Dr. Bauer has no disclosures

Learning Objectives

1. Describe the epidemiology of syphilis in California
2. Recognize varied manifestations of early syphilis
3. Identify patients who would benefit from screening
4. Discuss effective treatment regimens for all stages of syphilis

Today's Presentation

OVERVIEW
- Epidemiology

CLINICAL DISEASE
- Syphilis in adults
- Neurosyphilis

MANAGEMENT
- Syphilis serology
- Screening & staging
- Treatment

PARTNERS
- Partner management

Question: How would you describe the natural history of syphilis infection?

A. Most people have no symptoms and will clear the infection without treatment.
B. Syphilis is characterized by symptomatic and latent phases.
C. Treated infection confers lifelong immunity.
D. Syphilis cannot be spread through oral sex.
E. It's more important to think about the future than about history.

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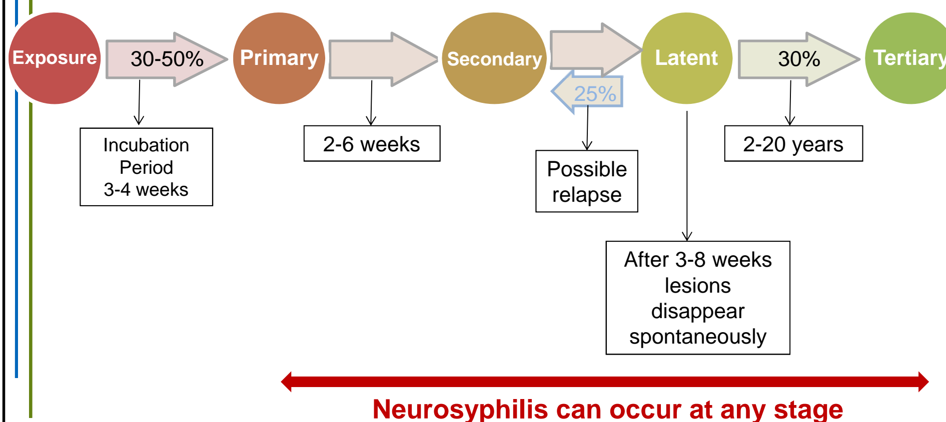
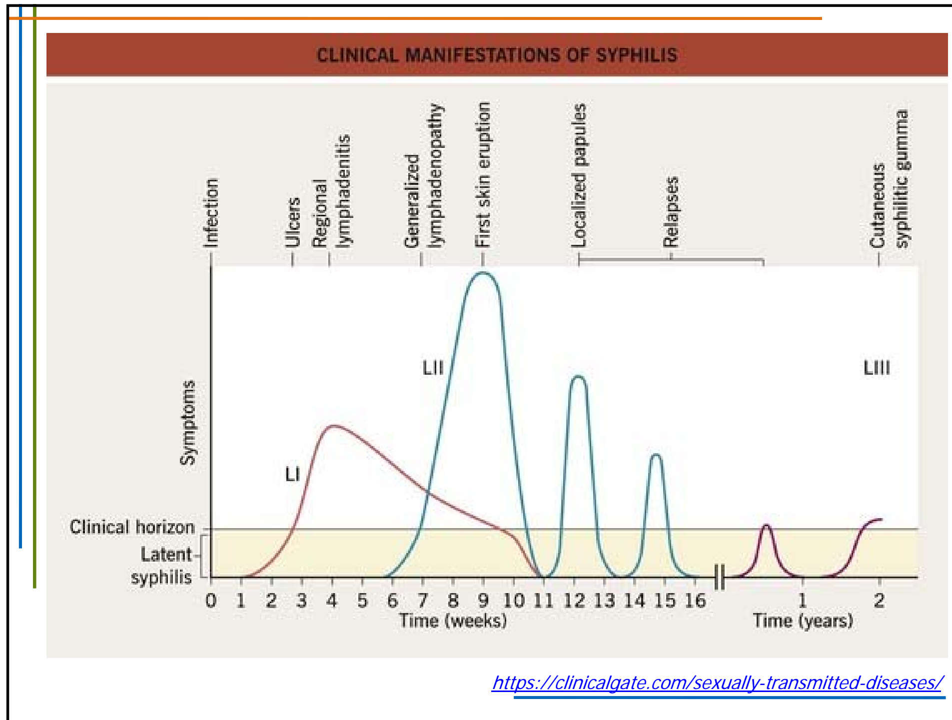
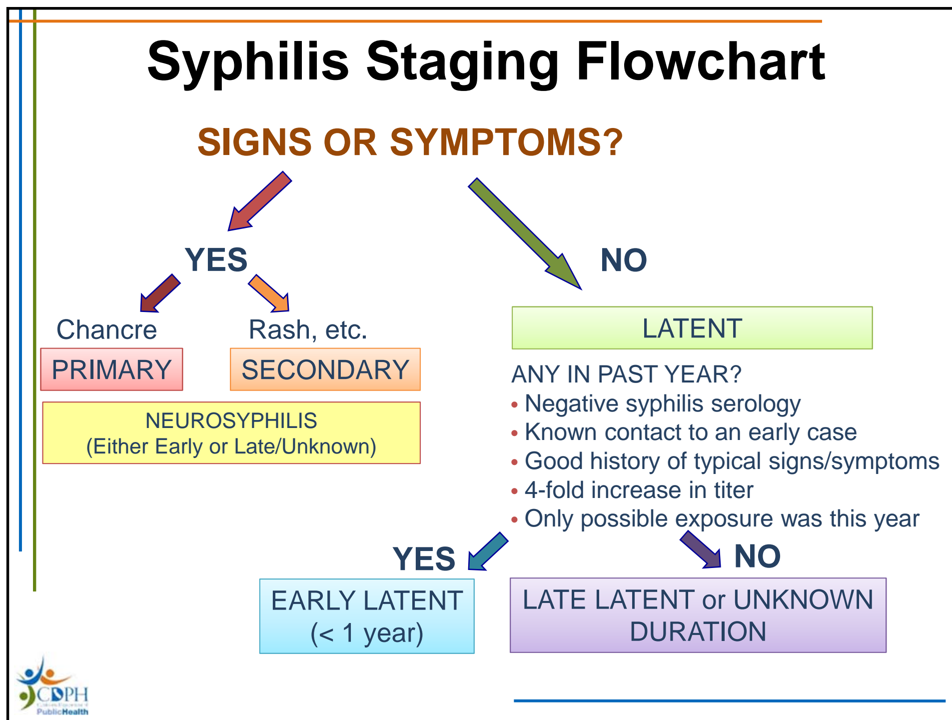
Syphilis Overview

- Causative organism: *Treponema pallidum*, spirochete bacterium, replicates in 30 hours
- Transmission: Direct contact to infectious lesion (mucosa or compromised skin), bloodborne, mother-to-child, semen or other bodily fluids?
- Incubation period: 10-90 days
- Causes systemic infection characterized by episodes of active disease and periods of latent infection
- Without treatment, remains chronic → progression of disease (tertiary) or it resolves (chronic latent), remains transmissible to fetus/newborn

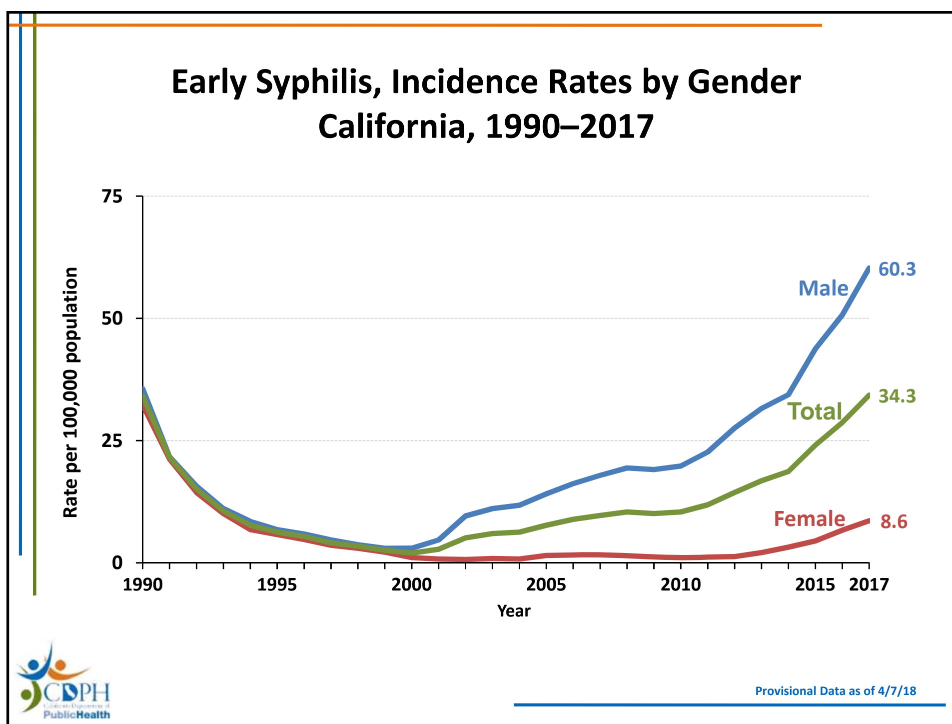
Syphilis Natural History



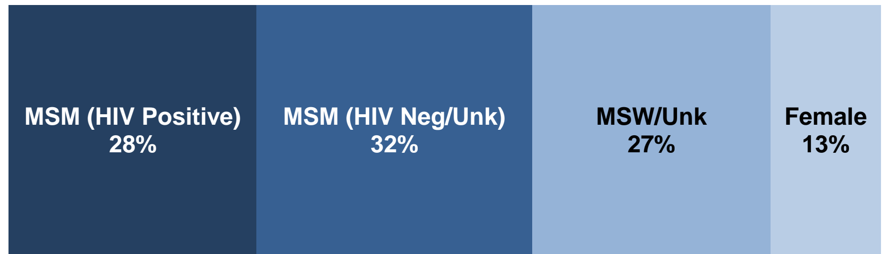

CLINICAL MANIFESTATIONS OF SYPHILIS
Infection
Ulcers
Regional lymphadenitis
Generalized lymphadenopathy
First skin eruption
Localized papules
Relapses
Cutaneous syphilitic gumma
Symptoms
LI
LII
LIII
Clinical horizon
Latent syphilis
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Time (weeks)
1 2
Time (years)
https://clinicalgate.com/sexually-transmitted-diseases/


Syphilis Staging Flowchart
SIGNS OR SYMPTOMS?
YES
NO
Chancre
Rash, etc.
PRIMARY
SECONDARY
NEUROSYPHILIS
(Either Early or Late/Unknown)
LATENT
ANY IN PAST YEAR?
• Negative syphilis serology
• Known contact to an early case
• Good history of typical signs/symptoms
• 4-fold increase in titer
• Only possible exposure was this year
YES
NO
EARLY LATENT
(< 1 year)
LATE LATENT or UNKNOWN
DURATION
CDPH

Epidemiology & Risk Factors
Inc.


Early Syphilis, Incidence Rates by Gender
California, 1990–2017
Rate per 100,000 population
75
50
25
0
1990
1995
2000
2005
2010
2015
2017
Year
Male
60.3
Total
34.3
Female
8.6
CDPH
PublicHealth
Provisional Data as of 4/7/18

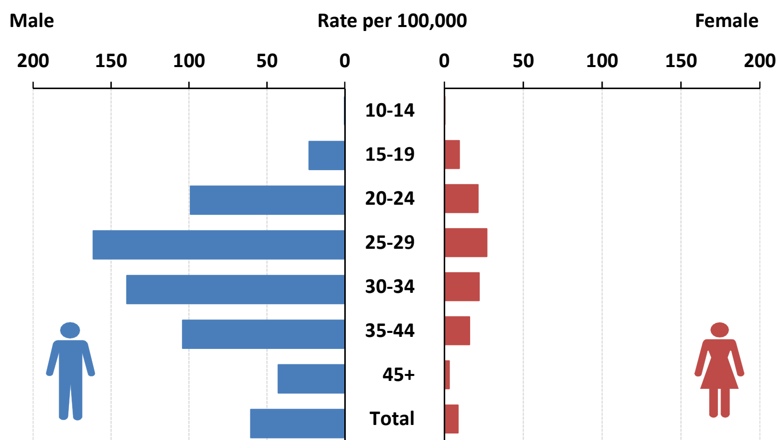
Early Syphilis* Cases by Sex and Gender of Sex Partners California, 2017



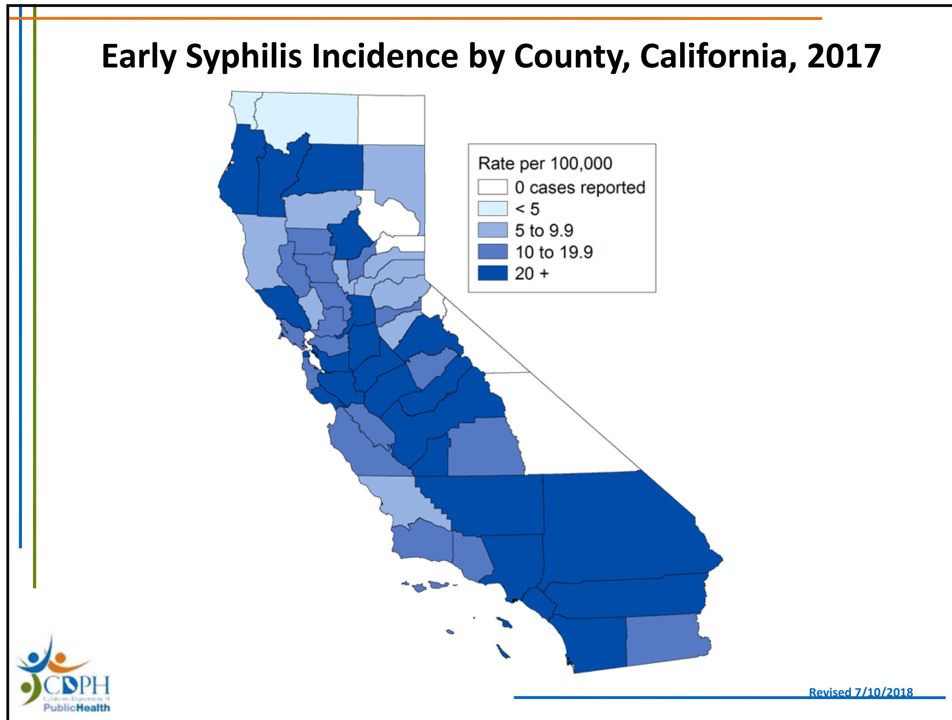
* Includes primary, secondary, and early latent syphilis.
MSM=Men who have sex with men
MSW/Unk=Men who have sex with women plus men of unknown sexual orientation

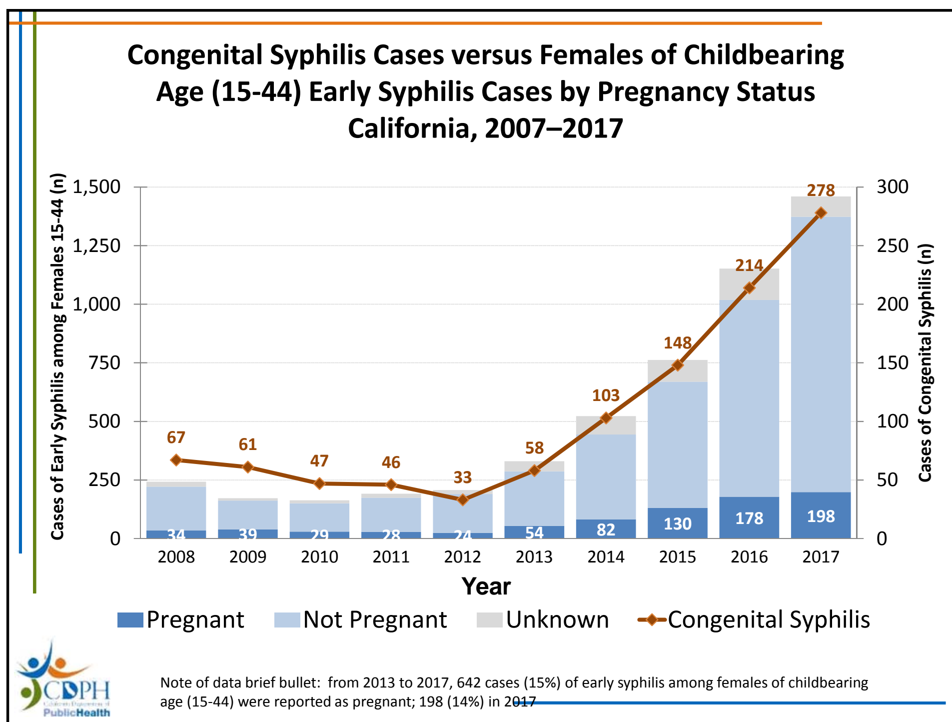
Provisional Data as of 4/7/18

Early Syphilis Incidence by Gender and Age Group, California, 2017



Provisional Data as of 4/7/18


Early Syphilis Incidence by County, California, 2017
Rate per 100,000
0 cases reported
< 5
5 to 9.9
10 to 19.9
20 +
CDPH
Revised 7/10/2018


Congenital Syphilis Cases versus Females of Childbearing Age (15-44) Early Syphilis Cases by Pregnancy Status California, 2007–2017
Cases of Early Syphilis among Females 15-44 (n)
Cases of Congenital Syphilis (n)
Year
2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
Pregnant: 34 39 29 28 24 54 82 130 178 198
Congenital Syphilis: 67 61 47 46 33 58 103 148 214 278
Pregnant
Not Pregnant
Unknown
Congenital Syphilis
CDPH
Note of data brief bullet: from 2013 to 2017, 642 cases (15%) of early syphilis among females of childbearing age (15-44) were reported as pregnant; 198 (14%) in 2017

Question: What is most challenging about diagnosing syphilis?

A. Patients present with a variety of symptoms (or none at all).
B. Many providers do not assess sexual risk, or even gender of partners.
C. Few providers have direct tests for *T. pallidum*.
D. The serology tests often remain positive after treatment.
E. All of the above.

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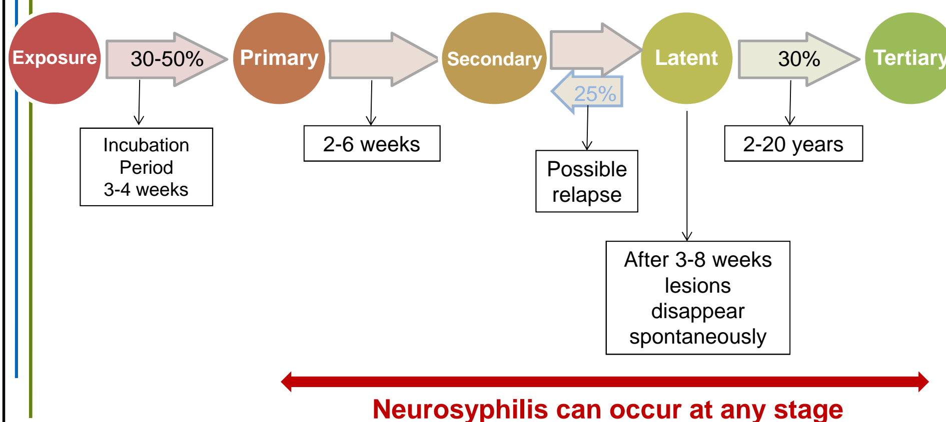
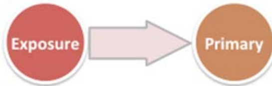
Syphilis Natural History

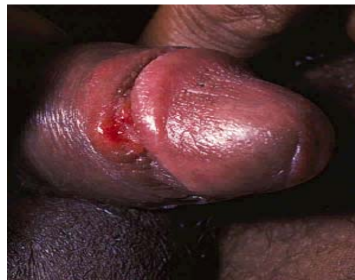


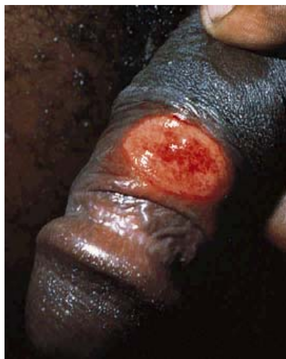
Primary Syphilis



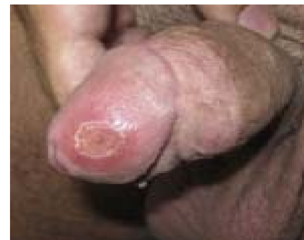
- Chancre (ulcer) appears 10-90 days after infection
  - Single, painless, indurated, clean-based lesion with rolled edges (textbook chancre)
  - More likely to be multiple lesions and persisting at the time of secondary syphilis in HIV-infected patients
  - Can go unrecognized, especially anal and vaginal
- Possible regional adenopathy (rubbery, bilateral, painless)

Primary Syphilis
Penile Chancre



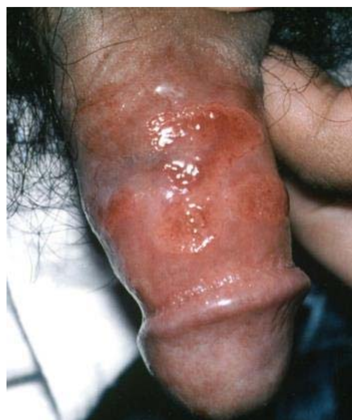
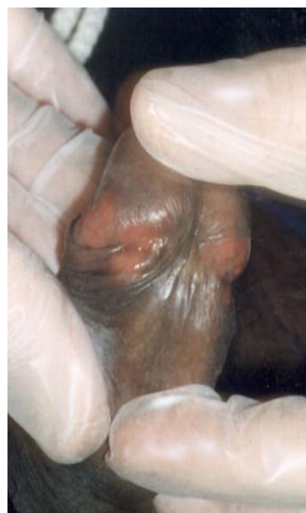


STD Atlas, 1997



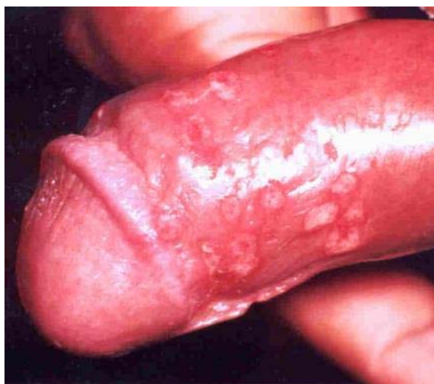
Bjekic et al Braz JID 2012

Primary Syphilis
Multiple Penile Chancres

SFCC
Courtesy: SF City Clinic

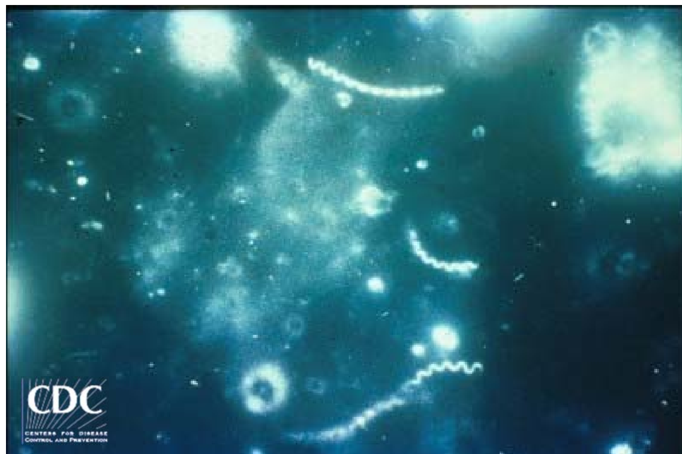
Primary Syphilis
Multiple Penile Chancres



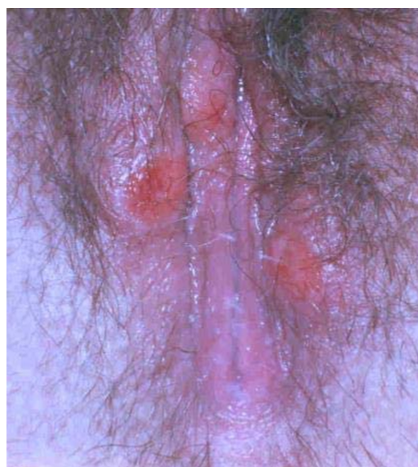
SFCC

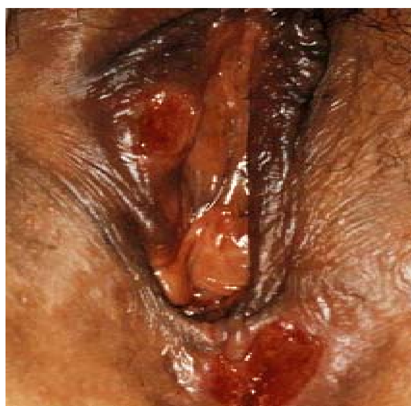
Mosby
STD Atlas, 1997

T. pallidum on Darkfield



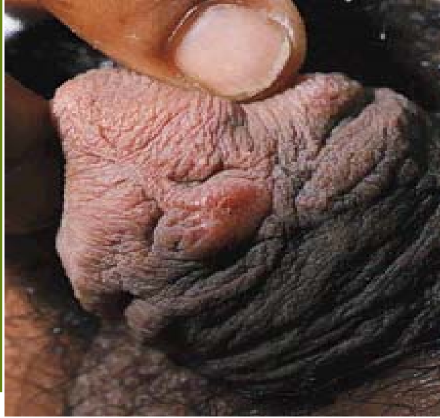
Primary Syphilis
Multiple Vulvar Chancres

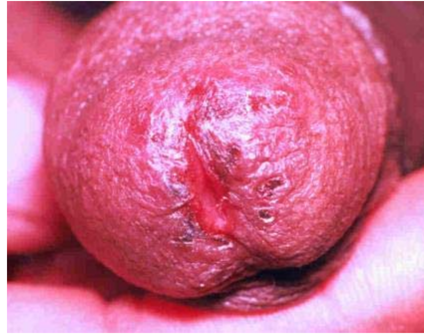




SFCC

Primary Syphilis
Healing Penile Chancre

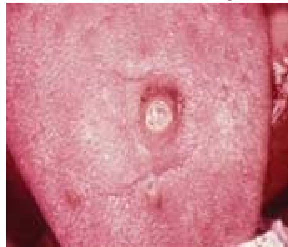


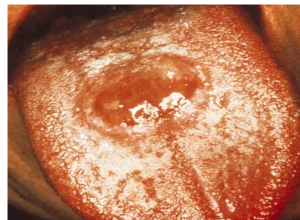


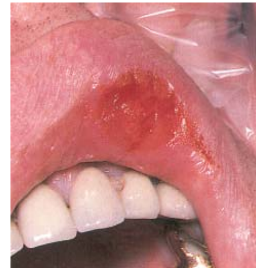
SFCC

STD Atlas, 1997

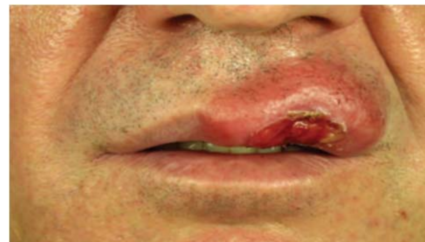
Primary Syphilis Oral Chancres





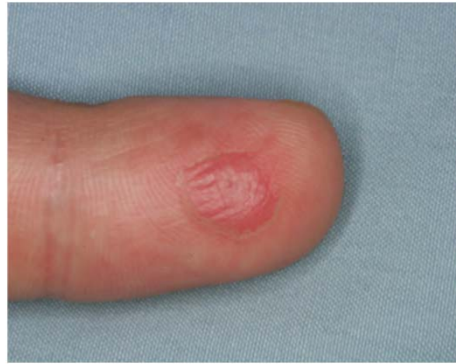


STD Atlas, 1997



Raguse et al. Ann Int Med March 2012.

Primary Syphilis-Extragenital Chancres



Raguse et al. Ann Int Med March 2012.

DDx Genital Ulcers

STD Causes	**Other Causes**
Herpes simplex	**Trauma**
Syphilis	**Behcet's**
Chancroid	**Scabies**
Lymphogranuloma venereum (LGV)	**Malignancy**
Granuloma inguinale (Donovanosis)	**Psoriasis**
Primary HIV infection	**Reiter's syndrome**
	Dermatitis

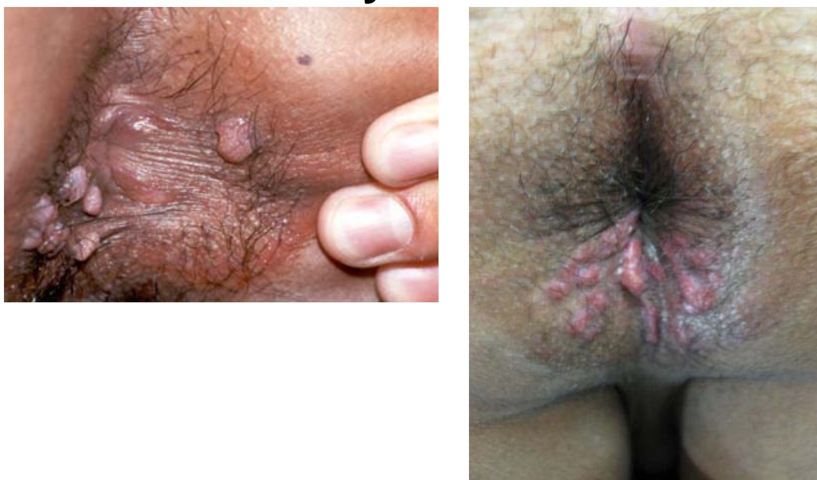
STD GUD: Laboratory Testing

STD	Direct Tests	Serology
Syphilis	Darkfield micro	Stat RPR
	T. pallidum PCR	POC EIA
	DFA *T. pallidum*	Non-trep (RPR, VDRL)
		Trep (TP-PA, FTA, EIA, CLIA)
Herpes	Culture	Type-specific HSV serology
	HSV NAATs	POC type-specific HSV serology
Chancroid	Culture	
	H. ducreyi PCR	

Secondary Syphilis

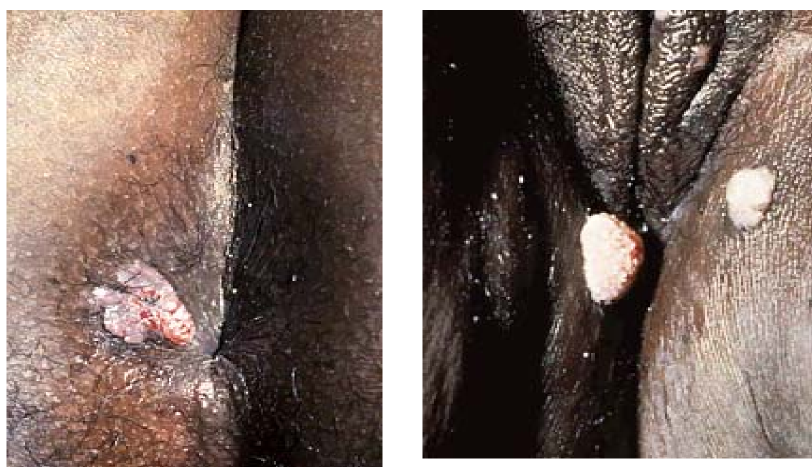
- Usually occurs 3-6 weeks after primary chancre
  - Rash (75-90%), involving palms/soles (60%)
  - Generalized lymphadenopathy (70-90%)
  - Constitutional symptoms (50-80%)
  - Mucous patches (5-30%)
  - Condyloma lata (5-25%)
  - Patchy alopecia (10-15%)
  - Symptoms of neurosyphilis (1-2%)
  - Less common: meningitis, hepatitis, arthritis, nephritis

Secondary Syphilis
Condyloma Lata



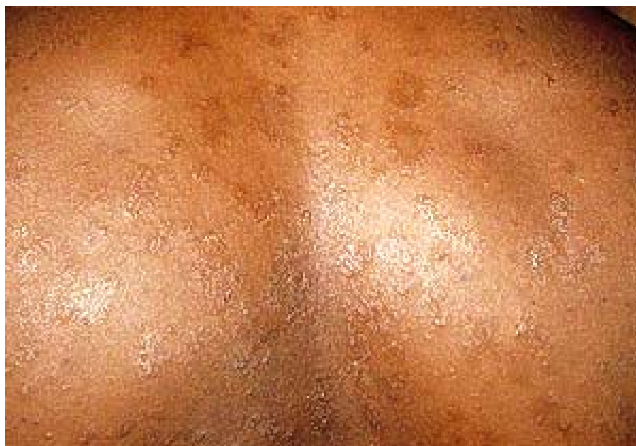
Courtesy: Gregory Melcher, UC Davis
Susan Philip, SF DPH & UCSF

Secondary Syphilis
Condyloma Lata



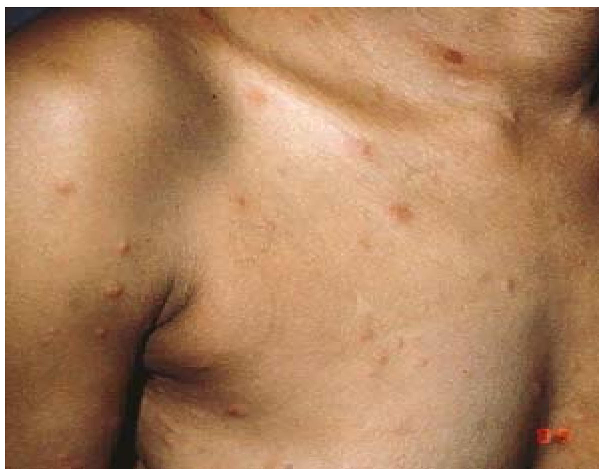
STD Atlas, 1997

Rash of Secondary Syphilis
Oval Macules, Upper Back



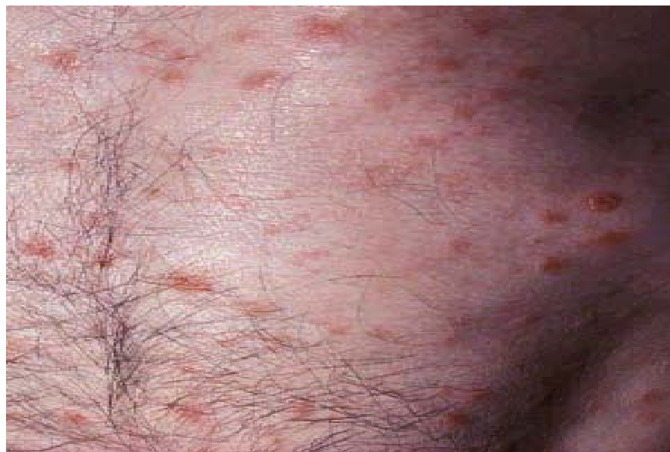
Mosby STD Atlas, 1997

Rash of Secondary Syphilis
Papular Form, Chest

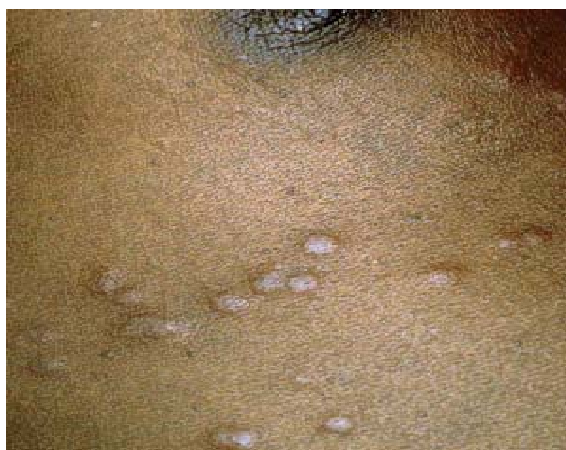


Mosby STD Atlas, 1997

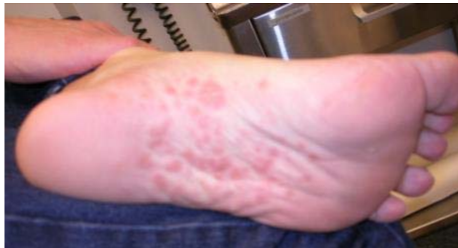
Rash of Secondary Syphilis
Papulosquamous Form, Chest

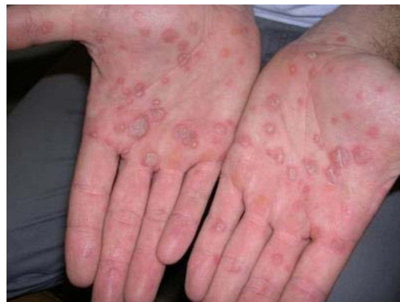


Rash of Secondary Syphilis
Lenticular Form, Chest



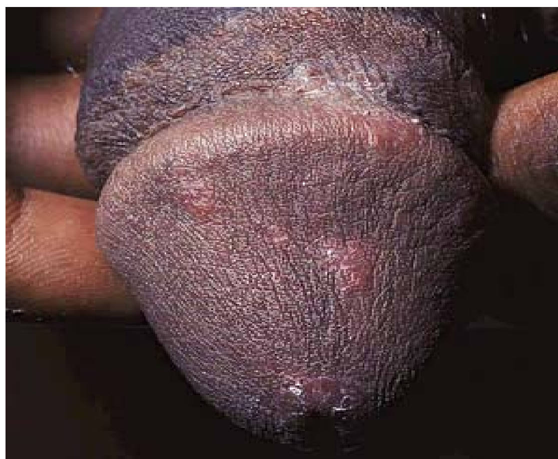
Secondary Syphilis: Rash on Palms and Soles





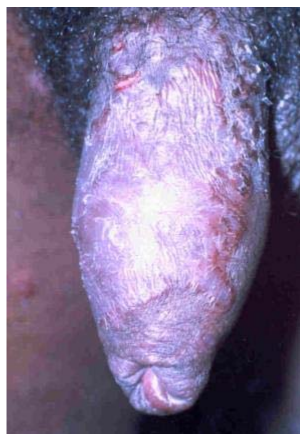
Courtesy: Gregory Melcher, UC Davis
Susan Philip, SF DPH & UCSF

Rash of Secondary Syphilis
Papulosquamous Form

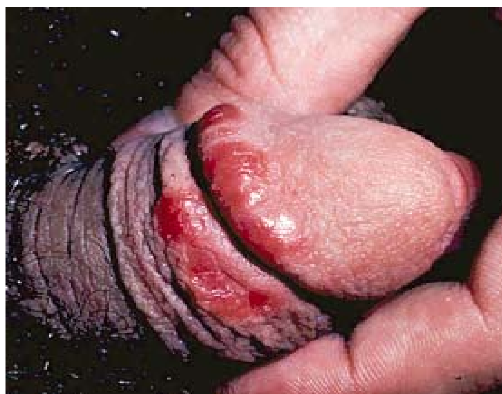


STD Atlas, 1997

Secondary Syphilis
Plaque-like Penile Lesion

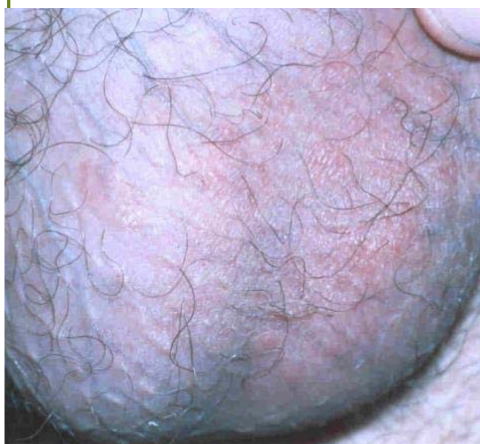


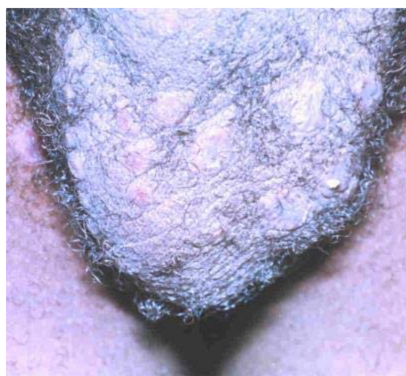
SFCC



Mosby STD Atlas, 1997

Secondary Syphilis
Scrotal Rash

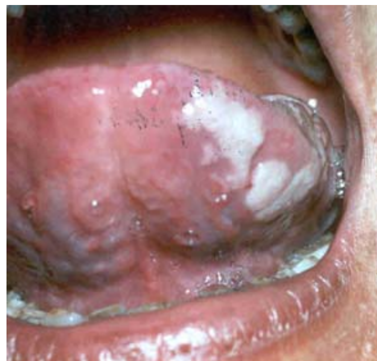


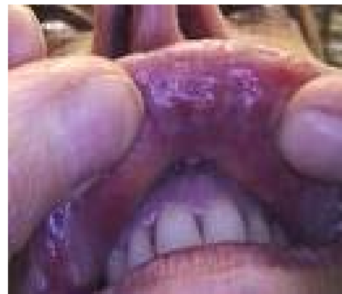


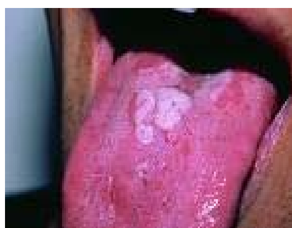
SFCC

Courtesy: SF City Clinic

Secondary Syphilis: Mucous Patches

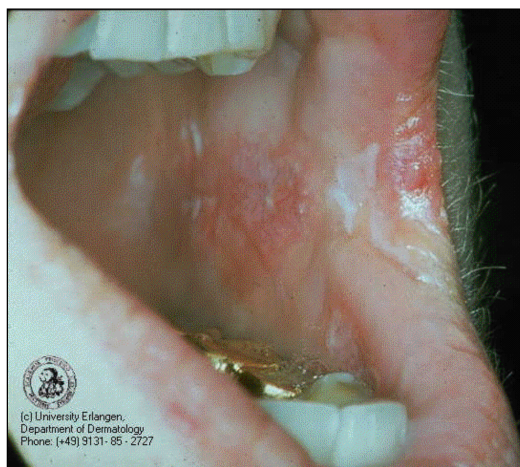






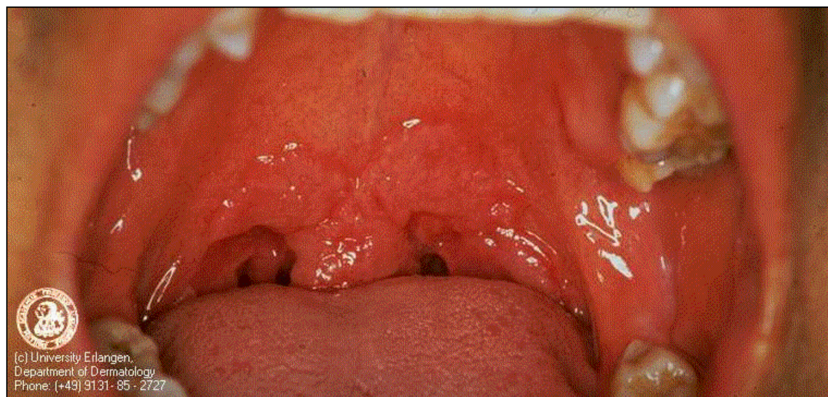
Courtesy: Gregory Melcher, UC Davis
Susan Philip, SF DPH & UCSF

Secondary Syphilis
Mucous Patches



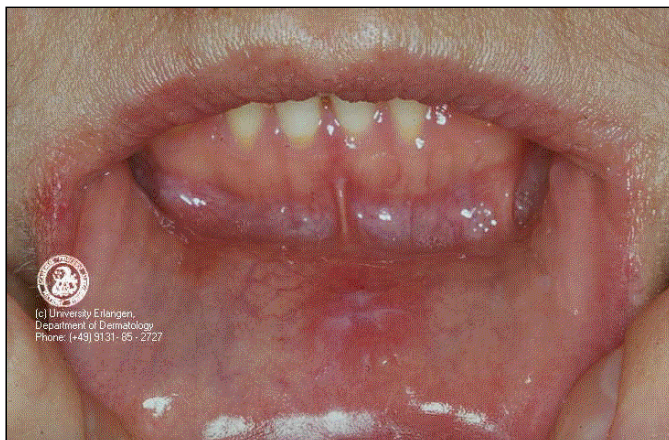
***DOIA** Website, 2000*

Secondary Syphilis
Mucous Patches, Palate



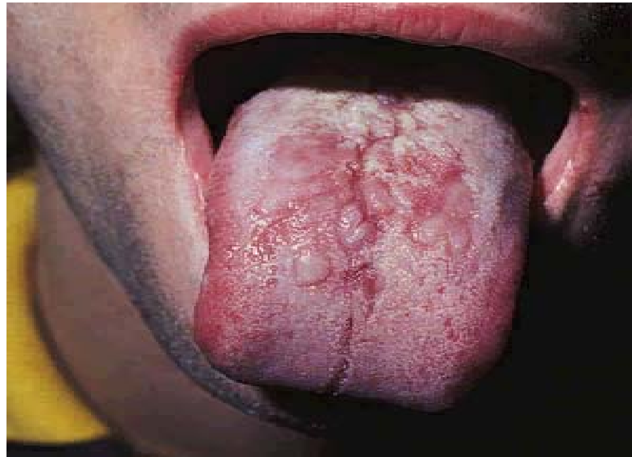
***DOIA** Website, 2000*

Secondary Syphilis
Mucous Patches, Inner Lower Lip



***DOIA** Website2000*

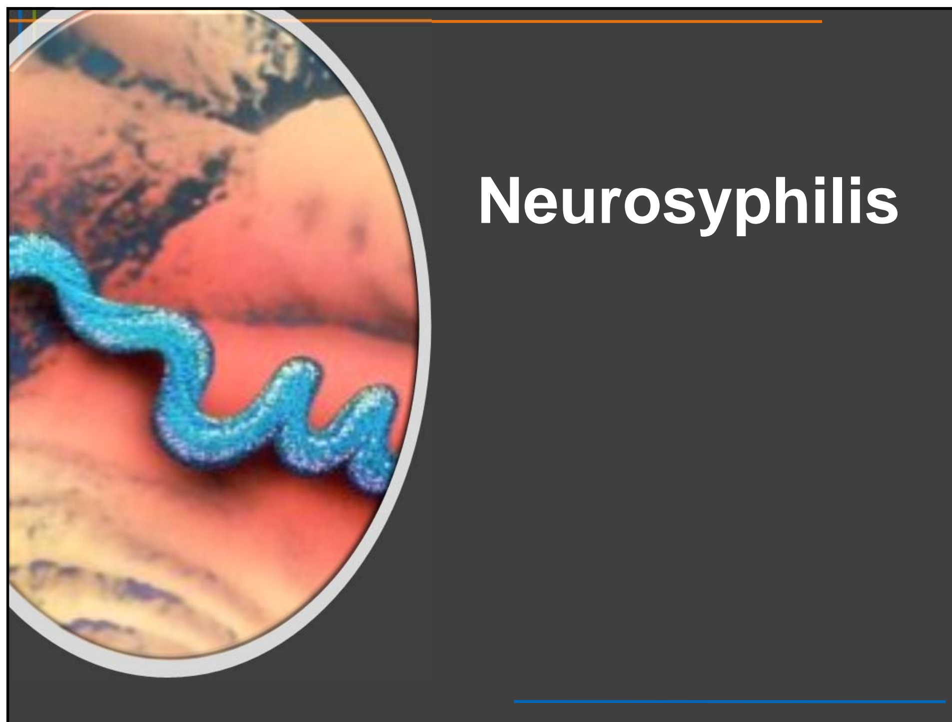
Secondary Syphilis
Mucous Patches, Tongue



STD Atlas, 1997

Secondary Syphilis
Patchy Alopecia

STD Atlas, 1997



Neurosyphilis: Can Occur at Any Stage of Syphilis

- All patients with syphilis should be evaluated for neurologic symptoms and signs
- Asymptomatic CNS invasion is common in early syphilis
- Early symptomatic forms (months to a few years):
  - Acute syphilitic meningitis (CN VI, VII, VIII)
  - Hearing loss
  - Ocular syphilis
  - Meningovascular (stuttering stroke)
  - Altered mental status
- Late symptomatic forms (> 2 years):
  - General paresis and tabes dorsalis

Criteria for CSF Examination

- Neurologic or **ophthalmic** symptoms/signs:
  - Auditory disease, cranial nerve dysfunction, meningitis, stroke, altered mental status, loss of vibration sense, iritis, uveitis
- Evidence of tertiary disease:
  - Aortitis, gumma
- Serologic treatment failure

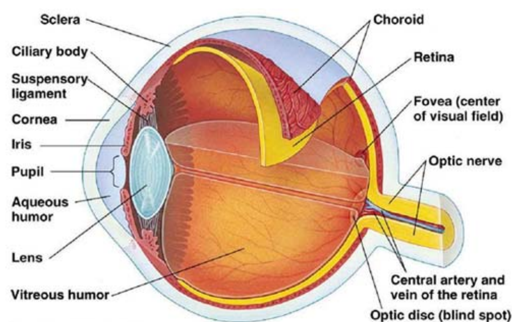
In HIV infection, unless neurologic symptoms, there is no evidence that CSF exam is associated with improved outcomes, so not recommended

CDC 2015 STD Treatment Guidelines
Guidelines for Prevention and Treatment of OI in HIV+ 2013

Ocular Syphilis

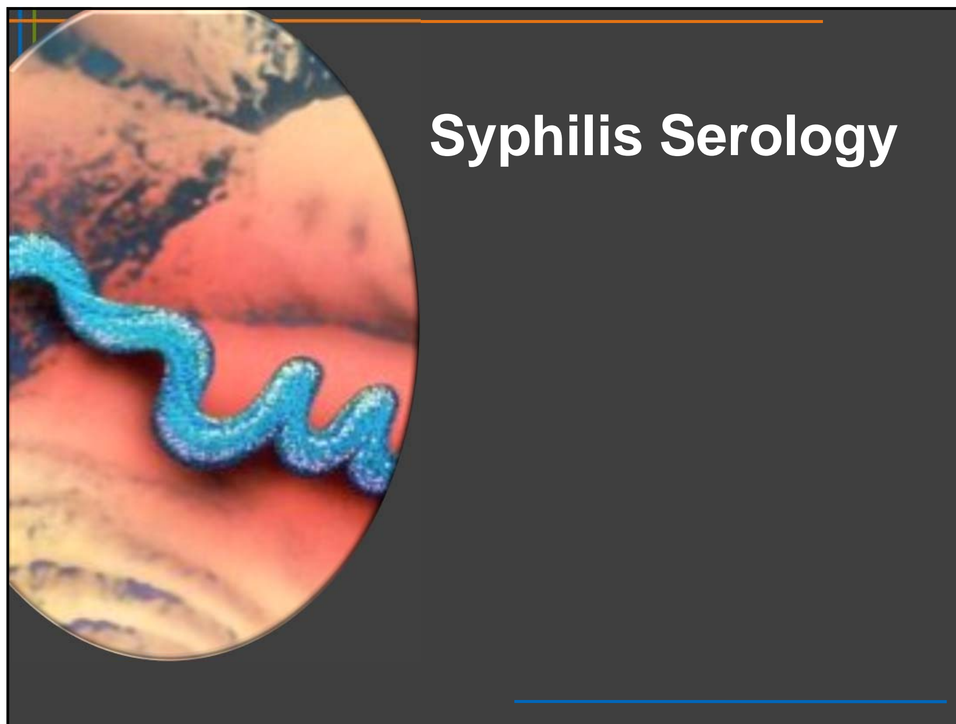
Manifestations:
- Conjunctivitis, scleritis, and episcleritis
- **Uveitis**: anterior and/or posterior
- Elevated intraocular pressure
- **Chorioretinitis**, retinitis
- Vasculitis

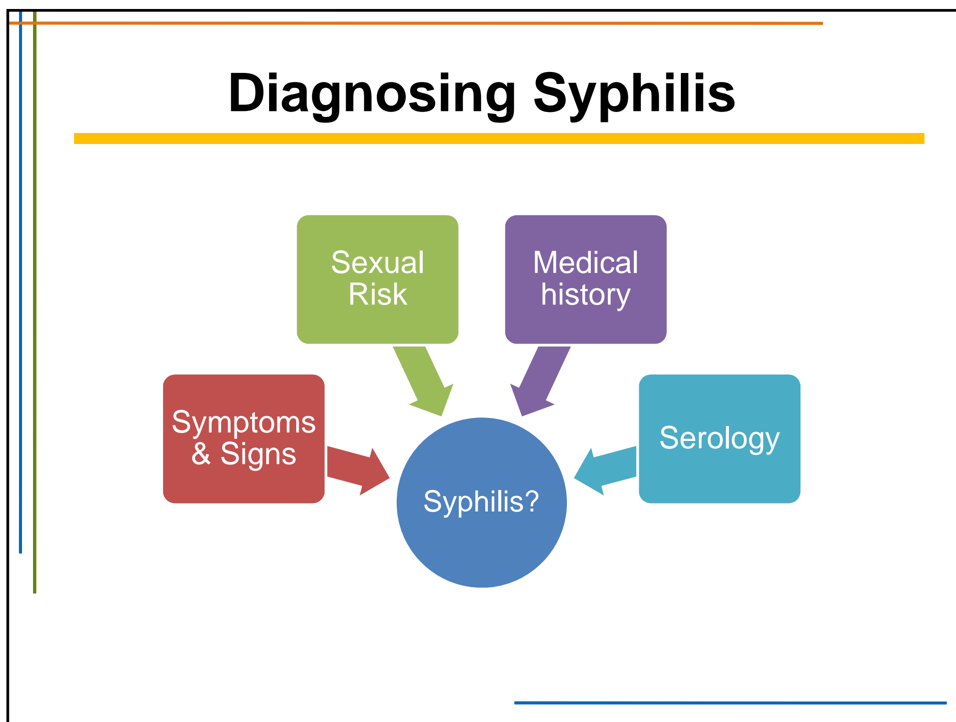
Symptoms:
- Redness
- Eye pain
- Floaters
- Flashing lights
- Visual acuity loss
- Blindness



Diagnosis:
- Ophthalmologic exam
- Serologies: RPR, VDRL, treponemal tests
- Lumbar puncture

Slide courtesy of Sarah Lewis, MD
Wender, JD et al. How to Recognize Ocular Syphilis. Review of Ophthalmology. 2008.


Syphilis Serology


Diagnosing Syphilis
Sexual Risk
Medical history
Symptoms & Signs
Serology
Syphilis?

Diagnostic Challenges

False negatives

- Early primary stage
  - Serology may be negative in up to 25% of primary syphilis cases
- Prozone reaction (RPR/VDRL)
- Untreated late latent

Biologic False Positives

(Non-trep test positive, but confirmatory trep test negative)

- Viral illnesses including HIV
- Recent immunizations
- Autoimmune and chronic diseases

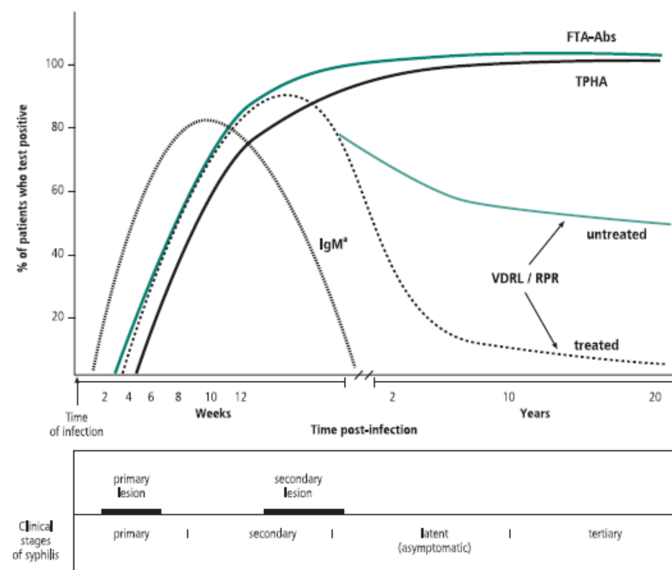
Discordant serology

(EIA or CIA + and RPR –)

- Untreated late latent
- Non-syphilis treponemal infection

*Jurado RL et al. Arch Intern Med 1993, **153:**2496–2498.*
*Geisler MG. South Med Jour 2004, **97**: 327-328.*

Common Patterns of Syphilis Serologic Reactivity



Peeling et al. / Bulletin of the World Health Organization / 2004 / Vol. 82 / No. 6

Syphilis Serology may be NEGATIVE in Primary Syphilis: Relative Sensitivity of Screening Tests

Testing Approach	Overall sensitivity	Sensitivity: HIV-	Sensitivity: HIV+	P Value
VDRL reflex TPPA	[illegible]	[illegible]	[illegible]	[illegible]
TPPA as first-line test	86%	88%	83%	.53

Bottom line:
Order BOTH Non-trep and Trep tests if primary syphilis is suspected

Creegan et al. STD 2007: 34: 1016-8.

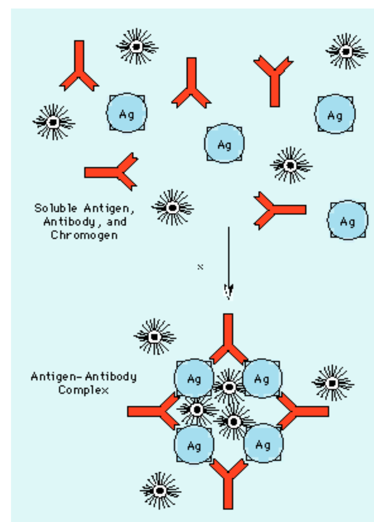
Syphilis Serology may be NEGATIVE in Secondary Syphilis: Prozone Reaction

False Negative RPR

- High Ab titers prevent antibody/antigenlattice formation

Rare

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

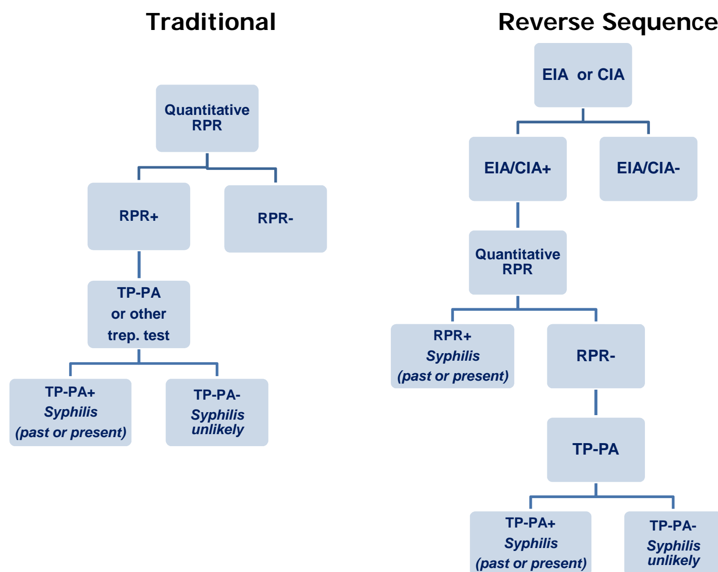


*Jurado RL et al. Arch Intern Med 1993, **153:**2496–2498.*
*Geisler MG. South Med Jour 2004, **97**: 327-328.*

Serologic Tests for Syphilis

- **Nontreponemal tests**
  - Rapid plasma reagin (RPR) test
  - Venereal Disease Research Laboratory (VDRL) test
  - Toluidine red unheated serum test (TRUST)
- **Treponemal tests**
  - Fluorescent treponemal antibody absorbed (FTA-ABS) test
  - Treponema pallidum article agglutination (TP-PA) test
  - Enzyme immunoassays (EIAs)
    - Trep-Check
    - Trep-Sure
  - Chemiluminescence immunoassays (CIAs)
    - LIAISON
    - Architect
  - Microbead immunoassays (MBIA)
    - BioPlex 2200 Syphilis IgM and IgG

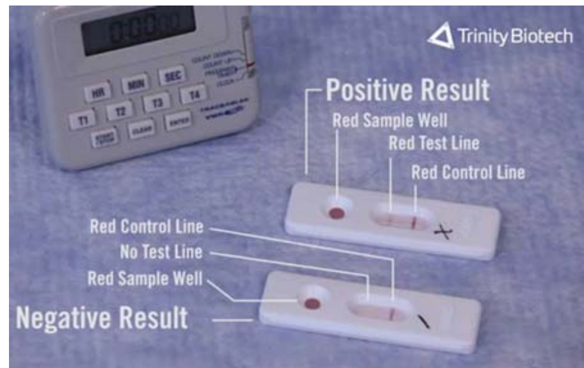
Syphilis Serologic Screening Algorithms

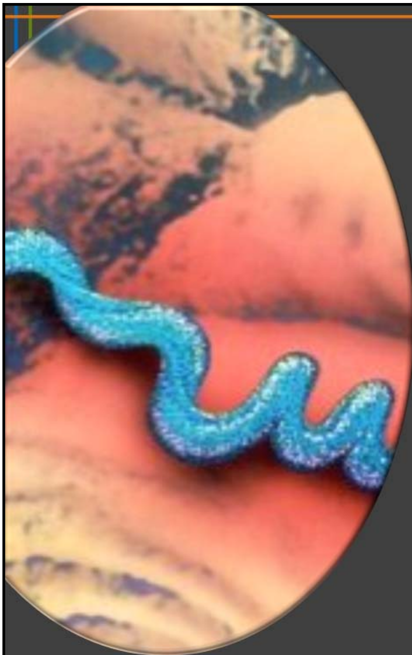


MMWR / February 11, 2011 / Vol. 60 / No. 5

New Point-of-Care Syphilis Test

- Syphilis Health Check (Trinity Biotech)
- Rapid Immunochromatographic Assays: lateral flow immunoassays
- Treponemal only (3rd gen EIA format, detects IgG and IgM)
- Results in 10 min
- FDA approved
- CLIA waived





Screening & Staging

Question: Who should be screened for syphilis?

A. Everyone applying for a marriage license in CA
B. All pregnant women at the first prenatal visit
C. Gay, bisexual and other MSM
D. Persons entering correction settings
E. Persons involved in commercial sex
F. B through E and anyone else at risk

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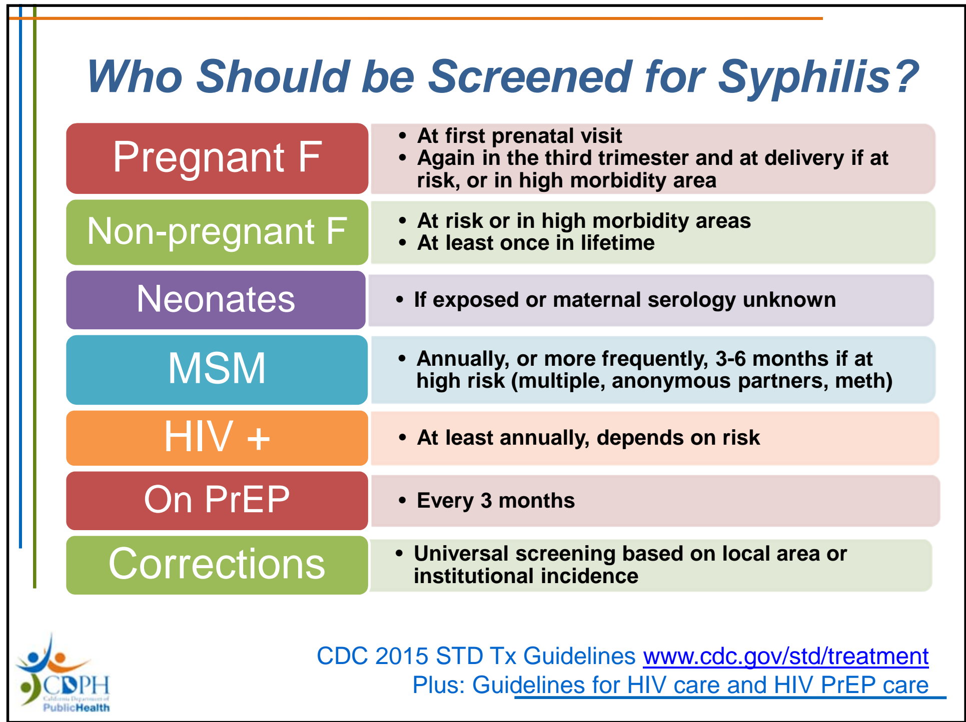
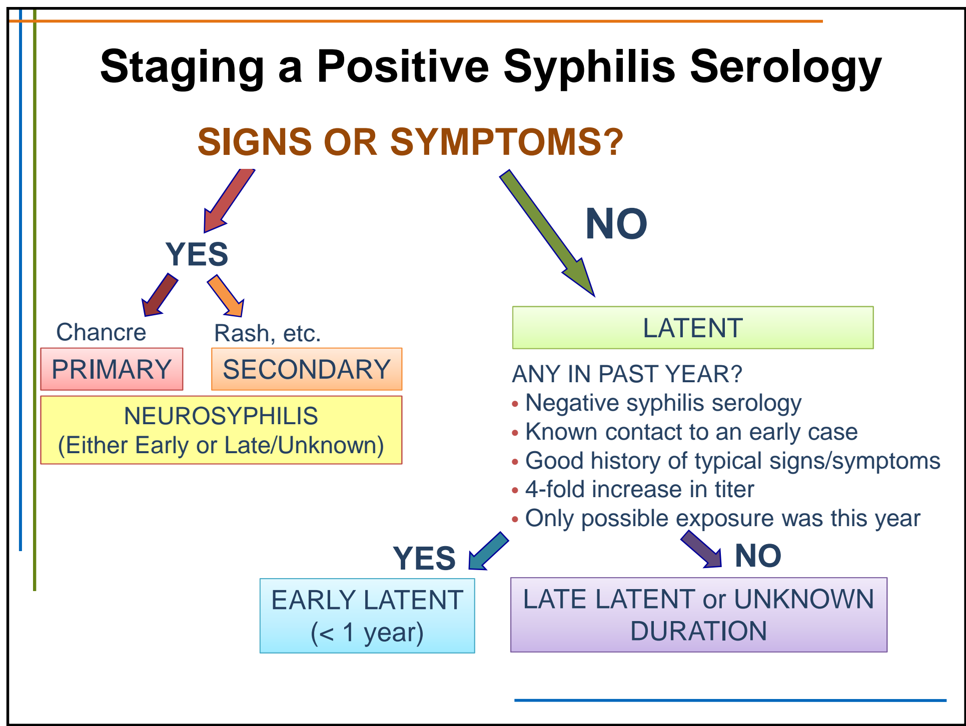
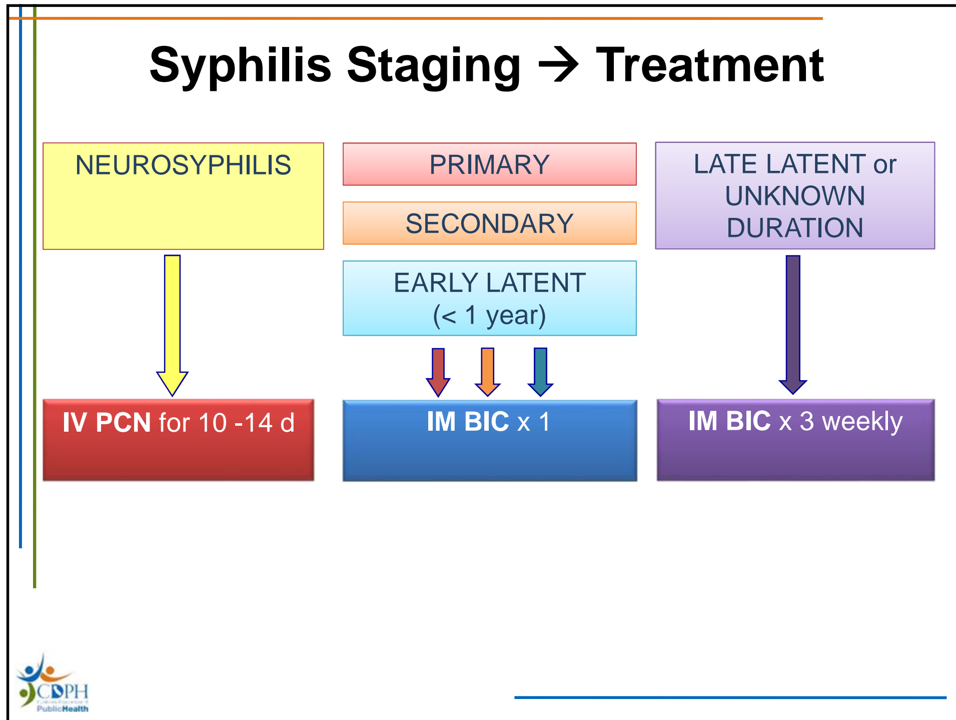
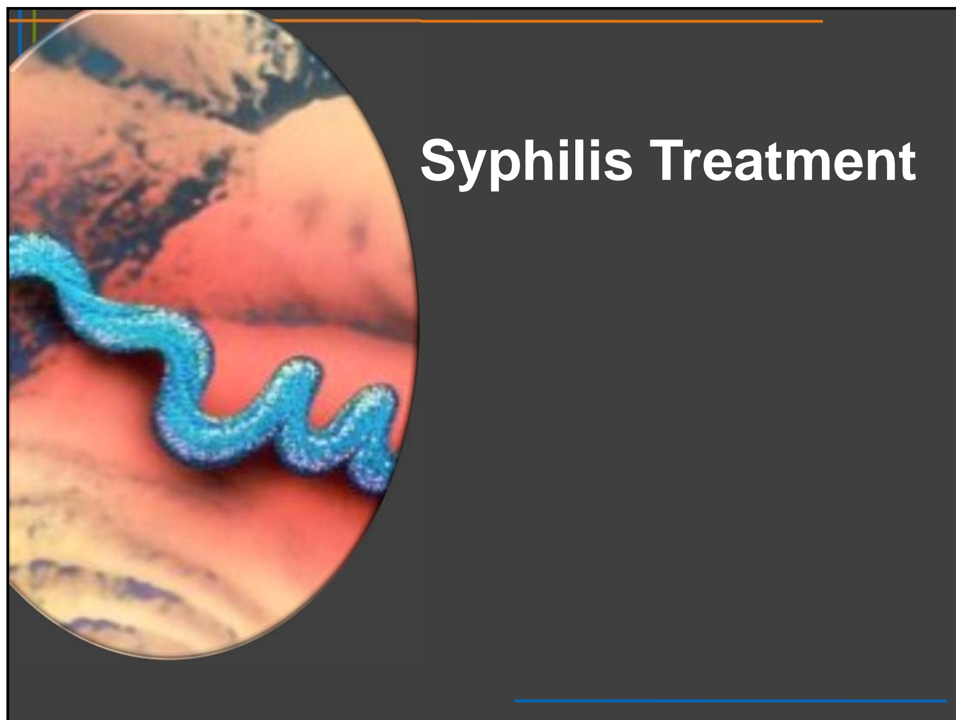

Who Should be Screened for Syphilis?
Pregnant F
• At first prenatal visit
• Again in the third trimester and at delivery if at risk, or in high morbidity area
Non-pregnant F
• At risk or in high morbidity areas
• At least once in lifetime
Neonates
• If exposed or maternal serology unknown
MSM
• Annually, or more frequently, 3-6 months if at high risk (multiple, anonymous partners, meth)
HIV +
• At least annually, depends on risk
On PrEP
• Every 3 months
Corrections
• Universal screening based on local area or institutional incidence
CDC 2015 STD Tx Guidelines www.cdc.gov/std/treatment
Plus: Guidelines for HIV care and HIV PrEP care
CDPH


Staging a Positive Syphilis Serology
SIGNS OR SYMPTOMS?
YES
NO
Chancre
Rash, etc.
PRIMARY
SECONDARY
NEUROSYPHILIS
(Either Early or Late/Unknown)
LATENT
ANY IN PAST YEAR?
• Negative syphilis serology
• Known contact to an early case
• Good history of typical signs/symptoms
• 4-fold increase in titer
• Only possible exposure was this year
YES
NO
EARLY LATENT
(< 1 year)
LATE LATENT or UNKNOWN DURATION


Syphilis Staging → Treatment
NEUROSYPHILIS
PRIMARY
SECONDARY
EARLY LATENT
(< 1 year)
LATE LATENT or
UNKNOWN
DURATION
IV PCN for 10 -14 d
IM BIC x 1
IM BIC x 3 weekly
CDPH


Syphilis Treatment

Question: Which of the following is true about treatment?

A. Treatment failure is common and follow up titers are essential to monitor treatment response
B. Knowing the titer on the day of treatment helps establish a baseline titer
C. Bicillin is superior to oral alternatives
D. On-site treatment recommended
E. Neuro and ocular syphilis require intravenous therapy
F. All of the above

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Syphilis Treatment

Primary, Secondary, & Early Latent

Benzathine penicillin G* 2.4 million units IM in a single dose

* Bicillin L-A is the trade name. DO NOT USE Bicillin C-R!

** No enhanced efficacy of additional doses of BPG, amoxicillin or other antibiotics even if HIV infected

Alternatives (non-pregnant penicillin-allergic adults):

- Doxycycline 100 mg po bid x 2 weeks
- Tetracycline 500 mg po qid x 2 weeks
- Ceftriaxone 1 g IV or IM qd x 10-14 d

CDC 2015 STD Treatment Guidelines
www.cdc.gov/std/treatment

Syphilis Treatment

Late Latent or Latent of Unknown Duration

Benzathine penicillin G* 7.2 million units IM total in 3 doses of 2.4 MU each at one week* intervals

* Maximum 10-14 day interval; 6-8 days in pregnancy.

Alternatives (non-pregnant penicillin-allergic adults):

- Doxycycline 100 mg po bid x 4 weeks
- Tetracycline 500 mg po qid x 4 weeks

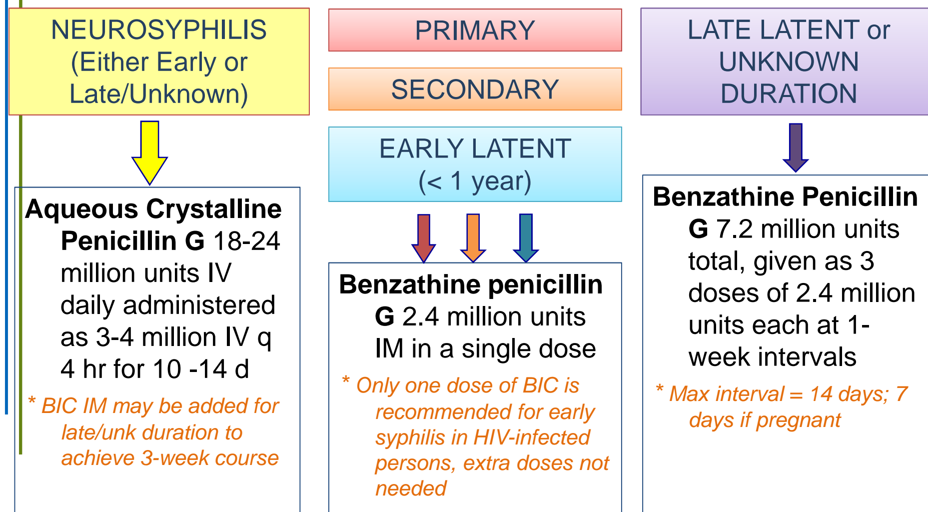
CDC 2015 STD Treatment Guidelines
www.cdc.gov/std/treatment

Neurosyphilis / Ocular Syphilis Treatment

Aqueous crystalline penicillin G 18-24 million units IV daily administered as 3-4 million units IV q 4 hr for 10-14 days

* Consider: BIC 2.4 million units IM once per week up to 3 weeks after completion of 10-14 day course for late syphilis

CDC 2015 STD Treatment Guidelines
www.cdc.gov/std/treatment



Treatment without Lab Confirmation

Diagnostic Challenges:

- Clinical presentation not specific
- Access to direct and stat tests limited
- Titer response slow: serology negative ~25% in early primary and majority of recently exposed contacts

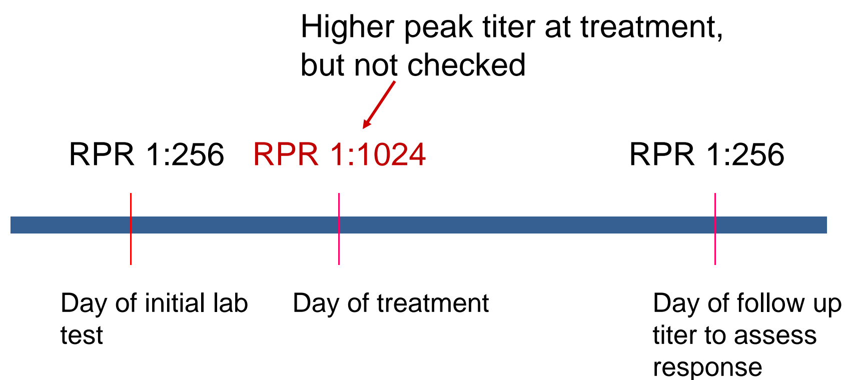
Empiric Treatment:

- Contact to early (with past 90 days, or uncertain follow up)
- Lesion is suspicious in high-risk patient and follow up is uncertain OR risk of ongoing transmission is high
- Symptoms and positive on point-of-care (stat RPR, trep)
- Get day of treatment titer

Watch and wait:

- Order serology and await results; ensure patient follow up
- If negative, repeat serology 2-4 weeks to rule out false negative

Importance of Day of Treatment Titer



Less than HALF of early syphilis cases in CA have a non-treponemal titer at the time of treatment!

Monitoring for Treatment Failure

- Best monitoring method = RPR at quarterly intervals
  - >4-fold decline best indicator of treatment effectiveness
  - Sustained >4-fold increase in titer strong indicator of treatment failure (sustained >2 week interval)
  - Lack of 4-fold decline – variable interpretation
  - If titer declines then increases 4-fold, consider treatment failure or reinfection
- Treatment failure most likely due to neuro-invasion
  - CSF necessary to evaluate treatment failure

Question: Which of the following is true about public health reporting?

A. Public health receives lab reports so provider reports are duplicative and unnecessary
B. Electronic medical records automatically send case reports to the health department
C. Timely reporting can make a difference in interrupting the spread of syphilis
D. Syphilis must be reported after treatment is complete

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D. Syphilis must be reported after treatment is complete

Provider STD Reporting Requirements
(Title 17, Section 2500)

1 working day:

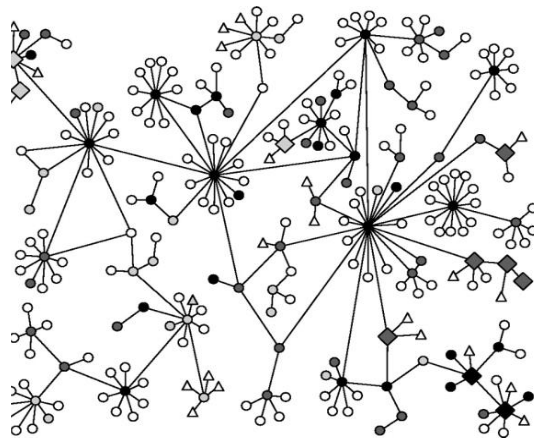
- **Syphilis**, including congenital syphilis
- **Acute HIV** infection
  - Additional HIV reporting requirements in Title 17, Section 2643.5

7 calendar days:

- Chancroid
- *Chlamydia trachomatis* infections, including lymphogranuloma venereum (LGV)
- Gonococcal infections
- HIV infection, stage 3 (AIDS)

Reports must be made by providers to via mail, phone, electronic report to the Local Health Officer (LHO) of the jurisdiction where the patient resides

Each report shall include the following information if known:
Date of onset and date of diagnosis
Name, address, telephone number
Occupation, race/ethnic group, sex, age, and date of birth
Provider contact information



Case Investigation and Contact Tracing

Goals:

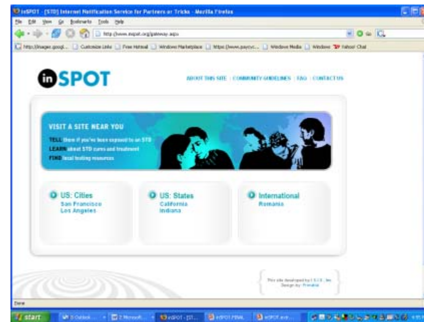
- Interrupt transmission
- Protect the community
- Prevent congenital syphilis

Online Anonymous Partner Referral

DONT SPREAD IT.COM

Anonymous STD/STI Notification via Text Message or Email

inspot.org



dontspreadit.com

Take Home Points: Syphilis

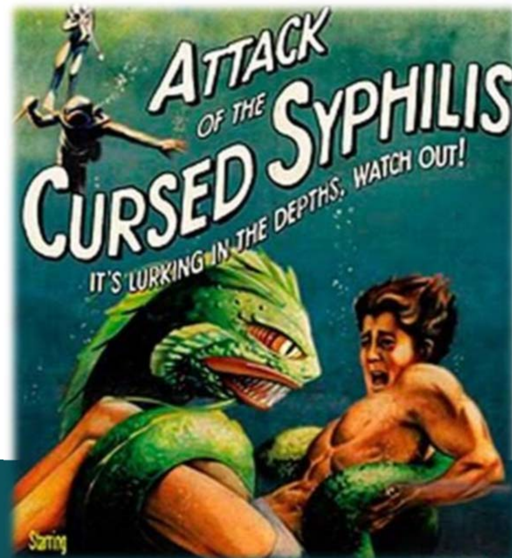
- Rates are increasing
- Recognize symptoms and signs
  - Evaluate for neuro/ocular signs
  - Empiric treatment if high suspicion
- Assess risk and screen
- Determine stage of disease to guide treatment
  - Get day-of-treatment titer
  - Follow titers to assess treatment
  - Use Bicillin L-A as first line
- Report to local health department

Clinical Guidelines and Consultation

CDPH Website:
www.std.ca.gov

STD Clinical Consult Line
www.stdccn.org

CDC STD Treatment Guidelines App
Available now, free
Search for "STD TX"



THANK YOU!

Heidi Bauer, MD MPH

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California Department of Public Health
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