

Syphilis – Rising RPR Titre: Distinguishing Reinfection from Serological Variation

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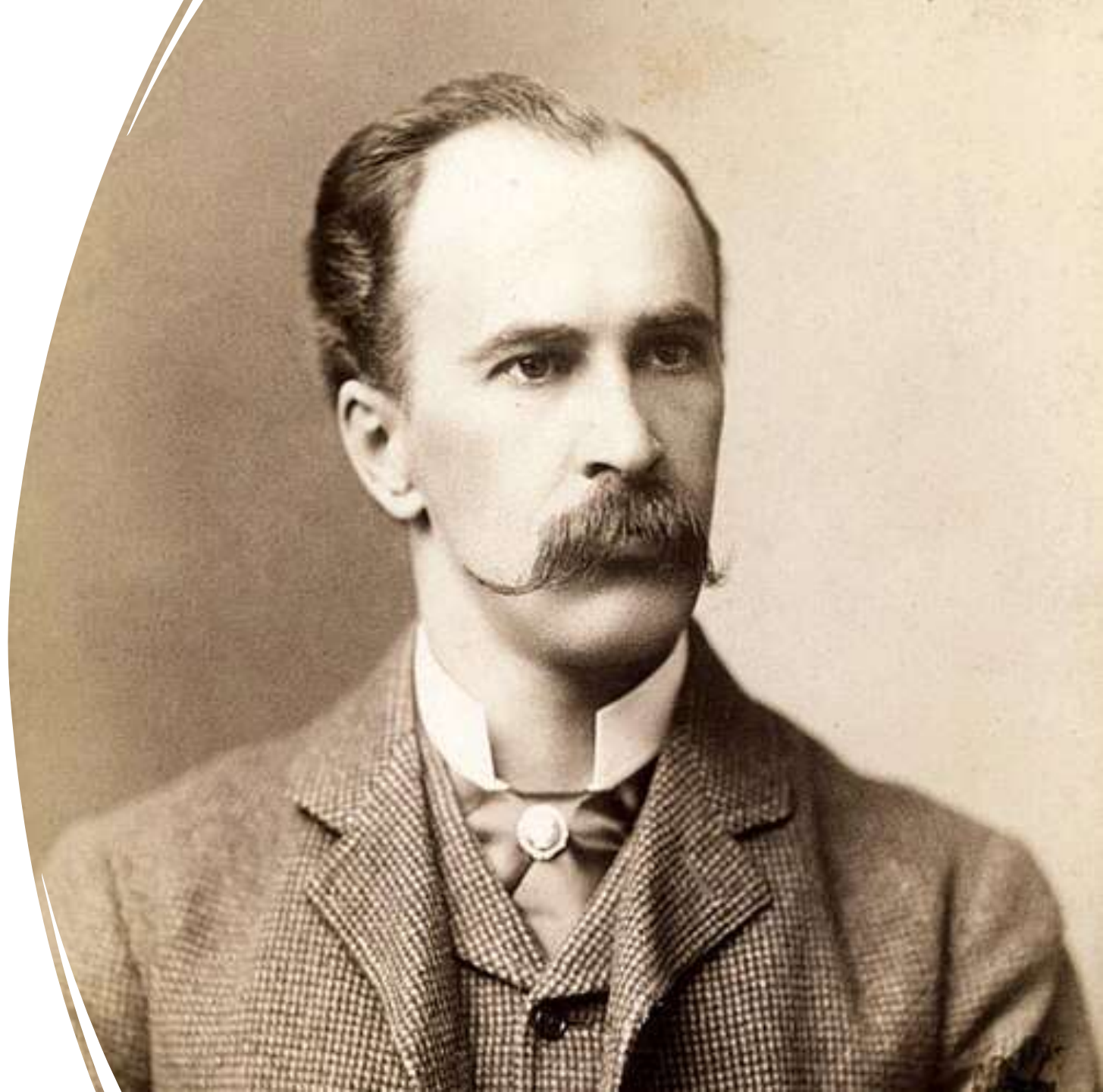
Disclosure

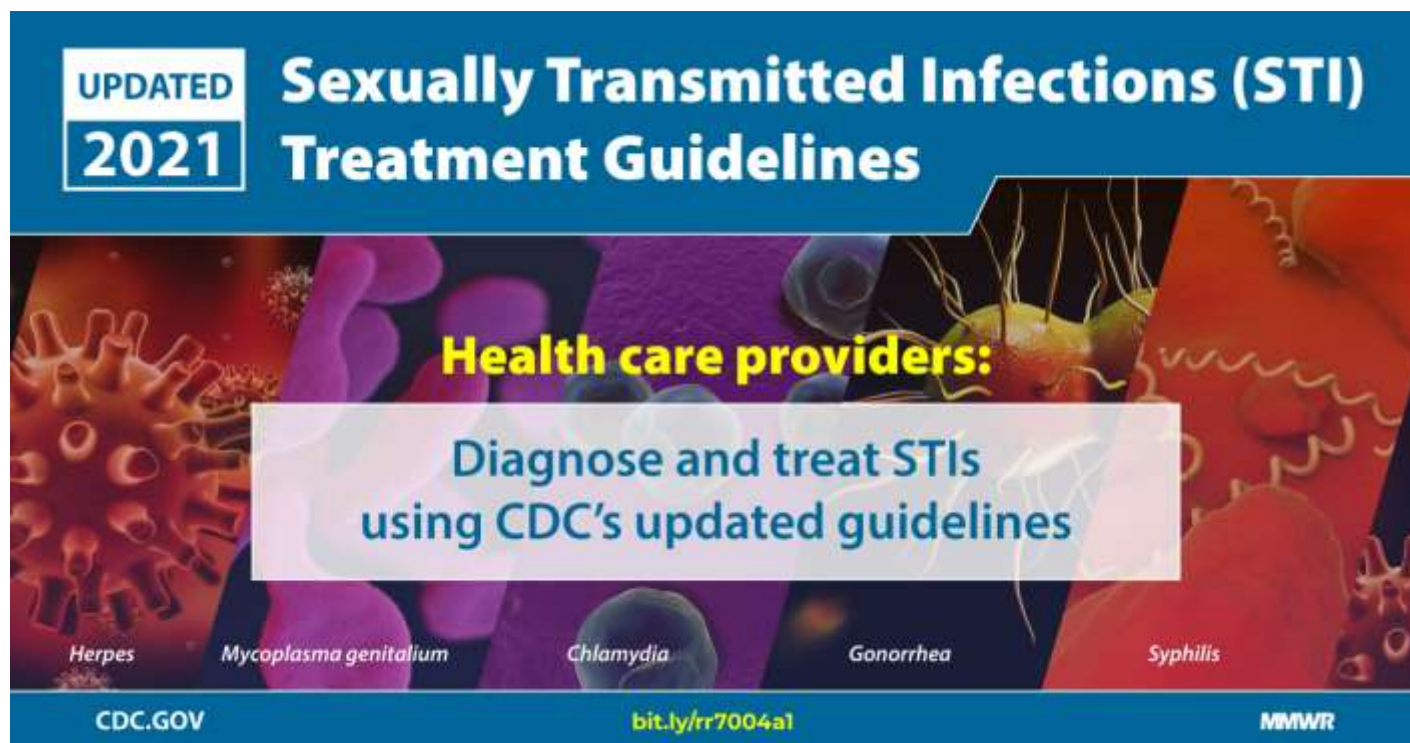
- Served as a speaker and or advisory board for Abbvie, Boehringer Ingelheim, DKSH, Galderma, GSK, Hyphens Pharma, Johnson and Johnson, Loreal, Novartis, Sanofi-Aventis, Taisho-HOE Pharma, Zuellig-Pharma

Syphilis:

The Greatest Mimicker

**“The physician that knows
syphilis knows medicine.”
– Sir William Osler**





Learning Objectives

Recognizing syphilis

Interpretation of RPR

Distinguish reinfection vs variation

Management

Follow up

Case scenarios

Introduction

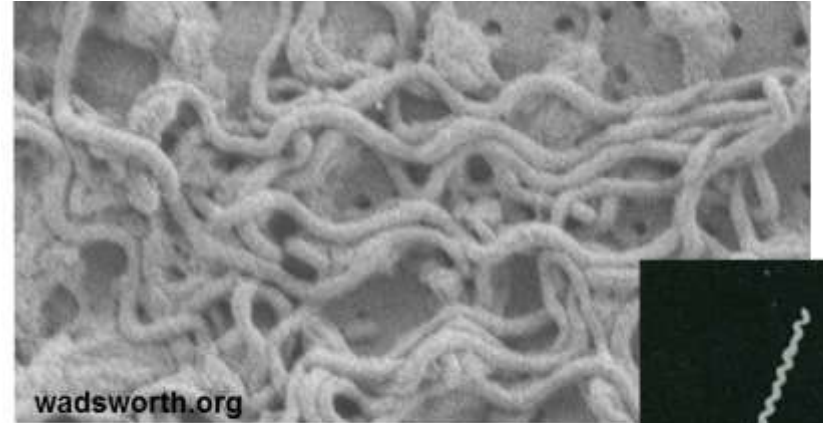
Causative organism: *Treponema pallidum*

Spirochete

Obligate human parasite

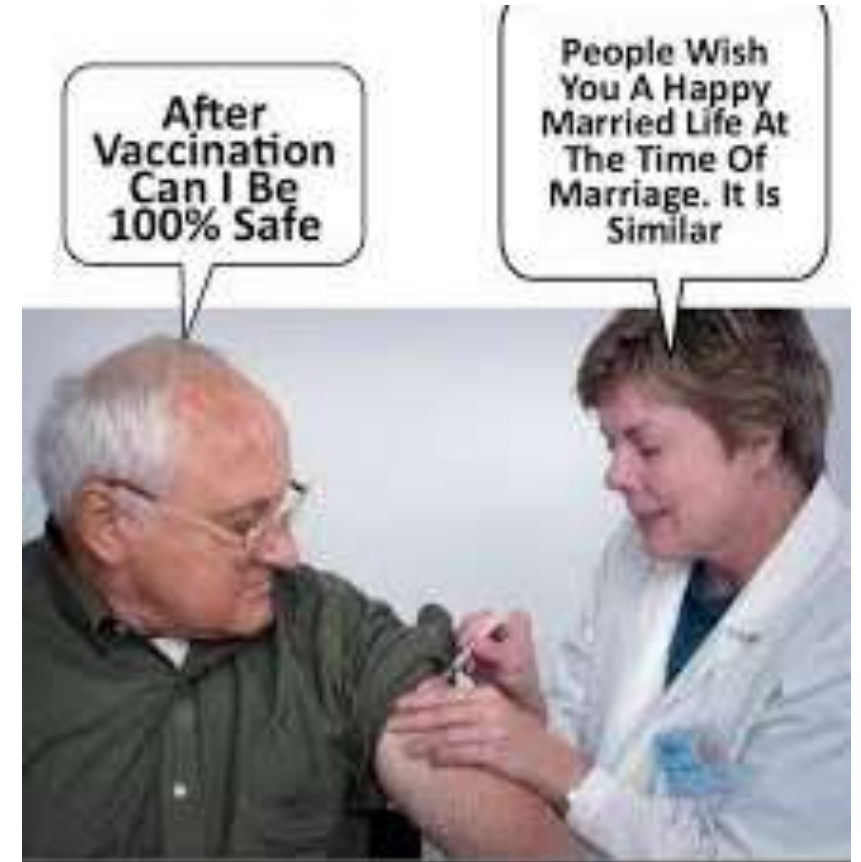
Transmission

- Sexual
- Trans-placental
- Percutaneous following contact with infectious lesions
- Blood Transfusion



Syphilis – The “Great Imitator”

- Incubation Period – 21 days (median)
- 3 clinical stages of syphilis
 - Primary:
 - Painless ulcer (chancre) at inoculation site
 - Secondary:
 - Rash, Fever, Lymphadenopathy, Malaise
 - Tertiary:
 - Gumma, cardiovascular syphilis
 - Latent:
 - Asymptomatic
- Neurosyphilis:
 - Can occur at any stage



Primary Syphilis

- Incubation period: 9-90 days
- **Chancre**
- painless, indurated with clean base
- Highly infectious
- Typically heals within 3-6 weeks
- Multiple lesions can occur
- Regional lymphadenopathy: bilateral, painless
- **Serologic tests for syphilis may not be positive** during early primary syphilis.



Secondary Syphilis

- Incubation period: 6 weeks to 6 months
- Clinical features:
 - **Rash (75%–100%)**
 - Lymphadenopathy (50%–86%)
 - Malaise
 - Mucous patches (6%–30%)
 - Condylomata lata (10%–20%)
 - Alopecia (5%)
- Serologic tests are usually highest in titer



Tertiary Syphilis

- Develop in untreated patient within 1 to 30 years
- Clinical features:
 - Gummatous lesions
 - Cardiovascular syphilis
- Non infectious



Neurosyphilis

- May occur at **any stage of syphilis**
- Can be asymptomatic
- Early neurosyphilis occurs a few months to a few years after infection
 - Clinical manifestations can include acute syphilitic meningitis, meningovascular syphilis, and ocular and auditory involvement
- Neurologic involvement can occur decades after infection and is rarely seen
 - Clinical manifestations can include general paresis, tabes dorsalis, and ocular involvement
- Ocular involvement can occur in early or late neurosyphilis.

Latent Syphilis

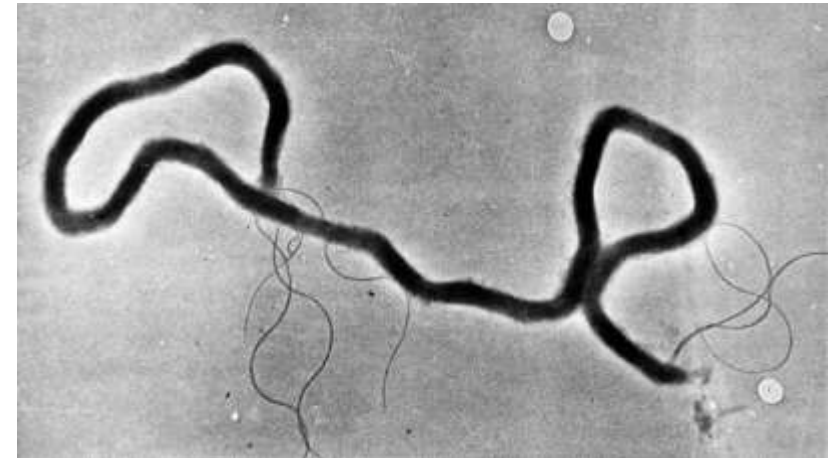
- Host suppresses infection, thus **no lesions are clinically apparent**
- Only evidence is a **positive serologic test**
- May occur between primary and secondary stages, between secondary relapses, and after secondary stage
- Categories:
 - Early latent: <1 year duration
 - Late latent: ≥ 1 year duration

Latent Syphilis

- **Criteria for early latent syphilis:** The following noted within the year preceding the evaluation
 - Documented seroconversion or 4-fold increase in comparison with a serologic titer
 - Symptoms of primary or secondary syphilis reported by patient
 - Contact to an infectious case of syphilis
 - Only possible exposure occurred within past 12 months
- Patients with latent syphilis of **unknown duration** should be managed clinically as if they have **late latent syphilis**.

Diagnosis

- History
- Physical examination
- **Serology**
 - Mainstay for syphilis testing
 - Two classes of serologic tests
 - Non-treponemal
 - Treponemal
- The use of only one type of serologic test is insufficient for diagnosis



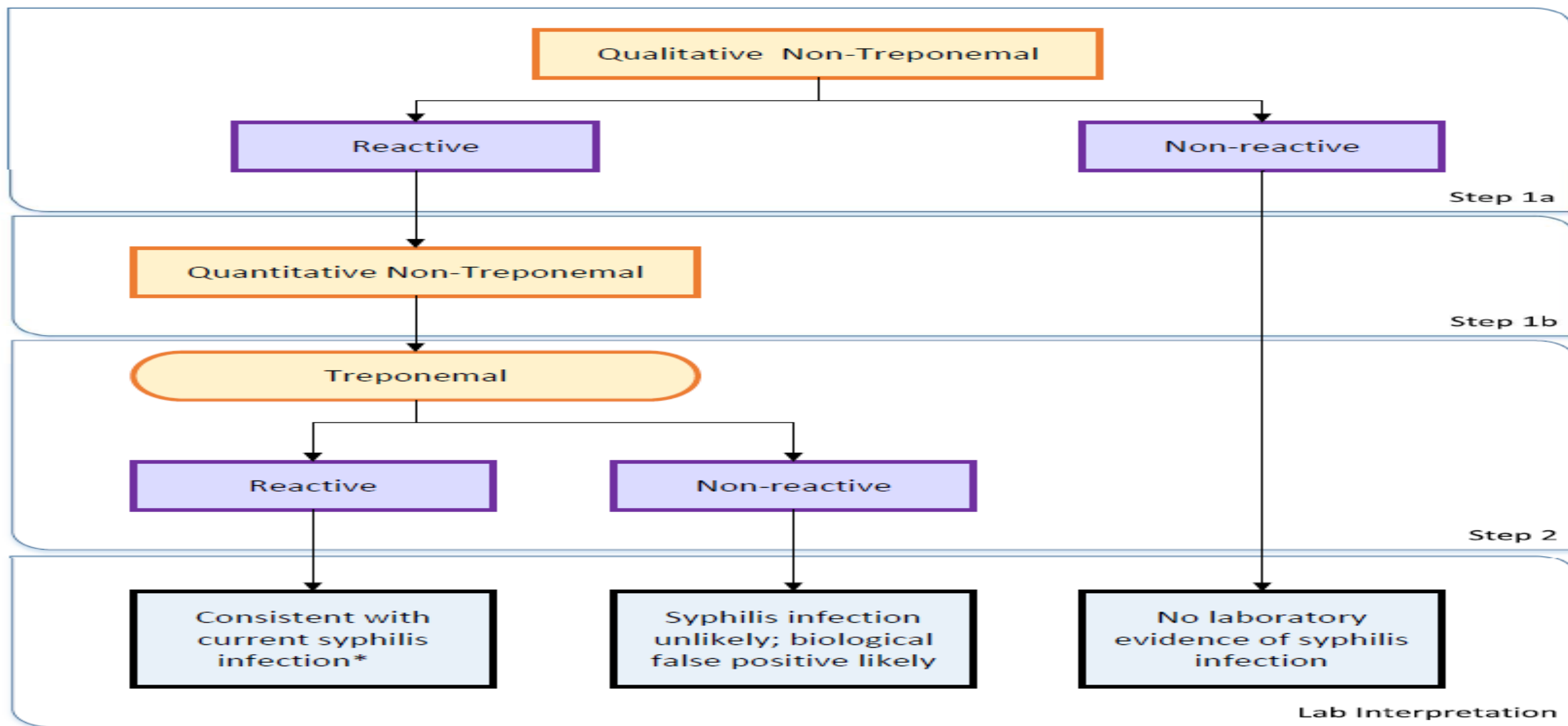
Nontreponemal Serologic Tests

- Principles
 - Measure antibody directed against a cardiolipin-lecithin-cholesterol antigen
 - **Not specific for *T. pallidum***
 - Used for **monitoring treatment** and **detecting reinfection**
 - May be reactive for life, referred to as “serofast”
- Nontreponemal tests include **VDRL, RPR, TRUST, USR**

Treponemal Serologic Tests

- Principles
 - Measure antibody directed against *T. pallidum* antigens
 - Qualitative
 - Usually **reactive for life**
 - Titers **should not be used to assess treatment response**
- Treponemal tests include **TP-PA**, FTA-ABS, EIA, and CIA
- Cannot differentiate between current and past infection.

Algorithm for Screening



**If titer <1:4 consider these values associated with possible serofast condition.²² Serofast is used to refer to those persons with early syphilis with non-treponemal titers that neither increase nor decrease 4-fold after treatment.^{2,3}*

Interpretation of Serological Tests

Non-Treponemal tests (RPR/VDRL)	Treponemal Tests (TP-PA/FTA-ADS)	Possible Explanation
+	+	Syphilis - recent or previous Yaws or pinta
+	—	No syphilis False positive
—	+	Consistent with previously treated or untreated Syphilis Yaws, Pinta, Bejel
—	—	No syphilis Syphilis in incubation period

False Positive Tests

- Viral infections (Infectious mononucleosis)
- Bacterial infections (pneumonia, TB)
- Connective tissue disease (rheumatoid arthritis, SLE)
- Elderly
- Pregnancy



Interpretation of Serological Tests



Initial screening may be negative in early primary syphilis.

If the history is strongly suggestive of syphilis then an RPR should be repeated in **3-4 weeks**



Most people become negative for RPR with adequate treatment.

some may maintain a **low titer RPR** (<1:8) for life despite adequate treatment. This is the **serofast state**.



Prozone phenomenon

false negative response resulting from overwhelming antibody titers associated with HIV, pregnancy and secondary syphilis

Treatment

Primary, secondary and early latent syphilis:

- IM Benzathine Penicillin G, 2.4 million units in a single dose.

Late latent syphilis / unknown duration:

- IM Benzathine Penicillin G, 2.4 million units weekly for 3/52 (max 10-14 days between doses)

If penicillin-allergy:

- Ceftriaxone 1g I.M. daily for 10 days
- Oral Doxycycline 100mg bd for 14 days (28 days for late latent)

Neurosyphilis

- IV Crystalline Penicillin G 3-4 MU 4 to 6 hourly (18-24 MU/day) for 10-14 days
- Alternative: IM procaine penicillin G 2.4 MU daily + oral probenecid 500mg daily for 10-14 days

Further management

NOTIFY and screen for other STIs

Follow up:

- Primary, secondary and early latent:
 - RPR titre at 6,12 months
- Late latent syphilis:
 - RPR titre at 6, 12, 24 months
- HIV more frequent, pregnancy closer monitoring

Neurosyphilis

- No need for repeat CSF at 6 months if adequate RPR response

Contact tracing:

- Examine and investigate sex partner - treat if contact within 3/12

Follow Up – Ask these 3 Questions

Did the titre fall appropriately?

Did it fall within the expected time?

Is there significant rise suggesting reinfection / treatment failure?

Did the titre fall appropriately?

- Use the **same test** (RPR/VDRL) and ideally **same lab**
- Not every rising RPR needs treatment
 - Need to ascertain if this is **reinfection**, **treatment failure**, or just **normal variation**
- Simple rule:
 - **≥4-fold decline** = adequate response
 - **≥4-fold rise** = reinfection / treatment failure
 - **<4-fold rise** = likely variation → observe

Did the titre fall within expected time?

- **Early Syphilis** (primary, secondary, early latent)
 - Follow up at 6, 12 months
 - Consider 3 monthly if high risk e.g. MSM, HIV
 - Expect **≥ 4 -fold drop within 6–12 months**
- **Late latent / unknown duration**
 - Follow up at 6, 12, 24 months
 - Expect slower decline, sometimes only by **24 months**

Special Group: Pregnancy

- Follow up monthly
- Expected serological response is the same as non-pregnant patients
- May not get a 4-fold drop before delivery, especially if late treatment
- Focus on:
 - **Adequate treatment given (penicillin)**
 - **Correct timing before delivery**
 - **Watch on any rise instead**
- Lower threshold to retreat

Special Group: HIV

- Follow up at 3, 6, 9, 12, 24 months
- Expected serological response is the same as non-HIV patients
- Slightly slower or fluctuating response possible
- When to consider LP?
 - Neurological / ocular / otic symptoms
 - Headache / confusion / Cranial nerve palsy / Visual symptoms / Hearing loss
 - Suspected treatment failure
 - No 4-fold RPR decline within expected time
 - Or 4-fold rise without clear reinfection

Treatment Failure / Reinfection

- Indications of probable treatment failure or reinfection include
 - Persistent or recurring clinical signs or symptoms
 - Sustained 4-fold increase in titer
 - Titer fails to show a 4-fold decrease at 12 months (24 months for late latent)
 - Persistently high titres (e.g. $\geq 1:32$)

Treatment Failure / Reinfection

- Ask these 5 questions:
 1. Are there any signs/symptoms or re-exposure?
 2. Is the partner treated?
 3. Was previous treatment adequate?
 4. Is there concurrent HIV / other STI?
 5. Is there any evidence of neurosyphilis?
- Treat if fourfold rise / new exposure / symptoms / pregnancy / uncertain follow up

Serofast State / Variation

Serofast:

- Low baseline titre ($\leq 1:8$)
- Stable low-level RPR / VDRL
- No symptoms
- No 4-fold rise

Variation:

- Small fluctuations (1 dilution)
- Usually in previously treated patients
- Lab variability



RPR Interpretation

- 1:64 → 1:16 at 6 months
 - Adequate response?
 - Yes (good response) -> 4-fold reduction
- 1:32 → 1:16 at 12 months (late syphilis)
 - Adequate response?
 - Acceptable (slow response) - need follow up until 24 months
- 1:128 → 1:64 at 12 months
 - Adequate response?
 - No (treatment failure)

The background is a complex, abstract pattern in shades of teal and dark green. It features a dense, repeating fractal-like structure that resembles marbled paper or a microscopic view of certain minerals. The pattern consists of numerous fine, curved lines that create a sense of depth and movement. The overall effect is a rich, textured backdrop for the central text.

CASE SCENARIOS

Case 1

- 28 year old man, HIV negative
- Treated for early syphilis 1 year ago
- RPR: 1:32 → 1:8 (after treatment)
- Currently came for review and RPR titre is 1:16
- No re-exposure, no symptoms
- Would you retreat?

Case 1 - Answer

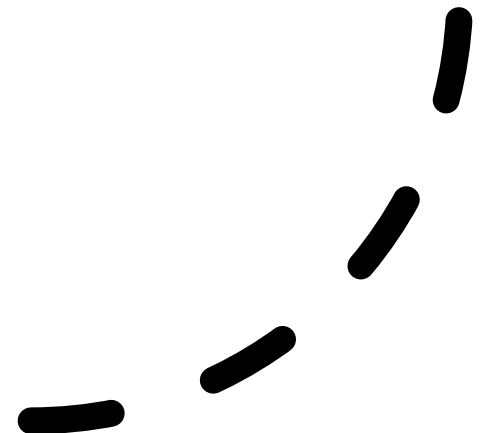
- No need to retreat
- Adequate decline earlier and not significant rise (only 2-fold)
- Likely serological variation
- May also be early re-infection (start with small rise first) – so need to repeat RPR in 2 to 4 weeks time
- Treat if further increase on repeat

Case 2

- 40 year old man, HIV negative
- Treated as early syphilis 6 months ago
- RPR 1:128 (baseline) → 1:64 (at 6 months) -> 1:64 (at 12 months)
- No re-exposure, no symptoms
- Would you retreat?

Case 2 - Answer

- Yes, need retreatment
- No fourfold decline by 12 months
- Consider neurosyphilis

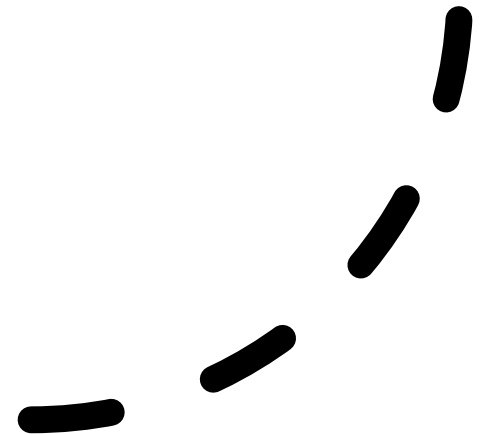


Case 3

- 30 year old lady, HIV negative
- Treated as late latent syphilis
- RPR trend:
 - RPR 1:8 (treated) -> RPR 1:16 (at 6 months) -> 1:8 (at 12 months)
- No re-exposure, no symptoms
- Would you retreat?

Case 3 - Answer

- No need treatment
- Lab variation with serofast state
- Apply the 4-fold rule strictly
- Follow up until 24 months for late latent syphilis

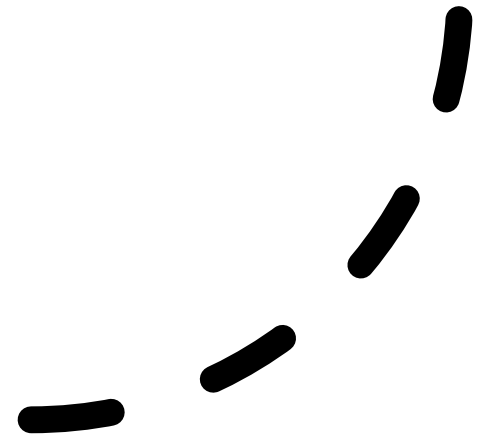


Case 4

- 28 year old lady, G1P0 at 20 weeks, HIV negative
- Baseline RPR at 16 weeks POA was 1:2 -> treated as late latent syphilis with benzathine penicillin
- RPR trend: 1:2 -> 1:4 -> 1:8
- No re-exposure, no symptoms
- Would you retreat?

Case 4 - Answer

- YES!
- 4-fold rise -> treat as reinfection
- Low threshold to treat in pregnancy



Conclusions



Always compare baseline vs current titre. Treat if ≥ 4 -fold rise from baseline



Do not react to 1 dilution (2-fold) change, need to repeat and see trend



Ask about partner treatment and re-exposure, concurrent HIV



In pregnancy, when in doubt, treat



It is not about making the titre negative – it is about ensuring a 4-fold decline within the expected time and watching for a 4-fold rise thereafter

THANK YOU

When someone has explained something to you three times and you still don't get. So you just smile politely

