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Chlamydia Trachomatis and Neisseria Gonorrhoeae

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A Brief Aside

- Several of the pictures used in this talk are not my own, but those of individuals who, over the years, have kindly given me copies to use
- Occasionally, some were obtained from the internet
- The figures and charts in the epidemiology section are from the 2005 CDC STD Surveillance Report which can be found at the following URL:
 - <http://www.cdc.gov/std/stats/trends2005.htm>



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Section A

Chlamydia Trachomatis

Chlamydia Trachomatis: Pathogenesis

- Obligate intracellular bacterium
- Has DNA and RNA, bacterial ribosomes, gram-negative-like cell wall
- Deficient in endogenous ATP production
- Has a dimorphic developmental cycle, which happens in an intracellular cytoplasmic inclusion
- Susceptible to antibiotics

Serological Classification

- A,B, Ba, C (Trachoma)
- D-K (genitourinary and ocular infections)
- L1-L3 (lymphogranuloma venereum)

Clinical Manifestations (D-K Serotypes): Men

- **Urethritis**
 - Discharge classically
 - may be asymptomatic
- **Epididymitis**
 - 70% due to CT

Clinical Manifestations (D-K Serotypes): Women

Cervicitis

- Majority—no signs or symptoms
- If present, signs include . . .
 - Discharge, ectopy, edema, induced bleeding
- 30-50% have mucopurulent cervicitis (>30 PMNs per oil immersion field)
- Pelvic Inflammatory Disease (PID)

Clinical Manifestations: Men and Women

Proctitis

- Caused by direct inoculation from unprotected anal sex
- Serovar D-K or LGV types
- Symptoms may include . . .
 - Rectal bleeding and pain
 - Mucous discharge
 - Diarrhea

Lymphogranuloma Venereum

- Worldwide distribution but higher prevalence in tropical and subtropical regions
- Endemic in Africa, India, SE Asia, the Caribbean, and Brazil
- Strains are more invasive
- Cause thrombolymphangitis
- Early disease—transient genital ulcer, buboes, inflammation; rectal pain/bleeding
- Late disease—abscesses, fistulas, genital elephantiasis, frozen pelvis, and rectal strictures

Trachoma: Serovars A, B, Ba, C

- Trachoma is a chronic keratoconjunctivitis
- Active disease occurs most commonly in preschool-aged children, with the highest prevalence in those children three to five years old
- Disease transmission occurs primarily between children and the women who care for them
- Repeated episodes of reinfection within the family cause chronic follicular conjunctival inflammation (active trachoma) resulting in corneal abrasions, corneal scarring and, ultimately, blindness
- Most common cause of preventable blindness worldwide
- In the U.S.
 - Endemic once in North America and Europe but has disappeared with improved living standards
- Internationally
 - Trachoma is endemic in Africa, Asia, the Middle East, and Aboriginal communities in Australia
 - Worldwide, 360 million people are affected

Chlamydia: Diagnosis

- Cell culture—sensitivity no more than 80% and “invasive”
- Non-amplified molecular tests (EIA, DFA) sensitivity up to 85%
- Amplified molecular tests [nucleic acid amplification tests (NAATs)]
 - Gold standard; can be performed on genital swabs (cervical, urethral, or vaginal) and on urine (i.e., less “invasive”)
 - Sensitivity > 90%
- Introduced in the mid 1990s

Interesting Question: How do we assess diagnostic accuracy of a test that is more sensitive than the gold standard?



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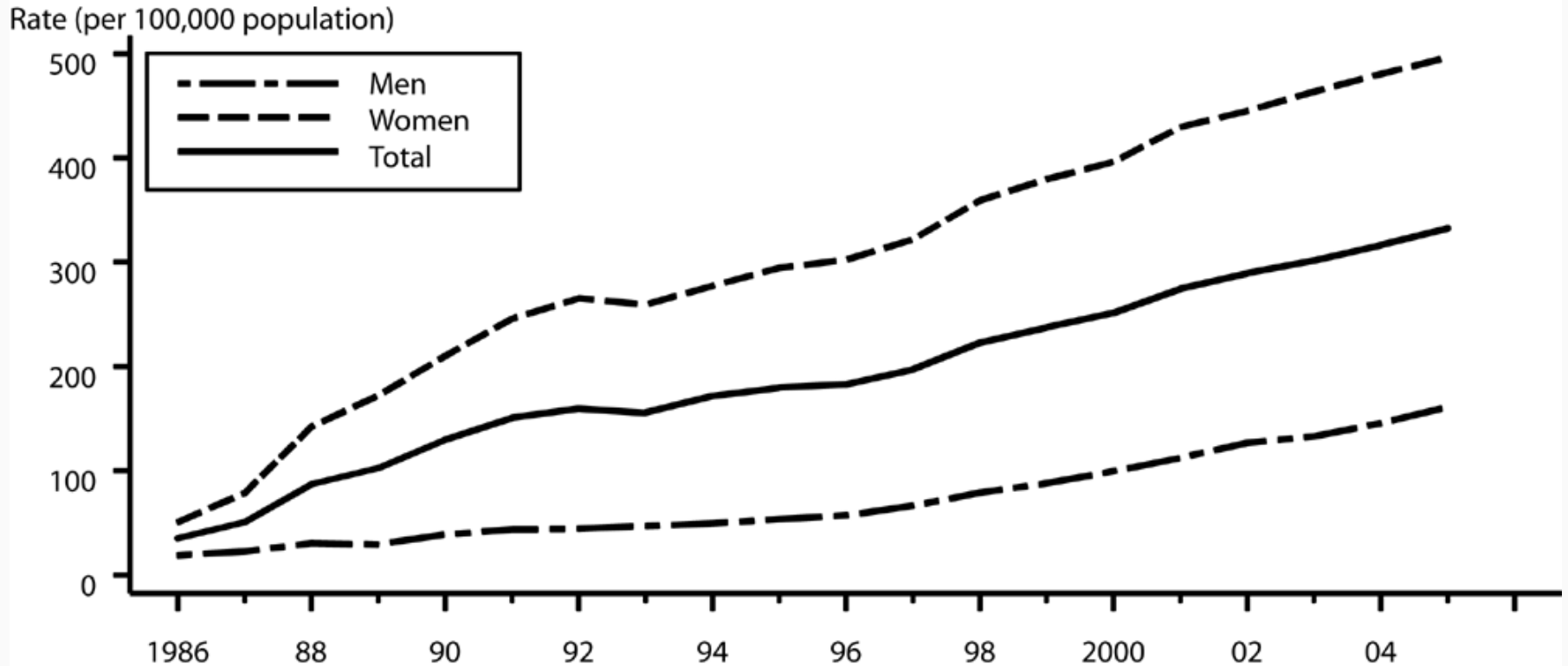
Section B

Chlamydia Trachomatis: Epidemiology

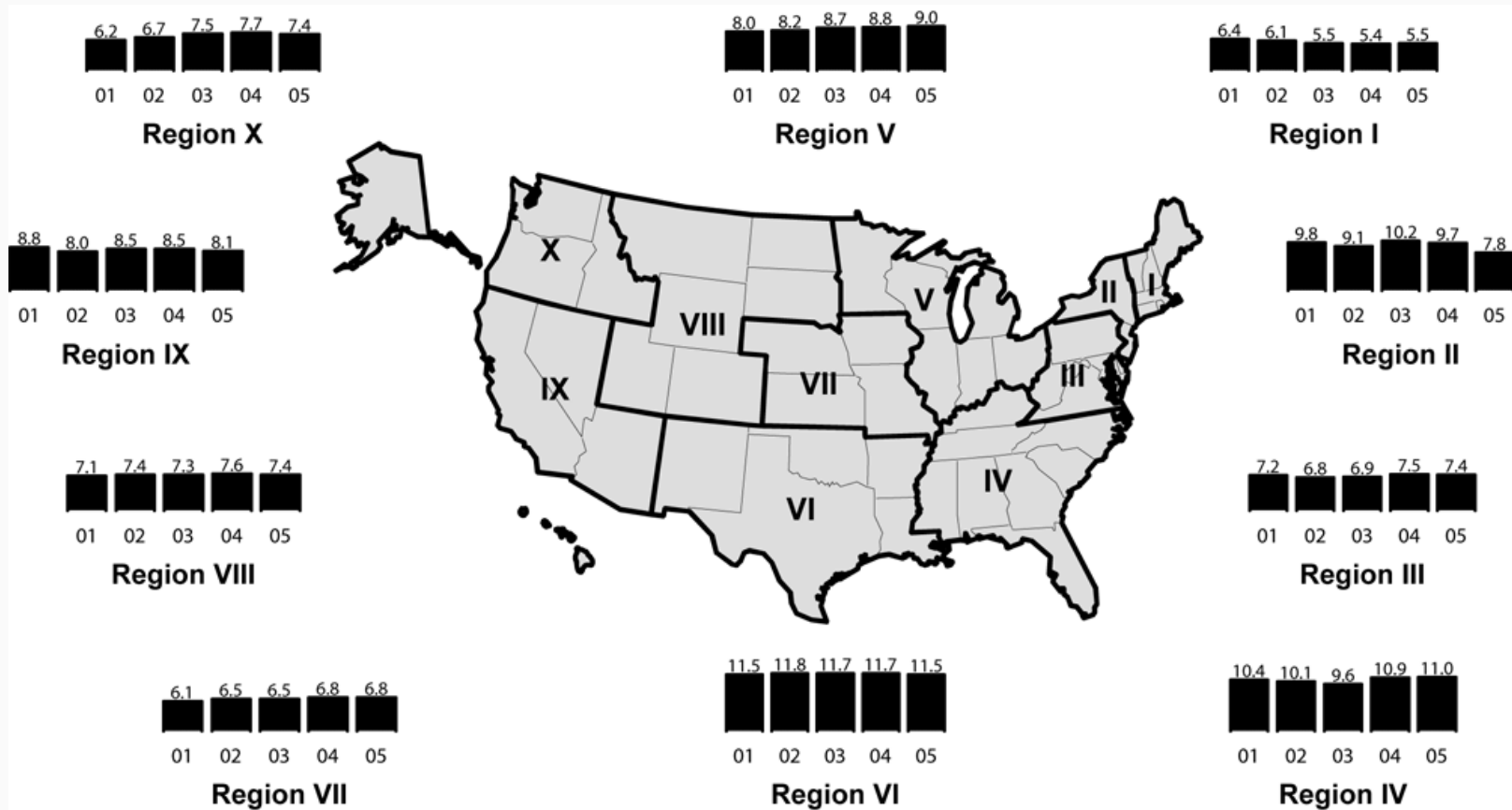
Overview

- Most commonly reported infectious disease in the U.S. (976,445 cases reported in 2005 to the CDC)
- “Approximately 5%-14% of routinely screened females aged 16-20 years and 3%-12% of women aged 20-24 years are infected with chlamydia”
- 335 commercial health maintenance organizations (HMOs) and point-of-service (POS) plans and 92 Medicaid HMO and POS plans reported chlamydia screenings
- These data accounted for 83% of enrollees in commercial HMO and POS plans and up to 30% of enrollees in Medicaid HMO and POS plans in the United States during this period MMWR October 29, 2004/53(42); 983-985

Chlamydia Rates: United States, 1986-2005

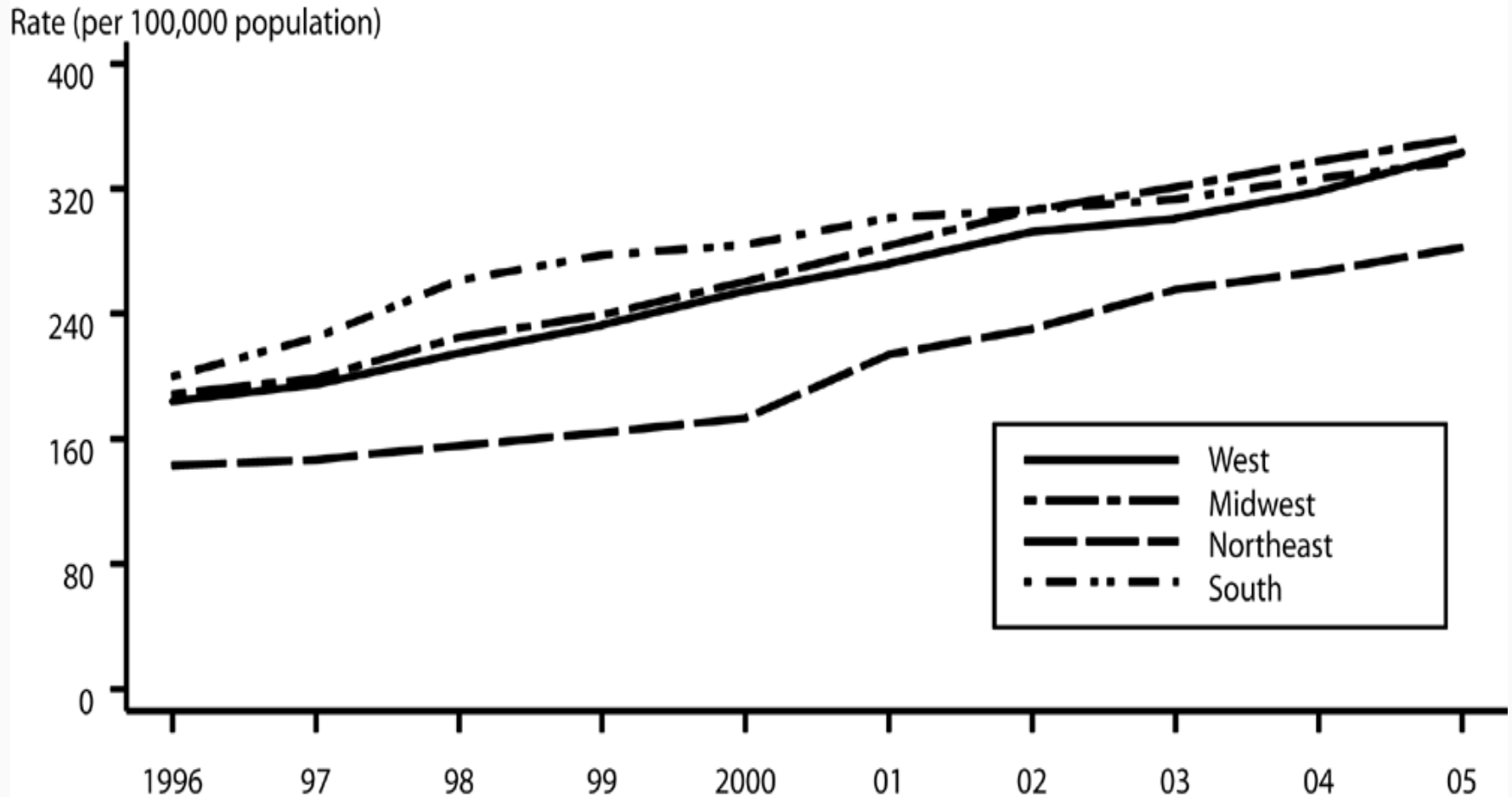


- The 2005 rates for the United States were calculated by dividing the number of cases reported from each area in 2005 by the estimated area-specific 2004 population

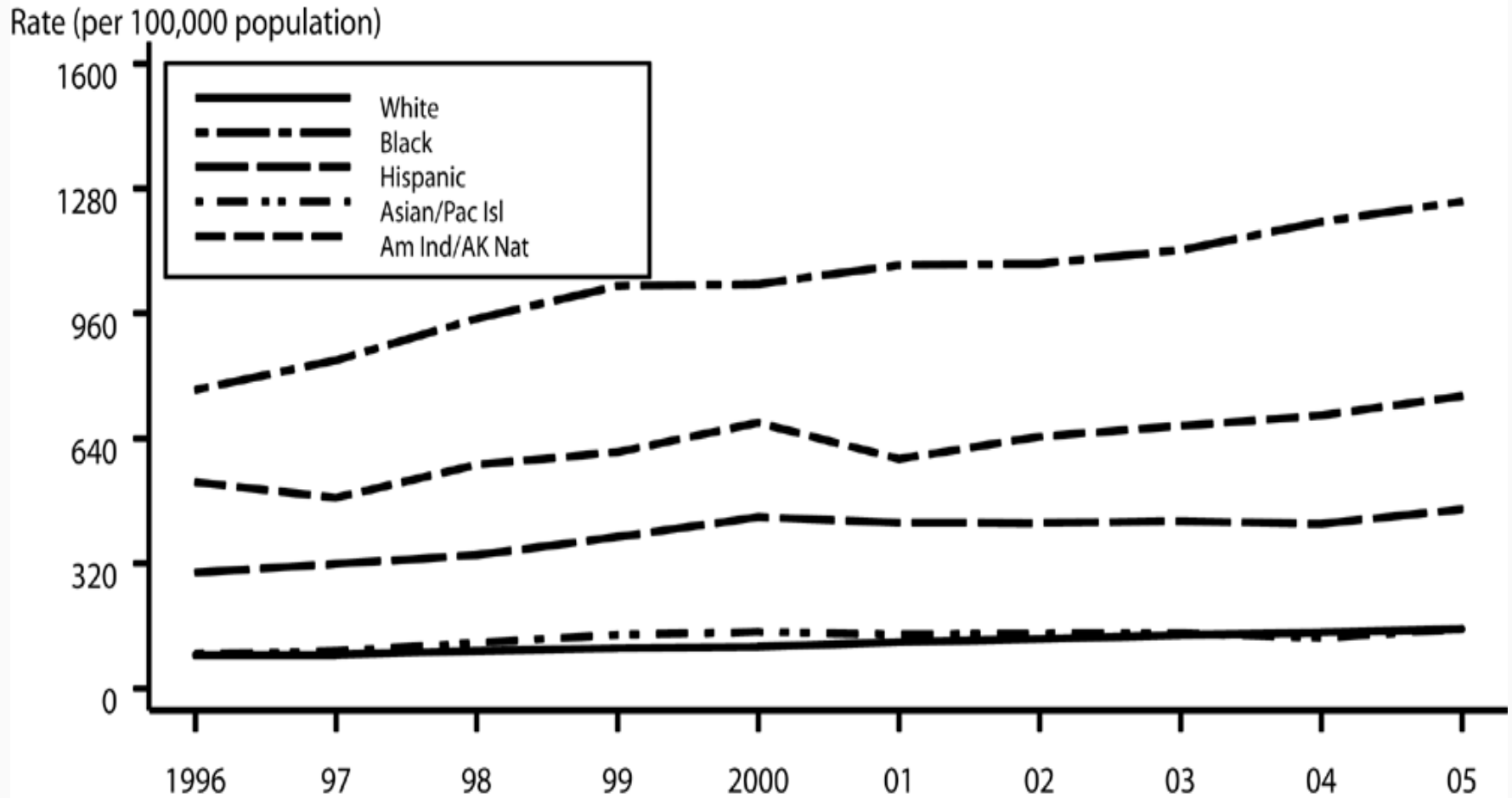


- Note—trends adjusted for changes in laboratory test method and associated increases in test sensitivity

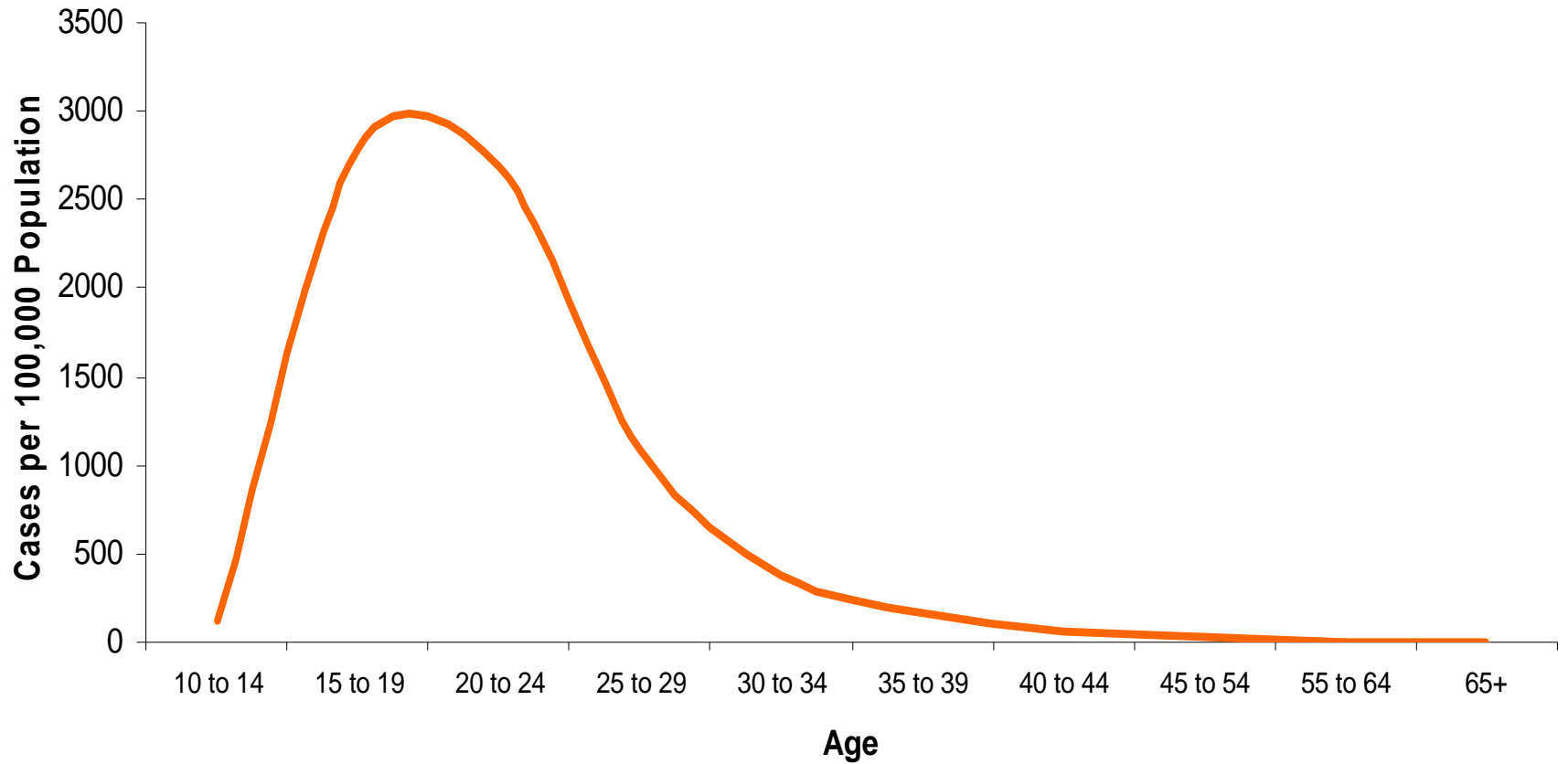
Chlamydia Rates by Region



Chlamydia Rates by Race



Female Chlamydia Rates, 2005



Epidemiology: Summary

- The increase in reported chlamydia infections during the last 10 years is due to the following:
 - The expansion of chlamydia screening activities
 - Increasingly sensitive diagnostic tests
 - Increasing emphasis on case reporting from both providers and laboratories
 - Improvements in the information systems for reporting
- Chlamydia screening and reporting are likely to expand further in response to the recently implemented Health Plan Employer Data and Information Set (HEDIS) measure for chlamydia screening of sexually active women 15 through 25 years of age who receive medical care through managed care organizations

Reporting of Chlamydia Cases

- “Trends in chlamydia morbidity reporting from many areas are more reflective of changes in diagnosis and reporting of cases rather than actual trends in disease incidence. Cases and rates of reported chlamydia in sex-specific tables are underestimated due to some reported cases with unknown sex. Despite problems with under-reporting, it is important to publish available data to emphasize the large numbers of cases of chlamydia being detected in the United States. As areas develop chlamydia prevention and control programs, including improved surveillance systems to monitor trends, the data should improve and become more representative of true trends in disease.”



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Section C

Chlamydia Trachomatis: Treatment and Screening

Recommended Regimens: CT

Recommended Regimens

- Azithromycin 1 g PO *or* . . .
- Doxycycline 100 mg PO BID for seven days

Alternative Regimens

- Seven day course of . . .
 - Erythromycin base 500 mg PO QID *or* . . .
 - Erythromycin ethylsuccinate 800 mg QID *or* . . .
 - Ofloxacin 300 mg PO BID

Other Considerations for Chlamydia Treatment

- Re-screen women for CT three to four months after treatment
- Screen sexually active women < = 25 years-old and high-risk women > 25 years old
- Refer all sex partners in the last 60 days for evaluation, testing, and therapy
- No sex until patient AND partner/partners are cured

Chlamydia Trachomatis: Infection and Re-Infection in 12-19 Year-Old Adolescent Women

- 3,202 sexually active women followed for 33 months
- Chlamydia infection in 24% of 1st visits and 14% of repeat visits
- Median time positive test
 - 1st positive—7.2 months
 - Repeat positive—6.3 months
- Screen sexually active adolescent females every six months

Does Screening Lead to Better Outcomes?

- Prospective study in group health, Seattle
 - 2,607 reproductive-age women
 - From 1990-1992 (did not use NAATs)
 - 1,009 randomized to screening intervention (but only 645 got tested)
 - 1,598 usual care (no active intervention)
 - Outcome—number of cases of PID in each group (ITT analysis)

Prevention of PID: Screening for Chlamydial Infection

	<u>Screening</u>	<u>Usual Care</u>	<u>Odds Ratio</u>
Number of Cases of PID	9	33	0.42 (0.20-0.89)

Per 10,000 woman-months

O.R. adjusted—age, marital status, douching



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Section D

Neisseria Gonorrhoea

Neisseria Gonorrhoeae (GC)

- Gram-negative diplococcus
- Fastidious—requires hemoglobin, CO₂
- Only causes disease in humans
 - No animal host
- Causes infection in columnar epithelial surfaces
- Multiple types—implications for vaccine

Gonococcal Syndromes

- Men—urethritis, epididymitis
- Women—cervicitis, salpingitis
- Men and women—proctitis, pharyngitis
- Newborns—ophthalmia, pneumonia
- Unusual—disseminated infection, adult ophthalmia, endocarditis, meningitis

Urethritis and Cervicitis

Urethritis

- Mostly seen in men [although urethritis may accompany cervicitis in women (~30%)]
- Symptoms—discharge of pus from the urethra & dysuria (pain on urination).
- Purulent discharge seen in > 80% of men with GC urethritis

Cervicitis

- 30-50% of women may be asymptomatic
- Symptoms—discharge, pruritus (itching), lower abdominal pain, dysuria, dyspareunia (painful intercourse)
- Several other diseases can mimic GC symptoms—chlamydia, herpes, trichomoniasis, BV, MPC

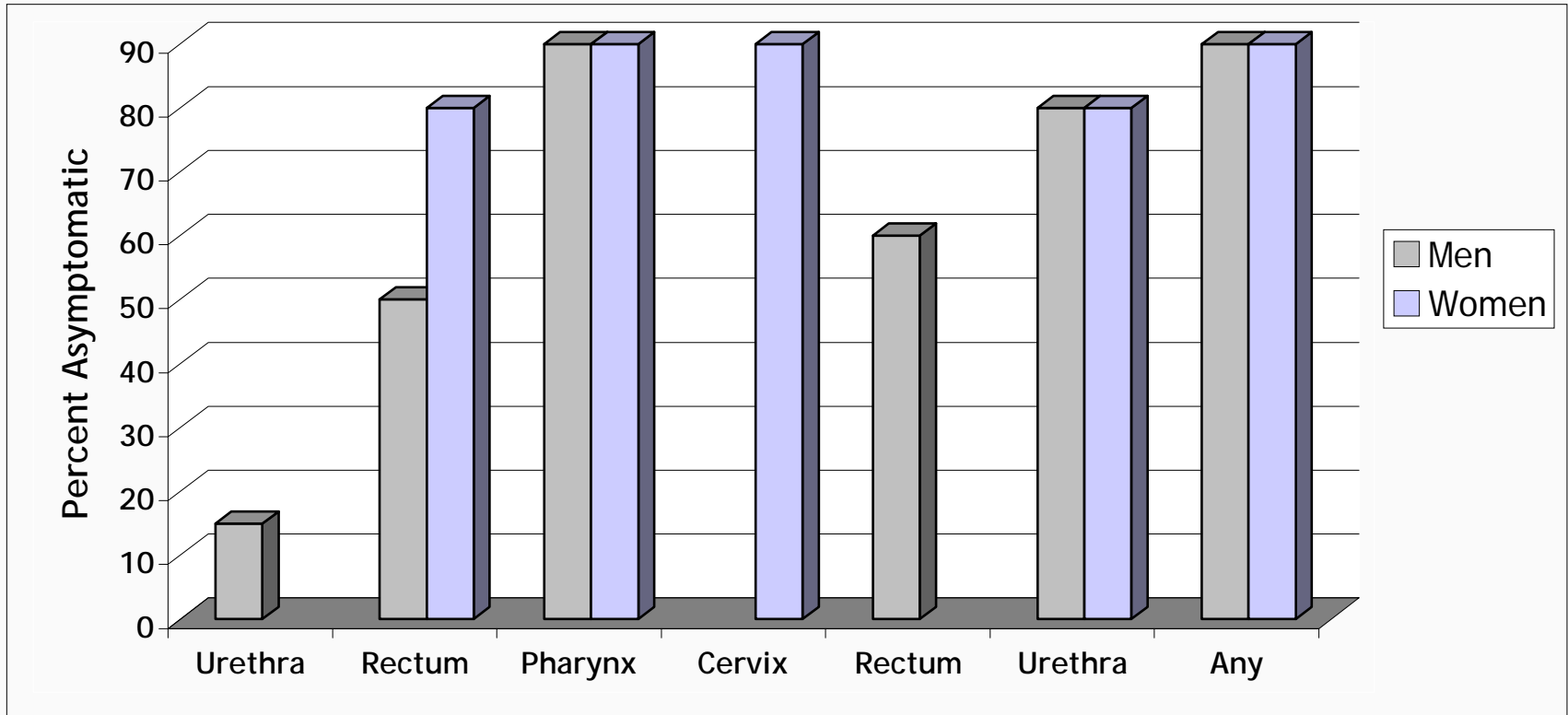
GC and HIV

- Retrospective and prospective studies demonstrate increased risk of HIV TRANSMISSION (HIV viral load in semen of GC infected men increases dramatically) and . . .
- ACQUISITION (increased number of immune cells in presence of GC infection)
- What are some potential problems with these studies?
 1. Behavioral confounding
 2. Selection bias
 3. Temporal bias
 - Think about other different types of biases in retrospective and prospective studies

GC Diagnosis

- Gram's stain has about 90% sensitivity in SYMPTOMATIC men
 - Sensitivity much lower in symptomatic women (~50%) and asymptomatic men and women (< 50%)
 - Specificity is about 95% in men, but lower in women
- Culture is still the gold standard; sensitivity > 90% and specificity > 99% (gender differences in sensitivity)
- Non-amplified molecular tests (EIA, etc.)
- Amplified molecular tests—NAATs (not FDA cleared for rectal and oropharyngeal samples)

Symptoms (or Lack of Symptoms)



Gonorrhea

Chlamydia

Herpes



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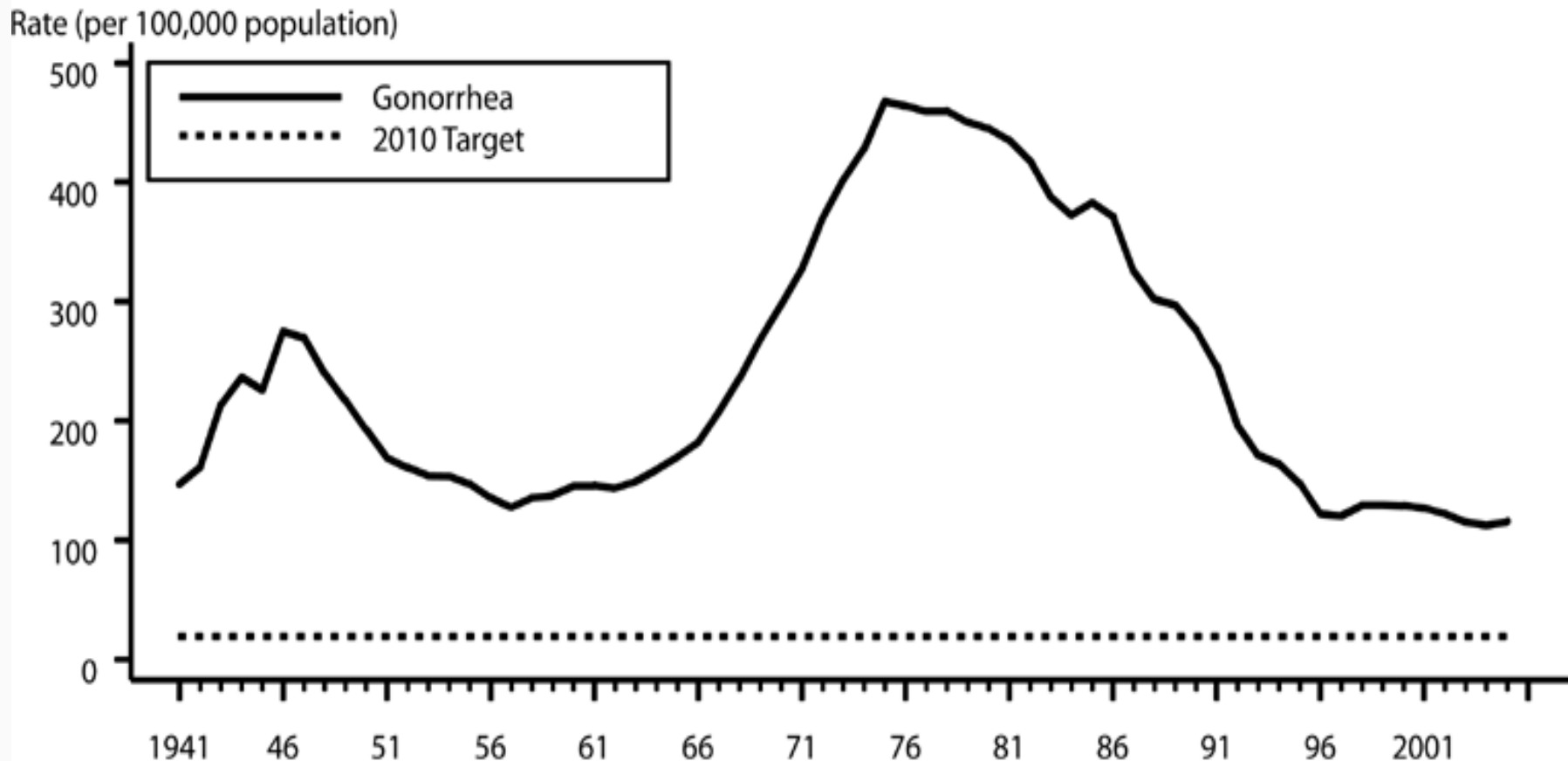
Section E

The Epidemiology of *Neisseria Gonorrhoeae*

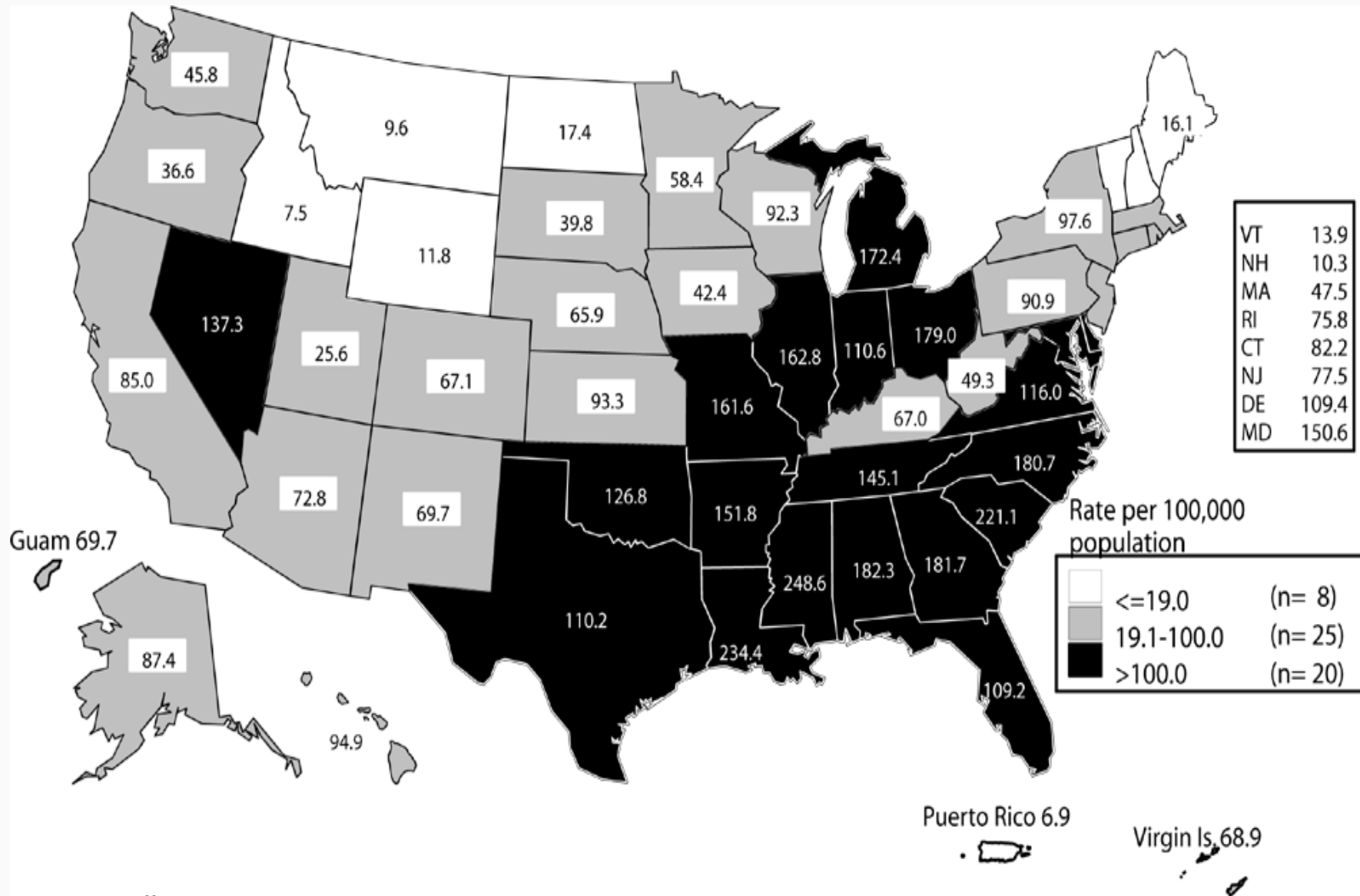
Overview

- Gonorrhea is the second most commonly reported notifiable disease in the United States (339,593 cases reported to the CDC in 2005)
- From 1975-1997, U.S. gonorrhea rates declined 74.3% following implementation of the national gonorrhea control program in the mid-1970s
- However, in 2005, rates increased slightly from 2004
- Rate increases or decreases may be masked by the following:
 - Changes in screening practices (affected by simultaneous testing for chlamydia)
 - Use of diagnostic tests with different sensitivities
 - Changes in reporting practices

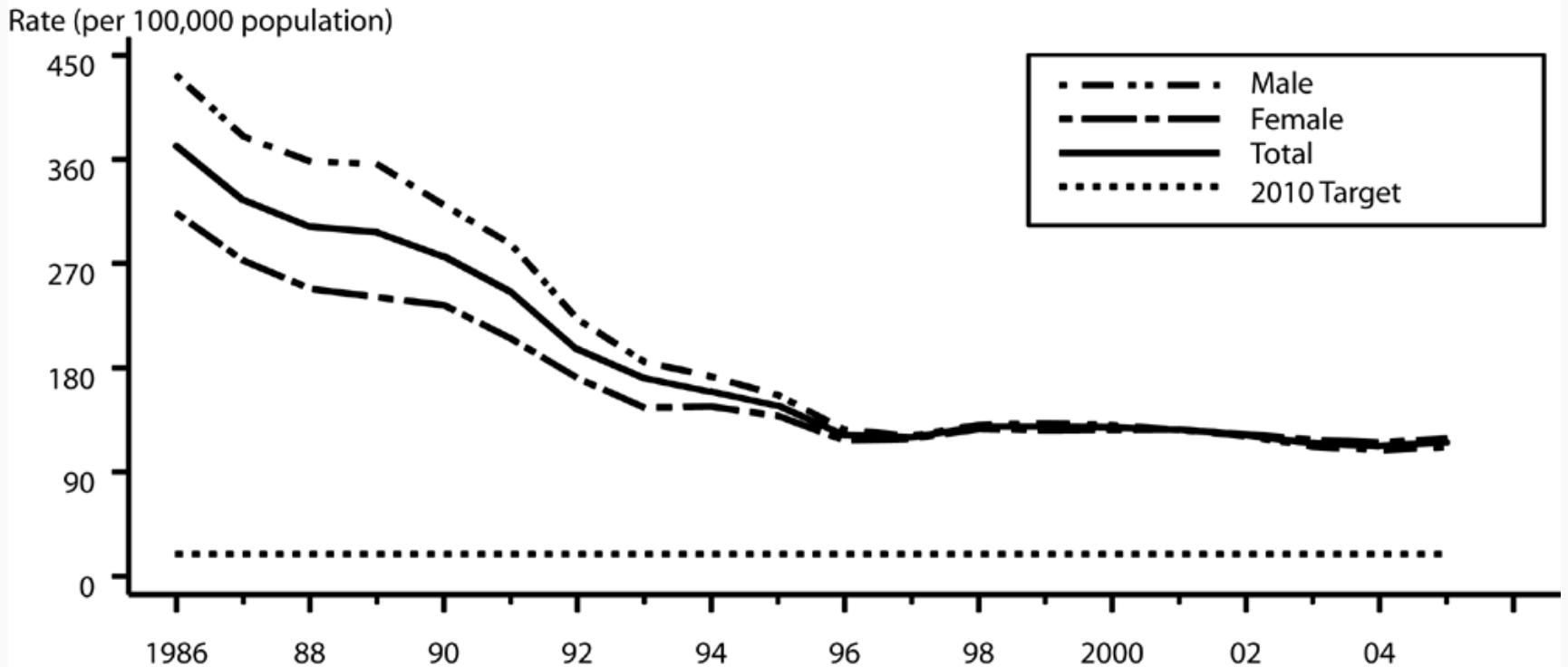
Gonorrhea Rates: United States 1941-2005 and the Healthy People 2010 Target



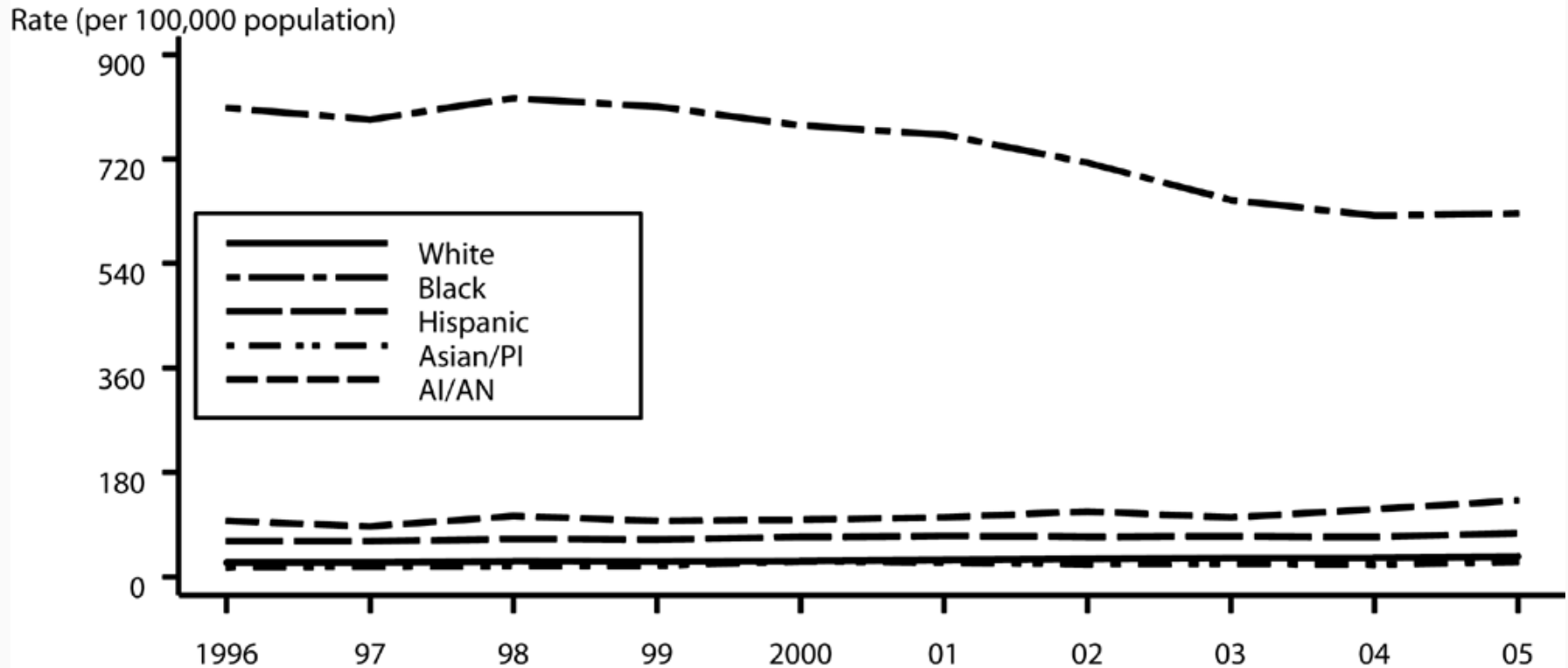
Gonorrhea Rates by State: United States (2005)



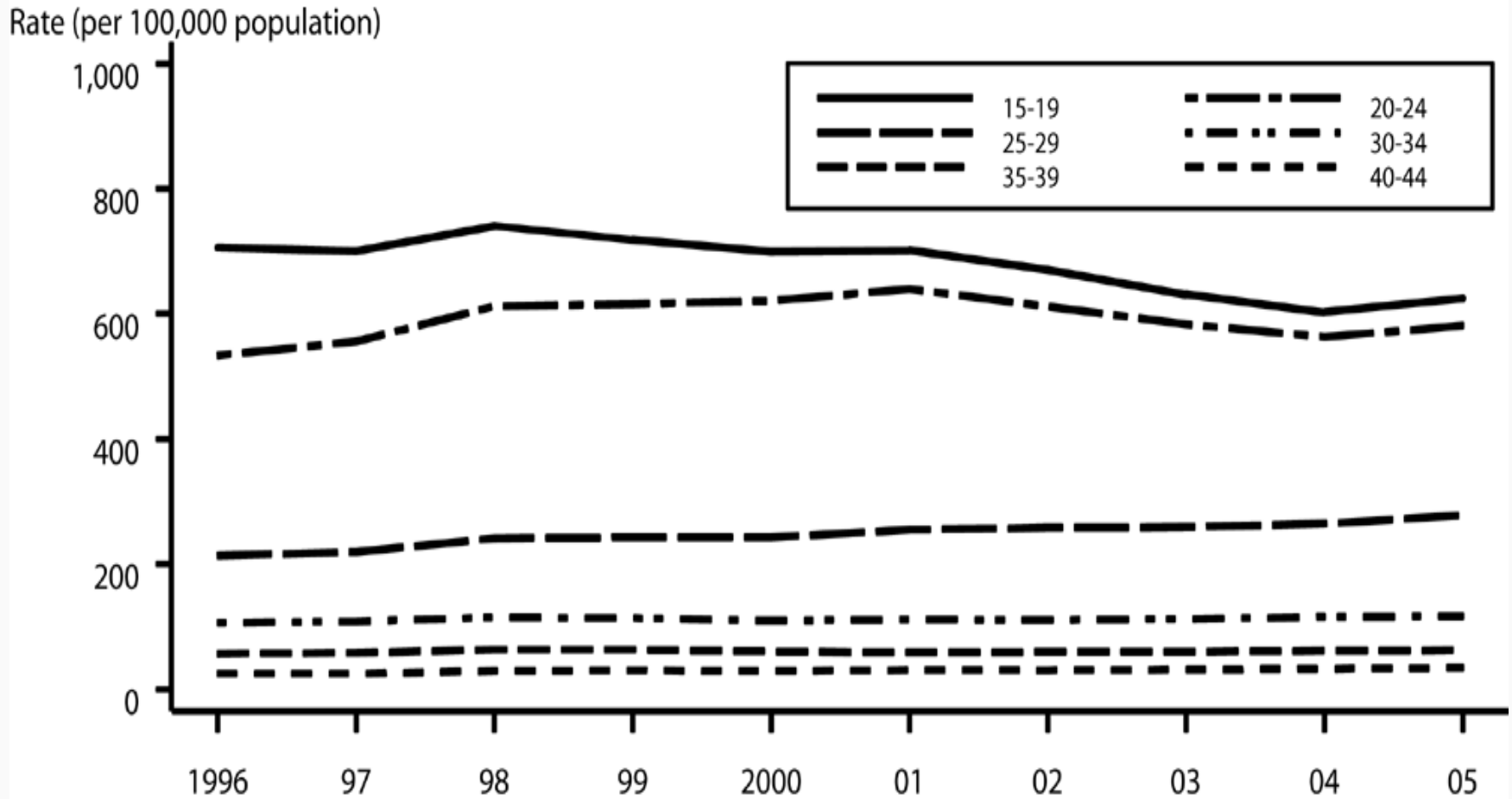
Gonorrhea Rates by Sex: United States, 1986-2005



Gonorrhea Rates by Race and Ethnicity: U.S., 1981-2004



Gonorrhea Positivity by Age





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Section F

Neisseria Gonorrhoeae: Treatment and Drug Resistance

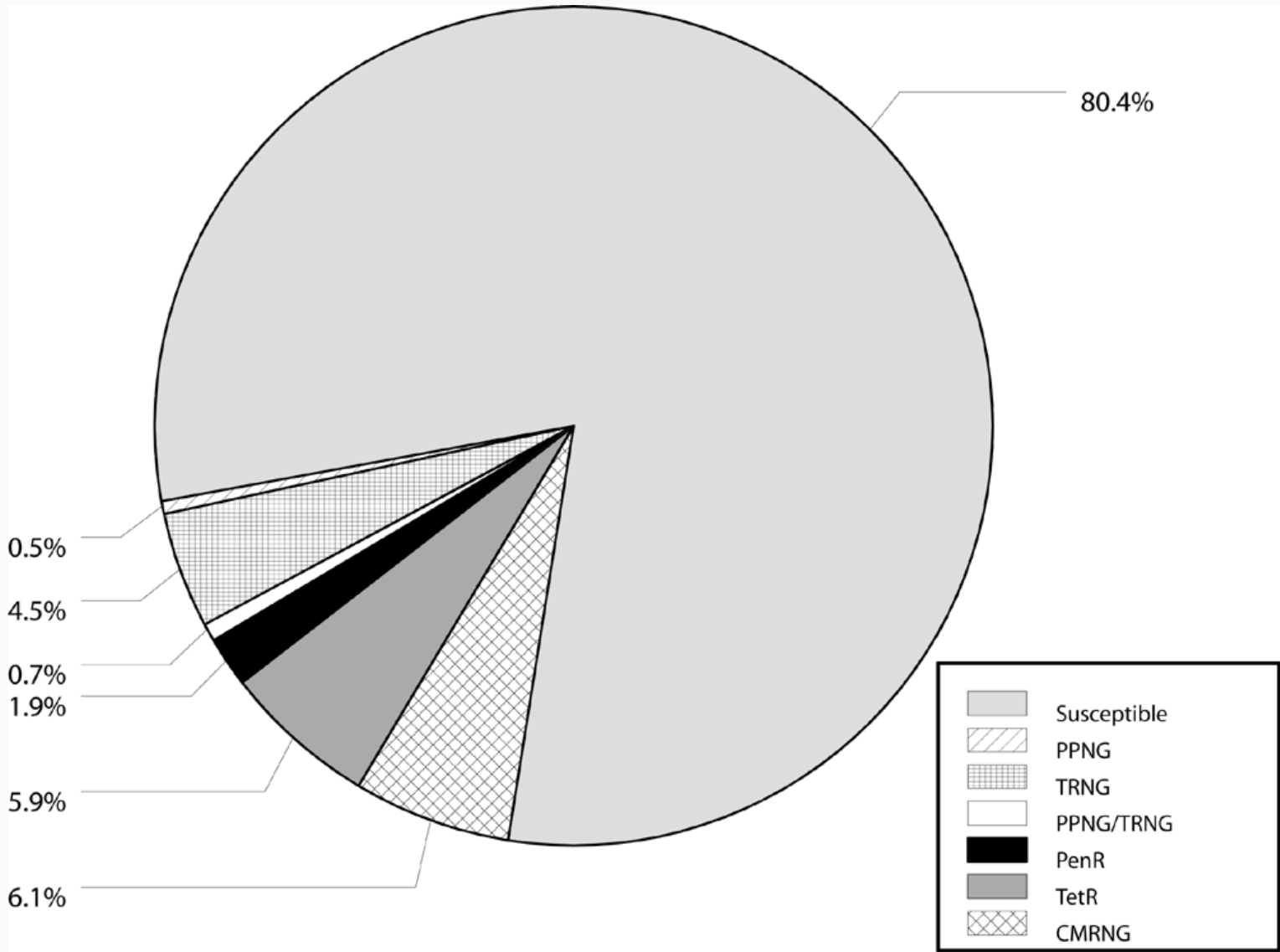
Therapy for Uncomplicated GC of the Cervix, Urethra and Rectum

- Cefixime 400 mg orally
- Ceftriaxone 125 mg intramuscular
- Ciprofloxacin 500 mg orally
- Ofloxacin 400 mg orally
- **PLUS**
- Doxycycline 100 mg orally twice a day x 1 week **OR** Azithromycin 1 gm orally x1

Partner Treatment Modalities

- None
- DIS (disease intervention specialists)
- Patient initiated REFERRAL of partners
- Novel method—patient initiated TREATMENT of partners

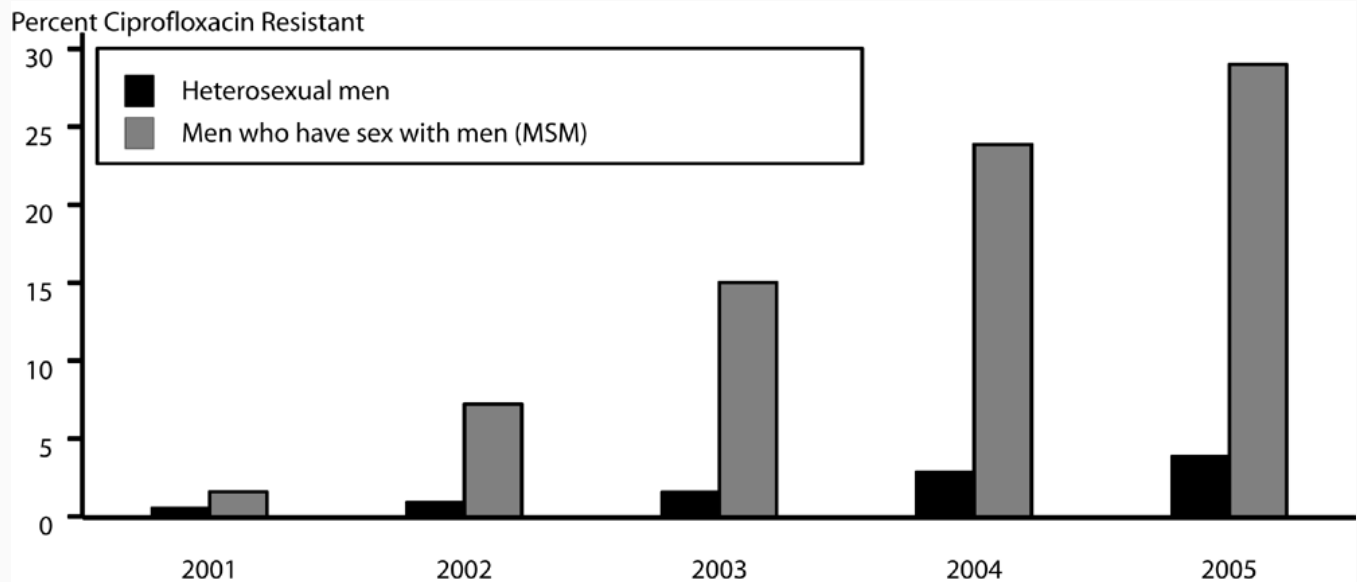
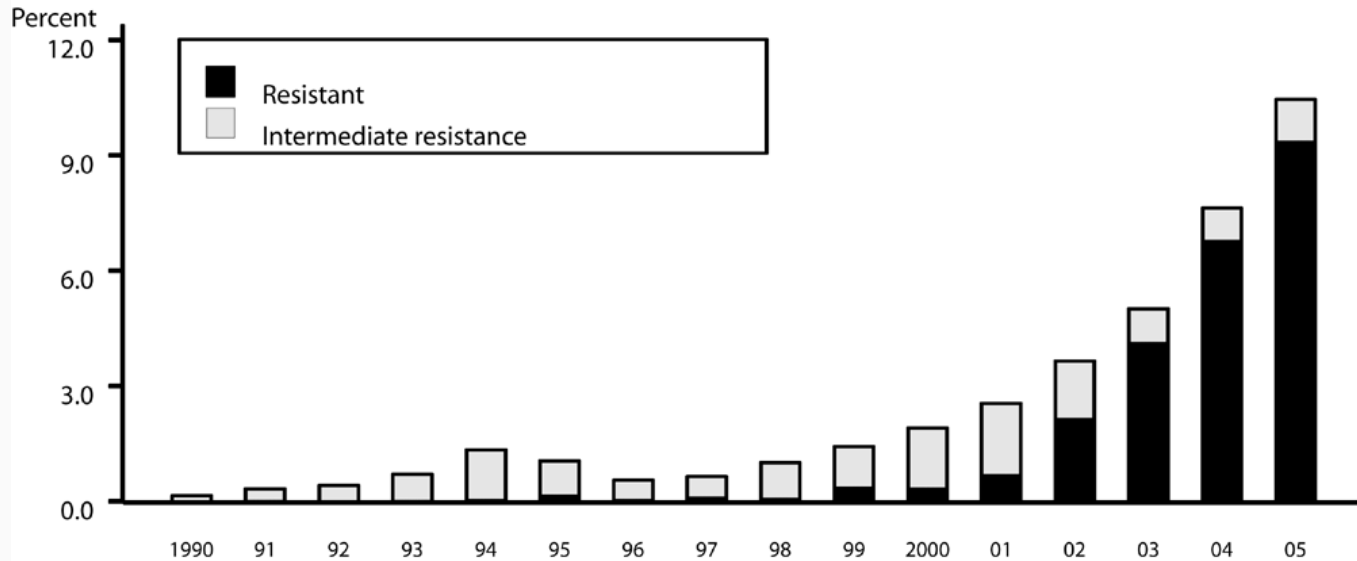
Antimicrobial Resistance



Quinolone Resistant Gonorrhea (QRNG)

- Rapidly increasing—especially in the Pacific Basin
- Change in treatment guidelines for the West Coast
- Quinolones recommended only since 1989
- Probably due to antibiotic overuse/misuse

Fluoroquinolone-Resistant Strains in the U.S.



GC: Summary of Major Epidemiological Trends

- Gonorrhea maintained in core groups
- Disproportionate impact on minorities
- Increases in gay men
- Emerging quinolone resistance
- “Repeater” impact
- Facilitate HIV infection

Future GC Issues that Need to be Addressed

- How much longer can we use fluoroquinolones?
- Will NAATs become the “new” gold standard in diagnosing neisseria gonorrhoeae?
- How will we follow susceptibility patterns of the organisms without culture testing?
- Where's the vaccine?