Emergency Medicine for Rural and Indigenous Communities Conference

September 15th - 17th, 2022

Syphilis Update

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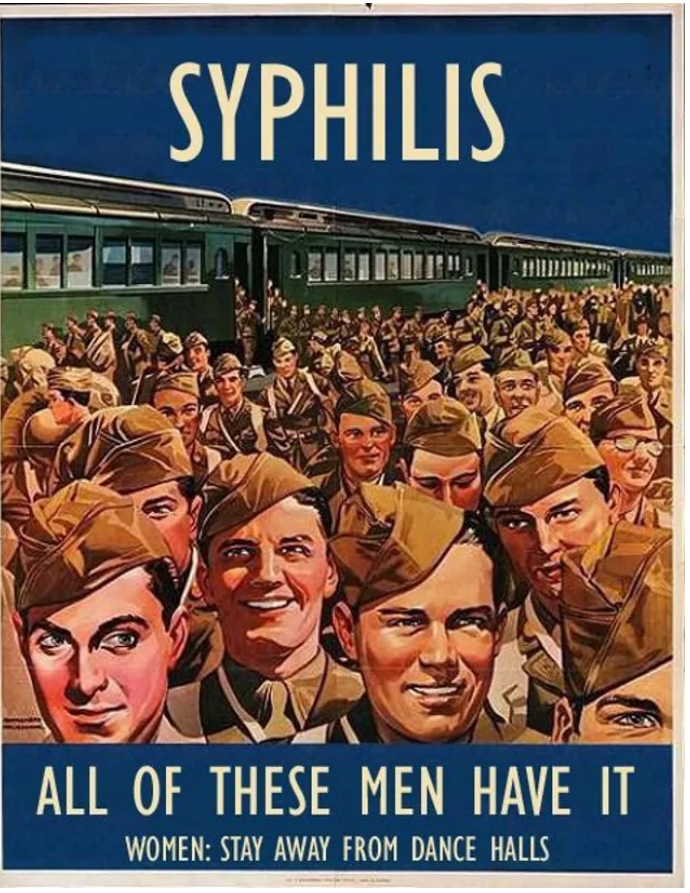
Whiteriver IHS

September, 16, 2022

Presentation prepared by:
Date prepared:



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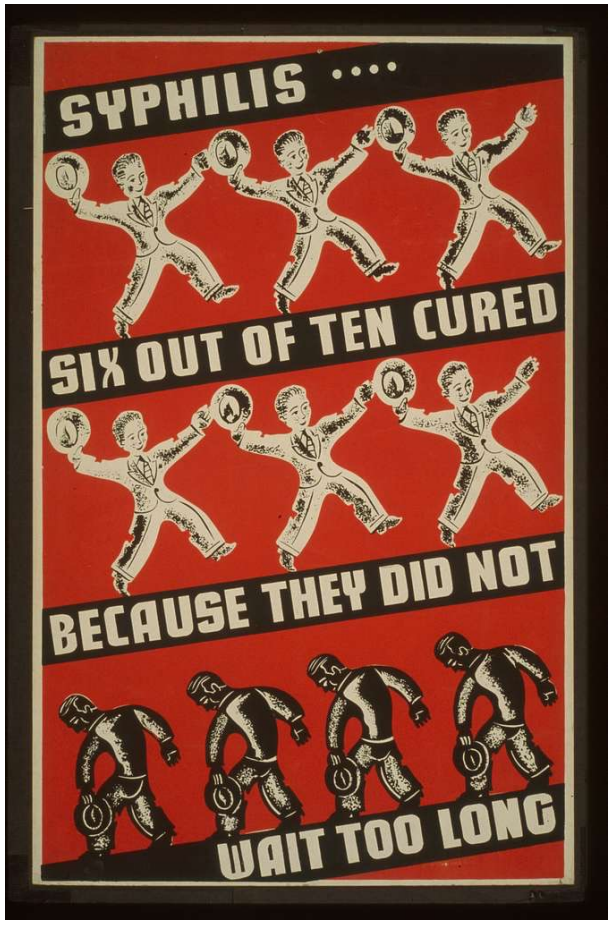
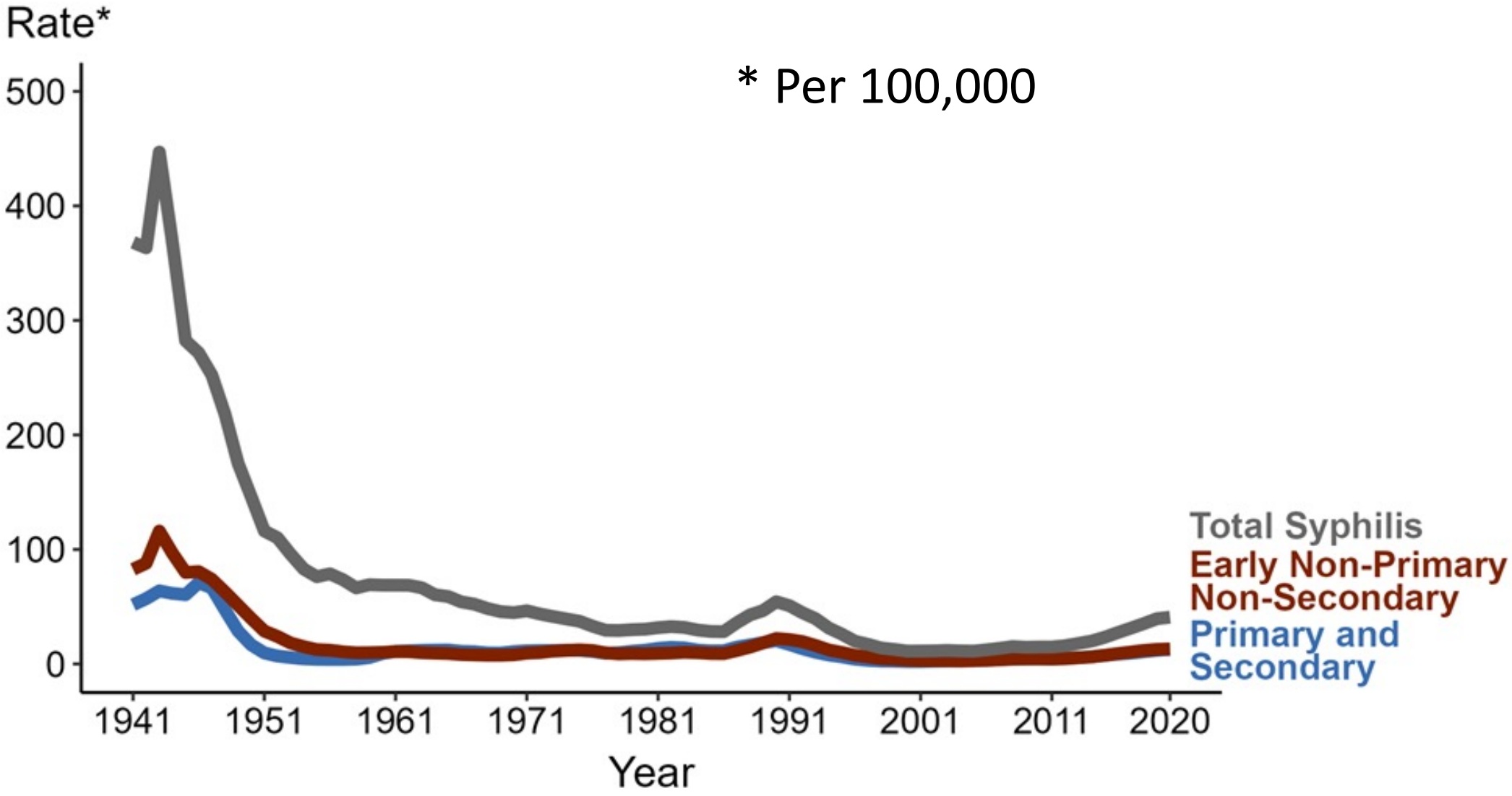


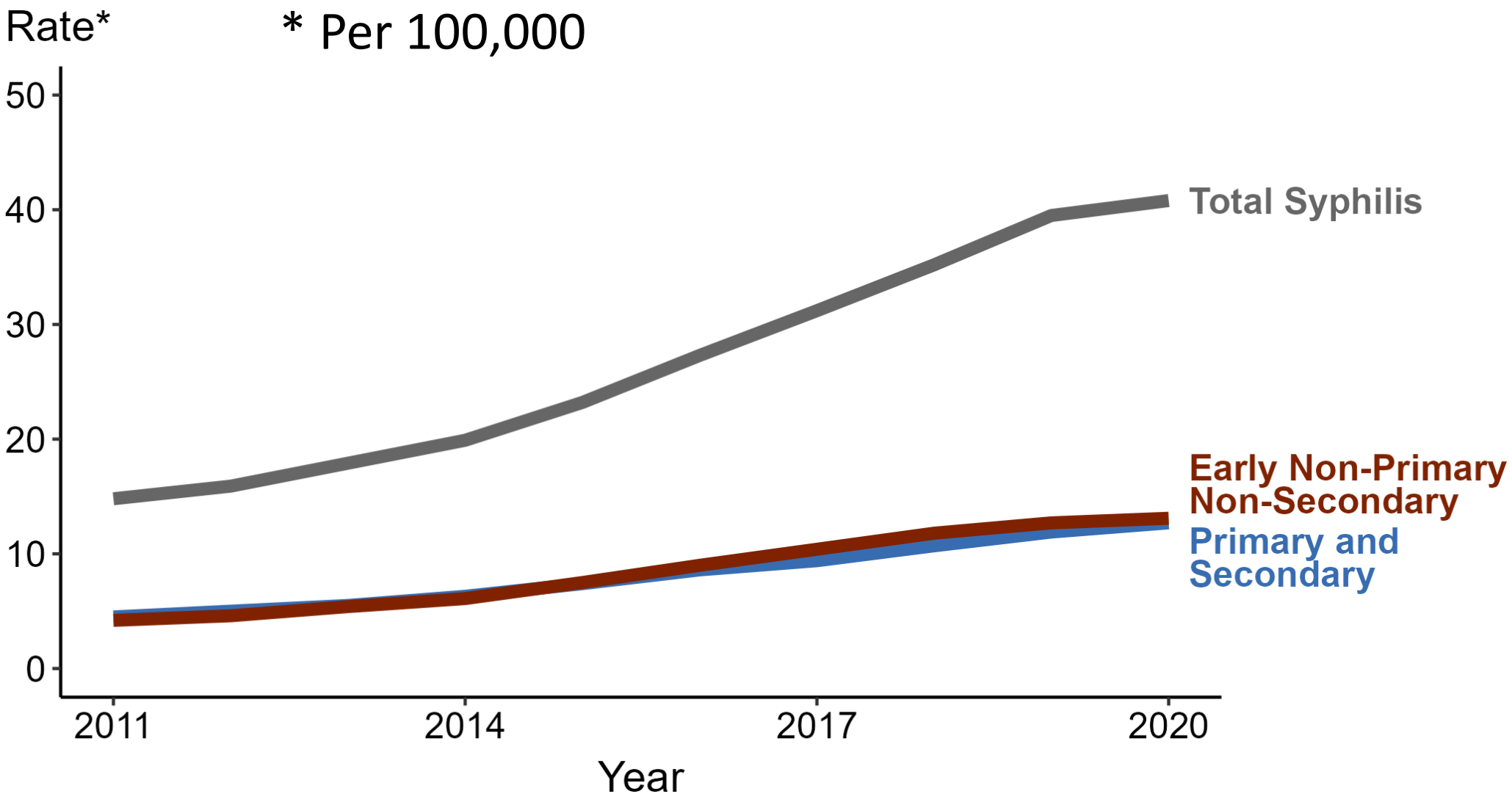
Overview

- Syphilis is back - raise your suspicion and test broadly
  - Any history or visualized genital lesions, unexplained rashes, neuro symptoms
  - Skin, GU and neuro exam
  - Risk factors for exposure
- The changing epidemiology of syphilis
- Staging and interpretation of labs is critical for appropriate treatment and follow up
- Congenital syphilis is devastating and preventable
  - Any woman tested for syphilis should have a pregnancy test
  - Any woman tested for pregnancy should have a syphilis test
- Recognize when to retest and identify treatment successes and failures

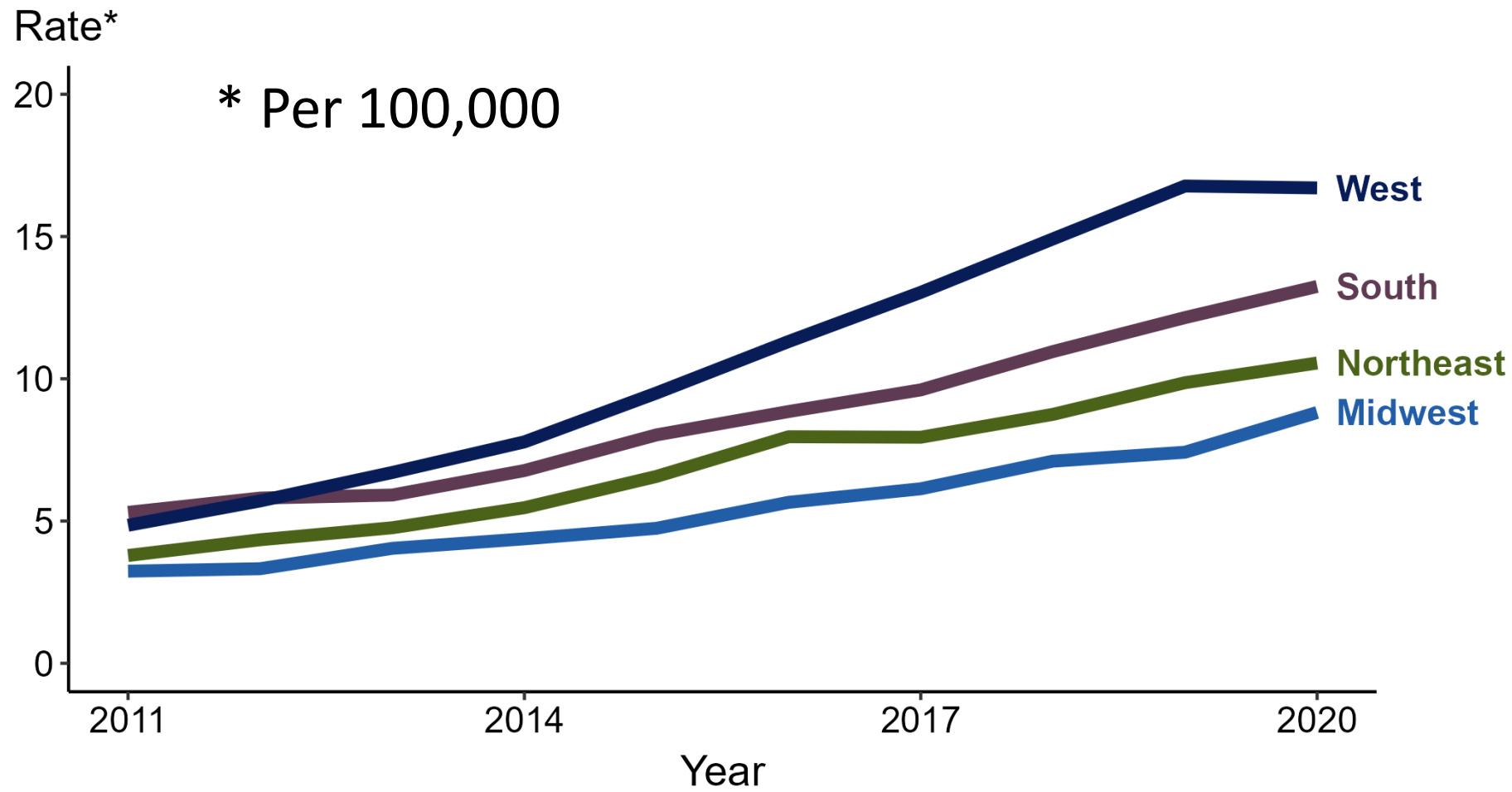
Syphilis — Rates of Reported Cases by Stage of Infection, United States, 1941–2020



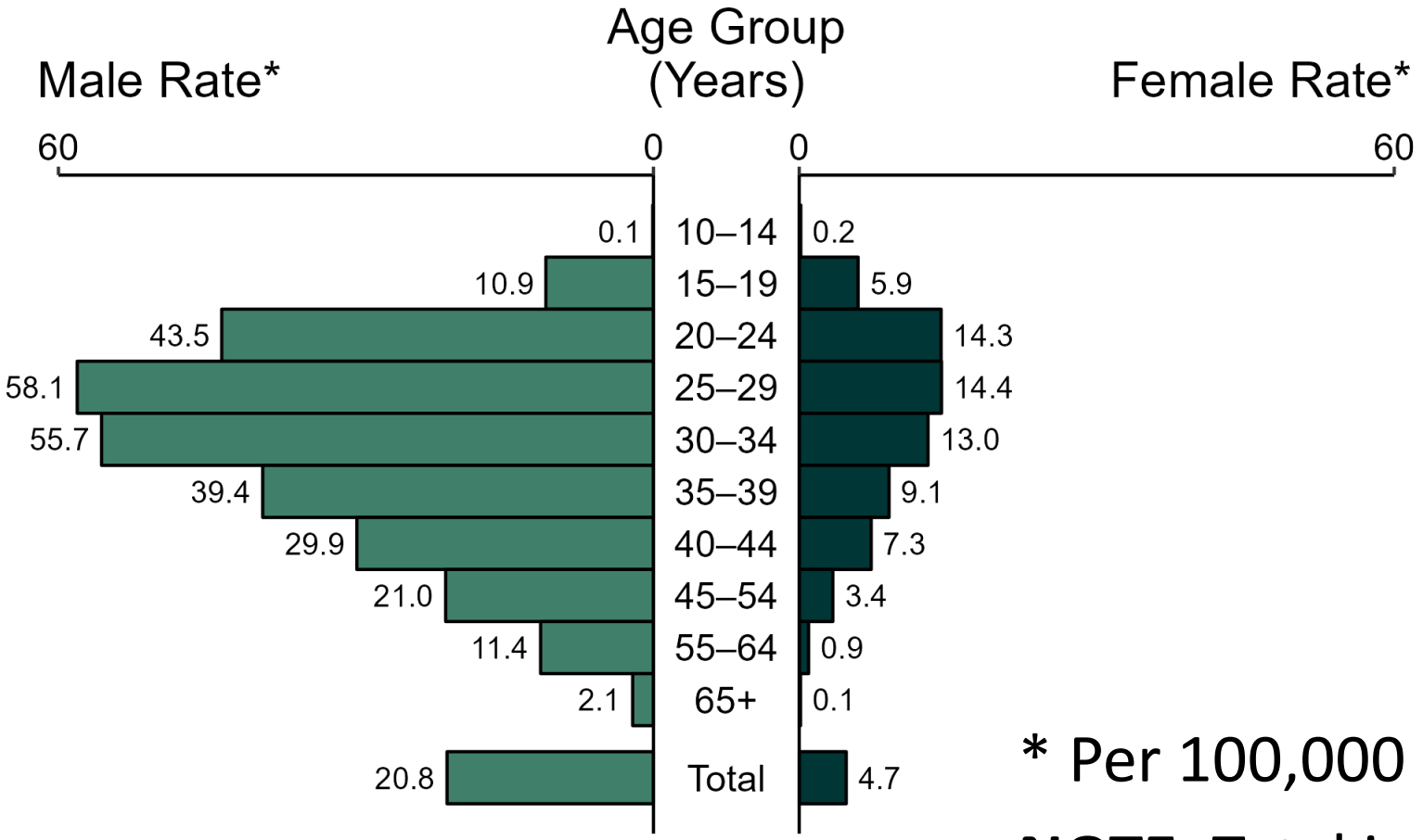
Syphilis — Rates of Reported Cases by Stage of Infection, United States, 2010–2020



Primary and Secondary Syphilis – rates of Reported Cases by Region, United States, 2011-2020



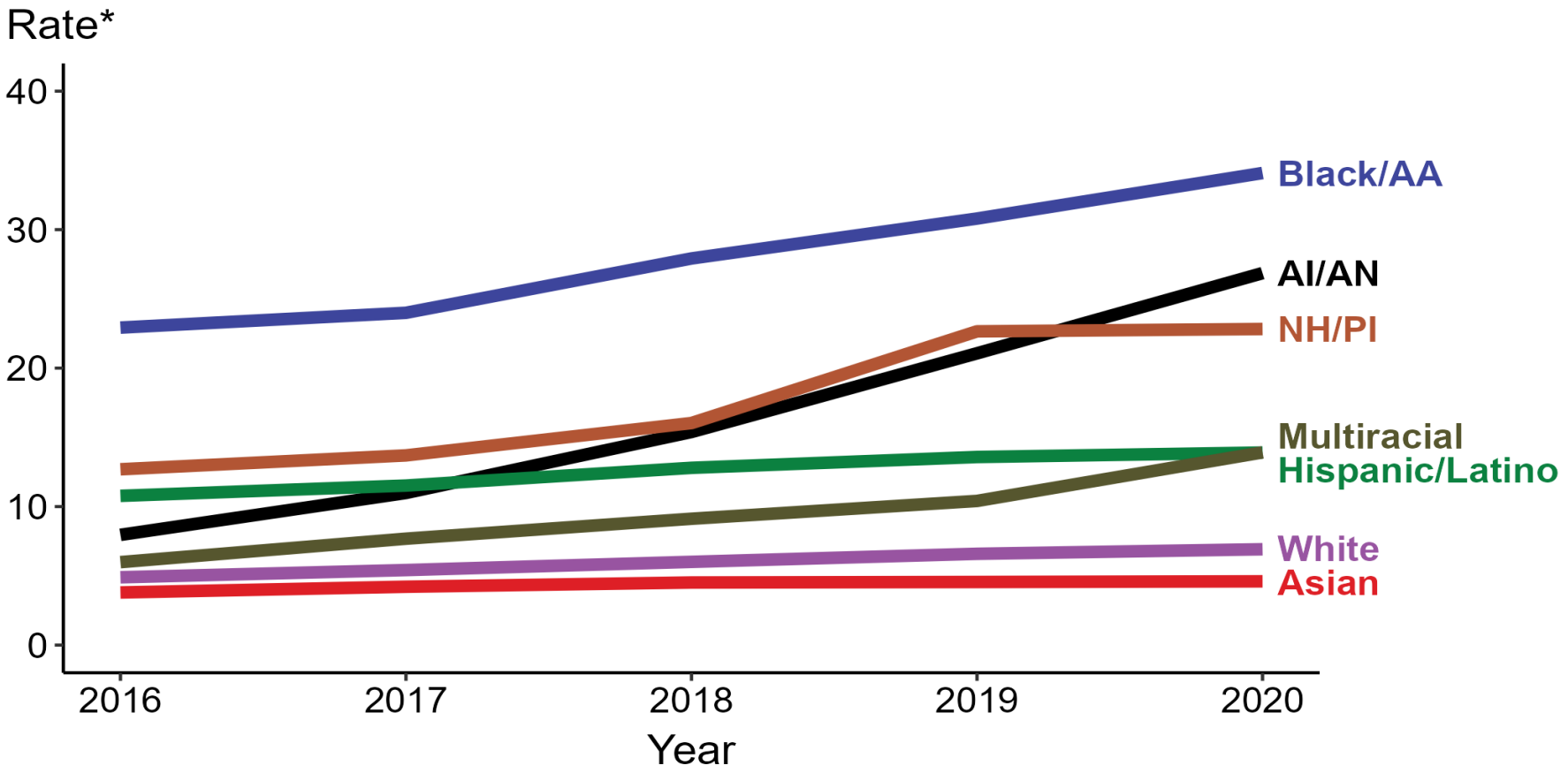
Primary and Secondary Syphilis — Rates of Reported Cases by Age Group and Sex, United States, 2020



* Per 100,000

NOTE: Total includes all ages.

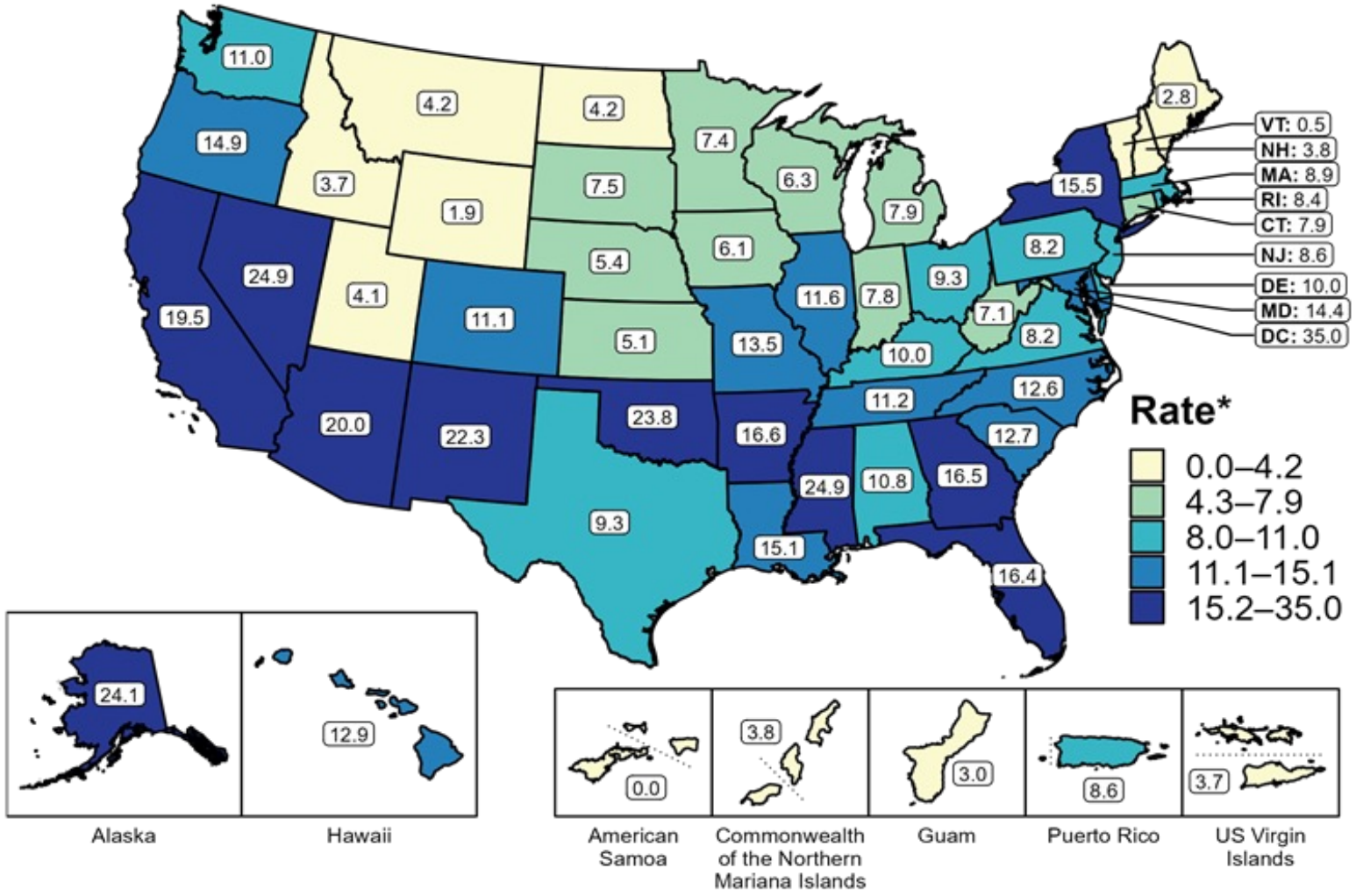
Primary and Secondary Syphilis — Rates of Reported Cases by Race/Hispanic Ethnicity, United States, 2016–2020



* Per 100,000

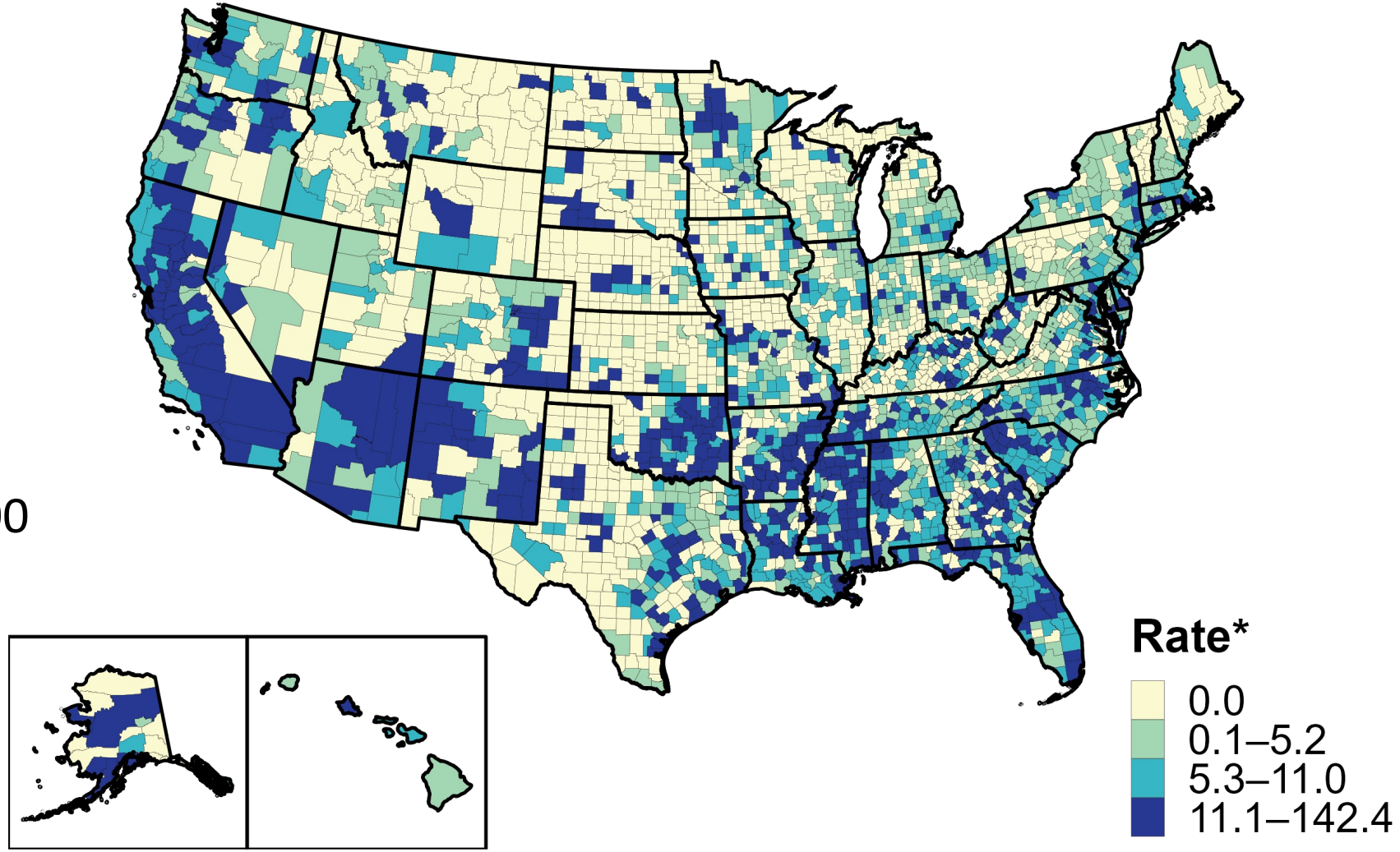
ACRONYMS: AI/AN = American Indian/Alaska Native; Black/AA = Black or African American; NH/PI = Native Hawaiian/Pacific Islander

Primary and Secondary Syphilis — Rates of Reported Cases by State, United States and Territories, 2020



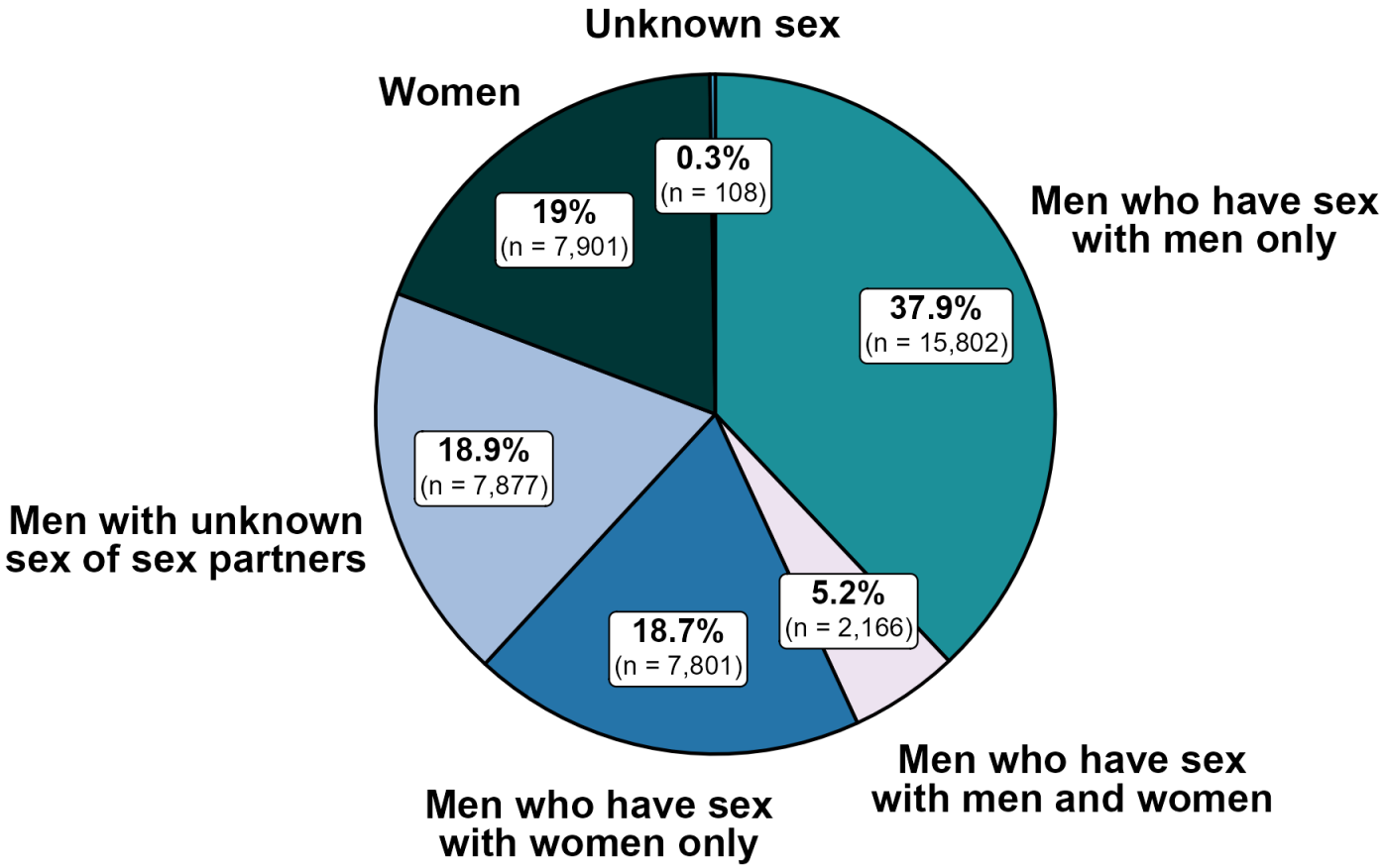
* Per 100,000

Primary and Secondary Syphilis — Rates of Reported Cases by County, United States and Territories, 2020

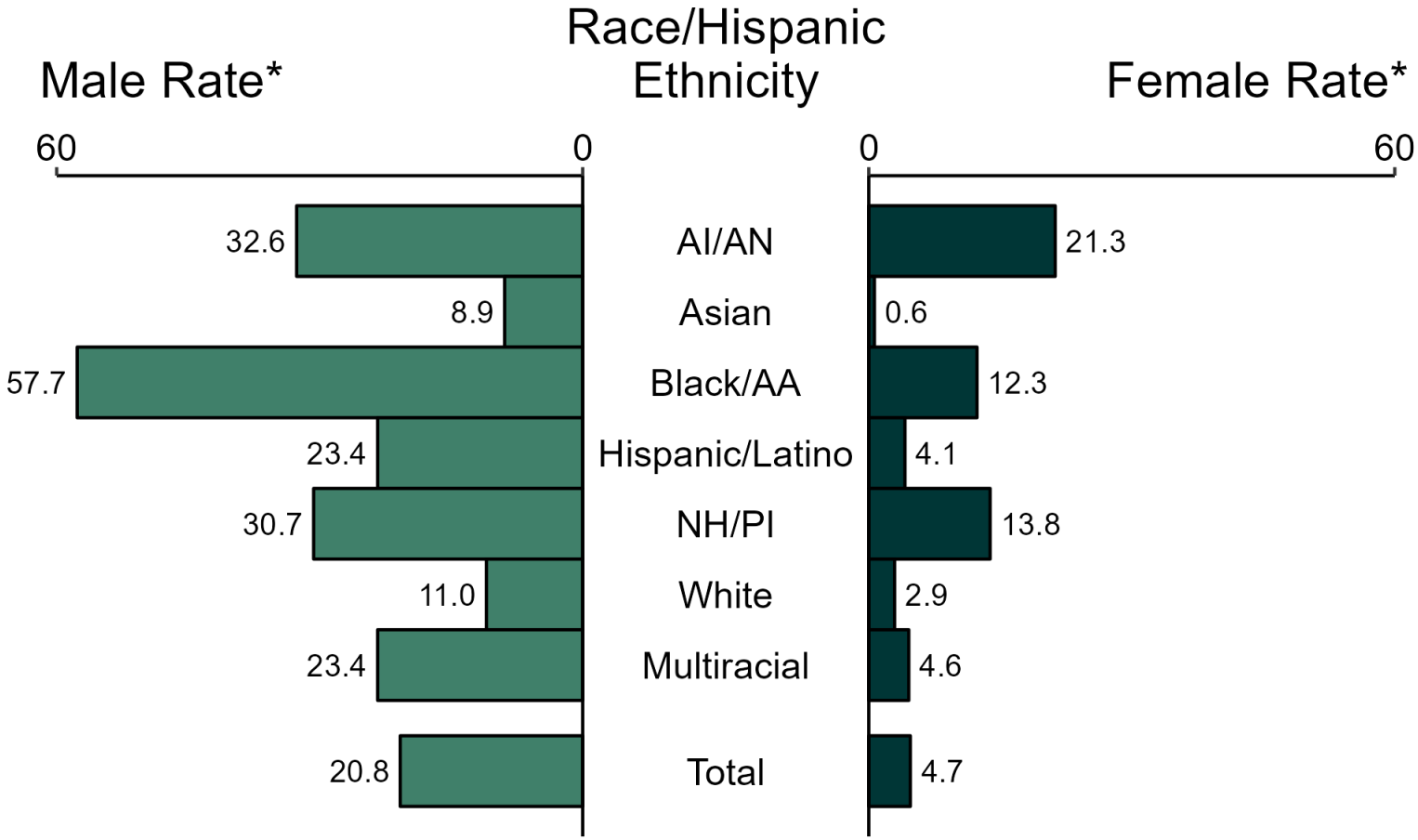


* Per 100,000

Primary and Secondary Syphilis — Distribution of Cases by Sex and Sex of Sex Partners, United States, 2020



Primary and Secondary Syphilis — Rates of Reported Cases by Race/Hispanic Ethnicity and Sex, United States, 2020

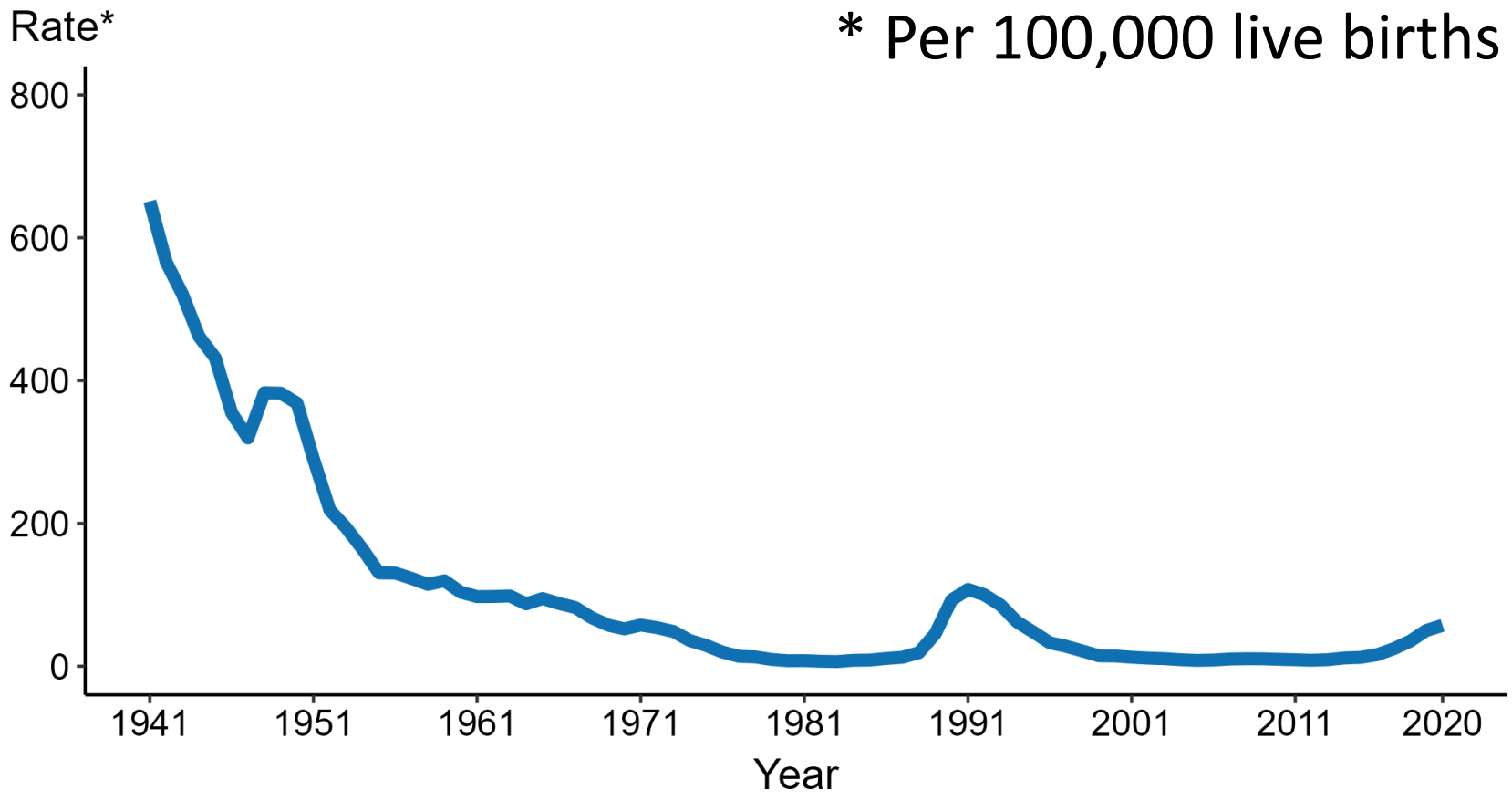


* Per 100,000

ACRONYMS: AI/AN = American Indian/Alaska Native; Black/AA = Black or African American; NH/PI = Native Hawaiian/Pacific Islander

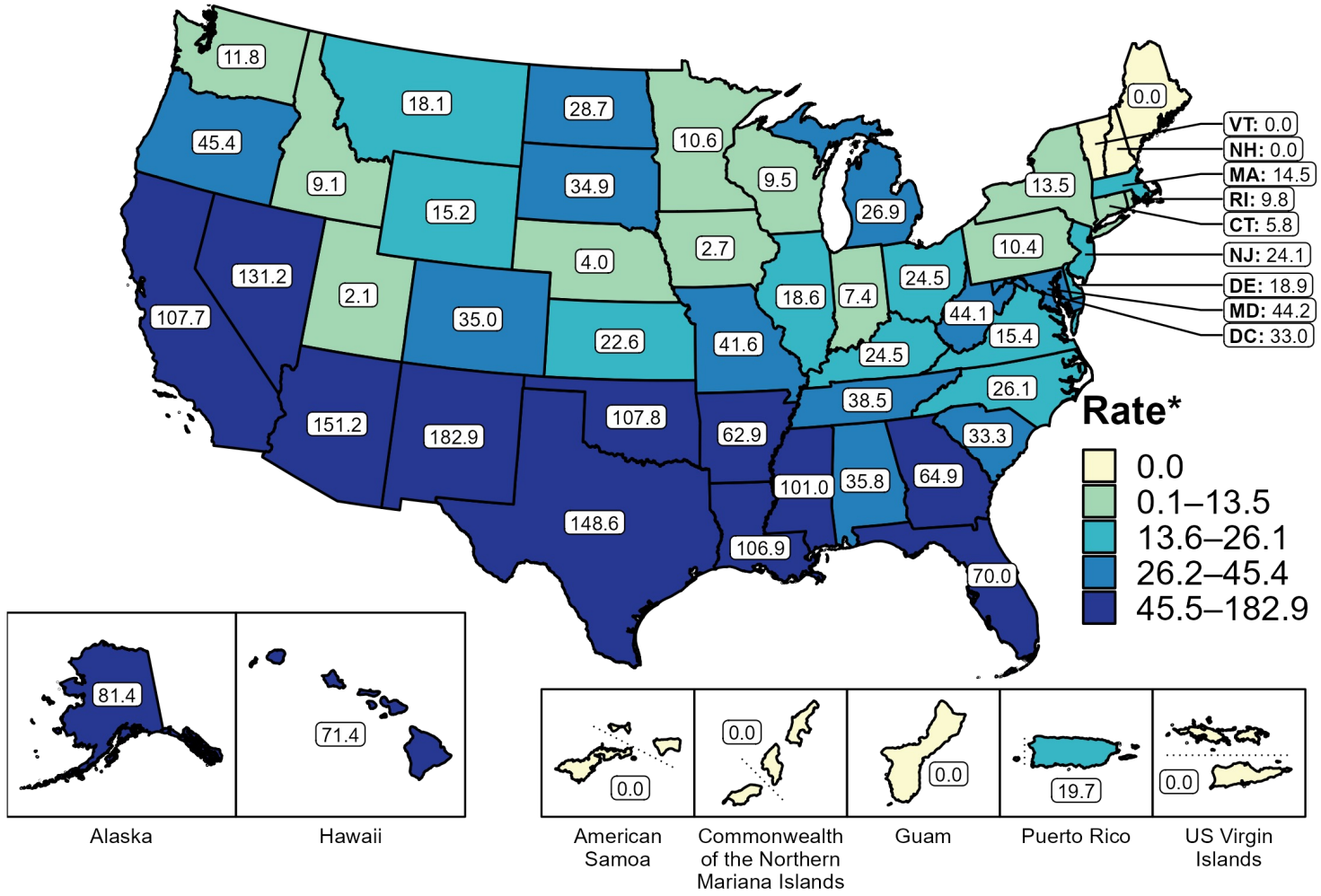
NOTE: Total includes all cases including those with unknown race/Hispanic ethnicity.

Congenital Syphilis — Rates of Reported Cases by Year of Birth, United States, 1941–2020

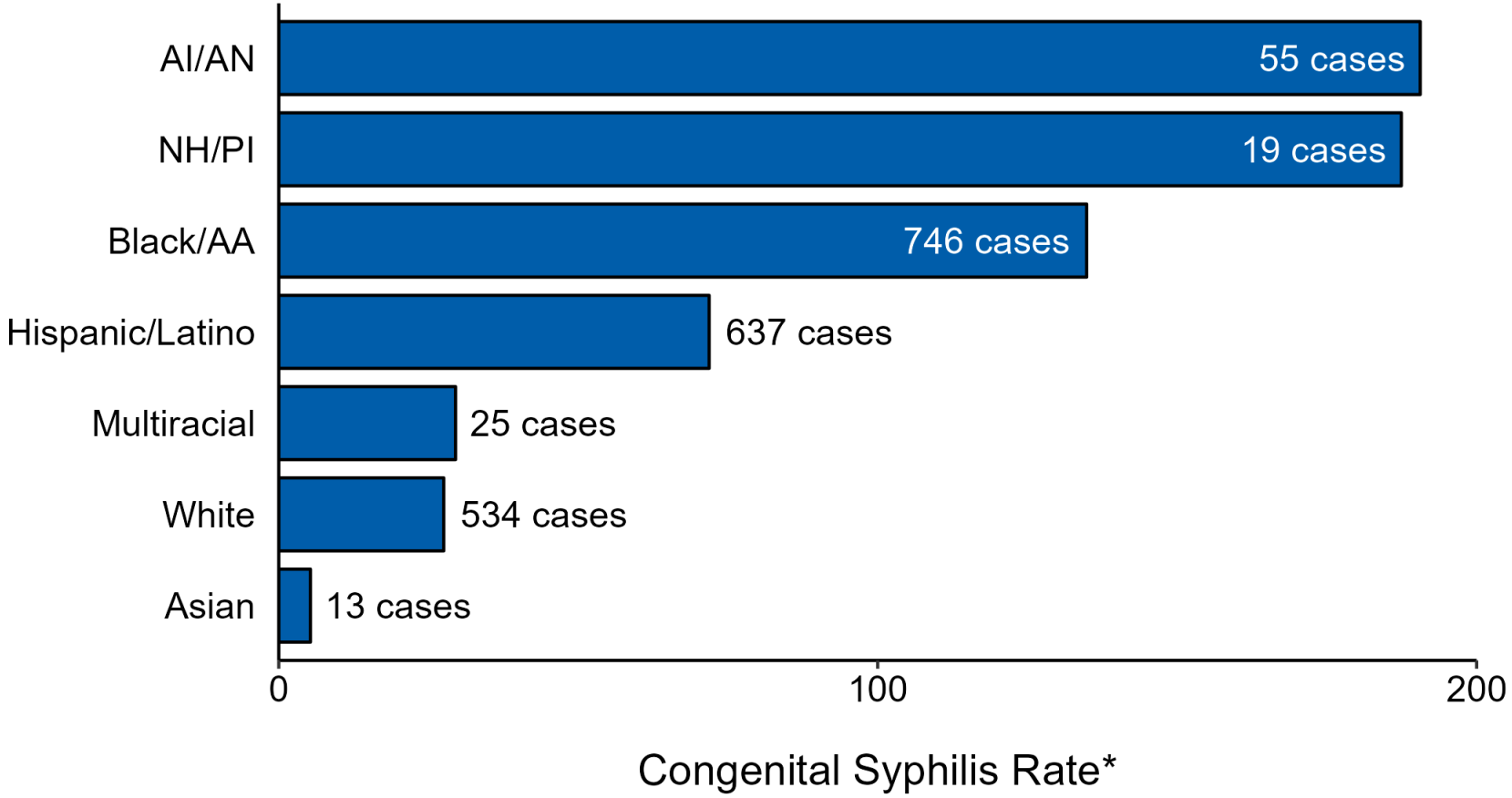


Congenital Syphilis — Rates of Reported Cases by Year of Birth and State, United States and Territories, 2020

* Per 100,000 live births



Congenital Syphilis — Case Counts and Rates of Reported Cases by Race/Hispanic Ethnicity of Mother, United States, 2020



* Per 100,000 live births

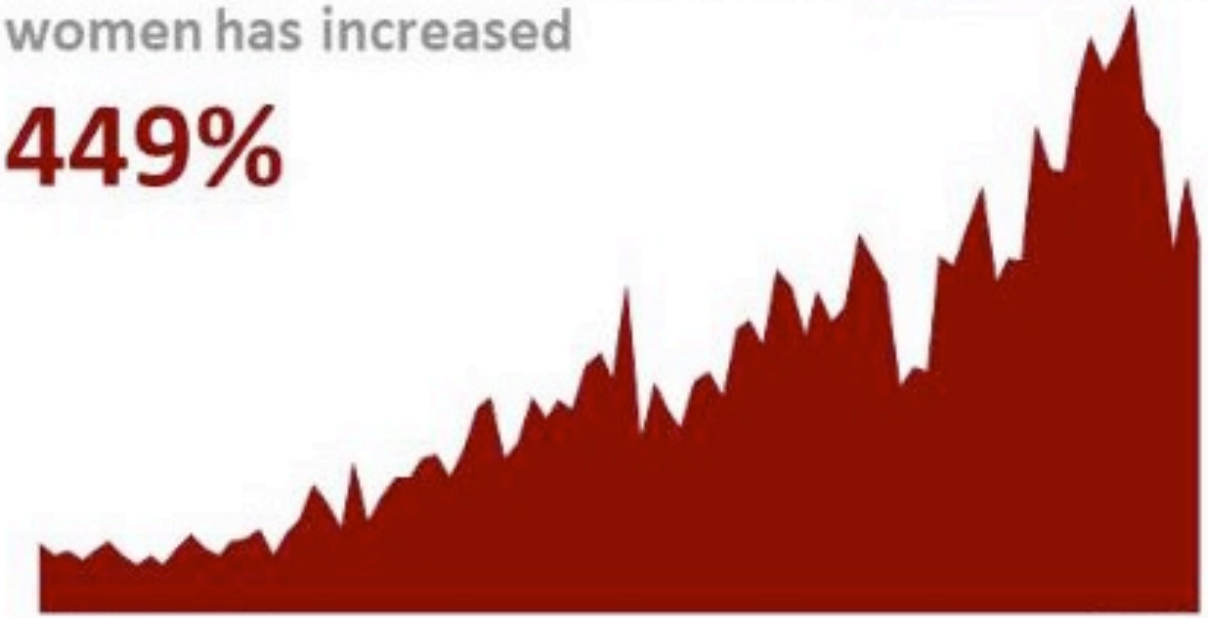
NOTE: In 2020, 119 cases (0.1%) were missing reported race and/or Hispanic ethnicity.

ACRONYMS: AI/AN = American Indian/Alaska Native; Black/AA = Black or African American; NH/PI = Native Hawaiian/Pacific Islander

Arizona has an outbreak of syphilis among women and babies

Since 2015, the yearly average of **syphilis** cases in women has increased

449%



Jan. 2015 Feb. 2022

How can you protect yourself?

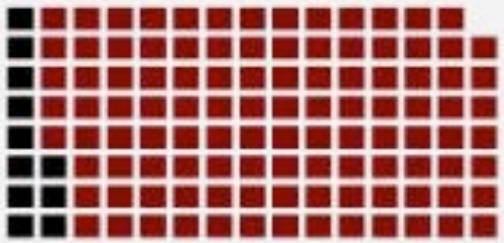
- **Use condoms** when having **ANY** type of sex
- **Reduce** number of sexual partners
- **Get tested** for STDs

2016 - 2019

The number of babies born with **syphilis doubled each year.**

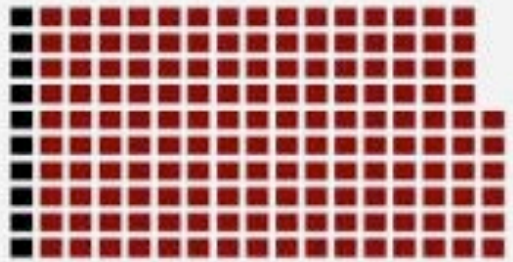
2020

Of the **119 babies born with syphilis** in 2020, **11 died.**

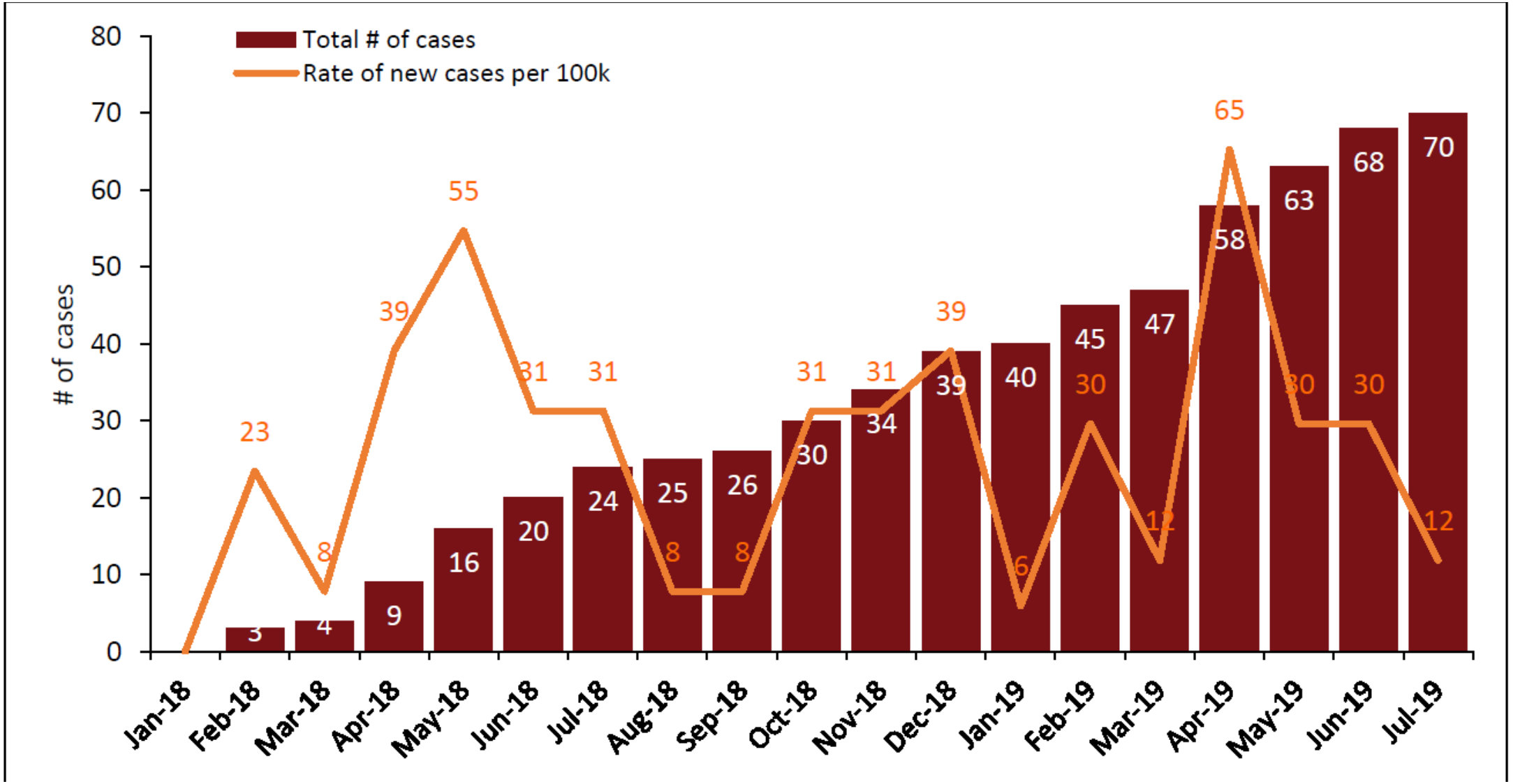


2021

Of the **166 babies born with syphilis** in 2021, so far **10 have died.**



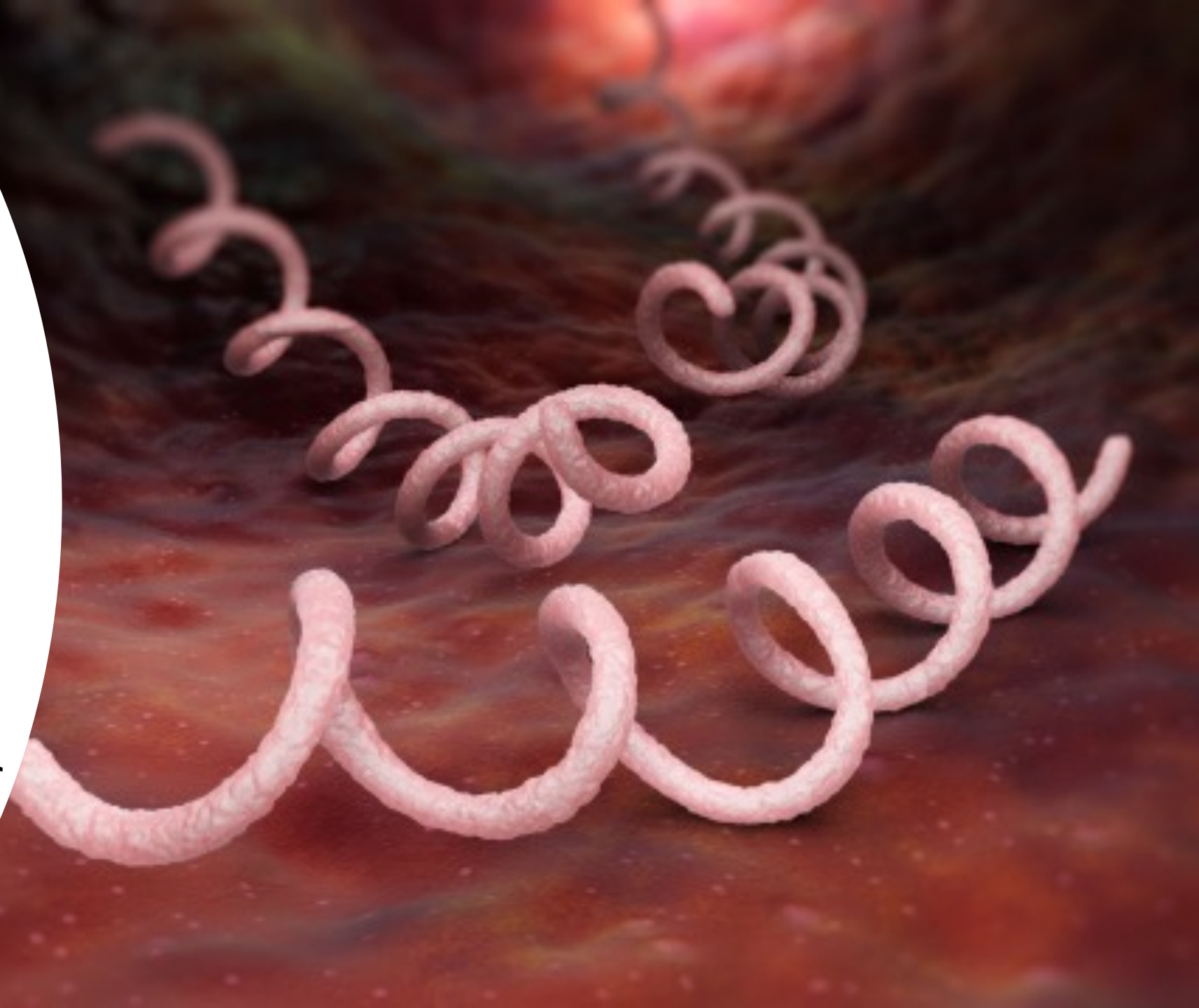
Cumulative cases of syphilis Whiteriver Jan 2018 – Jul 2019



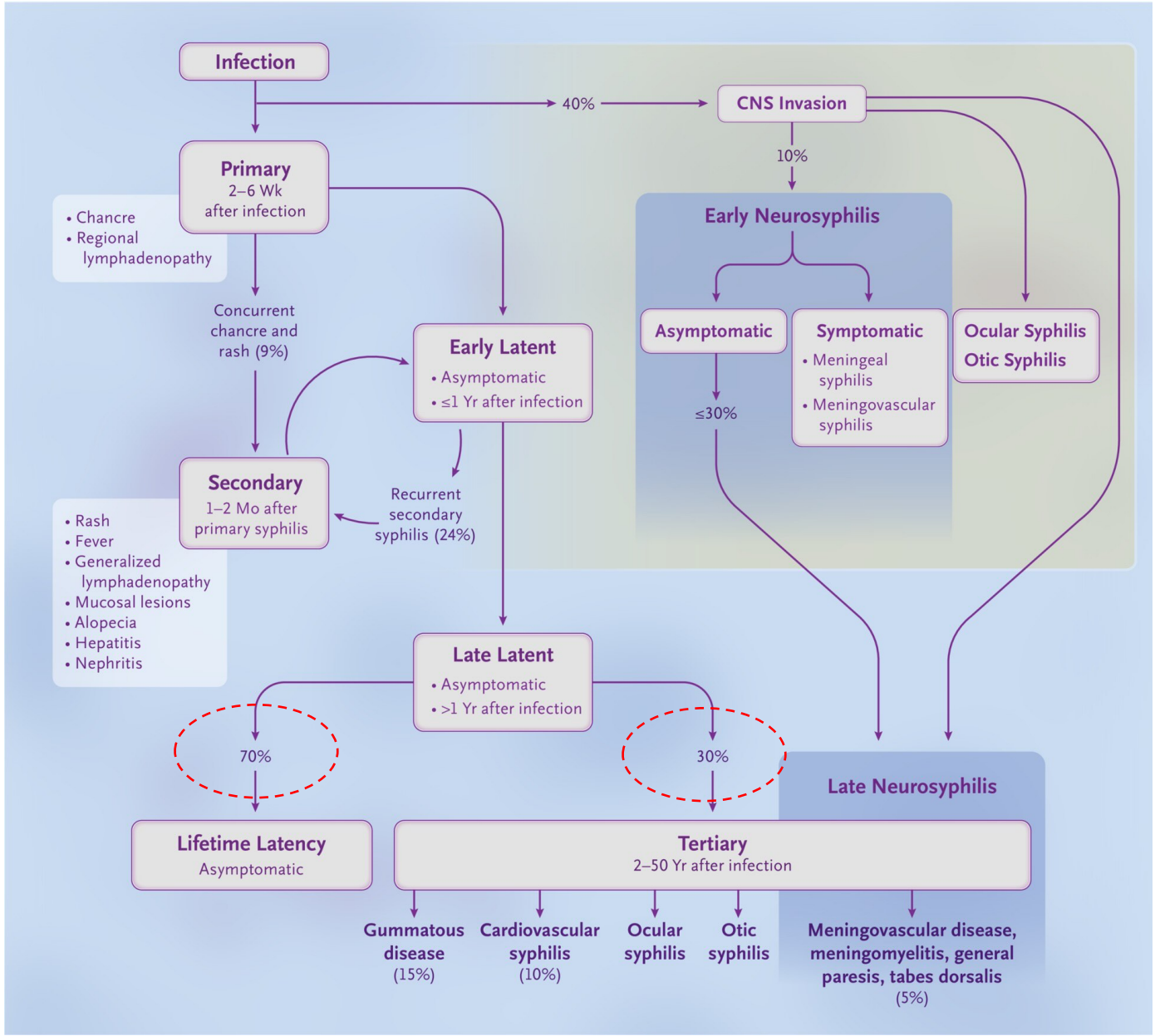
What is syphilis?

- ***Treponema pallidum***

- **Transmission:**
  - Sexual
  - Vertical
  - Non-sexual contact or transfusions (rare)

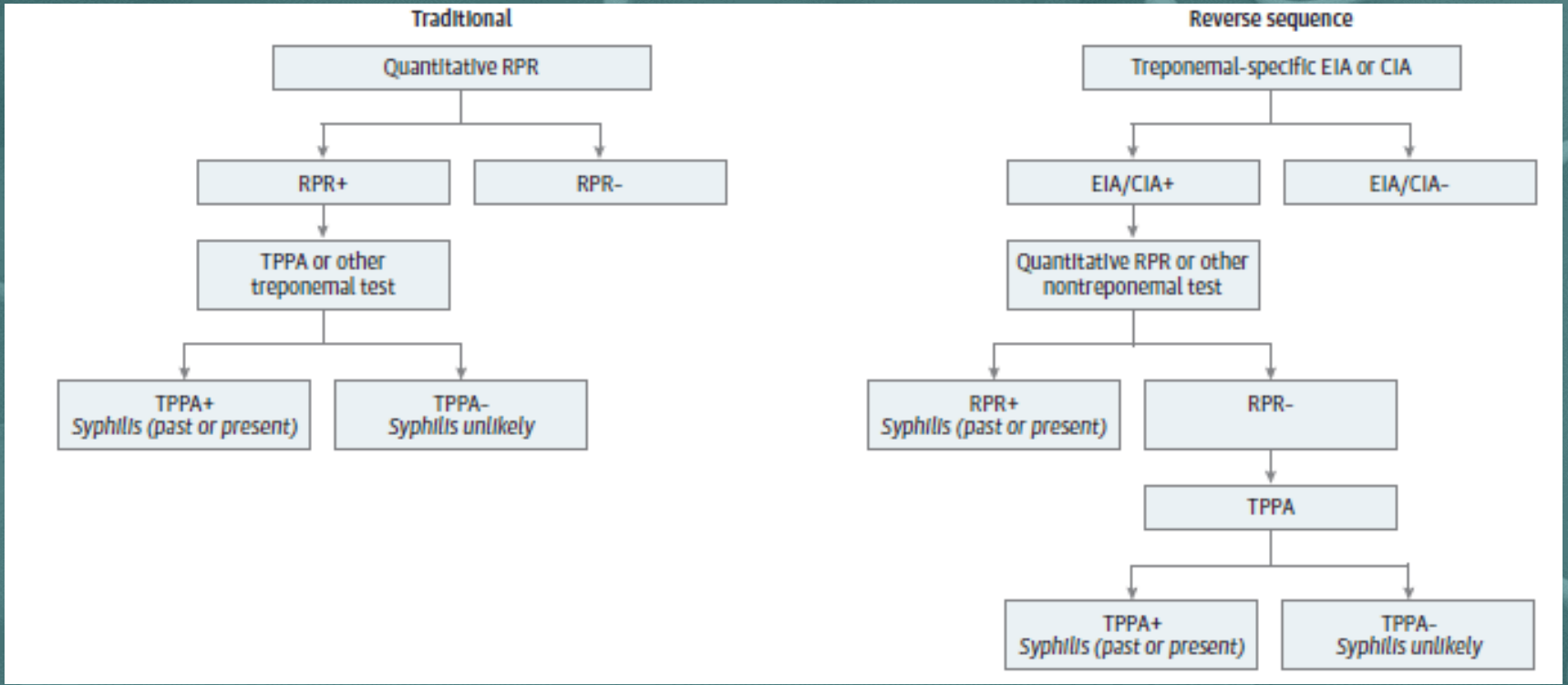


Natural History of Untreated Syphilis – *NEJM 2020;382:845-854*



Who should you test/screen?

- Patients with classic symptoms
- Patients with symptoms without an alternative diagnosis
- Patients in a high prevalence setting → ?



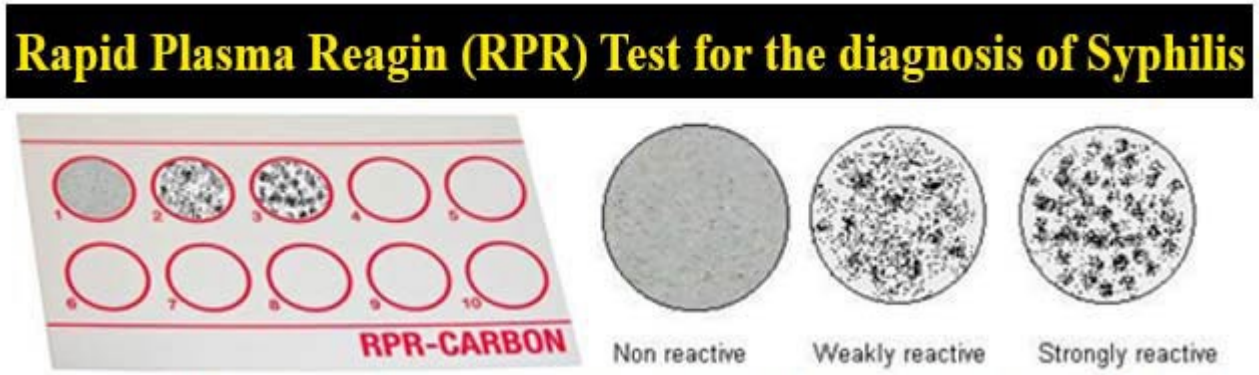


Table 1. Traditional and Reverse-Sequence Algorithms for Serologic Testing.*

Algorithm	NTT	TT	Confirmatory TT†	Interpretation‡
Traditional	Nonreactive			No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Treated or long-standing untreated syphilis
Traditional	Reactive	Nonreactive		Biologic false positive NTT§
Traditional and reverse-sequence	Reactive	Reactive		Untreated syphilis (likely) Treated syphilis (likely) Endemic treponematoses
Reverse-sequence	Nonreactive	Reactive	Nonreactive	Biologic false positive TT¶
Reverse-sequence	Nonreactive	Reactive	Reactive	Treated syphilis (most likely) Long-standing untreated syphilis Early primary syphilis (before NTT has turned positive) Prozone reaction (more common with VDRL test than with RPR test)
Reverse-sequence		Nonreactive		No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Long-standing treated syphilis if TT shows seroreversion

* The traditional algorithm starts with a nontreponemal test (NTT) followed, if reactive, by a confirmatory treponemal test (TT). The reverse-sequence algorithm starts with a TT (e.g., fluorescent treponemal-antibody absorption test, *Treponema pallidum* particle agglutination test, or automated enzyme or chemiluminescence immunoassay), followed, if reactive, by an NTT. RPR denotes rapid plasma reagin, and VDRL Venereal Disease Reference Laboratory.
† The confirmatory TT should be different from the TT performed initially.
‡ The likely or most likely interpretation of test results is noted for each algorithm.
§ Causes of a biologic false positive NTT include older age, autoimmune diseases, infections (e.g., human immunodeficiency virus infection), and drug use; pregnancy as a cause is controversial.
¶ Causes of a biologic false positive TT include infections (e.g., Lyme disease), autoimmune diseases, and older age.

Who to test

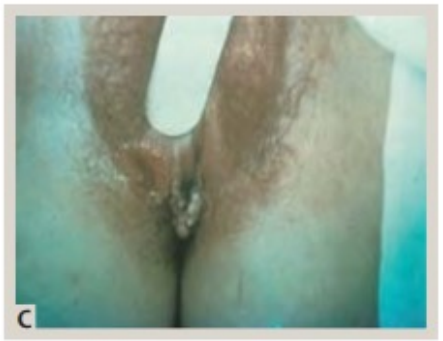
- Painless (or painful) genital ulcer
- Something you think you saw in the syphilis section of a textbook once
- Rash
  - Diffuse, symmetric maculopapular
  - Involving trunk and extremities
  - Palms and soles
- General paresis or tabes dorsalis

Who to test

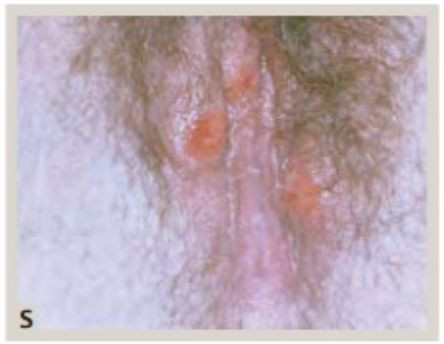
- Cranial nerve dysfunction
- Chronic Headache
- Meningitis, meningovascular disease or stroke
- Acute hepatitis
- Renal abnormalities
- Ocular findings (uveitis, retinal necrosis, optic neuritis)
- Aortic insufficiency

Frequently Test

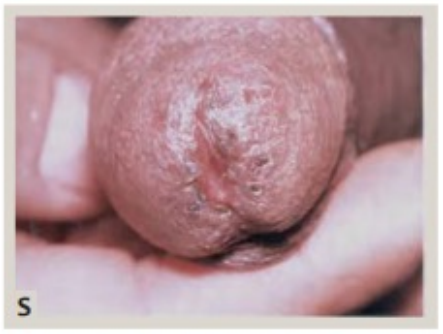
- Pregnant women
- Sexual partner with early syphilis
- Sexually active men who have sex with men (MSM)
- HIV positive individuals



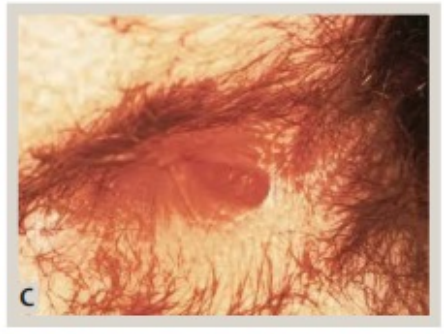
Syphilitic Ulcer, Vulva



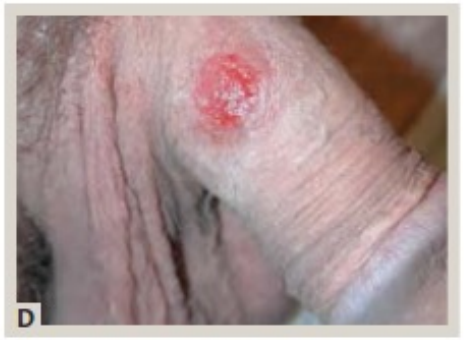
Multiple Syphilitic Ulcers, Vulva



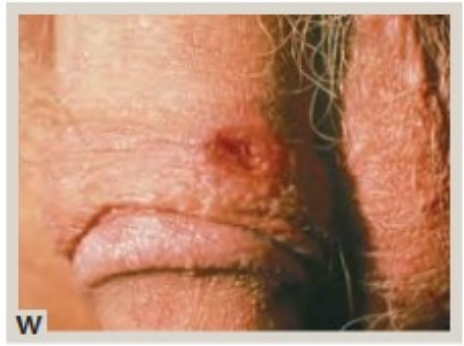
Crusted Syphilitic Ulcer, Urethra



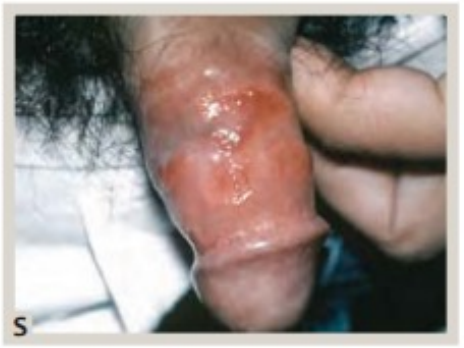
Syphilitic Ulcer, Perianal



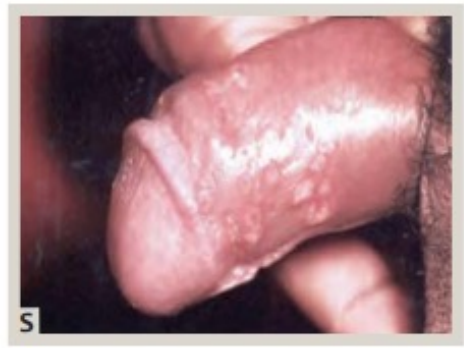
Syphilitic Ulcer, Shaft



Syphilitic Ulcer, Shaft



Multiple Syphilitic Ulcers, Shaft

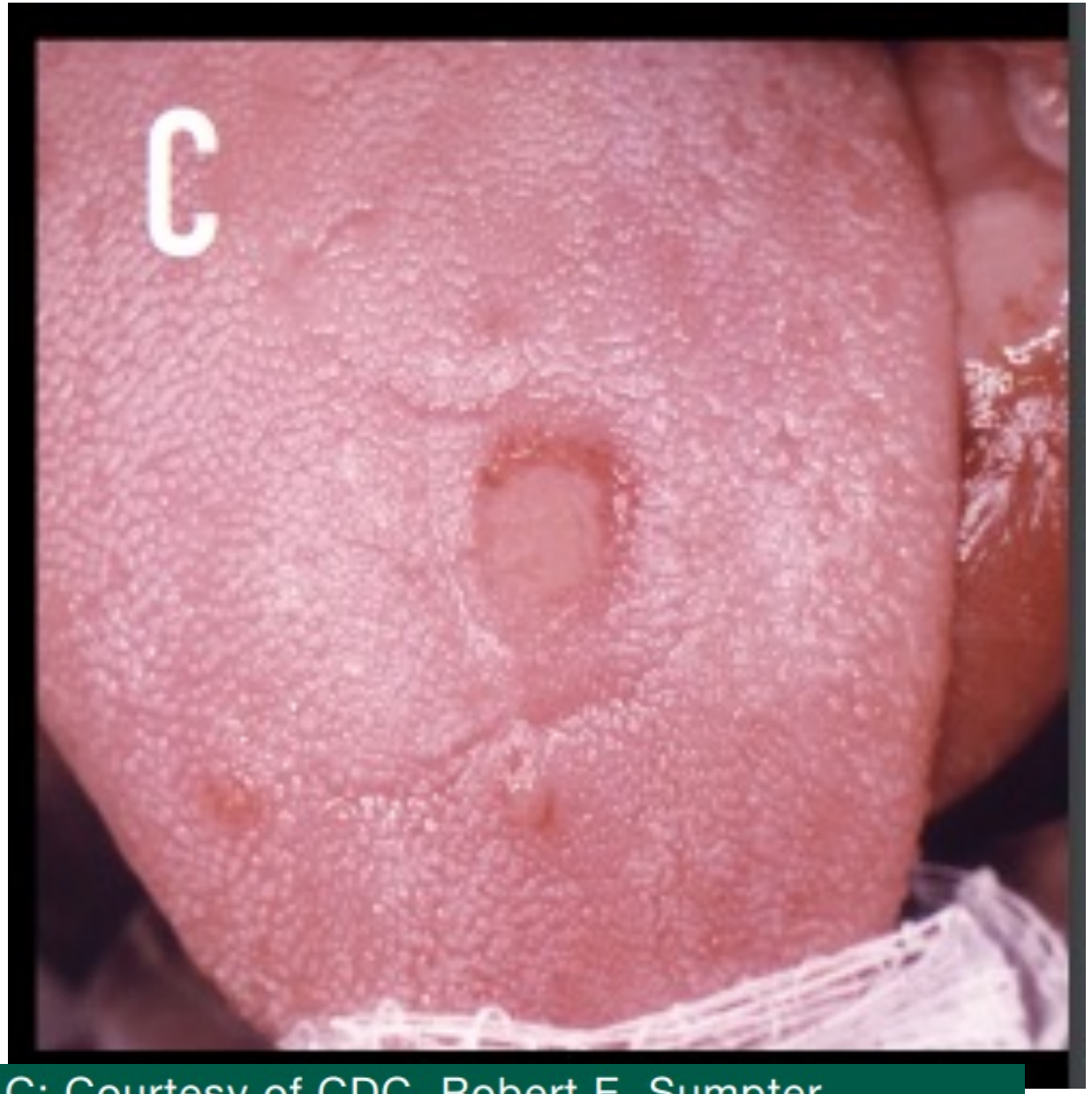


Multiple Syphilitic Ulcers Resembling Herpes

Syphilis Presentations and Stages – Primary

- Sexually transmitted
- Genital lesions
- Variable presentation
- Average time between acquisition and the start of symptoms is 21 days. Can range from **10 to 90 days**.
- Heal spontaneously within 3-6 weeks +/- treatment

Primary – Atypical Chancre



C: Courtesy of CDC, Robert E. Sumpter

CLINICAL PRESENTATIONS OF SECONDARY SYPHILIS

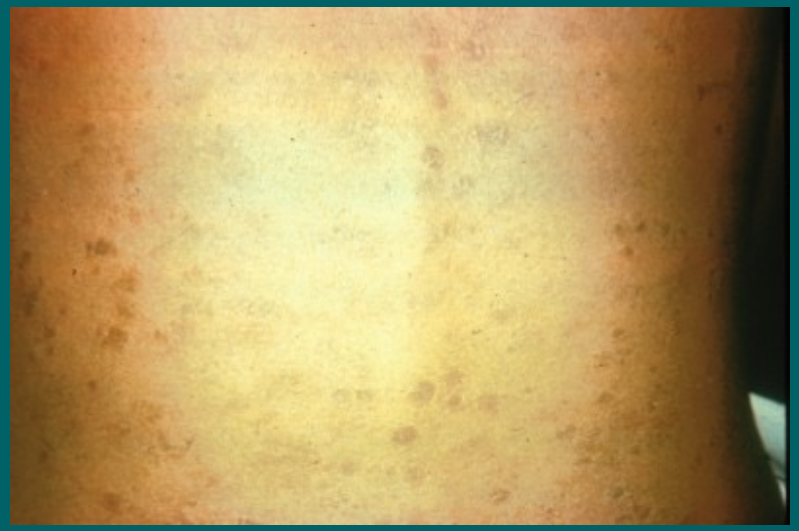
- Symptoms typically occur 3-6 weeks after primary stage (can overlap with primary); resolve in 2-10 weeks
- 25% may have relapse of signs & symptoms in first year

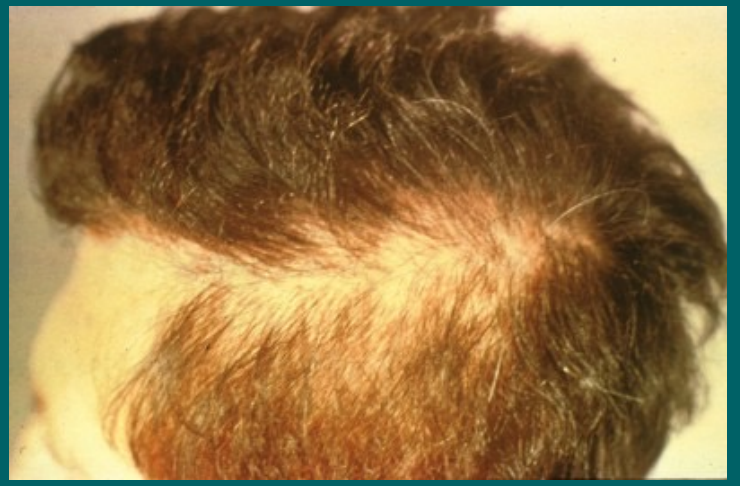
Signs & Symptoms of Secondary Syphilis

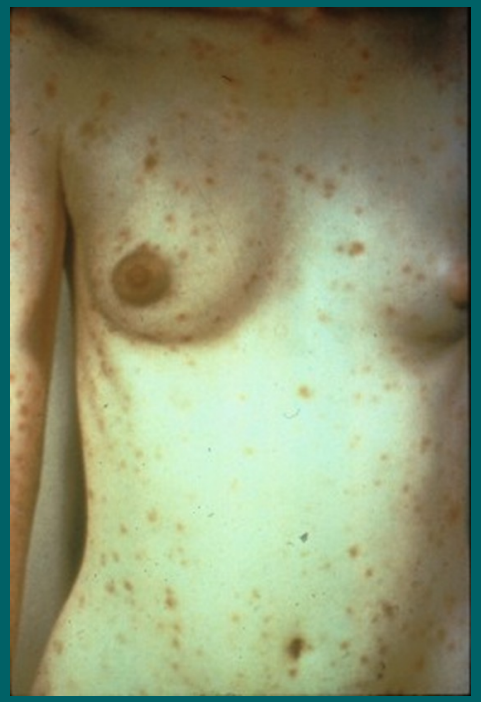
- **Rash:** most common feature (75-90%); can be macular, papular, squamous (scale), pustular (rare), vesicular (very rare) or combination; usually nonpruritic; may involve palms & soles (60%)
- **Lymphadenopathy:** (70-90%); inguinal, epitrochlear, axillary & cervical sites most commonly affected
- **Constitutional Symptoms:** (50-80%); malaise, fever
- **Mucous Patches:** (5-30%); flat gray-white patches in oral cavity & genital area
- **Condyloma Lata:** (5-25%); moist, heaped, wart-like lesions in genital, peri-rectal & rectal areas, & oral cavity
- **Alopecia:** (10-15%); patchy hair loss, loss of lateral eyebrows
- **Neurosyphilis:** (<2%); visual loss, hearing loss, cranial nerve palsies among other

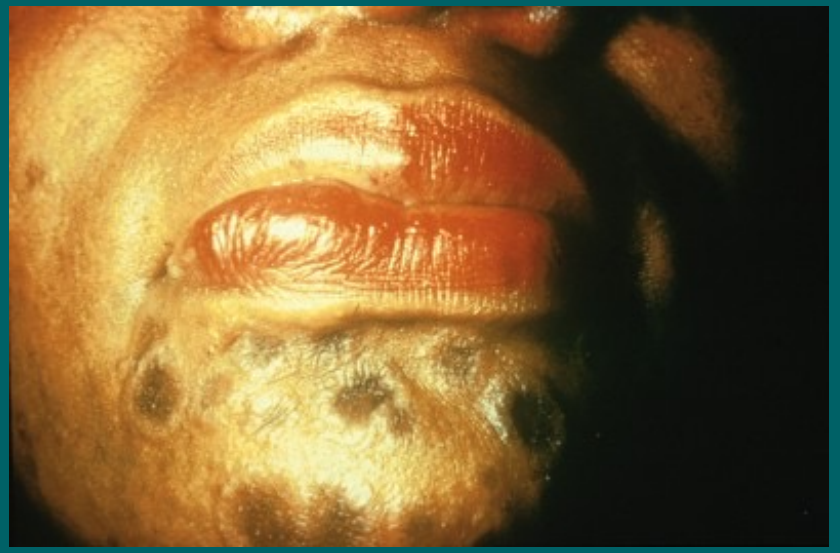
These symptoms will go away on their own without treatment

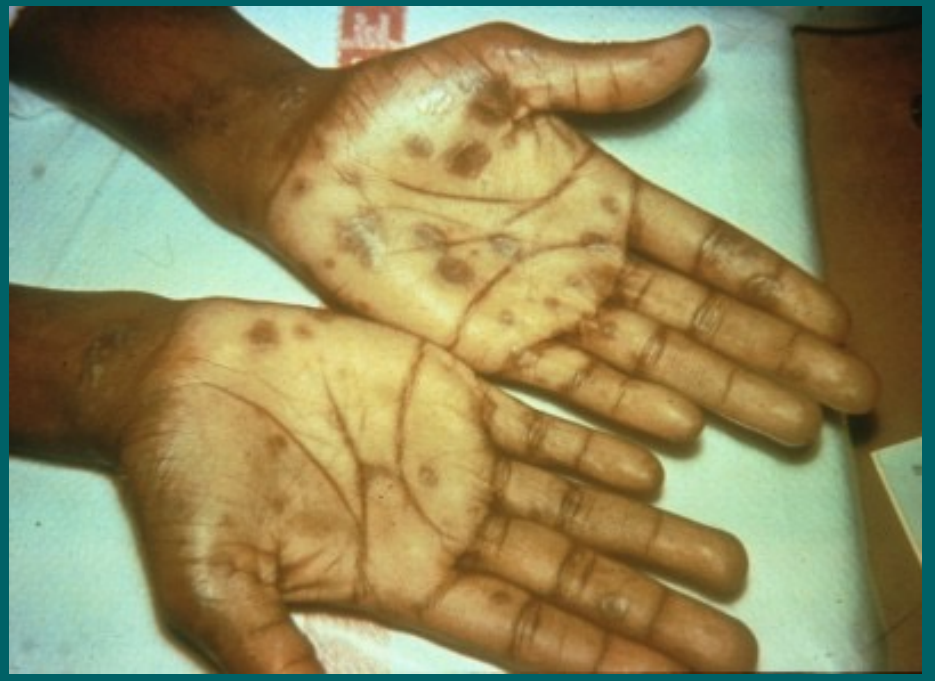
Secondary Syphilis

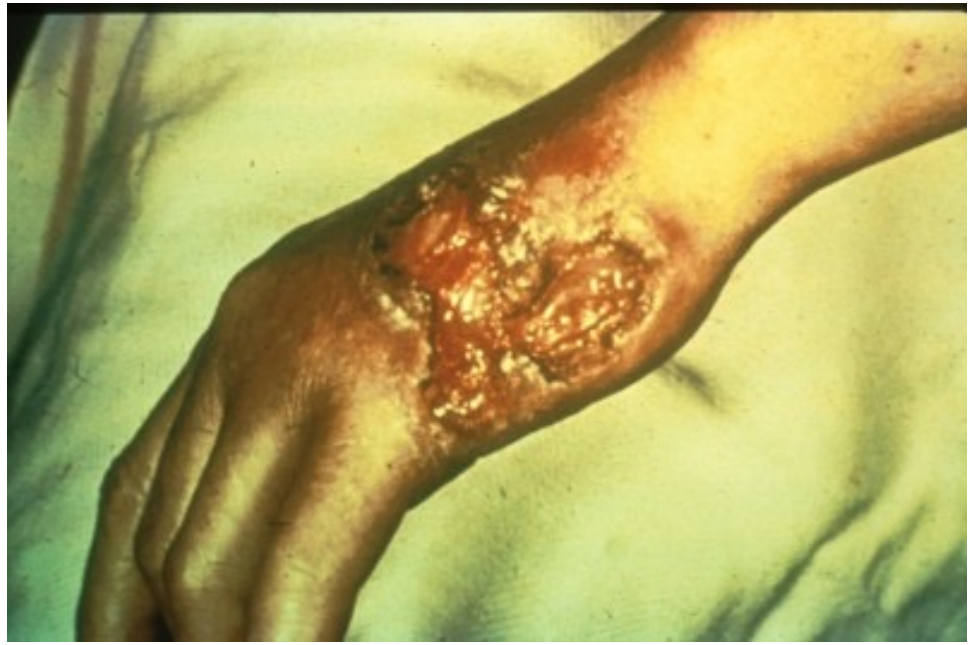


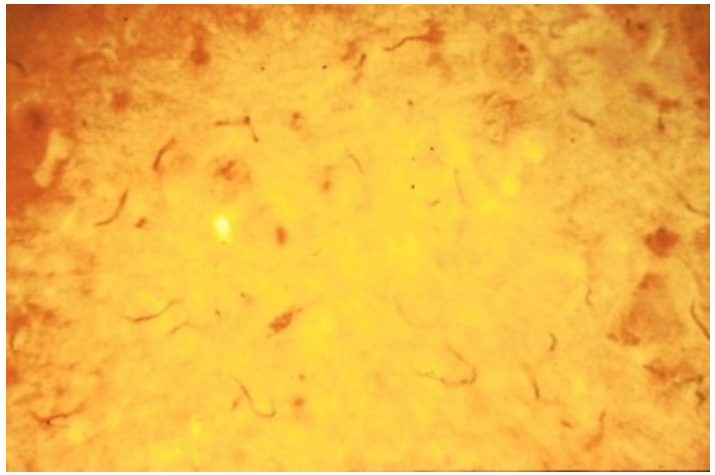










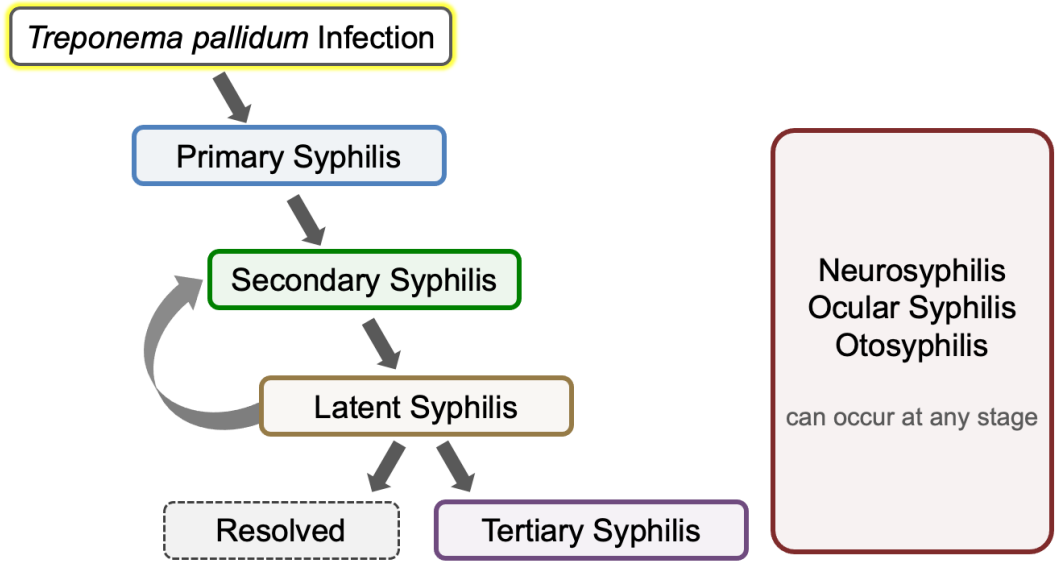


Tertiary

- Not sexually transmitted
- Decades after primary infection
- Cardiovascular
  - Dissection
  - HFrEF
- Gummas
  - Can occur anywhere
- CNS
  - Tabes doralis
  - General paraesis

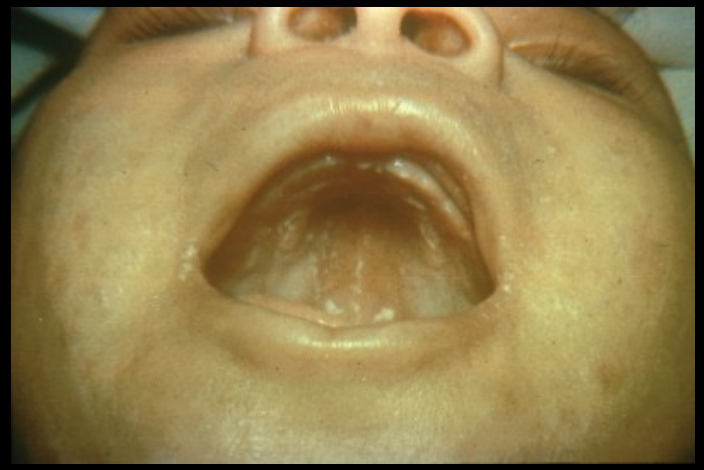
Latent Syphilis

- No symptoms
- **Early Latent**
  - **Infection within 1 year of last neg test → potentially infectious**
- **Late**
  - not infectious if truly late but may be in latent of unknown duration
  - **No negative RPR within past year**
- (sort-of) Important to differentiate for treatment
- 60-85% remain asx for years without treatment

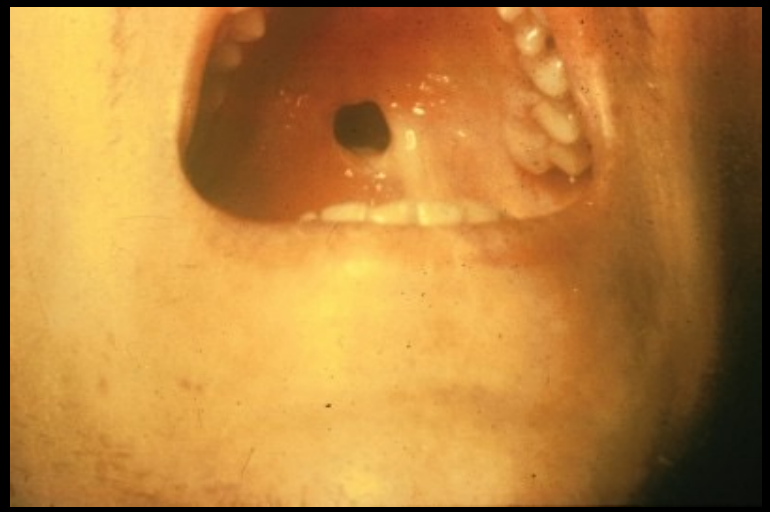


Syphilis in pregnancy

- Screen early and often in all pregnant women
- Treatment >30 d prior to delivery will likely prevent most cases of congenital syphilis
- Treat based on stage like anyone else
- Any stillborn/fetal death >20 weeks should be tested for syphilis



Congenital syphilis



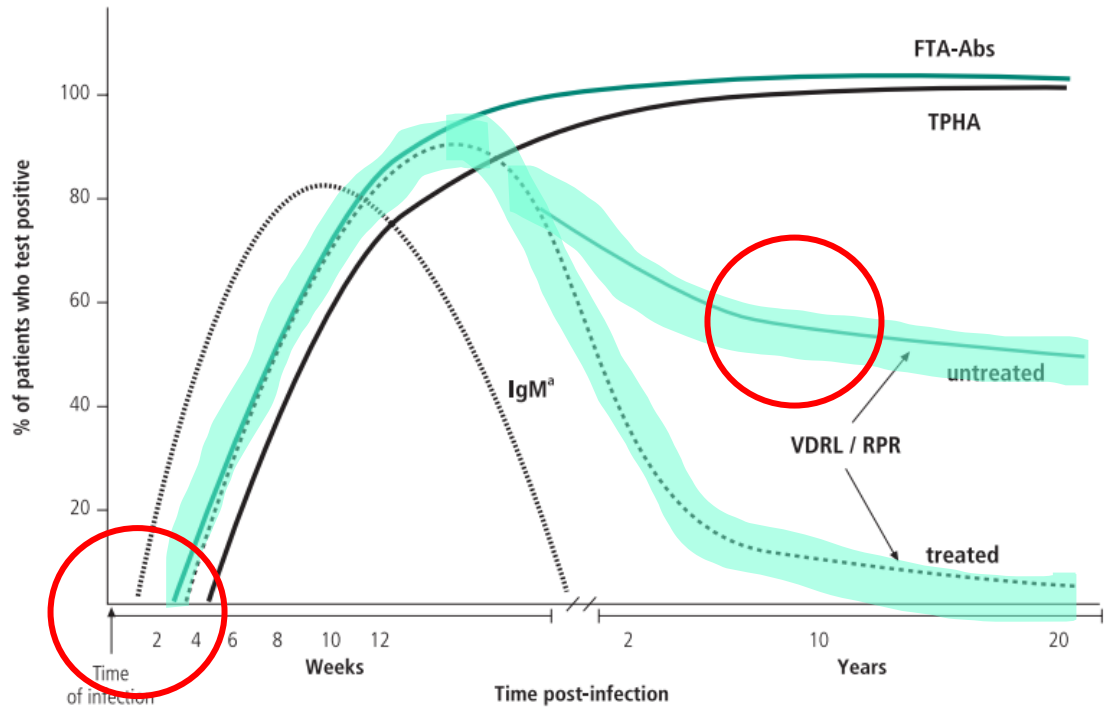
- Diagnosis can be difficult
- Maternal antibodies transferred through placenta to fetus, complicating interpretation of reactive serologic tests
- Treatment decisions based on:
  - identification of syphilis in the mother
  - adequacy of maternal treatment
  - presence of clinical, laboratory, or radiographic evidence of syphilis in the neonate
  - comparison of maternal (at delivery) and neonatal nontreponemal serologic titers (e.g., RPR or VDRL) by using the same test, ideally conducted by the same laboratory


How do you test?

Two types of serologic tests for syphilis

- **Non-treponemal**
  - **RPR, VDRL**
  - **Detects non-specific antibodies**
  - **Titers: quantitative**
    - Important for follow up
  - **Reflect disease activity**

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

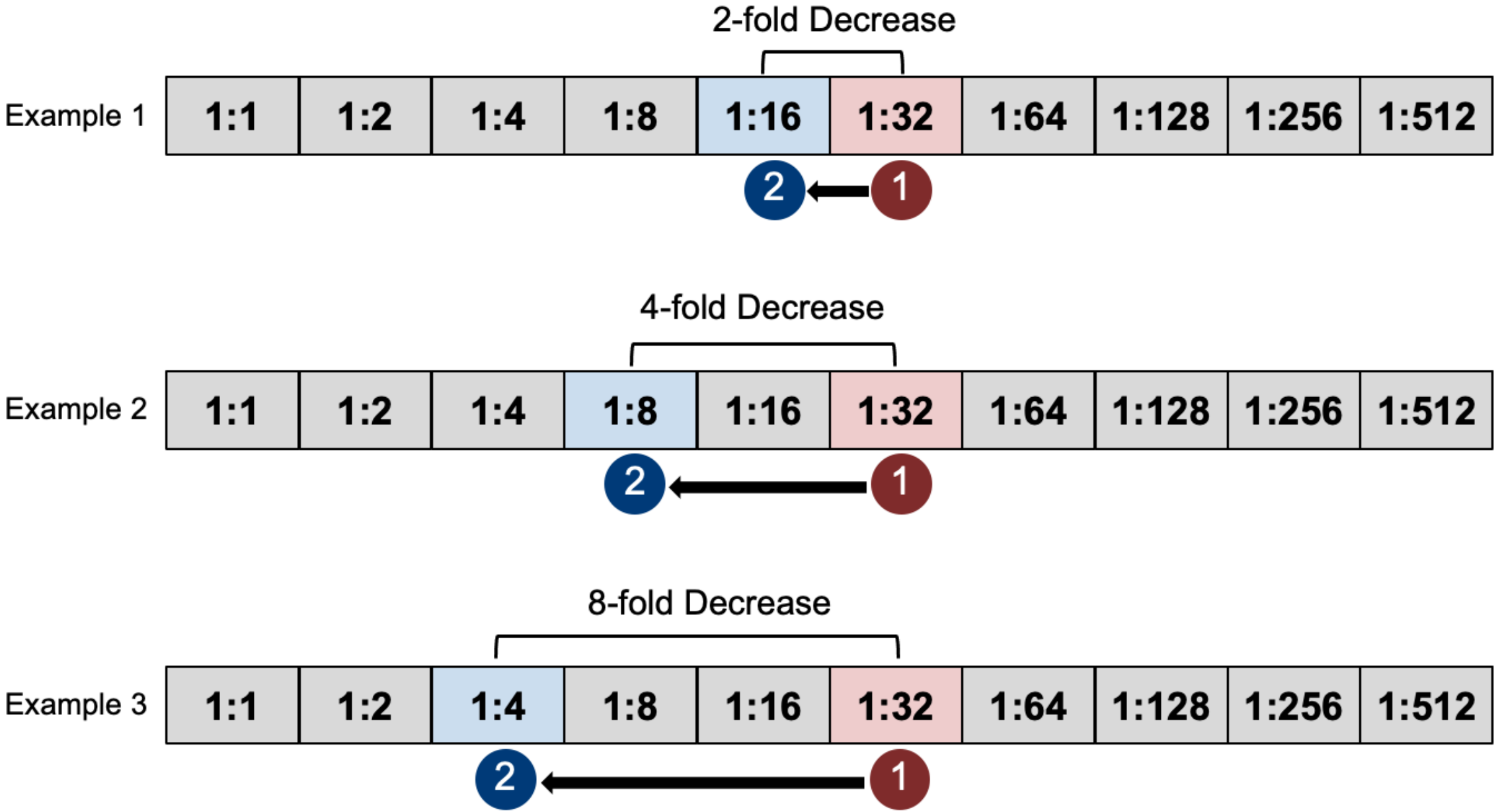


[a] IgM by ELISA or FTA-ABS 195 or immunoblot

WHO 04.69

Limitations of non-treponemal tests

- **False positives** due to other medical conditions
  - Eg SLE, TB, **Pregnancy**
- **False negatives** during incubation phase or with high titers
  - “Prozone effect” – overwhelming Ab titers interfere with test
- **Manual, labor intensive = no results immediately**


2-fold Decrease
Example 1
1:1
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
2
1
4-fold Decrease
Example 2
1:1
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
2
1
8-fold Decrease
Example 3
1:1
1:2
1:4
1:8
1:16
1:32
1:64
1:128
1:256
1:512
2
1

Two types of serologic tests for syphilis

- **Treponemal**
  - EIA, TPPA, FTA-ABS
  - Detects specific antibodies against *T. pallidum*
  - Qualitative (yes/no)
  - Automated = fast results

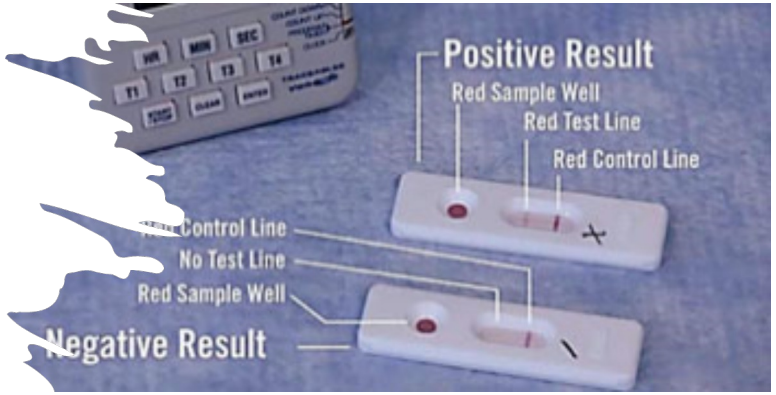
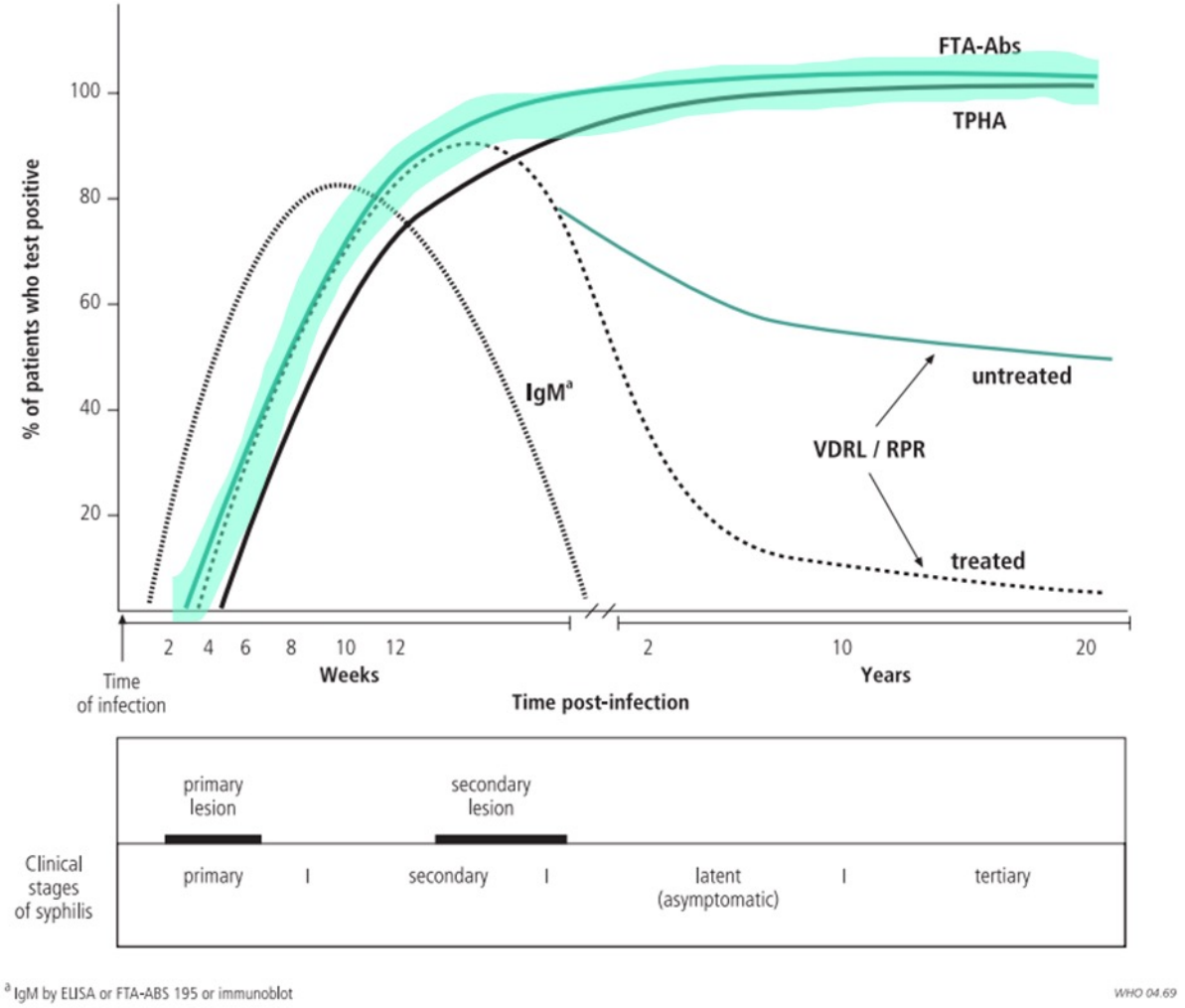


Fig. 1. **Common patterns of serological reactivity in syphilis patients**



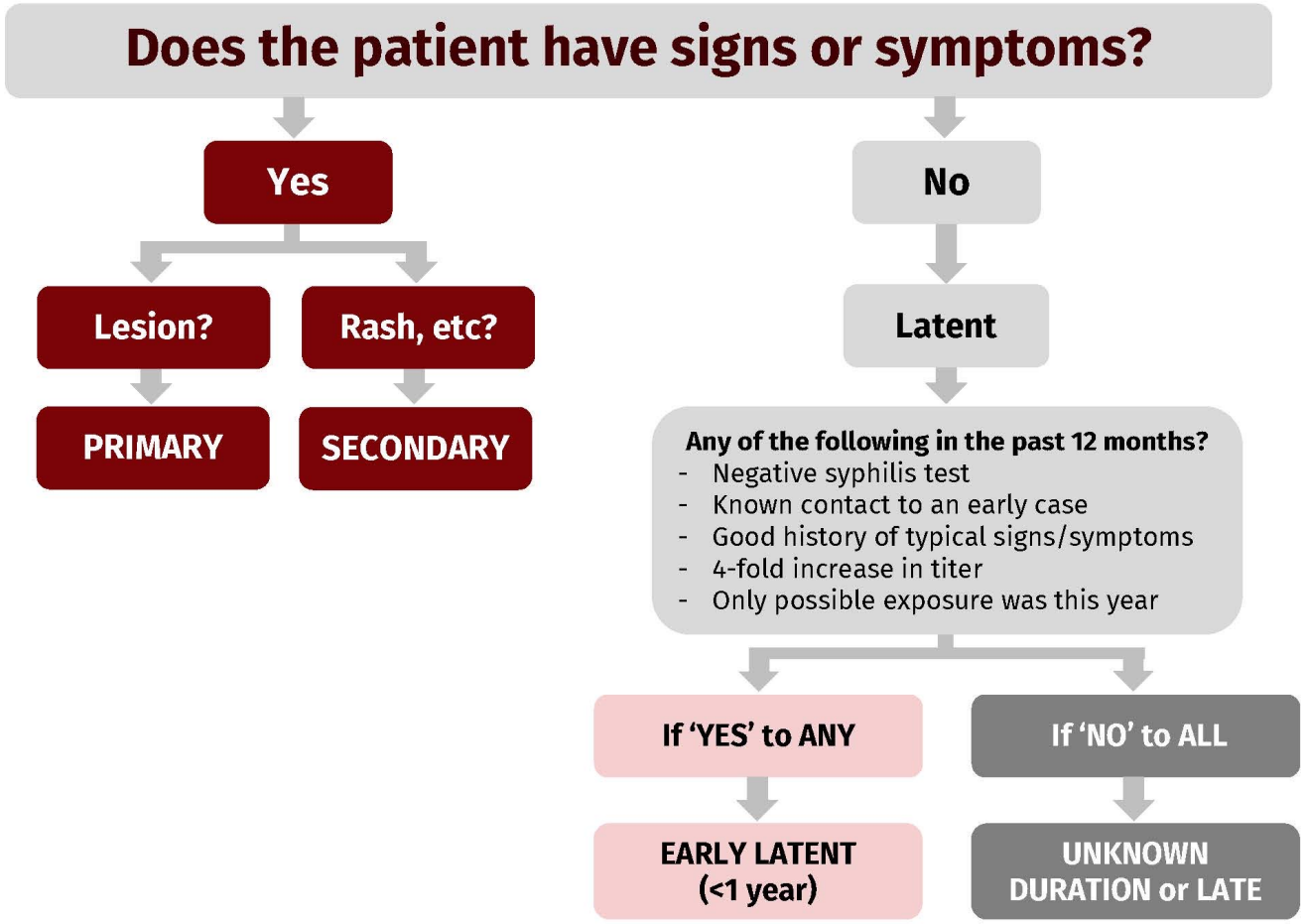
[a] IgM by ELISA or FTA-ABS 195 or immunoblot

WHO 04.69

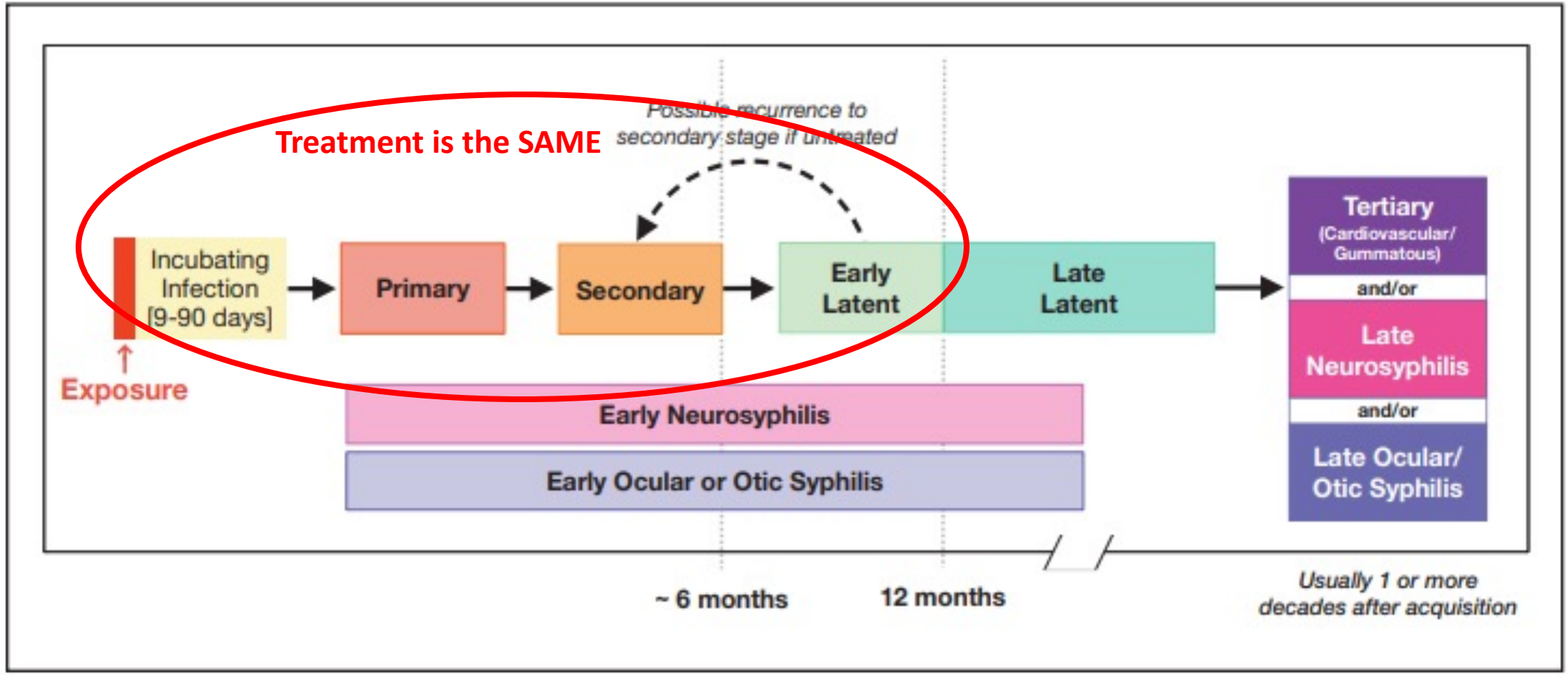
Pros and Cons of Treponemal tests

- **Automatic, faster results**
- **Persistent positive** after treatment – unable to determine treatment success
- **False negatives** during incubation phase

Syphilis Staging Flowchart



Clinical Stages

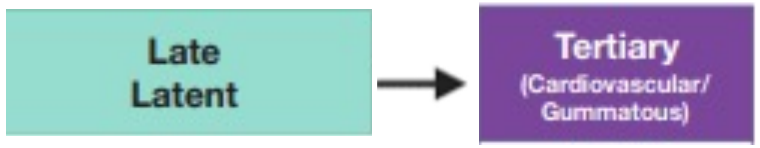


Early Syphilis

Treatment

Single dose of 2.4 million units
of **Benzathine Penicillin G**

Late Syphilis

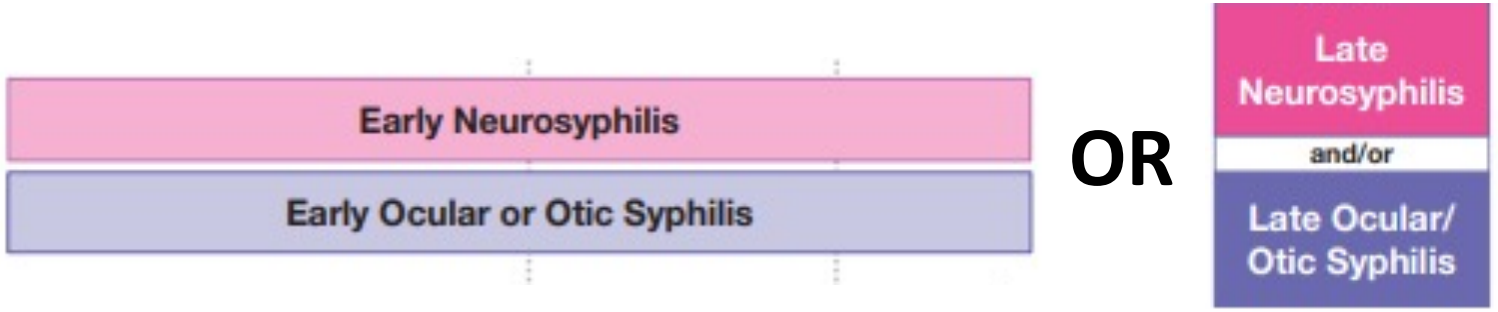


Asymptomatic and no documented negative test within last year or Tertiary symptoms

Treatment

3 doses of 2.4 million units of
Benzathine Penicillin G **one week apart**

Neurosyphilis



Treatment

IV Aqueous crystalline penicillin G 18 – 24 million units/day x 10-14 days

Table 2. Treatment Guidelines for Antimicrobial Management of Syphilis.*

For primary and secondary syphilis in nonpregnant adults, including HIV-infected adults:
Penicillin G benzathine, 2.4 million units in a single IM dose
Doxycycline, 100 mg orally twice a day for 14 days (first alternative)
Ceftriaxone, 1–2 g daily, IM or IV, for 10–14 days (second alternative)

For latent syphilis in nonpregnant adults, including HIV-infected adults:
Early latent: penicillin G benzathine, 2.4 million units in a single IM dose
Late latent: penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-week intervals
Doxycycline, 100 mg orally twice a day for 28 days (alternative)

For late syphilis (gummas and cardiovascular manifestations) but not neurosyphilis:
Penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-wk intervals

For neurosyphilis and ocular syphilis:
Aqueous crystalline penicillin G, 18–24 million units per day, administered in IV doses of 3–4 million units every 4 hr or as a continuous infusion, for 10–14 days
Penicillin G procaine, 2.4 million units in a single IM dose daily, plus probenecid, 500 mg administered orally four times a day, both for 10–14 days (alternative)

For primary and secondary syphilis in pregnancy:
Penicillin G benzathine, 2.4 million units in a single IM dose†

For latent syphilis in pregnancy:
Early latent: penicillin G benzathine, 2.4 million units in a single IM dose
Late latent: penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-wk intervals

* Treatment guidelines are from the Centers for Disease Control and Prevention (Workowski and Bolan[14]). IM denotes intramuscular, and IV intravenous.
† Some experts recommend an additional IM dose of 2.4 million units of penicillin G benzathine, given 1 week later.

Pregnant Women

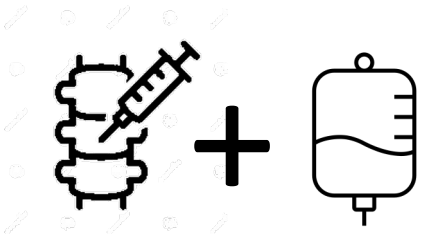
Treatment

According to Stage

CDC 2015 guidelines – 2 doses for early disease,
2021 Guidelines – 1 dose for early disease

If you treat the mother, you treat the baby

In summary:

- Early syphilis (primary, secondary early latent) = 1 dose IM 
- Pregnancy (2021 Guidelines) – same as nonpregnant
- Late syphilis = 3 doses IM a week apart 
- Neurosyphilis = LP+ IV (you should call a friend) 

Management of Sex Partners

Treat presumptively if:

- Exposure to primary, secondary, early latent < 90 days

  Single dose of Penicillin 2.4 million units IM
- Exposure to primary, secondary early latent > 90 days and no serology available
- Exposure to unknown latent syphilis

If serologies available treat according to results

- for instance, if no neg test in last year and positive without symptoms needs three doses

Treatment Follow-up

Early (Primary and Secondary)	Latent (Early, Late or Unknown)
• If lesions present, clinical exam in 1 week • Clinically evaluate and repeat RPR at 6 and 12 months • Suggest HIV test with repeat HIV test at 6 months • If known HIV+, repeat RPR at 3, 6, 9, 12 and 24 months	• Repeat RPR at 6, 12 and 24 months • If known HIV+, repeat RPR at 6, 12, 18 and 24 months

Retest at 3 months in pregnancy

What is Treatment Success

Four-fold decrease in titer = adequate response

Positive patient tested, titer 1:32

Treatment

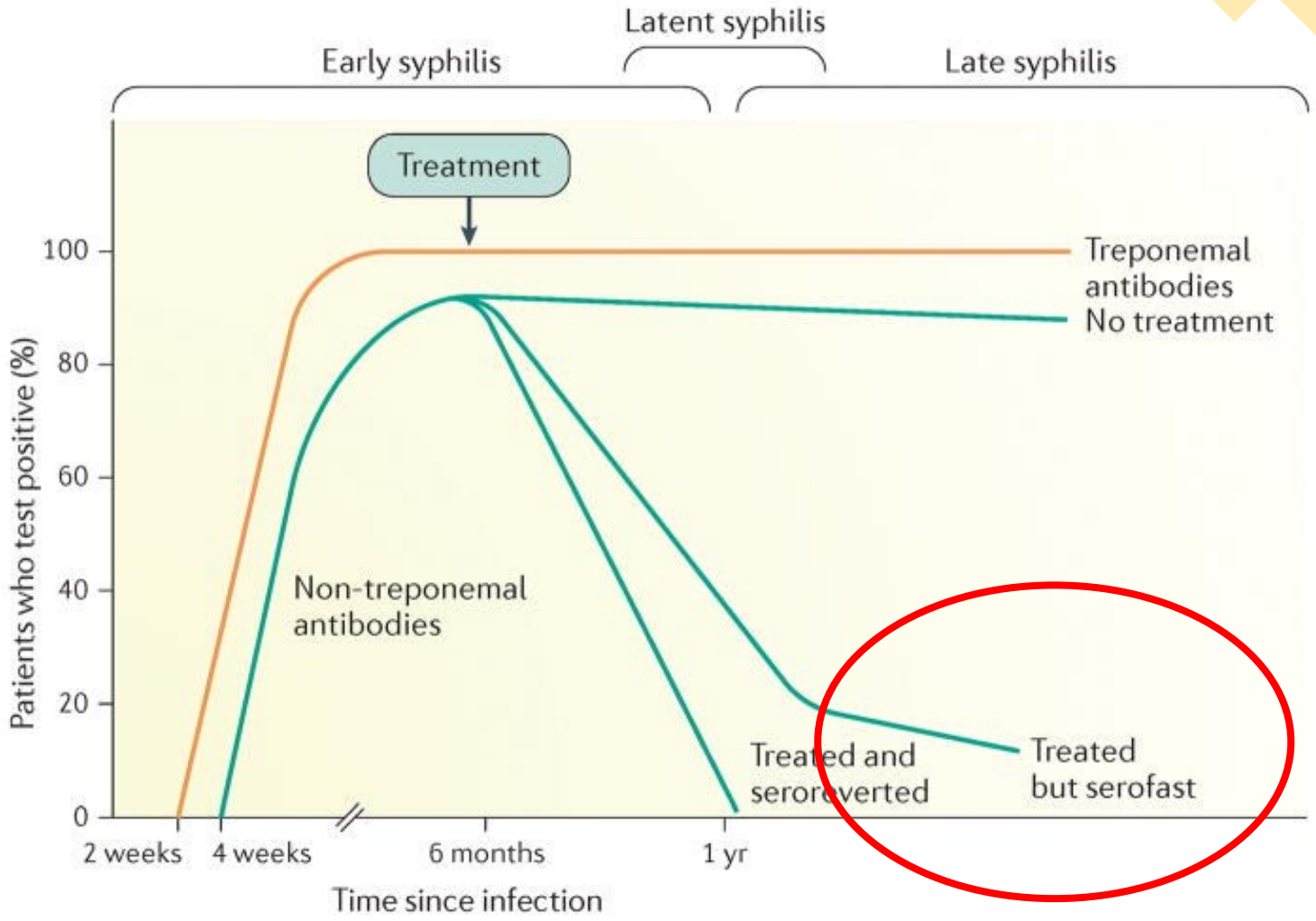
Retest in 6 mos, titer 1:8 **SUCCESS**

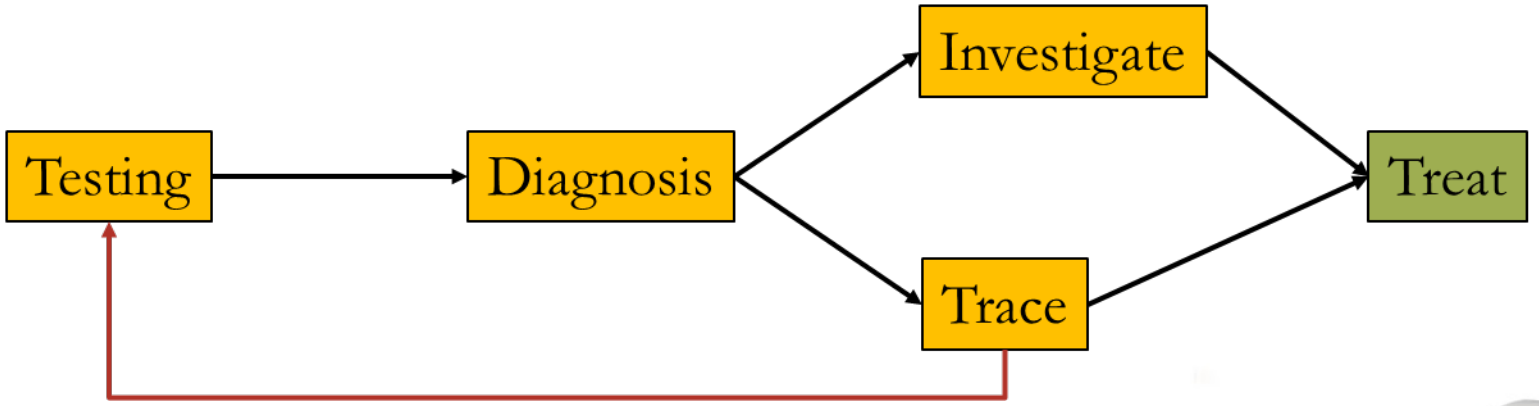
Adequate time must pass before declaring treatment failure

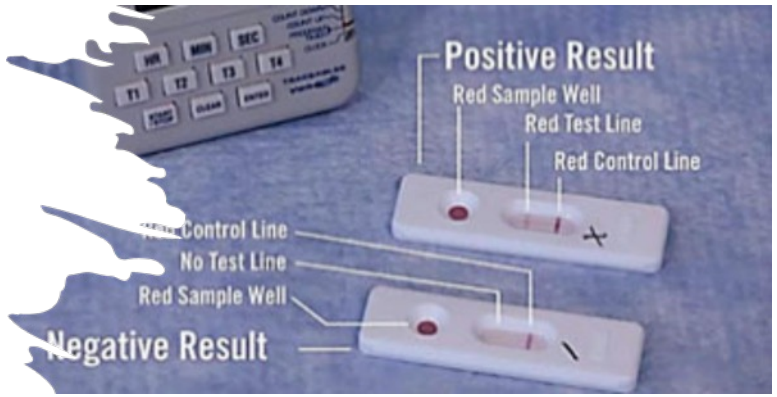
- 12 mos for Early Syphilis (primary, secondary, early latent)
- Up to 24 months for Late Syphilis

Serofast patients

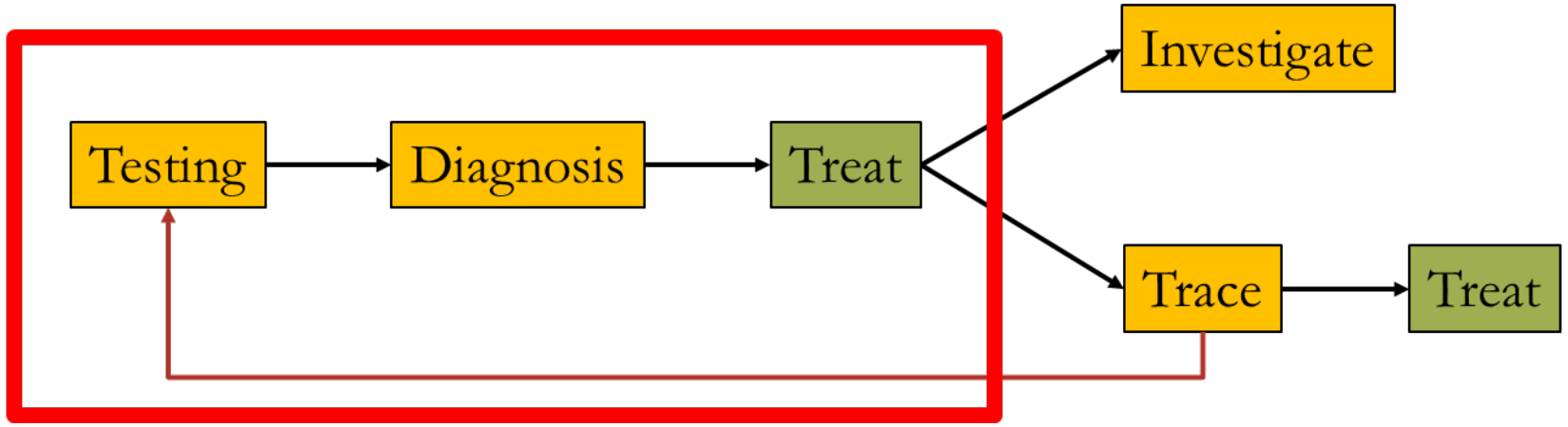
- Adequate decline in titers after treatment
- No change after 24 months
- 15-20% of early syphilis, up to 35% of late latent
- May never serovert
- Test for HIV
- Increases from baseline titer = reinfection





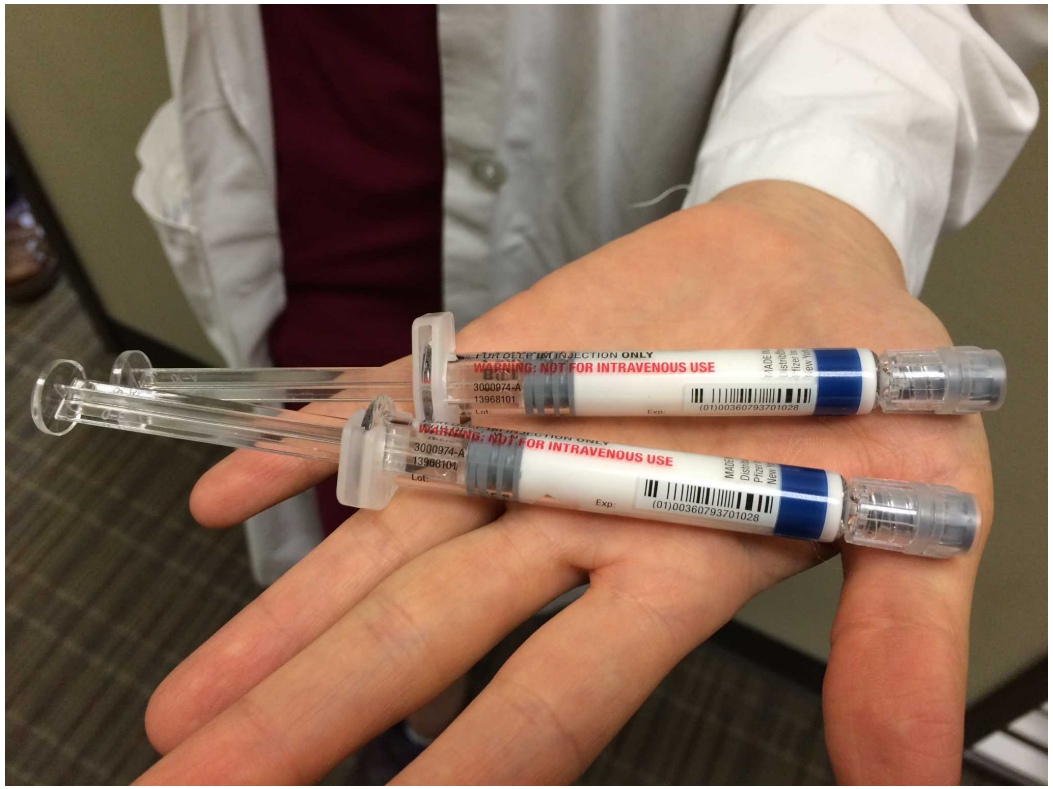


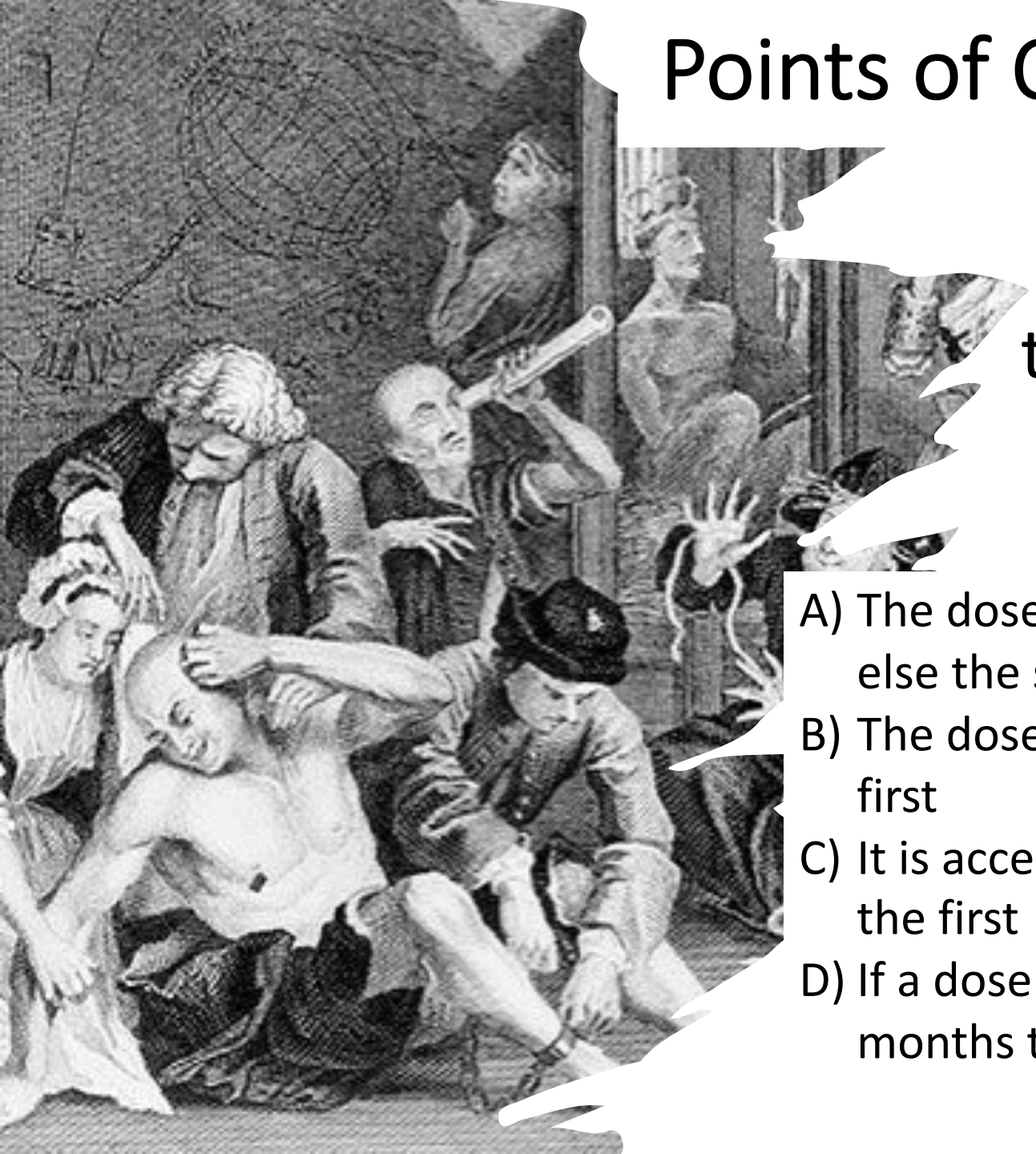
Paradigm Shift



Clinical environment and patient factors

- ER
  - Symptomatic vs seeking screening vs +/- syphilis sxs
  - Add Bicillin to your CTX/Doxy/Azithro regimen
    - **TREAT TREAT TREAT**
- Clinic
  - If ?symptoms or exposures – TREAT
  - If screening only, ensure good # or address for PHN visit
- Inpatient
  - Please screen everyone
  - There is time to review results
  - If questionable symptoms/exposures, draw serologies and TREAT
- Field
  - If any question/known contact - TREAT
  - Arrange f/u time/get info to f/u





Points of Confusion

What if the patient is late for their second or third shot in late latent cases?

A) The dose must be given within 7 days of the prior, or else the series must restart
B) The dose can be given any time within 14 days after the first
C) It is acceptable if the next dose is given within 9 days of the first
D) If a dose is >7 days late you must retest the patient at 6 months to determine if it was effective

Points of Confusion

Titers!

Problem #1

Titer not changing after treatment

Possible solutions:

1. Checked too early
2. Patient treated for wrong stage
3. Reinfection – any increase in titer after treatment
4. Patient sero-fast/sero-persister

The End

Questions?