POPULATION HEALTH DIVISION
SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH

Reverse Sequence Syphilis Screening Frequently Asked Questions

1) **What is a syphilis EIA or CIA?**

   A syphilis EIA is an "enzyme immunoassay." This is a blood test for syphilis that tests for antibodies directed at the syphilis organism (Treponema pallidum). The EIA is a treponemal test, like the TPPA or MHA-TP that have been used for many years. Syphilis CIAs ("chemoluminescence assays") are similar to EIAs. There are a number of syphilis EIAs and CIAs available.

2) **I always remember ordering an RPR when I wanted to test for syphilis. Why is my lab using a syphilis EIA or CIA?**
   Many commercial laboratories have adopted EIAs or CIAs for syphilis screening because they are highly automated tests, and thus are less expensive and more efficient to perform than RPRs or VDRLs. EIAs and CIAs are very sensitive and specific tests for syphilis and have a fast turn-around time.

3) **Why is screening with an EIA instead of an RPR sometimes referred to as Reverse Sequence Syphilis Screening?**
   Traditionally, syphilis screening is conducted with an RPR or VDRL. Unlike EIAs, the RPR and VDRL are *non-treponemal* antibody tests. They detect antibodies to proteins that are not part of the syphilis organism itself, but are similar to proteins found in the syphilis bacteria. RPRs or VDRLs must be confirmed with a treponemal test; most labs use a TPPA (treponemal pallidum particle assay) to confirm a positive RPR or VDRL. Screening with a non-treponemal test and confirming with a treponemal test is sometimes referred to as "traditional sequence" syphilis screening.

   Labs that screen with an EIA or CIA have "reversed" this algorithm. Rather than starting with a non-treponemal test and confirming with a treponemal test, they are starting with a treponemal test (the EIA or CIA) and confirming with a non-treponemal test (the RPR). Thus it is referred to as "reverse sequence" syphilis screening.

4) **If the EIA is positive, why do I need an RPR?**
   The RPR provides a *quantitative* result (known as a "titer") that is helpful for staging disease and for establishing a baseline for determining whether the patient responds appropriately to syphilis treatment. Once the EIA is positive (i.e., the first time someone is infected with syphilis), it remains positive for life in most people, and is therefore not useful for detecting reinfection, unlike the RPR, which fluctuates with disease activity.

5) **Will the EIA become negative after I treat the patient?**
   No, the EIA usually remains positive after treatment, but if the RPR decreases fourfold after treatment, the patient has likely been cured of syphilis. Remember that individuals can get syphilis more than once, so it is important to continue screening patients who are at risk for syphilis on a regular basis (q3-6 months).

6) **My patient's EIA is positive, but the RPR is not back yet, what should I do?**

   If your patient does not have any risk factors for syphilis and you are certain you can reach the patient if their RPR or TPPA are positive, one option is to send the patient home and wait for the rest of the test results to return.

If your patient does not have a prior history of syphilis and has risk factors for syphilis, or if the patient may be difficult to reach after the visit, we recommend having a low threshold for empiric treatment with benzathine penicillin G 2.4 mu IM.

7) What does it mean if the EIA is positive and the RPR is also positive?

This means the patient has untreated or previously treated syphilis. Determining whether a patient has an untreated syphilis infection and ascertaining the stage of syphilis relies on a combination of clinical history, diagnostic tests and physical examination. When interpreting syphilis tests, a provider should do the following:

1) Ask: Have you had a history of syphilis, recent symptoms (e.g. sore or rash), have any of your sex partners been diagnosed with syphilis?
2) Assess for risk factors for syphilis.
3) Examine: Physical examination for ulcers (primary syphilis) or rashes and/or mucocutaneous lesions (secondary syphilis) with attention to the mouth, skin, and anogenital areas.
4) Call: To obtain prior RPR titers or syphilis treatment history for patients who live in San Francisco, call SF City Clinic: 415-487-5531

8) What if the EIA is positive and the RPR is negative?

This is sometimes referred to as a “discordant” result. In this situation, the CDC recommends obtaining a third syphilis test to help resolve the situation. Many labs will automatically “reflect” to a third test in this situation. Typically, this is a TPPA. The following 2 scenarios can occur:

a. EIA positive, RPR negative, TPPA negative:

This is most likely a false positive EIA. No further action is necessary. If your clinical suspicion for syphilis is high, you should consider empiric treatment for syphilis, and repeat the syphilis tests in 2-4 weeks. The EIA is more sensitive for very early primary syphilis than the TPPA or RPR, so could theoretically turn positive before these other two tests.

b. EIA positive, RPR negative, TPPA positive:

There are several possible explanations for these results:

1. **The patient has a history of treated syphilis**. If this is the case, no treatment is necessary. If the patient is at risk for syphilis, they should continue to be screened every 3-6 months.
2. **The patient has late latent syphilis**. In this case, the patient should be treated with Benzathine Penicillin G 2.4 mu IM weekly x 3
3. **The patient was recently exposed to syphilis and the RPR has not yet turned positive**. If your patient is at risk for syphilis, bring the patient back to clinic, do a complete oral, skin and anogenital exam to look for signs of syphilis and repeat the syphilis tests. If the patient is asymptomatic and the RPR is still negative, and the patient has never been previously treated for syphilis, they should be treated for late latent syphilis.

9) My patient has a history of syphilis, what should I do?

If your patient has a history of syphilis, they should be screened with an RPR. At ZSFG, RPR alone can be ordered as: "Rapid Plasma Reagin (RPR) for prior history of syphilis." **This test is not indicated for initial laboratory evaluation of syphilis**.

10) How do I know if my patient is at risk for syphilis?

In 2019, approximately 90% of early syphilis cases in San Francisco were among men, and over 75% were among men have sex with men (MSM). While the majority of syphilis cases in San Francisco occur among men, between 2017 and 2019, the number of syphilis cases in women increased by 155%, and congenital syphilis is increasing across California and in San Francisco.

- Sexually active MSM and trans people who have sex with men should be screened for syphilis every 3 months
- Pregnant women should be screened for syphilis at least twice during pregnancy: once at either confirmation of pregnancy or at the first prenatal encounter, and again during the 3rd trimester (ideally during 28-32 weeks gestation). Patients should be screened again at delivery, except those at low risk who have a documented negative screen in the third trimester.
- Non-pregnant adults should be screened for syphilis at least annually if they report any of the following: Sex with a man who has sex with men, history of STI in the past year, methamphetamine use, unstable housing or homelessness, sex work, intimate partner violence, or incarceration.
- All sexually active people who could become pregnant should receive at least one lifetime screen for syphilis, with additional screening for those at increased risk