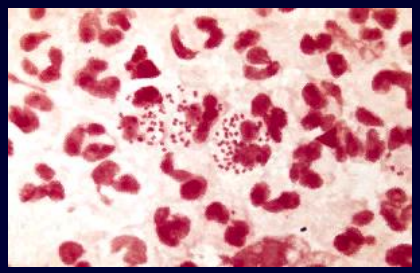
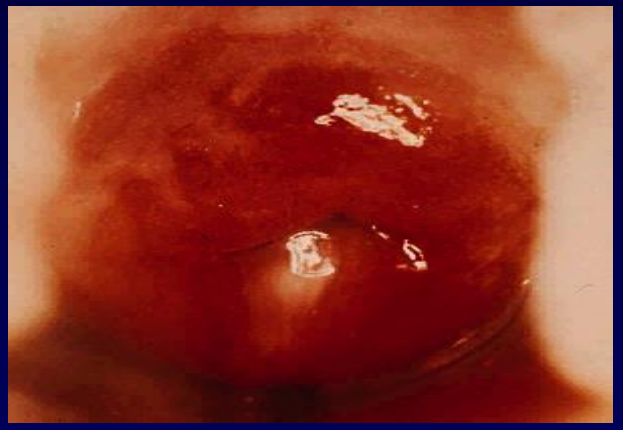


Pregnancy and STIs



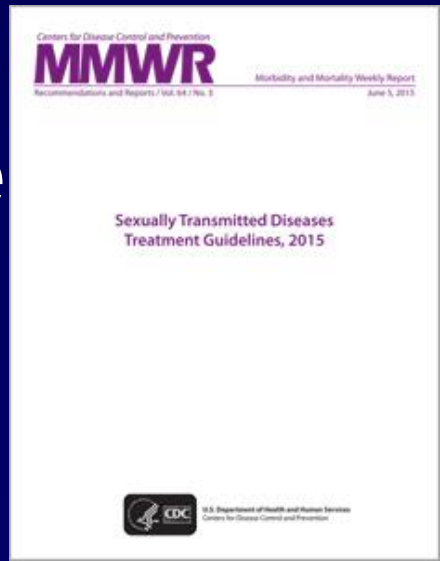
Jeanne S. Sheffield

Maternal-Fetal Medicine

Johns Hopkins Medicine

STD Treatment Guidelines

- 4/30-5/2/2013 Meeting in Atlanta to update the 2010 guidelines
- Clinical experts charged with reviewing and updating their “sections”
- CDC then developed the draft recommendations and a second independent panel reviewed these



Special Populations

- Pregnant women
- Adolescents
- Children
- Persons in correctional facilities
- MSM
- WSW
- Transgender men and women

Special Populations: Pregnancy

- Recommendations for screening pregnant women are based on disease severity and sequelae, prevalence, costs, medico-legal considerations
- Pregnant population screening recommendations are very broad

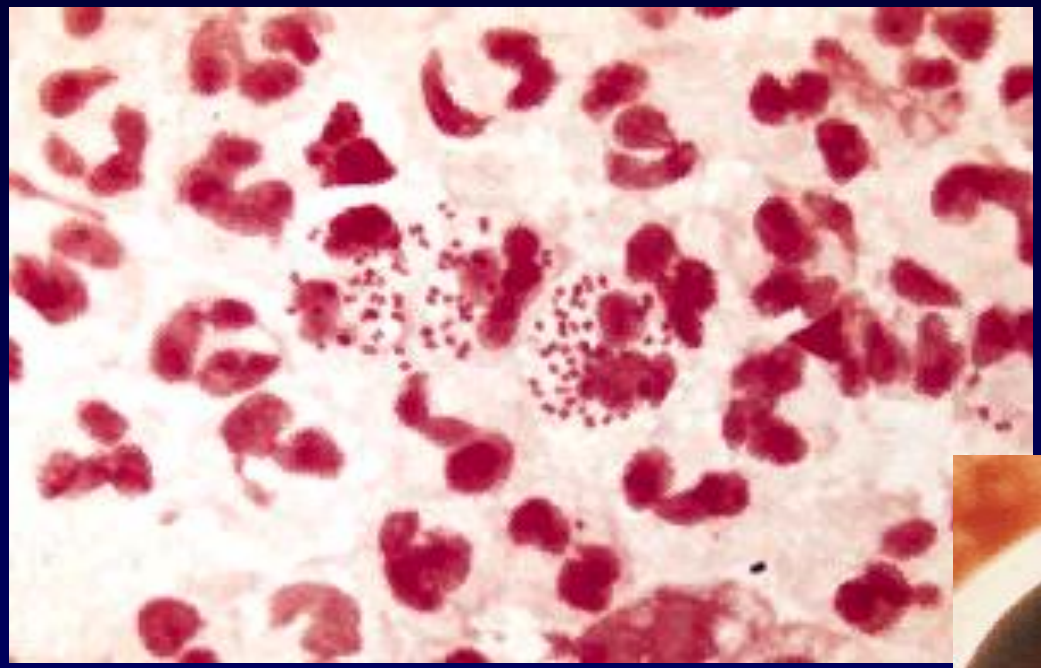
Special Populations: Pregnancy

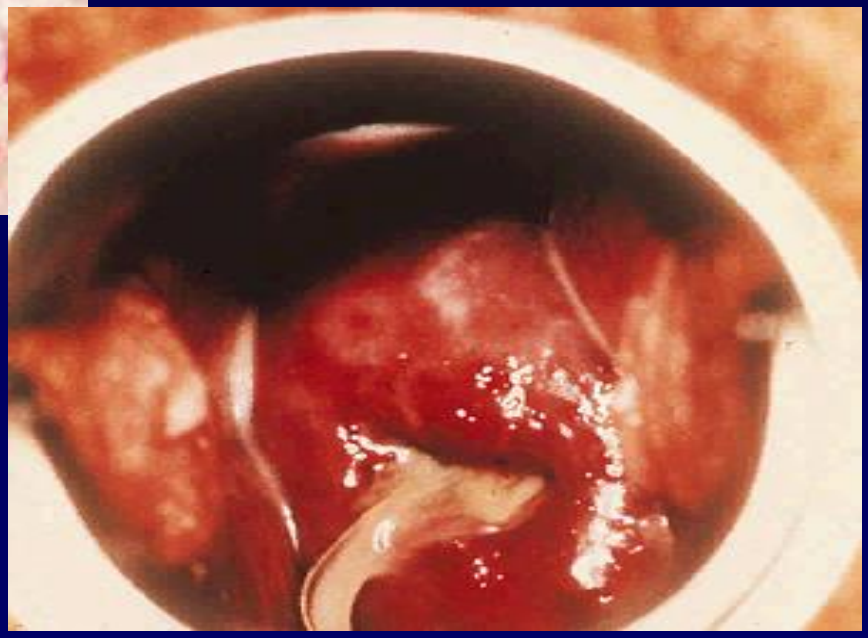
- Screen for
  - HIV first prenatal visit (opt out) and again in the third trimester in high risk populations
  - Syphilis first prenatal visit, third trimester and at delivery in high risk areas
  - HBsAg first prenatal visit and high risk people at delivery
  - Pregnant women <25 and older if high risk, screen for chlamydia first prenatal visit and third trimester
    - TOC 3-4 weeks and reinfection test at 3 months

Special Populations: Pregnancy

- Screen for
  - Gonorrhea women <25 and older if high risk first prenatal visit. Retest within 3 months of treatmentand again third trimester if high risk
  - HCV if at high risk for infection
  - Pap test
- Not enough information for screening for BV, trichomonas or HSV-2

GONORRHEA: GRAM NEGATIVE DIPLOCOCCUS

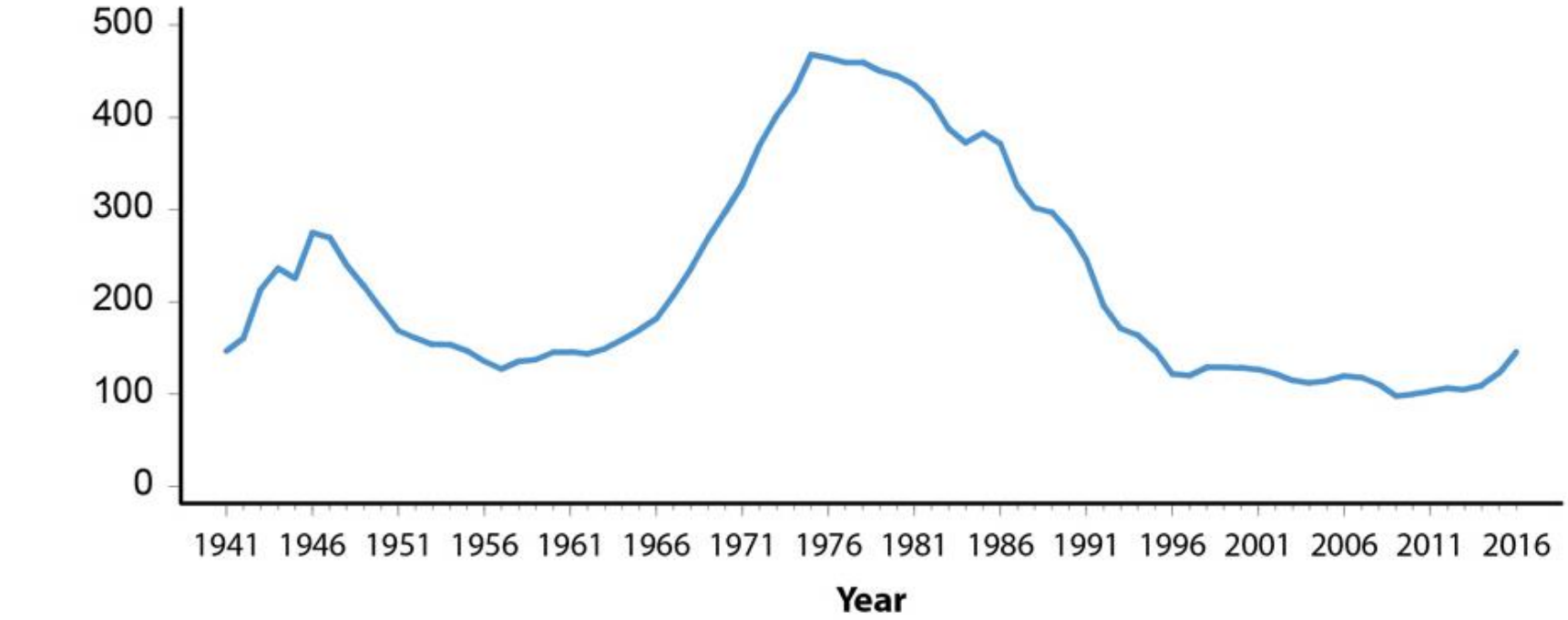




Gonorrhea Transmission

- Sexual contact
- Transmission efficiency
  - male to female 50 - 60%
  - female to male 20%
- Second most commonly reported bacterial STD
- Targeted screening of young women (i.e., those aged <25 years) at increased risk for infection is a primary component of gonorrhea control in the United States.

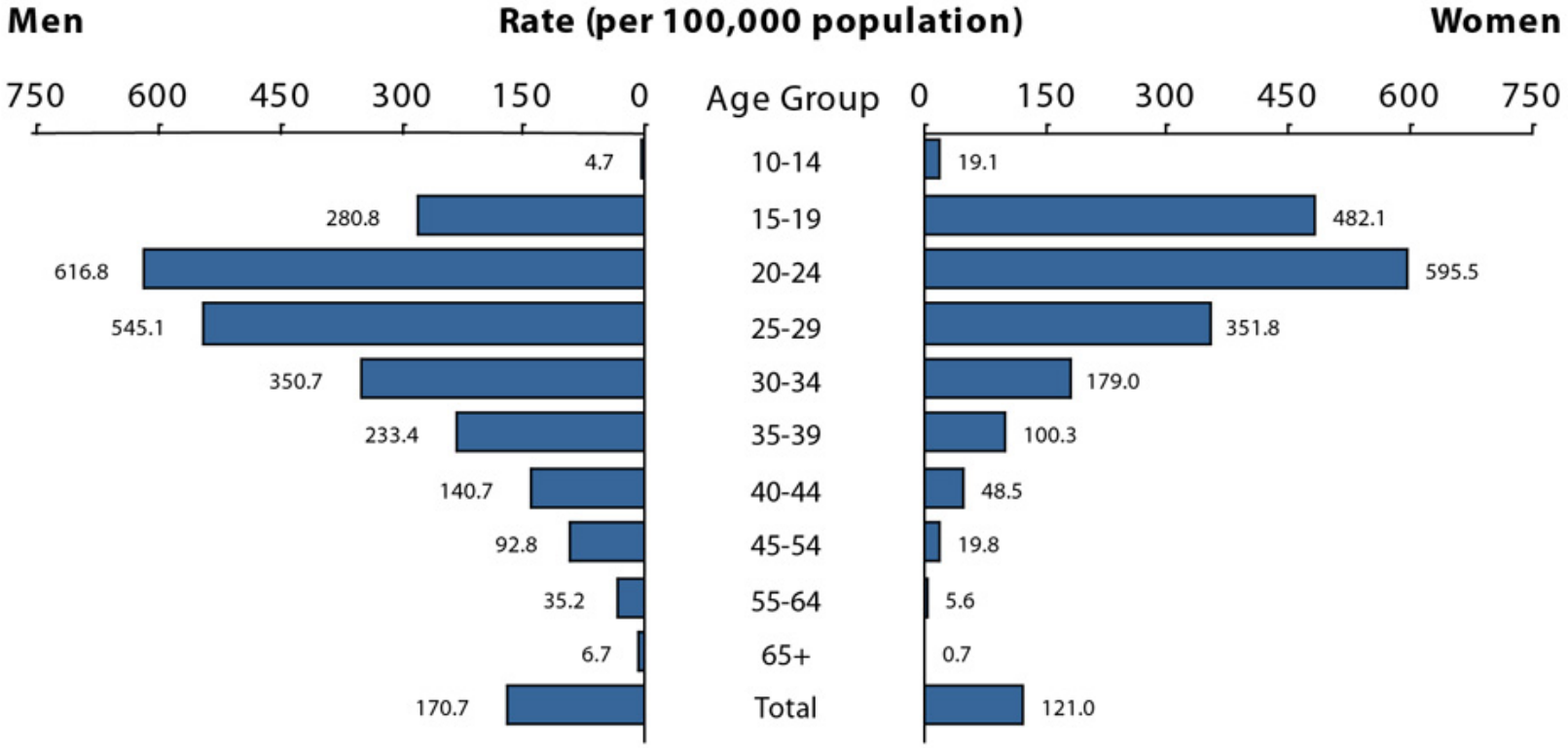
Figure 12. Gonorrhea — Rates of Reported Cases by Year, United States, 1941–2016



2016 Sexually Transmitted Diseases Surveillance

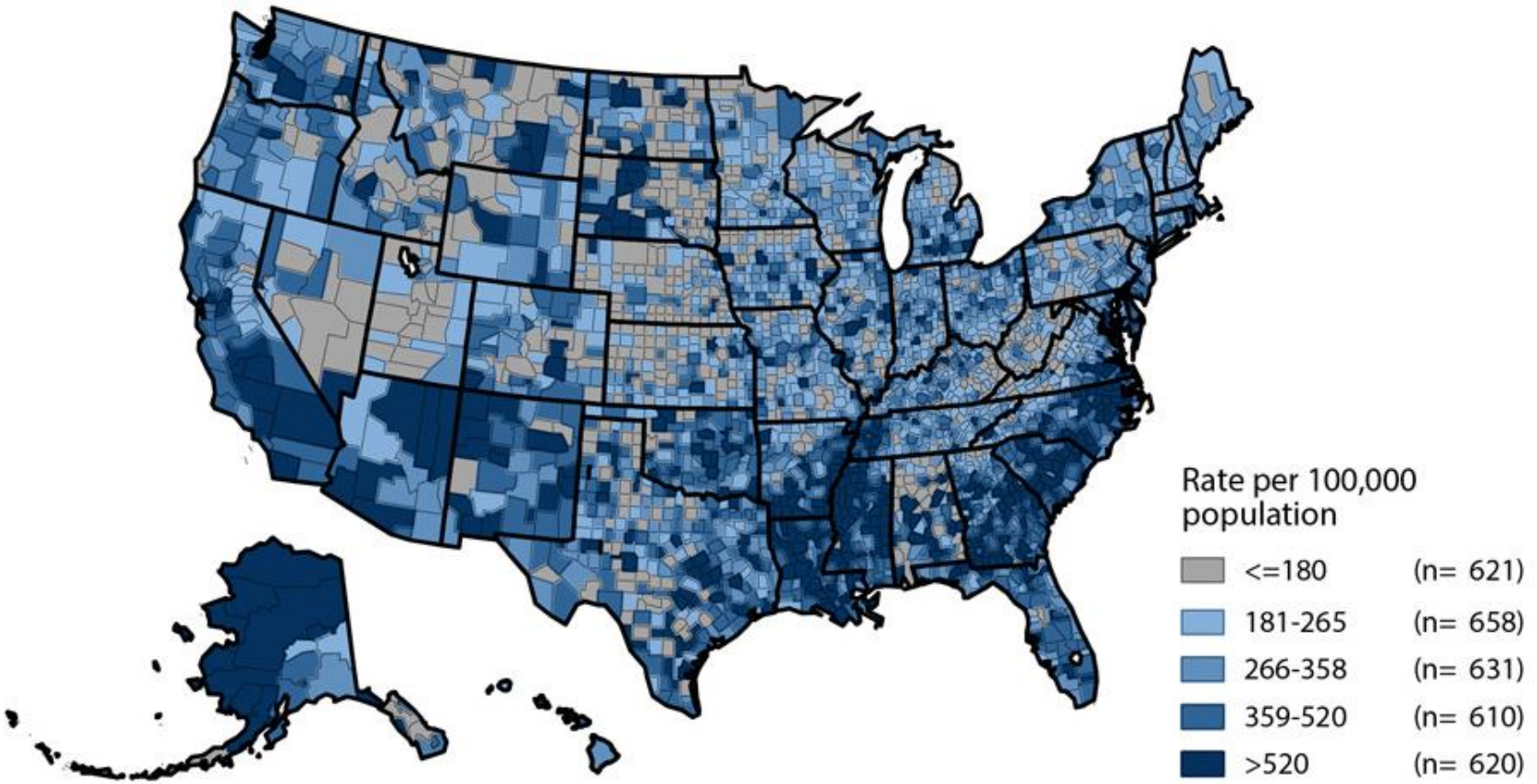
18.5% increase from 2015 to 2016
48.6% increase since historic low in 2009
Increase was in males and females and in all regions

Figure 17. Gonorrhea — Rates of Reported Cases by Age Group and Sex, United States, 2016

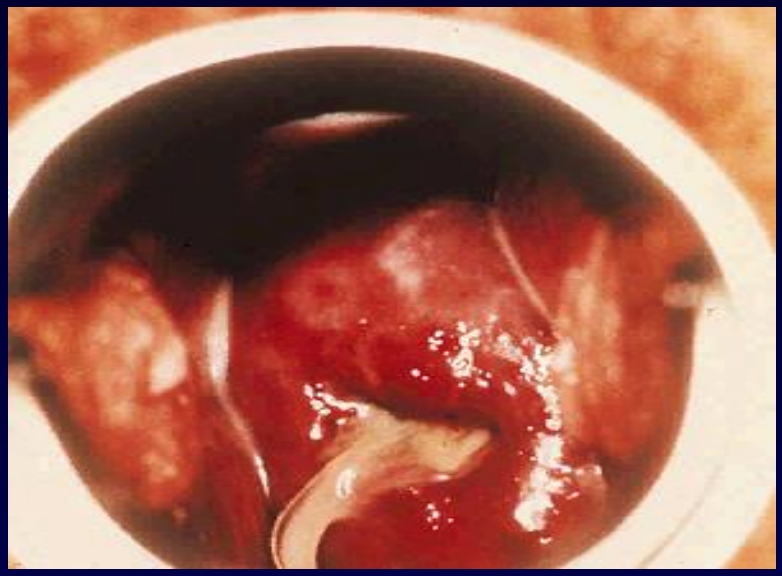


2016 Sexually Transmitted Diseases Surveillance

Figure 16. Gonorrhea — Rates of Reported Cases by County, United States, 2016



Clinical Findings



- Female
  - 2-5 days post-infection
  - urgency, frequency and dysuria
  - vaginal discharge (clear to purulent)
  - Rectal burning, itching, tenesmus (30%)
  - cervical os erythematous and/or friable
  - often asymptomatic (>50%) until complications arise (SCREEN)

Gonorrhea in Pregnancy

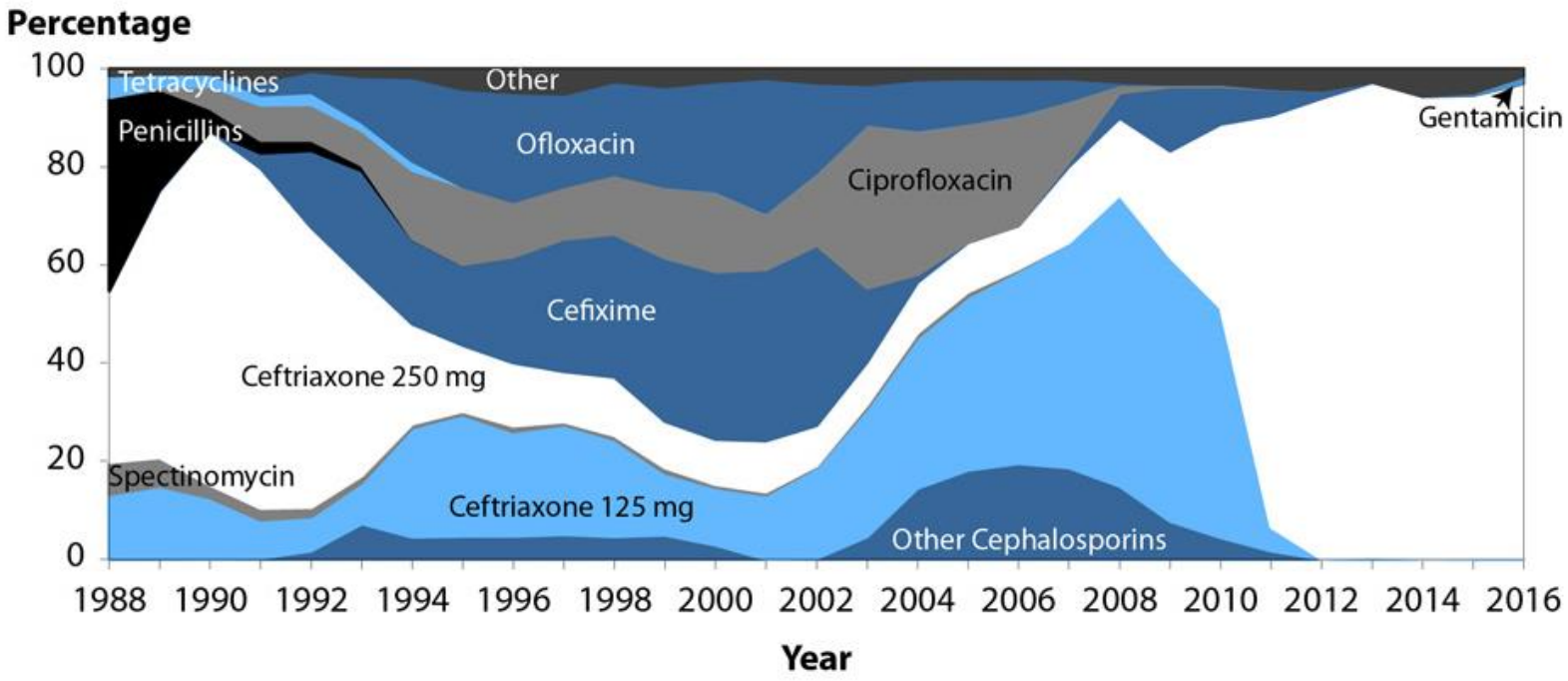
- Perinatal outcomes are not significantly affected by gonorrhea
- Ceftriaxone 250mg IM PLUS Azithromycin 1gm orally as a single dose.

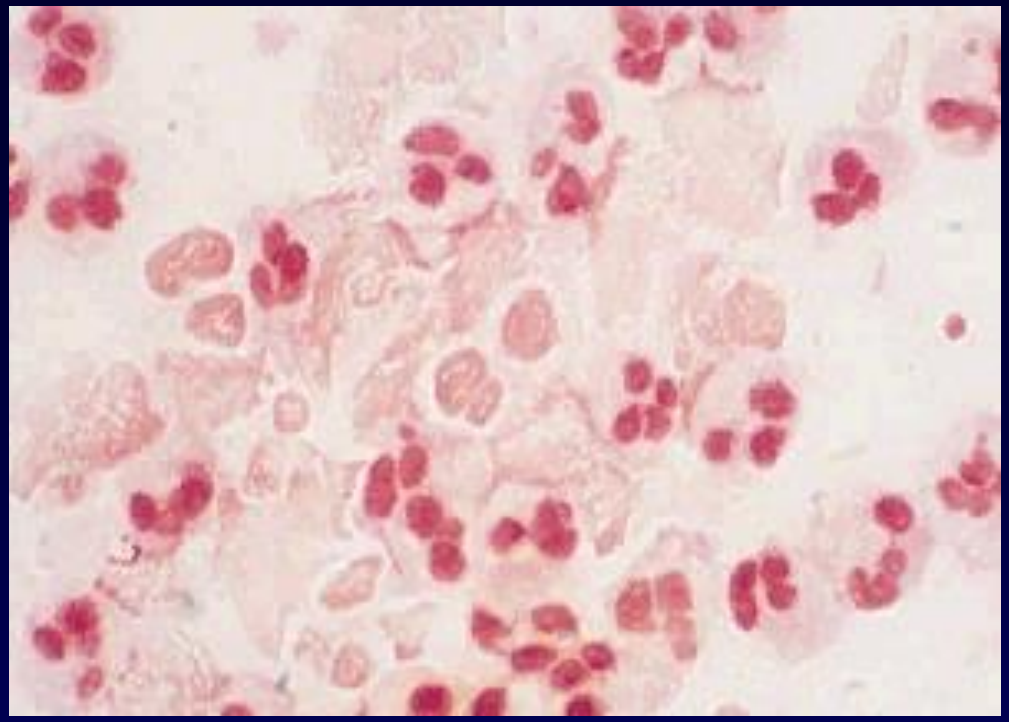
Neisseria gonorrhoeae
Antimicrobial Resistance

- Geographic variation in resistance to penicillin and tetracycline
- No significant resistance to ceftriaxone
- Fluoroquinolone resistance is now widespread in the United States – this class is no longer recommended for treatment of gonorrhea
- Surveillance is crucial for guiding therapy recommendations

MMWR 4/13/2007

Figure 29. Distribution of Primary Antimicrobial Drugs Used to Treat Gonorrhea Among Participants, Gonoc
Surveillance Project (GISP), 1988–2016





CHLAMYDIA

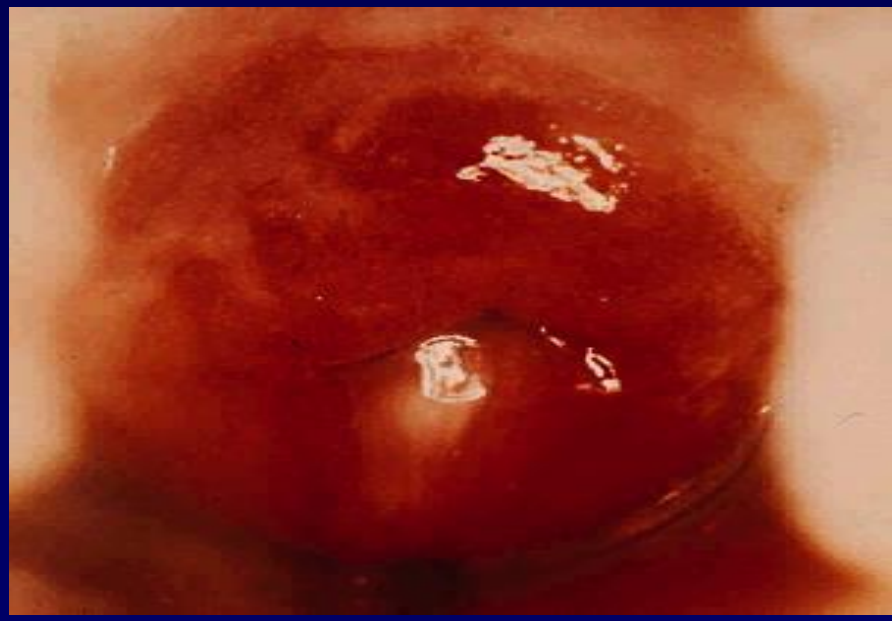
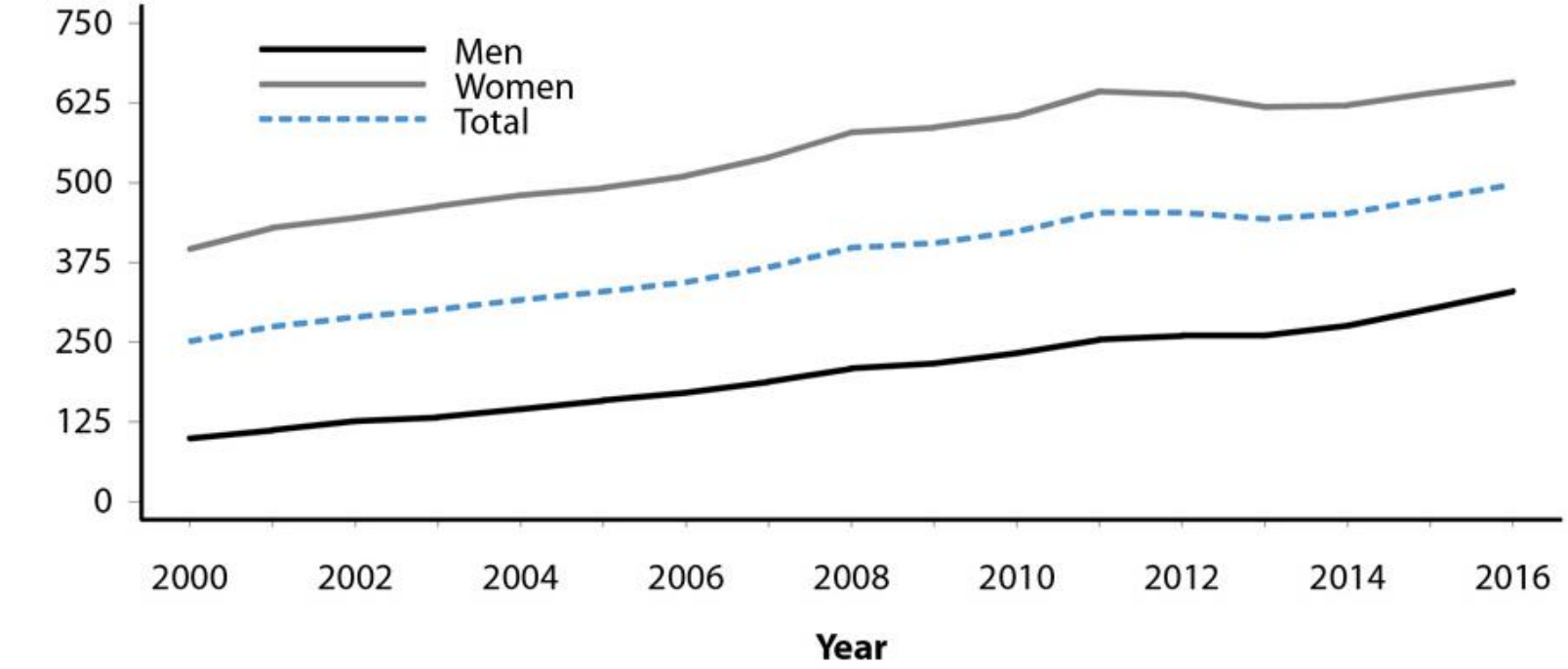
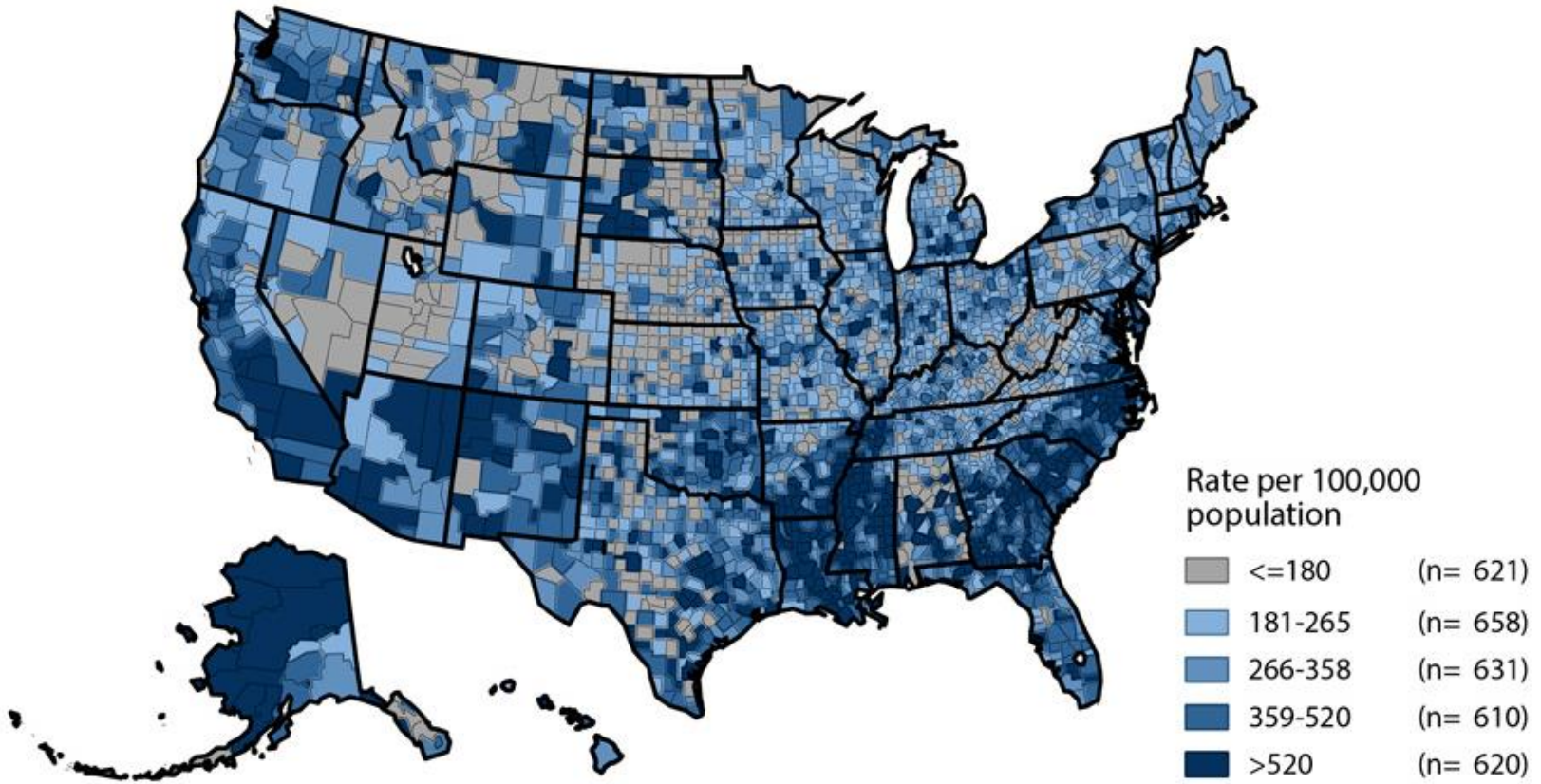


Figure 1. Chlamydia — Rates of Reported Cases by Sex, United States, 2000–2016



4.7% increase from 2015-2016

Figure 4. Chlamydia — Rates of Reported Cases by County, United States, 2016



2016 Sexually Transmitted Diseases Surveillance

Clinical Findings

- Female
  - 70% are asymptomatic
  - Nonspecific findings such as dysuria, vaginal discharge or pruritus
  - Friable cervix with mucopurulent discharge
  - acute urethral syndrome
    - abacteriuric pyuria in sexually active women

Clinical Sequelae

- Acute salpingitis
  - ascent from the lower genital tract
  - silent or clinical
  - fever, lower abdominal pain, uterine and adnexal tenderness
- Fitz-Hugh-Curtis syndrome
- Infertility
- Ectopic pregnancy
- ?Preterm delivery association in pregnancy

Diagnosis of Chlamydia

- Cell culture
- Direct fluorescent antibody (DFA)
- Enzyme immunoassay (EIA)
- PCR
- Ligase chain reaction (LCR)
- Urine testing (PCR or LCR)

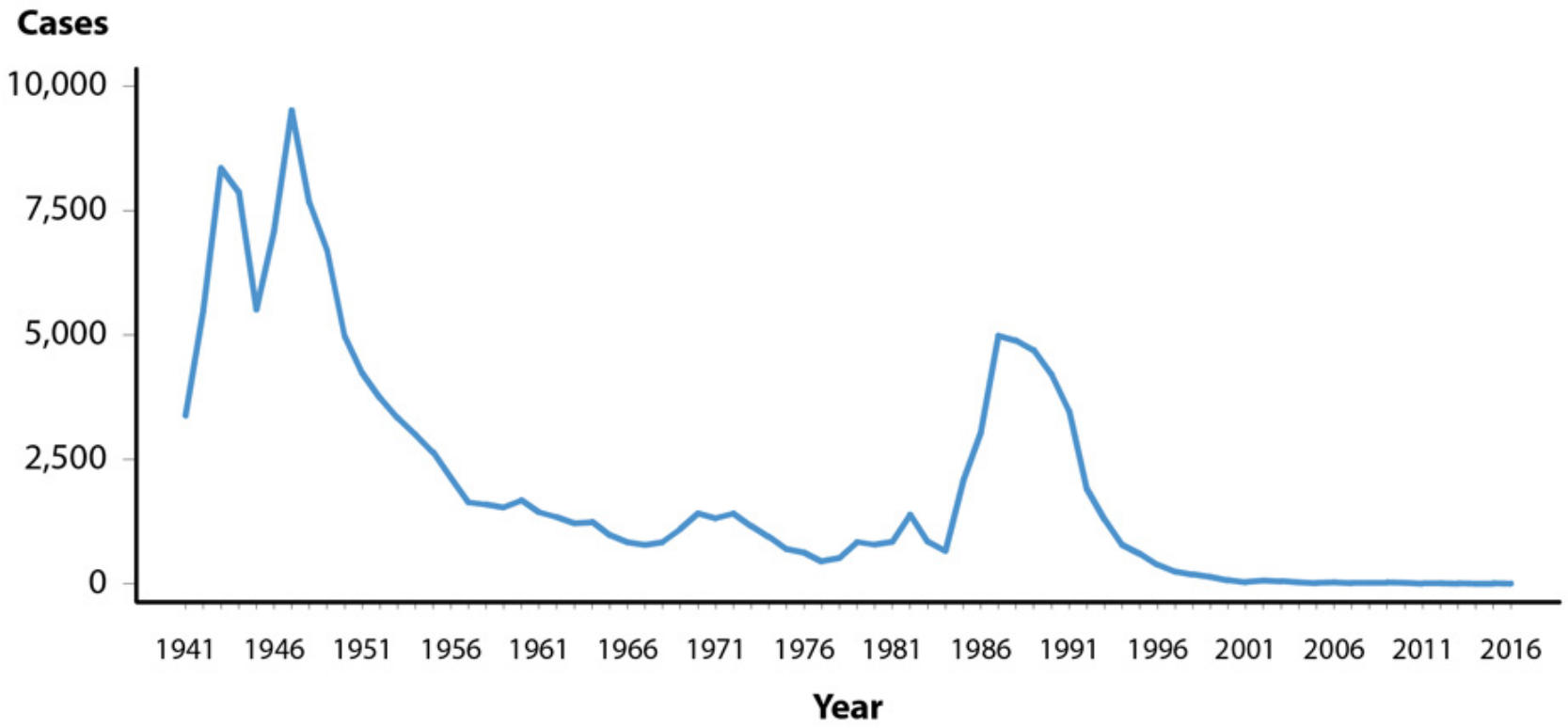
Chlamydia Updates

- Chlamydial infection is the most frequently reported infectious disease in the United States, and prevalence is highest in persons aged ≤24 years
- Azithromycin still the drug of choice for pregnancy
  - TOC 3-4 weeks afterwards
  - Retest 3 months after treatment
  - Amoxicillin is now an alternative regimen (500mg po tid x 7 days) as well as EES or erythromycin base
  - Doxy now a recommended regimen in NON-pregnant patients

Chancroid

- Usually in discrete outbreaks in the US
- *H. ducreyi* – special culture media
- Painful genital ulcer and tender suppurative inguinal adenopathy

Figure 45. Chancroid — Reported Cases by Year, United States, 1941–2016



Chancroid Updates

- Worldwide, chancroid appears to have declined, although infection might still occur in some regions of Africa and the Caribbean.
- A definitive diagnosis of chancroid requires the identification of *H. ducreyi* on special culture media that is not widely available from commercial sources; even when these media are used, sensitivity is <80%

Chancroid

- **Azithromycin** 1 g orally OR
- **Ceftriaxone** 250 mg IM OR
- **Ciprofloxacin** 500 mg BID for 3 days OR
- **Erythromycin base** 500 mg TID for 7 days

Chancroid

Management Considerations

- Examine and treat partner whether symptomatic or not if contact ≤ 10 days prior to onset
- Re-examination 3-7 days after treatment
- Time required for complete healing related to ulcer size

Granuloma Inguinale (Donovanosis)

- *Klebsiella granulomatis*
- Rare in the US
- Painless, progressive ulcerative lesions without regional LAD
  - Beefy red lesion
- Hard to culture – visualize on tissue crush prep looking for Donovan bodies

Granuloma Inguinale

Recommended Regimen:

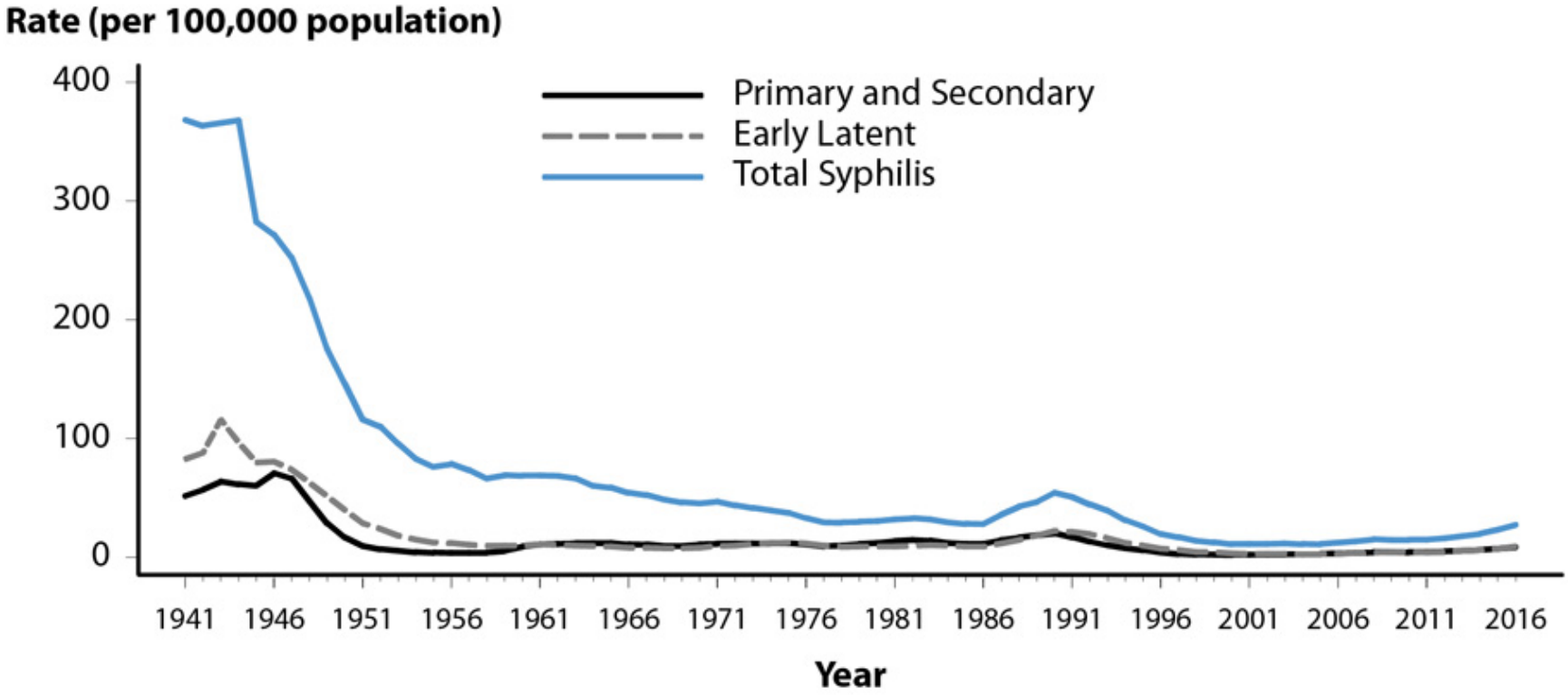
- Doxycycline 100 mg twice daily for NON-Pregnant
- Pregnant women should be treated with a macrolide regimen (EES or azithromycin) +/- an aminoglycoside of no improvement

-

Syphilis

- Systemic disease caused by the bacterium *Treponema pallidum*
- 2 stages
  - Early (<12 months from acquisition to diagnosis)
    - Primary syphilis
    - Secondary syphilis
    - Early latent syphilis
  - Late (>12 months acquisition to diagnosis)
    - Late latent syphilis

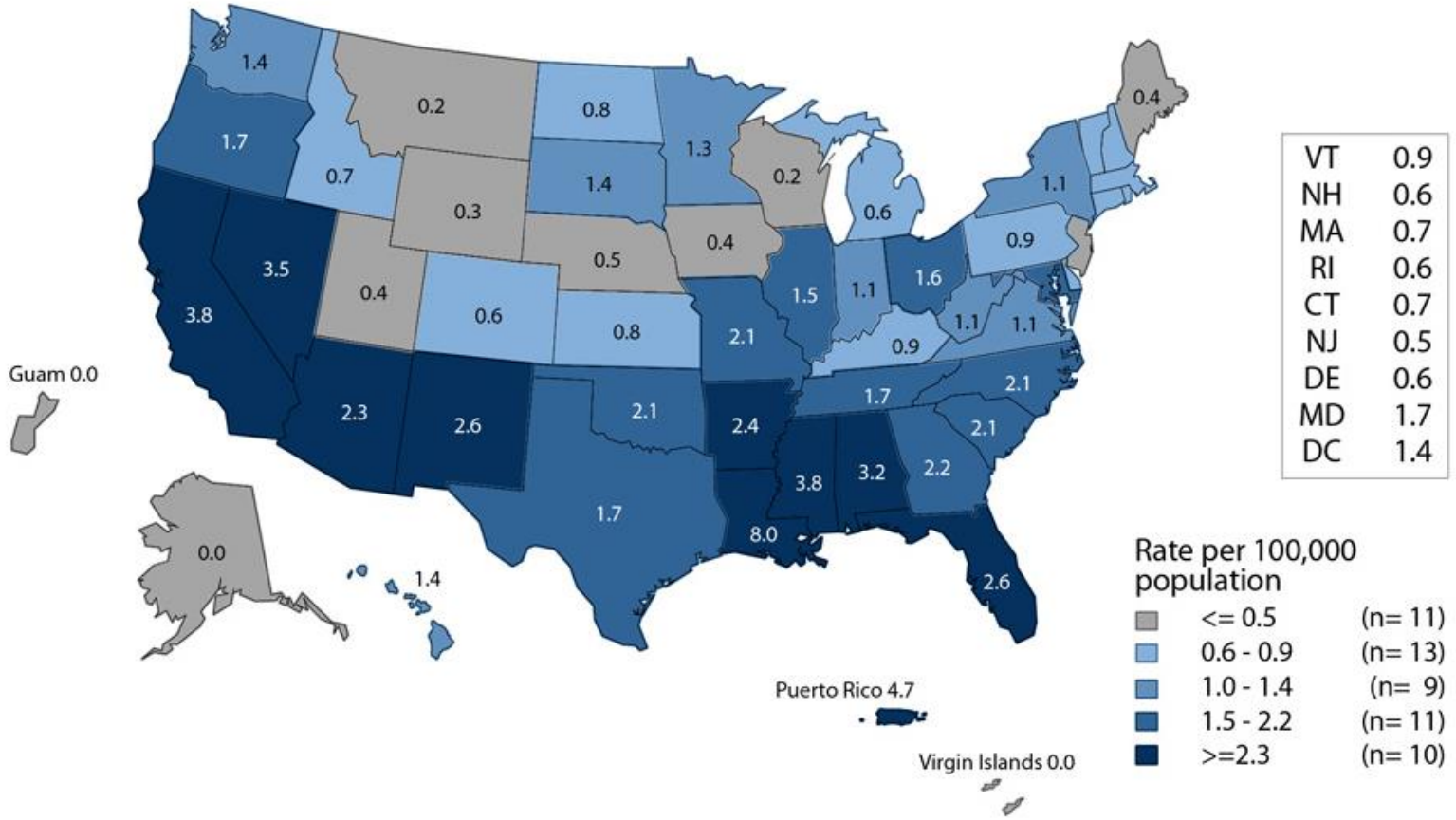
Figure 30. Syphilis — Rates of Reported Cases by Stage of Infection, United States, 1941–2016



2016 Sexually Transmitted Diseases Surveillance

17.6% increase from 2015 overall
All stages (total) highest since 1993

Figure H. Primary and Secondary Syphilis — Rates of Reported Cases Among Women by State, United Stat
Outlying Areas, 2016



35.7% increase from 2015 in women

Primary Syphilis

- Painless Chancre
  - raised, red firm border
  - smooth base
- Non-suppurative lymphadenopathy
- Resolves in 3-8 weeks without treatment

Secondary Syphilis

- Systemic dissemination
- 4-10 weeks after chancre appears
- Dermatologic (90%)
  - Diffuse macular rash
  - Plantar and palmar target-like lesions
  - Patchy alopecia
  - Mucous patches

Secondary Syphilis

- Genital Tract (20%)
  - Condylomata lata
  - generalized lymphadenopathy
- Constitutional (70%)
  - fever, malaise, anorexia, headache
  - arthralgias and myalgias
- CNS abnormalities (40%)
  - aseptic meningitis 1-2%

Early Latent Syphilis

- Asymptomatic stage
- Duration < 12 months
- Relapses 20-25%
- INFECTIOUS

Late Stage Syphilis

- Late Latent Syphilis
  - asymptomatic > 12 month duration
- Tertiary Syphilis (20-30% untreated)
  - Benign Late Syphilis
    - Gumma
  - Cardiovascular Syphilis
  - Neurosyphilis
    - Parenchymal and meningovascular

Clinical Features

- Pregnancy has little effect on the course of syphilis
- Syphilis has a major impact on the course and outcome of pregnancy
  - Abortion and Stillbirth
  - Preterm Delivery
  - Congenital Infection

Syphilis Updates

- Treatment – no updates. PCN still treatment of choice for pregnant women
  - Some evidence suggests that additional therapy is beneficial for pregnant women. For women who have primary, secondary, or early latent syphilis, a second dose of benzathine penicillin 2.4 million units IM can be administered 1 week after the initial dose

Primary & Secondary Syphilis

- **Benzathine penicillin G** 2.4 million units IM
- Penicillin allergy
  - Doxycycline 100 mg BID for 2 weeks
  - Tetracycline 500 mg QID for 2 weeks
  - Limited data: ceftriaxone, erythromycin or azithromycin (treatment failures)
- Repeat serology at 6 and 12 months

Latent Syphilis

Early latent

Benzathine penicillin G 2.4 million units IM

Repeat serology at 6, 12 and 24 months

Late latent

Benzathine penicillin G 2.4 million units IM weekly for 3 weeks

Repeat serology at 6, 12 and 24 months

Doxycycline 100 mg BID or **Tetracycline** 500 mg QID for 2 weeks (early) or 4 weeks (late) for penicillin allergy

Penicillin Desensitization

Dose	Penicillin V Suspension	Amount	Penicillin V Suspension	Cumulative Dose	Route
	Units/mL	*mL*	*Units*	*Units*	
1	1,000	0.1	100	100	P.O.
2	1,000	0.2	200	300	P.O.
3	1,000	0.4	400	700	P.O.
4	1,000	0.8	800	1,500	P.O.
5	1,000	1.6	1,600	3,100	P.O.
6	1,000	3.2	3,200	6,300	P.O.
7	1,000	6.4	6,400	12,700	P.O.
8	10,000	1.2	12,000	24,700	P.O.
9	10,000	2.4	24,000	48,700	P.O.
10	10,000	4.8	48,000	96,700	P.O.
11	80,000	1.0	80,000	176,700	P.O.
12	80,000	2.0	160,000	336,700	P.O.
13	80,000	4.0	320,000	656,700	P.O.
14	80,000	8.0	640,000	1,296,700	P.O.
Wait 30 minutes					
15	2,400,000 Units Benzathine Penicillin G				I.M.

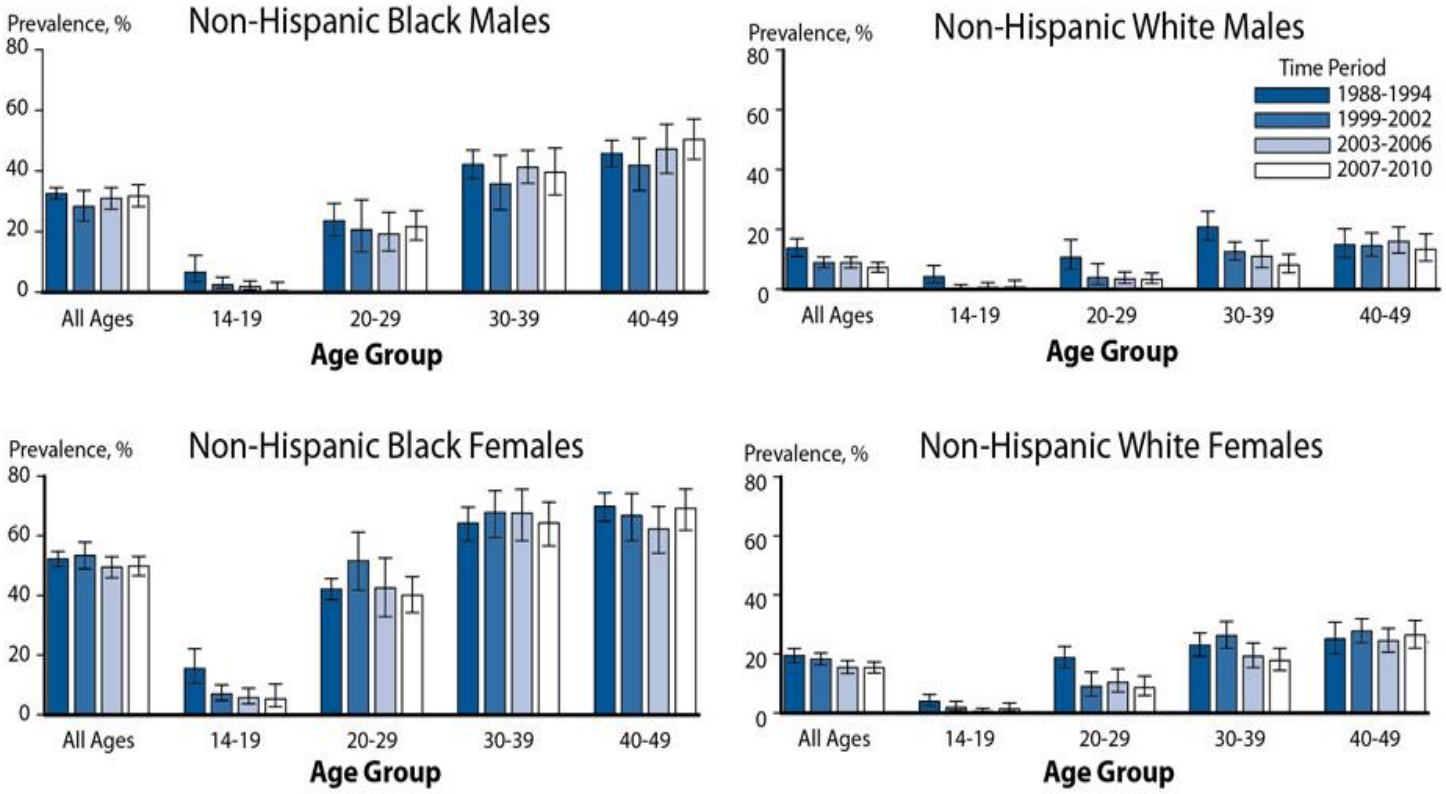
Wendel, GD et al. N Engl J Med
1985: 312:1229-32

Herpes Simplex Virus

Epidemiology

- 20-30% of the sexually active population have had genital herpes by serologic testing
- Often asymptomatic secondary to prior HSV-1 infection - antibodies are somewhat protective

Figure 49. Herpes Simplex Virus Type 2 — Seroprevalence Among Non-Hispanic Whites and Non-Hispanic Blacks by Sex and Age Group, National Health and Nutrition Examination Survey (NHANES), 1988–1994, 1999–2002, 2003–2006, and 2007–2010



HSV Microbiology and Transmission

- Encapsulated DNA viruses
- HSV-1 and HSV-2
  - 50% DNA sequence concordance
  - Prior infection with 1 type attenuated a new infection with the other type
- Transmission is usually secondary to intimate contact with an infected partner
- Incubation period mean 3 weeks (3-90 days)

Clinical HSV Classification

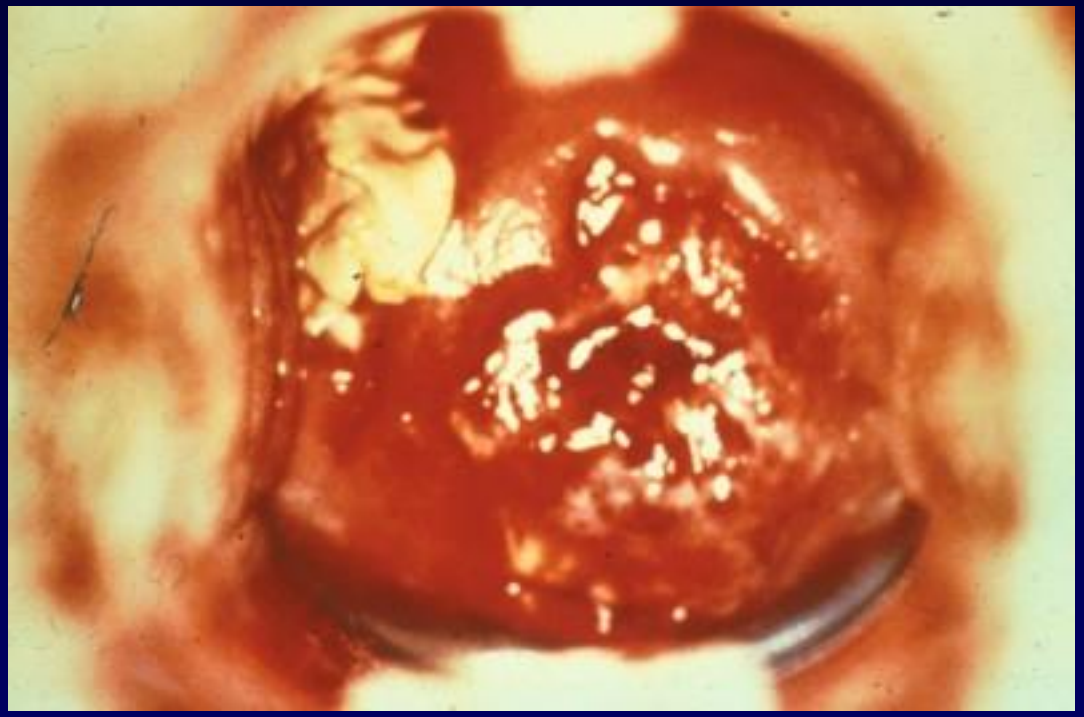
- First-episode primary infection
  - Isolation of HSV-1 or HSV-2 from genital secretions in the absence of HSV antibodies
- First-episode non-primary infection
  - Isolation of HSV-2 from genital secretions in the presence of HSV-1 antibodies in serum
- Reactivation disease
  - Isolation of HSV-1 or HSV-2 from the genital tract in the presence of same serotype antibodies
- Asymptomatic viral shedding (AVS)

Primary herpes

4 Days Later

Herpetic Whitlow

Herpes cervicitis

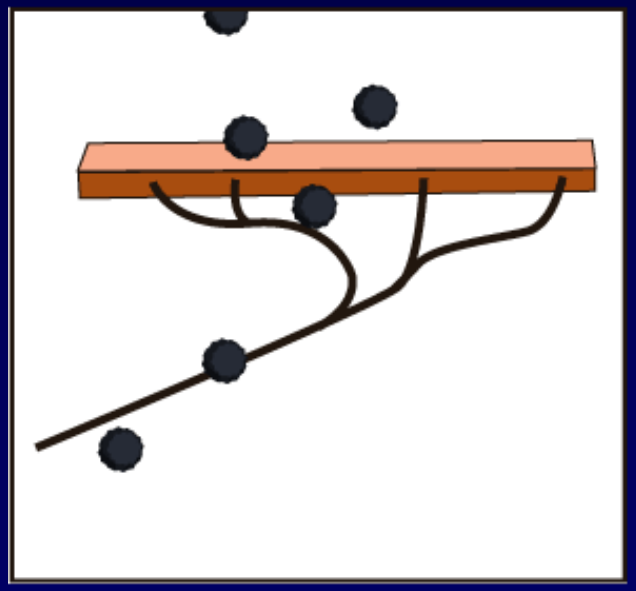


Recurrence Rate After Initial Genital Herpes

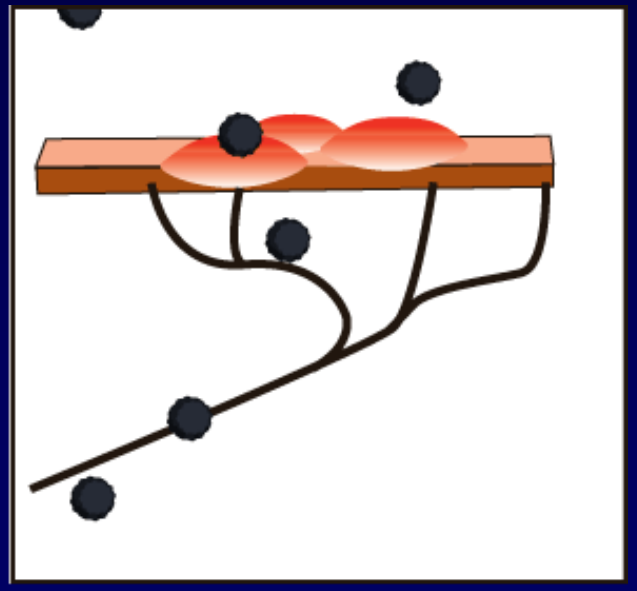
- **Mean recurrence rate in first year after initial genital HSV-2 infection (N = 457, median FU 391 days)**
  - **Men 5.2 episodes/yr**
  - **Women 4.0 episodes/yr**
- **≥6 recurrences in first year 38%**
- **≥10 recurrences in first year 20%**
- **Rate gradually declines over several years**
- **Recurrence after initial genital HSV-1 (N = 83)**
  - **Mean recurrences 1.3/yr 1, 0.7/yr 2 & beyond**
  - **38% had no recurrences**

Definition of Asymptomatic Viral Shedding

Presence of HSV as detected by viral culture or polymerase chain reaction (PCR) assay in the absence of signs or symptoms



Asymptomatic Shedding

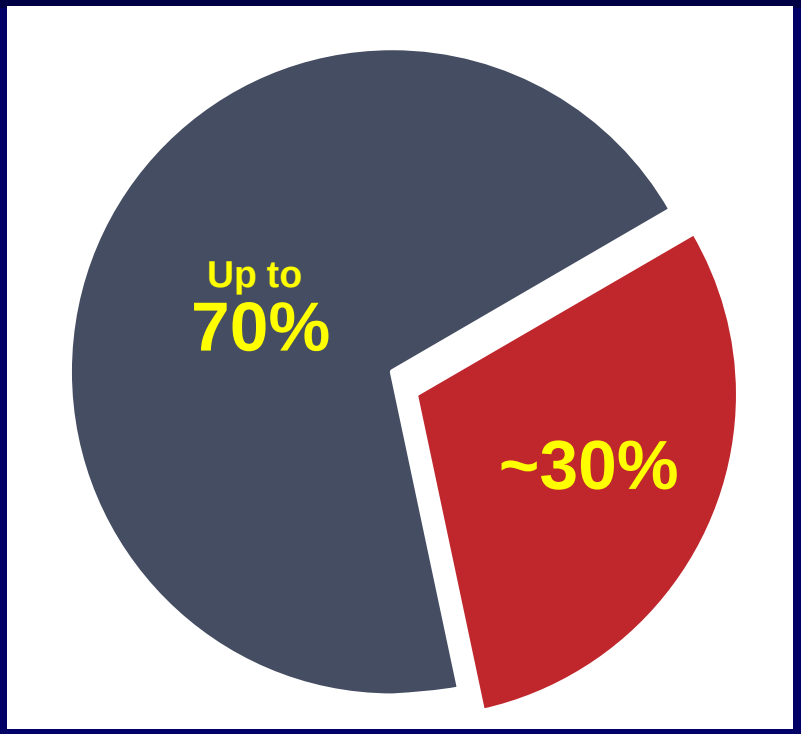


Symptomatic Outbreak

Role of Asymptomatic Shedding in Transmission

Up to 70% of transmissions occur during periods of asymptomatic shedding in adults with known infection

Transmission during asymptomatic shedding



Transmission during symptomatic outbreaks

Mertz et al. *Ann Intern Med.* 1992;116:197-202.

Characteristics of Asymptomatic Shedding

- Occurs on ~8% to 30% of days
- Is highest during the first year of infection
  - 42% of days in the first 6 months
- Occurs from any/all genital sites

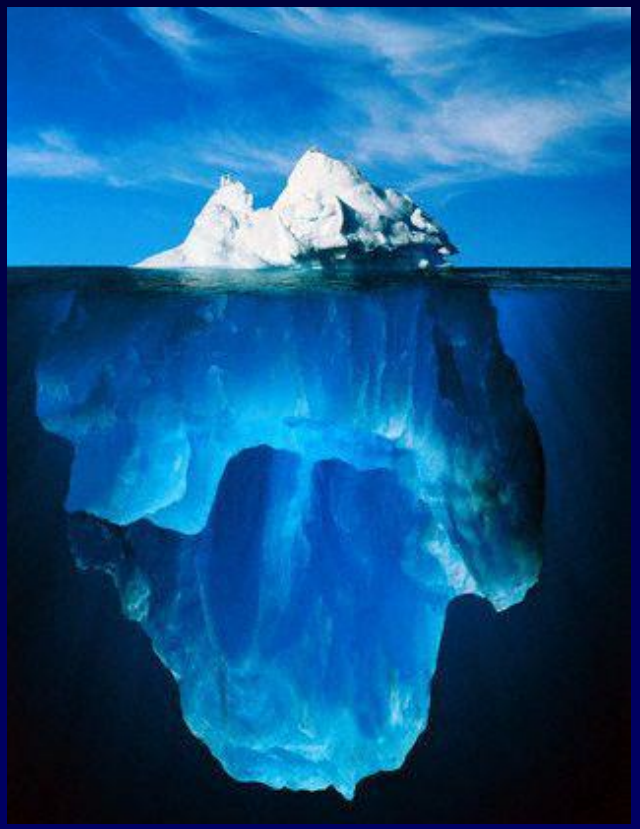
Corey and Wald. In: *Sexually Transmitted Diseases.* 1999:285-312. • Wald et al. *N Engl J Med.* 1995;333:770-775. • Mertz et al. *Ann Intern Med.* 1992;116:197-202.

Impact of Underdiagnosis and Asymptomatic Viral Shedding on Transmission

"The majority of genital herpes infections are transmitted by persons unaware that they have the infection or who are asymptomatic when transmission occurs."

CDC, *STD Treatment Guidelines 2010*

Underdiagnosis



Recognized HSV-2 infection 20%

Unrecognized HSV-2 infection 80%

With symptoms	Truly asymptomatic
60%	20%

Ashley and Wald. *Clin Microbiol Rev*. 1999;12:1-8.

Diagnosis

- Clinical exam
- HSV culture
- Tzank prep
- PCR rapidly becoming a diagnostic tool
- Screening protocols were not effective

HSV TREATMENT

- No cure
- Antiviral therapy
  - Acyclovir
  - Valacyclovir
  - Famciclovir

Special Considerations in Pregnant Women

Based on CDC's 2015 STD Treatment Guidelines

- Prevention of neonatal HSV depends on
  - Preventing maternal genital HSV acquisition during late pregnancy
    - Women without genital HSV should avoid intercourse during the third trimester with a partner known or suspected of having genital HSV
  - Avoiding exposure of the infant to herpetic lesions during delivery
    - Antiviral treatment in late pregnancy reduces the frequency of cesarean delivery by decreasing the frequency of recurrences
    - Women with recurrent genital HSV lesions at onset of labor should have cesarean delivery

HSV in Pregnancy

Risk of Recurrence at Delivery

- **30% for women having first episode during pregnancy**
- **15% for women with long-standing recurrent disease**
- **Asymptomatic shedding occurs in 3% (data by culture)**

Neonatal HSV

- Most devastating complication of genital HSV
- Occurs in up to 1 in 3200 live births
  - Disseminated or CNS disease in ~50% of cases
- 90% of cases are transmitted intrapartum
- High societal impact socially and economically
- Prevention strategies

Neonatal HSV Infection

- HSV-1 or HSV-2 (75% are HSV-2)
- High mortality rate
- ~40 - 50% survivors have serious morbidity
  - Microcephaly
  - Mental retardation and seizures
  - Retinal dysplasia
  - Meningitis and encephalitis
  - Hypertonia and coma

Risk Factors for Neonatal HSV

- HSV in the genital tract at delivery
- Stage of maternal infection
  - 60-80% of cases of neonatal HSV occur from women acquiring HSV in the third trimester - risk of neonatal HSV 30-50%
    - No protective transplacental antibodies
    - Highest viral loads
  - Symptomatic reactivation – neonatal HSV 3%
- Type of HSV (HSV-1>HSV-2) Most skin/eye/mouth, not CNS
- Invasive Obstetric procedures

Neonatal HSV Transmission

Rate of transmission depends on clinical characteristics of maternal disease

- **Symptomatic first episode 50%**
- **Asymptomatic first episode 33%**
- **Symptomatic recurrent 3%**
- **Asymptomatic recurrent 0.04%**