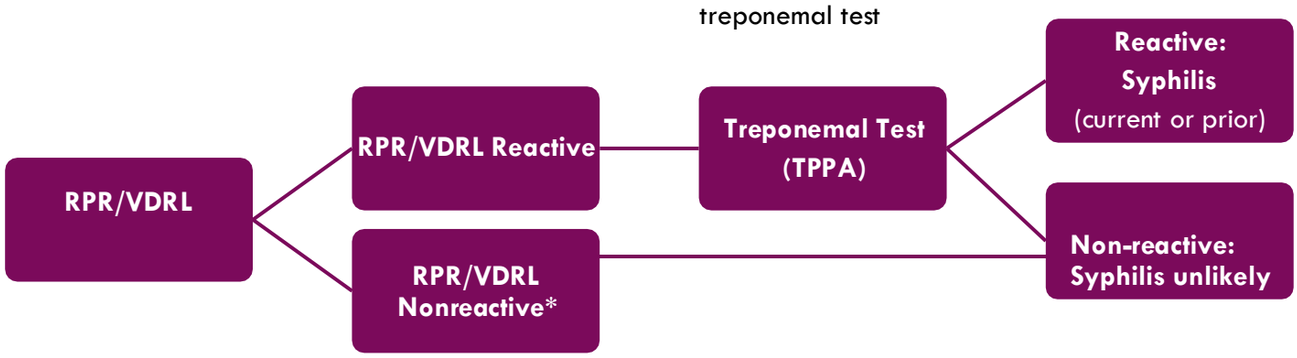
Clinical Interpretation of Syphilis Screening Algorithms

Testing: Traditional Algorithm[a]

1. Screen with non-treponemal test (RPR/VDRL)

2. Confirm reactive non-treponemal test with treponemal test



*Early primary syphilis and late untreated syphilis possible if RPR/VDRL are nonreactive; see below for recommended actions

Table 1: Interpretation of Syphilis Serologies, Traditional Algorithm

Non-Treponemal (RPR/VDRL)	Treponemal (TPPA)	Possible Interpretations	Recommended Actions
Nonreactive	Nonreactive or not done	1. No syphilis 2. Early/incubating syphilis (too early to be detected by serology)	▪ If syphilis unlikely, no further action needed. ▪ If early syphilis suspected, consider ordering a treponemal test (if not done initially) and repeating an RPR/VDRL in 1-2 weeks; if either test is reactive, treat for syphilis. ▪ If concerned for early syphilis (e.g., chancre present or known exposure) treat presumptively. If treating presumptively, repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
	Reactive	1. Prior treated syphilis 2. Untreated syphilis	▪ Treponemal tests (e.g., TPPA) often stay reactive for life; if patient has a history of adequate treatment for syphilis & no new exposures/ symptoms, no further action needed. ▪ If early syphilis suspected (e.g., chancre present or known exposure), treat presumptively according to stage. If treating presumptively, repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion. ▪ If no signs or symptoms, order a second treponemal test (e.g., EIA or CIA); see table 2 for recommendations based on results.
Reactive	Nonreactive	1. False positive RPR or VDRL	▪ Likely false positive (not syphilis).[b] ▪ In pregnancy or in patients at high risk for syphilis, consider rescreening with serologic testing in 2-4 weeks – if unchanged, no action needed.[c]
	Reactive	1. Current syphilis 2. Treated syphilis with residual/ persistent RPR/VDRL titer	▪ If RPR/VDRL is newly reactive, stage and treat. ▪ If previously treated and sustained (≥2 weeks) 4-fold rise in RPR/VDRL titer, manage as treatment failure versus re-infection.[d] ▪ Note that RPR/VDRL may still be reactive after treatment; if there is a fourfold decline within 12-24 months, treatment is considered to have been adequate even if RPR/VDRL remains reactive. ▪ Some treated patients may have a persistent low level RPR/VDRL titer for a prolonged period; re-treatment is not necessary in the absence of new exposures or symptoms.

[a] The traditional algorithm starts with a non-treponemal test (RPR or VDRL) which, if reactive, is followed by a confirmatory treponemal test (TPPA). In interpreting serologies, it is helpful to know which testing algorithm (traditional vs reverse) is being used in your lab.

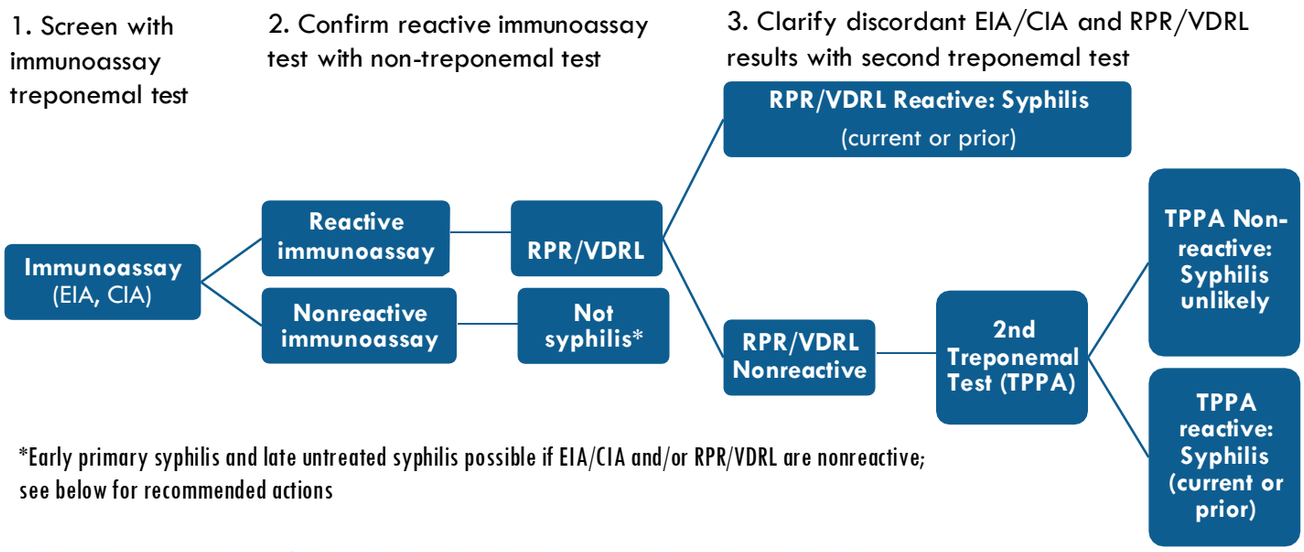
[b] False positives can be seen in pregnancy and/ in patients with autoimmune diseases, Lyme disease, certain viral infections (including HIV), injection drug use, and other conditions.

[c] In California, all pregnant people should be screened for syphilis at least twice during pregnancy: once at either confirmation of pregnancy or at the first pre-natal encounter, and again during the third trimester (ideally between 28-32 weeks). Patients should also be screened at delivery, except those at low risk who have a documented negative screen in the third trimester. See https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/California-STI-Screening-Recommendations.aspx.%20As%20of%20April%202024. As of April 2024, the American College of Obstetrics and Gynecology recommends screening all pregnant patients universally for syphilis three times: once at the first prenatal care visit, again during the third trimester, and again at birth.

[d] For patients determined to have new syphilis or treatment failure, refer to the Centers for Disease Control STD treatment guidelines at https://www.cdc.gov/std/treatment-guidelines/syphilis.htm for treatment and follow up recommendations.

Clinical Interpretation of Syphilis Screening Algorithms

Testing: Reverse Algorithm[a]



*Early primary syphilis and late untreated syphilis possible if EIA/CIA and/or RPR/VDRL are nonreactive; see below for recommended actions

Table 2: Interpretation of Syphilis Serologies, Reverse Screening Algorithm

Immuno-assay (CIA or EIA)	RPR/ VDRL	TPPA	Possible Interpretations	Recommended Actions
Non-reactive	Non-reactive or not done	Non-reactive or not done	1. Syphilis unlikely 2. Early/incubating syphilis (too early to be detected by serology)	▪ If syphilis unlikely, no further action needed. ▪ If immunoassay nonreactive but high clinical suspicion (such as a chancre or known exposure), treat presumptively for early syphilis. If treating presumptively, obtain RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
Reactive	Non-reactive	Non-reactive or not done	1. False positive immunoassay 2. Early/incubating syphilis 3. Latent or prior syphilis (treated or untreated)	▪ If no signs/symptoms and low risk for syphilis, most likely a false positive immunoassay.[b] No further action needed. ▪ If concerned for early infection or in pregnant patients, re-screen in 2-4 weeks.[c] ▪ If signs/symptoms or contact to syphilis, treat presumptively. Repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
		Reactive	1. Latent or prior syphilis (treated or untreated) 2. Early syphilis (prior to RPR/VDRL seroconversion)	▪ No further action needed if patient treated appropriately for syphilis in past, assuming no new exposures/symptoms and a negative clinical exam. ▪ If no symptoms and no known prior adequate treatment, treat presumptively for latent syphilis. ▪ If early syphilis suspected (symptoms or known exposure), treat presumptively. Obtain RPR/VDRL on day of treatment. If nonreactive, repeat in 2-4 weeks to assess for seroconversion.
	Reactive	Not done or Reactive	1. Current syphilis 2. Prior syphilis (treated or untreated)	▪ If RPR/VDRL is newly reactive, stage and treat. ▪ If previously treated and sustained (≥2 weeks) 4-fold rise in RPR/VDRL titer, manage as treatment failure versus re-infection.[d] ▪ If known prior adequate treatment for stage of infection and RPR/VDRL declining appropriately (i.e., a fourfold decline within 12-24 months), no further action needed. ▪ Some treated patients may have a persistent low level RPR/VDRL titer for a prolonged period; re-treatment is not necessary in the absence of new exposures or symptoms.

[a] The reverse algorithm starts with an immunoassay detecting syphilis antibodies which, if reactive, is followed by an RPR/VDRL. If there is a discrepancy between the immunoassay and RPR (one reactive, one nonreactive), a treponemal test (TPPA) serves as the tie-breaker. In interpreting serologies, it is helpful to know which testing algorithm (traditional vs reverse) is being used in your lab.

[b] False positive immunoassays can occur with Lyme disease or non-syphilis treponemal infections.

[c] In California, all pregnant people should be screened for syphilis at least twice during pregnancy: once at either confirmation of pregnancy or at the first pre-natal encounter, and again during the third trimester (ideally between 28-32 weeks). Patients should also be screened at delivery, except those at low risk who have a documented negative screen in the third trimester. See https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/California-STI-Screening-Recommendations.aspx.%20As%20of%20April%202024. As of April 2024, the American College of Obstetrics and Gynecology recommends screening all pregnant patients universally for syphilis three times: once at the first prenatal care visit, again during the third trimester, and again at birth.

[d] For patients determined to have new syphilis or treatment failure, refer to the Centers for Disease Control STD treatment guidelines at https://www.cdc.gov/std/treatment-guidelines/syphilis.htm for treatment and follow up recommendations.