years of observation after treatment suggests a treatment failure, reinfection, or a diagnostic error.

In any treatment situation, failure of the highest titer achieved (the highest titer may be reached a week or two after treatment is instituted) to decrease four-fold (two "tubes") within one year suggests a treatment failure and warrants reevaluation of the case. In cases wherein the epidemiologic and clinical information fails to support serologic findings, the diagnosis of syphilis should be doubted. A "biologic false positive" basis for seropositivity should be sought.

Biologic false positivity, meaning a non-syphilitic basis for reactive RPR or VDRL test, must be established by the use of a treponemal antigen test such as the MHA-TP. The RPR and the VDRL are two among many non-treponemal antigen tests. Among the non-treponemal tests, "false positivity" or "false reactivity" occurs in at least 1% of persons tested. Barring laboratory error, the treponemal antigen tests are seldom false positive. They are more complicated and expensive to perform, and there are relatively more false negative test results. *These tests are inappropriate for use as screening tests.*

The Bureau of Laboratories, Texas Department of Health, uses the MICRO-HEMAGGLUTINATION for TREPONEMA PALLIDUM (MHA-TP) test for routine confirmatory testing for syphilis. The specificity of the MHA-TP test is as good as or better than the FTA-Abs test. Usually, a nonreactive result on an MHA-TP test will establish the "biologic false positive" diagnosis. Transient (acute) false reactivity occurs in some patients due to intercurrent viral and bacterial infections, when the serum titer of heterophile antibodies is high. Infectious mononucleosis, viral hepatitis, smallpox vaccination, as well as herpes simplex infections, chancroid, and lymphogranuloma venereum, may be accompanied by biologic false positive serologic tests for syphilis. Long-term (chronic) biologic false positivity may be present in leprosy and collagen diseases, such as systemic lupus erytrhematosis and rheumatoid arthritis, as well as in narcotics addiction and in some forms of neoplasms. (A determination that a patient has a biologic false positive STS mandates a search for the medical basis of the positivity.) Serum controls used in the laboratory identify this activity, permitting further evaluation with the FTA-Abs test.

The Bureau of Laboratories will perform the FTA-Abs test, but only under the following circumstances:

1. In suspected cases of primary syphilis in which two nontreponemal tests performed five days apart have shown a static reactive titer and in which the MHA-TP test performed on the second specimen was Nonreactive. This must be documented when the specimen is sent for FTA-Abs testing.
2. In diagnostic problems arising from conflicts between the overall clinical impression and results from both nontreponemal and treponemal tests. (Such conflicts sometimes occur in cases of tertiary syphilis.) A brief written description of the diagnostic problem must accompany specimens sent for FTA-Abs testing.

The FTA-Abs test is performed twice per month, on the first and third Fridays. The MHA-TP test is performed three times per week, but only on specimens that are Reactive or Weakly Reactive in our VDRL Slide test or in cases where the results of nontreponemal tests are equivocal, and in which information describing this situation accompanies the specimen.

Unlike the non-treponemal antigen tests, the MHA-TP and the FTA-Abs do not revert to nonreactivity after successful treatment of syphilis. Once reactive, they almost always stay reactive. Therefore, a physician who might order repeated MHA-TP tests to check on his patient's progress would be wasting time, money, and the opportunity to get the desired information, which would be obtained through repetition of the VDRL Quantitative test.

Patients treated for OTHER venereal diseases should receive a serologic test for syphilis since such persons are obviously at relatively high risk for exposure to syphilis. Proper penicillin treatment for gonorrhea may abort incipient syphilis. In such situations, unless the STS becomes positive, further serologic study is not needed unless another exposure or new medical findings warrant. Following recommended treatment of gonorrhea with any drug other than one of the penicillins, a follow-up VDRL Quantitative test should be obtained at 3-6 months.

A reactive STS determined on serum raises the question as to whether testing of cerebrospinal fluid (CSF) is indicated. A spinal tap should NOT be done during an infectious stage of this disease (during the primary or secondary stages). Following proper penicillin therapy for syphilis, a favorable blood serologic response (four-fold titer drop) generally suggests that NO serologic examination for the CSF is required. Final judgment must be based on careful evaluation of the serologic response to treatment while following the serum titer for no less than 12 months, or to reversion to non-reactivity. "Fixed positive" (patients in whom the STS remains permanently reactive) cases should receive annual serologic tests. On the other hand, tests of the CSF (VDRL Quantitative) SHOULD be performed:

. . . in all cases of congenital syphilis,
. . . in the case of any syphilis patient with neurologic signs or symptoms, consistent with syphilis,
. . . in patients first treated after one year of disease (late syphilis) and who are not able to receive recommended therapy with PENICILLIN,
. . . despite the demonstration of a four-fold (2-tube) titer drop in the VDRL of patients in whom penicillin was used for treatment, a persistent VDRL titer of 1:8 or more after twelve months is indication of the need for a serologic examination of the CSF, and
. . . patients with primary or secondary syphilis treated with ANY DRUG OTHER THAN PENICILLIN should have a spinal tap and CSF serology one year after treatment.

A reactive VDRL performed on a sample of spinal fluid always represents syphilis unless proven otherwise. A diagnosis of central nervous system syphilis is supported by elevations of spinal fluid blood count and total protein. In general, spinal fluid serology is poorly understood; consultation with experts is often necessary.

If a VDRL performed on the cord blood of a newborn is reactive, it may be due to passive transfer of antibodies from the mother. A VDRL Quantitative test should be performed every month for three months to determine whether the titer is rising or falling. If the titer falls rapidly or becomes non-reactive, then passive transfer, not congenital syphilis, is to be regarded as the basis for the reactive serology.

References: Texas Morbidity This Week
Week No. 10 — Ending March 12, 1977
Texas Department of Health
Bureau of Communicable Disease Services

Syphilis — a synopsis
USDHEW, PHS Publ. No. 1660
January, 1968; pp. 112-113

TABLE - Summary of Recommended Follow-up

Stage	Treatment	Follow-up Posttreatment	
		Serology	Discharge[1]
Primary and Secondary	Yes	1st, 3rd, 6th, 12th months.	End of 1 year.
Contact of primary or secondary (even with negative RPR or VDRL)	Yes		
Latent, both Early and Late	Yes	As above, then every 6 months for second year.	End of 2 years.
Syphilis in Pregnancy[2]	Yes	Monthly until delivery, then as for appropriate stage.	End of 1-2 years, depending on stage.
Subsequent pregnancies. No change in titer[2]	No	Initial visit and monthly until delivery.	
Early Congenital (under 2 years)[3]	Yes	Same as primary or secondary.	End of 1 year.
Late Congenital (over 2 years)[3]	Yes	Same as primary or secondary; then every 6 months for 2 years.	End of 2 years.
Neurosyphilis Cardiovascular Syphilis Late Benign Syphilis	Yes	Every 3 months for 1st year. Every 6 months for 2nd year.	End of 2 years.

1. A spinal fluid examination is suggested at the time of discharge for all patients with other than primary or secondary syphilis as discharge patients should have either negative serologic tests for syphilis or fixed low titers. Neurosyphilis patients should have a spinal fluid examination at each follow-up visit.

2. Retreatment is indicated if there is any doubt concerning adequacy of previous treatment.

3. An appropriate medical specialist should be consulted regarding treatment of the complications of congenital syphilis.