

# **Treatment Recommendations for STIs**

## **~~2014~~ 2015 Guidelines**

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No Disclosures

# Overview

- Screening
  - USPSTF CT and GC
  - STI in MSM (early syphilis, rectal GC, LGV)
- New Directions
  - Emerging Issues (MG, HCV)
  - Treatment concerns (GC, CT)
  - Syphilis – NS definition, reverse testing algorithm
  - HPV management
  - Trichomonas management

# Clinical Prevention Guidance

- Behavioral and biologic risk assessment
- High intensity behavioral counseling (USPSTF)
- Pre-exposure vaccination (HPV, HAV,HBV)
- Male latex condoms
- Male circumcision
- Microbicides
- Emergency contraception
- **Preexposure prophylaxis for HIV**
- Retesting after treatment

# Pre-exposure prophylaxis (PrEP)

- Trial in MSM, persons with HIV+ partners, heterosexuals living in high HIV prevalence areas; IDUs show reduction in risk of HIV by 44-90% with daily use of tenofovir (300 mg)-emtricitabine (200 mg)=(Truvada)
- Truvada is well tolerated
  - tenofovir has been associated with acute and chronic kidney disease and declines in bone mineral density but not increased fractures
- Prior to initiation: HIV test or HIV RNA if recent high risk exposure; serum creatinine and UA; hepatitis B serologies, pregnancy test
- Give 90 day supply and monitor q 3 months HIV/STDs; creatinine; pregnancy

# Truvada as HIV PrEP

- When people are adherent, once-daily Truvada taken as PrEP provides up to 92% reduction in risk for HIV acquisition
- Recommended for persons:
  - In ongoing relationships with PLWH
  - Sharing injection drug use equipment
  - With a recent and/or repeat bacterial STIs
  - Having unprotected sex with persons of unknown serostatus

# PrEP Program Components

- Screening (risk assessment; insurance coverage)
- HIV Testing (to ensure patient is HIV negative)
- STI Testing and Treatment, Hep A&B vaccination
- Kidney Test
- Risk reduction counseling; condoms
- Side effects and adherence counseling
- 1, 3, 6, 9, and 12 month follow ups

# Paying for Truvada as PrEP

- No Income -  $\leq 138\%$  of FPL: Medicaid
- $\leq 139\%$  -  $\leq 400\%$  of FPL: Private Insurance (Subsidies on the Exchange)
- Underinsured
  - Gilead Co-Pay Program for Truvada (no income requirement)
  - Patient Access Network Co-Pay Program (up to  $\leq 500\%$  FPL)
- Uninsured
  - Gilead Medication Assistance Program
  - Partnership for Prescription Assistance

# Chlamydia and Gonorrhea Screening

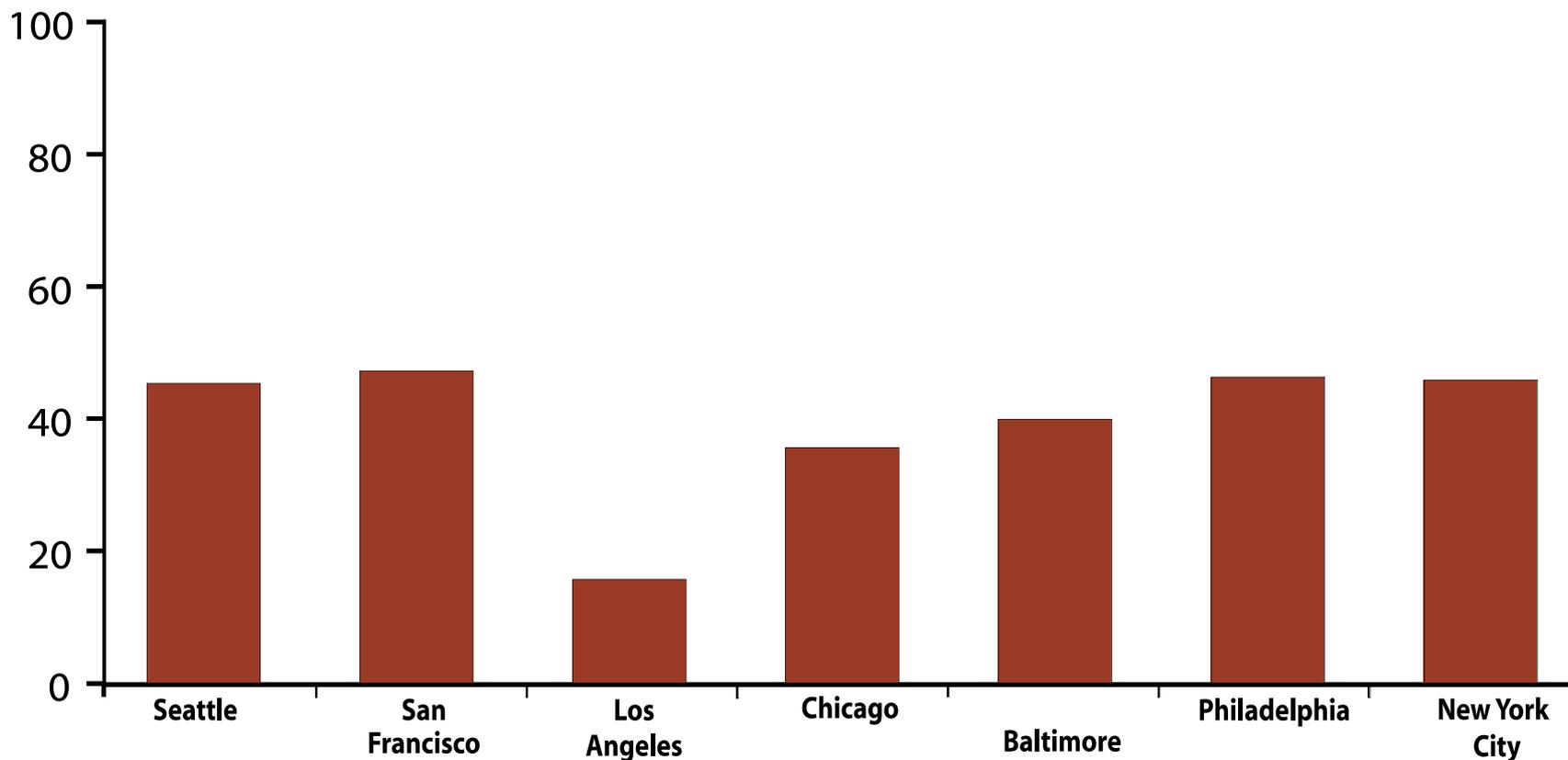
- Annual screening of sexually active women <25
- Screening of older women at increased risk
  - New sex partner, partner with concurrent partners or more than one partner, or partner with an STI
- Screening older women at low risk of infection not recommended
- CT screening sexually active men
  - Insufficient evidence for general screening; Consider in high prevalence (adolescent clinics, corrections, STD clinics)
- GC screening in men not recommended

# MSM

- Recent or concurrent STI and HIV infection
  - early syphilis (Zetola 2009, Solomon 2014, Pas-Bailey 2004, Pathela 2011)
  - rectal gonorrhea and chlamydia (Bernstein 2010, Pathela 2013)
  - Substance abuse, multiple anonymous partners, sex partners through internet
  - Resources for partner services
  - Educational materials and venues for risk reduction messages

# Primary and Secondary Syphilis and HIV—Proportion of MSM\* Attending STD Clinics with Primary and Secondary Syphilis Who Are Co-infected with HIV, STD Surveillance Network (SSuN), 2013

Percentage

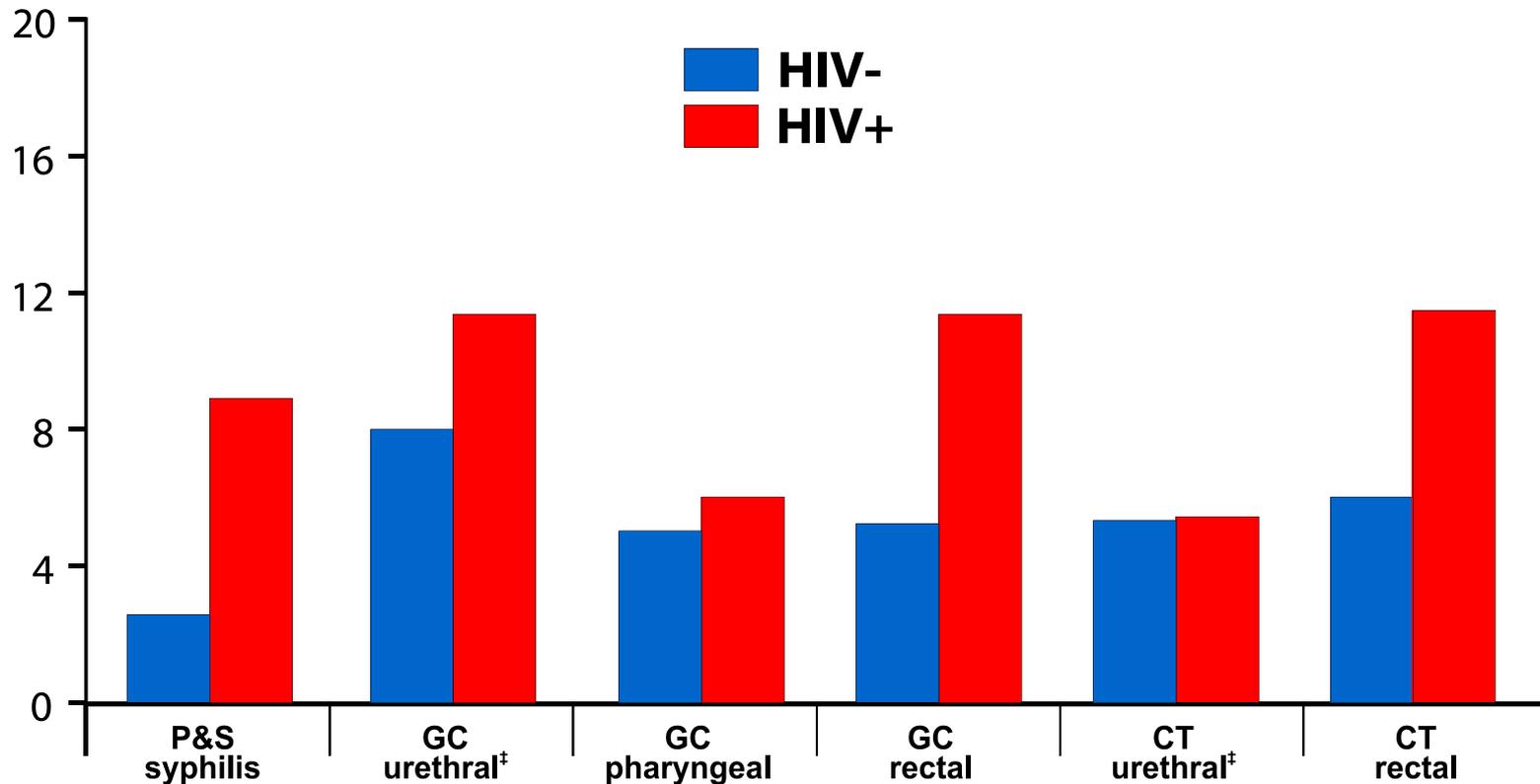


\*MSM=men who have sex with men.

**NOTE:** Includes sites that reported data on at least 25 MSM with primary and secondary syphilis in 2013. One jurisdiction (Chicago) contributed data from January through June 2013 and the remaining 6 jurisdictions contributed data for all of 2013.

# Proportion of MSM\* Attending STD Clinics with Primary and Secondary Syphilis, Gonorrhea or Chlamydia by HIV Status†, STD Surveillance Network (SSuN), 2013

Percentage



\*MSM=men who have sex with men.

† Excludes all persons for whom there was no laboratory documentation or self-report of HIV status.

‡ GC urethral and CT urethral include results from both urethral and urine specimens.

**NOTE:** Six jurisdictions (Birmingham, Chicago, Denver, Hartford/New Haven, New Orleans, and Richmond) contributed data from January through June 2013 and the remaining jurisdictions (Baltimore, Los Angeles, New York City, Philadelphia, San Francisco and Seattle) contributed data for all of 2013.

# STI Screening in MSM

- Sexually active MSM +/- HIV (at least yearly)
  - Syphilis serology
  - GC/CT NAAT (urine)
- Receptive oral
  - GC NAAT or culture
- Receptive anal
  - CT/GC NAAT
- Hepatitis A, B, C

**More frequent STI screening dependent on risk (3-6 mos)**

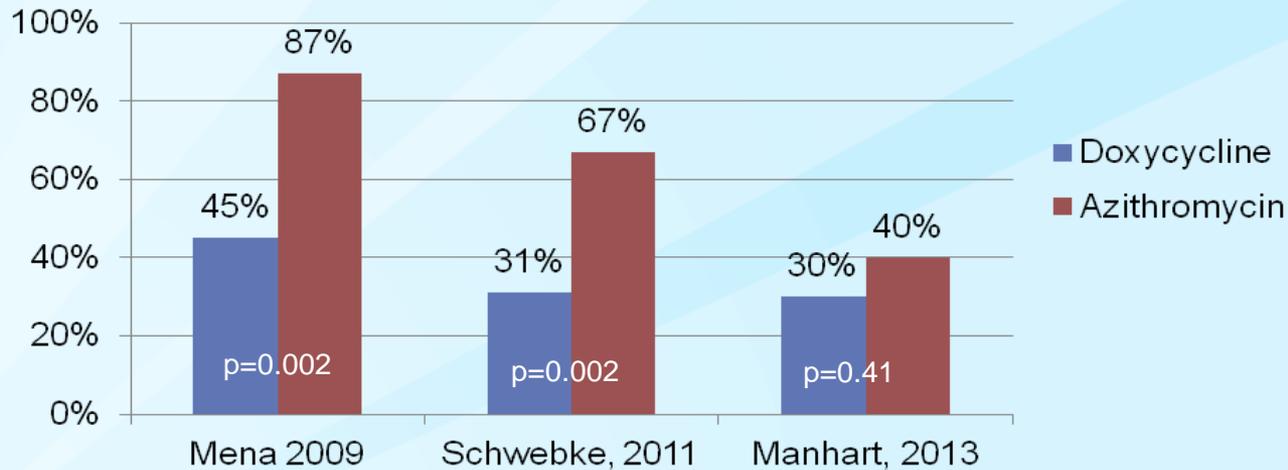
# New Section

- Emerging Issues
  - Role of *Mycoplasma genitalium*
    - Evidence of role in NGU (20%); role in cervicitis and PID emerging
    - No commercially available test (in house NAATs)
    - Treatment implications
      - azithromycin > doxycycline
      - Conflicting data on single dose vs extended dosing
      - Emerging resistance to azithromycin

# *Mycoplasma genitalium*

- **Observational studies** — DOX (7 studies; AZM (14 studies)
  - Microbiologic cure rates
    - **Doxycycline (7-9 days) :** 37% (median); range 17-94%
    - **Azithromycin (1g):** 91% (median); range 69-100%

- **RCTs**



- **Efficacy of AZM is not consistently high and declining**

# Efficacy of moxifloxacin

Study	Reason for treatment	Moxifloxacin dose	Micro Cure
Bradshaw 2006	AZM 1g treatment failures	400mg x 10 days	9/9 (100%)
Ross 2006	PID	400mg x 14 days	3/3 (100%)
Jernberg 2008	STD sx, or partner sx or MG+ or CT+	400mg x 7 days	3/3 (100%)
Bradshaw 2008	AZM 1g treatment failures	400mg x 14 days	8/8 (100%)
Terada 2012	Cervicitis	400mg x 7 days 400mg x 14 days	38/42 (91%) 42/42 (100%)
Twin 2012	AZM 1g treatment failures	400mg x 10 days	77/77 (100%)
Walker 2013	AZM 1g treatment failures	400mg x 10 days	3/3 (100%)
Anagrius 2013	AZM 1g treatment failures	400mg x 7 days	9/9 (100%)
Manhart 2013	Treatment failures (AZM1g, DOX, both)	400mg x 7 days	<b>17/20 (85%)</b>

# Emerging Issues

- **Sexually acquired HCV**

- Unprotected receptive anal intercourse
- Rough or poorly lubricated unprotected anal penetration(fisting)
- Ulcerative STIs (syphilis, LGV)

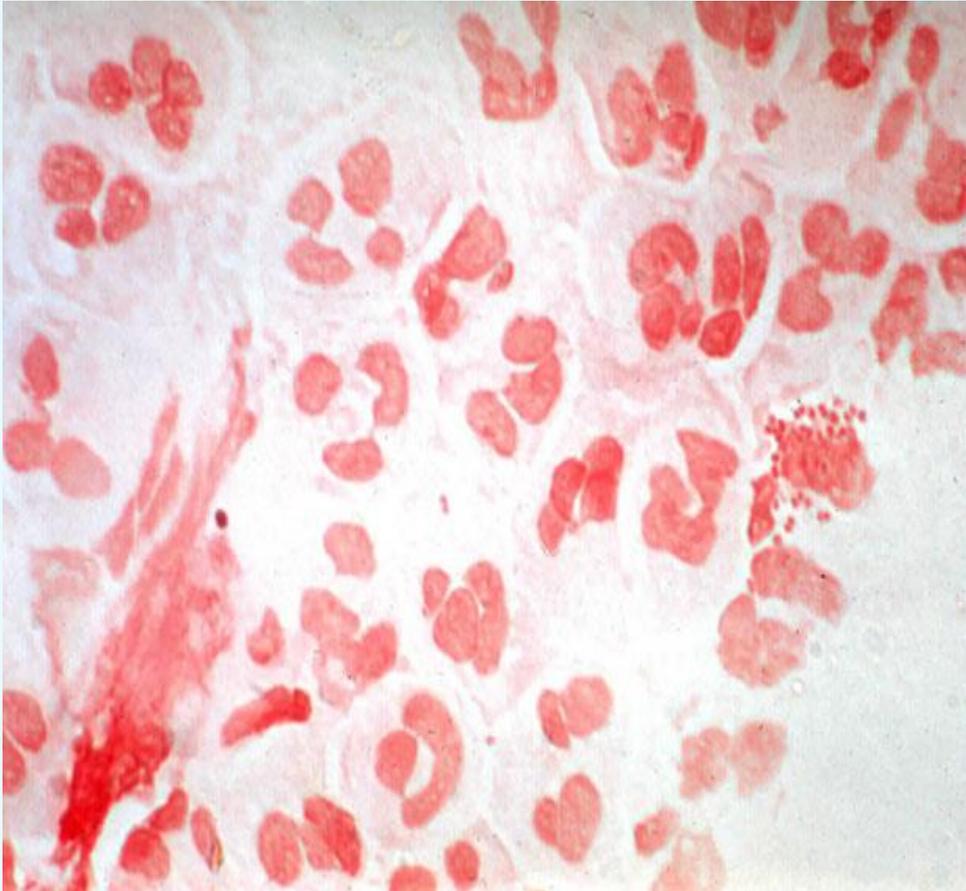
- **Annual screening**

- MSM +/-HIV infection
- Yearly testing with repeat test (HCV prevalence, high risk behavior, ulcerative STI or STI-related proctitis)

- **Acute HCV may be HCV Ab negative (CD4 <200)**

- HCV RNA with new LFT elevation

# Urethritis



- GC (5-20%)
- Chlamydia 15-40%
- *M. genitalium* 5-25%
- *Ureaplasma* 0-20%
- *Trichomoniasis* 5-20%
- HSV 15-30%,
- Adenovirus
- Enterics, *Candida*

# Urethritis

- Diagnosis of urethritis
  - Discharge
  - POC (gram stain  $\geq 2$  WBCs, **methylene blue or gentian violet**) or LE or first void urine
  - IF POC not available, who meet at least one criteria for urethritis, NAAT testing and treated for GC and CT
  - Sx but no signs of inflammation, NAAT testing may identify infection
    - GC or CT treat per recommendations
    - Empiric tx for high risk or unlikely follow-up

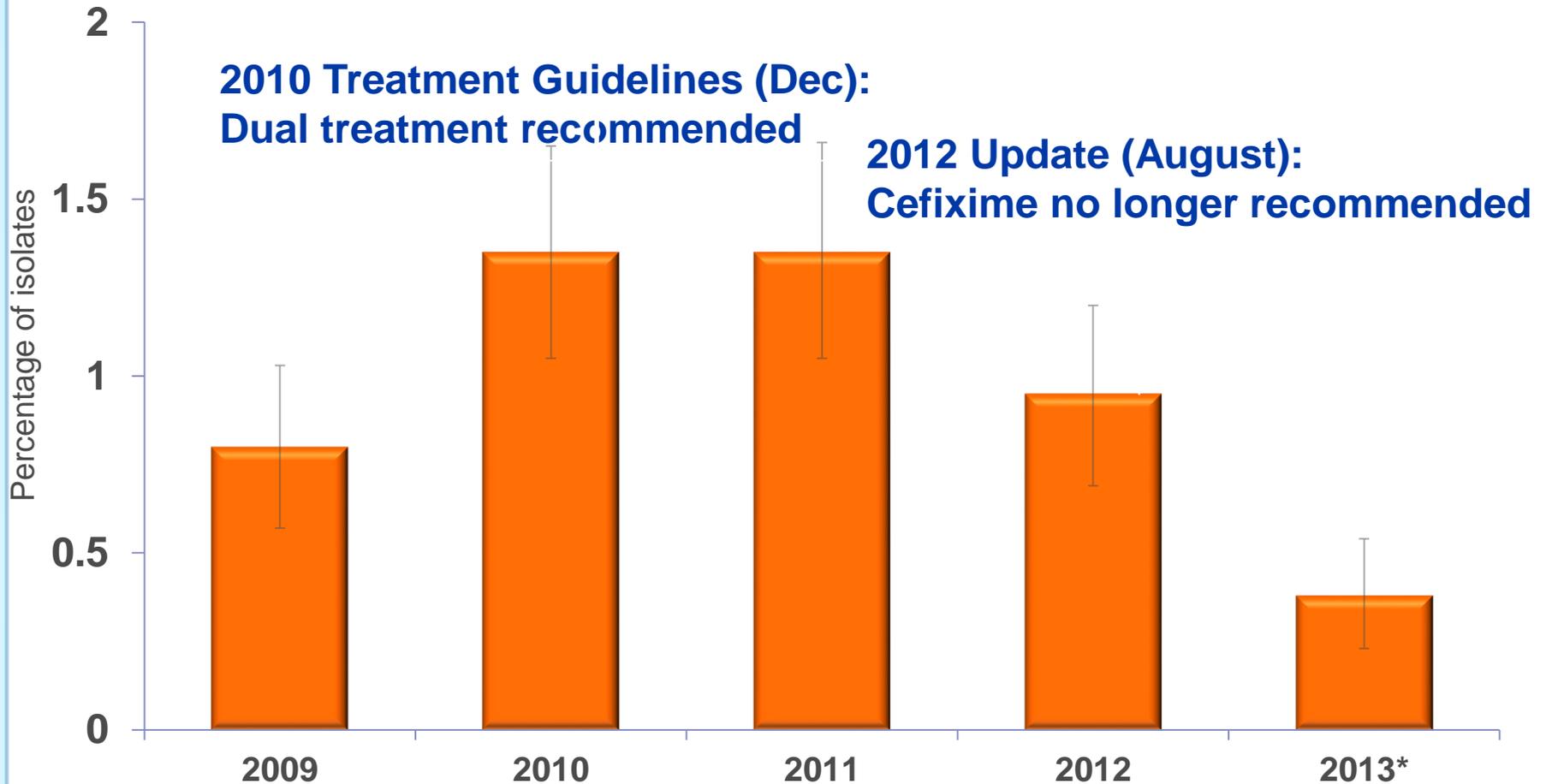
# **GONORRHEA**

# GISP sites and regional laboratories — United States

University of Washington



## Percentage of Isolates with Elevated Cefixime MICs ( $\geq 0.25$ $\mu\text{g/ml}$ ), United States, 2009–2013\*



\* Preliminary data

# Percentage of Isolates with Elevated Ceftriaxone MICs ( $\geq 0.125$ $\mu\text{g/ml}$ ), 2009–2013\*



\* Preliminary data

# **Uncomplicated Gonococcal Infections of Cervix, Urethra & Rectum**

**Ceftriaxone 250 mg as a single intramuscular  
dose**

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**PLUS**

**Azithromycin 1 g orally**

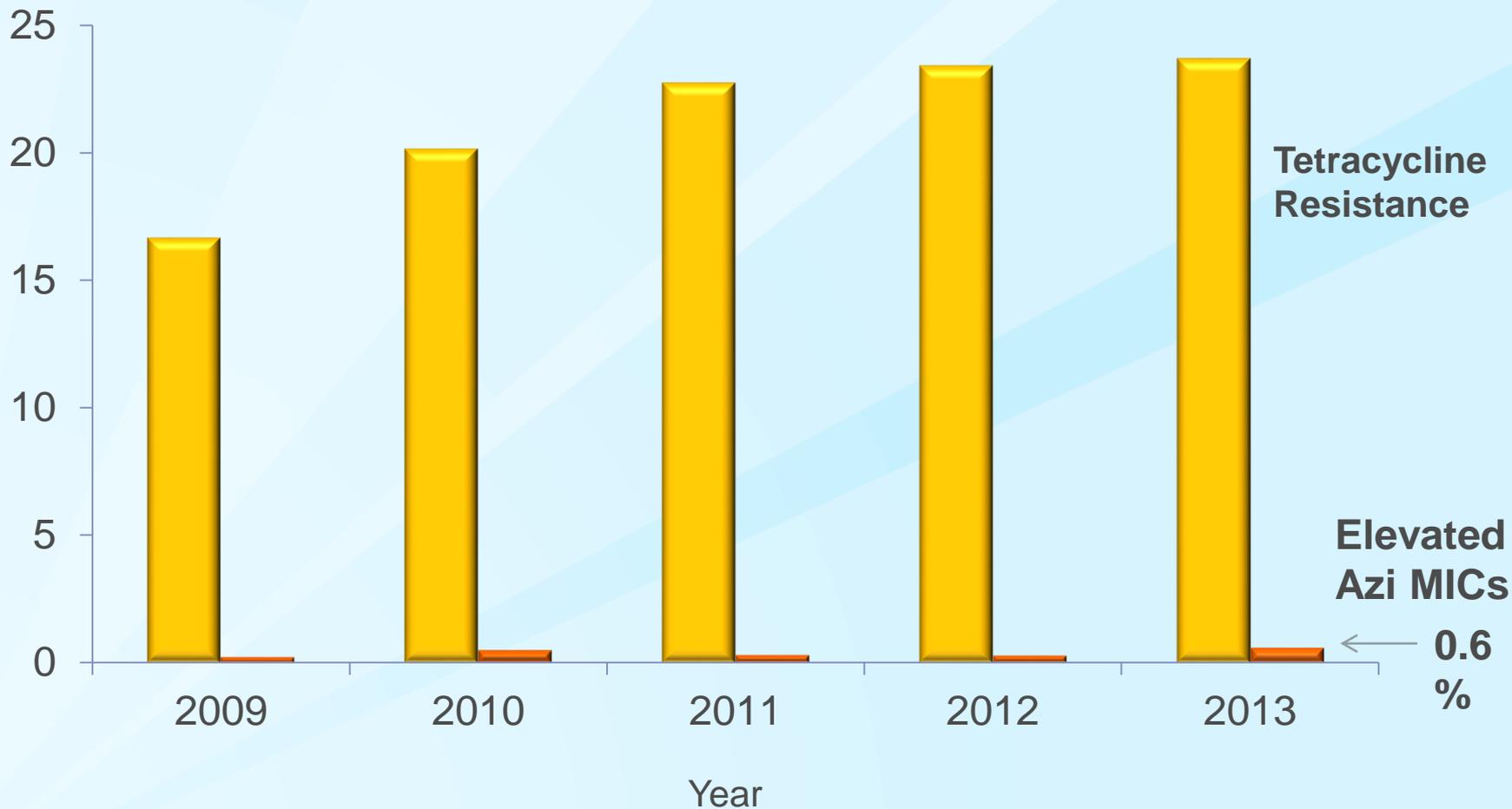
Alternative:

**If Ceftriaxone is not available:**

**Cefixime 400 mg PLUS azithromycin 1 gram**

# Proportion of GISP Isolates with Tetracycline Resistance or Elevated Azithromycin MICs ( $\geq 2 \mu\text{g/ml}$ ), 2009–2013

Percentage



# GC Treatment

- No clinical data to support increasing dose of ceftriaxone or azithromycin as part of dual therapy
- Higher ceftriaxone and/or azithromycin doses recommended outside US (UK, Japan) based on modeling not clinical data
- Ceftriaxone treatment failures rare- all outside US
- Azithromycin monotherapy effective not recommended - ease of resistance
- Test of cure not needed after treatment for urogenital or rectal infection (recommended/alternative); recommended for pharynx (alternative)

# New Treatment Option

- NIH sponsored RCT (Kirkaldy, CID 2014)
  - **Gentamicin 240 mg IM + azithromycin 2 g PO, OR**
  - **Gemifloxacin 320 mg PO + azithromycin 2 g PO**
- Rationale
  - Additive effect, gentamicin and azithromycin *in vitro*
  - Gemifloxacin more active against cipro resistance or GyrA and ParC mutations

	<u>Gentamicin / Azithromycin</u>		<u>Gemifloxacin / Azithromycin</u>	
	n/N	% (L 95% CI)	n/N	% (L 95% CI)
<b>Urethra/Cervix</b>	202/202	100% (98.5%)	198/199	99.5% (97.6%)
<b>Pharynx</b>	10/10	100%	15/15	100%
<b>Rectum</b>	1/1	100%	5/5	100%

# Suspect Treatment Failures

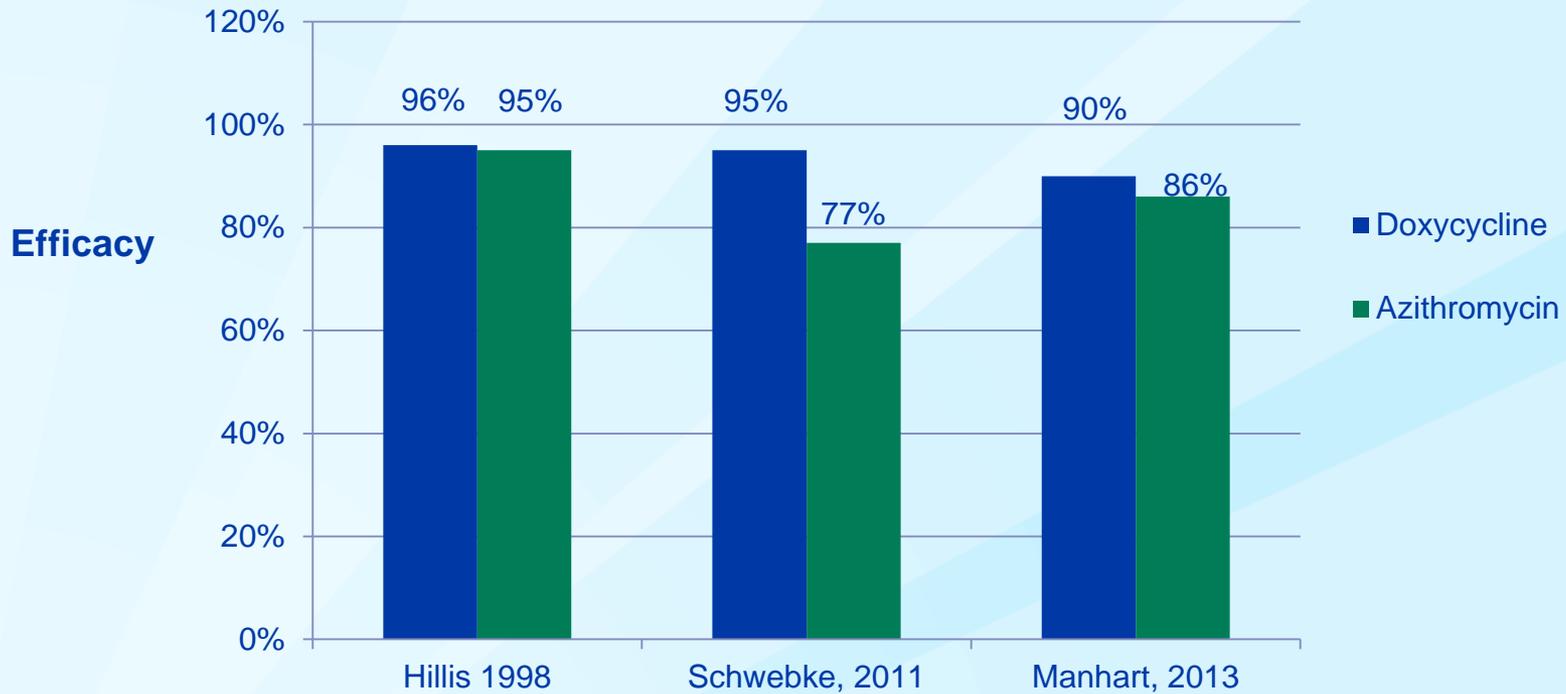
- **Most treatment failure likely due to reinfection**
- If tx failure suspect, obtain culture/ susceptibility test
- Treatment
  - If reinfection likely (ceftriaxone/azi ); Rx ceftriaxone 250 mg +azithromycin 1 gram
  - If reinfection likely (cefixime/azi) , Rx ceftriaxone 250 mg + azithromycin 2 gram
  - If tx failure suspected, Rx gemifloxacin 320 mg +azithromycin 2 g or gentamicin 240 IM + azithromycin 2g
- Report to local or state health department
- Test of cure 7-14 days after retreatment (culture/AST preferred with NAAT)
- Ensure partner tx

# **CHLAMYDIA**

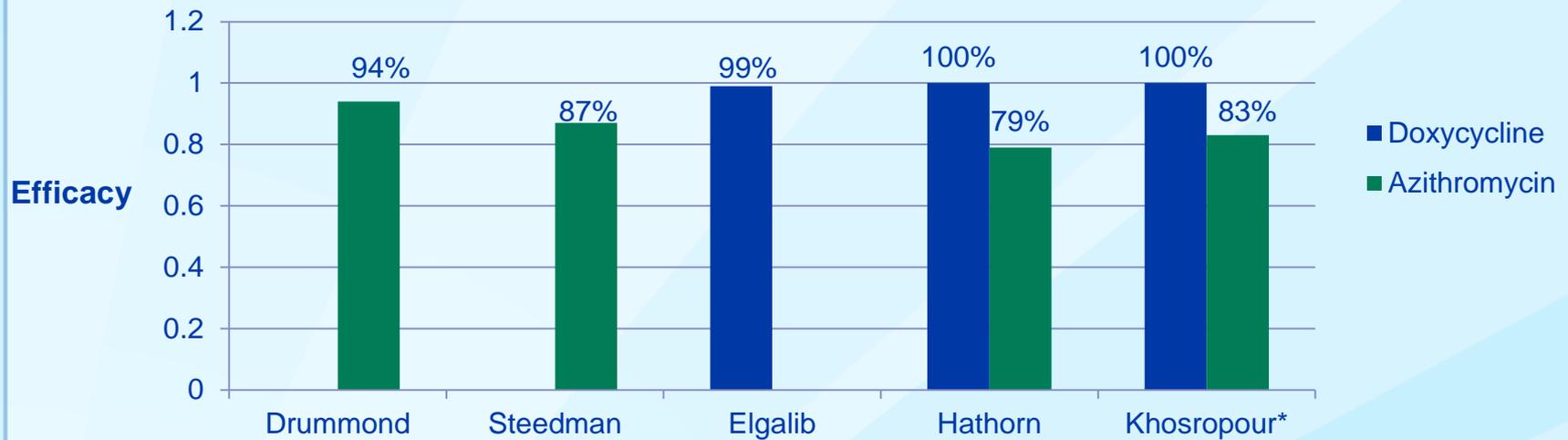
# Chlamydia Treatment

- Effectiveness of azithromycin < doxycycline
  - Data from one NGU trial and several rectal infection studies
- Doxycycline delayed release 200 mg tablets (Doryx)
- Amoxicillin moved to alternative regimen in pregnancy
  - In vitro studies demonstrate PCN induces persistent viable noninfectious *Chlamydia* forms that revert to infectious forms after PCN removal (Wyrick)
  - Earlier amoxicillin Rx studies in CT in pregnancy had major limitations
  - RCT by Kacmar et al. showed higher TOC by LCR w/ azithro vs. amox (95% vs. 80%),

# Azithro vs. Doxy RCTs using NAAT



# Azithro or Doxy for Rectal CT using NAAT



REF	CT + Cohort	Rx	TEST	TOC	Limitations
Drummond	85 MSM	Azithro	PCR	21-372 days	-Retrospective -45% tested >12 wks
Steedman	68 MSM	Azithro	PCR	Rec $\geq$ 21 days	-Retrospective -Most repeat CT+ sex after Rx -1/3 repeat CT+ tested $\leq$ 21 days
Elgalib	165 MSM	Doxy	SDA/TMA	Median 45d IQR 34-88d	-Retrospective -Long post-Rx test interval -Majority rectal CT pts excluded
Hathorn	82 MSM/women	42 Azithro 40 Doxy	TMA	Rec 42 days	-High lost-to-f/u (~50%) -Treatment bias in doxy Rx phase
Khosropour* (Unpublished)	89 MSM	69 Azithro 20 Doxy	Culture/TMA (majority culture)	21-42 days	-Retrospective, prelim data (unpublished) -Culture less sensitive assay -Possible bias of doxy group cultured more

\*Analysis shown restricted to 21-42 day interval (study included testing up to 180 days)

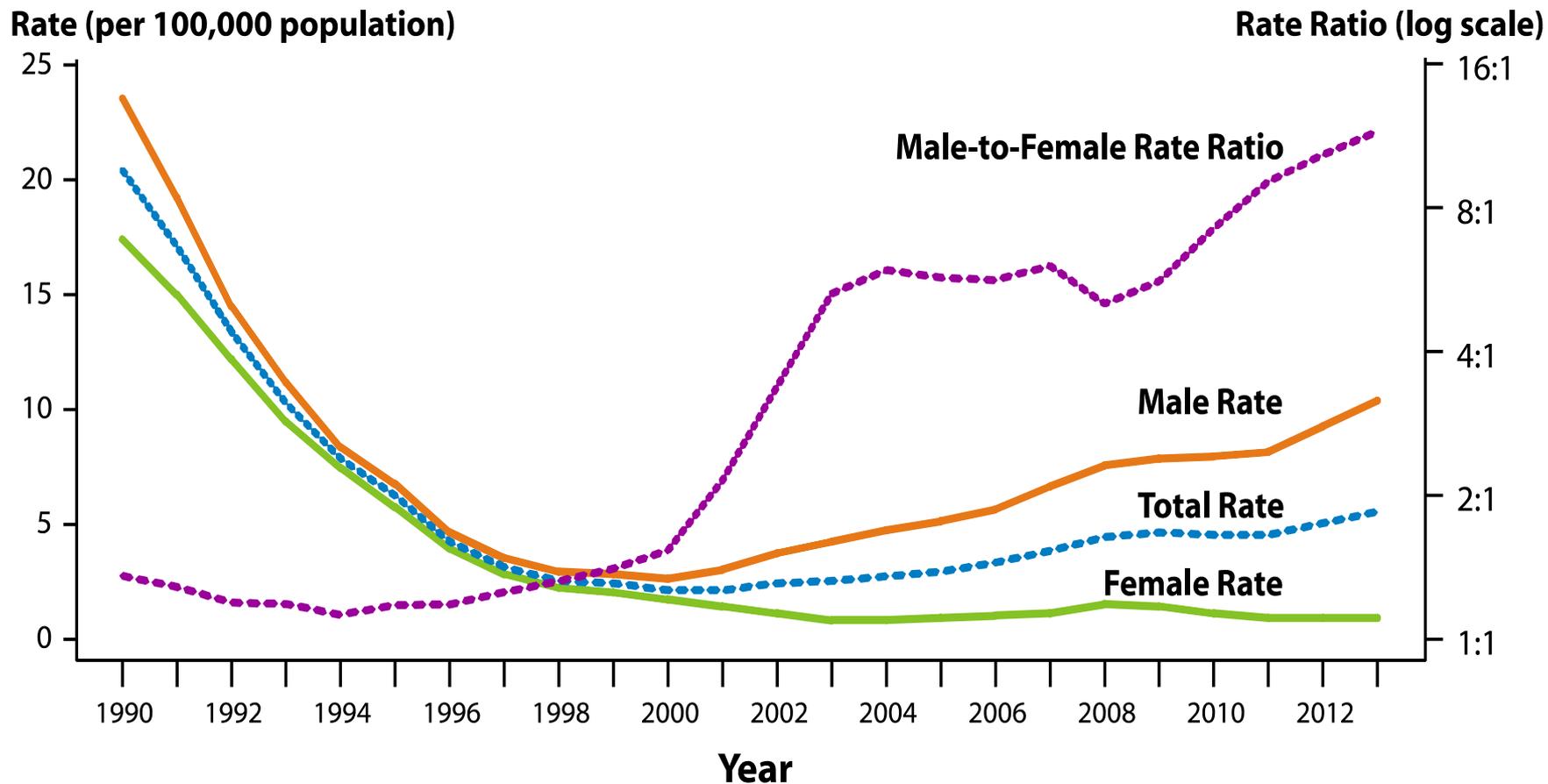
# Treatment of Genital Chlamydia Infection

*Hocking et al (University of Melbourne)*

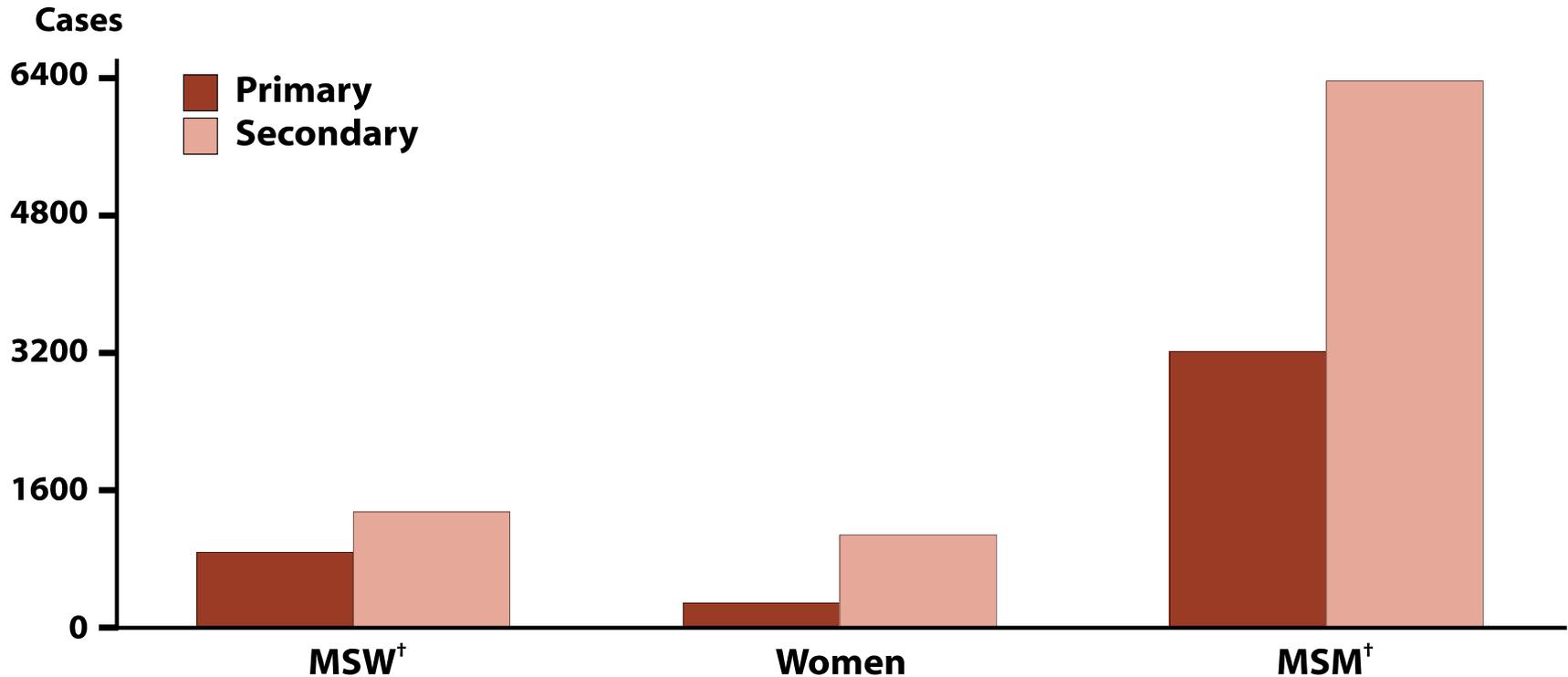
- **Meta-analysis** of 23 RCTs (through 2012) : 1065 individuals treated with azithromycin, 850 with doxycycline
- **Pooled cure rates: doxy 97.5%, azithro 94.4%**
- Pooled estimate favored doxy (2.2% - 2.7% more efficacious) especially in **men**
- **Conclusion: doxy marginally superior to azithro**
- Caveats in interpreting and comparing RCTs:
  - Differences in when endpoint was measured
  - Only 4 studies were double blind:
  - 20 RCTS – no sample size calculations
  - Most studies performed in high-risk population (generalizability?)

# **SYPHILIS**

# Primary and Secondary Syphilis—Rates of Reported Cases by Sex and Male-to-Female Rate Ratios, United States, 1990–2013



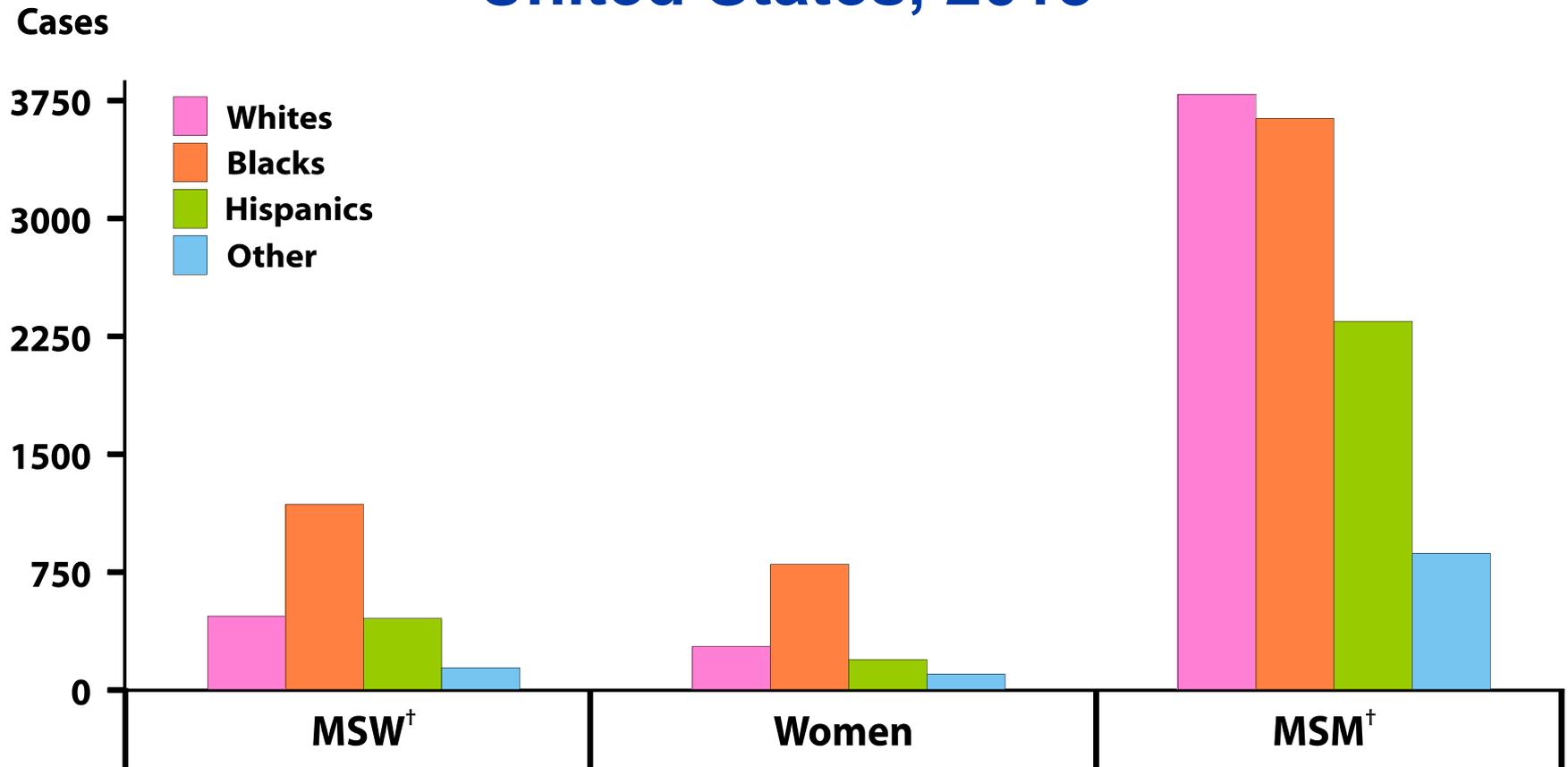
# Primary and Secondary Syphilis—Reported Cases\* by Stage, Sex, and Sexual Behavior, United States, 2013



\*Of the reported male cases of primary and secondary syphilis, 16.9% were missing sex of sex partner information.

†MSW=men who have sex with women only; MSM=men who have sex with men.

# Primary and Secondary Syphilis—Reported Cases\* by Sex, Sexual Behavior, and Race/Ethnicity, United States, 2013



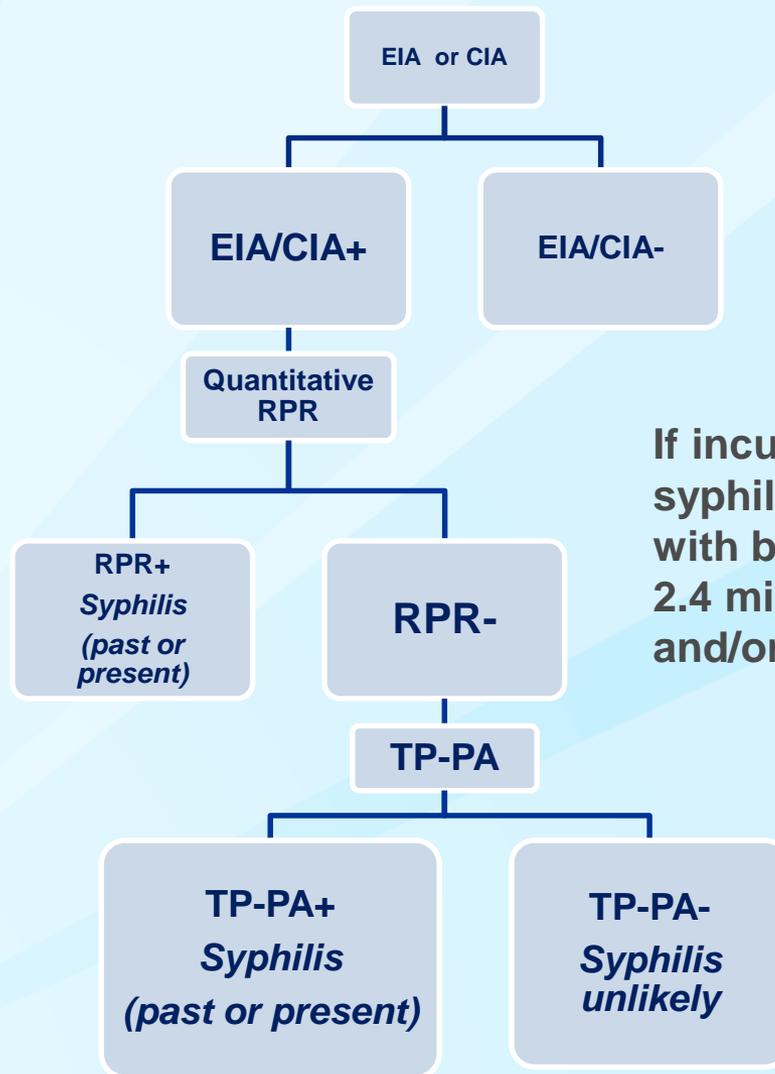
\*Of the reported male cases of primary and secondary syphilis, 16.9% were missing sex of sex partner information; 2.9% of reported male cases with sex of sex partner data were missing race/ethnicity data.

<sup>†</sup>MSW=men who have sex with women only; MSM=men who have sex with men.

# Syphilis

- No *T pallidum* detection tests available
- Serological response to tx (Sena 2011)
  - Stage (earlier stage more likely to decrease 4x)
  - titer (low titer less to decline than higher titer)
- Time between Benz pcn doses (LL)
  - <9 days is best based on limited PK (nonpregnant)
  - 7 days in pregnant women
    - 40% are below treponemicidal levels after 9 days
    - If a dose is missed, the entire series must be restarted

# Reverse Screening Algorithm



Evaluate clinically, determine if treated for syphilis in the past, assess risk of infection, and administer therapy according to guidelines if not previously treated

If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units IM x 1 and/or repeat in 2-4 weeks

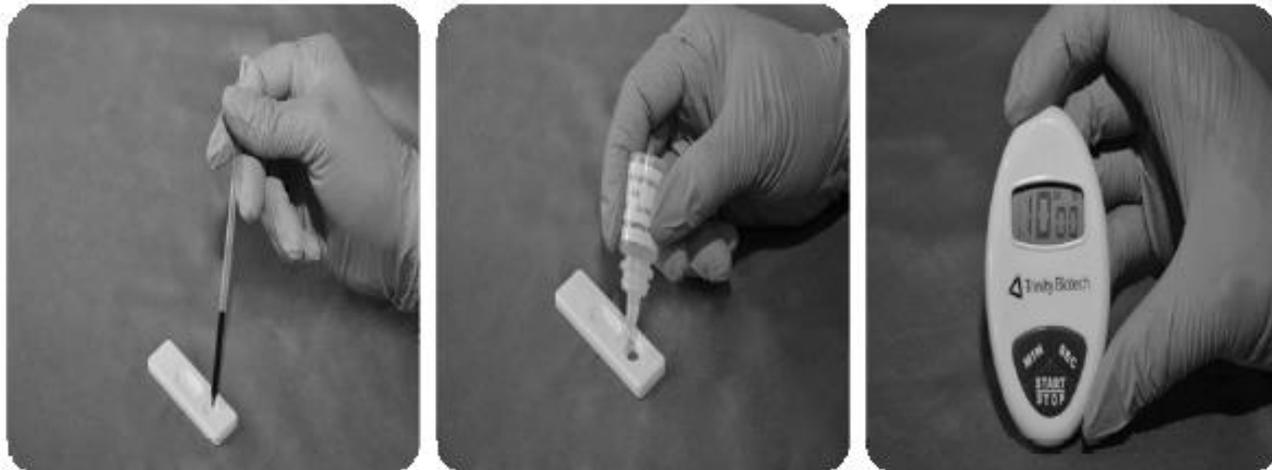
If at risk for syphilis, repeat RPR in 2 to 4 weeks

# Syphilis Health Check™ Venipuncture Procedure.....

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1. Collect Venipuncture Sample ( WB, serum, plasma)
2. Dispense 1 Drop of Sample into Sample Port (2 drops if WB or FS)
3. Add 4 Drops of Wash Solution
4. Read Test Device between 10 and 15 Minutes

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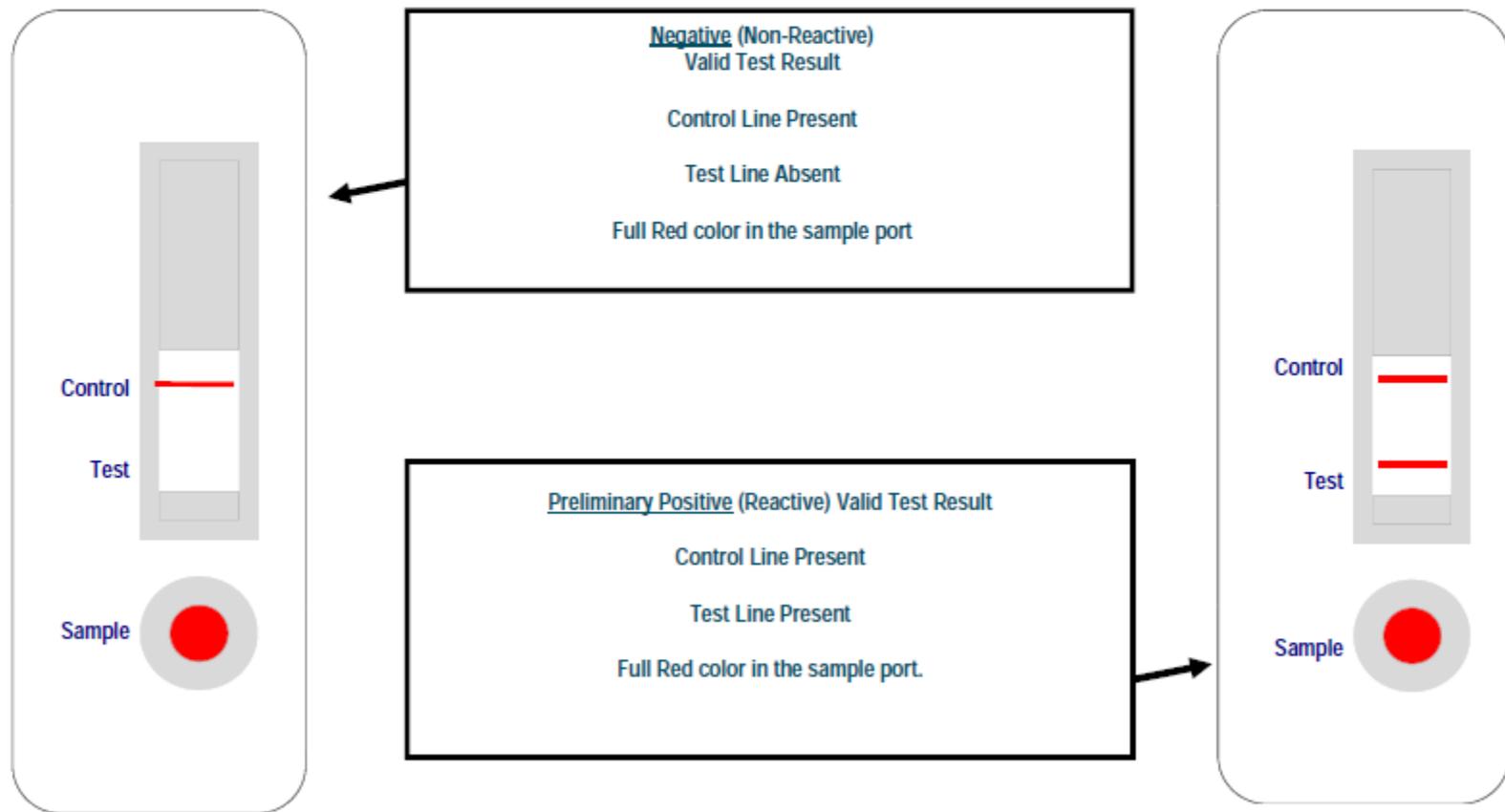
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# Syphilis Health Check™ Test Interpretation.....



# Syphilis Treatment

## Primary, Secondary, Early Latent

- Penicillin treatment of choice +/- HIV
  - Benz Pcn 2.4 mu IM x 1
- No benefit of additional therapy (Rofls 1997)
  - Enhanced (IM+oral)
- PCN alternatives
  - Doxycycline, ceftriaxone
  - Azithromycin 2 gm (A2058G mutation/tx failure)
    - MSM>MSW (Su, STD 2012)
    - Do not use in MSM or pregnancy

# Evaluation of CNS Involvement

- Clinical signs (neurologic, ocular, auditory, meningitis, stroke) warrant investigation
- CNS invasion in early syphilis +/- HIV is common
  - CSF abnormalities
  - Unknown clinical significance in absence of signs or sx
- **Neurosyphilis: CSF tests + reactive RPR + signs/sx**
- LP: neuro/ocular sx, serologic treatment failure, tertiary
  - Some studies in HIV+ showed association with CSF abnormalities\*
    - RPR  $\geq$  1:32 and/or CD4  $\leq$  350
  - Unless neurologic signs/sx, value of LP unknown.

\* Marra 2004; Libois A, *STD* 2007; Ghanem *CID*; Marra *CID* 2008

# HPV Infection

- ACIP HPV vaccine recommendations (*MMWR, 2014, Vol 63*)
- Podophyllin resin 10-25% (alternative)
  - Case reports of serious systemic toxicity (including death)
  - No clear efficacy benefit when compared with podophyllotoxin
- Case reports of inflammatory responses to imiquimod
  - Worsened inflammatory and autoimmune skin disease
    - **psoriasis, vitiligo, and lichenoid dermatoses**
- Imiquimod (3.75%) applied daily for genital warts

# Risk to Healthcare Workers Treating GW

- HPV DNA can be found in smoke plumes after laser or electrosurgical therapy on EGW, CIN, common warts
- 2 case reports of laryngeal papillomas reported in HCW exposed to smoke plumes during treatment of GW
- Appropriate infection control to prevent possible transmission for anogenital warts and anogenital intraepithelial neoplasias (e.g. CIN) with CO2 laser or electrosurgical procedures (local exhaust ventilation-smoke evacuator)

# Anal Cancer Screening

- HPV vaccination of MSM (ACIP 2014)
- Some clinical centers perform anal cytology in high risk populations
- Data are insufficient to recommend routine anal cancer screening with anal cytology
  - More evidence on best screening methods
  - Safety and response to treatment
  - Programmatic considerations
- High risk HPV tests not clinically useful for anal cancer screening (high prevalence of anal HPV infection)

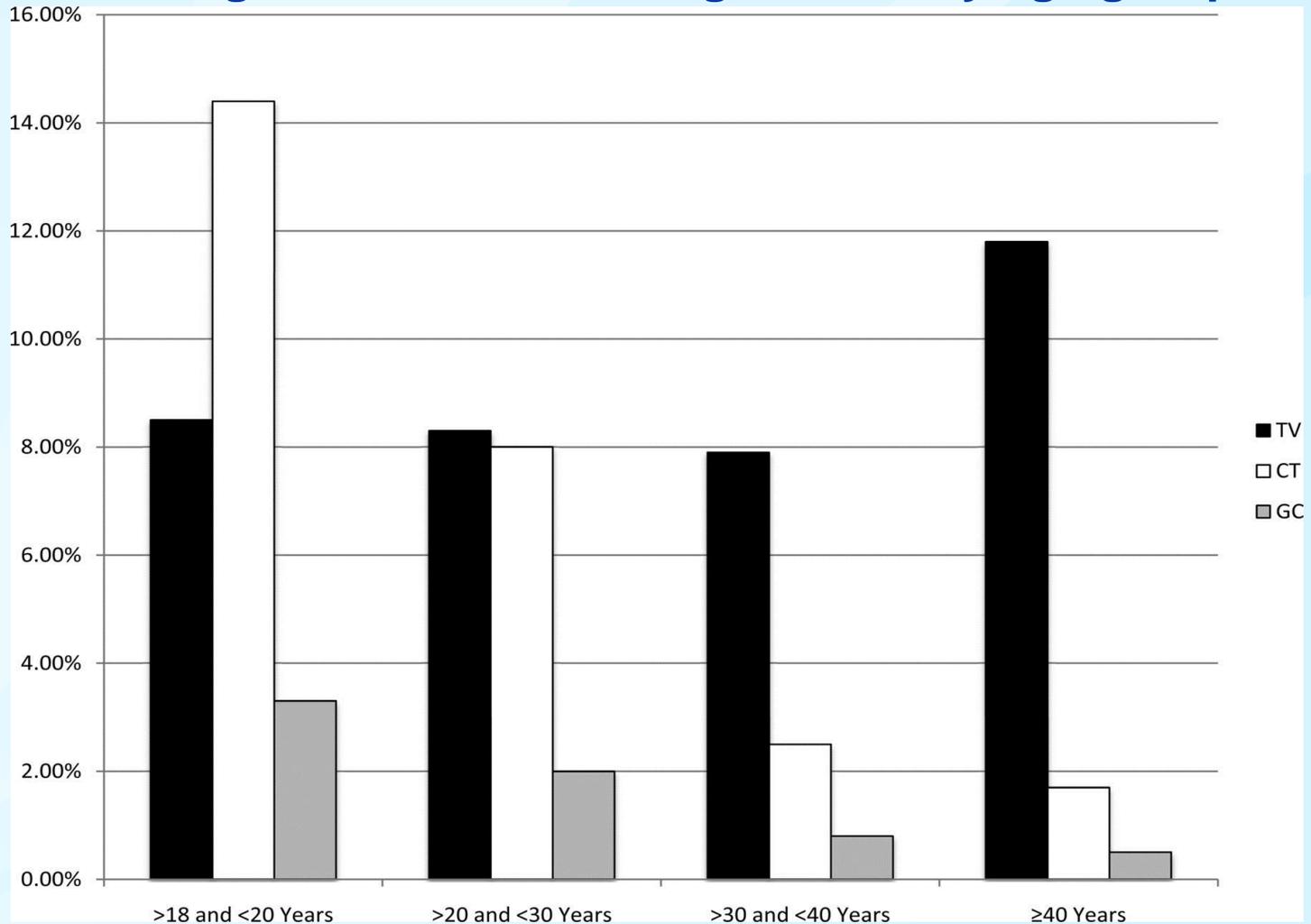
# 9vHPV (MMWR March 27,

Characteristic	Bivalent (2vHPV)	Quadrivalent (4vHPV)	9-valent (9vHPV)*
Brand name	Cevarix	Gardasil	Gardasil 9
VLPs	16,18	6,11,16,18	6,11,16,18,31,33,45,52,58
Manufacturer	GSK	Merck	Merck
Manufacturing	<i>Trichoplusia ni</i> insect cell line infected with L1 encoding recombinant baculovirus	<i>Saccharomyces cerevisiae</i> (Baker's yeast <sup>0</sup> , expressing Li	<i>Saccharomyces cerevisiae</i> (Baker's yeast <sup>0</sup> , expressing Li

- HPV routine vaccination at age 11 or 12
- Gardasil is licensed for males and females
- Also for females 13 through 26 and males 13 through 26, if not previously vaccinated
- Also for MSM through age 26 and for immunocompromised, if not previously vaccinated
- \*\*December 10, 2014 FDA approved for use in females ages 9-26 and males ages 9-15; ACIP also includes males up to 26 in MMWR

# Trichomonas Epidemiology

NAAT prevalence of TV, CT, and GC infections among 7593 U.S. women age 18–89, by age group



# *T vaginalis*

- Consider screening of those receiving care in high prevalence settings (STD clinics, corrections) or asymptomatic persons at high risk of infection (multiple sex partners)
  - Lack data on screening/tx to reduce adverse events or disparities
  - Screening decisions informed by epidemiology
- **NAATs for diagnostic testing**
  - APTIMA *T vaginalis*; BD Probe Tec TV Qx amplified DNA Assay
  - A molecular test-resolved algorithm (negative wet prep followed by NAAT - Aptima TV - sensitivity 87.5–96.6% , specificity of 97.7–100% (Nye)
- **Retesting 3 mo after treatment**
- Tx Metronidazole 2 g or Tinidazole 2 gm
- Nitroimidazole resistance 4-10% (Kirkaldy 2012, Schwebke 2006)

# ***Trichomonas vaginalis* and HIV in Women**

## **TV is an independent risk factor for HIV acquisition**

Increases probability of acquiring HIV	OR 2.6 (CI:1.4–4.7)	Hughes, 2012
More likely to test positive for HIV	HR 2.1 (CI:1.1–4.0)	Mavedzenge, 2010
Associated with incident HIV	OR 2.7 (CI:1.3–6.0)	Van der Pol, 2008

## **Maternal TV is a risk factor for vertical transmission**

Increases HIV vertical transmission risk	RR 1.7 (CI:1.0– 2.9)	Gumbo, 2010
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# *T vaginalis* and HIV infection

- Women with HIV infection should receive screening at entry to care and annually if sexually active
  - associated with PID (Moodley 2002)
  - Treatment reduces genital HIV shedding (Kissinger 2009, Anderson 2012)
- Longer treatment course better in women
  - metronidazole 500mg BID x7d (vs. 2g )-less TV at TOC/3 mo RR 0.46, CI:0.21–0.98 (*Kissinger, 2010*)
  - Potential factors- BV infection, arv, changes in vaginal ecology
- No data to recommend extended treatment in men
- **Retesting 3 mo after treatment**

# Bacterial Vaginosis

- Treatment- metronidazole oral or gel, clindamycin cream
- Recurrent BV
  - biweekly suppressive MTZ gel (RCT ) for 4-6 mo
  - oral metronidazole followed by boric acid and suppressive metrogel
  - Metronidazole (10-14 days with vaginal gel or oral tablets) or a weeklong course of oral tinidazole (limited data)
  - No data on suppressive tinidazole, oral clindamycin/vaginal cream
  - no support of any available probiotic as adjunctive or replacement therapy to antibiotics in BV
- Awaiting more data
  - Vitamin D deficiency; contraceptives and BV risk
  - *L. crispatus* vaginal capsule (LACTIN-V) for BV prevention

# Sexual Assault in Adults

- Initial exam individualized
  - NAAT for GC, CT; NAAT or POC test for trichomonas
  - HIV, syphilis, hepatitis B
- Prophylaxis
  - Empiric tx for GC, CT, trichomonas
  - Emergency contraception
  - Post exposure hepatitis B vaccination
  - HPV vaccination
  - HIV PEP individualized according to risk (algorithm)



# STD Treatment Guidelines Meeting

CDC Atlanta | April 30–May 2, 2013



# Look for the CDC's 2015 STD Treatment Guidelines on or after June 5!

A-Z Index **A** B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

## Sexually Transmitted Diseases (STDs)



### Diseases & Related Conditions

- Bacterial Vaginosis (BV)
- Chlamydia
- Gonorrhea
- Hepatitis, Viral
- Herpes, Genital
- HIV/AIDS & STDs
- Human Papillomavirus (HPV)
- Pelvic Inflammatory Disease (PID)
- STDs and Infertility
- Syphilis
- Trichomoniasis
- Other STDs

### How You Can Prevent STDs

- Basic prevention for all STDs

### Featured



**2013 Surveillance Report**

**Life Stages and Populations**

### What's New

**Public Health in a Hostile Environment: Racial Inequality and STD/HTV in the US** by Adara

<http://www.cdc.gov/std/>