Overview: CS Prevention

- A little bit of history
- Clinical manifestations
- CS trends in California
- Transmission
- Prevention
- Cases

Earliest depictions of syphilis

Woodcut 1497

Albrecht
Durer, 1496

Rembrandt's portrait of Gerard de Lairesse at age 25

Oil on canvas, ca. 1665-67
Metropolitan Museum of Art

Edvard Munch "The Inheritance" 1897-99

A lithograph from 1898 of an infant with congenital syphilis
Image: Wellcome Library, London

Congenital Syphilis Discovery Timeline

1780: Mercury used in specialized infant hospital in Paris

1905: T. pallidum discovered (Shaudinn & Hoffmann)

1789: Snuffles

1810: Periosteal bone disease

1863: Late CS

1910: Salvarsan (Erlich)

1942: Penicillin (Fleming; Lentz & Ingraham)

M. Obladen. 2013 Neonatology 103:274-80.

"The first thing to do completely, is to *wipe out congenital syphilis*. That is one job that doesn't need to take a generation."

Thomas Parran. **1937**.
Shadow on the Land: Syphilis.
New York, NY: Reynal & Hitchcock

8 decades, 3 generations later, we have failed

California Department of Public Health 2018

Congenital syphilis affects almost every organ system

Early manifestations:

- Bone abnormalities
- Enlargement of liver
- Skin rash
- Generalized lymphadenopathy
- Nasal discharge ("snuffles")
- Blood abnormalities
- Neurologic abnormalities
- Fetal and neonatal death

Late manifestations:

- Hearing loss
- Interstitial keratitis
- Vision loss
- Bone and facial abnormalities
- Tooth abnormalities
- Neurologic abnormalities
- Gummas in the skin or mucous membranes

Asymptomatic presentation at birth very common

Syphilitic Rhinitis

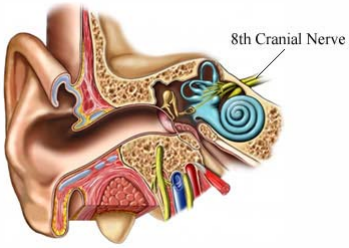
Syphilitic Rash

Photos courtesy of Public Health Image Library, CDC and Dr. Norman Cole

Hutchinson's Triad

Interstitial Keratitis

8th Nerve Deafness



Hutchinson's teeth: incisors narrow and notched

Photos courtesy of Public Health Image Library, CDC/Susan Lindsley and Robert Sumpter

Late Congenital Syphilis


Frontal bossing;
Saddle nose

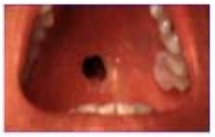

Interstitial keratitis


Hutchinson teeth


Rhagades


Mulberry molar


Saddle nose


Perforated hard palate


Saber shins

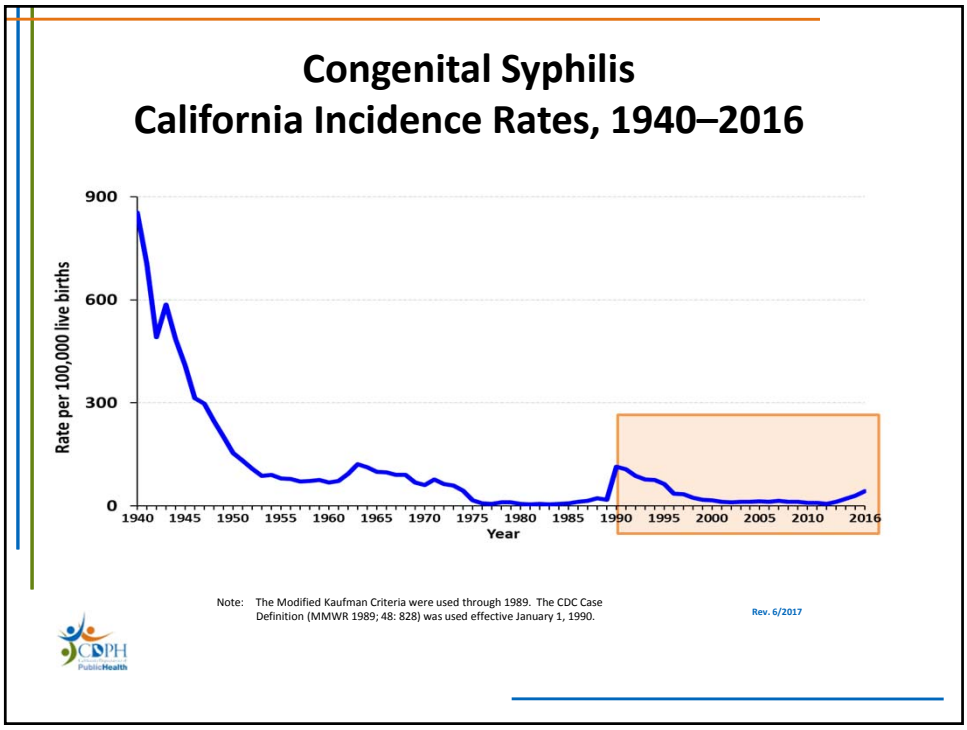
Mortality of Congenital Syphilis: Experience in Parkland Hospital Dallas, Texas

Case-fatality rate:

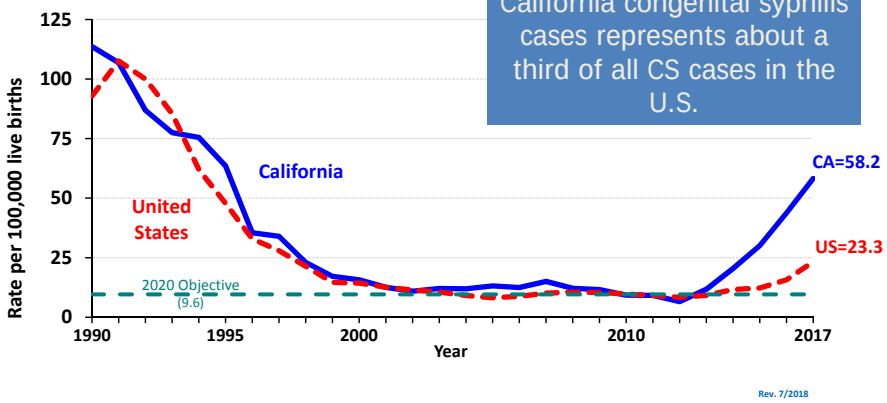
- Confirmed congenital syphilis: **35%** (67/191)
  - Stillbirths: 79% of deaths (53/67)
    - 74% of stillbirths occurred before 28 weeks' gestation

Courtesy of Pablo Sanchez, MD

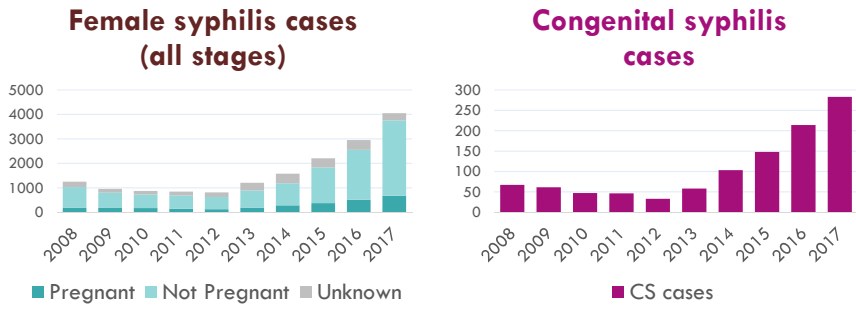

Re-emergence of Congenital Syphilis in California


Congenital Syphilis
California Incidence Rates, 1940–2016
Rate per 100,000 live births
900
600
300
0
1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2016
Year
Note: The Modified Kaufman Criteria were used through 1989. The CDC Case Definition (MMWR 1989; 48: 828) was used effective January 1, 1990.
Rev. 6/2017

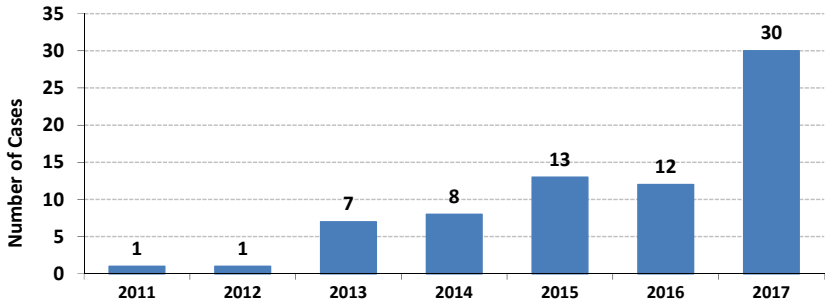
Congenital Syphilis, California versus United States Incidence Rates, 1990–2017



Syphilis in females and infants has been increasing in California since 2012

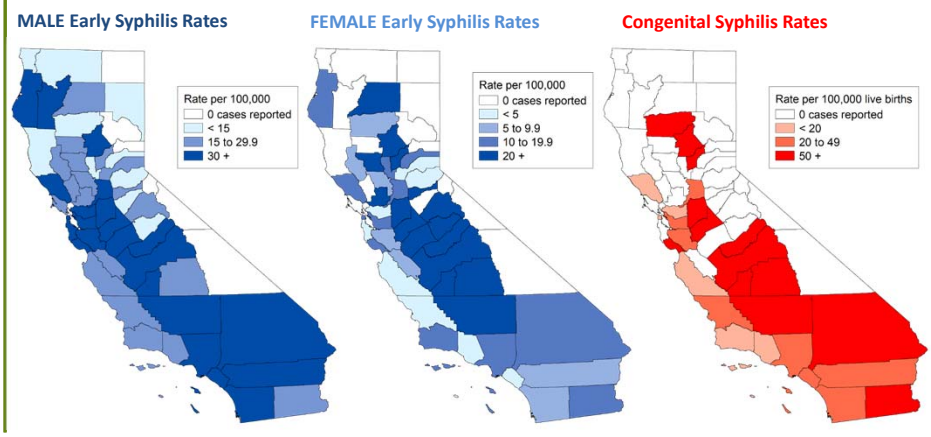


Congenital Syphilis Stillbirths California, 2011–2017



Rev. 7/2018

Early Syphilis* Incidence by County among Males, Females of Childbearing Age (15-44) & Congenital Syphilis, California, 2017

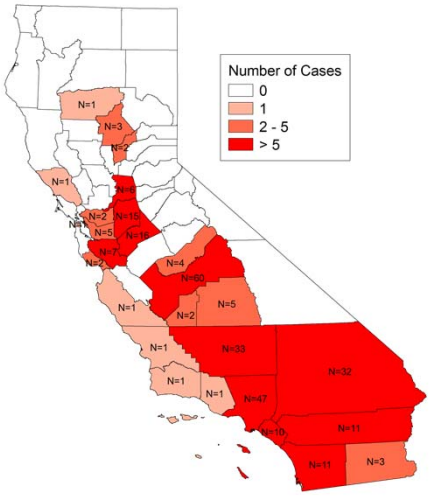


* Includes primary, secondary, and early latent syphilis.

Rev. 7/2018

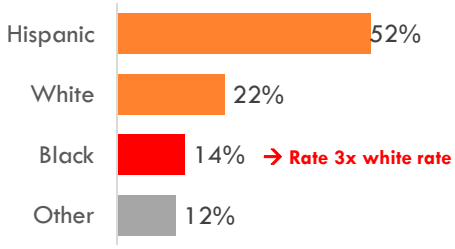
The highest morbidity counties are in Central and Southern California

Congenital Syphilis Cases by County, California, 2017

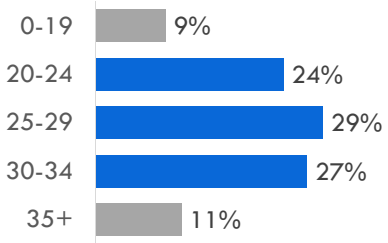


Majority of pregnant women with syphilis in California Hispanic or White and between age 20 and 34

Race/Ethnicity

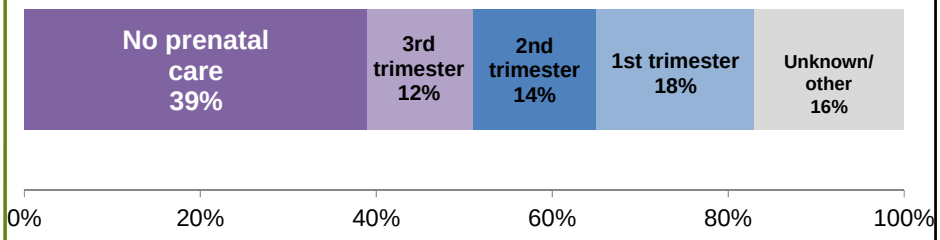


Age



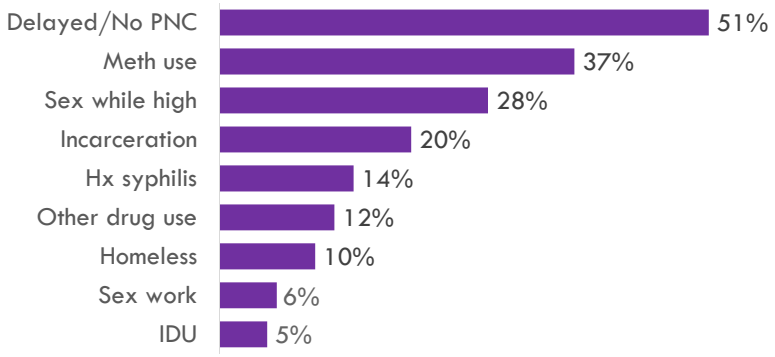
Source: 2016-2017 California surveillance data

Timing of first prenatal care visit, mothers of CS infants, California, 2016-2017

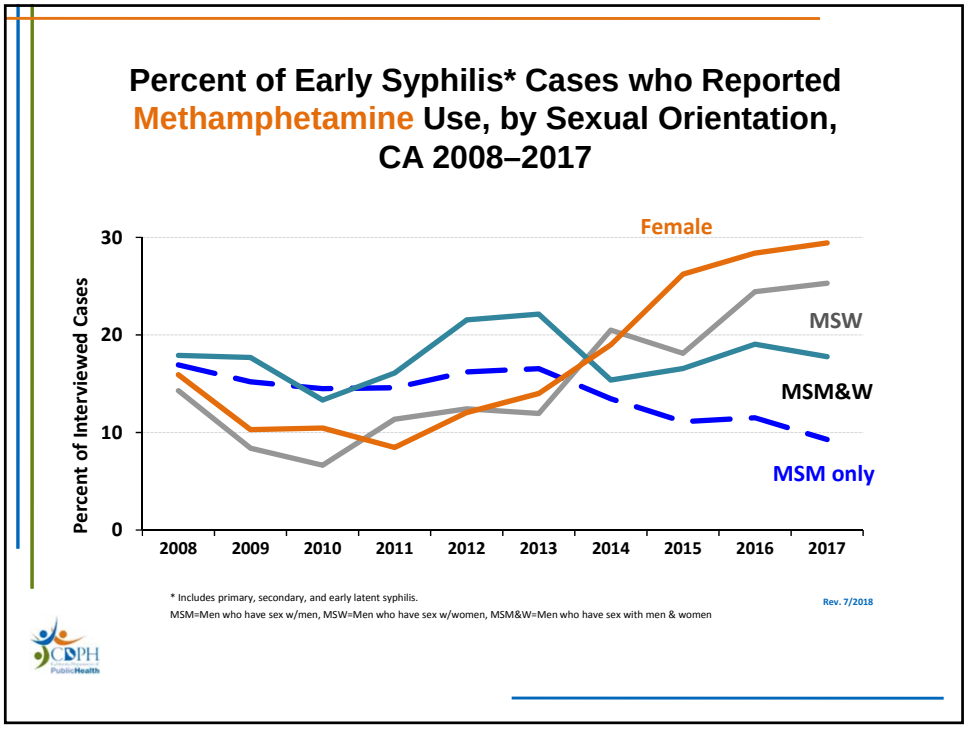


Source: 2016-2017 surveillance data, N=499

Maternal Risk Factors, interviewed mothers of CS infants

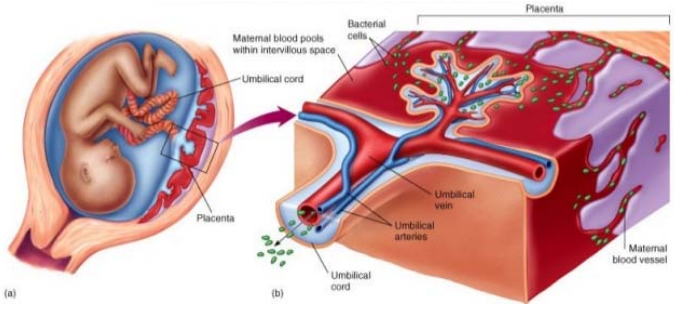


Source: 2016-2017 surveillance data, N=298


Percent of Early Syphilis* Cases who Reported Methamphetamine Use, by Sexual Orientation, CA 2008–2017
Female
MSW
MSM&W
MSM only
Percent of Interviewed Cases
30
20
10
0
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
* Includes primary, secondary, and early latent syphilis.
MSM=Men who have sex w/men, MSW=Men who have sex w/women, MSM&W=Men who have sex with men & women
Rev. 7/2018
CDPH PublicHealth

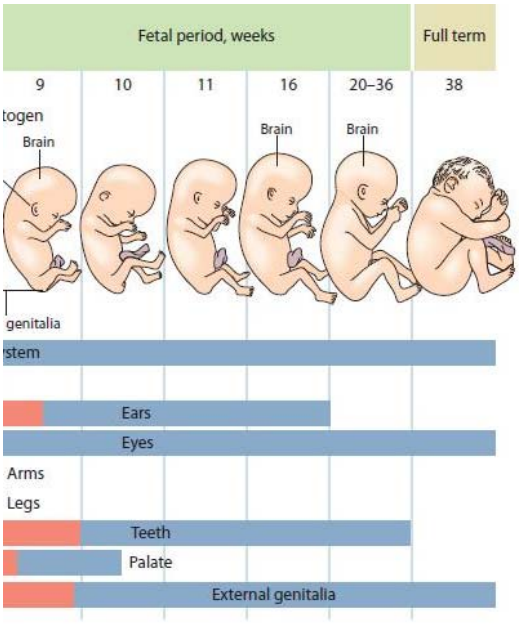

Maternal – Fetal Transmission

Mother to child transmission of syphilis can occur anytime during gestation



- Increased risk with early maternal stage of disease, spirochetemia (bacteria in the blood), and higher maternal titers
- Transmission can occur ANY time in pregnancy
- Latent including late latent infection can be transmitted vertically
- Earliest possible treatment is key to prevention

Timing of transmission affects disease outcome



-Peeling, Rosanna W., and Hnin Ye. "Diagnostic tools for preventing and managing maternal and congenital syphilis: an overview." *Bulletin of the World Health Organization* 82.6 (2004): 439-446.
-Santrock, John. *Children, 12th edition* McGraw Hill 2013

Congenital Syphilis Prevention Framework

Pre-pregnancy

- Screening/dx/tx
- Timely partner services
- Accessible highly effective contraception

During pregnancy

- Linkage to prenatal care
- Screening/dx
- Timely treatment appropriate for stage
- Timely partner services
- Case management
- Prevent and detect new infection

Birth

- Evaluation and treatment of baby

U.S. Preventive Services TASK FORCE

US Preventive Services Task Force | Evidence Report

September 4, 2018

Screening for Syphilis Infection in Pregnant Women
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Jennifer S. Lin, MD[1]; Michelle L. Eder, PhD[1]; Sarah I. Bean, MPH[1]

> Author Affiliations | Article Information

JAMA. 2018;320(9):918-925. doi:10.1001/jama.2018.7769

Editorial Comment | Related Articles

Abstract

Importance The incidence of syphilis and congenital syphilis in the United States has increased after reaching historic lows in the early 2000s.

Objective To systematically review literature on the effectiveness and harms of screening for syphilis in pregnancy and the harms of penicillin treatment in pregnancy to inform the US Preventive Services Task Force.

Data Sources MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials for relevant English-language literature, published from January 1, 2008, to June 2, 2017. Ongoing surveillance was conducted through November 22, 2017.

Study Selection Studies conducted in countries categorized as "high" or "very high" on the Human Development Index that explicitly addressed 1 of 3 a priori–defined key questions.

xtraction and Synthesis Independent critical appraisal and data abstraction by 2 reviewers. Data from included studies were narratively synthesized without pool-

nd Measures Incidence of congenital syphilis; any harms of screening or penicillin treatment in pregnancy.

JAMA
The Journal of the American Medical Association

Who Should be Screened for Syphilis?

Pregnant F	• At first prenatal visit • Again in the third trimester and at delivery if at risk, or in high morbidity area
Non-pregnant F	• At risk or in high morbidity areas • At least once in lifetime
Neonates	• If exposed or maternal serology unknown
MSM	• Annually, or more frequently, 3-6 months if at high risk (multiple, anonymous partners, meth)
HIV +	• At least annually, depends on risk
On PrEP	• Every 3 months
Corrections	• Universal screening based on local area or institutional incidence

CDPH California Department of Public Health

CDC 2015 STD Tx Guidelines www.cdc.gov/std/treatment
Plus: Guidelines for HIV care and HIV PrEP care

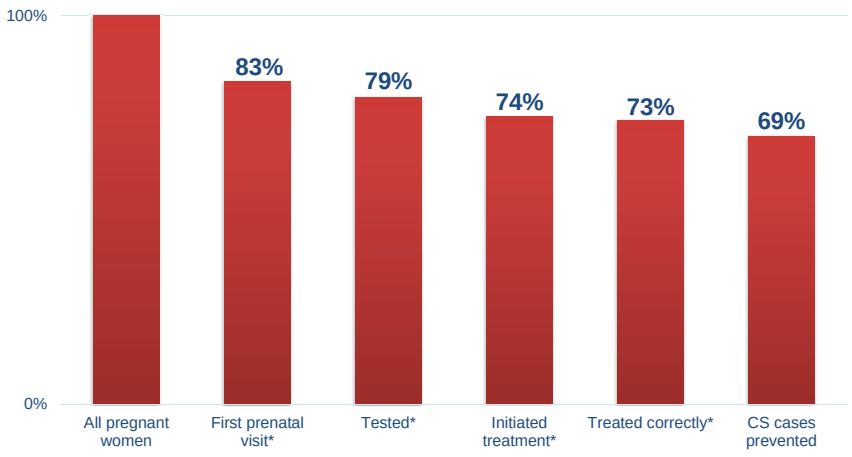
Syphilis Screening in Pregnancy

- **All pregnant women should be screened for syphilis at the first prenatal visit**
- Screening early in the third trimester (28-32 weeks) and at delivery is recommended for women at high risk for syphilis, live in areas of high syphilis morbidity, or are previously untested
- **No infant should leave the hospital without the maternal serologic status having been determined at least once during pregnancy, and again at delivery if at risk**
  - If mother presents at delivery with no prenatal care, STAT RPR should be performed
  - If baby was exposed, there is still an opportunity to treat the infant to prevent further progression of disease
- Any woman who delivers a stillborn infant should be tested for syphilis

High Risk for Syphilis:

- Diagnosed with an STD during pregnancy
- Receive late or limited prenatal care
- Partners who have other partners, or partners with male partners
- History of incarceration
- Marginally housed
- Involved with substance use, especially meth
- Exchange sex for money, housing, or other resources

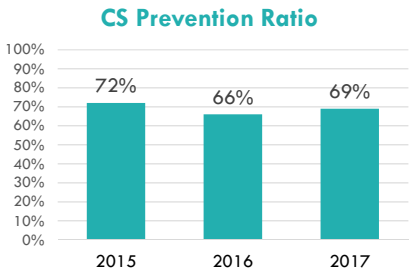
Congenital Syphilis Prevention Cascade, 2017

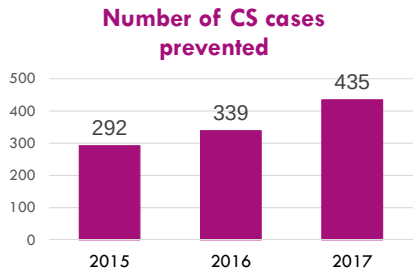


* ≥30 days prior to delivery

Source: Nicole Burghardt, 2017 CPA surveillance data

Congenital syphilis prevention over time





Source: Nicole Burghardt, 2015-2017 CPA surveillance data

Treatment of Syphilis in Pregnancy

- **The <u>only treatment</u> of syphilis in pregnancy is <u>penicillin</u>**
- Treatment should be appropriate for the stage of infection
  - Some experts recommend a 2nd dose of benzathine penicillin G be given a week after the initial dose in early syphilis
  - For late syphilis, **adherence to 6-8 day interval between doses** in pregnancy is necessary; otherwise must restart series
- Pregnant women with penicillin allergy should be desensitized and treated with penicillin
- All patients with syphilis should be **tested for HIV**
- Follow titer response: 28-32 weeks of gestation and at delivery; or monthly if high risk
- Clinical and serologic response should be appropriate for stage, though most women will deliver prior to 4-fold decline

CDC 2015 STD Treatment Guidelines
www.cdc.gov/std/treatment

Syphilis Treatment

Primary, Secondary, & Early Latent

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

* Bicillin L-A is the trade name. DO NOT USE Bicillin C-R!

Late Latent or Latent of Unknown Duration

Benzathine penicillin G* 7.2 million units IM total in 3 doses of 2.4 MU each at one week* intervals

* Maximum interval = 6-8 days in pregnancy.

CDC 2015 STD Treatment Guidelines
www.cdc.gov/std/treatment

Treatment failure highest with secondary stage of syphilis

Table 3. Success of Maternal Treatment to Prevent Congenital Syphilis by Stage of Infection

Stage	Success/Total treated	Percentage (95% CI)
Primary	27/27	100 (87.2, 100)
Secondary	71/75*	94.7 (86.9, 98.5)
Early latent	100/102	98 (93.1, 99.8)
Late latent	136/136	100 (97.3, 100)
Total	334/340	98.2 (96.2, 99.3)

CI = confidence interval.
* $P = .03$ compared with other groups, χ^2.

Alexander JM, Sheffield JS, Sanchez PJ, et al.. Efficacy of treatment for syphilis in pregnancy. Obstet Gynecol 1999;93:5–8.

Treatment EARLY in pregnancy highly effective in preventing CS

Table 4. Success of Maternal Treatment in Preventing Congenital Syphilis by Gestational Age

Gestational age	Success/Total treated	Percentage (95% CI)
≤20 wk	152/153	99.4 (96.4, 100)
21–25 wk	51/51	100 (93.0, 100)
26–30 wk	58/59	98.3 (90.9, 100)
31–35 wk	44/46	95.6 (85.2, 99.5)
36–40 wk	26/28	92.9 (76.5, 99.1)
41–42 wk	3/3	100 (29.2, 100)
Total	334/340	98.2 (96.2, 99.3)

CI = confidence interval.
P = not significant, χ^2.

Alexander JM, Sheffield JS, Sanchez PJ, et al.. Efficacy of treatment for syphilis in pregnancy. Obstet Gynecol 1999;93:5–8.

Meta-analysis: 80% reduction of CS stillbirths with treatment

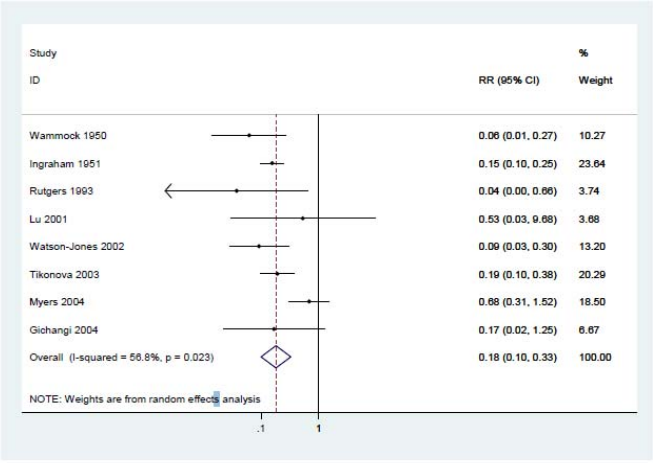


Figure 3 Meta analysis of 8 observational studies showing effect of penicillin on stillbirth in pregnant women with active syphilis.

Blencowe, Hannah, et al. *BMC public health* 11.3 (2011): S9.

Monitoring Titer Response in Pregnancy

- Repeat titer q 3 months, or monthly if high risk
- Repeat @ 28-32 weeks and at delivery
- Interpreting titer response:
  - >4-fold decline best indicator of treatment effectiveness
  - 4-fold increase in titer strong indicator of treatment failure
  - Lack of 4-fold decline – variable interpretation
  - If titer declines then increases 4-fold, consider treatment failure or reinfection
  - Many women will deliver prior to 4-fold decline

CDC 2015 STD Treatment Guidelines
www.cdc.gov/std/treatment

Evaluation and Treatment at Delivery

- **No mother or neonate should leave the hospital** without maternal serologic status having been documented **at least once** during pregnancy
- Even if RPR NR in pregnancy, if the mother is considered high risk, obtain RPR **at delivery**
- **All infants** born to women who were treated for syphilis during pregnancy should have **a thorough physical exam** for signs of CS, and a **RPR** for comparison to maternal RPR at delivery
- Any woman who has a **fetal death after 20 weeks'** gestation should be tested for syphilis

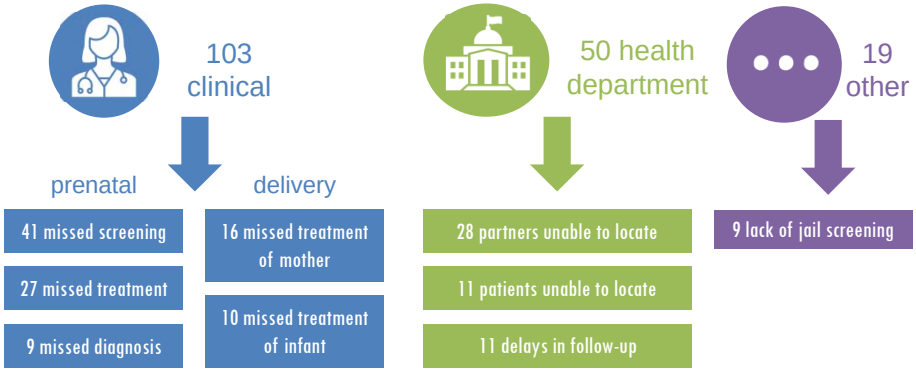
CDC 2015 STD Treatment Guidelines
www.cdc.gov/std/treatment

Each CS case should be examined for missed opportunities and upstream interventions to prevent future cases.

Congenital Syphilis Morbidity & Mortality Review (CS M&M Review):
Regular in-depth multidisciplinary review of CS cases

- Identify missed opportunities for prevention
- Follow-up actions aimed at systems level changes
- Multidisciplinary team from across health department

Among 69 CS cases reviewed by public health, 172 missed opportunities for prevention were identified



Source: Ashley Dockter, 2016-June 2018 CPA M&M Review Data

Congenital Syphilis Prevention Initiatives

- CS QA reviews and data feedback to LHJs
- Data reports to LHJs
- Syphilis screening in jails
- Collaborations/ partnerships
- Guidance, mentoring, training, TA
- Clinical training, consultation
- Patient and provider education materials
- Outbreak/cluster response

Slide credit: Ashley Dockter

Case Presentations

Case 1: Prenatal Care Visit #1

- 24 y.o. G2P1 Latina, single mom, employed
- Seen for first PNC visit on 2/10/17
- Estim. gestational age = 10 weeks
- Unplanned but desired pregnancy
- Used THC and other drugs but stopped
- FOB “out of town”
- Exam and labs normal (RPR NR, HIV-)
- Missed next PNV, assumed to be in care elsewhere

Urgent Care

- 5/19/17 (GA 24 weeks GA)
- Presented to urgent care with diffuse rash, fatigue, low grade fever, and muscle pain
- Routine labs, RPR, HIV
- 5/20: RPR 1:64, TP-PA+
- Reported to LHD 4/25
- Unable to contact, no treatment provided
- Delivery hospitals notified

Delivery Hospital

- 6/2/17 (GA 26 weeks)
- Presented for decreased fetal movement
- Diagnosed with fetal demise and delivered 700 g stillborn
- RPR 1:128, HIV-
- No further examination of placenta or fetus
- Mom treated with BIC x 1, scheduled for follow up

- *Qs: Could this case have been prevented?*

Case 2: Prenatal visit #1

- 29 y.o. G5P2 white female
- 1st PNC at 12 weeks GA, desired pregnancy
- History of syphilis in 2016:
  - RPR 1:64, staged as unknown duration
  - Treated BIC x 2
- Denies multiple partners, drug use
- Ob labs: RPR 1:4
- No treatment provided

- *Qs: Does the patient have syphilis? What is the risk to the fetus? What is recommended treatment plan?*

Treatment + Follow up

- At 14 weeks GA, treated w BIC x 3, 7 days apart
- Day of treatment titer 1:4
- FOB declined testing

- RPR at 22 weeks 1:4, fetal U/S normal, no treatment
- RPR at 32 weeks 1:8, no treatment
- Presented at 38 weeks, active labor, RPR 1:16

- *Qs: What's the differential for the increase in titer? Treatment plan? Infant evaluation plan?*

Case 3: Prenatal visit #1

- 26 y.o. G1P0 AfrAm married female
- GA 9 weeks, planned pregnancy
- No history of STDs, no reported risks
- RPR 1:128, TP-PA+

- *Qs: Stage? Treatment? Partner management?*

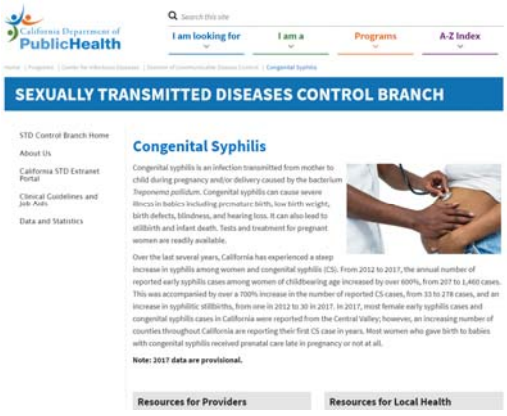
Management Plan

- Stage: unknown duration
- Treatment: BIC x 3 (6-8 days apart)
- Follow titers
- Husband: test and/or treat presumptively
- Fetal U/S, evaluation at birth

Take Home Points: Congenital Syphilis

- Rates are increasing
- **Prevention of congenital syphilis:**
  - Screening and treatment EARLY in pregnancy
  - Additional screening (for those testing negative at first PNC) at 28-32 weeks and at delivery may be needed
  - Bicillin is the only treatment
  - Interval between doses must be 6-8 days
  - Follow titers to assess treatment
  - Evaluate all exposed infants
- Report to local health department

Online resources @ STD.ca.gov



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