Syphilis Case Studies

HIV, HCV and Syphilis Diagnostic Testing Workshop

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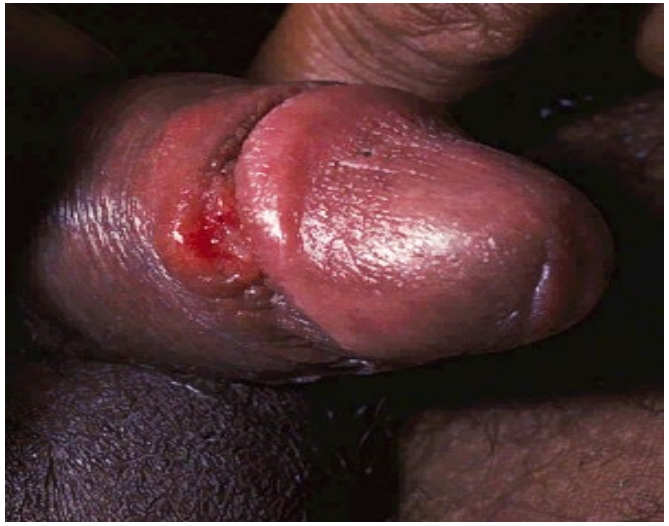
*Slides adapted from those courtesy of Megan Crumpler, PhD, HCLD

Disclosure Information

- I have no relevant financial relationships with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on patients

Case #1

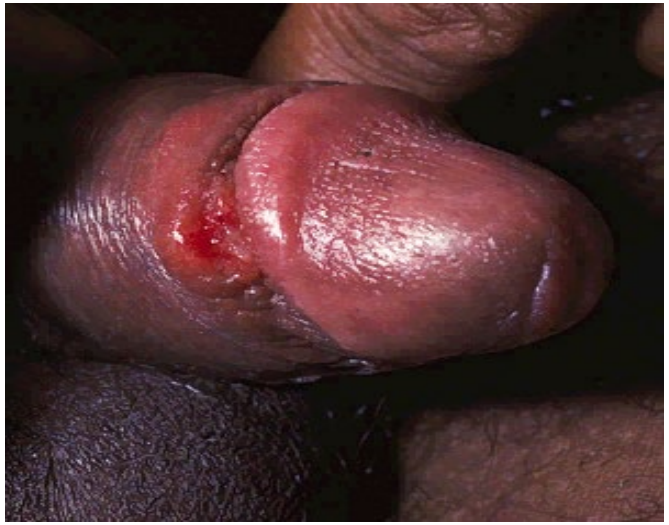
- A clinician sees a 36-year-old man living with HIV with a new painless solitary ulcer on his penis for 3 days. He reports 3 new male sexual partners in the past 2 months. He has no history of herpes or syphilis.



- The clinician orders an RPR as part of the traditional algorithm and both a HSV and mpox PCR
- Lab results: RPR: non-reactive; HSV PCR: negative; Mpox PCR: negative
- The clinician ask you, could this still be syphilis?

Case #1

- **Yes, this could still be syphilis!**
- Serology can be negative in up to ~25% primary syphilis
- RPR/VDRL may have slightly lower sensitivity than treponemal tests in syphilis
- **Recommend ordering TP-PA** with RPR/VDRL test when suspecting primary syphilis



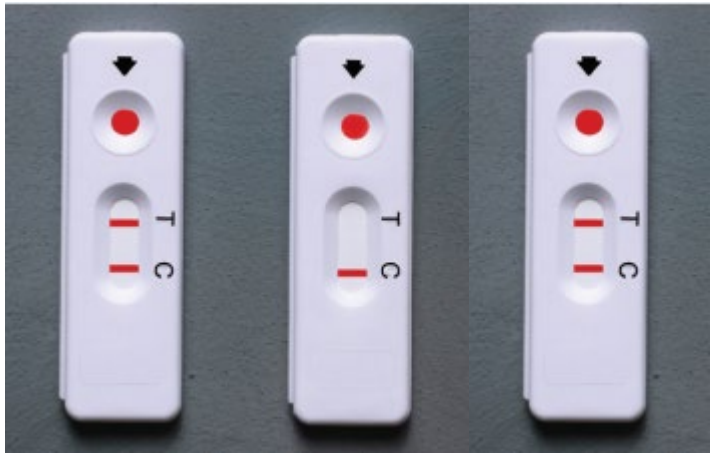
- If serology is negative and suspicion is low for syphilis AND follow-up is likely, repeat 2-4 weeks after onset of lesion
- If serology is negative and suspicion is high for syphilis, provider should empirically treat and can repeat serology 1 week after treatment

Case #2

- Your STD clinic has recently started performing a CLIA-waived rapid syphilis test. The physician calls you to make sure she is interpreting the test correctly. Based on the results below, what do you tell her?

The results are consistent with a case of syphilis infection at an undetermined time – it could be a current or past (treated) infection.

The currently available CLIA-waived rapid syphilis tests detect the presence of **treponemal** antibodies, therefore <u>when the infection occurred is unknown</u>. Treponemal tests alone cannot differentiate between current vs past infections.



Positive Control | Negative Control | Patient Result

Case #2

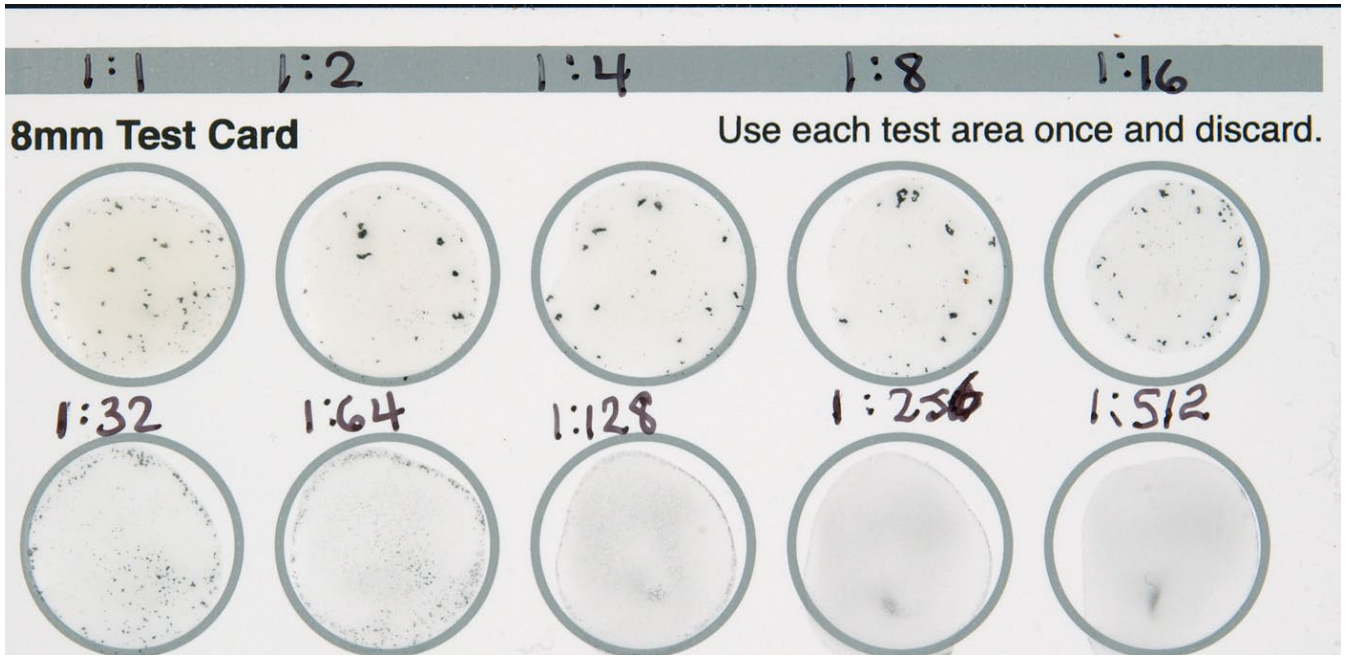
- The physician then tells you that the patient had previously been treated for syphilis, and his RPR result following treatment was 1:2. Should she do anything else to follow-up?
- Yes. Although the patient has a history of a past infection, there is still no way to know if she has a new infection without additional testing.
- What tests would you advise the physician to order next?

Qualitative RPR test, with reflex to quantitative if reactive.

In order to determine if the patient has a new infection, a RPR, both qualitative and quantitative, if reactive, is needed, to compare to the previous RPR result. When a patient has a past history of treated syphilis, comparing non-treponemal titers can be used to determine a new (current) infection.

Case #2

- The physician sends the blood specimen and the initial RPR Qualitative result was reactive so you perform serial dilutions to obtain a RPR titer.



Case #2

- You review the results with the physician and she wants to make sure she interprets the results correctly. What is the best interpretation to give her based on the information you already have?

Test	Results
RPR quantitative, post treatment, previous sample	Reactive 1:2
RPR qualitative this sample	Reactive
RPR quantitative, this sample	Reactive 1:64

The results are consistent with a new (current) syphilis infection

Because the past syphilis infection after treatment had a 1:2 titer with the RPR assay, this result with an increased titer of 1:64 **(equal or greater than a 4-fold increase in titer)** is indicative of a new (current) infection. The patient should have a careful physical exam to look for evidence of primary (chancre) or secondary syphilis (e.g., consistent rash).

Case #2

- Higher numbers correspond to higher level of antibodies in patient's serum
- **Two-fold change in titer** generally considered within margin of error of test
- **Four-fold change in titer** necessary to be a clinically significant difference
- Compare titer using <u>same</u> serologic test: *RPR often higher than VDRL*

1:1024
1:512
1:256
1:128
1:64
1:32 } 2-fold change
1:16
1:8
1:4 } 4-fold change
1:2
1:1

Case #3

- You receive a sample from a 30-year-old patient that had presented to her OB/GYN clinic after having tested positive with a home pregnancy test. As part of her prenatal workup, they screened her for chlamydia, gonorrhea, syphilis, HIV, hepatitis B surface antigen, and hepatitis C antibody. All of her other testing was negative, but the following results were obtained when testing for syphilis:

Test	**Results**
T. pallidum screening by EIA	Reactive

- What testing needs to be performed next to determine this patient's current syphilis status?

Non-treponemal test (RPR, VDRL), qualitative with reflex to quantitative if reactive

Case #3

- You perform the RPR and obtain the following results:

Test	Results
T. pallidum screening by EIA	Reactive
RPR, qualitative	Reactive
RPR, quantitative	Reactive 1:8

- What is the best final interpretation based on all of the testing for this patient?

The results are consistent with a current or past syphilis infection.

A reactive treponemal assay, and a reactive non-treponemal assay with a quantitative titer are consistent with current or past syphilis infection. A clinical evaluation is necessary to identify signs/symptoms or past history of syphilis or treatment to determine if this is a current or past infection.

If there is no history of treated syphilis, then the results would indicate current infection.

Case #4

- Your received another sample from a 30-year-old non-pregnant woman for routine STI testing. All of her other testing was negative, but the following results were obtained when testing for syphilis:

Test	Results
T. pallidum screening by EIA	Reactive

- What testing needs to be performed next to determine this patient's current syphilis status?

Non-treponemal test (RPR, VDRL), qualitative with reflex to quantitative if reactive

Case #4

- You perform the RPR and obtain the following results:

Test	Results
T. pallidum screening by EIA	Reactive
RPR, qualitative	Nonreactive

- What would you do next?
- You correctly perform a supplemental treponemal assay and obtain these results:

Test	Results
T. pallidum screening by EIA	Reactive
RPR, qualitative	Nonreactive
TP-PA	Nonreactive

- You report out the results and the next day the public health nurse calls for an explanation…What do you tell her?

Case #4

Test	Results
T. pallidum screening by EIA	Reactive
RPR, qualitative	Nonreactive
TP-PA	Nonreactive

Based on the test results, treponemal antibodies are not confirmed and the results are inconclusive. There is a potential that this is an early syphilis infection, but it is possibly a false positive immunoassay.

A clinical evaluation is necessary to identify any signs or symptoms, epidemiologic risk, recent exposures, and past history of syphilis or treatment. If a recent exposure is suspected, a sample should be redrawn in 2-4 weeks and tested through the laboratory algorithm.

If high clinical suspicion (presence of chancre or known exposure), treat presumptively and get day of treatment RPR. Otherwise, if the epidemiologic risk and clinical probability for syphilis are low, most likely a false positive immunoassay and further evaluation or treatment is not indicated.

Case #5

- You are at the laboratory and receive a call from a physician to discuss a case she wants to consult on.
- She tells you her patient is a 32-year-old man, who had been on a vacation in Miami about 12 weeks ago where he had multiple male sexual partners. He presented with a recent history of multiple painless sores on his penis that have disappeared, but now has a low-grade fever, reddish brown spots on the palms of his hands and soles of his feet.

You review the following results with her:

Test	Results
HIV 4th generation assay (Ag/AB combo)	Non-Reactive
VDRL, qualitative	Weakly Reactive
VDRL, quantitative	Reactive 1:1024
TP-PA	Reactive

Based on the patient history, symptoms and laboratory results, what would you tell the physician?

Case #5

Test	Results
HIV 4th generation assay (Ag/AB combo)	Non-Reactive
VDRL, qualitative	Weakly Reactive
VDRL, quantitative	Reactive 1:1024
TP-PA	Reactive

A reactive non-treponemal assay with a quantitative titer and reactive treponemal assay are consistent with a past or current syphilis infection.

However, because the doctor provided his sexual history and physical examination, the results are indicative of **current** infection, most likely in the **secondary stage (secondary syphilis)** because of the presence of the typical rash.

- The physician then asks you to explain the discrepancy between a weakly reactive qualitative result and the high titer quantitative result. What would you tell her?

These results are consistent with a **prozone** effect or phenomenon. The prozone phenomenon occur when there is a high level of antibodies in undiluted sera, which inhibits the antibody-antigen reaction

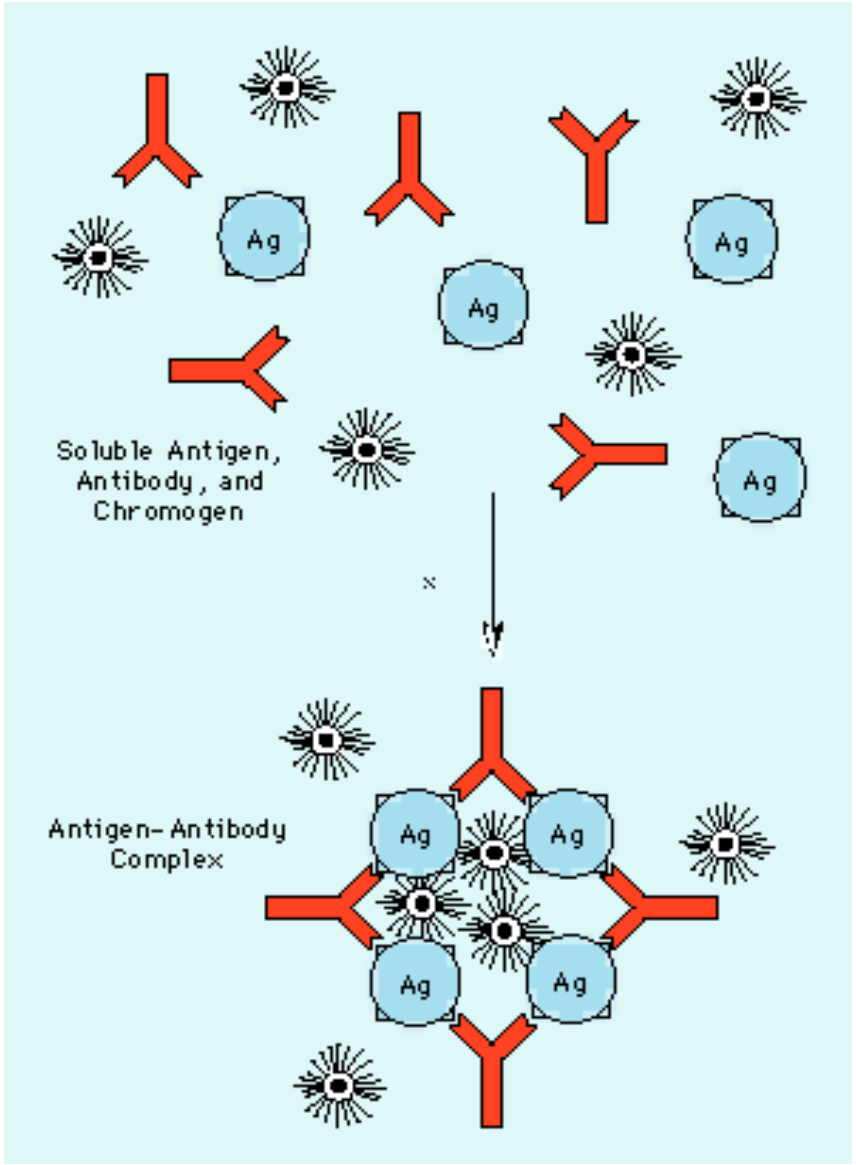
Prozone Phenomenon

False Negative (or weakly reactive) RPR

- High antibody titers prevent antibody/antigen lattice formation
- Important to perform 2-fold dilutions, particularly when there is a high-suspicion for syphilis

Rare

- Occurs ~0.3-2% (early / secondary syphilis)
- May be more common in HIV+ and neurosyphilis



*Jurado RL et al. Arch Intern Med 1993, **153:**2496–2498.*
*Geisler MG. South Med Jour 2004, **97**: 327-328.*
Liu LL et al. Clin Infect Dis 2014, 59:384-9.

Questions?