Syphilis 101

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Presenter Disclosures

• The author and their spouses/partners wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters.



PTC Disclaimer

Some terms in this presentation may have been modified to align with executive order requirements that this CDC-funded grant has received.





Objectives

- 1. Recognize the burden of syphilis
- 2. Identify the stages of syphilis infection
- 3. Interpret syphilis serologic tests
- 4. Determine appropriate syphilis treatments by stage
- 5. Summarize changes in syphilis diagnosis and treatment in special cases





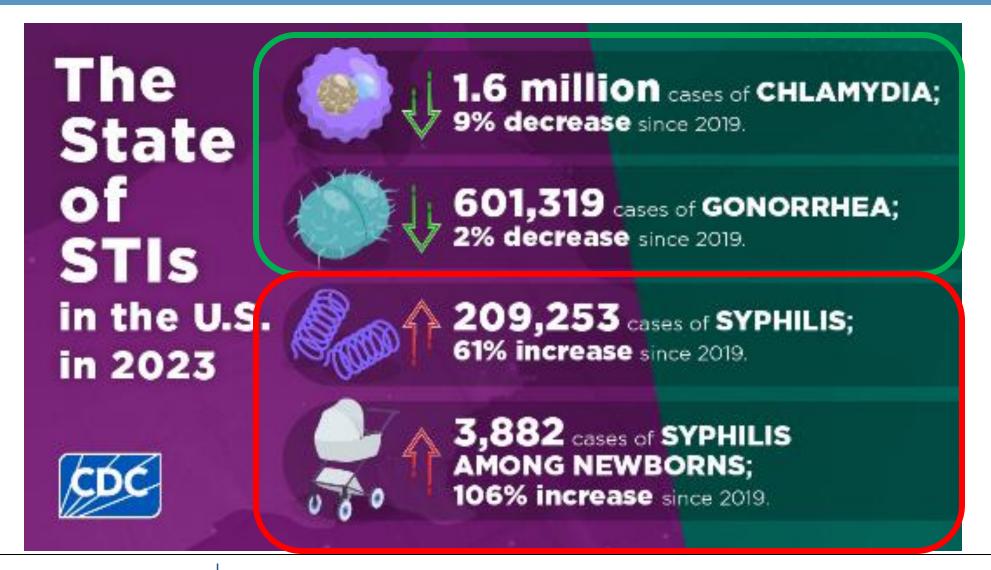
Not covered

- Congenital syphilis
- Syphilis in pregnancy
- Syphilis prevention e.g. Doxy PEP





Bacterial STIs in 2023—good news/bad news

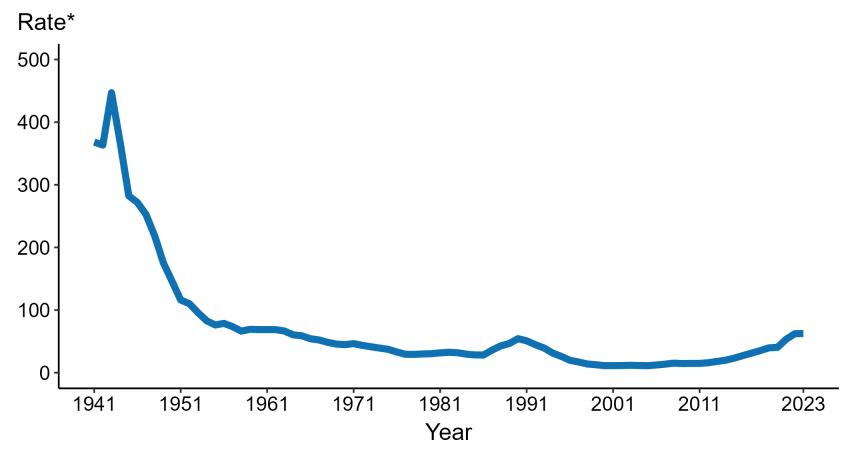






Syphilis: bouncing back

Syphilis — Rates of Reported Cases by Year, United States, 1941–2023



^{*} Per 100,000

NOTE: Total syphilis includes all stages of syphilis and congenital syphilis



The National Plan to Eliminate Syphilis

The National Plan to Eliminate Syphilis from the United States

October 1999

Division of STD Proportion

National Center for HIV, STD, and TB Preventio

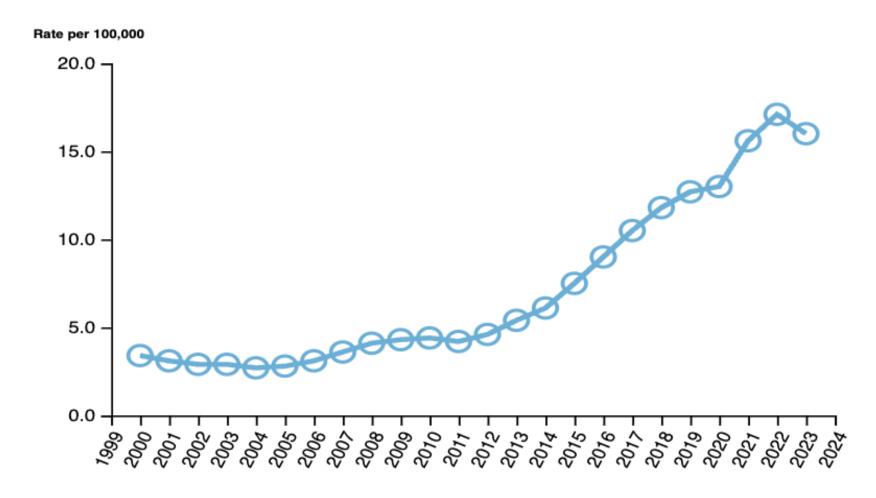
Centers for Disease Control and Prevention

s we approach the end of the 20th century, the United States is faced with a unique opportunity to eliminate syphilis within its borders. Syphilis is easy to detect and cure, given adequate access to and utilization of care. Nationally, it is at the lowest rate ever recorded and it is confined to a very limited number of geographic areas, primarily in the southern United States. Where syphilis does persist in the U.S., it disproportionately burdens African Americans living in poverty. Syphilis elimination is not only feasible, but also can have far-reaching public health implications by removing its devastating consequences-increased likelihood of HIV transmission and spontaneous abortions, stillbirths, and multi-system disorders caused by congenital syphilis acquired from mothers with syphilis.





Primary and Secondary Syphilis | 2023 | All age groups







Congenital and maternal syphilis

Congenital syphilis rates 2000-2023

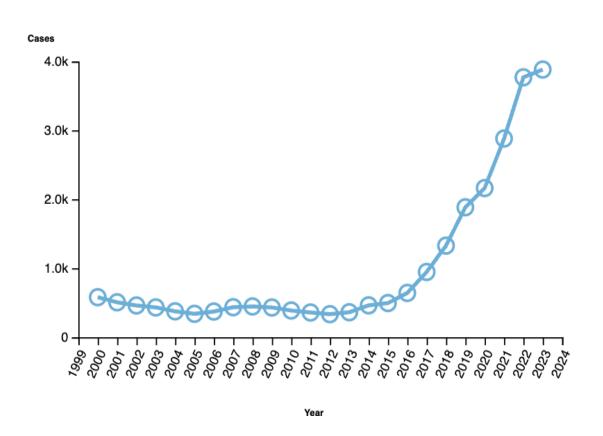
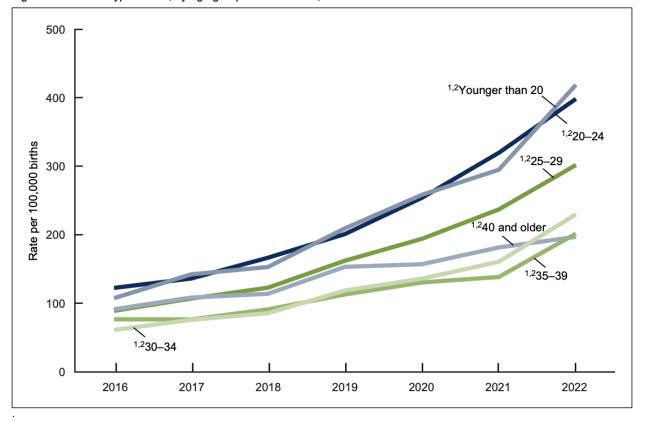


Figure 3. Maternal syphilis rate, by age group: United States, 2016–2022







What can we do?







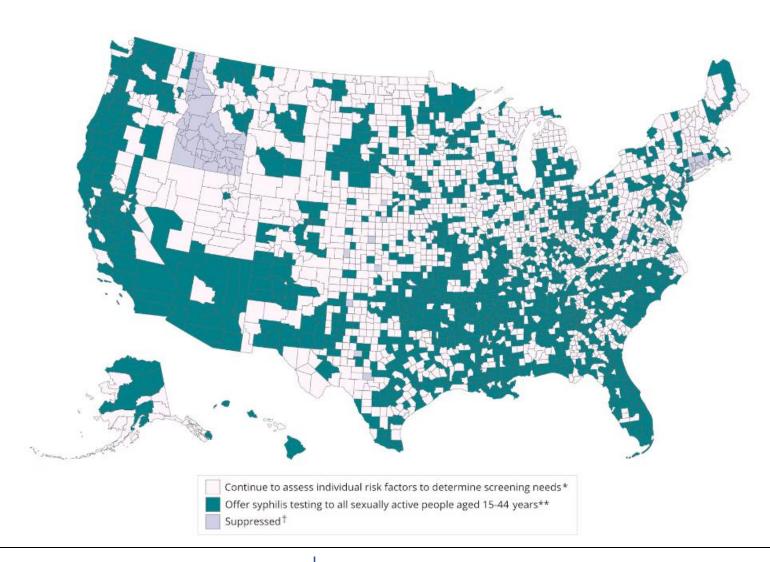
General Screening for Syphilis

Population	Recommendations
Men who have sex with men	 At least annually if sexually active Every 3-6 months based it increased risk*
Patients taking PrEP	 At initiation and every 3-6 months if increased risk*
Persons living with HIV	 At diagnosis and at least annually if sexually active, and more frequently depending on individual risk and local epidemiology*
Non-pregnant Women Non-MSM Men	 No national recommendation for routine screening Screen asymptomatic adults a increased risk*
Pregnant Women	 First prenatal encounter plus third trimester (28 weeks) and at delivery if increased risk or in a community with increased prevalence***





Syphilis rates are high (almost) everywhere



- Counties with syphilis rates >4.6 per 100,000 among females 15-44
- 72% of the US population



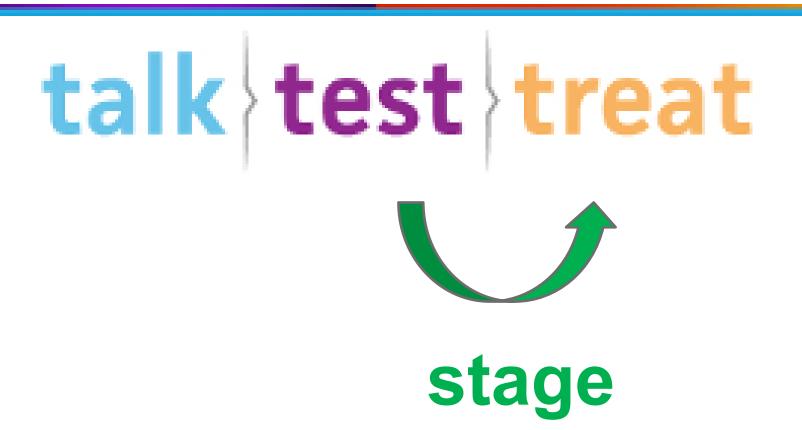
A case for increased screening

- In 2024, there were 144,805 cases of early non-primary, non-secondary syphilis and late syphilis/unknown duration i.e. "latent" infection
- The same year, there were 41,496 cases of primary or secondary syphilis i.e. symptomatic disease
- A large majority of new syphilis cases are diagnosed in people with no current symptoms
 - Screening is critical for preventing transmission and late complications!





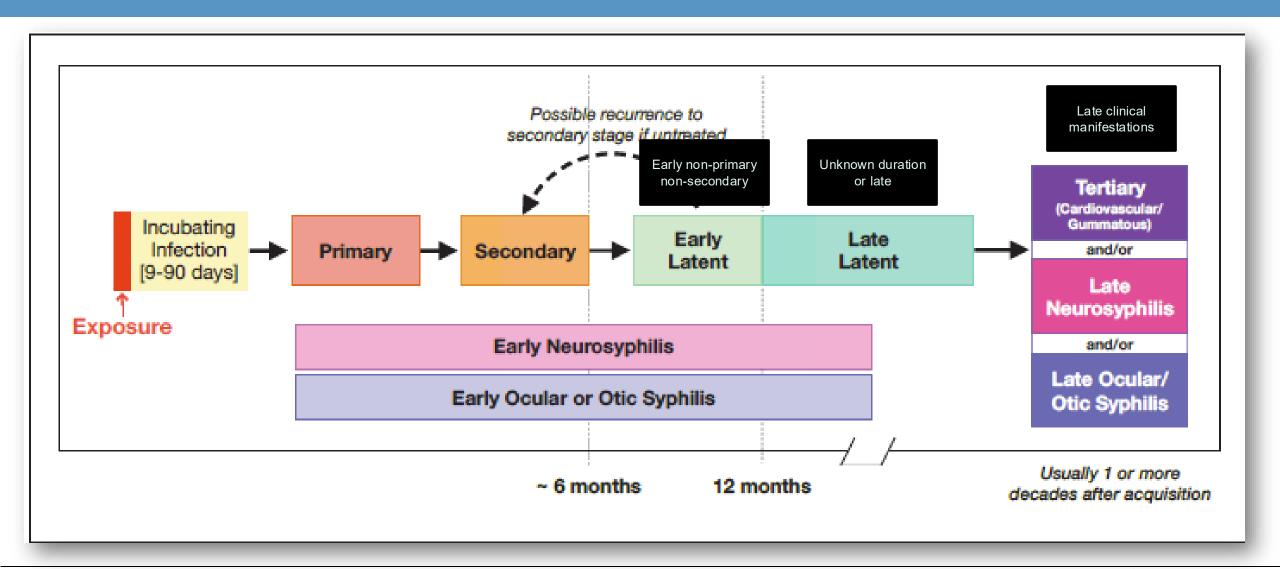
A missing step



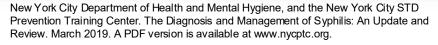




Syphilis – Natural History









Meet Joseph



- 24-year-old bisexual male
- Presents for "an ulcer on my penis"
- "It has been there for a few days but doesn't hurt"
- On exam had some inguinal lymphadenopathy

How to stage Joseph?





A stage of infection with *Treponema* pallidum characterized by one or more ulcerative lesions (e.g. chancre), which might differ considerably in clinical appearance







- Primary Syphilis
 - Local
 - One or more ulcers (chancres) at inoculation site
 - Painless
 - May go unnoticed
 - Often associated with regional or bilateral lymphadenopathy
 - Occur 10 90 days after infection
 - Highly infectious
 - Resolves in 1-6 weeks







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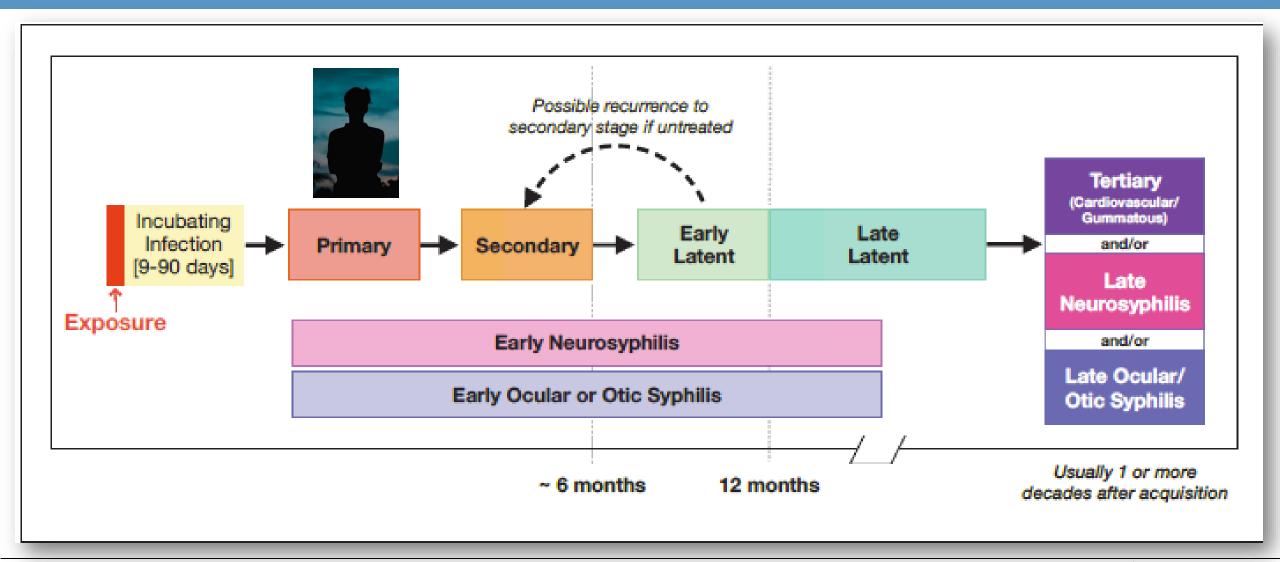
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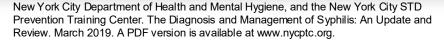




Primary Syphilis









2021 STI Guideline Updates to Primary Syphilis

- Classic Presentation
 - Single painless ulcer or chancre at the site of infection

- Atypical presentations
 - Multiple, atypical, or painful lesions at the site of infection

ORIGINAL ARTICLE

Painful and multiple anogenital lesions are common in men with *Treponema pallidum* PCR-positive primary syphilis without herpes simplex virus coinfection: a cross-sectional clinic-based study

Janet M Towns, ¹ David E Leslie, ² Ian Denham, ¹ Francesca Azzato, ² Christopher K Fairley, ^{1,3} Marcus Chen ^{1,3}





Meet Janice

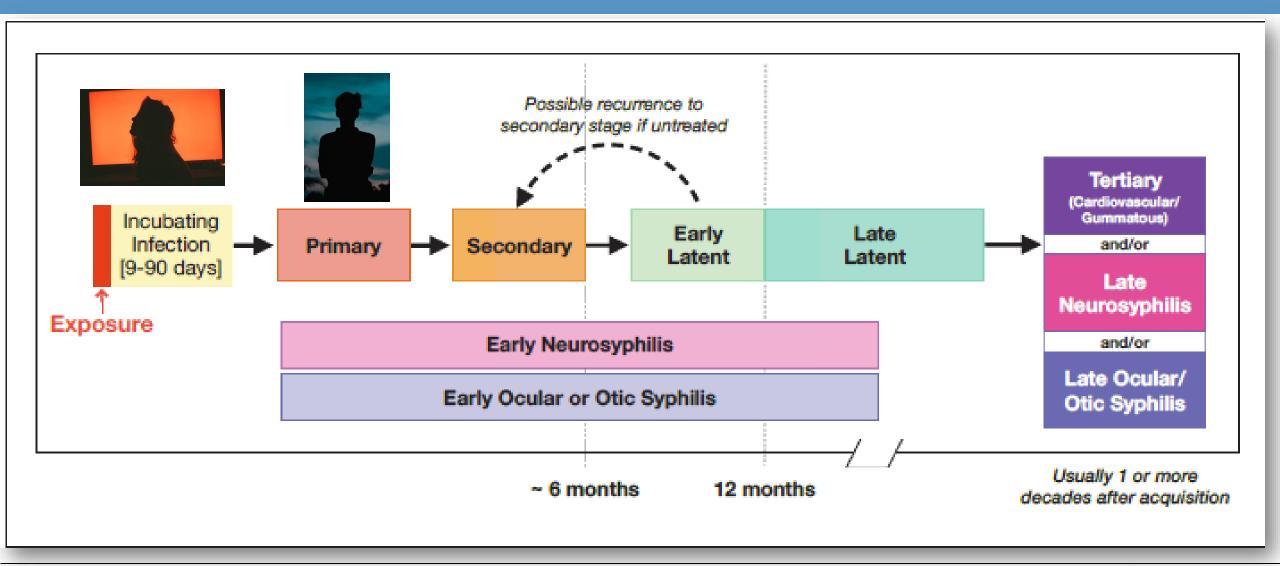


- 25-year-old female
- Presents for "routine STI testing"
- In a new (last 3 weeks) relationship with a bisexual male who was recently diagnosed with syphilis (Joseph)
- She reports no lesions, no rash, and her exam is benign

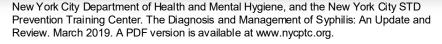




Syphilis – Incubation









Meet Jordan

- 30-year-old man who has sex with men who started PrEP 6 months ago
- Presents to clinic today for a routine PrEP visit and notes a recent history of diffuse skin rash that has now faded without any persistent symptom
- 6 weeks ago he presented to an urgent care when the rash appeared, and was sent home with a topical steroid cream







Jordan's Urgent Care Visit

- Diffuse, non-pruritic, non-painful, rash
- Erythematous macules and patches on his chest, axilla, abdomen, and bilateral upper and lower extremities





Jordan's Urgent Care Visit









Secondary Syphilis

A stage of infection caused by T.
 pallidum characterized by localized or
 diffuse mucocutaneous lesions (e.g.,
 rash – such as non-pruritic macular,
 maculopapular, papular, or pustular
 lesions), often with generalized
 lymphadenopathy

 Other signs can include mucous patches, condyloma lata, and alopecia

 The primary ulcerative lesion may still be present







Secondary Syphilis

- Secondary Syphilis
 - Bacterial Dissemination
 - Dermatologic manifestations
 - Systemic symptoms
 - Low-grade fever
 - Fatigue
 - Painless generalized adenopathy
 - Usually, 4-8 weeks after infection
 - Resolves in 6 weeks
 - Highly infectious







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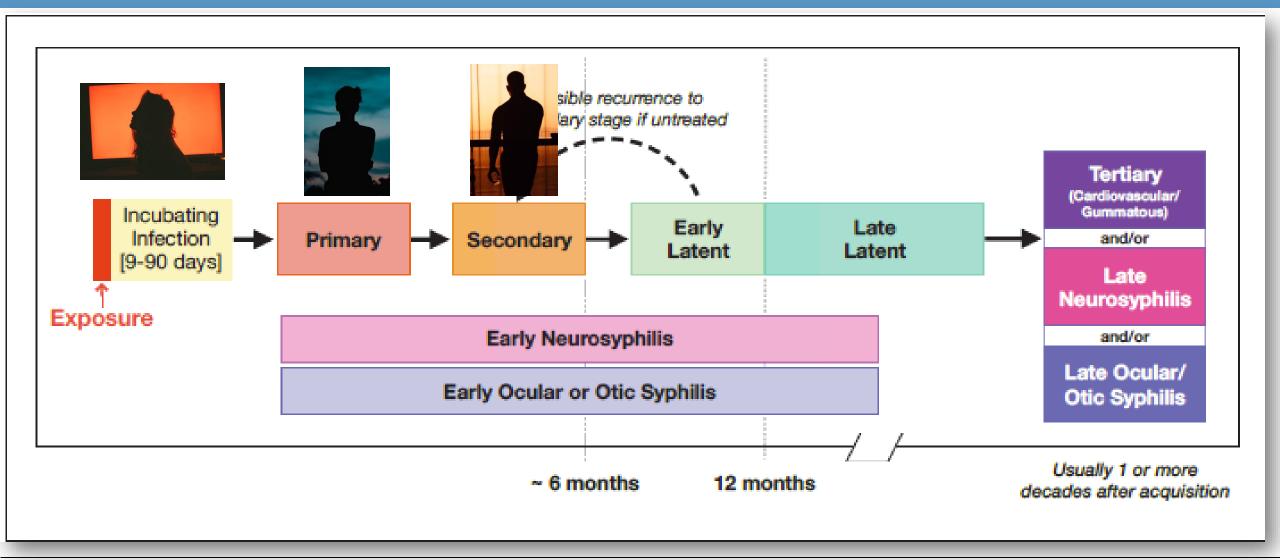
Syphilis - Secondary

Organ System	Clinical Findings
Skin and Mucous Membranes	Rash or other skin lesions with varied appearance frequently on palms/soles – Macular/papular/maculopapular – Annular – Psoriasiform – Necrotic (rare)
	 Condyloma lata: moist, gray-white, wart-like growths appearing in warm moist areas such as the perineum and the anus Patchy alopecia, often with a moth-eaten appearance Mucous patches: flat, silver-gray discrete macules, plaques or erosions involving the mouth, tongue, or ano-genital mucosa Split- or fissured-papules at the angles of the mouth and nasolabial folds (rare)
Systemic	Lymphadenopathy Systemic symptoms including: malaise, fever, and other nonspecific constitutional symptoms
Gastrointestinal	Gastric syphilis Hepatitis (usually subclinical)
Renal	Glomerulonephritis Nephrotic syndrome
Musculoskeletal	Arthritis Periostitis

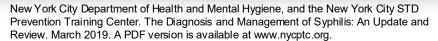




Syphilis – Secondary/Early Latent









Today's Visit with Jordan

- A few days ago Jordan felt like he was having a hard time hearing the TV
- Went to ED and was seen by ENT
 - "Asymmetric hearing loss, please get MRI"
 - MRI unremarkable
 - Told to follow-up outpatient





Today's Visit with Jordan

- At today's visit, Jordan notes that he's also having a hard time reading his homework
- A thorough neurologic exam reveals decreased visual and auditory acuity, but no other CN abnormalities
- You send him urgently to the ophthalmology clinic
- On the note from his fundoscopic exam:
 - "Panuveitis"







Clinical Descriptions of Ocular and Otic Manifestations

Ocular Syphilis

- Often presents as panuveitis
- Can involve any structure in the anterior and posterior segment of the eye including:
 - Conjunctivitis
 - Red eye/Pain
 - Anterior uveitis
 - Posterior interstitial keratitis
 - Optic neuropathy
 - Retinal vasculitis
- Can lead to permanent vision loss

Otosyphilis

- Typically presents with cochleo-vestibular symptoms including
 - Tinnitus
 - Vertigo
 - Sensorineural hearing loss
 - Unilateral/Bilateral
 - Have a sudden onset
 - Progress rapidly
- Can result in permanent hearing loss





Other neurosyphilis manifestations

NEUROSYPHILIS SYNDROME	ONSET	POSSIBLE SYMPTOMS & CLINICAL FINDINGS (Exam findings are listed in bold)	
Asymptomatic Neurosyphilis	Soon after infected	None	
Acute Syphilitic Meningitis	Within 1st year Can be seen during primary or secondary syphilis	 Meningismus (headache, nuchal rigidity, photophobia) Nausea, vomiting Focal neurologic symptoms (vision changes, tinnitus, hearing loss, facial weakness or other cranial nerve symptoms) Seizures 	 Symptoms of increased intracranial pressure Nuchal rigidity (+ Kernig/Brudzinski signs) Deafness (progressive or sudden) Cranial nerve deficits (3rd, 6th, 7th, 8th CN) Hemiplegia/Aphasia
Meningo-vascular Neurosyphilis (Rare spinal cord involvement)	Months to years (average 7 years)	Infarction-related focal neurologic symptoms • Paresthesias • Seizures • Hemiparesis, Hemiplegia • Aphasia • Hemianopsia (decreased vision or blindness in left or right half of visual field)	Pre-infarction symptoms • Headache • Dizziness/vertigo • Stuttering stroke-like symptoms (weakness, paresthesias) • Psychiatric manifestations (mood, personality, or behavioral changes; irritability) • Memory loss, slowed mentation & speech





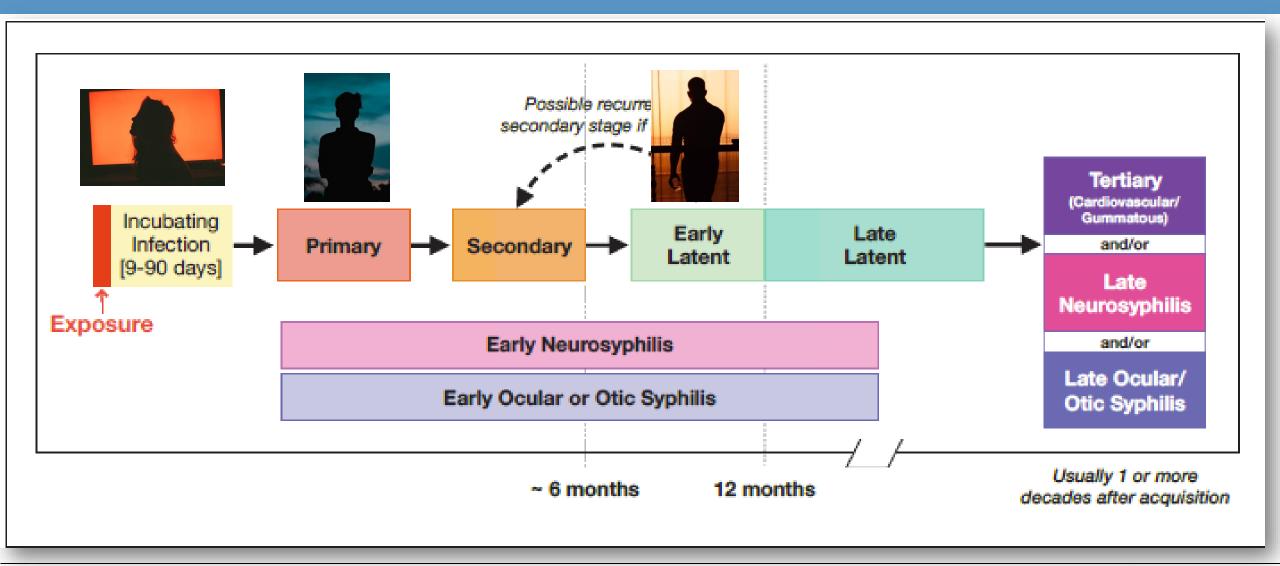
Screening for Neuro, Ocular, and Otic Syphilis

Screening Questions for Neurosyphilis (Including Ocular and Otosyphilis)				
Questions				
Symptoms of Otosyphilis				
 Have you recently had new trouble hearing? 	□ Yes – refer to ENT □ No			
2) Do you have ringing in your ears?	□ Yes – refer to ENT □ No			
 Symptoms of Ocular syphilis 3) Have you recently had a change in vision? 4) Do you see flashing lights? 5) Do you see spots that move or float by in your vision? 6) Have you had any blurring of your vision? 	□ Yes – refer to ophthalmology □ No			
Symptoms of neurosyphilis 7) Are you having headaches? 8) Have you recently been confused? 9) Has your memory recently gotten worse? 10)Do you have trouble concentrating? 11)Do you feel that your personality has recently changed? 12)Are you having a new problem walking? 13)Do you have weakness or numbness in your legs?	Yes			

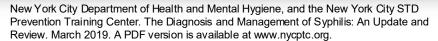




Syphilis – Secondary/Early Latent









Meet Jackie

- 29 year old female presents for a follow up visit
- She noted during a recent family planning visit that she was considering becoming pregnant
- Comprehensive STI testing was performed at that time at the discretion of the treating clinician, and included syphilis testing
- She has been referred to you for a positive result
- A pregnancy test from that visit was negative
- Prior syphilis testing two years ago was negative
- She notes no symptoms today, and has a normal exam







Syphilis – Latent

Latent Phase	Definition	
Syphilis, early non-primary non- secondary	Duration of infection <= 1 year	
Syphilis, unknown duration or late	Duration of infection >1 year	
	Unknown duration of infection	
***Latent syphilis requires no exam findings of primary, secondary		

- Early latent disease is differentiated due to the risk of relapsed or intermittent bacteremia
 - This can occur in up to 24% of patients
 - Manifests as symptoms of secondary syphilis including CNS disease
- Risk for infecting partners remains

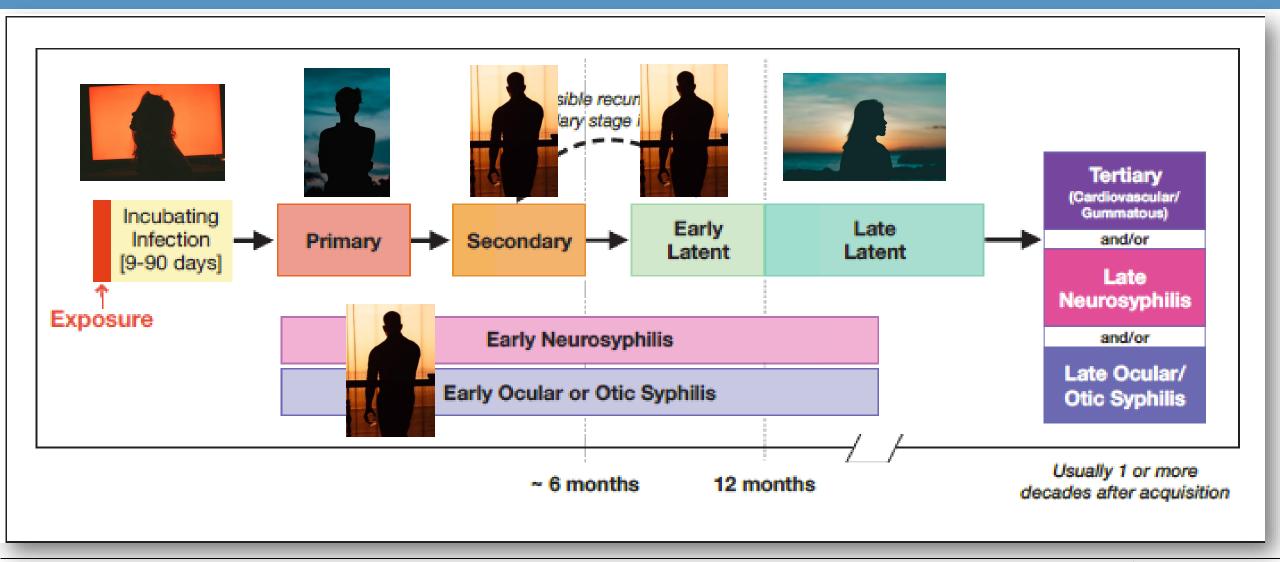
or tertiary syphilis

Risk of relapsed symptoms and infectiousness decreases after 1 year

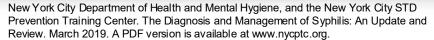




Syphilis – Secondary/Early Latent









Testing







How Do We Test for Syphilis?

- Multiple options exist to test directly for the presence of treponemes in primary syphilis lesions
 - Dark-field microscopy
 - Direct fluorescent antibody testing
 - T palladium NAAT
 - No FDA-approved tests are commercially available

Unfortunately, these are not available in most clinical settings





Serologic testing

Non-treponemal (lipoidal antigen) tests	Treponemal tests
Test serum reactivity (presence of antibodies) to cardiolipin-cholesterol-lecithin	Test serum reactivity against T. pallidum- specfic antigens
Antigen response is due both directly to bacteria and host tissue damage	More specific than non-treponemal tests
Up to 11% of positive tests in one series not due to T pallidum	Often remain positive for life
Degree of reactivity changes over disease course/after treatment	Generally automated
Generally manual	

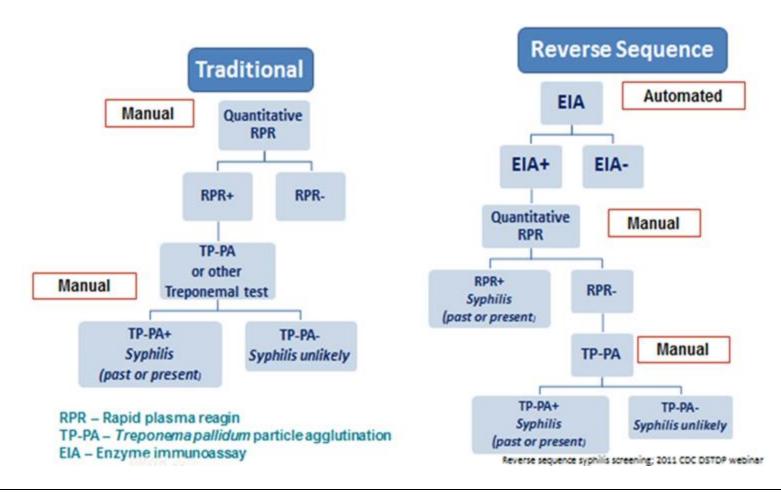


Serologic Testing

Non-treponemal (lipoidal antigen) tests	Treponemal tests
Rapid plasma reagin (RPR)	Enzyme Immunoassay (EIA)
Venereal disease research laboratory (VDRL)	Fluorescent treponemal antibody (FTA-ABS)
	Treponema pallidum particle agglutination (TP-PA)
	Chemiluminescence assay (CIA)



Serologic Testing

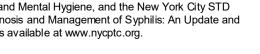


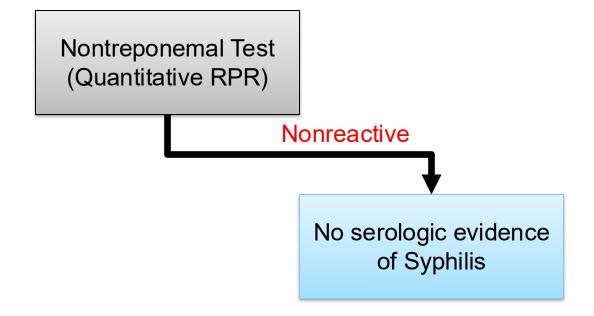




Nontreponemal Test (Quantitative RPR)

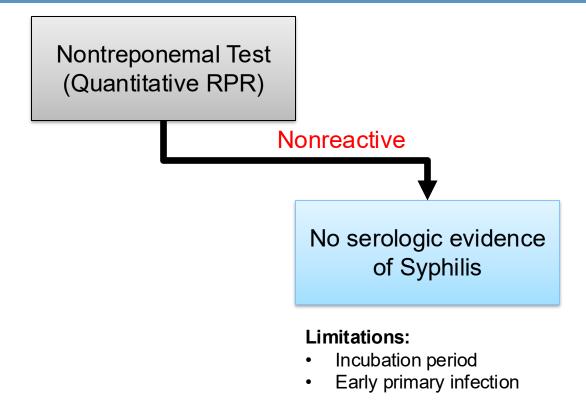




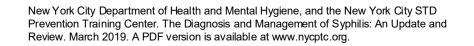




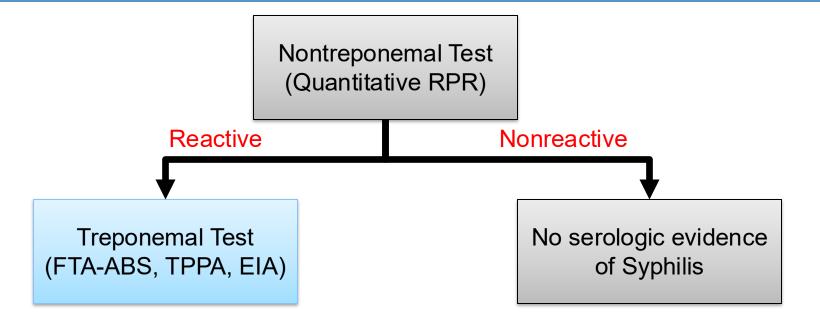






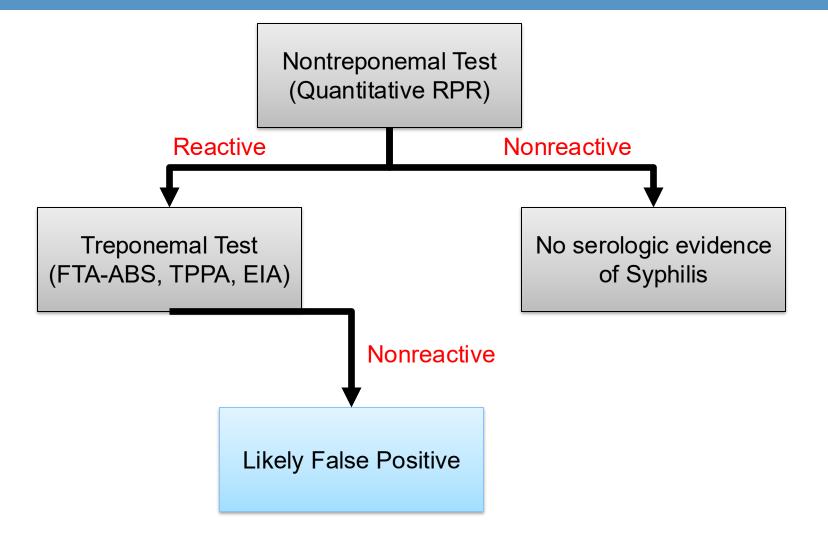




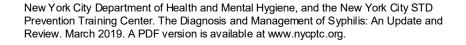




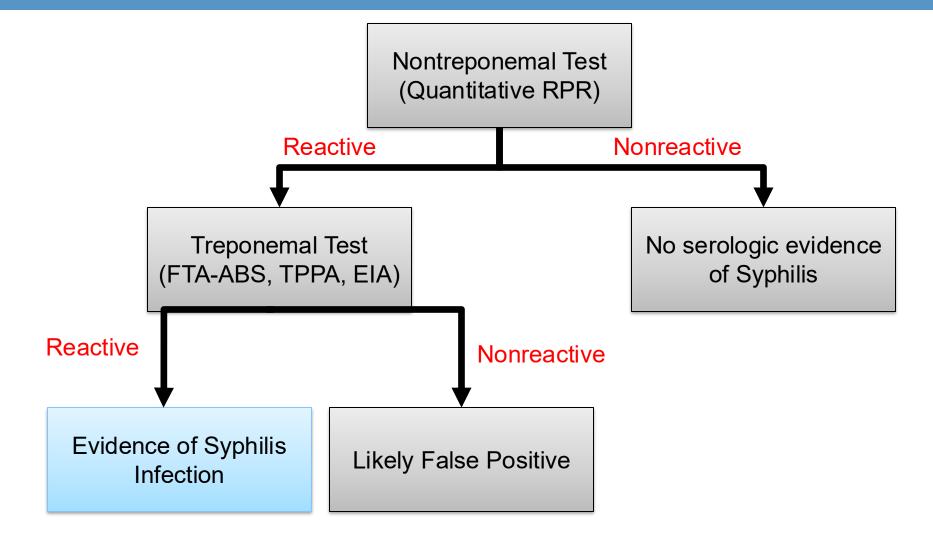




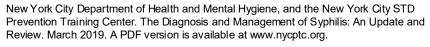


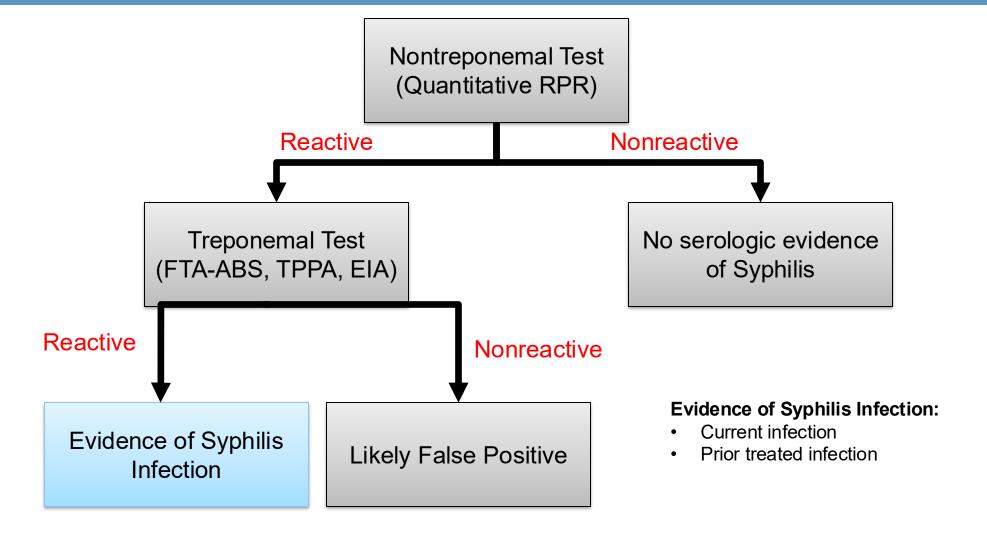




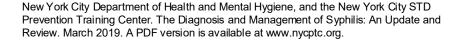










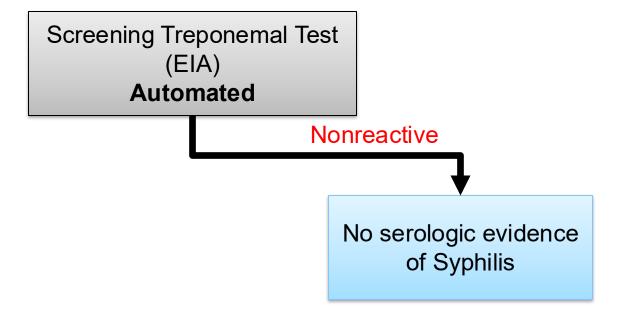




Screening Treponemal Test (EIA) Automated

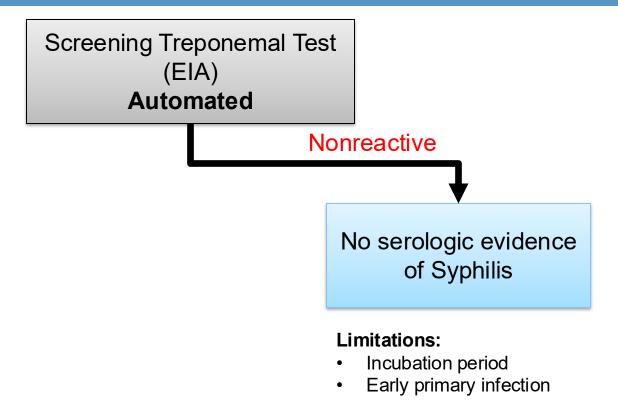




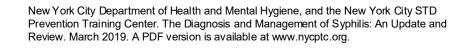




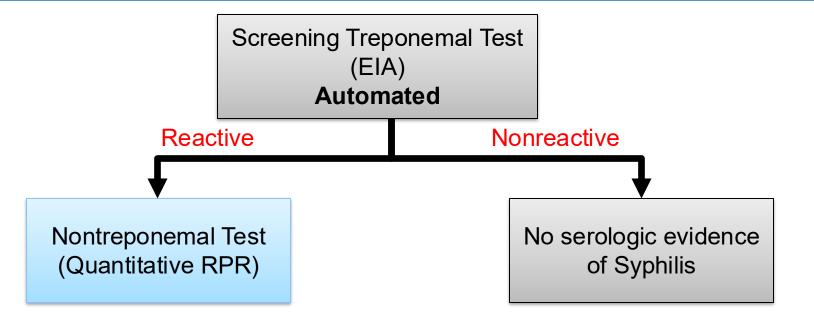






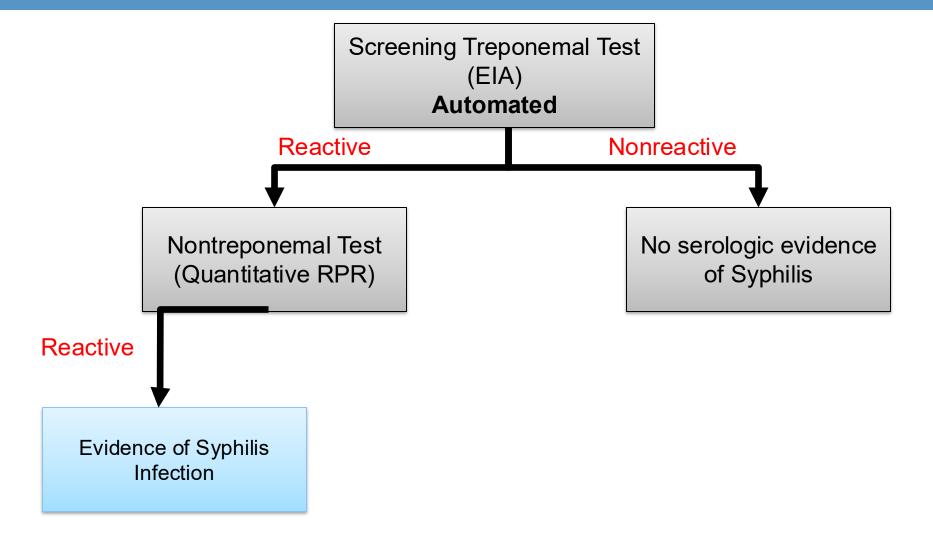




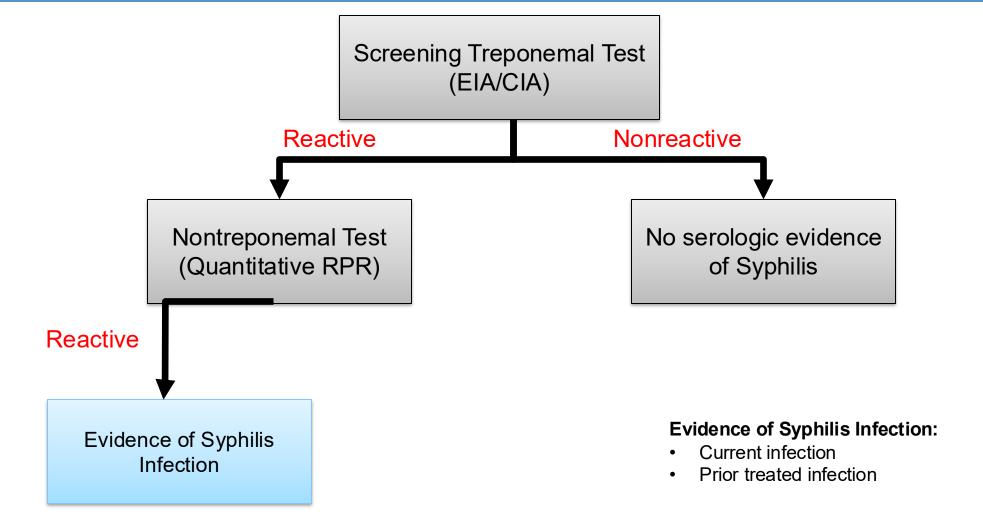




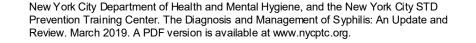




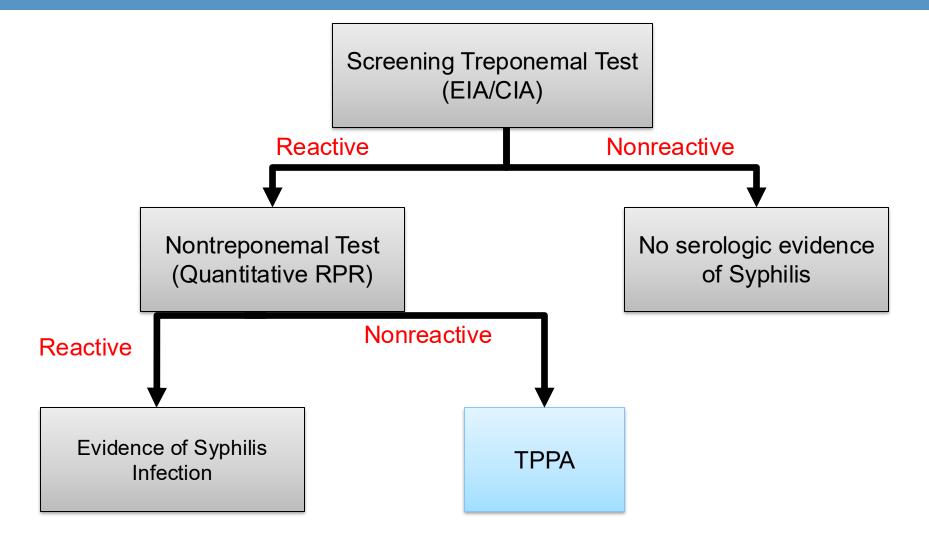




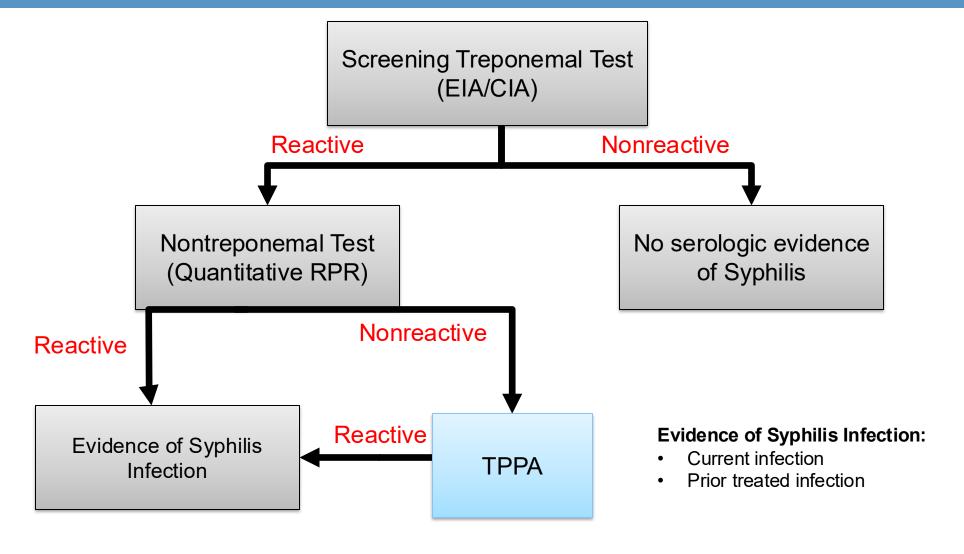








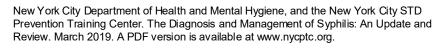


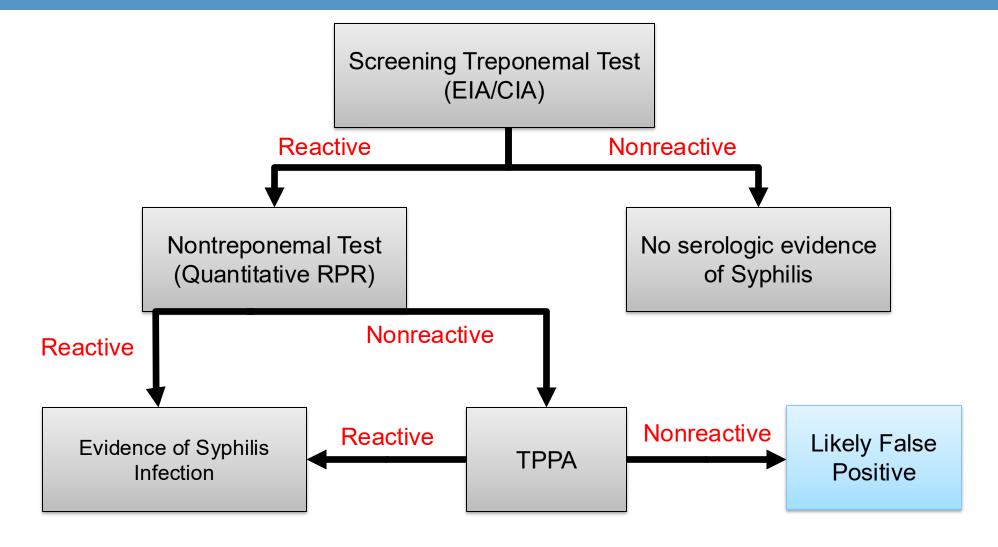


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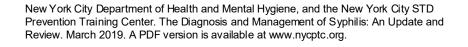
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FAQ: What about people with prior syphilis?

- Treponemal tests typically remain positive for life following syphilis infection, and RPR sometimes remains reactive as well
- Comparing RPR titers to prior results is an important way to evaluate for re-infection
- Stay tuned for more!





FAQ: What about CNS disease?

- Neurological disease previously always required diagnosis with CSF studies
- Hallmark CSF abnormalities include
 - Pleocytosis
 - >5 cells/mL in most patients
 - >20 cells/mL in people with HIV
 - Elevated protein
 - Limited sensitivity and specificity
 - Reactive CSF VDRL
 - Less than 80% sensitive, but specific







2021 Updates

Fewer Lumbar Punctures

- Isolated ocular symptoms and no cranial nerve dysfunction
 - CSF exam is not necessary
- Otic syphilis
 - CSF exam is not necessary
- Neuro syphilis
 - No repeat CSF exam at 6 months with adequate RPR response (HIV and HIV+/ART)







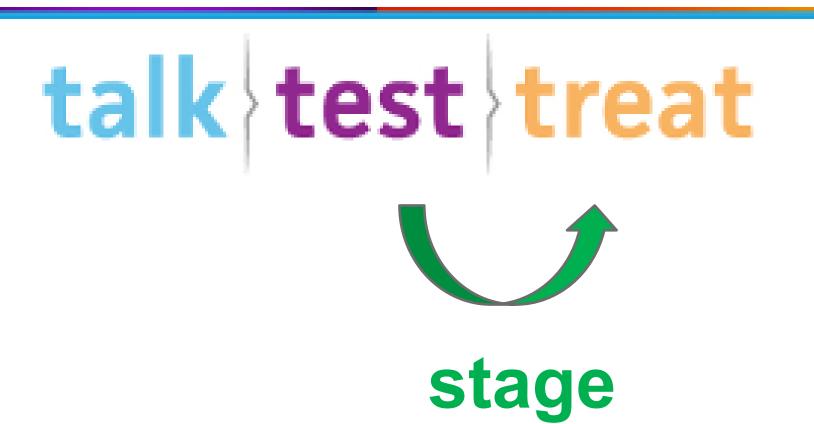
FAQ: When Do I Need to Report This?

- Processes for reporting new syphilis diagnoses vary by state/locality
- Always check with your local Department of Health regarding reporting requirements and processes





Treatment







Finally, treatment!

- Treatment continues to rely on penicillin, to which resistance has not been observed
- Long-acting benzathine penicillin-G sustains treponemocidal drug levels for 7-10 days
- Due to long generation times (33 hours), sustained drug levels are felt to be necessary for bacterial elimination
- Due to a recent shortage of this drug, doxycycline has been introduced as an alternative, supported primarily by retrospective studies
- On 1/16 the FDA announced that it would allow importation of Extencilline (an equivalent penicillin manufactured in Italy)





Syphilis Treatment – Early (uncomplicated)

Stage	Treatment	Alternative
Incubation	Benzathine penicillin G 2.4 million	Doxycycline 100mg twice
Primary	units intramuscular injection once	daily for 14 days
Secondary		
Syphilis, early non- primary non-secondary		



Incubation



Primary



Secondary/ early latent





Syphilis Treatment – CNS disease



Neurosyphilis, Ocular, or Otic Syphilis

Tertiary

Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units intravenously every 4 hours, or by continuous infusion, for 10–14 days Procaine penicillin G 2.4 million units IM once daily *PLUS* Probenecid 500mg 4 times daily for 10–14 days





Syphilis Treatment – Late Latent



Syphilis, unknown duration or late

Benzathine penicillin G 2.4 million units intramuscular injection 3 times at one week intervals

Doxycycline 100mg twice daily for 28 days





FAQ

How many days between injections is acceptable for latent syphilis?

General Population

- "If a person receives a delayed dose of penicillin in a course of weekly therapy for late latent syphilis or syphilis of unknown duration, the course of action that should be recommended is unclear"
- Interval of 7–9 days preferred
- An interval of 10–14 days between doses of benzathine penicillin for latent syphilis "might" be acceptable before restarting the sequence of injections
 - Check with local health departments for their policies

Pregnant women

- Optimal Interval is 7 days
- Missed doses >9 days between doses are not acceptable
- Missed doses = repeat the full course of therapy





Follow up and treatment failure

- Quantitative nontreponemal serologic tests should be repeated <u>at least</u> at:
 - 6 months
 - 12 months
 - 24 months (for latent disease)

- An inadequate serologic response after treatment is failure for titers to decrease by 4x:
 - 12 months after treatment for primary, secondary
 - 24 months after treatment for latent disease





1:2048

1: 1024

1:512

1: 256

1:128

1:64

1:32

1: 16

1:8

1:4

1:2

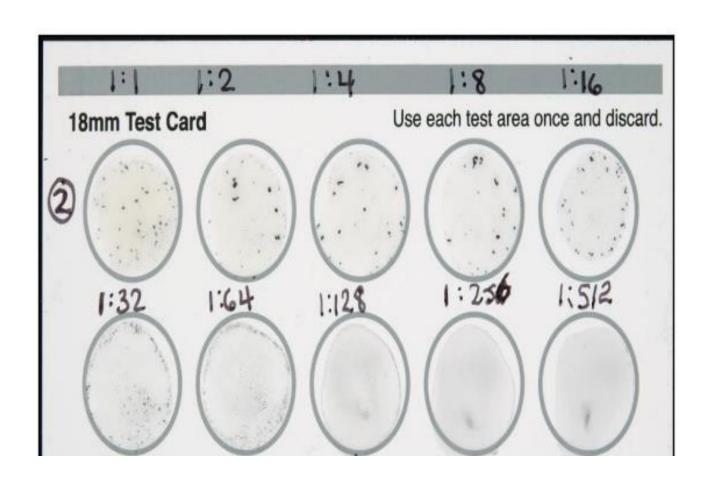
1: 1

Nonreactive





What Do Titers Mean?



1:2048

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1: 16

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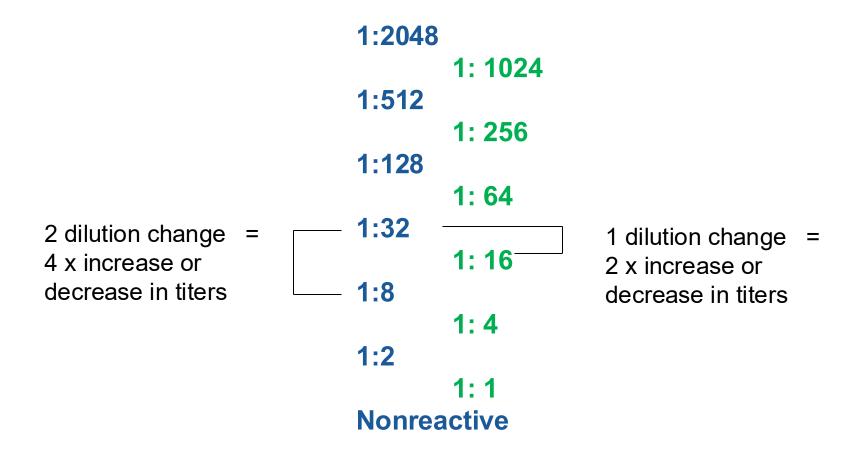
1:2

1: 1

Nonreactive

















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1:2048
       1: 1024
1:512
       1: 256
1:128
       1: 64
1:32
       1: 16
1:8
1:2
       1:1
Nonreactive
```





FAQ: Which partners to notify?

- Transmission
 - "Microscopically abraded" skin
 - Mucous membrane lesions
- Skin and mucous membrane lesions occur during the first year after infection and can be easily missed

STAGE OF INFECTION	MAXIMUM PERIOD OF INFECTIOUSNESS * (Prior to symptom onset or first serologic evidence of infection/reinfection)	MANAGEMENT OF CONTACTS AT RISK FOR EXPOSURE
Incubating Infection	Persons being treated presumptively for incubating infection following a known exposure, who lack any exam or serologic evidence of syphilis, are not considered infectious—but will become infectious if left untreated. Therefore, contacts of persons treated for incubating infection are not at risk of exposure but may benefit from syphilis/STI screening.	N/A
Primary Syphilis	3 months	Evaluation and presumptive treatment of contacts exposed within 3 months prior to the onset of symptoms or signs in the case patient.
Secondary Syphilis	6 months	Evaluation and presumptive treatment of contacts exposed within 6 months prior to the onset of symptoms or signs in the case patient.
Early Latent Syphilis	Since skin and mucous membrane lesions, which often go unrecognized by patients, occur predominately during the first year of infection, persons diagnosed with early latent syphilis are potentially infectious to contacts despite their lack of symptoms or exam findings at the time of treatment. ²³	Evaluation and presumptive treatment of contacts exposed <u>within 12 months</u> of first serologic evidence of infection or re-infection, in the case-patient.
Late Latent Syphilis	Persons diagnosed with late latent infection (ie, acquired > 1 year prior to treatment) are not considered to be infectious to current/recent sexual or needle-sharing contacts.	Long-term ongoing partners exposed to the case-patient more than 1 year ago may benefit from syphilis screening.
Latent Syphilis of Unknown Duration	If there is insufficient information to determine the duration of latent infection, the case-patient may have been infectious over the past year. Patients with latent syphilis of unknown duration who have high nontreponemal serologic titers (ie, > 1:32) have an increased likelihood of recent acquisition and of being infectious. ²³	Evaluation and presumptive treatment of contacts exposed within 12 months of first serologic evidence of infection, or re-infection in the case-patient.
Ocular, Otic, or Neuro- syphilis	Central nervous system, ocular and otic infection are not sexually transmissible.	If the case-patient also meets the diagnostic criteria for primary, secondary, early latent, or latent of unknown duration, contacts should be managed as noted above.
Tertiary Syphilis	Not considered infectious.	



FAQ: Partner management

- Primary, secondary, or early latent syphilis (<u>not</u> incubation period)
 - Partners exposed in the last 90 days: empiric therapy
- Secondary syphilis
 - Partners exposed 90 days-6 months+ symptom duration: serologies, treat if positive
- Early latent
 - Partners exposed 90 days-12 months: serologies, treat if positive
- Late latent
 - Long term sex partners should be tested, treat if positive
- Important!! Patients treated for primary, secondary, or early latent syphilis should abstain from sex until 7 days after they (and partners) start treatment





Summary

- Syphilis case rates are still high!
- Think about testing your patients
 - If vulnerable to infection (take a good history)
 - When screening for other sexually transmitted infections
- Knowing which syphilis testing algorithm is in use at your institution is important for diagnosis and staging
- Treatment is based on the stage of disease
 - Remember to screen for neurologic, ocular, and otic manifestations
- Identifying syphilis cases requires a high index of suspicion





NYC STI Prevention Training Center

The CDC-funded NYC STD Prevention Training Center at Columbia University provides a continuum of education, resources, consultation and technical assistance to health care providers, and clinical sites. www.nycptc.org

Didactic Presentations

Webinars, conferences, trainings and grand rounds presentations to enhance and build knowledge

Technical Assistance

Virtual and on-site technical assistance regarding quality improvement, clinic implementation and best practices around sexual health provision

For more information please contact: nycptc@cumc.columbia.edu



COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

Clinical Consultation Warmline

Clinical guidance regarding STD cases; no identifying patient data is submitted

https://stdccn.org/

Resources

Clinical guidance tools regarding the STD treatment guidelines, screening algorithms and knowledge books, such as the **Syphilis Monograph**.

To download a copy please visit:

https://www.publichealth.columbia.edu/file/15568/download?token=exDNYpJ-

