

Syphilis 101

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Disclosure Slide

- Gilead Sciences - Advisor/Researcher
- Merck - Researcher
- Abbvie Pharmaceutical - Researcher/Speaker
- Roche - Advisor

All relevant financial relationships listed have been mitigated

Outline

Trepanomatoses



A brief History of syphilis



Syphilis 101

Human treponematoses

Syphilis: *T. pallidum* spp. *pallidum*

- Globally distributed
- Sexually transmitted

Endemic Treponematoses:

Yaws: *T. pallidum* spp. *pertenuis*

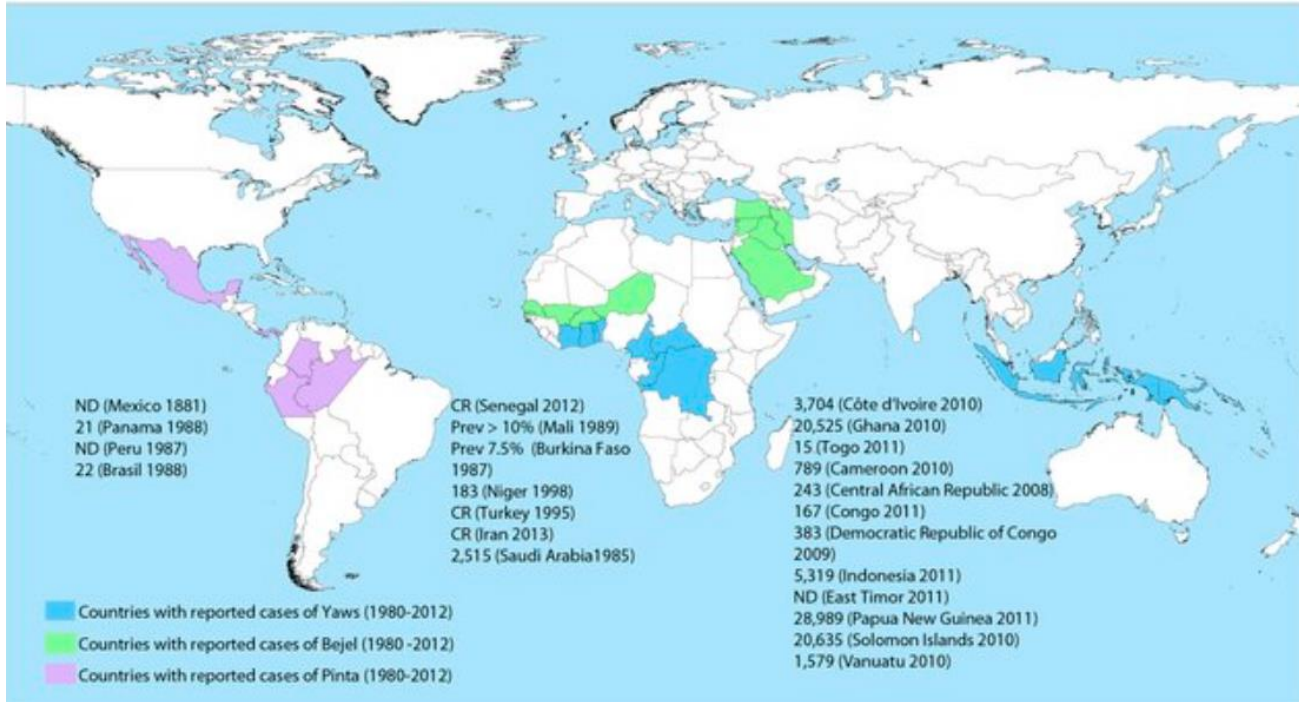
Bejel: *T. pallidum* spp. *endemicum*

Pinta: *T. pallidum* spp. *carateum*

- Mainly cause disease of the skin, joints, soft tissue, oral cavity and bone
- No evidence of vertical transmission

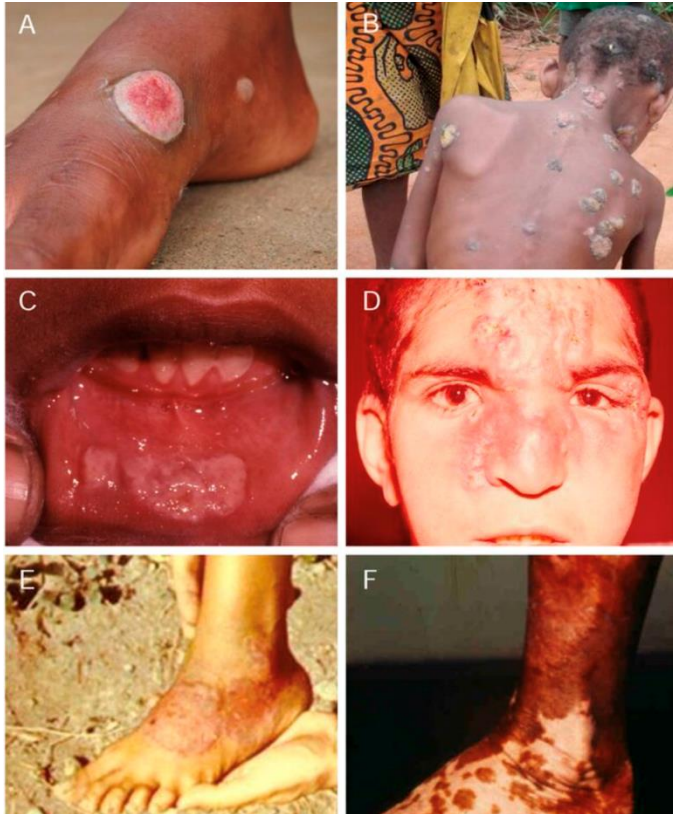


Yaws, Pinta and Bejel Distribution



- Countries with reported data on yaws, bejel, and pinta from 1980 to 2012
- In some countries the transmission may be restricted to small areas, rather than affecting the entire country.
- India interrupted transmission in 2004 and declared elimination in 2006.

Common yaws, bejel, and pinta lesions in 2013



A: Papillomatous primary yaws lesion

B: Disseminated papilloma of secondary yaws

C: labial mucosal plaques of primary bejel

D: Disfiguring infiltration of the nose, glabella, and forehead in a patient with secondary bejel

E: Squamous plaque of primary pinta

F: Late achromic pinta.

Sources of photographs: O. Mitjà, Papua New Guinea (A, B); A. Abdolrasouli, Iran (C, D); F. Gómez, Mexico (E, F). The individuals photographed for this publication were informed of the purpose of the photograph and they agreed to have their photograph taken and potentially published.

Human treponematoses

Probably have a clonal origin with a common ancestor

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graph TD; A[Probably have a clonal origin with a common ancestor] --> B[Are genomically, morphologically, and serologically similar]; B --> C[Infection occurs following an exposure of mucosal surfaces or traumatized skin to infected bodily fluids]; C --> D[After initial invasion, the organisms multiply and disseminate hematogenously or via lymphatic systems.];
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Are genomically, morphologically, and serologically similar

Infection occurs following an exposure of mucosal surfaces or traumatized skin to infected bodily fluids

After initial invasion, the organisms multiply and disseminate hematogenously or via lymphatic systems.

History of Syphilis

Origins of Syphilis: Columbian Hypothesis

- *T. pallidum* first arose in the Old World as a non-venereal infection and likely underwent genetic mutations giving rise to *T. pallidum* sp *pallidum*

Where does the name of Syphilis come from:

- A poem called "Syphilis, Sive Morbus Gallicus" ("Syphilis, or the French Disease"), written by Italian physician-poet Girolamo Fracastoro in 1530.

The "Great Imitator"

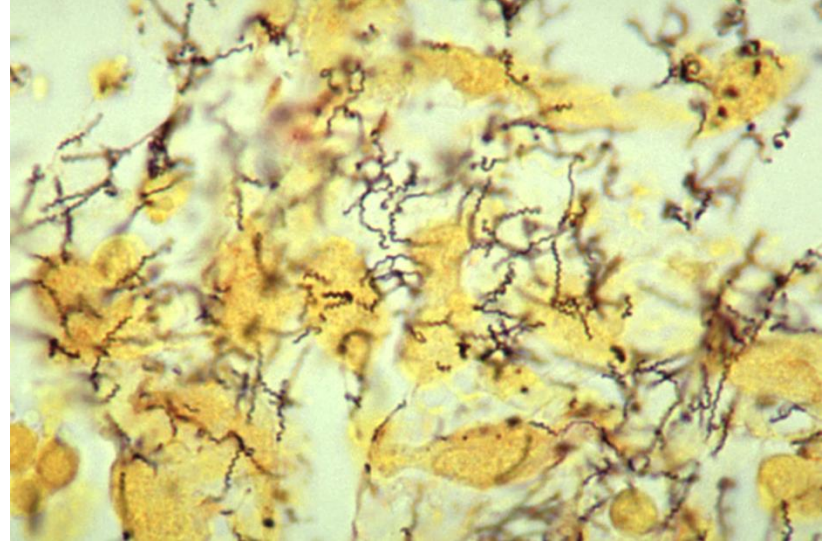
- Supposedly described by Sir William Osler

First reported outbreak:

- Among the French troops in Europe during the war of Naples in 1495

The Diagnostic History of Syphilis: Direct Detection of Organisms using Microscopy

After the turn of the 20th century *T. pallidum*, was first observed in diseased tissues by German zoologist Fritz Schaudinn and dermatologist Erich Hoffman.



Treponema pallidum spirochetes in a rabbit testicular tissue sample, prepared using the modified Steiner silver stain method. Source: CDC Public Health Image Library.

<https://asm.org/articles/2019/june/revisiting-the-great-imitator,-part-i-the-origi-a>

The Beginning of Laboratory Diagnosis of Syphilis: Direct Detection of Organisms using Microscopy

In 1906 Karl Landsteiner, along with Viktor Mucha, introduced the use of dark-field microscopy to detect the presence of syphilitic treponemes in infected specimens.



Karl Landsteiner



Treponema pallidum visualized using dark field microscopy.
Source: CDC Public Health Image Library.

Non-Treponemal Testing

In 1906 August Paul von Wassermann, Albert Neisser and Carl Bruck developed the first serologic test for the diagnosis of syphilis.

- It utilized the CF fixation method developed by Jules Bordet
- These “specific” antibodies were called Wassermann antibodies
- In the presence of antigens (liver extract of syphilitic fetus), the antibodies would form immune complexes and depletion of complement factors

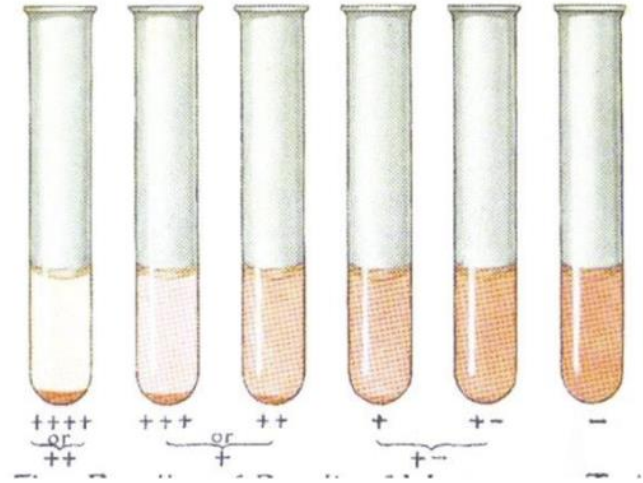


Figure 5. Wasserman test [19]

Non-Treponemal Testing

In 1907 Landsteiner elucidated the antibodies

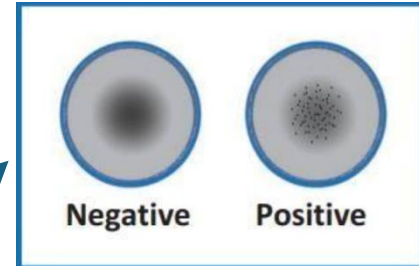
- They were directed against lecithin and cholesterol in non syphilitic tissue (non-specific)

In 1922 a flocculation test was developed

- Using an antigen of beef heart extract

In 1927 Dr. William Hinton improved the test

- Making headway for the development of the Rapid Plasma Reagin (RPR) and Venereal Disease Research Laboratory (VDRL) test.



<https://doi.org/10.32539/bsm.v5i8.339>



William Augustus Hinton

Non-Treponemal Testing

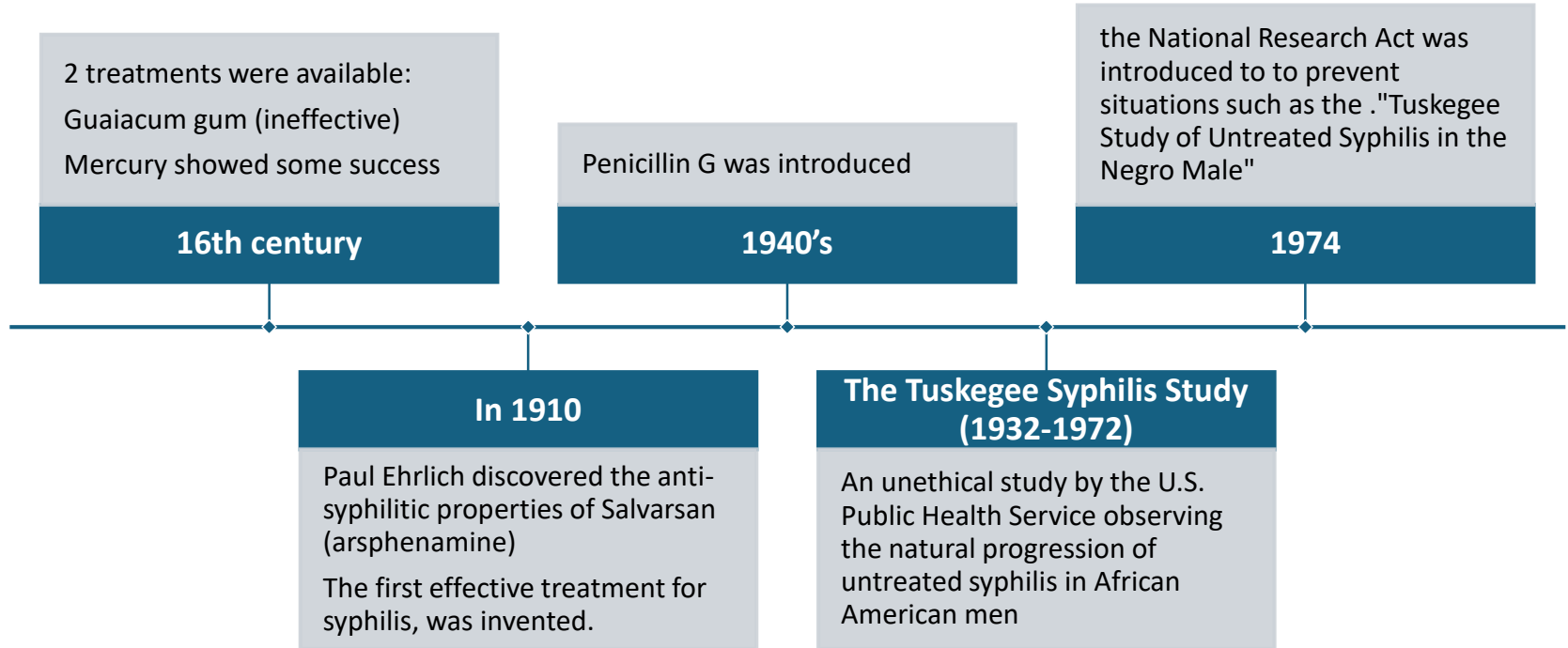
In 2018 A study found that *T. pallidum* contained a cardiolipin

- The increase in the Wasserman antibody (anti-phospholipid antibody) production was suggested to be a result of the combined effects of both the *T. pallidum* cardiolipin antigen and the damaged host-cell cardiolipin antigen during syphilis infection.

In the 1940s structure of the antigen in the Wassermann test was identified

- It is a diphosphatidylglycerol called cardiolipin
- Commonly found in normal non-syphilitic tissues

History of Syphilis: Treatment

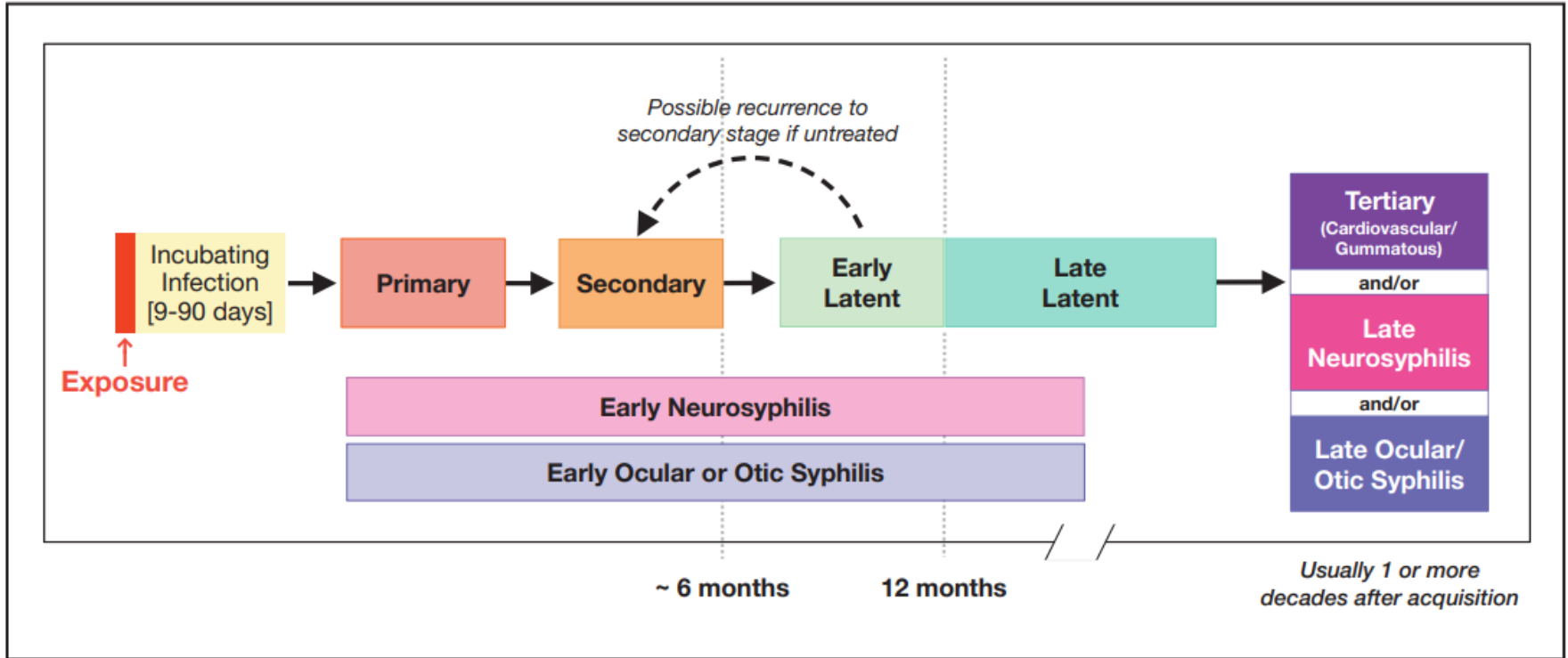


Syphilis

- **Sexual** (horizontal) and vertical transmission
- Average incubation period is **21 days** (can range from 10-90 days)
- **Four stages**
 - Primary
 - Secondary
 - Early (non-primary, non-secondary)
 - Unknown duration or late



The Natural History of Untreated Syphilis



Primary Syphilis

- **A single chancre** marks the onset of primary syphilis (can be multiple)
- **Usually firm, round, and painless** Located where syphilis enters the body
- Can appear in **difficult to notice** locations (anus, vagina)
- **Lasts 3 to 6 weeks** and heals regardless of whether a person receives treatment
- If untreated, **will progress** to the secondary stage



Secondary Syphilis

- Skin rashes and/or mucous membrane lesions (in the mouth, vagina or anus)
- Usually does not itch, may appear as rough, red, brown spots
- May be accompanied by fever, swollen lymph nodes, sore throat, hair loss, aches and pains
- Resolves regardless of whether a person receives treatment
- If untreated, will progress to the latent and possible tertiary stage



Latent Syphilis

Latent (hidden) stage of syphilis

- When there are no visible signs or symptoms of syphilis

Early latent syphilis

- Where infection occurs **within the past 12 months**

Late latent syphilis

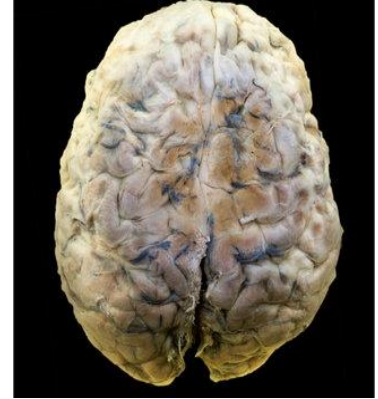
- Is where infection occurs **more than 12 months ago**

Latent syphilis of unknown duration

- When there is **not enough evidence** to confirm if initial infection was within the previous 12 months

Tertiary Syphilis

- Rare, develops in a subset of untreated syphilis infections
- Appears 10-30 years after infection, can be fatal
- Can affect multiple organ systems including brain, nerves, heart, blood vessels, eyes, liver, bones, joints



Neurologic Manifestations of Syphilis

- Can occur at any stage

Neurosyphilis (Nervous System)	Ocular Syphilis (Visual System)	Otosyphilis (Auditory/Vestibular System)
<ul style="list-style-type: none">- Severe headache- Trouble with muscle movements- Paralysis- Numbness- Altered mental status	<ul style="list-style-type: none">- Eye pain or redness- Floating spots in field of vision- Sensitivity to light- Can lead to permanent blindness	<ul style="list-style-type: none">- Ringing in ears (tinnitus)- Balance difficulties- Vertigo- Can lead to permanent hearing loss

Congenital Syphilis Transmission

How

- Transplacental during maternal spirochetemia
- Direct contact with an infectious lesion during birth
- Not transferred into breast milk

When during gestation?

- At any time during gestation with increasing frequency as gestation advances.

Transmission according to syphilis stage:

- | | |
|----------------------------------|----------------------------------|
| • Primary or secondary syphilis: | 60% to 90% |
| • Early latent: | 40% |
| • Late latent syphilis: | 10% (2% after four years) |

Serologic Tests for Syphilis

Nontreponemal

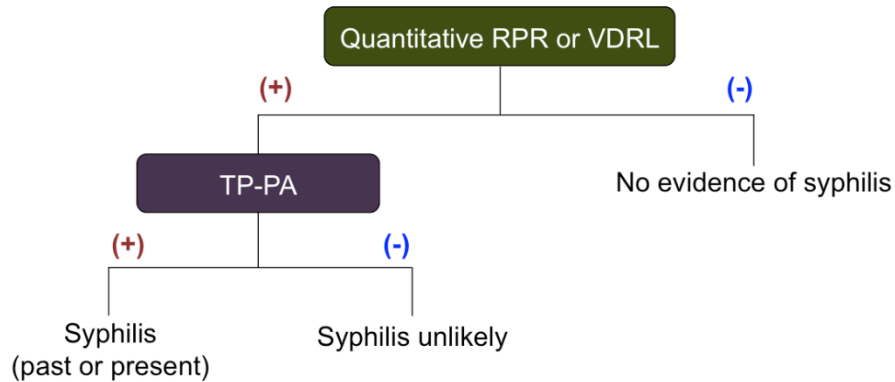
- VDRL, RPR
- Measure IgG and IgM to cardiolipin-cholesterol-lecithin antigen
- Qualitative or quantitative
- Used as a screening test
- Titer used to follow response to therapy

Treponemal

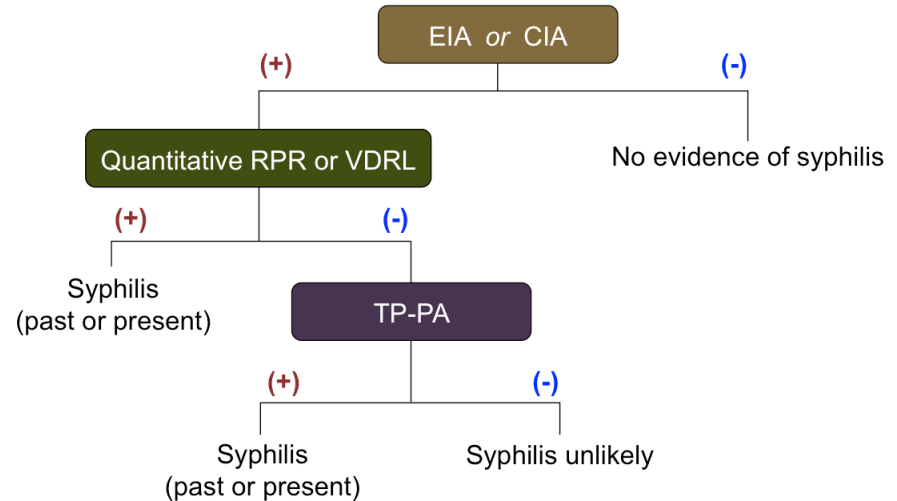
- CIE, EIA, FTA-ABS, TP-PA
- Measure IgG and IgM to Treponemal antigens
- Qualitative
- More specific
- Generally, remain reactive for life

Syphilis testing algorithms

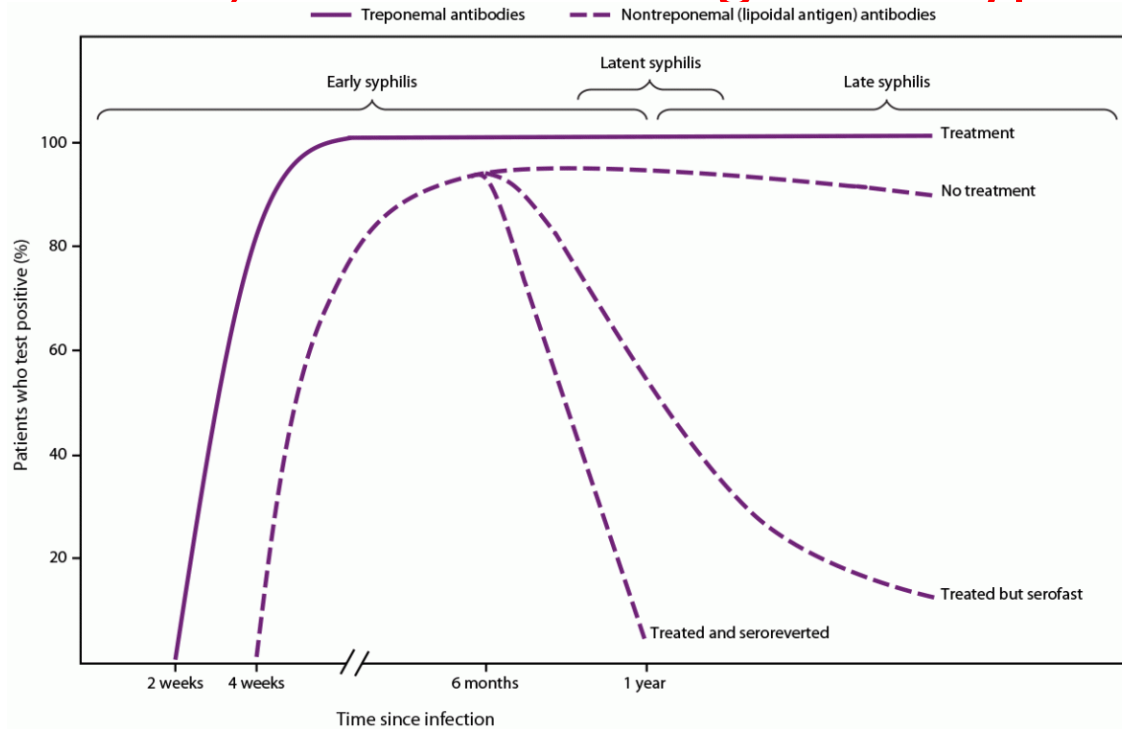
Traditional Sequence



Reverse Sequence



Serologic response to infection with *Treponema pallidum*, the causative agent of syphilis

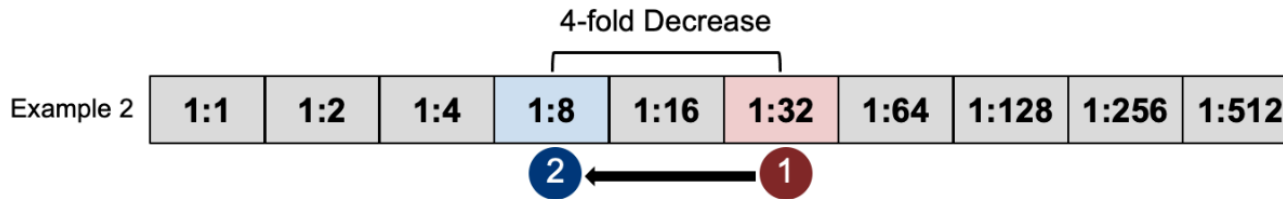


Treatment

STAGE		
<p>Primary & Secondary, Early non-primary, non secondary</p>	<p>Late Latent/or Unknown Duration</p>	<p>Neurosyphilis, ocular syphilis and otosyphilis</p>
<p>Benzathine penicillin 2.4 million units IM in a single dose</p> <p>Doxycycline 100mg BID for 14 days</p>	<p>Benzathine penicillin 2.4 million units total administered as 3 doses of 2.4 million units IM each at 1- week intervals</p> <p>Doxycycline 100mg BID for 28 days</p>	<p>Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units by IV every 4 hours or continuous infusion for 10-14 days</p> <p>Alternative: procaine penicillin G 2.4 million units IM 1x/day PLUS probenecid 500 mg orally 4x/day, both for 10-14 days</p>

Follow-up testing

- Adequate serologic response to treatment: ≥ 4 -fold decline in nontreponemal titer
 - Early Syphilis Primary/secondary/early latent: within 12 months
 - Late Syphilis: Late Latent, tertiary: within 24 months
 - Persons with HIV: within 24 months
- Serofast (lack of seroreversion): persistent nontreponemal titer after treatment



Who Wrote This?

"Something about the man's way of talking struck me and I watched him narrowly... a closer inspection showed me that one of his pupils was ever so little larger than the other. I did not say anything, for I had not the heart, but I knew that the fellow was as much condemned to death as though he were lying in the cell at Newgate."



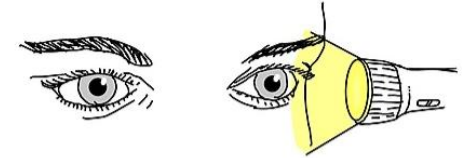
Who Wrote This?

Argyll Robertson pupils describe the physical exam findings associated with advanced stages of syphilis. Characterized by bilateral small irregular and asymmetric pupils that fail to constrict in response to bright light but exhibit constriction during near vision tasks, Argyll Robertson pupils are a diagnostic marker for tertiary syphilis.

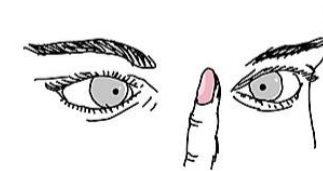


Sir Arthur Conan Doyle, the author of the 1894 short story, "A Medical Document"

Argyll Robertson pupil



Pupils DO **NOT** constrict when exposed to bright light. ("light reflex")



Pupils DO constrict on a near object. ("accommodation reflex")

Specialty

Neurology

Risk factors

A highly **specific** sign of **neurosyphilis**

Diagnostic method

Pupillary light reflex and accommodation reflex tests

References

- ❖ CDC STD 2021 Treatment Guideline: <https://www.cdc.gov/std/treatment-guidelines/default.htm>
- ❖ STD Prevention Training Centers: <https://www.cdc.gov/std/projects/nnptc.htm>
- ❖ STD online self-study: <https://www.std.uw.edu/>
- ❖ CDC self-study: <http://www.cdc.gov/std/training/std101/home.htm>
- ❖ USPS Task Force: <https://www.uspreventiveservicestaskforce.org/uspstf/>

Resources

- National Clinician Consultation Center
<http://nccc.ucsf.edu/>
 - HIV Management
 - Perinatal HIV
 - HIV PrEP
 - HIV PEP line
 - HCV Management
 - Substance Use Management
- Present on ECHO
<https://hsc.unm.edu/scaetc/programs-services/echo.html>
- AETC National HIV Curriculum
<https://aidsetc.org/nhc>
- AETC National Coordinating Resource Center
<https://targethiv.org/library/aetc-national-coordinating-resource-center-0>
- HIVMA Resource Directory
<https://www.hivma.org/globalassets/ektron-import/hivma/hivma-resource-directory.pdf>
- Additional trainings
scaetcecho@salud.unm.edu
- www.scaetc.org

IHS/Tribal Resources

- Sexually Transmitted Infections (STI) Initiative: STI Toolkit. https://www.ihs.gov/sites/nptc/themes/responsive2017/display_objects/documents/sti/Express-STI-Guide.pdf
- <https://www.indiancountryecho.org/resource-hubs/syphilis-resources/> The STOP SYPHILIS campaign offers free materials, including print materials, social media posts, and short educational videos.
- Go to www.stopsyphilis.org For questions about field testing and treatment policies and procedures, contact Tina Tah, Public Health Nursing Consultant, by e-mail at tina.tah@ihs.gov