

# Yale SCHOOL OF MEDICINE

## Syphilis 101 CT DPH STD Clinicians Meeting

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Dept of Internal Medicine/Infectious Diseases  
January 11, 2023

## Learning Objectives

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Describe	the current epidemiology of syphilis in US
Distinguish	between stages of syphilis based on clinical characteristics
Understand and apply	testing algorithms and interpretation of currently available syphilis tests
Apply	knowledge of syphilis staging to appropriate treatment recommendations

# Roadmap

- Epidemiology
- Clinical
- Diagnosis- reverse algorithm
- Management
- Reporting
- Cases- Test your retention!



Case-30 year old man presents with 7 days of a painless ulcer on his glans penis.



Differential?  
Diagnostics?  
Decision to tx?

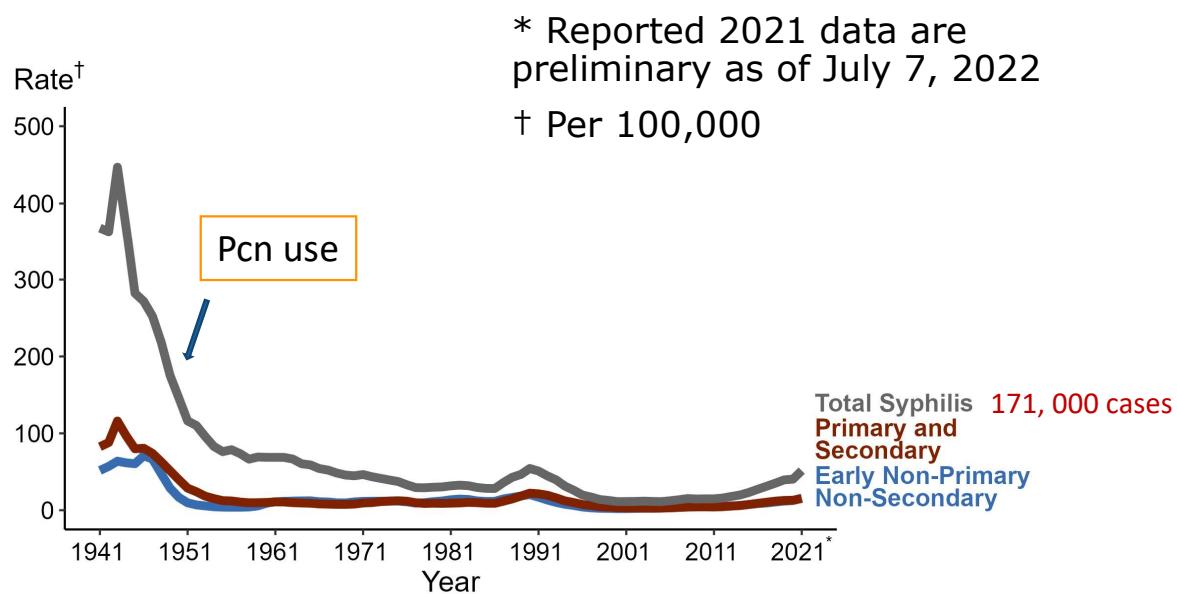
# Syphilis

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## Epidemiology



## Syphilis — Rates of Reported Cases by Stage of Infection, United States, 1941–2021\*

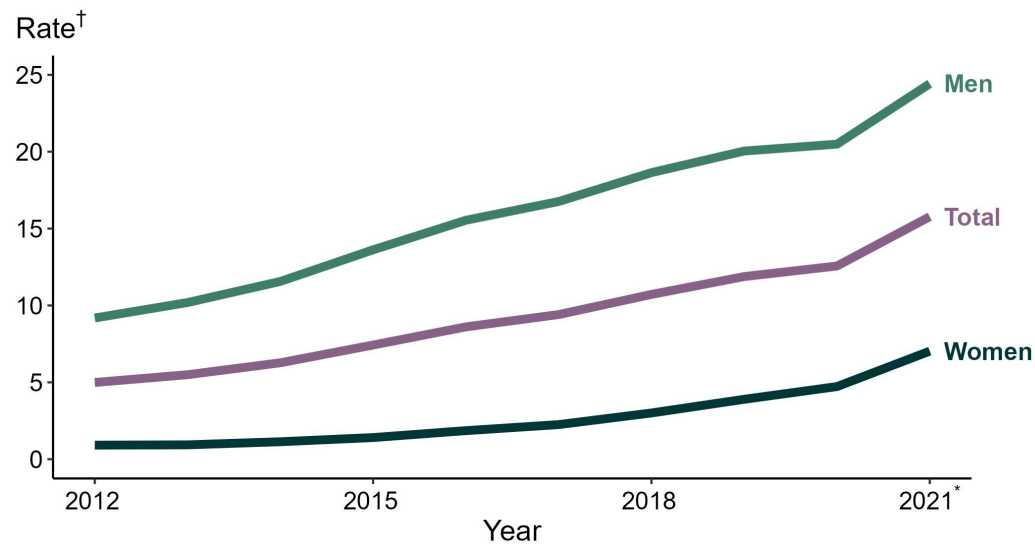


SUMMARY: Better c/w WW2 but on rise since 2001

# Primary and Secondary Syphilis — Rates of Reported Cases by Sex, United States, 2012–2021\*

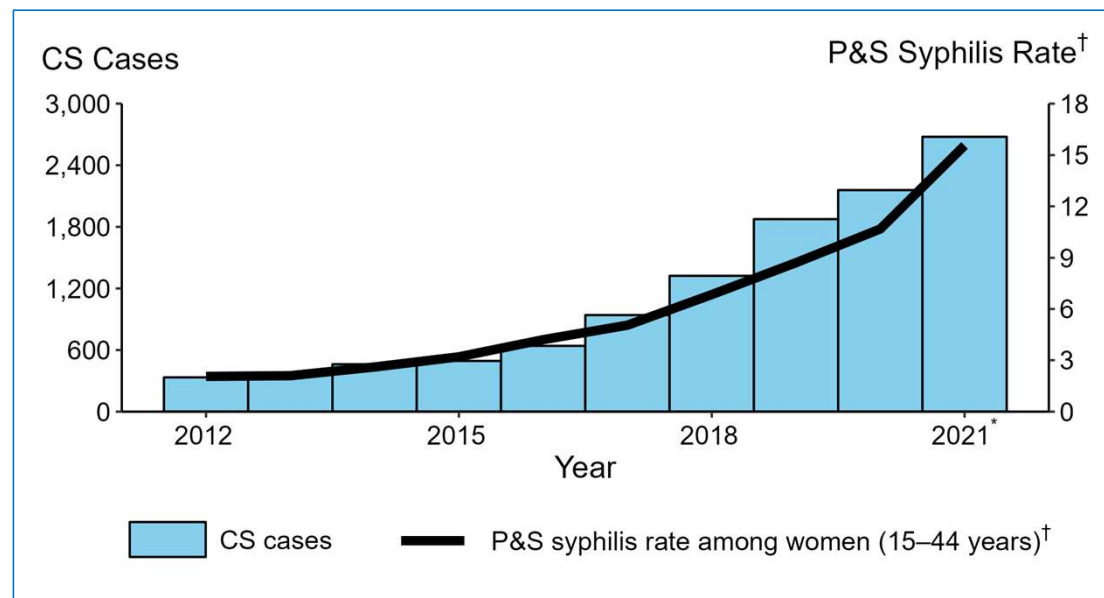
\* Reported 2021 data are preliminary as of July 7, 2022

† Per 100,000



Women: 2016-2021 **204 %** increase  
Men: 2016-2021 **45%** increase

## Congenital Syphilis — Reported Cases by Year of Birth and Rates of Reported Cases of Primary and Secondary Syphilis Among Women Aged 15–44 Years, United States, 2012–2021\*



**25% increase past year**  
**700% increase past 9 years.**

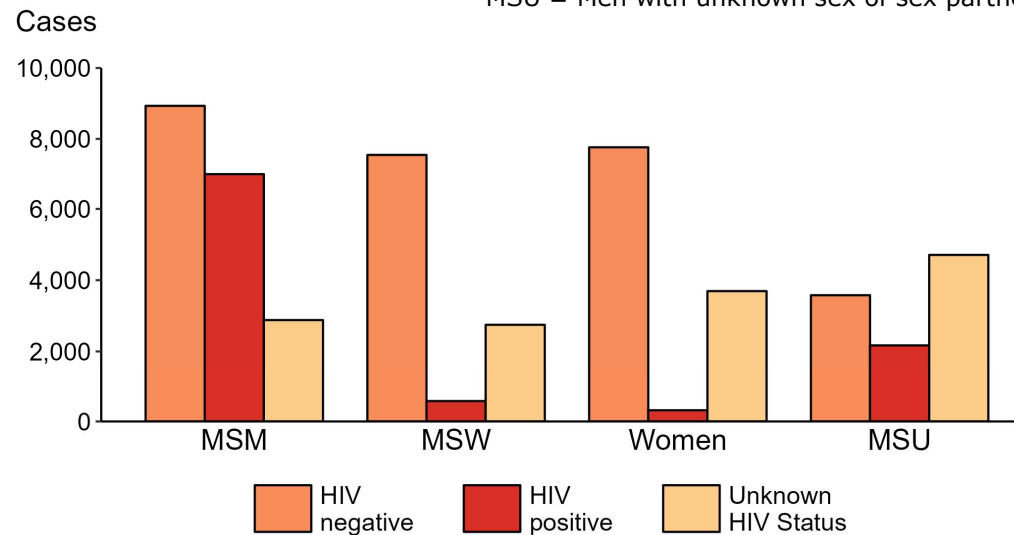


## Primary and Secondary Syphilis — Reported Cases by Sex, Sex of Sex Partners, and HIV Status, United States, 2021\*

\* Reported 2021 data are preliminary as of July 7, 2022

**NOTE:** Of all reported cases of primary and secondary syphilis, 0.8% were cases with unknown sex.

**ACRONYMS:** MSM = Gay, bisexual, and other men who have sex with men; MSW = Men who have sex with women only; MSU = Men with unknown sex of sex partners



High proportion HIV co-infection in MSM

# Epidemiology Summary

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- MSM predominant but women and MSW rates rising
- Congenital syphilis cases rising
- Lots of HIV co-infection

## Screening implications:

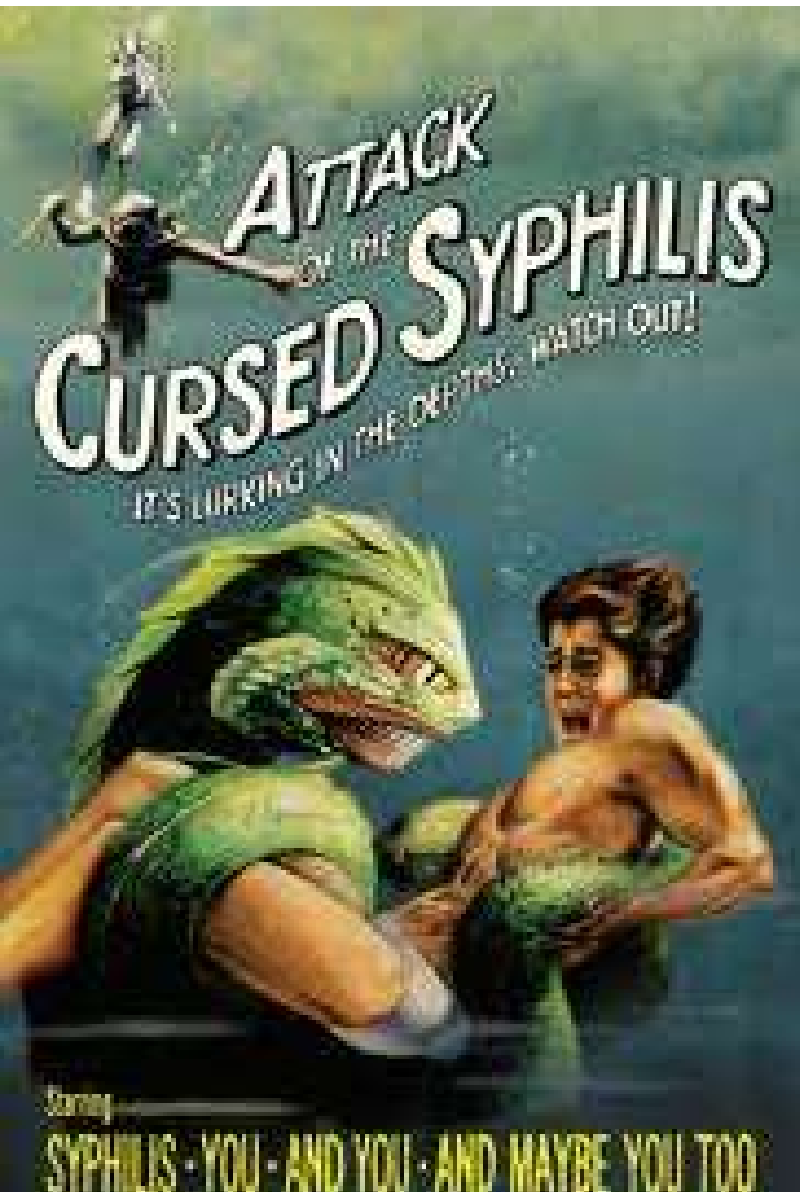
- ✓ MSM
- ✓ Sex partners of patients with infectious syphilis
- ✓ HIV+
- ✓ Pregnant

*JAMA. 2022 ;328(12):1250-1252 Updated USPSTF Recommendations-  
Screening for syphilis in non-pregnant adults*

## Syphilis-The organism

- *Treponema pallidum*
- Can be seen on darkfield or electron microscopy
- **Cannot** be cultured *in vitro*
- Culture *in vivo* by inoculating rabbit testicles





# Transmission and Incubation

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- Transmission-
  - Sexual
  - Vertical
  - Kissing
  - Blood transfusion
  - Inoculation
- Infectious= primary, secondary (when lesions/rash present)
- Incubation- 10-90 days; average 21 days.


## Syphilis- clinical

- **Early** syphilis
  - Primary
  - Secondary
  - Early Latent
- **Late** syphilis
  - Late latent
  - Tertiary syphilis
    - Cardiovascular
    - Neurologic
    - Gummatous




# The Stages of Syphilis

## Primary




The chancre lesion is the hallmark of primary syphilis. It may appear 10-90 days after exposure. Common sites include penis and labia. Other sites include anus, oral mucosa. Without treatment, chancre disappears in 2-8 weeks.

## Secondary

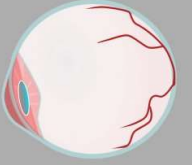


Rash, pink to brown macules. Involves palms/soles in 50% of cases.


Oral lesions called "mucous patches" resembling snail tracks.



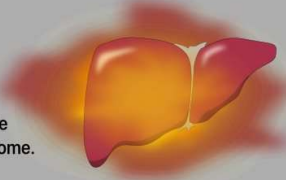
Symptomatic early neurosyphilis, cranial nerve deficits and/or aseptic meningitis presentation.



Ocular syphilis manifestations including anterior or posterior uveitis.



Genito-inguinal rashes, including tinea-mimicker or heaped-up wart-like lesions called condyloma lata.



Less common internal organ manifestations including acute hepatitis and nephrotic syndrome.

## Latent

Latent syphilis refers to asymptomatic infection after the period of primary and secondary syphilis (noticed or unnoticed) has passed.

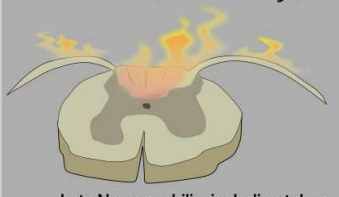
### Early Latent

Early latent refers to asymptomatic patients with positive testing, in whom history can confirm exposure to or symptoms of primary or secondary syphilis within the last year. This is group may receive single-dose penicillin like primary or secondary.


### Late Latent

Late latent patients have positive serology but do not meet criteria for early. Thus, multiple doses of penicillin.


## Late (Tertiary)



Late Neurosyphilis, including tabes dorsalis, gait impairments, and dementia. Tabes dorsalis damages the dorsal columns and sensory nerve roots, causing a syndrome of pain and sensory deficits similar to those of B12 deficiency.



Gumma are ulcerating granulomas on skin, bone, and internal organs.

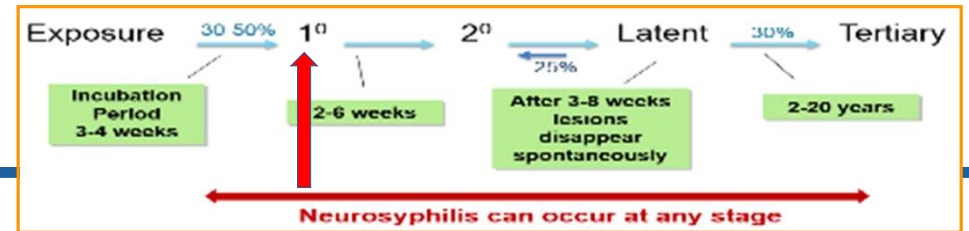


Cardiovascular effects of late syphilis include aortic aneurysm and coronary arteritis.

**THE CURB**  
**SIDERS**  
 INTERNAL  
 MEDICINE

Curbsiders Episode # 127!! Graphic by Bryan Brown, MD, MHS

## Primary Syphilis



- Incubation- 10-90 days
- Papule at exposed site which ulcerates= **Chancre**
- **Painless** chancre with regional painless lymphadenopathy
- DDx- HSV, chancroid, LGV, donovanosis, trauma, squamous cell cancer, furuncle.

penile



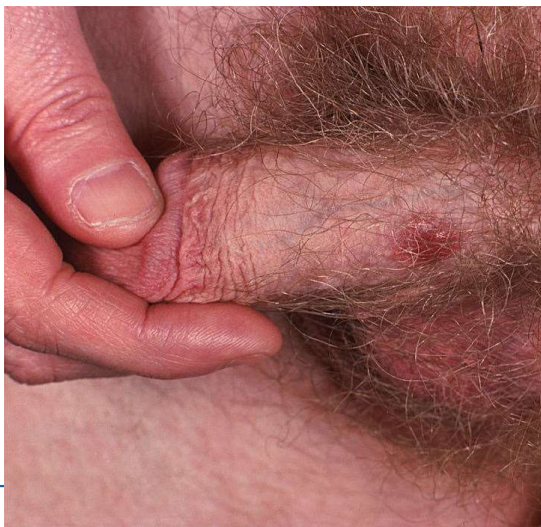
labial



cervical



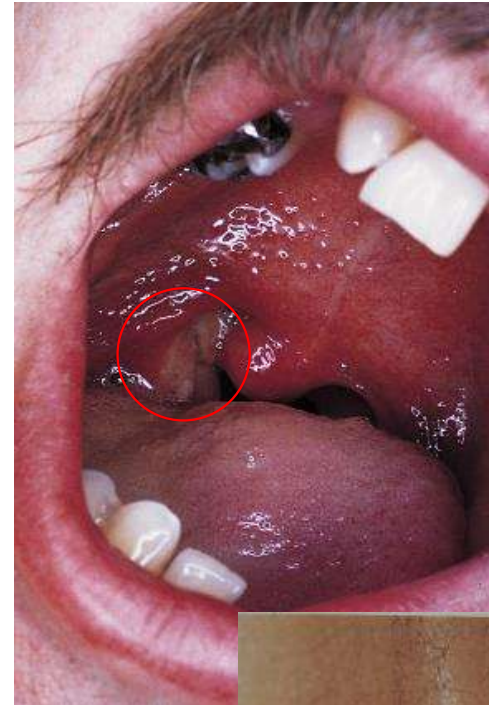




## Primary chancres



## Other chancres



## Secondary Syphilis

- Skin rash (75-90%)
  - Non-pruritic
  - Palms and soles in 60% of cases
  - 'nickel and dime' lesions





## Secondary syphilis

- sore throat, malaise, fever, **generalized lymphadenopathy, rash**
- Alopecia areata
- ~~Hepatitis~~
- Renal- nephrotic syndrome
- CNS involvement.



## Secondary syphilis: Mucous patches

Oral



of Nicholas Fiumara, MD

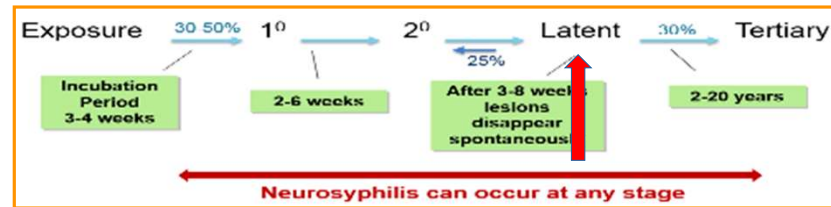
Genital



Condylomata lata- (5-25%)-heaped, moist papules in warm areas- gluteal folds, genitals, axillae



# Latent Syphilis



Definition- positive serology in absence of disease

- Early (EL)- <1 year duration
- Late (LL)- >1 year duration

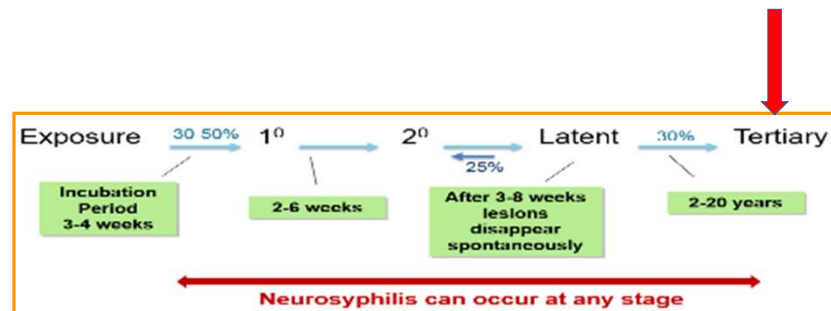
Diagnosis EL if-

- Documented seroconversion in past year
- Unequivocal si/sx of primary or secondary in last year
- Sex partner w/ primary, secondary, EL in last year
- A fourfold increase titer within last 12 months

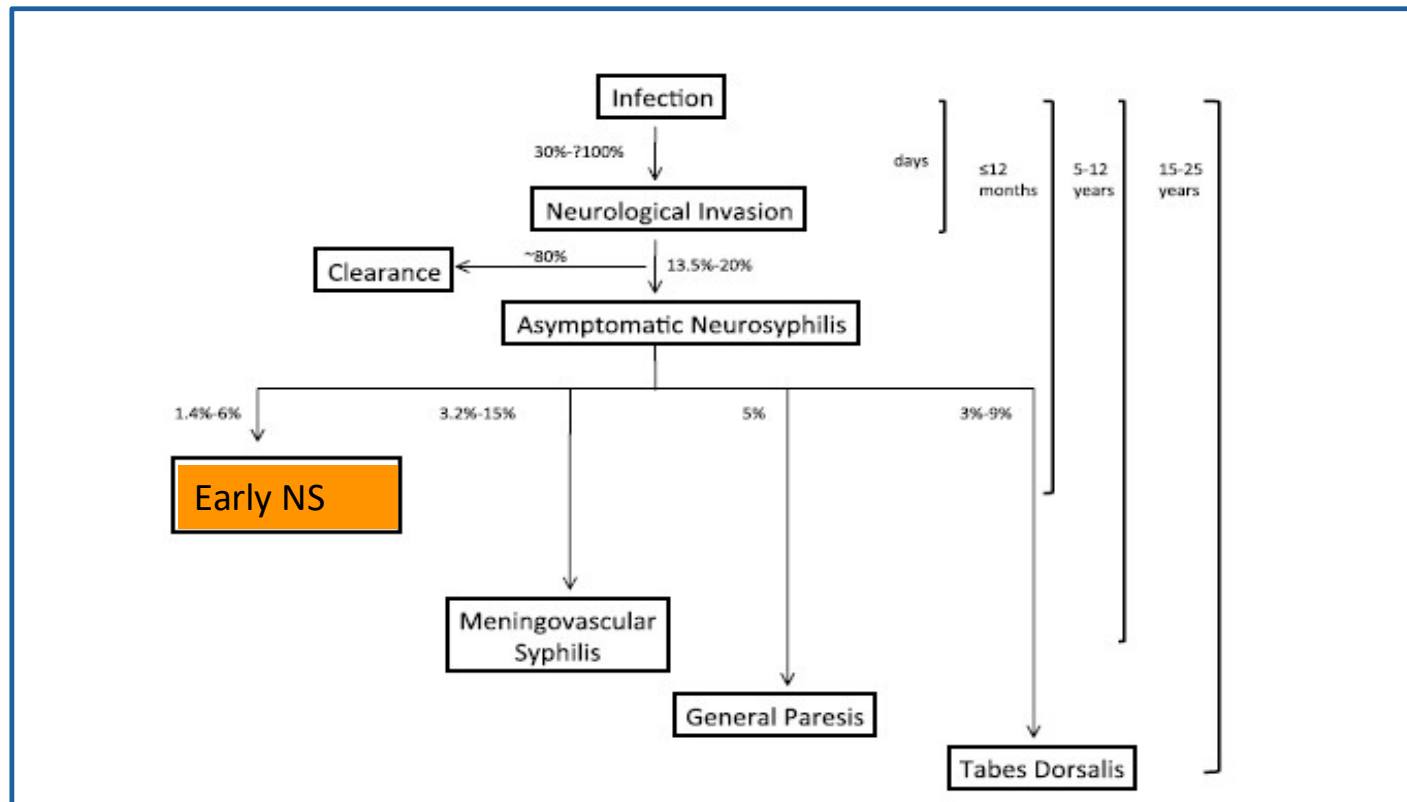
Everyone else should be presumed and treated for LL

## Tertiary Syphilis

- Cardiovascular- ascending aortic aneurysm, AI, CAD.
- Gummatous- inflammatory lesions in skin, bones, organs.



## Neurologic involvement with syphilis

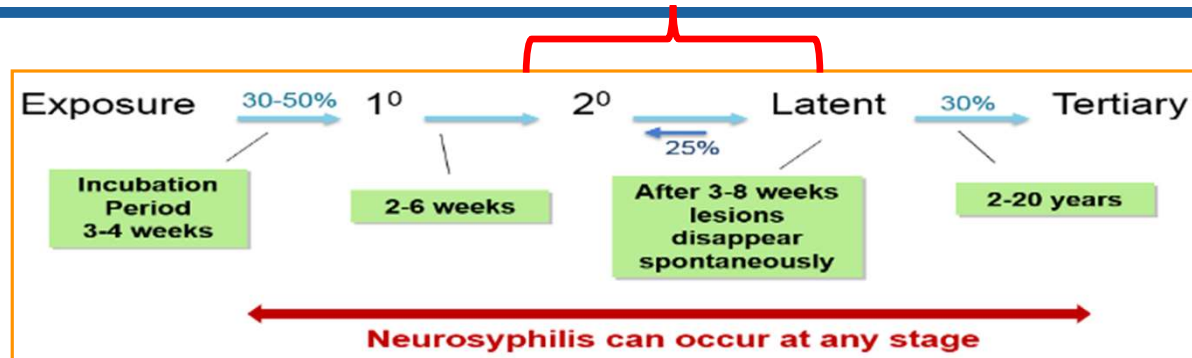


Ghanem 2010, CNS Neuroscience and Therapeutics

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# Syphilis- **Early** Neurologic disease



- Symptoms
  - Visual changes, hearing loss, facial weakness, stuttering stroke symptoms
- Entities- Symptomatic early neurosyphilis (SENS)
  - Ocular- uveitis, chorioretinitis most common
  - Otic- tinnitus, SNHL
  - Cranial Nerve involvement
  - Aseptic meningitis
  - Meningovascular

## Syphilis- **Late** (Parenchymatous) Neurologic disease

### General "Paresis"

Early	Late
Irritable, personality changes	Lability, impaired memory, confusion, delusions
	Argyll-Robertson Pupils

### Tabes Dorsalis

Symptoms	Signs
Ataxic gait Bladder dysfunction Lightening pains Failing vision	Argyll-Robertson Pupils Decreased reflexes Impaired vibration/proprioception <a href="#">Example</a>

# Syphilis Diagnosis Overview

## Direct

- Darkfield
- Tissue staining



## Indirect

- Nontreponemal (non specific)
  - RPR
  - VDRL
- Treponemal (specific)
  - "Trep Ab"
  - TP-PA



# Syphilis diagnosis- You need BOTH of these:

## **NON SPECIFIC**

### **Non-treponemal (VDRL, RPR)**

- detects antibodies to cardiolipin-lethicin-chol
- If used for screening must confirm w treponemal test
- titer generally reflects activity of disease- used for monitoring

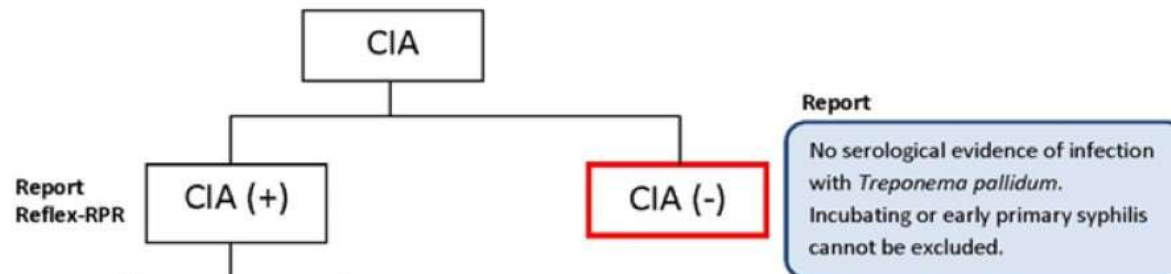
## **SPECIFIC**

### **Treponemal –(Older-FTA-ABS, TP-PA /Newer-Treponemal Ab-EIA/CIA/MBIA)**

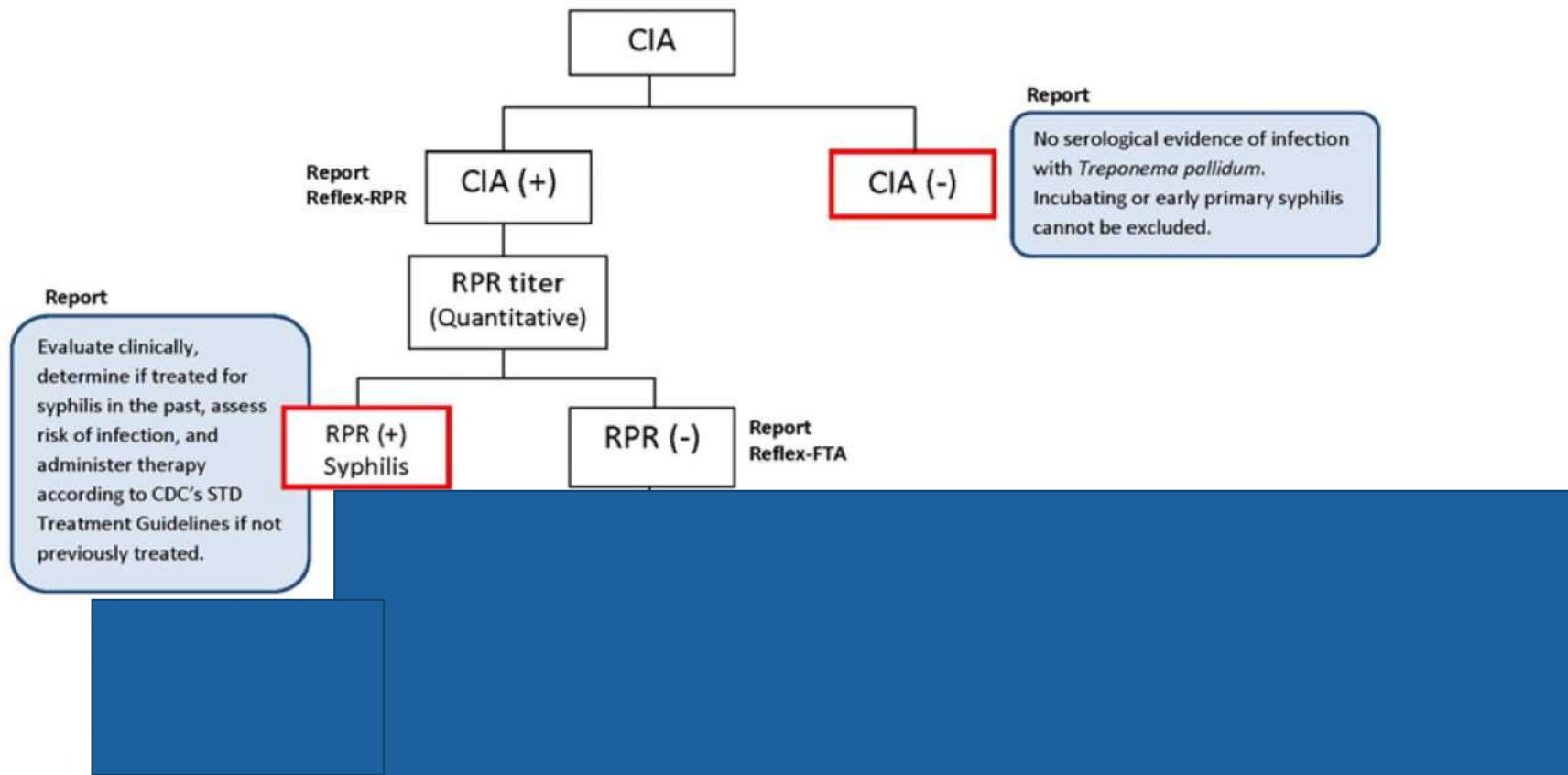
- detects antibodies to *T. pallidum*
- may stay positive for life after treatment



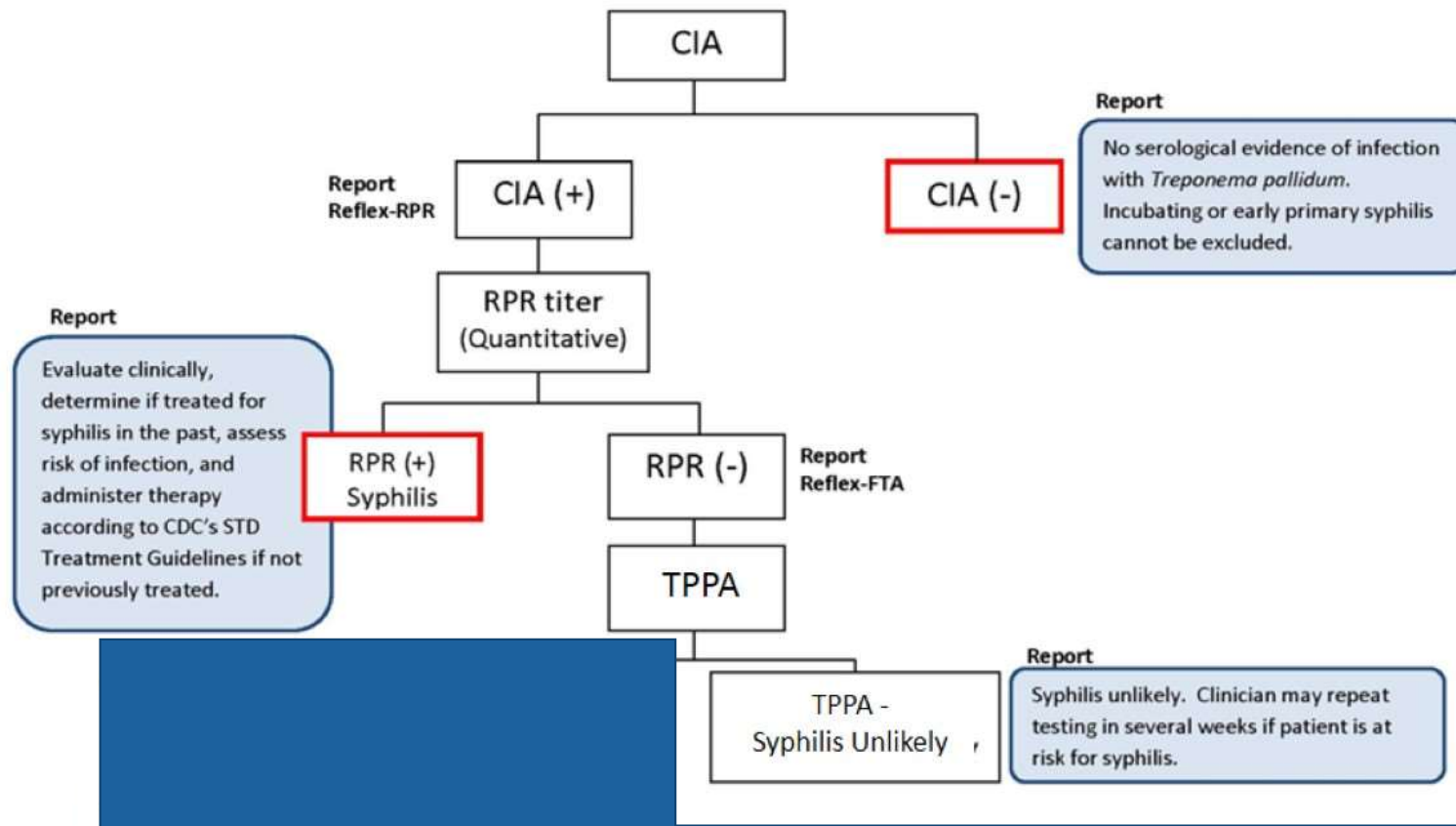
# Testing: The Reverse Sequence Algorithm



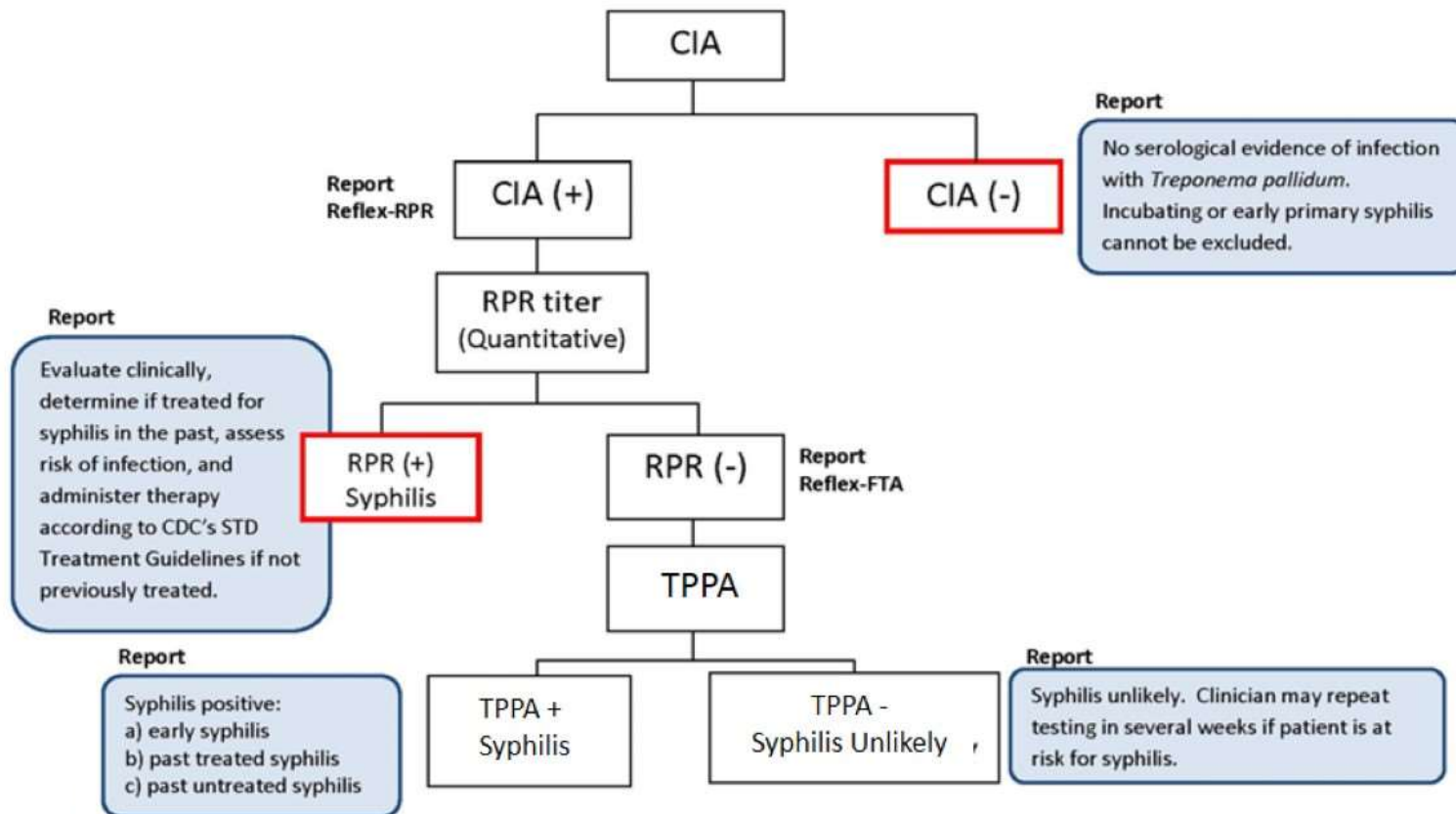
# Testing: The Reverse Sequence Algorithm



# Testing: The Reverse Sequence Algorithm

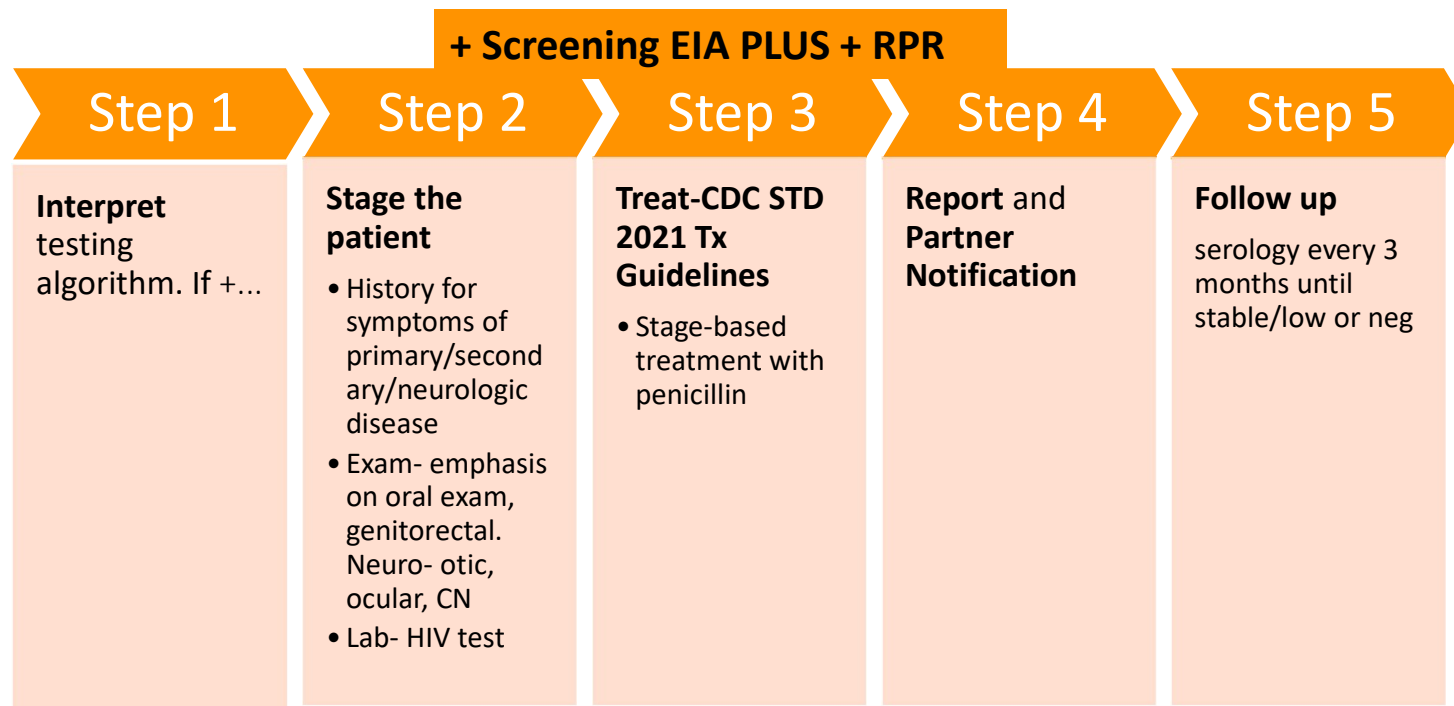


# Testing: The Reverse Sequence Algorithm





## 5-step approach to positive serology with confirmation



# Staging

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## History

- Last contact (time, sites)
- Symptoms (of primary, of secondary, includes GI, of neuro)
- Past hx of syphilis; treatment

## Physical

- Scalp (alopecia)
- OP- mucous patches, chancres
- Skin- rash, ulcers
- GU- chancre, (genital, anal), condylomata lata, mucous patches
- LAN
- Neuro

## New syphilis dx- Screening questions:

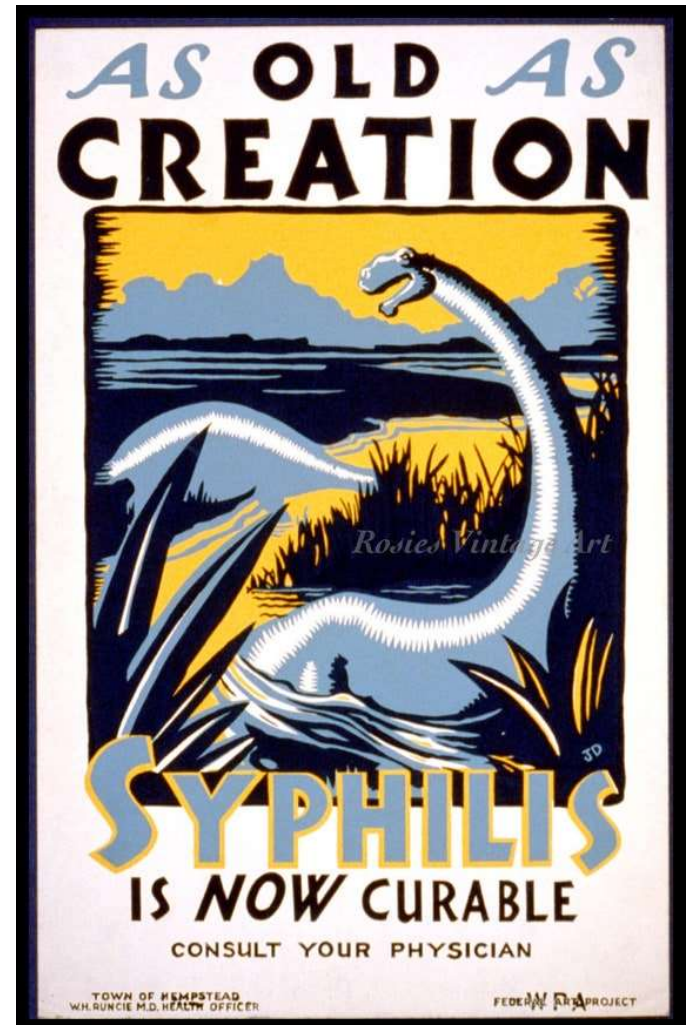
### Screening Questions for Neurosyphilis (Including Ocular and Ootosyphilis)

Questions	
<u>Symptoms of Ootosyphilis</u>	
1) Have you recently had new trouble hearing?	<input type="checkbox"/> Yes – refer to ENT <input type="checkbox"/> No
2) Do you have ringing in your ears?	<input type="checkbox"/> Yes – refer to ENT <input type="checkbox"/> No
<u>Symptoms of Ocular syphilis</u>	
3) Have you recently had a change in vision?	<input type="checkbox"/> Yes – refer to ophthalmology <input type="checkbox"/> No
4) Do you see flashing lights?	<input type="checkbox"/> Yes – refer to ophthalmology <input type="checkbox"/> No
5) Do you see spots that move or float by in your vision?	<input type="checkbox"/> Yes – refer to ophthalmology <input type="checkbox"/> No
6) Have you had any blurring of your vision?	<input type="checkbox"/> Yes – refer to ophthalmology <input type="checkbox"/> No
<u>Symptoms of neurosyphilis</u>	
7) Are you having headaches?	<input type="checkbox"/> Yes <input type="checkbox"/> No
8) Have you recently been confused?	<input type="checkbox"/> Yes <input type="checkbox"/> No
9) Has your memory recently gotten worse?	<input type="checkbox"/> Yes <input type="checkbox"/> No
10) Do you have trouble concentrating?	<input type="checkbox"/> Yes <input type="checkbox"/> No
11) Do you feel that your personality has recently changed?	<input type="checkbox"/> Yes <input type="checkbox"/> No
12) Are you having a new problem walking?	<input type="checkbox"/> Yes <input type="checkbox"/> No
13) Do you have weakness or numbness in your legs?	<input type="checkbox"/> Yes <input type="checkbox"/> No

Medical providers should consider evaluation and treatment for neurosyphilis in persons with new persistent headaches rated as moderate or greater; new change in vision, including loss, blurring, seeing spots or flashing lights; new change in hearing, including loss, muffling or tinnitus; new and persistent change in personality, memory or judgment; new numbness in both legs; or new gait incoordination.

# Treatment

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# Syphilis Treatment- (any HIV status)



- Early syphilis (primary/secondary/EL)

Benzathine PCN 2.4 million units IM x 1

Or

Doxycycline 100 mg po bid x 14 d\*

- Late syphilis (LL or non neuro tertiary)

Benzathine PCN 2.4 million units IM q week x 3

Or

Doxycycline 100 mg po bid x 28 d\*

2021 CDC STD Treatment Guidelines

\*if pcn allergic (except pregnancy)

# Syphilis Treatment- (any HIV status)



- Neuro and Ocular

Aqueous penicillin G 3-4 MU iv q 4hours x 10-14 d

- Tertiary (non neuro)

Benzathine PCN 2.4 million units IM q week x 3

Or

Doxycycline 100 mg po bid x 28 d\*

2021 CDC STD Treatment Guidelines

\*if pcn allergic (except pregnancy)

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# Follow Up

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## ***Serology***

***HIV-:*** Repeat RPR or VDRL at 6 and 12 months

***HIV+:*** Repeat RPR or VDRL at 3,6,9,12, months.

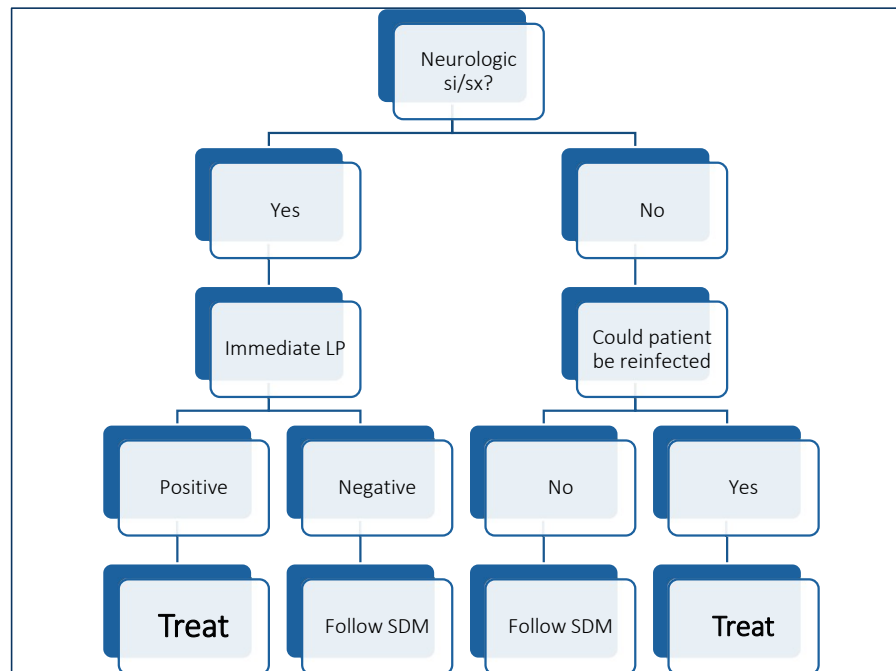
***CSF- if had been abnormal at initial LP, following peripheral serologies acceptable (NEW 2021)***

## ***Tx failure:***

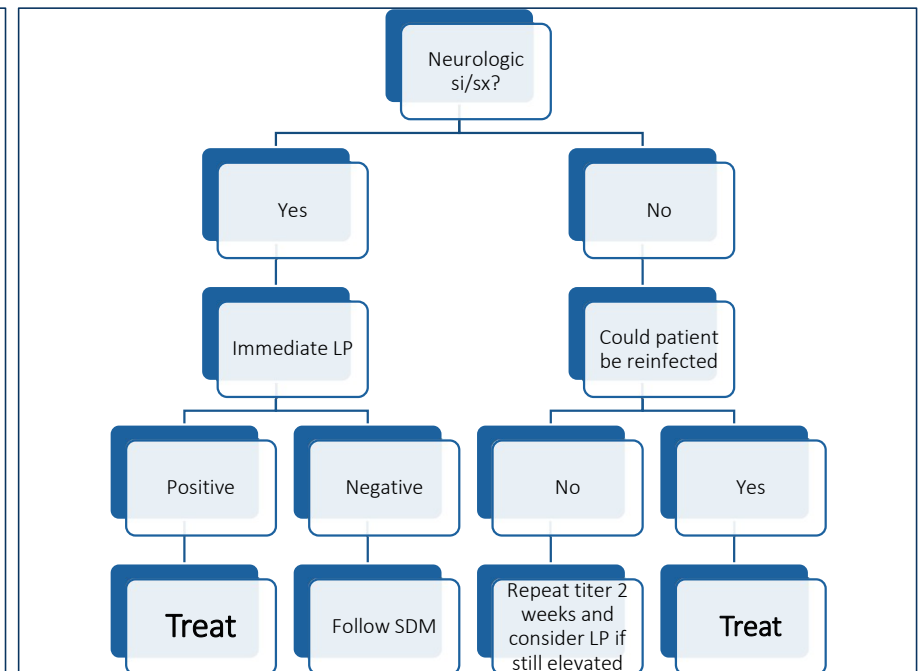
- 1.** Ongoing si/sx lasting longer than 2 weeks from tx
- 2.** Rise in NT 4x from treatment titer  
→ ***Recheck HIV, LP, retreat w 3 shots benzPCN***
- 3.** Failure to decrease 4x 6-12 months after early syphilis tx  
→ ***Recheck HIV, LP?, retreat w 3 shots benzPCN?***

What to do if titers don't respond appropriately?

**Lack of a fourfold decline** in titers after waiting a **full 12m (EL)** and a **full 24m (LS)**:



**A four-fold increase** in titers after appropriate therapy:







**Sexually Transmitted Disease  
Confidential Case Report  
Form STD-23**

(rev. 10/13/2020)

**STATE OF CONNECTICUT  
DEPARTMENT OF PUBLIC HEALTH  
STD CONTROL PROGRAM**  
410 Capitol Avenue, MS#11STD  
PO Box 340308  
Hartford, CT 06134-0308

☐ **Note:** Check this box to request forms

PATIENT INFORMATION												
Name (Last)	(First)	(MI)	Date of Birth	Home Phone Number	Other Phone Number							
Address (Number and Street)		(City or Town)		(State)	(Zip Code)							
Sex	<input type="checkbox"/> Male	<input type="checkbox"/> Female	<input type="checkbox"/> Unknown	Pregnant	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown	Marital Status	<input type="checkbox"/> Married	<input type="checkbox"/> Single	<input type="checkbox"/> Unknown	
Race	<input type="checkbox"/> White			<input type="checkbox"/> Black/African American			<input type="checkbox"/> Asian	Ethnicity	<input type="checkbox"/> Hispanic/Latino			
	<input type="checkbox"/> American Indian/Alaska Native			<input type="checkbox"/> Native Hawaiian/Other Pacific Islander					<input type="checkbox"/> Non-Hispanic/Latino			
	<input type="checkbox"/> Other, specify: _____			<input type="checkbox"/> Unknown					<input type="checkbox"/> Unknown			
Sex of Partners	<input type="checkbox"/> Men	<input type="checkbox"/> Women	<input type="checkbox"/> Both	<input type="checkbox"/> Unknown	Insurance Status	<input type="checkbox"/> Private	<input type="checkbox"/> Medicaid	<input type="checkbox"/> None	<input type="checkbox"/> Other			
DISEASE INFORMATION												
<input type="checkbox"/> <b>Gonorrhea</b> OR <input type="checkbox"/> <b>Chlamydia</b>				<input type="checkbox"/> <b>Syphilis</b>				<input type="checkbox"/> <b>Other STDs</b>				
<input type="checkbox"/> Symptomatic Uncomplicated				<input type="checkbox"/> Primary (Chancre Present)				<input type="checkbox"/> Late Latent – No SX (Duration > 1 Year)				<input type="checkbox"/> Neonatal Herpes (≤ 60 days of age)
<input type="checkbox"/> Asymptomatic				<input type="checkbox"/> Secondary (Rash, Lesions, etc.)				<input type="checkbox"/> Late – With SX				<input type="checkbox"/> Chancroid
<input type="checkbox"/> Pelvic Inflammatory Disease				<input type="checkbox"/> Early Latent – No SX (Duration < 1 Year)				<input type="checkbox"/> Congenital				
<input type="checkbox"/> Other, specify: _____												
PARTNER NOTIFICATION SERVICES				TREATMENT INFORMATION				DIAGNOSTIC INFORMATION				
Providers treating STDs are expected to counsel patients in prevention and identify and refer partners to medical care for examination and treatment.				Treatment Date: _____				Test Date: _____				
<input type="checkbox"/> Partners referred for exam and treatment by provider.				<input type="checkbox"/> Not Treated				<input type="checkbox"/> Laboratory Confirmed				
<input type="checkbox"/> Expedited Partner Therapy provided.				Specify Antibiotic and Dosage: _____				<input type="checkbox"/> Clinical Diagnosis-No Lab. Confirmation				
<input type="checkbox"/> Provider requesting assistance with partner notification from state health department. Please inform patient of this notification.				_____				Reporting Laboratory: _____				
				_____				Results or attach lab report: _____				
ATTENDING PHYSICIAN INFORMATION												
Name: _____		Address: _____		Phone Number: _____		Date Reported: _____						
If reporting from a Hospital or Facility, please complete the following: Name of person reporting (if different than above) _____												
Name of Hospital or Facility: _____ <input type="checkbox"/> Inpatient <input type="checkbox"/> ER/Urgent Care <input type="checkbox"/> Outpatient Clinic <input type="checkbox"/> OB/GYN <input type="checkbox"/> Family Planning												

## Case #1

- Painless Ulcer – dx and management questions
  - Work up/DDX
  - Empiric treatment or no?
  - With what
  - What else?



## Genital Ulcer- approach

### Take a (sex) history

- Time since last sexual contact
- Any RF for syphilis (MSM)
- Painful or painless
- Associated lymphadenopathy (and painful or not?)
- Travel

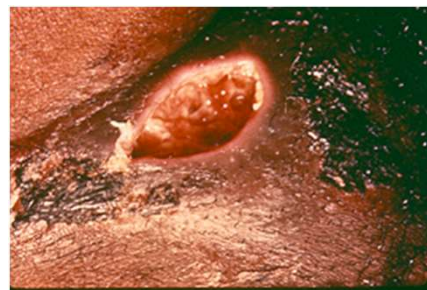
### Examine

- Rubbery, indurated feel vs shallow
- Associated LN? Where?
- Other- rash/skin, OP

### Diagnostic Testing

## Genital ulcer diagnostic work-up

- HSV- culture w typing or PCR *AND*
- Syphilis testing
  - Darkfield
  - Serology
- *Hemophilus ducryei*- culture if suspicious (painful and purulent, likely travel)



## Treatment

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- Empiric
  - **Treat the most likely diagnosis**
  - If serology negative and ulcer there <7 days:
    - Treat if still epidemiologically and clinically likely
    - Don't treat if unlikely but return in one week and repeat serology (and review HSV pcr results)
- What regimen?
  - A doxycycline 100 mg po bid x 7 d?
  - B ceftriaxone 125 mg IM x 1 ?
  - C azithromycin 2 gm po x 1 ?
  - **D penicillin 2.4 MU IM x 1?**
  - E penicillin 2.4 MU IM q week x 3?

## What else?

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1. Test for other STI including HIV
2. Recommend abstinence for 7 days
3. Partner referral
4. PrEP referral or prescription

CT STD Partner Notification Line  
1-860-509-7920 !!

## Case #2

- 54 year old man  
immigrated from Namibia.  
Screening blood test +  
**Trep Ab** and **reflex RPR**  
**neg**

1. What is next step?
2. How do you evaluate?
3. How do you treat?





## Case #2

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- 54 year old man immigrated from Namibia. Screening blood test + for syphilis (Treponemal Ab pos; RPR neg)

1. What is next step? – confirm with TP-PA (tie-breaker!); If pos →

2. How do you evaluate? – clinical exam/stage! HIV test

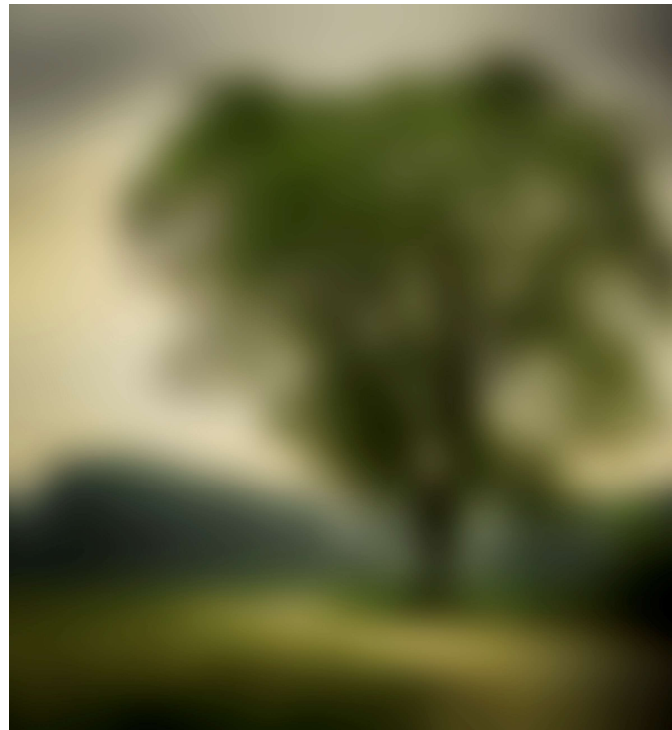
3. How do you treat?

- A doxycycline 100 mg po bid x 7 d?
- B ceftriaxone 125 mg IM x 1 ?
- C azithromycin 2 gm po x 1 ?
- D penicillin 2.4 MU IM x 1?
- E penicillin 2.4 MU IM q week x 3?

## Case #3

- 50 year old man presents with increasing blurry vision; had gone to HD because State called him. Trep Ab pos VDRL 1:64

1. What is ddx?
2. How to diagnose?
3. How to treat?
4. Anything else?



## Case 3- approach

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1. Take a history! Number and gender of partners, last time sexually active, HIV status, hx of STI
  - MSM, many partners
2. Always consider syphilis-
  - Remember stages; neuro involvement can be early (ocular, otic)
  - Uveitis common- seen by ophthalm; exam c/w post uveitis
  - Do an LP- this is a sign of NS
3. Treatment options
  - Treat for neurosyphilis with 10-14 d aqueous PCN iv
4. Other?
  - HIV test – remember high co-infection rate → +
  - Call DPH

## Take home points

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Always take a sexual history

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Know the current epidemiology to guide screening

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Ulcers- always check for HSV and syphilis, serology can be negative early. Empiric tx if high risk

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Always test for HIV

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Use penicillin whenever possible

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LP if symptoms but that means you have to ask questions

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Report, report, report

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# When to do an LP (HIV pos or neg)?

1. Si/sx of NS-
    1. Evidence of cranial nerve dysfunction
    2. ~~Auditory or ophthalmologic abnormalities~~ (NEW 2021)
    3. Meningitis
    4. Stroke
    5. Acute or chronic alteration in mental status
    6. Loss of vibration sense
  2. Diagnosis of Tertiary syphilis
  3. Not serologically responding to treatment
- Si/sx and Pos CSF-VDRL= diagnostic of neurosyphilis
- Si/sx with abn CSF (prot >40, WBC >5) with NEG CSF-VDRL = consider neurosyphilis. Negative CSF-TPPA *virtually* excludes neurosyphilis

CDC STD Tx Guidelines 2021

## Syphilis treatment- Pregnancy

Screen for syphilis at first prenatal visit; repeat RPR third trimester/delivery for those at high risk or high prevalence areas




Treat for the appropriate stage of syphilis



Missed doses (>9 days) **NOT ACCEPTABLE** when treating latent syphilis



Management and counseling may be facilitated by sonographic fetal evaluation for congenital syphilis in the second half of pregnancy



IF ALLERGIC NEED DESENSITIZATION! **ONLY USE PCN**