Syphilis Update:
Defense Against a Resurgent Foe

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Disclosures

- None

- Non FDA labeled uses:
  - Extragenital NAATs

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Objectives

- State at which stage(s) of syphilis neurologic involvement may be found
- State CDC's recommended therapy for primary, secondary, and late stages of syphilis
- State the criteria for a presumptive diagnosis of ocular syphilis
- Describe U.S. trends in syphilis incidence in the past decade among men and women
- State the baseline incidence of bacterial STI's among HIV PrEP users
- Describe the syphilis screening recommendations for persons taking HIV PrEP

Syphilis

https://www.cdc.gov/std/sam/2017syphilis.htm

Case A: 48 y.o. male with rash and LFT abnormalities

- Presents to office
  - Rash for 5 days
  - Nausea and poor appetite
  - History of chronic HCV and alcohol abuse
- Exam
  - Pustular rash on trunk & arms, sparing palms & soles
  - Normal mini-mental, no asterixis
- AST 52 U/L; ALT 58 U/L (baseline)
- **AP 1260 U/L**; T-bili 1.2 mg/dl (baseline 0.5)
- A test was performed…

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- AST 52 U/L; ALT 58 U/L (baseline)
- **AP 1260 U/L**; T-bili 1.2 mg/dl (baseline 0.5)
- **Serum Treponemal Ab reactive, RPR 1:128**
- Sexual HX: "Maybe a dozen" men & women / year

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Case B: 43 male with vision loss

- Progressive vision loss beginning 6 weeks ago
  - First-week R-sided only (blurriness, dark shapes), then left
  - Pain bilaterally, dry eye sensation, mild light sensitivity
  - No longer distinguishing faces – ophthalmologist (2 wk ago)
    - "Uveitis and possible infection"
    - Antibiotic eye drops and prednisone
  - Initial improvement, but now presents with worsening again
  - NO: h/a, neck stiffness, fevers, focal neuro, cognitive probs

- Other history
  - Immigrant from Central America, landscaper
  - Male and female partners, no further disclosure

- Office Exam: barely counting fingers

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Case B: 43 male with vision loss

- **Serum Treponemal Ab reactive, RPR 1:256**

- Ophthal Exam
  - Bilateral anterior & intermediate uveitis, vitritis
  - No retinal whitening
- LP
  - WBC 1 / 0; RBC 0 / 0
  - Pro 24, Glucose 63
  - VDRL (resulted 9 days later): Neg

- HIV pos; CD4 85, HIV RNA 731,000

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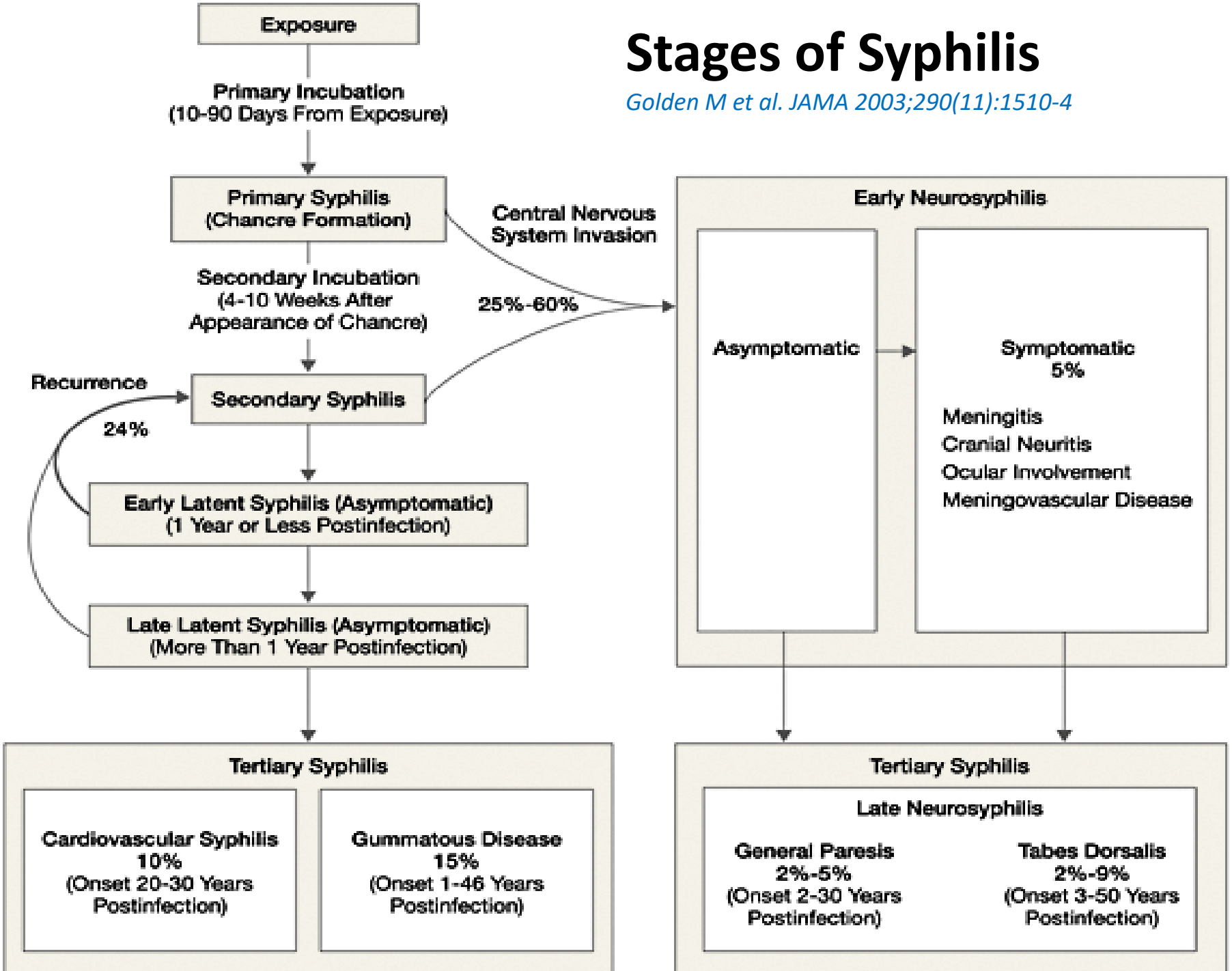
Stages of Syphilis

Golden M et al. JAMA 2003;290(11):1510-4



Serologic Tests for Syphilis

Non-treponemal Tests

- Flocculation tests (RPR, VDRL), complement fixation
- Detect antibodies to biomarkers released by cellular damage
- **Quantitative titers**

Treponemal Tests

- Fluorescent treponemal antibody absorption (FTA-ABS), Treponema pallidum hemaglutination assay (TPHA), Enzyme immunoassays (EIA), etc…
- Detect antibodies to *T. pallidum*
- **Qualitative, easier to run**
- **Increased sens/spec**

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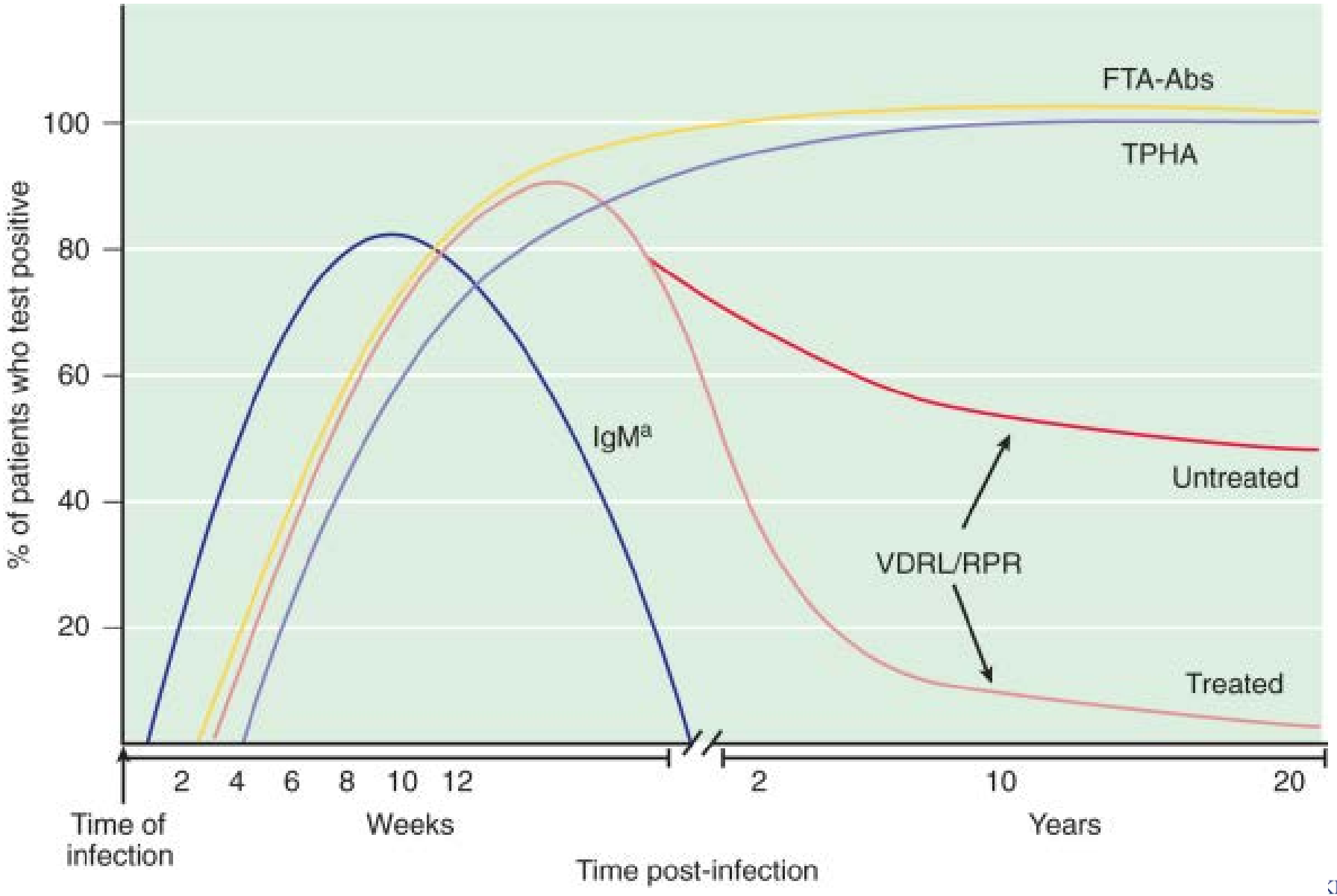
Time Course of Syphilis Serologies



Peeling et al. Bulletin of WHO 2004; 82(6):439-46

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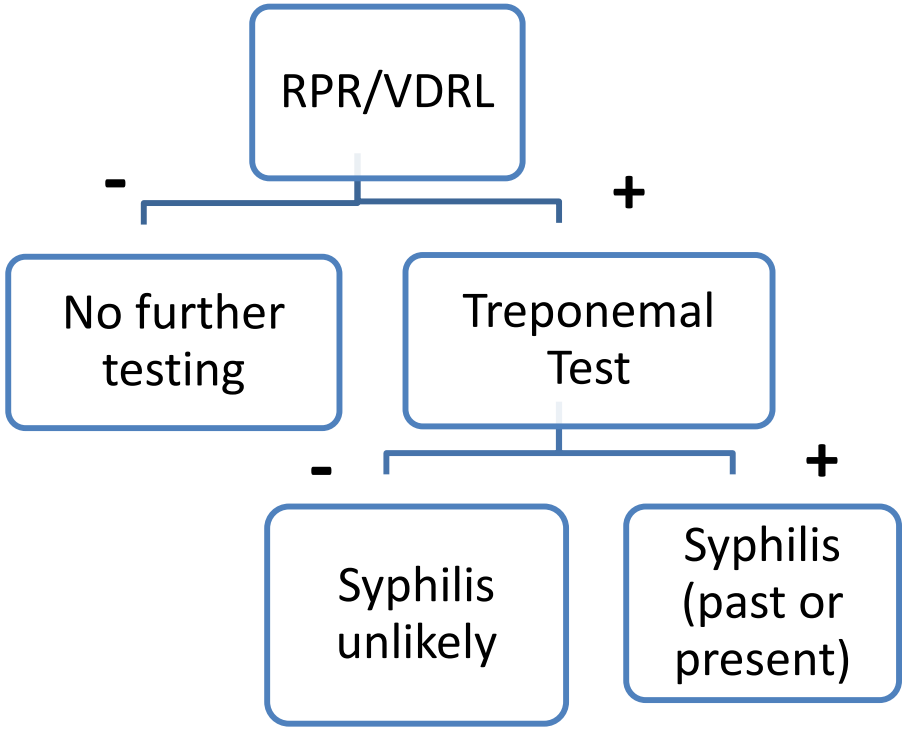
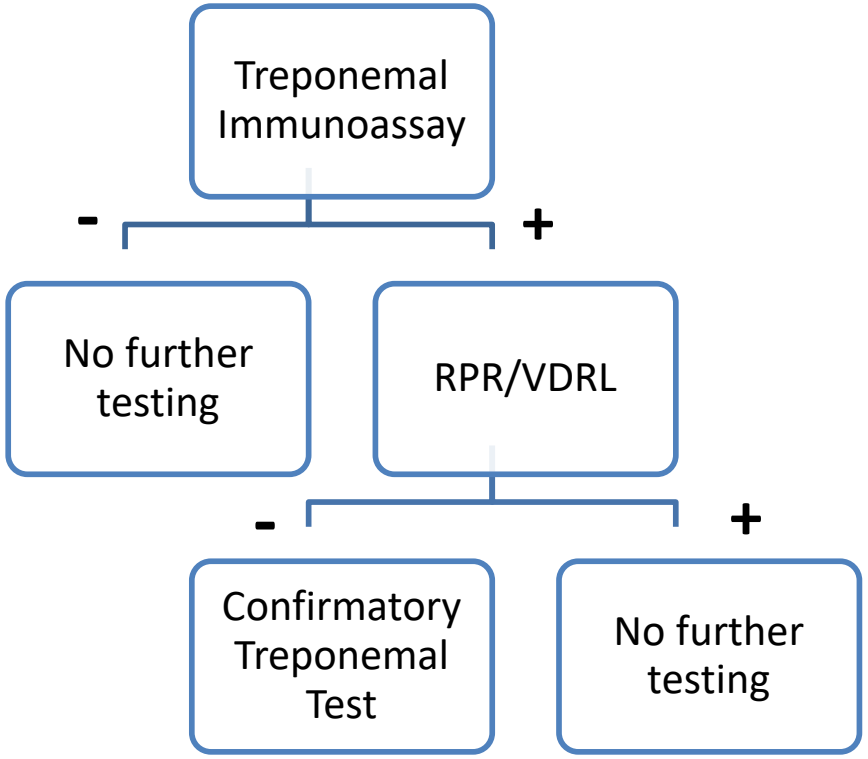
Syphilis Serology Algorithms

Traditional algorithm



Reverse algorithm



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Poll Question #1

Case A: 48 y.o. male with rash and LFT abnormalities

Serum Treponemal Ab reactive, RPR 1:128

What is the recommended therapy?

A. Benzathine PCN-G 2.4 MU IM x 1
B. Azithromycin 2000mg PO x 1
C. Benzathine PCN-G 2.4 MU IM qweek x 3
D. Aqueous PCN-G 3MU IV q4hr x 10-14 days

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Syphilis Therapy: 1°, 2°, Early latent (<1 yr)

- **Benzathine PCN 2.4 million units IM x1**
  - No documented resistance
  - Other PCN forms NOT substitutable
- **Penicillin allergies / reactions**
  - Doxycycline 100mg PO BID x 14 days
  - Ceftriaxone 1-2000mg qday IM or IV x 14 days
  - Azithromycin 2000mg PO x 1
    - NOT in MSM or pregnancy
    - Reports of treatment failures (23s rRNA mutations)
- **Pregnancy**: only use PCN! Desensitize if necessary

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Late (>1 yr) latent or latent with unknown duration

- **Benzathine PCN G 2.4 MU x3 doses (1 week intervals)**
  - Careful exam for lesions c/w prim, sec, or tertiary
  - Careful history and exam for neurologic findings
  - PCN-allergy: doxy (or tetra) for 28 days
- **What if they miss a week?**
  - One 10-14 day interval may be acceptable
  - Based on clinical experience, not pharmacology
- **Pregnancy**: only use PCN!
  - Desensitize if necessary
  - Repeat whole course if miss a 7-9 day interval

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Follow-up Testing

- Follow-up of quantitative non-treponemal titers
  - At least 6, 12, 24 months
  - Failure to decline 4-fold
    - CSF exam (for all?) but at least if starting ≥ 1:32
    - Repeat treatment (at least x 1)
- HIV-testing after any syphilis diagnosis
- NG/CT screening

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Tertiary

- Tertiary (cardiovascular or gummatous lesions)
  - CSF exam before treatment in all cases
  - If CSF negative, then treat as late latent
  - Some treat cardiovascular disease with CNS regimen

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Syphilitic Hepatitis

- **Early (primary and secondary) stage**
  - **LFT abnormalities 10-20%** (HIV neg and HIV pos)
  - Mostly asymptomatic
  - Hepatomagaly common
  - Disproportionately elevated AP typical, but not 100%
  - Treponemes identifiable in necrotic liver material
  - **Resolution with treatment (1-4 months)**

- **Late stage:** fibrosis, gummas, and hepar lobatum (pre-antibiotic era)

Lancet. 1975;2(7941):896-9

Int J STD AIDS. 2012;23(8):e4-6

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Poll Question # 2

Case B: 43 male with vision loss

- **Serum Treponemal Ab reactive, RPR 1:256**

What is the recommended therapy?

A. Azithromycin 2000mg PO x 1
B. Benzathine PCN-G 2.4 MU IM qweek x 3
C. Aqueous PCN-G 3-4 MU IV q4hr x 10-14 days
D. Ceftriaxone 2000mg IV qday x 10-14 days

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Ocular Syphilis

- **Every** part of the eye can be involved / **any** stage of the infection
- No eye findings are specific for syphilis
- **Presumptive diagnosis**
  - Objective (otherwise unexplained) eye findings
  - Active syphilis
- **Definitive diagnosis**
  - Treponemes in vitreal sample
  - CSF VDRL reactive

Semin Ophthalmol 2005; 20:161–167

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Ocular syphilis in 8 US Jurisdictions 2014-2015

Review all TP cases*

- 388 / 65,130 (0.6%)
- Range 0.17 – 3.9%
- Male 93%
- Known MSM 69%
- HIV-infected 51%

(Chart review, data not prospectively collected.
CA (partial), FL, IN, MD, NYC, NC, TX, WA

Characteristic	No.	(%)
Total	388	(100.0)
Stage of syphilis		
Primary	8	(2.1)
Secondary	101	(26.0)
Early latent	79	(20.4)
Late or latent of unknown duration	193	(49.7)
Unknown	7	(1.8)
Additional symptoms of neurosyphilis	87	(22.4)
Reported ocular symptoms (among 326 with symptoms)		
Blurry vision	210	(64.4)
Vision loss	107	(32.8)
Eye pain or red eye	46	(14.1)
CSF VDRL (among 174 with a documented result)		
Reactive	122	(70.1)
Nonreactive	52	(29.9)

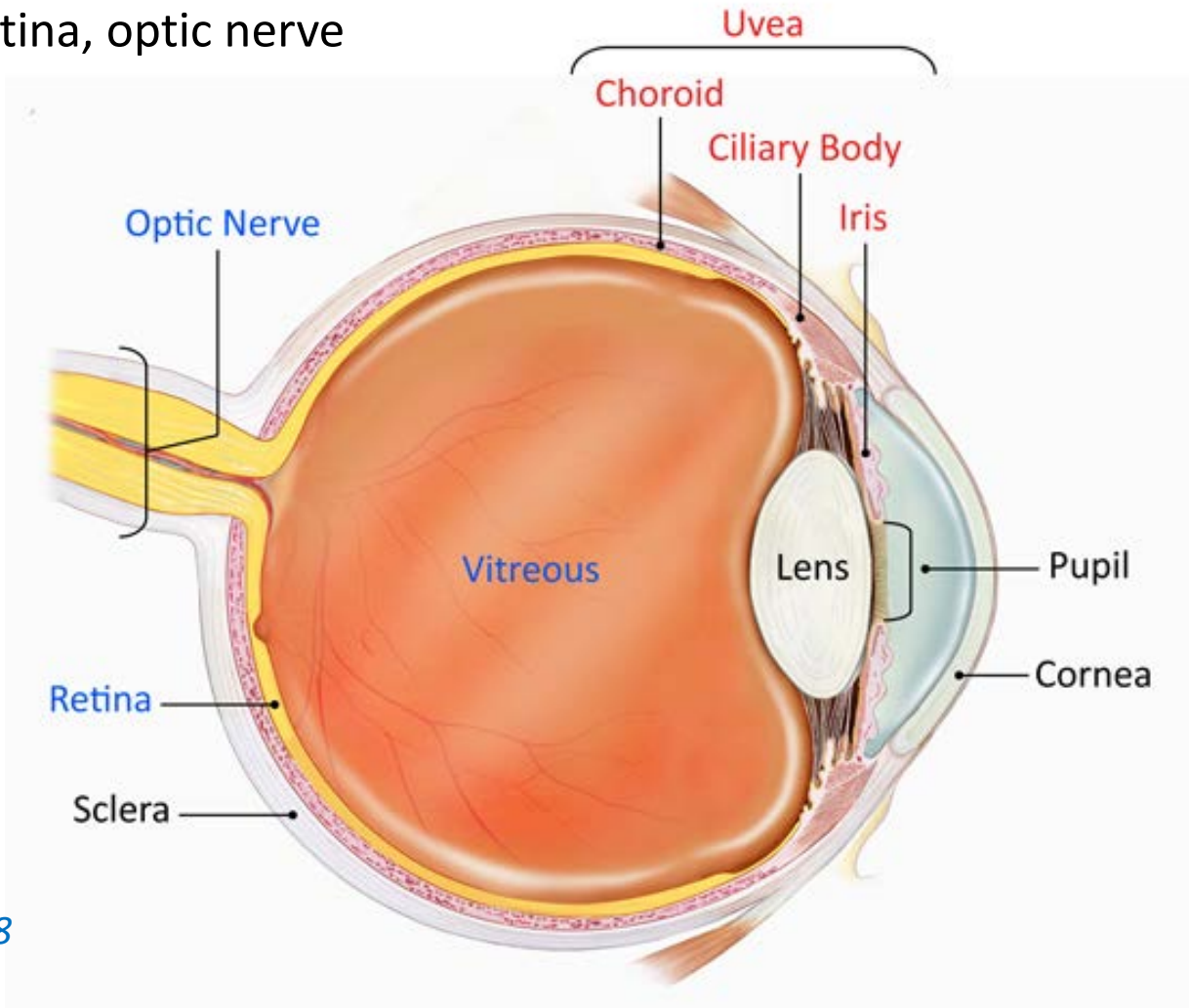
MMWR Nov 4, 2016; 65(43): 1185-88

Ocular Findings

Are ocular syphilis and neurosyphilis the same entity?

No, but a lot of co-occurrence (~70% have neurosyphilis)

Embyrologically, neuroectoderm forms
posterior layers of iris, retina, optic nerve



Ophthal findings (8 district review)

- Uveitis 46%
- Retinitis 13%
- Optic neuritis 11%
- Ret. detach. 4%

MMWR Nov 4, 2016; 65(43): 1185-88

Diagnosis of Ocular Syphilis

- **Presumptive diagnosis**
  - (Ocular signs in a person with syphilis)
  - Most diagnoses are presumptive
  - **Indicates a full treatment course!**

- Most patients will have positive serological tests
  - In late ocular syphilis, ~30% have a NEGATIVE serum RPR but all will have a positive serum treponemal test
  - VERY rarely, primary stage will have negative serologies (both treponemal and RPR) that will later turn positive

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Do you need to do an LP in someone who only has eye symptoms and no neurological symptoms?

- **YES**, and here's why:
  - CSF VDRL = DEFINITIVE diagnosis of ocular syphilis
    - Helpful in excluding other causes
    - Abnormal CSF profile with negative VDRL: still consistent with syphilis (but not definitive)
  - Practical
    - While the antibiotic regimen is the same for ocular and neurosyphilis, patients with neurosyphilis (about 70%) need follow-up LP(s)
    - Normalization of the CSF parameters is an objective way to track cure if visual symptoms fail to improve
- **Do not delay antibiotics waiting for the LP!**

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Ophthalmology involvement and steroids

- **Ophthalmologist:** recommended in all cases
  - In questionable cases, can help determine if objective eye signs
  - Help manage complications
  - Exam should be right away (24 hours?); in some cases ocular syphilis progresses rapidly to blindness (refer to ED if no urgent ophthalmologist available)
- **Do not delay antibiotics waiting for the ophthalmologist!**
- **Steroids**
  - No clear benefit or harm
  - Topical: adjunct for interstitial keratitis, anterior uveitis
  - Systemic: adjunct for posterior uveitis, scleritis, optic neuritis

Retina 2012; 32:1915–1941

Complications

- Incidence of **visual impairment**
  - 0.29/eye year for HIV uninfected
  - 0.21/eye year for HIV infected
- Incidence of **permanent blindness**
  - 0.07/eye year for HIV uninfected
  - 0.06/eye year for HIV infected

- **Risk factors for poor visual outcomes**: longer duration of untreated infection; macular chorioretinitis
- **Long-term complications**: glaucoma, cataract, epiretinal membrane and macular edema, choroidal neovascularization, widespread chorioretinal scarring

Am J Ophthalmol 2015; 159:334-43
Lancet Infect Dis 2004; 4(7):456-66

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Diagnosis of Neurosyphilis

- CSF exam if
  - Neurologic signs/symptoms
  - Ocular / otologic signs/symptoms
  - (During any stage of syphilis)

- Dx by any combination of
  - abnormal CSF cell count (> 5 WBC)
  - abnormal CSF protein
  - Reactive CSF-VDRL with or without symptoms
  - CSF-FTA reactive (More sensitive than CSF-VDRL, but less sensitive)

Neurosyphilis therapy

- **Recommended:** Aqueous crystalline PCN G 18-24 MU per day, divided 3-4 MU IV q4hr or continuous infusion for 10-14 days
- **Alternative:** Procaine PCN G 2.4 MU IM qday **PLUS** probenecid 500mg PO 4 times daily for 10-14 days
- **Penicillin allergy**
  - Consider ceftriaxone 2000mg qday IM or IV x 10 - 14 days, **OR**
  - Skin test and desensitize
- **Pregnancy**: only use PCN! Desensitize if necessary
- **Practical**: B PCN G in clinic while arranging for LP and IV therapy (if any chance LTFU after leaving clinic
- **Late stage**: consider B PCN G 2.4 MU IM qweek x3 after finishing IV

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Follow-up of neurosyphilis

- **Serial CSF exam q6 months**
  - Until cell count normal
  - Also follow protein +/- VDRL
    - Slower to normalize than WBC
    - Significance less clear

- **Consider retreatment**
  - WBC not decreased by 6 months
  - WBC or protein not normal after 2 years

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

CDC 2015 STD Surveillance Report

	Cases, 2015	Increase vs. 2014
Chlamydia*	1,526,658	6%
Gonorrhea	395,216	13%
Syphilis (P&S)	23,872	19%

* Most frequently reported infectious disease in U.S.

https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/std-trends-508.pdf

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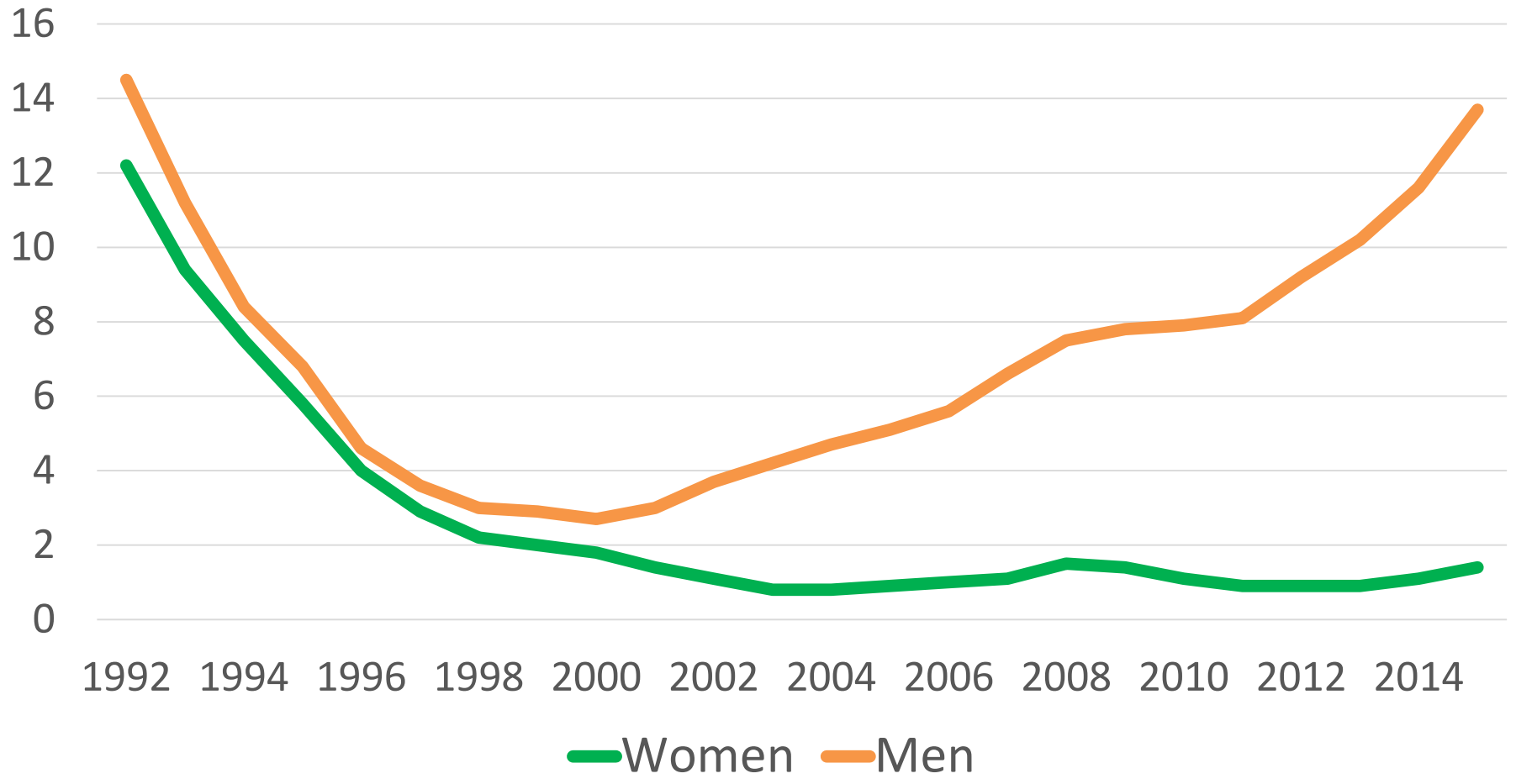
P&S Syphilis per 100,000, U.S.



CDC STD Surveillance reports 1996-2015

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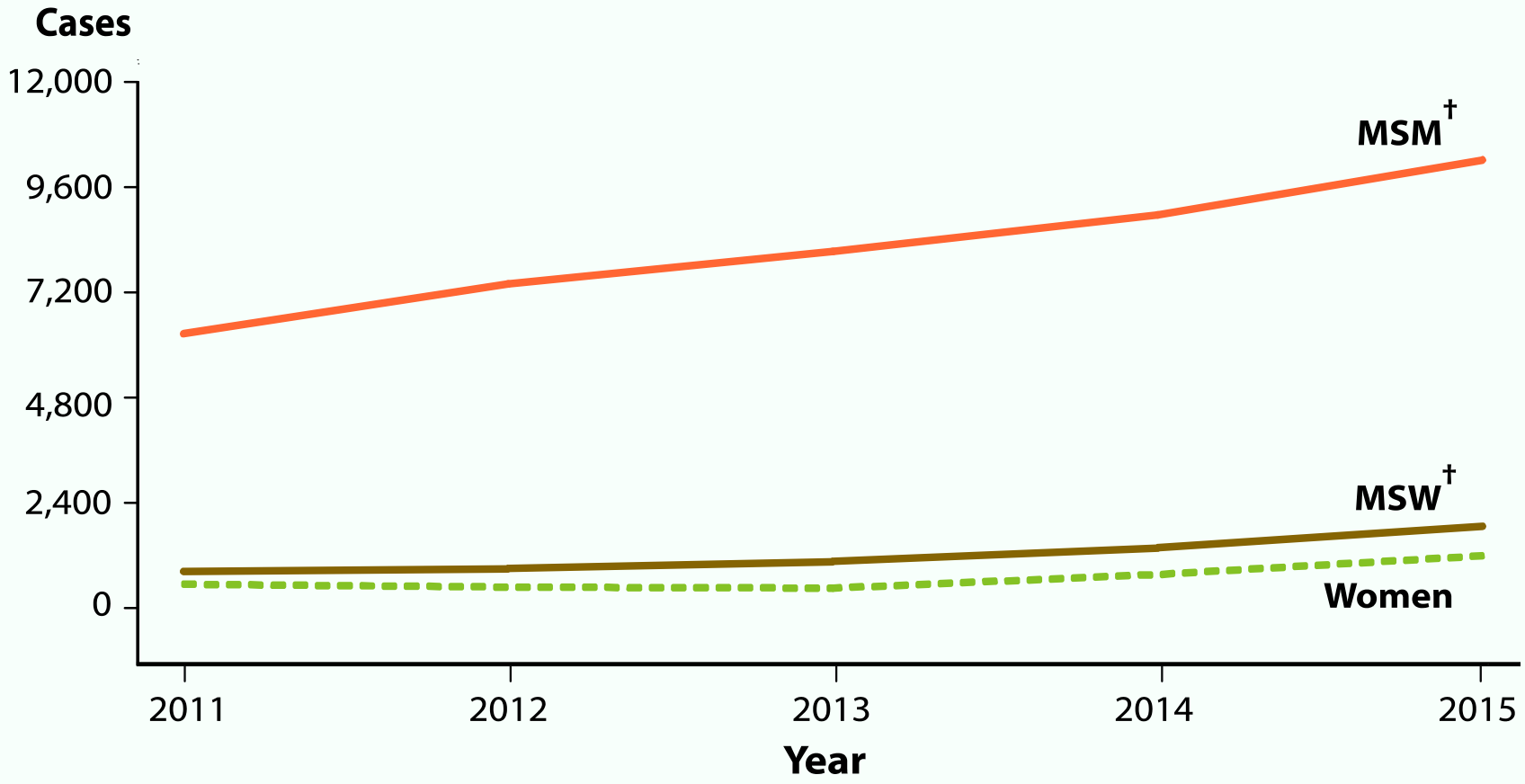
Primary and Secondary Syphilis — Reported Cases by Sex and Sexual Behavior, 37 States*, 2011–2015

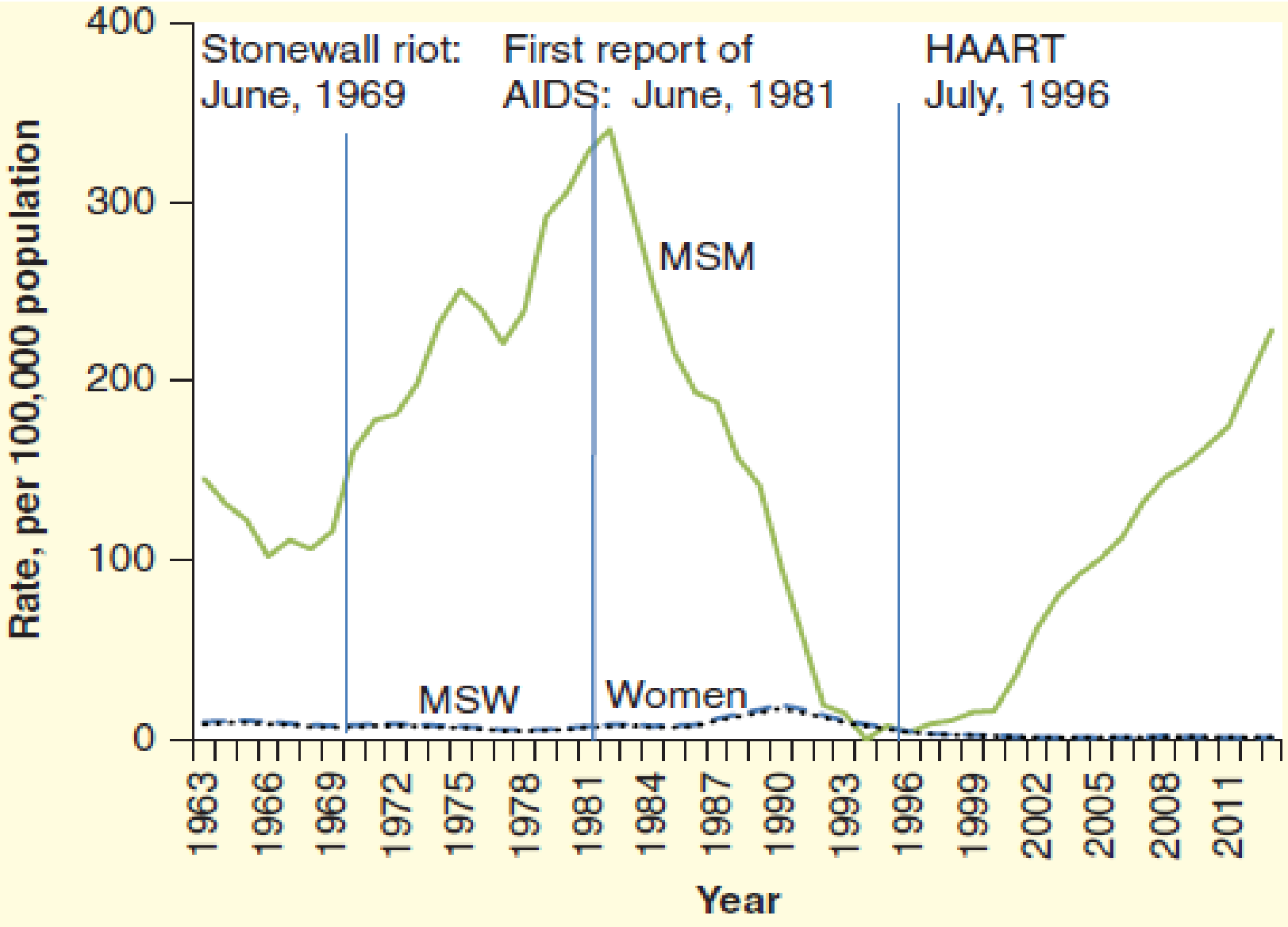


* 37 states were able to classify ≥70% of reported cases of primary and secondary syphilis as either MSM†, MSW†, or women for each year during 2011–2015.

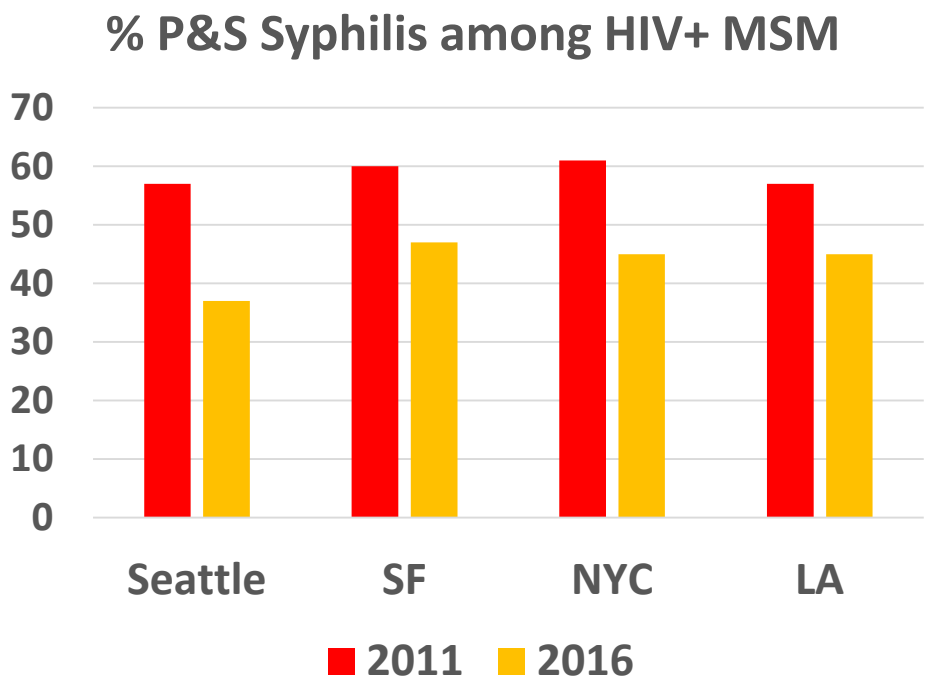
† MSM = Gay, bisexual, and other men who have sex with men (collectively referred to as MSM); MSW = Men who have sex with women only.

Estimated Annual Rate of P&S Syphilis

Peterman. Expert Rev Anti Infect Ther 2015; 13(2):161–168



Syphilis trends in HIV-uninfected MSM



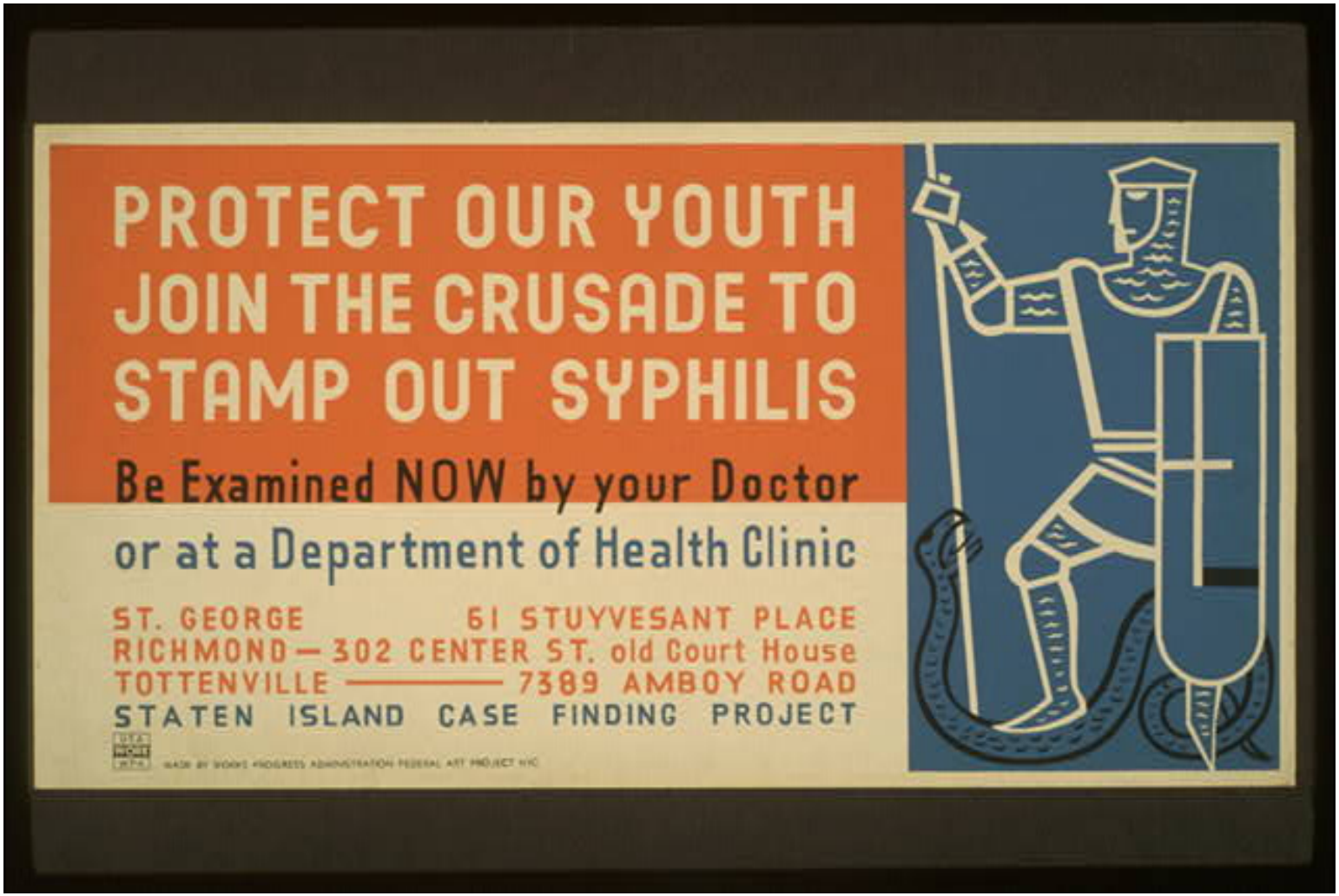
P&S Syphilis by HIV status and risk*, King County, WA

	2010	2016
HIV +, high risk	43%	26%
HIV +, low risk	17%	9%
HIV -, high risk	6%	10%
HIV -, low risk	**21%**	**38%**

*High risk: prior syphilis +/- meth use

Matthew Golden, Syphilis in the Era of Treatment as Prevention & PrEP, CROI 2017

Addressing the Ugly Trends



http://www.loc.gov/pictures/collection/wpapos/item/98514735/

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Risk compensation: anonymous partners via the internet

MSM who used the internet had ~2-fold higher odds of engaging in unprotected anal intercourse, a 3.4 higher odds of having anonymous sex, and a higher average number of partners in the past 6 months (10 vs 5)

Liau. Sex Transm Dis 2006;33:576–84
Taylor. Sex Transm Dis 2004;31:552–6
Ng. m J Public Health2013; 103:1450–6

Sex on demand: geosocial networking phone apps and risk of sexually transmitted infections among a cross-sectional sample of men who have sex with men in Los Angeles county

Beymer. Sex Transm Infect 2014;90:567–572

Recent outbreaks of infectious syphilis, United Kingdom, January 2012 to April 2014

"Targeting at-risk populations was complicated as many sexual encounters involved anonymous partners. **Outbreaks among MSM were influenced by the use of geospatial real-time networking applications** that allow users to locate other MSM within close proximity."

Simms. Euro Surveill. 2014;19(24):pii=20833

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HIV PrEP and STI risk - 1

- Baseline incidence for one or more NG, CT, or TP is 50-90/100PY (high!) among MSM initiating PrEP in real world settings
- How much does risk compensation due to PrEP contribute?

Meta-Analysis* STI's among MSM

	PrEP	No PrEP
NG	38%	4%
CT	38%	7%
TP	15%	1%

* PrEP studies recruit high risk, have more frequent monitoring

Incidence of STI's in PROUD*

	Immediate	Deferred
NG	39%	37%
CT	30%	22%
TP	11%	9%

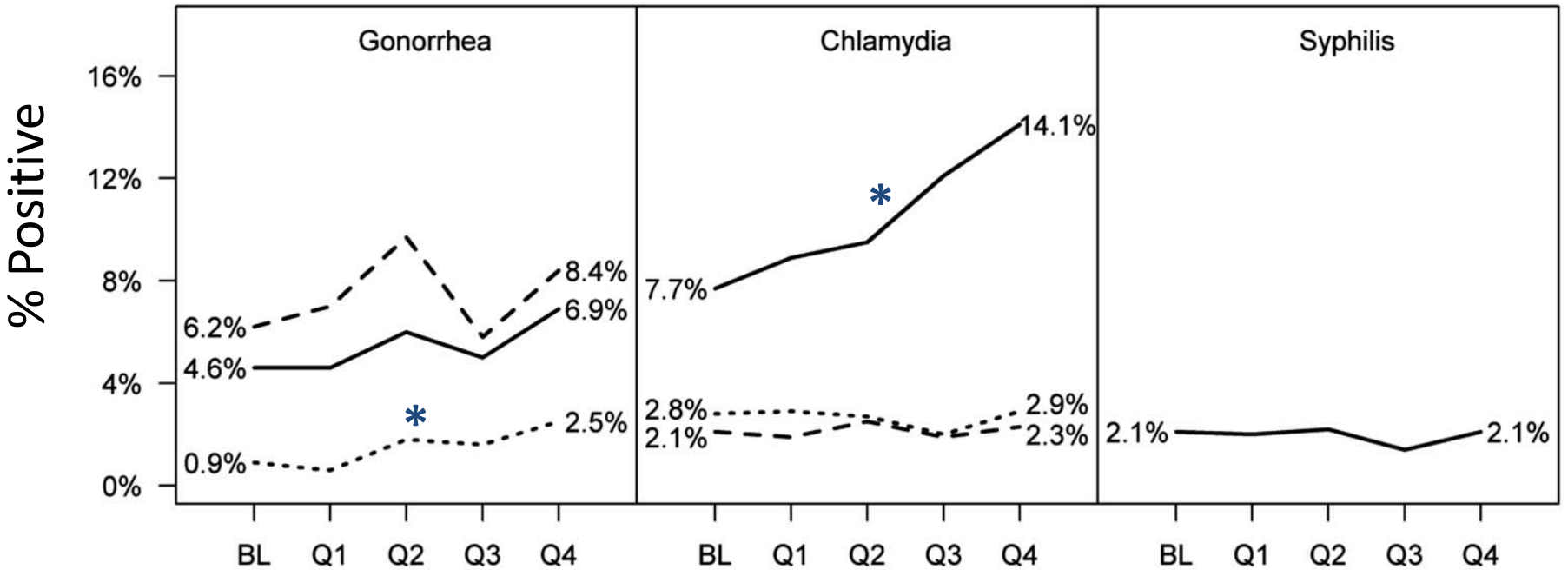
* RCT randomizing to immediate vs. 1-year deferral, stopped early b/c 86% effective

Lancet 2016:53, JAIDS 2016:540, JAMA Int Med 2016:75, AIDS 2016:2251

PrEP and STI risk - 2

PrEP Initiation, 972 Enrollees, Kaiser Northern CA 2012-2015

- Median annual: urine NG/CT 4.5, rectal NG/CT 3.6, oral NG/CT 3.8, syphilis 4.9
- 342/972 with ≥ 1 STI during follow-up, total 771 STI's (90.7 per 100PY)



* p<0.05 for increasing trend

JAIDS 2016:540

What to do about bacterial STI's among MSM?

1. Do nothing about asymptomatic STI's among MSM?

2. Screen **broadly, at every relevant body site**, **and frequently** as per guidelines?

3. Antibiotic prophylaxis for STI's?

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Do nothing about asymptomatic STI's among MSM?

1. Cannot conceive of leaving **syphilis** untreated, and we know our MSM patients are getting it!

% of Seattle Syphilis Cases *Confirmed* Neuro Disease 2012-13		
Early (489)	489	2.9%
Unknown/Late (84)	84	7.1%

2. Some asymptomatic NG/CT will progress

Sex Trans Dis 2015:702

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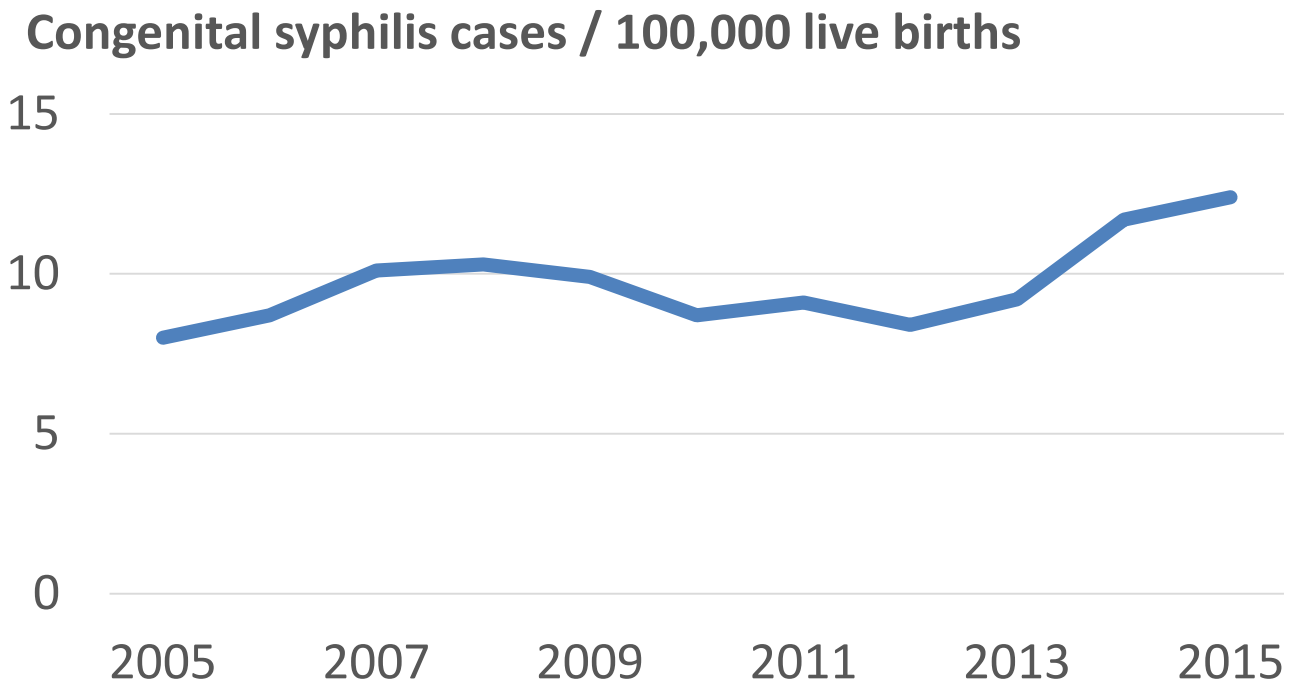
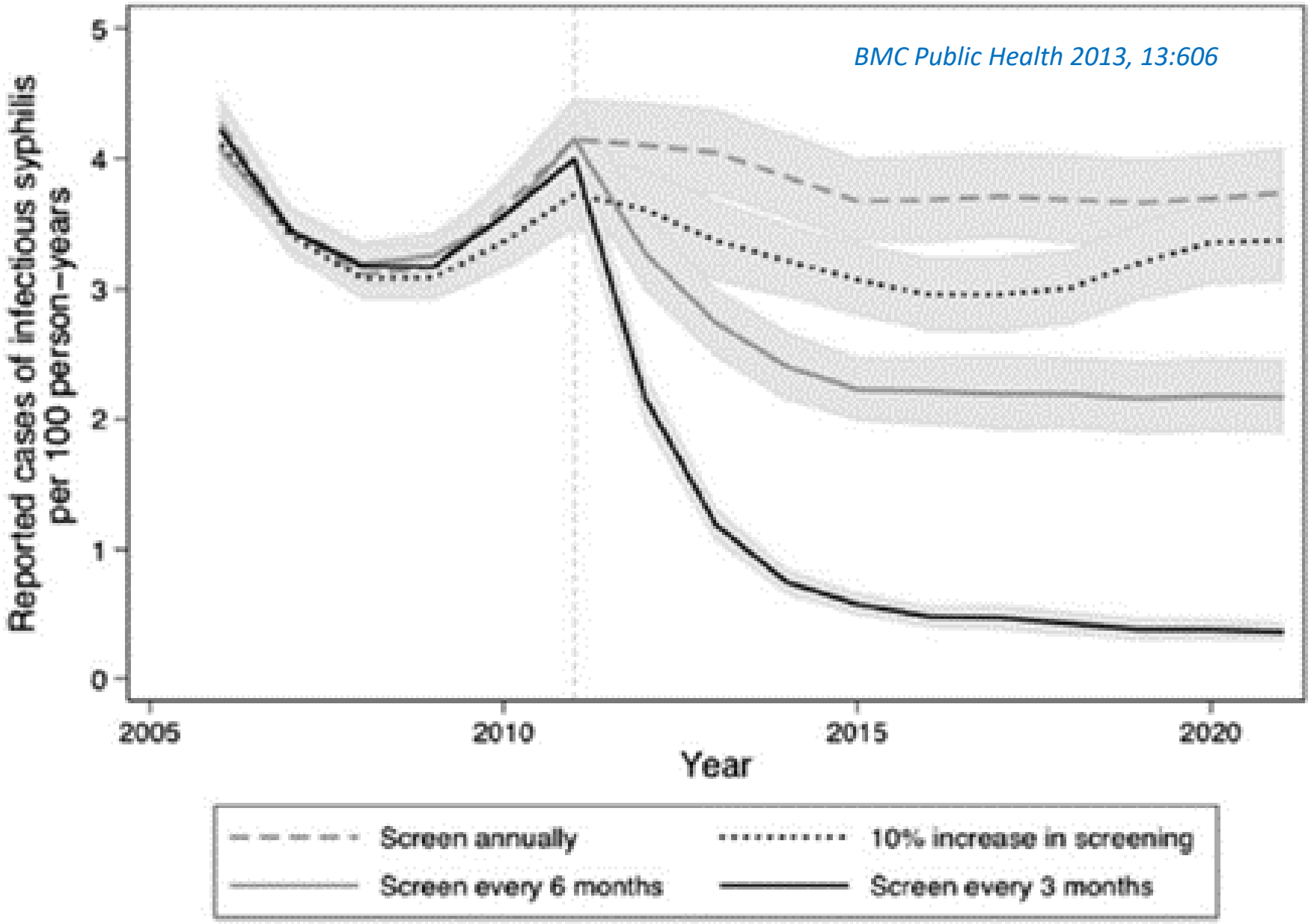
Women (and babies) will get these STIs

5-14% of MSM with syphilis report recent female partners*



Golden, CROI 2017; CDC STD Surveillance

Screening to Fight the Syphilis Trend



Frequent Syphilis Screening

- Simulation models of MSM populations
  - Syphilis elimination possible by q12 month screening of 62% or Q3 month screening of 23%
  - Q3 month screening of high-risk individuals much **more effective and cost-efficient than contact tracing or condom promotion**

Sex Transm Inf 2016, 92:49-54, Gray, *STD* 2010; 37:298-305; *J Publ Health Management Practice* 2011; 17:513-21, *Sex Transm Dis* 2011;38: 1151-1158

- Among 1268 HIV-uninfected MSM (National HIV Behavioral Surveillance System), Baltimore 2004 – 2011
  - 54% received an HIV test in previous 12 months
  - 31% had received a syphilis test
  - 72% of unscreened had seen a healthcare provider

AIDS Behav 2015, 19:2036

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CDC Screening Guidelines for Sexually Active Persons

	Syphilis	NG/CT	HIV
Women	Pregnancy	<25: annual ≥25: consider*	13-64 (opt-out) If other STI
MSW		Consider CT*	13-64 (opt-out) If other STI
MSM	≥ annual**	≥ annual** at sites of contact (**urethra, rectum, pharynx**) regardless of condoms	≥ annual if new partner(s) since last test
PLW HIV	≥ annual**	≥ annual**	

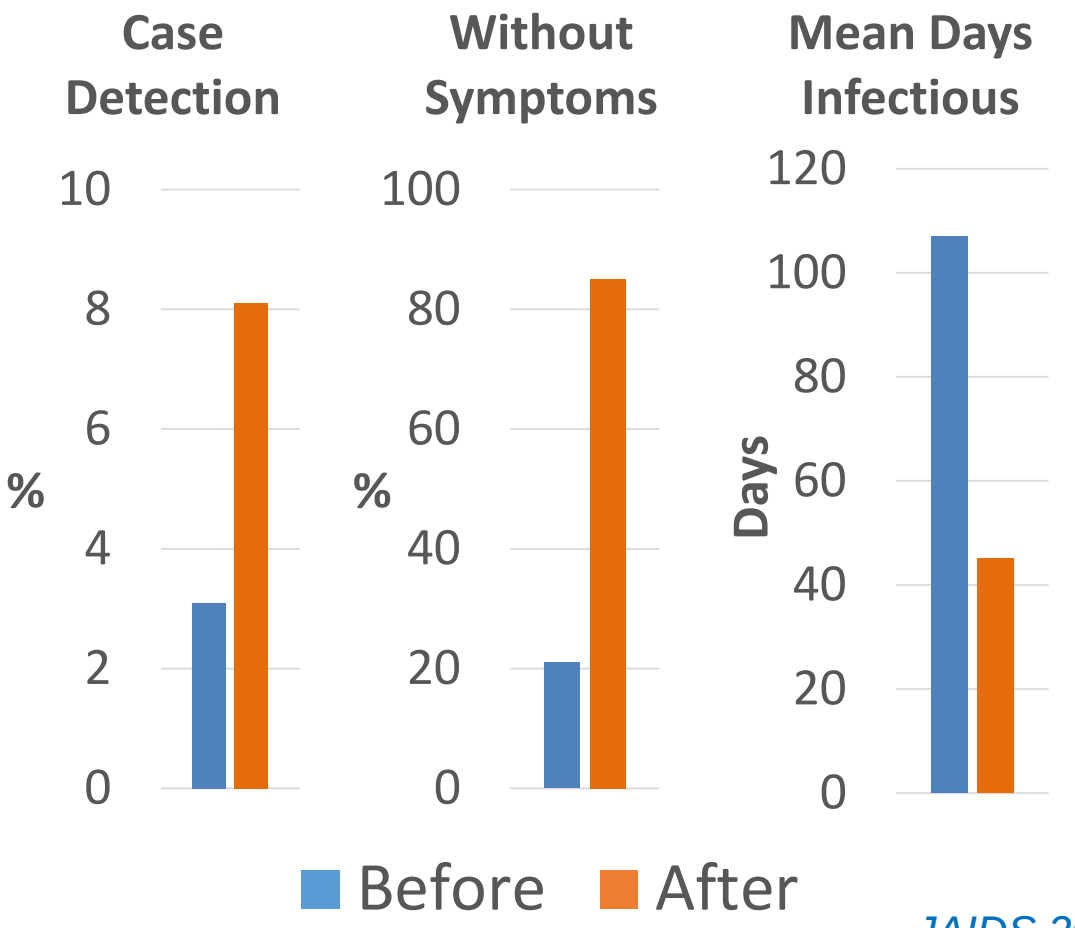
* New or multiple partners, transactional sex, partners with STI's

** q3-6 months based on risk factors above

https://www.cdc.gov/std/tg2015/screening-recommendations.htm

Frequent screening produces results

18 mon before/after **opt-out syphilis** screening for all bloods among 500 MSM, Melbourne HIV Clinic



JAIDS 2010:211

US Guidelines NG/CT and syphilis:

- "Q3-6 months if high risk"
- PrEP clinics "at least q6 months"

For me q3 months:

- Any prior bacterial STI and age <45
- Patients expect and request screening

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Doxycyline prophylaxis for high-risk MSM

- CT and syphilis resistance non-existent
- NG resistance already widespread
- Randomized, controlled, open-label pilot
  - Quarterly payments ($25-$100) for remaining syphilis-free vs. doxycycline 100mg daily
  - 30 HIV+ MSM with multiple prior syphilis infections

	$ incentives	Doxy prophylaxis	P-value
NG/CT	8	4	0.36
Syphilis	7	2	0.10
Any STI	15	6	0.02

- Two ongoing RCT's of daily doxy (NCT02864550, NCT02844634)

Sex Trans Dis 2015:98

On-Demand Doxy PEP, IPERGAY extension

- IPERGAY trial: on-demand TDF/FTC PrEP/PEP for HIV
- Randomized 232 participants in extension phase
  - No Doxy PEP, or
  - Doxy 200mg x1 at 24-72 hours after sex

	No PEP	Doxy PEP	Hazard Ratio
NG	25	22	0.83 (0.47, 1.47)
CT	21	7	**0.30 (0.13, 0.70)**
Syphilis	10	3	**0.27 (0.07, 0.98)**
Any STI	45	28	**0.53 (0.33, 0.85)**

- 83% of PEP arm used PEP, median 7 (3-15) pills/month
- No evidence of risk compensation
- Higher incidence of GI adverse events

Molina 91LB, CROI 2017

Summary

- Hepatic syphilis case
- Syphilis stages, serologic tests, and treatment regimens
- Ocular syphilis and overlap with neurosyphilis
- Syphilis, NG, CT at highest levels
- MSM with steepest increases in syphilis incidence
- **Broad, frequent screening** key to reversing current STD trends
- PrEP users (among others) should be screened q3-6 months

We have reached a decisive moment for the nation. STD rates are rising, and many of the country's systems for preventing STDs have eroded. We must mobilize, rebuild, and expand services – or the human and economic burden will continue to grow.

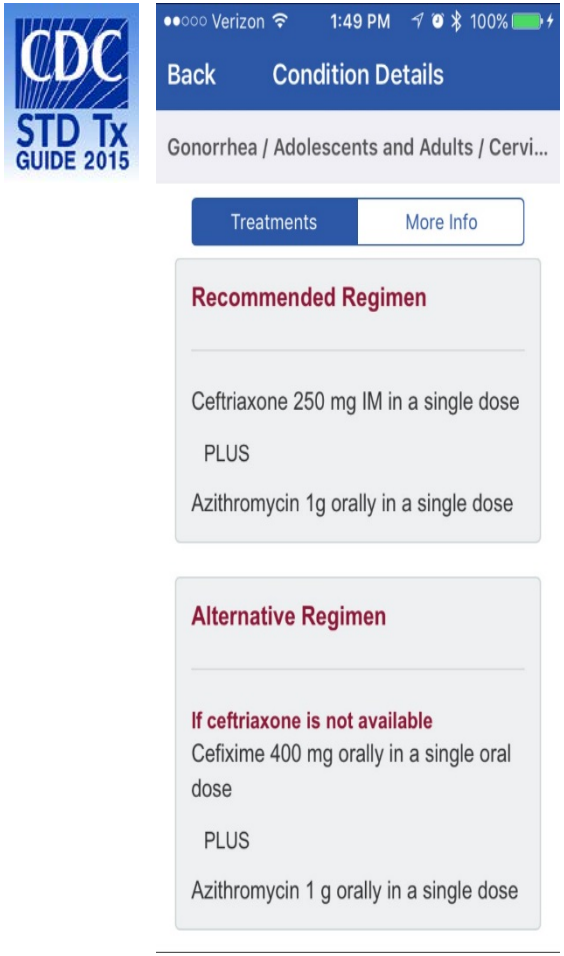
– Dr. Jonathan Mermin, Director

Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

JOHNS HOPKINS SCHOOL of MEDICINE

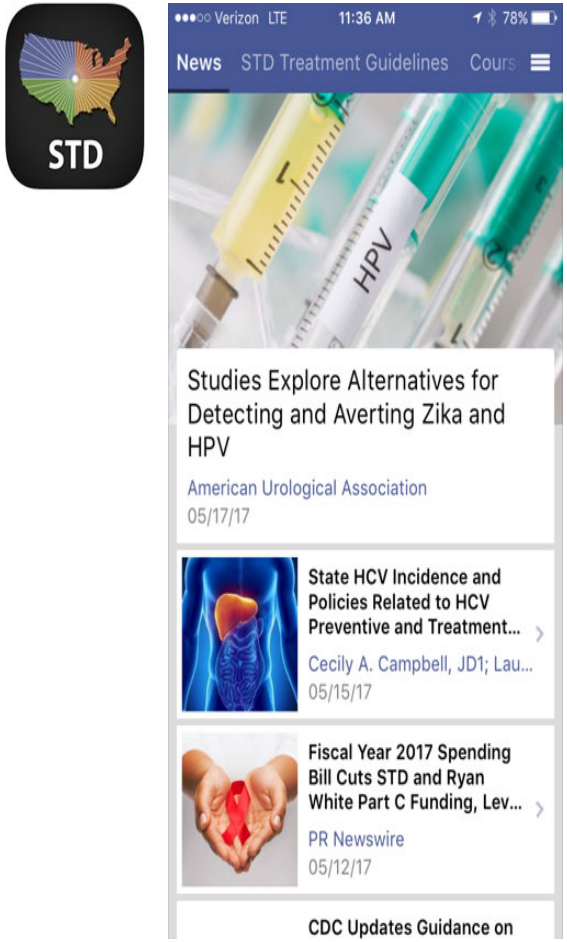
STD Treatment Guidelines Apps

STD Tx Guidelines



Available on iTunes & Google Play

STD Clinical Toolbox



Available on iTunes

STD Treatment Guidelines wall charts, pocket guides, and the full MMWR article at: www.cdc.gov/std/tg2015

The NNPTC provides:

- Clinical training
- STD clinical consultations
- Resources and tools for STD treatment

National Network of STD Clinical Prevention Training Centers

CDC
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Visit: www.nnptc.org

Questions?

THANK YOU!