The Emerging Threat of Cephalosporin (& Multidrug) Resistant Gonorrhea

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Centers for Disease Control and Prevention

Disclosure

- I do not have any financial interest or affiliation with any organization that would influence the content of this presentation

Objectives

- Understand current trends in *Neisseria gonorrhoeae* antimicrobial susceptibilities
- Comprehend public health and clinical implications of gonococcal cephalosporin susceptibility trends

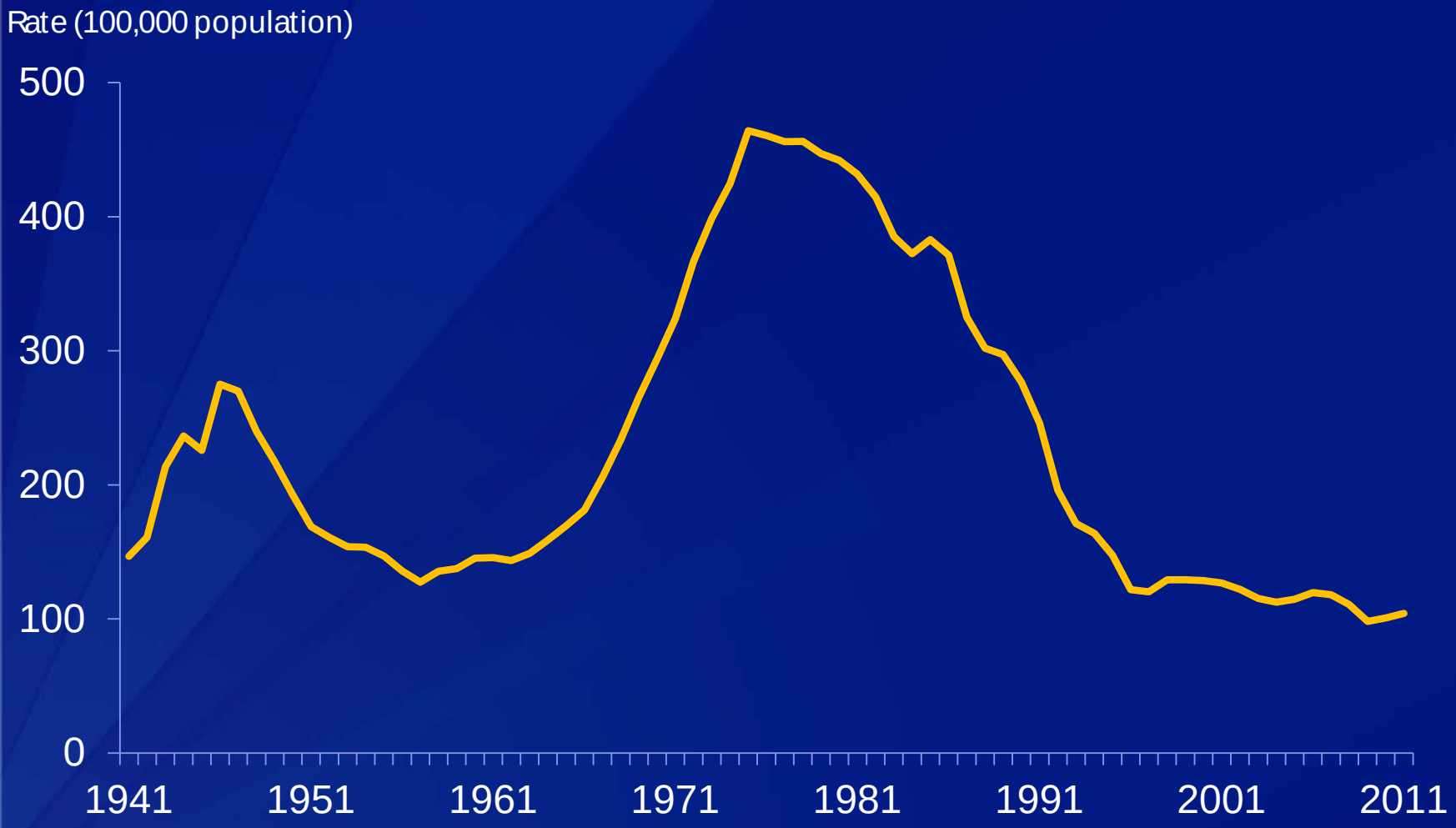
Overview

- Gonorrhea
- Resistance and treatment
- Surveillance of gonococcal resistance
- Emerging threat of cephalosporin resistance
- Conclusions

Gonorrhea

- One of the oldest known human diseases
  - Named by Galen (2nd century) ~ "flow of semen"
- Caused by *Neisseria gonorrhoeae*
- 2nd most commonly reported notifiable infection
- Can be asymptomatic
- Can cause
  - Pelvic inflammatory disease (PID)
  - Ectopic pregnancy
  - Infertility
- May facilitate HIV transmission

Gonorrhea Rates, United States, 1941–2011

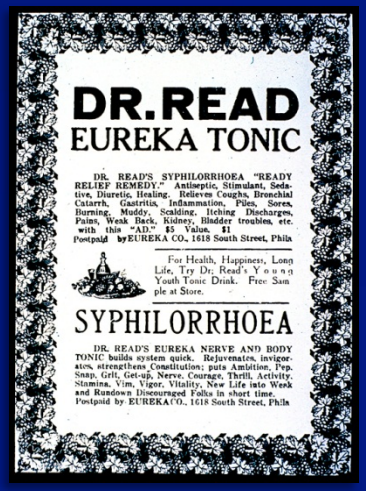


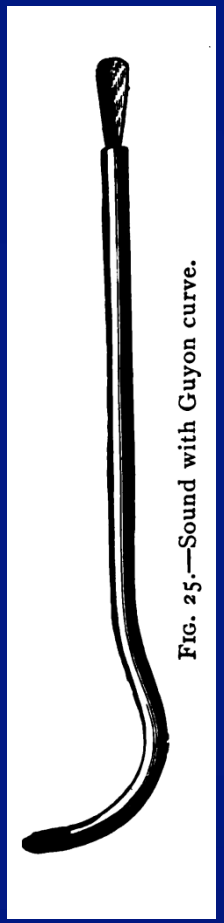
Neisseria gonorrhoeae (NG) Treatment

- **Prompt antimicrobial treatment limits sequelae, prevents transmission**
  - Detection & treatment is cornerstone of NG control
- **Antimicrobial resistance**
  - Undermines treatment success
  - Heightens risk of complications
  - Facilitates transmission *(by lengthening infectious period)*

Treatment of Gonorrhea in the Pre-Antimicrobial Era

- Patent Medicines
- Intraurethral irrigation
  - Mercurochrome
  - Nitric acid
  - Silver nitrate
- Mechanical removal of strictures
  - Sounds
  - Dilators





Baumann F. Gonorrhea: Its Diagnosis and Treatment. D. Appleton & Co. 1910

Antimicrobial Treatment of Gonorrhea

1930s

- **Sulfonamide therapy introduced**
  - Prontosil found to be effective
  - *N. gonorrhoeae* rapidly developed resistance within several years (~30% resistance)

Antimicrobial Treatment of Gonorrhea

1930s

- Sulfonamide therapy introduced

1940s

- Penicillin proved effective
  - Becomes treatment of choice

Antimicrobial Treatment of Gonorrhea

1930s

- Sulfonamide therapy introduced

1940s

- Penicillin proved effective

1970s

- Incremental penicillin resistance
  - Penicillin dosage increased
  - Probenicid added to extend half-life

Antimicrobial Treatment of Gonorrhea

1930s

- Sulfonamide therapy introduced

1940s

- Penicillin proved effective

1970s

- Incremental penicillin resistance

1980s

- High-level penicillin resistance (penicillinase-producing NG [PPNG])
  - Emerged in SE Asia and West Africa
  - Spread globally

Treatment Options after Emergence of PPNG

- Spectinomycin
  - No longer available in US

1980s – new antimicrobials became available

- Fluoroquinolones
  - Ciprofloxacin
  - Levofloxacin
- Third-generation cephalosporins
  - Ceftriaxone (injectable)
  - Cefixime (oral)

The Gonococcal Isolate Surveillance Project (GISP)

- CDC-supported US sentinel surveillance since 1987
- Monitors trends in *N. gonorrhoeae* susceptibility to antimicrobials
- Methods
  - Urethral isolates obtained from first 25 men per clinical site each month
  - Susceptibility testing conducted by regional laboratories
    - Minimum inhibitory concentrations (MICs) by agar dilution
  - Confirmatory testing by CDC
  - Limited demographic & clinical data

Gonococcal Isolate Surveillance Project — United States, 2012

Source: Gonococcal Isolate Surveillance Project

Measuring Antimicrobial Susceptibility

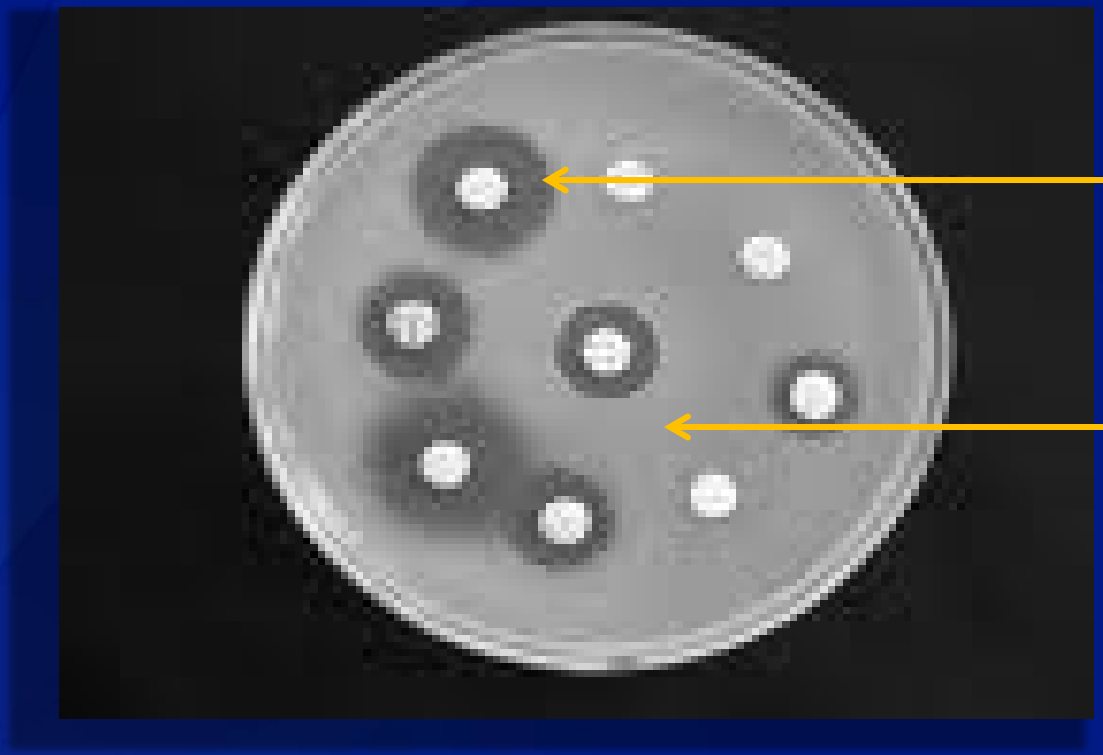
- **Agar dilution**
  - Grow bacteria on plates with varying antimicrobial concentrations
  - Requires culture
  - Gold standard but labor-intensive (done at reference laboratories)
  - Provides minimum inhibitory concentration (MIC) – lowest antimicrobial concentration that inhibits bacterial growth in lab
    - Low MICs ~ susceptible
    - High MICs ~ resistant
- **Disc diffusion (Kirby-Bauer)**
- **Etest**

Measuring Antimicrobial Susceptibility

- Agar dilution
  - Gold standard
  - Labor-intensive
  - Done at reference laboratories
  - Provides minimum inhibitory concentration (MIC) – lowest antimicrobial concentration that inhibits bacterial growth in lab
- Disc diffusion (Kirby-Bauer)

- Etest

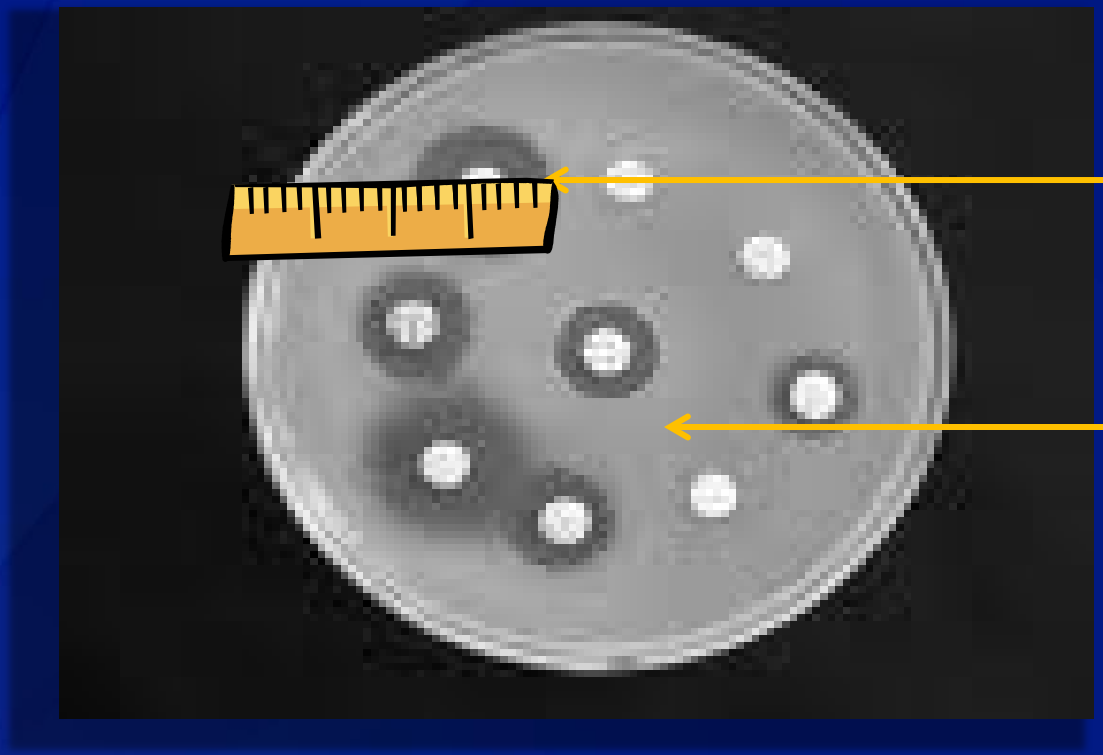
Disc Diffusion (Kirby-Bauer)

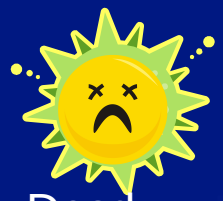


Dead bacteria

Live bacteria

Disc Diffusion (Kirby-Bauer)





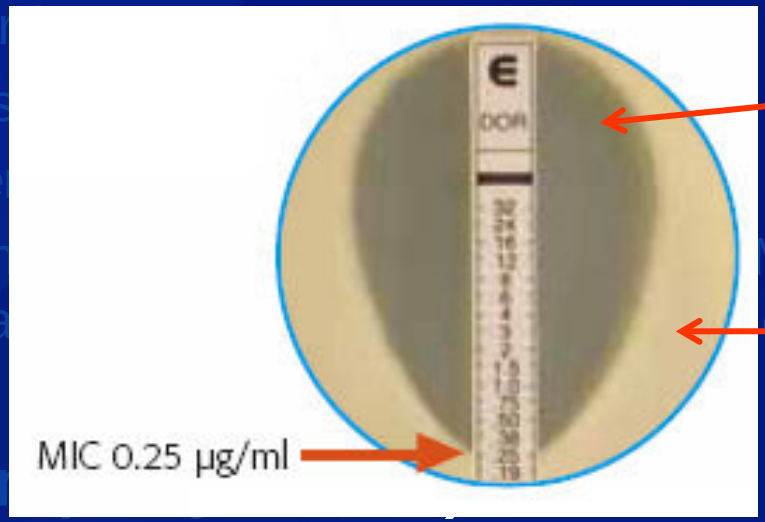
Dead bacteria

Live bacteria

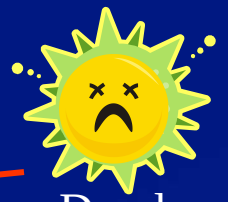
Results as diameter (in millimeters)

Measuring Antimicrobial Susceptibility

- Agar dilution
  - Gold standar
  - Labor-intens
  - Done at refer
  - Provides min MIC) – lowest antimicrobia erial growth in lab
- Disc diffusion
- Etest
  - Provides MIC

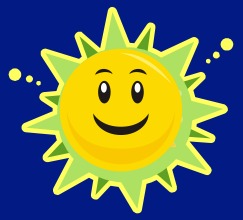


bioMérieux Clinical Diagnostics



Dead bacteria

Live bacteria



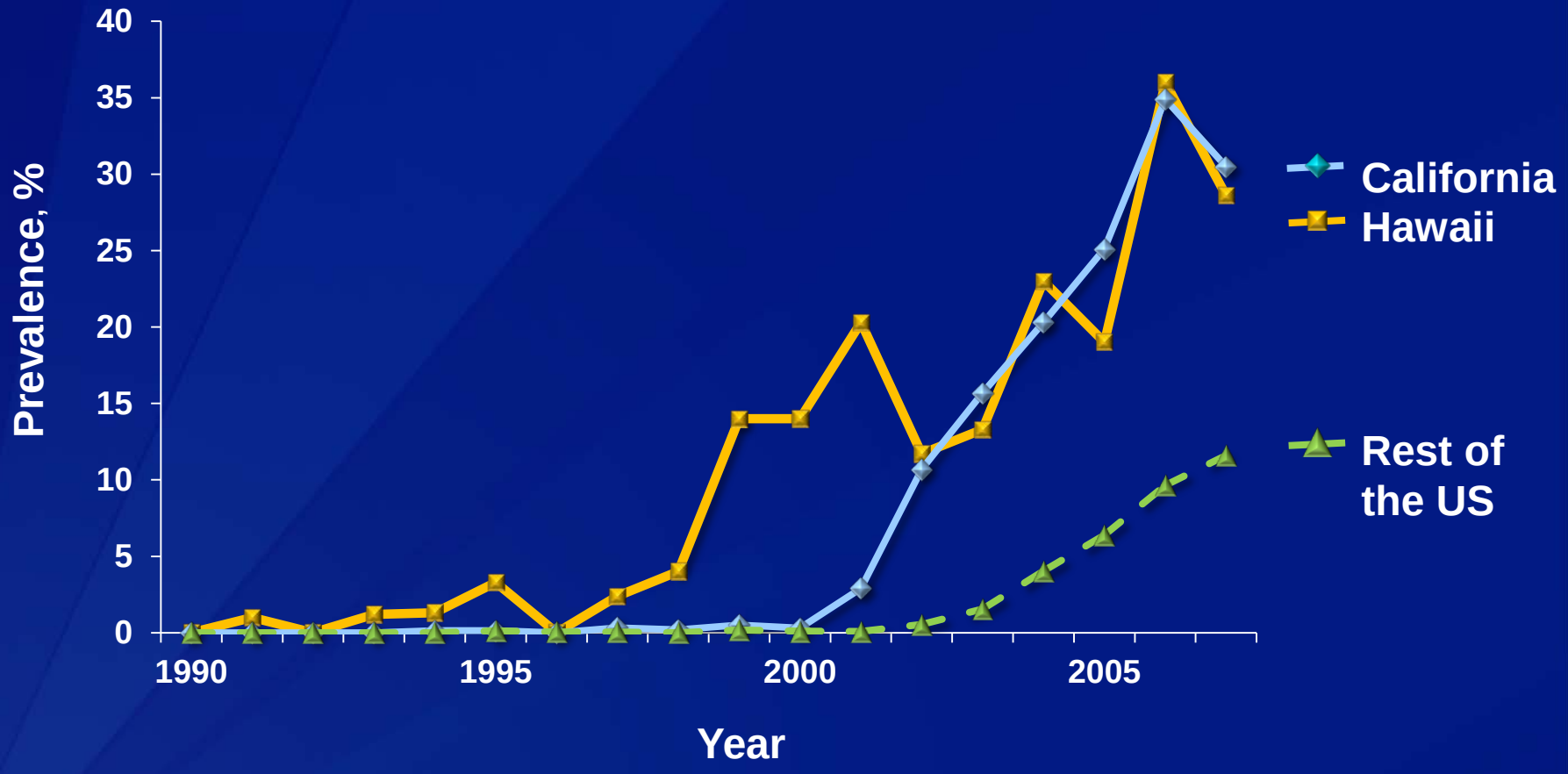
CDC STD Treatment Guidelines, 2002

- Cefixime 400 mg *(oral, single dose)*
- Ceftriaxone 125 mg *(injectable, single dose)*
- Ciprofloxacin 500 mg *(oral, single dose)*
- Ofloxacin 400 mg *(oral, single dose)*
- Levofloxacin 250 mg *(oral, single dose)*

- **If chlamydia is not ruled out:**
  - Azithromycin 1 g or
  - Doxycycline 100 mg BID x 1 week

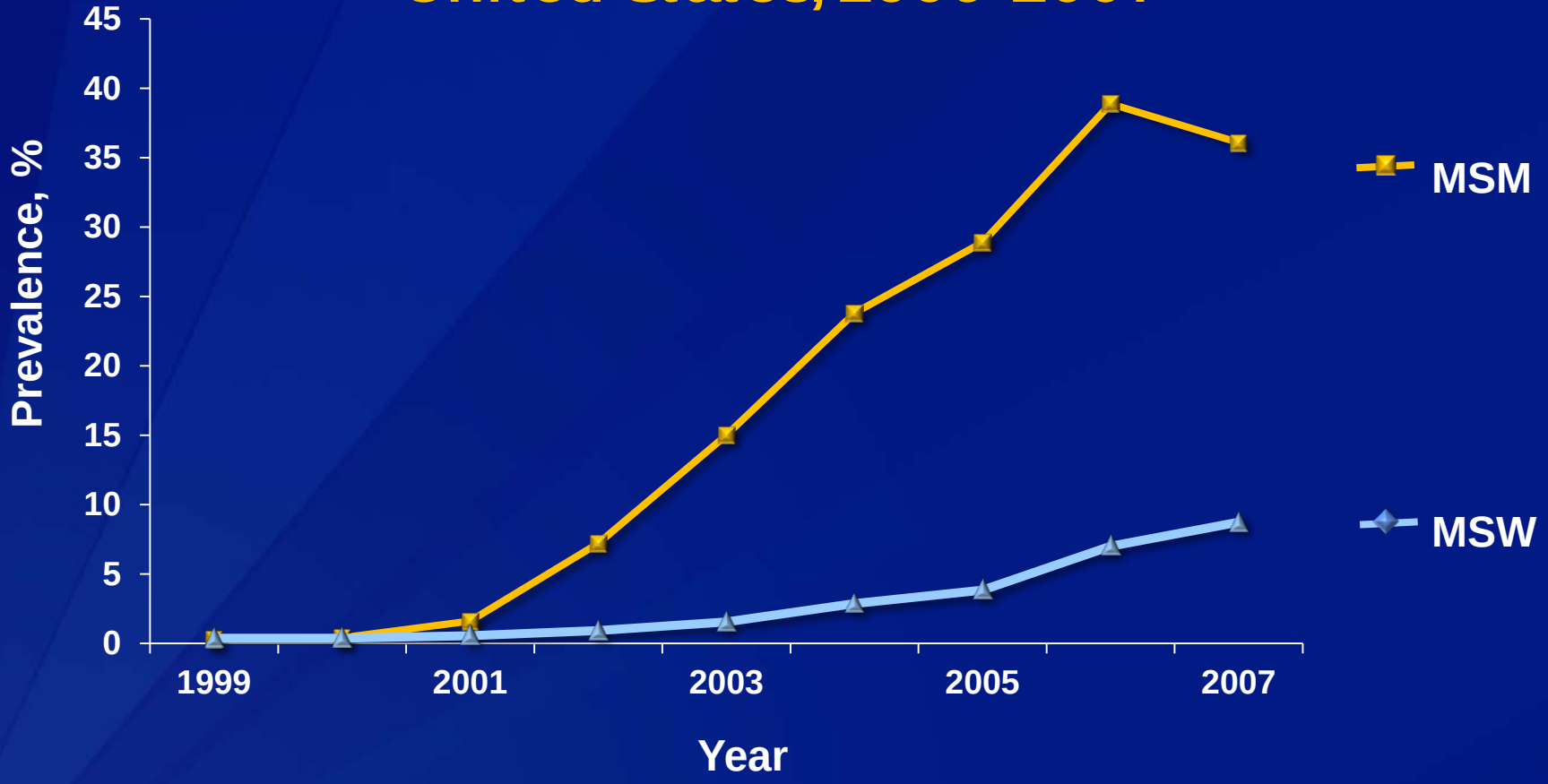
http://www.cdc.gov/std/treatment/default-2002.htm

Ciprofloxacin Resistance in *N. gonorrhoeae*, United States, 1990–2007



GISP, Gonococcal Isolate Surveillance Project, 1990–2007
Resistant isolates have ciprofloxacin MICs ≥1 µg/ml

Ciprofloxacin Resistance in *N. gonorrhoeae*, by Gender of Sex Partner, United States, 1999-2007



GISP, Gonococcal Isolate Surveillance Project, 1990–2007
Resistant isolates have ciprofloxacin MICs ≥1 µg/ml
MSM, men who have sex with men
MSW, men who have sex exclusively with women

CDC STD Treatment Guidelines, 2007

- Cefixime 400 mg po
- Ceftriaxone 125 mg IM
- ~~Ciprofloxacin 500 mg po~~
- ~~Ofloxacin 400 mg po~~
- ~~Levofloxacin 250 mg po~~

Cephalosporins are only remaining class

- & If CT is not ruled out
  - Azithro 1 g or
  - Doxycycline 100 mg BID x 1 week

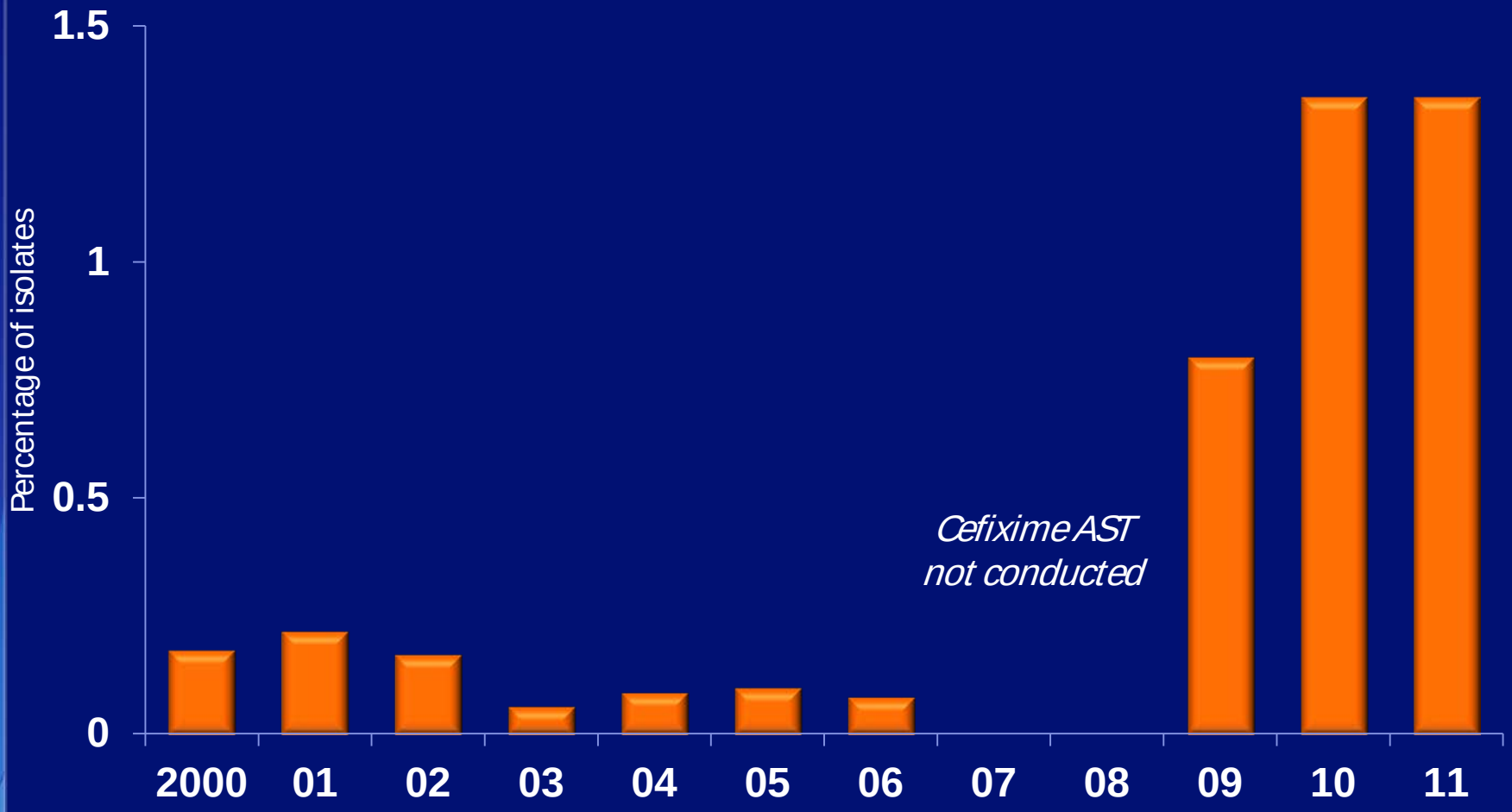
Global Emergence of Resistance to Cephalosporins

- First reported oral cephalosporin treatment failure – Japan (2001)
- Additional treatment failures with oral cephalosporins (east Asia)
- Increasing cephalosporin MICs – *early warning for potential resistance*
  - Japan
  - China
  - Australia

Global Emergence of Resistance to Cephalosporins

- Increasing oral cephalosporin MICs (late 2000s)
  - Europe
  - Canada
- 2009 – 1st high-level ceftriaxone resistant isolate (H041) from pharynx of CSW (Japan)
  - Cured, H041 has not since been detected
- Ceftriaxone-resistant isolates found in MSM in France, Spain
  - All were cured
- Treatment failures with cefixime among MSM identified in Toronto

Proportion of GISP Isolates with Elevated Cefixime MICs (≥0.25 µg/ml), United States, 2000–2011

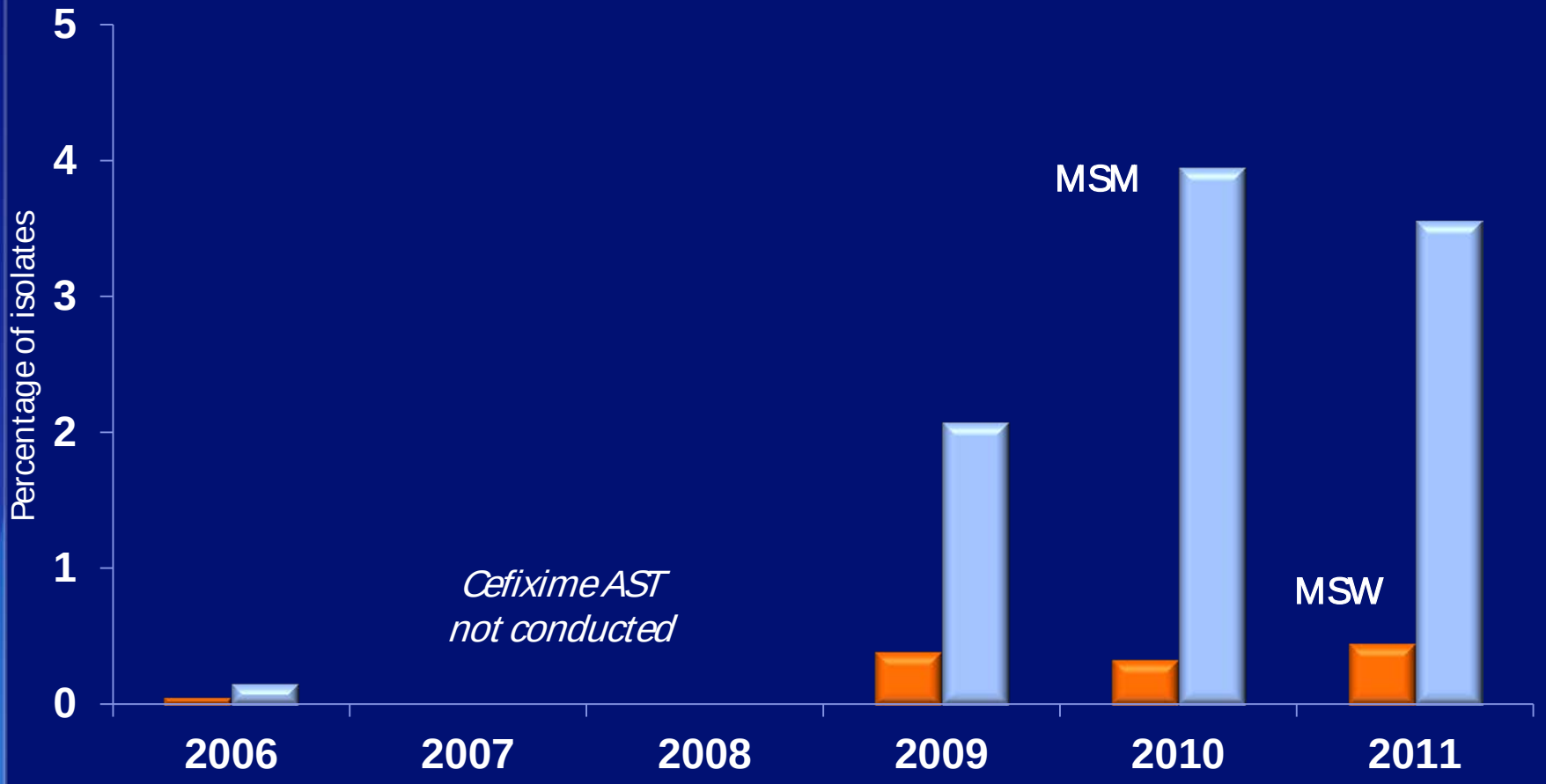


Source: Gonococcal Isolate Surveillance Project

Proportion of GISP isolates with Elevated Cefixime MICs (≥0.25 µg/ml) by Region, 2006–2011

Source: Gonococcal Isolate Surveillance Project

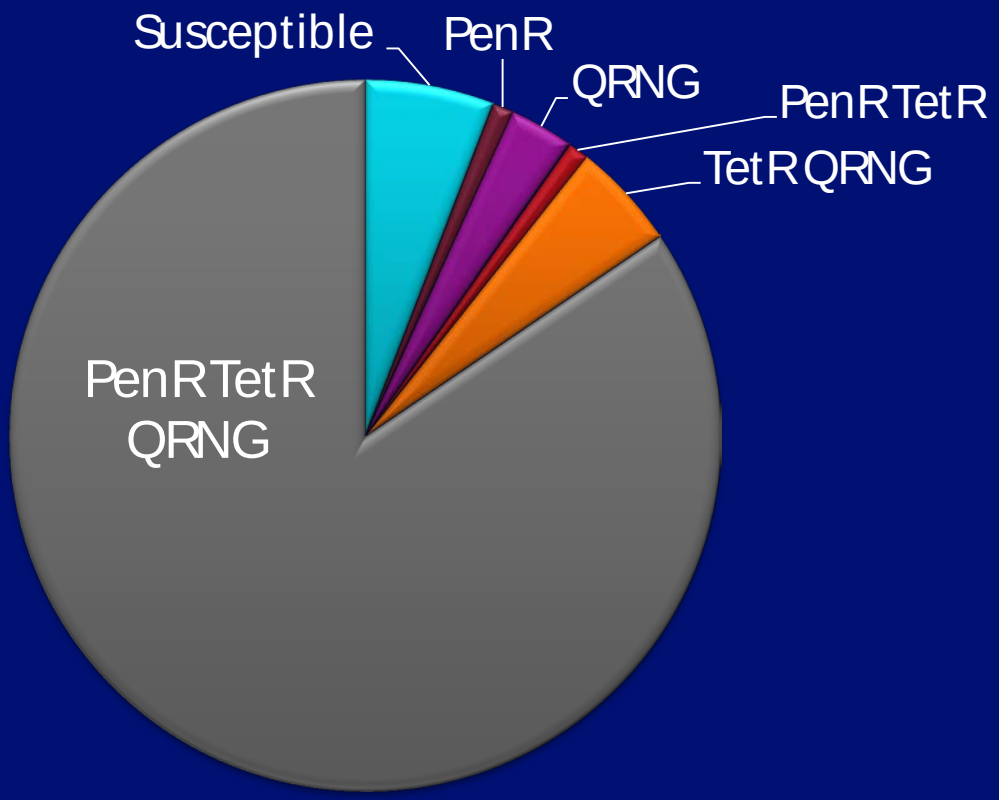
Proportion of GISP isolates with Elevated Cefixime MICs (≥0.25 µg/ml) by Gender of Sex Partner, US, 2006–2011



* Preliminary (Jan-June)
MSM = Men who have sex with men; MSW = Men who have sex exclusively with women

Source: Gonococcal Isolate Surveillance Project

Other Resistance in Isolates with Elevated Cefixime MICs, 2011–2012*

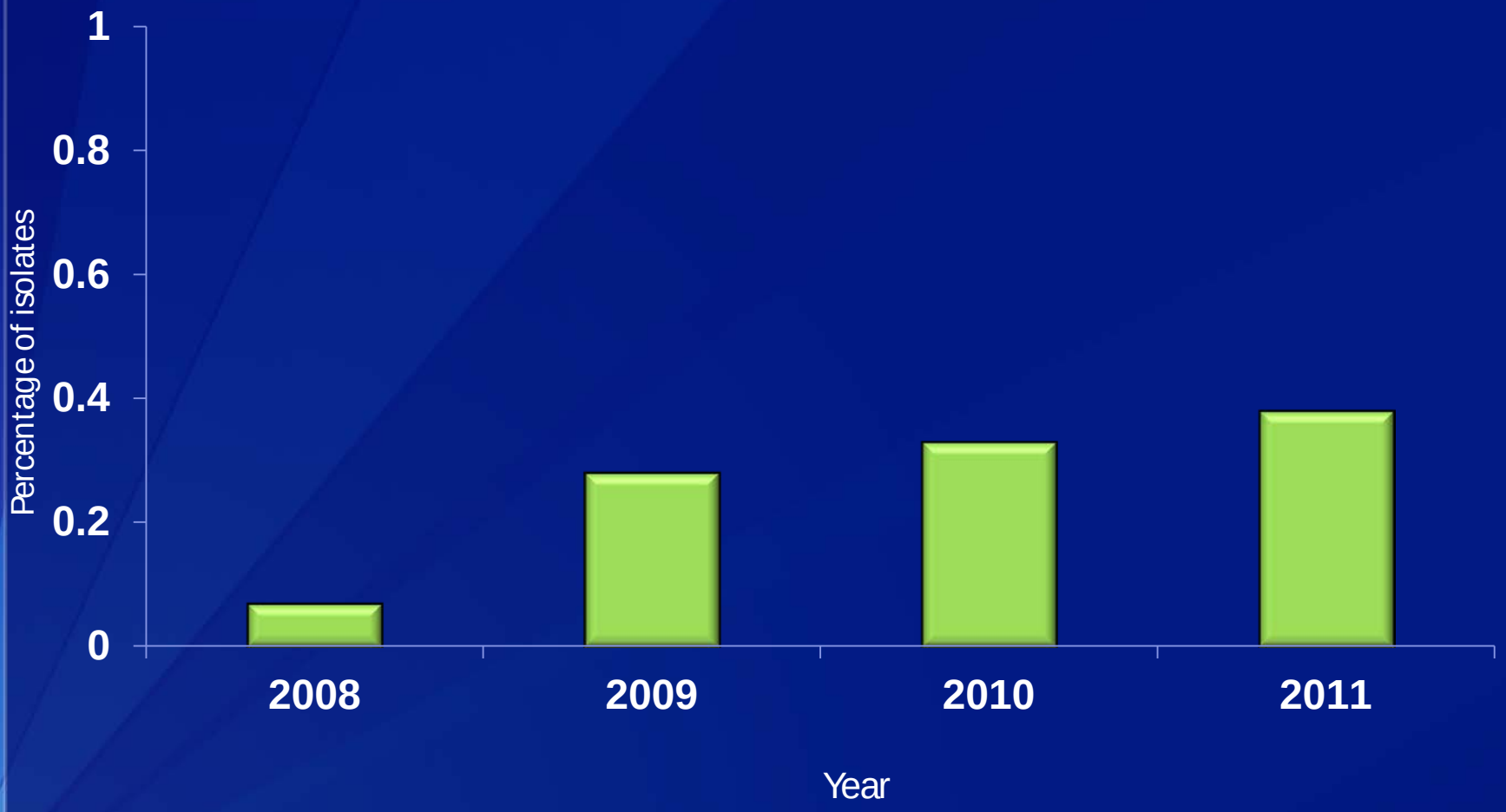


* Preliminary Jan-June

PenR=penicillin-resistant; QRNG = quinolone-resistant; TetR = tetracycline-resistant

Source: Gonococcal Isolate Surveillance Project

Percentage of Isolates with Elevated Ceftriaxone MICs (≥0.125 µg/ml), 2008–2011



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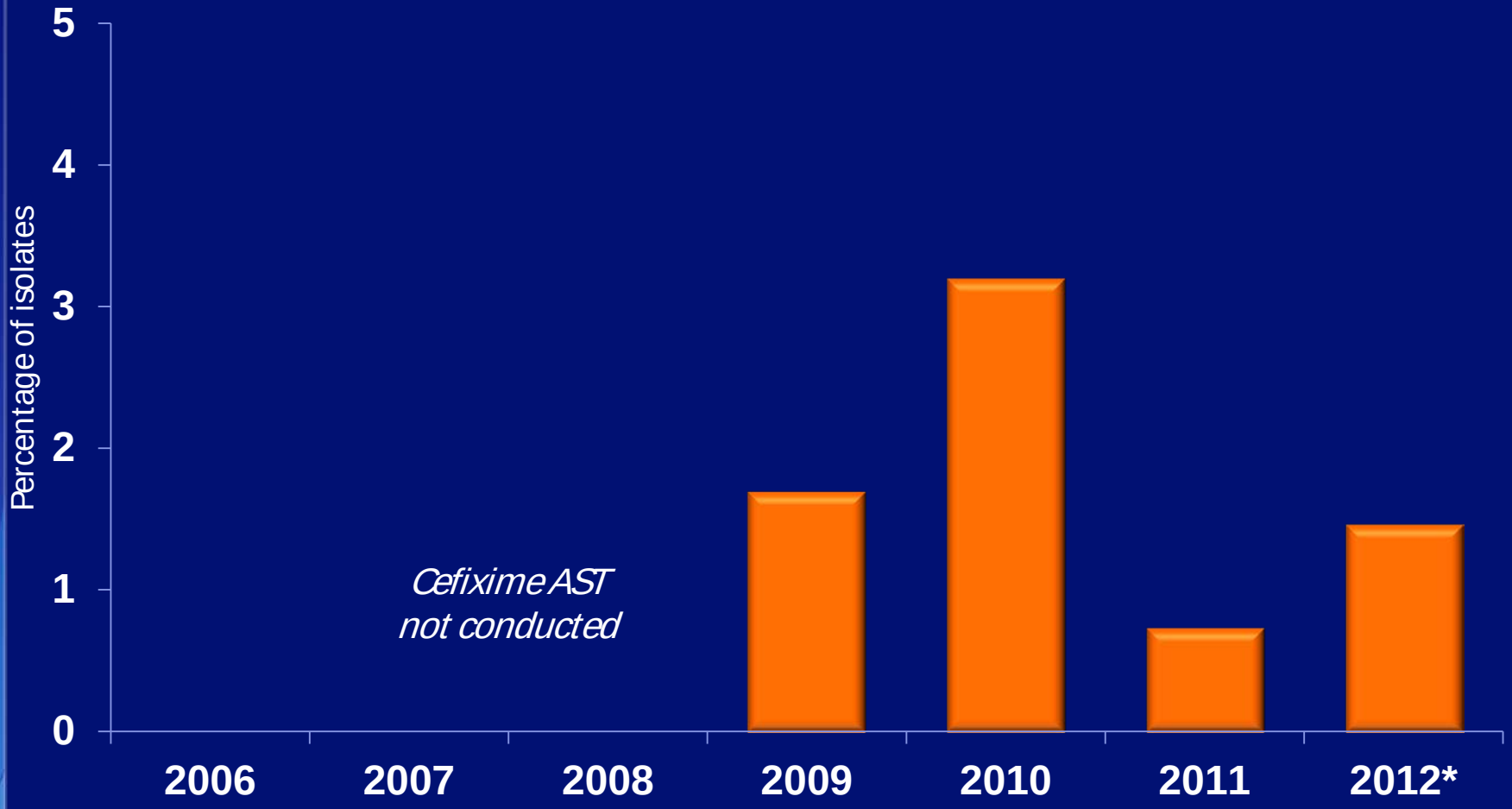
Source: Gonococcal Isolate Surveillance Project

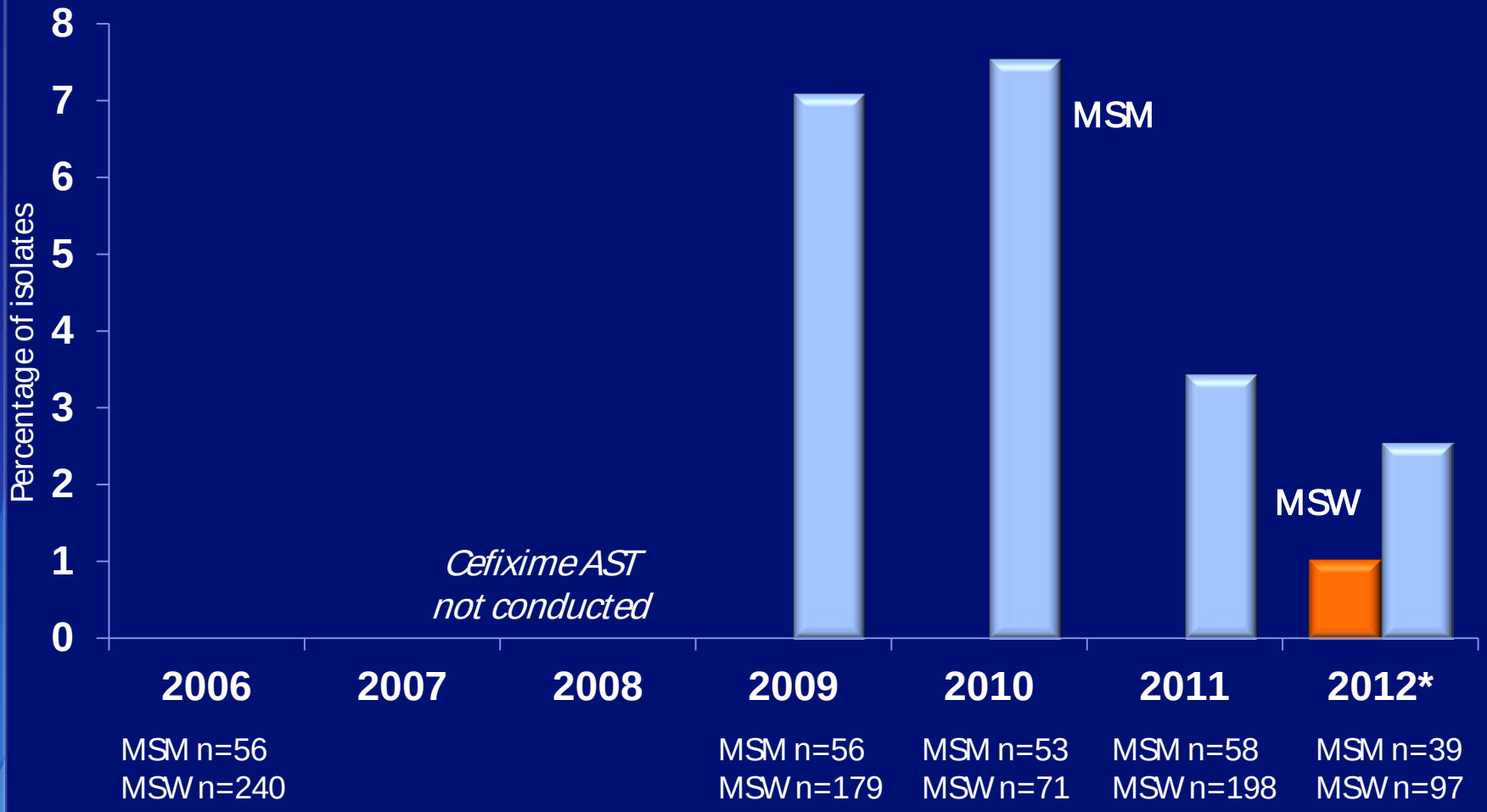
Proportion of Isolates with Elevated Cefixime MICs (≥0.25 µg/ml), Chicago, 2006–2012*



* Preliminary (Jan-June)

Source: Gonococcal Isolate Surveillance Project

Proportion of Isolates with Elevated Cefixime MICs (≥0.25 µg/ml) by Sex of Sex Partner, Chicago, 2006–2012*



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MSM = Men who have sex with men; MSW = Men who have sex exclusively with women

Source: Gonococcal Isolate Surveillance Project

Updated GC Treatment Guidelines, 2012

- Recommended
  - Ceftriaxone 250 mg IM PLUS
  - Azithro 1 g or Doxycycline

- Alternatives
  - Cefixime 400 mg PLUS Azithro/Doxy

    OR
  - Azithromycin 2 g

    PLUS
  - Test of cure

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Weekly / Vol. 61 / No. 31 August 10, 2012

Current Tobacco Use Among Middle and High School Students — United States, 2011

Tobacco use continues to be the leading preventable cause of death and disease in the United States, with nearly 443,000 deaths occurring annually because of cigarette smoking and exposure to secondhand smoke (*1*). Moreover, nearly 90% of adult smokers begin smoking by age 18 years (*2*). To assess current tobacco use among youths, CDC analyzed data from the 2011 National Youth Tobacco Survey (NYTS). This report describes the results of that analysis, which indicated that, in 2011, the prevalence of current tobacco use among middle school and high school students was 7.1% and 23.2%, respectively, and the prevalence of current cigarette use was 4.3%, and 15.8%, respectively. During 2000–2011, among middle school students, a linear downward trend was observed in the prevalence of current tobacco use (14.9% to 7.1%), current combustible tobacco use (14.0% to 6.3%), and current cigarette use (10.7% to 4.3%). For high school students, a linear downward trend also was observed in these measures (current tobacco use [34.4% to 23.2%], current combustible tobacco use [33.1% to 21.0%], and current cigarette use [27.9% to 15.8%]). Interventions that are proven to prevent and reduce tobacco use among youths include media campaigns, limiting advertisements and other promotions, increasing the price of tobacco products, and reducing the availability of tobacco products for purchase by youths. These interventions should continue to be implemented as part of national comprehensive tobacco control programs and should be coordinated with Food and Drug Administration (FDA) regulations restricting the sale, distribution, and marketing of cigarettes and smokeless tobacco products to youths (*2–6*).

NYTS is a school-based, self-administered, pencil-and-paper questionnaire given to middle school (grades 6–8) and high school (grades 9–12) students to collect information on key tobacco control outcome indicators used to monitor the impact of comprehensive tobacco control policies and programs (e.g., prevalence of tobacco use and smoking cessation, tobacco-related knowledge and attitudes, access to tobacco, exposure to tobacco advertising and promotions, and secondhand smoke exposure).* The survey has been conducted approximately every 2 years since 2000. The 2011 NYTS used a three-stage cluster sampling procedure to generate a cross-sectional, nationally representative sample of students in grades 6–12 from all 50 states and the District of Columbia.

Out of the 214 schools selected, 178 (83.2%) participated; this resulted in a sample of 18,866 (87.4%) out of 21,584 students. In 2011, the overall response rate was 72.7% from 2000 to 2011, response rates ranged from 72.7% to 84.8%. Respondents were asked about their use of cigarettes, cigars (e.g., premium cigars, cigarillos, and "little cigars"), smokeless tobacco, pipes, bidis (small brown cigarettes wrapped in a leaf), and kreteks (clove cigarettes)† within the last 30 days. For each product, current use was defined as use on at least 1 of the past 30 days. Current tobacco use was defined as current use of any

* Additional information available at http://www.cdc.gov/tobacco/tobacco_control_programs/surveillance_evaluation/key_outcome/pdfs/frontmaterial.pdf.

† Under the Family Smoking Prevention and Tobacco Control Act, kreteks (clove cigarettes) are banned.

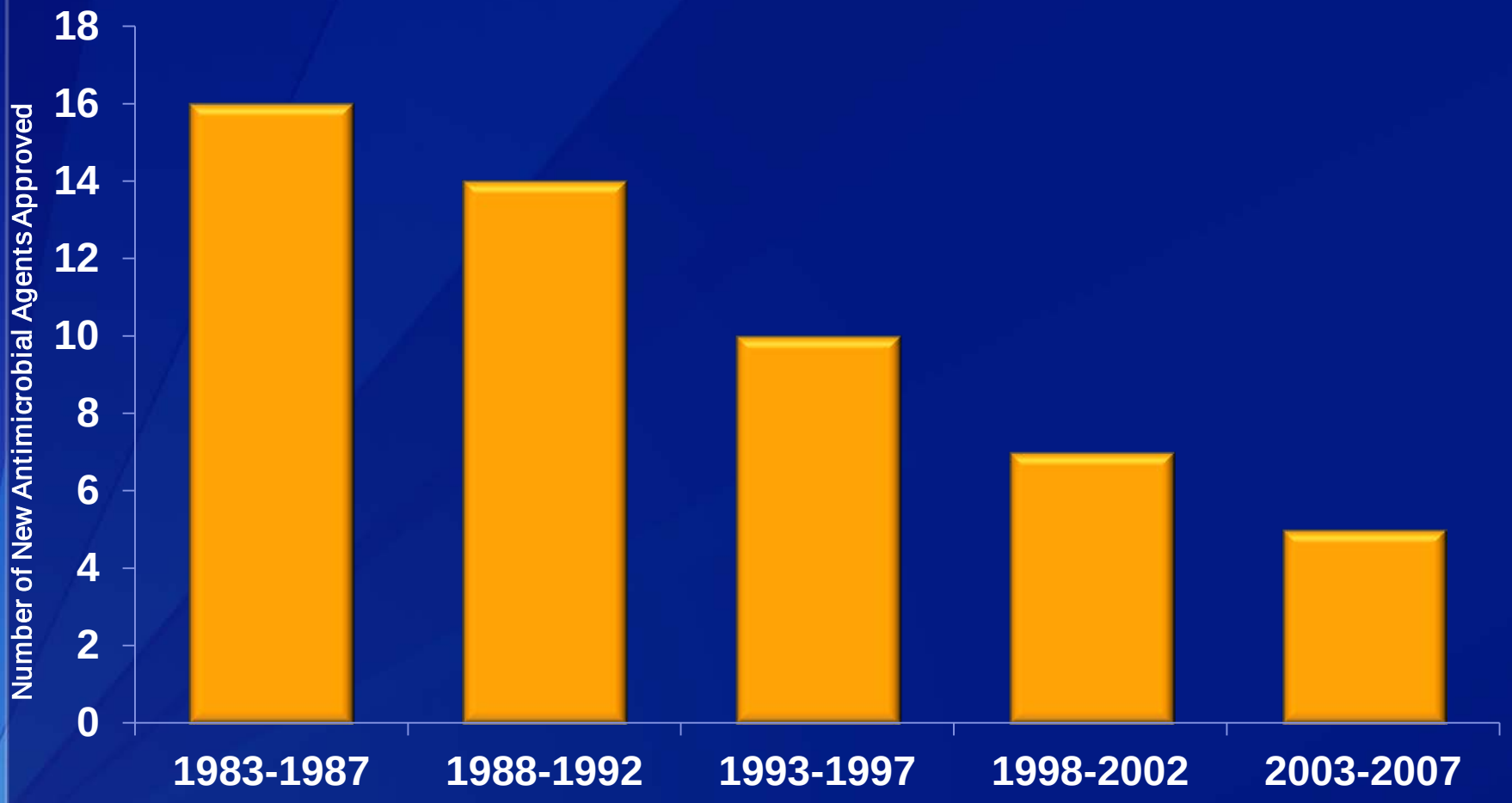
INSIDE

586 Interim Guidance for Clinicians Considering the Use of Preexposure Prophylaxis for the Prevention of HIV Infection in Heterosexually Active Adults
590 Update to CDC's *Sexually Transmitted Diseases Treatment Guidelines, 2010*: Oral Cephalosporins No Longer a Recommended Treatment for Gonococcal Infections
595 Vital Signs: Walking Among Adults — United States, 2005 and 2010
602 Announcement
603 QuickStats

Continuing Education examination available at http://www.cdc.gov/mmwr/cme/conted_info.html#weekly.

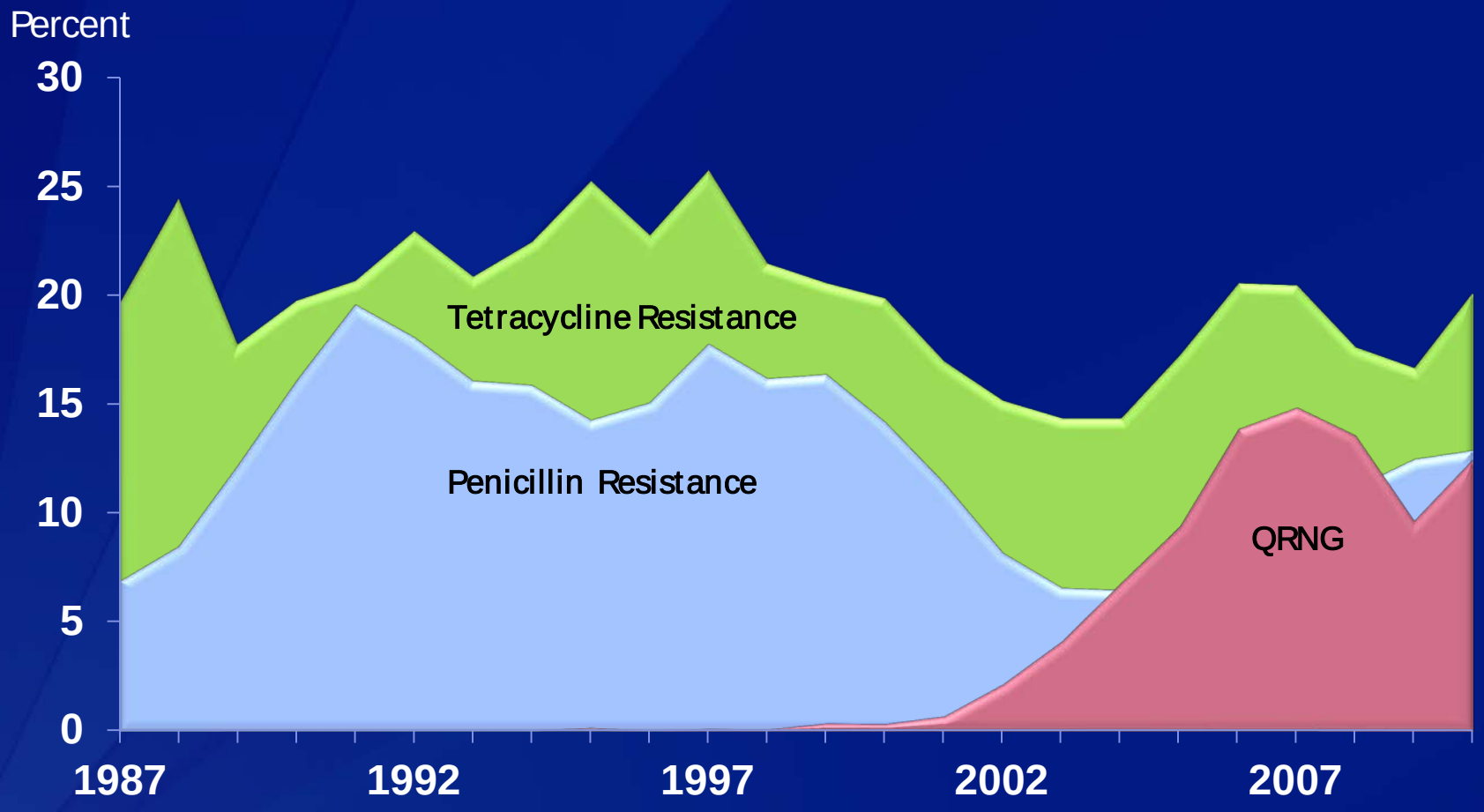
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

New Systemic Antibacterial Agents Approved by the FDA, 1983–2007



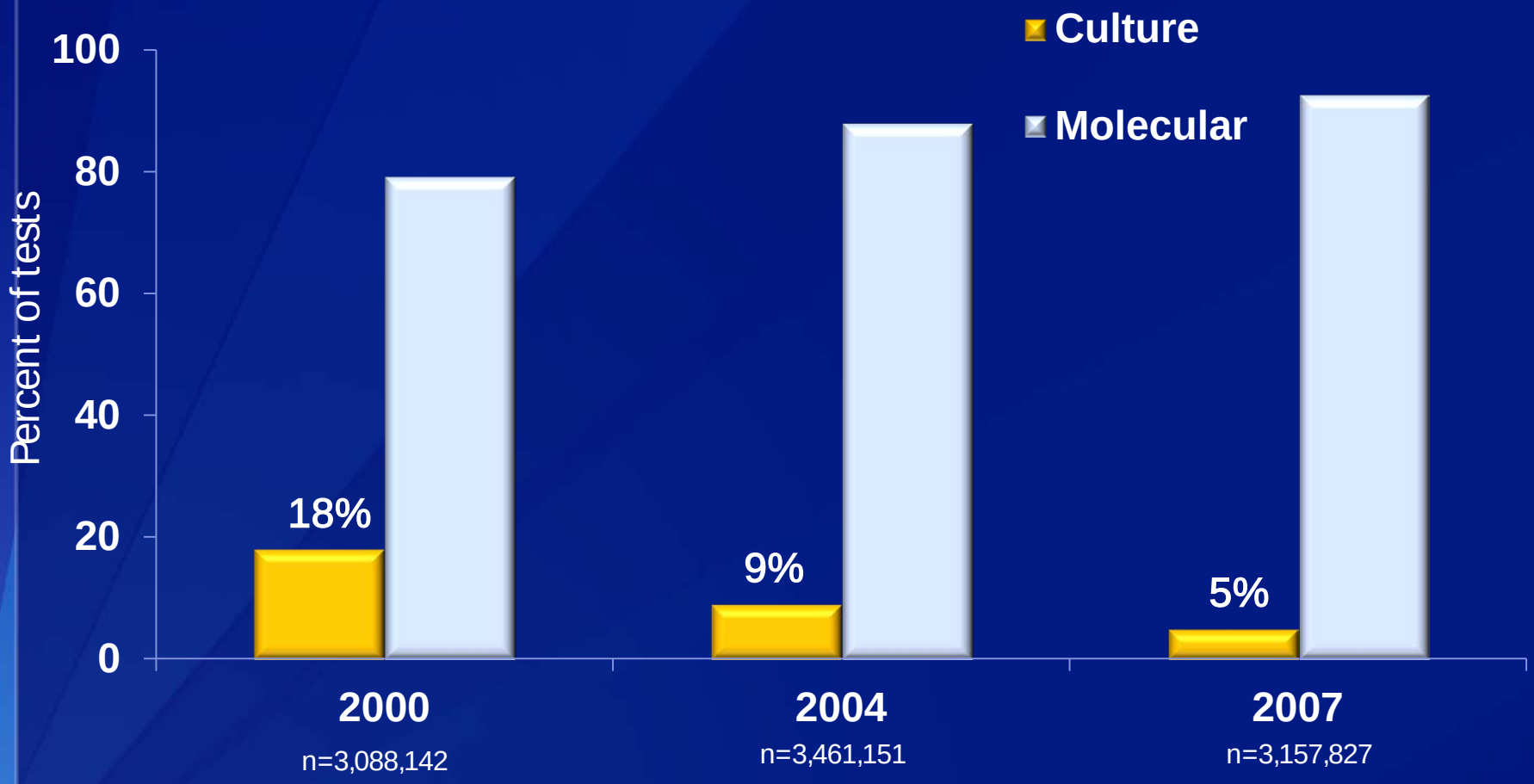
Spellberg B, Guidos R, Gilbert D et al. Clin Infect Dis 2008

Prevalence of Penicillin, Tetracycline and Fluoroquinolone Resistance, US, 1987–2010



Source: Gonococcal Isolate Surveillance Project (GISP)

Gonococcus Antimicrobial Susceptibility Testing U.S. Public Health Laboratories, 2000–2007



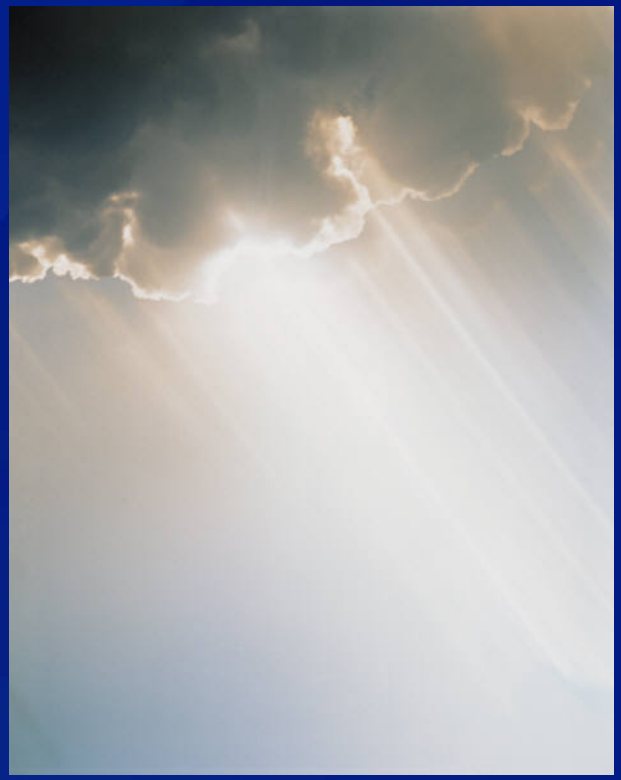
Dicker et al. STD 2004;31(5):259-264
Dicker et al. STD 2007; 34(1):41-46
http://www.cdc.gov/std/general/LabSurveyReport-2011.pdf .

Azithromycin Susceptibility

- In 2011, 0.3% isolates had elevated azithro MICs (≥2.0 µg/ml)
  - No clear temporal trends
- Macrolide resistance can emerge rapidly
- Have seen small number with reduced susceptibility/resistance in the US
  - San Diego: cluster of isolates from MSM with MICs 8–16
  - Hawaii: highly azithro-resistant infection (MIC > 512)
  - Portland: treatment failure after 2 g monotherapy (MICs 1, 8)

CDC. MMWR 2011
Katz AR et al. CID 2012
Soge O et al STD 2012

Yet, some recent cause for optimism



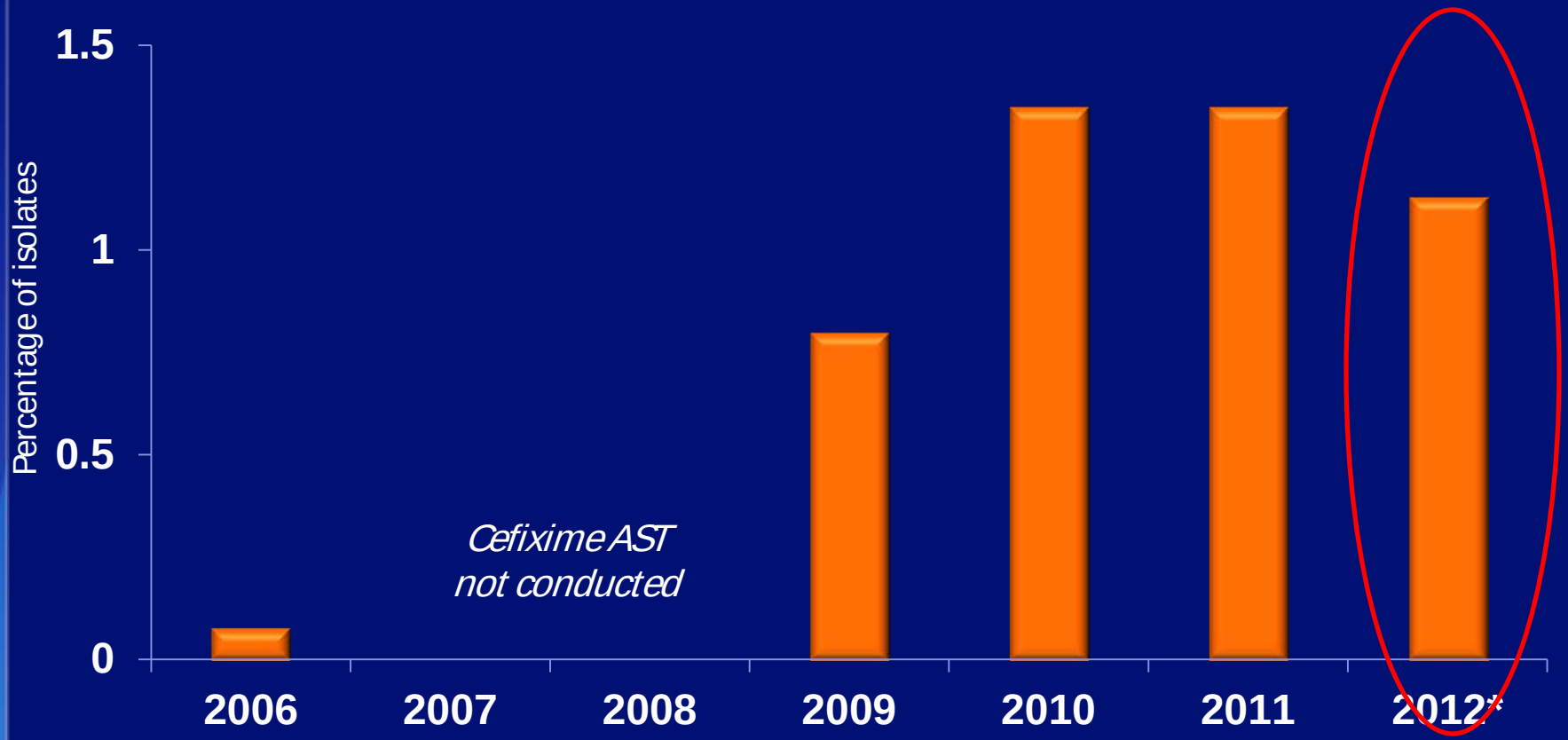
Recent developments

- No reported treatment failures yet in US
- Strains with elevated cephalosporin MICs do not appear to be more virulent or transmissible
- Heightened awareness
  - Media coverage (2011–present)
  - High level of awareness by public health STD programs
  - Increasing interest by drug developers
- GAIN Act (2012)
  - *N. gonorrhoeae* might be qualifying pathogen

GC Dual Therapy Clinical Trial for Salvage Therapy *(NCT00926796)*

- NIAID/NIH and CDC collaboration
- Investigating efficacy of 2 combinations for treatment of uncomplicated urogenital gonorrhea
  - Gentamicin 240 mg IM and Azithromycin 2 g po
  - Gemifloxacin 320 mg po and Azithromycin 2 g po
- Four clinical sites
  - San Francisco, CA
  - Birmingham, AL
  - Pittsburgh, PA
  - Los Angeles, CA
- Enrollment completed; data being analyzed

Proportion of GISP isolates with Elevated Cefixime MICs (≥0.25 µg/ml), 2006–2012*

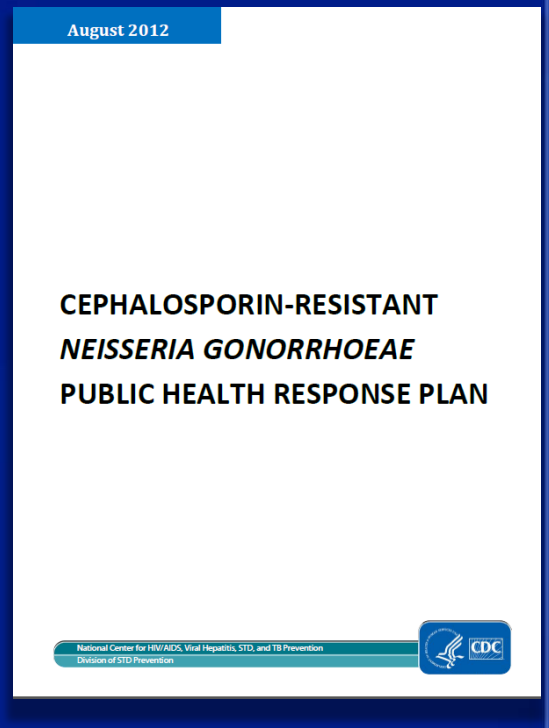


* Preliminary (Jan-June)

Source: Gonococcal Isolate Surveillance Project

Where do we go from here? (Short-term)

- **Surveillance**
  - GISP
  - Local GC detection & reporting
  - Enhanced local surveillance for GC AMR?
  - Clinician vigilance & reporting
- **Ability of labs to culture for GC**
- **Program preparedness and response**
- **Basic gonorrhea control**
- **Ensure appropriate clinical management**



Where do we go from here? (Longer-term)

- New antimicrobials or combinations
- New diagnostic approaches
  - Molecular detection of resistance determinants?
  - POC tests?
- Exploration of genome sequencing
- Vaccine?

Conclusions

- Emerging threat of cephalosporin-resistance *N. gonorrhoeae*
- Ceph R NG would severely complicate treatment
- Spread of resistance might be slowed by
  - Aggressive treatment
  - Prompt programmatic response
  - Driving down GC morbidity
- Local efforts are critical
- Preparedness now can enhance response later
- New treatment options urgently needed

Acknowledgements

CDC

- Hillard Weinstock
- Sarah Kidd
- John Papp
- David Trees
- Alesia Harvey
- Gail Bolan
- Kevin Pettus
- Samera Bowers
- Steve Shapiro

GISP Clinical Sites

- Englewood and Lakeview clinics

GISP PIs

- Ned Hook
- Olusegun (S.O.) Soge
- King Holmes
- Carlos del Rio
- Susan Harrington
- Susan Tanksley & Grace Kubin

Resources

www.cdc.gov/std

- CDC Cephalosporin-Resistant *Neisseria gonorrhoeae* Public Health Response Plan
- Updated gonorrhea treatment guidelines (MMWR, 2012)
- STD Surveillance Report, 2011 (contains aggregate GISP data)
- GISP home page (www.cdc.gov/std/gisp)
  - Annual site-specific profiles

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(404) 639-8659

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: http://www.cdc.gov

Percentage of Isolates with Elevated MICs or Resistance by Sex of Sex Partner, 2005–2010

Antibiotic	MSM n=8,117	MSW n=26,483	*p*
Ceftriaxone*	0.4	0.1	<0.01
Cefixime**	1.7	0.2	<0.01
Azithromycin†	0.9	0.2	<0.01
Tetracycline†	37.5	13.3	<0.01

* ≥0.125 μg/ml
** ≥ 0.25 μg/ml
† ≥ 2.0 μg/ml

Kirkcaldy RD et al. Annals Internal Medicine 2013

Gonorrhea—Rates by County, United States, 2011