

Review of Common Sexually Transmitted Infections (STIs) for the Primary Care Provider

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Course Objectives

1. Become familiar with current epidemiologic trends of common STIs and screening recommendations from the US Centers for Disease Control and Prevention (CDC)
2. Review common presentations, available diagnostic modalities, and recommended treatment regimens for common STIs

Overview

- Introduction
- STIs to be reviewed today:
 - *Chlamydia trachomatis* (CT)
 - *Neisseria gonorrhoeae* (GC)
 - *Trichomonas vaginalis* (TV)
 - Syphilis (*Treponema pallidum*; TP)
 - Herpes Simplex Virus (HSV)
 - Human Papillomavirus (HPV)
- STIs not covered: HIV, Hepatitis A, B, and C, mycoplasmas, ureaplasmas, chancroid, and bacterial vaginosis
- Speakers report no conflicts of interest or financial disclosures

Introduction

- STIs are “hidden epidemics” of enormous health and economic consequence in the United States
- STIs can be disruptive, painful, and lead to long-term negative health consequences; they also increase the risk of other detrimental reproductive morbidities
- All communities are impacted by STIs and all individuals directly or indirectly pay for the costs of these diseases

Sources: Eng TR, Butler WT, IOM, 1997; Holmes et al (editors), Sexually Transmitted Diseases, 4th ed, 2008

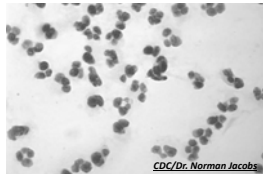
Chlamydia trachomatis (CT)

- Small gram-negative rod and obligate intracellular organism
- Most common reportable bacterial STI in the US
 - U.S. → 1,307,893 cases (Rate: 426.0 / 100,000)
 - Ohio → 51,150 cases (Rate: 443.1 / 100,000)
 - Columbus → 9,545 cases (Rate: 529.7 / 100,000)
- As of January 2000, regulations in all 50 states and D.C. require reporting all CT cases to CDC

Sources: <http://www.cdc.gov/std/stats10/tables/1.htm>;
<http://www.cdc.gov/std/stats10/tables/2.htm>; <http://www.cdc.gov/std/stats10/tables/6.htm>

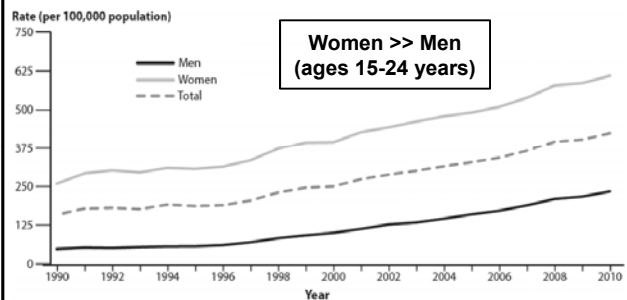
Case 1 – “Urethritis”

- 27 y/o African-American male presents with complaints of mild dysuria and clear penile discharge x 3 days. Denies constitutional symptoms.
- Patient reports multiple sex partners and unprotected vaginal and rectal intercourse with women only.
- Gram stain of discharge shows > 5 WBC (PMNs) / HPF. No organisms seen.



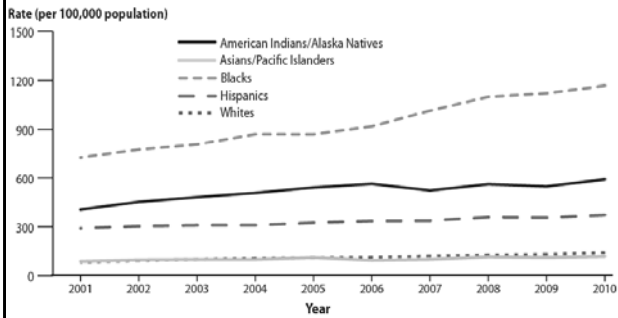
Source: <http://phil.cdc.gov/phil/home.asp>; <http://phil.cdc.gov/phil/details.asp>

CT Rate by Gender, US, 1990-2010



Source: <http://www.cdc.gov/std/stats10/figures/1.htm>;
<http://www.cdc.gov/std/stats10/figures/5.htm>

CT Rate by Race/Ethnicity, US, 2001-10



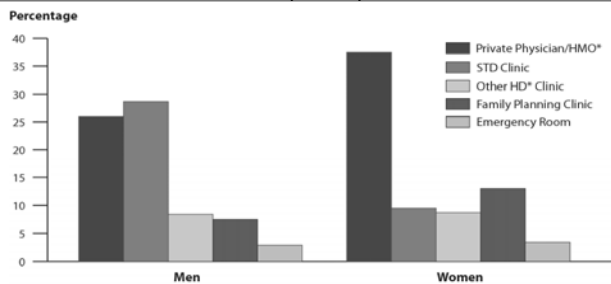
Source: <http://www.cdc.gov/std/stats10/figures/6.htm>

Neisseria gonorrhoeae (GC)

- Gram-negative diplococci
- Second most common bacterial STI in US:
 - U.S. → 309,341 cases (Rate: 100.8 cases / 100,000)
 - Ohio → 16,496 cases (Rate: 142.9 cases / 100,000)
 - Columbus → 3,351 cases (Rate: 186.0 cases / 100,000)
- As of January 2000, regulations in all 50 states and D.C. require reporting all gonorrhea cases to CDC.

Sources: <http://www.cdc.gov/std/stats10/tables/13.htm>; <http://www.cdc.gov/std/stats10/tables/14.htm>; <http://www.cdc.gov/std/stats10/tables/17.htm>

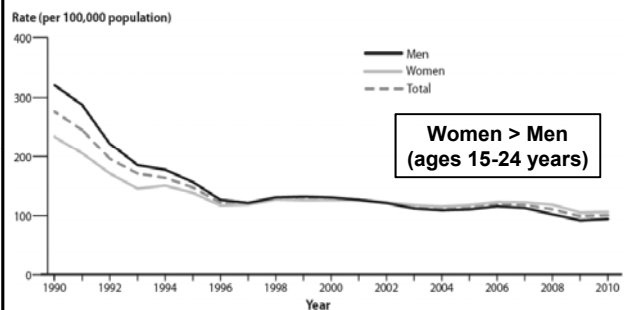
CT Prevalence by Sex & Reporting Source, US, 2010



* HMO = health maintenance organization; HD = health department
 These categories represent 72.5% of cases with a known reporting source
 11.6% of cases had a missing or unknown reporting source

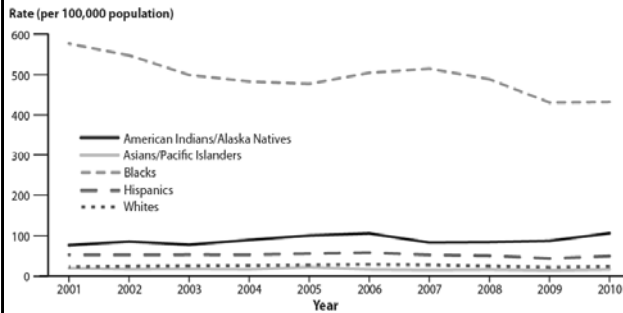
Source: <http://www.cdc.gov/std/stats10/figures/8.htm>

GC Rate by Gender, US, 1990-2010



Source: <http://www.cdc.gov/std/stats10/figures/15.htm>; <http://www.cdc.gov/std/stats10/figures/19.htm>

GC Rate by Race/Ethnicity, US, 2001-10



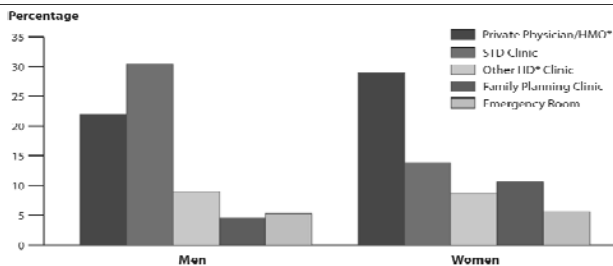
Source: <http://www.cdc.gov/std/stats10/figures/22.htm>

Risk factors: CT and GC

- Young age (adolescent into early adulthood)
- New or multiple partners, or partner with other partners in last 3 months
- Infrequent/non-use of barrier contraception
- Cervical ectopy
- Single (unmarried)
- Prior history of STIs (especially CT/GC)
- Low or intermediate education
- Low socioeconomic status
- Ethnic minority (especially African-American)
- Illicit drug use
- Commercial sex work

Sources: Gaydos CA, et al. *N Engl J Med.* 1998;339(11):739; Cook RL, et al. *Clin Infect Dis.* 1999;28(5):1002; Phillips RS, et al. *Am J Med.* 1989;86(5):515; Stergachis A, et al. *Am J Epidemiol.* 1993;138(3):143; Hook EW, et al. *Am J Epidemiol.* 1992;136(6):662; Mertz KJ, et al. *Am J Public Health.* 1997;87(9):1535; Klausner JD, et al. *J Infect Dis.* 1998;177(6):1766; Datta SD, et al. *Ann Intern Med.* 2007;147(2):89.

GC Prevalence by Sex and Reporting Source, US, 2010



* HMO = health maintenance organization; HD = health department
 These categories represent 69.5% of cases with known reporting source. Of all cases, 13.2% had missing or unknown reporting source

Source: <http://www.cdc.gov/std/stats10/figures/24.htm>

Screening Recommendations: CT

- All sexually active women ≤ 25 y/o, annually
- All sexually active women ≥ 26 y/o with risk factors (i.e. new or multiple sex partners), annually
- All pregnant women at 1st prenatal visit
- Sexually active young men? \rightarrow Not enough evidence to suggest routine screening, except in high risk settings (i.e. adolescent clinics, prison/jail, STD clinics)
- Primary focus of CT screening is to prevent complications in women (i.e. pelvic inflammatory disease)

Source: 2010 CDC STD Treatment Guidelines

Screening Recommendations: GC

- Target all sexually active women at risk for infection (i.e. previous STI, new or multiple sex partners, inconsistent condom use, commercial sex work, drug use, or living in high prevalence areas), annually
- All pregnant women at risk for infection (see above) at 1st pre-natal visit
- Sexually active young men? → Not enough evidence for routine screening except in high risk settings (i.e. adolescent clinics, jail/prison, STD clinics)
- Similar to CT, primary focus of GC screening and treatment effort is to prevent complications in women

Source: 2010 CDC STD Treatment Guidelines

Clinical Manifestations: CT and GC

- | | |
|---|--|
| • Non-gonococcal urethritis (NGU) | • Gonococcal urethritis |
| • Epididymitis / Orchitis / Prostatitis | • Epididymitis / Orchitis / Prostatitis |
| • Proctitis | • Proctitis |
| • Mucopurulent cervicitis (MPC) | • MPC / PID |
| • Pelvic inflammatory disease (PID) | • Pharyngitis |
| • Lymphogranuloma venereum (LGV; serovars L1, L2, and L3) | • Perihepatitis (Fitzhugh-Curtis Syndrome) |
| • Reactive arthritis (Reiter's Syndrome) | • Disseminated Gonococcal Infection (DGI) |
| • Infant pneumonia | • Meningitis / Endocarditis / Septic arthritis |
| • Ophthalmia neonatorum | • Ophthalmia neonatorum |
| • Asymptomatic infection >50%!!! | • Asymptomatic infection |

Sources: 2010 CDC STD Treatment Guidelines; Stamm WE, Holmes KK. Sex Transm Dis, 2nd Ed.,1990. p.181.

Screening in Men who have Sex with Men (MSM)

- In MSM who report in last 12 months:
 - Insertive anal intercourse → Urethral CT & GC, annually
 - Receptive anal intercourse → Rectal CT & GC, annually
 - Receptive oral intercourse → Oropharyngeal GC only, annually
- More frequent testing (every 3-6 months) if:
 - Multiple or anonymous sex partners
 - Sex with methamphetamine use
 - Sex partners report any of the above

Source: 2010 CDC STD Treatment Guidelines

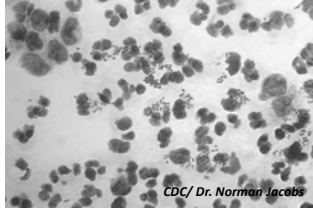
Diagnosis: CT

- Nucleic Acid Amplification (NAAT)
 - High sensitivity (80 – 100%) and specificity (≥94%)
 - Yield by site: Endocervical = Urine / Vaginal
 - Liquid-based cervical cytology and Pap-smear samples have lower sensitivity
 - Endocervical, vaginal, urethral and urine are FDA approved
 - Oropharyngeal and rectal specimens NOT FDA approved
- Tissue culture, Direct Fluorescent Antibody (DFA), and Enzyme Immunoassay (EIA)

Sources: 2010 CDC STD Treatment Guidelines; MMWR 2002;51(RR-15):1-27; Geisler WM. Clin Infect Dis 2011;53(S3):S92-8

Diagnosis: GC (1)

- Gram stain → PMNs with intracellular gram-negative diplococci:



- In symptomatic men
 - Sensitivity >95% and specificity >99%
- In asymptomatic men
 - Low sensitivity; does not rule out infection
- Not recommended for endocervical, pharyngeal, and/or rectal specimens

Sources: CDC. STD Treatment Guidelines 2010; <http://phil.cdc.gov/phil/home.asp>; <http://phil.cdc.gov/phil/details.asp>

CT Treatment

Uncomplicated urogenital infections

Non-Pregnant Patients

Recommended Regimens

Azithromycin 1 g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days
OR
Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days
OR
Levofloxacin 500 mg orally once daily for 7 days
OR
Ofloxacin 300 mg orally twice a day for 7 days

Pregnant Patients

Recommended Regimens

Azithromycin 1 g orally in a single dose
OR
Amoxicillin 500 mg orally three times a day for 7 days

Alternative Regimens

Erythromycin base 500 mg orally four times a day for 7 days
OR
Erythromycin base 250 mg orally four times a day for 14 days
OR
Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days
OR
Erythromycin ethylsuccinate 400 mg orally four times a day for 14 days

Source: 2010 CDC STD Treatment Guidelines

Diagnosis: GC (2)

- NAAT
 - High sensitivity and specificity, similar to CT.
 - Endocervical, vaginal, urethral (men), and urine specimens are FDA approved
 - Oropharyngeal, rectal, and/or conjunctival specimens are NOT FDA approved
- Culture → Allows for monitoring of antibiotic susceptibilities, but wide range of sensitivities (65 – 95%); higher for symptomatic vs. asymptomatic infections)

Sources: MMWR 2002;51(RR-15):1-27 ; 2010 CDC STD Treatment Guidelines; Buimer M, et al. J Clin Microbiol. 1996;34(10):2395; Koumans EH, et al. Clin Infect Dis. 1998;27(5):1171; Higgins SP, et al. Int J STD AIDS. 1998;9(1):21; Stary A, et al. J Clin Microbiol. 1997;35(1):239; Schink JC, et al. J Reprod Med. 1985;30(3 Suppl):244.

GC Treatment

Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum

Recommended Regimens

Ceftriaxone 250 mg IM in a single dose
OR, IF NOT AN OPTION
Cefixime 400 mg orally in a single dose
OR
Single-dose injectible cephalosporin regimens
PLUS
Azithromycin 1g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

Uncomplicated Gonococcal Infections of the Pharynx

Recommended Regimens

Ceftriaxone 250 mg IM in a single dose
PLUS
Azithromycin 1g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

- GC/CT co-infection rates ~46%
- If PCN or cephalosporin allergy → Azithromycin (AZM) 2g PO x 1 (must limit use!!)

• Fluoroquinolones (ofloxacin, levofloxacin) no longer recommended

Source: 2010 CDC STD Treatment Guidelines; Datta SD, et al. Ann Intern Med. 2007;147(2):89.

CT and/or GC Follow-up (1)

- No sex for 7 days after single dose or until completion of 7-day treatment regimens
- Notify and treat all sex partners from last 60 days and/or most recent partner even if >60 days
- Test of Cure (TOC) at 3 – 4 weeks is **NOT recommended** in men or **non-pregnant** women, unless...
 - Compliance with initial treatment is questionable (non-issue with DOT)
 - Symptoms persist
 - Re-infection suspected (common)
- Risk of false (-) and false (+) results with repeat NAAT < 3 weeks after treatment

Source: 2010 CDC STD Treatment Guidelines

Trichomonas vaginalis (TV)

- Motile flagellated protozoan
- Most prevalent curable STI in US and worldwide
- Overall prevalence 3.1% (95% CI, 2.3-4.3%)
 - African-American women; 14-49 year-olds (13.3%)
 - Women attending STD clinics (13-34%)
 - Men attending STD clinics (3-17%)
 - Women co-infected with HIV (6.1-52.6%)
- In 2010 → 149,000 initial visits to physician offices due to trichomoniasis

Sources: WHO Geneva 2001; Sutton M et al. Clin Infect Dis 2007;45(10):1319-26; Helms DJ, et al. Sex Transm Dis 2008;35:484-8; 2010 CDC STD Guidelines

CT and/or GC Follow-up (2)

- Re-testing (women and men) recommended at **3 months** after treatment (or whenever medical care is sought within next 12 months) due to high risk of re-infection
- In pregnant women:
 - TOC for CT with NAAT, **3 – 4 weeks after treatment**
 - If diagnosed with CT and/or GC during 1st trimester, re-test 3-6 months after treatment (preferably during 3rd trimester)
 - If negative for CT and/or GC during 1st trimester, but remains at high risk, re-test during 3rd trimester

Source: 2010 CDC STD Treatment Guidelines

TV Screening Recommendations

- Women complaining of vaginal discharge, especially if high risk (i.e. new or multiple sex partners, prior STI, commercial sex work, injection drug use)
- All sexually active HIV-positive women (at entry to care, then annually)
 - TV infection increases HIV shedding from vaginal secretions, while TV treatment decreases HIV shedding
- No optimal studies evaluating costs & benefits of screening asymptomatic STD clinic patients

Sources: Bachman LH, et al. Clin Infect Dis 2011;53(53):S160-72; 2010 CDC STD Treatment Guidelines

TV Clinical Manifestations

- NGU
- Prostatitis
- Epididymitis
- Vaginitis (diffuse, yellow-green, and malodorous vaginal discharge)
- Cervicitis (“strawberry cervix”)
- Prolonged asymptomatic carriage (women)
- Transient asymptomatic carriage (men)
- PID
- Post-hysterectomy cellulitis
- Infertility
- Premature rupture of membranes (PROM)
- Pre-term delivery
- Low birthweight
- Neonatal respiratory and/or genital infection

Sources: Soper DE, et al. Am J Obstet Gynecol. 1990;163(3):1016; Soper D. Am J Obstet Gynecol. 2004;190(1):281; Bachman LH, et al. Clin Infect Dis 2011;53(S3):S160-72; 2010 CDC STD Treatment Guidelines

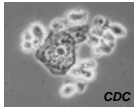
TV Diagnosis (2)

- Point-of-Care Tests
 - Rapid Antigen Test & Nucleic-Acid Probe Hybridization
 - Sensitivity → >83%, specificity → >97%
- NAAT: Transcription-mediated amplification (TMA)
 - Sensitivity → 74-98%
 - Specificity → 87-98%
- NAAT: Polymerase chain reaction (PCR)
 - Sensitivity → 88-97%
 - Specificity → 98-99%

Sources: Bachman LH, et al. Clin Infect Dis 2011;53(S3):S160-72; 2010 CDC STD Treatment Guidelines

TV Diagnosis (1)

- Microscopy of vaginal secretions
 - “Wet prep”
 - Low cost, simple
 - Requires rapid examination after collection
 - Sensitivity → 60-70%
- Culture (Diamond’s media): current Gold Standard
 - Sensitivity with vaginal secretions → 75-95%
 - Sensitivity of male urethra samples (swab, urine, or semen) → 28-56%
- Liquid-based cervical cytology / PAP-smears
 - May require confirmatory testing
 - Overall poor sensitivity



CDC

Sources: Bachman LH, et al. Clin Infect Dis 2011;53(S3):S160-72; 2010 CDC STD Treatment Guidelines; <http://phil.cdc.gov/phil/home.asp>; <http://phil.cdc.gov/phil/details.asp>

TV Treatment and Follow-up

Recommended Regimens	Alternative Regimen
Metronidazole 2 g orally in a single dose	Metronidazole 500 mg orally twice a day for 7 days*
OR	
Tinidazole 2 g orally in a single dose	

* Patients should be advised to avoid consuming alcohol during treatment with metronidazole or tinidazole. Abstinence from alcohol use should continue for 24 hours after completion of metronidazole or 72 hours after completion of tinidazole.

- Notify, test, and treat all sex partners
- Re-screen at 3 months due to high re-infection rate (~17% positive again at 3 months)
 - Treatment failure 1 month post-treatment is 7% in HIV (-) women, 10% in HIV (+) women
- Low-level metronidazole (MNZ) resistance: ~2 – 5%
 - High-level resistance is rare.
- No data to support re-screening men diagnosed with TV infection

Sources: 2010 CDC STD Treatment Guidelines; Peterman TA, et al. Ann Intern Med 2006;145:564-72; Kissinger P, et al. Clin Infect Dis 2008;46:994-9; Bachman LH, et al. Clin Infect Dis 2011;53(S3):S160-72

TV Management: Adverse Reactions

- Allergy or adverse reactions to 5-nitroimidazoles
 - Severe reactions do not always reoccur, but we cannot predict who will react with re-challenge
 - Avoid 5-nitroimidazoles in patients with history of allergic reactions
 - Alternative treatments have poor response rates (<50%)
 - Can consider consult with allergist or immunologist for desensitization if history of immediate-type hypersensitivity reaction

Sources: Bachman LH, et al. Clin Infect Dis 2011;53(S3):S160-72; 2010 CDC STD Treatment Guidelines

Case 1 – Urethritis

- Presumptive diagnosis: NGU
- Urine CT NAAT – Positive
- Urine GC NAAT – Negative
- Urine TV culture – Negative
- Rapid HIV test – Negative
- Treatment: Azithromycin 1g PO x 1
- Notification and treatment of sex partners
- Re-testing in 3 months or whenever care is sought within next 12 months
- Counseling regarding safer sex practices

TV Management: Treatment Failure

- Exclude re-infection
- If no response to MNZ 2g PO x 1, treat with MNZ 500mg PO BID x 7 days
- If no response, then MNZ or TNZ 2g PO daily x 5 days
- If no response, consult with ID specialist and CDC for susceptibility testing of TV isolate: [404-718-4141](tel:404-718-4141) or <http://www.cdc.gov/std>
- Treat male sex partners of women who experience treatment failure with MNZ 500mg PO BID x 7 days OR TNZ 2g PO x 1

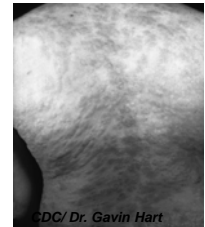
Sources: 2010 CDC STD Treatment Guidelines

Case 2 – “Rash and Sores”

- 36 y/o white HIV + gay male presents with 3-week history of generalized malaise, low-grade fevers, oral ulcers, and whole body rash
- Has had a steady partner (also HIV+) for 4 months, but reports that they both engage in unprotected anal and oral intercourse with each other and with anonymous partners met online



CDC/ Robert Sumpter



CDC/ Dr. Gavin Hart

Sources: <http://phil.cdc.gov/phil/home.asp>; <http://phil.cdc.gov/phil/details.asp>

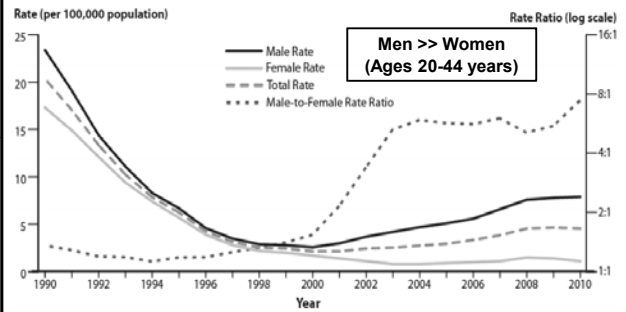
Syphilis

- Etiologic agent is *Treponema pallidum*
- Microaerophilic or anaerobic gram-negative rod
- Cannot survive outside host, difficult to grow *in vitro*
- Very slow growth rate (doubling time 30-36 hours)
- Stages of infection:
 - Primary (PS)
 - Secondary (SS)
 - Early Latent (ELS; < 1 year)
 - Late Latent (> 1 year)
 - Tertiary
 - Neurosyphilis (can occur at any stage)
 - Syphilis of “Unknown Duration”

“Early Syphilis,” (ES)
(Increased risk of transmission to susceptible partners)

Sources: Infectious Diseases. Cohen J, et al. 3rd Ed, 2010. Chapter 161; Vol. 2: pp. 1590-7.

Primary and Secondary Syphilis Rates by Sex, US, 1990–2010



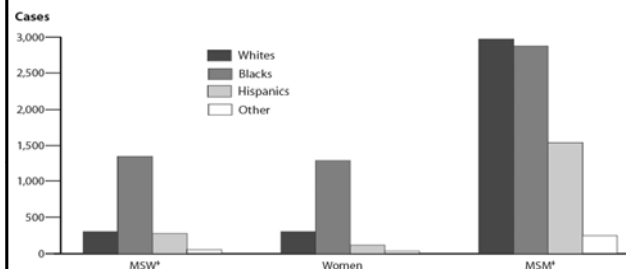
Sources: <http://www.cdc.gov/std/stats10/figures/35.htm>;
<http://www.cdc.gov/std/stats10/figures/39.htm>

Syphilis Rates, US, 2010

- All Stages: 45,834 cases (Rate: 14.9 cases / 100,00)
- Primary & Secondary Syphilis (PS & SS):
 - U.S. → 13,774 cases (Rate: 4.5 cases / 100,000)
 - Ohio → 528 cases (Rate: 4.6 cases / 100,000)
 - Columbus → 120 cases (6.7 cases / 100,000)
- Early Latent Syphilis (ELS):
 - U.S. → 13,604 cases (Rate: 4.4 cases / 100,000)
 - Ohio → 193 cases (Rate: 1.7 cases / 100,000)*
 - Columbus → 37 cases (Rate 4.8 cases / 100,000)*

Sources: <http://www.cdc.gov/std/stats10/syphilis.htm>; *Ohio Department of Health, STD Surveillance. Data reported through 01/01/2012.

Primary and Secondary Syphilis Cases by Sex, Behavior and Race/Ethnicity, US, 2010



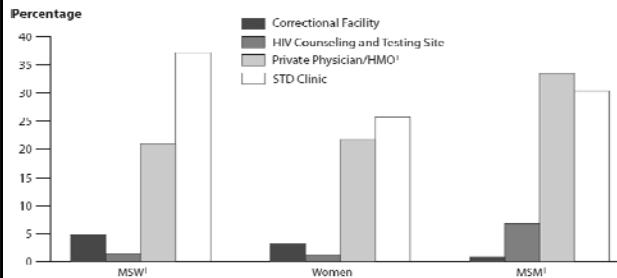
* Of the reported male cases of P&S syphilis, 18.3% were missing sex of sex partner; 2.0% of male cases with sex of sex partner data were missing race/ethnicity data.

† No imputation done for race/ethnicity

‡ MSW = men who have sex with women only; MSM = men who have sex with men

Sources: <http://www.cdc.gov/std/stats10/figures/44.htm>

Primary and Secondary Syphilis Cases by Sex, Behavior, and Reporting Sources, US, 2010



* Of reported male cases of P&S syphilis, 18.3% were missing sex of sex partner; 2.7% of male cases with sex of sex partner data were missing source.
 † HMO = health maintenance organization; MSW = men who have sex with women only; MSM = men who have sex with men

Sources: <http://www.cdc.gov/std/stats10/figures/46.htm>

Syphilis Screening

- Routine screening of asymptomatic adolescents is NOT recommended
- Certain groups should be screened:
 - Pregnant women
 - MSM (especially with risk factors present)
 - HIV-positive patients
 - Inmates at correctional facilities, depending on local prevalence of infectious ES

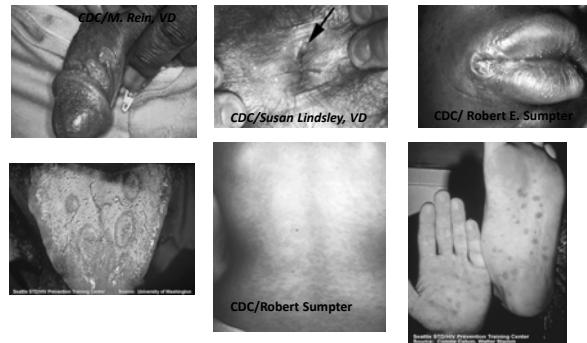
Sources: 2010 CDC STD Treatment Guidelines

Risk Factors for Early Syphilis (ES)

- HIV-positive status (OR 7.3)
 - Co-infection ~20 – 60%
- Anonymous sex partners (OR 2.0)
- “Barebacking” (OR 2.6)
- Recreational illicit and/or prescription drug use
 - Crystal meth (OR 3.2)
 - Viagra® (OR 2.1)
 - Crystal meth + Viagra® (OR 6.2)
- Oral sex (“safe sex”?)
 - Risk for syphilis vs. HIV transmission (13.7% vs. 0.31%)
- Availability of HAART = False sense of security
 - Patients with HIV and syphilis report being on HAART (69%) and having an undetectable VL (58%)

Sources: Zetola et al. CID 2007;44:1222-8.; Paz-Baiely et al. Sex Transm Dis 2004;31:581-6; Katz et al. Am J Public Health 2002;92:388-94; Kim et al. AIDS 2002;16:1425-8; Page-Shafer et al. AIDS 2002;16:2350-2; CDC MMWR 2004;53:966-8.

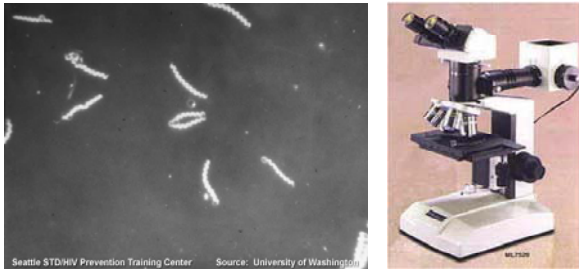
Primary & Secondary Syphilis



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

Tissue Diagnosis

- Dark-field microscopy examination and/or Direct Fluorescent Antibody (DFA) testing of lesion



Sources: Infectious Diseases. Cohen J, et al. 3rd Ed, 2010. Chapter 161; Vol. 2; pp. 1590-7; Darkfield Microscopy. St. Louis STD/HIV Prevention Training Ctr. Washington Univ. School of Medicine; http://depts.washington.edu/nnptc/online_training/std_handbook/gallery/index.htm

Serologic Diagnosis: Confirmatory Tests

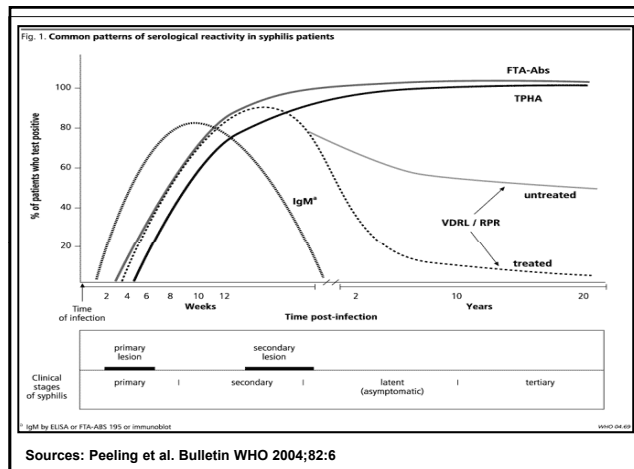
- **Specific Treponemal tests**
 - Fluorescent Treponemal Antibody Absorbed assay (FTA-ABS)
 - *Treponemal pallidum* particle agglutination assay (TP-PA)
 - Immunoassays (EIA, CIA, and MBIA)
 - Once positive, usually remain so for life
- False (+) can occur! (i.e. low prevalence populations, autoimmune conditions, endemic treponematoses, etc.)
- False (-) can also occur! (i.e. early treatment)

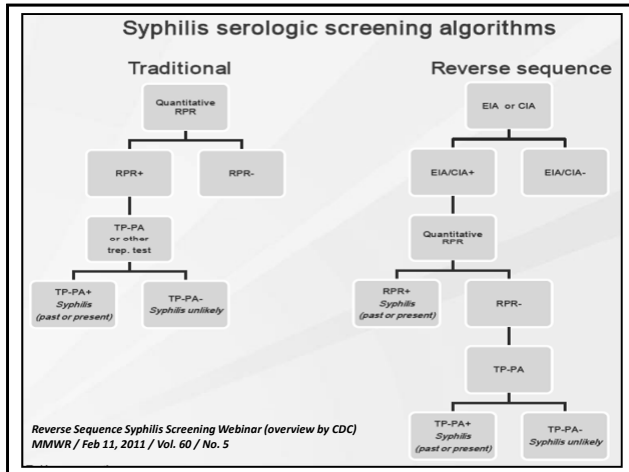
Sources: Infectious Diseases. Cohen J, et al. 3rd Ed, 2010. Chapter 161; Vol. 2; pp. 1590-7 <http://dermatology.cdlib.org/124/letters/syphilis/larranaga.html>; Peter et al. J Clin Micro 1979;9(3):369-372

Serologic Diagnosis: Screening Tests

- **Non-Treponemal tests**
 - Rapid Plasma Reagin (RPR)
 - Venereal Disease Research Laboratory (VDRL)
 - Reported as highest dilution titer at which agglutination is visibly appreciated (i.e. NR, 1:1, 1:2, 1:4, ... 1:256, etc.)
 - Markers of disease activity
 - Used to monitor response to treatment
- False (+) can occur! (i.e. autoimmune conditions, pregnancy, older age, IVDU, other spirochetal infections, etc.)
- False (-) can also occur! (i.e. early PS, “prozone” reaction, late latent untreated infection; early treatment)

Source: 2010 CDC STD Treatment Guidelines; Infectious Diseases. Cohen J, et al. 3rd Ed, 2010. Chapter 161; Vol. 2; pp. 1590-7; Larsen SA, et al. Clin Microbiol Rev. 1995;8(1):1.





Early Syphilis Follow-Up

- **PS & SS** → Repeat RPR/VDRL at 6 and 12 months for HIV (-) and 3, 6, 9, 12, and 24 months for HIV (+) patients
- **ELS** → Repeat RPR/VDRL at 6, 12, and 24 months for HIV (-) and 6, 12, 18, and 24 months for HIV (+) patients
- **Appropriate serologic response to treatment:**
 - **PS & SS** → ≥4-fold decrease in RPR/VDRL titer between **6 and 12 months**
 - **ELS** → ≥4-fold decrease in RPR/VDRL titer between **12 and 24 months**.
- **Response to treatment is variable** and a slower decrease in titers may be seen in patients with prior history of syphilis and/or HIV infection

Sources: 2010 CDC STD Treatment Guidelines

Treatment of Early Syphilis

- **PS & SS** → Benzathine PCN-G 2.4MU IM x 1
- **ELS** → Benzathine PCN-G 2.4MU IM x 1
- **PCN-Allergy**
 - Doxycycline 100mg PO BID x 14 days
 - Tetracycline 500mg PO QID x 14 days
- **Additional non-traditional regimens**
 - Ceftriaxone 1g IM/IV QD x 10-14 days
 - Azithromycin 2g PO x 1 (not recommended in MSM or pregnant women)
- **Pregnancy** – only use PCN!!
- **Recommended Benzathine PCN-G regimens are same for HIV (-) and HIV (+) patients**

Sources: 2010 CDC STD Treatment Guidelines

Need for Lumbar Puncture in ES

- Patients with **NEUROLOGIC SYMPTOMS** (i.e. cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, CN palsies, symptoms of meningitis)
- Patients who meet criteria for **suspected treatment failure:**
 - **Recurrence or persistence of symptoms**
 - **PS & SS** → Lack of ≥4-fold decrease in RPR/VDRL titer
 - **ELS** → If pre-treatment RPR ≥1:32 and lack of ≥4-fold decrease in titer
 - **≥4-fold increase in titer at any time after treatment**
- **No data to support routine LP of HIV-positive patients with ES and with RPR ≥1:32 and/or CD4 count ≤ 350 cells/mL and no neurologic symptoms**

Sources: 2010 CDC STD Treatment Guidelines

Follow-Up with Sex Partners

- Notification and screening of sex partners:
 - PS → Last 90 days + symptom duration
 - SS → Last 6 months + symptom duration
 - ELS → Last 1 year
- Presumptive treatment of exposed sex partners:
 - All partners exposed < 90 days before diagnosis of PS, SS, and ELS.
 - All partners exposed >90 days before diagnosis of PS, SS, and ELS, if screening results not available immediately or follow-up is questionable.
 - Partners of patients diagnosed with “Syphilis of Unknown Duration” and RPR ≥1:32, should be managed as ELS

Sources: 2010 CDC STD Treatment Guidelines

HSV Risk Factors

Table 4. Multiple logistic regression analyses for significant variables associated with antibodies to herpes simplex virus type 1 or 2.

Antibodies, demographics	Odds ratio	95% Confidence interval
HSV-1		
Female gender	2.29	1.73-3.03
Black race	1.69	1.16-2.48
Blue-collar origin	1.45	1.04-2.02
First intercourse at <15 y	1.64	1.05-2.58
Sexual experience		
1-2 y	1.44	1.02-2.02
3-5 y	1.71	1.19-2.45
≥6 y	3.03	1.72-5.34
History of STD	2.04	1.22-3.40
History of partner with oral sores	2.39	1.42-4.02
HSV-2		
Black race	4.62	1.80-11.90
Sexual experience		
3-5 y	18.36	1.49-226.39
≥6 y	108.13	9.03-1293.80
History of STD	3.43	1.32-8.91

Sources: Gibson et al. J Infect Dis 1990;162:306

Herpes Simplex Virus (HSV)

- Most prevalent ulcerative STI in the US
- Life-long chronic infection with intermittent episodic outbreaks of mucocutaneous and/or genital ulcers.
- Two subtypes:
 - HSV-1 → orolabial infection (but, increasing rates of anogenital infection in MSM and young women)
 - HSV-2 → genital infection
- U.S. → ~50 million people infected w/ genital HSV-2
 - Majority have never been diagnosed due to mild or subclinical infection
 - Viral shedding from genital tract (even when asymptomatic) accounts for majority of transmissions

Sources: Ryder N, et al. Sex Transm Infect 2009;85:416-9; Roberts CM, et al. Sex Transm Dis 2003;30:797-800; Xu F, et al. JAMA 2006;296:964-73; 2010 CDC STD Treatment Guidelines

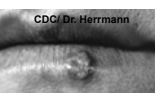
HSV Screening Recommendations

- Serologic screening for HSV-1 and HSV-2 not recommended in general population
- Type-specific serologic screening considered for:
 - Recurrent anogenital ulcers or atypical symptoms with negative HSV cultures
 - Clinical diagnosis of anogenital HSV without lab confirmation
 - Sex partner reports anogenital HSV infection
 - Persons with multiple partners that present for STI evaluation
 - HIV-positive individuals
 - MSM at high risk for HIV infection

Sources: 2010 CDC STD Treatment Guidelines

HSV Clinical Manifestations

- **Primary infection**
 - Infection of a previously seronegative patient
 - Mild (can be asymptomatic!) to severe
 - Multiple painful ulcers/vesicles
 - Systemic symptoms (i.e. fevers, HAS, lymphadenopathy, etc.)
 - May have neurologic involvement
- **Non-primary infection**
 - Infection with HSV-2 in person already seropositive for HSV-1 or vice-versa
 - Symptoms usually milder than with primary infection



Sources: Corey L, et al. *Ann Intern Med* 1983;98(6):958; Eberhardt O, et al. *Neurology*. 2004;63(4):758; Kimberlin DW, Rouse DJ. *N Engl J Med*. 2004;350(19):1970; 2010 CDC STD Treatment Guidelines; <http://phil.cdc.gov/phil/home.asp>; <http://phil.cdc.gov/phil/details.asp>

HSV Diagnosis

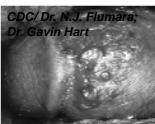
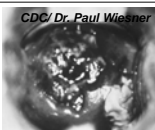
- **Clinical diagnosis**
 - Low sens and spec
- **Cytologic detection, i.e. Tzanck Smear**
 - Low sens and spec
- **Cell Viral Culture**
 - Low sensitivity
 - Sensitivity decreases as lesions heal and with recurrent lesions
 - Allows for viral typing (HSV-1 vs. HSV-2)
- **HSV DNA PCR**
 - High sens and spec
 - Allows for viral typing (HSV-1 vs. HSV-2)
 - Useful in late clinical lesions
 - Test of choice in CSF
- **Type specific glycoprotein-G serologic assays (IgG)**
 - Sensitivity 80-98%
 - Specificity $\geq 96\%$
 - False (-) in early infection
 - False (+) in patients with low likelihood of infection

Testing for IgM is not useful or recommended!!

Sources: 2010 CDC STD Treatment Guidelines

HSV Clinical Manifestations

- **Recurrent infection**
 - Reactivation of latent infection (outbreaks)
 - Milder than primary or non-primary infection
 - May be subclinical or asymptomatic (~25%)



Sources: Corey L, et al. *Ann Intern Med* 1983;98(6):958; Eberhardt O, et al. *Neurology*. 2004;63(4):758; Kimberlin DW, Rouse DJ. *N Engl J Med*. 2004;350(19):1970; 2010 CDC STD Treatment Guidelines; <http://phil.cdc.gov/phil/home.asp>; <http://phil.cdc.gov/phil/details.asp>

Genital HSV Treatment (Some Examples)

- **First Clinical Episode (always treat, even if mild symptoms)**
 - Acyclovir 400mg PO TID x 7 – 10 days
 - Valacyclovir 1g PO BID x 7 – 10 days
- **Episodic Recurrences (start w/ prodrome or w/in 24hr of vesicle appearance)**
 - Acyclovir 400mg TID OR 800mg BID x 5 days
 - Valacyclovir 500mg PO BID x 3 days
- **Suppressive Therapy (decreases recurrences by ~70-80% and subclinical viral shedding by ~95%)**
 - Acyclovir 400mg PO BID
 - Valacyclovir 500mg* or 1g PO daily (*may be less effective if very frequent recurrences reported; ≥ 10 episodes/year)

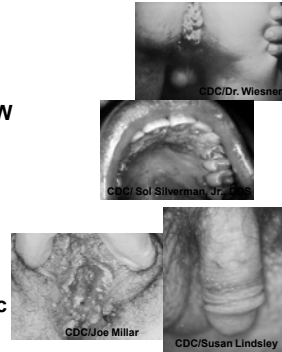
Sources: 2010 CDC STD Treatment Guidelines; Diaz-Mitoma F, et al. *JAMA* 1998;280:887-92; Mertz GJ, et al. *Arch Intern Med* 1997;157:343-9; Reitano M, et al. *J Infect Dis* 1998;178:603-10; Romanowski B, *Sex Transm Dis* 2003;30:226-231.

Case 2 – “Rash and Sores”

- RPR 1:1,024 and Reactive FTA-ABS
- Diagnosis – Secondary Syphilis with characteristic body rash and mucous patches in tongue
- Benzathine PCN-G 2.4MU IM x 1
- Follow-up RPRs at 3, 6, 9, and 12 months
- Attempt to notify, screen, and treat any sex partners met online within last 6 months with the help of Disease Intervention Specialists (DIS)
- Education and counseling regarding safer sexual practices and modes of syphilis transmission

HPV and Genital Warts (GW): Diagnosis and Clinical Manifestations

- Majority of HPV infections are subclinical, completely asymptomatic, and clear spontaneously.
- When present, diagnosis of GW is mainly clinical by visual inspection
- GW are highly infectious (64% of contacts develop GW).
- GW are usually asymptomatic, but may be pruritic or bleed.
- Large GW may cause anatomic obstruction



Sources: 2010 CDC STD Treatment Guidelines; ; Oriol JD. Br J Vener Dis 1971;47:1-13; Dunne EF, et al. Clin Infect Dis 2011;53(S3):S143-52; <http://phil.cdc.gov/phil/home.asp>; <http://phil.cdc.gov/phil/details.asp>

Human Papillomavirus (HPV)

- >50% of sexually active people are infected at least once in life.
- >100 types of HPV and >40 are known to infect the genital area.
- Oncogenic or High-Risk (HR-HPV types 16 and 18)
 - Cause majority of cervical, anal, penile, vulvar, and vaginal CA
 - Oropharyngeal CA (HPV type 16)
- Non-Oncogenic or Low-Risk (LR-HPV types 6 and 11)
 - Cause ~90% of genital warts (GW)
- Efficient rates of transmission among sex partners
 - Penis → Cervix (4.9 infections / 100 person-months)
 - Cervix → Penis (17.4 infections / 100 person-months)
- Limited data on transmission via non-intercourse sexual contact

Sources: 2010 CDC STD Treatment Guidelines; Myers ER, et al. Am J Epidemiol 2000;151:1158-71; Dunne EF, et al. Clin Infect Dis 2011;53(S3):S143-52; Clifford GM, et al. Br J Cancer 2003;88:66-73; Parkin DM, et al. Vaccine 2006;24(Suppl 3):S3/11-25; Kreimer AR, et al. Cancer Epidemiol Biomarkers Prev 2005;14:467-75; Garland SM, et al. J Infect Dis 2009;199:805-14; Winer RL, et al. Am J Epidemiol 2003;157:218-26; Hernandez BY, et al. Emerg Infect Dis 2008;14:888-94.

Genital Wart (GW) Treatment

Table 2. Recommended Treatment Regimens for Anogenital Warts Based on Anatomic Location*

Anatomic location	Patient-applied				Provider-administered			
	Podofilox ^b	Imiquimod ^b	Sinecatechins ^b	Cryotherapy	Podophyllin ^b	TCA/BCA	Surgical removal	Other
External genital	X	X	X	X	X	X	X	†
Meatus				X	X			†
Vagina				X		X		†
Cervix/ectocervix								Biopsy, consult a specialist
Anal/perianal				X		X	X	Digital rectal exam, anoscopy

Abbreviation: TCA/BCA, trichloroacetic acid or bichloroacetic acid 80%–90%.
 * Adapted from the 2010 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines.
^b Podofilox, podophyllin, imiquimod, and sinecatechins are not recommended during pregnancy.
[†] Alternative regimens include intralosomal interferon, laser therapy, topical cidofovir, and other.
[‡] Some experts recommend use of podofilox or imiquimod, but limited data exist.

Sources: Dunne EF, et al. Clin Infect Dis 2011;53(S3):S143-52; 2010 CDC STD Treatment Guidelines

HPV DNA Tests: General Overview

- **Recommended:**
 - Triage of women ≥ 21 years who have ASC-US cytology results
 - Routine adjunctive testing in combination with cervical cytology for women ≥ 30 years.
- **Not Recommended:**
 - **LR-HPV DNA testing (No clinical indications)**
 - STD screening for HPV (including sex partners)
 - Deciding whether to administer vaccine or not.
 - Testing adolescents < 21 years old.
 - Screening for primary cervical CA as stand-alone test (i.e. w/o cervical cytology)
 - Triaging Low-grade squamous intraepithelial lesions (LSIL)

Source: 2010 CDC STD Treatment Guidelines

Final Thoughts

- We all share the responsibility of helping to fight the epidemic of STIs that affect this country.
- We must inquire about specific risk factors for common STIs (i.e. Syphilis).
- Implement a guideline-based STI screening protocol for your at-risk patient population.
- Consult with your local health department, sexual health clinic, ID physician, and/or the 2010 CDC STD Treatment Guidelines for the latest diagnostic and treatment recommendations.

HPV Vaccine Recommendations

Table 1. Quadrivalent and Bivalent Human Papillomavirus Vaccines*

	Quadrivalent HPV vaccine (Gardasil, Merck & Co)	Bivalent HPV vaccine (Cervarix, GlaxoSmithKline)
Licensed in United States	2006 (females) 2009 (males)	2009 (females)
ACIP recommendations/guidance	Routine vaccination: 11- or 12-year-old girls ^b May be given to 9-26-year-old males	Routine vaccination: 11- or 12-year-old girls ^b
VLP types	6/11/16/18	16/18
Adjuvant	AAHS: 225 μ g amorphous aluminum hydroxyphosphate sulfate	ASO4: 50 μ g 3-O-desacyl-4'-monophosphoryl lipid A, 600 μ g Al in total, (Al(OH) ₃)
Efficacy against HPV 16/18-related CIN2+	$\geq 98\%$	$\geq 93\%$
Efficacy against HPV 6/11-related genital lesions	$\sim 99\%$...
Seroconversion to vaccine types	$>99\%$	$>99\%$
Duration of protection		Unknown, follow-up has occurred upto 6-10 years found no evidence of waning protection

Abbreviations: ACIP, Advisory Committee on Immunization Practices; HPV, human papillomavirus; VLP, virus-like particles.

* Source: adapted from ACIP presentation, 21 October 2009. Available at: <http://www.cdc.gov/vaccines/imz/downloads/091021hpv.pdf>.

^b Either vaccine is recommended for girls aged 11 or 12 years; vaccine is recommended for persons aged 13-26 years who have not started or completed the vaccine series. Vaccine can be given beginning at age 9 years.

Sources: Dunne EF, et al. Clin Infect Dis 2011;53(S3):S143-52;
2010 CDC STD Treatment Guidelines