

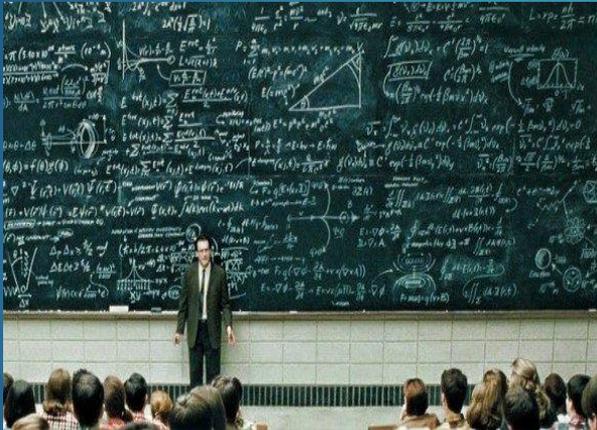
Tackling the syphilis epidemic in North Carolina: Key issues in clinical and public health management

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Overview



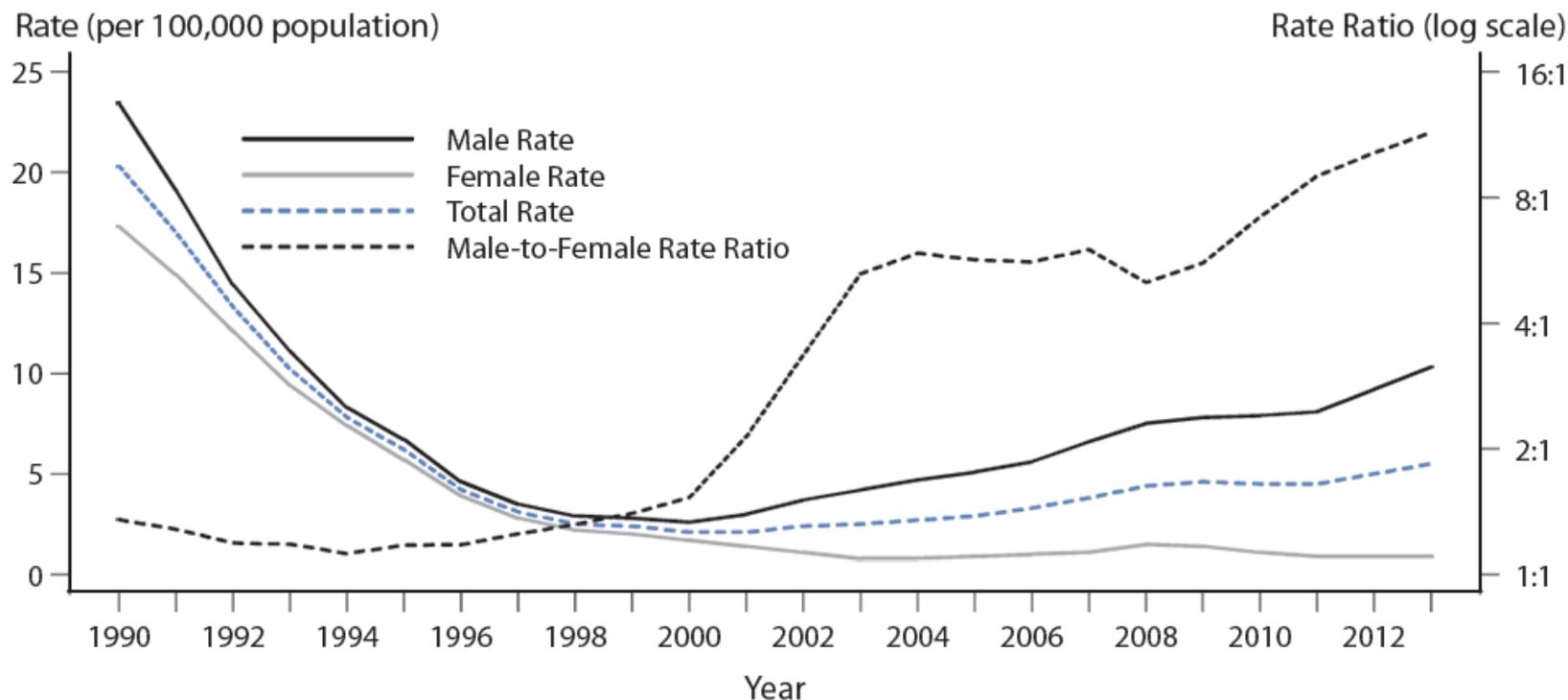
- ▶ **The Problem (s):**
 - ▶ Epidemiology of syphilis
 - ▶ Clinical presentations
 - ▶ Laboratory diagnosis

- ▶ **The Solution (s):**
 - ▶ Treatment
 - ▶ Partner services
 - ▶ Prevention

- ▶ **QA Session**

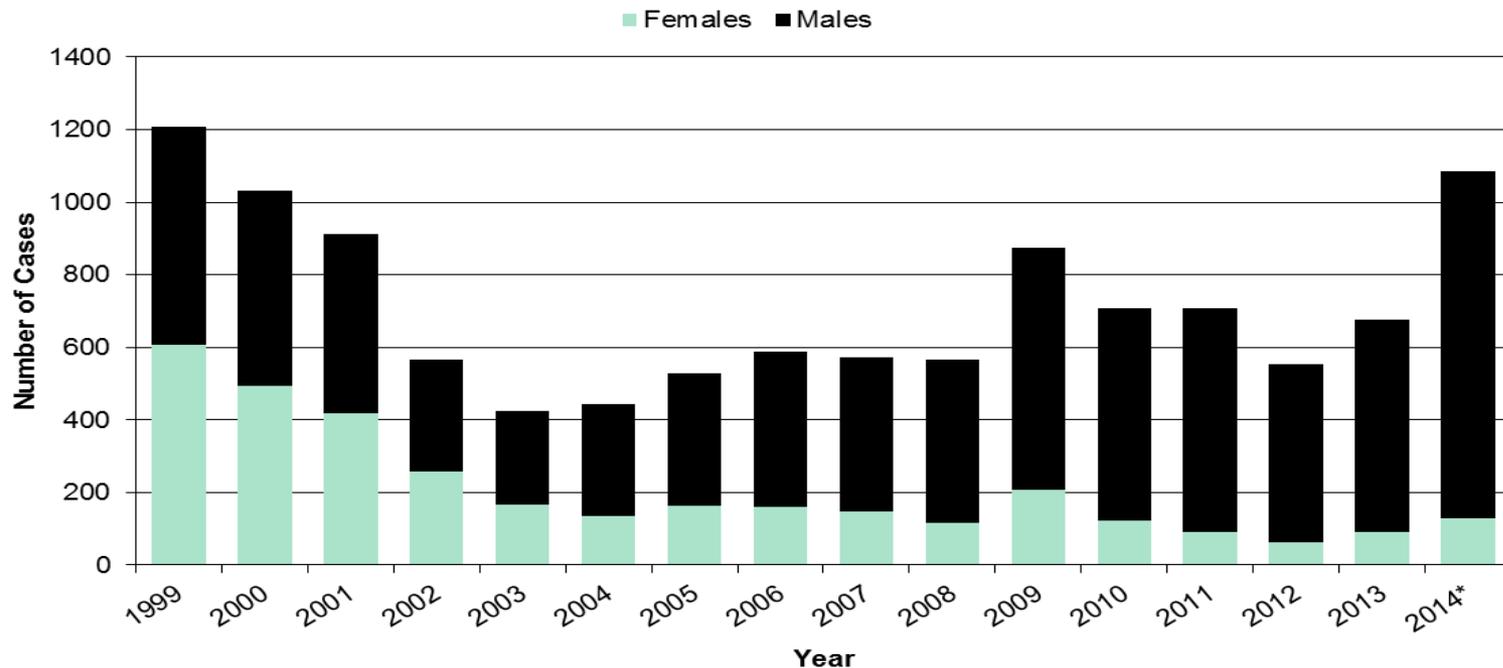
The Public Health PROBLEM

Primary and Secondary Syphilis — Rates of Reported Cases by Sex and Male-to-Female Rate Ratios, United States, 1990–2013



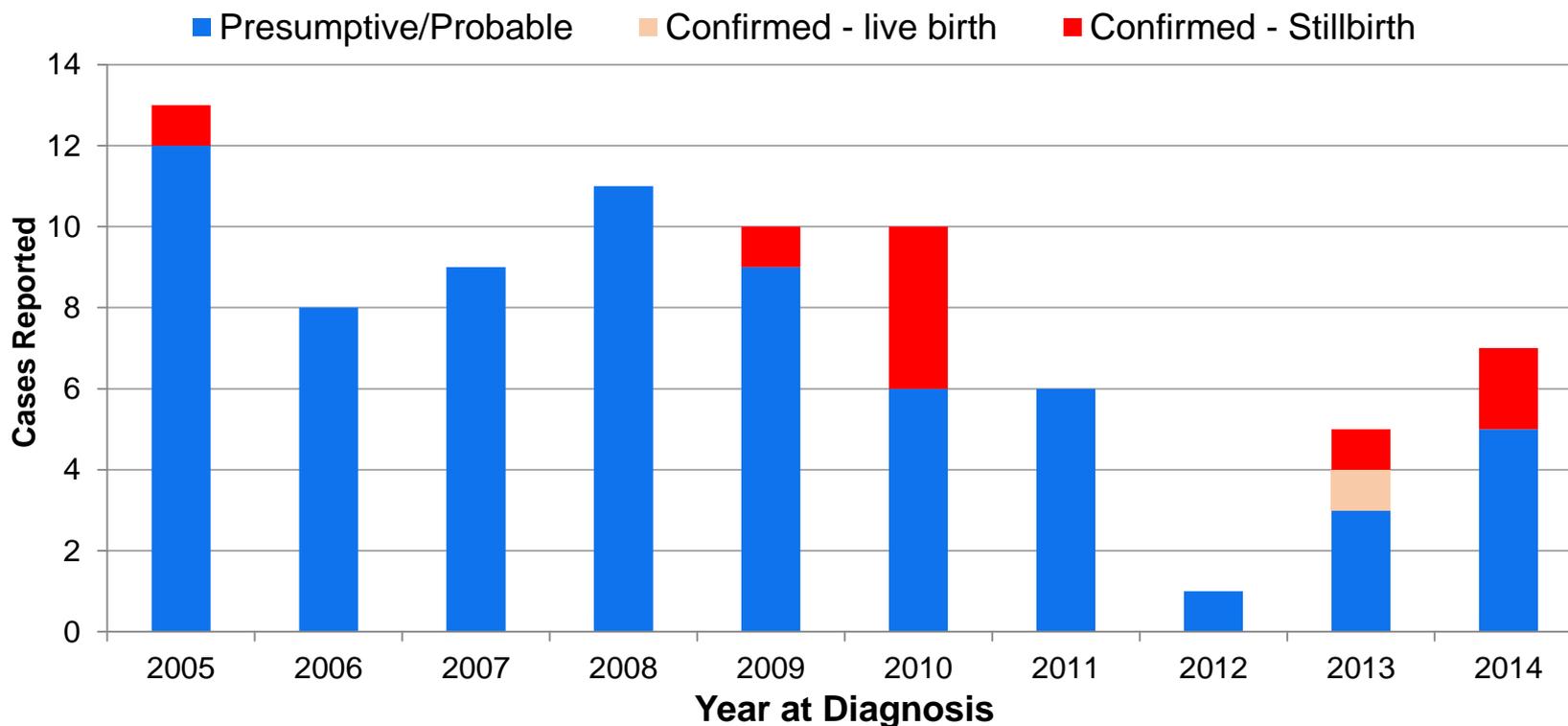
Syphilis in North Carolina

North Carolina Primary, Secondary, and Early Latent Syphilis Infections by Gender, 1999-2014



*2014 data are preliminary

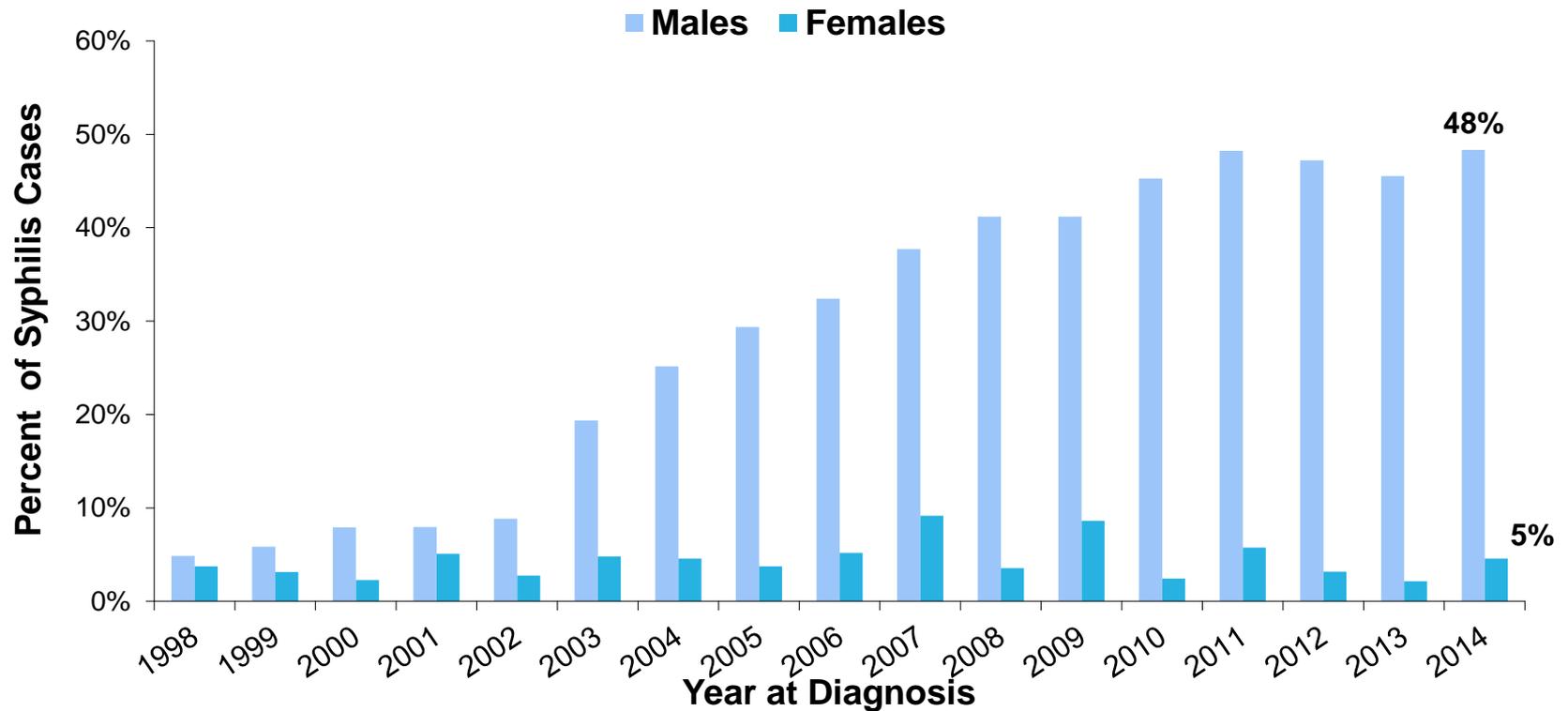
Congenital Syphilis, Cases by Birth Year, North Carolina, 2005-2014



Data Source: Sexually Transmitted Disease Management Information System (STD*MIS) and North Carolina Electronic Disease Surveillance System (NC EDSS) (data as of July 17, 2015).

HIV/STD Surveillance Unit

Primary, Secondary, and Early Latent Syphilis, Percentage of Cases with HIV by Gender, 1998-2014



*HIV diagnosed prior to OR within 30 days of syphilis diagnosis.

Data Source: North Carolina Electronic Disease Surveillance System (NC EDSS) (data as of May 7, 2015) and enhanced HIV/AIDS Reporting System (eHARS) (data as of June 25, 2015).

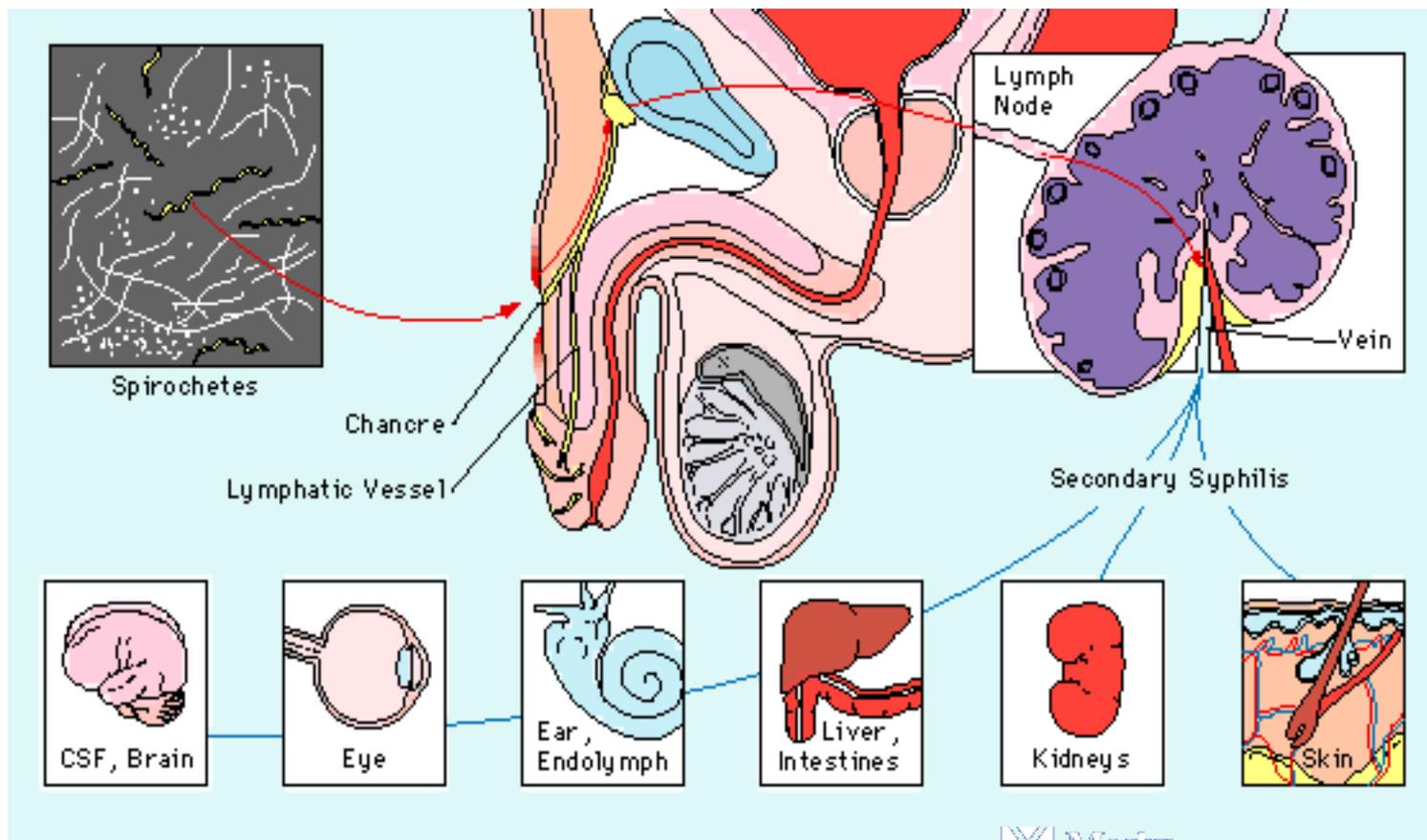
HIV/STD Surveillance Unit

The Microbiologic PROBLEM

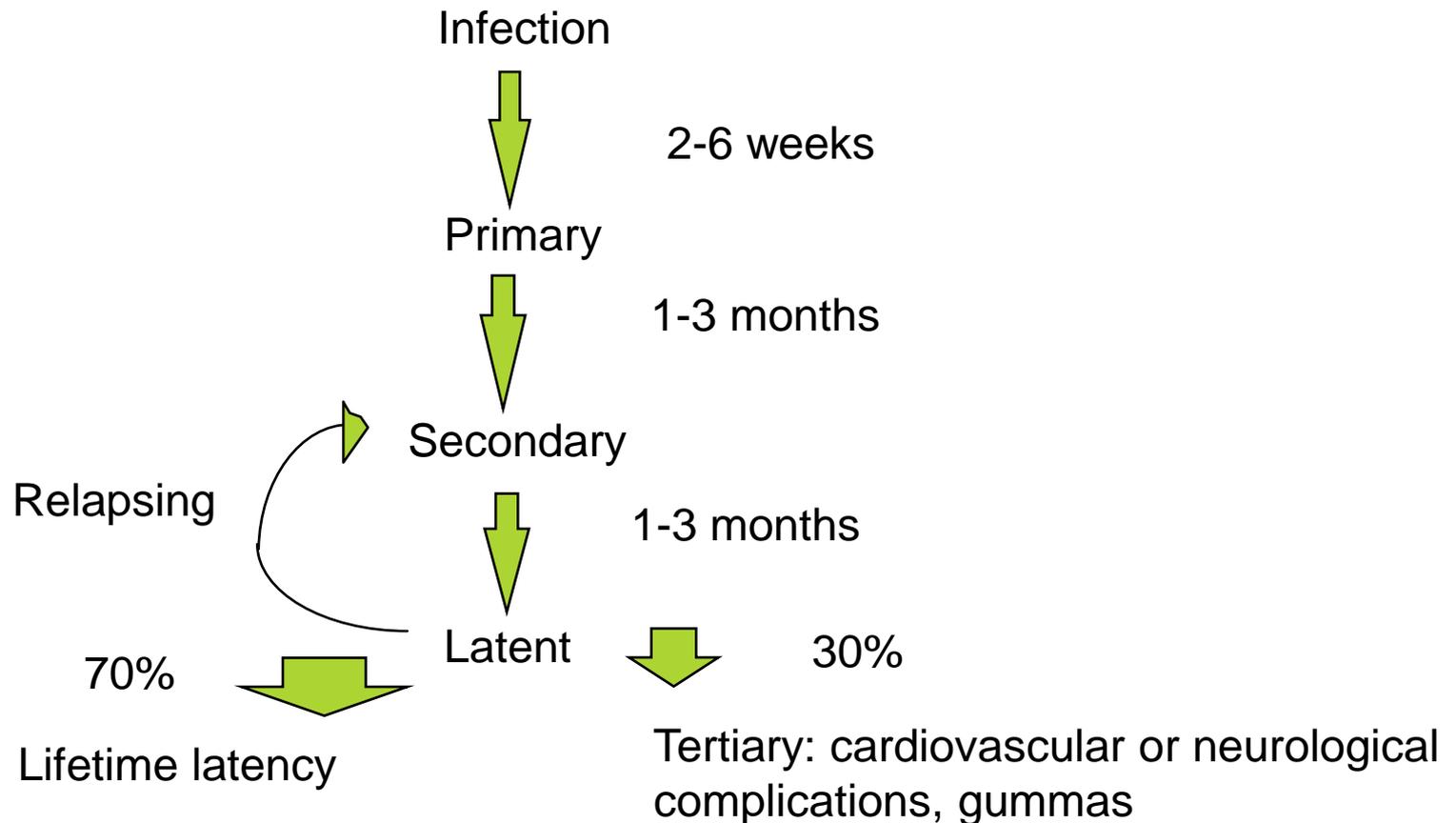
- ▶ *Treponema pallidum* is causative agent of syphilis; humans are the natural host.
- ▶ Cannot be cultured *in vitro*; therefore, diagnosis based on serological assays.
- ▶ Estimate of the risk of sexual transmission is 30% among sexual contacts to syphilis (Schroeter *et. al.* JAMA 218, 1971)



Invasiveness of *T. pallidum*



Natural history of syphilis



Question 1: How do you stage syphilis?

- ▶ Primary (#710): chancres with a reactive serologic test (*probable*) and/or direct detection of *T. pallidum* (*confirmed*)
- ▶ Secondary (#720): mucocutaneous lesions with a reactive serologic test (*probable*) and/or direct detection of *T. pallidum* (*confirmed*)
- ▶ Latent: asymptomatic with reactive serologic tests (*probable*)
 - ▶ Early latent (#730) : disease \leq 1 year duration
 - ▶ Late latent (#745) : disease of more than 1 year duration

Syphilis: Primary Stage



- ▶ 10-60 day incubation (mean 21 days)
- ▶ Lesion at site of entry of *T. pallidum*.
- ▶ Anogenital skin and mucous membranes.
- ▶ Red macule --> papule --> indurated ulcer
- ▶ Painless chancre
 - ▶ resolves in 1-6 weeks

Secondary Syphilis

- ▶ Hematogenous spread of spirochetes
- ▶ Usually 3-6 weeks after disappearance of chancre
- ▶ Rash seen in 75-100% - typically maculopapular, involves the palms and soles, may have superficial scaling



Secondary Syphilis Rash



Source: Cincinnati STD/HIV Prevention Training Center



Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Secondary Syphilis

- ▶ Systemic symptoms: malaise, myalgias, fever, headache, lymphadenopathy, sore throat, hair loss, hepatitis
- ▶ Condyloma lata and mucous patches



Tertiary Syphilis (Late Syphilis with Symptoms)

- ▶ Without therapy 1/3 of patients will develop some manifestation of tertiary syphilis
- ▶ Occurs 10-30 years after infection
- ▶ Neurosyphilis: 8-10%
- ▶ Cardiovascular: 10%
- ▶ Gummatous: 15%



The Clinical PROBLEM

▶ **Symptomatic early neurosyphilis**

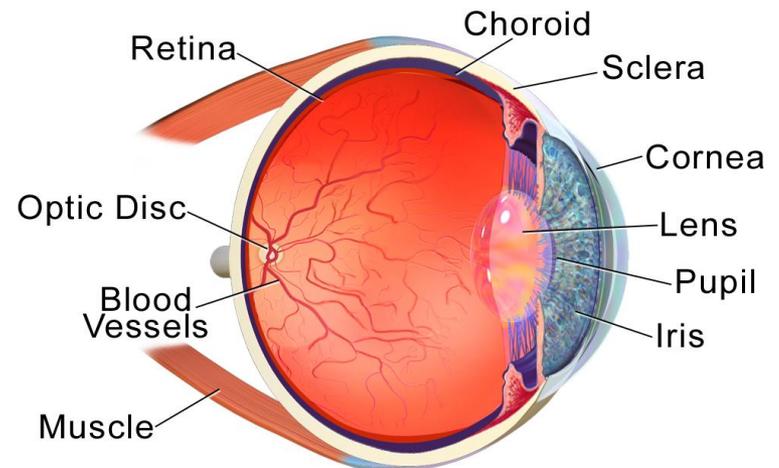
- ▶ Presenting with 12 months of exposure with headache, nausea, photophobia, cranial nerve palsies, seizures and abnormal CSF findings
- ▶ Initially reported among HIV-positive MSM in 2007 from Los Angeles, San Diego, Chicago, New York City

▶ **Ocular syphilis**

- ▶ Clinical symptoms or signs consistent with ocular disease with syphilis of any stage.
- ▶ Reported among MSM and HIV-positive persons in Seattle and Los Angeles in 2014-2015
- ▶ In NC, increasing number of possible ocular syphilis since 2013.

Presentations of Ocular Syphilis

- ▶ Uveitis (uvea= iris, choroid body, choroid)
 - ▶ Eye redness and irritation, blurred vision, eye pain, increased sensitivity to light, floating spots
- ▶ Chorioretinitis
 - ▶ Blurred vision, sensitivity to light
- ▶ Optic neuritis
 - ▶ Eye pain, vision loss, flashing lights
- ▶ Interstitial keratitis
 - ▶ Eye pain, excessive tearing, sensitivity to light

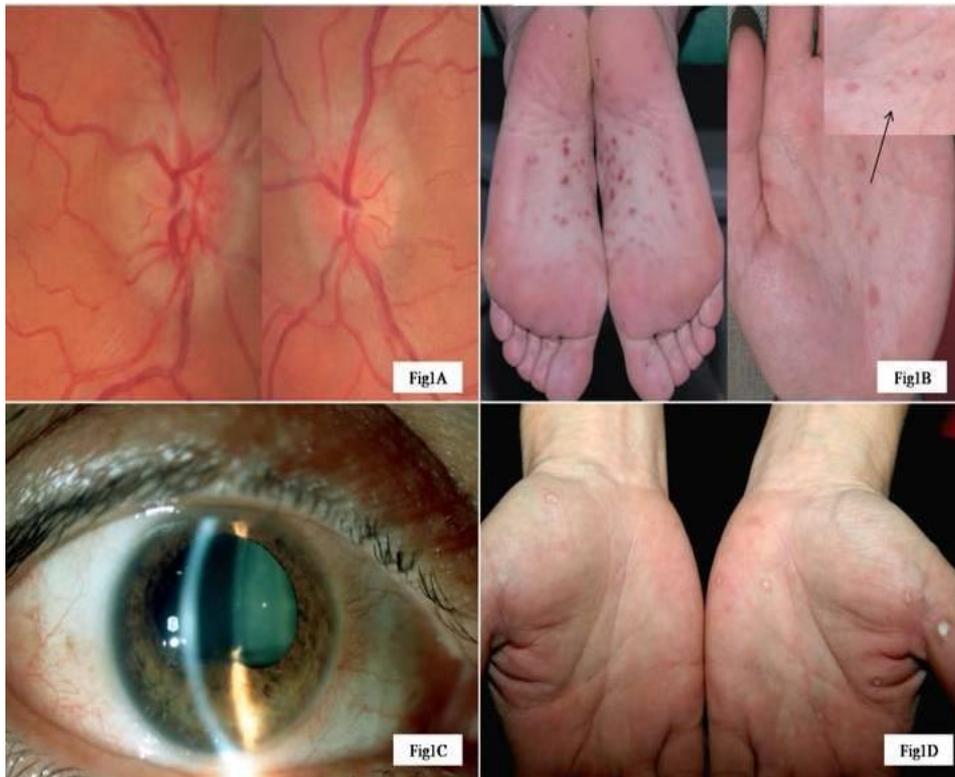


Anatomy of the Eye

Question: What should you do for patients with ocular syphilis?

- ▶ **Refer** patients with syphilis and ocular symptoms for immediate ophthalmologic evaluation.
- ▶ **Refer** for a lumbar puncture with cerebrospinal fluid (CSF) examination.
- ▶ **Report** suspected cases of ocular syphilis to the state within 24 hours of diagnosis.
- ▶ If possible, pre-antibiotic clinical samples (whole blood, primary lesions and moist secondary lesions, CSF or ocular fluid) should be saved and stored at -80°C for molecular typing.
- ▶ Management for ocular syphilis should include similar treatment as for neurosyphilis.

Ocular Syphilis in HIV Patients



- ▶ Association of palmo-plantar eruption and ocular findings in HIV-infected patients.
 - ▶ Fig 1 A: Bilateral papilledema,
 - ▶ Fig 1 B: Papulosquamous palmoplantar rash
 - ▶ Fig 1 C: Anterior granulomatous uveitis
 - ▶ Fig 1 D: Pustulous palmoplantar eruption

The Laboratory Problem: Syphilis Antibody Detection

- ▶ Infection with *T. pallidum* results in a complex immune response, which doesn't always correlate with disease activity.
- ▶ Two general types of antibodies are produced in infected persons:
 - ▶ Non-specific antibodies that react primarily with lipids from *T. pallidum* and damaged host cells during inflammatory process
 - ▶ Detected by RPR, VDRL, TRUST
 - ▶ Treponemal specific antibodies
 - ▶ Detected by EIAs, TPPA, FTA-ABS

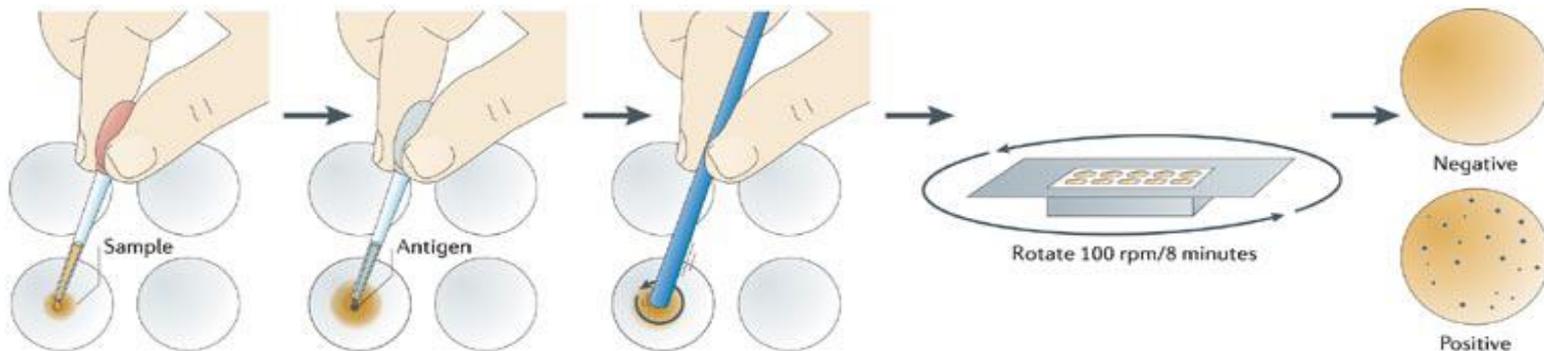
Direct Detection of *T. pallidum*

- ▶ Direct detection:
 - ▶ Darkfield microscopy
 - ▶ Direct fluorescent antibody –*T. pallidum*
 - ▶ Silver staining
 - ▶ PCR
- ▶ Limitations
 - ▶ Requires lesion swabs or biopsies
 - ▶ Not widely available
 - ▶ PCR sensitivity limited in blood and CSF specimens



Non-treponemal Antibody Tests

- ▶ Non-treponemal tests detect nonspecific antibodies to reagin (cardiolipin and lecithin) and require confirmation with a treponemal test.
- ▶ Limitations:
 - ▶ Low sensitivity in early primary and late syphilis stages
 - ▶ Biologic false positives (e.g. viral infections, autoimmune conditions)
 - ▶ Lab variation in quantitative titers (+/- one dilution)
 - ▶ Prozone reaction



Sensitivity of serological tests

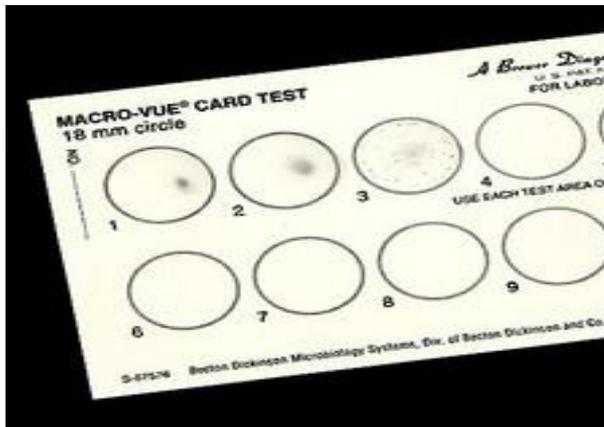
Stage of Disease (Percent Positive [Range])

Test	Primary	Secondary	Latent	Tertiary
VDRL	78 (74–87)	100	95 (88–100)	71 (37–94)
RPR	86 (77–99)	100	98 (95–100)	73
FTA-ABS*	84 (70–100)	100	100	96
Treponemal Agglutination*	76 (69–90)	100	97 (97–100)	94
EIA	93	100	100	

*FTA-ABS and TP-PA are generally considered equally sensitive in the primary stage of disease.

Question: What is the prozone reaction?

- ▶ Prozone: false negative response resulting from high antibody titer which interferes with formation of antigen-antibody



The Precipitin Curve

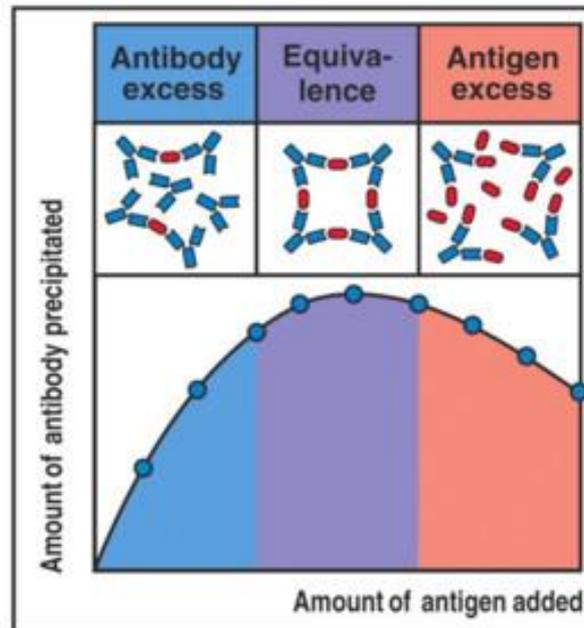


Figure A-9 Immunobiology, 6/e. (© Garland Science 2005)

Fig A.9 Janeway & Travers Immunobiology

In the precipitin reaction various amounts of soluble antigen are added to a fixed amount of antibody in a fine tube.

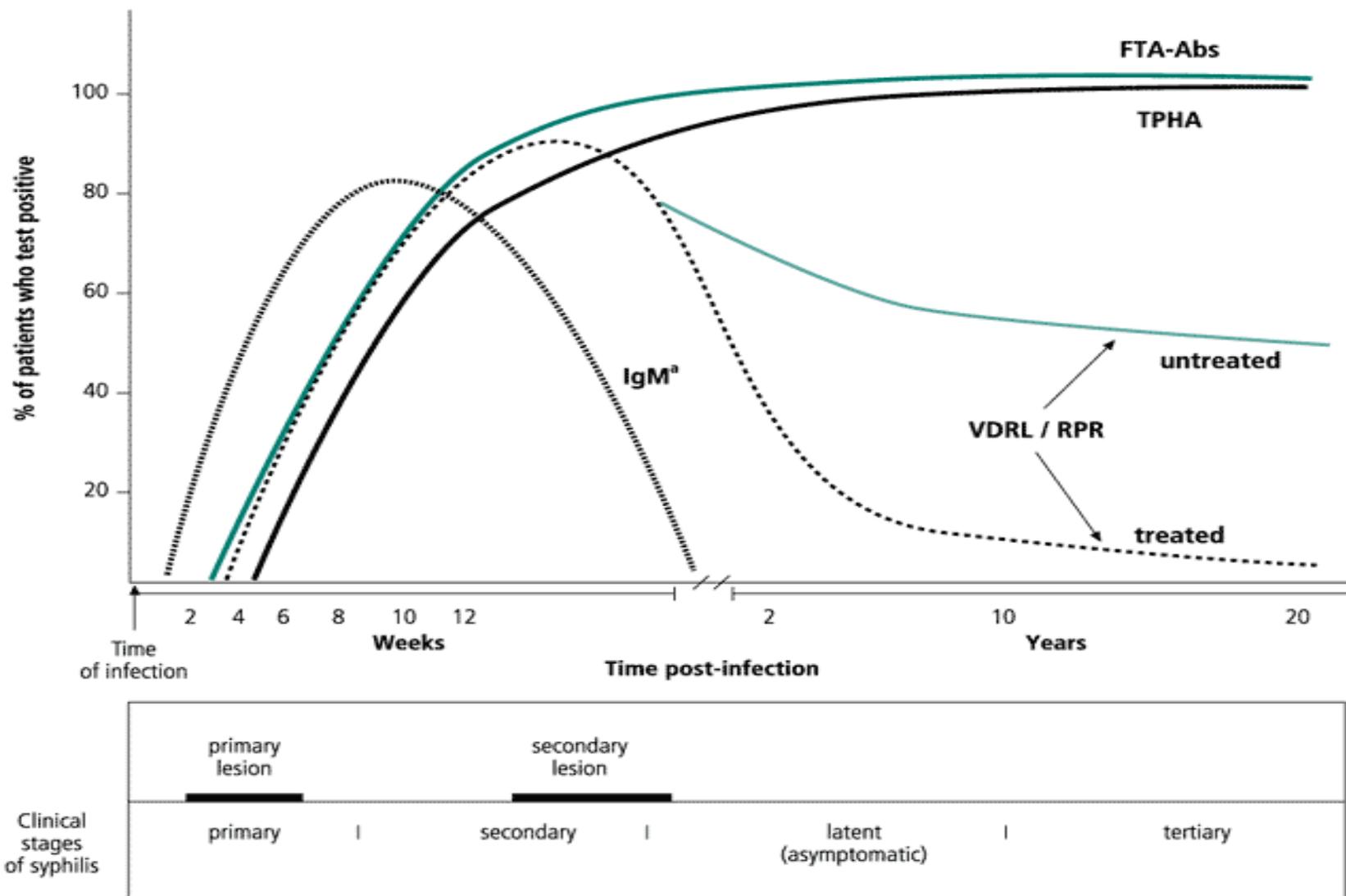
As antigen \uparrow the amount of precipitate produced also \uparrow .

This increases until a maximum amount is reached and then the amount of precipitate \downarrow , despite further \uparrow antigen added.

This gives rise to the curve opposite with 3 clear zones produced:

Prozone, the zone of equivalence and the postzone.

Fig. 1. Common patterns of serological reactivity in syphilis patients



^a IgM by ELISA or FTA-ABS 195 or immunoblot

Response to Syphilis Treatment

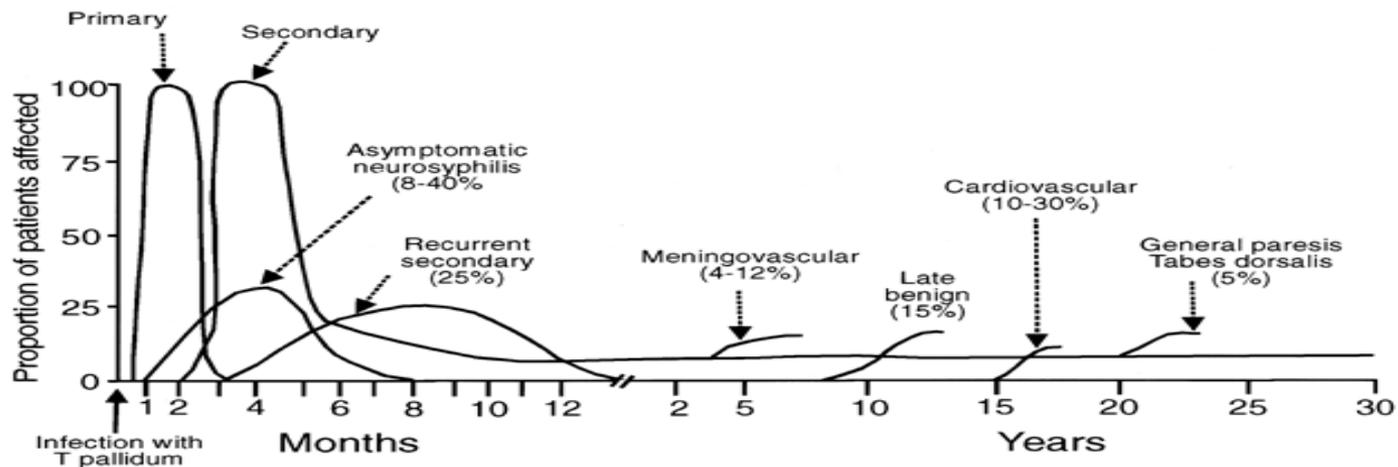
- Serological cure or response (~ 80%) - a negative RPR (seroreversion) or ≥ 4 -fold (2 dilution) decrease in RPR titers at 6-24 months after treatment (ex: 1:64 to 1:16)
- Serological non-response or serofast (~ 15%): < 4 -fold decrease in titers or persistent low-level titers after treatment
- Treatment failure or reinfection (~5%): Sustained 4-fold increase in RPR titers compared with the baseline titer at time of treatment

A Clinical SOLUTION: Treatment for Syphilis

- ▶ Primary, secondary, early latent syphilis
 - ▶ Benzathine penicillin G 2.4 mu IM x 1 dose
 - ▶ For PCN –allergic:
 - Doxycycline 100mg PO BID or tetracycline 500 mg PO QID x 14 days
 - Ceftriaxone 1-2 g daily either IM or IV for 10–14 days
- ▶ Late latent syphilis
 - ▶ Benzathine penicillin G 2.4 mu IM q weeks x 3 weeks
 - ▶ For PCN-allergic: Doxycycline 100mg PO BID or tetracycline 500mg PO QID x 28 days
- ▶ Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin.

Question: Why does DIS recommend three doses of PCN in patients with positive serologies but no symptoms?

- ▶ Latent syphilis: Longer durations of benzathine PCN may be required to treat *T. pallidum* that has disseminated and may result in tertiary syphilis.
- ▶ Although latent syphilis cannot be transmitted sexually, goals are to prevent complications including neurosyphilis and congenital syphilis.



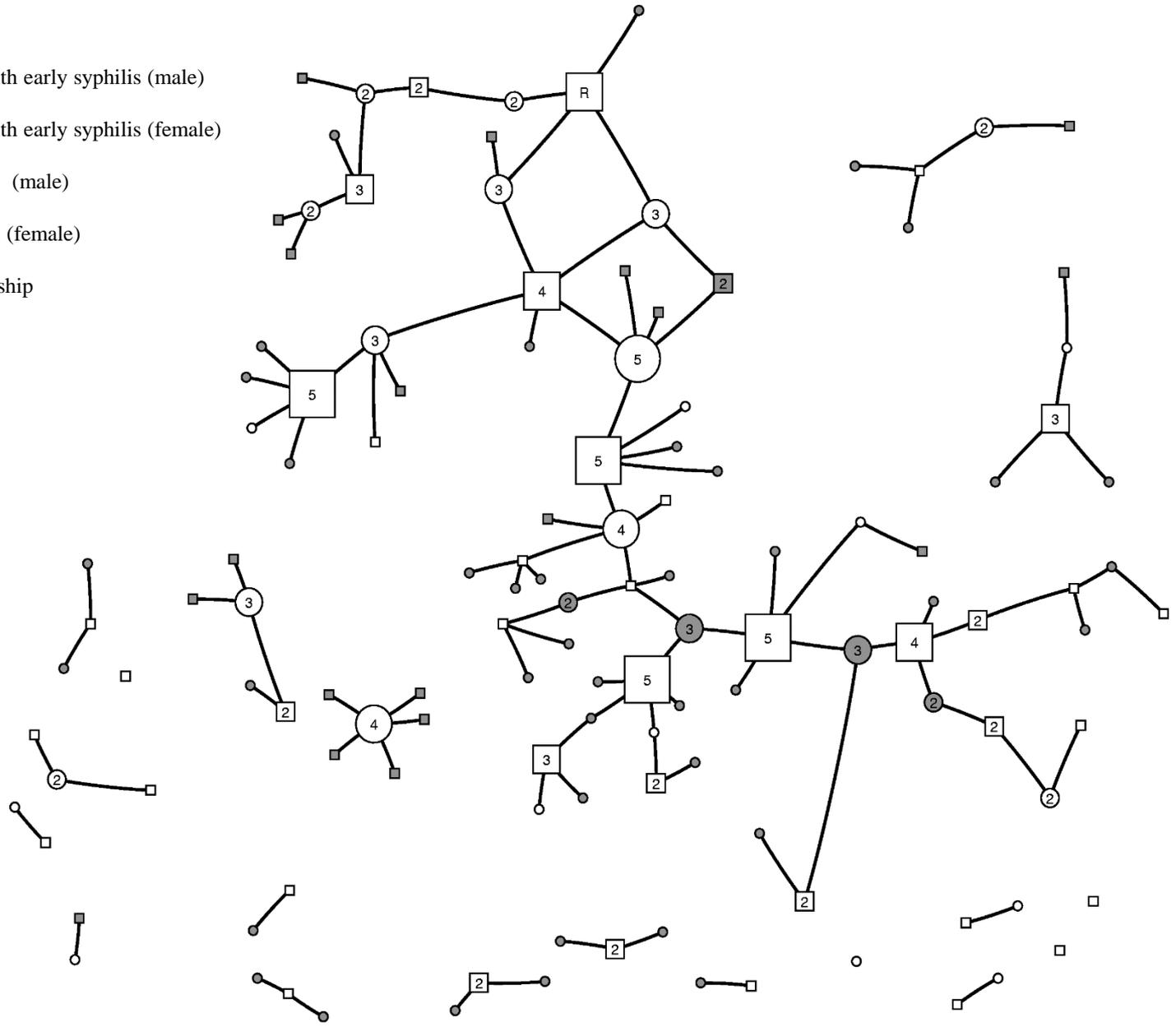
A Public Health SOLUTION: Management of Sex Partners

- ▶ For sexual partners of patients with syphilis in any stage
 - ▶ Obtain syphilis serology and perform physical exam
- ▶ For sex partners of patients with primary, secondary, or early latent syphilis exposed ≤ 90 days prior
 - ▶ Treat presumptively as for early syphilis, even if serologic tests are negative.
- ▶ For partners of patients with late latent syphilis
 - ▶ Treat based on serologic tests

Question: Why is it important to test and possibly treat associates and suspects?

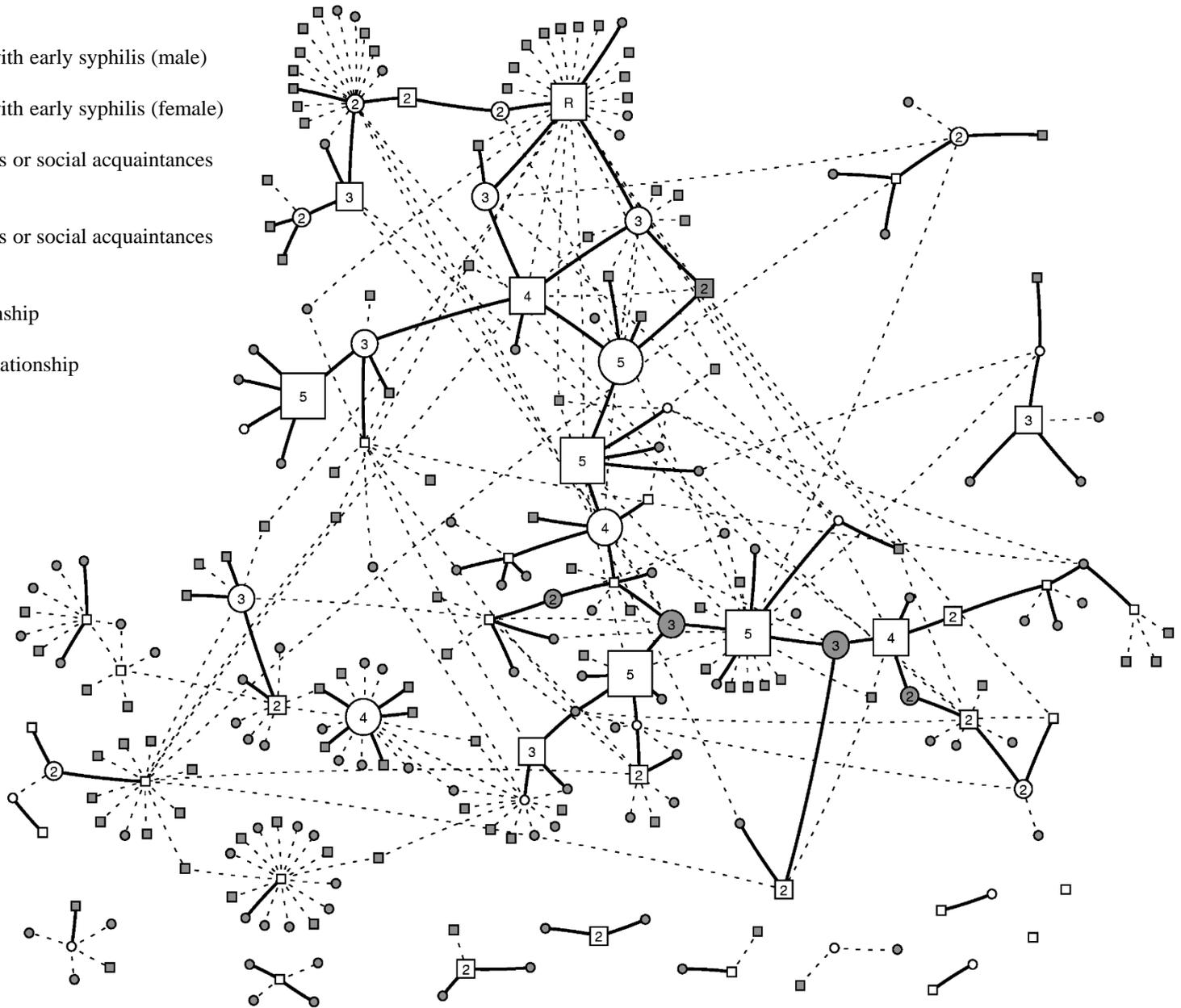
- ▶ Disease Intervention Specialists (DIS)
 - ▶ Interview cases and conduct partner notification
 - ▶ Suspects and associates refer to social contacts
 - ▶ Perform “clustering” during outbreaks to identify other persons in social groups with risky behaviors
- ▶ Network analysis
 - ▶ Hypothesis that transmission of syphilis occurs in a broader social context.
 - ▶ Illustrates interactions between infected and uninfected in socio-sexual networks

-  case-patient with early syphilis (male)
-  case-patient with early syphilis (female)
-  sexual partners (male)
-  sexual partners (female)
-  sexual relationship





-  case-patient with early syphilis (male)
-  case-patient with early syphilis (female)
-  sexual partners or social acquaintances (male)
-  sexual partners or social acquaintances (female)
-  sexual relationship
-  non-sexual relationship



Summary: Key Clinical Points

- ▶ Recognize and know how to manage syphilis infections.
- ▶ Screen frequently for syphilis, especially among men who have sex with men, HIV infected persons and pregnant women.
- ▶ Ask about neurologic and ocular symptoms in all patients with syphilis.
- ▶ If a patient presents with a genital ulcer/rash suspicious for syphilis and RPR is negative, treat presumptively.
 - ▶ Ask the lab to do additional dilutions on the RPR/ VDRL
 - ▶ Consider sending a treponemal test
 - ▶ Advise the patient to return for follow-up and have sexual partners evaluated.

Syphilis Prevention

“It takes a
village...”

IF YOU ARE A HEALTH CARE PROVIDER, A COMMUNITY LEADER
OR A POLICY MAKER, VISIT WWW.CDC.GOV/STD/SEE/ TO FIND
OUT HOW TO GET INVOLVED.



The Syphilis Elimination Effort (SEE) is a national initiative to eliminate syphilis and wipe out one of our nation's biggest racial disparities in health. Right now, syphilis is concentrated in a small number of counties in the United States. Ours is one of them.



Public Health Strategies

- ▶ Educate your patients about syphilis prevention and risk for HIV infections.
- ▶ Plan outreach and increased screening among high risk groups in your community.
- ▶ Work with community based organizations and local health care providers to increase awareness about syphilis in the area.
- ▶ Work with regional or local DIS to ensure partner evaluation and treatment.

Case Presentation 1

- ▶ 26 yo African-American man, previously healthy presents with one week of mild scalp pain, hypersensitivity to sounds and left sided facial droop. He went to the ER and was diagnosed with Bell's palsy, presumptive shingles and treated with acyclovir and prednisone. However, he developed oral thrush and a centripetal maculopapular rash involving his palms and soles, along with fever, malaise, and headache.
- ▶ He denied sexual contact of any kind and reported being a virgin. He had no other significant exposures including travel. What should be your initial thoughts about the cause of his symptoms?
 - 1) Rocky Mountain spotted fever
 - 2) Secondary syphilis
 - 3) Secondary syphilis and early neurosyphilis
 - 4) Secondary syphilis, HIV co-infection, and early neurosyphilis

Case Presentation 1

- ▶ Patient had HIV and syphilis testing, and was given doxycycline for 10 days by the ER.
- ▶ RPR returned at a titer of 1:512, and HIV antigen/antibody test was positive. He was referred for a lumbar puncture and was found to have abnormal CSF findings with a WBC count of 33.
- ▶ He was hospitalized for penicillin G 18-24 mu IV for 14 days.
- ▶ The patient was adamant that he had no prior sexual contact.
- ▶ Key points:
 - ▶ Syphilis can mimic symptoms of other diseases as the “great imitator.”
 - ▶ HIV and syphilis can present together at initial presentation.
 - ▶ Early neurosyphilis can occur in patients with HIV.

Case Presentation 2

- ▶ 33 year old White male, presents with photophobia and blurred vision two weeks prior to admission. He was seen in the ER and had a CT head suggestive of sinusitis. He was discharged with Bactrim and told to follow-up with an ophthalmologist. The patient now reports worsening photophobia, a new periorbital and frontal headache and ocular pain. He also noted worsening eczema.
- ▶ The patient lives with his fiancée and has had extensive prior travel in the Navy overseas. He denies prior syphilis history. What does this patient need for further evaluation?
 - 1) Quantitative RPR with confirmatory treponemal testing
 - 2) Lumbar puncture
 - 3) Immediate ophthalmology exam
 - 4) Outpatient ophthalmology exam after completion of his antibiotics
 - 5) 1, 2, and 3 above

Case Presentation 2



- ▶ Skin: hyperkeratotic scaly plaques on torso, buttocks, palms, soles

- ▶ Eyes:

- ▶ pupils dilated, sluggish, conjunctival injection L >> R,
- ▶ Visual acuity: left – counts fingers at 4 feet, right – counts fingers at 2 feet
- ▶ Visual fields: Left:  Right: 

- ▶ Slit lamp exam:

- ▶ Panuveitis
- ▶ Bilateral acute retinal necrosis



Case Presentation 2

- ▶ Patient was found to have an RPR 1:512, TP-PA positive but HIV negative. He underwent lumbar puncture and had + CSF VDRL 1:2, and elevated CSF WBCs of 75.
- ▶ He was diagnosed with secondary and ocular syphilis.
- ▶ He was treated with penicillin G 18-24 mu IV for 14 days.
- ▶ Unfortunately, patient had little improvement in vision prior to discharge.
- ▶ Key points:
 - ▶ Ocular syphilis has no “classic” presentation.
 - ▶ Patients with suspected syphilis and ocular symptoms need immediate ophthalmology evaluation.
 - ▶ Ocular syphilis is treatable but can result in significant sequelae including blindness.

Questions?

