The Top 10 STD Updates For 2016

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*No commercial disclosures or conflicts of interest

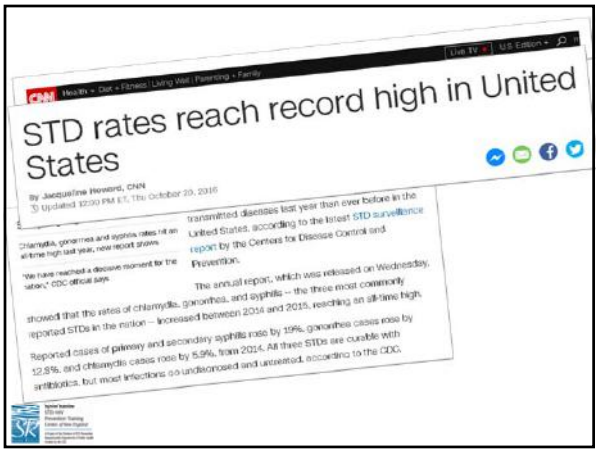
Disclosures

- In the past 12 months, Dr. Hsu has **NOT** had significant financial interests or other relationships with manufacturer(s) of product(s) or provider(s) of service(s) that will be discussed in this presentation.
- This presentation will include discussion of pharmaceuticals or devices that have not been approved by the FDA.
  - "Off-label" use of extra-genital (rectal and pharyngeal) nucleic acid amplification tests (NAATs) for gonorrhea and chlamydia

Goals

- Distinguish relevant updates to epidemiology, diagnosis, and treatment for bacterial, viral, and other STDs
- Highlight areas of 2015 CDC STD Treatment Guidelines that should be read carefully for detailed recommendations

10. STD Rates Are At Unprecedented Highs


STD rates reach record high in United States

By Jacqueline Howard, CNN
Updated 12:00 PM ET, Thu October 20, 2016

Chlamydia, gonorrhea and syphilis rates hit an all-time high last year, new report shows

"We have reached a decisive moment for the nation," CDC official says

transmitted diseases last year than ever before in the United States, according to the latest STD surveillance report by the Centers for Disease Control and Prevention.

The annual report, which was released on Wednesday, showed that the rates of chlamydia, gonorrhea, and syphilis -- the three most commonly reported STDs in the nation -- increased between 2014 and 2015, reaching an all-time high.

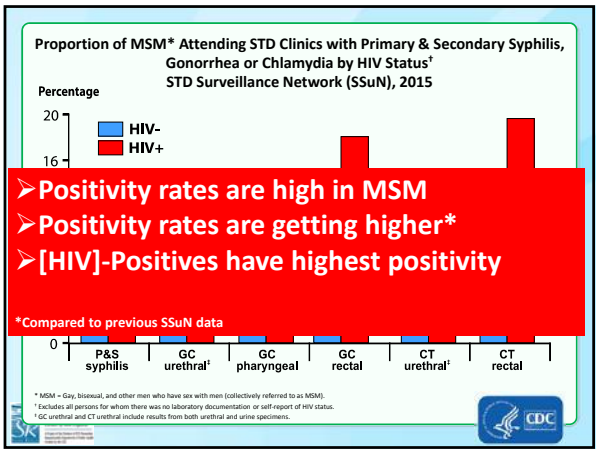
Reported cases of primary and secondary syphilis rose by 19%, gonorrhea cases rose by 12.8%, and chlamydia cases rose by 5.9%, from 2014. All three STDs are curable with antibiotics, but most infections go undiagnosed and untreated, according to the CDC.

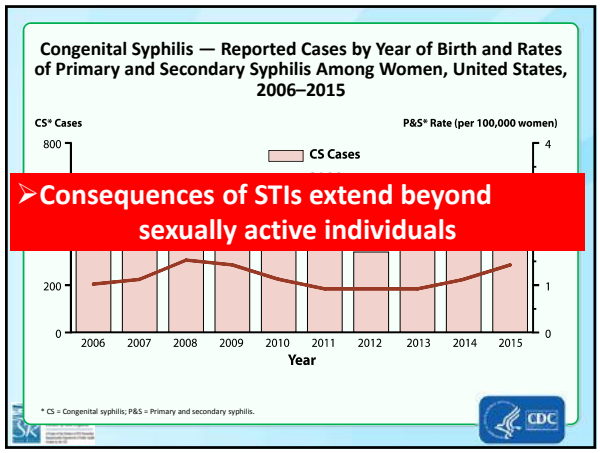
2015 STD Surveillance Report Press Release October 19, 2016

- Total combined cases of chlamydia, gonorrhea, and syphilis reported in 2015 reached highest number ever

➢**Turning the tide will require a strong, sustained public health commitment**

- Americans ages 15 to 24 years old accounted for nearly two-thirds of chlamydia diagnoses and half of gonorrhea diagnoses
- MSM accounted for the majority of new gonorrhea and P&S syphilis cases (82 percent of male cases with known gender of sex partner)
  - Antibiotic-resistant gonorrhea may be higher among MSM
- Women's rate of syphilis diagnosis increased by more than 27% from 2014 to 2015
- Reported congenital syphilis increased by 6%





9. The Specter of MDR GC

The NEW ENGLAND JOURNAL of MEDICINE

June 23, 2016

Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea

Letter to the Editor:

- GC treatment failure at pharyngeal site in heterosexual man in United Kingdom (Ceftriaxone 500mg IM x 1 plus azithromycin 1gm PO x 1)
- Individual had traveled to Japan and had female partner from Japan
- Isolates from d 15, 79 and 98 identical with 4 major mutations in each
- Ultimately successfully treated with Ceftriaxone 1gm + 2g Azithromycin PO x 1

Cluster of Hawaii Gonorrhea Isolates with Diminished Susceptibility to Multiple Antibiotics, Including Very High Azithromycin MIC and Alert-Value Ceftriaxone MIC April-May, 2016

Minimum Inhibitory Concentrations, µg/mL			
	azithro*	ceftriax*	cefix*
1	> 256	0.125	0.094
2	> 256	0.125	0.094
3	> 256	0.190	0.190
4	> 256	0.125	0.125
5	> 256	0.094	0.094
6	> 256	0.125	0.125
7	> 256	0.125	0.094

*Hawaii State Laboratories Division
**Seattle GISP Reference Lab

Epi-X June 2016

Gonorrhea Treatment

Uncomplicated Genital, Rectal, or Pharyngeal Infections

Ceftriaxone 250 mg IM in a single dose **PLUS*** Azithromycin 1 g orally

*** Regardless of CT test result**

Doxycycline demoted from recommended to alternative, because of tetracycline resistance in U.S. GISP isolates

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

Gonorrhea Treatment Alternatives Just for *Anogenital* Infections

IF CEFTRIAXONE UNAVAILABLE

- Cefixime 400 mg orally once

PLUS

- Dual treatment with azithromycin 1 g

IN CASE OF ALLERGY TO AZITHROMYCIN:

- Cefixime 400 mg orally once

PLUS

- Dual treatment with doxycycline 100 mg BID x 7 days

Azithromycin 2 g orally removed as an alternative regimen

Prior TOC recommendation: Test of cure in 1 week for anyone treated w/ alternative regimens

New TOC recommendations: Limit TOC only to pharyngeal GC not treated with recommended regimen, perform TOC at 14 days with either NAAT* or culture

**Not FDA-approved for extragenital testing, but has been validated*

Back-Pocket GC Treatment Regimens:
Alternatives for cephalosporin-allergic patients

- **Trial conducted in Baltimore, Birmingham, Pittsburgh, San Francisco**
- **401 men and women 15 - 60 yrs**
- **202 received gent 240 mg IM + azithro 2 g PO: 100% effective**
- **199 received gemiflox 320 mg PO + azithro 2 g PO: 99.5% effective**

Probably fine for urogenital gonorrhea
Trial not powered for extragenital gonorrhea, though it worked in the few cases enrolled

Efficacy limited by tolerance
8% vomited in the gemiflox + azithro group and needed re-treatment with standard cftx + azithro

Kirkcaldy RD et al. *CID* 2014

8. Re-screening for STIs in those previously infected, reaches those at HIGHEST STI risk

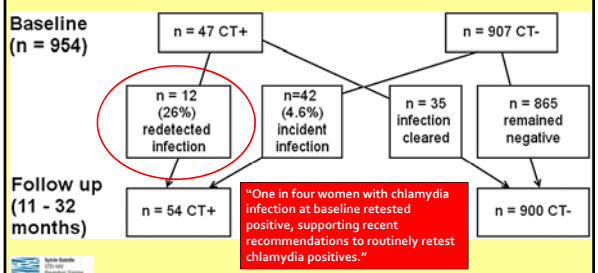
Repeat Testing after an STD infection

- Current CDC STD screening guidelines for GC and CT recommend screening persons at-risk, including those with a prior STD
- Among sex workers with baseline GC, CT or trichomonas infection, the adjusted HR for any of these at follow up was 2.6 (95% CI 2.1-3.1) (Turner 2010)
- Project RESPECT in US STD clinic patients:
  - 25.8% of women had 1 or more new infections with CT, GC, or Trich at one year of follow up.
  - 14.7% of men had a new GC or CT infection.
  - Conclusion: patients with GC/CT or trich infections should return at 3 months because they are at high risk for new infections (Peterman 2006)

Frequency and risk factors for incident and redetected *Chlamydia trachomatis* infection in sexually active, young, multi-ethnic women: a community based cohort study

Adamma Aghaizu,[1,2] Fiona Reid,[1] Sally Kerry,[3] Phillip E Hay,[4] Harry Mallinson,[5] Jorgen S Jensen,[6] Sarah Kerry,[1] Sheila Kerry,[1] Pippa Oakeshott[1]

- Sexually active female students 15-27 years old, enrolled in the British Prevention of Pelvic Infection (POPI) trial between 2004-06, who self-collected 2 vaginal swab specimens



"One in four women with chlamydia infection at baseline retested positive, supporting recent recommendations to routinely retest chlamydia positives."

Aghaizu A et al. *STI* 2014

Repeat Screening after an STD infection

- *Women with CT, GC or trich should be rescreened at 3 months after treatment.*
- *Men with CT or GC should be rescreened at 3 months after treatment.*
- *Patients diagnosed with syphilis should undergo follow up serologic serology per current recommendations.*
- *HIV testing should also be considered in all patients with a prior STD history*

Effective Practice Changes to Increase Uptake of Re-Screening

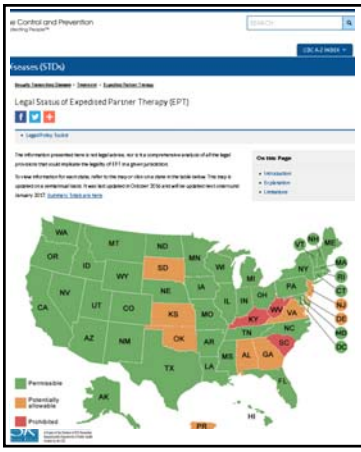
- Implementation of pop-up reminders at six large family planning clinics in California
  - retesting rates for chlamydia and gonorrhea among those patients who returned to the clinic increased by 23% (from 70 to 86%)
- Western New York, University at Buffalo student health clinic implemented a three-step Treatment-Letter-Reminder (email, phone calls) in those with chlamydia infection
  - re-testing rates went from 16 to 89%

Howard et al., Burstein et al., 2012 National STD Prevention Conference Abstracts

7. Treating sex partners sight unseen (EPT) is LEGAL (mostly)

Chlamydia, Gonorrhea, and EPT

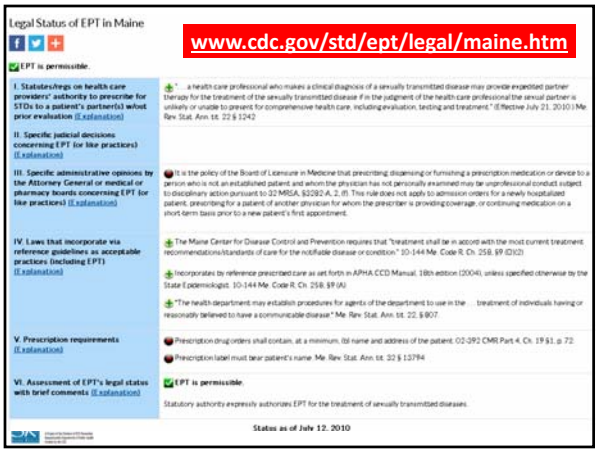
- EPT is supported by the CDC and permissible in at least 35 states
- Standard partner treatment for chlamydia infection is one oral dose of 1g of the antibiotic azithromycin
- Standard partner treatment for gonorrhea is one oral dose of 1g of the antibiotic azithromycin PLUS one oral dose of 400 mg of cefixime
- EPT has been shown to be safe and effective in the treatment of sex partners
- Most states with long-standing EPT programs also have had no reports of adverse events



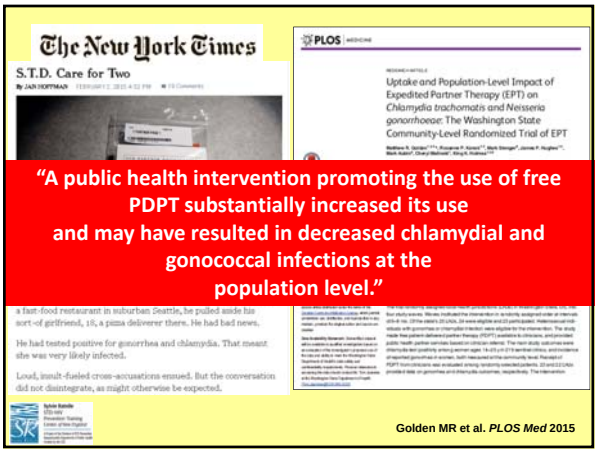
CDC EPT guidelines

"PDPT can prevent reinfection of index case and has been associated with a higher likelihood of partner notification…"

www.cdc.gov/STD/EPT



www.cdc.gov/std/ept/legal/maine.htm



"A public health intervention promoting the use of free PDPT substantially increased its use and may have resulted in decreased chlamydial and gonococcal infections at the population level."

Golden MR et al. *PLOS Med* 2015

www.maine.gov/dhhs/mecdc/infectious-disease/hiv-std/ept/index.shtml

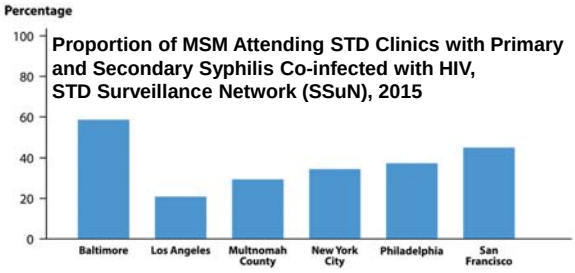
6. The epidemic of syphilis (& HIV co-infection) in MSM continues

HIV and Syphilis Diagnoses Have Increased in Young MSM

- Survey of trends in HIV and syphilis diagnoses in 73 large metro areas, 2004/2005 and 2007/2008
- Primary and secondary syphilis rates increased in 70% of areas
- Average increases in young black men
  - HIV: 68%
  - Syphilis: 203%

Torrone et al, *JAIDS*, 2011

Syphilis/HIV Co-infection Common



CDC, *Sexually Transmitted Diseases Surveillance*, 2015

SYPHILIS – PARTNER MANAGEMENT

- Exposed within 90 days to primary, secondary or early latent syphilis
  - Treat, even if seronegative
- Exposed >90 days to primary, secondary or early latent syphilis
  - Treat, if serologic test results not available immediately and follow-up is uncertain
- Exposed to late latent syphilis or syphilis of unknown duration
  - Evaluate clinically and serologically, treat if syphilis suspected
- **Discuss and partner with your public health colleagues to do contact tracing and treatment!**

Can We Screen for Syphilis Control?

- Syphilis screening *can* lead to decreases in MSM population prevalence

$$R_o = T \cdot C \cdot D$$

- How do we scale up screening in MSM?

Stay tuned …

Don't forget the q3mth "triple dip" for at-risk MSM

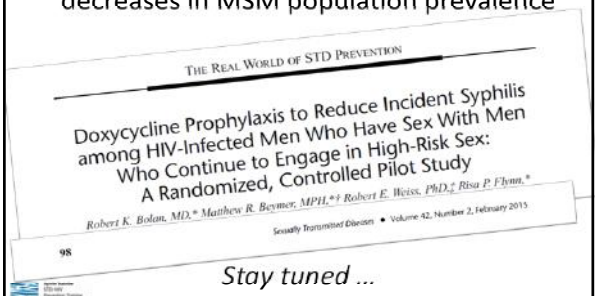
- HIV/Syphilis/ HepC* Serologies
- Pharyngeal GC NAAT**
- Urine GC/CT NAAT
- Rectal GC/CT NAAT**

*In HIV-coinfected individuals, screen hep C at least annually

**Off-label use - not FDA-approved for testing at extragenital sites, but many reference labs have validated the assay for use

Can We Prophylax for Syphilis Control?

- Prophylaxis for syphilis *might* also lead to decreases in MSM population prevalence


THE REAL WORLD OF STD PREVENTION

Doxycycline Prophylaxis to Reduce Incident Syphilis among HIV-Infected Men Who Have Sex With Men Who Continue to Engage in High-Risk Sex: A Randomized, Controlled Pilot Study

Robert K. Bolan, MD,* Matthew R. Beymer, MPH,*† Robert E. Weiss, PhD,‡ Risa P. Flynn,*

Sexually Transmitted Diseases • Volume 42, Number 2, February 2015

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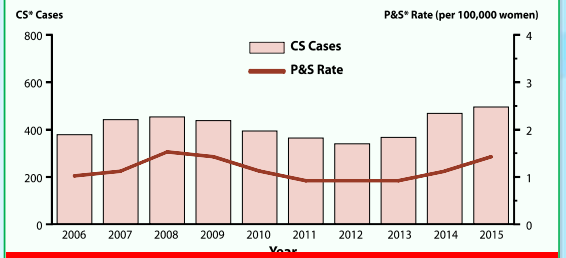
Stay tuned …

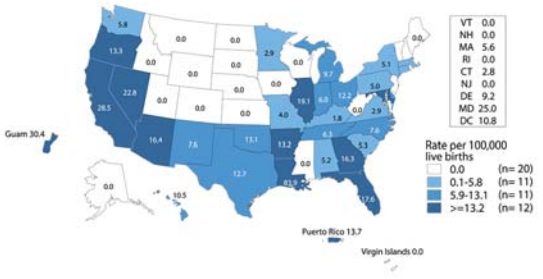
5. CONGENITAL SYPHILIS IS BACK

Congenital Syphilis — Reported Cases by Year of Birth and Rates of Primary and Secondary Syphilis Among Women, United States, 2006–2015



- In 2015, 487 reported cases of congenital syphilis
- National congenital syphilis rate now 12.4 cases per 100,000 live births
- Increase in 2015 represents 6% increase relative to 2014 and 36% increase relative to 2011

Congenital Syphilis — Rates of Reported Cases by Year of Birth and State, United States and Outlying Areas, 2015



NOTE: The total rate of congenital syphilis for infants by year of birth for the United States and outlying areas (Guam, Puerto Rico, and Virgin Islands) was 12.4 per 100,000 live births.

Syphilis Screening Recommendations: Pregnant Women

- **A serologic test for syphilis should be performed for all pregnant women at first prenatal visit**
- When access to prenatal care is not optimal, RPR card test screening (and treatment, if that test is reactive) should be performed at time pregnancy is confirmed
- **Women at high risk for syphilis or who live in areas of high syphilis morbidity should be screened again early in 3rd trimester (~28 wks gestation) and at delivery**
- **Some states require all women to be screened at delivery**
- Neonates should not be discharged from hospital unless syphilis serologic status of mother has been determined at least once during pregnancy and preferably again at delivery if at risk
- Any woman who delivers a stillborn infant should be tested for syphilis

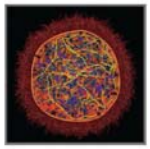
Screen, treat, and partner with the health department, to contact trace and prevent reinfection in pregnant women

4. *MYCOPLASMA GENITALIUM* HAS EMERGED

What is *Mycoplasma genitalium*?

- Mollicute
  - Lacks a cell wall
- Smallest known genome[1,2]
  - 580 kb translating to <500 genes
- First identified in 1981 from 2 of 13 men with NGU[3]
- Extremely fastidious
  - Culture only achieved by ~3-4 laboratories worldwide
  - Takes ~6 months[4]

Scanning electron micrograph

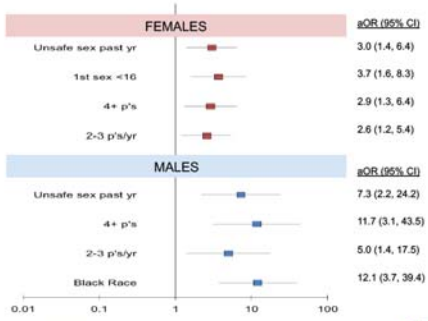


Computer assembled & generated 3D model

Slide courtesy of LE Manhart

[1]Glass et al, PNAS 2006; [2]Gibson et al, Science 2008; [3] Tully et al, Lancet 1981, [4]Jensen et al, J Clin Micro 1996

Who's at risk for *M. genitalium*? (British NATSAL-3)



Sonnenberg et al. Int J Epi 2015

Slide courtesy of LE Manhart

M. genitalium testing – No FDA-approved test

	Sensitivity %	Specificity %	PPV %	NPV %
Aptima TMA (CE Mark)				
Male Urine	100.0	97.9	90.0	100.0
Female Vaginal Swab	96.9	98.4	94.0	99.2
Diagenode S-DiaMGTV (CE Mark)				
Urine	100.0	100.0	-	-
Swab	100.0	96.3		
SpeeDx (CE-IVD Mark)				
Specimen type not specified	99.1	96.5	99.7	96.7

Adapted from Charlotte Gaydos

Slide courtesy of LE Manhart

Mycoplasma genitalium: Clinical Syndromes

- Cause of male urethritis
  - 15-20% of non-gonococcal urethritis (NGU) cases
  - 20-25% of non-chlamydial NGU
  - 30% of persistent or recurrent urethritis
  - More common than *N. gonorrhoeae* but less common than *C. trachomatis*
  - Co-infection with *C. trachomatis* is not uncommon
- Unknown whether it can cause male infertility or other male anogenital tract disease syndromes
- Pathogenic role in women less clear
  - Found more commonly in those with cervicitis or PID than those without cervicitis or PID

CDC 2015 STD Treatment Guidelines

"The **1-g single dose of azithromycin** was significantly more effective against *M. genitalium* than doxycycline in two randomized urethritis treatment trials and is **preferred over doxycycline.** However, **resistance** to azithromycin appears to be **rapidly emerging**….

Moxifloxacin (400mg daily x 7, 10, or 14 days) has been successfully used to treat *M. genitalium* in men and women with previous treatment failures….

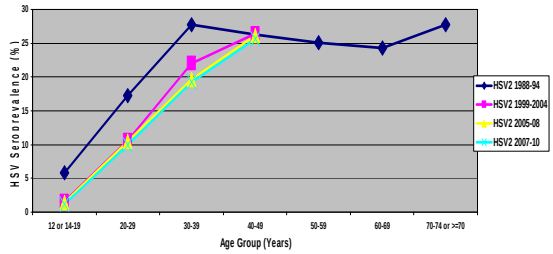
Although generally considered effective, studies in Japan, Australia, and the United States have reported **moxifloxacin treatment failures after the 7 day regimen.**"

CDC 2015 STD Treatment Guidelines

Slide courtesy of LE Manhart

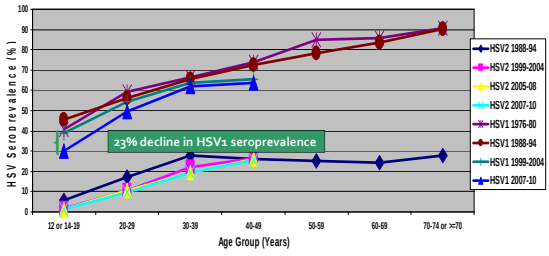
3. GENITAL HSV EPIDEMIOLOGY IS CHANGING

NHANES HSV2 Seroprevalence



Johnson et al. *NEJM* 321:7-12, 321, 1989
Schillinger et al. *STD* 31:753-60, 2004
Fleming et al. *NEJM* 337:1105-11, 1997
Xu et al. *JAMA* 296:964-73, 2006
Xu et al. *MMWR* 59:456-9, 2010
Bradley et al. *JID 209:325-33*, 2014

NHANES HSV1&2 Seroprevalence



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Xu et al. *MMWR* 59:456-9, 2010
Bradley et al. *JID 209:325-33*, 2014

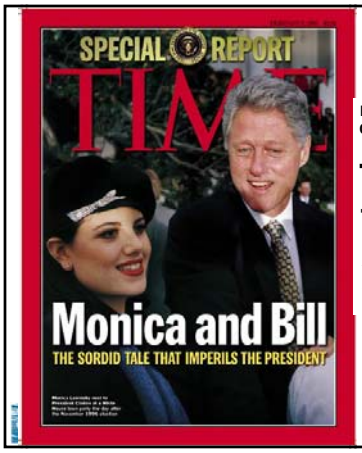
"Almost 1 in 10 adolescents who 10 years ago already would have acquired HSV1 earlier in life now are vulnerable to getting a primary infection as they enter their sexually active years."
Kimberlin, JID 2013

What About Genital HSV-1?

- **HSV1 now causes MOST of first genital HSV episodes in young adults**
  - Among >3400 HSV double-seronegative women 18-30 yrs from control arm of herpes vaccine trial who acquired disease during a 20 month period:
    - 5.3% became infected
    - HSV1 2.3x *more common* than HSV2 infection
    - Genital HSV1 2.5x *more common* than oral HSV1
  - Increasing proportion of anogenital herpetic infections have been attributed to HSV-1 infection in women and MSM
- Primary genital HSV1 and HSV2 remain *indistinguishable* clinically, and are treated with the same antiviral regimens
- Genital HSV1 does not recur as often as genital HSV2 **(?)**

What are the implications for genital HSV vaccine development?

Bernstein DI et al., *CID* 2013
Whitley RJ, *CID* 2013
Ryder N et al., *STI* 2009
Roberts CM et al., *STD* 2003



Monica Lewinsky & Bill Clinton Feb. 2, 1998

They are in the majority, *not* the minority …

Sexual Exploration

- We don't teach infants to crawl or walk by moving their limbs for them
  - although they are inefficient at first, this is something they have to do for themselves
- Of course, we want to minimize risk
  - *"if crawling is unsafe because the floor is dirty or littered with broken glass, the appropriate response is not to confine and restrict the child from crawling, but to clean up the mess."*

Bay-Cheng L et al. , "Not Always a Clear Path": Making Space for Peers, Adults, and Complexity in Adolescent Girls' Sexual Development," from *Sexualization of Girls and Girlhood,* Zurbriggen EL and Roberts T-A, eds., Oxford University Press, 2012.

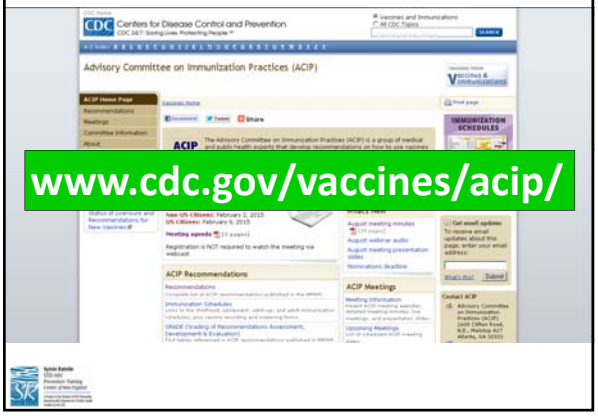
"Rather than trying to eliminate adolescent risk taking via abstinence programs or training in social skills or social norms – strategies that have not proven successful to date – a better tactic might be to reduce costs of adolescent risk taking by limiting access to particularly harmful risk-taking situations, while providing opportunities to engage in risky and exciting activities under circumstances designed to lessen changes for harm."

Spear LP, Adolescent neurodevelopment, *JAdolHealth*, 2013

Adolescent STI/HIV Prevention

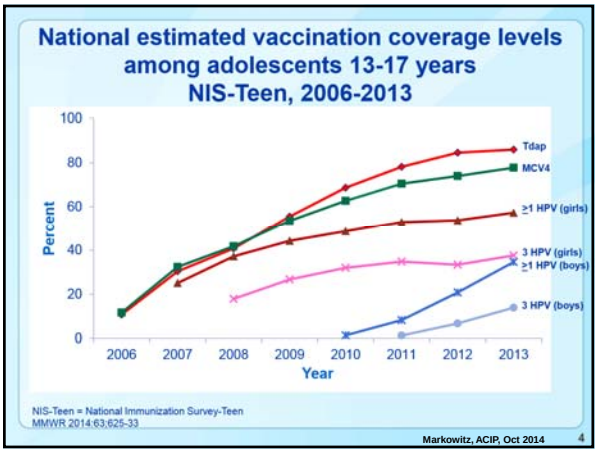
- ☑ "Clean up the floor" by encouraging immunizations, including HPV, HAV and HBV
- ☑ Provide information on STI/HIV infection, testing, transmission, and implications of infection to all adolescents as part of health care
- ☑ Integrate sexuality education into clinical practice
  - USPSTF recommends high-intensity STD prevention behavioral counseling for all sexually active adolescents twice yearly
- ☑ Re-channel adolescent risk-taking into safer avenues

2. HPV9 VACCINE 2-DOSE REGIMEN IS HERE (9-14 YEAR OLDS)



ACIP Meeting October 2016

- **Persons initiating vaccination before the 15th birthday (9-14 yrs):**
  - Recommended AND FDA-approved (as of 10/2016) immunization schedule is 2 doses old HPV vaccine
  - Second dose should be administered 6-12 months after the first dose (0, 6-12 schedule)
  - Minimum interval is 5 months between the first and the second dose
- **Persons initiating vaccination on or after the 15th birthday (15-26 yrs):**
  - Recommended AND FDA-approved immunization schedule is 3 doses of HPV vaccine
  - Second dose should be administered 1-2 months after the first dose, and the third dose should be administered 6 months after the first dose (0, 1-2, 6 month schedule)
- **Additional persons who should still receive 3 doses (up thru age 26 yrs):**
  - Primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, such as B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, HIV infection, malignant neoplasm, transplantation, autoimmune disease, or immunosuppressive therapy
  - Immune response to vaccination may be attenuated



"Pediatrician-Tested, Parent-Approved Messaging"

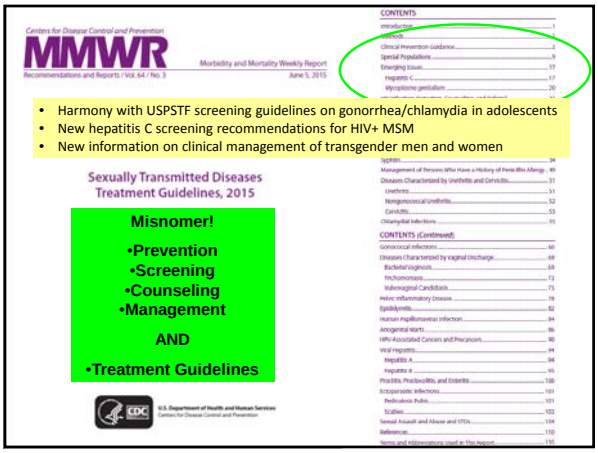
(CDC Formative Behavioral Research)

Drum roll please …

2. HPV9 2-dose vaccine regimen is here (9-14 year olds)
3. Genital HSV epidemiology is changing
4. *Mycoplasma genitalium* has emerged
5. Congenital syphilis is back
6. The epidemic of syphilis (& HIV co-infection) in MSM continues
7. Treating sex partners sight unseen (EPT) is legal (mostly)
8. Re-screening for STIs in those previously infected, reaches those at highest STI risk
9. The Specter of MDR GC
10. STD Rates are at unprecedented highs

1. CDC STD Treatment Guidelines:

A rose by any other name …



- Harmony with USPSTF screening guidelines on gonorrhea/chlamydia in adolescents
- New hepatitis C screening recommendations for HIV+ MSM
- New information on clinical management of transgender men and women

Sexually Transmitted Diseases Treatment Guidelines, 2015

Misnomer!

•Prevention
•Screening
•Counseling
•Management

AND

•Treatment Guidelines

CDC STD Treatment Guidelines Development

- Evidence-based on principal outcomes of STD therapy
  1. Microbiologic eradication
  2. Alleviation of signs & sx
  3. Prevention of sequelae
  4. Prevention of transmission
- Recommended regimens preferred over alternative regimens
- Alphabetized unless there is a priority of choice
- Reviewed April 2013; published 2015
- www.cdc.gov/std/treatment
  - Pocket guides, teaching slides, charts, app

Language in yellow highlighted boxes reflects changes between 2010 and 2015 guidelines

Want to know more about STDs?

There's an app for that.

CDC STD Treatment Guidelines App for Apple and Android

Available now, **FREE!** (accept no competitors)

Search "STD Treatment" in App store

STD Clinical Consultation Network (STDCCN)

- NEW!!!!!
- Provides STD clinical consultation services within 1-5 business days, depending on urgency, to healthcare providers nationally
- Your consultation request is linked to your regional PTC's STD faculty
- Just a click away!
- www.STDCCN.org