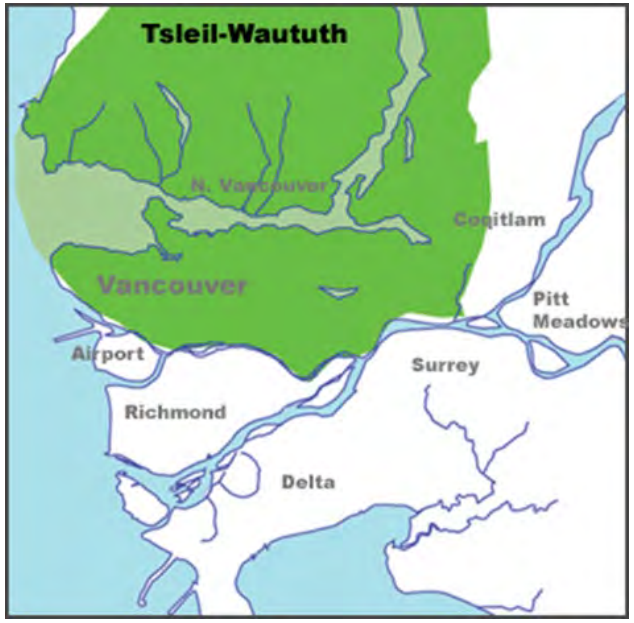
We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



Unveiling the latest in STI Updates and Navigating the Syphilis Surge

Sarah Malleson MBBS, CCFP

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January 24 2024

Disclosures

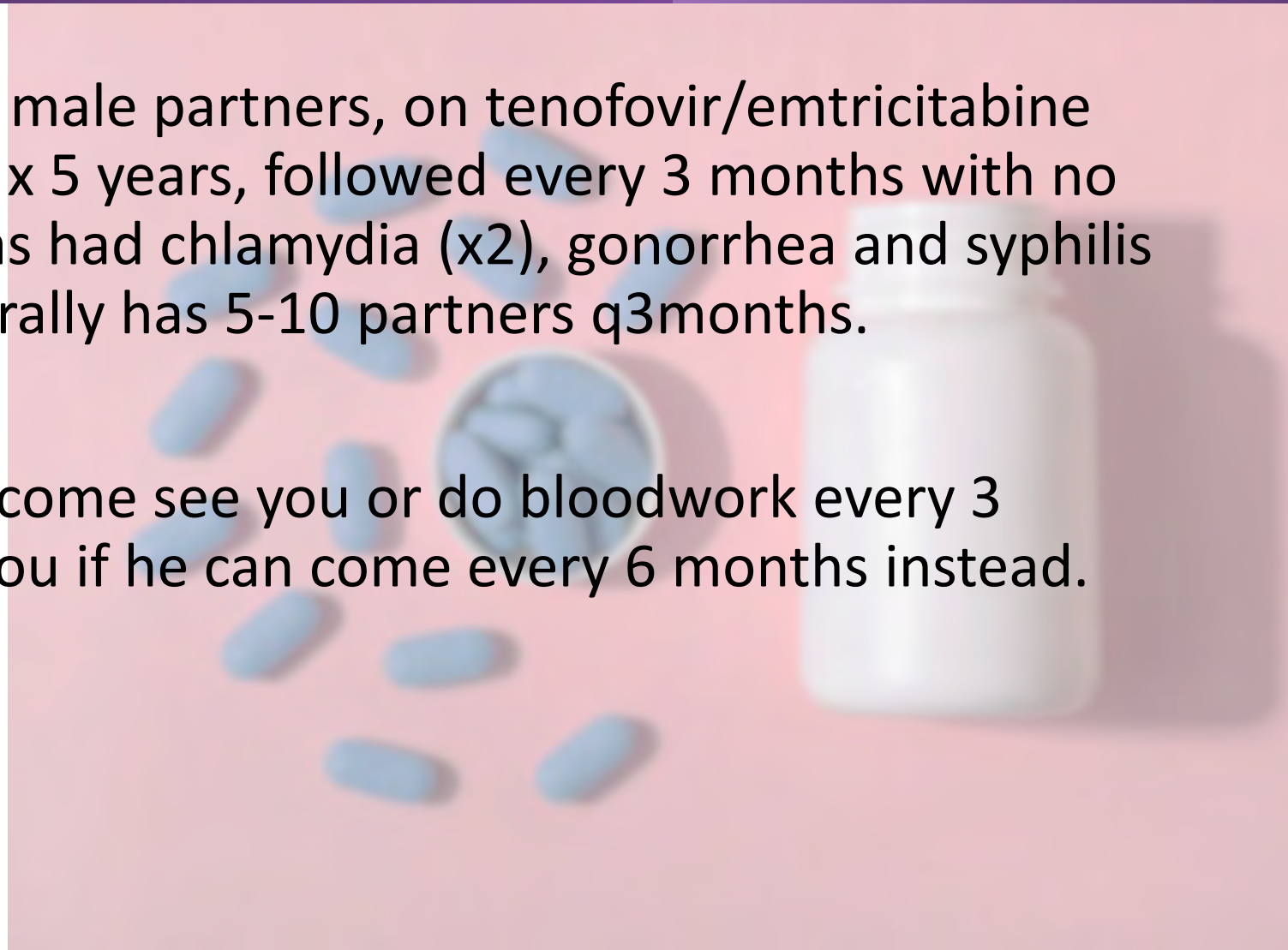
- No conflicts of interest to declare
- Slides developed with support of Dr. Troy Grennan
- ***I will be discussing the off-label use of doxycycline for STI prevention***

OBJECTIVES

- Reviewing the recommendations for screening of STIs
- Understanding the evolving treatment recommendations and challenges of chlamydia and gonorrhoea management
- DoxyPrEP/PEP – what you need to know
- Recognizing the changing epidemiology of the syphilis epidemic
- Reviewing testing, treatment and follow-up strategies to address the syphilis surge

STI TESTING: HOW OFTEN?

CASE 1

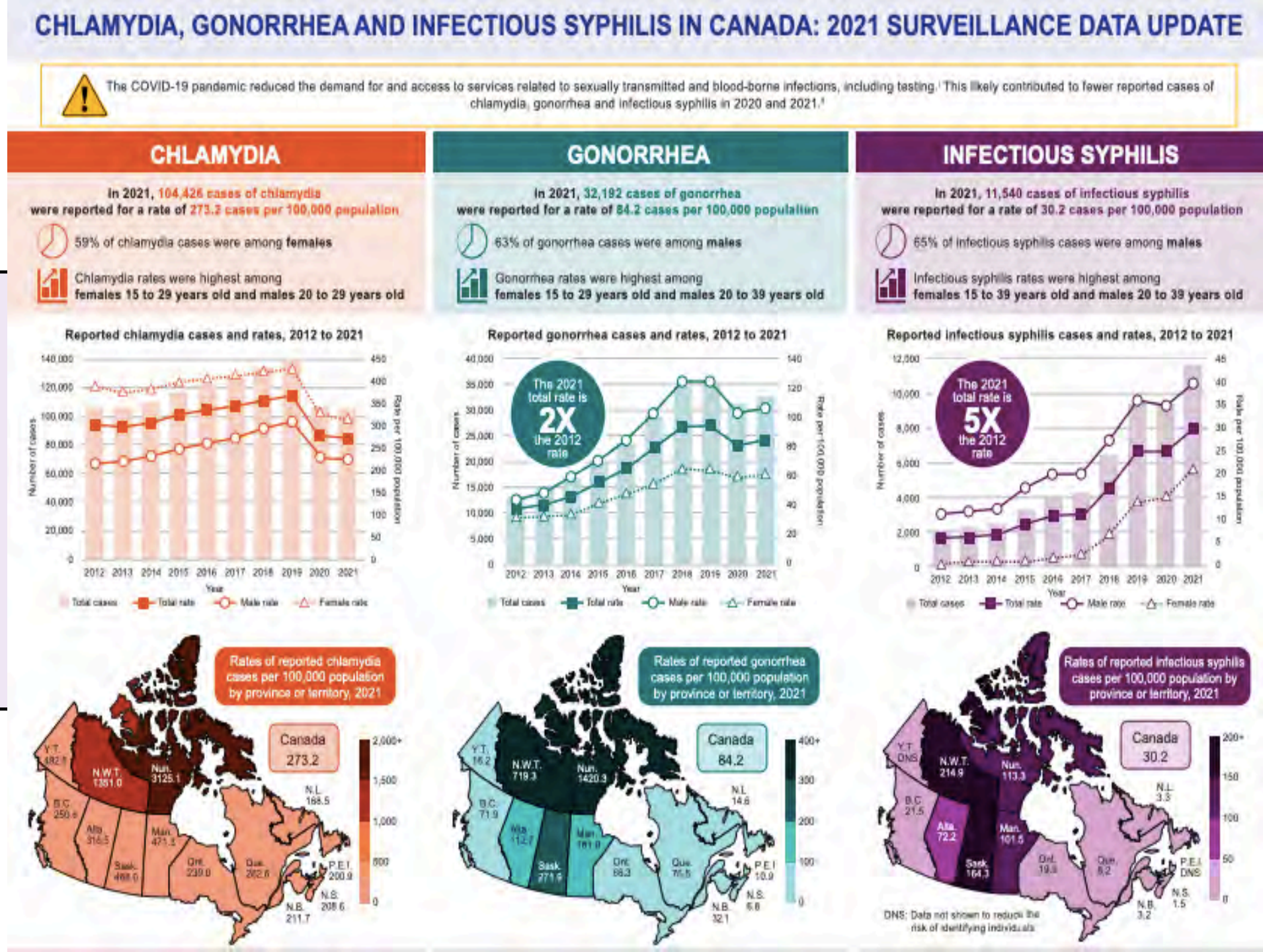


26-year-old male, with male partners, on tenofovir/emtricitabine (TDF/FTC) for HIV PrEP x 5 years, followed every 3 months with no issues. Stable eGFR. Has had chlamydia (x2), gonorrhea and syphilis in last two years. Generally has 5-10 partners q3months.

He no longer wants to come see you or do bloodwork every 3 months and is asking you if he can come every 6 months instead.

What do you think?

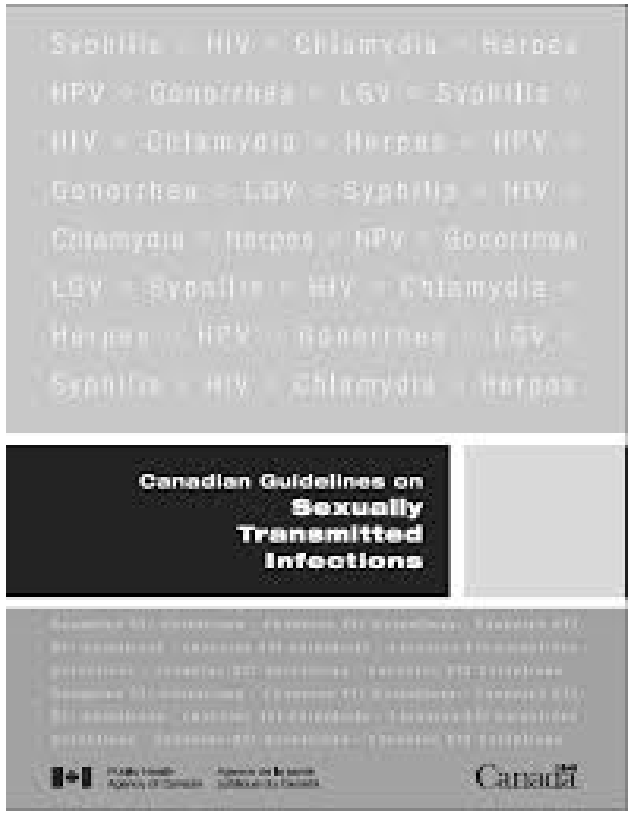
Increases of ***26% in chlamydia***, ***171% in gonorrhea***, and ***389% in syphilis*** in last decade.

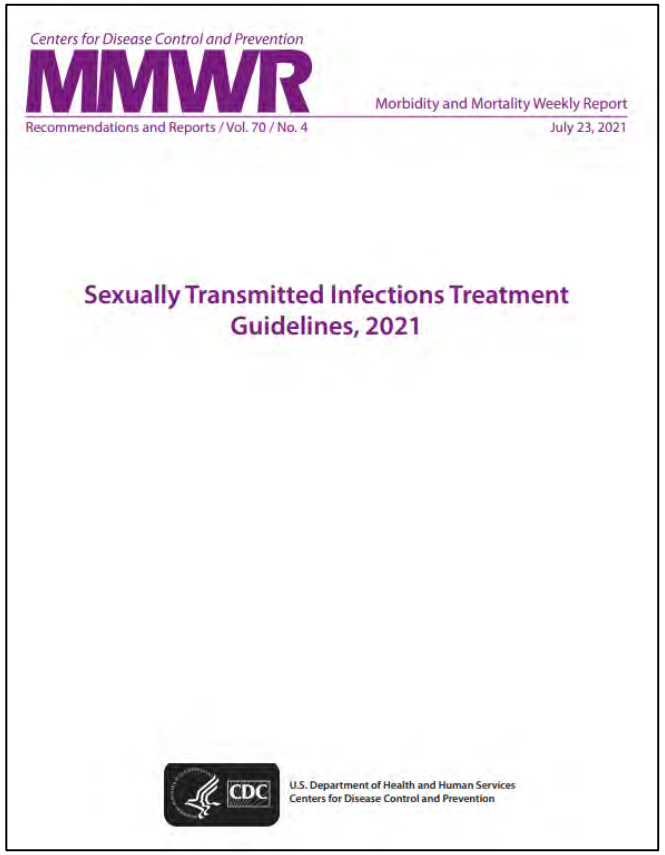


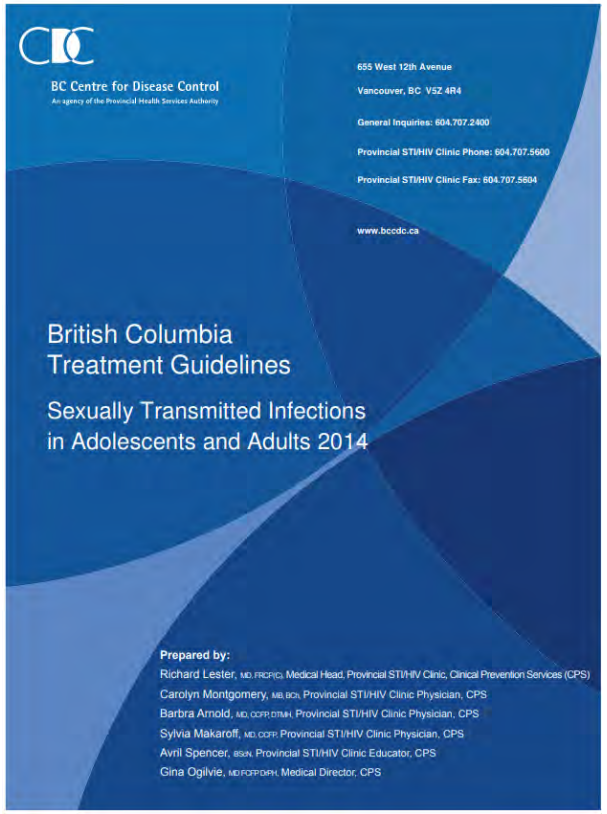
STI testing frequency: Why is this important?

- Rates of bacterial STIs in BC and elsewhere are **increasing significantly**
- Frequent testing could be an **effective STI control strategy**
  - Earlier diagnosis
  - Earlier treatment
  - Decreased onward transmission
  - Reduced morbidity

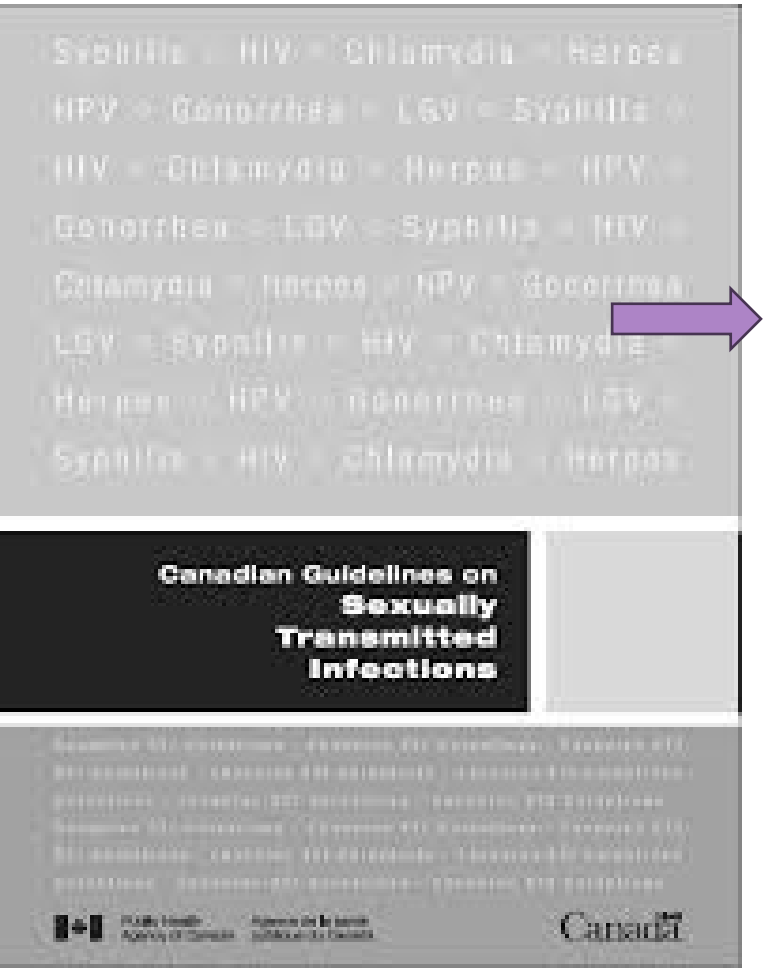
STI Guidelines: What do they say about testing frequency?







Canadian Guidelines

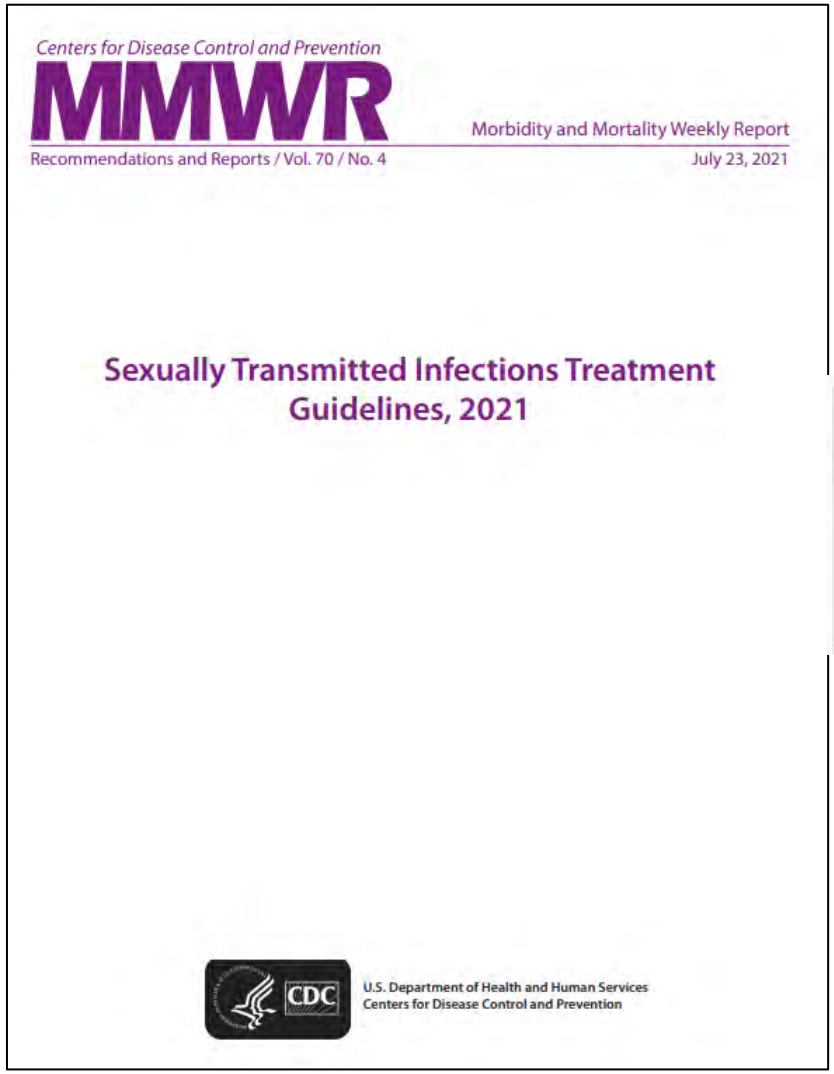


11. Following up

Ideally, follow-up should be conducted by the same health care provider to ensure resolution of symptoms, follow-up testing as indicated and follow-through on partner notification to reduce the likelihood of reinfection. Where this is not possible, patients should be directed to the appropriate community resources, counselled on when to get follow-up (especially if tests were done) and advised of indicators of treatment failure. (See infection-specific chapters for follow-up recommendations.)

For individuals identified at ongoing risk for STIs, recommend screening for gonorrhea, chlamydia, syphilis and HIV at 3-month intervals and reinforce safer sexual practices.

US CDC Guidelines, 2021



Men Who Have Sex With Men	• At least annually for sexually active MSM at sites of contact (urethra, rectum) regardless of condom use[2] • Every 3 to 6 months if at increased risk (i.e., MSM on PrEP, with HIV infection, or if they or their sex partners have multiple partners)[2]

Is there any evidence to support specific testing frequency?

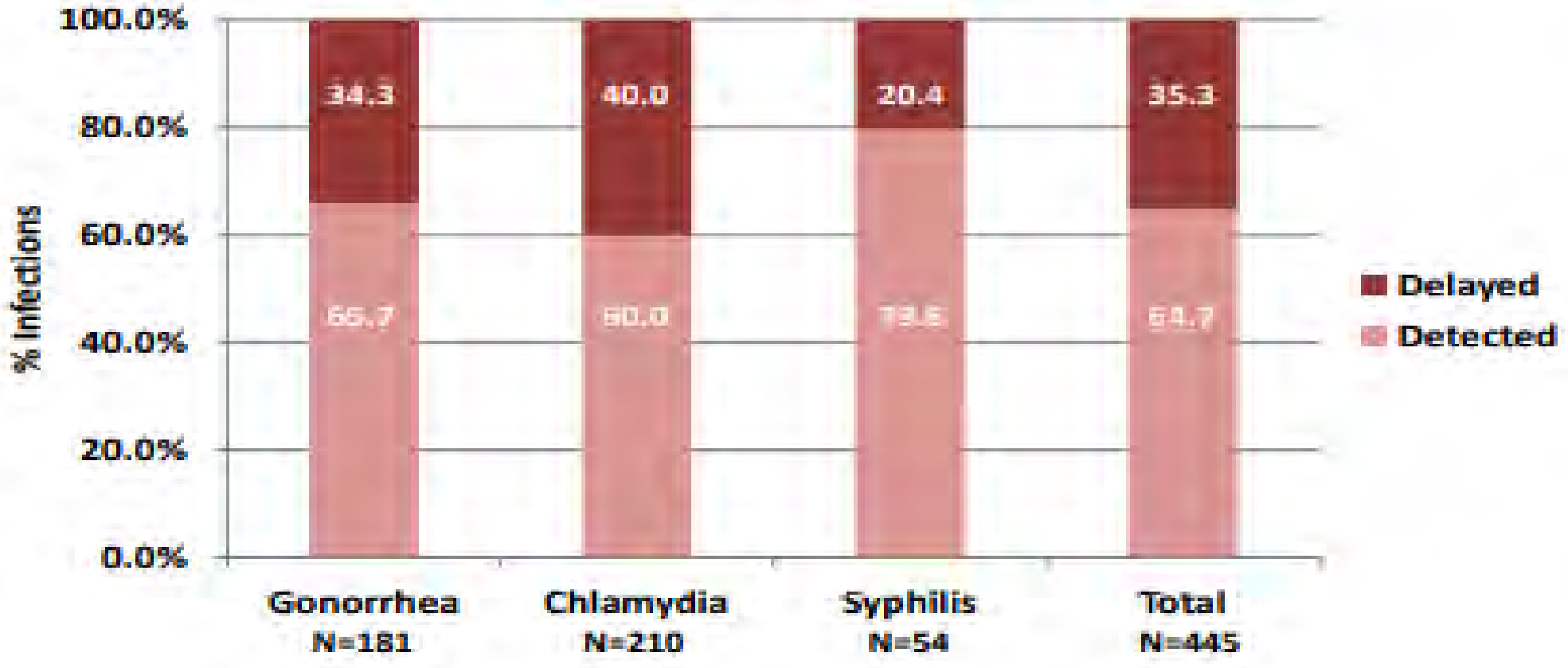
Quarterly Screening Optimizes STI Detection Among PrEP Users in the Demo Project

Stephanie E. Cohen, MD, MPH[1,2]; Eric Vittinghoff, PhD[2]; Susan S. Philip, MD, MPH[1,2]; Susanne Doblecki-Lewis, MD[3]; Oliver Bacon, MD, MPH[1,2]; Wairimu Chege, MD, MPH[4]; Richard Elion, MD[5,6]; Susan Buchbinder, MD[1,2]; Michael A. Kolber, PhD, MD[3]; Albert Y. Liu, MD, MPH[1,2]
[1]San Francisco Department of Public Health; [2]University of California, San Francisco;
[3]University of Miami, Miller School of Medicine; [4]National Institutes of Health, Division of AIDS; [5]Whitman-Walker Health; [6]Washington DC, Department of Health

- **Objective:** To determine the percent of gonorrhea (GC), chlamydia (CT), and syphilis infections for which treatment would have been delayed without quarterly (q3mo) screening.

Results

Figure 1. Percent infections for which treatment would have been delayed with q6 month, as opposed to q3 month, screening



Other not “high-risk” individuals

GUIDELINE CPD

Recommendation on screening for chlamydia and gonorrhea in primary care for individuals not known to be at high risk

Ainsley Moore MD MSc, Gregory Traversy MSc, Donna L. Reynolds MD MSc, John J. Riva DC PhD, Guylène Thériault MD, Brenda J. Wilson MB ChB MSc MRCP (UK), Melissa Subnath MSc, Brett D. Thombs PhD; for the Canadian Task Force on Preventive Health Care

■ Cite as: *CMAJ* 2021 April 19;193:E549-59. doi: 10.1503/cmaj.201967

CMAJ Podcasts: author interview at www.cmaj.ca/lookup/doi/10.1503/cmaj.201967/tab-related-content

The guideline is available in French at www.cmaj.ca/lookup/doi/10.1503/cmaj.201967-f; see related article at www.cmaj.ca/lookup/doi/10.1503/cmaj.210604

- Target population: asymptomatic individuals not clearly belonging to a category with elevated STI risk
- Conditional recommendation, very-low certainty evidence:
  - *Screen sexually active individuals <30y for chlamydia and gonorrhea opportunistically at primary care visits*

Canadian Task Force on Preventive Health Care

Key Recommendation

•*We recommend **opportunistic screening of sexually active individuals under 30 years of age** who are not known to belong to a high-risk group, annually, for chlamydia and gonorrhea at primary care visits, using a self- or clinician-collected sample*

Syphilis Screening

Executive Summary on Syphilis Screening, PHAC, 2023

Sexually active adults and adolescents

Screen all sexually active persons with a new or multiple partners, and/or upon request of the individual. Screening **every 3 to 6 months** is recommended in individuals with multiple partners.

High prevalence groups and communities

Due to stigma and prior negative experiences with the healthcare system, patients may not be fully transparent when discussing their sexual health. Health care providers should consider implementing an "opt-out" approach to screening to remove the need for an in-depth discussion on the person's sexual history. These programs have experienced greater success compared to "opt-in" programs in certain settings. Applying opt-out programs normalize STBBI screening and can help reduce stigma related to sexual health.

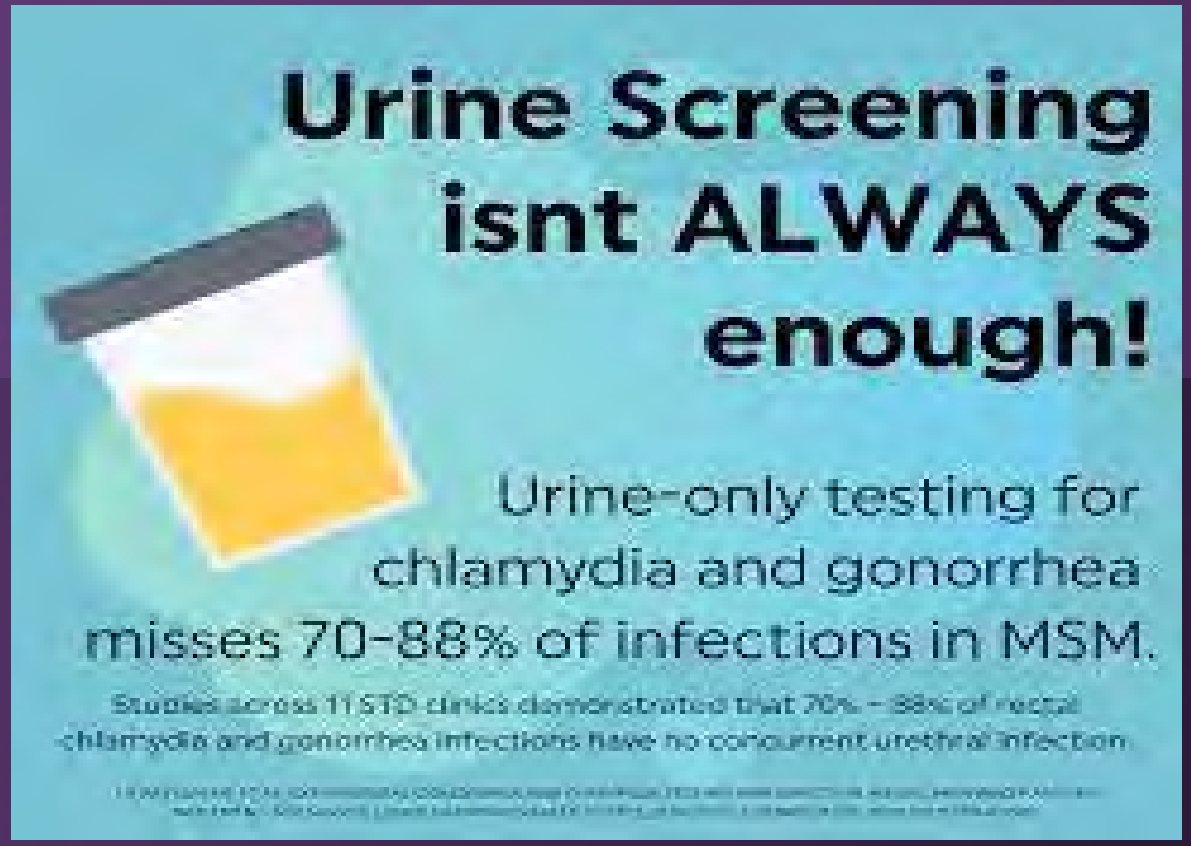
Targeted "opt-out" screening programs should be considered as frequently as every 3 months when serving population groups and/or communities experiencing high prevalence of syphilis (and other STBBI), such as:

- Gay, bisexual, and other men who have sex with men
- People living with HIV
- Person who is or has been incarcerated
- People who use substances and/or access addiction services
- Some Indigenous communities

It is important to consider aligning screening with other health services ("opportunistic screening") for individuals living with HIV and other individuals at increased risk accessing care services. Opportunistic screening is defined as offering screening when an individual is accessing non-emergency health services and has not undergone recent STBBI testing.

Consider local epidemiology when determining which groups/communities to target and for a specific individual, travel history and patient risk factors need to be considered [2].

How important are extragenital sites when screening for STIs?



Case 2

36-year-old healthy female, married to a male partner. Attends swinger parties 2-3 times per month; generally has 3-5 male partners per month (aside from husband).

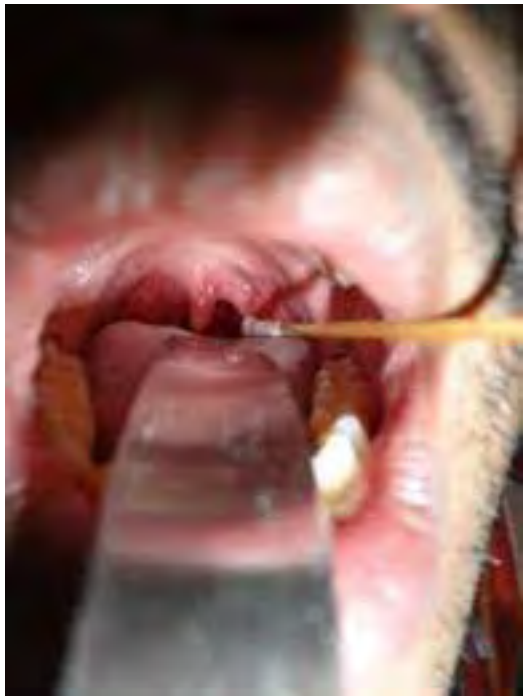
You see her for her quarterly STI screening and she reports no symptoms. You have her do a vaginal self-swab for CT/GC NAAT and draw blood for HIV and syphilis.

By not doing pharyngeal or rectal swabs, how much CT and GC are you potentially missing?

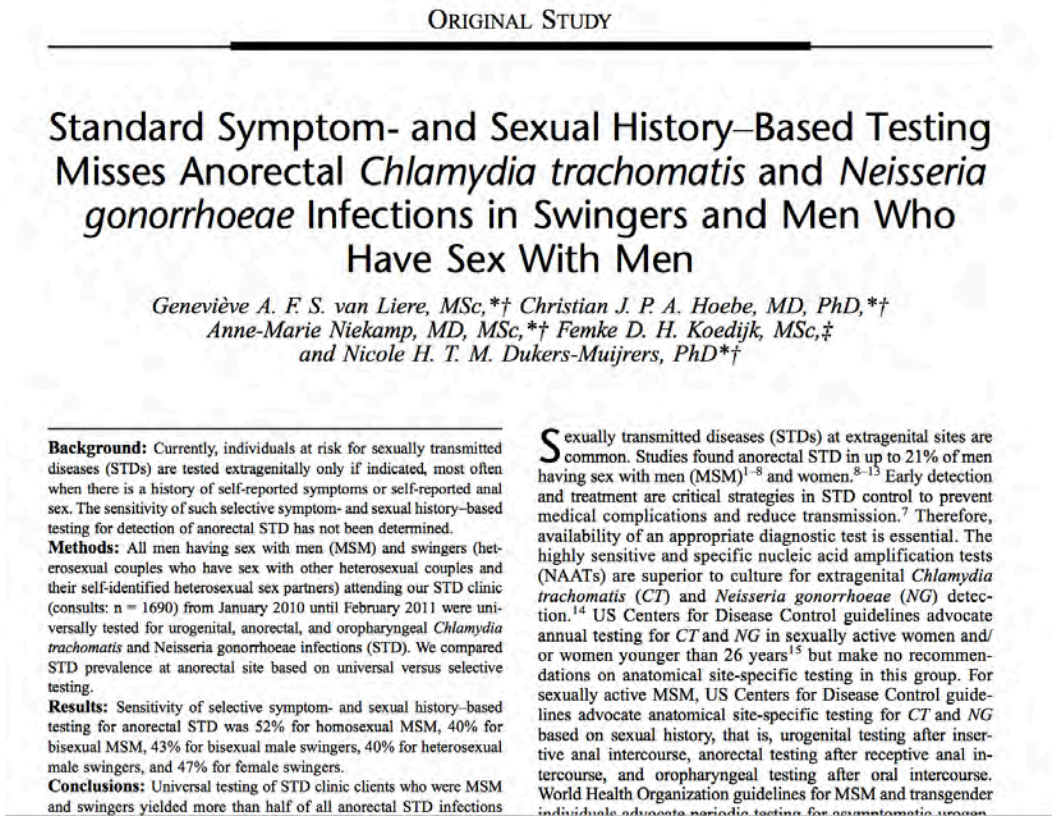
1. 10%
2. 25%
3. 50%
4. 75%
5. 90%

Extra-genital Sites : Why should we care?

- These sites are often asymptomatic
- Can increase HIV risk
- Treatment can be slightly more challenging
  - E.g. tissue penetration of drug
- May act as a reservoir for antimicrobial resistance



Is it really *that* important to test rectal and throat samples in asymptomatic MSM?



ORIGINAL STUDY

Standard Symptom- and Sexual History–Based Testing Misses Anorectal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Infections in Swingers and Men Who Have Sex With Men

Geneviève A. F. S. van Liere, MSc,† Christian J. P. A. Hoebe, MD, PhD,*† Anne-Marie Niekamp, MD, MSc,*† Femke D. H. Koedijk, MSc,‡ and Nicole H. T. M. Dukers-Muijrers, PhD*†*

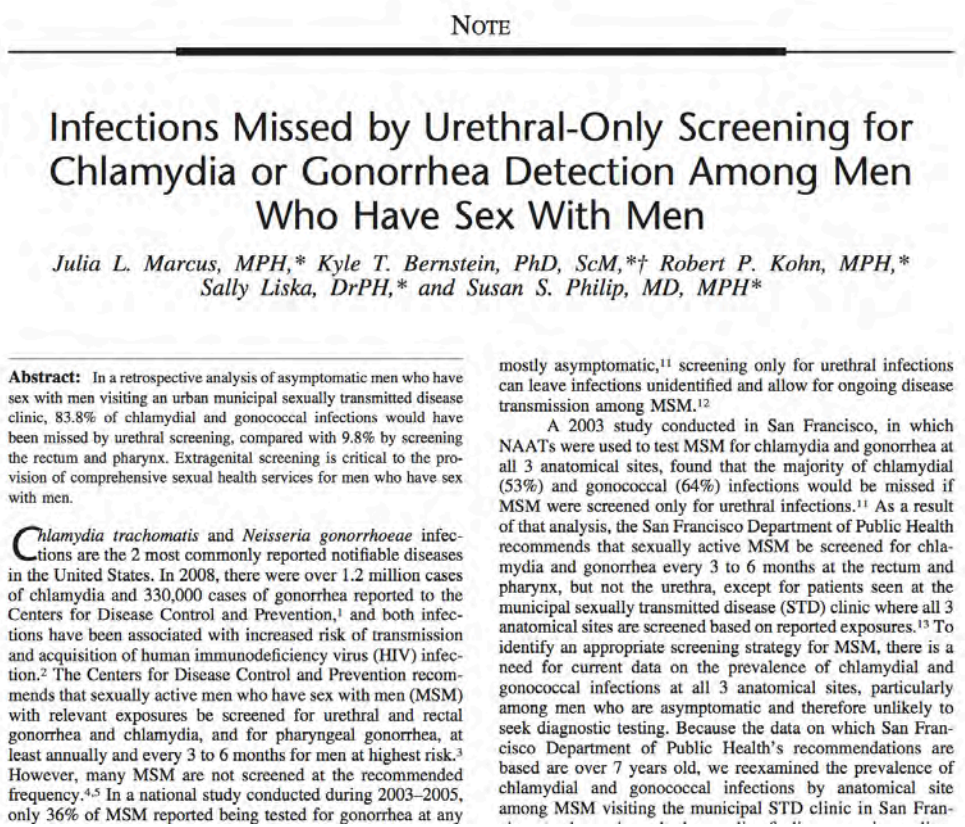
Background: Currently, individuals at risk for sexually transmitted diseases (STDs) are tested extragenitally only if indicated, most often when there is a history of self-reported symptoms or self-reported anal sex. The sensitivity of such selective symptom- and sexual history–based testing for detection of anorectal STD has not been determined.

Methods: All men having sex with men (MSM) and swingers (heterosexual couples who have sex with other heterosexual couples and their self-identified heterosexual sex partners) attending our STD clinic (consults: n = 1690) from January 2010 until February 2011 were universally tested for urogenital, anorectal, and oropharyngeal *Chlamydia trachomatis* and Neisseria gonorrhoeae infections (STD). We compared STD prevalence at anorectal site based on universal versus selective testing.

Results: Sensitivity of selective symptom- and sexual history–based testing for anorectal STD was 52% for homosexual MSM, 40% for bisexual MSM, 43% for bisexual male swingers, 40% for heterosexual male swingers, and 47% for female swingers.

Conclusions: Universal testing of STD clinic clients who were MSM and swingers yielded more than half of all anorectal STD infections

Sexually transmitted diseases (STDs) at extragenital sites are common. Studies found anorectal STD in up to 21% of men having sex with men (MSM)[1–8] and women.[8–13] Early detection and treatment are critical strategies in STD control to prevent medical complications and reduce transmission.[7] Therefore, availability of an appropriate diagnostic test is essential. The highly sensitive and specific nucleic acid amplification tests (NAATs) are superior to culture for extragenital *Chlamydia trachomatis* (*CT*) and *Neisseria gonorrhoeae* (*NG*) detection.[14] US Centers for Disease Control guidelines advocate annual testing for *CT* and *NG* in sexually active women and/or women younger than 26 years[15] but make no recommendations on anatomical site-specific testing in this group. For sexually active MSM, US Centers for Disease Control guidelines advocate anatomical site-specific testing for *CT* and *NG* based on sexual history, that is, urogenital testing after insertive anal intercourse, anorectal testing after receptive anal intercourse, and oropharyngeal testing after oral intercourse. World Health Organization guidelines for MSM and transgender individuals advocate periodic testing for asymptomatic urogen-



NOTE

Infections Missed by Urethral-Only Screening for Chlamydia or Gonorrhea Detection Among Men Who Have Sex With Men

Julia L. Marcus, MPH, Kyle T. Bernstein, PhD, ScM,*† Robert P. Kohn, MPH,* Sally Liska, DrPH,* and Susan S. Philip, MD, MPH**

Abstract: In a retrospective analysis of asymptomatic men who have sex with men visiting an urban municipal sexually transmitted disease clinic, 83.8% of chlamydial and gonococcal infections would have been missed by urethral screening, compared with 9.8% by screening the rectum and pharynx. Extragenital screening is critical to the provision of comprehensive sexual health services for men who have sex with men.

Chlamydia trachomatis and *Neisseria gonorrhoeae* infections are the 2 most commonly reported notifiable diseases in the United States. In 2008, there were over 1.2 million cases of chlamydia and 330,000 cases of gonorrhea reported to the Centers for Disease Control and Prevention,[1] and both infections have been associated with increased risk of transmission and acquisition of human immunodeficiency virus (HIV) infection.[2] The Centers for Disease Control and Prevention recommends that sexually active men who have sex with men (MSM) with relevant exposures be screened for urethral and rectal gonorrhea and chlamydia, and for pharyngeal gonorrhea, at least annually and every 3 to 6 months for men at highest risk.[3] However, many MSM are not screened at the recommended frequency.[4,5] In a national study conducted during 2003–2005, only 36% of MSM reported being tested for gonorrhea at any mostly asymptomatic,[11] screening only for urethral infections can leave infections unidentified and allow for ongoing disease transmission among MSM.[12]

A 2003 study conducted in San Francisco, in which NAATs were used to test MSM for chlamydia and gonorrhea at all 3 anatomical sites, found that the majority of chlamydial (53%) and gonococcal (64%) infections would be missed if MSM were screened only for urethral infections.[11] As a result of that analysis, the San Francisco Department of Public Health recommends that sexually active MSM be screened for chlamydia and gonorrhea every 3 to 6 months at the rectum and pharynx, but not the urethra, except for patients seen at the municipal sexually transmitted disease (STD) clinic where all 3 anatomical sites are screened based on reported exposures.[13] To identify an appropriate screening strategy for MSM, there is a need for current data on the prevalence of chlamydial and gonococcal infections at all 3 anatomical sites, particularly among men who are asymptomatic and therefore unlikely to seek diagnostic testing. Because the data on which San Francisco Department of Public Health's recommendations are based are over 7 years old, we reexamined the prevalence of chlamydial and gonococcal infections by anatomical site among MSM visiting the municipal STD clinic in San Fran-

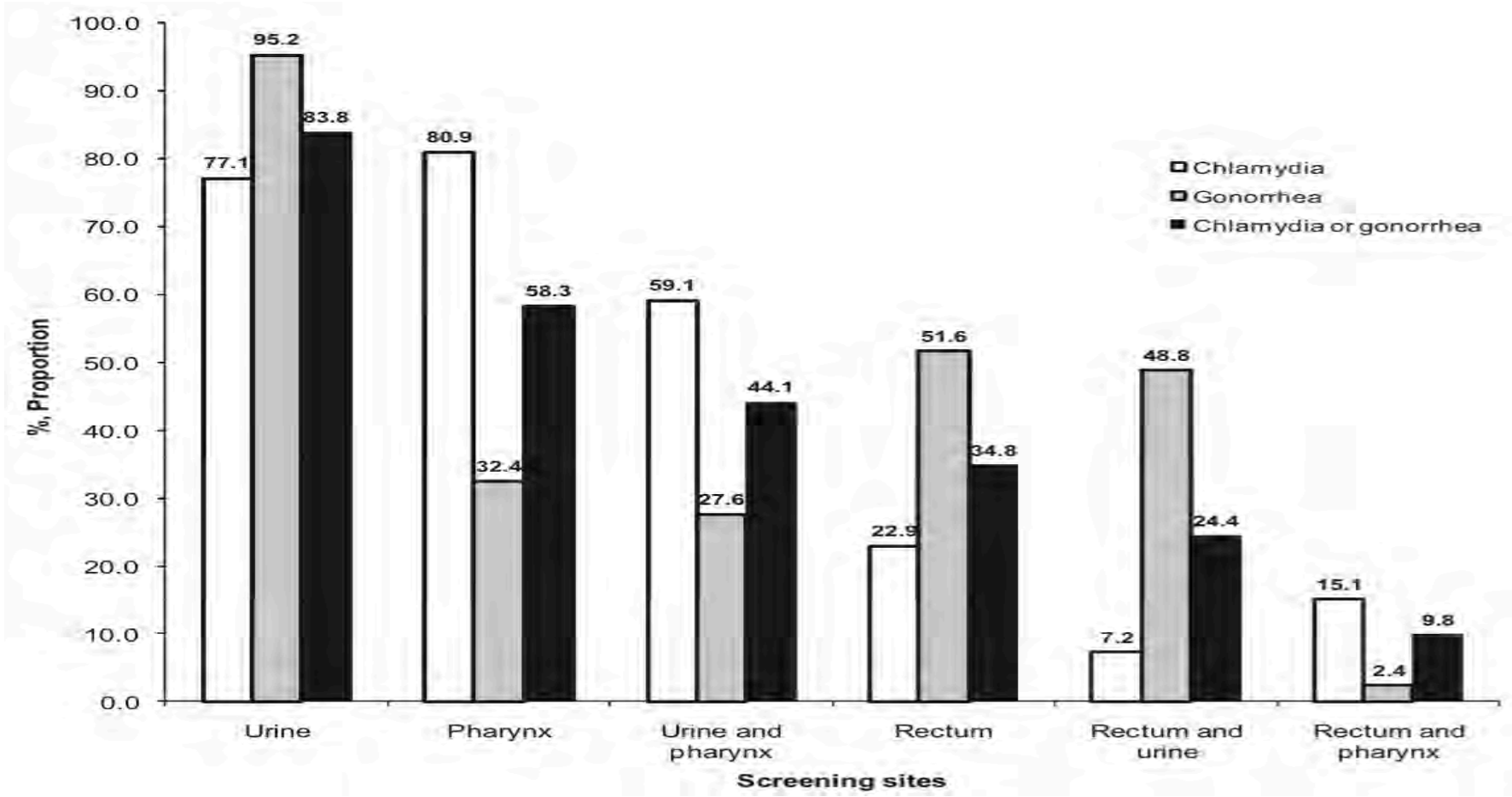
CT and GC Prevalence, by Site

TABLE 1. Prevalence of Chlamydial and Gonococcal Infection by Anatomic Site Among Asymptomatic Men Who Have Sex With Men (N = 3398)—San Francisco City Clinic, 2008–2009

Site of Infection	Chlamydia, % (95% CI)	Gonorrhea, % (95% CI)
Urethra	2.3 (1.8–2.9)	0.4 (0.2–0.6)
Rectum	7.8 (6.9–8.8)	3.6 (3.0–4.2)
Pharynx	1.9 (1.5–2.5)	5.0 (4.3–5.8)

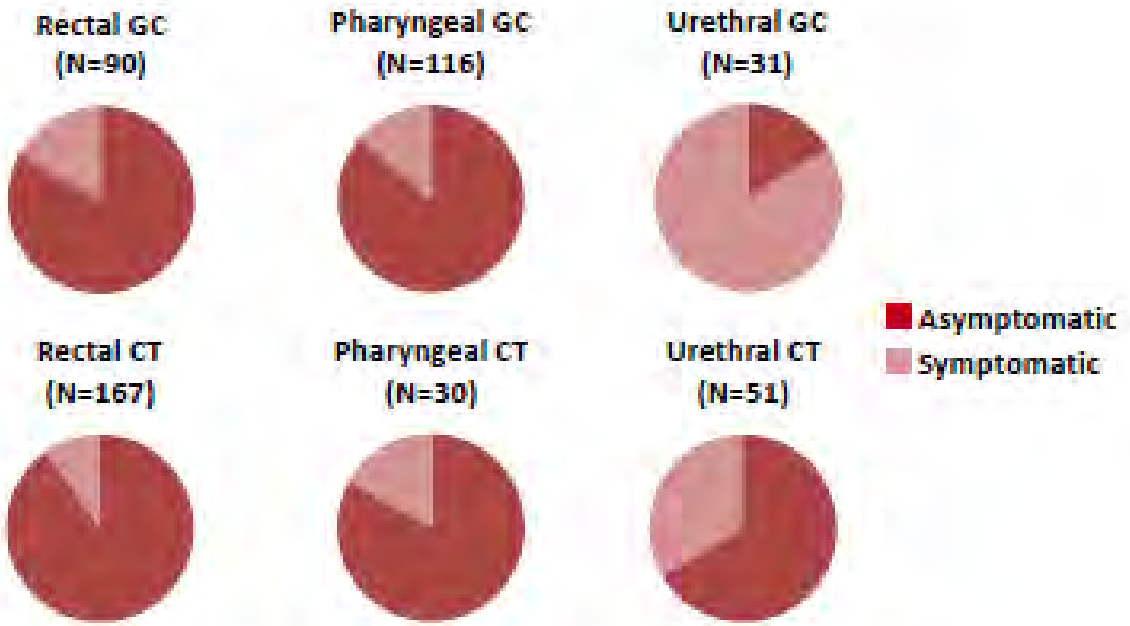
CI indicates confidence interval.

Proportion of missed infections, by screening method



Back to the Demo Project…

Figure 2. Percent of R, P and U- GC and CT Infections that were asymptomatic



N (%) of infections missed without extra-genital screening

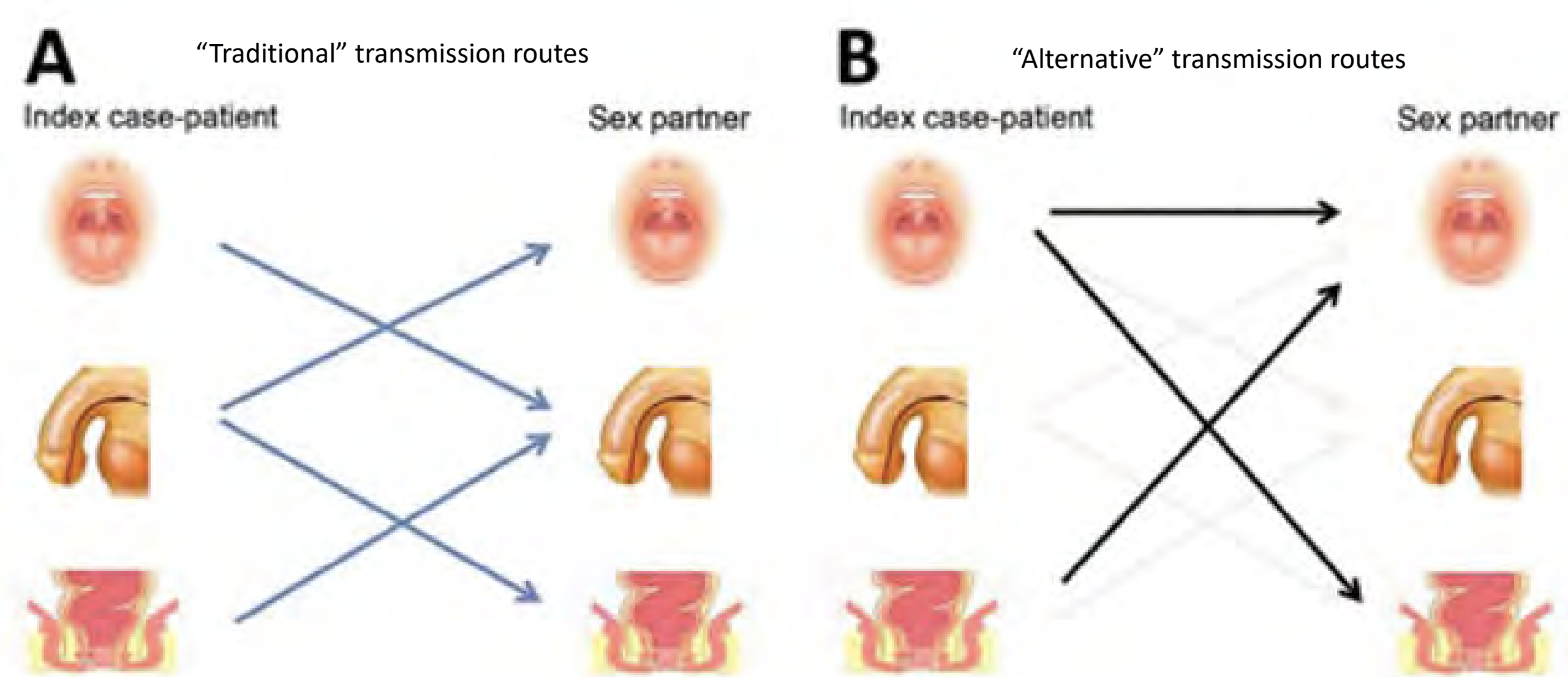
- 150/181 (82.9%) GC infections
- 159/210 (75.7%) CT infections

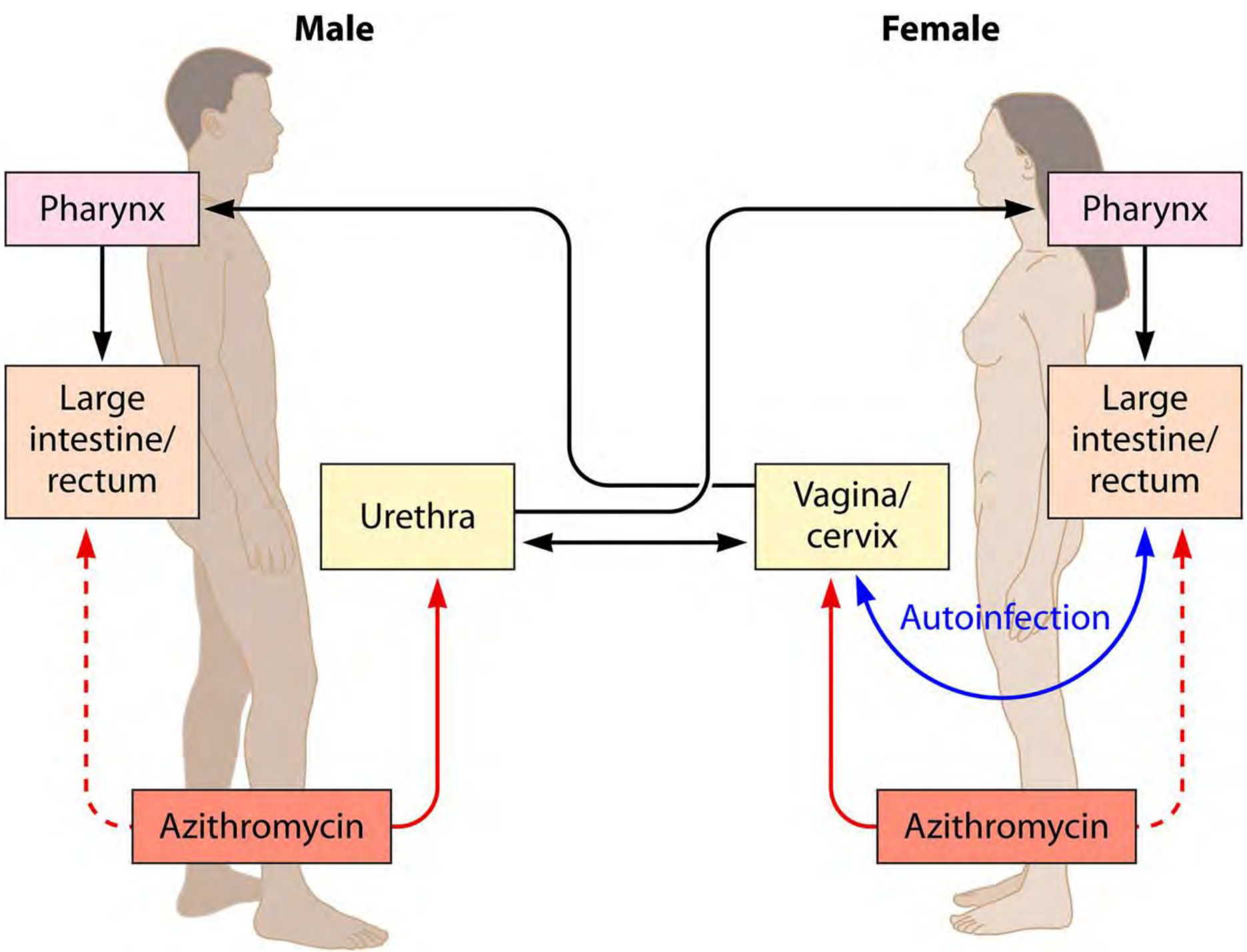
TABLE 3. Absolute Numbers and Prevalences of Anorectal *CT*, *NG*, and *CT/NG* by Universal Testing and Selective Testing With Sensitivity Estimates in 5 Different Risk Group Categories

	Homosexual MSM (n = 674)	Bisexual MSM (n = 95)	Bisexual Male Swingers (n = 157)	Heterosexual Male Swingers (n=303)	Female Swingers (n = 461)	*P*
CT						
Universal						
n	60	7			31	
%	8.9	7.4			6.7	*
Selective						
n	27	4			16	
%†	4.0	4.2			3.5	†
Sensitivity selective, % (CI)‡	45.0				1.6	
NG						
Universal						
n	28	3			5	
%	4.2	3.2			1.1	*
Selective						
n	20	0	0	1	1	
%	3.0	0	0	0.3	0.2	§
Sensitivity selective, % (CI)‡	71.4	0	0	100	20.0	
CT/NG						
Universal						
n	83	10	7	5	34	
%	12.3	10.5	4.5	1.7	7.4	*
Selective						
n	43	4	3	2	16	
%	6.4	4.2	1.9	0.7	3.5	†
Sensitivity selective, % (CI)‡	51.8	40.0	42.9	40.0	47.1	

Symptom- or history-based testing missed 51.1% (71/139; CI, 43-59%) of CT/GC infections

*$P < 0.0001$.
†$P < 0.05$.
‡Calculated as the proportion of anorectal infections diagnosed by symptom- and sexual history–based testing versus universal testing.
§$P < 0.01$.


A
“Traditional” transmission routes
Index case-patient
Sex partner
B
“Alternative” transmission routes
Index case-patient
Sex partner

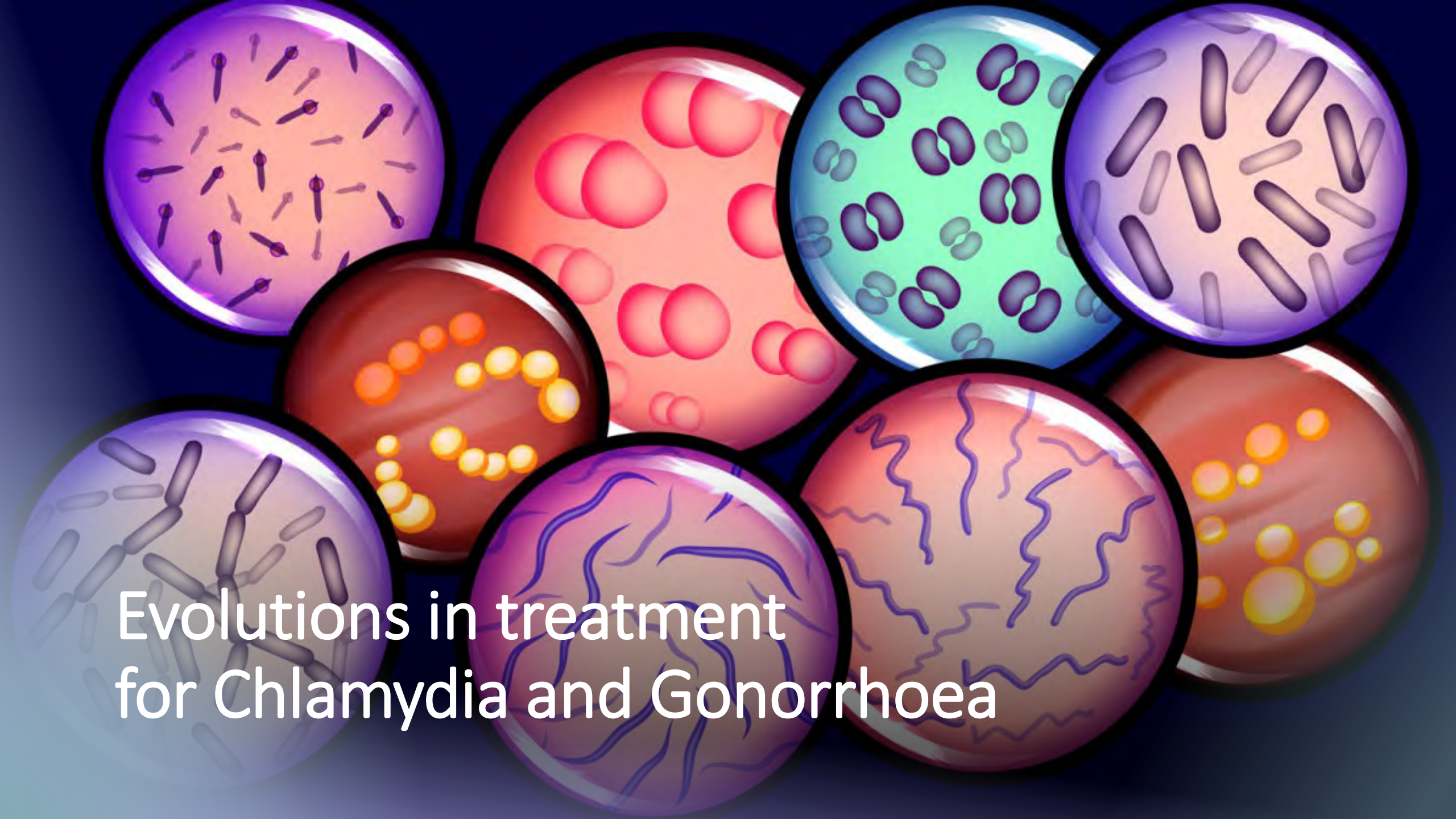

Male
Female
Pharynx
Large intestine/ rectum
Urethra
Vagina/ cervix
Pharynx
Large intestine/ rectum
Autoinfection
Azithromycin
Azithromycin

The Bottom Line

Especially for MSM and other patients at risk, CT and GC testing should be *at least considered* – and usually done – in all three anatomic sites.

- Several studies have shown that you will miss most infections by focusing on urethral samples only.

You can't always rely on history; use clinical judgment, but consider "universal testing" for some risk groups.



Evolutions in treatment for Chlamydia and Gonorrhoea

Current PHAC GC Management Recommendations

- Antimicrobial treatment
  - Ceftriaxone 250mg IM (or *Cefixime 800mg PO*) PLUS
    - Azithromycin 1g PO OR
    - (*Doxycycline 100mg PO bid x 7d*)

- What is the rationale for dual therapy?
    - Chlamydia co-infection is common AND incubation period is longer so may be missed by test early on.
    - Theoretical idea that if you treat gonorrhea with a drug with a different mechanism of action, you may reduce the risk of resistance development at population level.

    - **WARNING: THIS WILL (most likely) CHANGE!**

Gonorrhea: US CDC recommends monotherapy

- Ceftriaxone 500mg IM
  - Co-treat with doxycycline 100mg bid x 7d if CT not excluded
  - Co-treatment no longer universally recommended due to increasing azithromycin resistance
- Key differences in US CDC vs Canadian vs BC (and other provincial) guidelines
- What is the rationale for Monotherapy?
  1. Antimicrobial stewardship : affects on commensals and concurrent pathogens
  2. Increasing incidence of azithromycin resistance

What about Chlamydia? Shift towards Doxycycline

- Consider how repeated Azithromycin exposure affects the reservoir of antimicrobial resistance genes in the body

- Increasing concern for the efficacy of Azithromycin to treat Chlamydial infections, especially rectally

- **Doxycycline should be first-line for rectal Chlamydia, with better tissue penetration**

J Antimicrob Chemother 2015; **70**: 1290–1297
doi:10.1093/jac/dku574 Advance Access publication 29 January 2015

Journal of Antimicrobial Chemotherapy

The efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection: a systematic review and meta-analysis

Fabian Yuh Shiong Kong[1]*, Sepehr N. Tabrizi[2,3], Christopher Kincaid Fairley[4,5], Lenka A. Vodstrcil[1,2,5], Wilhelmina M. Huston[6], Marcus Chen[5], Catriona Bradshaw[5] and Jane S. Hocking[1]

- Pooled efficacy from 8 observational studies on treatment of rectal CT
  - 99.6% doxycycline vs. 82.9% azithromycin

Comparing Azithromycin and Doxycycline for the Treatment of Rectal Chlamydial Infection: A Retrospective Cohort Study

Christine M. Khosropour, MPH, Julia C. Dombrowski, MD, MPH,†‡ Lindley A. Barbee, MD, MPH,†‡ Lisa E. Manhart, PhD,*§ and Matthew R. Golden, MD, MPH*†‡*

- Retrospective cohort study on rectal CT treatment
  - Azithromycin-treated men had a significantly higher risk of persistent/recurrent infection aRR 5.2 (1.3-21.0)

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association

Doxycycline Versus Azithromycin for the Treatment of Rectal Chlamydia in Men Who Have Sex With Men: A Randomized Controlled Trial

Julia C. Dombrowski,[1,2] Michael R. Wierzbicki,[3] Lori M. Newman,[4] Jonathan A. Powell,[3] Ashley Miller,[5] Dwyn Dithmer,[2] Olusegun O. Soge,[6] and Kenneth H. Mayer[7,8]

- RCT, placebo-controlled in 177 MSM with rectal CT
  - 100% efficacy of doxycycline vs 74% azithromycin

JOURNAL ARTICLE

Azithromycin Versus Doxycycline for the Treatment of Genital Chlamydia Infection: A Meta-analysis of Randomized Controlled Trials

FREE

F. Y. S. Kong, S. N. Tabrizi, M. Law, L. A. Vodstrcil, M. Chen, C. K. Fairley, R. Guy, C. Bradshaw, J. S. Hocking

Clinical Infectious Diseases, Volume 59, Issue 2, 15 July 2014, Pages 193–205, https://doi.org/10.1093/cid/ciu220
Published: 11 April 2014 **Article history**

- Pooled efficacy from 23 observational studies on treatment of urogenital CT
  - Increased efficacy of up to 3% for doxy; 7% in symptomatic men.

A few more thoughts/predictions

- Changes to guidelines and clinical practice will be driven by a desire to be better antimicrobial stewards
  - Reduce macrolide use
  - Respond to AMR in GC
  - Emergence of mycoplasma genitalium
- Move away from dual treatment for GC
- Move away from empiric treatment when follow-up is likely
- Treatment should be guided by local AMR patterns
  - Continue to do C&S
  - Resistance-guided therapy

The Role of Doxycycline in STI Prevention

Emerging Paradigm:
Doxycycline for Bacterial STI Prevention

SCIENCE | HEALTH CARE | PUBLIC HEALTH

There's a morning-after pill to prevent sexually transmitted infections

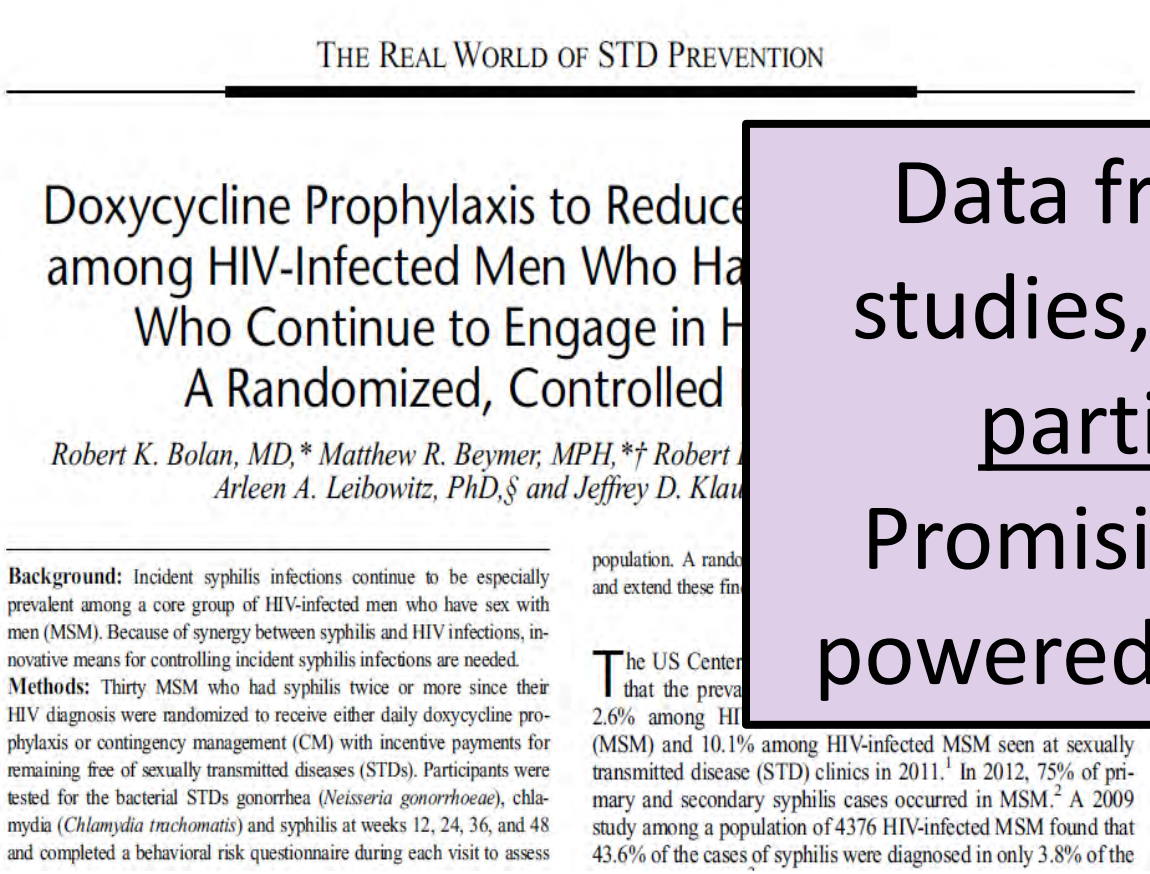
The CDC is getting close to recommending it to prevent STIs like chlamydia and syphilis.

By Keren Landman | @landmanspeaking | Updated Oct 13, 2023, 8:53am EDT

SHARE

New Engl J Med 2023; 388: 1296-1306.

DoxyPrEP: doxycycline 100mg PO daily



THE REAL WORLD OF STD PREVENTION

Doxycycline Prophylaxis to Reduce
among HIV-Infected Men Who Ha
Who Continue to Engage in H
A Randomized, Controlled

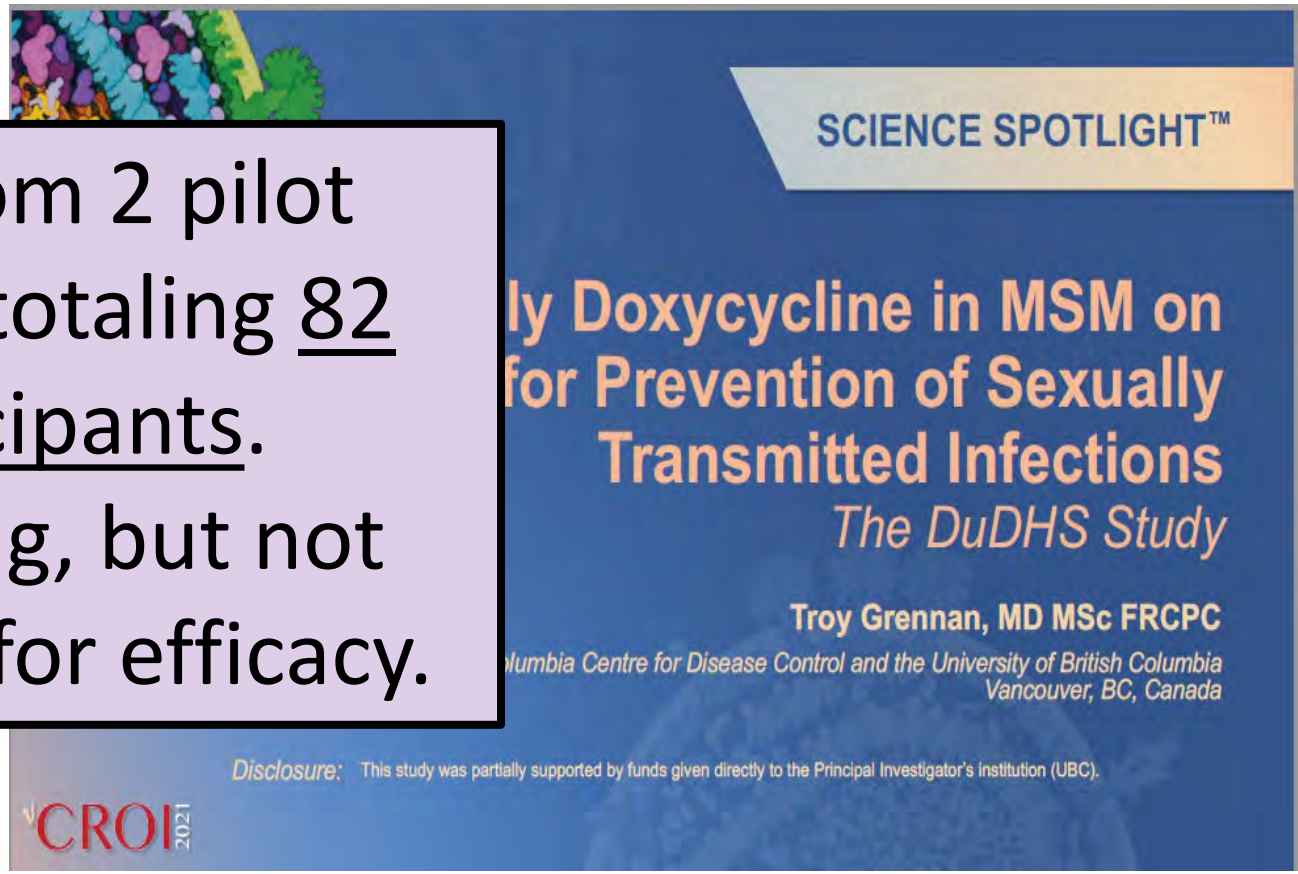
Robert K. Bolan, MD, Matthew R. Beymer, MPH,*† Robert*
Arleen A. Leibowitz, PhD,§ and Jeffrey D. Klau

Background: Incident syphilis infections continue to be especially prevalent among a core group of HIV-infected men who have sex with men (MSM). Because of synergy between syphilis and HIV infections, innovative means for controlling incident syphilis infections are needed.
Methods: Thirty MSM who had syphilis twice or more since their HIV diagnosis were randomized to receive either daily doxycycline prophylaxis or contingency management (CM) with incentive payments for remaining free of sexually transmitted diseases (STDs). Participants were tested for the bacterial STDs gonorrhea (*Neisseria gonorrhoeae*), chlamydia (*Chlamydia trachomatis*) and syphilis at weeks 12, 24, 36, and 48 and completed a behavioral risk questionnaire during each visit to assess

population. A rando
and extend these fin

The US Center
that the preva
2.6% among HI
(MSM) and 10.1% among HIV-infected MSM seen at sexually transmitted disease (STD) clinics in 2011.[1] In 2012, 75% of primary and secondary syphilis cases occurred in MSM.[2] A 2009 study among a population of 4376 HIV-infected MSM found that 43.6% of the cases of syphilis were diagnosed in only 3.8% of the

Data from 2 pilot studies, totaling 82 participants. Promising, but not powered for efficacy.



SCIENCE SPOTLIGHT™

ly Doxycycline in MSM on
for Prevention of Sexually
Transmitted Infections
The DuDHS Study

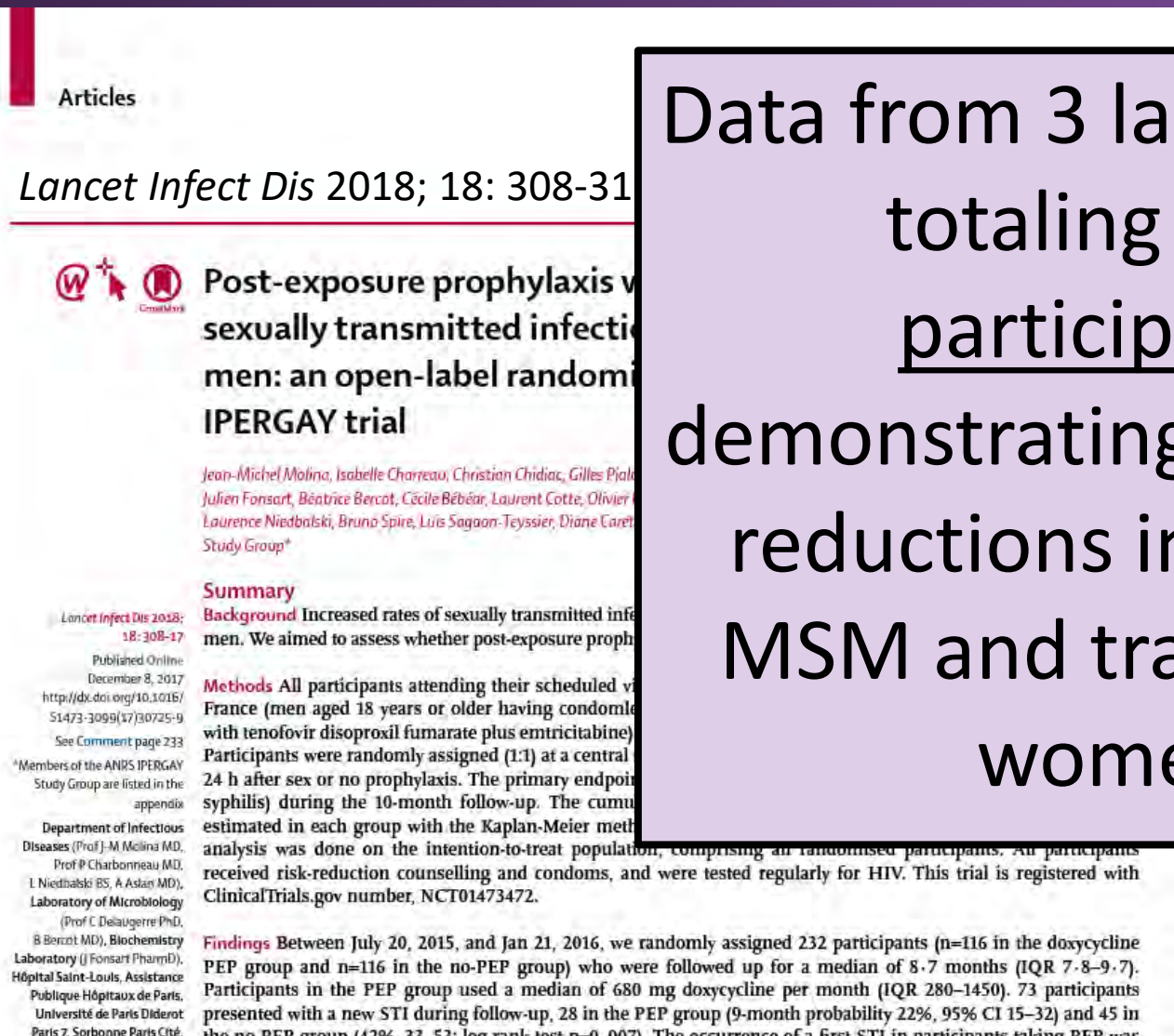
Troy Grennan, MD MSc FRCPC
lumbia Centre for Disease Control and the University of British Columbia
Vancouver, BC, Canada

Disclosure: This study was partially supported by funds given directly to the Principal Investigator's institution (UBC).

CROI 2021

DoxyPEP: Doxycycline 200mg within 72 h of sex

Data from 3 large studies, totaling 1279 participants, demonstrating significant reductions in all STI in MSM and transgender women.



Articles

Lancet Infect Dis 2018; 18: 308-31

Post-exposure prophylaxis v
sexually transmitted infecti
men: an open-label randomi
IPERGAY trial

Jean-Michel Molina, Isabelle Charreau, Christian Chidiac, Gilles Pial
Julien Fonsart, Béatrice Bercot, Cécile Bébéar, Laurent Cotte, Olivier
Laurence Niedbalski, Bruno Spire, Luis Sagaon-Teyssier, Diane Caret
Study Group*

Summary

Background Increased rates of sexually transmitted infe
men. We aimed to assess whether post-exposure proph

Methods All participants attending their scheduled v
France (men aged 18 years or older having condoml
with tenofovir disoproxil fumarate plus emtricitabine)
Participants were randomly assigned (1:1) at a central
24 h after sex or no prophylaxis. The primary endpoi
syphilis) during the 10-month follow-up. The cumu
estimated in each group with the Kaplan-Meier meth
analysis was done on the intention-to-treat population, comprising all randomised participants. All participants
received risk-reduction counselling and condoms, and were tested regularly for HIV. This trial is registered with
ClinicalTrials.gov number, NCT01473472.

Findings Between July 20, 2015, and Jan 21, 2016, we randomly assigned 232 participants (n=116 in the doxycycline PEP group and n=116 in the no-PEP group) who were followed up for a median of 8·7 months (IQR 7·8–9·7). Participants in the PEP group used a median of 680 mg doxycycline per month (IQR 280–1450). 73 participants presented with a new STI during follow-up, 28 in the PEP group (9-month probability 22%, 95% CI 15–32) and 45 in

Lancet Infect Dis 2018; 18:308–17
Published Online December 8, 2017 http://dx.doi.org/10.1016/S1473-3099(17)30725-9
See Comment page 233
*Members of the ANRS IPERGAY Study Group are listed in the appendix
Department of Infectious Diseases (Prof J-M Molina MD, Prof P Charbonneau MD, L Niedbalski BS, A Aslan MD), Laboratory of Microbiology (Prof C Delaugerre PhD, B Bercot MD), Biochemistry Laboratory (J Fonsart PharmD), Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris, Université de Paris Diderot Paris 7, Sorbonne Paris Cité,

l J Med 2023; 388: 1296-1306.

NGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

re Doxycycline to Prevent
ally Transmitted Infections

meyer, M.D., Deborah Donnell, Ph.D.,
M.D., M.P.H., Stephanie Cohen, M.D., M.P.H.,
, Clare E. Brown, Ph.D., Cheryl Malinski, B.S.,
P.H., Melody Nasser, B.A., Carolina Lopez, B.A.,
n P. Buchbinder, M.D., Hyman Scott, M.D., M.P.H.,
.P.H., Diane V. Havlir, M.D., Olusegun O. Soge, Ph.D.,
and Connie Celum, M.D., M.P.H., for the DoxyPEP Study Team*

Reference Links: • Lexi-Comp

Product: **DOXYCYCLINE HYCLATE 100 MG CAPSULE** View Available Strengths

Sig Method: Specify Dose, Route, Frequency | Taper/Ramp | Combination Dosage | Use Free Text

Dose: 200 mg | 100 mg

Calculated dose: 2 capsule

Route: oral | oral

Frequency: Daily PRN | Daily | BID

PRN is important as can distinguish doxy-PEP use from other doxycycline use

PRN Comment: Take within 24 hours after condomless sexual contact, and no later than 72 hours after sex.

Duration: Doses | Days | 30 days | 3 months | 1 year

Starting: 10/17/2022 Ending: First fill:

Dispense: Days/Fill: Full (0 Days) | 30 Days | 90 Days

Quantity: 60 capsule Refill: 0

Consider 30 days with no refill for initial dispensing & assess usage and tolerability

☐ Dispense As Written

Mark long-term: ☐ DOXYCYCLINE HYCLATE

⚠ Patient Sig: Take 2 capsules (200 mg total) by mouth 1 time each day if needed (Take within 24 hours after condomless sexual contact, and no later than 72 hours after sex.). Not to exceed 200 mg in a 24 hour period. Take large glass of water, do not lie down for 30 minutes after.

Doxy-PEP specific instructions

Edit the additional information appended to the patient sig

ⓘ The sig contains both discrete and free text elements. Review the final sig above.

Class: Normal | Normal | Print | Phone In | No Print | Sample

ⓘ This medication will not be e-prescribed. Invalid items: Pharmacy

Providence Health Care

Drug Treatment Program

DOXYCYCLINE FOR BACTERIAL SEXUALLY TRANSMITTED INFECTION (B-STI) PREVENTION ENROLMENT & PRESCRIPTION FORM

STIP ID #
CFE/PrEP ID #

☐ B-STI Prevention Initial Enrolment
☐ B-STI Prevention Prescription Refill

Please return completed form by Fax 604-806-8044

Patient & Prescriber Information

Patient (Legal First or Given Names): | Patient (Legal Last Name): | Telephone:

Patient's Address: | Postal Code: | BC Personal Health Number or Other Billing #:

Sex at Birth: ☐ Male ☐ Female | Gender Identity: ☐ Man ☐ Woman ☐ Other | Date of Birth

Does this individual self-identify as an Indigenous person? ☐ Yes ☐ No ☐ Unknown ☐ Prefer not to answer
If Yes, ☐ First Nations ☐ Métis ☐ Inuit ☐ Other

If this individual does not self-identify as an Indigenous person, how does this individual self-identify? (Check all that apply)
☐ Black ☐ East Asian ☐ Latin American ☐ Middle Eastern ☐ South Asian ☐ Southeast Asian
☐ White ☐ Other: ☐ Unknown ☐ Prefer not to answer

Prescriber Information College ID number (CPSID)
Prescriber Name: MSP number
Prescriber Address: Telephone:
Fax:

Initial Program Eligibility Program information can be found at bccfe.ca/drug-treatment-program

BC-CfE Drug Treatment Program participant: (Must be currently enrolled in one of the following programs)
☐ HIV Pre-Exposure Prophylaxis Program (HIV PrEP) or ☐ HIV Treatment Program (Person living with HIV)

Identifies with one of the following groups:
☐ Gay, bisexual and other men who have sex with men or ☐ Transgender women
If other group, provide clinical justification:

B-STI risk: (Select all that apply)
☐ History of B-STI in the past year and / or ☐ Clinically assessed increased risk of B-STI

Medical Information

Most recent B-STI screening test date:
☐ Confirmed no currently active B-STI (prior to starting doxycycline prophylaxis)

Most recent B-STI(s) diagnosed in the past 12 months (check all that apply):
☐ None ☐ Syphilis ☐ Chlamydia ☐ Gonorrhea

Drug Allergies/ Intolerance (specify):
☐ None

Medication Prescription

Doxycycline 100 mg capsule or tablet — **Take two capsules or tablets (2 x 100 mg) as soon as possible (up to 72 hours) after condomless sex. Maximum 200 mg per 24 hours.**

Quantity: ☐ Initial prescription ☐ 30 Continuation ☐ 30 ☐ 60 ☐ 100 capsules / tablets
(one dose dispensed in BC pharmacy)

Pick-up site: ☐ St. Paul's Hospital Ambulatory Pharmacy, 8B1E3-1081 Burrard Street, Vancouver BC, Telephone: 1-800-947-9822
☐ Healthcare site (outside Vancouver):
Please specify pick-up date:

Prescriber's signature: MSC#: Date:

Reviewer initials: Date:

PRESCRIPTION FORM VALID FOR 1 YEAR FROM PRESCRIPTION DATE

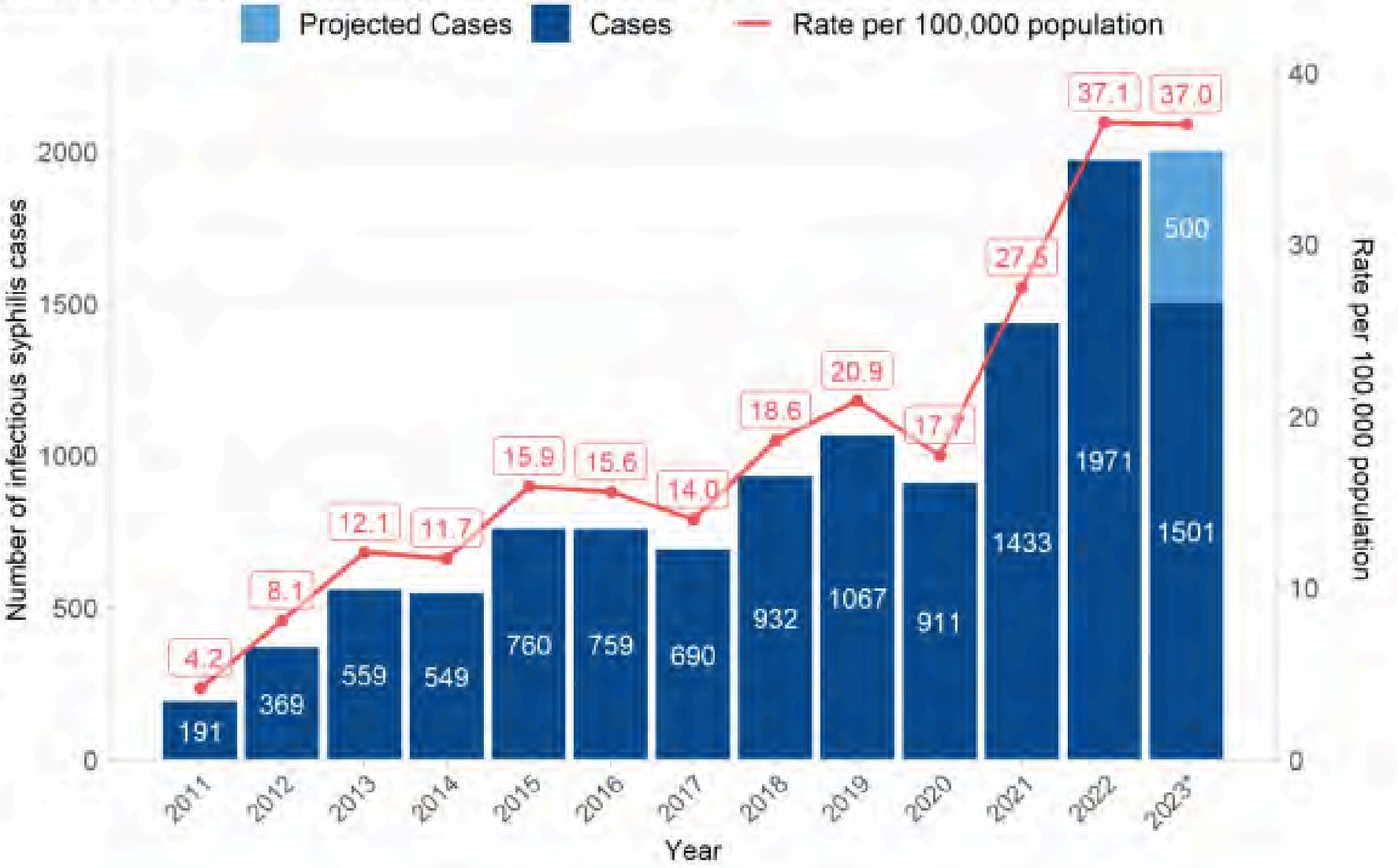
https://bccfe.ca/doxycycline-for-sti-prevention

Reminders and Unanswered Questions

- Chronic use of doxycycline for other indications : generally safe and well-tolerated, but limited info for STI prevention
- Remember Doxycycline side-effects:
  - Photosensitivity, GI symptoms, Pill esophagitis, Yeast infections, Benign Intracranial Hypertention (rare)
- What is the impact of Doxycycline on antimicrobial resistance?
- What is the impact of Doxycycline on the human microbiome?
- Will Doxy PrEP/PEP perform in other populations?

The changing epidemiology of the syphilis epidemic

1. Infectious syphilis case reports in BC, 2011-2023*



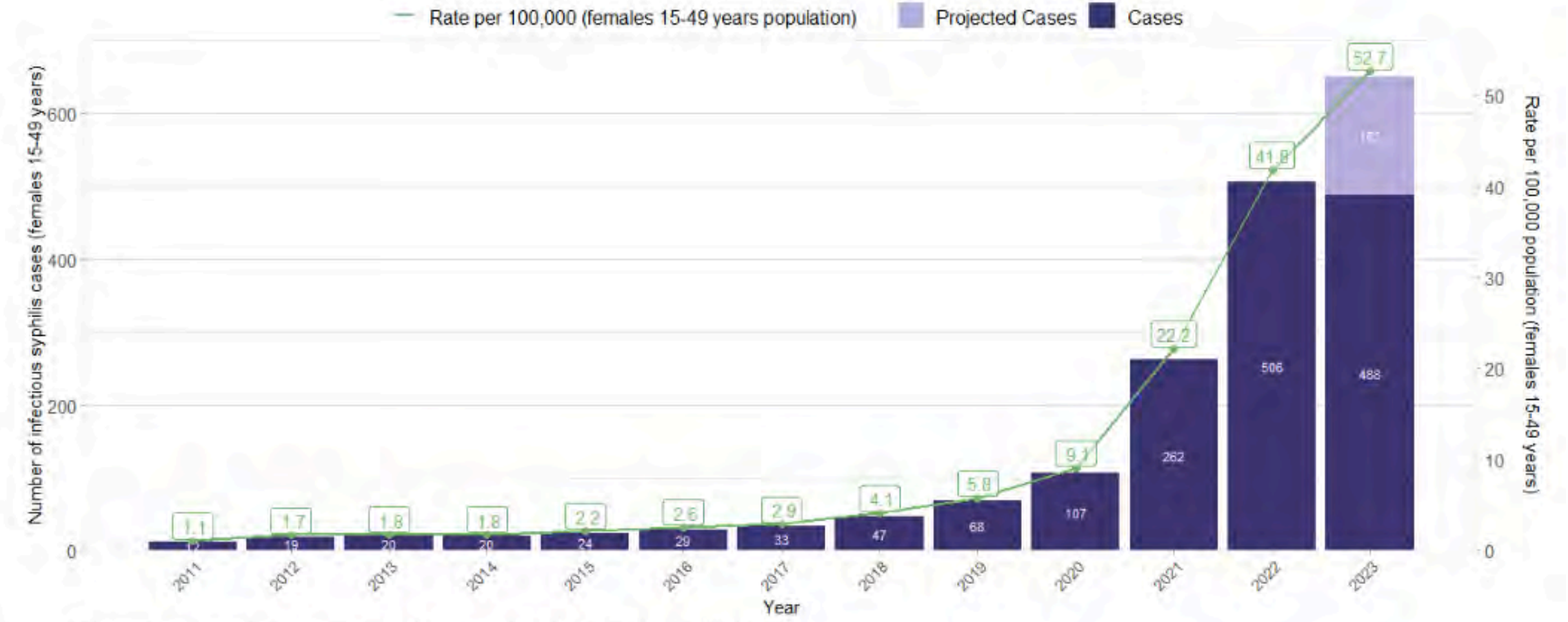
*Projected case counts/rates assume that the average number of reported cases per month year to date (YTD) remain contact throughout 2023.

Infectious syphilis case reports in BC by gender, 2011-2023*

Gender	Cases YTD 2023	Cases YTD 2022	% Change Cases YTD	Projected Annual Incidence 2023	Annual Incidence 2022	% Change Annual Incidence	Proportion YTD 2023	Proportion YTD 2022
Female	530	393	34.9	25.8	20.5	25.9	**35.3**	26.4
Male	960	1087	-11.7	48.0	53.6	-10.4	**64.0**	72.9
Transgender	7	9	-22.2	NA	NA	NA	0.5	0.6
Unknown	4	2	100.0	NA	NA	NA	0.3	0.1

Data are preliminary and subject to change

Infectious syphilis case reports in BC among females 15-49 years, 2011-2023

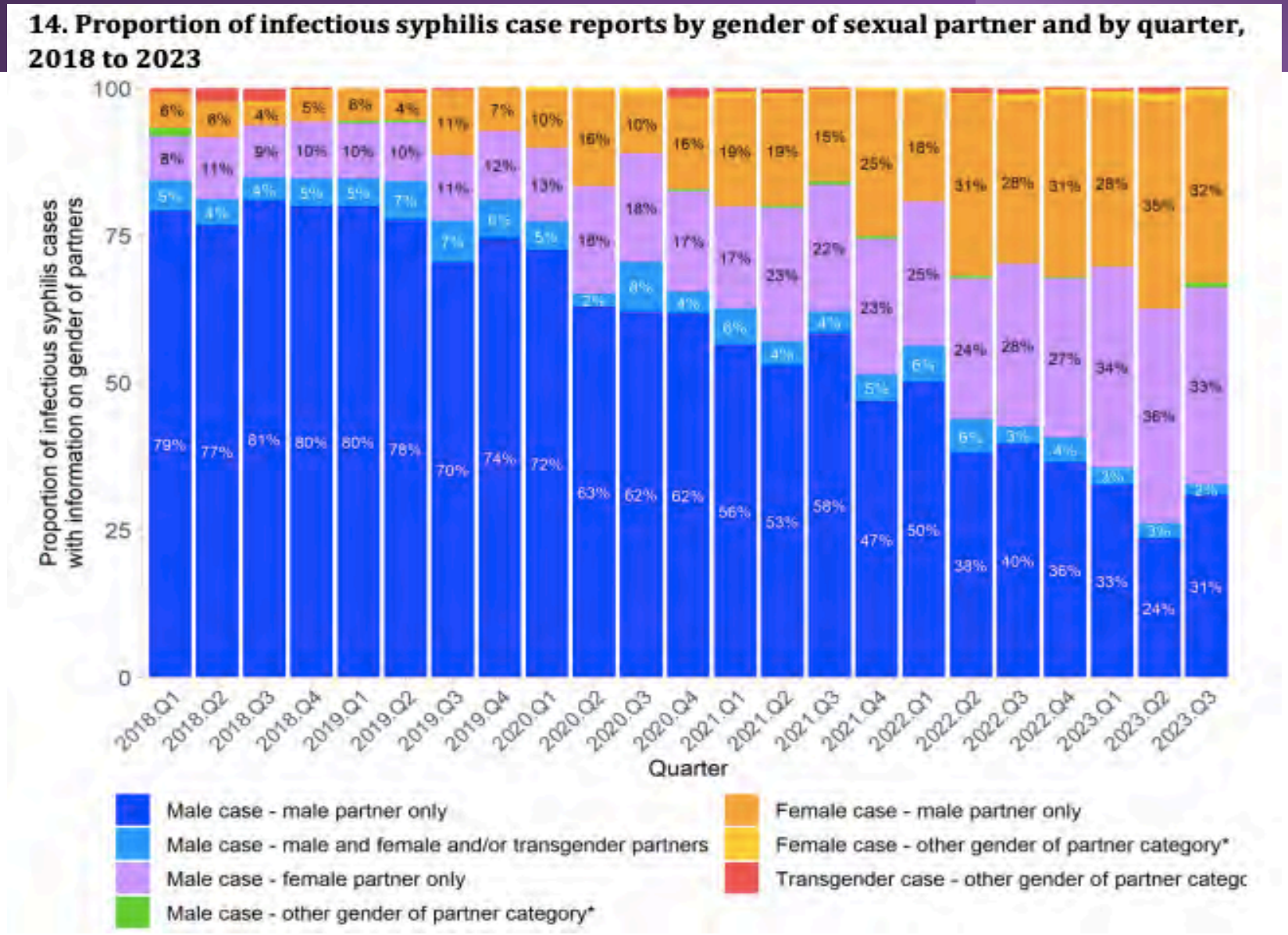


*Rate projected based on current year's case counts up to and including 2023 Q3.

Infectious Syphilis Cases in Females

- March 2018 – Dec 2020
- 83.9% - documented mental illness
- 71.1% - housing instability
- 71.9% - street involvement
- 68.2% - concurrent substance use
- 61.9% - transactional sex
- 42.9% - recent STI diagnosis

Infectious Syphilis by Gender and Gender of Sexual Partner



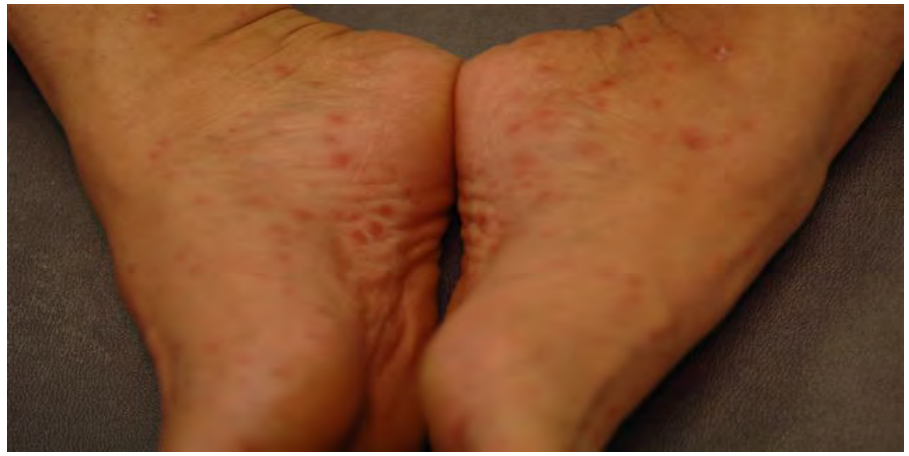
Testing, Treatment and Follow-up to address the Syphilis Surge

Case 3

30-year-old male with both male and female sexual partners. Healthy, on HIV PrEP. Diffuse maculopapular rash incl palms/soles. Progressively worsening headache, and a clinical picture consistent with meningitis.

Current syphilis serology:

- EIA reactive
- RPR 1:256
- TPPA reactive



Syphilis serology negative three months ago.

How worried are you about neurosyphilis?

Syphilis clinical manifestations: Important to keep an open mind!

Altered Clinical Presentation of Early Syphilis in Patients with Human Immunodeficiency Virus Infection

Catherine M. Hutchinson, MD; Edward W. Hook, 3d, MD; Mary Shepherd, MS; Janice Verley, MD; and Anne M. Rompalo, MD, ScM

Annals of Internal Medicine®

Human Immunodeficiency Virus Seropositivity and Early Syphilis Stage Associated With Ocular Syphilis Diagnosis: A Case-control Study in British Columbia, Canada, 2010–2018

Hasan Hamze,[1] Venessa Ryan,[2] Emma Cumming,[2] Christine Lukac,[2] Jason Wong,[2] Morshed Muhammad,[2] and Troy Grennan[2]

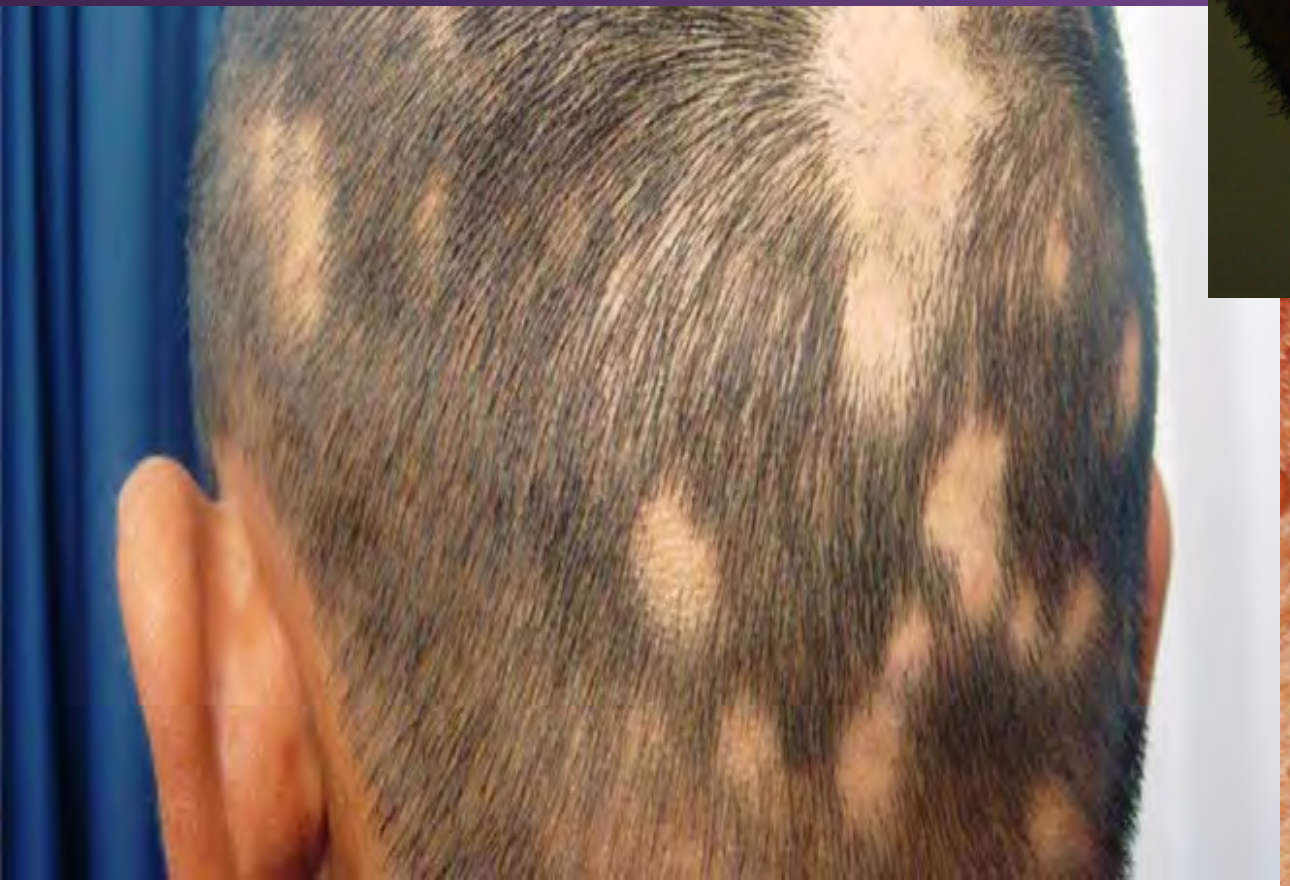
Clinical Infectious Diseases

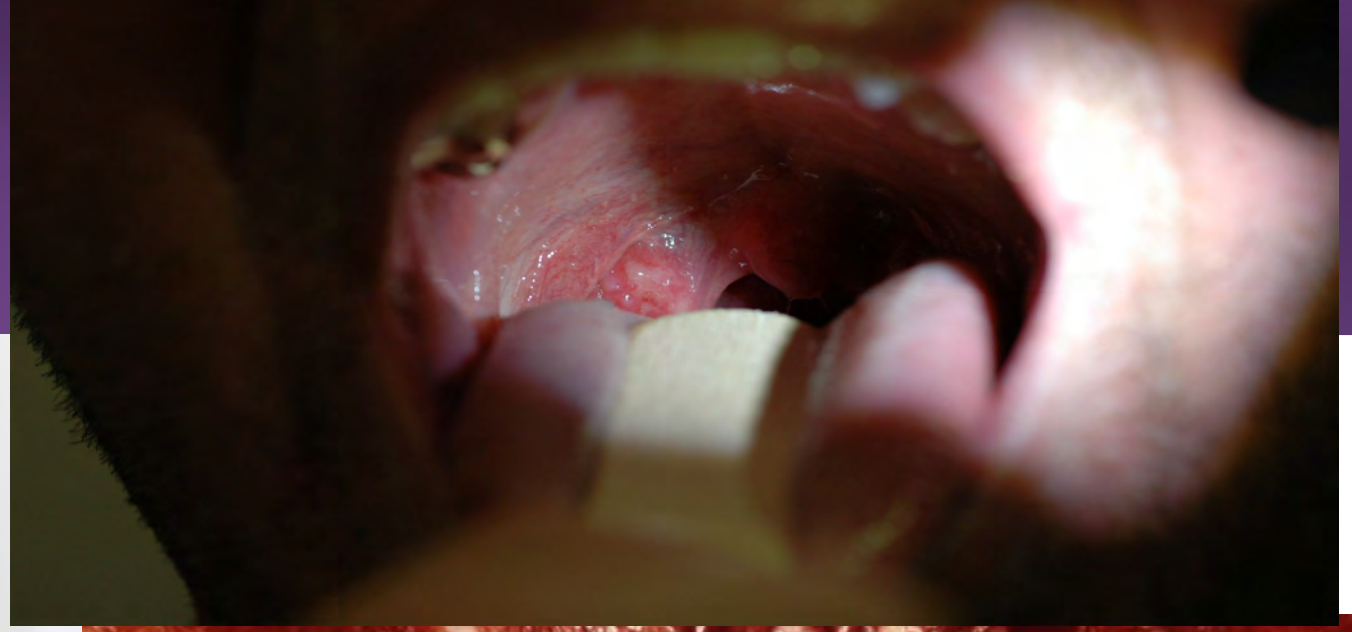
ORIGINAL ARTICLE

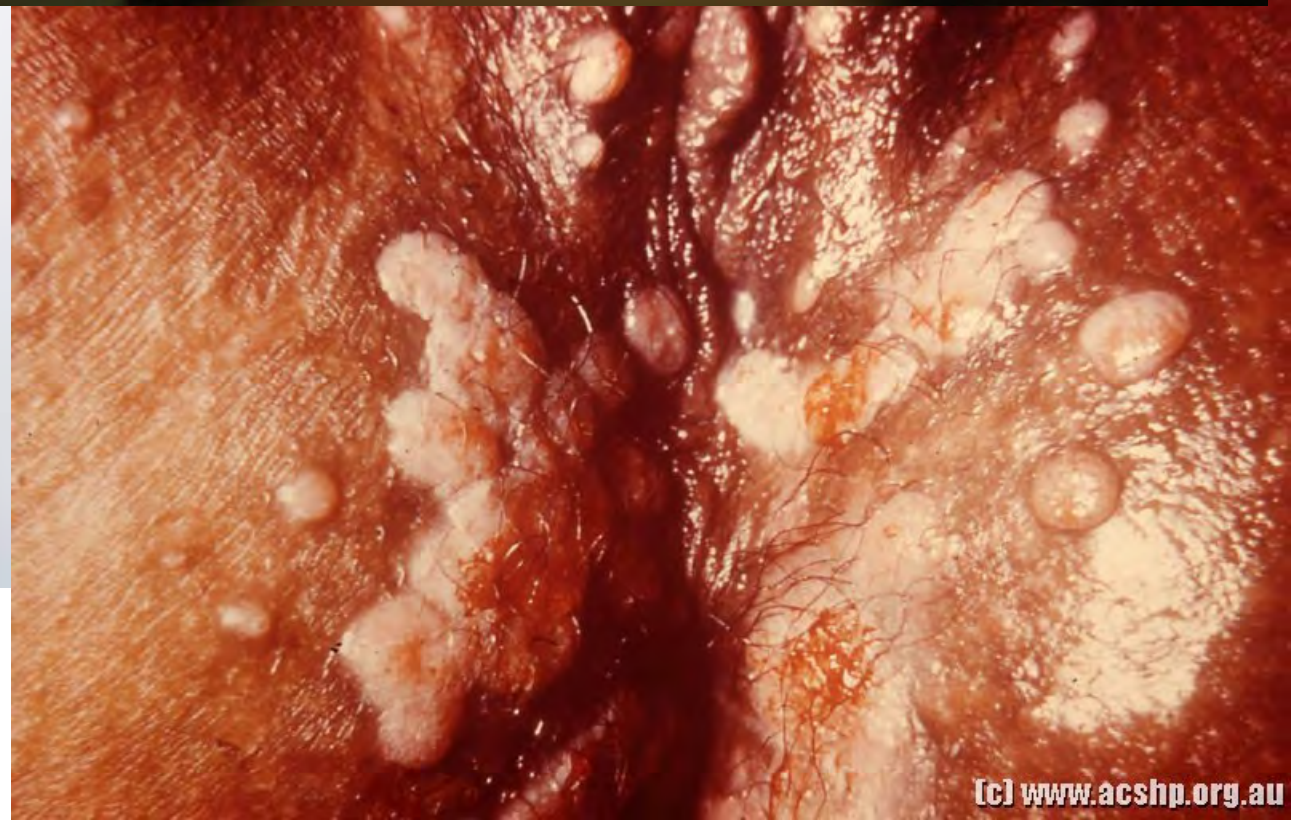
Sexually Transmitted Infections

Painful and multiple anogenital lesions are common in men with *Treponema pallidum* PCR-positive primary syphilis without herpes simplex virus coinfection: a cross-sectional clinic-based study

Janet M Towns,[1] David E Leslie,[2] Ian Denham,[1] Francesca Azzato,[2] Christopher K Fairley,[1,3] Marcus Chen[1,3]






(c) www.acshp.org.au

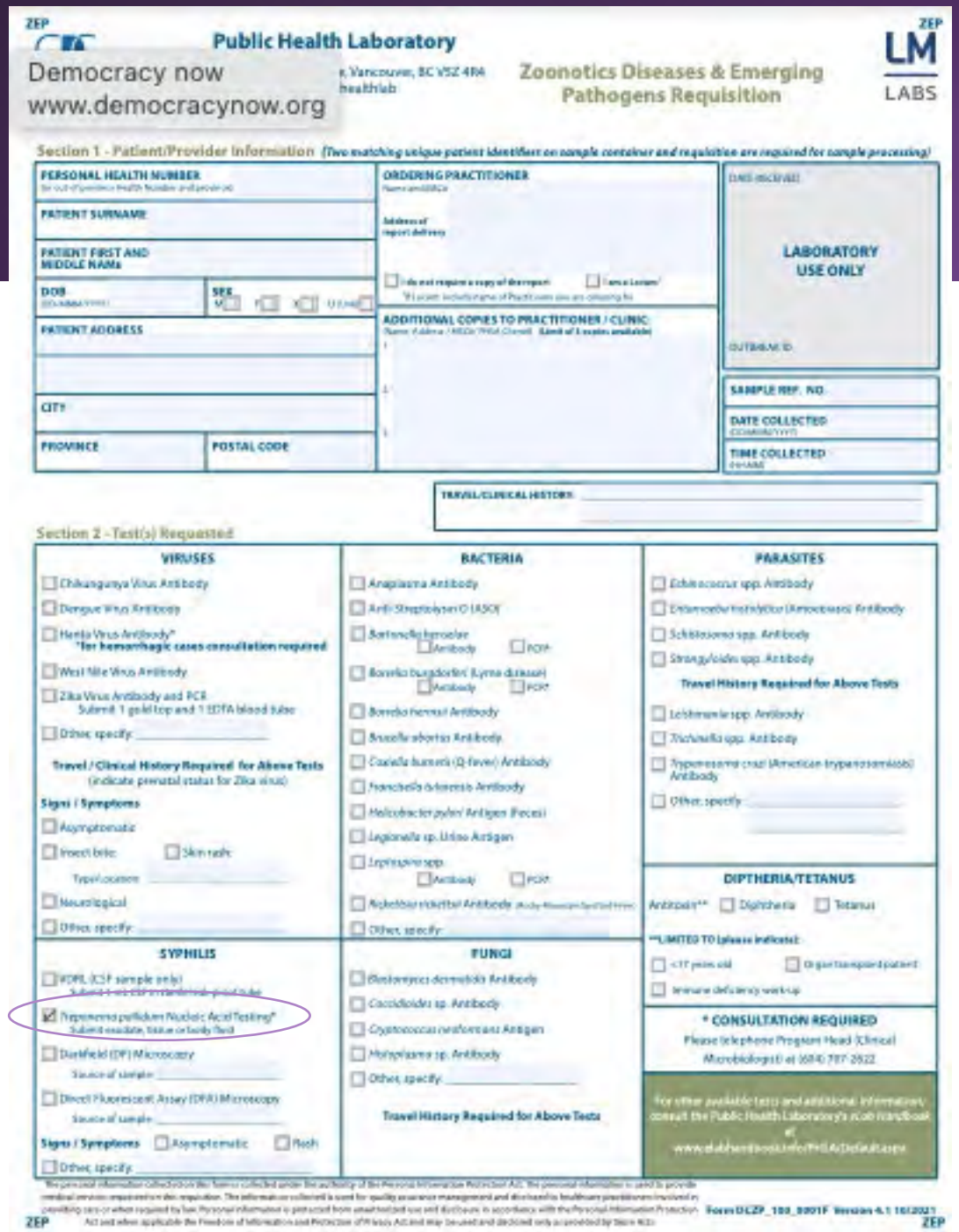
What organ systems can be involved in early syphilis?

- General: fever, malaise, lymphadenopathy
- H +N: pharyngitis
- GI: hepatitis (10%), high ALP, ALT/AST usually N or slightly up; diffuse GI tract infiltration and/or ulceration. Syphilis proctitis.
- GU: immune-complex nephropathy with nephrotic syndrome
- MSK: myalgias, arthralgias; periostitis
- Derm: any type of eruption possible (except vesicular); alopecia; mucous patch; chancre; condyloma lata; “malignant lues”
- Neurologic: headache; CNS involvement common (pleocytosis in up to 30%); symptomatic meningitis rare (2-5%); tinnitus, vertigo, ocular manifestations

Syphilis Serology : Key reminders

- **Treponemal tests: EIA, CLIA, TPPA, FTA-ABS**
  - Nonreactive in up to 30% of primary syphilis
  - False-positives: endemic treponematoses, other infections, inflammatory diseases
  - Remains reactive for life, so not a useful diagnostic test post-infection #1
- **Nontreponemal tests: RPR, VDRL**
  - Nonreactive in up to 30% of primary syphilis
  - Can become nonreactive over time, regardless of treatment history
  - False positives: autoimmune diseases, HIV, other infections, pregnancy, acute illness
  - Aids with diagnosis for re-infection

Don’t forget to swab!



Public Health Laboratory

Zoonotics Diseases & Emerging Pathogens Requisition

LM LABS

Section 1 - Patient/Provider Information (Two matching unique patient identifiers on sample container and requisition are required for sample processing)

PERSONAL HEALTH NUMBER

PATIENT SURNAME

PATIENT FIRST AND MIDDLE NAMES

DOB

SEX

PATIENT ADDRESS

CITY

PROVINCE

POSTAL CODE

ORDERING PRACTITIONER

ADDITIONAL COPIES TO PRACTITIONER / CLINIC

LABORATORY USE ONLY

SAMPLE REF. NO.

DATE COLLECTED

TIME COLLECTED

TRAVEL/CLINICAL HISTORY:

Section 2 - Test(s) Requested

VIRUSES

- Chikungunya Virus Antibody
- Dengue Virus Antibody
- Hanta Virus Antibody* *for hemorrhagic cases consultation required
- West Nile Virus Antibody
- Zika Virus Antibody and PCR Submit 1 gold top and 1 EDTA blood tube
- Other, specify:

Travel / Clinical History Required for Above Tests (indicate prenatal status for Zika virus)

Signs / Symptoms

- Asymptomatic
- Insect bite
- Skin rash
- Neurological
- Other, specify:

BACTERIA

- Anaplasma Antibody
- Anti-Streptolysin O (ASO)
- Bartonella henselae Antibody / PCR
- Borrelia burgdorferi (Lyme disease) Antibody / PCR
- Borrelia hermsii Antibody
- Brucella abortus Antibody
- Coxiella burnetii (Q Fever) Antibody
- Francisella tularensis Antibody
- Helicobacter pylori Antigen (Feces)
- Legionella sp. Urine Antigen
- Leptospira spp. Antibody / PCR
- Rickettsia rickettsii Antibody
- Other, specify:

PARASITES

- Echinococcus spp. Antibody
- Entamoeba histolytica (Amoebiasis) Antibody
- Schistosoma spp. Antibody
- Strongyloides spp. Antibody

Travel History Required for Above Tests

- Leishmania spp. Antibody
- Trichinella spp. Antibody
- Trypanosoma cruzi (American trypanosomiasis) Antibody
- Other, specify:

DIPHTHERIA/TETANUS

Antitoxin** Diphtheria Tetanus

**LIMITED TO (please indicate):

- <17 years old
- Organ transplant patient
- Immune deficiency work-up

SYPHILIS

- VDRL (CSF sample only)
- Treponema pallidum Nucleic Acid Testing*
- Darkfield (DFA) Microscopy
- Direct Fluorescent Assay (DFA) Microscopy

Signs / Symptoms: Asymptomatic Rash

- Other, specify:

FUNGI

- Blastomyces dermatitidis Antibody
- Coccidioides sp. Antibody
- Cryptococcus neoformans Antigen
- Histoplasma sp. Antibody
- Other, specify:

Travel History Required for Above Tests

* CONSULTATION REQUIRED

Please telephone Program Head (Clinical Microbiologist) at (604) 707-2622

For other available tests and additional information, consult the Public Health Laboratory's eLab Handbook at www.ehandbook.info/PHL/eDefault.aspx

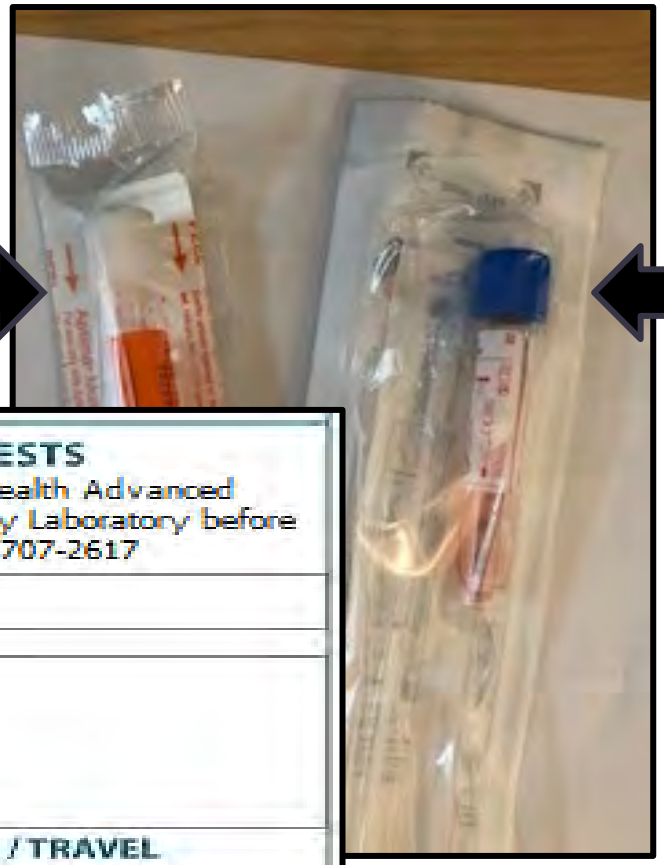
Form BCZP_100_0001F Version 4.1 10/2021

ZEP

Democracy now
www.democracynow.org

TP PCR & LGV

HSV



OTHER TESTS

Consult with Public Health Advanced Bacteriology and Mycology Laboratory before ordering at 604-707-2617

Sample Type:

Test Requested:

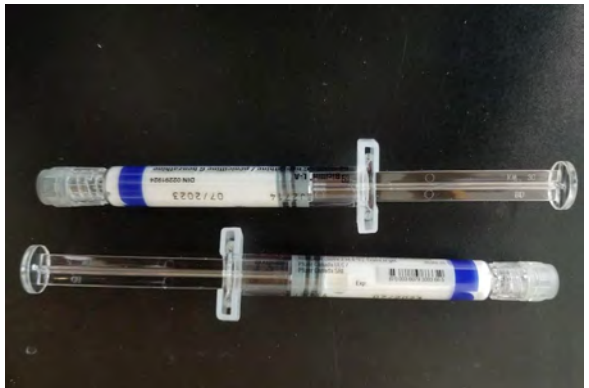
TP PCR
Attn: Dr. Morshed

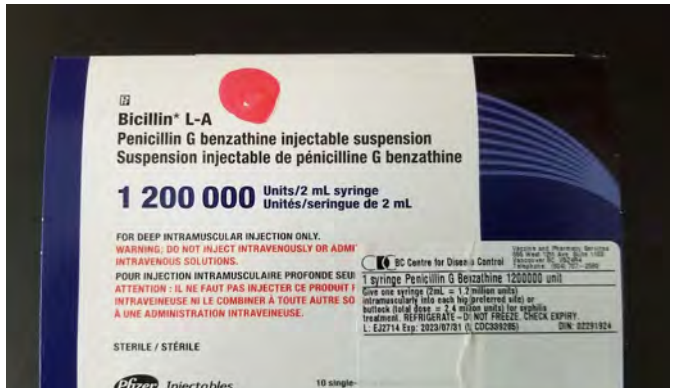
ADDITIONAL CLINICAL / TRAVEL INFORMATION:

Syphilis Treatment Tips

Bicillin…

- Ventrogluteal*
- Warm up medication prior to injection
- J-H reaction





Doxycycline…

- Avoid in pregnancy
- Tips for managing adherence challenges
- Consider allergy testing
  - Dropthelabel.ca

Case 4

42-year-old transgender woman living with HIV (CD4 1050, VL < 40), on antiretroviral therapy, presents for routine HIV follow-up. Treated 12 months ago for secondary syphilis with 2.4 million U benzathine penicillin. No reinfection risk. RPRs as follows:

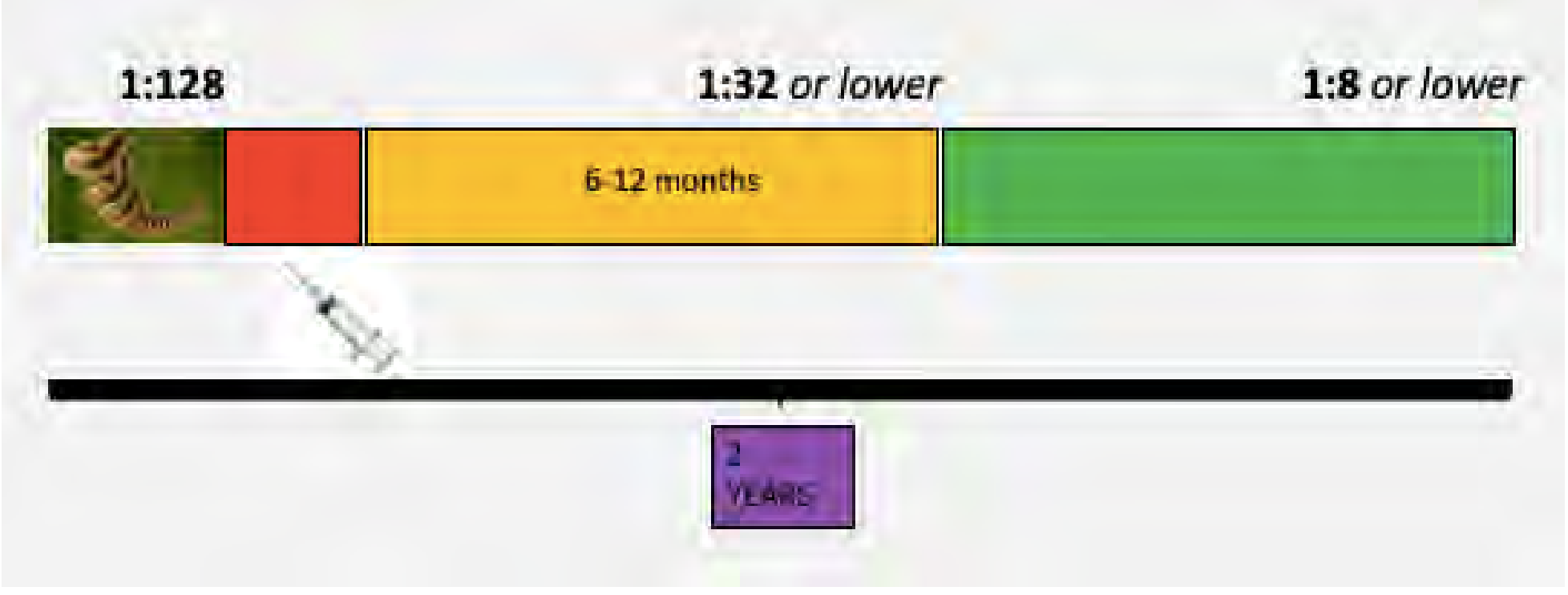
- At diagnosis: 1:128
- 3 months: 1:128
- 6 months: 1:64
- 9 months: 1:64
- Today: 1:64

Are you worried? What do you do?

How do you gauge an appropriate treatment response?

- Within 6-12 months* of treatment = 4-fold (or 2-dilution) drop in RPR.
- At 2 years, RPR <1:8.

*for individuals living with HIV or in those with late latent syphilis, may take up to 24 months



What if you don’t see an adequate RPR drop?

- Are there any neurological signs/symptoms?
  - If yes, needs LP.
- Is there a chance of reinfection?
  - If yes, retreat.
- If no neurological symptoms or concerns re: reinfection then:
  - Discuss with BCCDC physician
  - Possible ID referral and LP
  - Monitoring titre may be appropriate

What is the best approach?

EXPERIMENTAL AND THERAPEUTIC MEDICINE 19: 255-263, 2020

Is repeated retreatment necessary for HIV-negative serofast early syphilis patients?

YONG LIU[1-4], QUEQIAO BIAN[1-4], SHUHUAN ZHANG[1-4], JUN WANG[1-4], ZHENMING WANG[2-5] and JUNYUE LI[2-5]

Outcomes From Re-Treatment and Cerebrospinal Fluid Analyses in Patients With Syphilis Who Had Serological Nonresponse or Lack of Seroreversion After Initial Therapy

Xiaohui Zhang, MD, Andrea Shahum, MD, PhD,*† Li-Gang Yang, MD, MSc,* Yaohua Xue, PhD,* Liuyuan Wang, MD,* Bin Yang, MD, PhD,* Heping Zheng, PhD,* Jane S. Chen, MSPH,† Justin D. Radolf, MD,‡ and Arlene C. Seña, MD, MPH†*

Bottom line from these observational studies: No short-term benefits from re-treatment of those not achieving a four-fold drop in RPR. Long-term impacts unknown.

Response to Therapy Following Retreatment of Serofast Early Syphilis Patients With Benzathine Penicillin

Clinical Infectious Diseases 2013;56(3):420–22

Arlene C. Seña,[1] Mark Wolff,[2] Frieda Behets,[1,3] Kathleen Van Damme,[3] David H. Martin,[4] Peter Leone,[1] Linda McNeil,[5] and Edward W. Hook[6]

J Antimicrob Chemother 2018; **73**: 1348–1351
doi:10.1093/jac/dky006 Advance Access publication 31 January 2018

Journal of Antimicrobial Chemotherapy

Serological response to therapy following retreatment of serofast early syphilis patients with benzathine penicillin

Zhong-Shuai Wang, Xiao-Ke Liu and Jun Li*

Original research article

INTERNATIONAL JOURNAL OF STD & AIDS

No improvement in serological response among serofast latent patients retreated with benzathine penicillin

International Journal of STD & AIDS
2016, Vol. 27(1) 58–62
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sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0956462415573677
std.sagepub.com

SAGE

Rong-Xin Ren[1], Lin-Na Wang[2], He-Yi Zheng[1] and Jun Li[1]

Syphilis : Key Points

- Up to 1/3 may have atypical presentation of primary syphilis
- Persons with recent syphilis less likely to be symptomatic
- Always ask about neurologic symptoms, regardless of how subtle
- Serious syphilis complications occur in early syphilis – including neurologic manifestations!
- Different expectations for treatment response in HIV and for late syphilis
- Don’t forget TP PCR swabs!
- Test frequently and call us! (604-707-5610)

Summary

- Test q3mthly if high risk, annually for others ; site-based testing is key!
- Move away from Azithromycin and empiric treatment when F/U is likely
  - Always consider AMR patterns in your treatment decisions
    - We still must provide cultures in GC
- Don’t be afraid of using doxycycline for prevention in those who qualify (i.e. MSM or TW with STI in last year)
- Syphilis continues to surge – with rising rates in women and heterosexuals
  - Test frequently, keep an open mind, don’t forget TP PCR

References

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