Sexually Transmitted Diseases Update

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Why Diagnose and Treat STIs?

- 20 millions new infections in the US annually
- 110 million total STIs among men and women
- Health consequences of untreated STIs
  - Women's reproductive health
    - Untreated CT or GC may lead to PID
    - Leading infectious cause of infertility in the US
  - Infant mortality/morbidity
    - Neonatal HIV, HSV and congenital syphilis
  - HIV transmission
- Direct medical cost
  - $16 billion (2010)*

*Estimate incorporates minor corrections in the Persp Sex Rep Hlth 2010

Populations at Greatest Risk for STDs

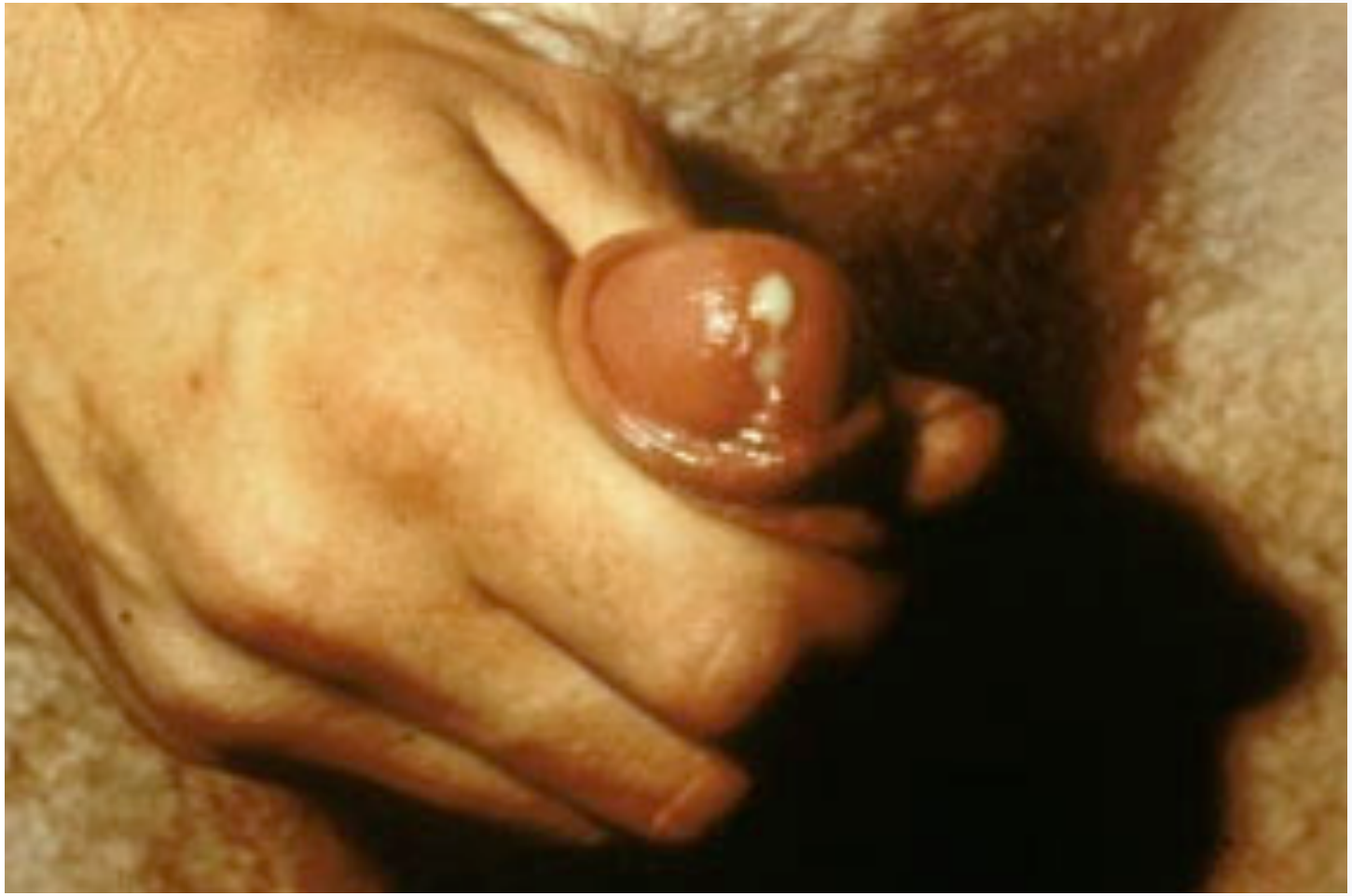
- Youth
  - ~50% of STDs to occur in 15-24 years old
- Racial/ethnic minorities
  - STDs among highest or all racial/ethnic health disparities
  - AA 71% GC, 48% CT, 52% syphilis
  - Over last 5 years syphilis cases increased more than 150% among young African American men.
- MSM
  - Accounted for 72% of all primary and secondary syphilis cases in 2014 (5 in 10 also HIV)
  - High rates of HIV co-infection

STD Prevention: Clinician Role

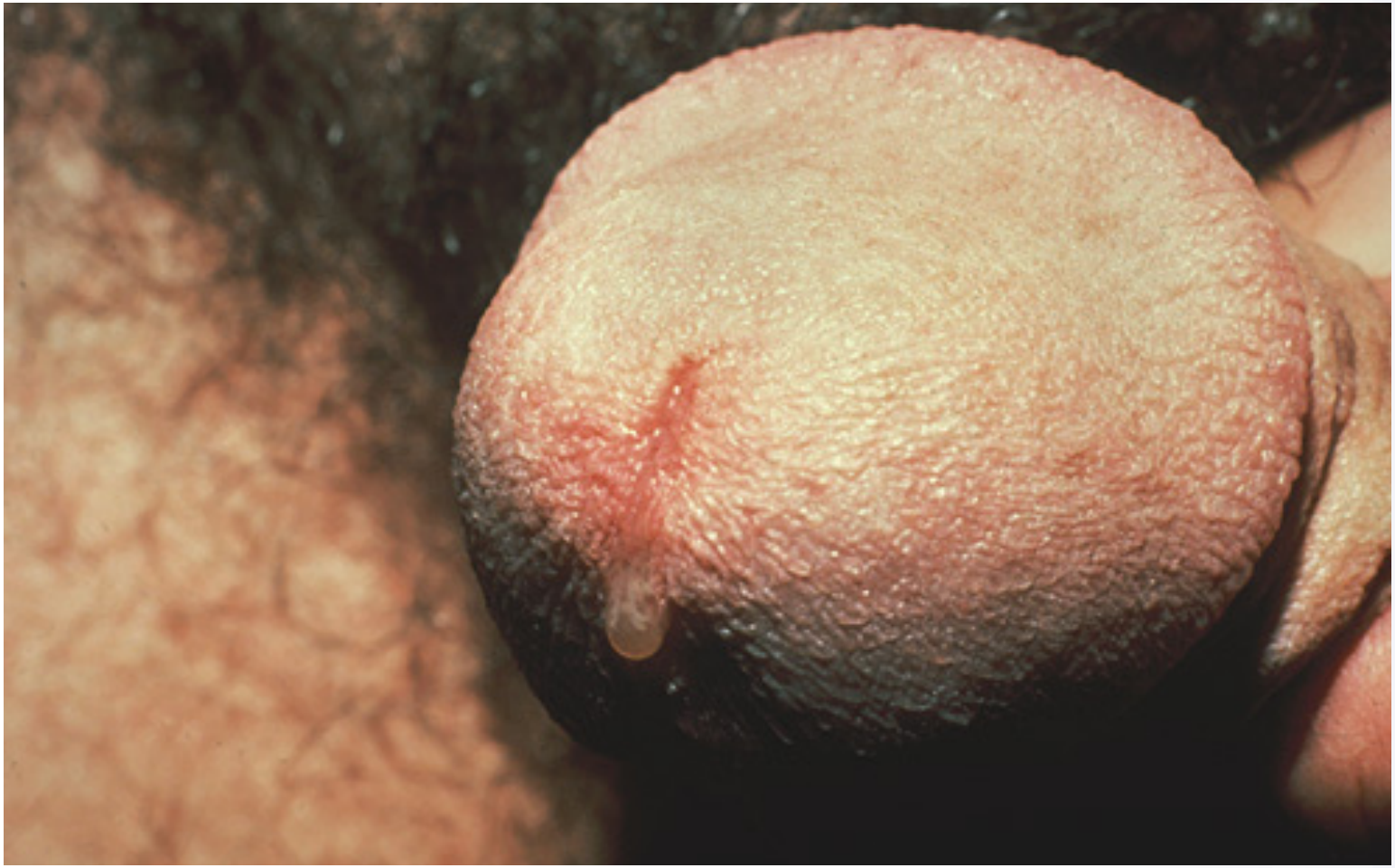
- Take sexual history in all patients
- Assess patients' risk and test accordingly
- Talk to patients about pre-exposure vaccination
- Provide or refer for prevention/risk reduction counseling (ie. PrEP for MSM with high HIV risk)
- Diagnose and treat infected patients
- Provide or refer for partner management/services
- Report STDs and HIV in accordance with state and local requirements
- Keep STD/HIV report confidential

Male Urethritis

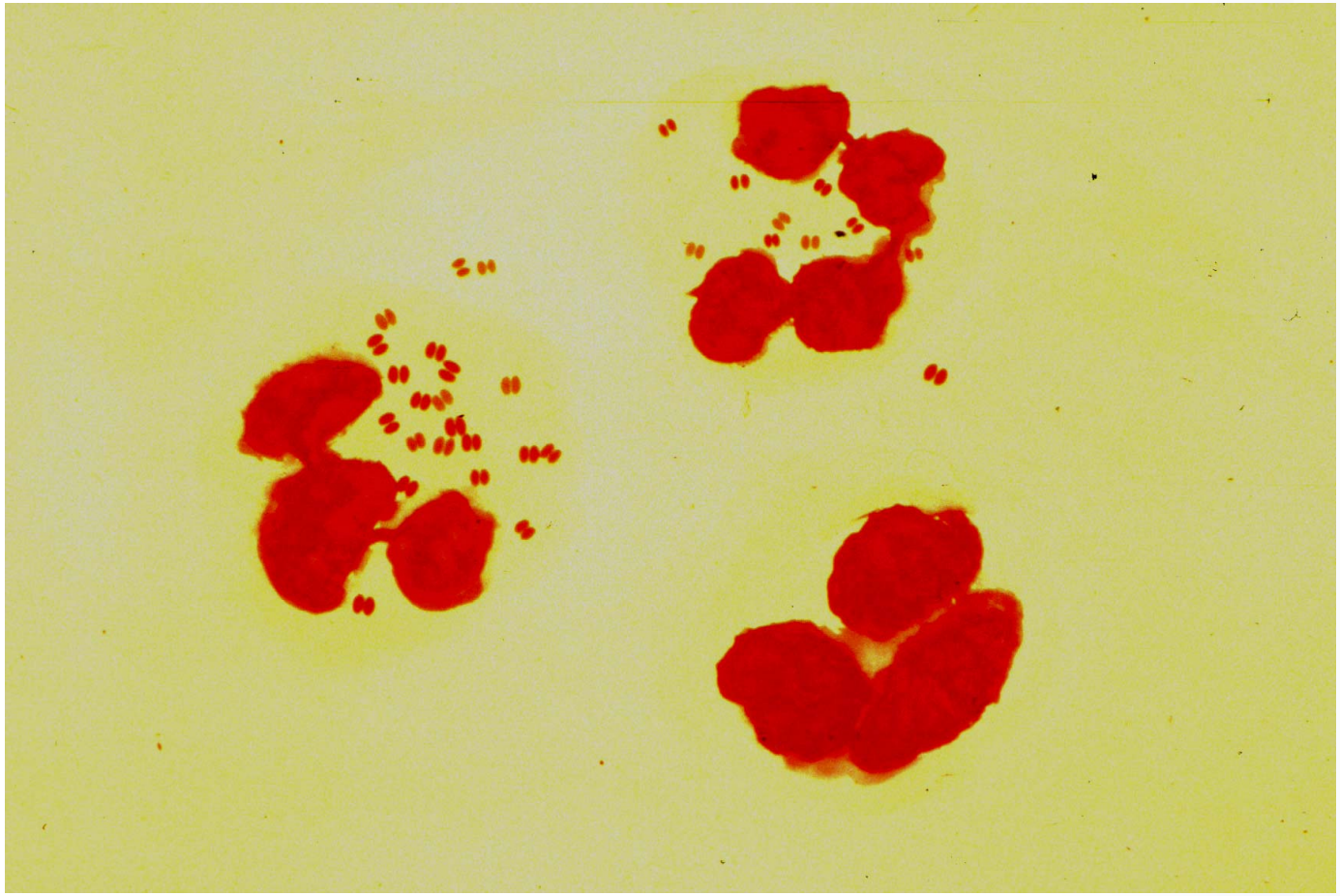
Gonococcal Urethritis



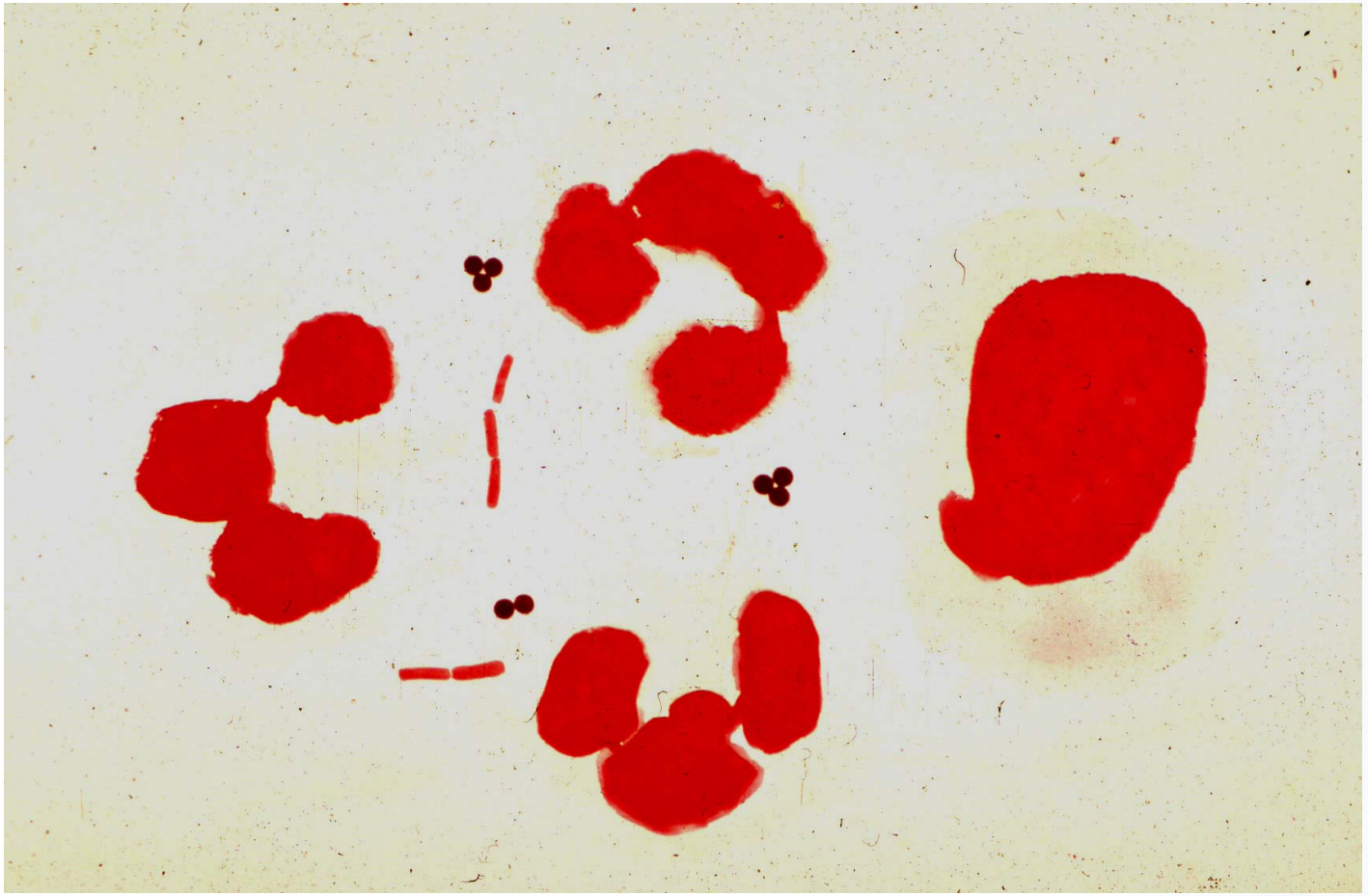
Nongonococcal Urethritis



Gram Negative Intracellular Diplococci (GNID)



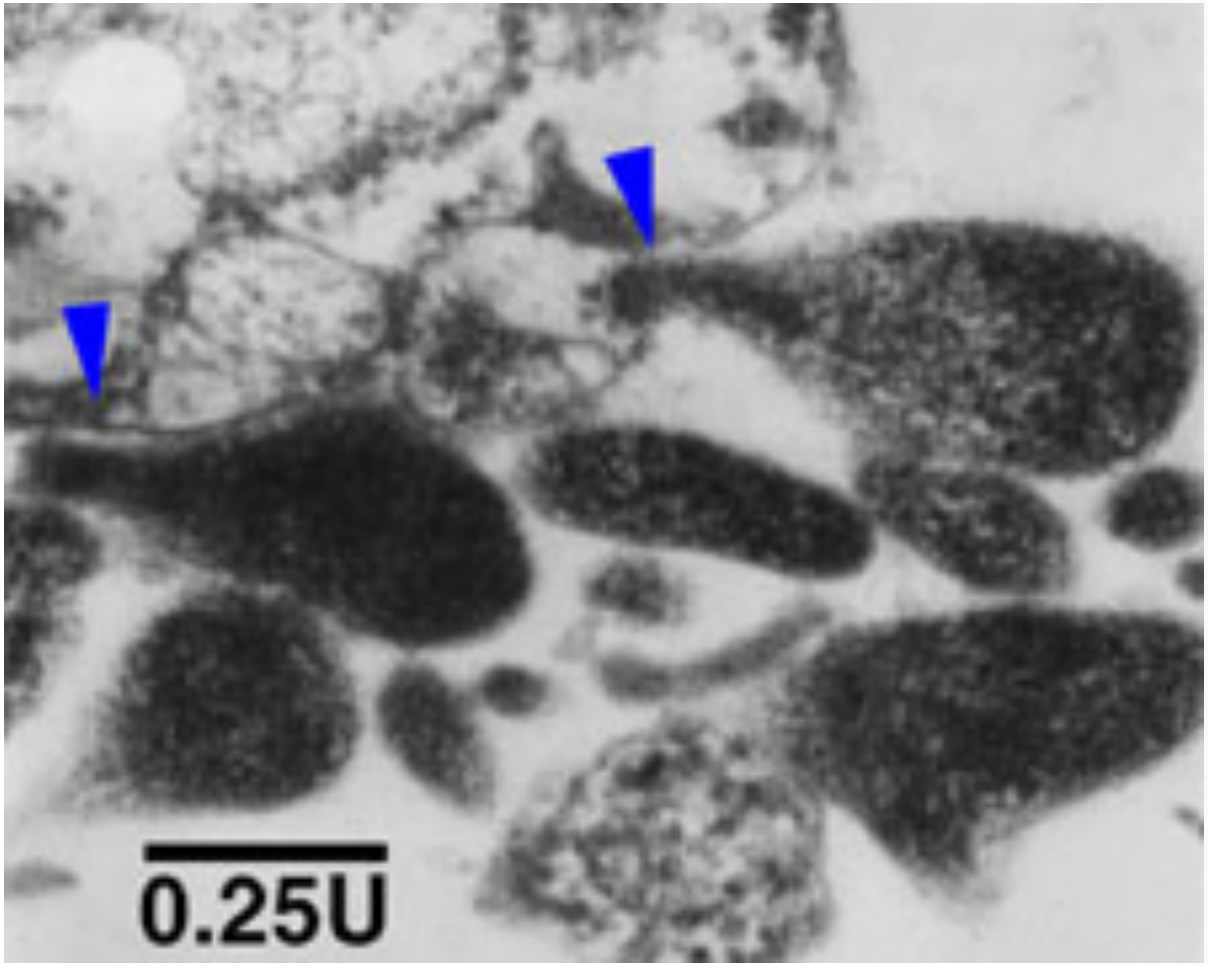
Inflammation Without GNID



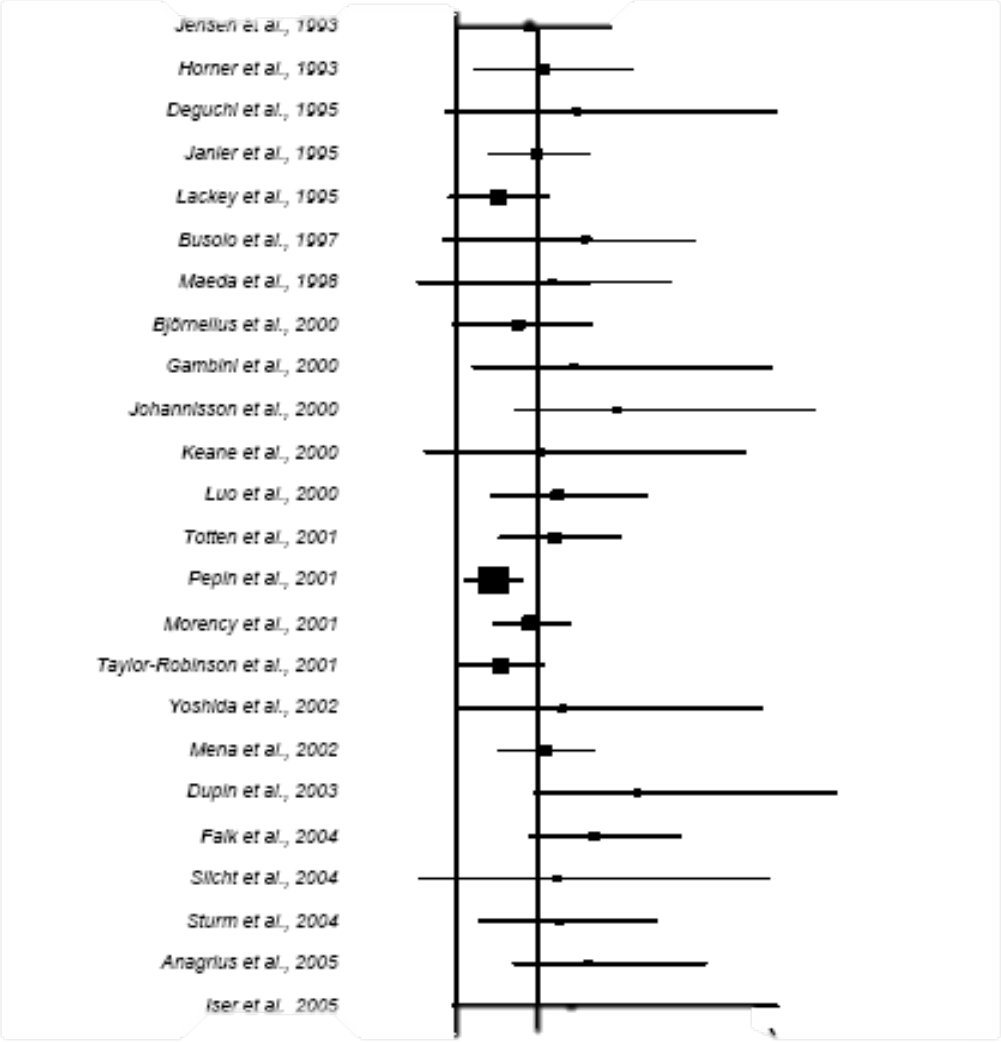
Etiology of Nongonococcal Urethritis - 2016

Chlamydia trachomatis	20-40%
Ureaplasma urealyticum	10-20%
Trichomonas vaginalis	5-15%
Herpes simplex virus	1-2%

Mycoplasma genitalium



Association between *M. genitalum* and male NGU



2015 CDC STD Treatment Guidelines

Nongonococcal Urethritis (NGU)

Recommended Regimens

Azithromycin 1 gram, orally, single dose

Doxycycline 100 mg orally 2 times a day for 7 days

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

F. Y. S. Kong,[1] S. N. Tabrizi,[2] M. Law,[3] L. A. Vodstrcil,[1,2] M. Chen,[4,5] C. K. Fairley,[5] R. Guy,[3] C. Bradshaw,[4,5] and J. S. Hocking[1]

[1]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne; [2]Murdoch Children's Research Institute, Parkville; [3]Kirby Institute, University of New South Wales, Sydney; [4]Sexual Health Unit, Melbourne School of Population and Global Health

Conclusions. There may be a small increased efficacy of up to 3% for doxycycline compared with azithromycin for the treatment of urogenital chlamydia and about 7% increased efficacy for doxycycline for the treatment of symptomatic urethral infection in men. However, the quality of the evidence varies considerably, with few double-blind placebo-controlled trials conducted. Given increasing concern about potential azithromycin failure, further well-designed and statistically powered double-blind, placebo-controlled trials are needed.

Clinical Infectious Diseases 2014;59(2):193–205

ORIGINAL ARTICLE

Azithromycin versus Doxycycline for Urogenital *Chlamydia trachomatis* Infection

William M. Geisler, M.D., M.P.H., Apurva Uniyal, M.A., Jeannette Y. Lee, Ph.D., Shelly Y. Lensing, M.S., Shacondra Johnson, B.S.P.H., Raymond C.W. Perry, M.D., M.S.H.S., Carmel M. Kadrnka, D.O., and Peter R. Kerndt, M.D., M.P.H.

ABSTRACT

BACKGROUND

Urogenital *Chlamydia trachomatis* infection remains prevalent and causes substantial reproductive morbidity. Recent studies have raised concern about the efficacy of azithromycin for the treatment of chlamydia infection.

METHODS

We conducted a randomized trial comparing oral azithromycin with doxycycline for the treatment of urogenital chlamydia infection among adolescents in youth correctional facilities, to evaluate the noninferiority of azithromycin (1 g in one dose) to doxycycline (100 mg twice daily for 7 days). The treatment was directly observed. The primary end point was treatment failure at 28 days after treatment initiation, with treatment failure determined on the basis of nucleic acid amplification testing, sexual history, and outer membrane protein A (OmpA) genotyping of *C. trachomatis* strains.

RESULTS

Among the 567 participants enrolled, 284 were randomly assigned to receive azithromycin, and 283 were randomly assigned to receive doxycycline. A total of 155 participants in each treatment group (65% male) made up the per-protocol population. There were no treatment failures in the doxycycline group. In the azithromycin group, treatment failure occurred in 5 participants (3.2%; 95% confidence interval, 0.4 to 7.4%). The observed difference in failure rates between the treatment groups was 3.2 percentage points, with an upper boundary of the 90% confidence interval of 5.9 percentage points, which exceeded the prespecified absolute 5-percentage-point cutoff for establishing the noninferiority of azithromycin.

CONCLUSIONS

In the context of a closed population receiving directly observed treatment for urogenital chlamydia infection, the efficacy of azithromycin was 97%, and the efficacy of doxycycline was 100%. The noninferiority of azithromycin was not established in this setting. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00980148.)

From the Department of Medicine, University of Alabama at Birmingham, Birmingham (W.M.G.); the Departments of Preventive Medicine (A.U., P.R.K.) and Internal Medicine (P.R.K.), University of Southern California, and Los Angeles County Department of Health Services, Juvenile Court Health Services (R.C.W.P., C.M.K.) — both in Los Angeles; the Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock (J.Y.L., S.Y.L.); and FHI 360, Durham, NC (S.J.). Address reprint requests to Dr. Geisler at the University of Alabama at Birmingham, 703 19th St. S., 242 Zeigler Research Bldg., Birmingham, AL 35294-0007, or at wgeisler@uab.edu.

N Engl J Med 2015;373:2512-21.
DOI: 10.1056/NEJMoa1502599

A 24 y.o. male treated for NGU 2 weeks ago with azithromycin returns stating that his symptoms have persisted. He denies sexual intercourse since treatment. On exam a small amount of grayish discharge is visible at the urethral meatus. Gram stain shows numerous PMNL's but no GNID. What would you do now?

1. Treat with doxycycline for a week.
2. Give a 5 day course of azithromycin.
3. Metronidazole 2 gm as a single dose.
4. Don't treat. Tell him he needs to use condoms.

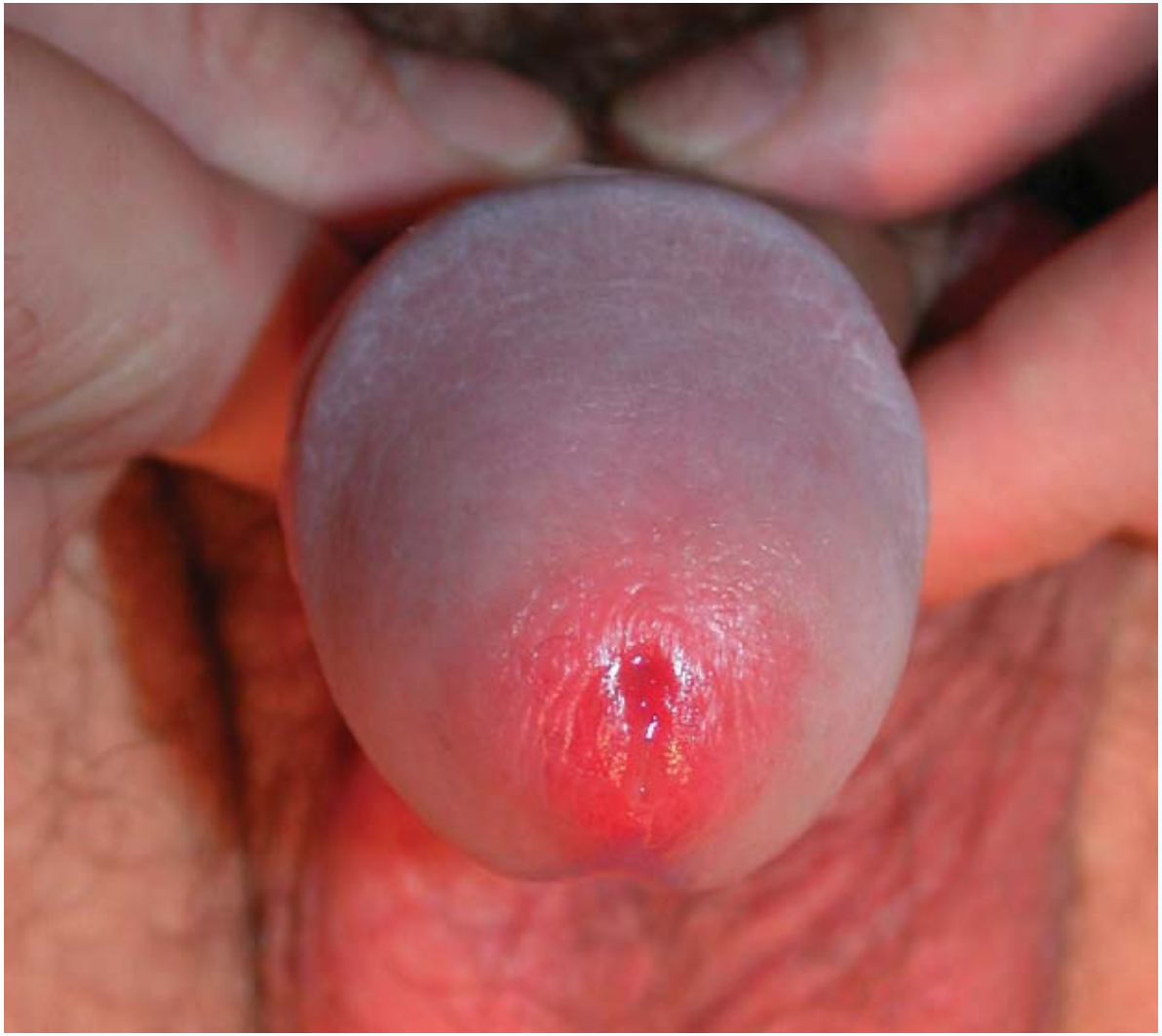
Recurrent NGU

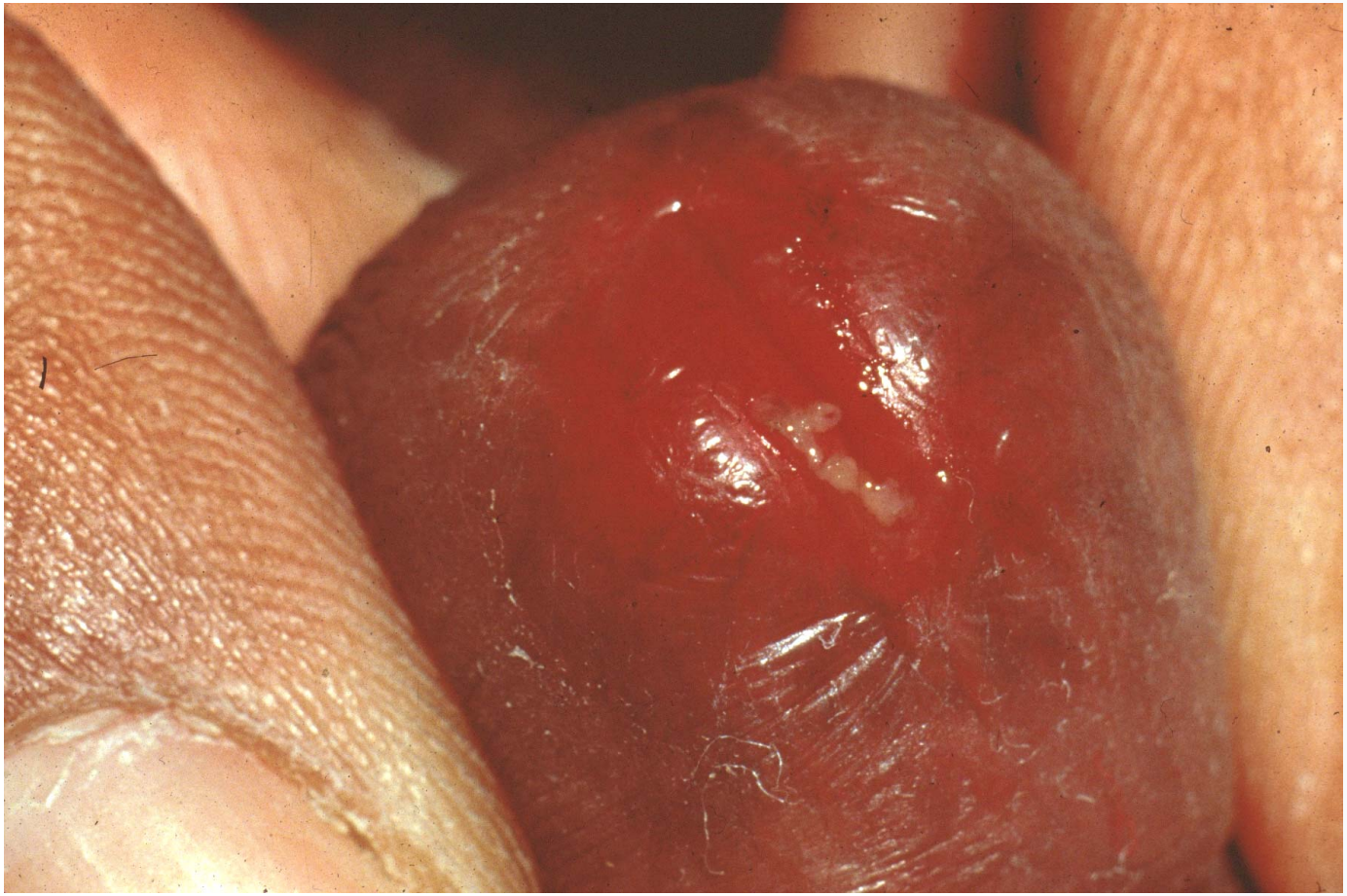
- MSW > MSM (*T. vaginalis)*
- Urethral meatus (HSV); insertive rectal IC (*E coli*)
- ***Mycoplasma genitalium***
  - no FDA cleared test
  - Azithromycin>doxycycline (3 RCTs)
  - Azithromycin efficacy declining (Manhart, CID 2013)
  - Moxifloxacin for recurrence (resistance reported)

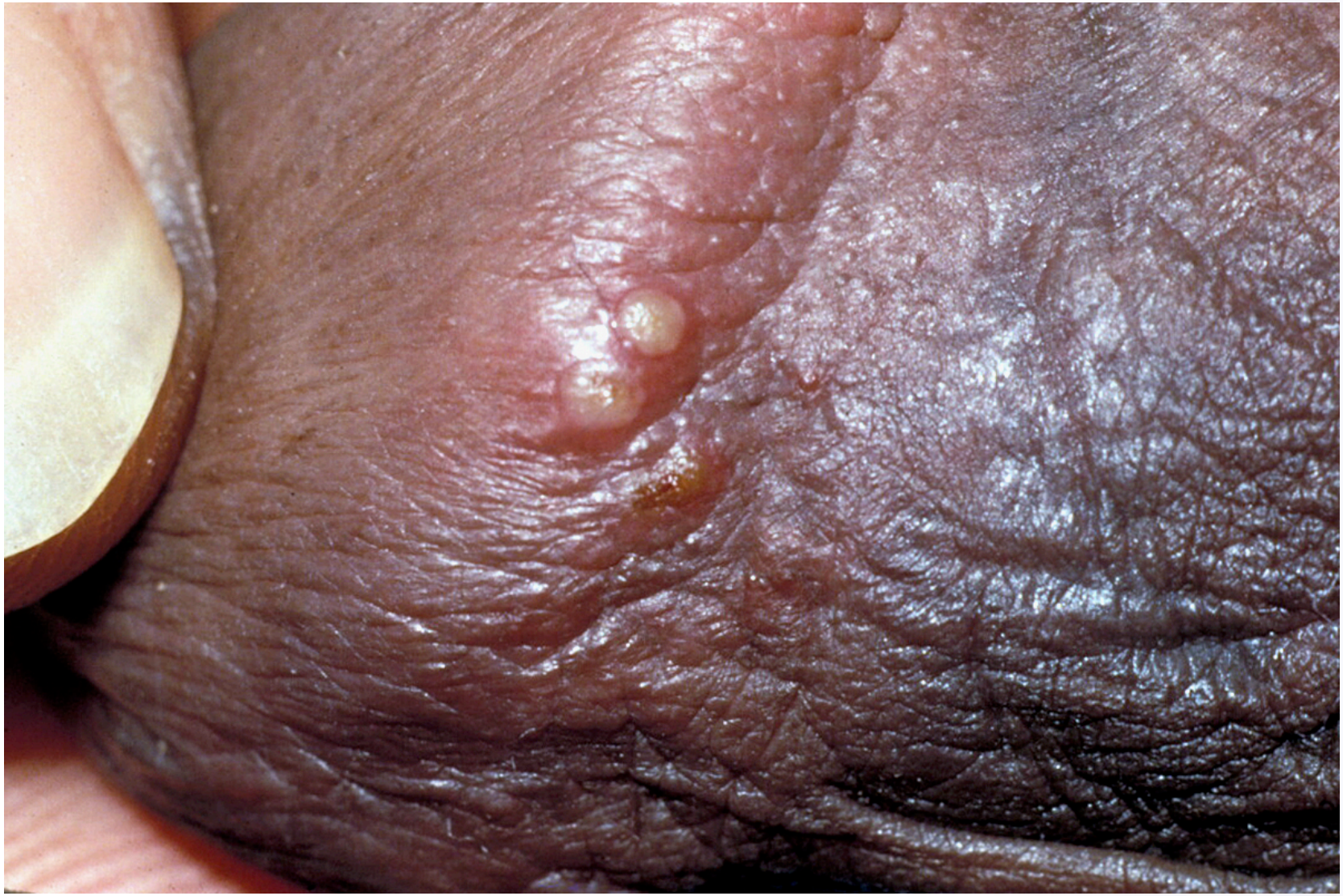
Etiology of Nongonococcal Urethritis - 2008

Chlamydia trachomatis	20-40%
Mycoplasma genitalium	15-25%
Ureaplasma urealyticum	10-20%
Trichomonas vaginalis	5-15%
Herpes simplex virus	1-2%

Adenovirus Urethritis







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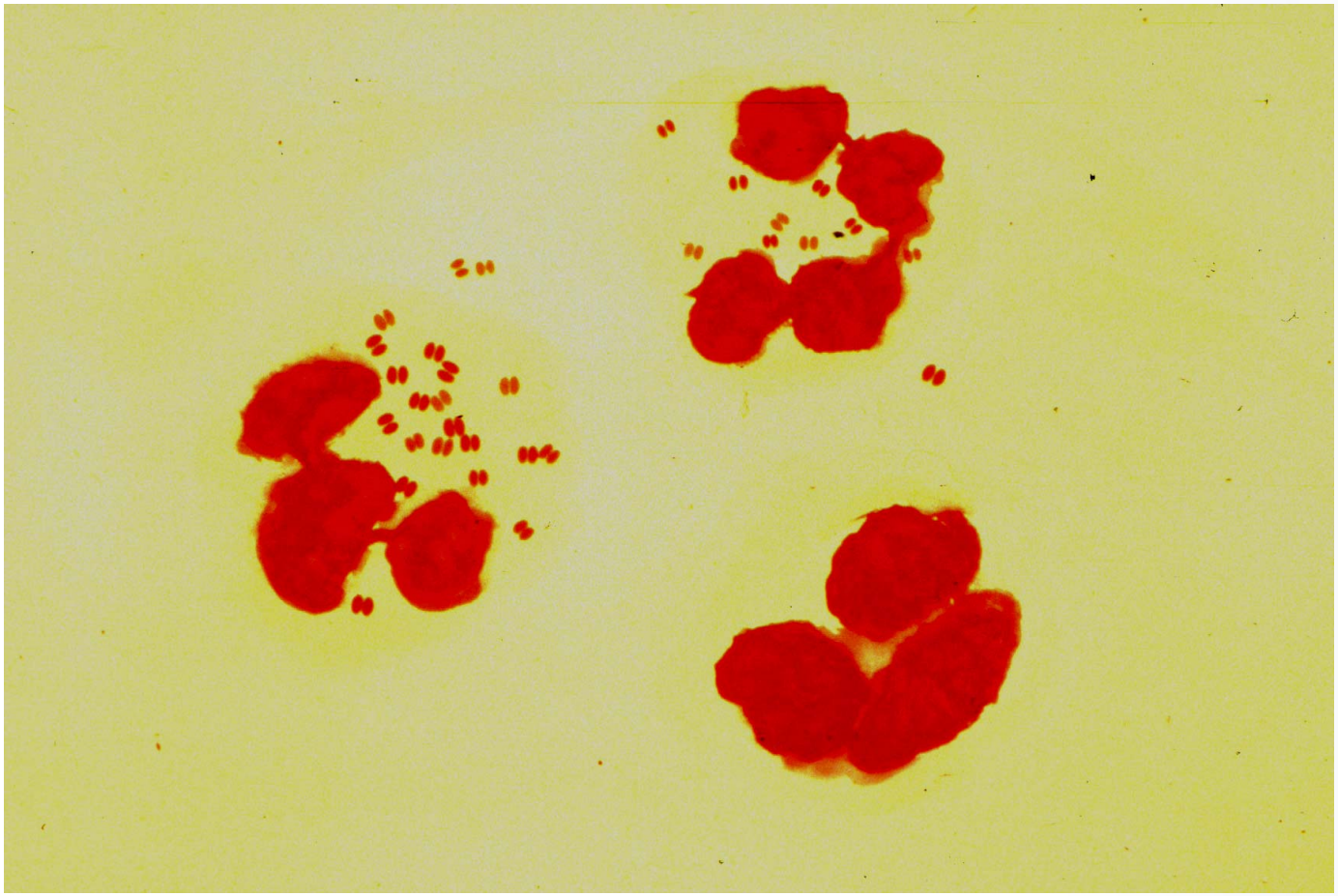
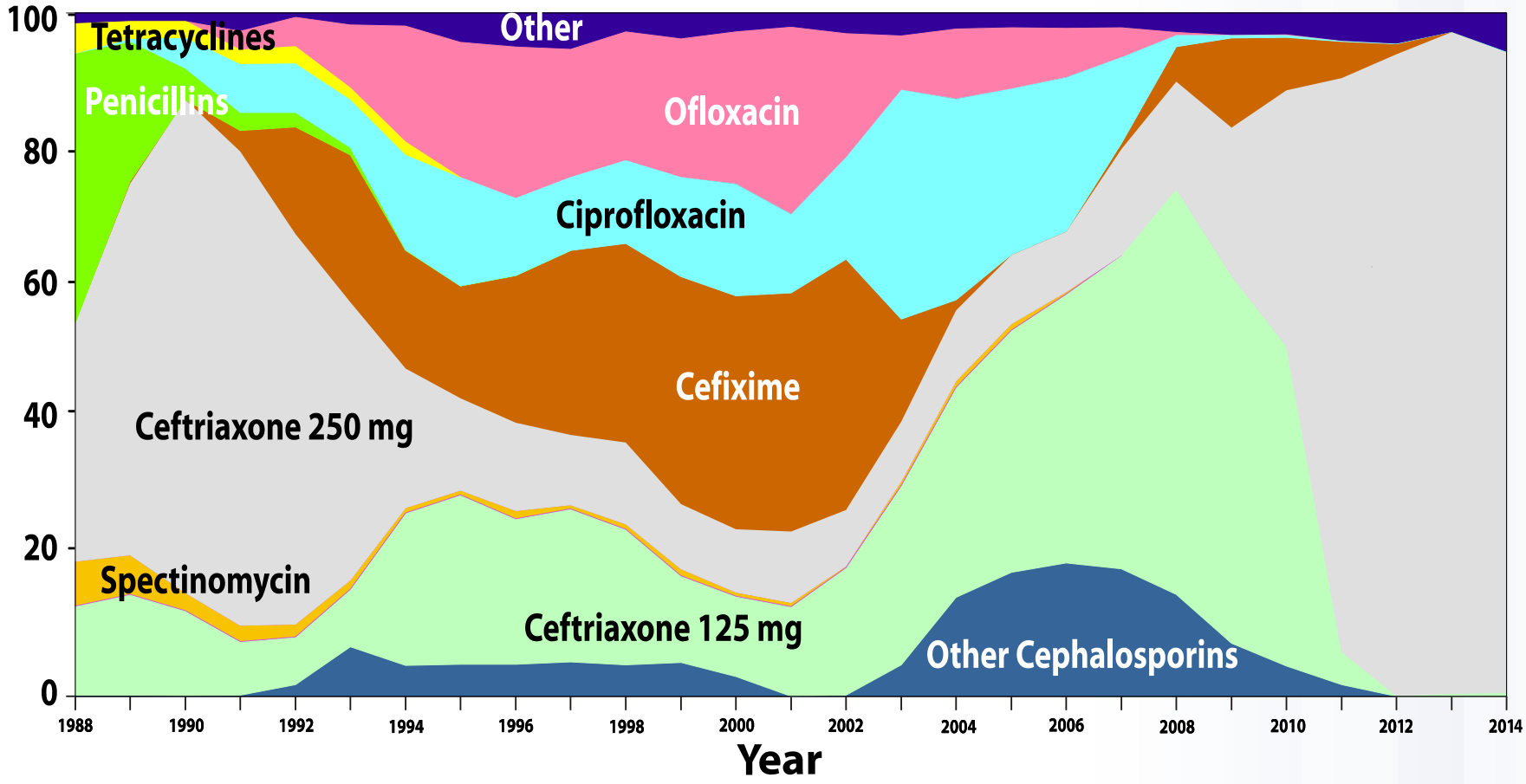


Primary Antimicrobial Drugs Used to Treat Gonorrhea Among Participants, Gonococcal Isolate Surveillance Project (GISP), 1988-2014



NOTE: For 2014, "Other" includes clinical trial study drugs (2.9%), azithromycin 2g (1.9%), no therapy (0.7%), and other less frequently used drugs (0.1%).

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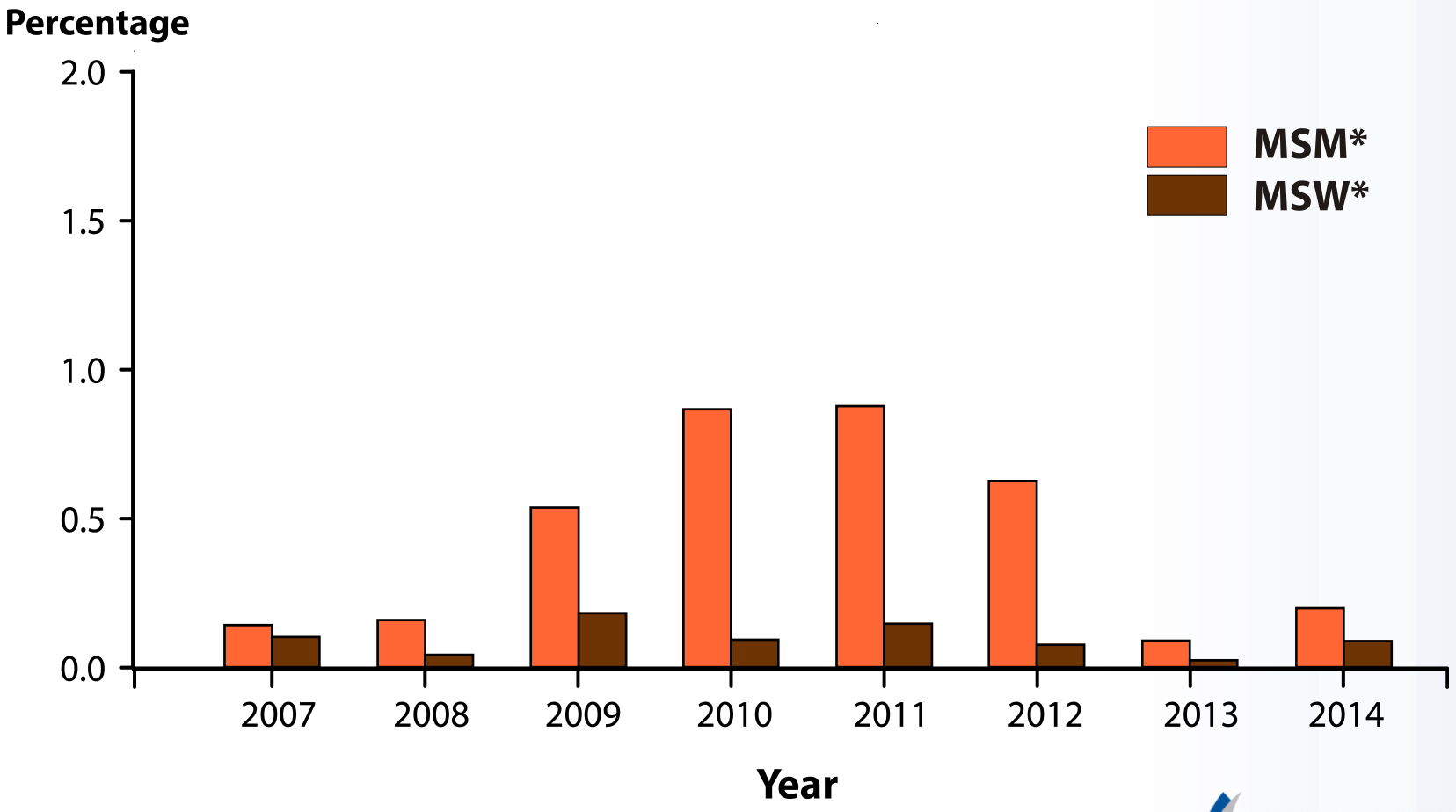
Neisseria gonorrhoeae — Percentage of Urethral Isolates with Elevated Ceftriaxone Minimum Inhibitory Concentrations (MICs) (≥0.125 µg/ml) by Reported Sex of Sex Partner, Gonococcal Isolate Surveillance Project (GISP), 2007-2014



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

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2013-Fig Z. SR Pg. 75.

Uncomplicated Gonococcal Infections of Cervix, Urethra, Pharyngeal & Rectum

Ceftriaxone 250 mg as a single IM dose

PLUS

Azithromycin 1 g orally

Alternative:

If Ceftriaxone is not available:

- **Cefixime 400 mg PLUS azithromycin 1 gram**
- **Gemifloxaxine 320 mg Plus azithromycin 2 gram**
- **Gentamicin 240 mg IM PLUS azithromycin 2 grams**

Test of cure not needed after treatment for urogenital/ rectal infection, but for pharynx (alternative)

Genital Ulcer Disease: The Big Three

Syphilis

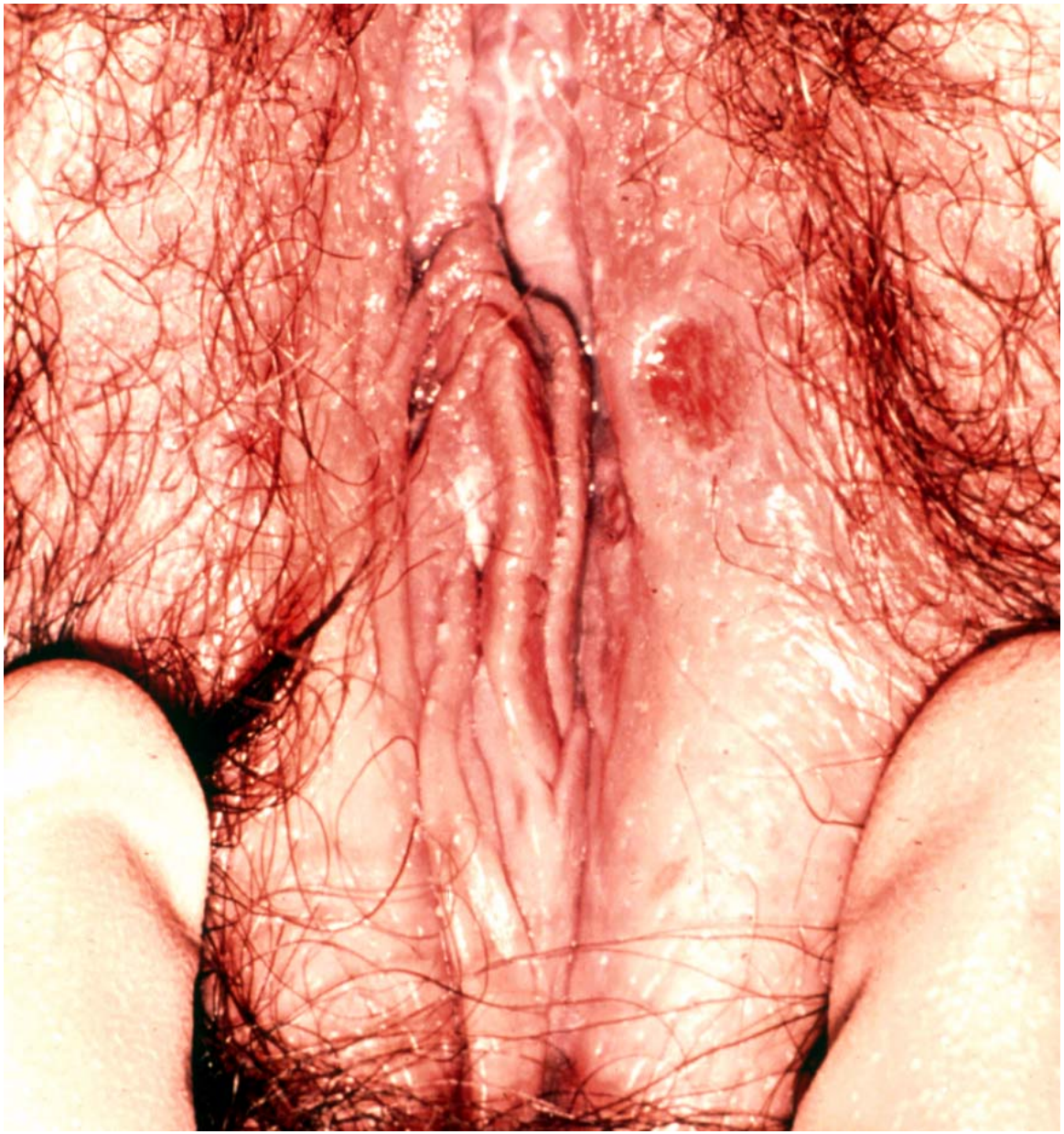
Chancroid

Genital Herpes

Classic Signs of Genital Ulcer Disease

Syphilis

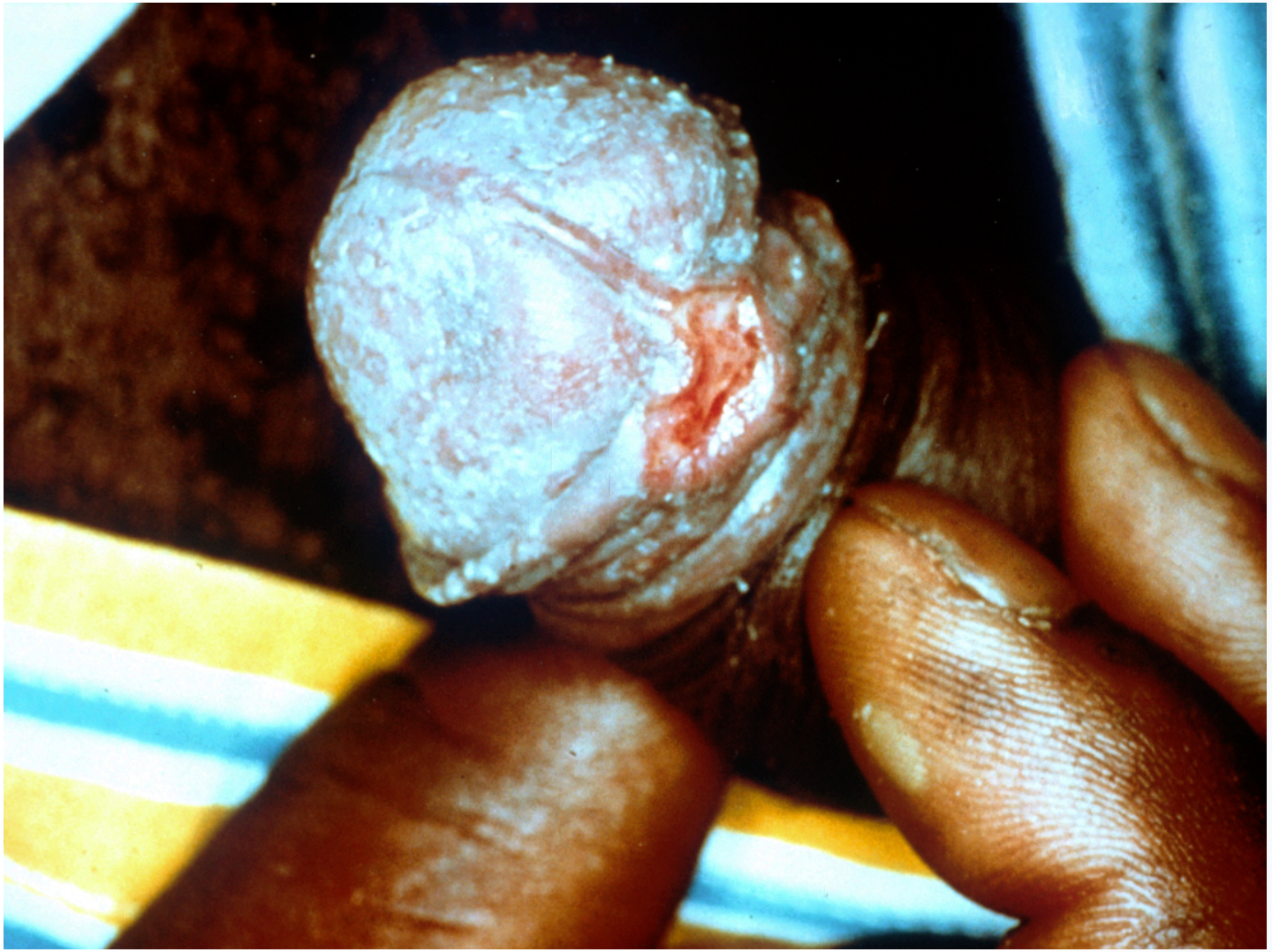
- Induration
- Painless lesion
- Clean based lesion

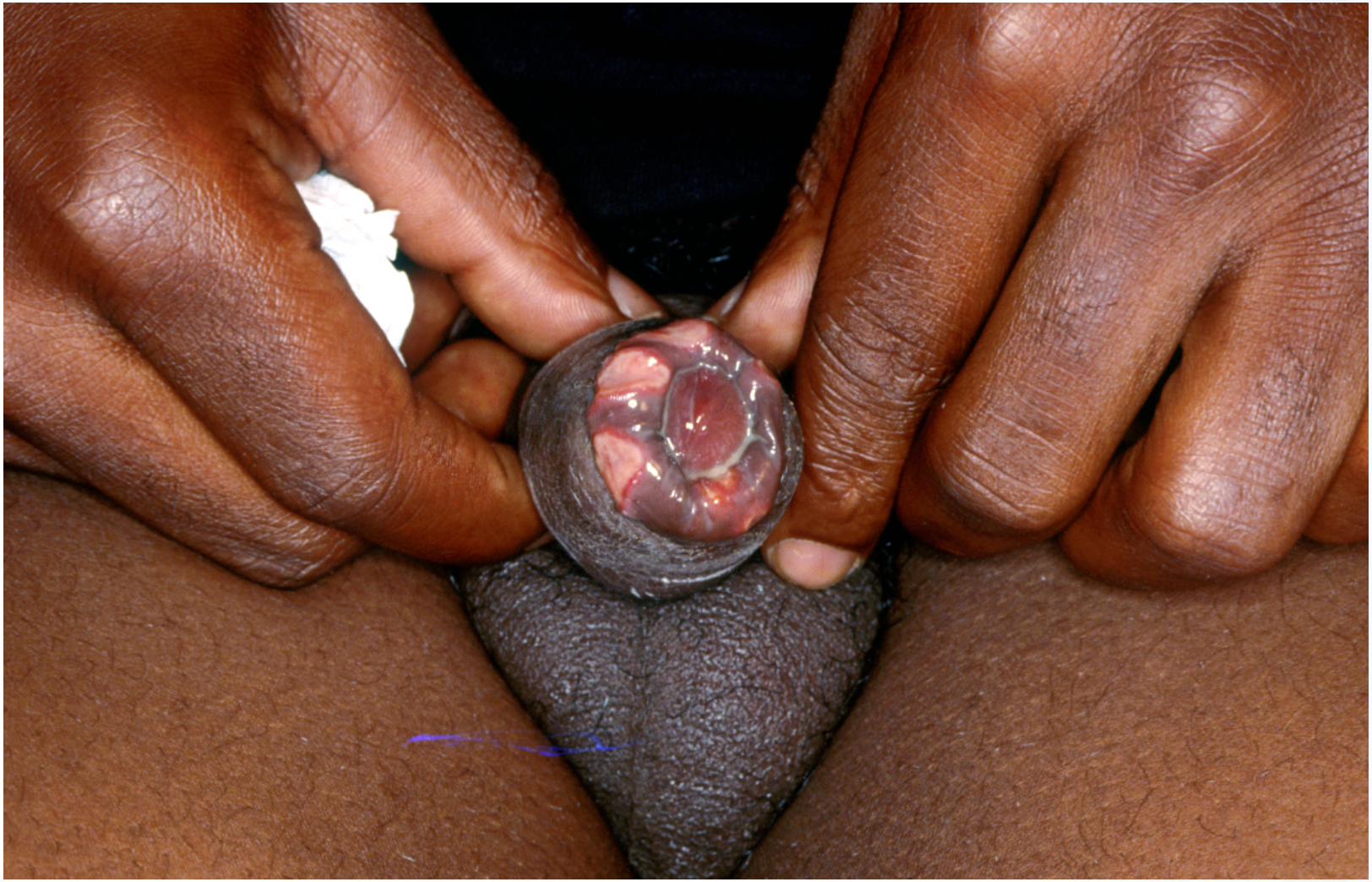


Classic Signs of Genital Ulcer Disease

Chancroid

- Undermined lesion border
- Painful lesion
- Purulent exudate

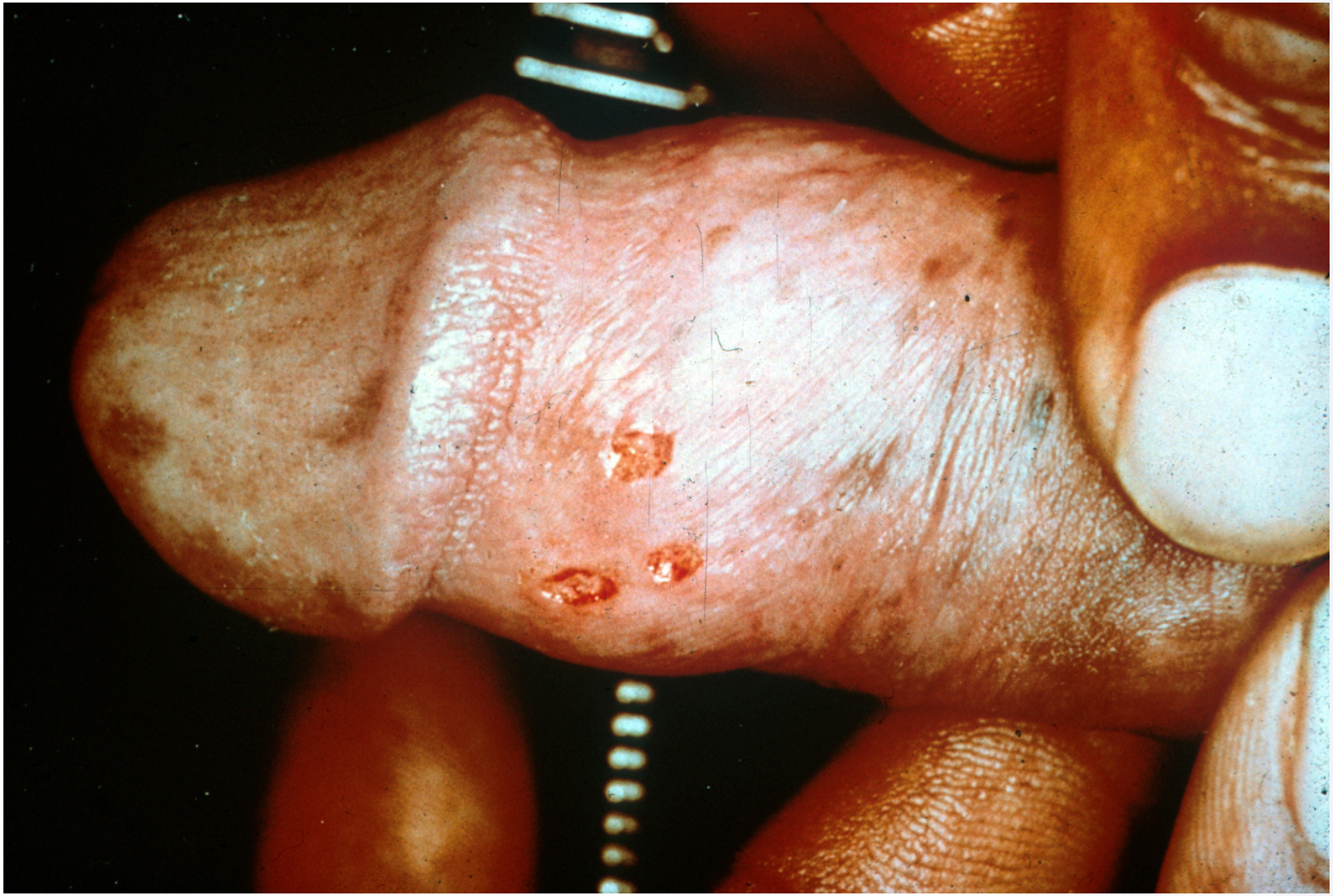


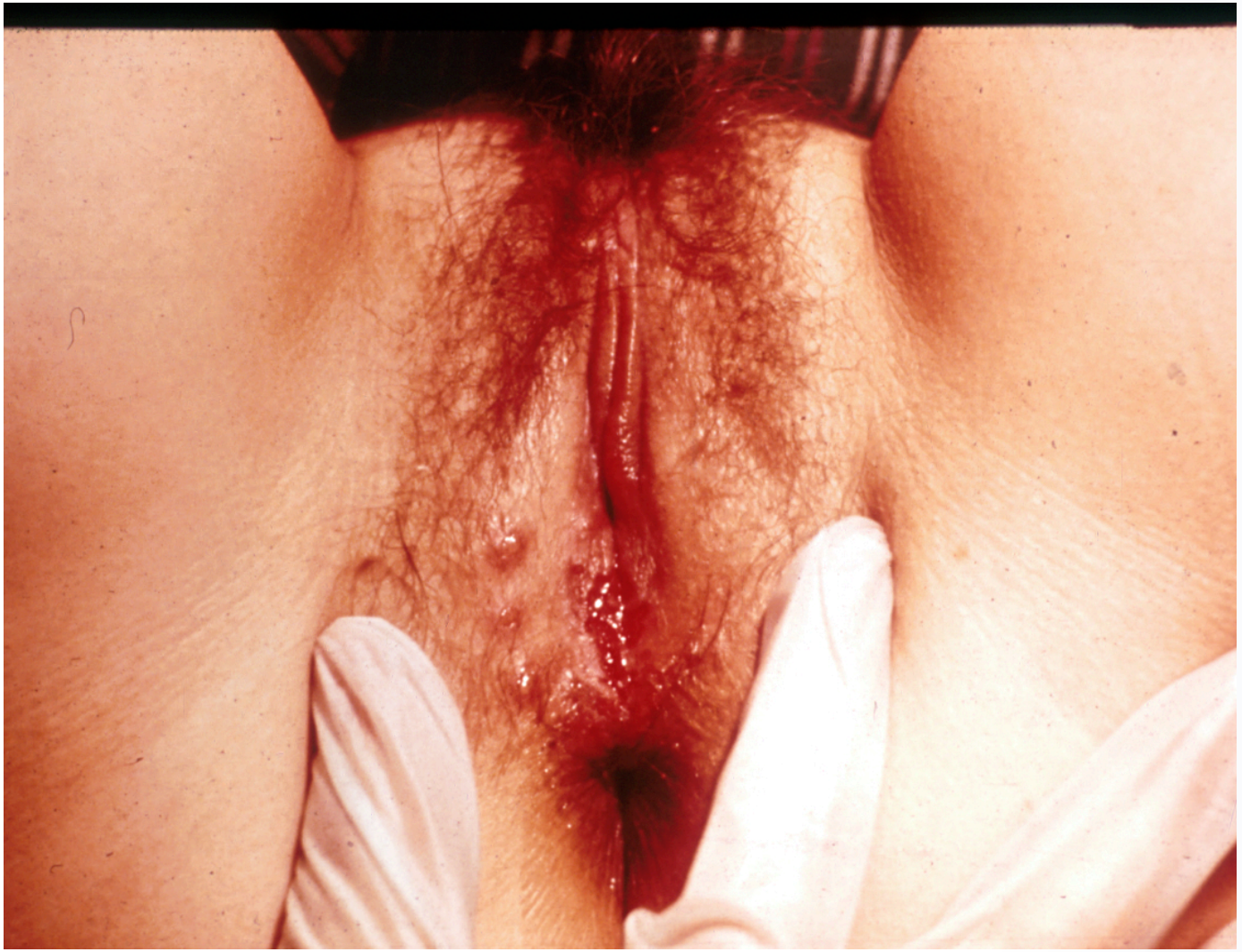


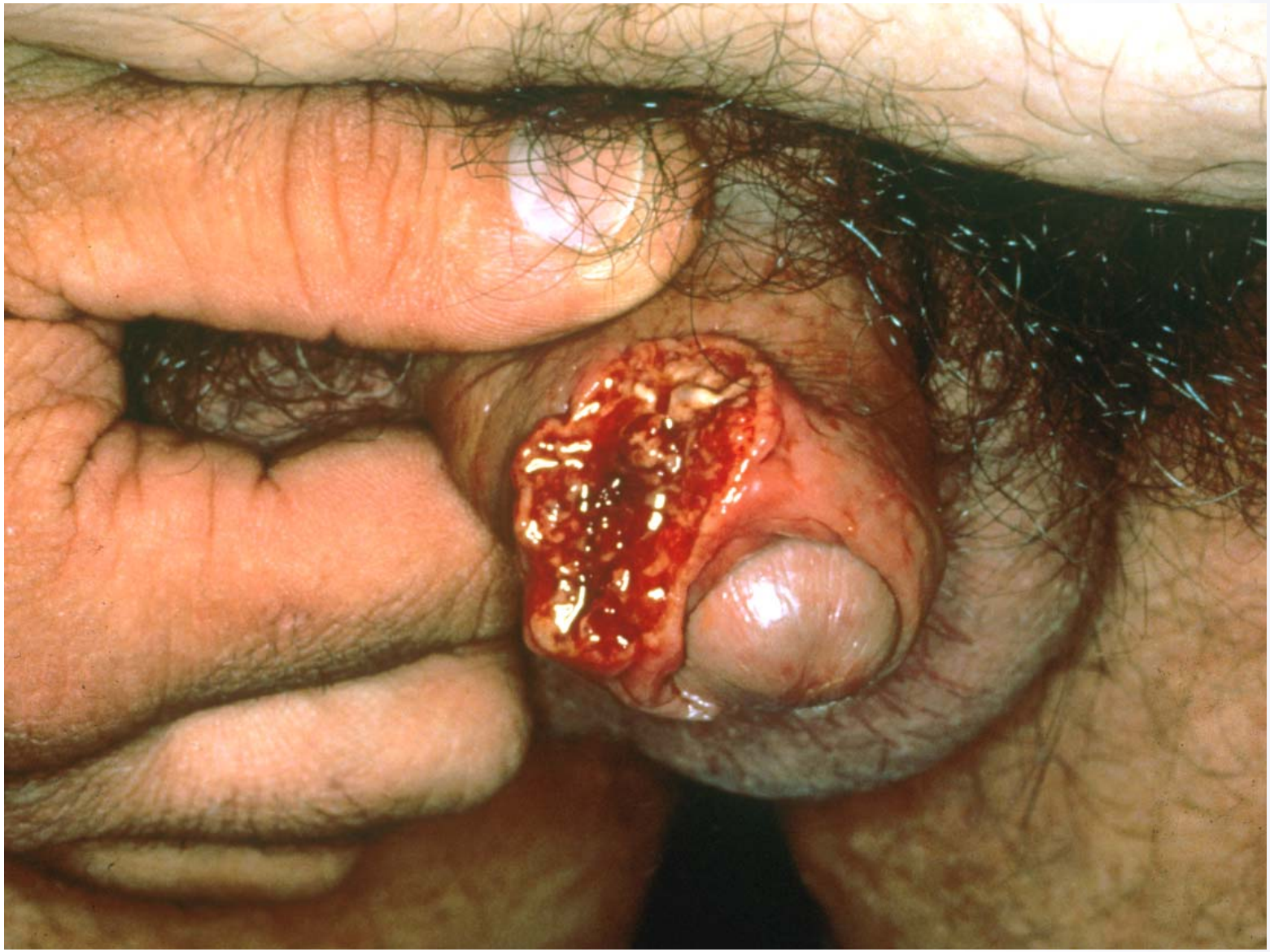
Classic Signs of Genital Ulcer Disease

Genital Herpes

- Multiple ulcers
- Shallow lesions
- Painful lesions





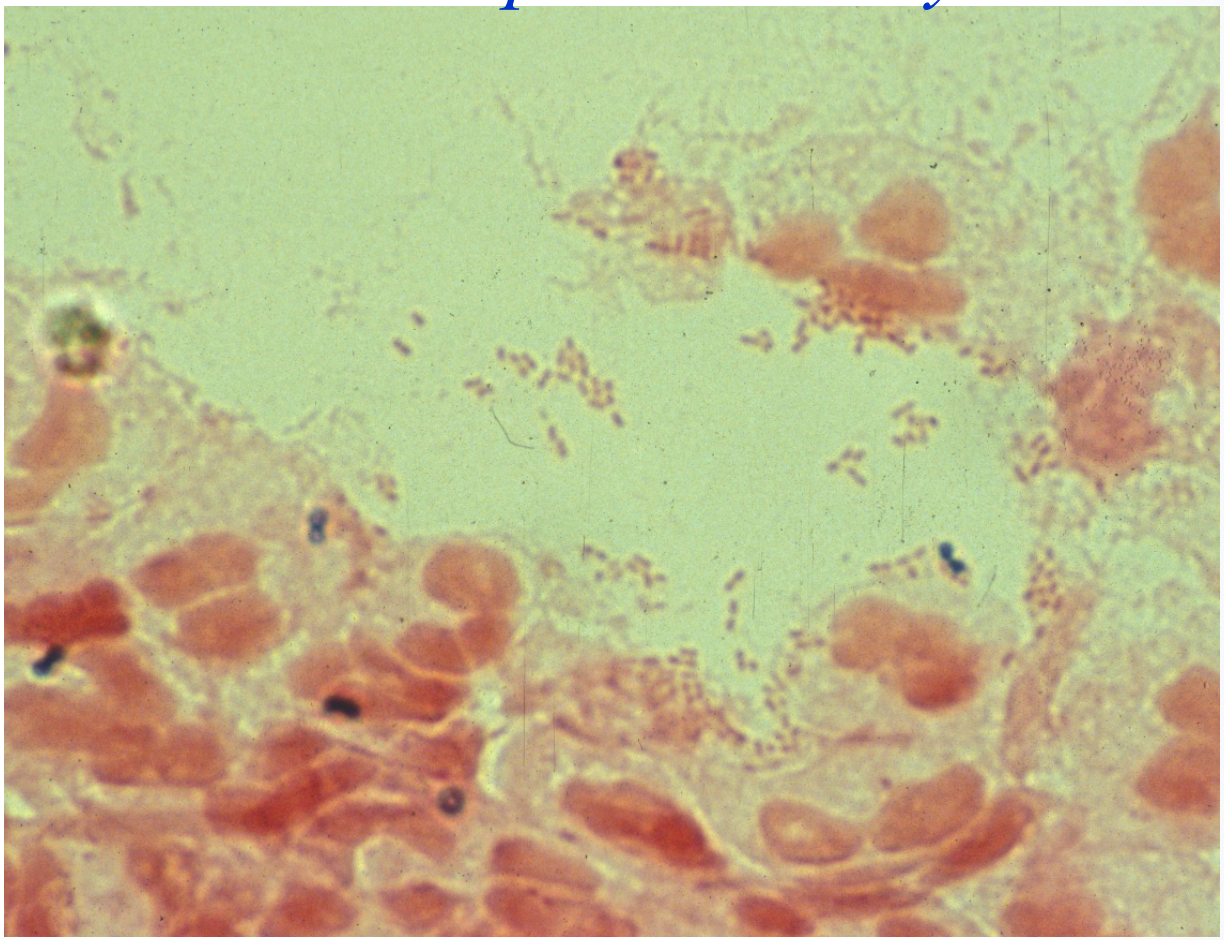


Utility of "Classic" GUD Signs for the Diagnosis of Genital Ulcer Disease

	Sensitivity	Specificity
Syphilis	31%	98%
Chancroid	34%	94%
Genital herpes	35%	94%

DiCarlo RP and Martin DH, Clin Infect Dis 1997;25:292-8.

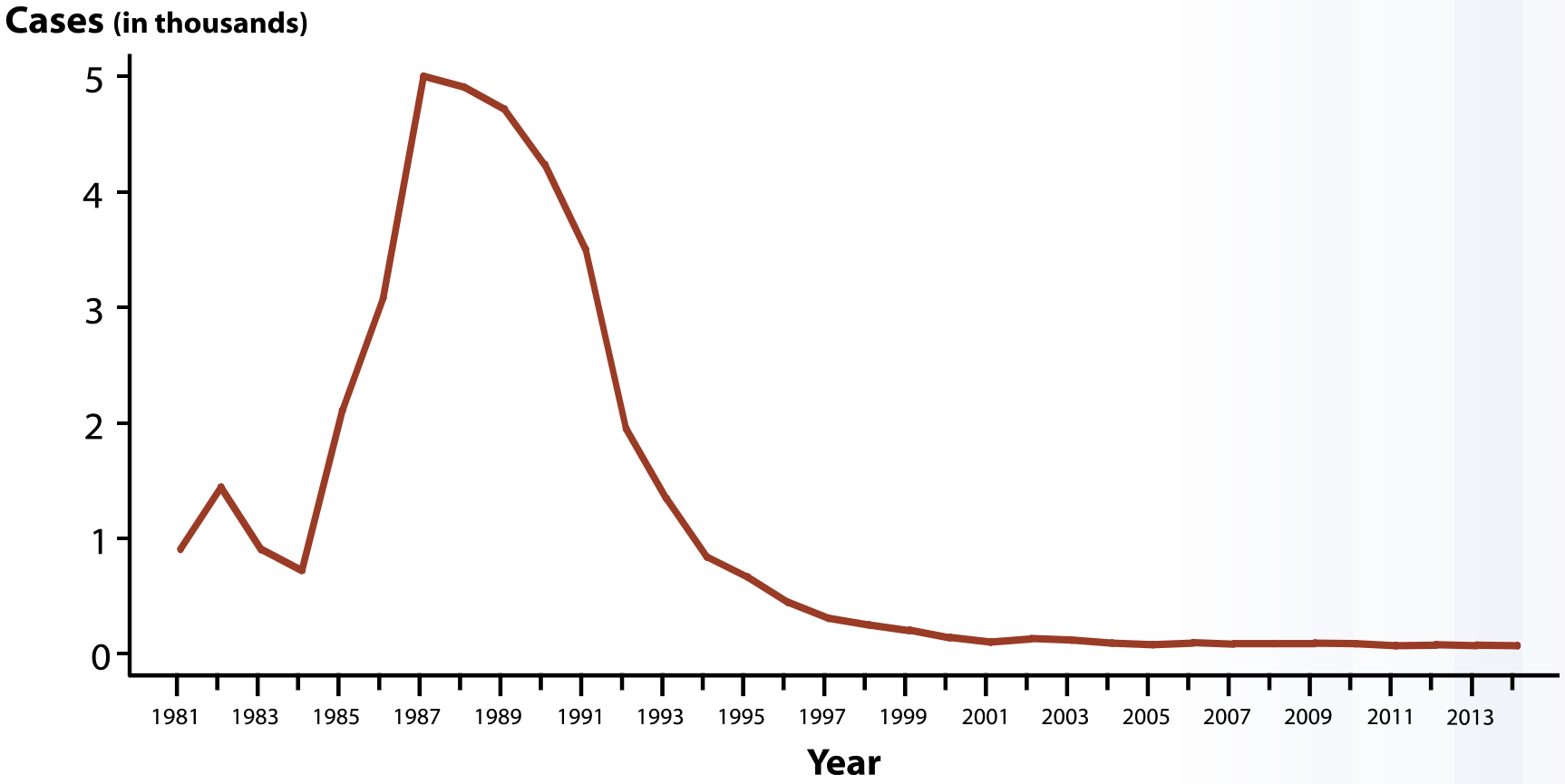
Lesion Swab Gram Stain Showing *Haemophilus ducreyi*



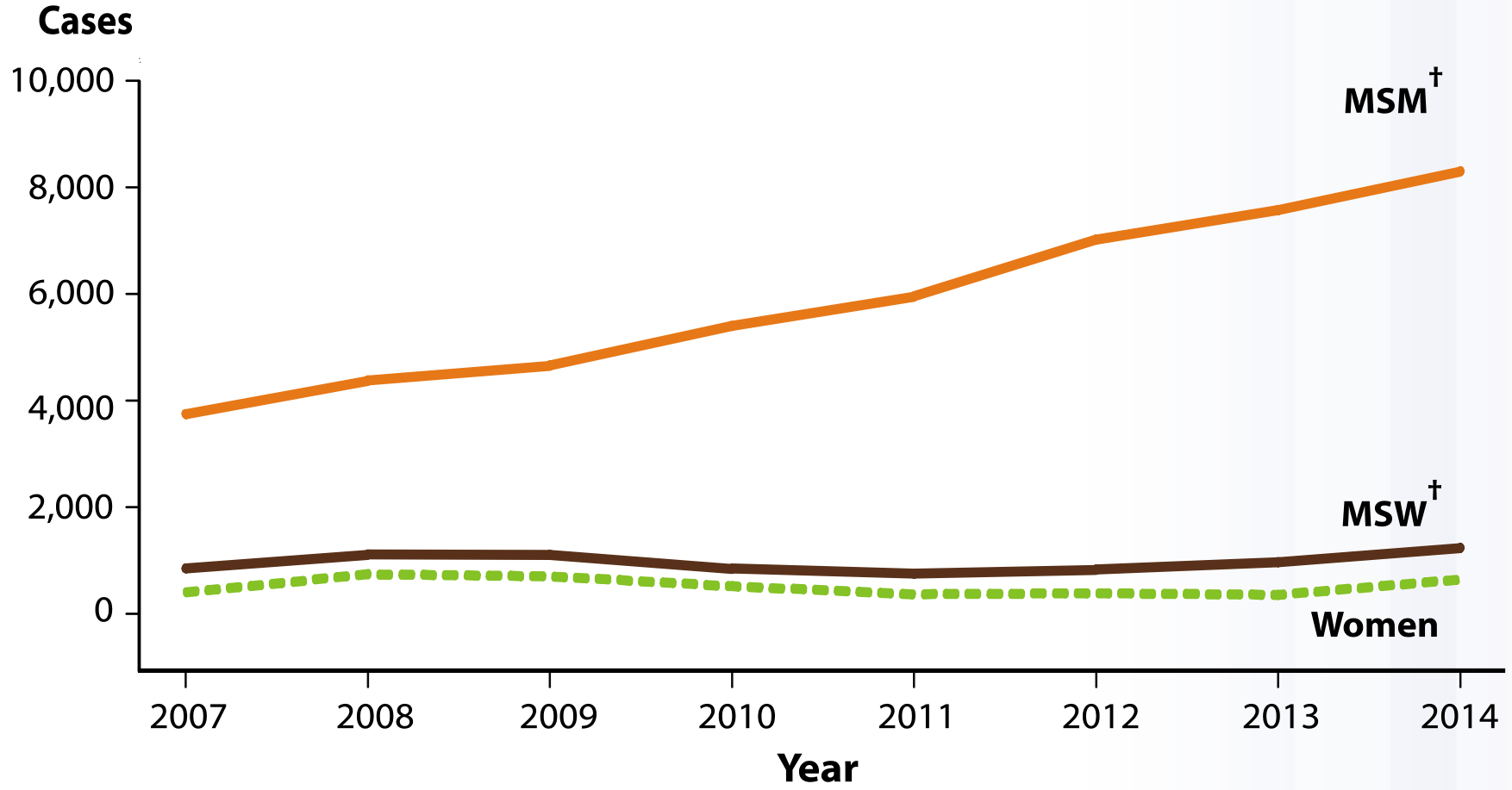
Expected Results of Serologic Testing in Patients With Untreated Syphilis

	% Positive at Disease Stage		
	Primary	Secondary	Late
Reagin test (e.g. RPR, VDRL)	70	100	70
Treponemal test (e.g. TP-PA, EIA, etc.)	85	100	98

Chancroid — Reported Cases by Year, United States, 1981-2014



Primary and Secondary Syphilis — Reported Cases by Sex and Sexual Behavior, 27 Areas*, 2007-2014



*27 states reported sex of partner data for 70% of reported cases of primary and secondary syphilis for each year during 2007–2014.

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

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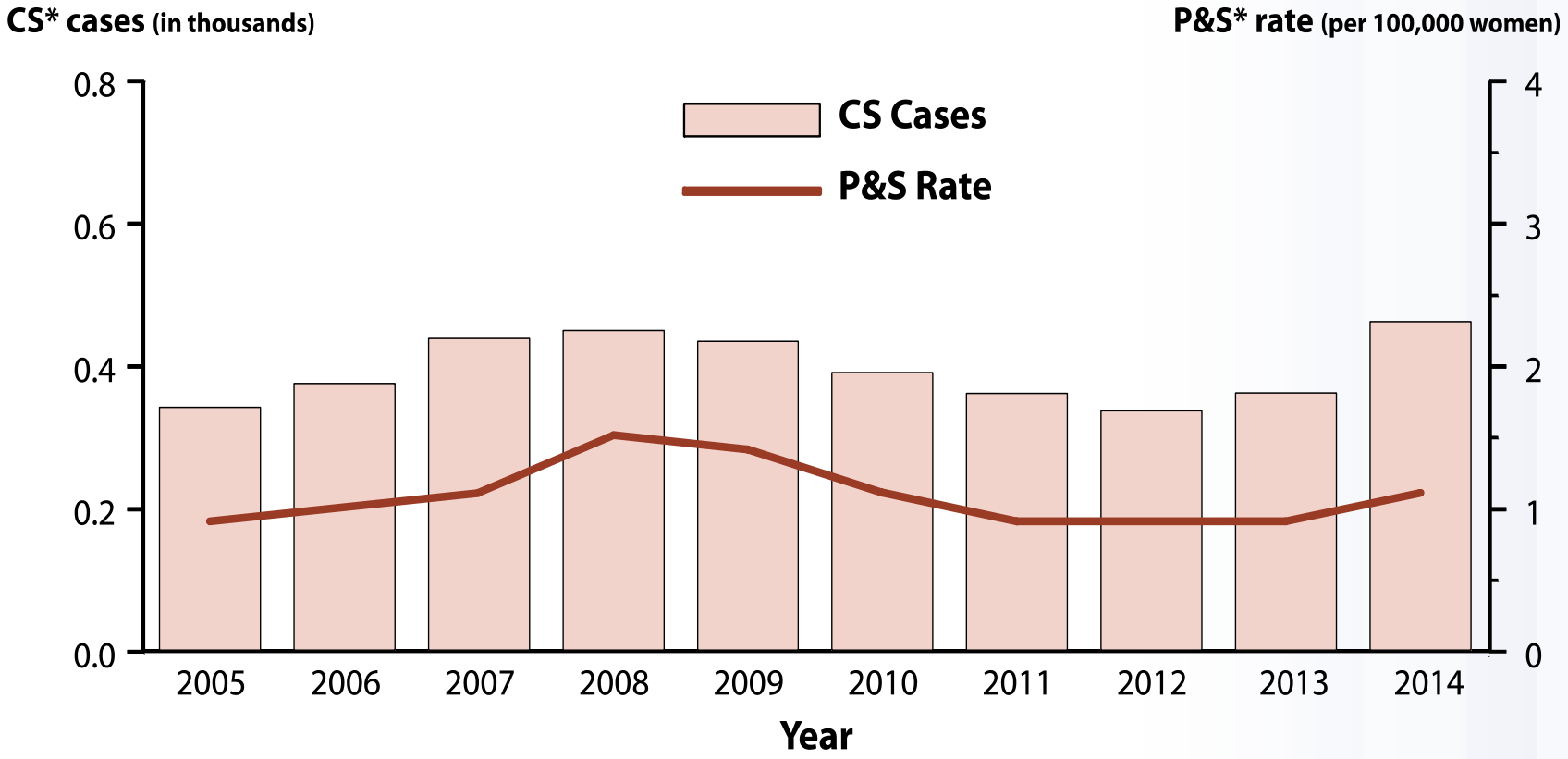
Congenital Syphilis — Reported Cases by Year of Birth and Rates of Primary and Secondary Syphilis Among Women, United States, 2005-2014



* **CS**=congenital syphilis; **P&S**=primary and secondary syphilis.

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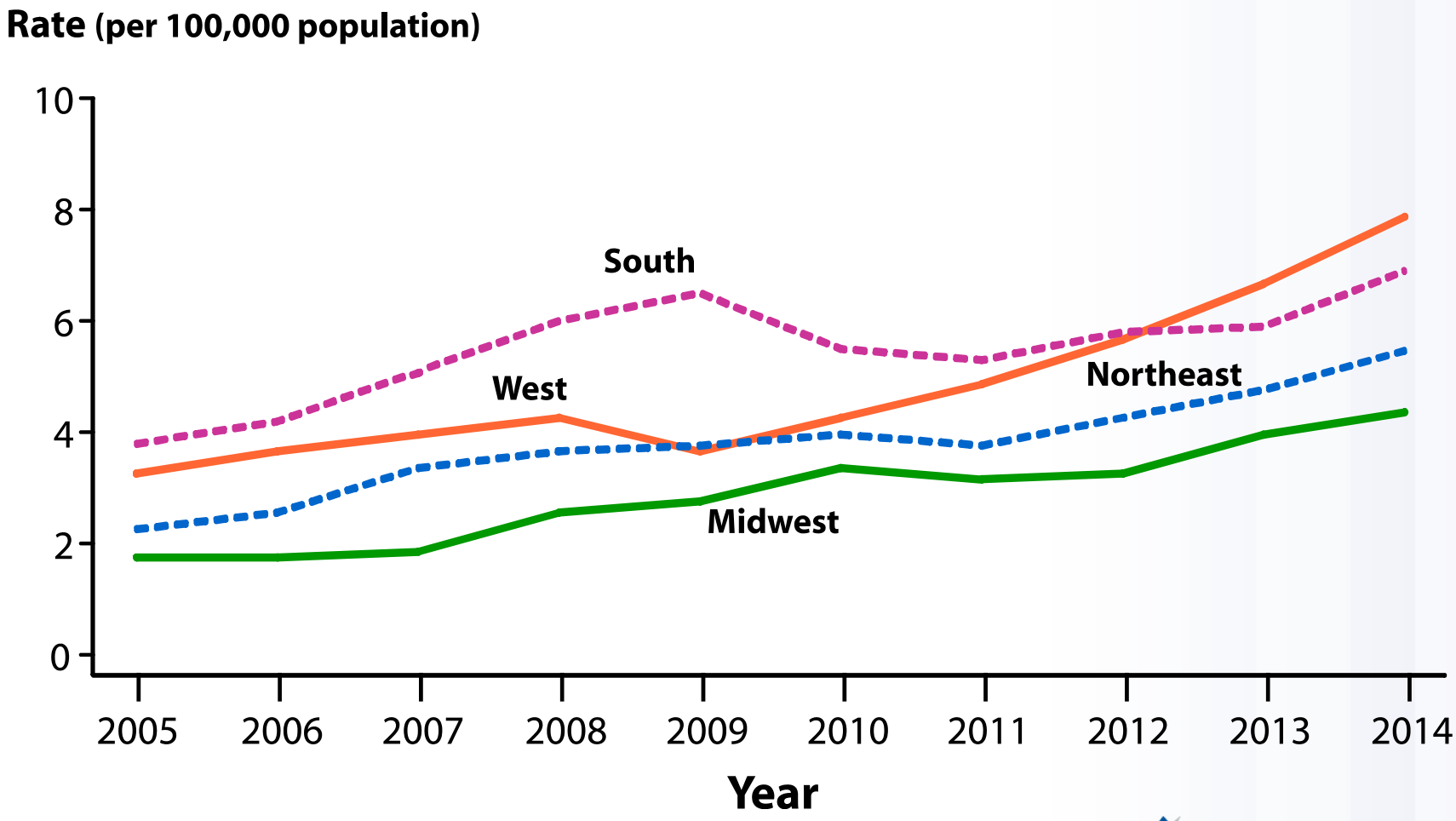
Primary and Secondary Syphilis — Rates of Reported Cases by Region, United States, 2005-2014



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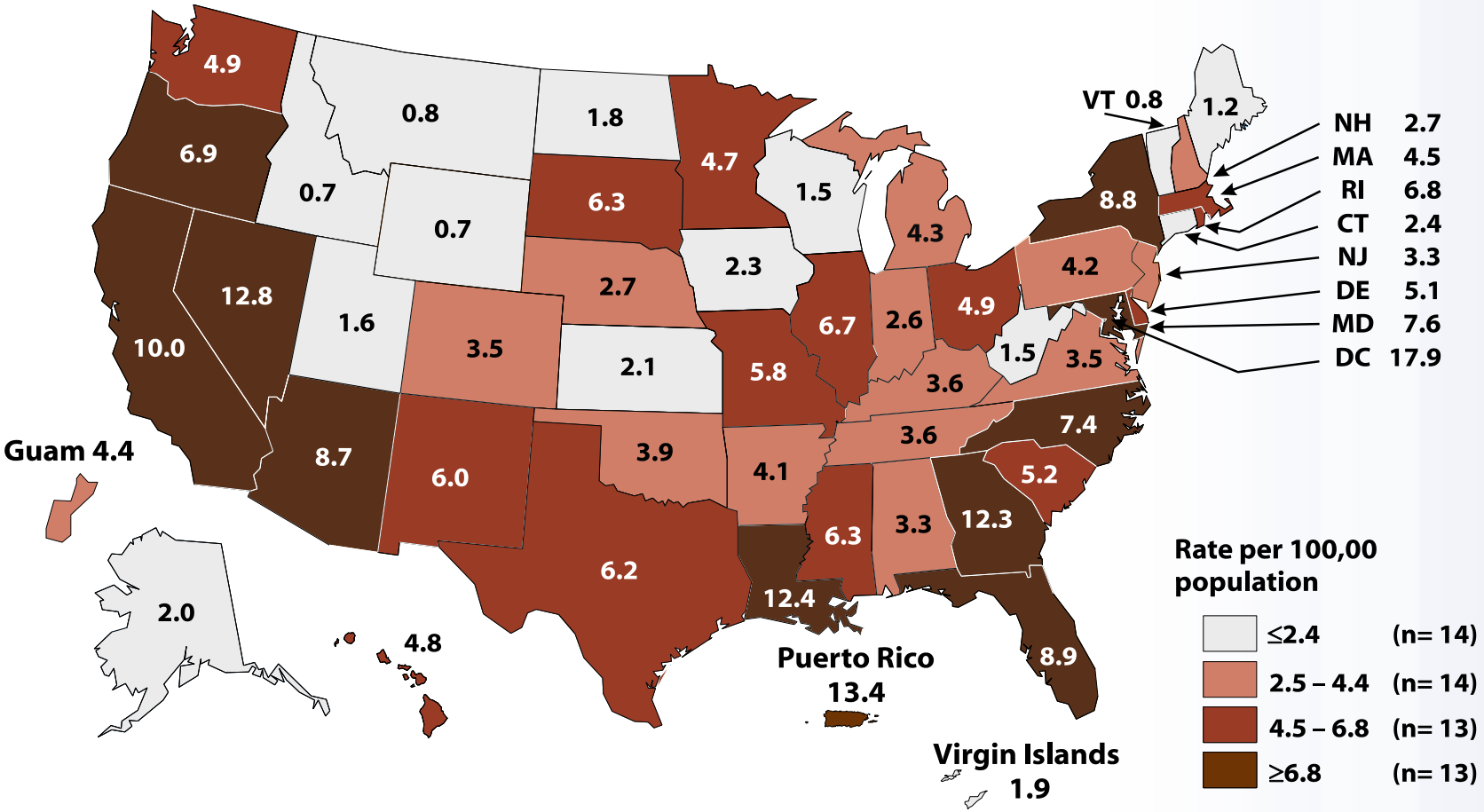
Primary and Secondary Syphilis—Rates of Reported Cases by State, United States and Outlying Areas, 2014



NOTE: The total rate of primary and secondary syphilis for the United States and outlying areas (Guam, Puerto Rico, and Virgin Islands) was 6.4 per 100,000 population.

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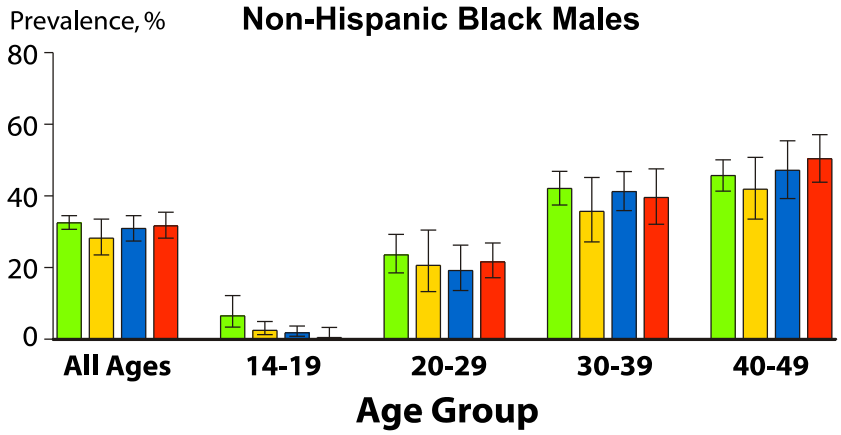
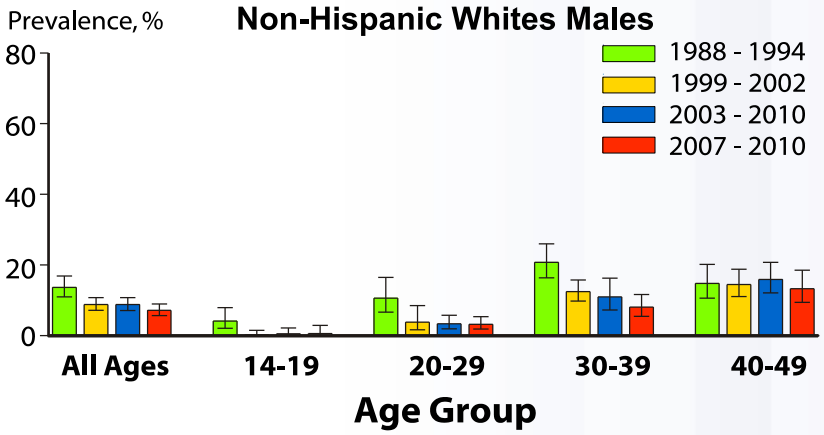
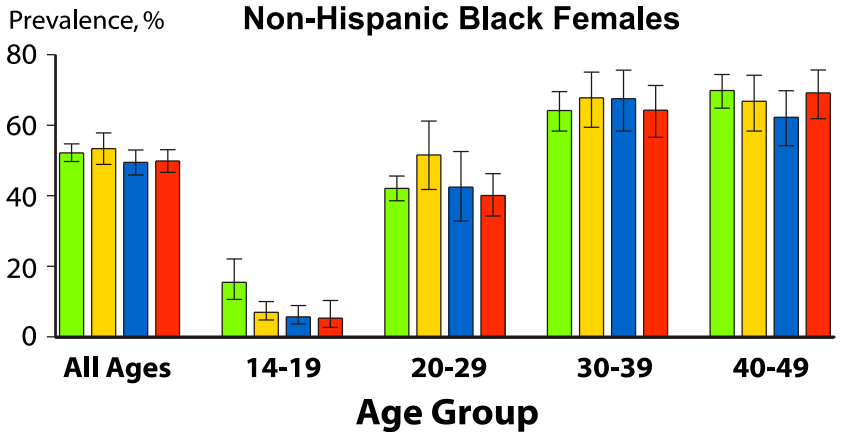
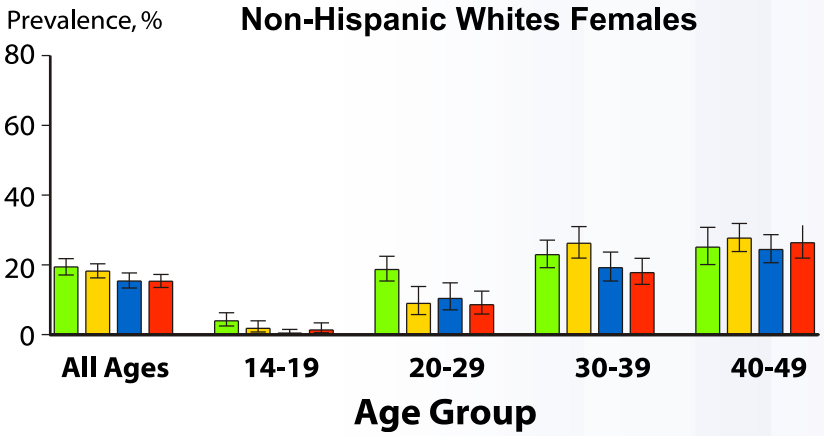
Herpes Simplex Virus Type 2—Seroprevalence Among Non-Hispanic Whites and Non-Hispanic Blacks by Sex and Age Group, National Health and Nutrition Examination Survey, 1988-1994, 1999-2002, 2003-2006, and 2007-2010



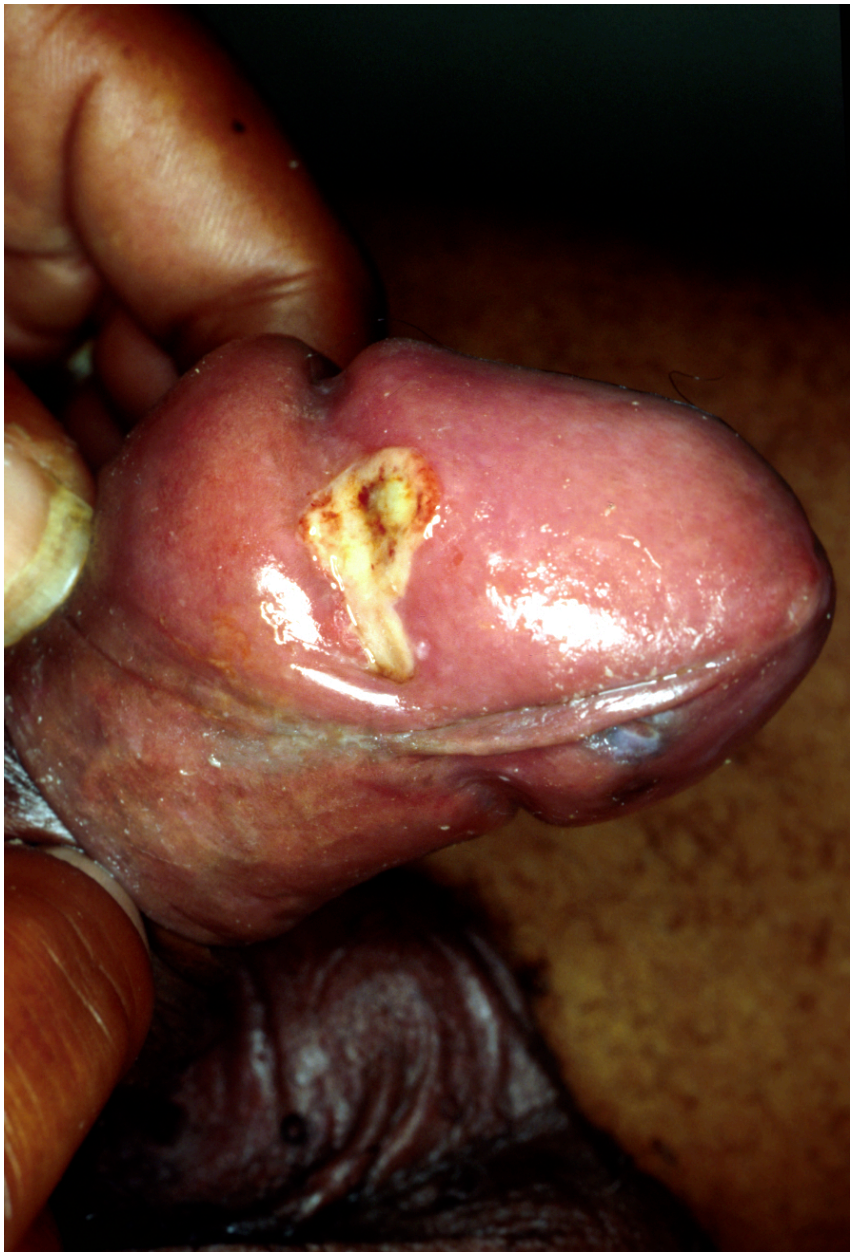






NOTE: Error bars indicate 95% confidence interval.

SOURCE: Fanfair RN, Zaidi A, Taylor LD, Xu F, Gottlieb S, Markowitz L. Trends in seroprevalence of herpes simplex virus type 2 among non-Hispanic blacks and non-Hispanic whites aged 14 to 49 years — United States, 1988 to 2010. Sex Transm Dis. 2013;40(11):860-4.

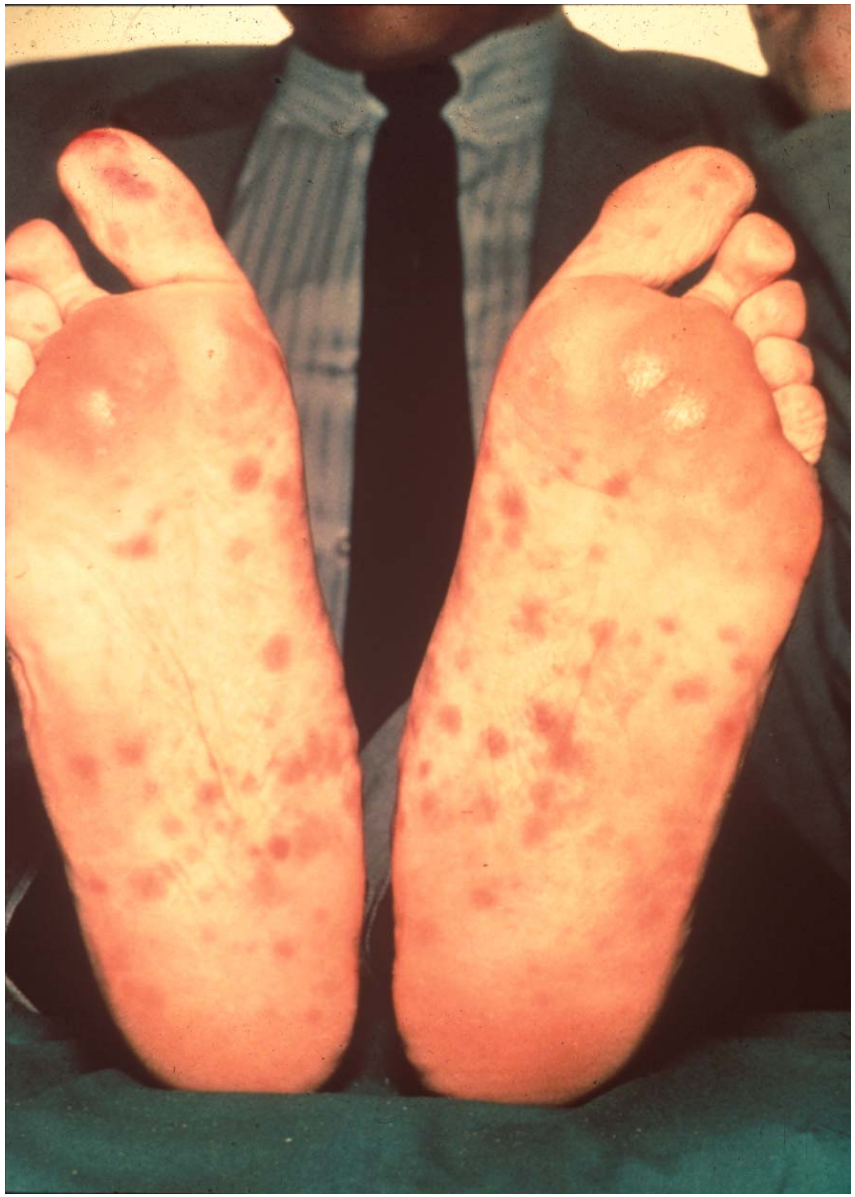


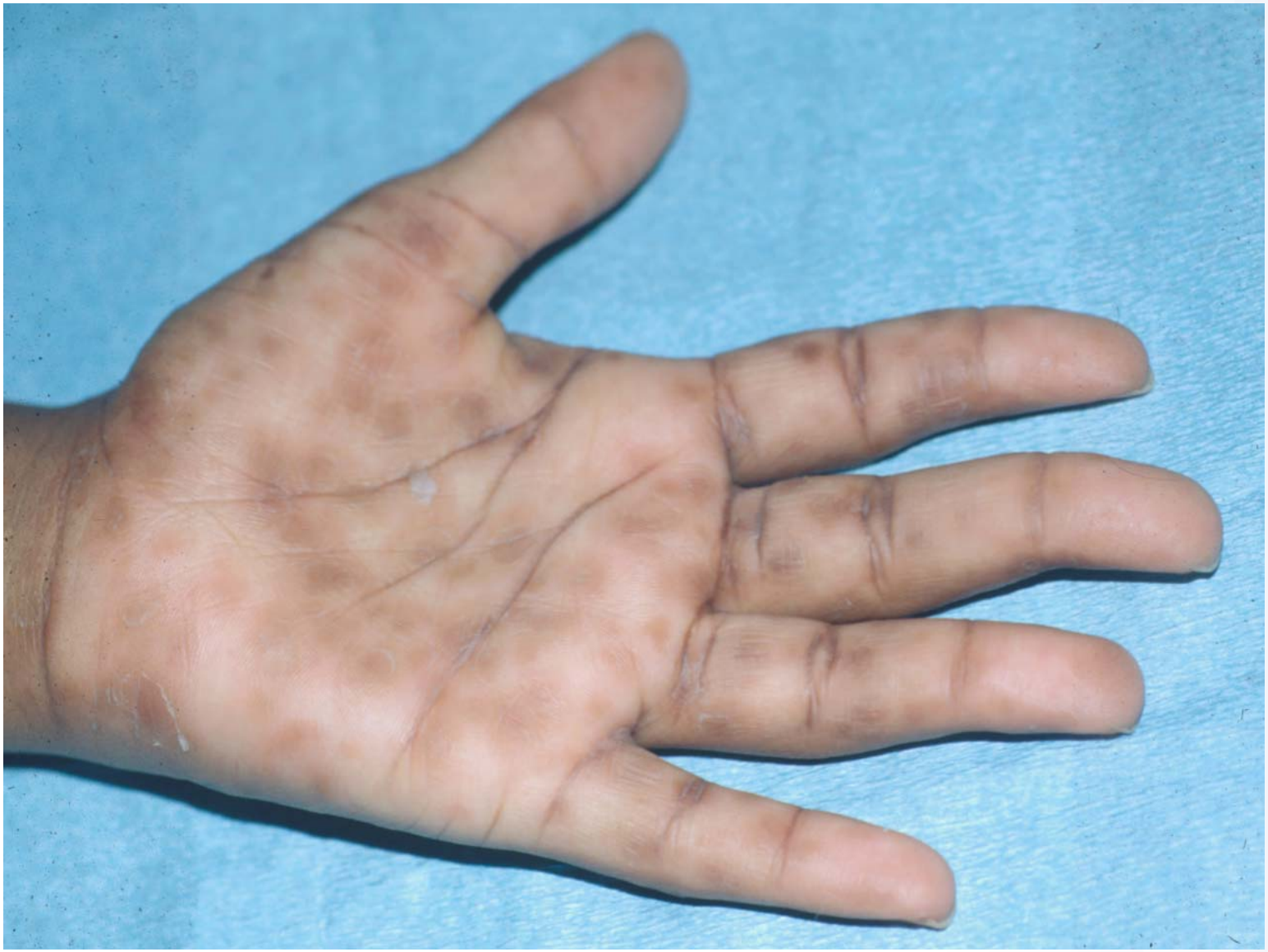
Empiric Management of Atypical GUD in 2016

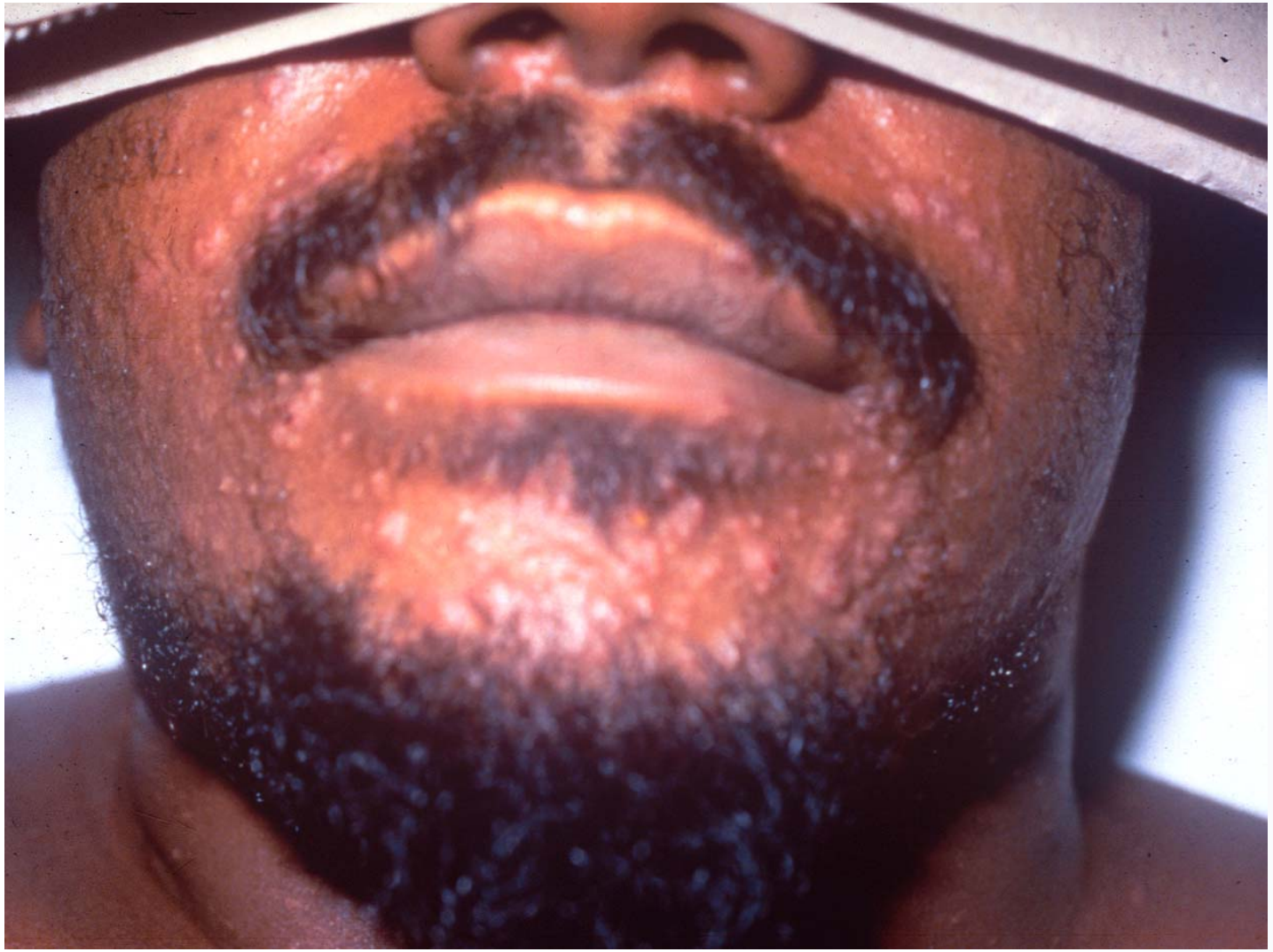
- Swab lesion HSV PCR (superior to culture).
- If rapid reagin test is positive treat for primary syphilis. If not treat for HSV.
- Treat for primary syphilis in MSM and sex workers regardless of syphilis serology result.
- *H. ducreyi* PCR if suggested by epidemiology

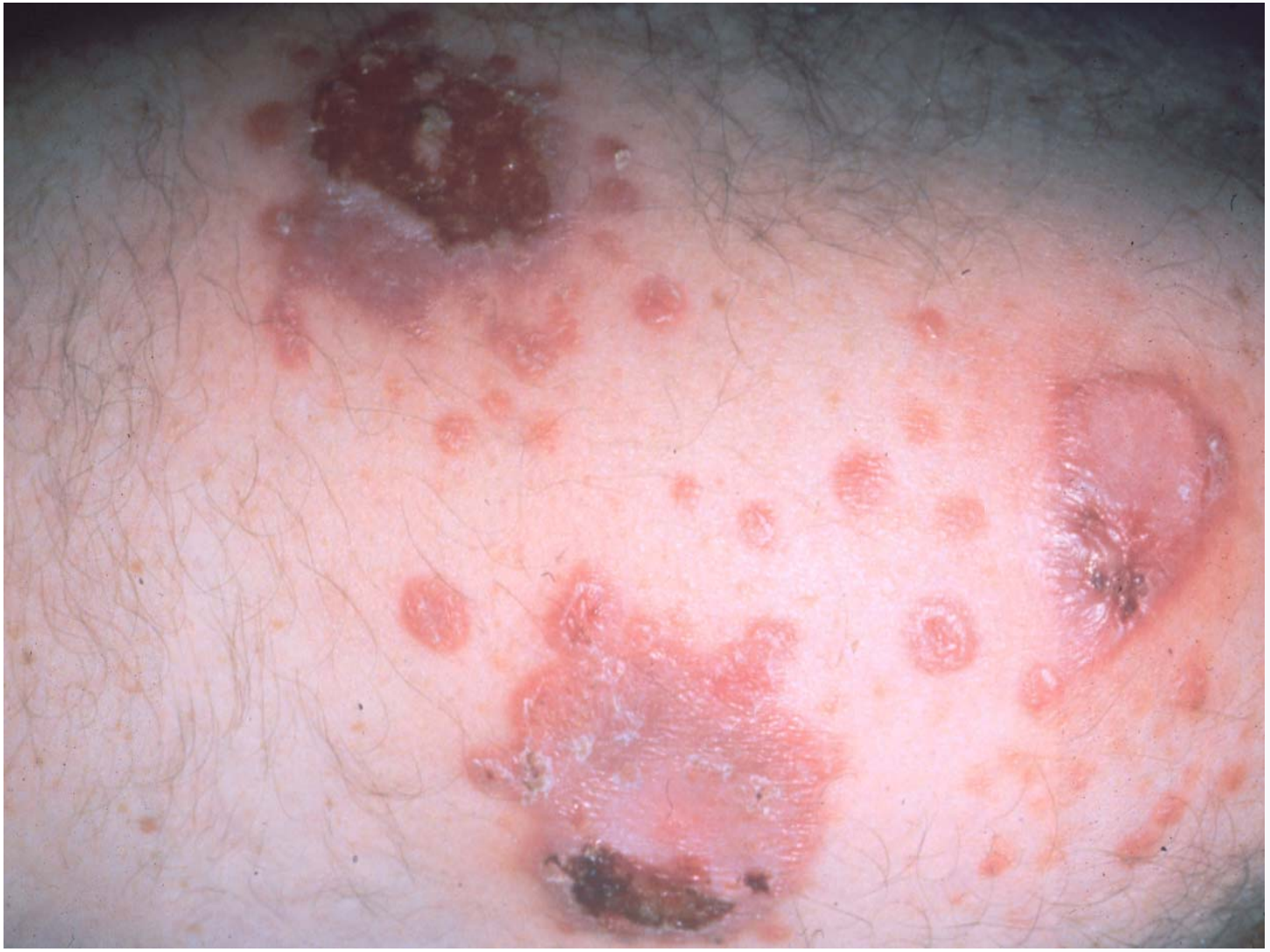
Expected Results of Serologic Testing in Patients With Untreated Syphilis

	% Positive at Disease Stage		
	Primary	Secondary	Late
Reagin test (e.g. RPR, VDRL)	70	100	70
Treponemal test (e.g. TPPA, EIA, etc.)	85	100	98









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Causes of False-Positive Reactions in Serologic Tests for Syphilis

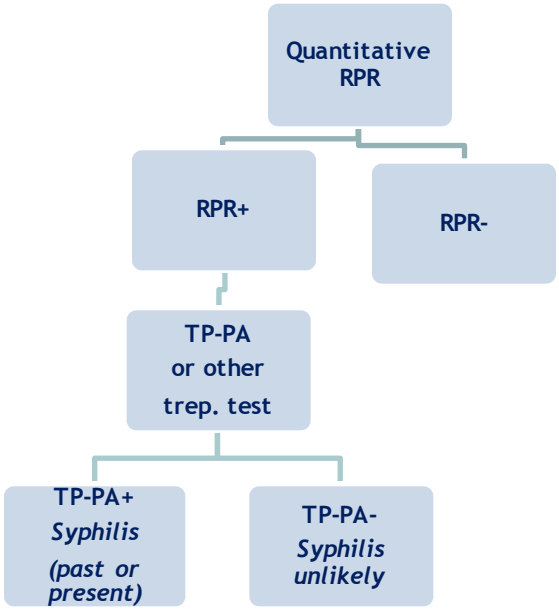
Disease	RPR/VDRL	FTA-ABS	TP-PA
Age		Yes	
Autoimmune Diseases	Yes	Yes	
Cardiovascular Disease		Yes	Yes
Dermatologic Diseases	Yes	Yes	--
Drug Abuse	Yes	Yes	
Febrile Illness	Yes		
Glucosamine/chondroitin sulfate		Possibly	
Leprosy	Yes	No	--
Lyme disease		Yes	
Malaria	Yes	No	
Pinta, Yaws	Yes	Yes	Yes
Pregnancy	Yes*		
Recent Immunizations	Yes	--	--
STD other than Syphilis		Yes	

*May cause increase in titer in women previously successfully treated for syphilis

Source: Syphilis Reference Guide, CDC/National Center for Infectious Diseases, 2002

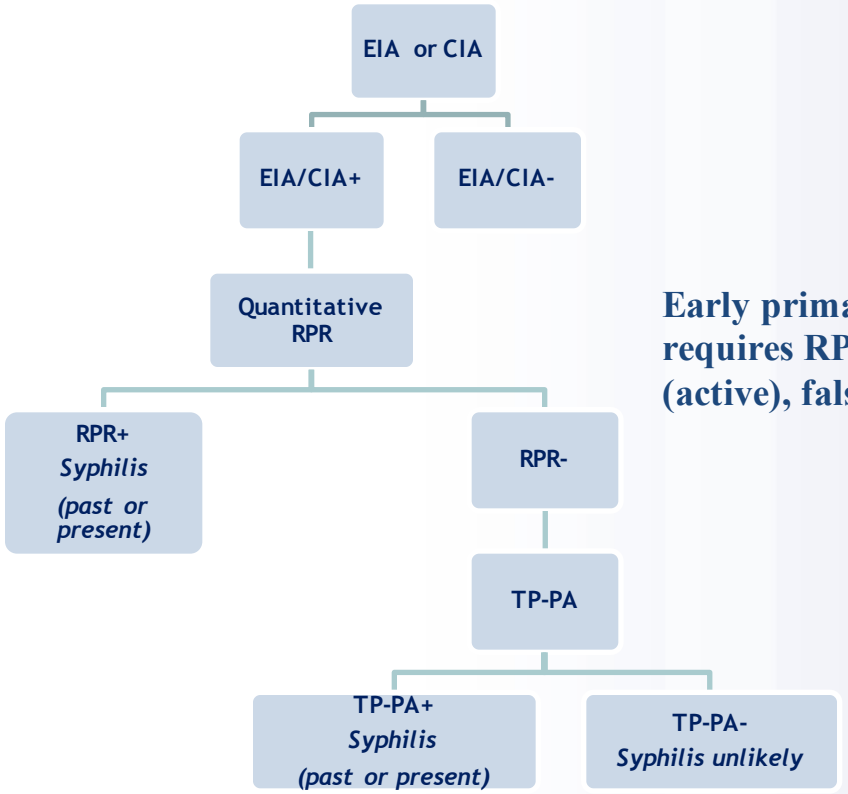
Syphilis serologic screening algorithms

Traditional



Active infection, F+, miss early

Reverse sequence



Early primary, requires RPR (active), false +

Consequences of Automated EIA Syphilis Screening

- Many more treponemal test positive/reagin test negative cases are being identified.
- Treponemal tests remain positive for life in 85% of treated syphilis cases so many more of these individuals also are being identified.
- Approach to the patient with a positive treponemal test but a negative reagin test.
  - Take a careful history
  - If there is no history of treatment or if in doubt, treat for late latent syphilis.
  - Counseling – infectivity is very low but partners should be tested.

Evaluation of CNS Involvement

- Neurologic, ocular, auditory signs/sxs
- CNS invasion in early syphilis +/- HIV or neuro
  - Clinical significance unknown (protein, pleocytosis)
  - Neurosyphilis - combination of tests + clinical
    - Higher cut off for CSF >20 WBCs may improve specificity of NS diagnosis
- LP: neuro/ocular sx, serologic treatment failure, tertiary
  - Some studies - clinical and CSF consistent with NS
    - RPR ≥ 1:32 and/or CD4 ≤350
  - Unless neurologic sx, CSF exam has not been associated with improved clinical outcomes

2015 STD Treatment Guidelines; Marra 2004; Libois A, *STD* 2007 ; Ghanem CID;Marra CID 2008

April 3, 2015
CDC Clinical Advisory: Ocular Syphilis in the United States

- Since December 2014
- 15 cases of ocular syphilis from California and Washington have been reported to the CDC
- 5 Other states have suspect cases under investigation
- **MSM with HIV** and a few cases have occurred among HIV-uninfected persons including heterosexual men and women
- Several of the cases have resulted in significant sequelae including blindness
- Previous research supports evidence of neuropathogenic strains of syphilis, it remains unknown if some *Treponema pallidum* strains have a greater likelihood of causing ocular infections

Signs and Symptoms of Infectious Syphilis and Acute HIV

Disease	Signs and Symptoms	Recommended Testing
Primary Syphilis	• A small, usually painless, ulcerated lesion in or around the genitals, mouth, or anal region • A typical primary chancre will last three weeks and resolve on its own after which begins a latent period of four weeks	RPR (Serological Nontreponemal) AND FTA or TP-PA (Treponemal antigen testing)
Secondary Syphilis	• Palmer/plantar rash • Body rashes, typically of the torso and extremities • Condylomata lata (flat, raised papules) • Mucous patches • Lymphadenopathy • Alopecia	
Acute HIV Infection	• Fever • Lymphadenopathy • Skin rash • Myalgia/arthralgia • Headache • Diarrhea • Oral ulcers • Leucopenia • Thrombocytopenia • Transaminase elevation	HIV RNA test

Genital Herpes: FDA-Approved Type-Specific Serologic Tests

Type of Test	Sensitivity* (%)	Specificity* (%)	
HerpeSelect™ 2 ELISA IgG	91-93	96-100	97-100
HerpeSelect™ 1 ELISA IgG		92-100	
HerpeSelect™ Immunoblot 2	99-100	95-100	
Immunoblot 1	97-100	98	

Antibody tests become positive as early as three weeks, and by 16 weeks almost all tests of those infected are positive

*Based on comparison with the results of Western blot test. Percentages given for HerpeSelect, and Immunoblot, are for HSV-2 antibodies

HerpeSelect™ is a trademark of Focus Diagnostics

Adapted from Ashley RL. *Sex Transm Infect.* 2001;77:232-237.

Ashley-Morrow R et al. *Am J Clin Pathol;* 2003;120

Who Is a Candidate for HSV Serologic Testing?

- Patient with typical GH lesion; culture not done or negative
- Patient with recurrent clinical symptoms suggestive of GH, but without typical GH lesions
- Sexual partners of patients with GH
- Patient request to know infection status
- STD screening
- Prenatal screening
- Patient with HIV infection

Is IgM Useful in Distinguishing New vs. Recurrent GH Infection?

- No! Do not order IgM antibodies to diagnose new vs. recurrent GH infection. Often laboratories automatically do IgM test
- Why aren't IgM tests helpful in determining the recency of GH infection?
  - IgM tests are not type-specific – IgM could be from HSV-1 or HSV-2!
  - Each of the many episodes of viral reactivation can produce new IgM and IgG, making it difficult to interpret results as to acuity of infection. For example, some first infections can have no IgM (only IgG) and some recurrent infections can have IgM.

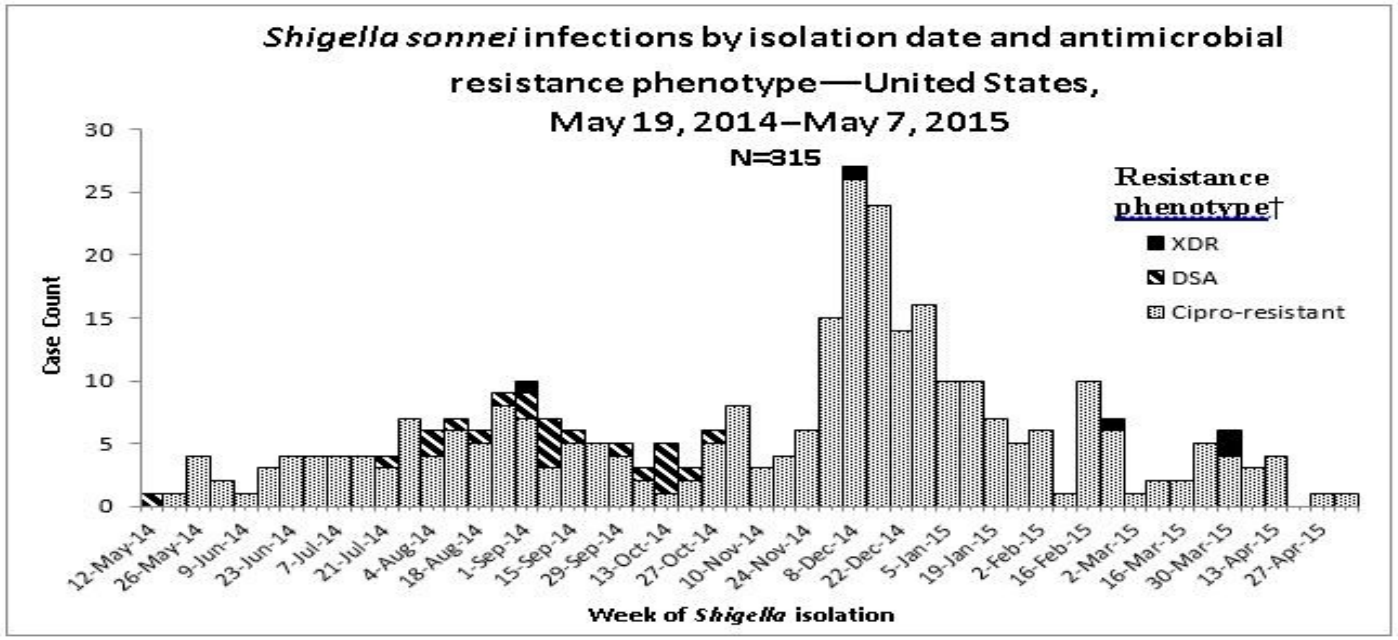
Antimicrobial Resistant Shigella in MSM

Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: a cross-sectional study

Kate S Baker, Timothy J Dallman, Philip M Ashton, Martin Day, Gwenda Hughes, Paul D Crook, Victoria L Gilbart, Sandra Zittermann, Vanessa G Allen, Benjamin P Howden, Takehiro Tomita, Mary Valcanis, Simon R Harris, Thomas R Connor, Vitali Sintchenko, Peter Howard, Jeremy D Brown, Nicola K Petty, Malika Gouali, Duy Pham Thanh, Karen H Keddy, Anthony M Smith, Kaisar A Talukder, Shah M Faruque, Julian Parkhill, Stephen Baker, François-Xavier Weill, Claire Jenkins, Nicholas R Thomson

Summary

Background Shigellosis is an acute, severe bacterial colitis that, in high-income countries, is typically associated with travel to high-risk regions (Africa, Asia, and Latin America). Since the 1970s, shigellosis has also been reported as a sexually transmitted infection in men who have sex with men (MSM), in whom transmission is an important component of shigellosis epidemiology in high-income nations. We aimed to use sophisticated subtyping and international sampling to determine factors driving shigellosis emergence in MSM linked to an outbreak in the UK.



Gardasil 9

- Vaccine approved December 2014
- Females ages 9 through 26
- Males ages 9 through 15
- It is approved for the prevention of cervical, vulvar, vaginal and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, and for the prevention of genital warts caused by HPV types 6 or 11

Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis

Dorothy A Machalek, Mary Poynten, Fengyi Jin, Christopher K Fairley, Annabelle Farnsworth, Suzanne M Garland, Richard J Hillman, Kathy Petoumenos, Jennifer Roberts, Sepehr N Tabrizi, David J Templeton, Andrew E Grulich

Summary

Background Men who have sex with men (MSM) are at greatly increased risk of human papillomavirus (HPV)-associated anal cancer. Screening for the presumed cancer precursor, high-grade anal intraepithelial neoplasia (AIN), followed by treatment in a manner analogous to cervical screening, has been proposed. We aimed to assess available data for anal HPV disease that can inform pre-cancer screening programmes.

Methods We searched PubMed, OVID Medline, and Embase for all studies published before Nov 1, 2011, that reported prevalence and incidence of anal HPV detection, AIN, and anal cancer in MSM. We calculated summary estimates using random-effects meta-analysis.

Findings 53 studies met the inclusion criteria, including 31 estimates of HPV prevalence, 19 estimates of cytological abnormalities, eight estimates of histological abnormalities, and nine estimates of anal cancer incidence. Data for incident HPV and high-grade AIN were scarce. In HIV-positive men, the pooled prevalence of anal HPV-16 was 35·4% (95% CI 32·9–37·9). In the only published estimate, incidence of anal HPV-16 was 13·0% (9·6–17·6), and clearance occurred in 14·6% (10·2–21·2) of men per year. The pooled prevalence of histological high-grade AIN was 29·1% (22·8–35·4) with incidences of 8·5% (6·9–10·4) and 15·4% (11·8–19·8) per year in two estimates. The pooled anal cancer incidence was 45·9 per 100 000 men (31·2–60·3). In HIV-negative men, the pooled prevalence of anal HPV-16 was 12·5% (9·8–15·4). Incidence of HPV-16 was 11·8% (9·2–14·9) and 5·8% (1·9–13·5) of men per year in two estimates. The pooled prevalence of histological high-grade AIN was 21·5% (13·7–29·3), with incidence of 3·3% (2·2–4·7) and 6·0% (4·2–8·1) per year in two estimates. Anal cancer incidence was 5·1 per 100 000 men (0–11·5; based on two estimates). There were no published estimates of high-grade AIN regression.

Interpretation Anal HPV and anal cancer precursors were very common in MSM. However, on the basis of restricted data, rates of progression to cancer seem to be substantially lower than they are for cervical pre-cancerous lesions. Large, good-quality prospective studies are needed to inform the development of anal cancer screening guidelines for MSM.

Take Home Messages

- *M. genitalium* is clearly associated with NGU in men. It is a likely cause relapse following doxycycline treatment.
- Gonorrhea should be treated with high dose ceftriaxone and azithromycin.
- Remember the proper interpretation of syphilis serologic tests.
- Empiric therapy for GUD depends on knowledge of current epidemiology of the individual causative agents.
- HSV 2 specific serologic tests are available and useful in limited circumstances.
- HPV Vaccination prevents cancer!

Educational and Training Resources

- NNTPC
  - www.nnptc.org
- 2015 STD Treatment Guidelines
  - www.cdc.gov/std/treatment/2015
  - cdcinfo@cdc.gov or 800.CDC.INFO (800.232.4636)
- CDC Division of STD Prevention
  - www.cdc.gov/std/training
  - stdstraining@cdc.gov or 404.639.8360

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