

“Sexually Transmitted Infections (STIs): Update on Chlamydia, Gonorrhea, and Syphilis”

Jose A. Bazan, DO
Medical Director, Sexual Health Clinic
Columbus Public Health (CPH)
Assistant Professor, Clinical Internal Medicine
Division of Infectious Diseases
The Ohio State University Wexner Medical Center

Learning Objectives

- **Describe the recent epidemiologic trends for Chlamydia, Gonorrhea, and Syphilis in the United States**
- **Recognize and describe risk factors, clinical manifestations, screening/diagnosis, and management of Chlamydia, Gonorrhea, and Syphilis**

Introduction

- Sexually transmitted infections (STIs) are hidden epidemics of enormous health and economic consequence
 - ✓ Estimated annual direct medical cost = \$17 billion U.S. dollars, 2010 (range: \$14 – 23 billion)
- Disruptive, painful, and associated with long-term negative health consequences
- Increase risk of other reproductive morbidities (e.g. infertility)
- All communities are impacted by STIs – all individuals directly or indirectly pay for the costs of these diseases

Eng TR, Butler WT, IOM, 1997; Holmes, et al. (editors), STD, 4th Ed. 2008; Chesson HW, et al. STD 2011

Why Focus on Chlamydia, Gonorrhea, and Syphilis?

CNN Health » Diet + Fitness | Living Well | Parenting + Family

STD rates reach record high in United States

By Jacqueline Howard, CNN
Updated 12:09 PM ET, Thu October 20, 2016

She may be..
a bag of
TROUBLE
SYPHILIS - GONORRHEA

shots HEALTH NEWS FROM NPR

PUBLIC HEALTH

STD Infections Rise To New Highs After States Close Health Clinics

OCTOBER 20, 2016 3:51 PM ET
ANGUS CHEN

The New York Times

U.S.

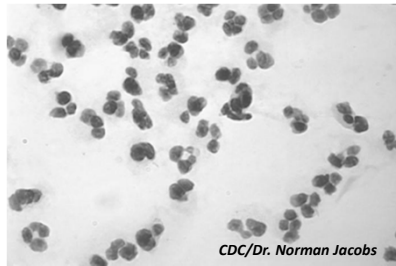
Reported Cases of Sexually Transmitted Diseases Are on Rise

By ABBY GOODNOUGH OCT. 18, 2016

WASHINGTON — There were more cases of sexually transmitted diseases reported in the United States last year than ever before, according to new federal data. Rates of chlamydia, gonorrhea and syphilis — three of the most common S.T.D.s — grew for the second consecutive year, with sharper increases in the West than other regions. And while all three diseases are treatable with antibiotics, most cases continue to go undiagnosed, potentially causing infertility and other problems.

Case

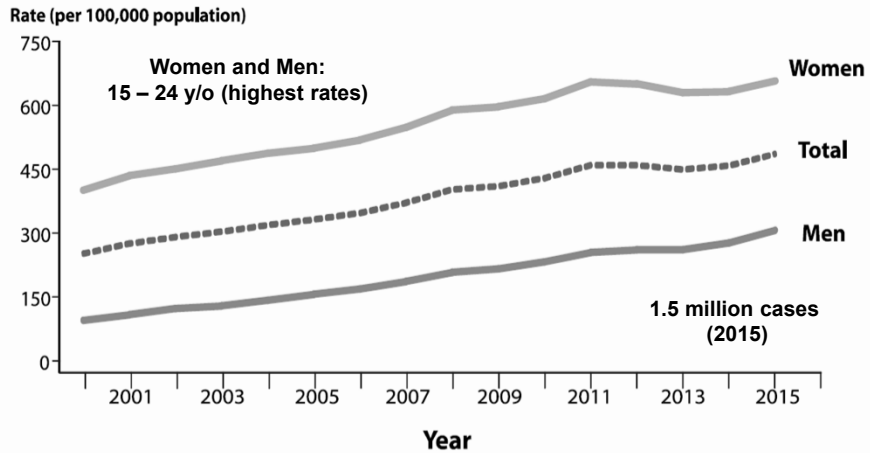
- 27 y/o African American male presents with complaints of a clear penile discharge x 3 days (top picture)
- Patient reports having multiple female sex partners and practices unprotected vaginal and anal sex
- Gram stain of urethral discharge is shown (bottom picture).
- Urine nucleic acid amplification test is positive for chlamydia and negative for gonorrhea



<http://phil.cdc.gov/phil/home.asp>

Chlamydia

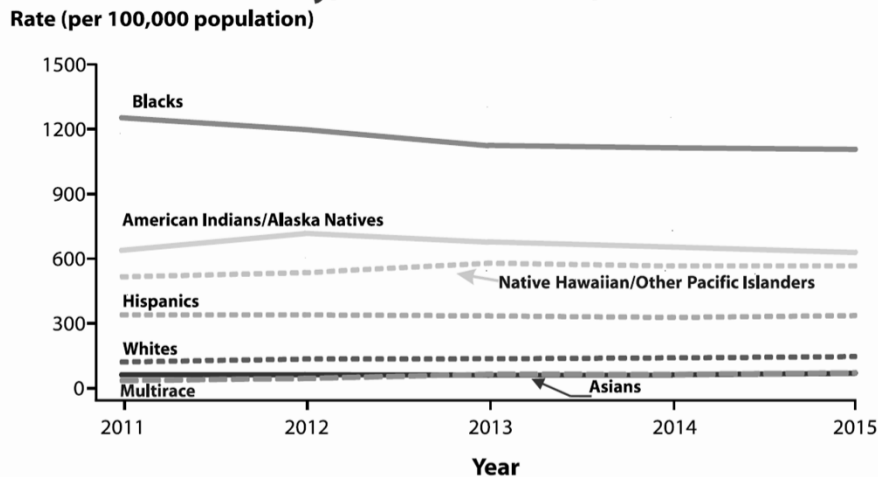
Chlamydia — Rates of Reported Cases by Sex, United States, 2000–2015



NOTE: Data collection for chlamydia began in 1984 and chlamydia was made nationally notifiable in 1995; however, chlamydia was not reportable in all 50 states and the District of Columbia until 2000. Refer to the National Notifiable Disease Surveillance System (NNDSS) website for more information: <https://www.cdc.gov/nndss/conditions/chlamydia-trachomatis-infection/>.



Chlamydia — Rates of Reported Cases by Race/Ethnicity, United States, 2011–2015



NOTE: Includes 45 states reporting race/ethnicity data in Office of Management and Budget compliant formats during 2011–2015.



Chlamydia: Risk Factors

- Adolescents and young adults (<25 y/o)
- New sex partner
- Multiple sex partners
- Sex partner with other sex partners
- Previous STI or sex partner with an STI
- Inconsistent condom use (non-monogamous)
- Ethnic minority
- Low or intermediate education

Workowski KA, et al. MMWR 2015; LeFevre ML. AIM 2014; Gaydos CA, et al. NEJM 1998; Cook RL, et al. CID 1999; Phillips RS, et al. AJM 1989; Stergachis A, et al. AJE 1993; Hook III EW, et al. AJE 1992; Datta SD, et al. AIE 2007

Chlamydia: Manifestations

- Asymptomatic infection (common in men and women)
- Cervicitis
- Pelvic Inflammatory Disease (PID)
 - Infertility
 - Ectopic pregnancy
 - Chronic pelvic pain
- Peri-hepatitis
- Urethritis
- Epididymitis
- Prostatitis
- Proctitis
- Inclusion conjunctivitis (adults and neonates)
- Pneumonia (mainly infants)
- Lymphogranuloma venereum (LGV serovars)
- Reactive arthritis

Mandell, et al. (editors), PPID, 8th Ed. 2015; Workowski KA, et al. MMWR 2015

Chlamydia: Screening Recommendations

- All sexually active women <25 y/o (annually)
- Older sexually active women with risk factors (annually)
- All pregnant women <25 y/o and those older with risk factors
 - 1st prenatal visit
 - 3rd trimester if <25 y/o or if at high-risk for infection
- Incarcerated women ≤35 y/o and men <30 y/o (at intake)
- Sexually active young men (?)
 - Not enough evidence to suggest routine screening, except in high risk settings (e.g. adolescent clinics, prison/jail, STD clinics) or high-burden populations (e.g. men who have sex with men)

Chlamydia screening programs reduce rates of PID in women

Workowski KA, et al. MMWR 2015; LeFevre ML. AIM 2014; Scholes D, et al. NEJM 1996; Kamwendo F, et al. STD 1996

Chlamydia: Diagnosis

- Nucleic acid amplification testing (NAAT)
 - High sensitivity ≥90% and specificity ≥99%
- Women
 - Vaginal swabs[†] ≥ Endocervical swab > First-catch urine[‡]
 - † Self-collected or clinician-collected (equivalent)
 - ‡ Can miss up to 10% of infections
- Men
 - First-catch urine[§]
 - § Equivalent/superior to urethral swab

MMWR Morbidity and Mortality Weekly Report
March 14, 2015

Recommendations for the Laboratory-Based Detection of Chlamydia trachomatis and Neisseria gonorrhoeae — 2014



cdc U.S. Department of Health and Human Services



CPH/Dr. Bazan

Papp J, et al. MMWR 2014; Workowski KA, et al. MMWR 2015

Chlamydia: Treatment

- **2002 Meta-analysis (n = 12 studies)**
 - **Equal efficacy: azithromycin (97%) and doxycycline (98%) for urogenital infections**
 - **Older testing methods, underestimated failure rates, adherence to doxycycline not ensured, repeat exposures (?), single TOC**
- **2014 Meta-analysis (n = 23 studies)**
 - **Marginal superior efficacy (up to 3%) for doxycycline (97.5%) vs. azithromycin (94.4%) for urogenital infections**
 - **Considerable variability in evidence quality**
 - **Few double-blind placebo controlled trials**
- **2015 Meta-analysis (n = 8)**
 - **Observational studies; azithromycin was less efficacious than doxycycline for rectal infections (82.9% vs. 99.6%)**

Workowski KA, et al. MMWR 2015; Geisler WM, et al. NEJM 2015 ; Lau CY, et al. STD 2002; Kong FY, et al. CID 2014; Kong FY, et al. JAC 2015.

THE NEW ENGLAND JOURNAL of MEDICINE

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.

**Still very good!
(DOT advantage)**

- **Doxycycline (n = 155) → 100% efficacy**
 - **No treatment failures**
- **Azithromycin (n = 155) → 97% efficacy**
 - **5 treatment failures**
 - **Failure rate difference, 3.2% (1-sided 90% CI, 0 – 5.9)**
 - **Did NOT establish “non-inferiority”**

Geisler WM, et al. NEJM 2015.

Chlamydia: Treatment

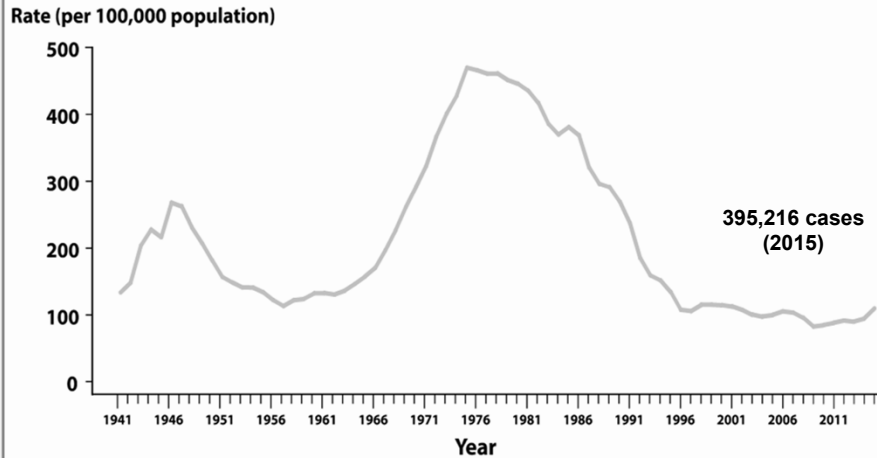
- **Non-Pregnant Patients**
 - **Recommended Regimen**
 - Azithromycin 1 g PO x 1
 - Doxycycline 100 mg PO BID x 7 days
 - **Alternative Regimen (one example)**
 - Levofloxacin 500 mg PO QD x 7 days
- **Pregnant Patients***
 - **Recommended Regimen**
 - Azithromycin 1 g PO x 1
 - **Alternative Regimen (one example)**
 - Amoxicillin 500 mg PO TID x 7 days

**Test of cure (TOC) in
3 – 4 weeks with NAAT*

Workowski KA, et al. MMWR 2015

Gonorrhea

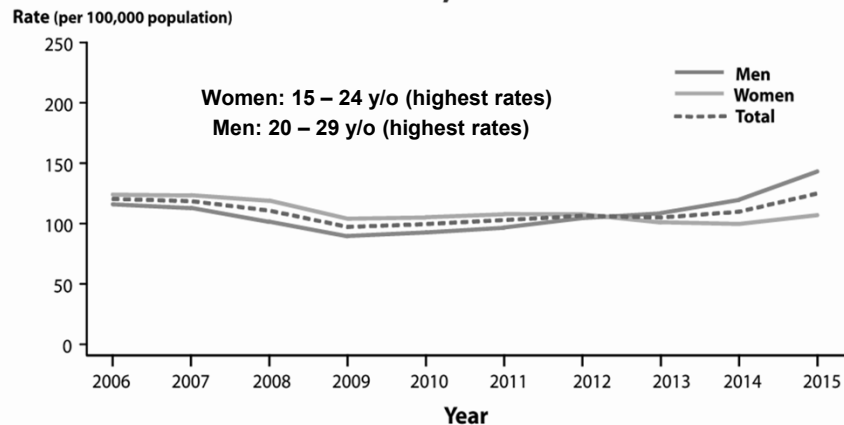
Gonorrhea — Rates of Reported Cases by Year, United States, 1941–2015



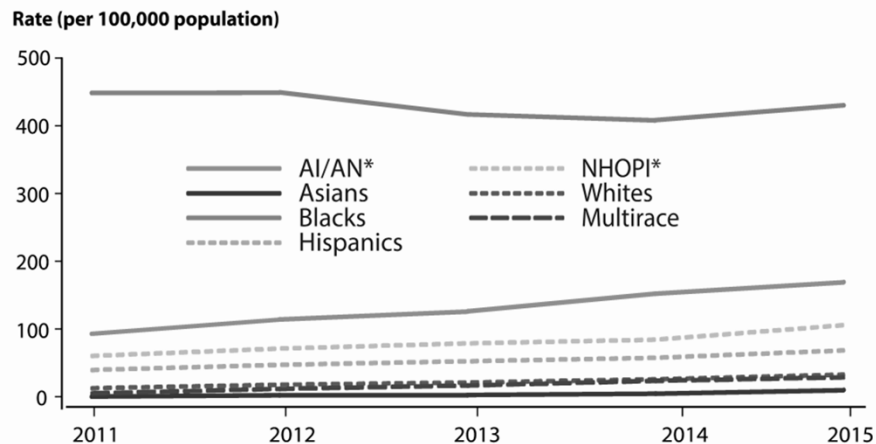
NOTE: Data collection for gonorrhea began in 1941; however, gonorrhea became nationally notifiable in 1944. Refer to the National Notifiable Disease Surveillance System (NNDSS) website for more information: <https://www.cdc.gov/nndss/conditions/gonorrhea/>.



Gonorrhea — Rates of Reported Cases by Sex, United States, 2006–2015



Gonorrhea — Rates of Reported Cases by Race/Ethnicity, United States, 2011–2015



* AI/AN = American Indians/Alaska Natives; NHOPI = Native Hawaiian/Other Pacific Islanders.

NOTE: Includes 45 states reporting race/ethnicity data in Office of Management and Budget compliant formats during 2011–2015



Gonorrhea: Risk Factors

- Adolescents and young adults (<25 y/o)
- New sex partner, multiple sex partners, or sex partner with other sex partners
- Previous/co-existing STI or sex partner with an STI
- Inconsistent condom use (non-monogamous)
- Ethnic minority
- Low or intermediate education
- Commercial sex work (sex for money or drugs)
- High prevalence of gonorrhea at provider's site

Workowski KA, et al. *MMWR* 2015; LeFevre ML. *AIM* 2014; Hook III EW, et al. *AJE* 1992; Mertz KJ, et al. *AJPH* 1997; Klausner JD. *JID* 1998; Datta SD, et al. *AIM* 2007.

Gonorrhea: Manifestations

- Asymptomatic infection (common in women)
- Cervicitis
- Pelvic Inflammatory Disease (PID)
 - Infertility
 - Ectopic pregnancy
 - Chronic pelvic pain
- Peri-hepatitis
- Urethritis
- Epididymitis
- Proctitis
- Pharyngitis
- Disseminated gonococcal infection (DGI)
- Conjunctivitis (adults and neonates)

Mandell, et al. (editors), PPID, 8th Ed. 2015; Workowski KA, et al. MMWR 2015

Gonorrhea: Screening Recommendations

- All sexually active women <25 y/o (annually)
- Older sexually active women with risk factors (annually)
- All pregnant women <25 y/o and those older with risk factors
 - 1st prenatal visit
 - 3rd trimester if at high-risk for infection
- Incarcerated women ≤35 y/o and men <30 y/o (at intake)
- High-risk men who have sex with men (MSM)
- No screening of older women or men at low risk

Workowski KA, et al. MMWR 2015; LeFevre ML. AIM 2014

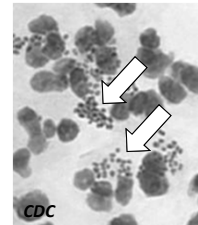
Gonorrhea: Diagnosis

- Nucleic acid amplification testing (NAAT)
 - Sensitivity $\geq 90\%$, Specificity $\geq 99\%$
- Women
 - Vaginal swabs \geq Endocervical swab $>$ First-catch urine
- Men
 - First-catch urine
 - Urethral Gram stain with GNID in symptomatic men
 - Sensitivity $>95\%$, Specificity $>99\%$
- Culture
 - Antibiotic susceptibility testing

MMWR
 Recommendations for the Laboratory-Based
 Detection of *Chlamydia trachomatis* and
Neisseria gonorrhoeae — 2014



CDC

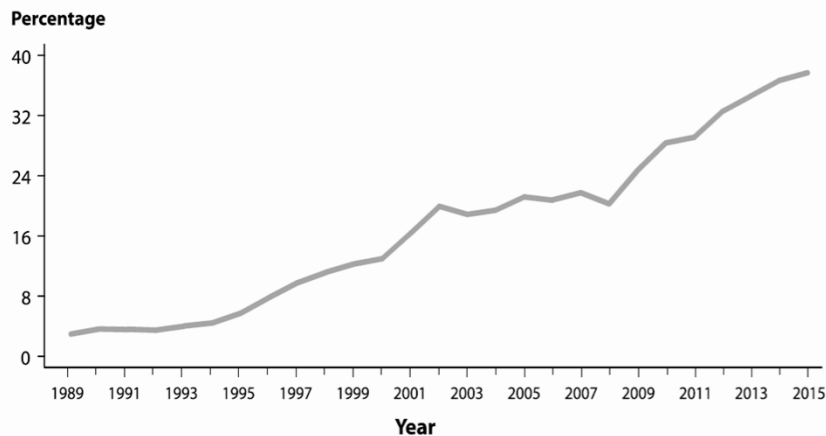


CDC

Gram negative
 intracellular diplococci
 (GNID)

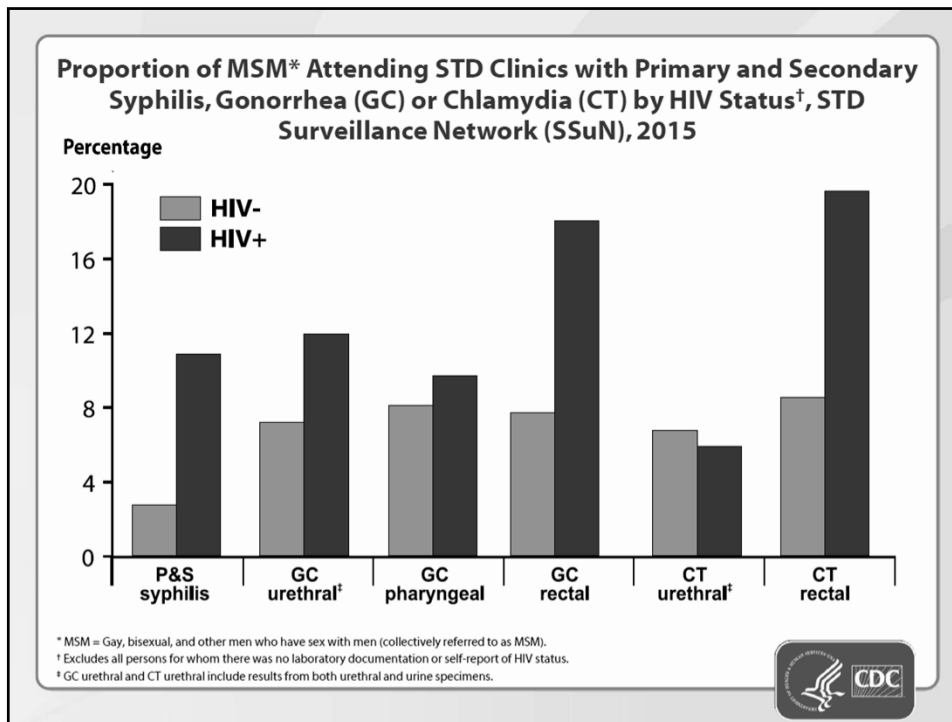
Papp J, et al. *MMWR* 2014; Workowski KA, et al. *MMWR* 2015

Neisseria gonorrhoeae — Percentage of Urethral Isolates
 Obtained from MSM* Attending STD Clinics, Gonococcal
 Isolate Surveillance Project (GISP), 1989–2015



* MSM = Gay, bisexual, and other men who have sex with men (collectively referred to as MSM).





Extragenital Chlamydia and Gonorrhea Infections in MSM

- Frequently asymptomatic
- High proportion of MSM with extragenital chlamydia and gonorrhea infections have negative urethral/urine chlamydia and gonorrhea test result (74% pharyngeal GC, 72% rectal GC, 92% pharyngeal CT, 88% rectal CT)
- Rectal chlamydia or gonorrhea infections increase risk of HIV seroconversion in MSM (8-fold if ≥ 2 episodes of rectal infection in the previous 2 years)

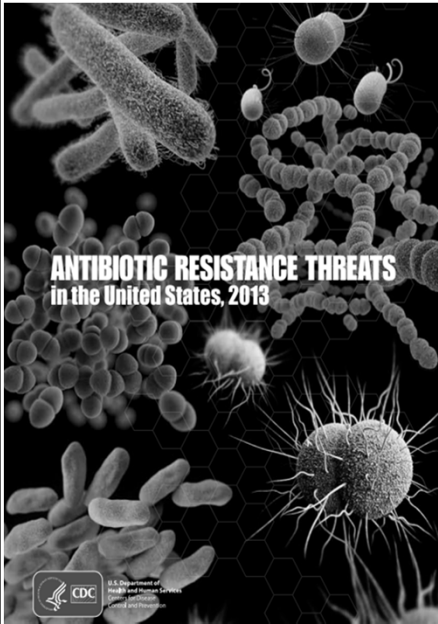
Patton ME, et al. CID 2014; Bernstein KT, et al. JAIDS 2010

Chlamydia and Gonorrhea Screening in MSM

- Reported behaviors in the last 12 months:
 - Insetive intercourse
 - Urethral Chlamydia and Gonorrhea (annually)
 - Receptive anal intercourse
 - Rectal Chlamydia and Gonorrhea (annually)*
 - Receptive oral intercourse
 - Oropharyngeal Gonorrhea only (annually)*
- More frequent testing (every 3 – 6 months) if patient or sex partner has multiple partners or sex while using illicit drugs

**NAAT recommended (Not FDA-cleared)*

Workowski KA, et al. *MMWR* 2015; Patton ME, *CID* 2014



Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae* ←

Serious Threats

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β -lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

Gonorrhoea: Treatment Failures

J Antimicrob Chemother
doi:10.1093/jac/dkt017

Failure of 500 mg of ceftriaxone to eradicate pharyngeal gonorrhoea, Australia

Marcus Y. Chen^{1,2,†*}, Kerrie Stevens^{3,†}, Robin Tideman¹, Angelo Zai³, Takehiro Tomita³, Christopher K. Fairley^{1,2}, Monica Lahra^{4,5}, David Whitley^{6,7} and Geoff Hogg³

RAPID COMMUNICATIONS

Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010

CA Ison (catherine.ison@hpa.org.uk), J Hussey¹, KN Sankar², J Evans³, S Alexander⁴
1. Sexually Transmitted Bacteria Reference Laboratory, Health Protection Agency, London, United Kingdom
2. Carlton Street Clinic, Blyth, Northumberland, United Kingdom
3. New Croft Centre, Newcastle upon Tyne, United Kingdom
4. Health Protection Agency North East, Newcastle General Hospital, Newcastle upon Tyne, United Kingdom

Citation style for this article:
Ison CA, Hussey J, Sankar KN, Evans J, Alexander S. Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010. *Euro Surveill*. 2011;16(4):pii=19833. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19833>

CASE REPORT

Emergence of Increased Azithromycin Resistance During Unsuccessful Treatment of *Neisseria gonorrhoeae* Infection With Azithromycin (Portland, OR, 2011)

Olusegun O. Soge, PhD,* Doug Harger, BS,† Sean Schafer, MD,† Kim Toews, MPH,‡
Kathie A. Raisler, MT,‡ Kathy Vinator, FNP,‡ King K. Holmes, MD, PhD,*
and Robert D. Kirkcaldy, MD, MPH§

Chen MY, et al. *JAC*. 2013; Ison CA, et al. *Euro Surveill*. 2011; Soge OO, et al. *STD* 2012.

Gonococcal Isolate Surveillance Project (GISP)

- Surveillance study sponsored by CDC since 1986
- Tracks gonorrhoea antibiotic susceptibility trends in the U.S.
- Informs national treatment recommendations



CDC GISP

Gonorrhea: 2014 GISP Results

- 5,093 urethral gonorrhea isolates analyzed
- Tetracycline-R = 25%
- Ciprofloxacin-R = 19%
- Penicillin-R = 16%
- Azithromycin-RS = 2.5% (up from 0.6% in 2013)
 - ✓ Greatest increase in Midwestern U.S.
 - ✓ MSM > MSMW > MSW
- Cefixime-RS = 0.8% (up from 0.4% in 2013)
- Ceftriaxone-RS = 0.1%

R = Resistance
RS = Reduced Susceptibility

Kirkcaldy RD, et al. MMWR 2016

Gonorrhea Treatment

- Uncomplicated urethral, cervical, and rectal infections:
 - Ceftriaxone 250 mg IM + Azithromycin 1g PO x 1 (Recommended)
 - Cefixime 400 mg PO + Azithromycin 1g PO x 1 (Alternative)
 - No test of cure (TOC) necessary
- Uncomplicated oropharyngeal Infections:
 - Ceftriaxone 250 mg IM + Azithromycin 1g PO x 1 (Recommended)
 - Alternative → TOC in 14 days (NAAT or Culture)*

** Perform susceptibility testing if positive*

Workowski KA, et al. MMWR 2015

Gonorrhea: Treatment

- **Dual therapy ALWAYS recommended**
 - Treats chlamydia co-infection (20 – 40%) and prevents development of drug-resistant gonorrhea
 - Azithromycin preferred over doxycycline* due to high prevalence of tetracycline resistance (25%)
 - *Doxycycline 100 mg PO BID x 7 days (azithro allergy)
- **Azithromycin (2 g) monotherapy not recommended**
 - Resistance can develop easily (at least in-vitro)
 - Multiple documented treatment failures
 - Options for patients with “Cephalosporin-allergy”?

Workowski KA, et al. MMWR 2015; Lyss SB, et al. AIM 2003; Habib AR, et al. Int J STD AIDS 2004; Kirkcaldy RD, et al. MMWR 2016; Ison CA, et al. Euro Surveill. 2011; Soge OO, et al. STD 2012; Waters LJ, et al. Int J STD AIDS 2005; McLean CA, et al. STD 2004; Chisholm SA, et al. JAC 2009.

Gonorrhea: Treatment (New Options)

**National shortage*

- **Gemifloxacin 320 mg* + Azithromycin 2 g PO x 1**
 - 99.5% cure rate for urogenital infections (n = 199)
- **Gentamicin 240 mg IM + Azithromycin 2 g PO x 1**
 - 100% cure rate for urogenital infections (n = 202)
- **Study not powered to detect efficacy for extra-genital infections (rectum or pharynx)**
- **Solithromycin 1 g OR 1.2 g PO x 1 (Phase II Trial)**
 - 100% cure rate among patients (n = 46) with culture positive urogenital, rectal, and pharyngeal infections

Kirkcaldy RD, et al. CID 2014; <http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm#G>; Hook III EW, et al. CID 2015

Chlamydia and Gonorrhea: Follow-up

- No sex for 7 days after treatment
- Notify, screen, and treat all sex partners in the last 60 days
 - Screen and treat most recent sex partner even if last sexual contact was >60 days
- Re-screen in 3 months after treatment due to high risk of re-infection (if not possible, re-screen whenever medical care is sought within next 12 months)

Workowski KA, et al. MMWR 2015

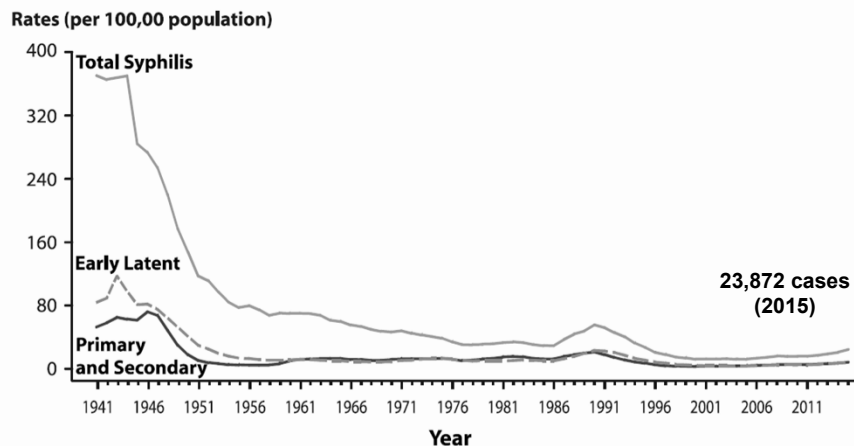
Syphilis

Case

- 28 y/o African American male presents with whole body rash, malaise, and mouth ulcers for the last 4 weeks
- Reports having sex with women and men (~8 sex partners in last 6 months), uses the internet to find sex partners, engages in anonymous sex, uses methamphetamines, and reports unprotected insertive/receptive anal sex and receptive oral sex
- RPR = 1:256
- FTA-ABS = Reactive
- Rapid HIV antibody = Positive (Western Blot +) – Negative 3 months prior



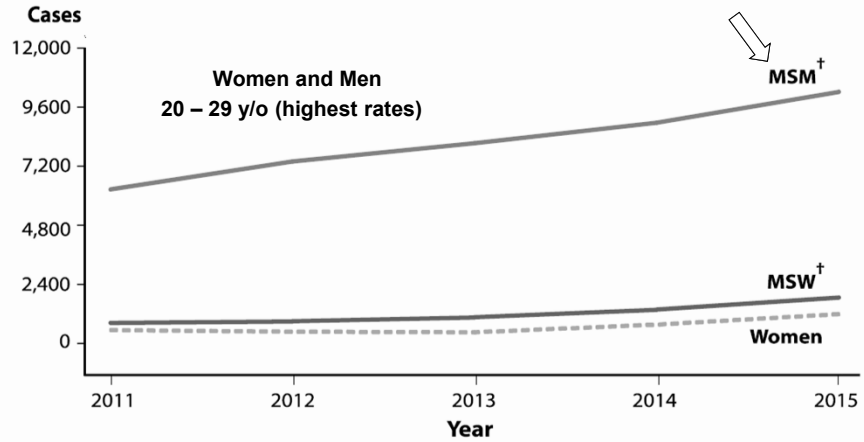
Syphilis — Rates of Reported Cases by Stage of Infection, United States, 1941–2015



NOTE: Data collection for syphilis began in 1941; however, syphilis became nationally notifiable in 1944. Refer to the National Notifiable Disease Surveillance System (NNDSS) website for more information: <https://www.cdc.gov/nndss/conditions/syphilis/>.



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

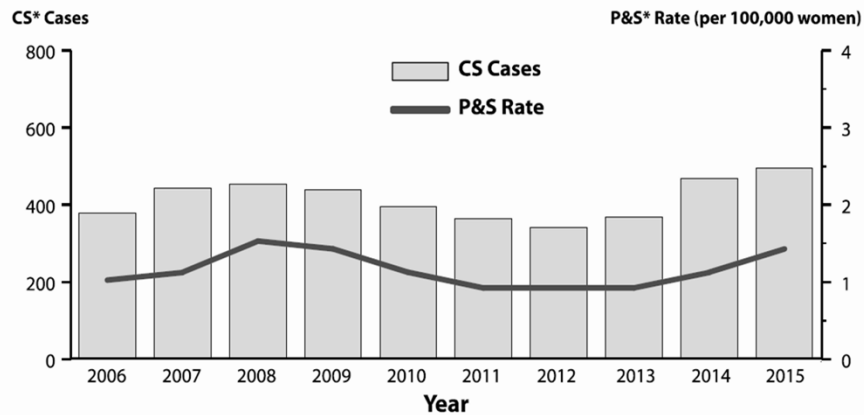


* 37 states were able to classify $\geq 70\%$ of reported cases of primary and secondary syphilis as either MSM[†], MSW[†], or women for each year during 2011–2015.

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



Congenital Syphilis — Reported Cases by Year of Birth and Rates of Primary and Secondary Syphilis Among Women, United States, 2006–2015



* CS = Congenital syphilis; P&S = Primary and secondary syphilis.



Syphilis: Risk Factors in MSM

- Non-white race (OR: 2.1, 95% CI: 1.1–4.4)
- Income >\$30,000 per year (OR: 2.7, 95% CI: 1.4–5.2)
- Unprotected anal sex (OR: 2.6, 95% CI: 1.4 – 4.8)
- Stronger gay community affiliation (OR: 2.3, 95% CI: 1.2–4.6)
- Recent internet sex partners (OR: 2.1, 95% CI: 1.0–4.3)
- Methamphetamine use (OR: 3.2, 95% CI: 1.3–7.6)
- Methamphetamine + Sildenafil use (OR: 6.2, 95% CI: 2.6–14.9)
- HIV-positive (OR: 7.3, 95% CI: 3.5–15.4)

Wong W, et al. STD 2005; Paz-Bailey G, et al. STD 2004.

Syphilis and HIV

- Approximately 20 – 60% of MSM with primary and secondary syphilis are HIV infected
- Syphilis can increase risk of HIV transmission and acquisition
 - ✓ Incident syphilis strongly associated with HIV acquisition (iPrEx) – HR 2.6 (95% CI: 1.6 – 4.4)
 - ✓ Offer HIV pre-exposure prophylaxis (PrEP) to individuals diagnosed with syphilis
- Atypical clinical manifestations and serologic responses; transient increase in HIV viral load and decline in CD4 counts
- Early manifestations of neurosyphilis (median ~9 months)

SSuN 2015 (<http://www.cdc.gov/std/stats15/figures/x.htm>); Solomon MM, et al. CID 2014; Zetola NM, et al. CID 2007; Ghanem KG, et al. AIDS 2008

Syphilis: Screening Recommendations

- **Pregnant women (1st trimester, 3rd trimester, and delivery)**
 - **Women who deliver stillborn infants >20 weeks gestation**
- **Sexually active MSM and HIV-positive patients**
 - **Screen at least annually, but every 3 – 6 months if high-risk (e.g. multiple sex partners, anonymous sex partners, sex partner with multiple partners, etc.)**
- **All at-risk (asymptomatic) non-pregnant adults and adolescents (e.g. history of incarceration, commercial sex work, highly affected races/ethnicities, men <29 y/o, living in areas with increased risk)**

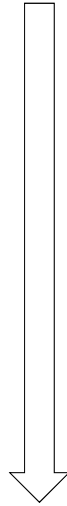
Workowski KA, et al. MMWR 2015; USPSTF. JAMA 2016.

Syphilis: Screening Recommendations

- **Other high-risk groups (e.g. sexual contacts of patients diagnosed with early syphilis, patients diagnosed with chlamydia and gonorrhea)**
- **Inmates at correctional facilities (depending on local prevalence of infectious early syphilis)**

Workowski KA, et al. MMWR 2015; USPSTF. JAMA 2016.

Syphilis: Manifestations



Infection

*~30% of individuals with
Latent Syphilis progress to
Tertiary Syphilis*

Primary Syphilis (chancre)

Secondary Syphilis (rash, lymphadenopathy, etc.)

Latent Syphilis

Early Latent Syphilis (<1 year duration)

Late Latent Syphilis (>1 year duration)

Tertiary Syphilis

Benign gummatous syphilis

Cardiovascular syphilis

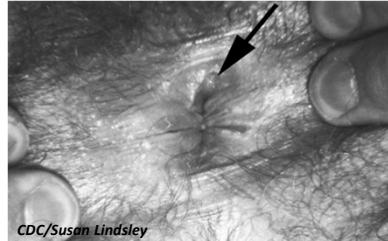
LaFond RE, Lukehart SA. Clin Micro Rev 2006

Neurosyphilis

- **Can occur at any stage!**
- **CNS invasion occurs early in the course of infection (30 – 100%; clearance in ~80%)**
- **Early Neurosyphilis**
 - ✓ **Asymptomatic (14 – 20% within 1st year)**
 - ✓ **Early meningeal syphilis (1 – 6% within 1st year)**
 - ✓ **Meningovascular syphilis (3 – 15% between 5 – 12 years)**
- **Late Neurosyphilis**
 - ✓ **General Paresis (5% within 15 – 20 years)**
 - ✓ **Tabes Dorsalis (3 – 9% within 20 – 25 years)**

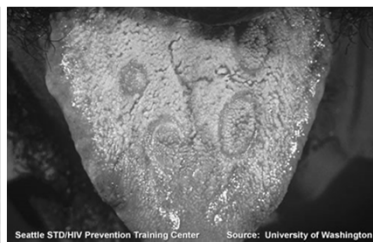
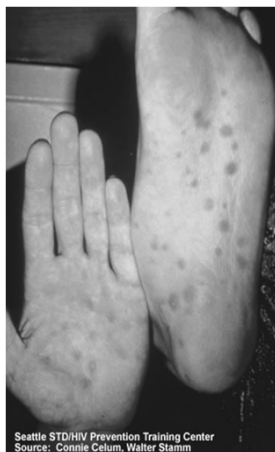
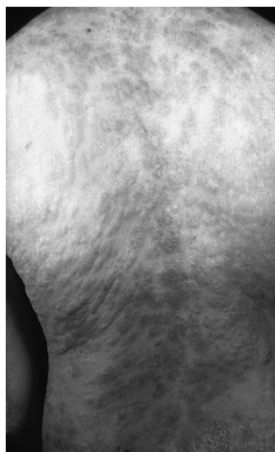
Ghanem KG. CNS Neurosci Ther. 2010

Primary Syphilis



<http://phil.cdc.gov/phil/home.asp>

Secondary Syphilis

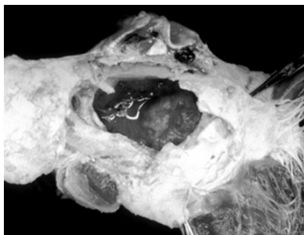
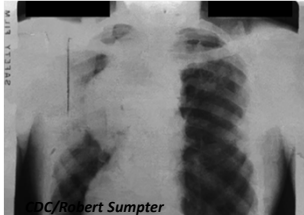


<http://phil.cdc.gov/phil/home.asp>; http://depts.washington.edu/nnptc/online_training/std_handbook/gallery/index.html

Secondary Syphilis with Ocular Manifestations



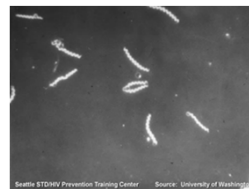
Tertiary Syphilis



<http://phil.cdc.gov/phil/home.asp>

Syphilis: Diagnosis

- Direct detection from tissue
 - Dark-field microscopy
 - Polymerase chain reaction (PCR)
- Non-treponemal tests*
 - Rapid Plasma Reagin (RPR)
 - Venereal Disease Research Laboratory (VDRL)
- Treponemal tests*
 - *T. pallidum* particle agglutination assay (TPPA)
 - Fluorescent treponemal antibody absorbed test (FTA-ABS)
 - Enzyme immunoassays (EIA), chemiluminescence immunoassays (CIA), and microbead immunoassays (MBIA)



**Traditional and Reverse Sequence screening algorithms*

Workowski KA, et al. MMWR 2015; CDC MMWR 2011; <https://www.cdc.gov/std/syphilis/syphilis-webinar.htm>*

Syphilis: Treatment

- Primary, Secondary, and Early Latent Syphilis
 - Benzathine PCN-G 2.4 MU IM x 1
 - Doxycycline 100 mg PO BID x 14 days (PCN allergy)
- Late Latent Syphilis
 - Benzathine PCN-G 2.4 MU IM Q weekly x 3
 - Doxycycline 100 mg PO BID x 28 days (PCN allergy)
- Tertiary Syphilis (Benign Gummatous and Cardiovascular*)
 - Benzathine PCN-G 2.4 MU IM Q weekly x 3 (if CSF exam is normal)
- Neurosyphilis (All forms)
 - Aqueous Crystalline PCN-G 18–24 MU IV QD x 10–14 days
 - Procaine PCN-G 2.4 MU IM QD + Probenecid 500 mg PO QID x 10–14 days

Syphilis in Pregnancy (ONLY USE PCN)

**Some may treat as neurosyphilis*

Workowski KA, et al. MMWR 2015

Syphilis: Post-Treatment Follow-up

- **Primary and Secondary Syphilis**
 - HIV negative → RPR at 6 and 12 months
 - HIV positive → RPR at 3, 6, 9, 12, and 24 months
 - ≥4-fold decline in RPR titer by 6 – 12 months*
- **Latent Syphilis**
 - HIV negative → RPR at 6, 12, and 24 months
 - HIV positive → RPR at 6, 12, 18, and 24 months
 - ≥4-fold decline in RPR titer by 12 – 24 months
- **Neurosyphilis**
 - If CSF pleocytosis present, repeat CSF every 6 months until normal
 - Decline in CSF WBC by 6 months
 - Normal CSF WBC and protein at 2 years
 - Normalization of CSF protein and VDRL is much slower

**Lack of 4-fold decline in RPR by 12 months (~15 – 20%)*

Workowski KA, et al. MMWR 2015; Rolfs RT, et al. NEJM 1997; Sena AC, et al. CID 2011; Marra CM, et al. CID 2004; Marra CM, et al. CID 2008.

Syphilis: Need for Lumbar Puncture

- **Patients with manifestations of TERTIARY SYPHILIS**
- **Patients with NEUROLOGIC SYMPTOMS**
 - Cognitive dysfunction, motor/sensory deficits, ophthalmic/auditory symptoms, cranial nerve palsies, symptoms of meningitis, stroke, etc.
- **Patients with SUSPECTED TREATMENT FAILURE**
 - Recurrence and persistence of signs and symptoms
 - Sustained (>2 weeks) ≥4-fold increase in RPR after treatment
 - *PS and SS → Lack of ≥4-fold decline in RPR (6 – 12 months in HIV negative and 12 – 24 months in HIV positive individuals)
 - *LS → Lack of ≥4-fold decline in RPR (if ≥1:32) (12 – 24 months in HIV negative and after 24 months in HIV positive individuals)

**Primary Syphilis (PS), Secondary Syphilis (SS), Latent Syphilis (LS)*

Workowski KA, et al. MMWR 2015; Rolfs RT, et al. NEJM 1997; Sena AC, et al. CID 2013

Syphilis: Sex Partner(s) Follow-up

- **Notification and screening**
 - Primary Syphilis → Last 90 days + Symptom duration
 - Secondary Syphilis → Last 6 months + Symptom duration
 - Early Latent Syphilis → Last 12 months
 -
- **Presumptive treatment**
 - All SP exposed <90 days before diagnosis of Early Syphilis
 - All SP exposed >90 days before diagnosis of Early Syphilis if screening results not available or follow-up is questionable
 - SP of patients diagnosed with Late Latent Syphilis with RPR $\geq 1:32$, manage as contact to Early Syphilis

Workowski KA, et al. MMWR 2015

Expedited Partner Therapy (EPT)

Expedited Partner Therapy (EPT)

- Also known as *Patient Delivered Partner Therapy (PDPT)*
- Associated with reduction in both chlamydia (20%) and gonorrhea (50%) prevalence at follow-up
- Potential role in management of trichomoniasis
- No role in management of syphilis
- Most data from heterosexual men and women
 - Limited data among MSM (NOT routinely recommended)
- Legal status of EPT in U.S. → permissible (38 states), potentially allowable (8 states), and prohibited (4 states)

Workowski KA, et al. MMWR 2015; Trelle S, et al. BMJ 2007; Golden MR, et al. NEJM 2005; Schillinger JA, et al. STD 2003; Kissinger P, et al. CID 2005; Kissinger P, et al. STD 2006; Schwebke JR, et al. STD 2010; Stephens SC, et al. STD 2010; Kerani RP, et al. STD 2011; <https://www.cdc.gov/std/ept/legal/default.htm>

EPT: Ohio Bill Summary

VENEREAL DISEASES PRESCRIPTION AUTHORITY –
“Regarding the authority to prescribe without examination a drug for a sexual partner of a patient diagnosed with chlamydia, gonorrhea, or trichomoniasis.”

- Authorizes a physician, APRN, or PA to prescribe or personally furnish a drug for up to two sexual partners of a patient without examining the sexual partner
- Authorizes pharmacist to dispense the prescription
- Grants immunity from civil liability for those acting in good faith

House Bill 124, 131st General Assembly, Ohio

When is EPT appropriate?

- **Recipient is a sexual partner of the prescriber's patient**
- **Patient has been diagnosed with chlamydia and gonorrhea**
- **Patient reports that the sexual partner(s) is unable or unlikely to be evaluated or treated by a health professional**
- **Administering appropriately packaged medications is preferred over a written prescription**
- **Must include treatment instructions, medication warnings (e.g. pregnancy, allergies, etc.), health counseling, and instructions to seek evaluation for STI symptoms (e.g. PID)**

Workowski KA, et al. MMWR 2015

Issuing an EPT Prescription in Ohio

- **If known, must include the sexual partner's name and address**
- **If unable to obtain the partner's name and address, then patient's name and address along with the words "expedited partner therapy" or the letters "EPT"**
- **Includes a written, electronic, or verbal orders**

House Bill 124, 131st General Assembly, Ohio

Take Home Points

- **Chlamydia, gonorrhea, and syphilis cases are on the rise**
 - ✓ **Adolescents, young adults, MSM, and ethnic minorities**
 - ✓ **Monitor for early neurological complications of syphilis (e.g. ocular involvement)**
 - ✓ **All 3 are associated with incident HIV (must screen for HIV!)**
- **Important to identify risk factors, screen appropriately, and treat promptly**
- **Screening and treatment of sex partners is important to prevent re-infection**
- **EPT is legal in most states, including Ohio**
 - ✓ **Additional tool for management of sex partners of patients diagnosed with chlamydia and gonorrhea**