STI Clinical Update: Introduction to Syphilis

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Learning Objectives

STI update through case-based approach

Case Presentation

- 35-year-old bisexual male presents to your clinic with genital ulcers.
- The ulcers are a little bit painful. They are not pruritic. There are several of them.
- The patient's physical exam reveals the following findings . . .

OC health CARE AGENCY

What is the most likely diagnosis?

- A. Genital herpes
- B. Primary syphilis
- C. Secondary syphilis
- D. Chancroid
- E. Pityriasis rosea

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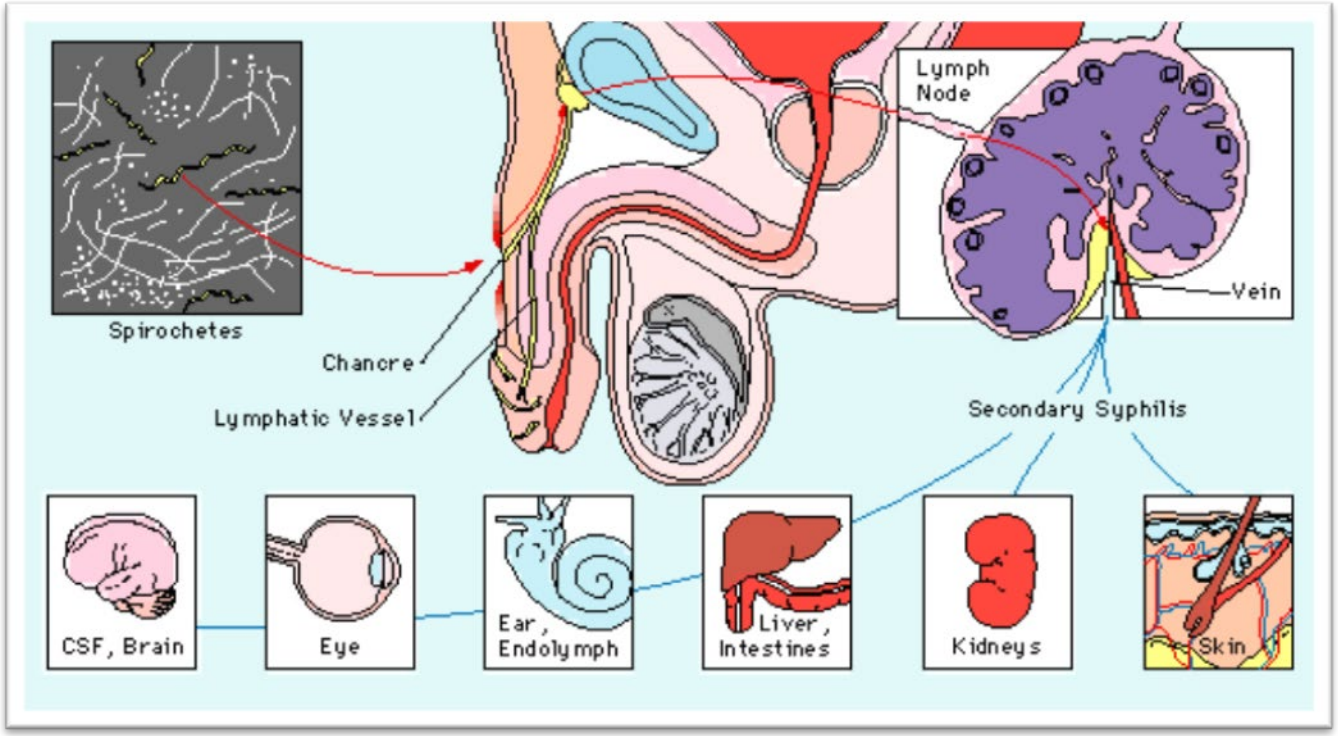
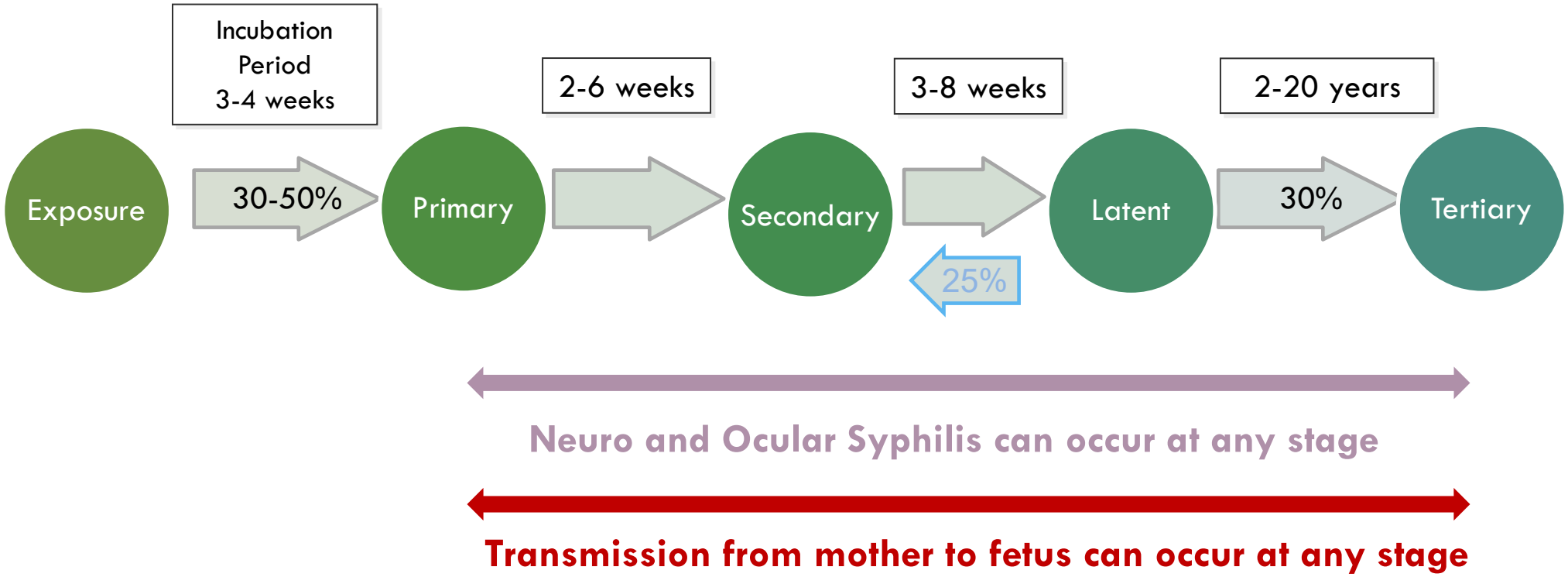
Syphilis Overview

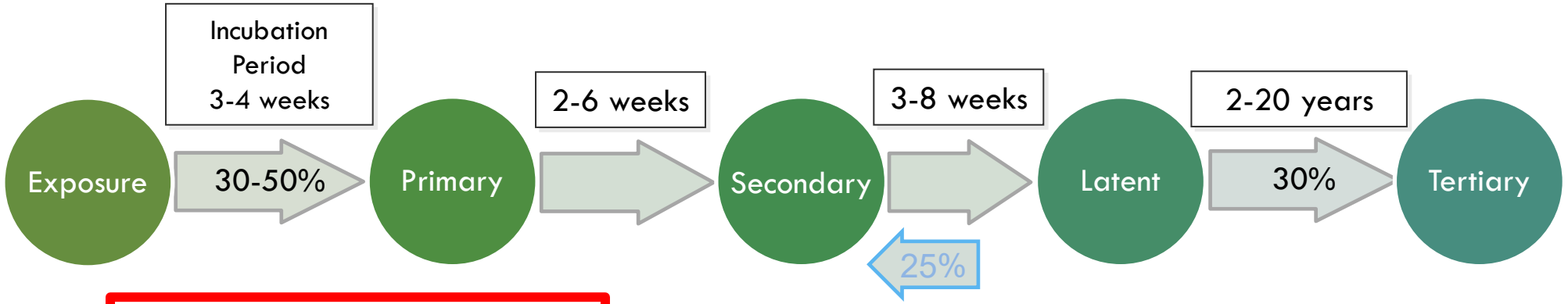
- **Causative organism:** *Treponema pallidum*, spirochete bacterium
- **Transmission:** direct contact to infectious lesion, blood-borne, mother-to child
- Incubation: ~3-4 weeks; range 10-90 days
- Causes systemic infection, episodes of active disease interrupted by periods of latent infection



Natural History of Syphilis



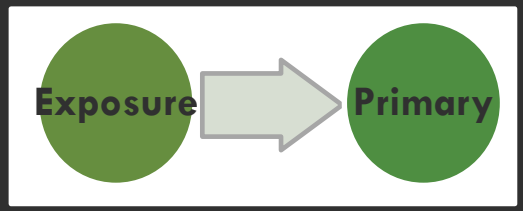
Natural History of Syphilis: Primary Syphilis



Chancre (ulcer)

- Single, painless, indurated, clean-based lesion with rolled edges.
- Can go unrecognized, esp if in the rectum or vagina
- Possible regional adenopathy (rubbery, bilateral, painless)

Primary Syphilis

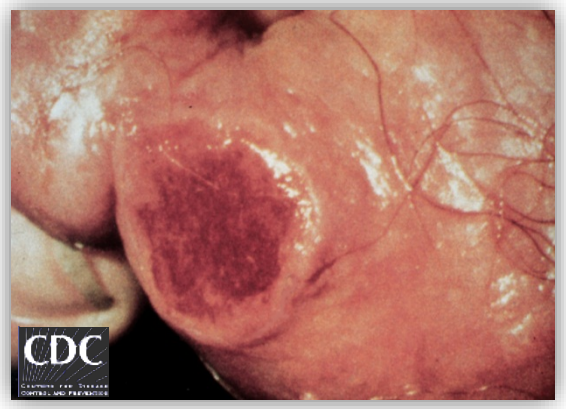


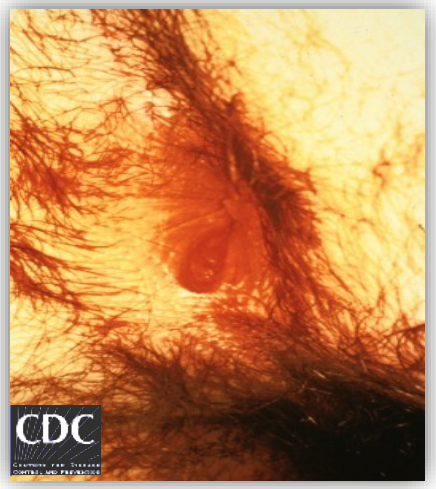
Mosby *STD Atlas, 1997*

Dr. Joseph Engelman, San Francisco City Clinic

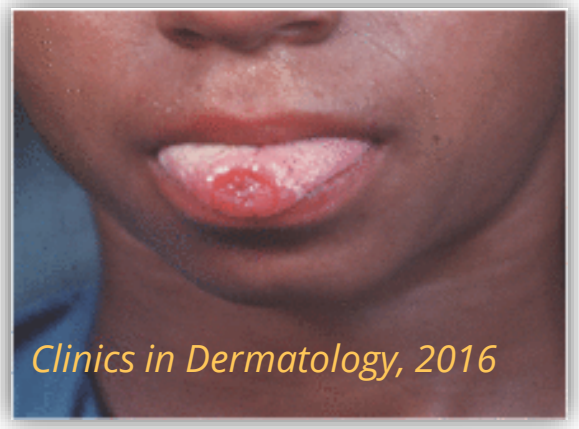
Courtesy: SF City Clinic

Primary Syphilis





Primary Syphilis: Extragenital Chancres



Back to our patient…

- After examining the patient's genital ulcers, the provider suspects genital herpes.
- The patient is prescribed acyclovir.
- His ulcers resolve entirely; he feels well.
- He returns a few weeks later, this time with a diffuse but subtle non-pruritic rash.
- The appearance of the rash is as shown:


DMHC

What is the most likely diagnosis?

- A. Secondary syphilis
- B. Tinea versicolor
- C. Coxsackie virus (hand-foot-mouth disease)
- D. Atopic dermatitis
- E. Contact dermatitis

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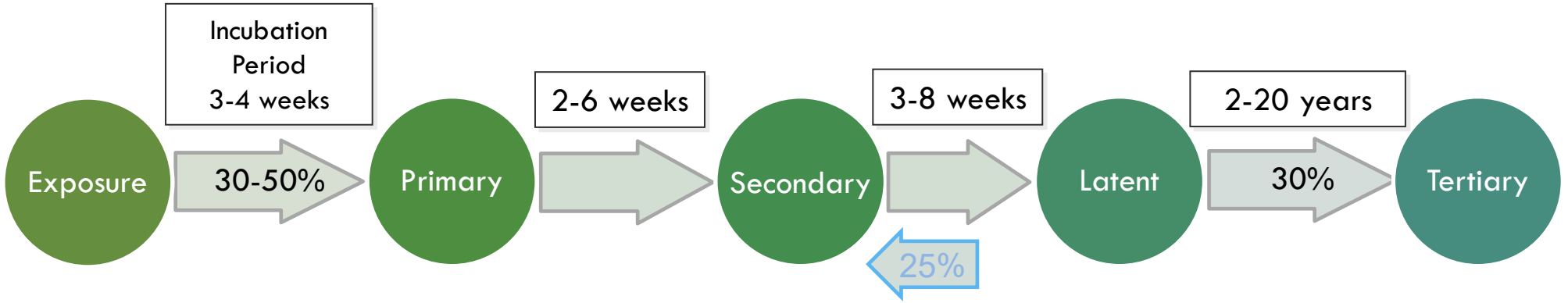
Natural History of Syphilis: Secondary Syphilis



Secondary signs

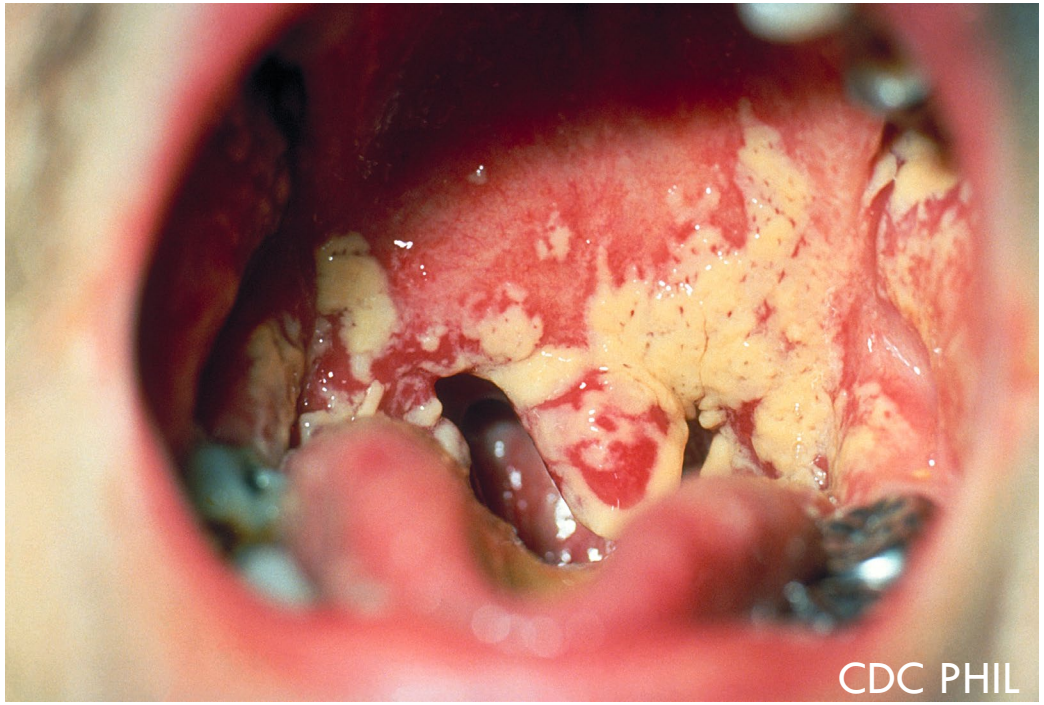
- Rash (75-90%),
  - Involving palms/soles (60%)
- Generalized lymphadenopathy (70-90%)
- Constitutional symptoms (50-80%)
- Mucous patches (5-30%)
- Condyloma lata (5-25%)
- Patchy alopecia (10-15%)
- Symptoms of neurosyphilis (1-2%)

Secondary Syphilis: Rash

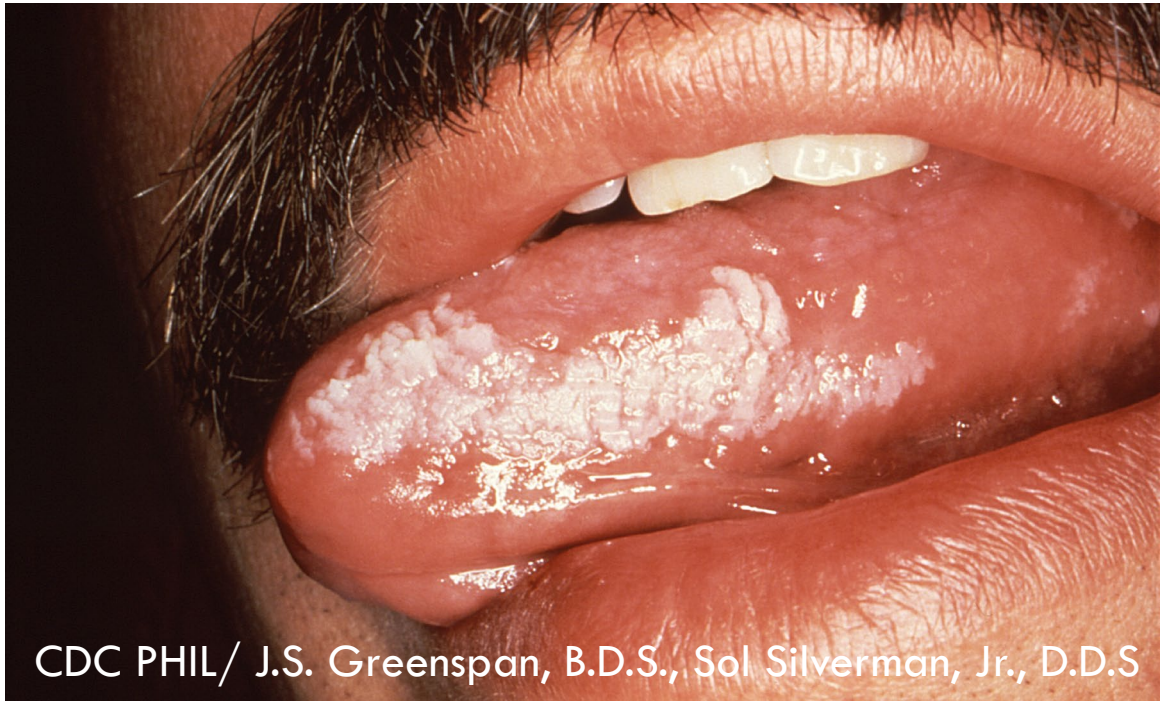
Secondary Syphilis: Mucous Patches

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

Mucus Patches: Differential Diagnosis



Oropharyngeal candidiasis / Thrush



Oral hairy leukoplakia

https://phil.cdc.gov/details.aspx?pid=1217; https://phil.cdc.gov/details.aspx?pid=6061

Secondary Syphilis: Patchy Alopecia

Mosby *STD Atlas, 1997*

Secondary Syphilis: Condyloma lata

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

Forbes CD, Jackson WF. *Color Atlas and Text of Clinical Medicine*, 3rd ed. London: Mosby; 2003

Differential diagnosis: Condyloma acuminata

https://www.std.uw.edu/go/pathogen-based/hpv/core-concept/all#clinical-manifestations

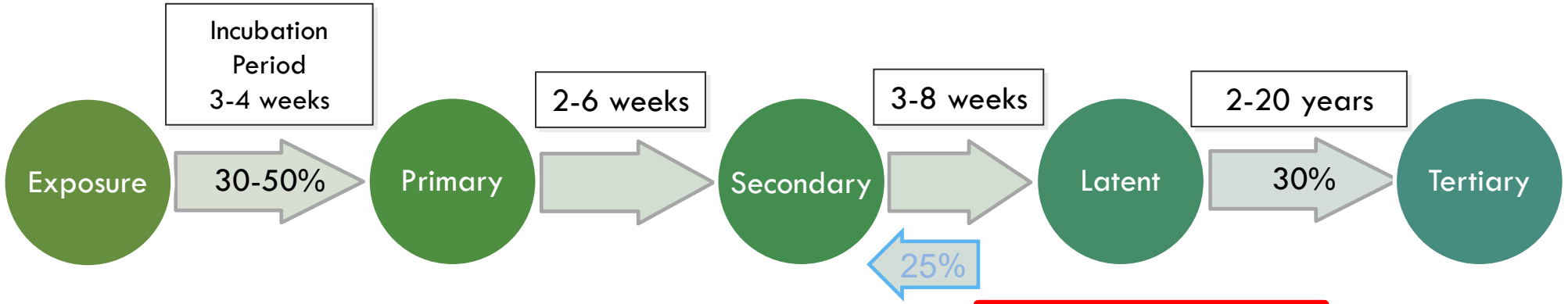
Back to our case…

- After evaluating the patient's rash, the provider suspects contact or allergic dermatitis.
- A topical steroid is prescribed.
- The patient is adherent to steroid treatment.
- His rash resolves and he feels well.

Case, Continued

- The patient returns for a routine physical exam and check-up a few months later.
- He has no acute concerns.
- A sexual history is not taken, and he is not screened for sexually transmitted infections.

Natural History of Syphilis: Early latent



Early latent
Latent w/evidence of infection within the past 12 months

Otherwise: Considered **Late-Latent or Unknown Duration**

Back to our patient . . .

- Two years after resolution of his rash, the patient returns to clinic with slight hearing loss and new mild headaches.
- The provider tests the patient's hearing in office and does not find any obvious deficits.
- No further testing is pursued.
- The patient is reassured that there is nothing to worry about.
- He is told to return to clinic if his symptoms worsen.

What is the most likely diagnosis?

For the hearing loss and headaches:

- A. Cholesteatoma
- B. Otitis media
- C. Neurosyphilis
- D. Age-related sensorineural hearing loss

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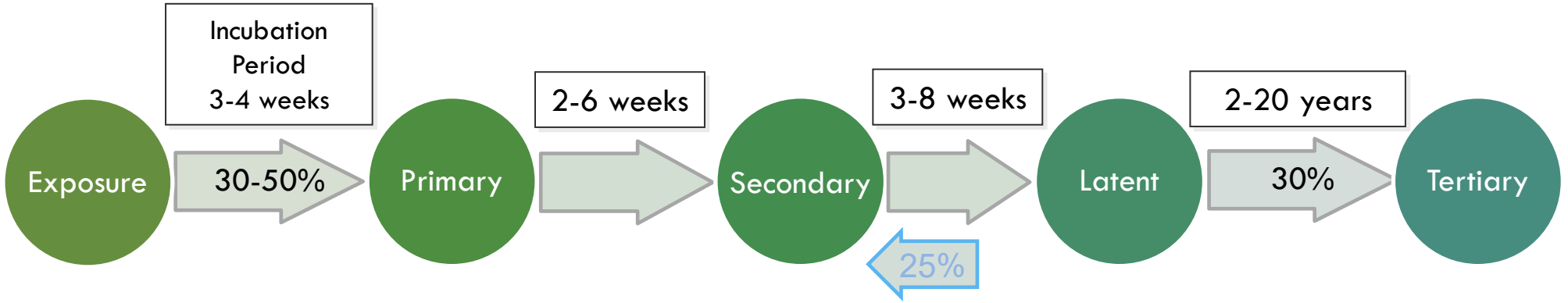
Natural History of Syphilis



Neuro and Ocular Syphilis can occur at any stage

Neurosyphilis

- Can occur at **any** stage of syphilis
- **Early** manifestations (months to years after infection)
  - Cranial nerve dysfunction, meningitis, stroke, AMS, hearing or vision changes
  - Otosyphilis – hearing loss w/wo tinnitus
  - Ocular – range of visual symptoms
- **Late** manifestations (10-30 years after infection)
  - Tabes dorsalis and general paresis
- **Note: in untreated HIV or AIDS- Neuro and ocular syphilis timelines are shortened considerably**
- **All patients with syphilis should be assessed for neurological signs and symptoms**
  - Neuro exam, including assessment of ophthalmic and auditory symptoms
  - If clinical evidence of neurologic involvement is observed, perform LP

Case Continued

- The patient presents to the ED a few days after his last clinic discharge
- His headaches have worsened to the point of becoming severe.
- The ED physician now does a CT brain and LP.
- A cerebrospinal fluid VDRL is sent as part of the routine work up for meningitis.
- The VDRL results positive, and the patient is diagnosed with neurosyphilis.
- He is admitted for treatment with IV penicillin.

Case conclusion…

- Meanwhile, a few months after our patient's last clinic visit, one of the patient's female partners delivers an infant at 38 weeks pregnant.
- The mother received no pre-natal care.
- The newborn appears ill, with copious nasal discharge, hepatosplenomegaly, lymphadenopathy, a rash, and jaundice.
- CSF analysis reveals a positive VDRL, confirming a diagnosis of congenital syphilis.

CDC: "Up to 40% of babies born to women with untreated syphilis may be stillborn, or die from the infection"

Early CS physical findings (birth-8 weeks, but up to 2 years)

- **Hepatomegaly** (enlarged liver)
- **Splenomegaly** (enlarged spleen)
- **Snuffles** (copious nasal secretions – infectious!)
- **Mucocutaneous lesions** (infectious!)
- **Pneumonia Alba**
- **Osteochondritis**
- **Pseudoparalysis**
- **Edema**
- **Rash, lymphadenopathy**
- **Hemolytic anemia or thrombocytopenia**

Snuffles

Cutaneous lesion

Mucous patches

Pneumonia Alba

Umbilical lesion

Courtesy CDC Public Health Image Library

Congenital Syphilis Physical Findings: Late (2 years +)

- **Interstitial keratitis** (5–20 years of age)
- **Eighth cranial nerve deafness** (10–40 years of age)
- **Hutchinson teeth** (peg-shaped, notched central incisors)
- **Mulberry molars**
- **Anterior bowing of the shins**
- **Frontal bossing**
- **Saddle nose**
- **Rhagades** (perioral fissures)
- **Clutton joints** (symmetric, painless swelling of the knees)

Interstitial keratitis

Hutchinson's teeth

Frontal bossing

Clutton's joints

Courtesy CDC Public Health Image Library

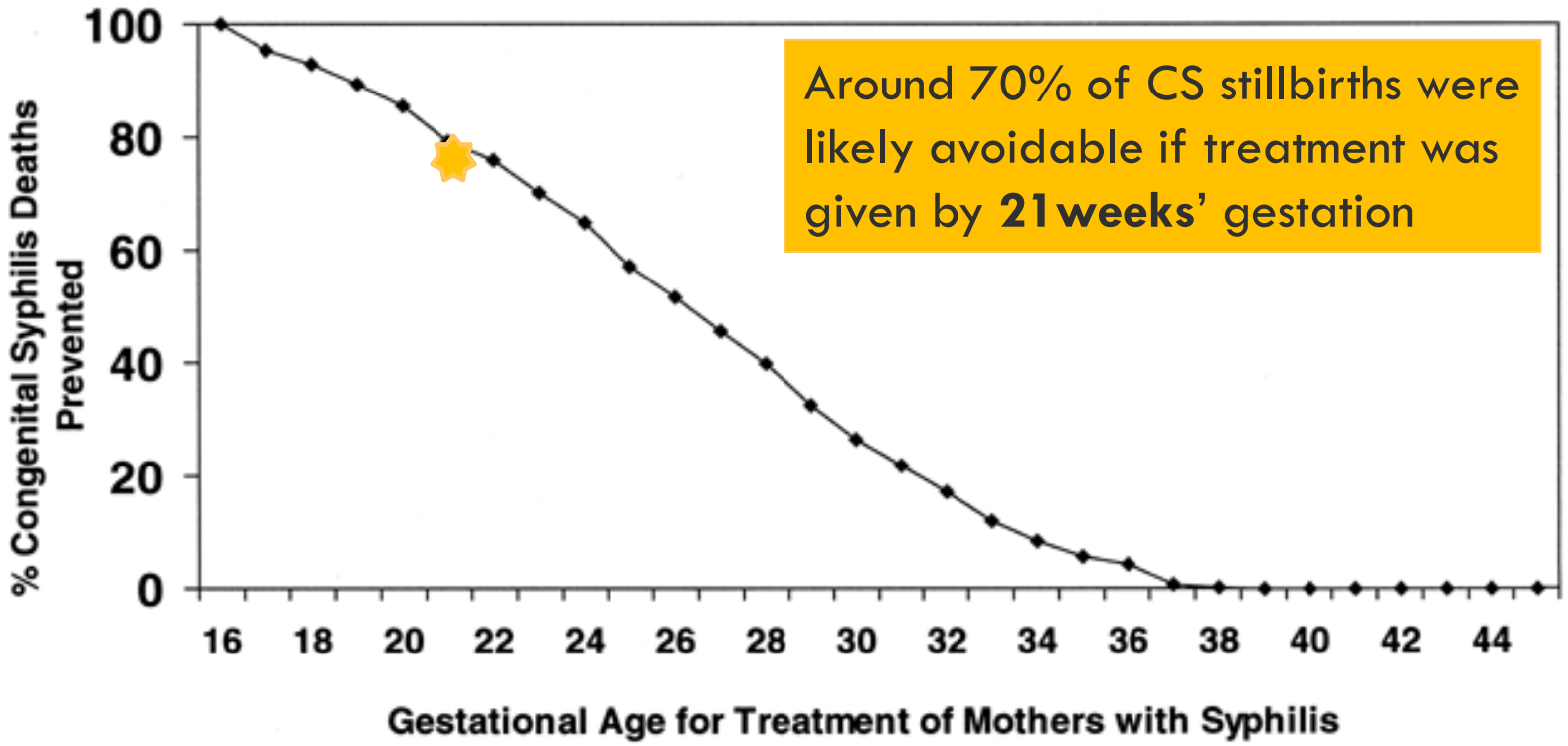
"Saber shins"

Rhagades

Citation: 1. L. Pessoa and V. Galvao, "Unusual presentation of more common disease/injury: clinical aspects of congenital syphilis with Hutchinson's triad," BMJ Case Reports, vol. 2011, pp. 1–3, 2011.

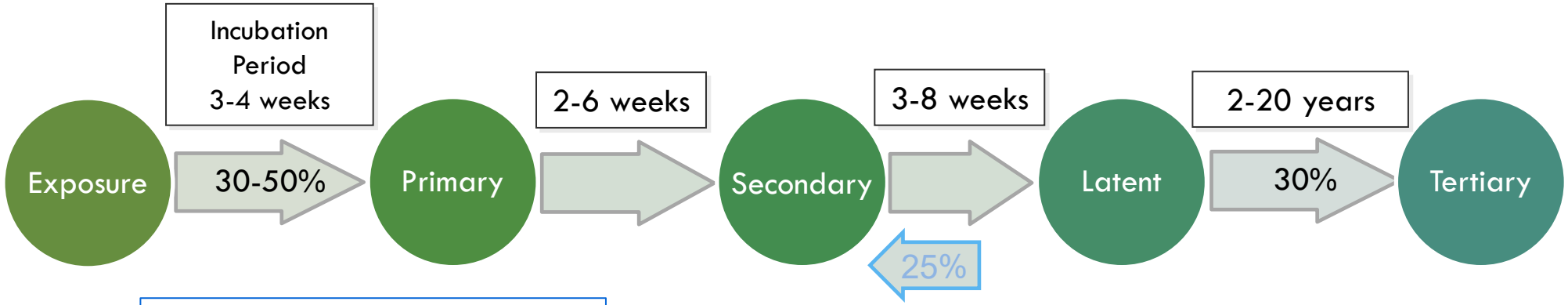
Mathematical model: Early Rx = Fewer CS Infant Deaths

% CS deaths preventable by treating pregnant women with syphilis at a given gestational age.



(Gust DA, Levine WC, St. Louis, M, *et al*. Mortality associated with congenital syphilis in the United States, 1992-1998. Pediatrics, 2002; 109(5):E79-9.)

Natural History of Syphilis



Chancre (ulcer)

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Otherwise: Considered **Late-Latent or Unknown Duration**

Neuro and Ocular Syphilis can occur at any stage

Transmission from mother to fetus can occur at any stage

Syphilis Diagnosis

California Department of PublicHealth

Syphilis Diagnostics

What test(s) is/are needed to diagnose syphilis?

- A) A treponemal test, such as a treponema pallidum particle agglutination (TPPA), Enzyme immunoassay (EIA), or chemiluminescence immunoassay (CIA) detecting antibodies to syphilis
- B) A non-treponemal test such as an RPR or VDRL
- C) Both a non-treponemal test and at least one treponemal test

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Serology and stage: Need both a treponemal AND a non-treponemal tests

Non-treponemal tests

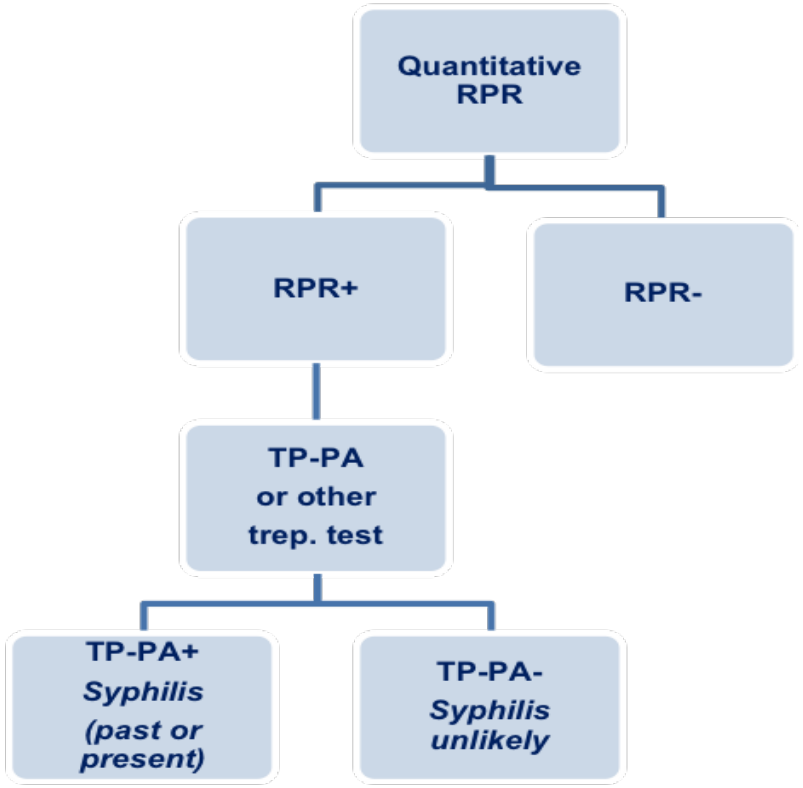
- Examples: RPR and VDRL
- Quantitative tests, allowing for assessment of disease burden, treatment adequacy, and re-infection
- Non-specific (can be positive in patients with other conditions)

Treponemal tests

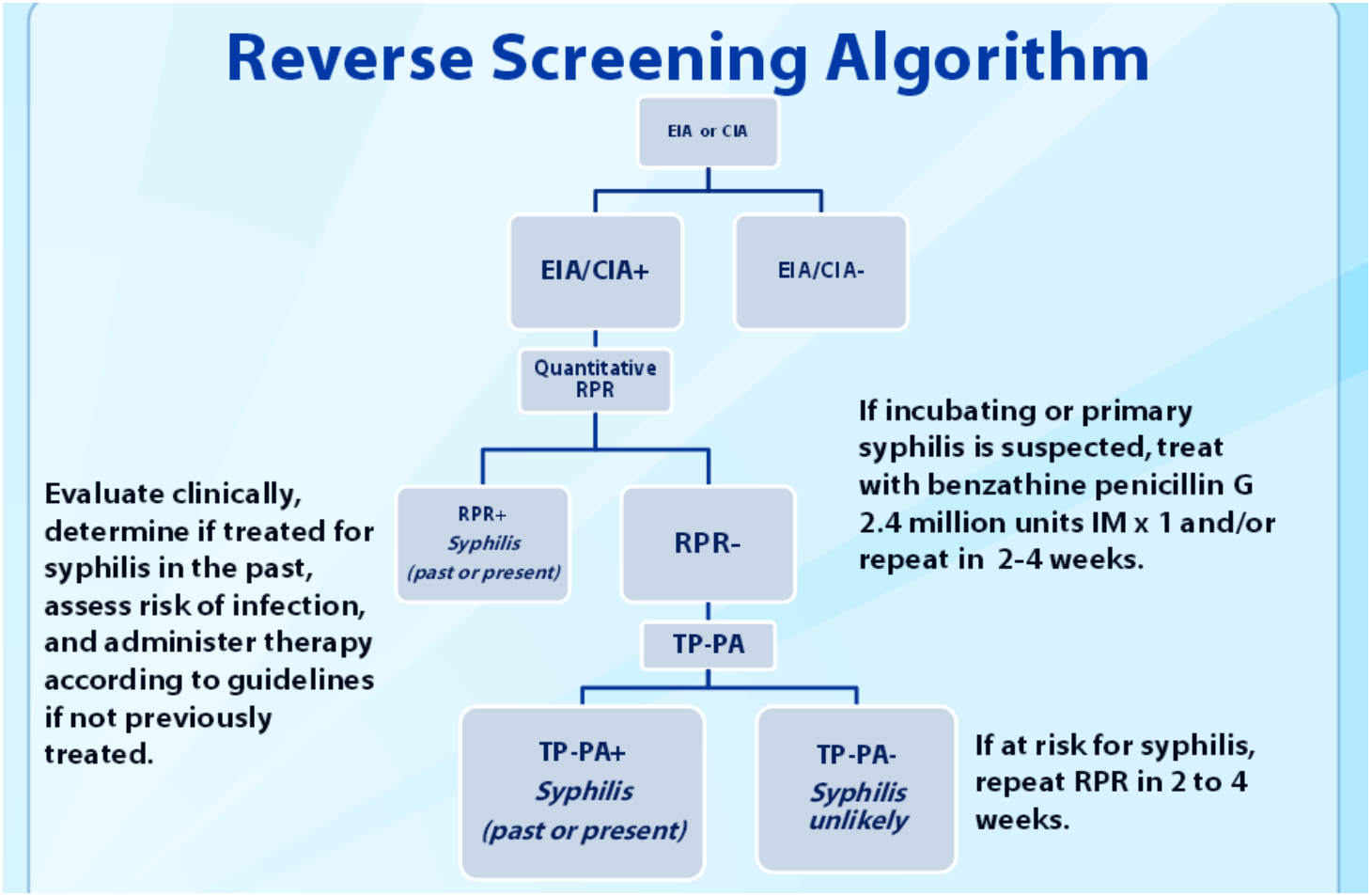
- Examples: **TPPA, TPHA, FTA-ABS, EIA, CIA**
- Detect antibodies specific to T. pallidum
- Antibodies usually stay positive for life after initial infection
- Not quantitative; cannot be used to assess for reinfection or response to treatment

Serologic Screening for Syphilis: Traditional vs Reverse Algorithms

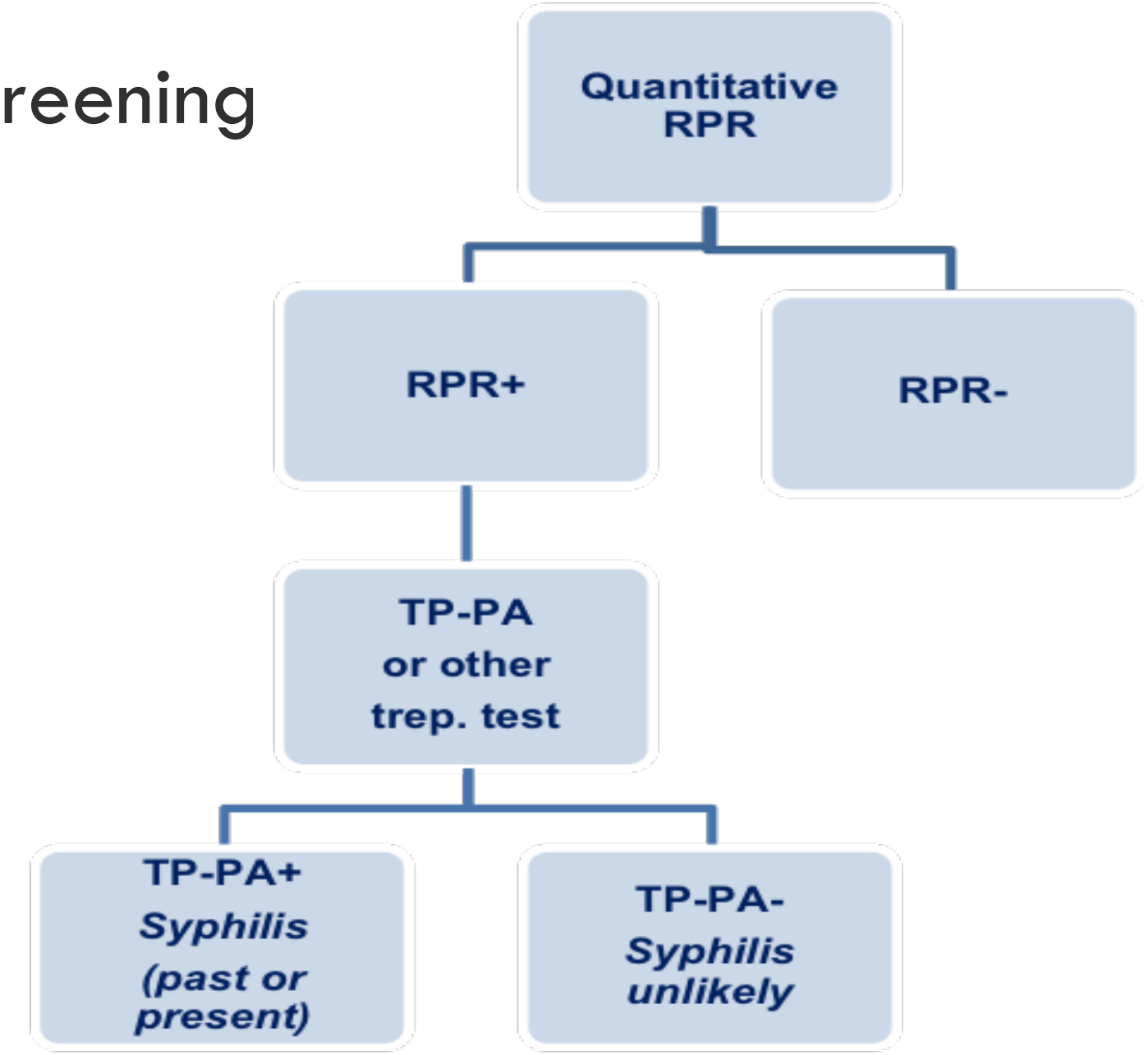
TRADITIONAL



Reverse Screening Algorithm



Traditional screening algorithm



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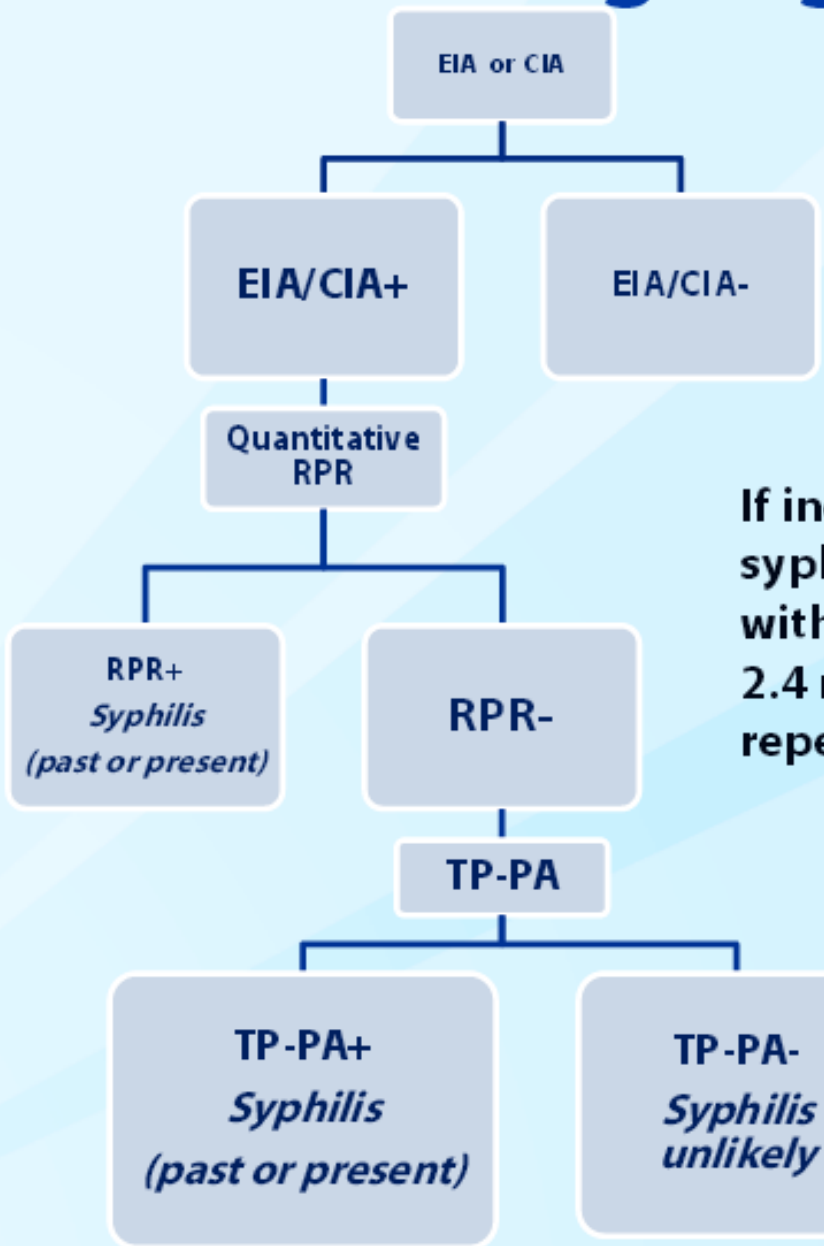


Evaluate clinically, determine if treated for syphilis in the past, assess risk of infection, and administer therapy according to guidelines if not previously treated.

If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units IM x 1 and/or repeat in 2-4 weeks.

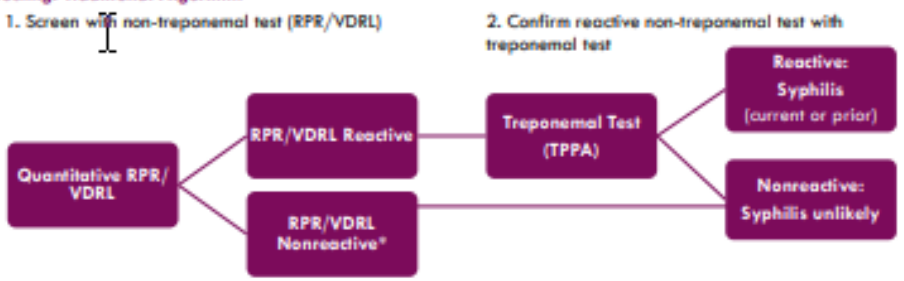
If at risk for syphilis, repeat RPR in 2 to 4 weeks.

Clinical Interpretation of Syphilis Screening Algorithms: A Resource for Local Health Jurisdictions

https://californiaptc.com/wp-content/uploads/2021/09/Syphilis-Diagnostics_V2-4_8.31.21-LB_508.pdf

Clinical Interpretation of Syphilis Screening Algorithms
A Resource for Local Health Jurisdictions

Testing: Traditional Algorithm[a]



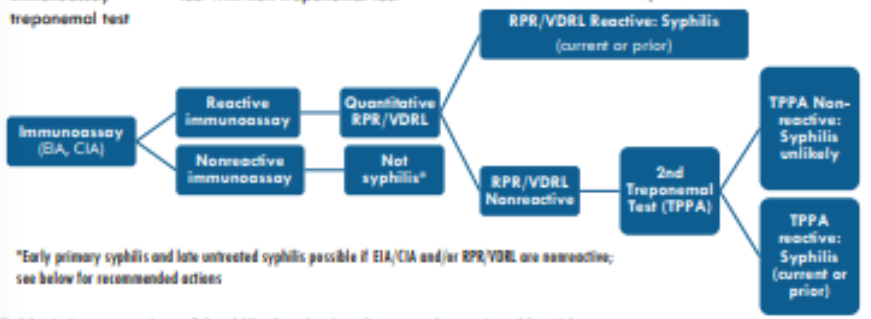
*Early primary syphilis and late untreated syphilis possible if RPR/VDRL are nonreactive; see below for recommended actions

Table 1: Interpretation of Syphilis Serologies, Traditional Algorithm

Non-Treponemal (RPR/VDRL)	Treponemal (TPPA)	Possible Interpretations	Recommended Actions
Nonreactive	Nonreactive or not done	1. No syphilis 2. Early/incubating syphilis (too early to be detected by serology)	• If syphilis unlikely, no further action needed. • If early syphilis suspected, consider ordering a treponemal test (if not done initially) and repeating an RPR/VDRL in 1-2 weeks; if either test is reactive, treat for syphilis. • If concerned for early syphilis (e.g., chancre present or known exposure) treat presumptively. If treating presumptively, repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
	Reactive	1. Prior treated syphilis 2. Untreated syphilis	• Treponemal tests (e.g., TPPA) often stay reactive for life; if patient has a history of adequate treatment for syphilis & no new exposures/ symptoms, no further action needed. • If early syphilis suspected (e.g., chancre present or known exposure), treat presumptively according to stage. If treating presumptively, repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion. • If no signs or symptoms, order a second treponemal test (e.g., EIA or CIA); see table 2 for recommendations based on results.
Reactive	Nonreactive	1. False positive RPR or VDRL	• Likely false positive (not syphilis).[b] • In pregnancy or in patients at high risk for syphilis, consider rescreening with serologic testing in 2-4 weeks – if unchanged, no action needed.[c]
	Reactive	1. Current syphilis 2. Treated syphilis with residual/ persistent RPR/VDRL titer	• If RPR/VDRL is newly reactive, stage and treat. • If previously treated and sustained (≥2 weeks) 4-fold rise in RPR/VDRL titer, manage as treatment failure versus re-infection.[d] • Note that RPR/VDRL may still be reactive after treatment; if there is a fourfold decline within 12-24 months, treatment is considered to have been adequate even if RPR/VDRL remains reactive. • Some treated patients may have a persistent low level RPR/VDRL titer for a prolonged period; re-treatment is not necessary in the absence of new exposures or symptoms.

Clinical Interpretation of Syphilis Screening Algorithms
A Resource for Local Health Jurisdictions

Testing: Reverse Algorithm[a]



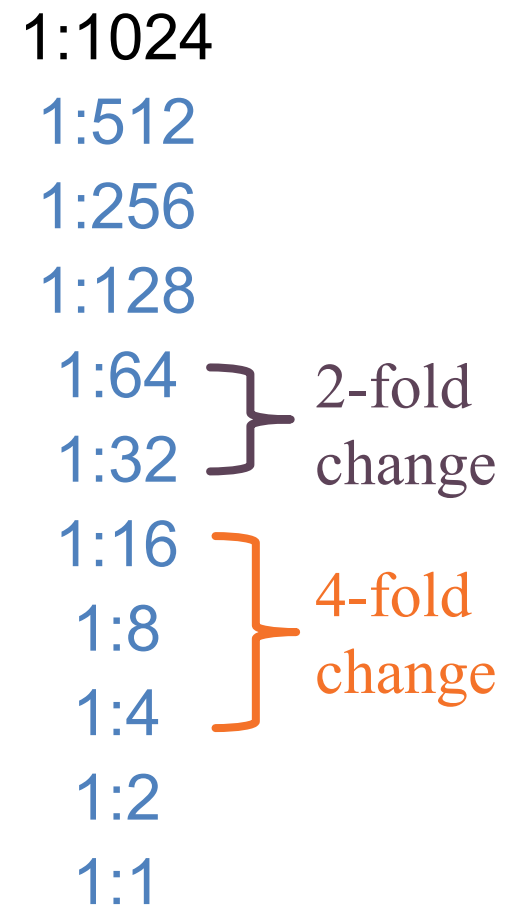
*Early primary syphilis and late untreated syphilis possible if EIA/CIA and/or RPR/VDRL are nonreactive; see below for recommended actions

Table 2: Interpretation of Syphilis Serologies, Reverse Screening Algorithm

Immuno-assay (CIA or EIA)	RPR/ VDRL	TPPA	Possible Interpretations	Recommended Actions
Non-reactive	Non-reactive or not done	Non-reactive or not done	1. Syphilis unlikely 2. Early/incubating syphilis (too early to be detected by serology)	• If syphilis unlikely, no further action needed. • If immunoassay nonreactive but high clinical suspicion (such as a chancre or known exposure), treat presumptively for early syphilis. If treating presumptively, obtain RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
Reactive	Non-reactive	Non-reactive or not done	1. False positive immunoassay 2. Early/incubating syphilis 3. Latent or prior syphilis (treated or untreated)	• If no signs/symptoms and low risk for syphilis, most likely a false positive immunoassay.[b] No further action needed. • If concerned for early infection or in pregnant patients, re-screen in 2-4 weeks.[c] • If signs/symptoms or contact to syphilis, treat presumptively. Repeat RPR/VDRL on day of treatment and, if nonreactive, again in 2-4 weeks to assess for seroconversion.
		Reactive	1. Latent or prior syphilis (treated or untreated) 2. Early syphilis (prior to RPR/VDRL seroconversion)	• No further action needed if patient treated appropriately for syphilis in past, assuming no new exposures/symptoms and a negative clinical exam. • If no symptoms and no known prior adequate treatment, treat presumptively for latent syphilis. • If early syphilis suspected (symptoms or known exposure), treat presumptively. Obtain RPR/VDRL on day of treatment. If nonreactive, repeat in 2-4 weeks to assess for seroconversion.
	Reactive	Not done or Reactive	1. Current syphilis 2. Prior syphilis (treated or untreated)	• If RPR/VDRL is newly reactive, stage and treat. • If previously treated and sustained (≥2 weeks) 4-fold rise in RPR/VDRL titer, manage as treatment failure versus re-infection.[d] • If known prior adequate treatment for stage of infection and RPR/VDRL declining appropriately (i.e., a fourfold decline within 12-24 months), no further action needed. • Some treated patients may have a persistent low level RPR/VDRL titer for a prolonged period; re-treatment is not necessary in the absence of new exposures or symptoms.

What about patients with a history of syphilis, how do you interpret non-treponemal (RPR/VDRL) titers?

- Higher numbers correspond to higher level of antibodies in patient's serum
- **Two-fold change:** Generally considered within margin of error of test
- **Four-fold change:** Sustained for at least 2 weeks considered to be significant
- Compare titers using the **same** serologic test: *RPR often higher than VDRL*



Syphilis Treatment

California Department of PublicHealth

Primary, Secondary, and Early Latent Syphilis

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!**

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

Syphilis of Late Latent or Unknown Duration

Benzathine penicillin G 2.4 million units IM weekly* x 3

***Maximum 10-14 day interval in non-pregnant patients (7-9 days ideal)**

***7-day interval optimal in pregnancy**

Alternatives (non-pregnant penicillin-allergic adults):

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

Syphilis in Pregnancy

Penicillin is the only treatment for syphilis in pregnancy

- Treat with the penicillin regimen appropriate for stage of infection
  - Some experts recommend a 2nd dose of benzathine penicillin G 2.4 mu IM (7 days after 1st dose in early syphilis for pregnant people)
- Pregnant people with history of penicillin allergy should be desensitized and treated with penicillin
- All patients with syphilis should be tested for HIV

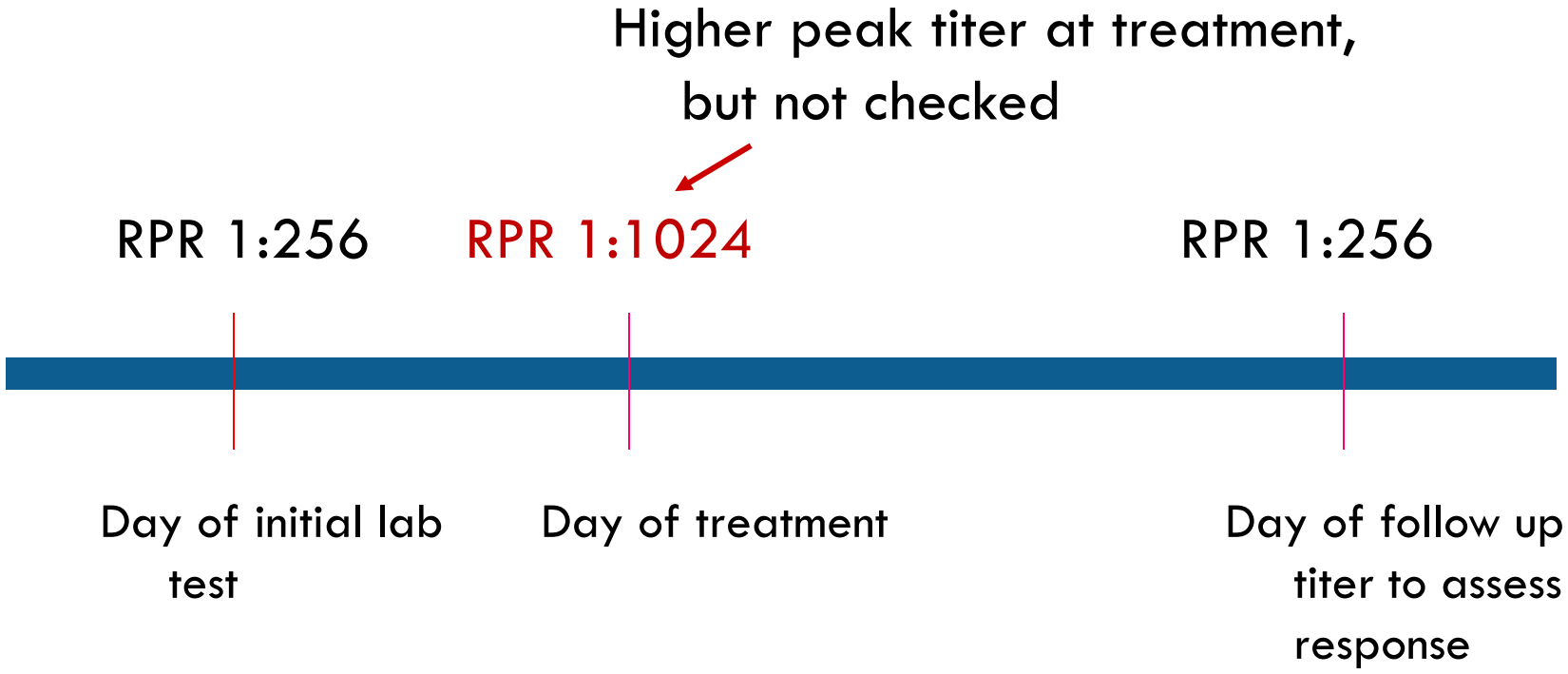
Neurosyphilis & Ocular Syphilis

Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days

Alternative Regimen *(use only if compliance with therapy can be ensured)*

- Procaine penicillin G 2.4 million units IM once daily PLUS
- Probenecid 500 mg orally four times a day, both for 10–14 days

Importance of Day of Treatment Titer



Establishes baseline to compare response post treatment

Frequently forgotten and without baseline makes assessment of titer response difficult

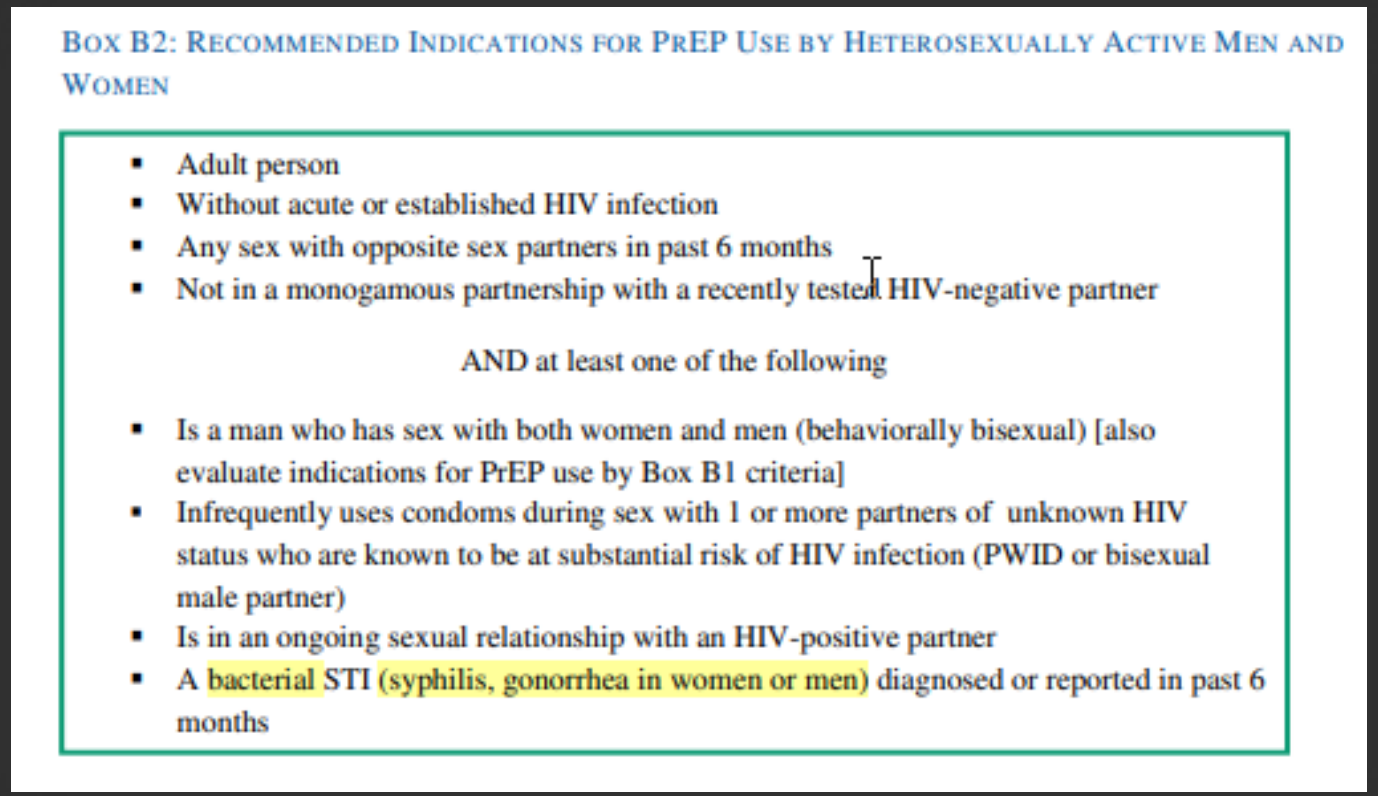
Conclusions

- 1) Syphilis presents differently in different stages of disease and can easily be misdiagnosed.
- 2) Left untreated, patients progress through stages of active disease interspersed by periods of latent disease.
- 3) The outcomes of untreated primary, secondary, and latent syphilis can be as severe as congenital syphilis, neurosyphilis, and ocular syphilis
- 4) Neurosyphilis and maternal-fetal syphilis transmission can occur at any stage of disease.
- 5) The diagnosis of syphilis involves both treponemal and non-treponemal tests.
- 6) Syphilis is treated differently depending on the stage of disease; penicillin is the drug of choice.
- 7) Remember to include syphilis on your differential diagnoses and to screen broadly.

CDC Indications for HIV PrEP

HIV PrEP should be offered to sexually active individuals with syphilis (and/or any other bacterial STI) diagnosed or reported in the past 6 months

https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

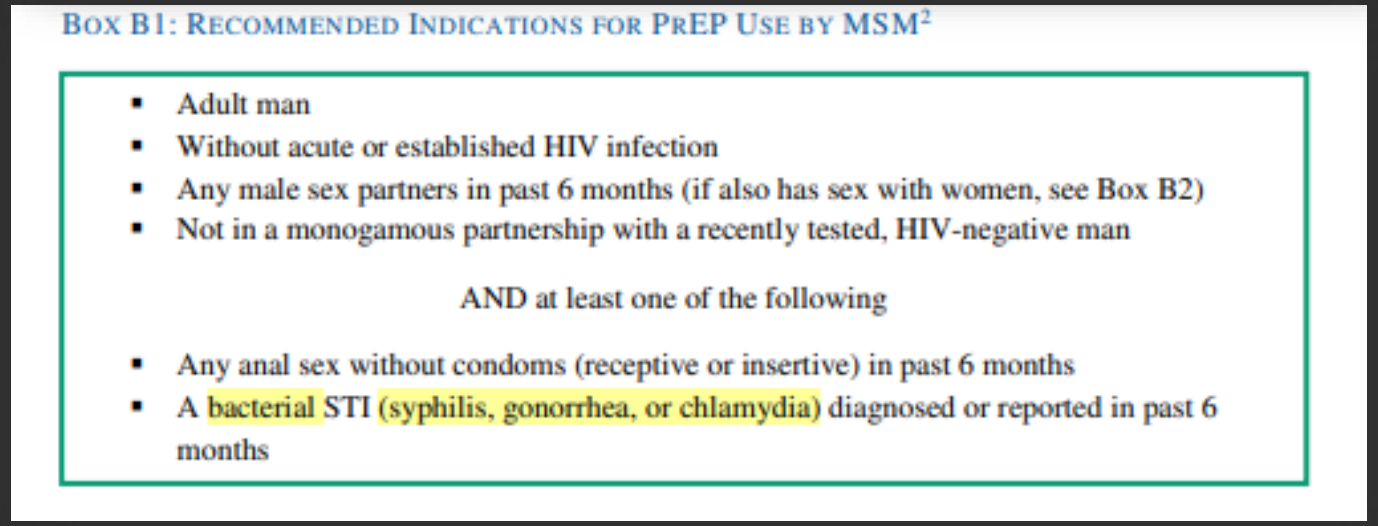


BOX B2: RECOMMENDED INDICATIONS FOR PREP USE BY HETEROSEXUALLY ACTIVE MEN AND WOMEN

- Adult person
- Without acute or established HIV infection
- Any sex with opposite sex partners in past 6 months
- Not in a monogamous partnership with a recently tested HIV-negative partner

AND at least one of the following

- Is a man who has sex with both women and men (behaviorally bisexual) [also evaluate indications for PrEP use by Box B1 criteria]
- Infrequently uses condoms during sex with 1 or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (PWID or bisexual male partner)
- Is in an ongoing sexual relationship with an HIV-positive partner
- A bacterial STI (syphilis, gonorrhea in women or men) diagnosed or reported in past 6 months



BOX B1: RECOMMENDED INDICATIONS FOR PREP USE BY MSM[2]

- Adult man
- Without acute or established HIV infection
- Any male sex partners in past 6 months (if also has sex with women, see Box B2)
- Not in a monogamous partnership with a recently tested, HIV-negative man

AND at least one of the following

- Any anal sex without condoms (receptive or insertive) in past 6 months
- A bacterial STI (syphilis, gonorrhea, or chlamydia) diagnosed or reported in past 6 months

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