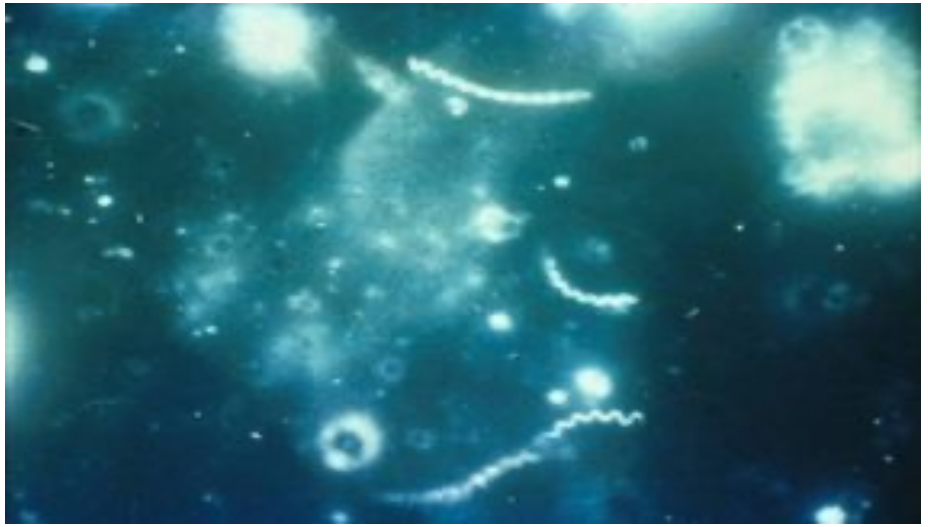
Congenital Syphilis: Diagnosis and Management

Hafsah Tootla
Clinical Microbiologist
National Health Laboratory Service
Red Cross War Memorial Children's Hospital

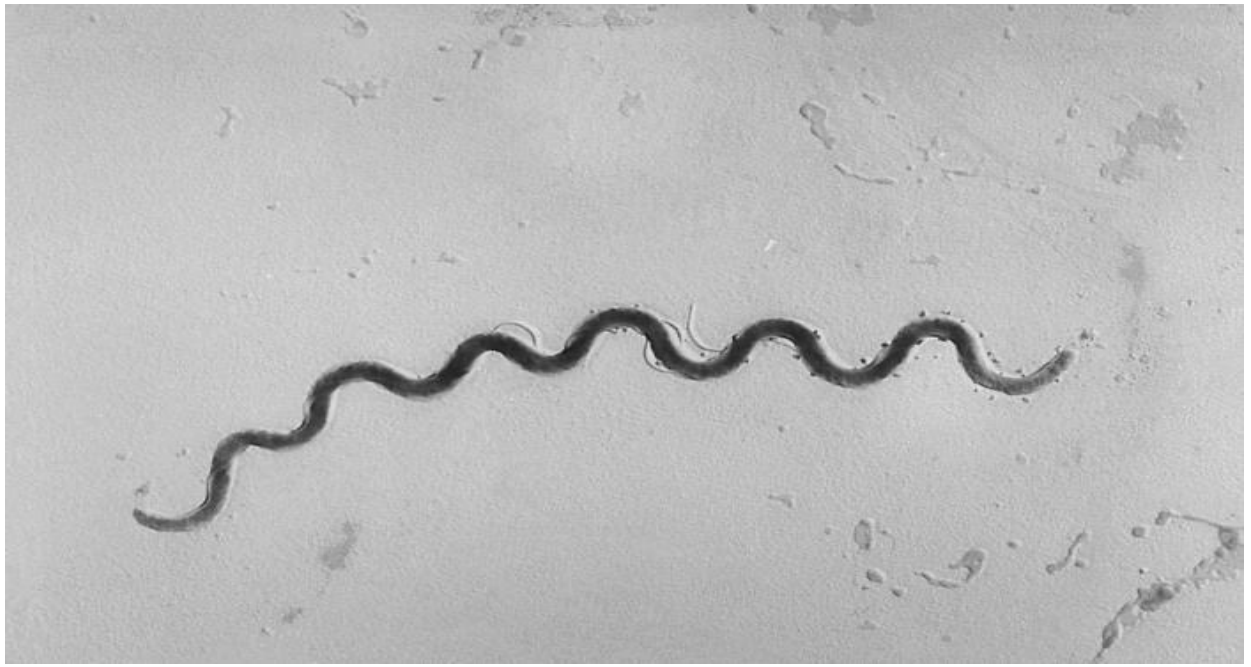
NATIONAL HEALTH
LABORATORY SERVICE

Microbiology and Transmission

- Spirochete - *Treponema pallidum* subspecies *pallidum* - ‘great imitator’ or ‘imposter’
- Stealth pathogen – outer membrane lacks protein and lipopolysaccharides – capacity for immune evasion allowing replication and dissemination.



https://www.cdc.gov/std/syphilis/images.htm



https://phil.cdc.gov/Details.aspx?pid=14969

doi:10.1371/journal.pone.0143304
WHO GUIDELINE ON SYPHILIS SCREENING AND TREATMENT FOR PREGNANT WOMEN: 2017
doi:10.1007/s40471-018-0138-z
doi.org/10.1371/journal.pone.0205863.t001

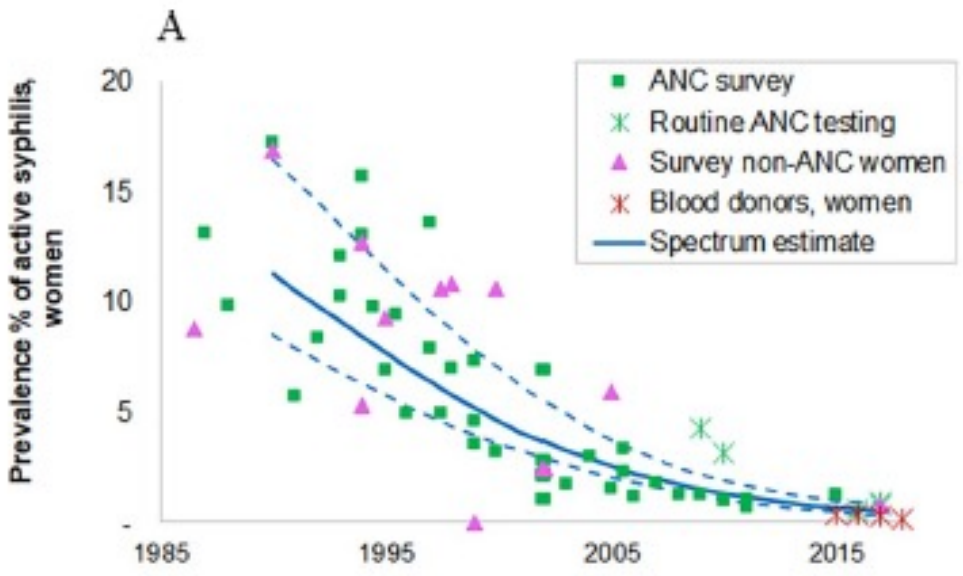
Burden of disease

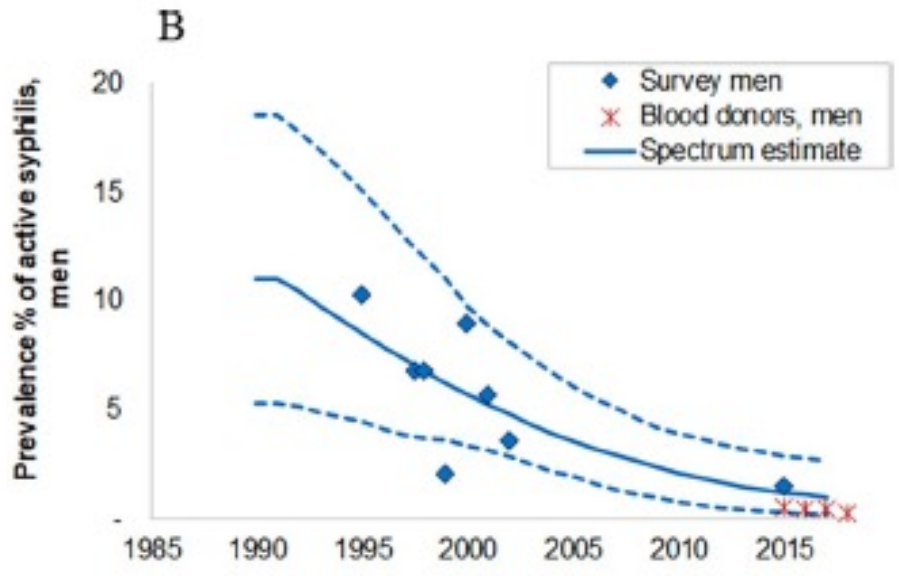
- 6 million new adult cases of syphilis annually (2012)
- Highest prevalence in Africa
- 930 000 maternal infections resulting in 350 000 adverse outcomes
  - Still births
  - Neonatal deaths
  - Preterm births
  - Infected infants
- 3.5-6.5% prevalence in pregnant women in Africa (2018)
- In SA (2017)

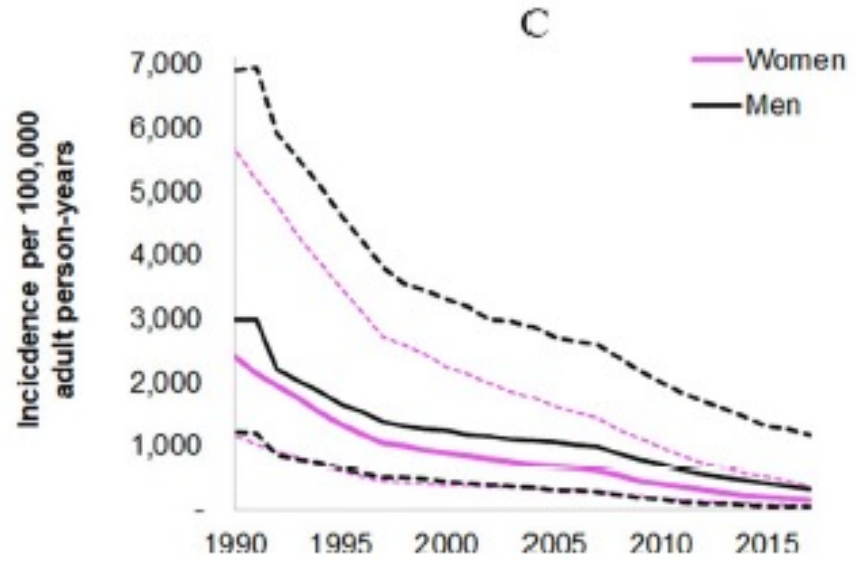
Table 1. Spectrum-estimated STI prevalence, incidence rates and incident case numbers, in South African women and men 15–49 years in 2017.

STI	Metric	Women		Men	
		Point estimate	95% CI	Point estimate	95% CI
Active syphilis	Prevalence	0.50%	0.32% to 0.80%	0.97%	0.19% to 2.38%
	Incidence rate per 100 000 adult person-years	153	65 to 414	316	34 to 1,162
	New incident cases	23,175	9,900 to 62,500	47,500	5,100 to 173,000

Prevalence of syphilis in South Africa







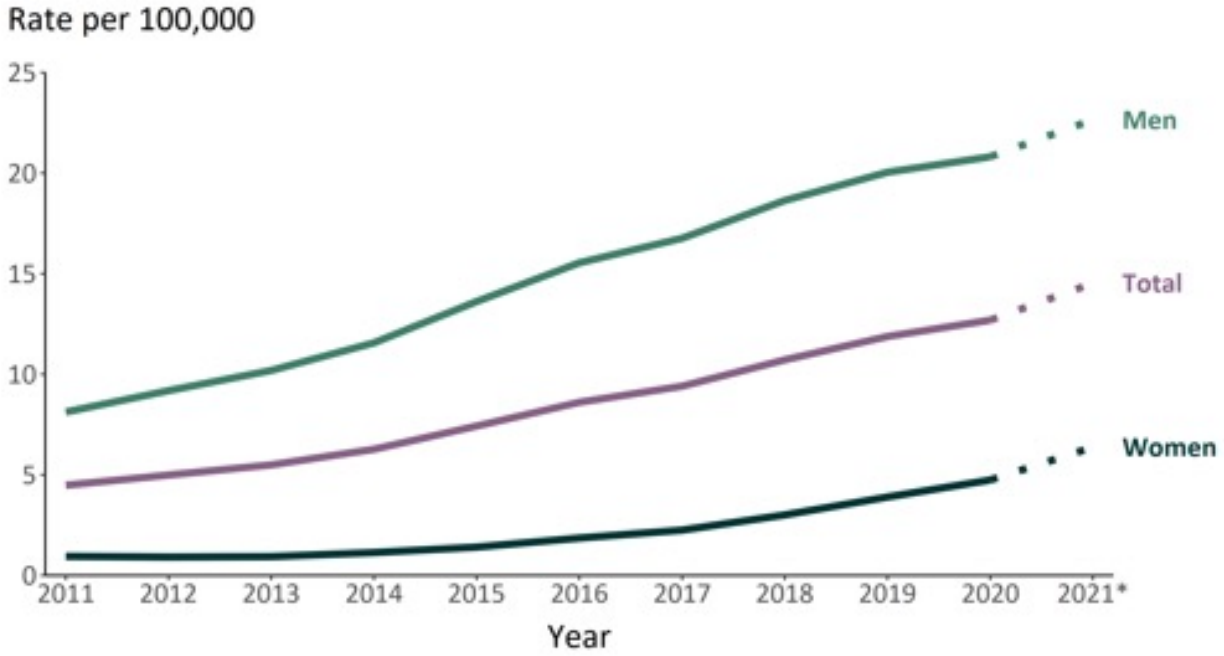
Syndromic management of STIs
Availability of diagnostic tests – lab based and point-of-care test
Screening – ANC and high risk populations

https://doi.org/10.1371/journal.pone.0205863.t001

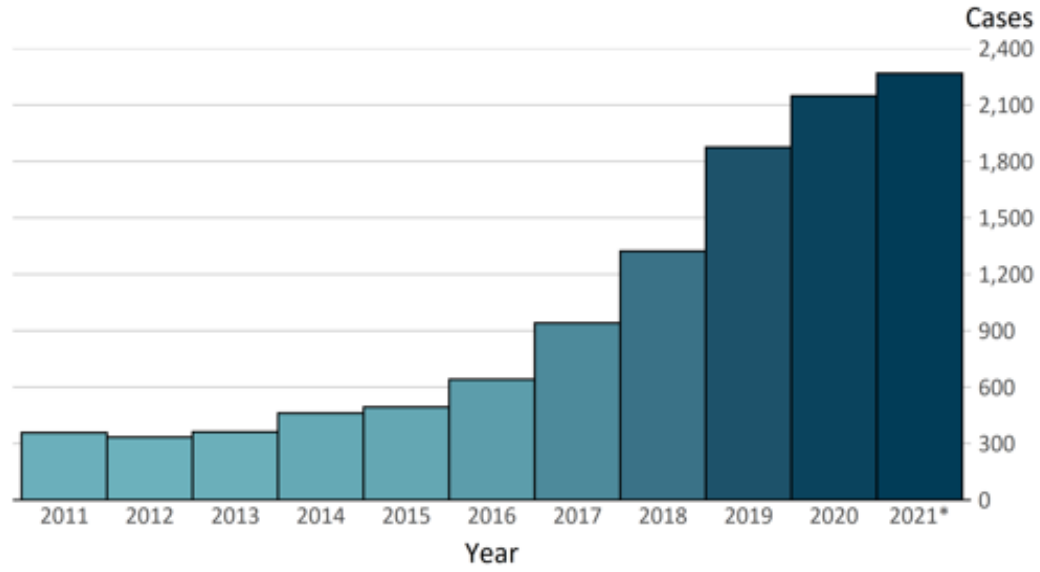
Increasing numbers of CS cases in SA

CONGENITAL SYPHILIS QUARTERLY SURVEILLANCE REPORT DECEMBER 2020 (NICD)

Increasing trends in incidence and number of cases in the US



* Reported 2021 primary and secondary syphilis data are preliminary as of March 9, 2022.



* Reported 2021 congenital syphilis data are preliminary as of March 9, 2022.

Congenital Syphilis — Reported Cases by Year of Birth, United States, 2011–2021*

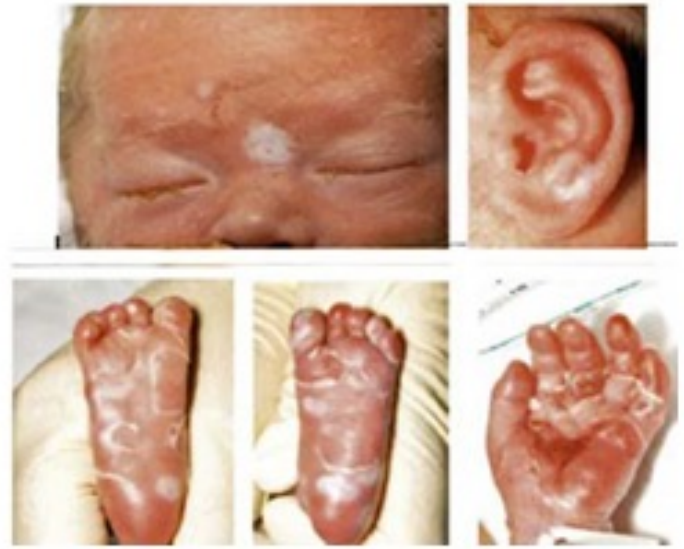
https://www.cdc.gov/std/syphilis/stats.htm

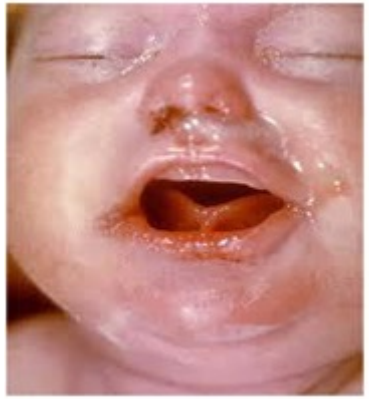
Why is it important

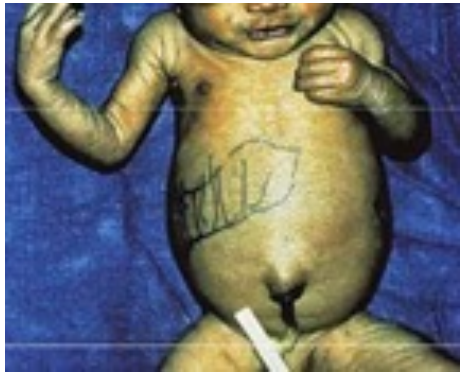
- Congenital syphilis is preventable
- Easily treatable – to prevent serious morbidity and mortality in the infant
- Transmissions most commonly occurs transplacentally, but can also occur during delivery if the neonate comes into contact with infectious lesions
- Untreated syphilis in the mom results in CS
  - In primary syphilis 60%
  - In secondary syphilis 90%
  - In early latent syphilis 40%
  - In late latent syphilis 10%
- Disease severity also depends on classification of disease in the mother, RPR titre, GA when transmission occurred (increased risk in older GA)

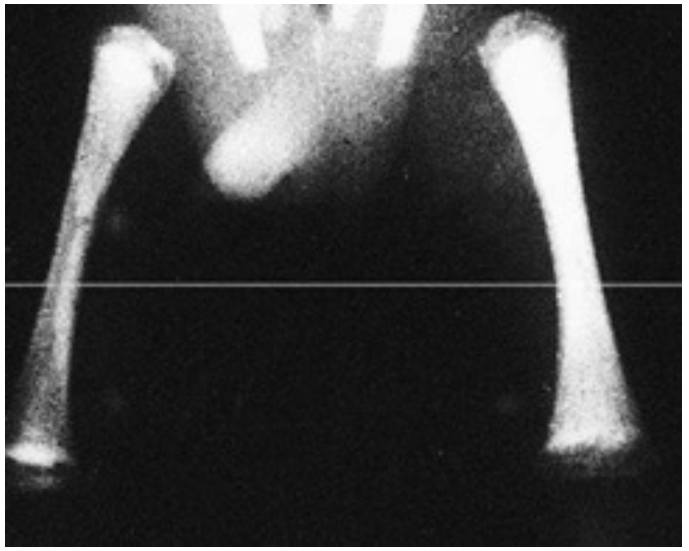
Clinical features in the infant

- Severe infection – still birth/neonatal death/ clinical features on US or birth
- Most are ASYMPTOMATIC at birth with symptoms developing in the first 4-8 weeks of life
    - desquamating rash
    - lymphadenopathy
    - hepatosplenomegaly
    - nasal discharge ‘snuffles’/rhinitis
    - Jaundice
    - Central nervous system involvement: elevated cell count or elevated protein in cerebrospinal fluid
    - Pneumonitis
    - Intrauterine growth retardation
    - Periosteitis/epiphysitis
    - Anaemia
    - Non-immune hydrops









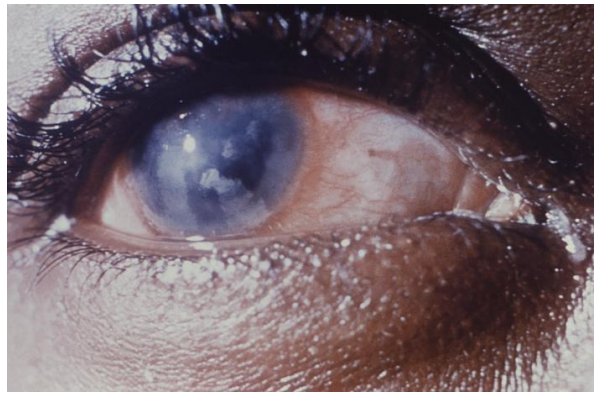
Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases. 9th ed. 2020.

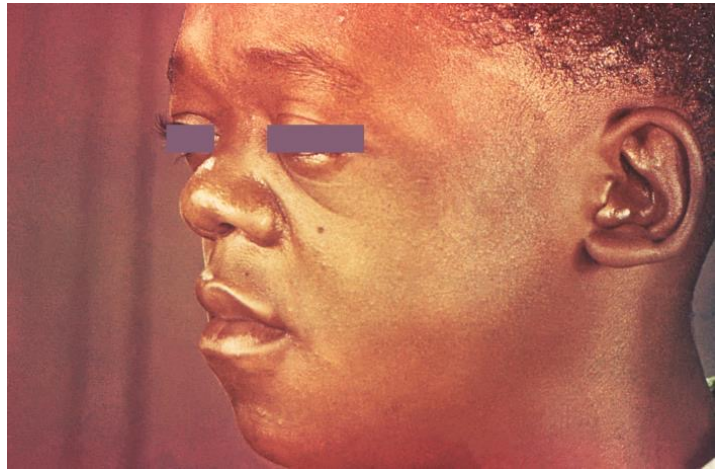
https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-5/chapter5-2.html

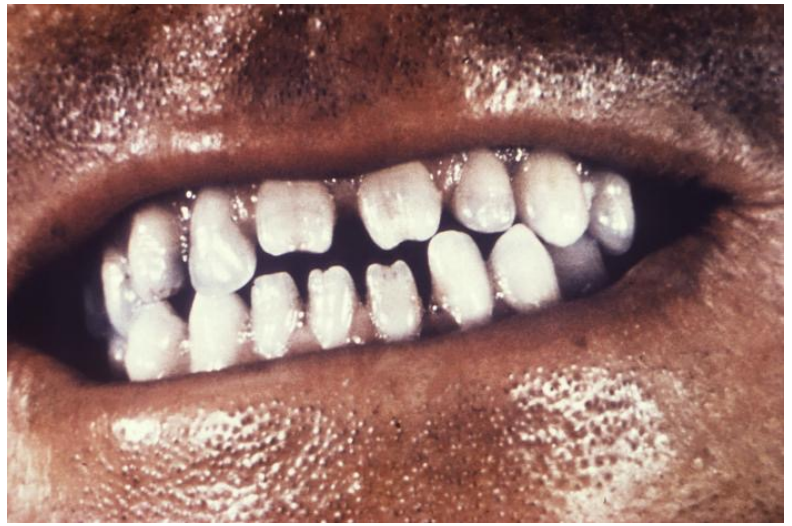
Late congenital syphilis

Late Congenital Syphilis

Frontal bosses
Short maxillas
Saddle nose
Protruding mandible
Interstitial keratitis
Eighth nerve deafness
High palatal arch
Hutchinson incisors
Mulberry molars
Sternoclavicular thickening (Higoumenaki sign)
Clutton joints (bilateral painless swelling of knees)
Saber shins
Flaring scapulas







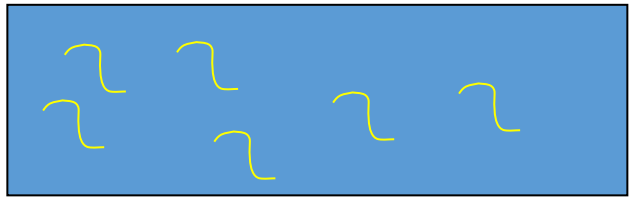
https://phil.cdc.gov/Details.aspx?pid=17626
https://phil.cdc.gov/Details.aspx?pid=12600
https://phil.cdc.gov/Details.aspx?pid=12599
https://phil.cdc.gov/Details.aspx?pid=3823

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. 2020.

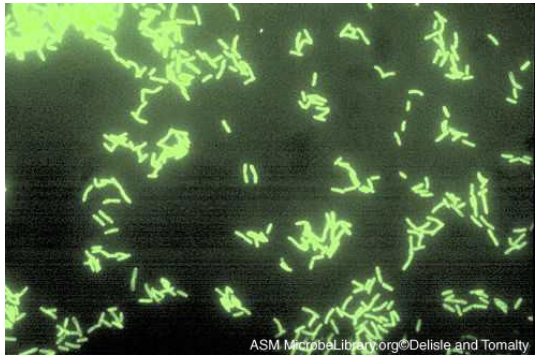
Laboratory Diagnosis

- Routine diagnostics like microscopy and culture is not helpful
  - Spirochetes are too small and thin to be visualised using routine light microscopy – need specialised dark-field microscopy or fluorescent microscopy
  - Unable to culture it on artificial media – the rabbit infectivity test is the gold standard method for diagnosis
- Molecular tests like PCR – research settings
- Serology is the main method used to test for syphilis
  - Diagnosis by made by detecting antibodies (treponemal and non-treponemal)
- Histology
  - Placenta – macroscopic (large, pale) and microscopic findings (villitis, small gummas). Visualisation of spirochetes using silver and immunohistochemistry staining techniques

Treponemal serology (specific tests)



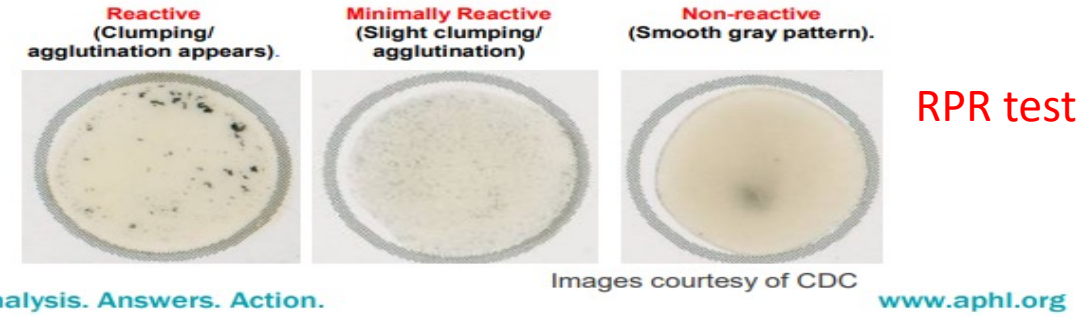
FTA: slide coated with treponema organisms



- Specific to *Treponema pallidum*
- **Remains positive for life in most cases – cannot differentiate current disease from past disease**
- Examples:
  - FTA-abs – fluorescent Treponemal antibody test-absorbed
  - TPHA – *Treponema pallidum* haemagglutination test
  - Newer ELISA based *T. pallidum* tests (TPAB)
- IgM antibodies against T. pallidum appear first, followed by IgG antibodies
  - 6 – 14 days after infection
  - IgM declines. IgG is usually positive life-long, even with treatment

Figure: Courtesy of Dr Elizabeth Prentice

Non-treponemal serology



RPR test

- Non-specific tests: Antibodies to non-treponemal antigens
- IgM and IgG are produced against material released from dying host cells (cardiolipin, phospholipids)
  - Start to become positive 10-15 days after infection but the window period for detection is typically 6 weeks
  - Without treatment, titres peak at 1-2 years after infection and decrease slightly and remain positive even in late disease
  - After treatment titres decline fourfold but this can take long (usually 6 months)
- Examples: VDRL – venereal diseases research laboratory, RPR – rapid plasma reagin
- Biological false-positive reactions
  - Febrile illness, pregnancy, connective tissue disorders
  - Auto-immune conditions, hepatitis C
  - Important to monitor titres to differentiate from syphilis
  - Usually low titres (<1:8)
- Advantage of non-treponemal tests = measure disease activity (titres) and can use trends to monitor response to treatment

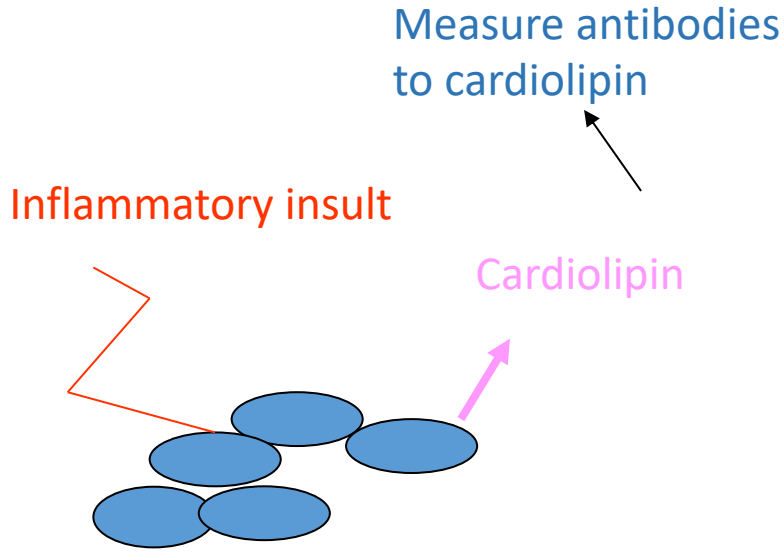
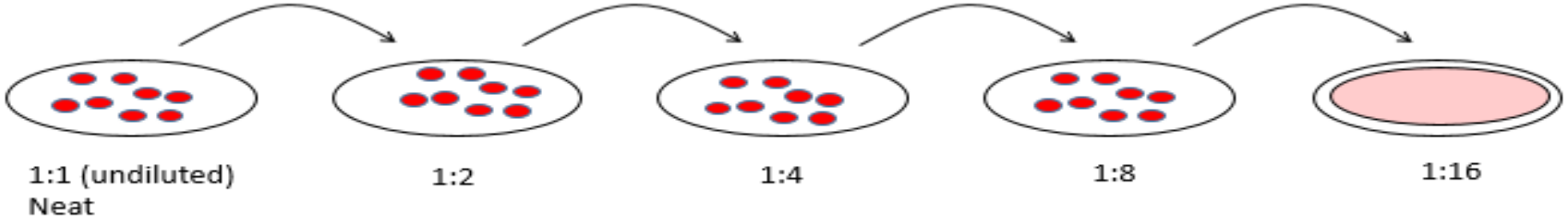
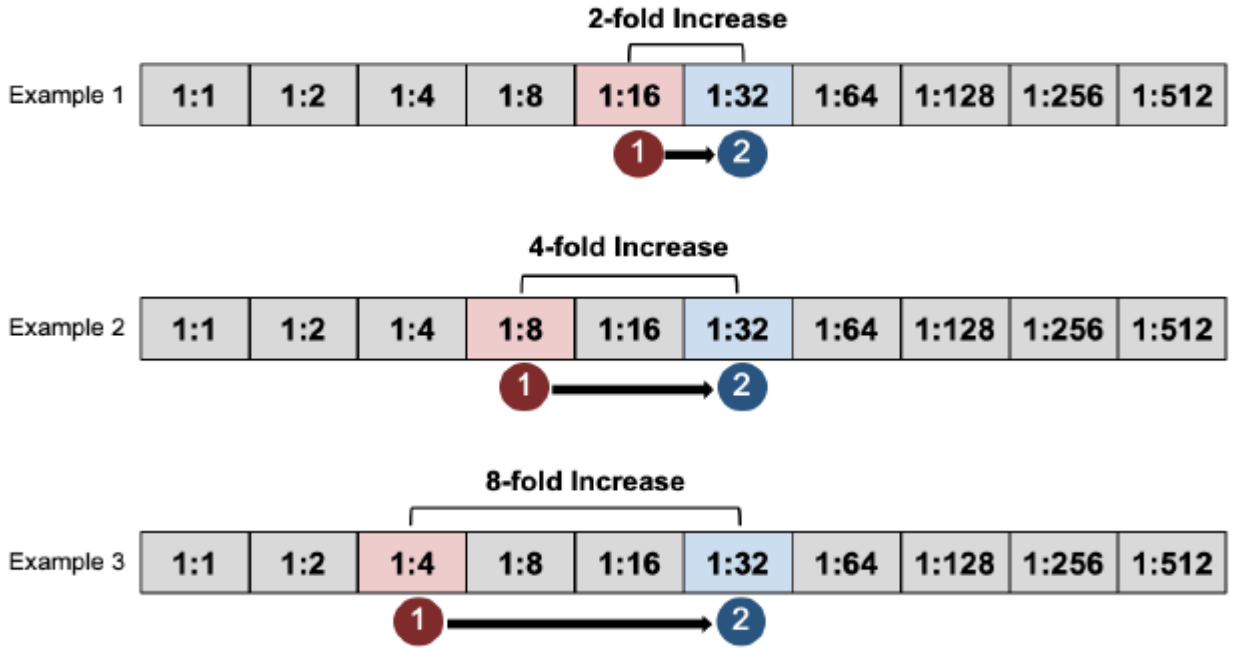


Figure: Courtesy of Dr Elizabeth Prentice

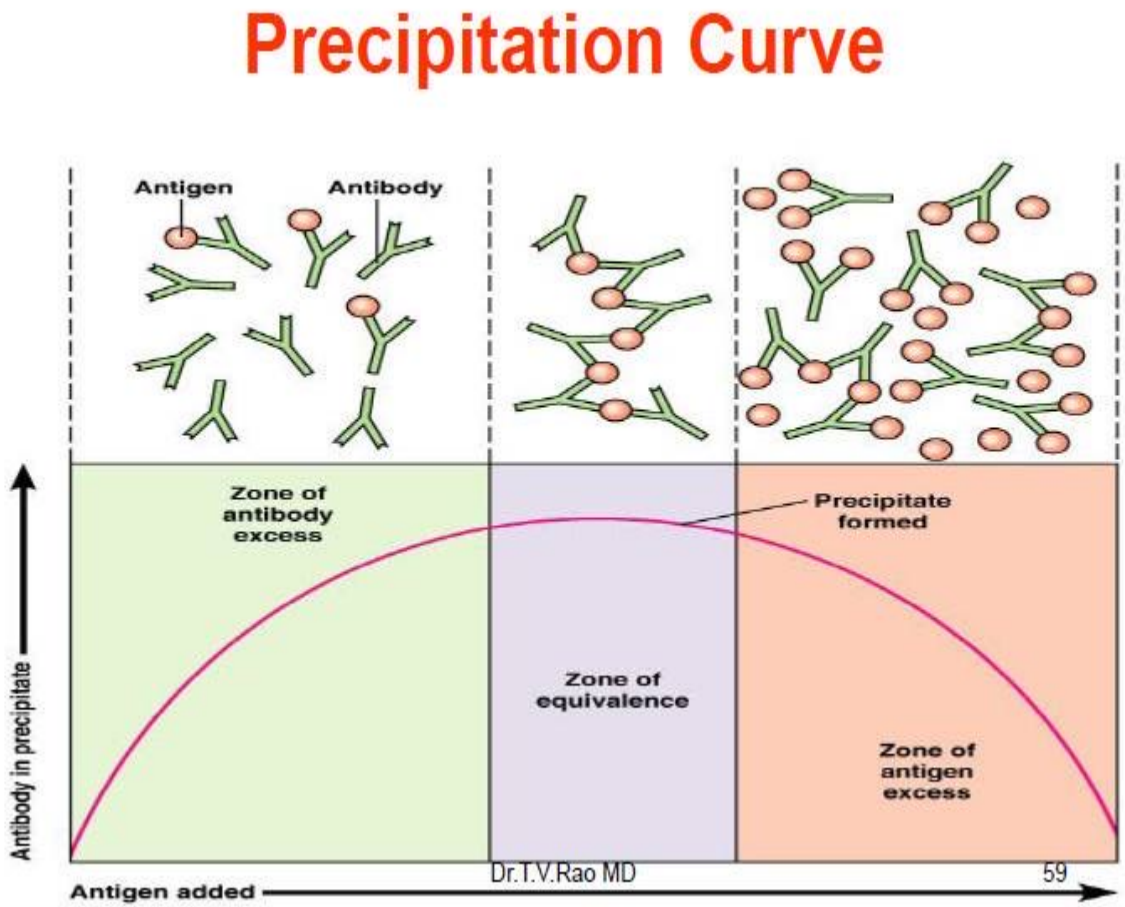
Measuring titres



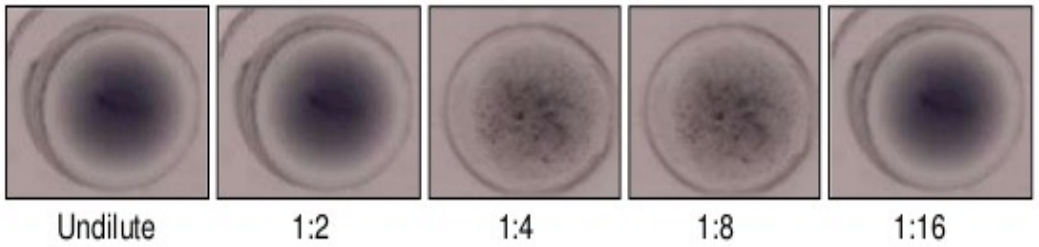


First figure: Courtesy of Dr Elizabeth Prentice
https://www.std.uw.edu/go/comprehensive-study/syphilis/core-concept/all.

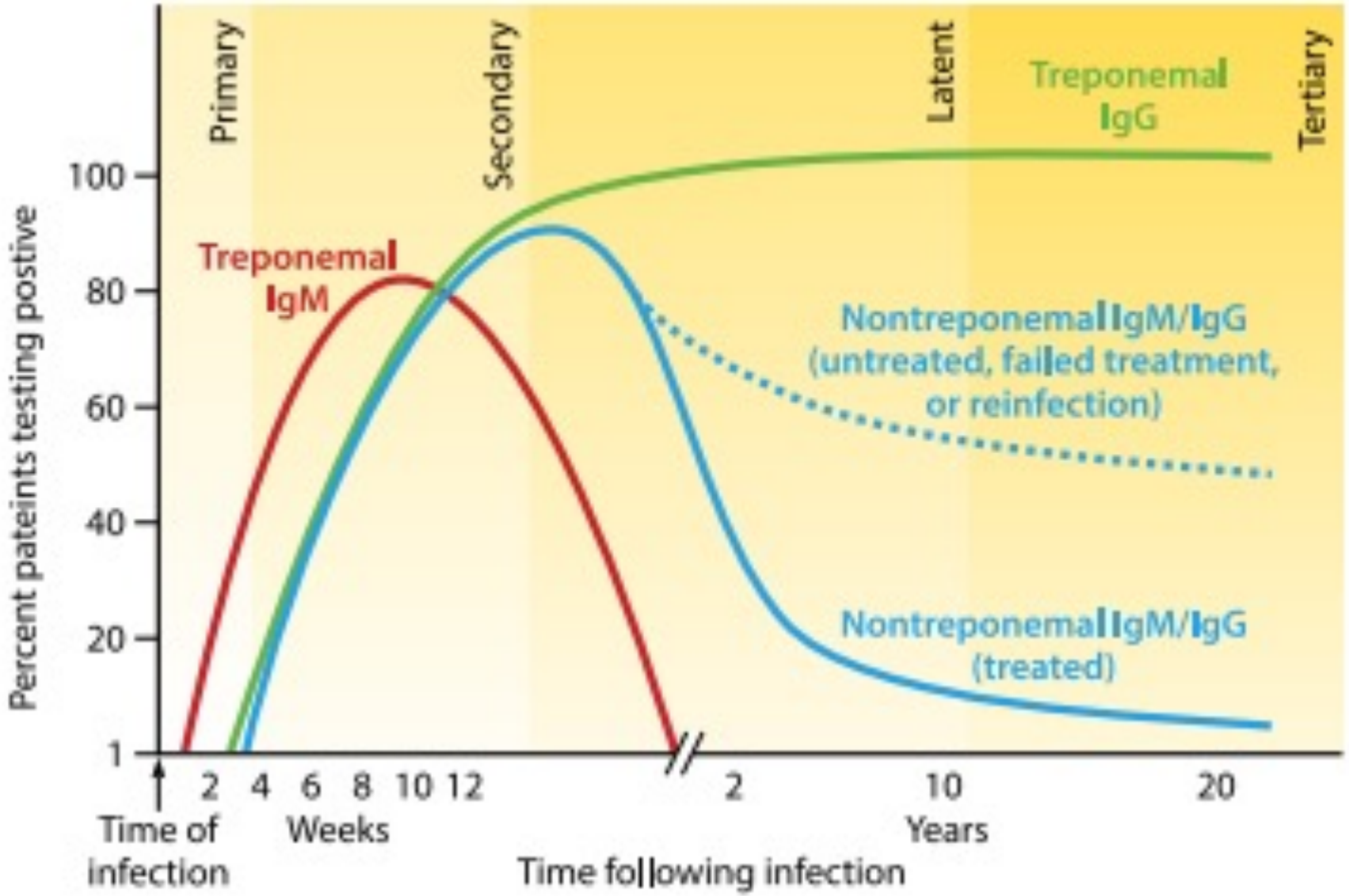
Prozone effect – RPR false negative results



- Possibility for prozone effect
  - High levels of antibody may inhibit the agglutination reaction
  - To identify prozone, labs must serially dilute samples

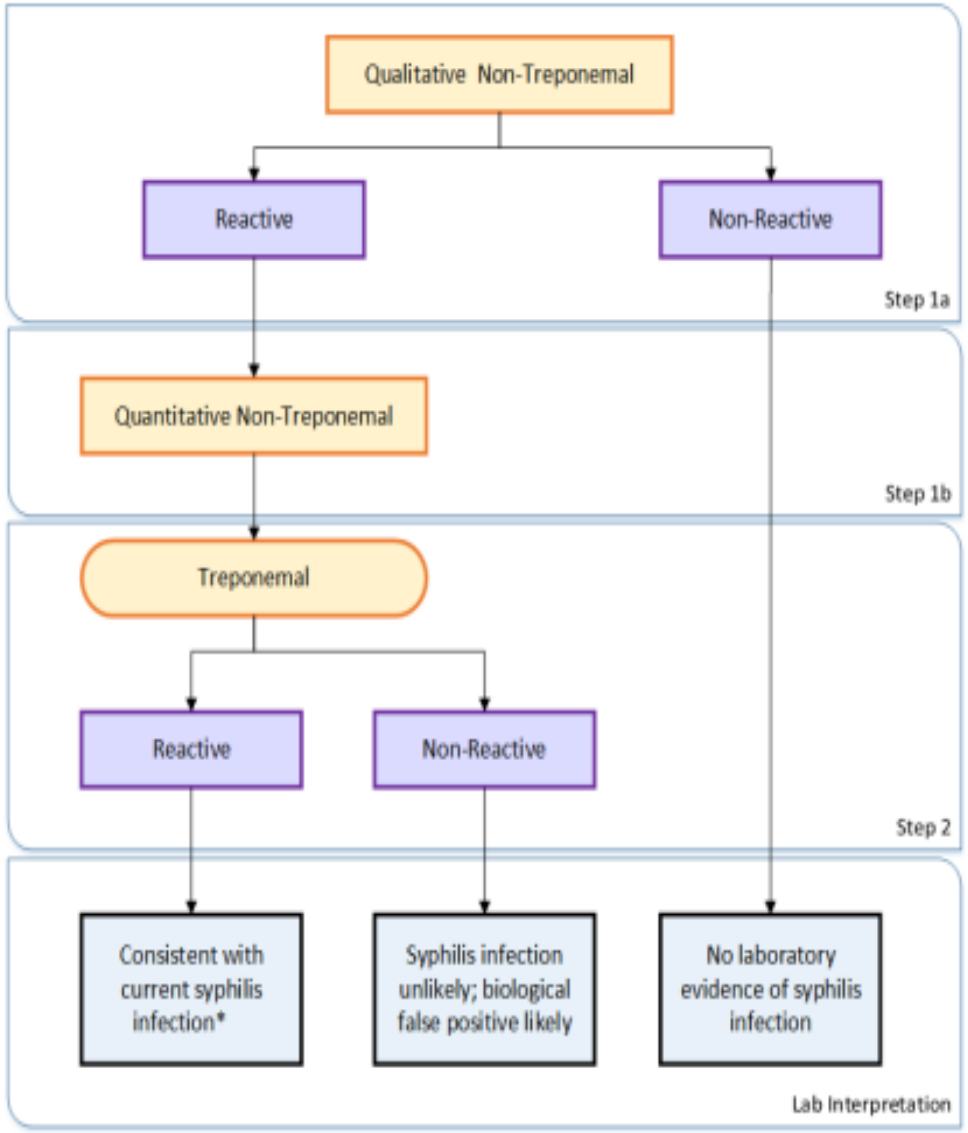


Serology through the stages of disease

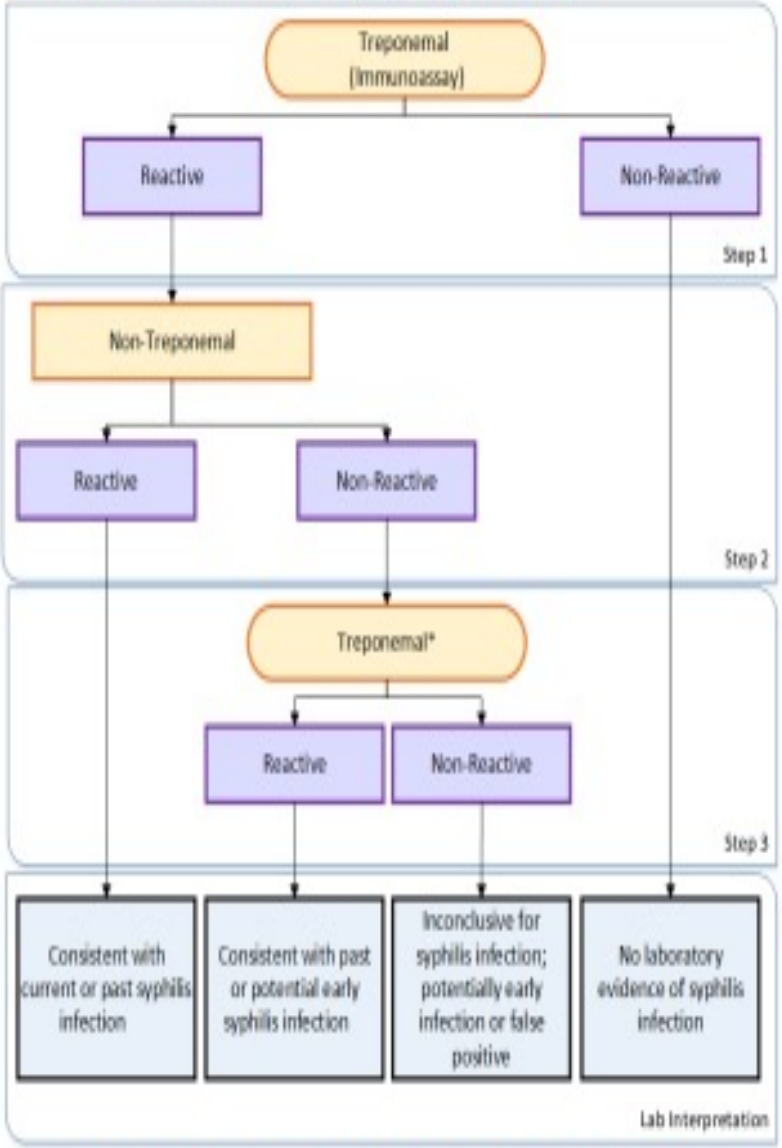


https://doi.org/10.1016/j.clinmicnews.2014.12.001

Traditional Syphilis Algorithm



Reverse Syphilis Algorithm



www.aphl.org

Diagnosis of congenital syphilis

Case Definition of Early Congenital Syphilis: A condition affecting an infant or child (< 2 years) **whose mother had untreated or inadequately treated* syphilis at delivery, regardless of signs in the infant** OR An infant or child who has a **reactive non-treponemal test for syphilis (RPR), AND any one of the following:**

- Any evidence of congenital syphilis on physical examination: hepatosplenomegaly, skin rash, jaundice, anaemia, mucosal lesions, nasal discharge
- Any evidence of congenital syphilis on x-ray of long bones: e.g. periostitis, tibial erosions
- An elevated cerebrospinal fluid (CSF) white cell count and protein (without other cause)
- A reactive cerebrospinal fluid (CSF) venereal disease research laboratory test (VDRL) test
- A reactive serum IgM antibody test (e.g. FTA-Abs IgM)

a) Infant's non-treponemal (RPR) titer is higher (preferably four-fold higher) than that of mother when both blood samples are drawn at the time of delivery
b) Infant has a reactive non-treponemal serologic titre which is equal to or less than the maternal titre, if the mother has been untreated or inadequately treated for syphilis during pregnancy
c) Infant's non-treponemal titer persists or increases after birth when serial tests are performed
d) Infant's treponemal antibody (TPHA, TPPA, TPAb) titre remains positive at 12-18 months of age.
e) Infant has a reactive serum non-treponemal test and a reactive serum IgM antibody test (e.g. FTA-Abs IgM)

NICD: Congenital Syphilis FAQ_20170531

Treatment

5. How is Congenital Syphilis treated?

WHO recommends that treatment of congenital syphilis in developing countries should be based on the following:

- Identifying maternal syphilis (by RPR) during pregnancy and/or at time of delivery
- Determining the quantitative RPR result of the infant
- Identifying whether a sero-reactive infant has clinical features compatible with early congenital syphilis.
- Determining whether an infected mother was adequately treated for syphilis during pregnancy i.e. received at least **1 dose** of benzathine penicillin **more than 30 days before** delivery.

Category	Treatment Protocol	Alternative Treatment
Symptomatic neonates	IV or IM aqueous crystalline penicillin G 50, 000 units/kg every 12 hours for the first 7 days of life, then every 8 hours after 7 days of life to complete 10-14 days of treatment	IM procaine penicillin 50, 000 units/kg as a single daily dose for 10days
Symptomatic Infants at least 4 weeks of age or older children	Aqueous crystalline penicillin G 50,000 units/kg/dose every 6 hours IV for 10-14 days	
Asymptomatic infants born to RPR positive mothers	Single IM dose Benzathine Penicillin G 50, 000 units/kg given	

NICD: Congenital Syphilis FAQ_20170531

Less likely or unlikely syphilis

Scenario 3: Congenital Syphilis Less Likely

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal or less than fourfold of the maternal titer at delivery (e.g., maternal titer = 1:8, neonatal titer ≤1:16) and both of the following are true:

- The mother was treated during pregnancy, treatment was appropriate for the infection stage, and the treatment regimen was initiated ≥30 days before delivery.
- The mother has no evidence of reinfection or relapse.

Recommended Evaluation

No evaluation is recommended.

Recommended Regimen, Congenital Syphilis Less Likely
Benzathine penicillin G 50,000 units/kg body weight/dose IM in a single dose*

* Another approach involves not treating the newborn if follow-up is certain but providing close serologic follow-up every 2–3 months for 6 months for infants whose mothers' nontreponemal titers decreased at least fourfold after therapy for early syphilis or remained stable for low-titer, latent syphilis (e.g., VDRL <1:2 or RPR <1:4).

Scenario 4: Congenital Syphilis Unlikely

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold of the maternal titer at delivery§ and both of the following are true:

- The mother's treatment was adequate before pregnancy.
- The mother's nontreponemal serologic titer remained low and stable (i.e., serofast) before and during pregnancy and at delivery (e.g., VDRL ≤1:2 or RPR ≤1:4).

Recommended Evaluation

No evaluation is recommended.

Recommended Regimen, Congenital Syphilis Unlikely
No treatment is required. However, any neonate with reactive nontreponemal tests should be followed serologically to ensure the nontreponemal test returns to negative (see Follow-Up). Benzathine penicillin G 50,000 units/kg body weight as a single IM injection might be considered, particularly if follow-up is uncertain and the neonate has a reactive nontreponemal test.

CDC STI guidelines 2021

Follow up

- Reactive nontreponemal tests: examinations and serologic testing (i.e., RPR or VDRL) every 2–3 months until nonreactive.
- RPR titers should decrease and be nonreactive by 6 months
- If not, re-evaluate (with CSF analysis). Retreatment with a 10-day course of a penicillin G regimen might be indicated.
- Neonates with a negative nontreponemal test at birth and whose mothers were seroreactive at delivery should be retested at age 3 months to rule out serologically negative incubating congenital syphilis at the time of birth.
- Treponemal tests should not be used to evaluate treatment response because the results are qualitative, and passive transfer of maternal IgG treponemal antibody might persist for >15 months

CDC STI guidelines 2021

Screening and Prevention

- Elimination of mother-to-child transmission
  - Effective early screening and treatment
  - ANC: first visit, 32 weeks, (delivery in high risk mothers)
  - Lesions in the neonate are highly infectious. Need to be handled with gloves until at least 24 hours on treatment
  - Notify
  - Don’t forget the partner
  - Don’t forget siblings