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An update on Congenital syphilis



Amruta Padhye MD, FAAP
Asst Prof of Child Health, Pediatric Infectious Diseases
MU Children's Hospital, Columbia

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DISCLOSURES

- Site principal investigator: Moderna TX, COVID-19 vaccine trial
- Physician on the MO DHSS Syphilis advisory group
- I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.



LEARNING OBJECTIVES

Recognize

- The scale of the ongoing epidemic of syphilis

Describe

- The different stages of syphilis and presentation in newborns and children

Select

- Appropriate tests for evaluation of syphilis in all ages

Ensure

- Ensure appropriate syphilis screening in mother of newborn

Manage

- Newborn/infants at risk for congenital syphilis (screen & treat)



OUTLINE



Origins and cure: brief history

Natural course of syphilis

Presentation in newborn and children

Epidemiology of syphilis in the US and Missouri

CDC/ Redbook algorithm

Cases

Bienvenu, C. Y. & Federal Art Project, S. *Their health depends on you Destroy syphilis* // C.Y. Bienvenu. Louisiana, None. [Louisiana: wpa war services of la., between 1941 and 1943] [Photograph] Retrieved from the Library of Congress, <https://www.loc.gov/item/98518284/>.



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HUMAN TREPONEMATOSES

Initial infection:

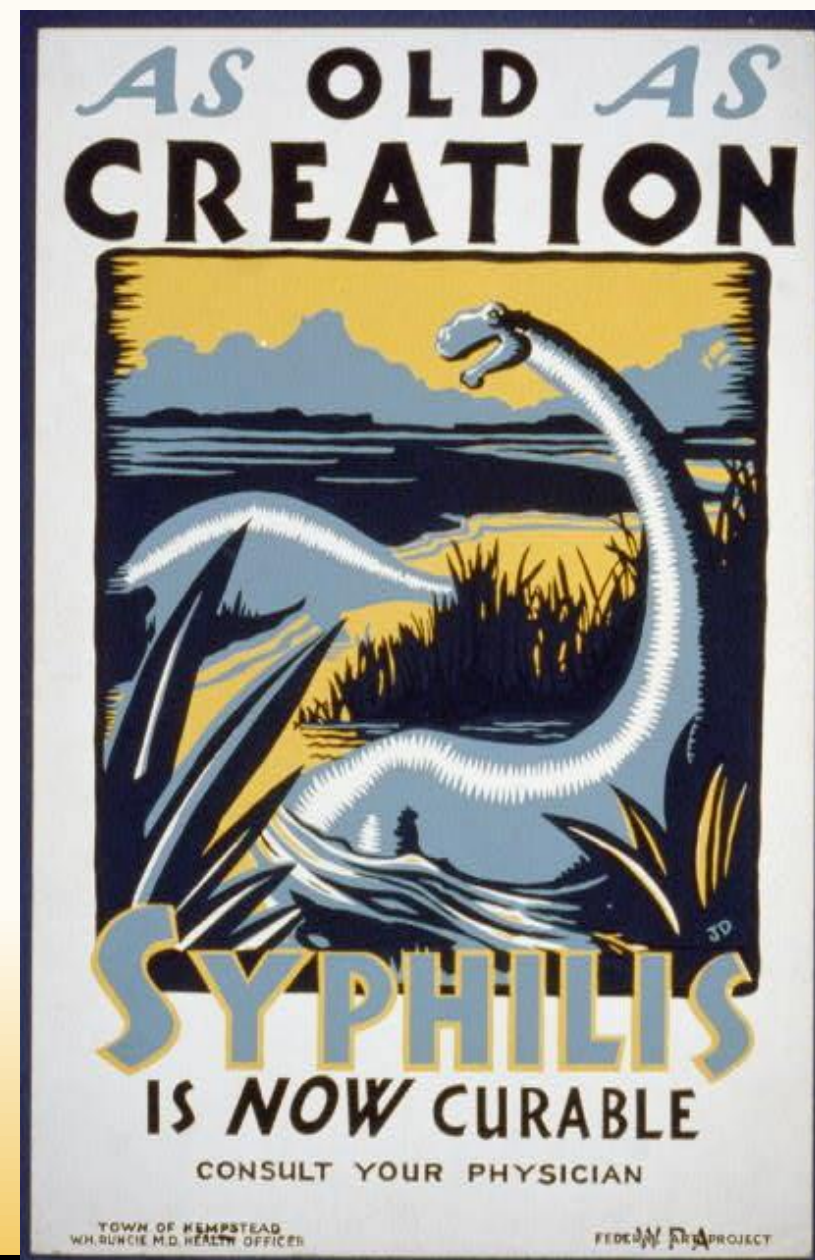
- exposure of mucosal surfaces or traumatized skin to bodily fluids containing pathogenic treponemes

Spread

- invasion of epithelia or mucosal membrane → multiply → disseminate by blood or lymphatics
- **Syphilis:** *T. pallidum* spp. *pallidum*
- **Global distribution**
- **Transmission:** sexual, vertical
- **Untreated:** many late-stage complications including CNS
- **Endemic treponematoses: Geographic distribution**
 - Yaws: *T. pallidum* spp. *pertenue*
 - Bejel (endemic syphilis): *T. pallidum* spp. *endemicum*
 - Pinta: *T. carateum*
- **Yaws:** Equatorial distribution
 - disease of the skin, joints, soft tissue, and bone
 - transmitted by skin-to-skin contact, no vertical
 - initial papillomatous lesions in lower extremities → ulcers
 - CNS complications rare
 - Untreated: severe destructive osteitis → deformity



NOT THAT OLD...



(1936) *As old as creation Syphilis is now curable: Consult your physician* // JD. Hempstead New York, 1936.
[New York: WPA Federal Art Project, or 1937] [Photograph] Retrieved from the Library of Congress,
<https://www.loc.gov/item/98516350/>.



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HISTORY OF SYPHILIS

In 1495 an epidemic of a new and terrible disease broke out among the soldiers of Charles VIII of France when he invaded Naples in the first of the Italian Wars, and its subsequent impact on the peoples of Europe was devastating – this was syphilis, or *grande verole*, the “great pox”



French troops under Charles VIII entering Florence, 17 November 1494, by [Francesco Granacci](#)



- Columbus sailed the ocean blue in 1492.
- But on returning home, his sailors unknowingly were carrying a disease never before known in Europe, syphilis.
- By 1495, the disease, called the "Great Pox," had spread across Europe, killing five million people.

Read more: <http://www.digitaljournal.com/life/health/did-columbus-bring-syphilis-back-from-the-new-world/article/420611#ixzz5oj8gi9dS>



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- The poem recounted the mythical origin of syphilis. A shepherd named Syphilus tended the sheep of Alcithoüs, the king of Atlantis. In an act of devotion to his master, Syphilus overturned the altars dedicated to Apollo and rededicated them to King Alcithoüs. Apollo gave Syphilus the venereal disease as punishment for his transgressions. The Atlantians named the disease after their cursed shepherd.
- The shepherd was cured by ingesting the bark of the guaiacum tree.
- A Syrian hunter named Ilceus also appeared in the poem and was stricken by syphilis but found his cure via mercury treatments.

The term "syphilis" was coined in 1530 by Girolamo Fracastoro in his 1530 poem *Syphilis sive morbus gallicus*



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WHAT SYPHILIS WAS CALLED BEFORE IT WAS CALLED SYPHILIS?



TREATMENTS FOR SYPHILIS

- Early 16th century
 - Guaiacum, or holy wood
 - Mercury skin inunctions or ointments [used since 1363 for epidemics]
 - ‘A night with Venus, lifetime with mercury’
 - Sweat baths (induced salivation and sweating eliminated the syphilitic poisons)
- Treatment was the province of barber and wound surgeons
- Inoculation (inoculating syphilis like vaccinia for small pox)



The Martyrdom of Mercury. The scourge of Venus and Mercury, represented in a treatise of the venereal disease. John Sintelaer. 1709. London: G. Harris

THE ORGANISM “TREPONEMA PALLIDUM”



- 1905: Spirochaeta pallida discovered by
 - Fritz Richard Schaudinn, a German zoologist &
 - Erich Hoffmann, a dermatologist,
- 1906:
 - August Paul von Wassermann, a German bacteriologist and an assistant of Robert Koch, developed a complement fixation serum antibody test for syphilis – the “Wasserman reaction”

TREATMENTS FOR SYPHILIS

- Paul Ehrlich (started working on Arsenic in 1906, Compound #606 in 1909)
- In 1909, Salvarsan and in 1910, Neosalvarsan
- Ehrlich awarded Nobel prize in 1908 for the discovery of this 'magic bullet'
 - Long treatment courses
 - Cured only primary and secondary syphilis
- In 1917, Julius Wagner, Austrian physician used Malariotherapy, infecting the patient with malaria, then treating the malaria with quinine
- In 1936, 'Electropyrexia'

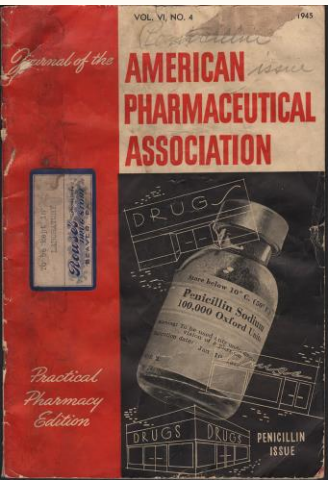


Salvarsan treatment kit for syphilis, Germany, 1909-1912
(Wikipedia Commons)



CURRENT TREATMENT OF SYPHILIS

- **1928: Discovery of penicillin Alexander Fleming**
- **1941: First used in patient**
- **1943: Introduced as treatment for syphilis by John Mahoney, Richard Arnold and AD Harris.**
 - Mahoney and his colleagues at the US Marine Hospital, Staten Island, treated four patients with primary syphilis chancres with IM penicillin four-hourly for 8 days by which time the syphilis had been cured.



THE story of Penicillin is a shining example of international cooperation for the good of mankind.

From Fleming's observations in 1929, through the pioneer work of Florey's research team, to the large-

individual British and American scientists, the Rockefeller Foundation, the National Research Council, the U. S. Department of Agriculture, the War Production Board, the American Pharmaceutical Industry, and the

1943: Bristol-Myers acquires Cheplin Laboratories in Syracuse, New York, enabling it to mass produce penicillin during WWII.
1944: Squibb opens **the world's largest penicillin production** facility in New Brunswick, New Jersey..



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PENICILLIN – HOW COME SYPHILIS IS STILL SUSCEPTIBLE?

- 1941: Penicillin used for S aureus
- 1942: Penicillin resistance detected in S aureus
- 1943: Penicillin used for Syphilis
- 2022: Penicillin resistance still never reported
- **T pallidum lacks Mobile genetic elements (plasmids, bacteriophage, transposons)**
Nobody has shared a penicillinase with T pallidum
- Why?
 - Adaptation to a specific host (us!)
 - Genome size reduction (1.14 Mb compared to E coli 4.6 Mb)
 - Loss of ability to replicate outside of the host
- T pallidum does contain a PCN binding protein, Tp47 with beta-lactamase activity
- Tp47 hydrolyzes PCN and creates byproducts that also bind Tp47 more strongly than PCN

PATHOPHYSIOLOGY: *GREAT IMITATOR*

William Osler:

“I often tell my students that it is the only disease which they require to know thoroughly. Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you.”



USPHS SYPHILIS STUDY AT TUSKEGEE

- Intended to observe the natural history of untreated syphilis
- Did not collect informed consent
- Did not offer treatment even after widely available
- 1974, the National Research Act was signed into law, creating the [National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research](#) : identified basic principles of research conduct and suggested ways to ensure those principles were followed.

Timeline

1932

The U.S. Public Health Service (USPHS) engages the Tuskegee Institute in Macon, AL in the USPHS Tuskegee Syphilis Study.²

Mid-1940s

Penicillin [becomes treatment of choice for syphilis](#), but men in study are not treated.

1972

[First news article](#) [↗](#) about the study.

[The study ends](#) [↗](#), on recommendation of an Ad Hoc Advisory Panel convened by the Assistant Secretary for Health and Scientific Affairs.

1997

President Clinton issues a [formal Presidential apology](#) [↗](#).

<https://www.cdc.gov/tuskegee/faq.htm>

Vonderlehr to Clark, October 20, 1932, Records of the USPHS Venereal Disease Division, Record Group 90, National Archives, Washington National Record Center, Suitland, Maryland.

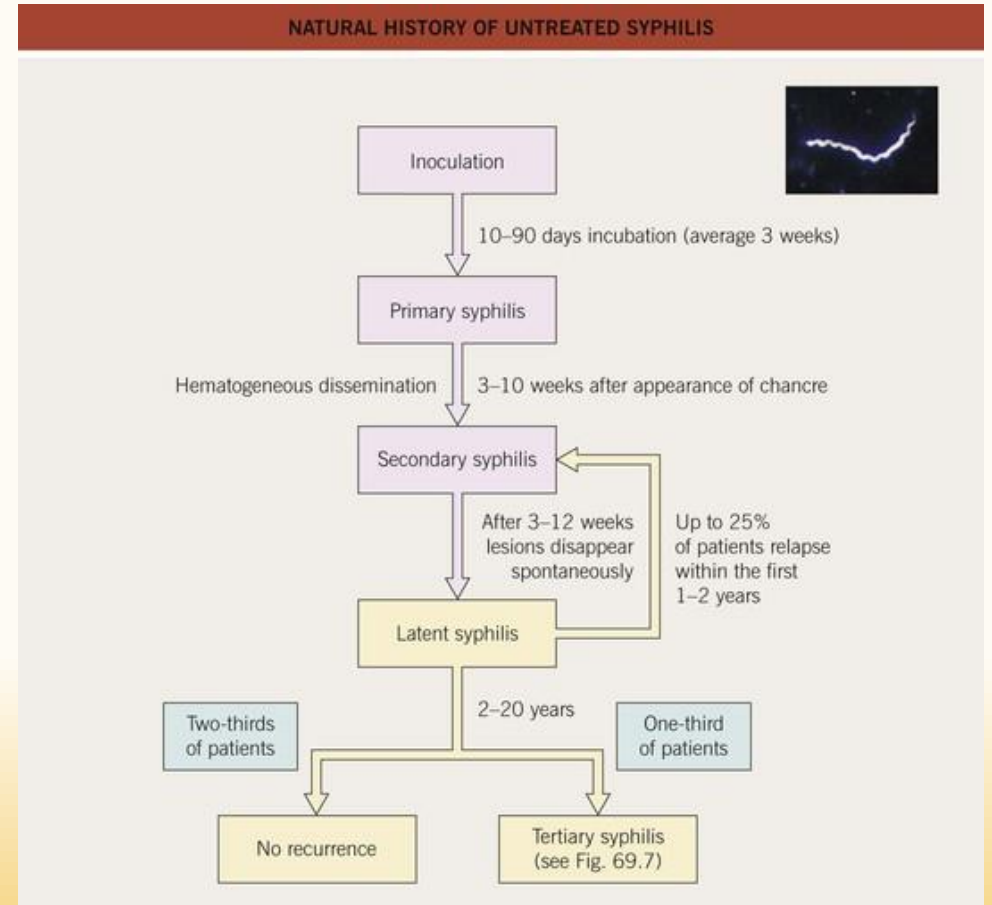
Gray, Fred D. The Tuskegee Syphilis Study: An Insider's Account of the Shocking Medical Experiment Conducted by Government Doctors against African American Men. Montgomery: Fred D. Gray, 2013.



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NATURAL HISTORY OF UNTREATED SYPHILIS

- Chancres spontaneously resolve after a few weeks
- In patients with no recurrence:
 - RPR becomes negative in 50% and remains positive in 50%.



• Adapted from Rein MF, Musher DM. Late syphilis. In: Rein MF (Ed.), *Atlas of Infectious Diseases, Vol. V: Sexually Transmitted Diseases*. New York: Current Medicine, 1995:10.1–10.13. Inset figure: Adapted from Morse SA, et al. *Atlas of Sexually Transmitted Diseases and AIDS*, 3rd ed. London: Mosby; 2003. <https://clinicalgate.com/sexually-transmitted-diseases/>



ACQUIRED SYPHILIS: PRIMARY STAGE (OR “PRIMARY SYPHILIS”)

- 1 or more painless indurated ulcers (chancres) of skin / mucous membranes at site of inoculation
- Most commonly appear on genitalia but may appear elsewhere, depending on the sexual contact responsible for transmission (eg, oral, anal)
- Average 3 weeks after exposure (10–90 days) and heal spontaneously in a few weeks
- Adjacent lymph nodes frequently enlarged but are nontender.
- Chancres sometimes are not recognized clinically and sometimes still are present during the secondary stage
 - **Why painless?** Infects the nerves



Tongue lesion



SECONDARY STAGE (OR “SECONDARY SYPHILIS”)

- 1 to 2 months later: fever, sore throat, muscle aches, rash, mucocutaneous lesions, and generalized lymphadenopathy (50-85%).
- **Polymorphic maculopapular rash** is generalized and typically includes the palms and soles
- In moist areas around the vulva or anus, hypertrophic papular lesions (**condyloma lata**) can occur and can be confused with condyloma acuminata secondary to HPV
- Malaise, splenomegaly, headache, alopecia, and arthralgia also can be present.
- Secondary syphilis can be mistaken for other conditions, because its **signs and symptoms are nonspecific**.
- **Resolves spontaneously** without treatment in approximately 3 to 12 weeks, leaving the infected person completely asymptomatic.



LATENT SYPHILIS

- Variable latent period follows
- Period after infection when patients are seroreactive but demonstrate no clinical manifestations of disease.
- Sometimes interrupted in first few years by recurrences of symptoms of secondary syphilis.
- **Early latent:** syphilis acquired within the preceding year
- **Late latent:** syphilis > 1yr or unknown duration



TERTIARY SYPHILIS

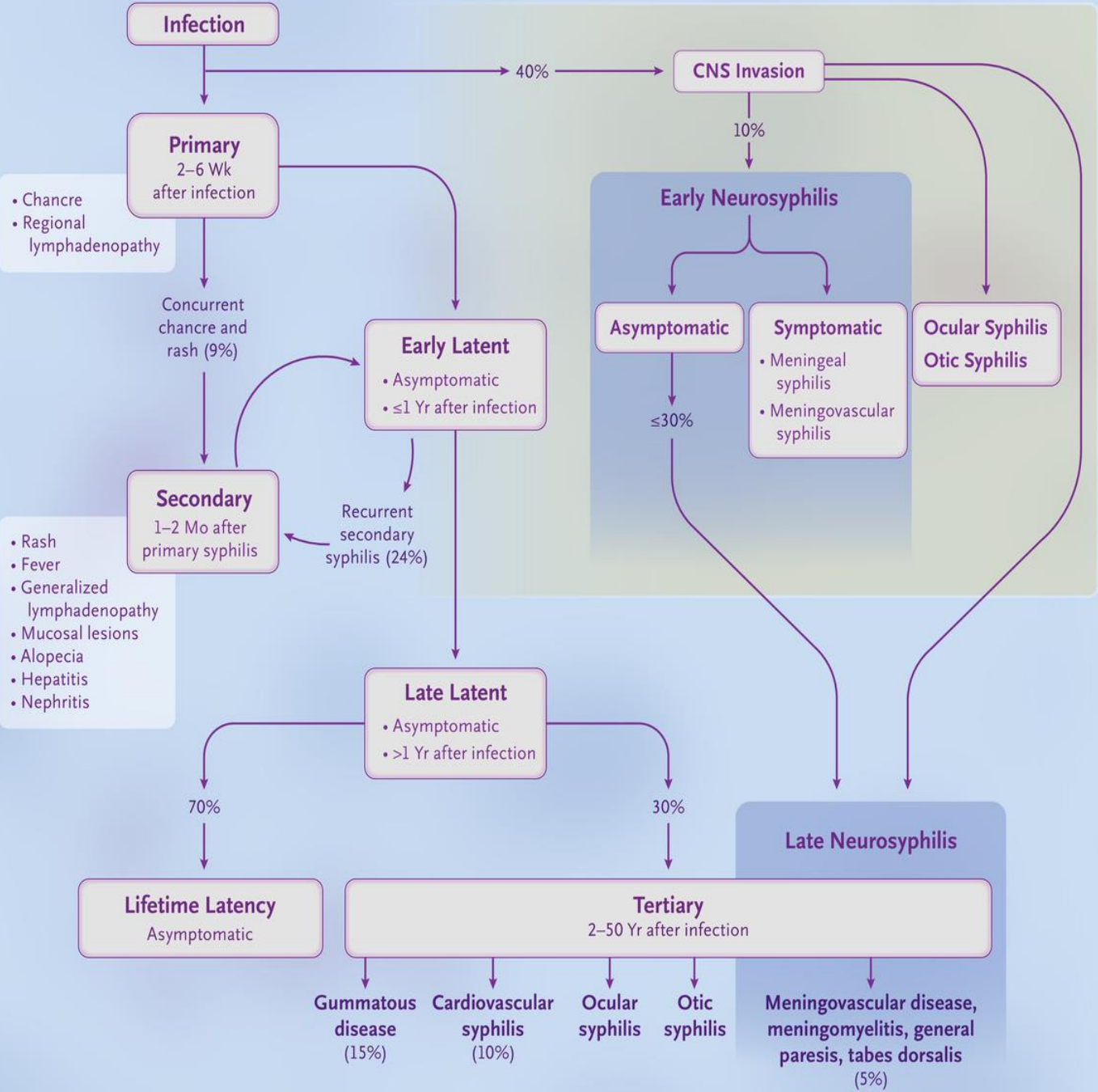
- 15 to 30 years after the initial infection
- Gumma formation (soft, noncancerous growths that can destroy tissue)
- Cardiovascular involvement (including aortitis).

NEUROSYPHILIS

- CNS infection can occur at any stage of infection
- Especially in people infected with HIV and neonates with congenital syphilis.
 - Syphilitic meningitis
 - Uveitis
 - Seizures
 - Optic atrophy
 - Dementia
 - Posterior spinal cord degeneration (tabes dorsalis, including a characteristic high-stepping gait with the feet slapping the ground with each step because of loss of proprioception).



Natural History of Untreated Syphilis.



KG Ghanem et al. N Engl J Med 2020

SYPHILIS IN PREGNANCY

- Maternal risk factors
 - sex with multiple partners
 - sex in conjunction with drug use or transactional sex
 - late entry to prenatal care (i.e., first visit during the second trimester or later) or no prenatal care
 - methamphetamine or heroin use
 - incarceration of the woman or her partner
 - unstable housing or homelessness
 - HIV infection (also syphilis co-infection increases risk of maternal to child HIV)
- Providers should obtain information concerning
 - risk behaviors
 - treatment of sex partners to assess t risk for reinfection.



CONGENITAL SYPHILIS TRANSMISSION

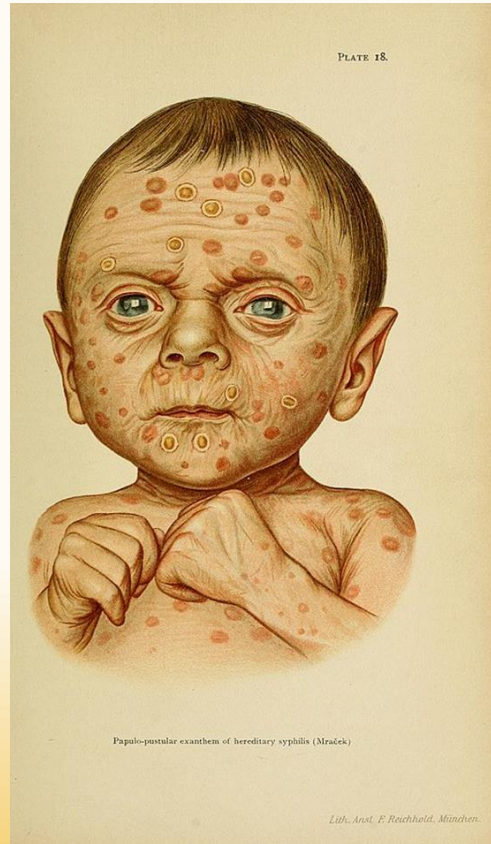
- At any stage of maternal infection via transplacental transmission at any time
- Contact with maternal lesions at the time of delivery
- Untreated early syphilis in pregnancy:
 - Up to 40% of will result in spontaneous abortion, stillbirth, or perinatal death
 - Rate of maternal-fetal transmission
 - Primary and secondary: 60% to 100%
 - Early latent: 40%
 - Late latent: <8%
- Risk of transmission increases directly with gestation at time of maternal infection
- Not transmitted by milk but may occur if infected lesion on breast



CONGENITAL SYPHILIS

Intrauterine infection

- Stillbirth
- Hydrops fetalis
- Preterm birth
- Asymptomatic at birth



Symptomatic at birth

- Hepatosplenomegaly
- Snuffles (copious nasal secretions)
- Lymphadenopathy
- Muco-cutaneous lesions
- Pneumonia
- Osteochondritis
- Periostitis
- Pseudoparalysis
- Edema
- Rash (maculopapular consisting of small dark red-copper spots that is most severe on the hands and feet)
- Hemolytic anemia
- Thrombocytopenia at birth or within the first 4 to 8 weeks of age

Plate description reads: 'Papulopustular Exanthema. Hereditary Syphilis.'

A manual of syphilis and the venereal diseases,
By Hyde, James Nevins, 1840-1910; Montgomery, Frank Hugh, 1862-1908



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CONGENITAL SYPHILIS

Untreated infants: late manifestations, which usually appear after 2 years of age

- central nervous system (CNS)
- bones and joints, teeth, eyes, and skin
- interstitial keratitis (5–20 years of age)
- eighth cranial nerve deafness (10–40 years of age)
- Hutchinson triad - Hutchinson teeth (peg-shaped, notched central incisors), anterior bowing of the shins, frontal bossing
- mulberry molars
- saddle nose
- rhagades (perioral fissures)
- Clutton joints (symmetric, painless swelling of the knees)

Late manifestations can be prevented by treatment of early infection





Portrait of Gerard de Lairesse, 1665–67

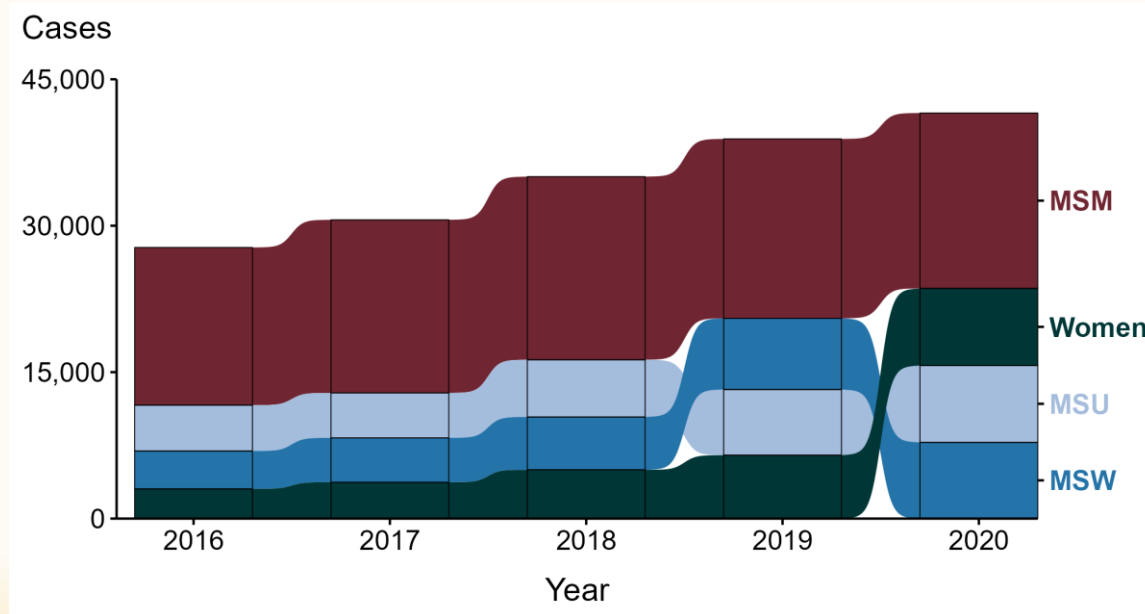
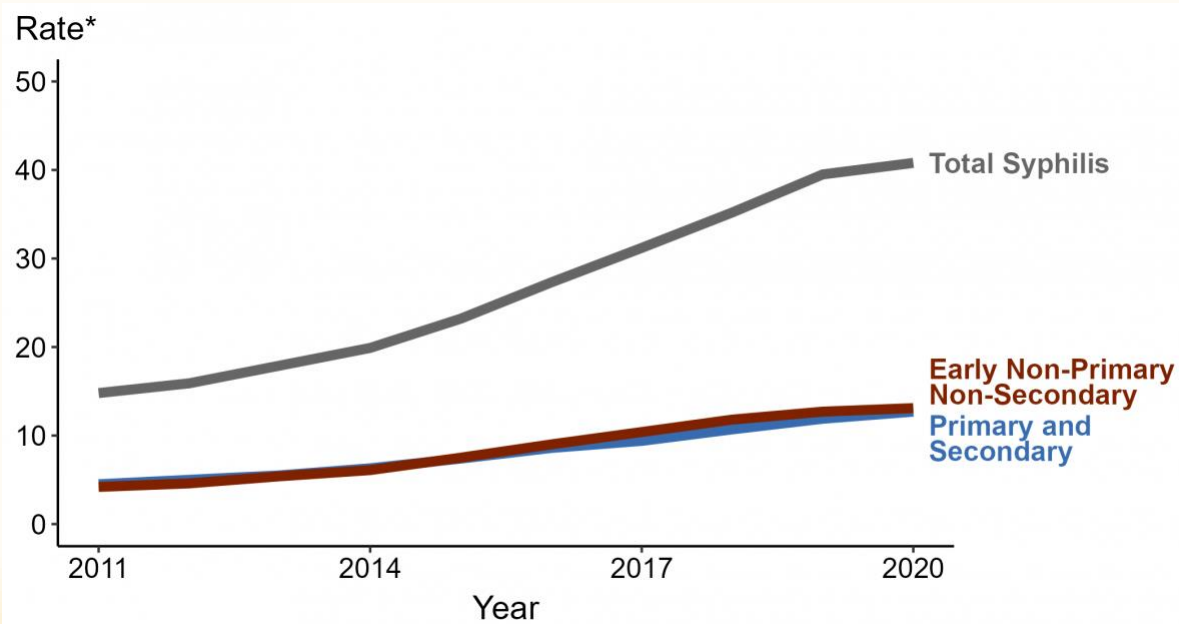
by his contemporary Rembrandt
(both Dutch Golden age painters)



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Sexually Transmitted Disease Surveillance 2020

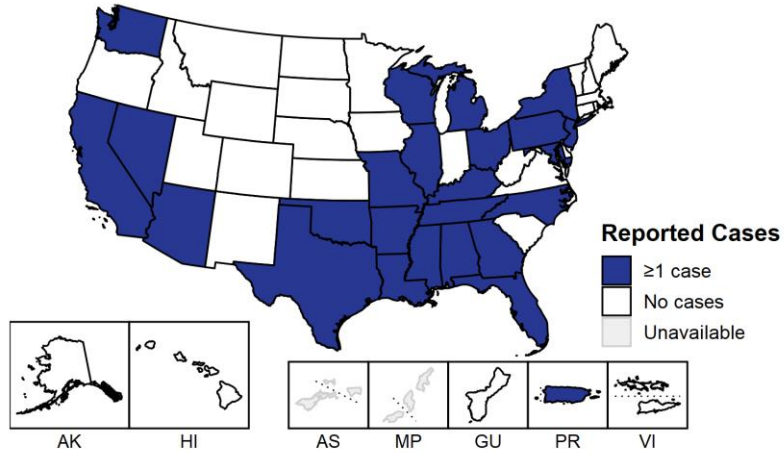
Sexually Transmitted Disease Surveillance 2020



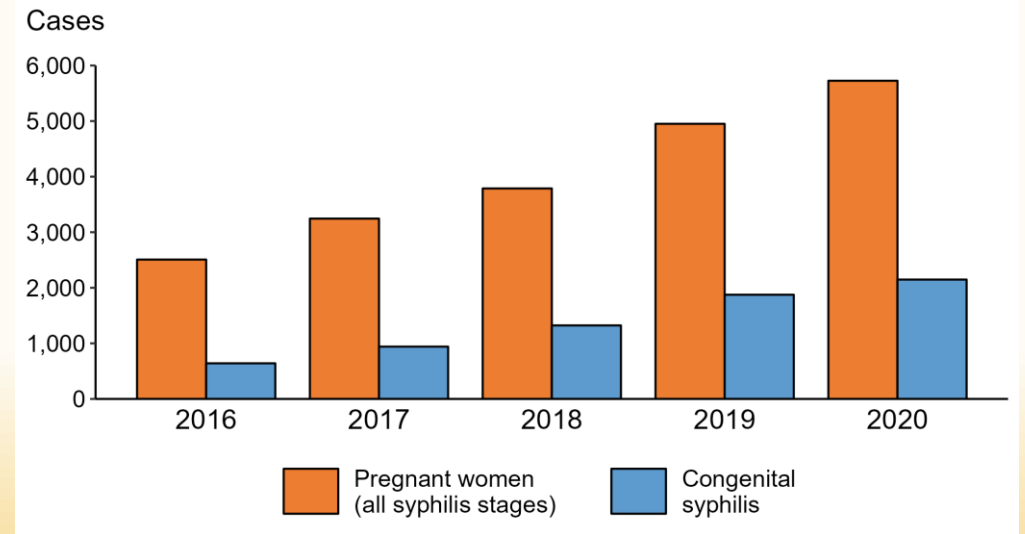
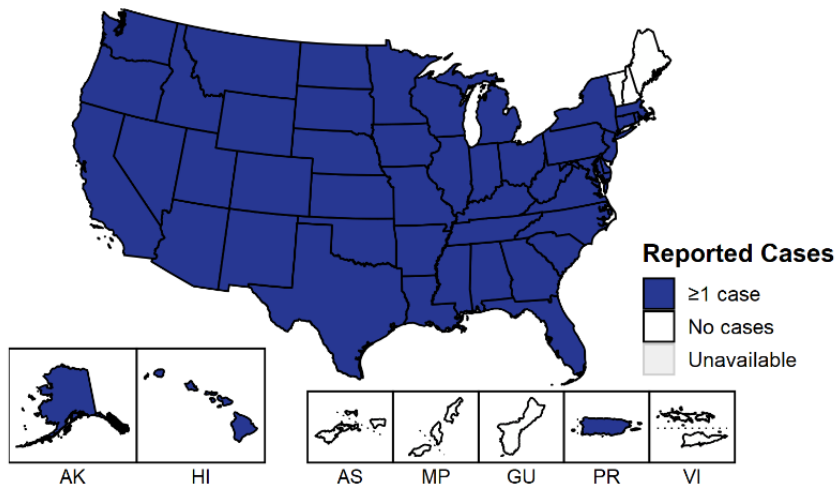
Congenital syphilis rate in 2020

- **57.3 cases per 100,000 live births**
- 15% increase from 2019
- 254% increase from 2016
- Mirrored increase in P&S syphilis in women (15-44yr)

2011



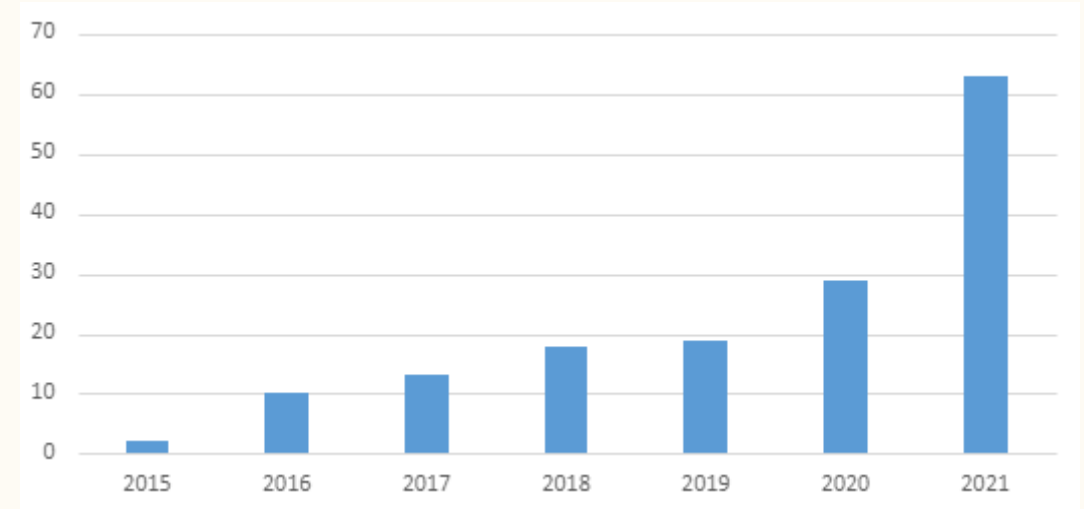
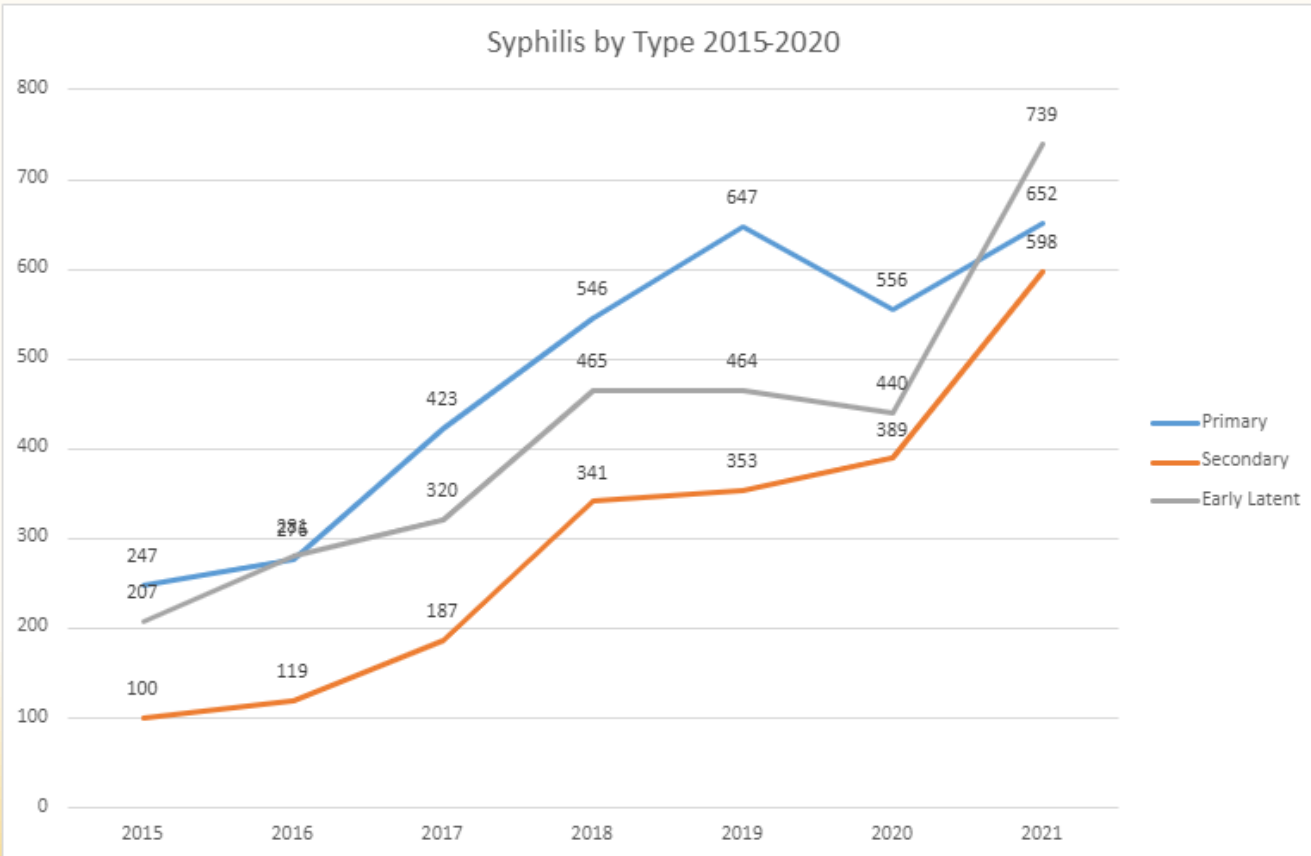
2020



MISSOURI

Data courtesy: MO DHSS

Congenital syphilis 2015-2020



2015	2
2016	10
2017	13
2018	18
2019	19
2020	29
2021	63



SEROLOGIC TESTS FOR SYPHILIS

- Two antibody types are detected to determine syphilis diagnosis:
 - Treponemal antibodies
 - Antibodies directed against *T. pallidum*
 - Non-treponemal antibodies
 - Antibodies directed against antigens such as cardiolipin, cholesterol, and lecithin
 - Released in response to *T. pallidum* active infection



TREPONEMAL AND NON-TREPONEMAL TESTS

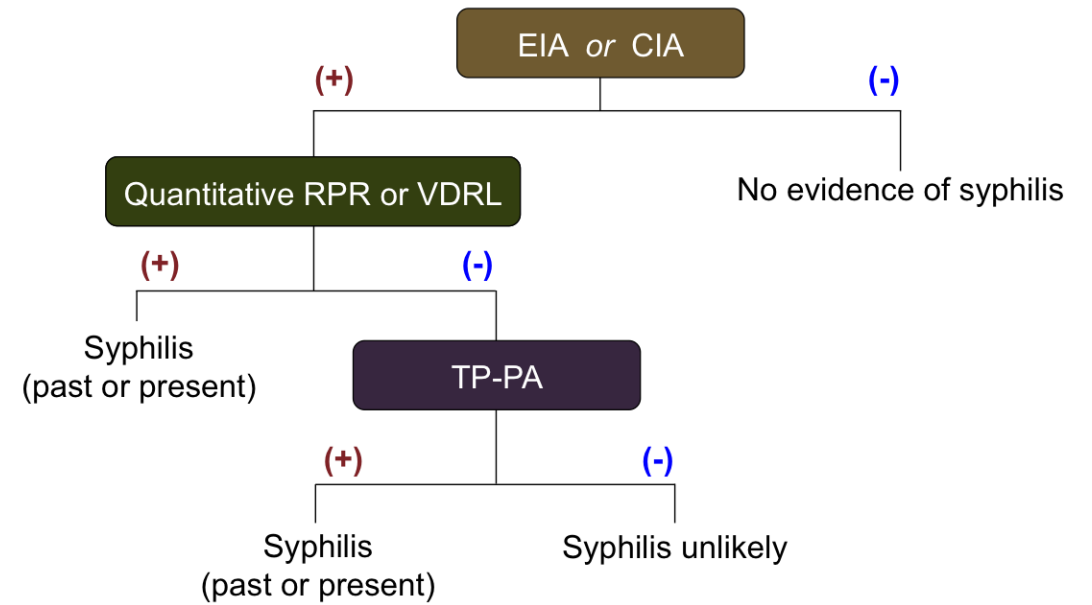
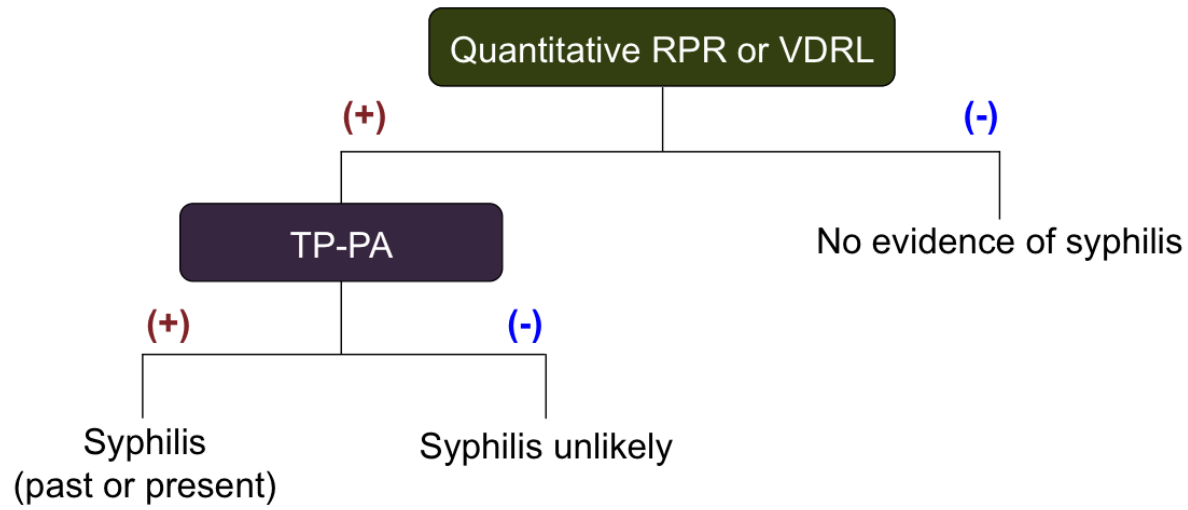
Treponemal serologic tests

- Treponema pallidum particle agglutination (TP-PA)
- Enzyme immunoassay (EIA)
- Chemiluminescent immunoassay (CLIA)
- Fluorescent treponemal antibody absorption (FTA-ABS)

Non-treponemal serologic tests: Quantitative tests to evaluate treatment progress

- Venereal Disease Research Laboratory (VDRL)
- Rapid plasma reagin (RPR)
- Unheated serum regain (USR)
- Tolidine red unheated serum (TRUST)





Screening for Syphilis Infection in Pregnant Women: A Reaffirmation Evidence Update for the U.S. Preventive Services Task Force

Evidence Synthesis, No. 167

Investigators: Jennifer S. Lin, MD, MCR, Michelle Eder, PhD, and Sarah Bean, MPH.

Rockville (MD): [Agency for Healthcare Research and Quality \(US\)](https://www.evidencebasedpractice.org/); 2018 Sep. Report No.: 18-05238-EF-1



REVERSE ALGORITHM ADVANTAGES

- Treponemal IgG screening tests are highly sensitive and specific
 - fewer false negatives than non-treponemal assays (presumably due to detection of latent syphilis)
- Can be performed on automated platforms
 - Increased testing volume while reducing labor cost
- More effective for diagnosis of secondary, latent, and late syphilis
 - Treponemal assays are not subject to prozone reactions which have been reported as a rare occurrence in nontreponemal (RPR) assays



PEARLS OF LABORATORY MEDICINE

Diagnosis of Syphilis Using the Reverse Algorithm

Gregory J. Berry, PhD

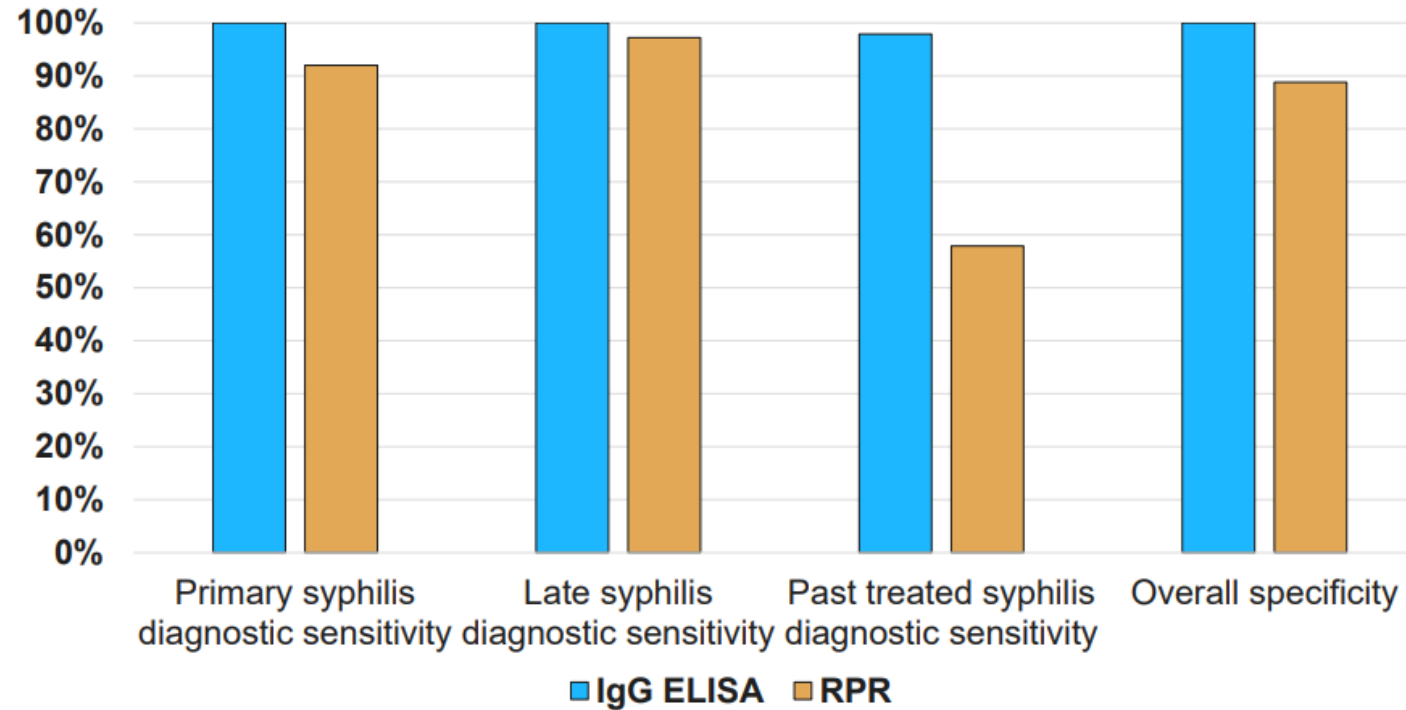
University of Texas Medical Branch

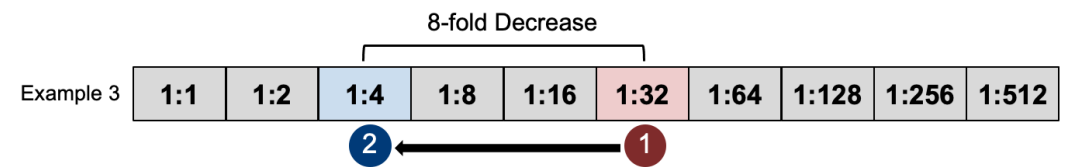
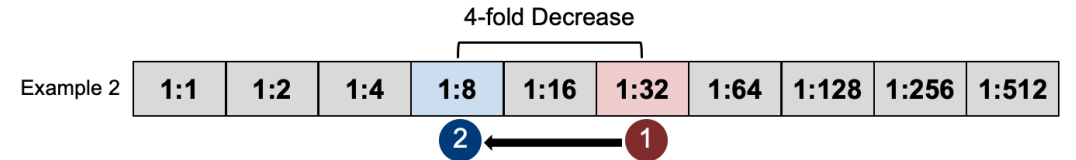
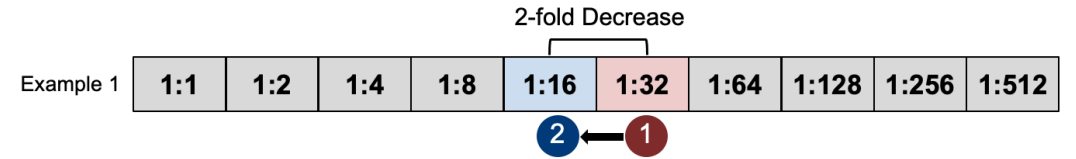
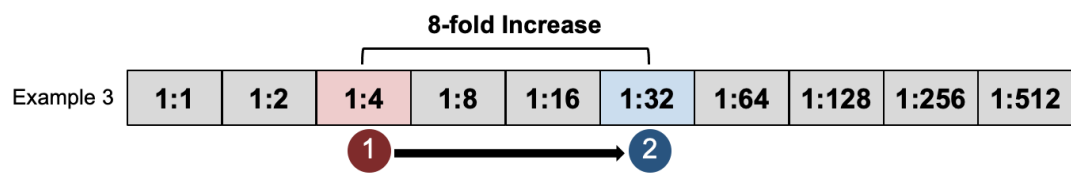
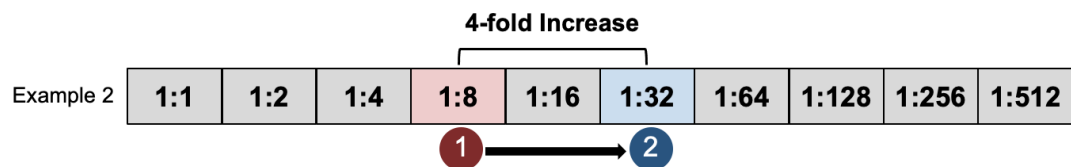
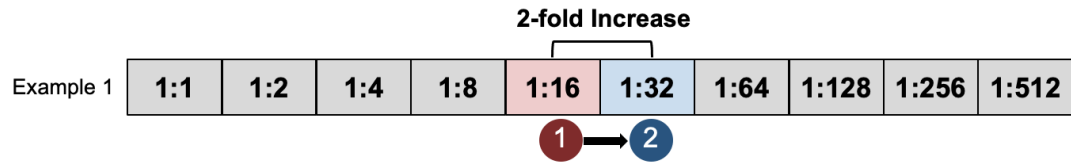
DOI: 10.15428/CCTC.2015.252692

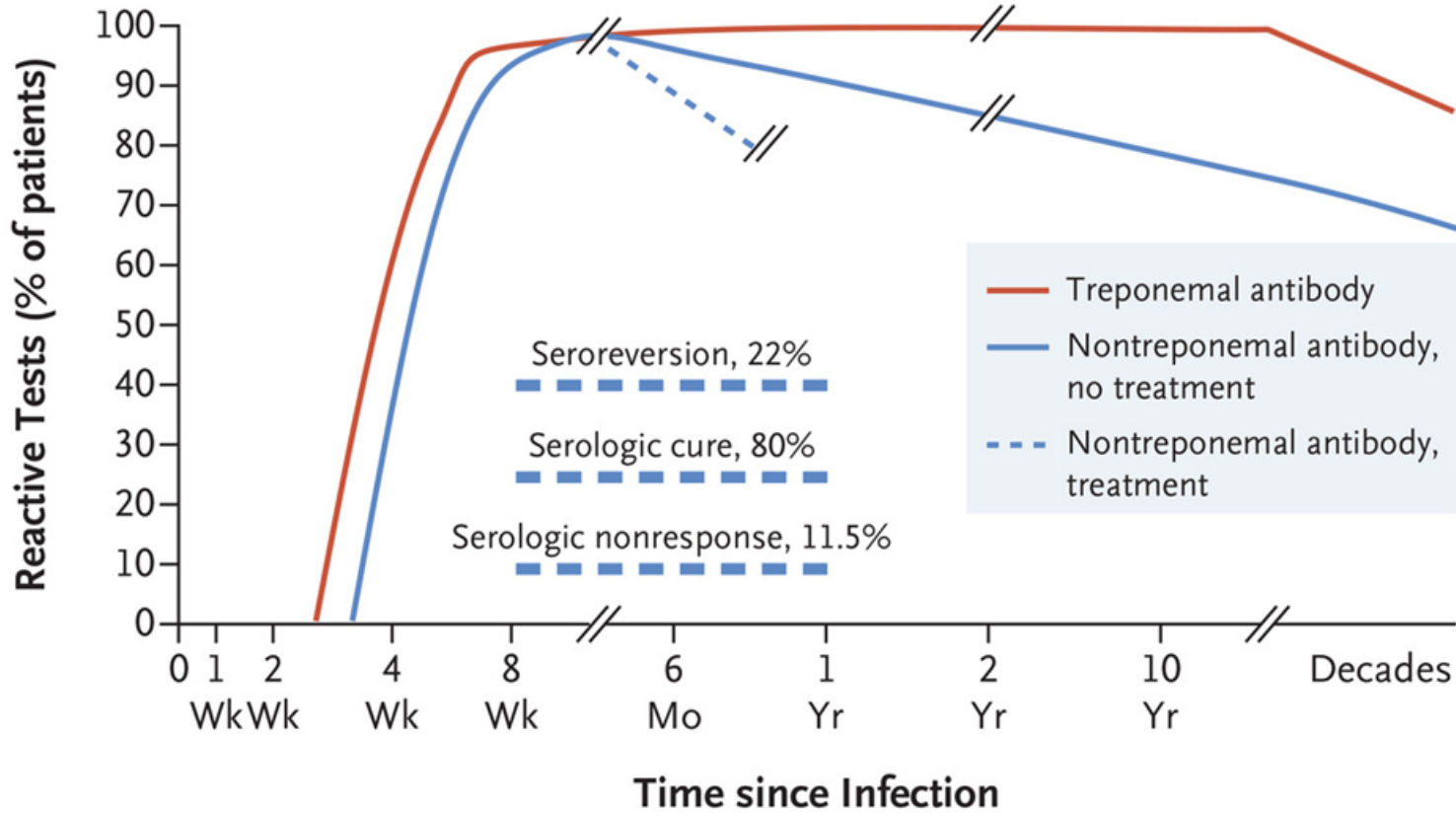
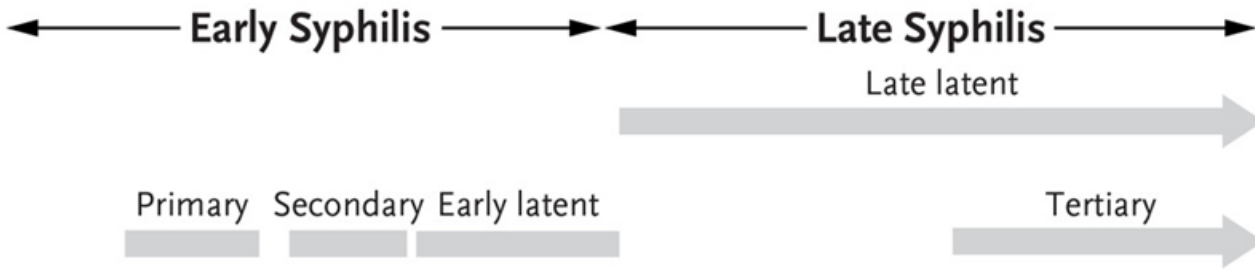


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Sensitivities and specificities of RPR test and IgG ELISA in comparison to results of FTA-Abs test for IgG







Serologic Responses (in Serum) throughout the Natural History of Treated and Untreated Syphilis.

KG Ghanem et al. N Engl J Med 2020

Sexually Transmitted Infections Treatment Guidelines, 2021

STI Treatment Guidelines

2021 RECOMMENDATIONS NOW AVAILABLE



CDC's Sexually Transmitted Infections (STI) Treatment Guidelines, 2021 provides current evidence-based prevention, diagnostic and treatment recommendations that replace the 2015 guidance. The recommendations are intended to be a source for clinical guidance. Healthcare providers should always assess patients based on their clinical circumstances and local burden.



STI Treatment Guide Mobile App

Now available for Apple and Android devices.



SYPHILIS



POCKET GUIDE FOR PROVIDERS



U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

TREATMENT

Primary, Secondary, or Early Latent (<1 year)

- Benzathine penicillin G 2.4 million units IM in a single dose

Late Latent (>1 year), Latent Syphilis of Unknown Duration, or Tertiary Syphilis with Normal CSF Examination

- Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

Pregnant women

- Pregnant women should be treated with the penicillin regimen appropriate for their stage of infection. (See CDC STD Treatment Guidelines)

TREATMENT (CONTINUED)

Neurosyphilis, Ocular Syphilis

- Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days
- Additional doses of benzathine penicillin are not indicated in patients with HIV infection.
- Additional doses of penicillin in pregnant women with early syphilis may be indicated if evidence of fetal syphilis on ultrasound.

Note: For treatment information on congenital syphilis and syphilis in children, please see CDC STD Treatment Guidelines at www.cdc.gov/std/treatment/.

Penicillin Allergies

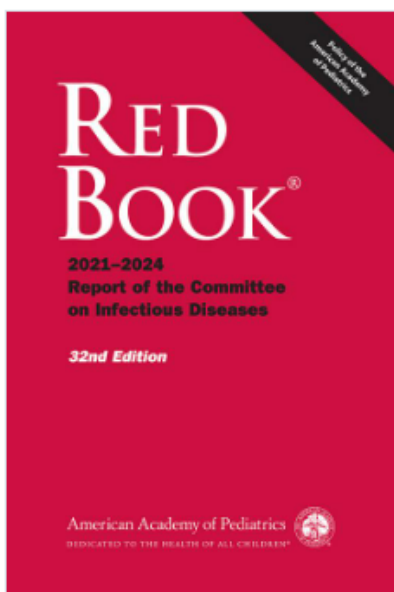
- See CDC STD Treatment Guidelines

Penicillin Shortages

- See www.cdc.gov/std/treatment/drugnotices/bicillinshortage.htm



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Red Book: 2021–2024 Report of the Committee on Infectious Diseases (32ND EDITION) ✓

By Committee on Infectious Diseases, American Academy of Pediatrics;
David W. Kimberlin, MD, FAAP; Elizabeth D. Barnett, MD, FAAP; Ruth Lynfield, MD, FAAP;
Mark H. Sawyer, MD, FAAP

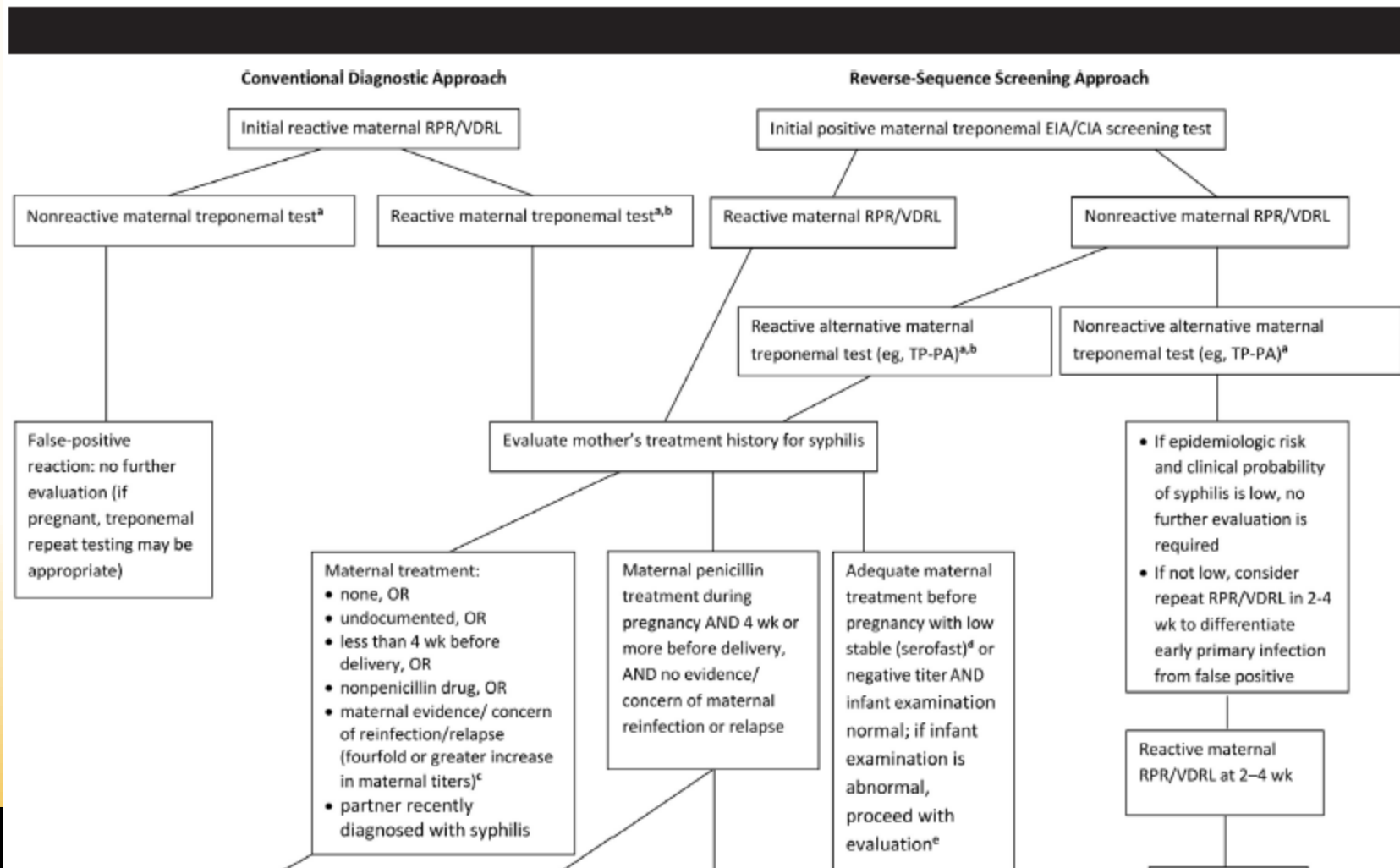
American Academy of Pediatrics
ISBN electronic: 978-1-61002-578-2
Publication date: January 2021

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 Tools ▾



FIG 3.15. ALGORITHM FOR DIAGNOSTIC APPROACH OF INFANTS BORN TO MOTHERS WITH REACTIVE SEROLOGIC TESTS FOR SYPHILIS.



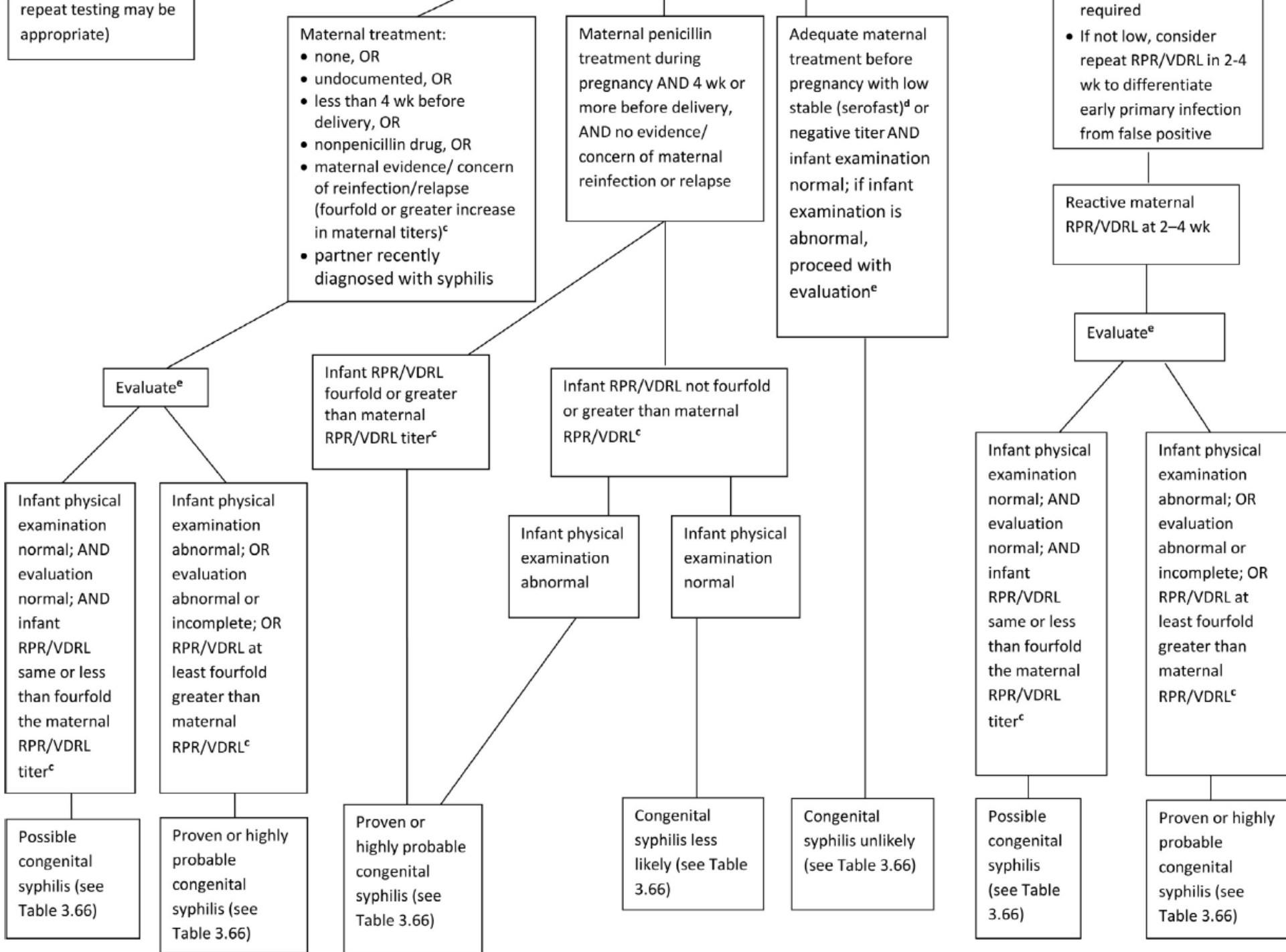


Table 3.66. Evaluation and Treatment of Infants Up To 1 Month of Age With Possible, Probable, or Confirmed Congenital Syphilis^a

Category	Findings	Recommended Evaluation	Treatment
Proven or highly probable congenital syphilis	Abnormal physical examination consistent with congenital syphilis	CSF analysis (CSF VDRL, cell count, and protein)	Aqueous crystalline penicillin G, 50 000 U/kg, IV, every 12 hours (1 wk or younger), then every 8 h for infants older than 1 wk, for a total of 10 days of therapy ^b (preferred)
	OR	CBC count with differential and platelet count	
	A serum quantitative nontreponemal serologic titer fourfold higher than the mother's titer	Other tests (as clinically indicated):	OR
	OR	Long-bone radiography Chest radiography Aminotransferases	Procaine penicillin G, 50 000 U/kg, IM, as single daily dose for 10 days
	A positive result of darkfield test or PCR assay of lesions or body fluid(s)	Neuroimaging Ophthalmologic examination Auditory brain stem response	



Table 3.66. Evaluation and Treatment of Infants Up To 1 Month of Age With Possible, Probable, or Confirmed Congenital Syphilis,^a continued

Category	Findings	Recommended Evaluation	Treatment
Possible congenital syphilis	Normal infant examination	CSF analysis (CSF VDRL, cell count, and protein)	Aqueous crystalline penicillin G, 50 000 U/kg, IV, every 12 h (1 wk or younger), then every 8 h for infants older than 1 wk, for a total of 10 days of therapy ^b (preferred) OR Procaine penicillin G, 50 000 U/kg, IM, as single daily dose for 10 days OR Benzathine penicillin G, 50 000 U/kg, IM, single dose (recommended by some experts, but only if all components of the evaluation are obtained and are normal ^c and follow-up is certain
	AND	CBC count with differential and platelet count	
	A serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer	Long-bone radiography	
	AND ONE OF THE FOLLOWING:		
	Mother was not treated, was inadequately treated, or had no documentation of receiving treatment;		
	OR		
	Mother was treated with a regimen other than recommended in the guideline (ie, a nonpenicillin regimen)		
	OR		
	Mother received recommended treatment <4 wk before delivery		



Table 3.66. Evaluation and Treatment of Infants Up To 1 Month of Age With Possible, Probable, or Confirmed Congenital Syphilis,^a continued

Category	Findings	Recommended Evaluation	Treatment
Congenital syphilis less likely	Normal infant examination	Not recommended	Benzathine penicillin G, 50 000 U/kg, IM, single dose (preferred)
	AND		
	A serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer		
	AND		
	Mother was treated during pregnancy, treatment was appropriate for stage of infection, and treatment was administered >4 wk before delivery		
AND		Alternatively, infants whose mothers' nontreponemal titers decreased at least fourfold after appropriate therapy for early syphilis or remained stable at low titer (eg, VDRL ≤1:2; RPR ≤1:4) may be followed every 2–3 mo without treatment until the nontreponemal test becomes nonreactive	
AND		Nontreponemal antibody titers should decrease by 3 mo of age and should be nonreactive by 6 mo of age; patients with increasing titers or with persistent stable titers 6 to 12 mo after initial treatment should be reevaluated, including a CSF examination, and treated with a 10-day course of parenteral penicillin G, even if they were treated previously	
	Mother has no evidence of reinfection or relapse		



Table 3.66. Evaluation and Treatment of Infants Up To 1 Month of Age With Possible, Probable, or Confirmed Congenital Syphilis,^a continued

Category	Findings	Recommended Evaluation	Treatment
Congenital syphilis is unlikely	Normal infant examination	Not recommended	None, but infants with reactive nontreponemal tests should be followed serologically to ensure test result returns to negative
	AND		
	A serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer		
	AND		
	Mother was treated adequately before pregnancy		Benzathine penicillin G, 50 000 U/kg, IM, single dose can be considered if follow-up is uncertain and infant has a reactive test (some experts)
	AND		
	Mother's nontreponemal serologic titer remained low and stable (ie, serofast) before and during pregnancy and at delivery (eg, VDRL \leq 1:2; RPR \leq 1:4)		

PCR indicates polymerase chain reaction; CSF, cerebrospinal fluid; CBC, complete blood cell count; VDRL, Venereal Disease Research Laboratory; IV, intravenously; IM, intramuscularly; RPR, rapid plasma reagin.

Adapted and modified from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(RR-3):45-47.

^aFor treatment of infants \geq 1 month of age with congenital syphilis, see text on p 735.

^bIf 24 hours or more of therapy is missed, the entire course must be restarted.

^cIf CSF is not obtained or uninterpretable (eg, bloody tap), a 10-day course is recommended.



MISSOURI DHSS HEALTH ADVISORY FEB 2019

Missouri Department of Health & Senior Services

Health Advisory:

Sustained Increase in Syphilis Cases in Missouri

February 15, 2019

This document will be updated as new information becomes available. The current version can always be viewed at <http://www.health.mo.gov>.

The Missouri Department of Health & Senior Services (DHSS) is now using 4 types of documents to provide important information to medical and

Health Advisory
February 19, 2019

FROM: RANDALL W. WILLIAMS, MD, FACOG
DIRECTOR

SUBJECT: Sustained Increase in Syphilis Cases in Missouri

The Missouri Department of Health and Senior Services (DHSS) continues to observe a sustained increase in the number of syphilis cases reported in the state. The number of early syphilis cases reported in Missouri in 2017 (930 cases) increased by 38% over the number of cases in 2016 (676 cases), and has increased 218% since 2012 (292 cases). Provisional data indicate that this upward trend continued in 2018 with the number of reported cases through December 31, 2018, up 40% over the same time period in 2017. The purpose of this DHSS Health Advisory is to alert health care providers of the significant increase in rates of syphilis among multiple populations including gay, bisexual, and other men who have sex with men; people who use drugs; and heterosexual men and women. A significant increase has also been observed in the number of reported congenital syphilis cases.

public health professionals, and to other interested persons:

Health Alerts convey information of the highest level of importance which warrants immediate action or attention from Missouri health providers, emergency responders, public health agencies, and/or the public.

Health Advisories provide important information for a specific incident or situation, including that impacting neighboring states; may not require immediate action.

Health Guidances contain comprehensive information pertaining to a particular disease or condition, and include recommendations, guidelines, etc. endorsed by DHSS.

Health Updates provide new or updated information on an incident or situation; can also provide information to update a previously sent Health Alert, Health Advisory, or Health Guidance; unlikely to require immediate action.

Office of the Director
912 Wildwood
P.O. Box 570
Jefferson City, MO 65102
Telephone: 800-392-0272
Fax: 573-751-6041

Website: <http://www.health.mo.gov>

Background

Syphilis is a sexually transmitted disease (STD) that can have very serious complications for adults and newborns if left untreated. Initial symptoms of syphilis include a sore and/or rash that goes away after a few weeks without treatment, though serious health issues may emerge later without appropriate treatment. Syphilis can be treated and cured with antibiotics yet many cases go undiagnosed and untreated, leading to increased transmission and future negative health consequences. Congenital syphilis occurs when a mother with untreated syphilis passes the infection on to her baby during pregnancy – causing miscarriages, premature births, stillbirths, or death of newborn babies. Babies born with congenital syphilis can experience serious health complications that may present at delivery or later in life.

Missouri's increase in syphilis cases was initially observed among gay, bisexual, and other men who have sex with men, though other groups, including heterosexual women, have also experienced an increase in cases recently. While the initial increase in cases occurred primarily in the Kansas City and St. Louis metropolitan areas, other areas including smaller metropolitan areas and rural counties throughout Missouri are also experiencing a steep increase in cases, particularly among people who use drugs and their partners. With the increase in cases in women, Missouri has seen a corresponding increase in the number of babies born with, or stillborn due to, syphilis. In 2017, 13 congenital syphilis cases were reported in Missouri, representing the highest number of cases reported since 1998. Missouri has also experienced an increase in ocular syphilis, which can cause blurry vision and/or blindness. Syphilis can cause ocular and neurological issues at any stage of infection.

The increasing rates of STDs in Missouri, including syphilis and congenital syphilis, mirror nationwide trends seen in recent years. Ongoing public health efforts to reverse current trends will require a renewed commitment from, and continued partnership with, healthcare providers.

Health Update:

Update 1: Sustained Increase in Syphilis Cases in Missouri

June 15, 2022

This document will be updated as new information becomes available. The current version can always be viewed at <http://www.health.mo.gov>.

The Missouri Department of Health & Senior Services (DHSS) is now using four types of documents to provide important information to medical and public health professionals, and to other interested persons:

Health Alerts convey information of the highest level of importance which warrants immediate action or attention from Missouri health providers, emergency responders, public health agencies or the public.

Health Advisories provide important information for a specific

Health Update
June 15, 2022

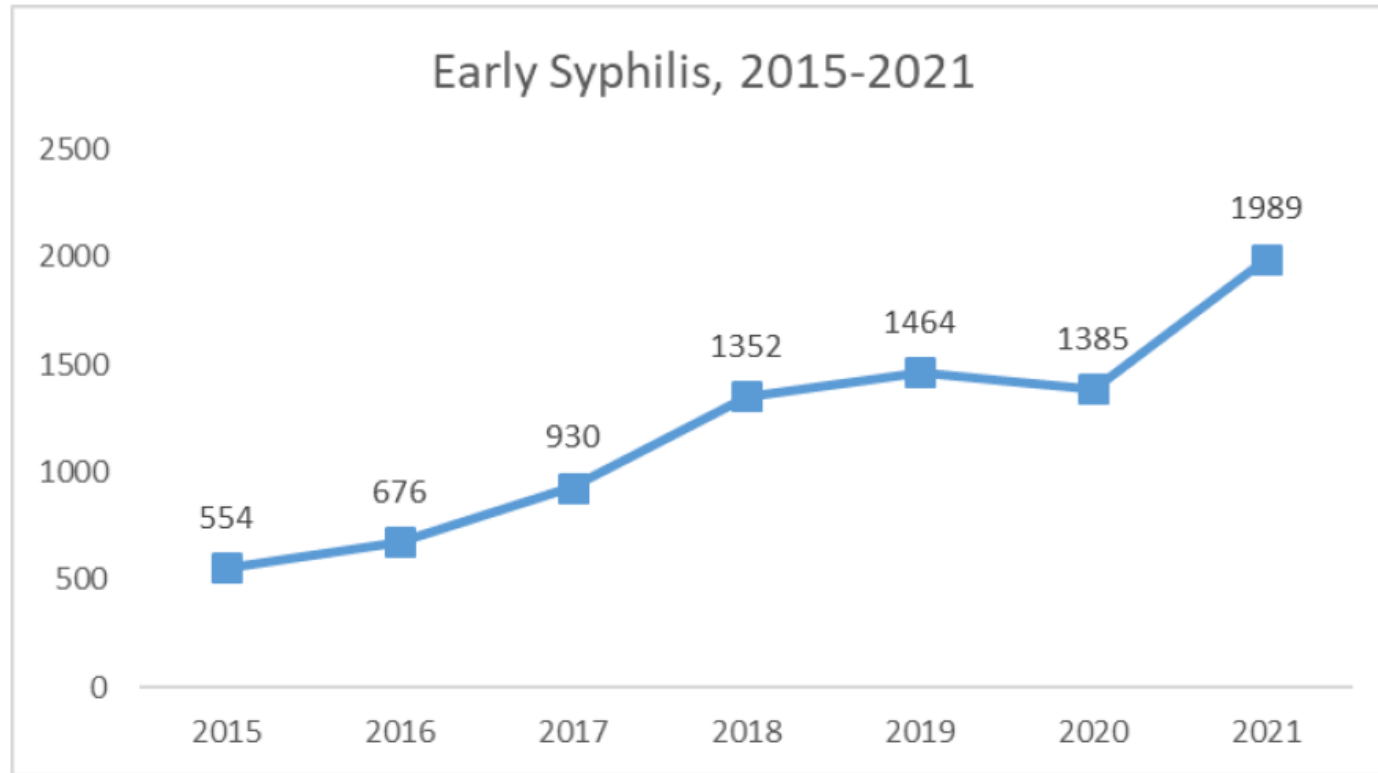
FROM: PAULA F. NICKELSON
ACTING DHSS DIRECTOR

SUBJECT: **Update 1: Sustained Increase in Syphilis Cases in Missouri**

On February 19, 2019, the Missouri Department of Health and Senior Services (DHSS) released a Health Advisory entitled “Sustained Increase in Syphilis Cases in Missouri.” The purpose of that DHSS Health Advisory was to alert health care providers of the significant increase in rates of syphilis among multiple populations including gay, bisexual, and other men who have sex with men; people who use drugs; and heterosexual men and women. A significant increase has also been observed in the number of reported congenital syphilis cases. This notification is available at: <https://health.mo.gov/emergencies/ert/alertsadvisories/pdf/advisory21919.pdf>.

The Missouri Department of Health and Senior Services (DHSS) continues to observe a sustained increase in the number of syphilis cases reported in the state. **The number of early syphilis cases reported in Missouri increased by 259% from 2015 to 2021.** The purpose of this DHSS Health Advisory is to alert health care providers of the significant increase in rates of syphilis among multiple populations including gay, bisexual, and other men who have sex with men; people who use drugs; and heterosexual men and women. A significant increase has also been observed in the number of reported congenital syphilis cases.

The graph below shows the trend in Missouri syphilis cases over the last seven years, with 2020 likely underestimating the disease burden due to decreased testing that occurred during the COVID-19 pandemic.



Source: Missouri Department of Health and Senior Services, Office of Epidemiology, Missouri Health Surveillance Information System (WebSurv). Based on data as of May 24, 2022.



Recommendations

- Providers should assess the sexual health of all patients and discuss STD risks for the patient and partners of the patient.
- Providers should routinely test for syphilis in individuals who have signs or symptoms suggestive of infection. Individuals exposed to syphilis within the past 90 days should receive testing and preventive treatment, even if testing is initially negative.
- Sexually active gay, bisexual, and other men who have sex with men should be tested for syphilis annually or more frequently depending on risk.
- All pregnant women in Missouri should be tested at the first prenatal visit, in the third trimester (28 weeks), and at delivery regardless of perceived risk. Bicillin LA is the only CDC-recommended treatment for pregnant women, including those who are allergic to penicillin. Pregnant women who are allergic to penicillin should be desensitized and treated with Bicillin LA.



- Any woman who has a fetal death after 20 weeks gestation should be tested for syphilis.
- Individuals who are living with HIV who are sexually active should be tested for syphilis annually.
- Patients with diminished visual acuity, blindness, uveitis, panuveitis, optic neuropathy, interstitial keratitis, anterior uveitis, and retinal vasculitis should be tested for syphilis and referred to an ophthalmology specialist. If ocular syphilis is suspected, the patient should be treated according to the Centers for Disease Control and Prevention's (CDC's) 2021 treatment recommendations (see below under Additional Resources) for neurosyphilis and, if they have other neurological symptoms, should undergo a lumbar puncture with cerebrospinal fluid (CSF) examination.

Questions should be directed to the Missouri Department of Health and Senior Services' Bureau of HIV, STD, and Hepatitis at 573-751-6439, or via email at STD@health.mo.gov .



CASE 1:

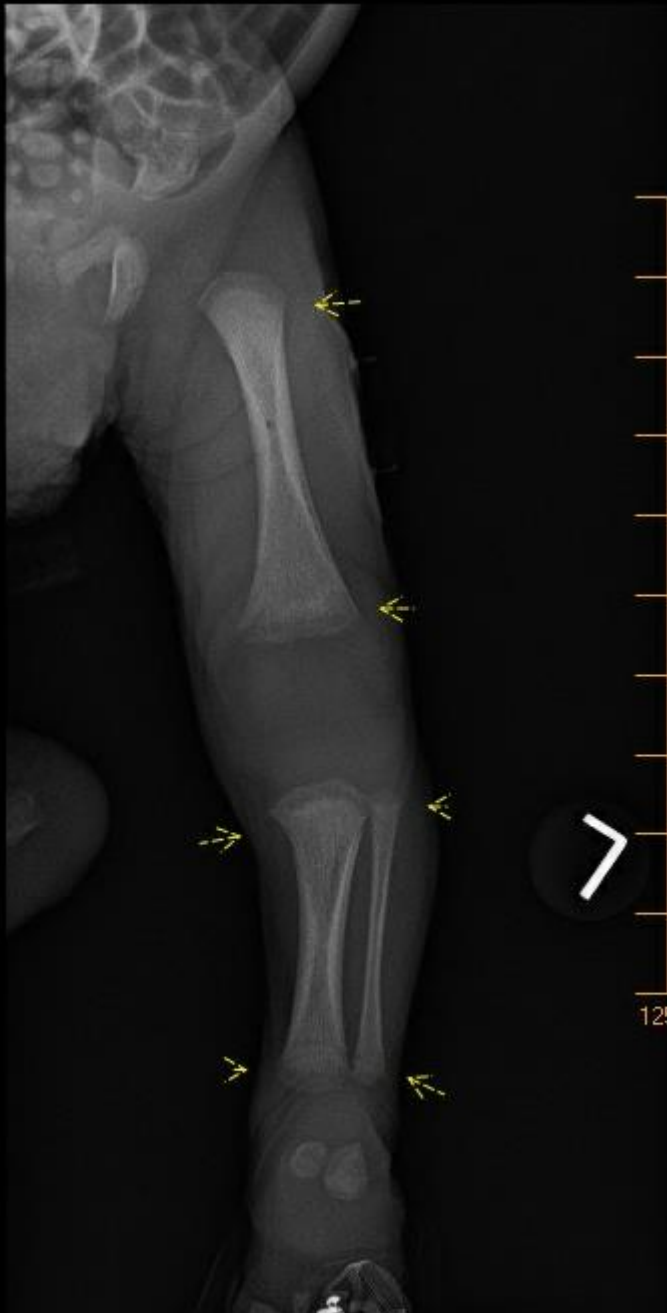
- Mother G5P2 at 28 weeks EGA with fetal ascites seen on US
- Cholestasis of pregnancy and started on ursodiol, transaminitis
- Rash on her hands, arms, belly, and feet, itchy present for one month, on admission noted lesion ?gumma on lip
- Admitted with non-immune fetal hydrops and concern for congenital syphilis versus CMV.
- RPR 1:128, TP-PA positive, HIV negative
- IM penicillin 2.4 million units
- Continuous IV penicillin infusion – 3 days
- Live birth



CASE 2:

- Preterm born at 32 wk, Late maternal prenatal care: titre 1:512, birth RPR 1:64
- Father incarcerated (had HIV), Mother negative for HIV Ab/Ag at delivery
- Neurosyphilis –
 - CSF profile - WCC 10, RBC 16, Elevated protein 204 mg/dl
 - Abnormal MRI- diffuse bilateral cerebral restricted diffusion of leptomeninges and cortex (early neurosyphilis)
 - Positive CSF VDRL 1:1
 - Bone involvement
 - Treated with 10 days of IV penicillin
 - High risk HIV prophylaxis – Zidovudine 6 weeks, Nevirapine 3 doses
- Mother's repeat HIV Ab/Ag neg at 4 weeks after delivery
- 4 months: RPR negative, developmental delay - mild hyperreflexia and clonus, keeping hands fisted on exam
- 6 months: CSF evaluation at follow up reassuring





- Non-specific metaphyseal lucent bands involving the bilateral humerus, bilateral radius, bilateral ulna and bilateral femurs, bilateral tibia and fibula.
-
- Smooth periosteal reaction involving the diaphysis of the bilateral femur, bilateral tibia, most likely physiologic.



CASE 3: 3 MO WITH RASH FOR ONE MONTH

- Almost 3 mo with rash onset ?5weeks of age (unsure) on face, trunk
- Antifungal Rx at ER visit → rash 'increased from 30 spots to over 100'
- 5 days later saw Pediatrician who recognized diagnosis
- Maternal prenatal testing was negative for Hep B, Hep C, RPR, HIV, Ur GC/chlamydia at 27 weeks gestation
- Prior pregnancy had Chlamydia that was treated





- Mother and baby RPR 1:128
- Mother with rash for probably one month on palms and soles
- Mother started Infliximab 6 weeks after delivery for Rheumatoid arthritis (off therapy for years in interim)
- Father also with rash on palms - mild
- Baby evaluation: normal LFT, CSF, long bone radiograph, eyes
- Treated with 10 days iv penicillin, IM Penicillin x 1 at end of course



CASE 4

- 2 mo in foster care with fever, irritability and progressive rash for one month in infant
- Unknown prenatal history (?neg maternal testing)
- Recent URI – suctioning
- Lethargy
- Seen providers twice
- RPR 1:512, TPPA positive
- Proven Congenital syphilis



CASE 5

- Maternal prenatal testing negative for syphilis
- At birth, mother had positive RPR 1:1, pending TPPA
- Transferred baby – RPR neg
- Mother's TPPA positive
- Baby work up negative: Treated baby with ten days iv penicillin
- Possible Congenital syphilis



CASE 6

- Maternal treatment before pregnancy (3mo prior to conception) RPR 1:64
- During pregnancy 1:16 at multiple times
- At delivery mother 1:16, baby 1:4
- Congenital syphilis Unlikely
- However, with reactive RPR and 'not low titers' in mother, given baby Benzathine Penicillin IM x 1 dose



CASE 7: PRESCHOOLER WITH RASH FOR 1 MONTH

- Previously healthy child with onset of rash 1 month prior on abdomen and upper thighs, 'red itchy flat lesions'
- 3 days of fever to 102F at onset of rash which self resolved
- Papules appeared to spread to her palms after scratching abdomen
- 2 weeks prior developed lesion on lips and rash persisted
- Urgent care visit: likely breakthrough chicken pox vs dermatitis (rx topical triamcinolone, topical nystatin)
- With triamcinolone individual lesions darkened
- 1 week prior developed oral lesions increased on tongue and inside of cheeks, mildly uncomfortable with acidic foods





TREATMENT IN NEONATE

- If more than 1 day of therapy is missed, entire course should be restarted
- Data supporting use of other antimicrobial agents (eg, ampicillin) for treatment of congenital syphilis are not available
- When possible, a full 10-day course of penicillin is preferred, even if ampicillin initially was provided for possible sepsis



FOLLOW UP OF NEONATES

- All infants with reactive serologic test or born to sero-reactive mother should have careful f/u at 2, 4, 6, 12mo
- Use RPR (not treponemal test as these may persist till 15mo) – check every 2-3 mo until non-reactive
- Typically decrease by 3mo, should be non-reactive by 6 mo
- Response may be slower for infants treated after the neonatal period.
- Increasing titers or persistent stable titers 6-12 months after initial treatment should be reevaluated, including CSF
- Retreatment with 10-day course of IV penicillin G may be indicated, even if they were treated before
- Neonates with a negative nontreponemal test at birth whose mothers were sero-reactive at delivery should be retested at 3 months to rule out incubating congenital syphilis
- Neonates whose initial CSF evaluations are abnormal do not need repeat lumbar puncture unless they have positive RPR at 6-12mo



REAL WORLD PROBLEMS

- Knowledge of current epidemiology
- Non availability of reverse algorithm platform
- Turn around time for RPR and quantitation
- Transfer of maternal care (lack of records)
- Incorrect transcribing of dates after transfer of care
- Availability of neonatal facilities – for admission for 10 days, LP, imaging, ophthalmology



SUMMARY

- Syphilis along with other sexually transmitted infections is on the rise
- Maternal syphilis testing in 1st trimester (prenatal visit), 3rd trimester and at delivery regardless of perceived risk
- Screen mother for other STI and substance abuse
- Obtain information on maternal testing and treatment → ask for help
- F/u for newborn with positive RPR, repeat every 2-3 months until neg
- F/u for newborn with mother +RPR, infant neg → repeat at least at 3 months



THANK YOU

- MO AAP
- MO DHSS

CLINICAL FEATURES OF SECONDARY SYPHILIS

- Prodromal symptoms and signs
 - Weight loss
 - Low-grade fever
 - Malaise
 - Headache (meningeal irritation)
 - Sore throat
 - Conjunctivitis (iritocyclitis)
 - Arthralgia (periostitis)
 - Myalgias, bone pain
 - Hepatosplenomegaly (mild hepatitis)
- Generalized lymphadenopathy with indolent enlargement of lymph nodes (50–85%)
- Skin manifestations
 - Early (10%): generalized eruption; non-pruritic, roseola-like, discrete macules, initially distributed on the flanks and shoulders
 - Late (70%): generalized maculopapular and papulosquamous eruptions; more infiltrated lesions, often copper-colored; annular plaques on the face; corymbose arrangement (satellite papules around a larger central lesion); occurs in successive waves and is polymorphic
 - Localized syphilids (specific infiltrations of treponemes; positive darkfield examination):
 - palms and soles: symmetric papules and plaques with a collarette of scale (collarette of Bièrré)
 - anogenital area: condylomata lata
 - seborrheic area: 'corona veneris' along the hairline
 - Hypopigmented macules, mainly on the neck (postinflammatory; 'necklace of Venus')
- Manifestations involving mucous membranes (30%)
 - Syphilitic perlèche, split papules
 - Mucous patches: 'plaques muqueuses' in the oropharynx (equivalent to condylomata lata in the genital area)
 - Syphilitic sore throat: inflammation of the whole pharynx
- Patchy alopecia (7%): 'moth-eaten' localized areas of hair loss; toxic telogen effluvium

