Sexually Transmitted Diseases: Hiding in Plain Sight?

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- A 21 year old woman comes to clinic asking for STD tests. You'll order:

- Depends on how many partners she's had
- Depends on her symptoms
- Urine Gonorrhea/Chlamydia
- Cervix Gonorrhea/Chlamydia
- Throat Gonorrhea/Chlamydia
- Blood for syphilis
- Blood for HIV
- Urine for *Mycoplasma genitalium*
- Herpes antibody test

STD are increasing! 2018 in US:

1.7 million cases of chlamydia

580,000 gonorrhea

115,000 syphilis

1306 congenital syphilis: 185% increase since 2014

http://www.cdc.gov/std/stats/default.htm

Different Organisms, Similar Diseases

- Chlamydia
  - Urethritis
  - Cervicitis
  - PID
  - Epididymitis
  - Proctitis, prostatitis?
  - Conjunctivitis, trachoma
  - Reactive arthritis
  - Neonatal pneumonia, conjunctivitis
- Gonorrhea
  - Urethritis
  - Cervicitis
  - PID
  - Epididymitis
  - Proctitis
  - Conjunctivitis
  - Pharyngitis
  - Disseminated infection
  - Neonatal conjunctivitis

Majority of all infections have no symptoms!

Urethritis: Inflammation of the Urethra

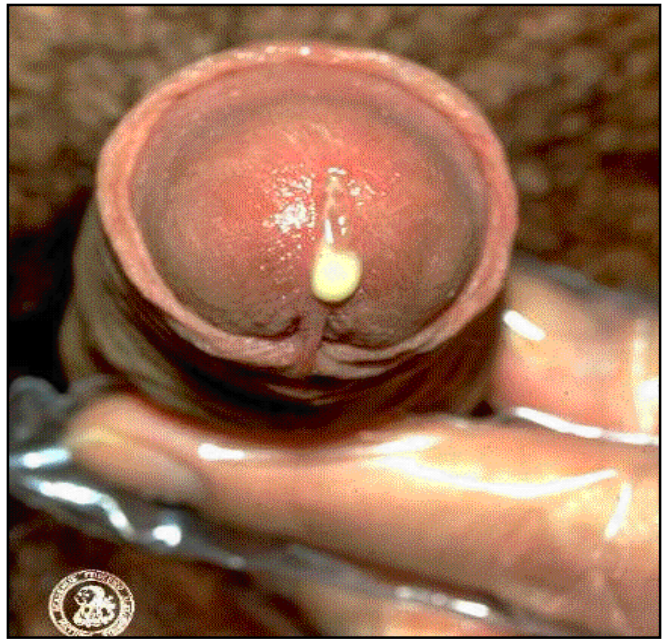
Symptoms/signs:

- Urethral discharge
- Dysuria
- WBC (>5/highpower field)

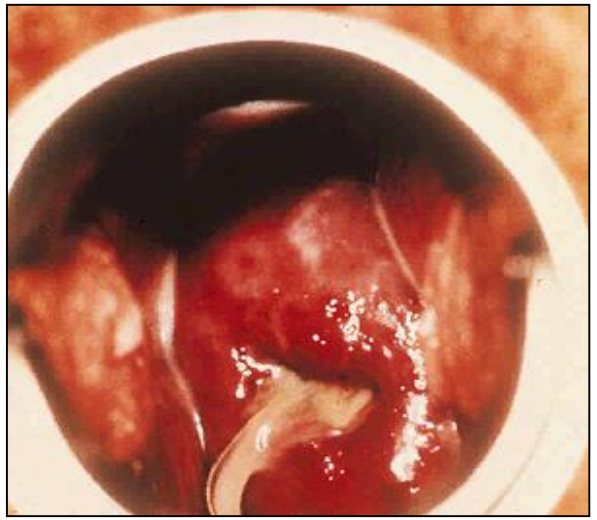
May progress to epididymitis

Causes:

- Gonorrhea
- Chlamydia
- Mycoplasma genitalium
- Trichomonas
- Herpes
- Other??

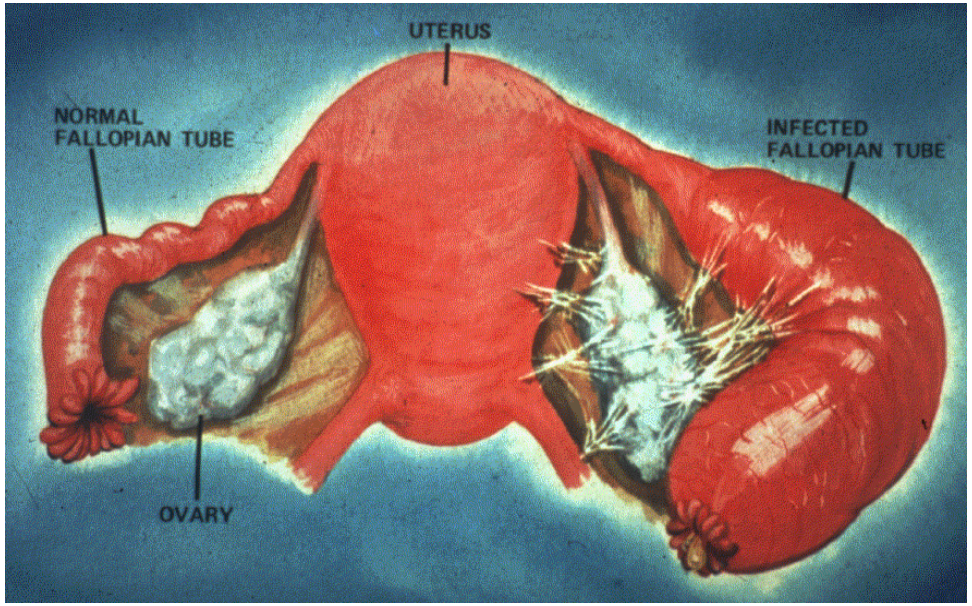


Cervicitis: may have vaginal discharge, bleeding, or no symptoms



Pelvic Inflammatory Disease: abdominal pain, leads to scarring of fallopian tubes

Causes: chlamydia, gonorrhea, maybe other mixed flora, mycoplasmas, etc.



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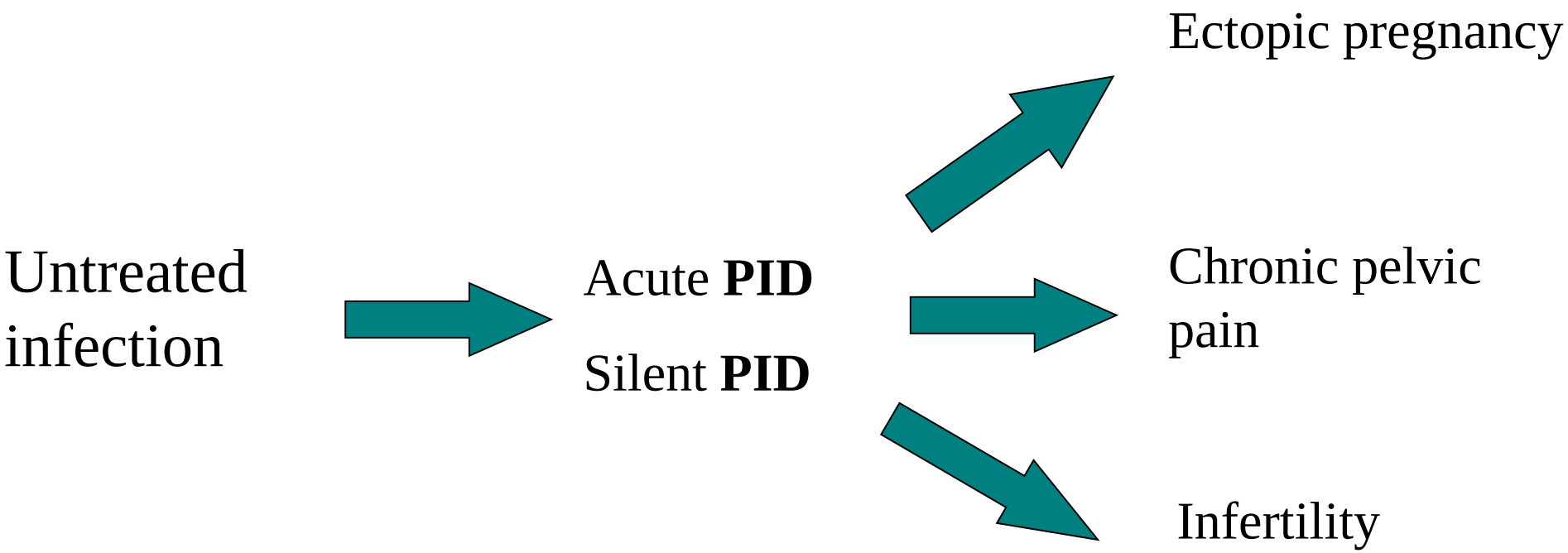
Complications of Chlamydia and Gonorrhea in Women



Screening and treating for asymptomatic infection is cost-saving!

Yearly Chlamydia Screen for Any Woman Who:

Is sexually active and age ≤ 25

Is sexually active, of any age, and:

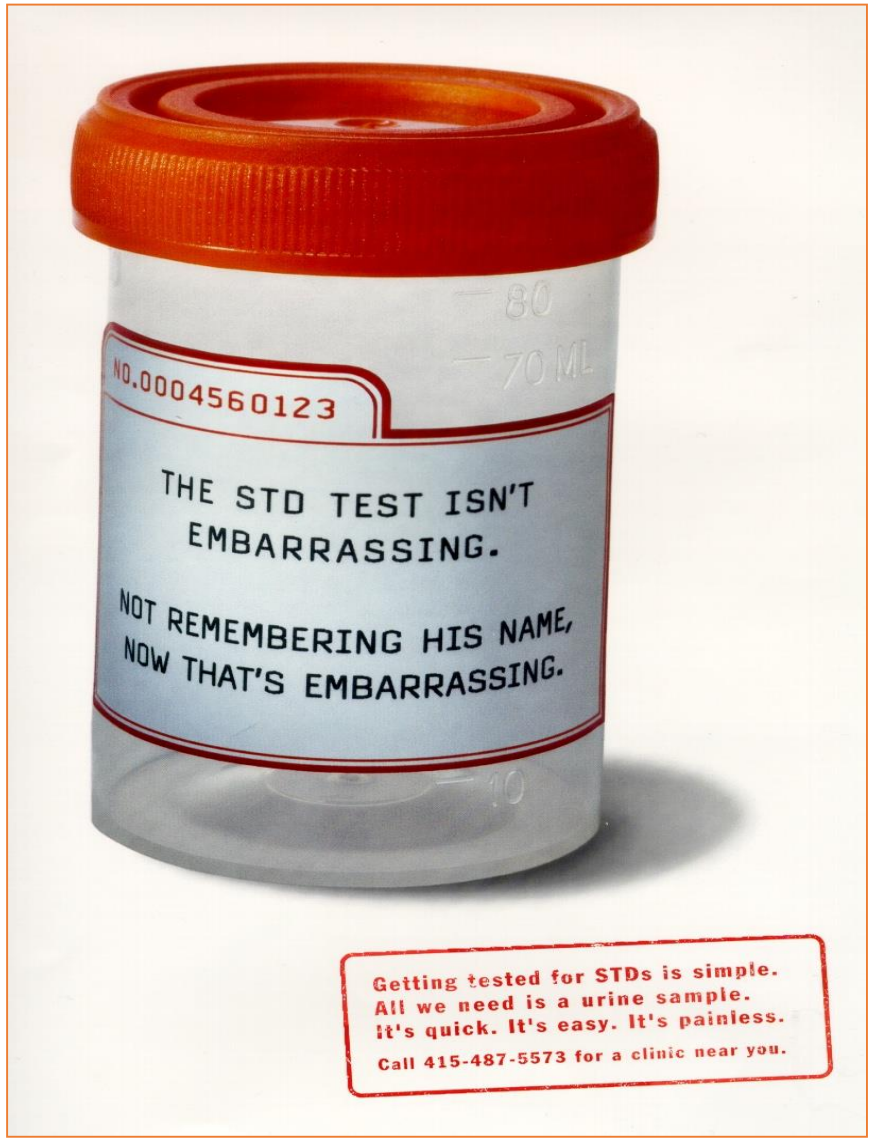
- **Has had an STD before OR**
- **Has more than one sexual partner OR**
- **Does not use condoms consistently and correctly**

Guideline endorsed by CDC, AMA, American Acad. of USPS Task Force, ACOG, etc.

Proven to reduce PID (NEJM 334:1362, 1996)

Less than half of eligible women get screened!

Nucleic-acid Amplification Tests for Gonorrhea and Chlamydia



- Very sensitive
- Urine, urethral, cervical, vaginal, anal, pharyngeal
  - Triple screen for MSM
- Can screen asymptomatic males
- Can use in non-clinical settings
- Can self-collect
- DOESN'T test for resistance
- Know what kind of test your lab offers

Extragenital sites in women: Sex Transm Dis. 42:233, 2015

Self-collection: Sex.Transm.Dis. 38:1107, 2011; Sex.Transm.Dis. 36:493, 2009

Chlamydia Treatment: CDC 2015 guidelines

Recommended regimens:

- Azithromycin 1 g PO x 1 (watch for vomiting)
- Doxycycline 100 mg PO BID x 7 d (watch for nonadherence)

Alternatives:

- Erythromycin base 500 mg PO QID x 7 d
- Erythromycin ethylsuccinate 800 mg PO QID x 7 d
- Ofloxacin 300 mg PO BID x 7 d
- Levofloxacin 500 mg PO QD x 7 d

- Good review of concerns about equivalence of doxy and azithro:
  Dombrowski et al., Sex Transm Dis 43: 603, 10/2016

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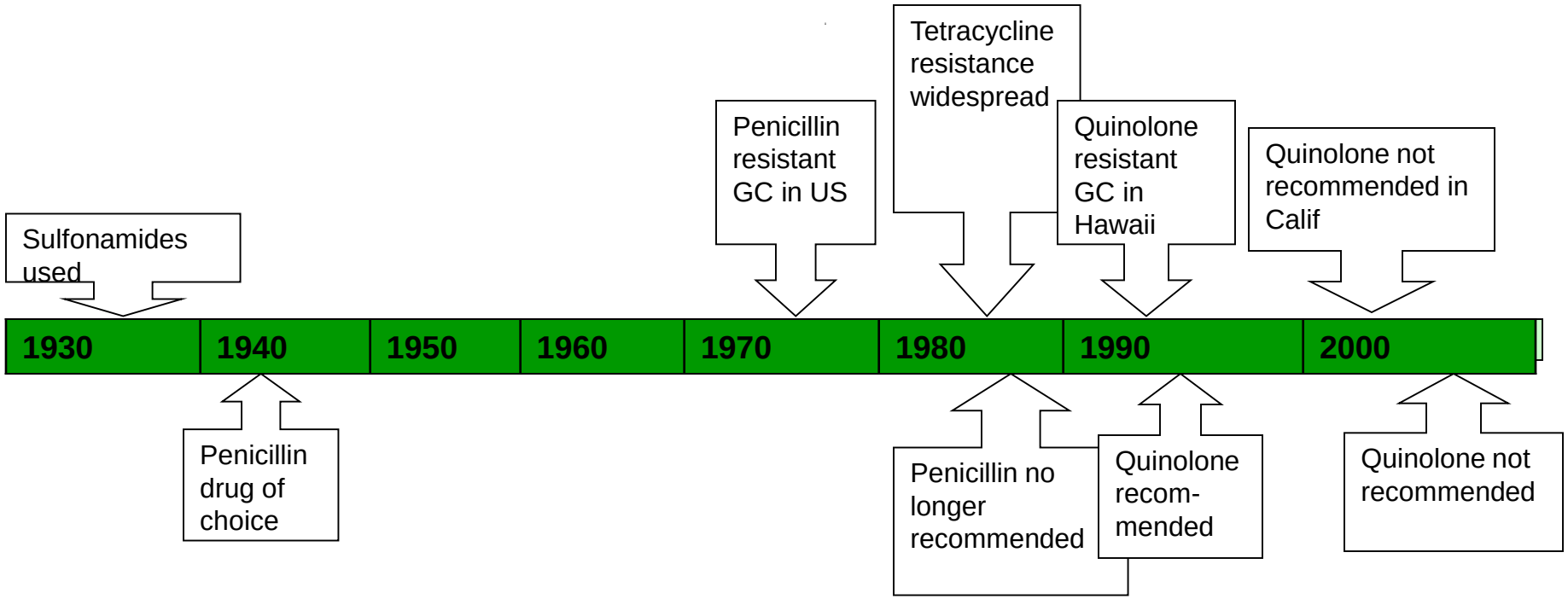
Gonorrhea: evolution of resistance

Has acquired multiple plasmid and chromosomal resistance mutations



Now rare reports of gonorrhea resistant to all antibiotics usually used!

Adapted from Workowski et al., Ann.Int.Med 2008, 148(8):606

Gonorrhea Treatment: www.cdc.gov/std/gonorrhea/

Uncomplicated gonorrhea of cervix, urethra, or rectum
Ceftriaxone 250 mg IM once *PLUS*
Azithromycin or doxycycline as for chlamydia
(EVEN if chlamydia test negative)

Alternative regimens: **ONLY IF ceftriaxone not available:**
Cefixime 400 mg single oral dose *PLUS*
Azithromycin or doxycycline as for chlamydia
PLUS Test of cure in 1 week

Serious cephalosporin allergy:
Consult expert, and test of cure

Gonorrhea and Chlamydia: Re-testing after treatment

- Test of cure not needed unless pregnant or second-line tx
- Nucleic acid amplification tests positive up to 2 weeks after treatment (CID 62:1348, 2016)

- Re-infection rate
  - Chlamydia - women 7-25%; men 13%;
  - Gonorrhea - women: 12-24%; men 9%

- Retesting recommendation (CDC)
  - Women: retest 3 mo after treatment, or at next visit within 12 mo
  - Less evidence for men (suggest retest in 3 mo)

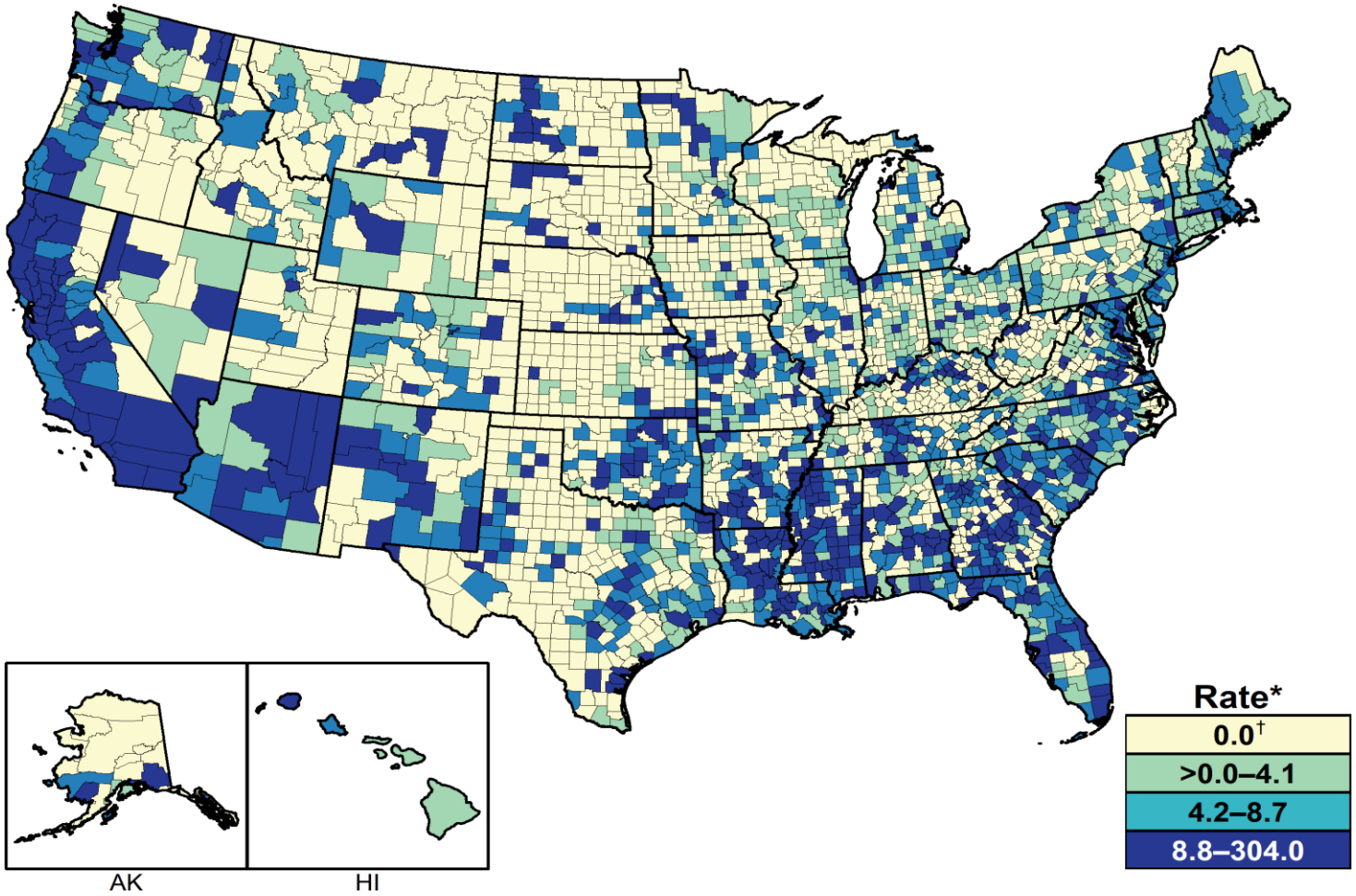
- A young man who has had sex with multiple men comes in with urethral burning and a scant penile discharge. You treat him with azithromycin. His tests come back negative for GC and CT. He comes back a month later. His symptoms got a little better but then came back.

Mycoplasma genitalium: uncertain significance!

- Organism associated with urethritis, cervicitis, PID, preterm birth, infertility, HIV transmission
- But LESS strongly than CT and GC, so causative role uncertain
- New nucleic amplification test recently approved
- Screening NOT currently recommended
- Consider testing symptomatic cases, especially if failing treatment
- Poor response to doxycycline; increasing resistance to azithromycin
  - Moxifloxacin? - though some resistance reported

J Infec. Dis. supplement 2, 2017

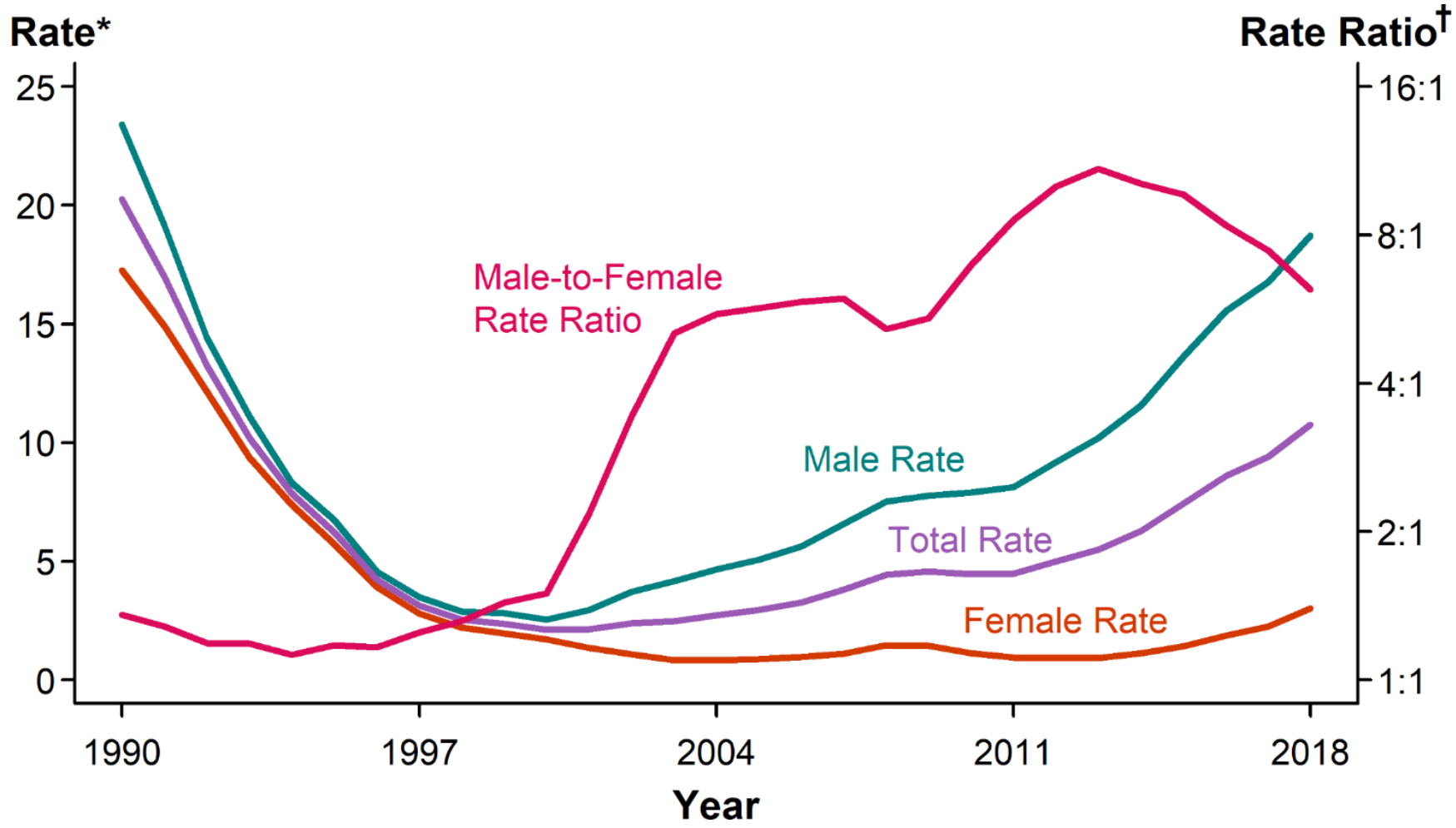
Primary and Secondary Syphilis: Rates of Reported Cases by County, 2018



* Per 100,000.

† In 2018, 1,498 (47.7%) of 3,142 counties in the United States reported no cases of primary and secondary syphilis. See section A1.4 in the Appendix for more information on county-level rates.

Primary and Secondary Syphilis — Rates of Reported Cases by Sex and Male-to-Female Rate Ratios, United States, 1990–2018



* Per 100,000.
† Log scale.

Why isn’t Syphilis gone?

- Easy to treat – no antibiotic resistance
- Targets people with less access to health care
- Can’t be seen on Gram stain or grown in the lab
- Long periods with no symptoms, yet causes serious disease
- Diagnosis depends on serology (blood antibody) tests with many pitfalls in interpretation

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Syphilis Serology

- Traditionally: nontreponemal first, if positive confirm with treponemal
- Some labs now do a new treponemal Ab first

Nontreponemal	Treponemal
RPR, VDRL	TPPA, MHA-TP, FTA, new Trep-Sure
Quantitative	Qualitative
Titers go down with treatment – Can be negative in early or late disease	Stays + for life, with or w/o treatment
False positives and negatives	More specific

From Park IU et al., CID 2019

Table 2. Sensitivity and Specificity of Treponemal Assays for Detection of Syphilis, by Stage and Overall

Assay	Sensitivity by Stage				Overall Sensitivity (n = 262)	Overall Specificity (n = 403)
	Primary (n = 55)	Secondary (n = 98)	Early Latent (n = 41)	Late Latent (n = 68)		
FTA-ABS	**78.2**[a] (65.0–88.2)	**92.8**[a] (85.7–97.0)	100 (90.7–100)	92.6 (83.7–97.6)	**90.8**[a] (86.7–94.0)	98.0 (96.1–99.1)
TPPA	94.5 (84.9–98.9)	100 (96.2–100)	100 (90.7–100)	**86.8**[b] (76.4–93.8)	95.4 (92.1–97.6)	100 (99.0–100)
Centaur CIA	94.5 (84.9–98.9)	100 (96.2–100)	100 (90.7–100)	94.1 (85.6–98.4)	97.3 (94.6–98.9)	95.5 (93.0–97.3)
Trep-Sure EIA	94.5 (84.9–98.9)	100 (96.2–100)	100 (90.7–100)	98.5 (92.1–99.9)	98.5 (96.1–99.6)	**82.6**[c] (78.4–86.1)
LIAISON CIA	96.4 (94.5–98.2)	100 (96.2–100)	97.6 (87.4–99.9)	92.6 (83.7–97.6)	96.9 (94.1–98.7)	94.5 (91.8–96.5)
Bioplex MBIA	96.4 (94.5–98.2)	100 (96.2–100)	95.1 (83.8–99.4)	94.1 (85.6–98.4)	96.9 (94.1–98.7)	96.7 (94.4–98.2)
INNO-LIA	96.4 (94.5–98.2)	100 (96.2–100)	100 (90.7–100)	91.1 (81.7–96.7)	96.9 (94.1–98.7)	98.5 (96.8–99.5)

Data are presented as % (95% confidence interval).

Abbreviations: CIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption test; LIA, line immunoassay; MBIA, microbead immunoassay; TPPA, *Treponema pallidum* particle agglutination assay.

[a]FTA-ABS was less sensitive than other assays for primary syphilis (all $P \leq .01$) and secondary syphilis ($P = .007$). Combining all stages, FTA-ABS was less sensitive than TPPA ($P = .038$) or the immunoassays (all $P < .001$).

[b]TPPA significantly less sensitive than Trep-Sure EIA for late latent syphilis ($P = .009$); all other comparisons were not statistically significant.

[c]Trep-Sure EIA was significantly less specific than all other assays (all $P < .001$).

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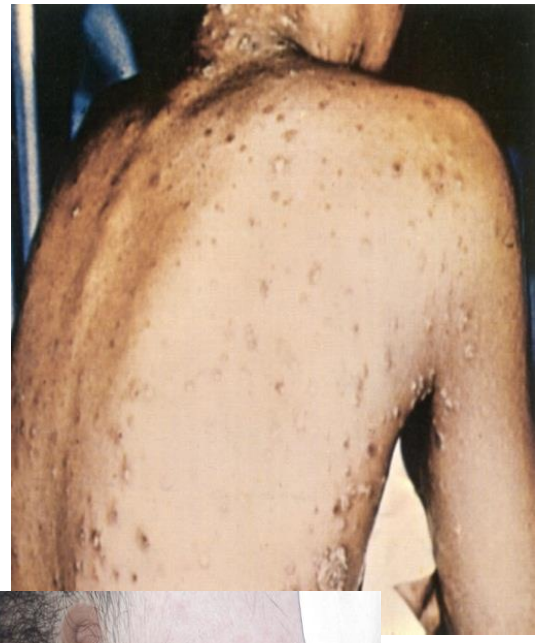
Syphilis: Primary Chancre

Images from: *STD Atlas, 1997*

Rash of Secondary Syphilis – can look like anything!!



Mosby *STD Atlas, 1997*

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Secondary Syphilis: Other clues

Patchy alopecia

Condyloma lata

Mucous patches

Images from: *STD Atlas, 1997*

Determining syphilis stage is critical for management

Incubating syphilis
- Recent exposure, may be infected; blood test may not be positive yet

Primary: 3-6 weeks after infection - Chancre, localized lymphadenopathy

Secondary: 6-12 weeks after infection
- Rash, lymphadenopathy, fever, mucous patches, alopecia, headache, hepatitis, nephritis, etc.!

Early Latent
- No signs and symptoms, < 1 year after infection **TX: LA Bicillin x 1**
- Can still be infectious; secondary signs may recur

Late Latent
- No signs and symptoms, > 1 year after infection
- Less infectious, symptoms probably will not recur

Latent unknown duration
- Positive serology, no signs/symptoms, unknown time of infection **TX: LA Bicillin x 3**

Tertiary Syphilis – years later: neurological, cardiovascular, gummatous lesions

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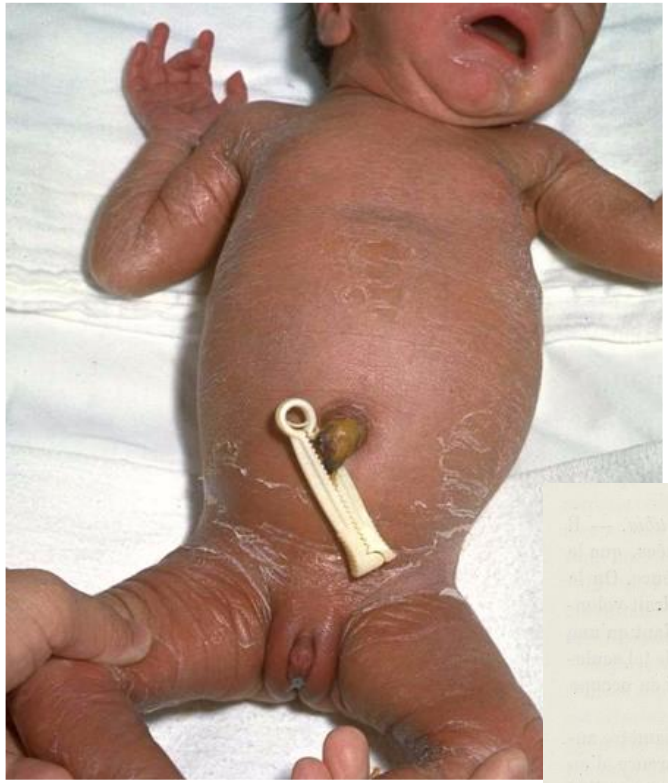
Neurosyphilis
- Can happen at ANY stage **TX: IV penicillin 14 days**
- Eye or ear disease - treat same as neurosyphilis

Syphilis in Pregnancy

- Screen ALL pregnant
- Transmission more common in 2nd & 3rd trimester
- Treatment effective if completed in time
- Outcome in untreated early syphilis
  - 25% intrauterine death
  - 25% perinatal death
  - 50% congenital syphilis
- How does congenital syphilis happen?:
  - No prenatal care
  - Incomplete, late, or interrupted care
  - Misinterpretation or miscommunication of tests
  - Woman infected after testing
  - Wrong, too-late or incomplete treatment



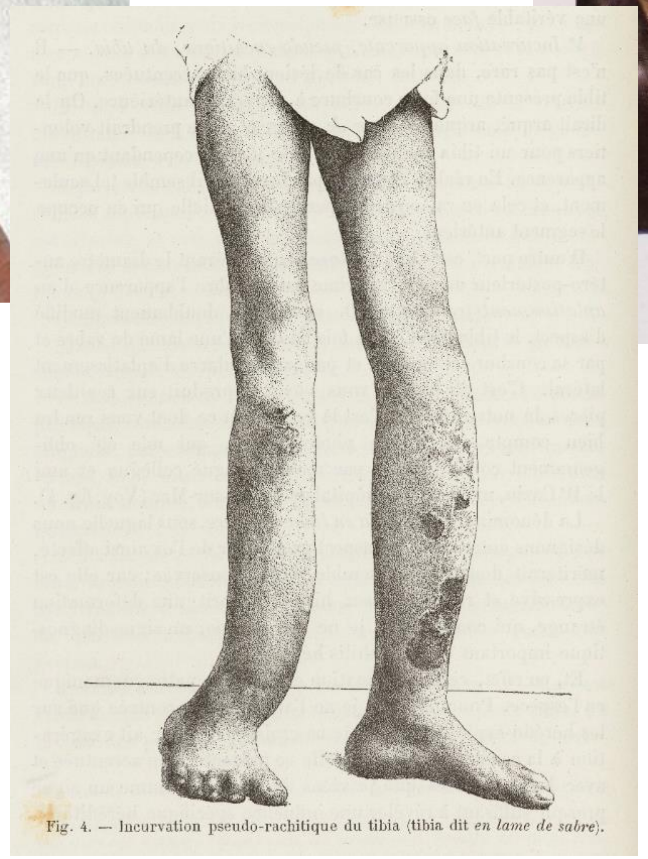
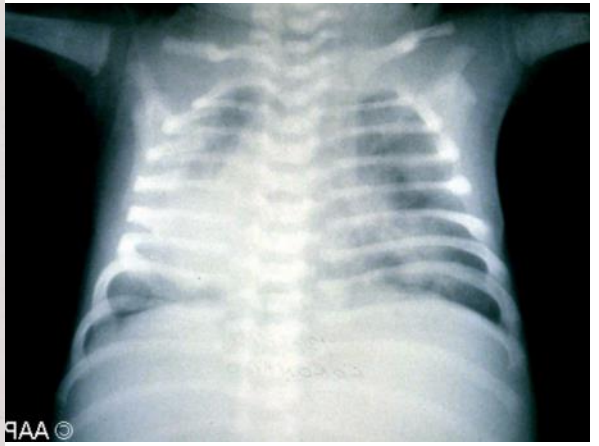


Fig. 4. — Incurvation pseudo-rachitique du tibia (tibia dit *en lame de sabre*).

CONGENITAL SYPHILIS.



Many Bad Outcomes – Early and Late

Testing in Pregnancy

- All women must be tested at first prenatal visit
- Either treponemal or nontreponemal screen
- False positives do happen, need careful evaluation
- “High-risk” women or those in “high-risk area” should be tested again in 3rd trimester and at delivery
- No newborn should leave hospital without maternal tests known

Syphilis Management: CDC Guideline

- Careful history and exam, including neurologic, eye
- Treat according to disease stage
- Followup RPR at 3, 6, 12 months to look for 4-fold drop
- Penicillin allergy? Take a good history; many are not truly allergic
- Doxycycline alternative if PCN-allergic, except:
- Pregnancy or neurosyphilis – ONLY pencillin; get expert advice!
- Pregnancy: RPR monthly till delivery; coordinate with OB and Pediatrics
- Help from Health Department to ensure partners treated

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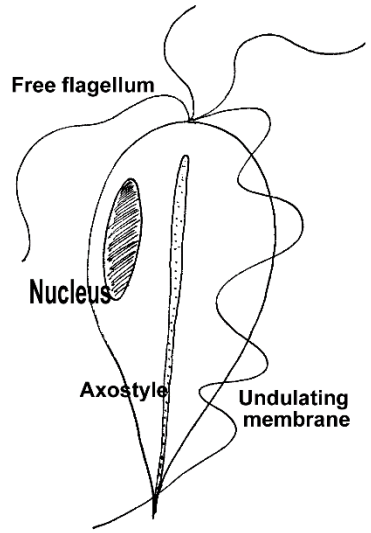
Herpes Simplex

- Type 1 *usually* oral, Type 2 *usually* genital
- US adult HSV-2 Seroprevalence (NHANES): 17%
- Most who have it don't know it
- Can be transmitted by asymptomatic shedding
- Can seriously infect neonates – skin, CNS, or disseminated (rare)
- Acyclovir, valacyclovir, famciclovir:
  - episodically for outbreaks or
  - daily for suppression

Trichomonas (a CDC "neglected parasite")

- Prevalence: ~3% in women 14-49 yo; older age range than gonorrhea and chlamydia
- Many asymptomatic
- Associated with:
  - postpartum endometritis, low birth weight, preterm labor, PROM
  - HIV transmission/acquisition
- Metronidazole resistance increasing though still uncommon
  - Higher dose metronidazole or tinidazole may cure
- No great options for true metronidazole allergy – consider desensitization
- Metronidazole-alcohol interaction is probably rare
- 500 mg BID x 7 days better than 2 gm x 1
- Topical metronidazole less effective
- Must treat the partner(s)!
- Diagnosis in men has been a barrier; Tricore Lab can do on urine



Satterwhite CL, STD 40:187, 2013; Kirkcaldy RD, Emerg.Infec.Dis. 18:939, 2012; Soper D, AJOG 190:281, 2004 review; Cudmore SL, Clin. Micro Rev 17:783, 2004 (resistance); Helms, Am J Obst. Gyn. 2008;198:370; Bachmann LH, Clin.Infec.Dis. 53:S160, 2011 review

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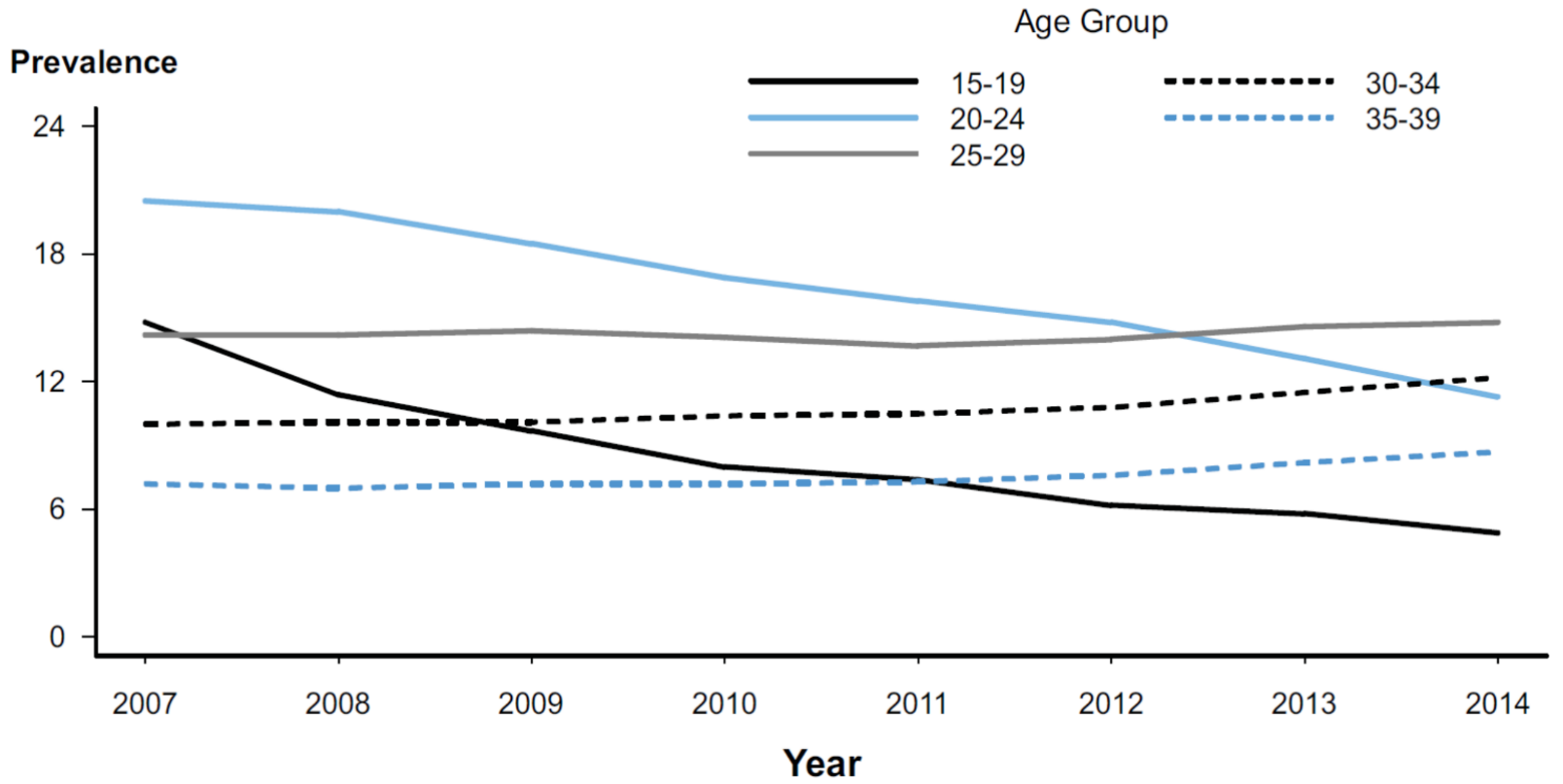
Human Papilloma Virus and Genital Warts

- Very common; mostly asymptomatic
- Some strains mostly warts, others cause dysplasia/cancer
- Infection, and warts, may spontaneously resolve
- Worse in immunocompromised
- Vaccine is very effective and safe!

CIN 2 and 3 (cervical dysplasia): Prevalence/1000 Person-Years, Females in Private Health Plans, 2007–2014



SOURCE: Flagg EW, Torrone EA, Weinstock H. Ecological association of human papillomavirus vaccination with cervical dysplasia prevalence in the United States, 2007–2014. Am J Public Health 2016; 106(12):2211–2218.

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Principles of STI Management

- Follow CDC treatment guidelines
  - www.cdc.gov/std/treatment/default.htm
- Test patient for other STI, **including HIV**
- Notify Public Health Department (reportable diseases)
- Evaluate and treat all recent partners
- Educate patient: treatment failure, prevention, rescreening
- Condoms reduce risk
- Discuss HIV PrEP if at risk

What will you do differently as a result of this talk?

- Screen more young people routinely for GC/CT?
- Check what kind of GC/CT test your facility uses? Throat/rectal?
- Test for syphilis and HIV too?
- Check whether your lab uses treponemal or nontreponemal test?
- Ask patients more about their sexual history?
- Find out where people can get PrEP in your area?
- Re-test patients 3 months after a GC or CT diagnosis?
- Re-test pregnant women in 3rd trimester and at delivery?
- Education/outreach about STD to your community?

Resources and Reading

CDC STD 2015 Treatment Guideline: www.cdc.gov/std/treatment/default.htm

STD Prevention Training Centers - resources and online self-study,

for example: http://californiaptc.com/online-learning/ and https://www.std.uw.edu/

CDC self-study: http://www.cdc.gov/std/training/std101/home.htm

USPS Task Force: https://www.uspreventiveservicestaskforce.org/Page/Name/uspstf-recommendations-for-sti-screening

New MexicoExpedited Partner Therapy guideline: https://nmhealth.org/publication/view/help/1602/

Herpes review: Gupta et al., Lancet 370:2127, 2007

Chlamydia review: Weisenfeld HC, N Engl J Med 2017;376:765

Lutz AR, LGBT Health. 2015;2:27. Screening for Asymptomatic Extragenital Gonorrhea and Chlamydia in Men Who Have Sex with Men: Significance, Recommendations, and Options for Overcoming Barriers to Testing.

California STD/HIV Screening Recommendations in Pregnancy 2017: https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/CaliforniaSTD-Sxand-Tx-inPregnancy2017.pdf

JAMA, "Why are mothers still passing syphilis to their babies?" https://jamanetwork.com/journals/jama/article-abstract/2724373