Syphilis Testing and Treatment in Pregnancy

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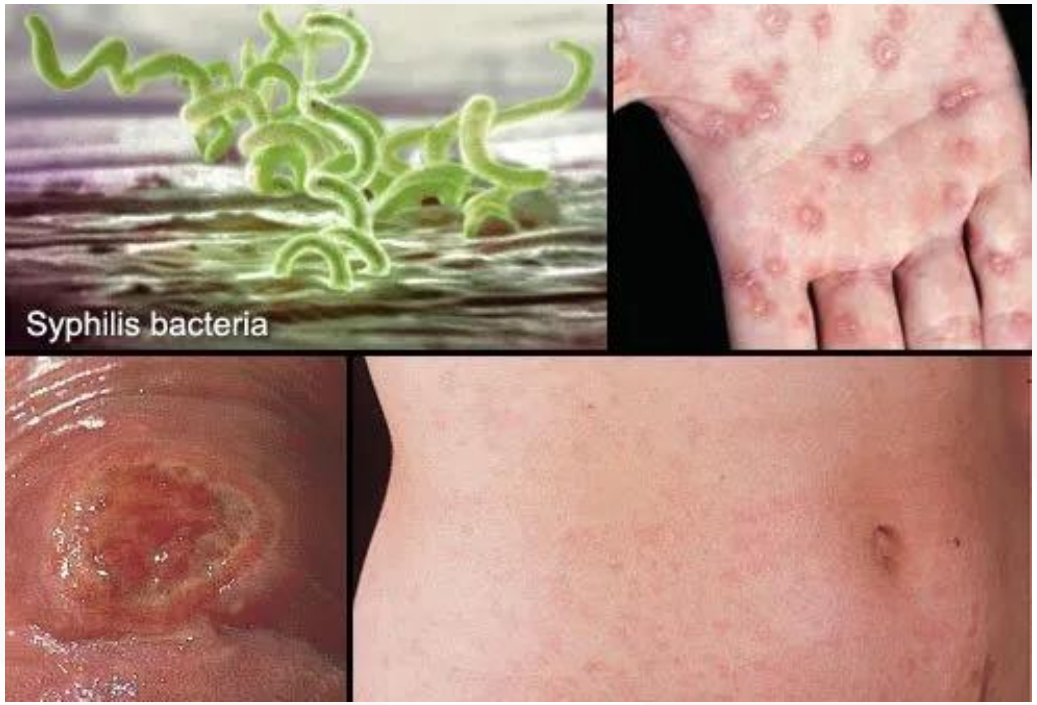


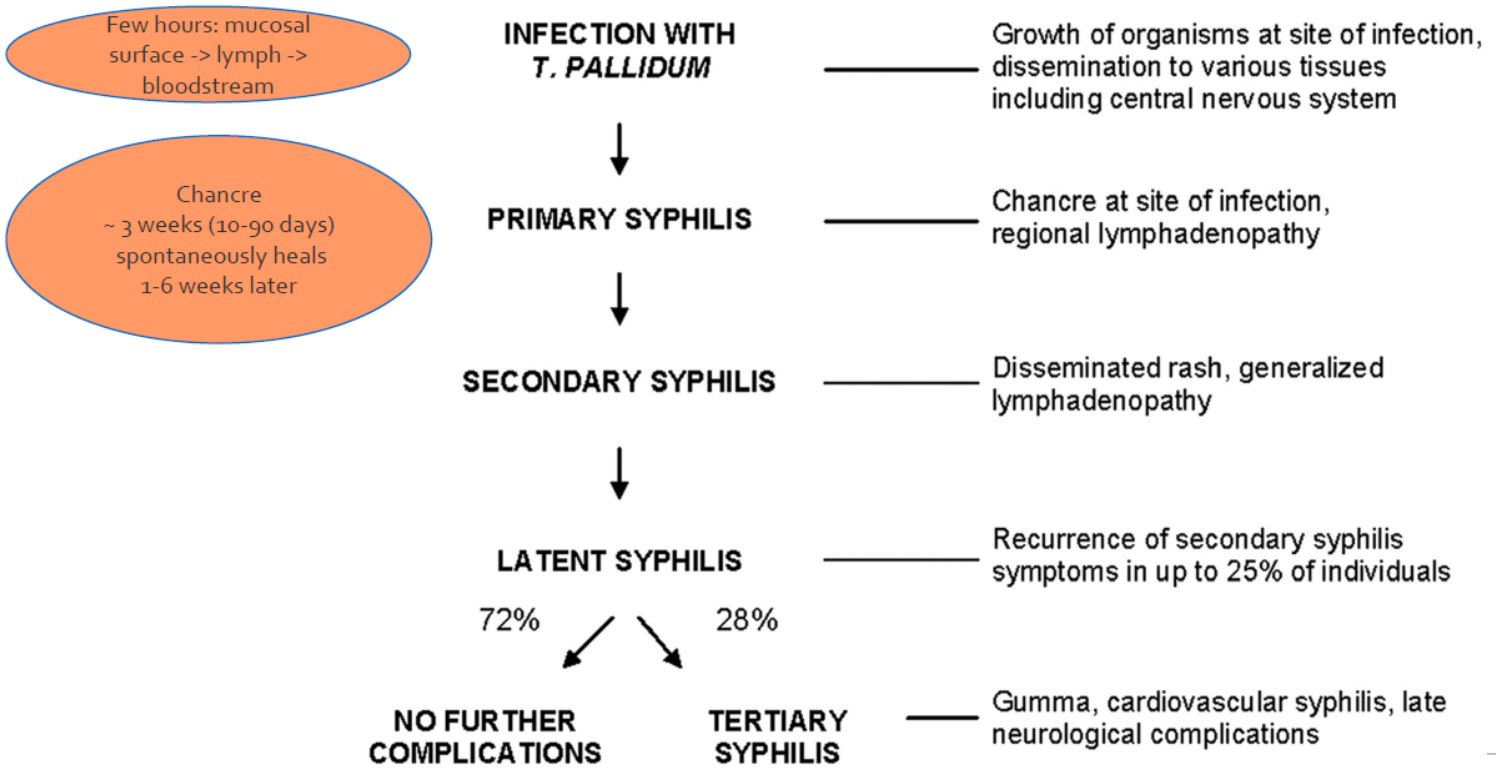
St Luke's®

Syphilis an ancient disease

- Defined by positive treponemal serology in the absence of clinical manifestations
- •Early Latent: Infected less than one year Negative syphilis serology in past year Known contact to an early case of syphilis

- •Late Latent (infected > 1 year or unknown duration)No syphilis serology in past year
- No contact to syphilis case or history of signs/symptoms in past year

Syphilis – A Brief Refresher



Gaps in diagnosis and treatment

CDC 2018

1. Lack of timely prenatal care with no timely syphilis testing (28.2%)
2. Lack of timely syphilis testing despite timely prenatal care
3. Lack of adequate maternal treatment despite a timely syphilis diagnosis (30.7%)
4. Late identification of seroconversion during pregnancy (identified <30 days before delivery)

Gaps and Timing for pregnancy

- Complex and confusing testing algorithms
- 25% - Inadequate treatment in one group
- 35% - Loss of post-treatment surveillance
  - ✓ *Language barriers*
  - ✓ *Socioeconomic – High association with Substance use*
- Best outcomes with early detection and treatment

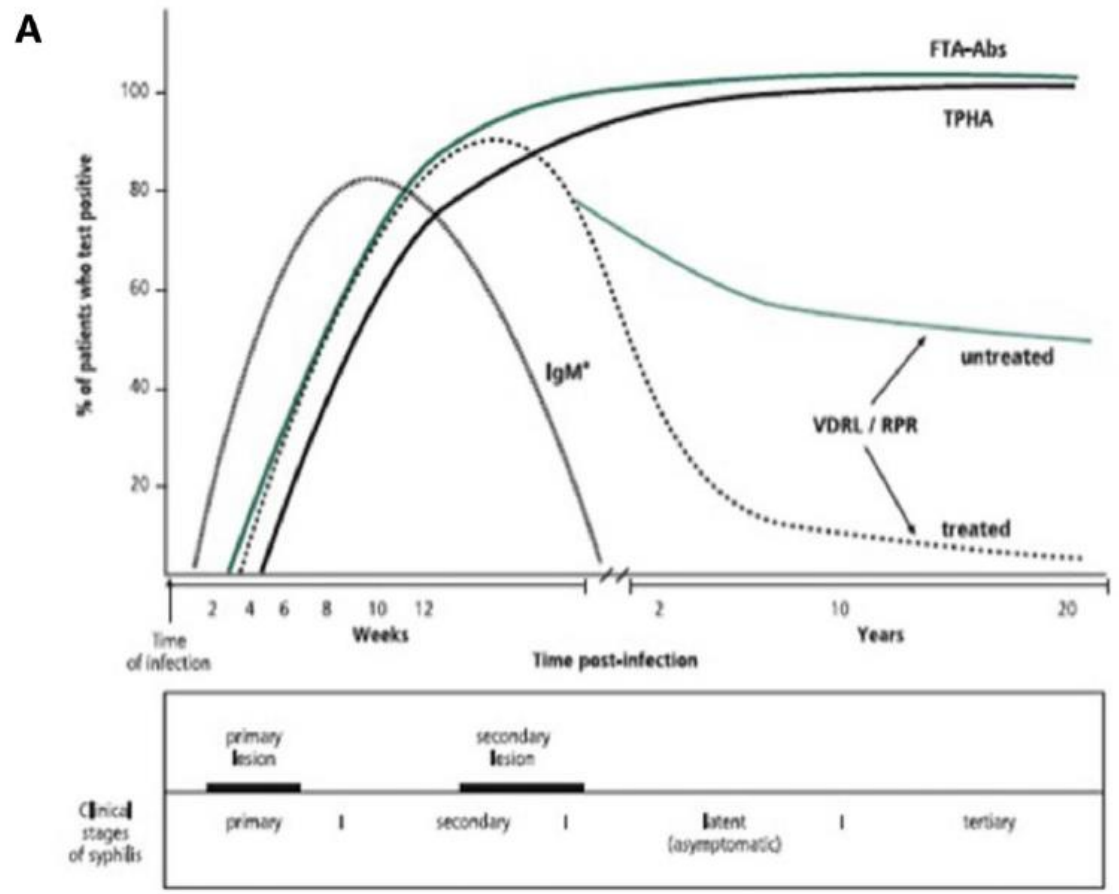
Treponemal Tests

- **Treponemal Tests**
- Serofast for life
- FTA-ABS
- TP-PA
- EIA/CIA

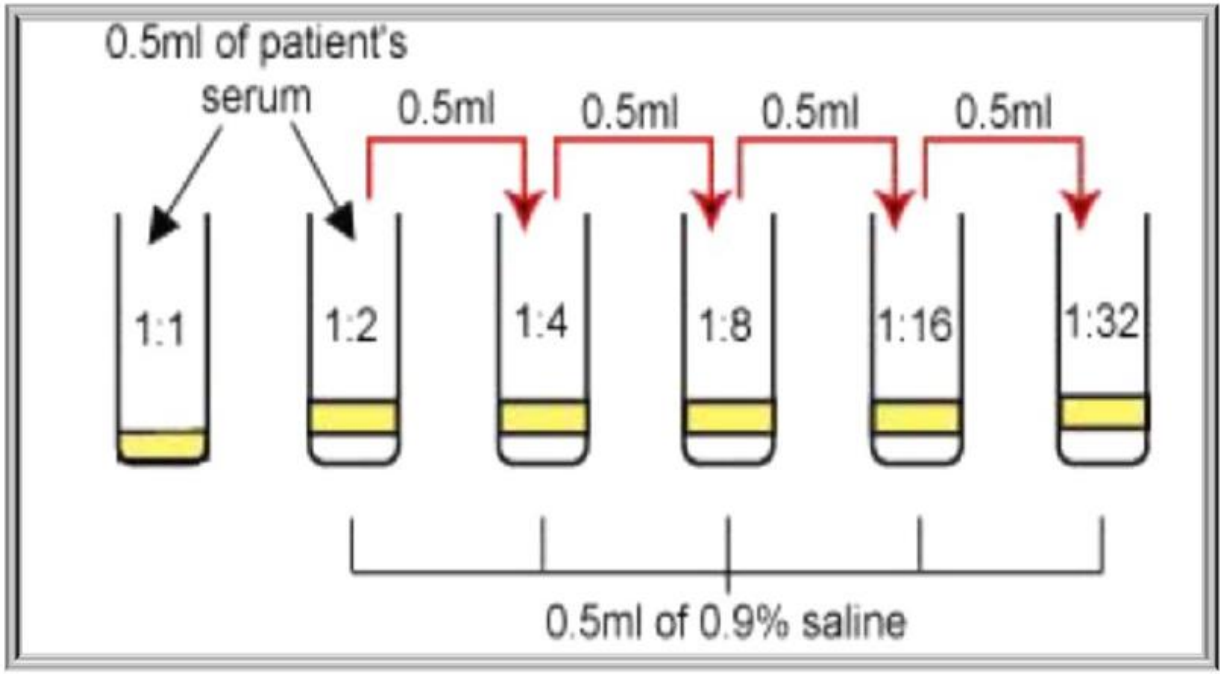
Newer Tests may be more sensitive to primary syphilis but less available

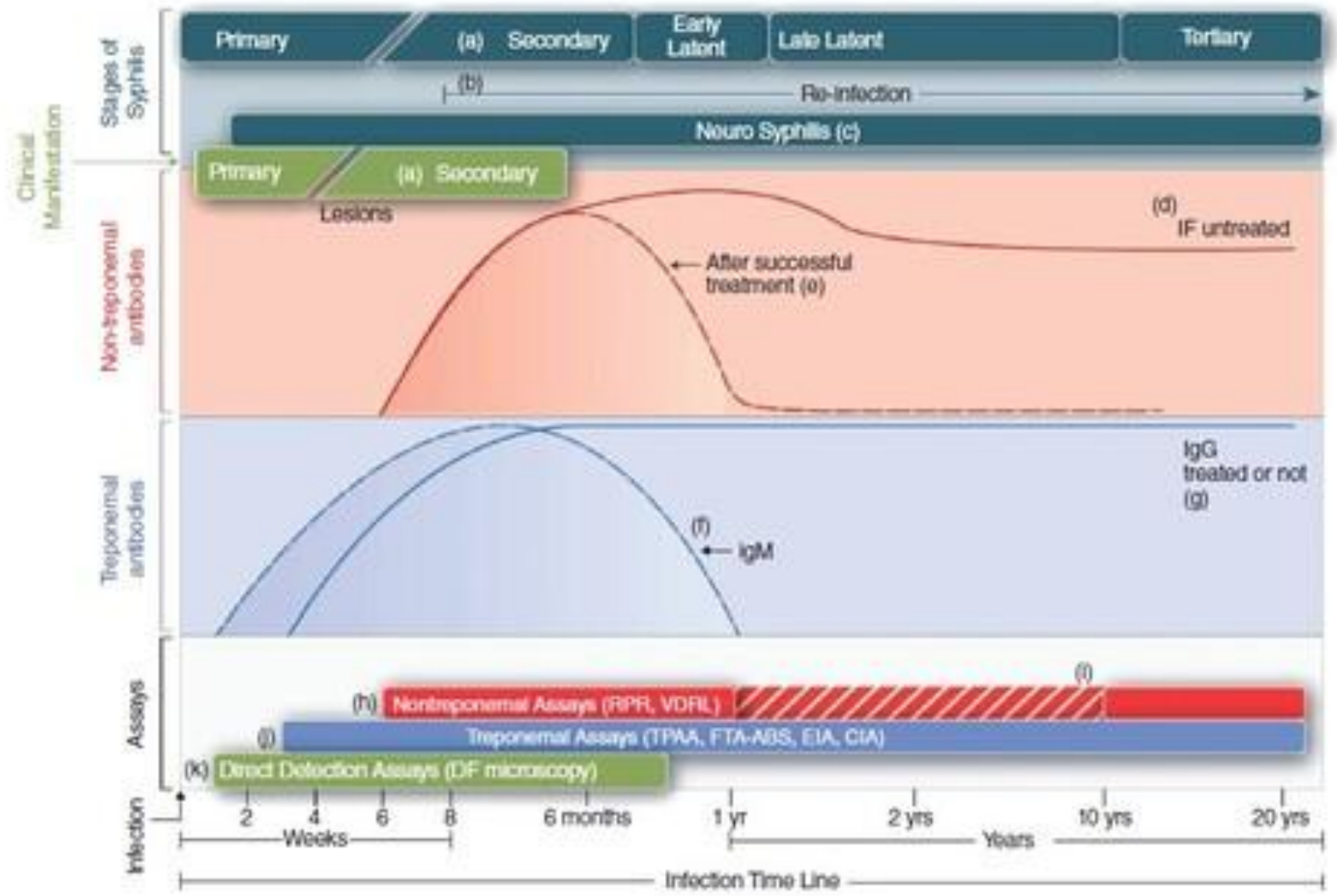
- **Non-Treponemal Tests**
- Fluctuate according to disease activity but may be sero fast (1:1)
- RPR - Rapid Plasma Reagin
- VDRL - Venereal Disease Research Laboratory
  - Non-specific products of cell wall damage
    - Lecithin/Cholesterol/Cardiolipins

Timeline of syphilis testing positivity and testing algorithms



Titers.....


0.5ml of patient's serum
0.5ml
0.5ml
0.5ml
0.5ml
1:1
1:2
1:4
1:8
1:16
1:32
0.5ml of 0.9% saline


Clinical Manifestation
Stages of Syphilis
Primary
(a) Secondary
Early Latent
Late Latent
Tertiary
(b)
Re-infection
Neuro Syphilis (c)
Primary
(a) Secondary
Lesions
Non-treponemal antibodies
(d)
IF untreated
After successful treatment (e)
Treponemal antibodies
IgG
treated or not
(g)
(f)
IgM
Assays
(h) Nontreponemal Assays (RPR, VDRL)
(i)
(j) Treponemal Assays (TPAA, FTA-ABS, EIA, CIA)
(k) Direct Detection Assays (DF microscopy)
Infection
2
4
6
8
Weeks
6 months
1 yr
2 yrs
10 yrs
20 yrs
Years
Infection Time Line

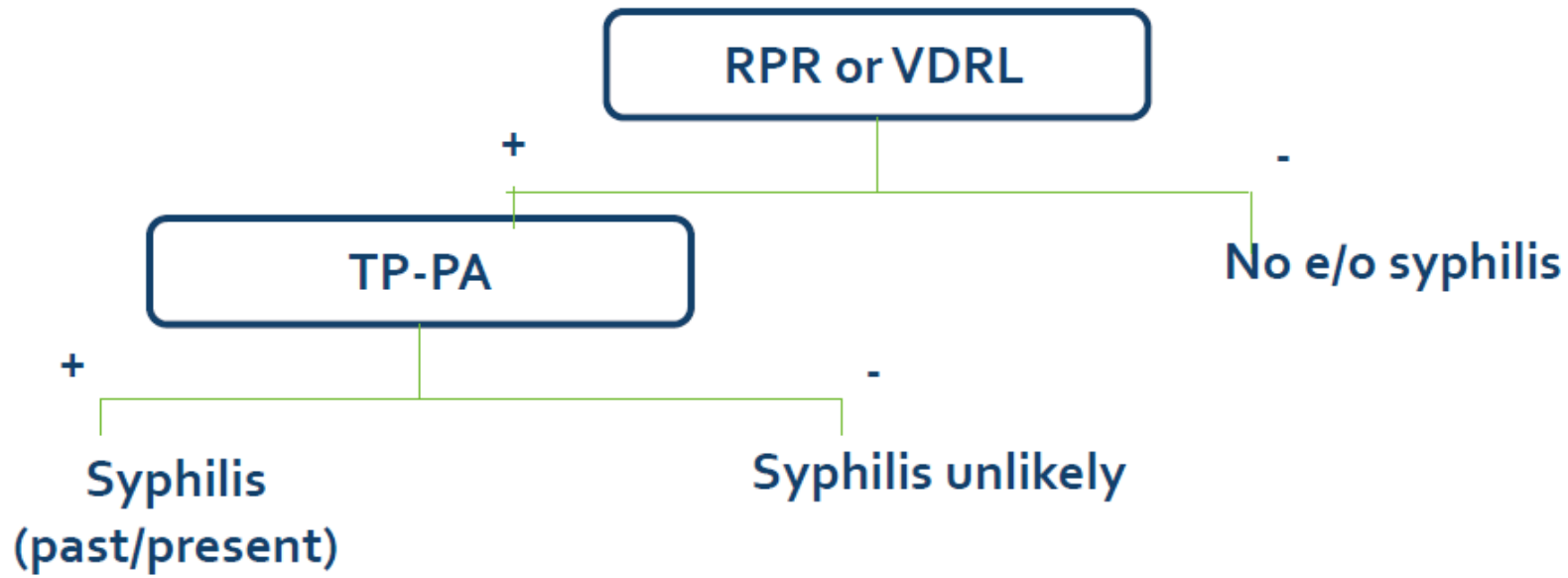
Early exposure can be tricky.

- Incubation can last from 10 to 90 days with an average incubation period of 21 days. During this period, the serologic testing for syphilis will be non-reactive but known contacts to early syphilis (that have been exposed within the past 90 days) should be preventatively treated.

Serological Testing for Syphilis

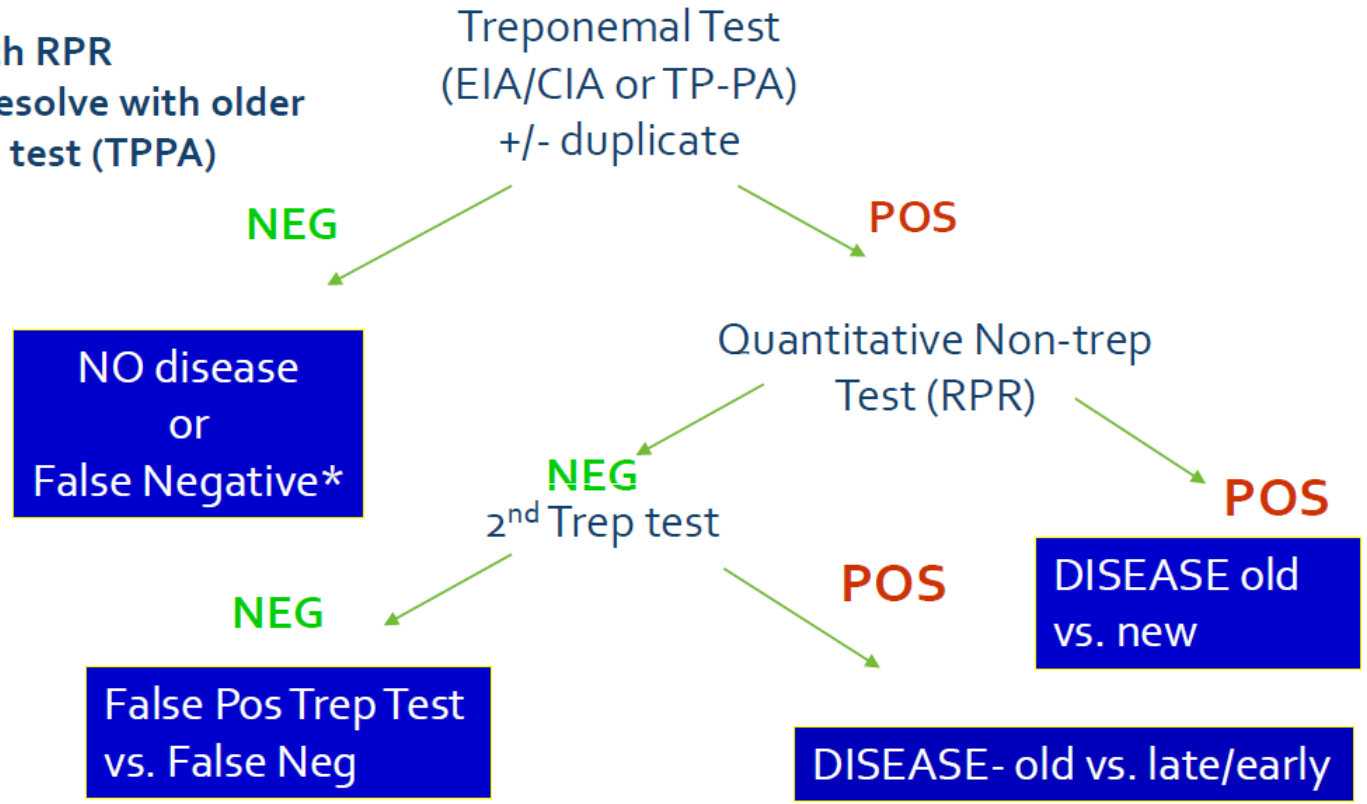
Nontreponemal	Treponemal
RPR, VDRL	MHATP, FTA-ABS, TPPA, EIA/CIA
(Quantitative, goes down with treatment)	(Good for screening but once positive, positive for life)

- Traditional: 2 serologic tests
  - Screen with nontreponemal test (RPR or VDRL)
  - Confirm with a treponemal specific test (TPPA, MHATP)



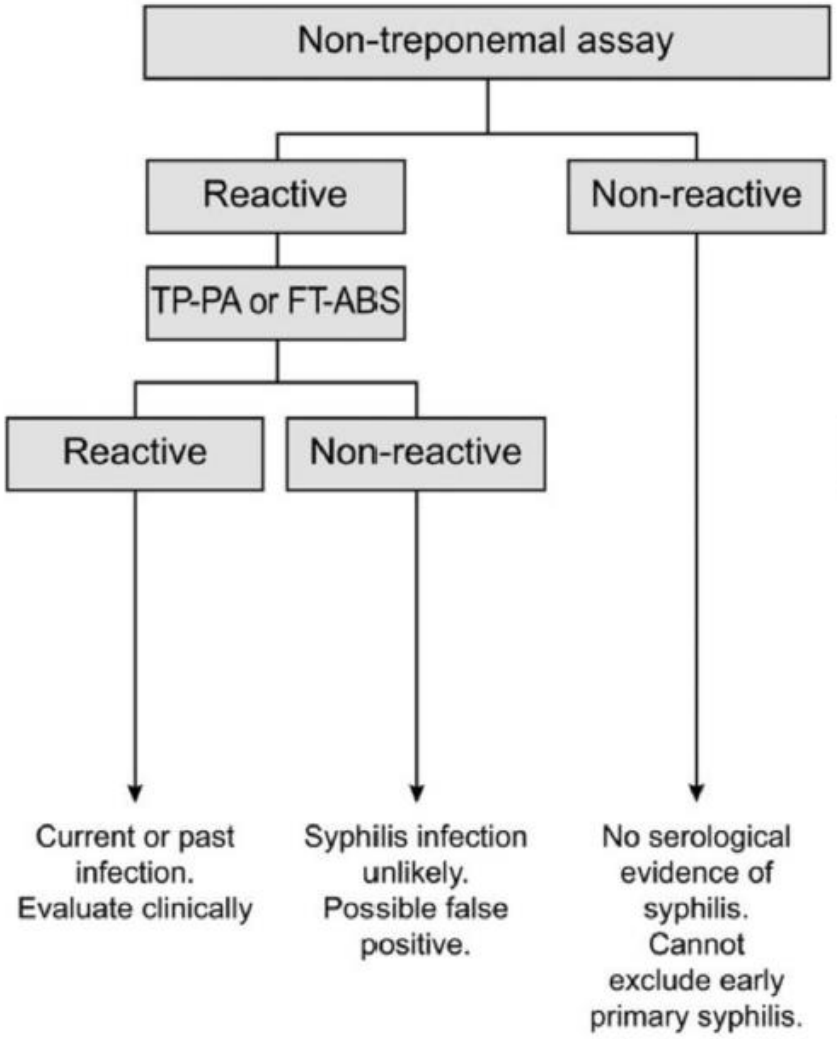
Reverse Algorithm

- **Screen with treponemal specific EIA**
- **Confirm with RPR**
- **If conflict: resolve with older treponemal test (TPPA)**

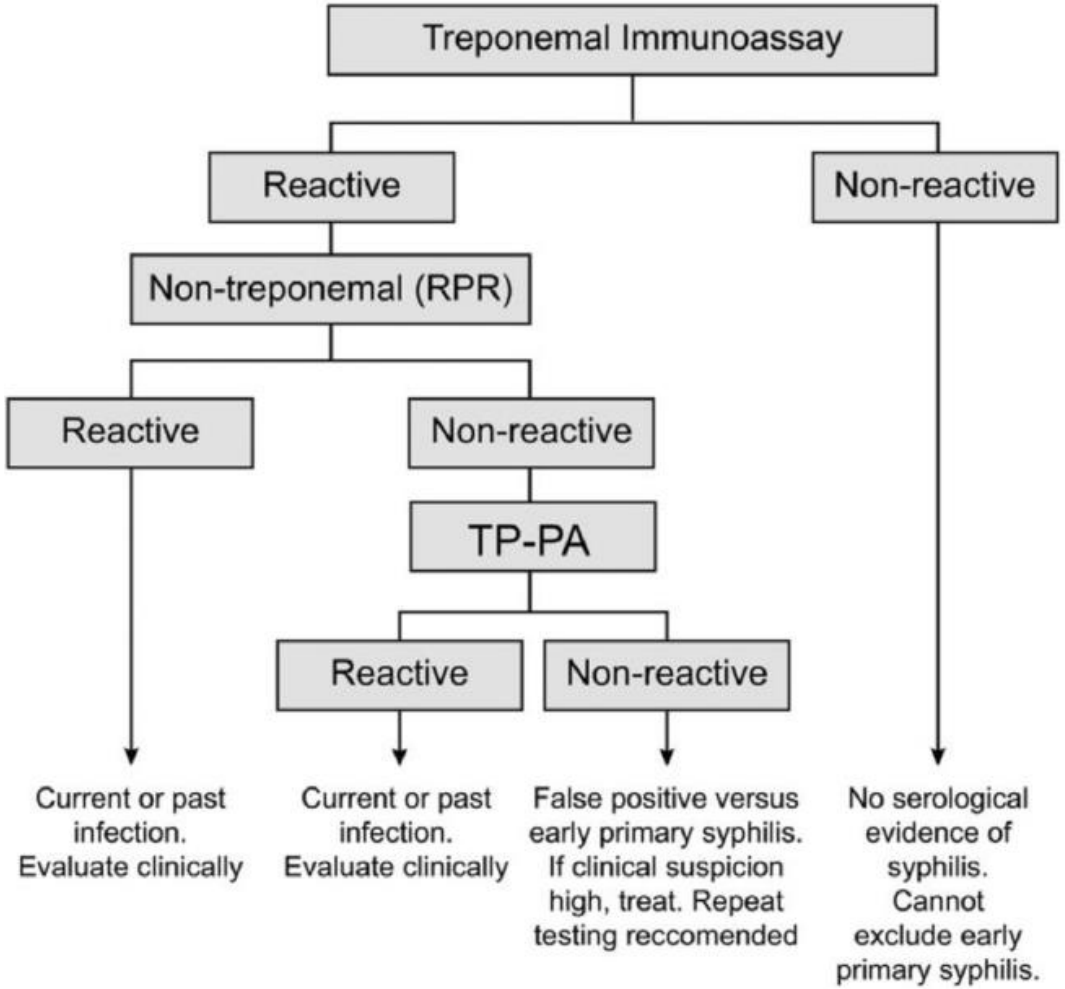


- Do not use EIA in patients with a history of syphilis and in newborns
- False negatives occur in early disease. If high clinical suspicion, repeat tests.

Traditional



Reverse



Risk of Congenital Syphilis

Vertical Transmission

- Correlates with Stage
  - ✓ *Primary Syphilis – 50%*
  - ✓ *Secondary – 40%*
  - ✓ *Latent – 10%*
- Gestational Age at treatment
  - ✓ *Third Trimester – 41%*
  - ✓ *Second Trimester – 18%*
  - ✓ *First trimester – 10%*

Untreated Outcomes

TABLE 2
Summary estimates of adverse pregnancy outcomes in untreated maternal syphilis

Qin et al (2014)[33]	Summary estimate (95% CI)
All adverse pregnancy outcomes	76.8% (68.8–83.2)
Congenital syphilis	36.0% (28.0–44.9)
Preterm birth	23.2% (18.1–29.3)
Low birthweight	23.4% (12.8–38.6)
Miscarriage	14.9% (11.4–19.4)
Stillbirth or fetal loss	26.4% (21.9–31.4)
Neonatal death	16.2% (10.1–25.1)
Gomez et al (2013)[31]	
All adverse pregnancy outcomes	66.5% (58.0–74.1)
Clinical evidence of syphilis	15.5% (7.5–29.0)
Prematurity or low birthweight	12.1% (3.9–31.8)
Stillbirth and fetal loss	25.6% (18.5–34.2)
Neonatal death	12.3% (9.3–16.2)

Adapted from Qin et al,[33] and Gomez et al.[31]

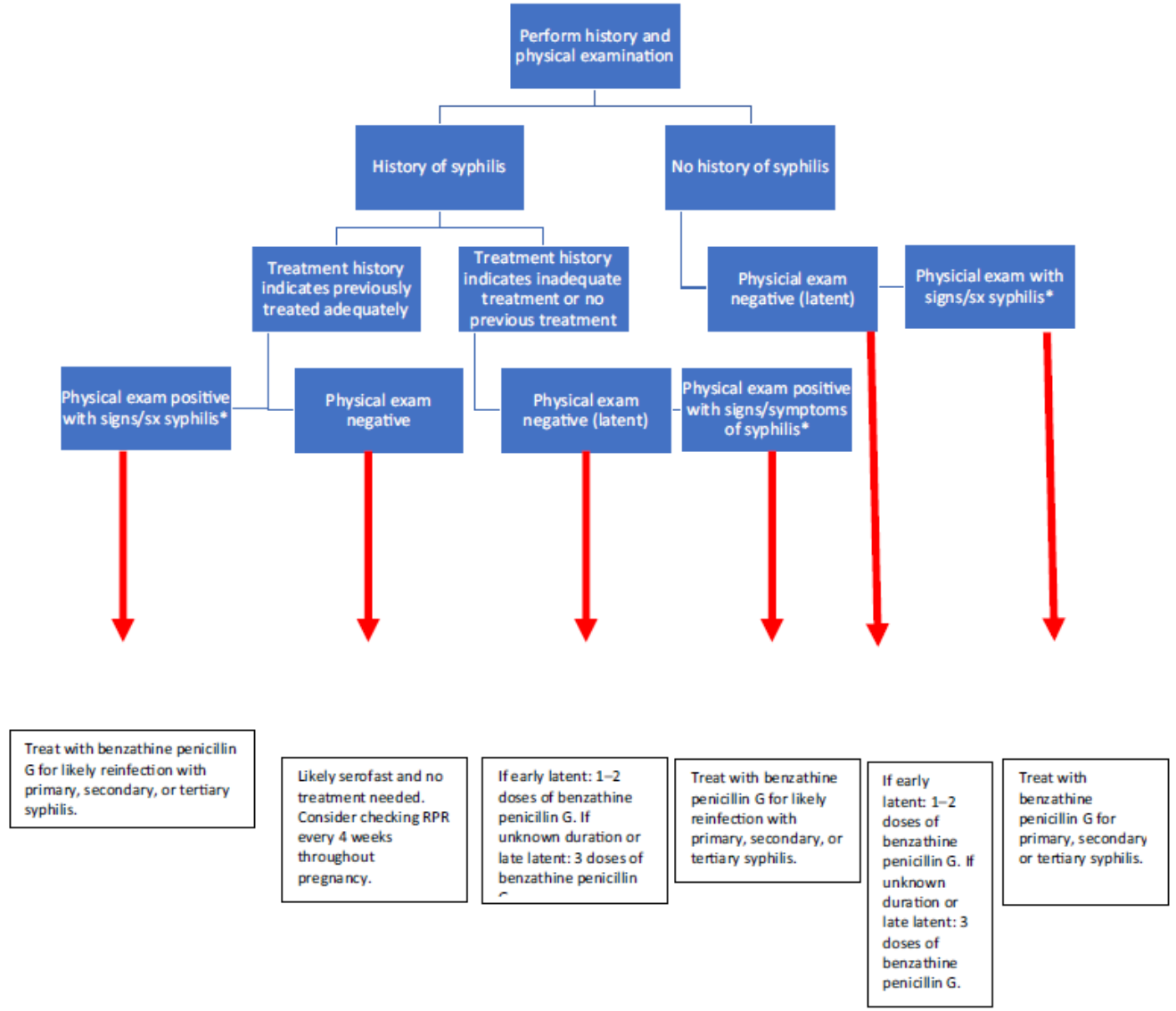
CI, confidence interval.

Eppes. Syphilis in pregnancy. Am J Obstet Gynecol 2022.

Treatment In Pregnancy

- Benzathine Penicillin G (BPG) – 98.7% Effective
- Alternative Alternatives are not acceptable in pregnancy
- (Ceftriaxone, doxycycline, tetracycline, azithromycin, erythromycin, amoxicillin)
- Cefixime may be useful in resource limited countries – studies are ongoing

FIGURE 4
Management algorithm for patients with positive treponemal and nontreponemal antibodies



The *asterisk* represents that if at any point in the evaluation, clinical evidence of neurologic infection is observed, a cerebrospinal fluid examination to rule out neurosyphilis should be considered.

RPR, rapid plasma reagin.

Eppes. Syphilis in pregnancy. Am J Obstet Gynecol 2022.

TABLE 3

Treatment of syphilis during pregnancy[7]

Stage of syphilis	Treatment
Primary syphilis	BPG 2.4 million units IM once
Secondary syphilis	
Early latent syphilis	Expert opinion recommends a second dose of BPG of 2.4 million units IM, 1 week after the initial dose (total of 4.8 million units)
Late latent syphilis	BPG of 7.2 million units total, given as 3 doses of 2.4 million units IM, each at 1-week intervals[a]
Syphilis of unknown duration	
Reinfection	

Adapted from Workkowski et al.[38]

BPG, benzathine penicillin G; *IM*, intramuscularly.

[a] An interval of >9 days between doses is unacceptable during pregnancy, and if present the treatment regimen should be restarted.

Eppes. Syphilis in pregnancy. Am J Obstet Gynecol 2022.

Treatment

- Each dose must be administered on a weekly basis or the entire treatment course must be restarted
  - ✓ *(Maximum interval 9 days)*
- Single Dose – Only 36% of patients retain treponemocidal levels in one week.
- Second dose – Treponemocidal level present at 100 days
- Spriochetemia is highest during early stages so a second or third dose is very reasonable.

Treatment Follow up

- Non Treponemal Titers should decrease Four-Fold
- For example - RPR 1:64 → 1:16
- Pretreatment titers <1:8 may not achieve timely fall.
- CDC suggests rate of fall:
- Early syphilis 6-12 months
- Late syphilis or Unknown Duration up to 24 Months
- HIV positive: Up to 24 months regardless of stage

Treatment Follow up

Beyond the CDC Recommendations in Pregnancy

- Check Titers every 4 weeks:

  - ✓ *Detect inappropriate decline, plateau, rising*
  - ✓ *Maybe a treatment failure that needs retreatment*
  - ✓ *Prior infection may blunt presentation and course of reinfection*

Jarisch-Herxheimer Reaction

- Release of endotoxins, lipopolysaccharides, prostaglandins, cytokines etc. leading to inflammatory response, ie sepsis and should be treated supportively
- Response is more likely to occur in early infections
- Occurs in 2-8 hours and abate by 24 hours
- Consider EFM/Hospitalization for first treatment

Newborn Plan

Determined by a complicated amalgam of factors:

1. Change in newborn NTTs relative to maternal titers
2. Maternal treatment status (adequately treated, sub-optimally treated, untreated)
3. Duration of maternal treatment (< or > 28 days before birth)
4. Newborn signs and symptoms
5. Placental pathologic evaluation

Newborn Treatment

Congenital Syphilis

- Non-Treponemal Titers for both mother and baby
- CDC guidelines require follow-up of the exposed newborn every 2-3 months for 18 months
- 40% of neonates with undetected CS develop stigmata
- St. Luke’s Children’s Hospital Pediatric Infectious Disease are an invaluable resource.

Summary

- Diagnosis and Treatment algorithms are complex
- Please reach out to MFM or Infectious Disease
- Pediatric Infectious Disease for neonatal planning !