

Extra-Genital Testing: What Are We Missing?

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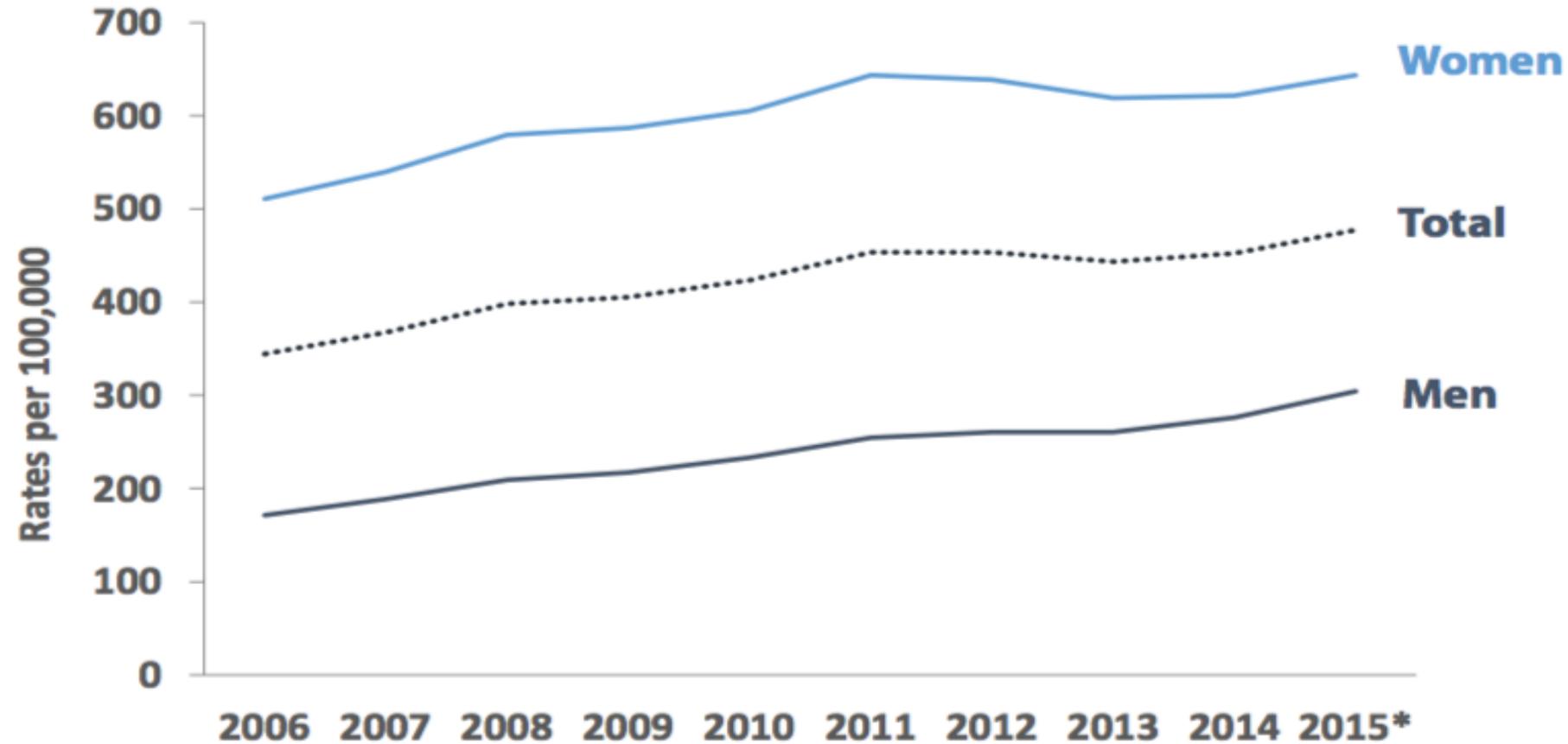
Medical Director, STD/HIV Prevention Training Center at Johns Hopkins

Special thanks to Kyle Bernstein, Ph.D.
for sharing his slides with me

Extragenital GC and Ct

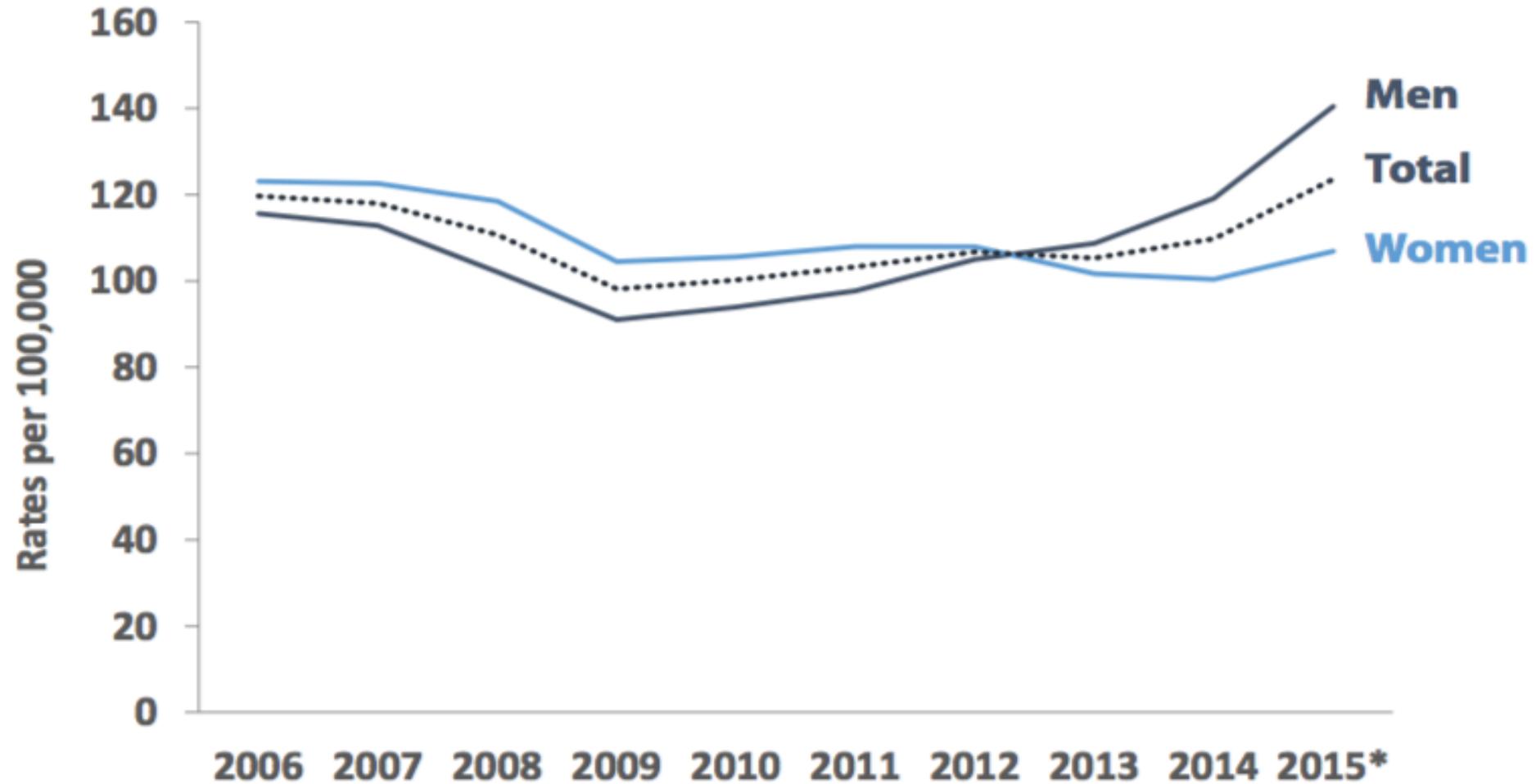
- Prevalence
- Public Health Implications
- Importance
 - HIV
 - Resistant gonorrhoea
- Future Directions

Chlamydia — Rates of Reported Cases by Sex, United States, 1994–2015*



*2015 Data are preliminary as of May 5, 2016

Gonorrhea — Rates of Reported Cases by Sex, United States, 1994–2015*



*2015 Data are preliminary as of May 5, 2016

National Case Based Surveillance

- Person based
 - Extragenital infections may be underestimated
- Site of infection
 - Data not available at national level

GENITAL & EXTRA-GENITAL TESTING CAPACITY AT DHMH LABS - 2016

- NAATs (Chlamydia lab)
 - endocervical swabs
 - male urethral swabs
 - urine first void (male and female)
 - rectal swabs
- Culture tests (GC Lab)
 - Endocervix
 - Urethra
 - Conjunctival
 - Nasopharynx
 - throat
 - rectal

What do we know?

Why do extragenital testing?

- From July 2003 until February 2007, 441 rectal test sets were collected from individuals attending a sexually transmitted disease clinic and three HIV clinics
 - who gave a history of anal intercourse or
 - were women at high risk for *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infections.
- What would we have missed by NOT testing the rectum?
 - Over 60% and 80% of gonococcal and chlamydial infections in MSM
 - Over 20% of chlamydial infections in women

Extragenital Screening in Men Who Have Sex With Men Diagnoses More Chlamydia and Gonorrhea Cases Than Urine Testing Alone

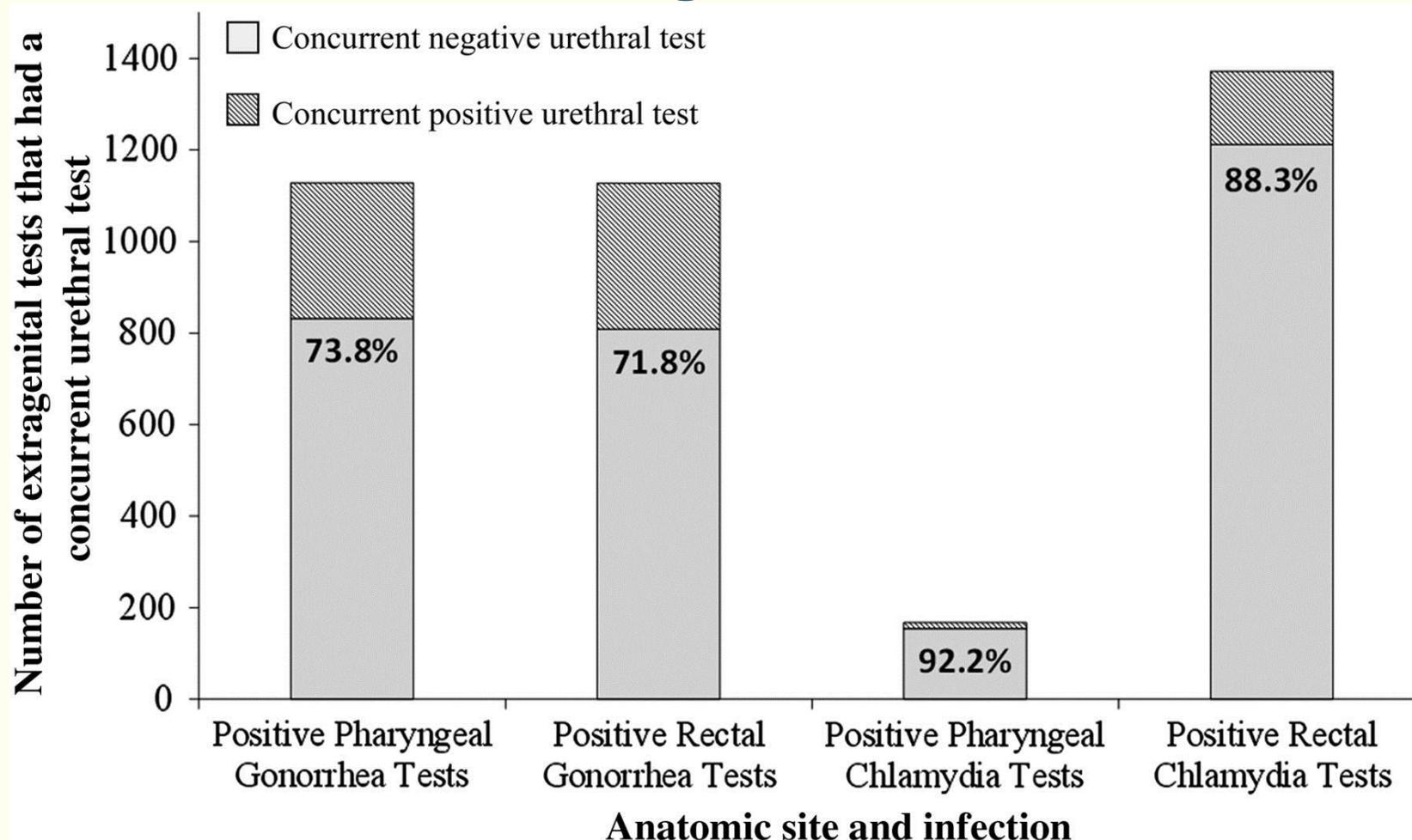
Greta L. Anschuetz, MPH, Eric Paulukonis, BA,† Ron Powers, BA,† and Lenore E. Asbel, MD**

TABLE 1. Gonorrhea and Chlamydia Infections Identified From Extragenital Screening Compared to Urine Testing Alone Among MSM Seen at 2 Clinics Between 7/1/2014 and 6/30/2015

	n			Gonorrhea					Chlamydia				
				Urine Negative					Urine Negative				
	Urine Tested	Pharyngeal Tested	Rectal Tested	Urine Positive	Pharyngeal Positive	Rectal Positive	Both Positive	% Potentially Missed	Urine Positive	Pharyngeal Positive	Rectal Positive	Both Positive	% Potentially Missed
Washington West Program	1731	1619	1124	37	80	42	33	80.7	48	13	99	14	72.4
Health Center #1 STD Clinic	1025	886	639	29	59	50	36	83.3	40	12	88	8	73.0

% Potentially missed is defined as the number of pharyngeal, rectal, or both infections that would not have been diagnosed if only urogenital testing was available.

Proportion of extragenital gonorrhea and chlamydia infections associated with concurrent negative urethral tests.



Monica E. Patton et al. Clin Infect Dis. 2014;58:1564-1570

21,994 MSM attending 42 STD Clinic in US 2011-2012

Neisseria gonorrhoeae and Chlamydia trachomatis Among Women Reporting Extragenital Exposures

Joshua D. Trebach, BS,* C. Patrick Chaulk, MD,*† Kathleen R. Page, MD,*† Susan Tuddenham, MD, MPH,* and Khalil G. Ghanem, MD, PhD*

- **Methods:** All patients who reported extragenital exposures in the preceding 3 months, who presented for care between June 1, 2011, and May 31, 2013, and who were tested for GC and CT using nucleic acid amplification tests at all sites of
- **Results:** A total of 10,389 patients were included in this analysis (88% African American; mean age, 29 years; 42% women; 7% MSM; 2.5% HIV infected)
 - The prevalence estimates of any extragenital GC and CT were as follows:
 - 2.4% GC and 3.7% CT in women
 - 2.6% GC and 1.6% CT in men who have sex with women
 - 18.9% GC and 11.8% CT in MSM.
- Among women, 30.3% of GC infections and 13.8% of CT infections would have been missed with urogenital-only testing.
- Unlike MSM, age ≤ 18 years was the strongest predictor of extragenital infections in women.

Trebach JE, Chaulk CP, Page KR, Tuddenham S, Ghanem KG. *Sex Transm Dis* 2015;42:233-239 A summary of studies that assessed prevalence of GC and CT in women

Study First Author	Year	Population/Setting	GC Prevalence Throat (95% CI)	GC Prevalence Rectum (95% CI)	CT Prevalence Throat (95% CI)	CT Prevalence Rectum (95% CI)	% missed CT and GC ^Δ (95% CI)
Trebach JD, et al. (current study)	2014	Baltimore City Health Department Eastern Health District and Druid Health Center, Maryland	2.09 (1.68–2.57) N=4203	2.95 (1.76–4.62) N=611	2.59 2.10–3.16 N=3662	8.64 (6.52–11.17) N=602	CT: 13.8% (10.7–17.6) GC: 30.3% (23.4–37.9)
Van Liere, G et al. ¹⁶	2014	South Limburg Public Health Service STI clinic, Netherlands	2.3% (1.54–3.23) N=1321	0.9% (0.47–1.58) N=1321	1.4% 0.87–2.23 N=1321	4.8% (3.68–6.06) N=1321	CT: 22.8% (14.72–32.75) GC: 58.5 (42.11–73.68)
Garner AL, et al. ⁴	2014	Manchester Centre for Sexual Health, UK	0.6% (0.17–1.59) N=642	1.1% (0.03–5.97) N=91	2.5% (1.43–4.02) N=642	6.6% (2.46–13.80) N=91	CT: 12.9% (5.74–23.85) GC: 28.5% (3.67–70.96)
Ladd J, et al. ¹⁷	2014	Home testing using iwantthekit.org	N/A	2.4% (0.80–5.60) N=205	N/A	12.7% (8.45–18.03) N=205	N/A
Jenkins WD, et al. ³⁰	2014	Memorial Medical Center Emergency Department, IL	0.66% (0.18–2.38) N=301	N/A	0.66% (0.18–2.38) N=301	N/A	Pharyngeal CT: 0% Pharyngeal GC: 9.09% (2.53–27.81)
Shaw SG, et al. ¹⁸	2013	STI center in the United Kingdom	0.28% (0.03–0.49) N=1799	0.64% (0.08–2.30) N=312	1.3% (0.81–1.91) N=1799	7.1% (4.47–10.48) N=312	N/A

Study First Author	Year	Population/Setting	GC Prevalence Throat (95% CI)	GC Prevalence Rectum (95% CI)	CT Prevalence Throat (95% CI)	CT Prevalence Rectum (95% CI)	% missed CT and GC ^Δ (95% CI)
Koedijk FDH, et al. ⁵	2012	STI centers in the Netherlands	1.20% (1.15–1.25) N = 206,513	1.20% (1.15–1.25) N = 207,134	2.70% (2.63–2.77) N = 206,720	9.3% (9.18–9.43) N = 206,720	CT: 12.9% (N/A) GC: 30.0% (N/A)
Javanbakht M, et al. ⁶	2012	STD clinics in Los Angeles County, CA	N/A	3.0% (2.27–3.80) N=2026	N/A	14.6% (12.29–16.32) N=1203	CT: 25% (19.41–32.14) GC: 18.5% (10.75–28.70)
Rodriguez-Hart C, et al. ³	2012	Adult film performers	22.32% (15.00–31.16) N=112	16.96% (10.53–25.22) N=112	N/A	3.57% (0.98–8.89) N=112	CT & GC: 15% (N/A)
Karlsson A, et al. ¹⁹	2011	Porsö Health Care Centre and Gällivare Centre for Young Persons, Sweden	N/A	N/A	12% (6.12–20.39) N=92	N/A	N/A
Peters RP, et al. ²⁰	2011	STD Clinic-The Hague	0.8% (0.54–1.14) N = 3750	1.7% (0.96–2.81) N = 876	1.9% (1.48–2.38) N = 3750	8.7% (6.90–10.74) N = 876	N/A

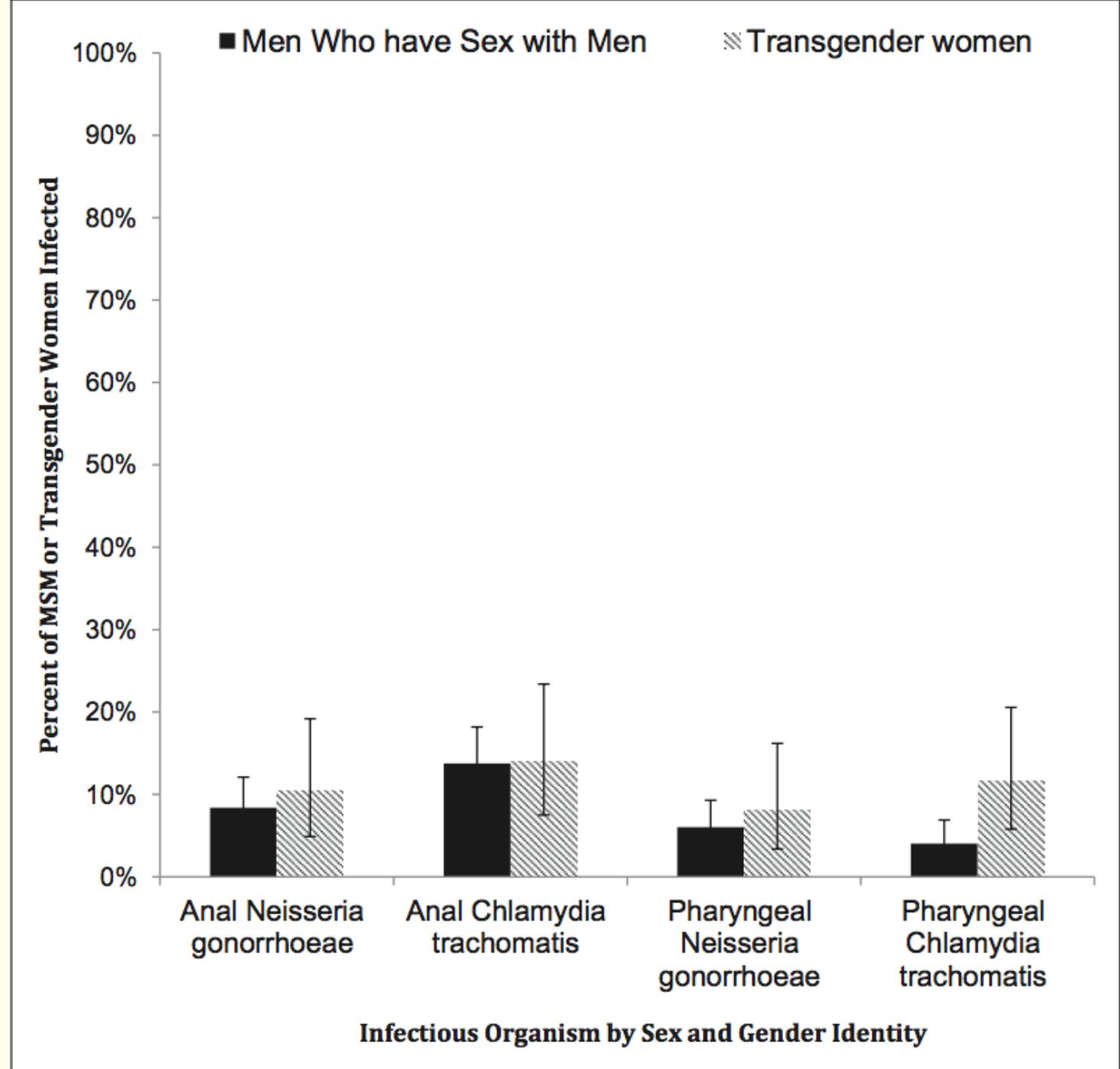
Study First Author	Year	Population/Setting	GC Prevalence Throat (95% CI)	GC Prevalence Rectum (95% CI)	CT Prevalence Throat (95% CI)	CT Prevalence Rectum (95% CI)	% missed CT and GC ^Δ (95% CI)
Bachmann LH, et al. ²¹	2010	Clinics in AL and IL	N/A	16.46% (9.88–26.15) N=79	N/A	32.14% (23.12–42.72) N=84	Rectal CT: 23.33% (11.79–40.92) Rectal GC: 15.79% (5.52–37.57)
Tipple C, et al. ²²	2010	UK STI Center	N/A	N/A	1.9% (1.05–3.05) N=805	N/A	N/A
Giannini CM, et al. ²³	2010	Adolescent hospital STD Clinic (adolescents) STD Clinic (Adults)	3.5% (1.0–6.2) N= 195; 6.8% (3.8–9.9) N= 263; 2.5% (1.4–3.5) N=887	2.9% (0.1–5.7) N=140; 13.4% (3.9–23) N=52; 5.2% (2.7–7.7) N=308	N/A	N/A	Adolescents GC: 14–26% (N/A) Adolescents (hospitalized): 11% (N/A) Adults GC: 20–40% (N/A)
Hunte T, et al. ²	2010	Miami Dade Health Department STD Clinic	N/A	13.4% (7.33–21.83) N=97	N/A	17.5% (10.55–26.57) N=97	Rectal CT: 6% (0.15–28.69) Rectal GC: 38% (13.86–68.42)
Barry PM, et al. ²⁴	2010	San Francisco STD Clinic	N/A	1.7%; (1.06–2.54) N=1308	N/A	4.7% (3.65–6.03) N= 1308	Rectal GC: 0.1% (0.0–0.43) Rectal CT : 1.0% (0.53–1.69)
Raychaudhuri M, et al. ²⁵	2010	STI clinic; UK	N/A	35.83% (27.29–45.10) N=120	N/A	N/A	GC 5.8% (2.38–11.65)

Study First Author	Year	Population/Setting	GC Prevalence Throat (95% CI)	GC Prevalence Rectum (95% CI)	CT Prevalence Throat (95% CI)	CT Prevalence Rectum (95% CI)	% missed CT and GC ^Δ (95% CI)
Van der Helm JJ, et al. ²⁶	2009	Clients of Amsterdam and South Limburg STI outpatient centers	N/A	1.9% (1.1–3.2) N=697	N/A	9.4% (7.7–11.5) N=901	N/A
Bachmann LH, et al. ²⁷	2009	Public STD clinic, HIV clinic, university-based HIV clinic; Alabama.	9.1% (6.18–13.17) N=264	N/A	N/A	N/A	N/A
Ostergaard L, et al. ²⁸	1997	Rudolph Bergh Hospital, Denmark	N/A	N/A	1.53% (0.52–4.40) 3/196	5.61% (3.16–9.77) 11/196	CT: 13.04% (4.54–32.12)
Jones RB, et al. ²⁹	1985	Indiana STD clinics	N/A	N/A	3.2% (1.96–4.89) N=626	5.2% (4.04–6.61) N=1227	N/A

Trebach JE, Chaulk CP, Page KR, Tuddenham S, Ghanem KG. *Sex Transm Dis* 2015;42:233-239

High prevalence of extra-genital CT or GC among MSM and transgender women in Lima, Peru

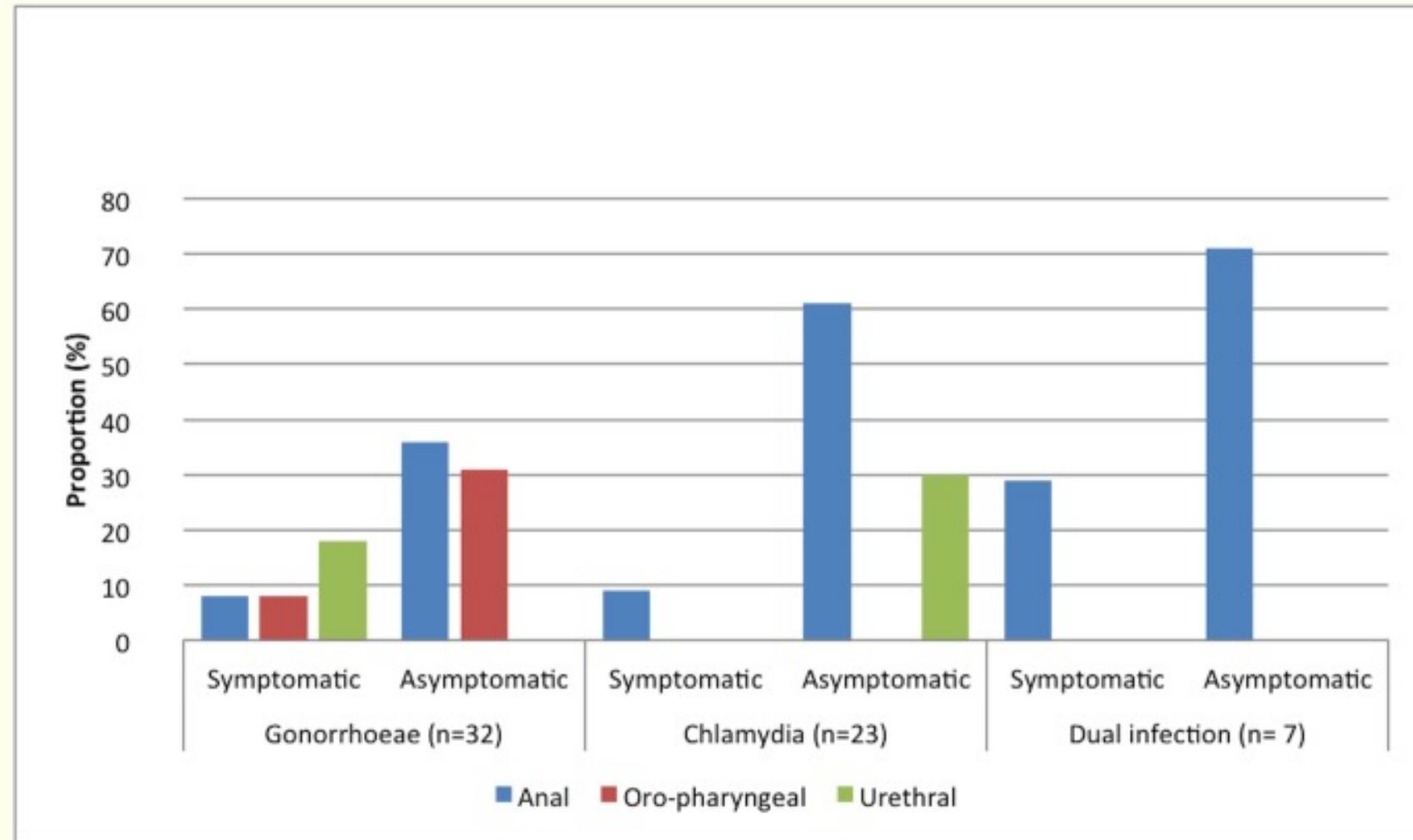
Allan-Blitz et al. Int J STD AIDS 2016



GC and CT infections among MSM in Cape Town, SA

Rebe K et al PLoS One 2015;10:e0138315

- 200 MSM
 - 57 (29%) symptoms
 - 10 (5%) urethral discharge
 - 26 (13%) oropharynx pain
 - 22 (11%) anal discharge or pain



Pharyngeal CT and GC Positivity among MSM – San Francisco 2010

TABLE 1. Pharyngeal Chlamydia and Gonorrhea Positivity Among Men Who Have Sex with Men, San Francisco, 2010

Clinical Site	N	CT Positivity (%)	95% CI (%)	GC Positivity (%)	95% CI (%)
HIV testing site	816	1.1	0.5–2.1	3.4	2.3–4.9
STD clinic	3949	2.3	1.8–2.8	7.0	6.2–7.9
Community clinics	505	1.4	0.6–2.8	4.0	2.4–6.1
Gay men's health center	6556	1.4	1.2–1.7	5.5	4.9–6.0
HIV care clinic	633	1.7	0.9–3.1	5.6	3.9–7.6

Park J, et al. Sentinel Surveillance for Pharyngeal Chlamydia and Gonorrhea Among Men Who Have Sex with Men – San Francisco, 2010. Sex Transm Dis 2012;39:482-484.

Prevalence and Incidence of Pharyngeal GC

- Project EXPLORE (MSM)
 - Prevalence 5.5%
 - Incidence 11.2/100 person-years

Prevalence and Incidence of Pharyngeal Gonorrhoea
in a Longitudinal Sample of Men Who Have Sex
with Men: The EXPLORE Study

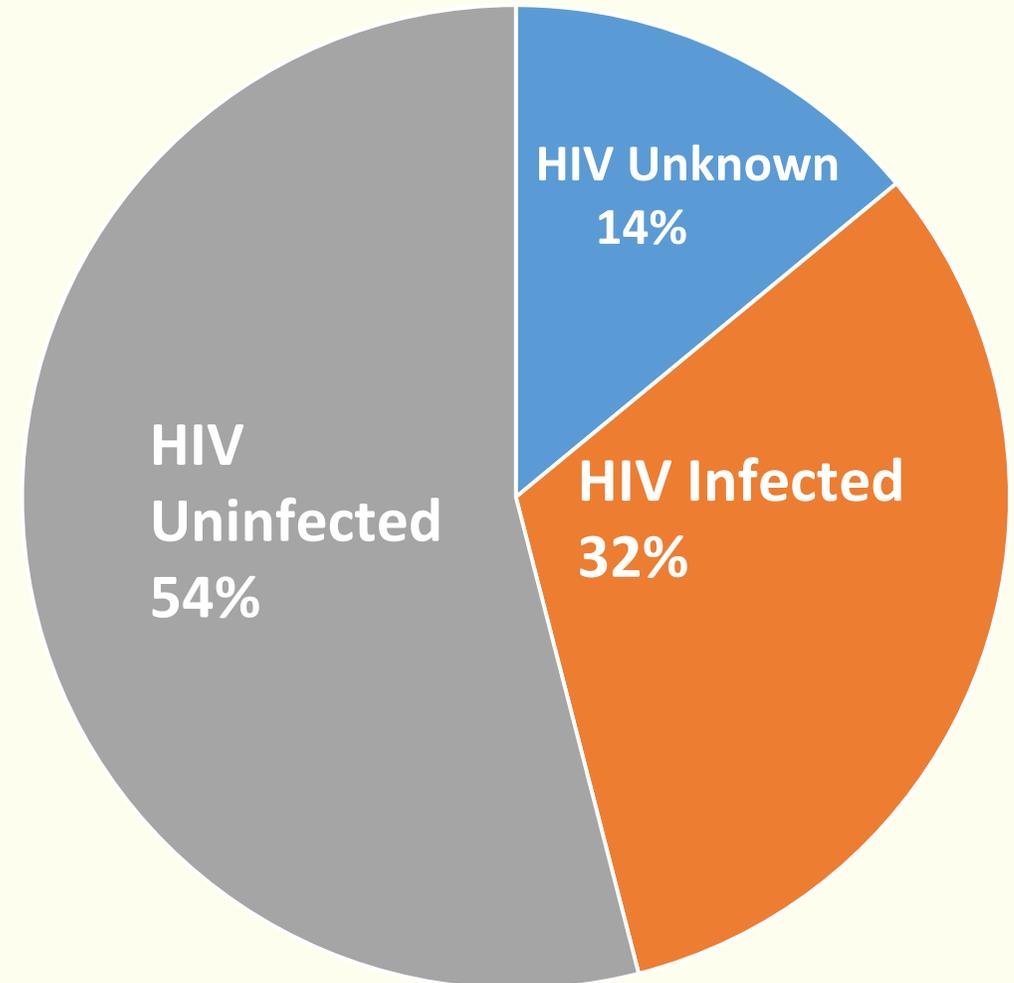
CID 2006;43:1284-1289

Sheldon R. Morris,¹ Jeffrey D. Klausner,² Susan P. Buchbinder,² Sarah L. Wheeler,² Beryl Koblin,⁴ Thomas Coates,³ Margaret Chesney,⁵ and Grant N. Colfax²

¹Department of Community and Family Medicine, University of California San Francisco, and ²San Francisco Department of Public Health, San Francisco, and ³University of California, Los Angeles, California; ⁴New York Blood Center, New York, New York; and ⁵National Center of Complementary and Alternative Medicine, Bethesda, Maryland

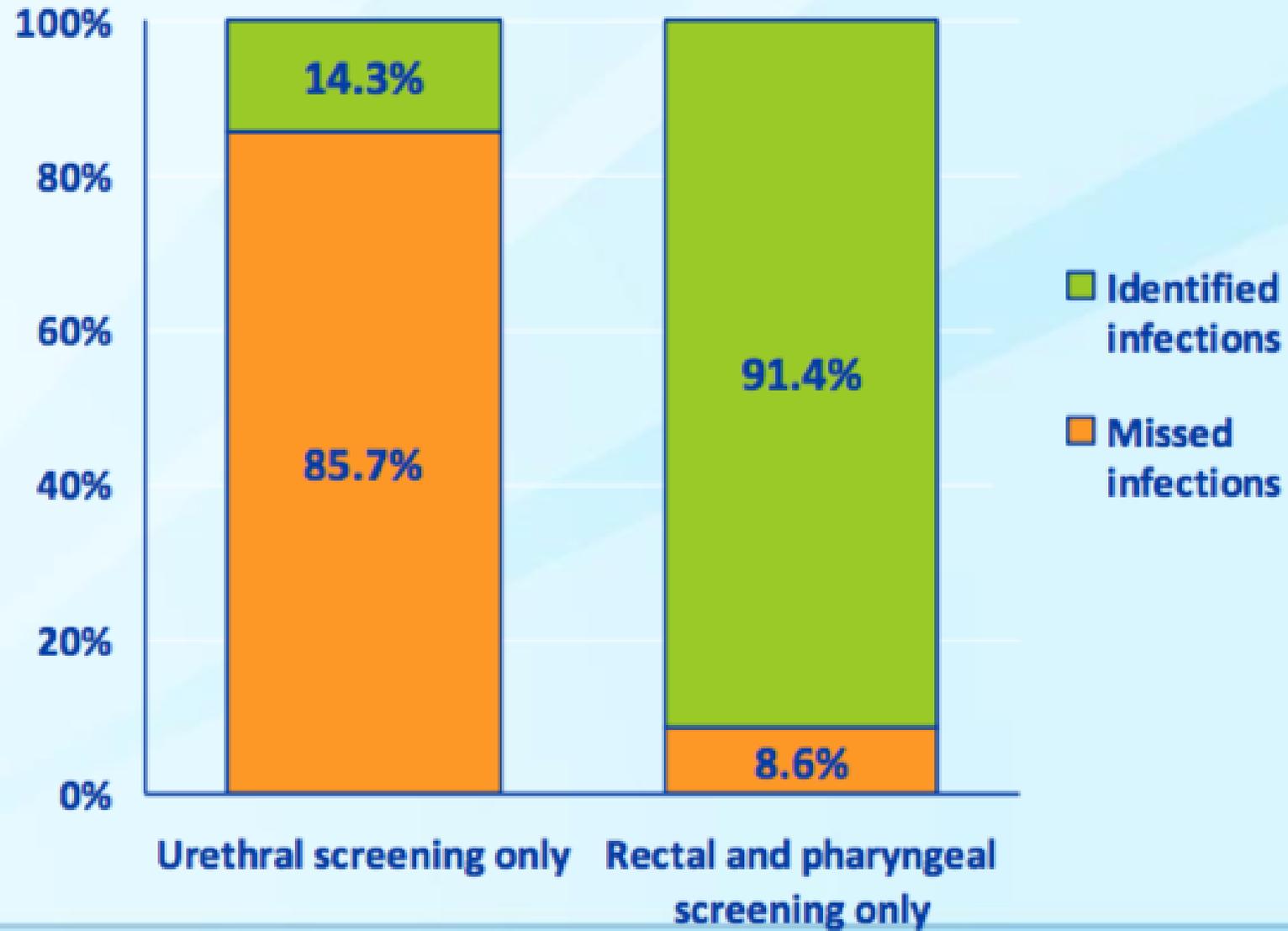
Rectal CT and GC by HIV Status: San Francisco STD Clinic, 2009

- HIV-infected at higher risk for rectal infections than HIV-uninfected
- RR CT = 1.7 (1.3-2.2)
- RR GC = 1.8 (1.3-2/5)



Rectal and pharyngeal screening
without urogenital screening?

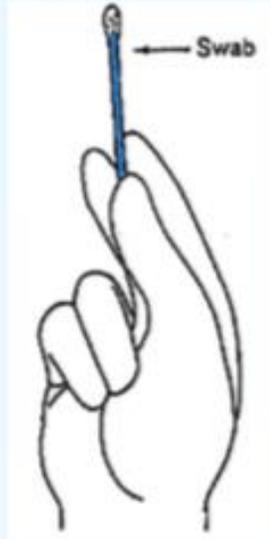
Proportion of chlamydial and gonococcal infections among asymptomatic men who have sex with men that would be identified and missed by different screening algorithms—San Francisco City Clinic, 2008–2009



2015 CDC STD Treatment Guidelines

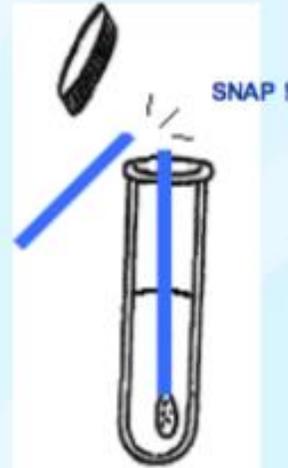
- Sexually active MSM should be screened at least annually for GC and CT at sites of exposure (urethra, rectum, pharynx*)
 - Pharyngeal CT screening not recommended
- MSM at increased risk should be screened every 3-6 months

Rectal Self-Swab Collection Instructions



Step 1.

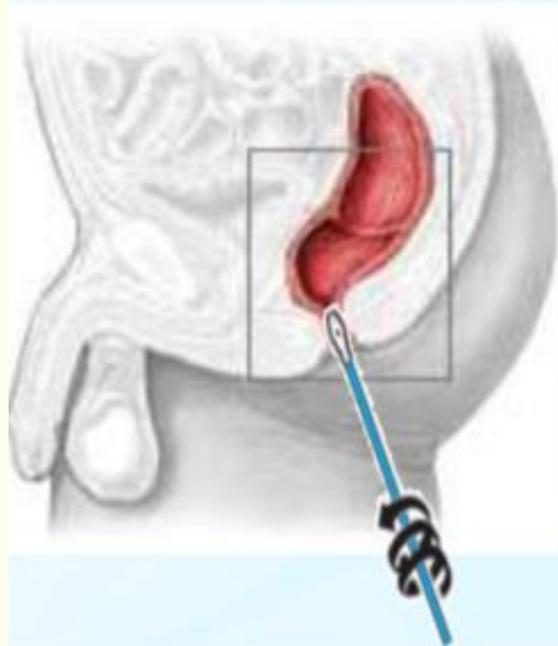
Open kit and remove tube and package with green writing. Remove the swab with the **BLUE** shaft. **USE BLUE SHAFT SWAB ONLY.**



Step 3.

Remove cap from test tube. Place swab in test tube. Do not puncture the foil cap.

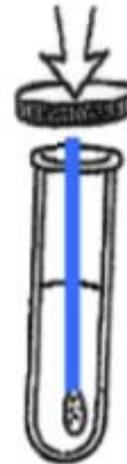
Break swab shaft at the score mark.



Step 2.

Insert swab 1 inch into the anus and turn for 5 – 10 seconds.

If needed, before inserting swab, wet swab with water or saline solution.



Step 4.

Put cap back tightly on test tube to prevent any leaking. Try not to splash the liquid out the tube.

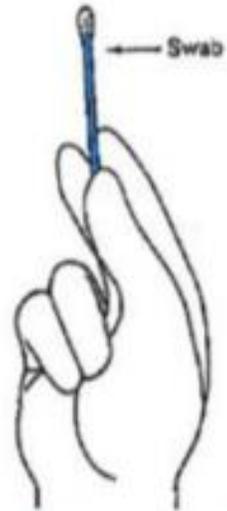
Step 5.

Discard wrapper and unused swab. **Wash your hands.** Return the tube to the health worker.

Pharyngeal Swab Collection Instructions



A landmark in prevention

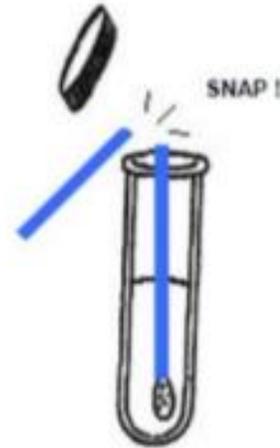


Step 1.

Open kit and remove tube and package with green writing. Remove the swab with the **BLUE** shaft. **USE BLUE SHAFT SWAB ONLY.**

Step 2.

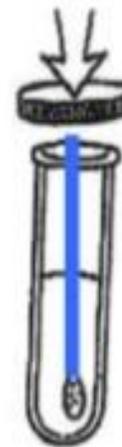
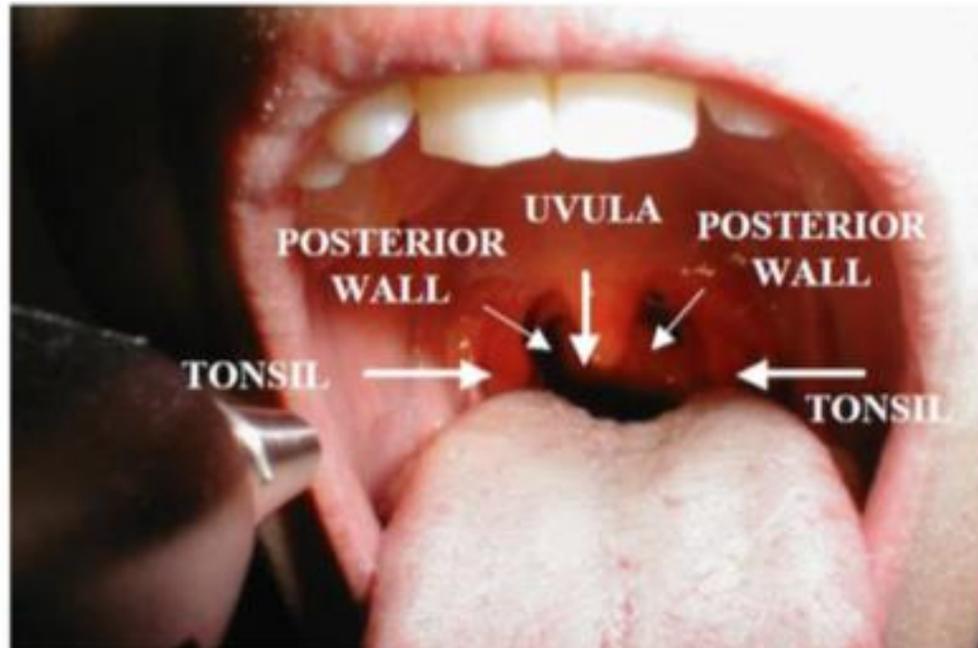
Instruct patient to open mouth widely. Be sure to make good contact with 5 key areas of the throat (See below).



Step 3.

Remove cap from test tube. Place swab in test tube. Do not puncture the foil cap.

Break swab shaft at the score mark.



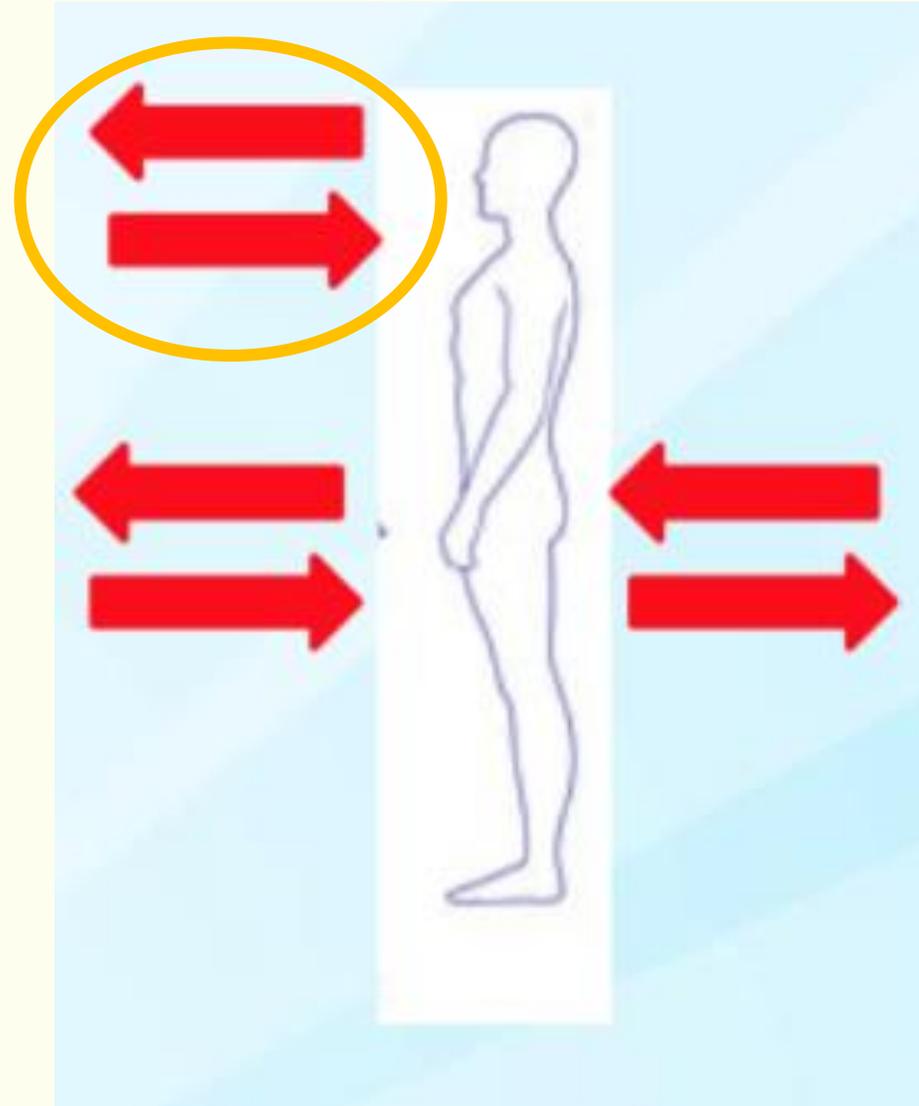
Step 4.

Put cap back tightly on test tube to prevent any leaking. Try not to splash the liquid out the tube.

Step 5.

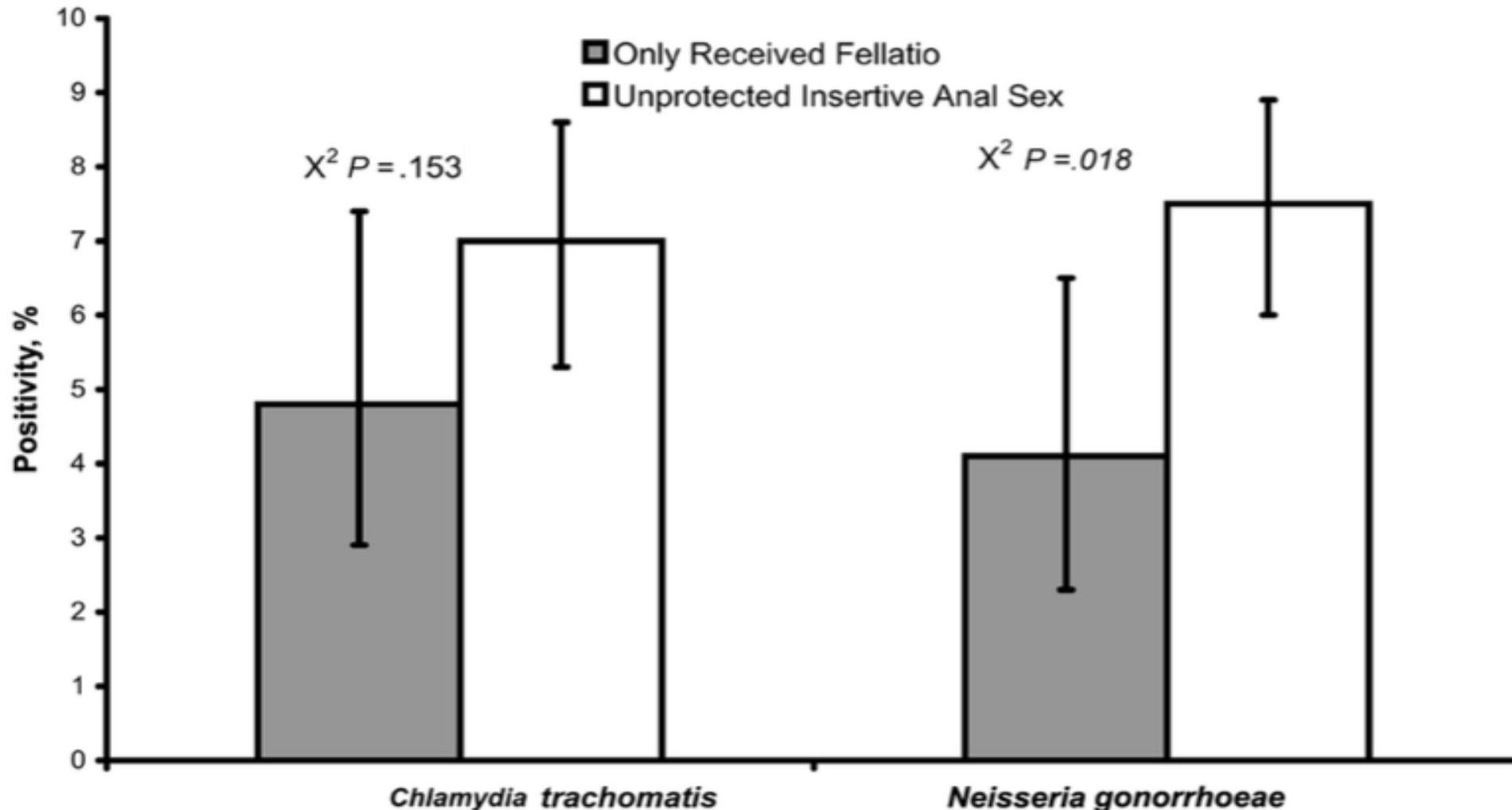
Discard wrapper and unused swab. **Wash your hands.**

Transmission Opportunities



Positivity of urethral CT and GC among MSM San Francisco City Clinic 2007

Bernstein CID 2009;49:1793



Positivity of Urethral CT and GC among MSW – San Francisco City Clinic 2006-10

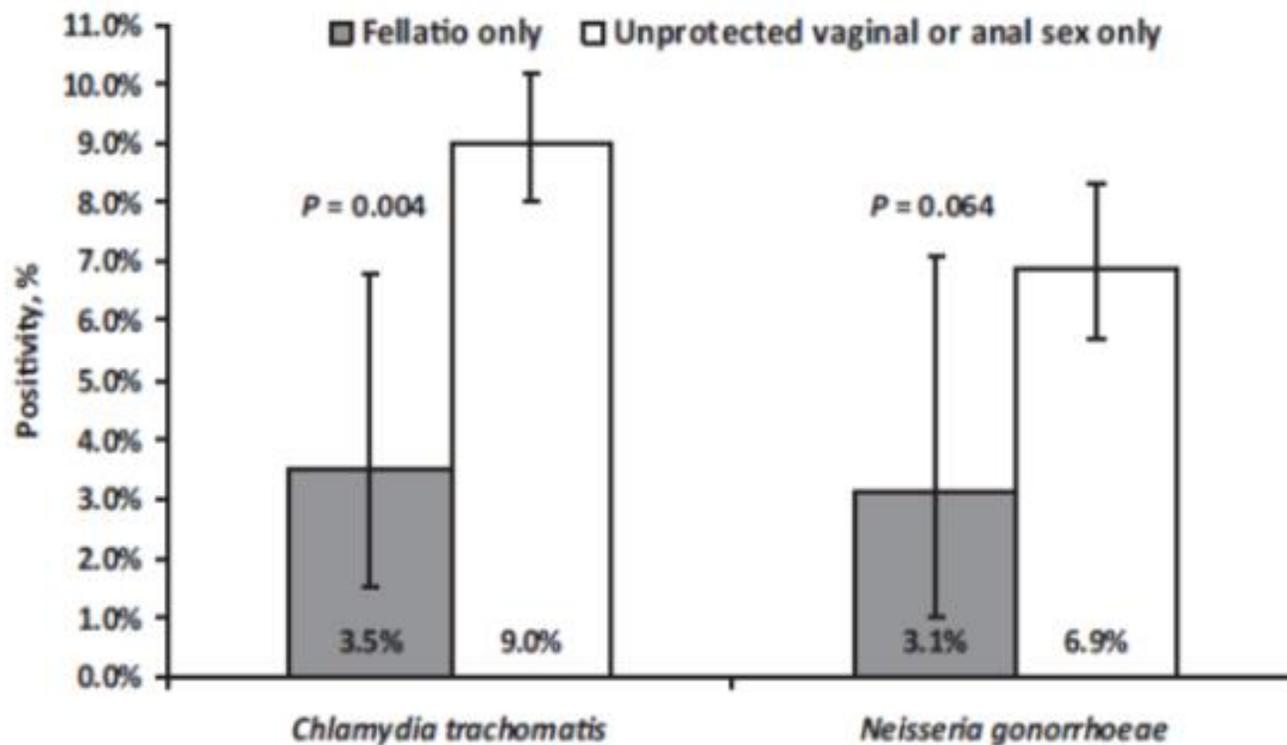


Figure 1. Urethral *Chlamydia trachomatis* and *Neisseria gonorrhoeae* positivity among men who have sex with women who visited the San Francisco City Clinic, 2006–2010.

Population Attributable Risk Percentage for Oropharyngeal Exposure, MSM Seattle 2001-13

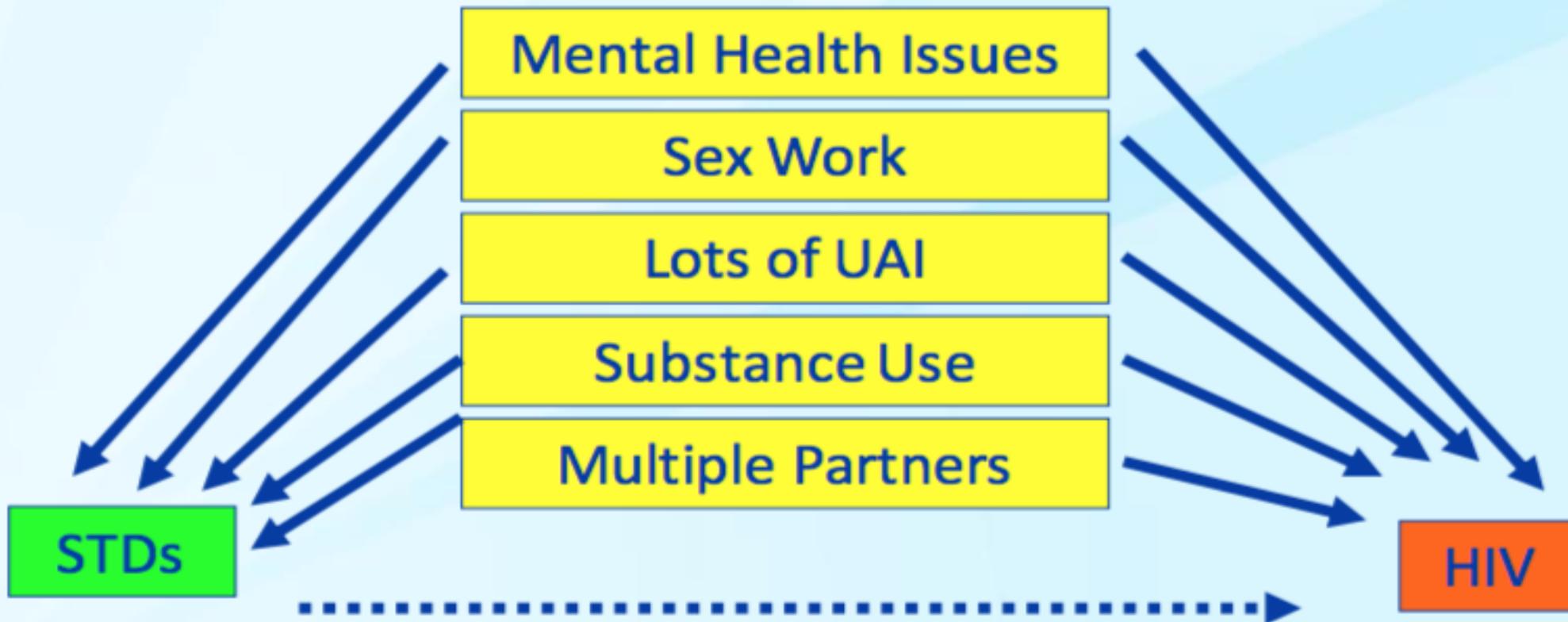
- **Case-control study of new patient MSM visits**
 - Case-MSM visits with urethritis
 - Control – MSM visits with no urethral infections
- **Gonococcal Urethritis – 33.8%**
- **Chlamydial urethritis – 2.7%**
- **Non-gonococcal, non-chlamydial urethritis – 27.1%**

Duration of Extragenital GC and CT Infections among MSM

- Pharyngeal GC – 114.1-137.8 days
- Rectal GC – 346.0 days
- Pharyngeal CT – 667.1 days
- Rectal CT – 578.7 days

Don't ask, won't tell
Don't look, won't find

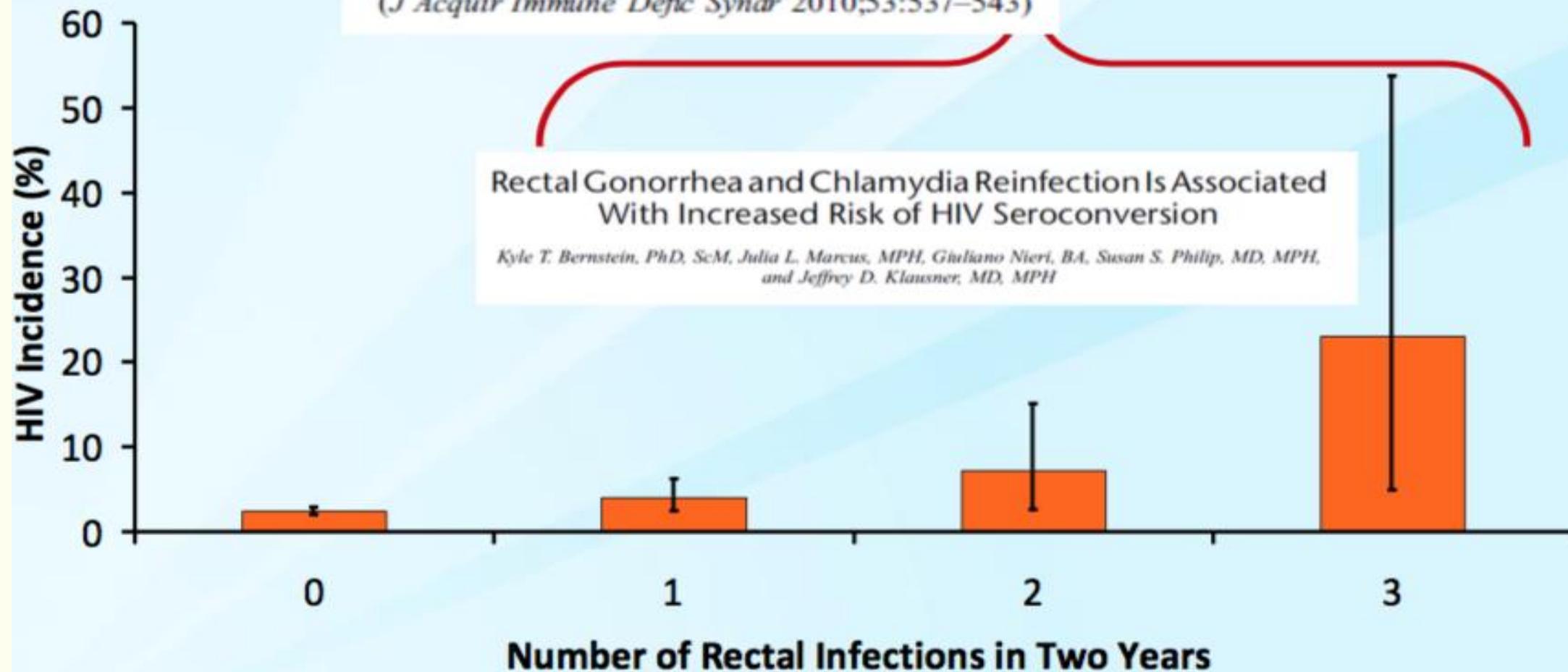
Are STDs Causally Associated with HIV?



Cumulative HIV Incidence Among HIV-uninfected MSM, San Francisco City Clinic

17.7%

(J Acquir Immune Defic Syndr 2010;53:537–543)



Bernstein KT, et al. Rectal Gonorrhea and chlamydia reinfection is associated with increased risk of HIV seroconversion. JAIDS 2010 Apr 1;53(4):537-43.

Do extragenital STDs → HIV?

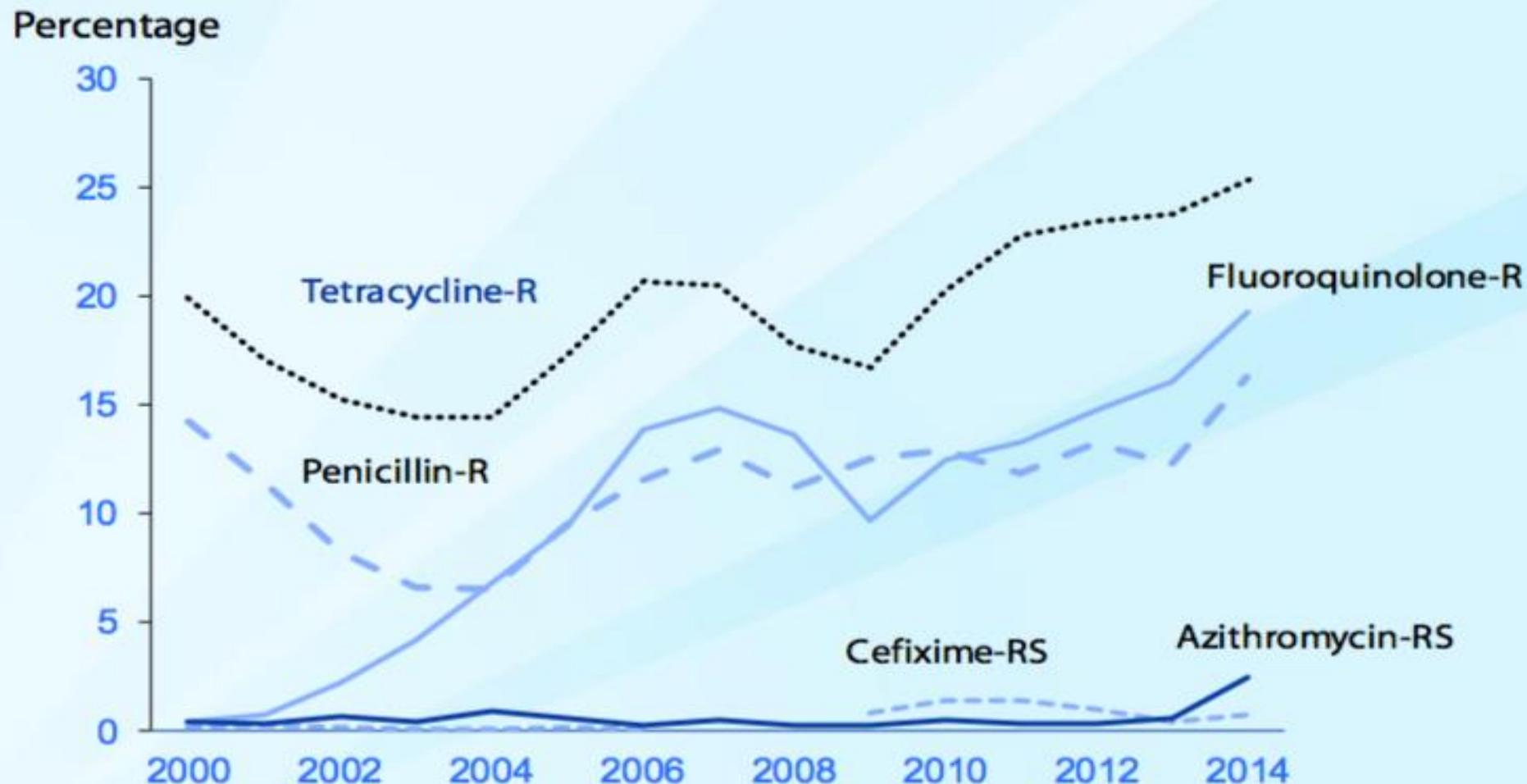
- We may never know
 - Randomized trial of infection or treatment of STDs = unethical!
 - Randomized trial of prophylactic treatment of bacterial STDs = unethical (?), abx resistance?
 - Marginal structural models of observational data
 - Every visit needs rectal STD testing and HIV testing
 - Sufficient number of HIV seroconversions for appropriately power analysis

Do extragenital STDs → HIV?

- Maybe it doesn't matter
 - If rectal STDs *cause* HIV, then preventing STDs is good HIV prevention
 - Even if rectal STDs *do not cause* HIV, MSM with rectal STDs are at higher risk for HIV
 - Way to identify high-risk subpopulations for intervention
 - Less subjective marker of risk than self-reported sexual or substance use behaviors

Extragenital GC and Antibiotic Resistance

Prevalence of resistance to penicillin, tetracycline or fluoroquinolone, or reduced cefixime or azithromycin susceptibility by year — Gonococcal Isolate Surveillance Project (GISP), United States, 2000–2014



Azithromycin Reduced Susceptibility (RS) = MIC $\geq 1 \mu\text{g/ml}$ (2000-2004); $\geq 2 \mu\text{g/ml}$ (2005-2014); Cefixime-RS = MIC $\geq 0.25 \mu\text{g/ml}$;
Fluoroquinolone Resistance (R) = Ciprofloxacin MIC $\geq 1 \mu\text{g/ml}$; Penicillin-R = MIC $\geq 2 \mu\text{g/ml}$ or β -lactamase positive; Tetracycline-R = MIC $\geq 2 \mu\text{g/ml}$

NOTE: Cefixime susceptibility not testing in 2007 and 2008

Unemo BMC Infectious Diseases 2015;15:364

Table 1 Characteristics of verified gonorrhoea treatment failures with ceftriaxone (250–1000 mg × 1) and causing gonococcal strain

Country, year	Ceftriaxone Therapy	Ceftriaxone MIC (mg/L)	$fT_{>MIC}$ hours ^a	MLST/NG-MAST	Site of failure	Final successful treatment
Australia (n = 2), 2007 [31]	250 mg × 1	0.016-0.03 (Agar dilution)	41.4-50.3	ND/ST5, ST2740	Pharynx	Ceftriaxone 500 mg × 1/ Ceftriaxone 1 g × 1
Japan (n = 1), 2009 [30]	1 g × 1	4.0 ^b (Etest, XDR)	0	ST7363/ST4220	Pharynx	None ^c
Sweden (n = 1), 2010 [34]	250 mg × 1 and 500 mg × 1	0.125-0.25 ^b (Etest)	15.6-32.8	ST1901/ST2958	Pharynx	Ceftriaxone 1 g × 1
Australia (n = 1), 2010 [32]	500 mg × 1	0.03-0.06 (Agar dilution)	41.3-49.9	ND/ST1407, ST4950 (genogroup 1407)	Pharynx	Azithromycin 2 g × 1
Slovenia (n = 1), 2011 [36]	250 mg × 1	0.125 ^b (Etest)	24.3	ST1901/ST1407 (genogroup 1407)	Pharynx	Ceftriaxone 250 mg × 1 plus azithromycin 1 g × 1
Australia (n = 2), 2011 [33]	500 mg × 1	0.03-0.06 (Agar dilution)	41.3-49.9	ST1901/ST225, new variant of ST225	Pharynx	Ceftriaxone 1 g × 1 plus azithromycin 2 g × 1 or Ceftriaxone 1 g × 1
Sweden (n = 3), 2013–2014 [35]	500 mg × 1	0.064-0.125 ^b (Etest)	32.8-41.3	ST1901/ST3149, ST3149, ST4706 (genogroup 1407)	Pharynx	Ceftriaxone 1 g × 1

^aSimulation of time of free ceftriaxone above MIC ($fT_{>MIC}$) based on mean pharmacokinetic parameter values. Data from Chisholm et al. [52]

^bGenetic cephalosporin resistance determinants (*penA*, *mtrR*, *penB*) elucidated [3, 5–8]

^cThe infection was considered to have resolved spontaneously within 3 months

MIC minimum inhibitory concentration, MLST multilocus sequence typing, NG-MAST *Neisseria gonorrhoeae* multi-antigen sequence typing, ND not determined, ST sequence type, XDR extensively drug-resistant [9]

A Phase 2 Trial of Oral Solithromycin 1200 mg or 1000 mg as Single-Dose Oral Therapy for Uncomplicated Gonorrhea

Edward W. Hook III,¹ Matthew Golden,² Brian D. Jamieson,³ Paula B. Dixon,¹ Hanne S. Harbison,¹ Sylvan Lowens,² and Prabhavathi Fernandes³

¹University of Alabama at Birmingham; ²University of Washington, Seattle; and ³Cempra Inc, Chapel Hill, North Carolina

- 58 participants enrolled and treated: 28 participants received 1200 mg of solithromycin and 31 received 1000 mg

Table 2. Microbiologic Outcomes Following Solithromycin Therapy for Uncomplicated Gonorrhea^a

Organism and Site	Solithromycin 1200 mg (n = 24)		Solithromycin 1000 mg (n = 22)	
	Culture	NAAT	Culture	NAAT
<i>Neisseria gonorrhoeae</i>				
Urogenital	22/0	23/2	20/0	20/4
Rectal	2/0	9/0	2/0	11/0
Throat	5/0	9/3	3/0	7/1
Total	29/0	41/5	25/0	37/5
<i>Chlamydia trachomatis</i>				
Urogenital	NA	8/1	NA	2/1
Rectal	NA	1/0	NA	1/0

Outcomes are shown as positive at enrollment/positive at follow-up.

Abbreviations: NA, not applicable; NAAT, nucleic acid amplification test.

^a Participants were tested at all potential sites of sexual exposure. Several participants had positive tests for *N. gonorrhoeae* or *C. trachomatis* at >1 site.

Future Directions

- **Estimates of population burden of disease outside of clinic-based convenience samples**
- **Epidemiology of sequelae of untreated extragenital infections**
 - Biome?
 - Immune response?
- **Role of extragenital GC in development of resistance**
- **Molecular epidemiology of GC**
- **Avenues of intervention**

GENITAL & EXTRA-GENITAL TESTING CAPACITY AT DHMH LABS - 2016

- NAAT tests (Chlamydia lab):
 - endocervical swabs
 - male urethral swabs
 - urine first void (male and female)
 - rectal swabs
- Culture tests (GC Lab):
 - Endocervix
 - Urethra
 - Conjunctival
 - Nasopharynx
 - throat
 - rectal

Thank you

