UNIVERSITY OF WASHINGTON
STD Prevention Training Center

Syphilis in pregnancy and congenital syphilis

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Slides courtesy: Matt Golden, Julie Dombrowski, Sue Szabo, Sheila Lukehart, Jared Bartschi, Joseph Hilinski, Tara Reid, Meena Ramchandani

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Disclosures

Stockholder: Gilead and Merck

***Caveat**: Language is evolving, and though our aim is to change accordingly, we acknowledge that CDC guidelines are written using binary language with respect to gender.*

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Syphilis among women and congenital cases in South Dakota, 2021

Dr. Mary Carpenter

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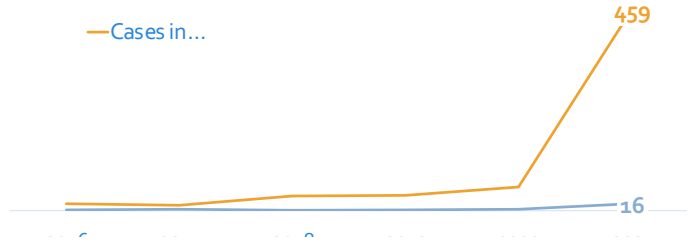
The increase in congenital cases is a result of the increase in syphilis among women

Provisional Data, January – December 2021

Cases of Syphilis (all stages). SD, 2016-2021.



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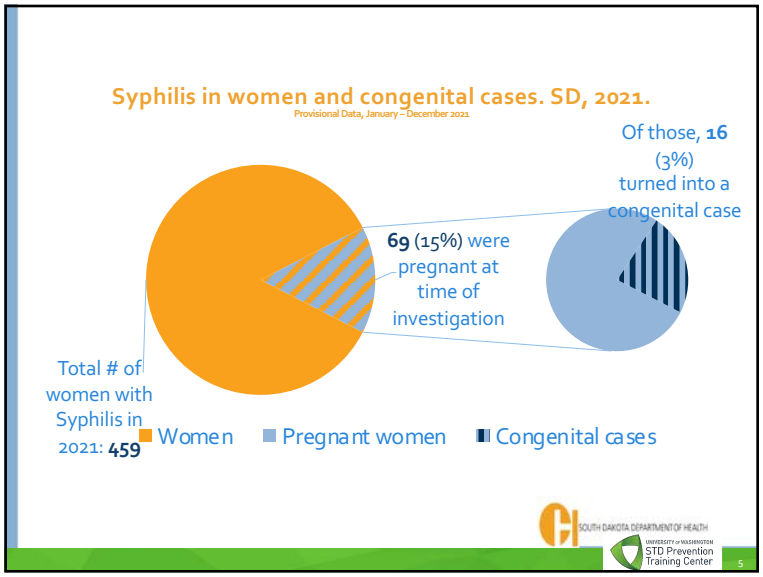
Syphilis in women and congenital cases. SD, 2021.
Provisional Data, January – December 2021
Of those, 16 (3%) turned into a congenital case
69 (15%) were pregnant at time of investigation
Total # of women with Syphilis in 2021: 459
Women
Pregnant women
Congenital cases
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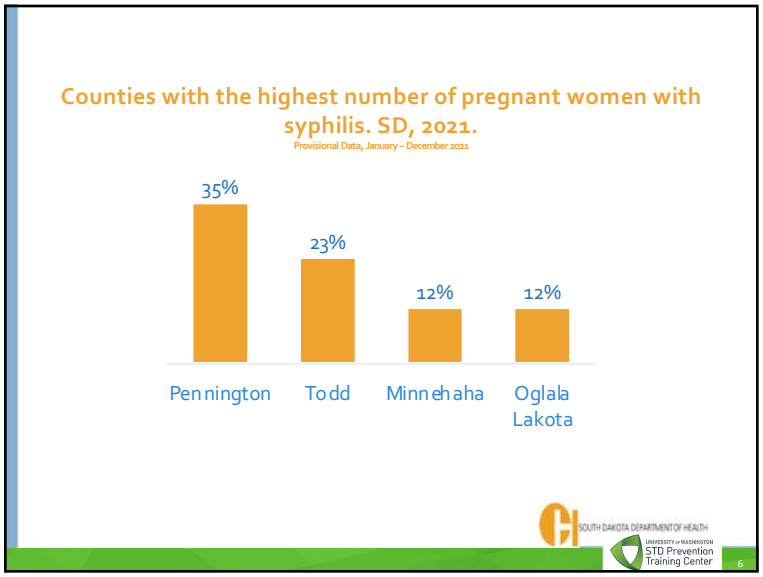
Counties with the highest number of pregnant women with syphilis. SD, 2021.
Provisional Data, January – December 2021
35%
23%
12%
12%
Pennington
Todd
Minnehaha
Oglala Lakota
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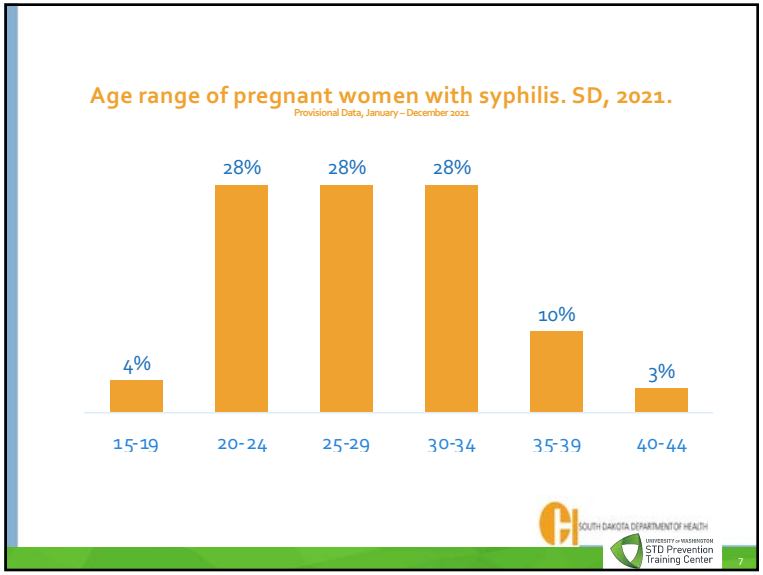
Age range of pregnant women with syphilis. SD, 2021.
Provisional Data, January – December 2021
4%
28%
28%
28%
10%
3%
15-19
20-24
25-29
30-34
35-39
40-44
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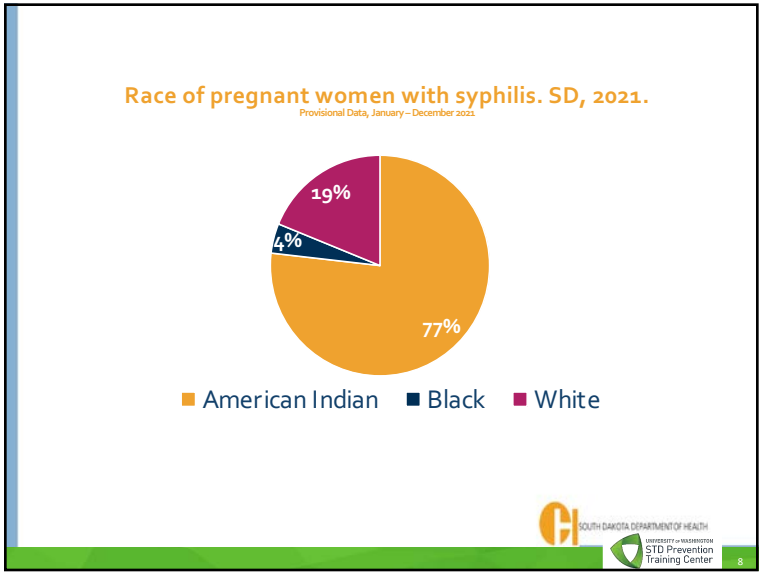
Race of pregnant women with syphilis. SD, 2021.
Provisional Data, January – December 2021
19%
4%
77%
American Indian
Black
White
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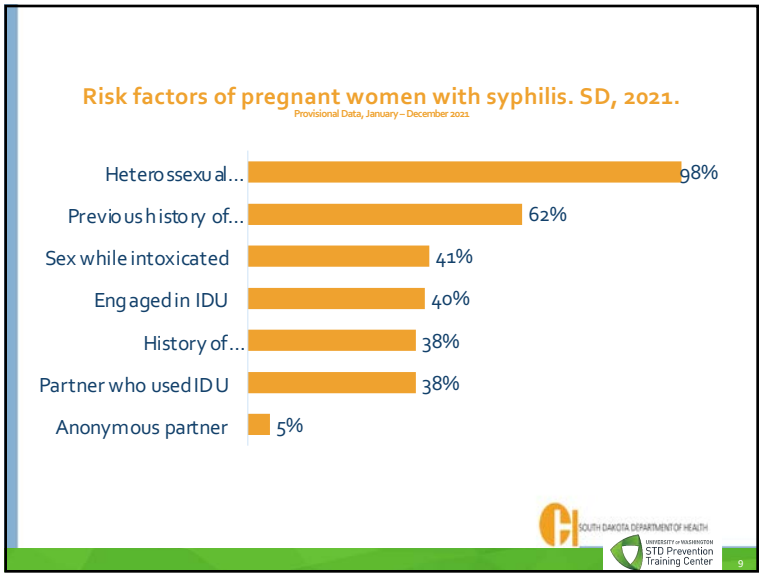
Risk factors of pregnant women with syphilis. SD, 2021.
Provisional Data, January – December 2021
Heterosexual...
98%
Previous history of...
62%
Sex while intoxicated
41%
Engaged in IDU
40%
History of...
38%
Partner who used IDU
38%
Anonymous partner
5%
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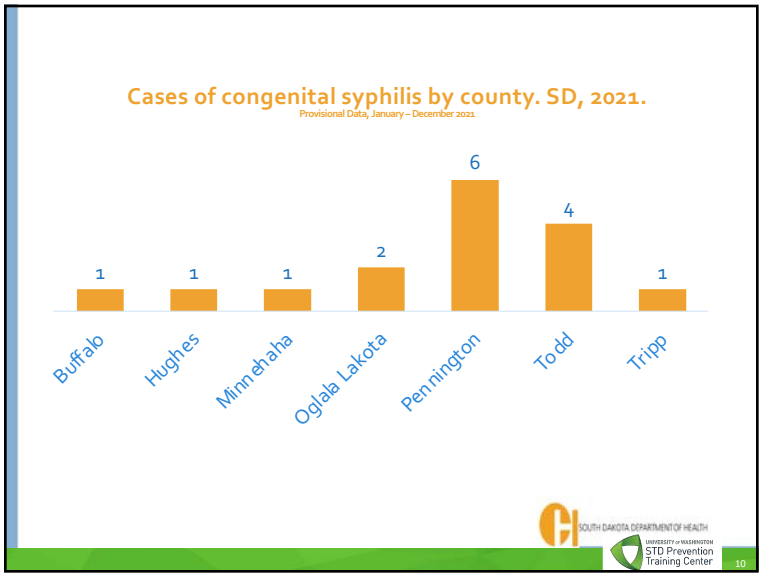
Cases of congenital syphilis by county. SD, 2021.
Provisional Data, January – December 2021
1
1
1
2
6
4
1
Buffalo
Hughes
Minnehaha
Oglala Lakota
Pennington
Todd
Tripp
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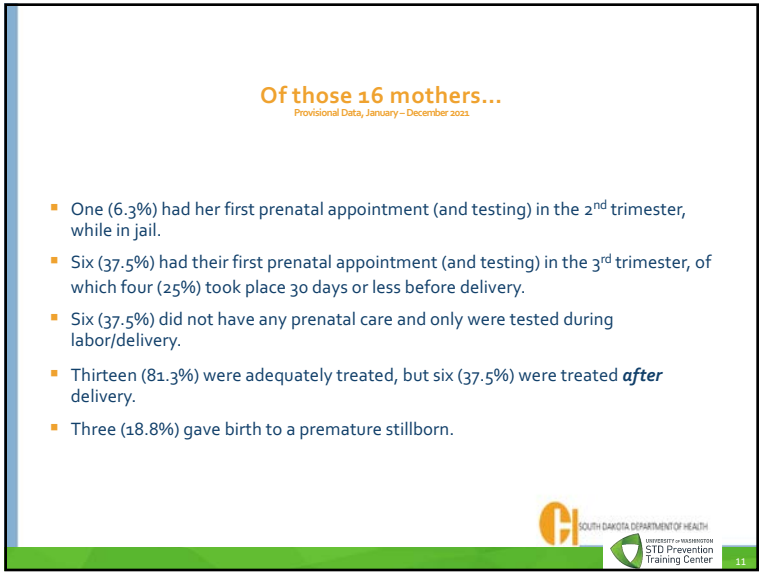
Of those 16 mothers...
Provisional Data, January – December 2021
One (6.3%) had her first prenatal appointment (and testing) in the 2nd trimester, while in jail.
Six (37.5%) had their first prenatal appointment (and testing) in the 3rd trimester, of which four (25%) took place 30 days or less before delivery.
Six (37.5%) did not have any prenatal care and only were tested during labor/delivery.
Thirteen (81.3%) were adequately treated, but six (37.5%) were treated after delivery.
Three (18.8%) gave birth to a premature stillborn.
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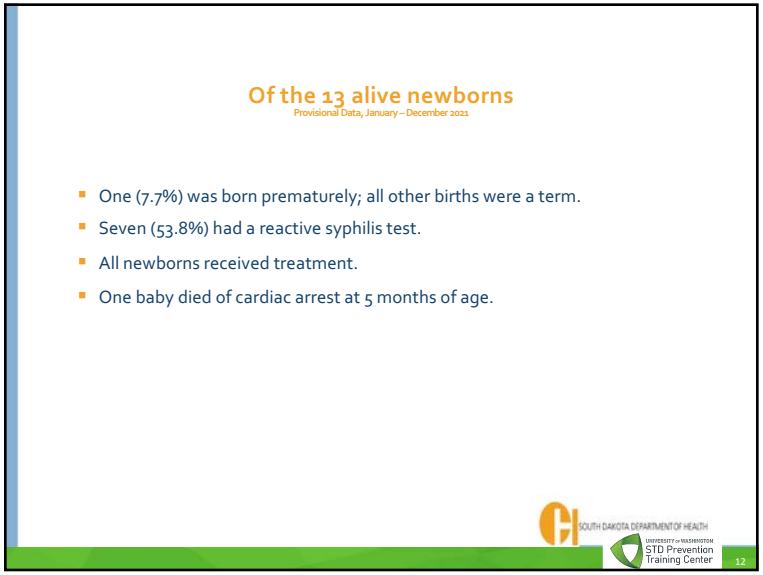
Of the 13 alive newborns
Provisional Data, January – December 2021
One (7.7%) was born prematurely; all other births were a term.
Seven (53.8%) had a reactive syphilis test.
All newborns received treatment.
One baby died of cardiac arrest at 5 months of age.
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Overview

Focus on pregnant people and congenital syphilis

- Epidemiology
- Clinical manifestations of syphilis in adults and newborns
- Syphilis diagnosis in adults and newborns
  - Serologic testing
  - Diagnostic pathways and neonate management
- Treatment and follow-up

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Epidemiology

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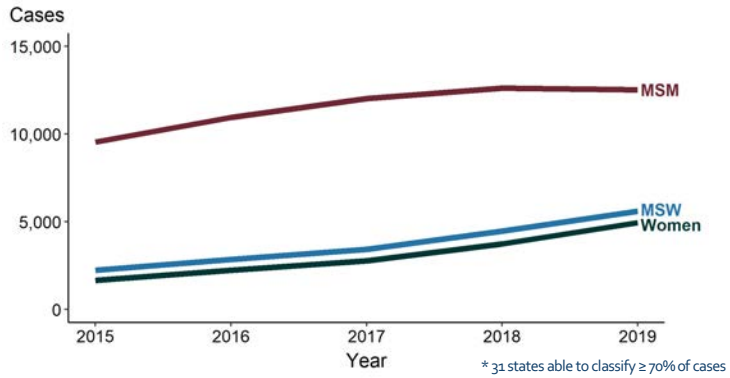
Primary & Secondary Syphilis – Reported Cases by Sex and Sex Behavior*, 2015-2019



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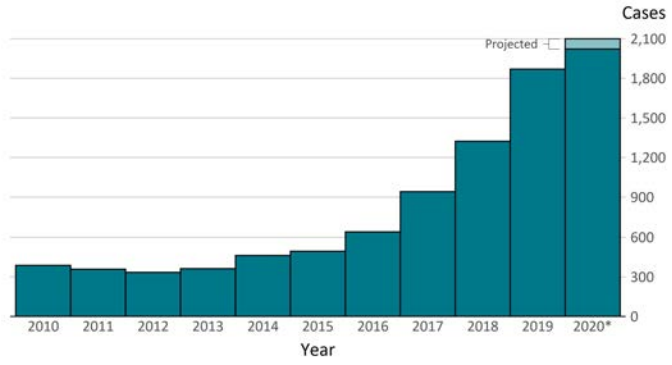
Congenital Syphilis — Reported and Projected Cases by Year of Birth, US, 2010–2020



* Reported and projected 2020 congenital syphilis data are preliminary as of July 29, 2021.

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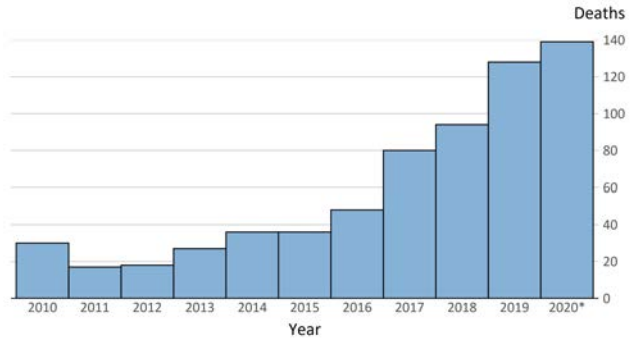
Congenital syphilis – reported stillbirths and infant deaths, US, 2010-2020*



* Reported 2020 congenital syphilis data are preliminary as of July 29, 2021.

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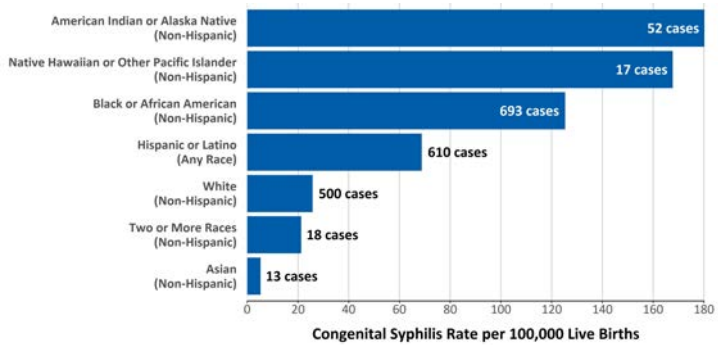
Congenital syphilis – case counts and rates of reported cases by race/ethnicity, US, 2020*



* Reported 2020 congenital syphilis data are preliminary as of July 29, 2021.

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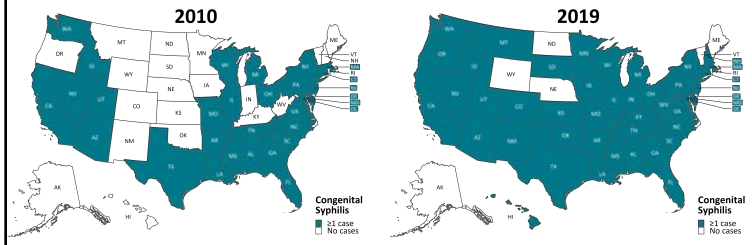
Congenital Syphilis — spread across the US, 2010–2019



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SYPHILIS IN SOUTH DAKOTA

2021 DATA	
ADULT SYPHILIS	**CONGENITAL / SYPHILITIC STILLBIRTHS**
874 Infections Reported 622% Increase from 2020 1,050% Increase from 5-Year Median	16 Congenital and 4 Syphilitic Stillbirths 300% Increase from 2020 700% Increase in 5-Year Median

RISK FACTORS:

- 93% heterosexual exposure
- 45% history of other STIs
- 45% history of incarceration
- 75% American Indian
- 59% Reported age range of 25-39 years-old
- 36% sex while intoxicated
- 27% used IV drug use
- 21% cases reported among an institutionalized population

This is a preventable disease: awareness, aggressive screening, appropriate and timely treatment is key to prevention

Talk to public health if suspected case and call early!

Courtesy of South Dakota Department of Health

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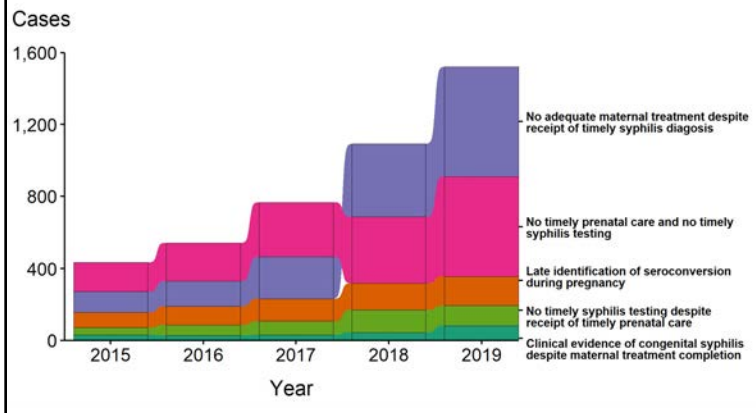
Congenital Syphilis — Missed Prevention Opportunities among Mothers of Infants with Congenital Syphilis, United States, 2015–2019



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Clinical manifestations and Staging

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Patient Case

- Your patient is a 37 year old pregnant woman who presents to your clinic for routine testing.
- She has no symptoms, but has a positive RPR titer of 1:8 found on routine screening.
- Her confirmative TPPA is also reactive.
- She tests on occasion, and her last test was negative 2 years ago.

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Polling Question 1

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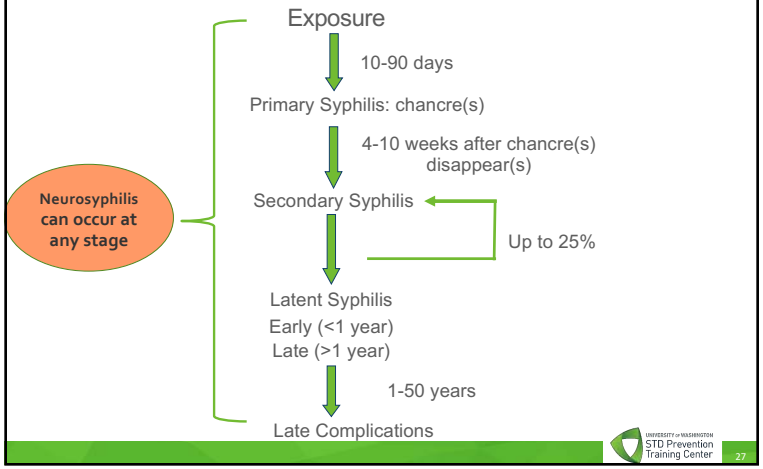
Natural history and clinical staging of syphilis



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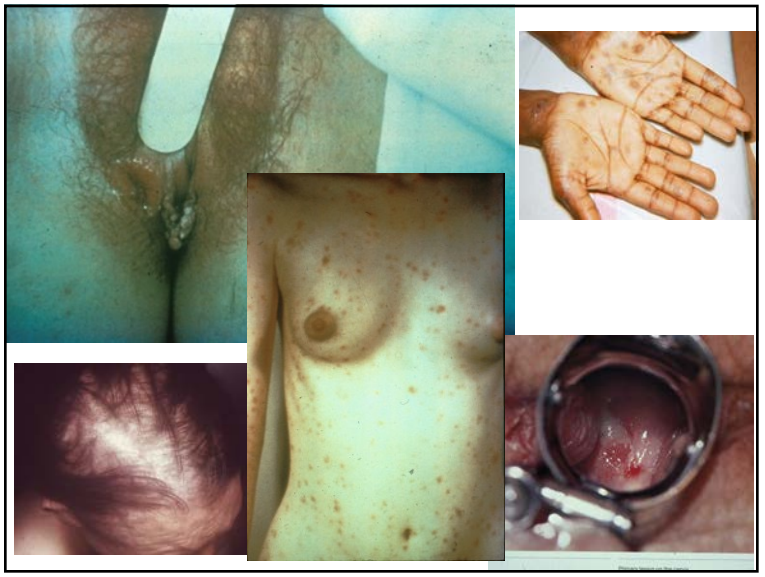

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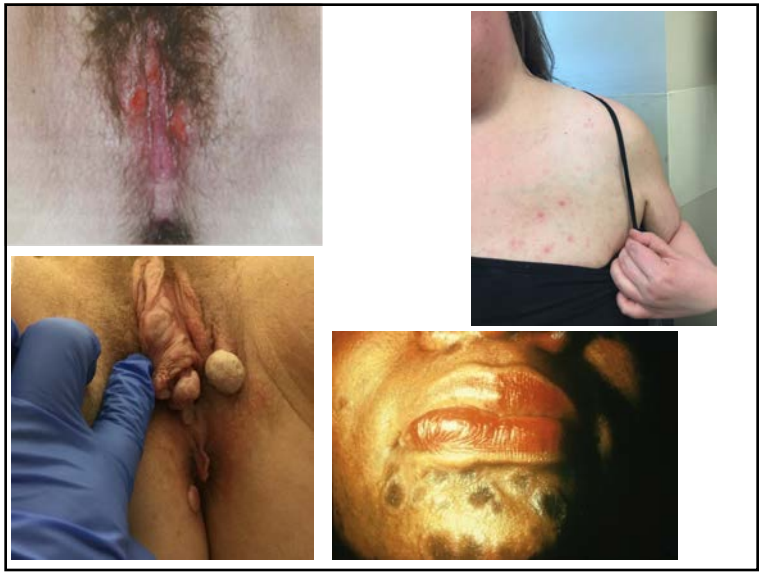

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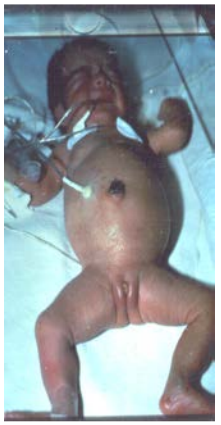
Congenital syphilis

- Transplacental infection can occur during any stage of syphilis and at any time during gestation
- Results in spontaneous abortion, stillbirth, infant with active or latent syphilis
  - High morbidity and mortality



Bates' Guide to Physical Examination and History Taking, 8th ed; eurorad.org

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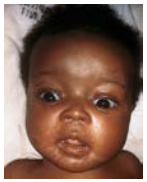
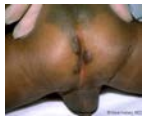
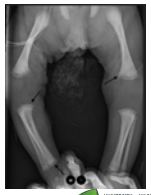
Congenital syphilis

- Early Disease: detected before 2 years of age
  - 60% of infected infants symptomatic at birth
  - Symptoms: Stillbirth, HSM and liver dysfunction, Skeletal involvement, rash, CNS infection, nephrotic syndrome, rhinorrhea (snuffles), others
  - Leads to great morbidity/mortality
- Late Disease: detected after 2 years of age
  - Bony and/or teeth malformations, deafness, keratitis, neurosyphilis
- Get help from Pediatric ID if questions and call early!



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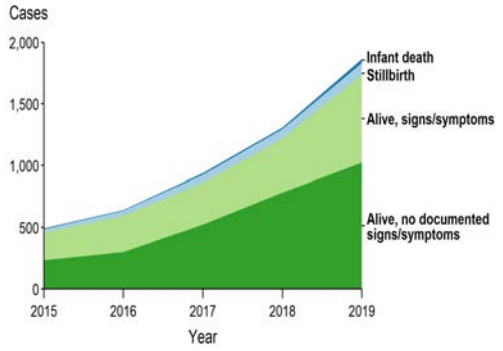
Congenital Syphilis — Number of Reported Cases by Vital Status and Clinical Signs and Symptoms* of Infections, United States, 2015–2019



* Signs/symptoms include long bone changes, snuffles, condylomata lata, syphilitic skin rash, pseudoparalysis, hepatosplenomegaly, edema, jaundice, hepatitis, reactive CSF-VDRL, elevated CSF WBC or protein, or evidence of direct detection of T. Pallidum.

NOTE: Of the 5,269 congenital syphilis cases reported during 2015–2019, 23 (0.4%) did not have sufficient information to be categorized

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Testing

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Syphilis testing in pregnant adults

- **Syphilis screening should occur 3 times during pregnancy!**
  - First prenatal visit (or at time of pregnancy confirmation)
  - Third trimester (~28 weeks)
  - Delivery (and post-partum visit, if ongoing risk)
- Risk factors for syphilis acquisition in pregnancy
  - Sex with multiple partners
  - Transactional sex or sex + drug use
  - Late entry into prenatal care (first visit in 2nd trimester or later)
  - No prenatal care
  - Meth or heroin use
  - Incarceration of pregnant individual or their partner
  - Unstable housing or homelessness

Workowski et al. Sexually Transmitted Infections Treatment Guidelines. MMWR Recomm Rep 2021;70 (4)

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Syphilis testing in pregnant adults, cont.

- Either algorithm is permitted. Use same quantitative NTT (and same lab, if possible) for adult/baby pair
- Serofastness is not uncommon. Higher titers (>1:8) might raise suspicion for re-infection and/or treatment failure
- If syphilis diagnosed in 2nd half of pregnancy, fetal sono recommended to evaluate for congenital abnormalities
- Testing recommended for any fetal death >20 wks EGA
- Neonates should not be dc'd unless syphilis status of mother has been determined

Workowski et al. Sexually Transmitted Infections Treatment Guidelines. MMWR Recomm Rep 2021;70 (4)

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Syphilis testing in Pregnancy

- For evaluating pregnant persons/baby pairs near delivery:
  - Traditional Strategy might be more useful
  - Rapid comparison of maternal/infant RPR/VDRL (use only one test for comparison)
  - Implement management quickly
  - When access to prenatal care is not optimal→do RPR at time pregnancy is confirmed and treat if positive
- Can then follow testing with a treponemal specific test afterwards
- Second half of pregnancy: sonographic fetal evaluation for congenital syphilis.
  - This evaluation should not delay therapy
  - Sonographic signs: hepatomegaly, ascites, hydrops, fetal anemia, or a thickened placenta indicate a greater risk for fetal treatment failure
  - consultation with obstetric specialists and peds ID
- Call public health→they can help you!

Adapted from Dr. Joseph Hilinski, CDC: https://www.cdc.gov/std/tg2015/syphilis-pregnancy.htm

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Case

- 29 yo pregnant woman seen for first pregnancy visit. Her syphilis screening comes back with a reactive RPR (1:2) and a syphilis IgG that is positive.
- She recalls that she was treated for secondary syphilis 2 years ago. You obtain records and see that her initial titer was 1:256.
- After treatment, the RPR had fallen to 1:16 at six months, then to 1:2 at 1 year.
- The titer remained at 1:2 two years later.

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Polling Question 2

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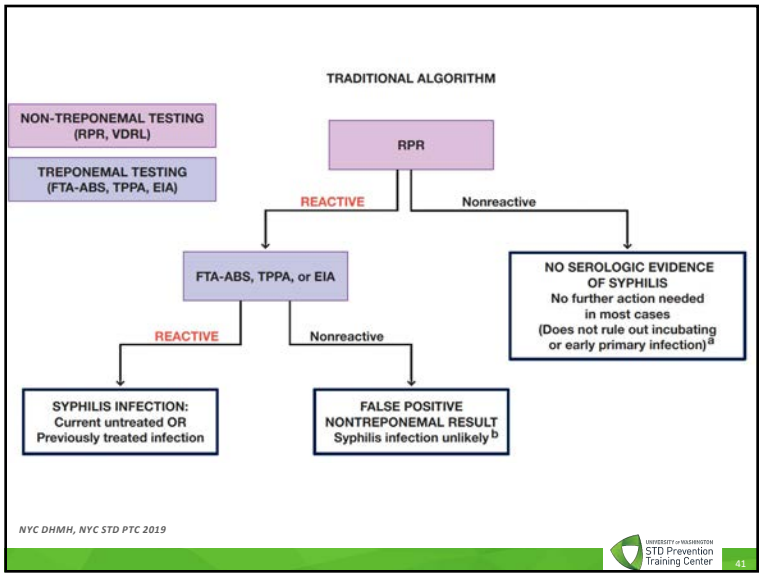
TRADITIONAL ALGORITHM
NON-TREPONEMAL TESTING (RPR, VDRL)
TREPONEMAL TESTING (FTA-ABS, TPPA, EIA)
RPR
REACTIVE
Nonreactive
FTA-ABS, TPPA, or EIA
NO SEROLOGIC EVIDENCE OF SYPHILIS
No further action needed in most cases
(Does not rule out incubating or early primary infection)a
REACTIVE
Nonreactive
SYPHILIS INFECTION:
Current untreated OR
Previously treated infection
FALSE POSITIVE NONTREPONEMAL RESULT
Syphilis infection unlikelyb
NYC DHMH, NYC STD PTC 2019
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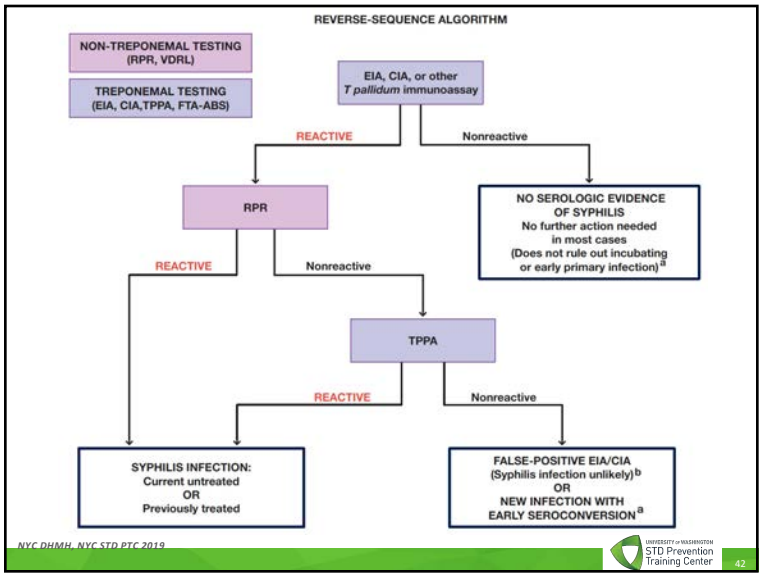
REVERSE-SEQUENCE ALGORITHM
NON-TREPONEMAL TESTING (RPR, VDRL)
TREPONEMAL TESTING (EIA, CIA,TPPA, FTA-ABS)
EIA, CIA, or other T pallidum immunoassay
REACTIVE
Nonreactive
RPR
NO SEROLOGIC EVIDENCE OF SYPHILIS
No further action needed in most cases
(Does not rule out incubating or early primary infection)a
REACTIVE
Nonreactive
TPPA
REACTIVE
Nonreactive
SYPHILIS INFECTION:
Current untreated
OR
Previously treated
FALSE-POSITIVE EIA/CIA
(Syphilis infection unlikely)b
OR
NEW INFECTION WITH EARLY SEROCONVERSIONa
NYC DHMH, NYC STD PTC 2019
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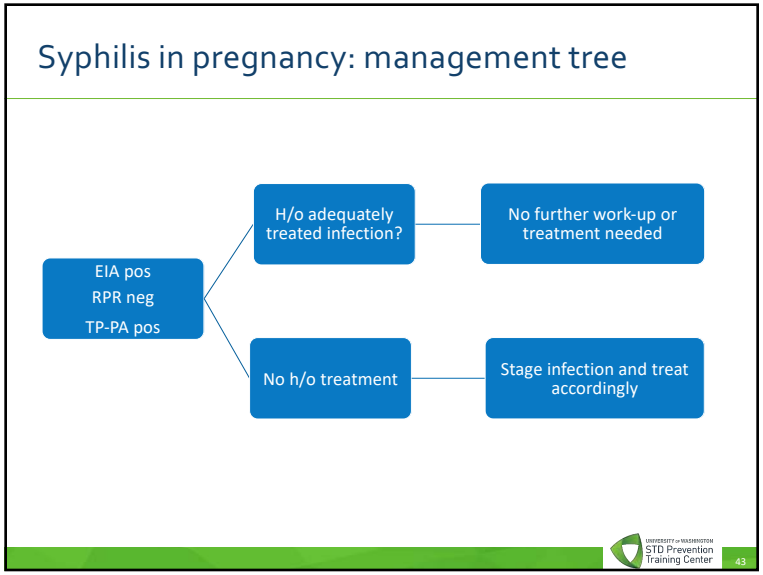
Syphilis in pregnancy: management tree
EIA pos
RPR neg
TP-PA pos
H/o adequately treated infection?
No further work-up or treatment needed
No h/o treatment
Stage infection and treat accordingly
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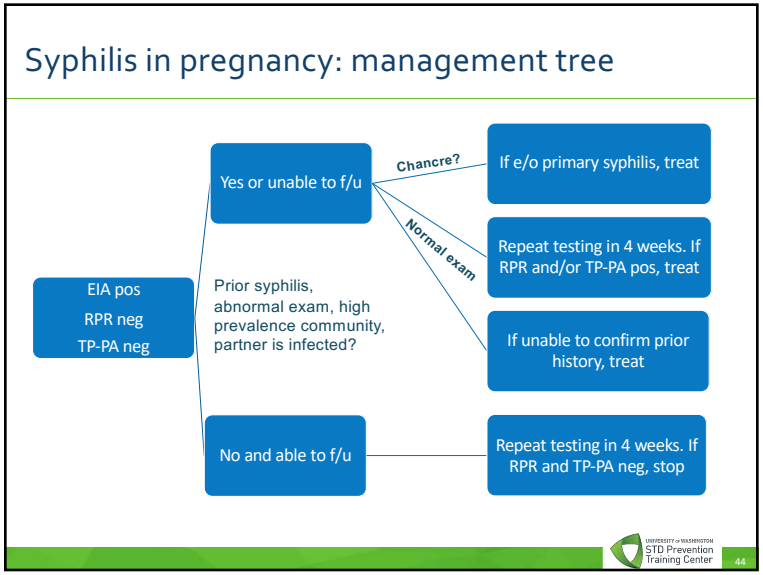
Syphilis in pregnancy: management tree
EIA pos
RPR neg
TP-PA neg
Prior syphilis, abnormal exam, high prevalence community, partner is infected?
Yes or unable to f/u
Chancre?
If e/o primary syphilis, treat
Normal exam
Repeat testing in 4 weeks. If RPR and/or TP-PA pos, treat
If unable to confirm prior history, treat
No and able to f/u
Repeat testing in 4 weeks. If RPR and TP-PA neg, stop
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Neonatal syphilis testing

- Transplacental antibodies may persist for days to >15 months: use quantitative NTT, not treponemal!
- Serum specimen is preferred over cord blood or Wharton's jelly
- Key elements for neonatal diagnosis
  - Serology and CSF evaluations
  - Detailed physical examination, including radiology
  - Placental or cord histopathology, including PCR testing*
  - Darkfield microscopy* of skin lesions or body fluids (nasal discharge, etc.)

Call pediatric ID for help!

Workowski et al. Sexually Transmitted Infections Treatment Guidelines. MMWR Recomm Rep 2021;70 (4)

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Diagnostic scenarios and management of neonate

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Neonatal evaluation and treatment scenarios

Scenario	Exam	Titer relative to mother	Other considerations	Management[Δ]
Proven/ Probable	Abnl*	≥4x	**or** Positive darkfield, PCR, silver stain from placenta, cord, lesions, body fluid	Aqueous crystalline PCN G **IV** x10 days or procaine PCN G **IM** daily x10 days
Possible	Normal *	≤4x	+ Mother inadequately treated (non-PCN tx) or within 30 days of delivery	May treat as above or with benzathine PCN G **IM** x1
Less likely	Normal	≤4x	+ Mother appropriately treated >30 days prior, no relapse/reinfection	Benzathine penicillin G **IM** x1 or monitor for RPR decline
Unlikely	Normal	≤4x	+ Mother appropriately treated and titer low/stable	No treatment, follow serologically

* Further eval with CSF, CBC w/ diff, long bone XR, other clinically indicated tests
[Δ] No missed doses permitted. *Ceftriaxone IV may be ok if aqueous crystalline PCN shortage, no significant bilirubinemia, infant unable to tolerate IM – consult pediatrician/ID*

Workowski et al. Sexually Transmitted Infections Treatment Guidelines. MMWR Recomm Rep 2021;70 (4)

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Other management considerations

- Always ok to err on side of treatment if any concern for undertreatment or re-exposure in parent
- Ampicillin ≠ benzathine/aqueous/procaine PCN
- Scenario 2 (possible): single dose benzathine PCN only if other testing is nl, CSF non-bloody and f/u is certain
- If neonate's RPR is NR + parent is "low risk" – may consider benzathine PCN x1 w/o addl. eval for "incubating" syphilis

Workowski et al. Sexually Transmitted Infections Treatment Guidelines. MMWR Recomm Rep 2021;70 (4)

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Treatment and follow-up

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Syphilis treatment in pregnant adults

Table. Treatment recommendations for syphilis during pregnancy		
Primary Secondary Early non-primary, non-secondary Or if fetal abnormalities on sono	Benzathine penicillin G 2.4 million units intramuscularly (IM) x 2	For HIV-positive women, administer at least two doses of benzathine penicillin G 2.4 million units IM and strongly consider three doses
Late syphilis (>1 year or unknown duration)	Benzathine penicillin G 2.4 million units intramuscularly (IM) weekly x 3	
Neuro or ocular syphilis	Penicillin 4 million units intravenously every 4 hours for 10-14 days	

- Avoid tetracyclines in 2nd and 3rd trimester
- Optimal timing between doses is 7 days; up to 9 days *may be* permitted, otherwise restart course
- If PCN-allergic: urgent skin testing to confirm → desensitization
- *Engage OHA or local HD for partner services to get contacts tested and treated!*

Oregon Health Authority (Tim Menza), 2018

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Treatment in Pregnancy

- Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy
  - Penicillin allergies
    - Skin testing to confirm allergy
    - Induce drug tolerance (desensitization)
  - Treat appropriate to stage and manifestations
- Some evidence: a second dose of benzathine PCN 2.4 million units IM can be administered after initial dose for primary, secondary or early latent syphilis
- Missed doses not acceptable for treatment for late latent disease.
  - Need to restart treatment
- Treat partners, contacts to syphilis

https://www.cdc.gov/std/tg2015/syphilis-pregnancy.htm

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Jarisch-Herxheimer reaction

- Pregnancy: >20 weeks are at risk for premature labor and/or fetal distress (stillbirths are rare)
- Acute febrile reaction after initiation of antibiotics for the treatment of spirochetal infections, due to release of endotoxins and lipoproteins
- May cause malaise, nausea, vomiting, chills, exacerbation of rash.
- Seek obstetric attention if fever, contractions, or decreased fetal movement
- Typically resolves within 24 hours with supportive care; steroids not beneficial

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IMPORTANT: Contacts to syphilis (sex partners)

Partners Needing Evaluation

- Primary, secondary, early latent syphilis - 3 months plus the duration of symptoms

Partner Testing and Treatment

- Contacts– sex in 90 days preceding onset of case's symptoms
  - Test and treat with 1st dose Benzathine PCN without waiting for test results
- Contacts - >90 days since last sex
  - Test – Treatment based on results and staging
  - Treat if testing not available or follow-up uncertain
- Late latent syphilis
  - Test partners

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Follow up for the pregnant adult

- If syphilis, always test for HIV!
- Monitoring is based on stage of pregnancy at diagnosis
  - Before/at 24 weeks EGA: soonest to repeat titers is 8 weeks after tx (unless new signs/sx of 1ry or 2ry syphilis)
  - After 24 weeks EGA: repeat titers at delivery
- Consider monthly titer checks for those with ongoing risk factors
- Many may not achieve fourfold decrease before delivery
- Concern for re-infection or tx failure: if sustained (>2 wks) fourfold titer increase after tx

Workowski et al. Sexually Transmitted Infections Treatment Guidelines. MMWR Recomm Rep 2021;70 (4)

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Follow up for the neonate

- If syphilis, always test for HIV!
- Physical exam and NTT titers every 2-3 mos. until neg
- Scenarios 3 & 4: NTT titers should decrease by 3 mos. and be neg by 6 mos. If still positive → treat infant
- If persistent NTT titers ≥6 months despite tx, consult OHA/pediatric ID and consider CSF eval
- If concern about "incubating" syphilis (initial NTT was neg), retest at 3 mos.

Workowski et al. Sexually Transmitted Infections Treatment Guidelines. MMWR Recomm Rep 2021;70 (4)

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Late congenital syphilis

- Children >1 month with positive serologies
  - Evaluation including CSF VDRL, cell count, protein, CBC
  - Other tests as clinically indicated
- Parent's serologies and records to differentiate congenital vs acquired syphilis
- Child should be tested for HIV
- Consider endemic treponematoses in adoptees, immigrants, refugee children from endemic countries
- Assess for sexual assault and child abuse – report!

Kimball et al. Congenital Syphilis Diagnosed Beyond the Neonatal Period in the United States: 2014–2018. Pediatrics. 2021;148(3)

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Summary and conclusions

- Rates of syphilis are increasing – both congenital syphilis and in adults of childbearing potential
- Be aware of your local epidemiology and risk factors in pregnancy. If in doubt, always ok to treat (and test)!
- Screening for syphilis and appropriate treatment are imperative in pregnancy
  - PCN is drug of choice
  - Treat index patients and all contacts
- Congenital syphilis *can be prevented*! Public health can provide support for diagnosis and treatment

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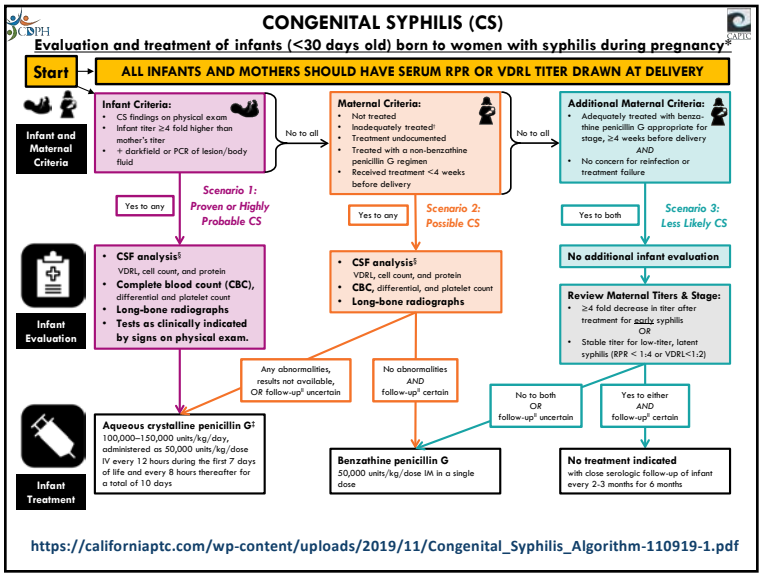

https://californiaptc.com/wp-content/uploads/2019/11/Congenital_Syphilis_Algorithm-110919-1.pdf

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South Dakota Recommendations

PRENATAL CARE PROVIDERS

- ☐ All pregnant women should be screened for syphilis **three times** during pregnancy during this outbreak setting:
  - At first prenatal appointment or at time of initial pregnancy diagnosis if concerned for poor follow up
  - At 28 weeks
  - At delivery
- ☐ All pregnant women delivering a stillbirth (gestational age ≥20 weeks)

In an effort to stop congenital syphilis **SD-DOH recommends enhancing syphilis screening to emergency room departments and urgent care.** In 2021 South Dakota mothers associated with congenital/syphilitic stillbirths had insufficient, late, or no prenatal care, however, some of those same women and/or their partners were seen in emergency rooms and urgent care for reasons other than prenatal care. Screening women of reproductive age (15-45 years) and sex partners to women of reproductive age can reduce congenital syphilis.

ADEQUATE TREATMENT FOR INFECTED CASE DURING PREGNANCY

- Completion of a penicillin-based regimen, appropriate for stage of infection, initiated 30 or more days before delivery.
- Pregnant women MUST be treated with penicillin. If allergic, she must be desensitized and treated to stage of illness.

No infant should leave the hospital without the mother's serological status documented at delivery

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Your best friends

DISEASE INTERVENTION SPECIALIST (DIS) CONTACT INFORMATION

Contact your local DIS with syphilis questions or if you need assistance contacting a client for testing, treatment, and counseling for syphilis, HIV/AIDS, and other sexually transmitted infections.

Aberdeen 402 S. Main St. Aberdeen, SD 57401-4127 Toll-free: 1-866-805-1007	**Mobridge** 210 East Grand Crossing, Suite A Mobridge, SD 57601 Toll-free: 1-833-618-2740	**Sioux Falls** 4101 West 38th St., Suite 102 Sioux Falls, SD 57106 Toll-free: 1-866-315-9214
Pierre 740 E. Sioux, Suite 107 Pierre, SD 57501-3395 Toll-free: 1-866-229-4927	**Rapid City** 909 E. St. Patrick, Suite 10 Rapid City, SD 57701 Toll-free: 1-866-474-8221	**Watertown** 2001 9th Ave. SW #500 Watertown, SD 57201-4038 Toll-free: 1-866-817-4090
Mitchell 1420 North Main St. Mitchell, SD 57301 605-995-8051	**Main office** Toll-Free: 800-592-1861	

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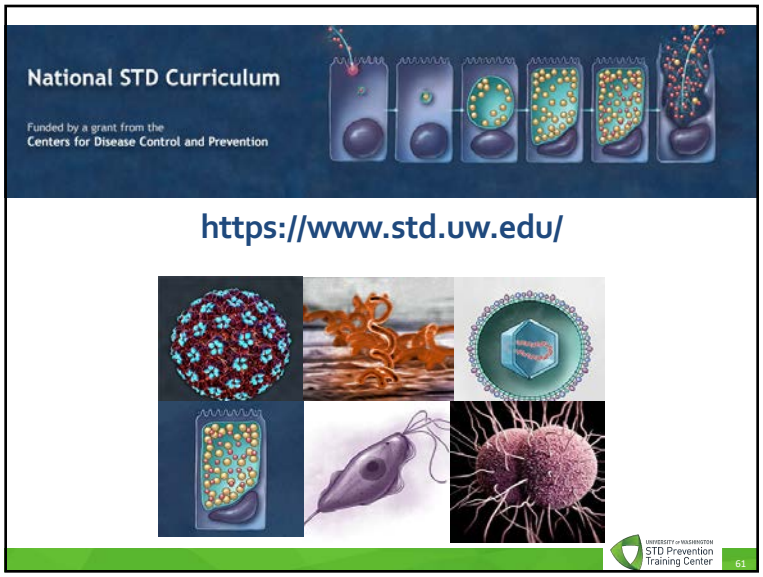
National STD Curriculum
Funded by a grant from the
Centers for Disease Control and Prevention
https://www.std.uw.edu/
STD Prevention Training Center
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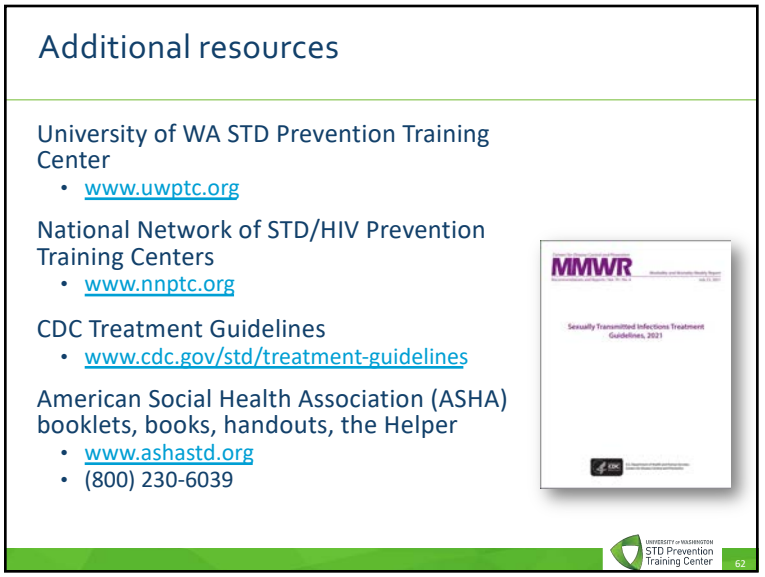
Additional resources
University of WA STD Prevention Training Center
• www.uwptc.org
National Network of STD/HIV Prevention Training Centers
• www.nnptc.org
CDC Treatment Guidelines
• www.cdc.gov/std/treatment-guidelines
American Social Health Association (ASHA) booklets, books, handouts, the Helper
• www.ashastd.org
• (800) 230-6039
MMWR
Sexually Transmitted Infections Treatment Guidelines, 2021
STD Prevention Training Center
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