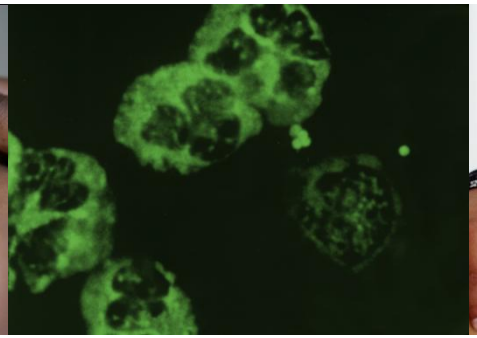
THE GROWING THREAT OF MULTIDRUG-RESISTANT GONORRHEA

Accessible version: https://youtu.be/rE2th3A0Oxs

- **Edward W. Hook, III, MD**
  University of Alabama, Birmingham
  Neisseria gonorrhoeae Infections and the Emergence of Antimicrobial Resistance
- **William Shafer, PhD**
  Emory University
  Molecular Basis of *N. gonorrhoeae* Resistance to Antimicrobials
- **Carolyn Deal, PhD**
  National Institute for Allergy and Infectious Disease, National Institutes of Health
  New Tools to Combat Multidrug Resistance
- **Robert D. Kirkcaldy, MD, MPH**
  National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC
  What Public Health Can Do Now and in the Future

Neisseria gonorrhoeae Infections and the Emergence of Antimicrobial Resistance

Edward W. Hook, III, MD

Professor of Medicine

University of Alabama at Birmingham

Jefferson County Department of Health

Birmingham, Alabama

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

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

Disclosure

- Receive grant support for clinical trials from Cepheid, Becton Dickinson, Roche Molecular GenProbe, and Cempra Pharmaceuticals
- Receive fees from MedHelp.org for serving as a content expert

Outline

- ***N. gonorrhoeae*** **(gonococcus) infections**
- **Evolution of antimicrobial treatment**
- **Surveillance for antimicrobial resistance**
- **Current treatment recommendations**
- **The emerging threat of cephalosporin-resistant *N. gonorrhoeae***

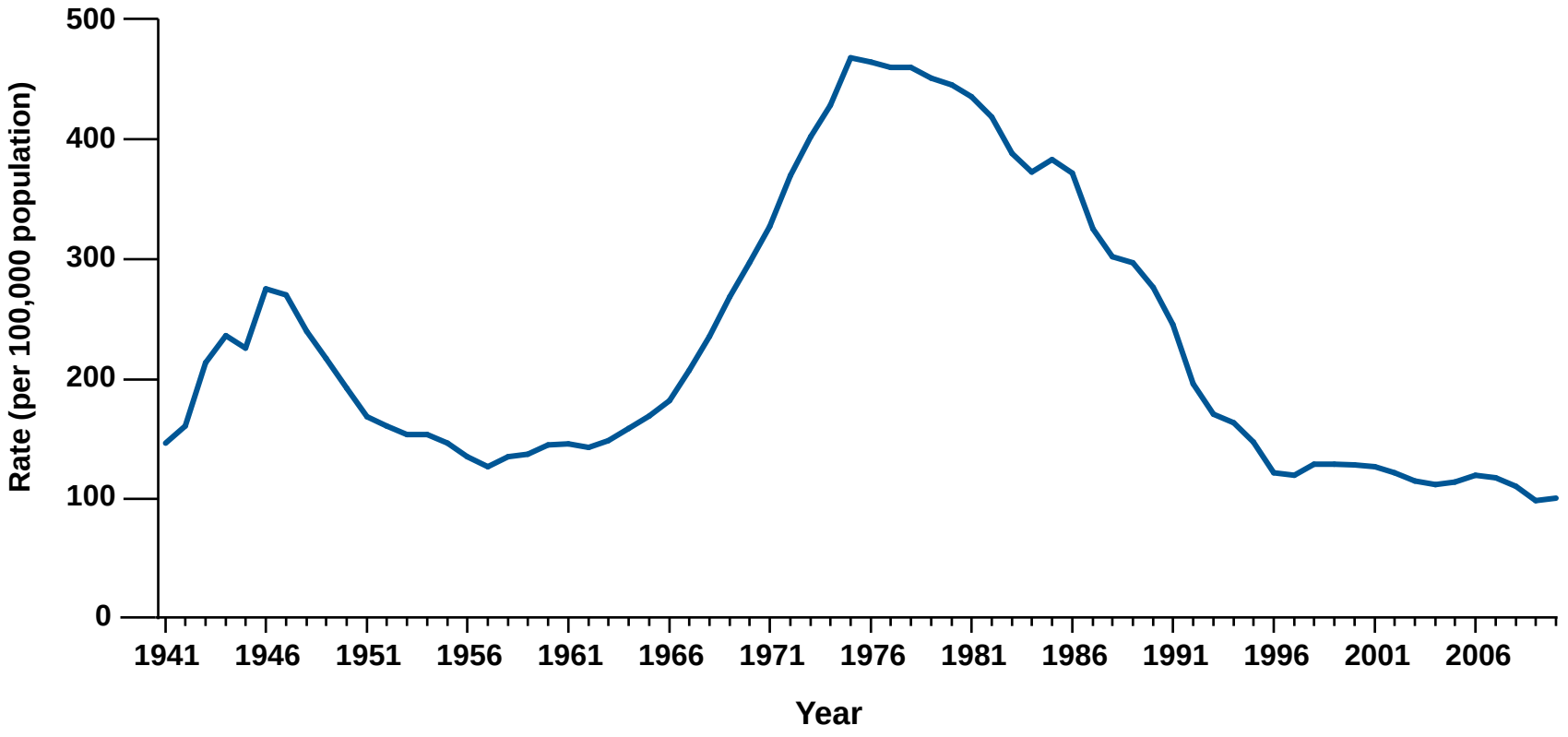
Burden of Gonococcal Disease in the United States

- **>300,000 cases reported in 2010**
  - Approximately 50% underestimation
- **The spectrum of gonococcal infections**
  - Uncomplicated local disease (urethrititis/cervicitis)
  - Complications disproportionately impact women

Complications of Untreated Gonorrhea

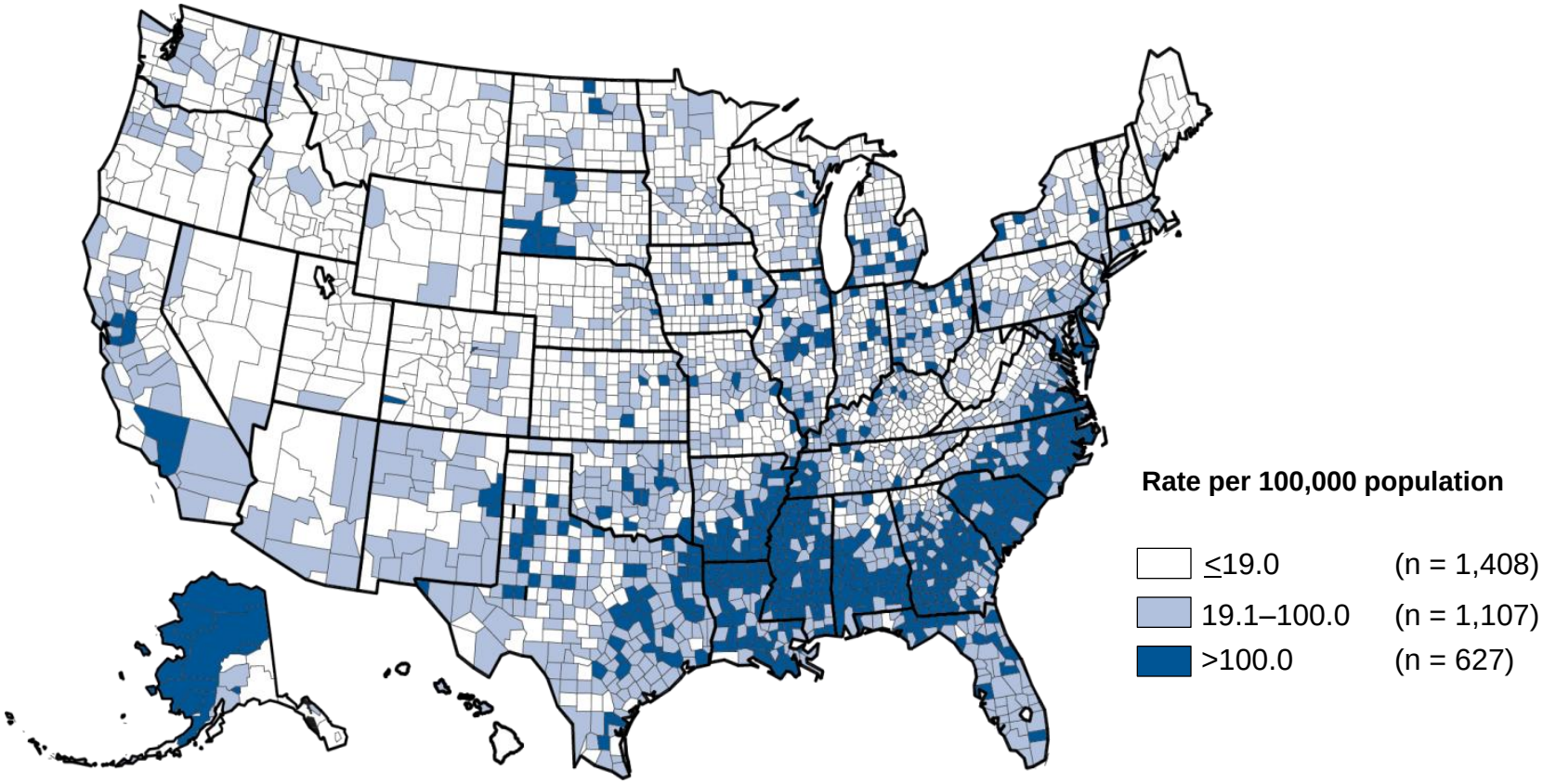
- **Pelvic inflammatory disease (PID) leads to scarring and**
  - Infertility
  - Ectopic pregnancy
  - Chronic abdominal pain
- **Disseminated gonococcal infection**
- **Childhood blindness (neonatal infection)**
- **Increased risk for HIV transmission and acquisition**

Gonorrhea Case Report Rates United States, 1941–2010



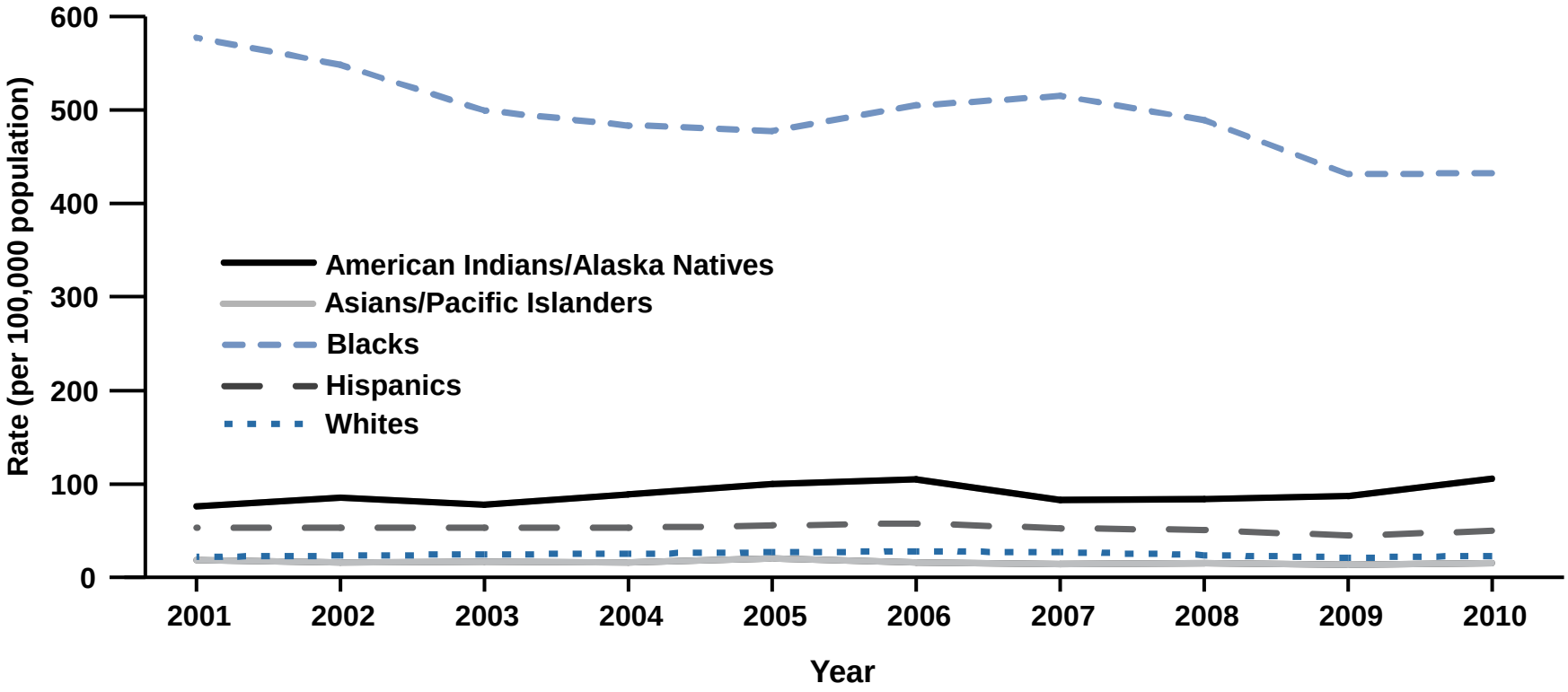
CDC. Sexually Transmitted Disease Surveillance 2010. Atlanta: U.S. Department of Health and Human Services; 2011

Gonorrhea Case Report Rates by County, 2010



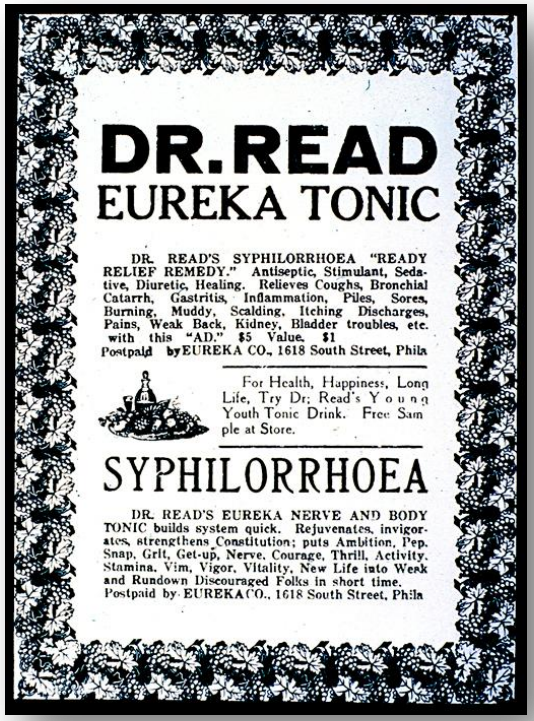
CDC. Sexually Transmitted Disease Surveillance 2010. Atlanta: U.S. Department of Health and Human Services;2011

Gonorrhea Case Report Rates by Race/Ethnicity, 2001–2010



CDC. Sexually Transmitted Disease Surveillance 2010. Atlanta: U.S. Department of Health and Human Services; 2011

Treatments for Gonorrhea Before 1937 Were Ineffective and/or Toxic



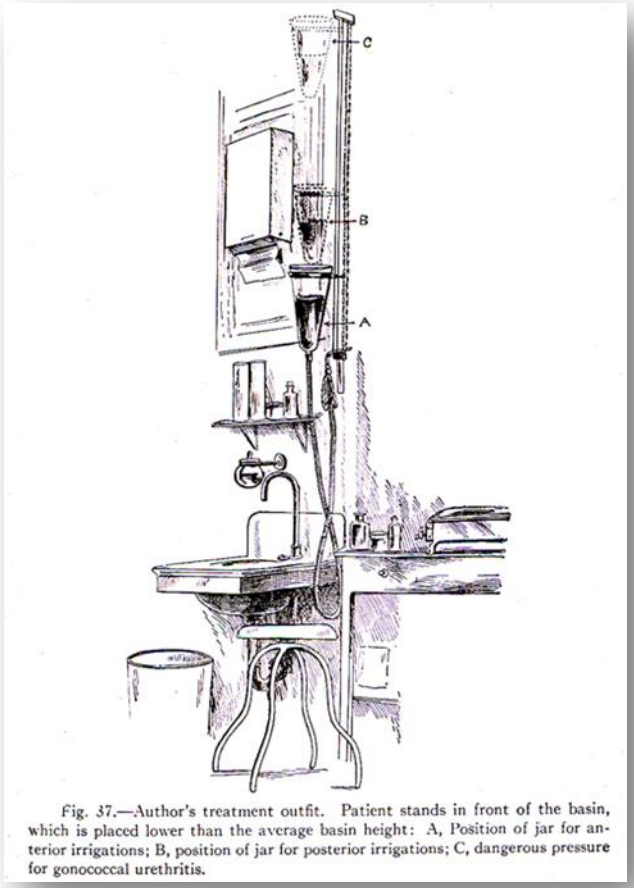


Fig. 37.—Author's treatment outfit. Patient stands in front of the basin, which is placed lower than the average basin height: A, Position of jar for anterior irrigations; B, position of jar for posterior irrigations; C, dangerous pressure for gonococcal urethritis.

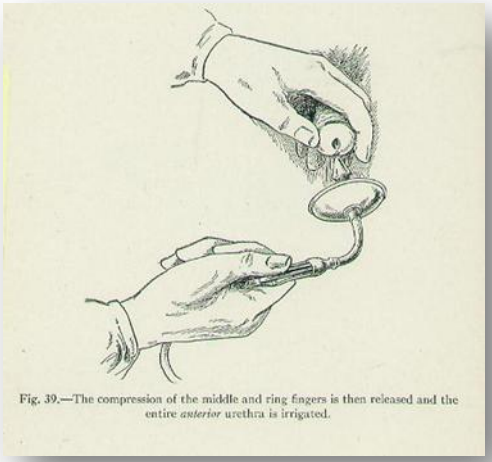


Fig. 39.—The compression of the middle and ring fingers is then released and the entire *anterior* urethra is irrigated.

Sulfonamides and Penicillin for Treatment of Gonorrhea

1937

- Sulfonamide therapy introduced

1940s

- Penicillin proved effective
- Sulfonamide resistance in 34% of patients

1972

- Penicillin dosage increased; probenicid added

1989

- Penicillin no longer drug of choice

Antimicrobials Previously Recommended for Treatment of Gonorrhea

- Sulfonamides
- Penicillin

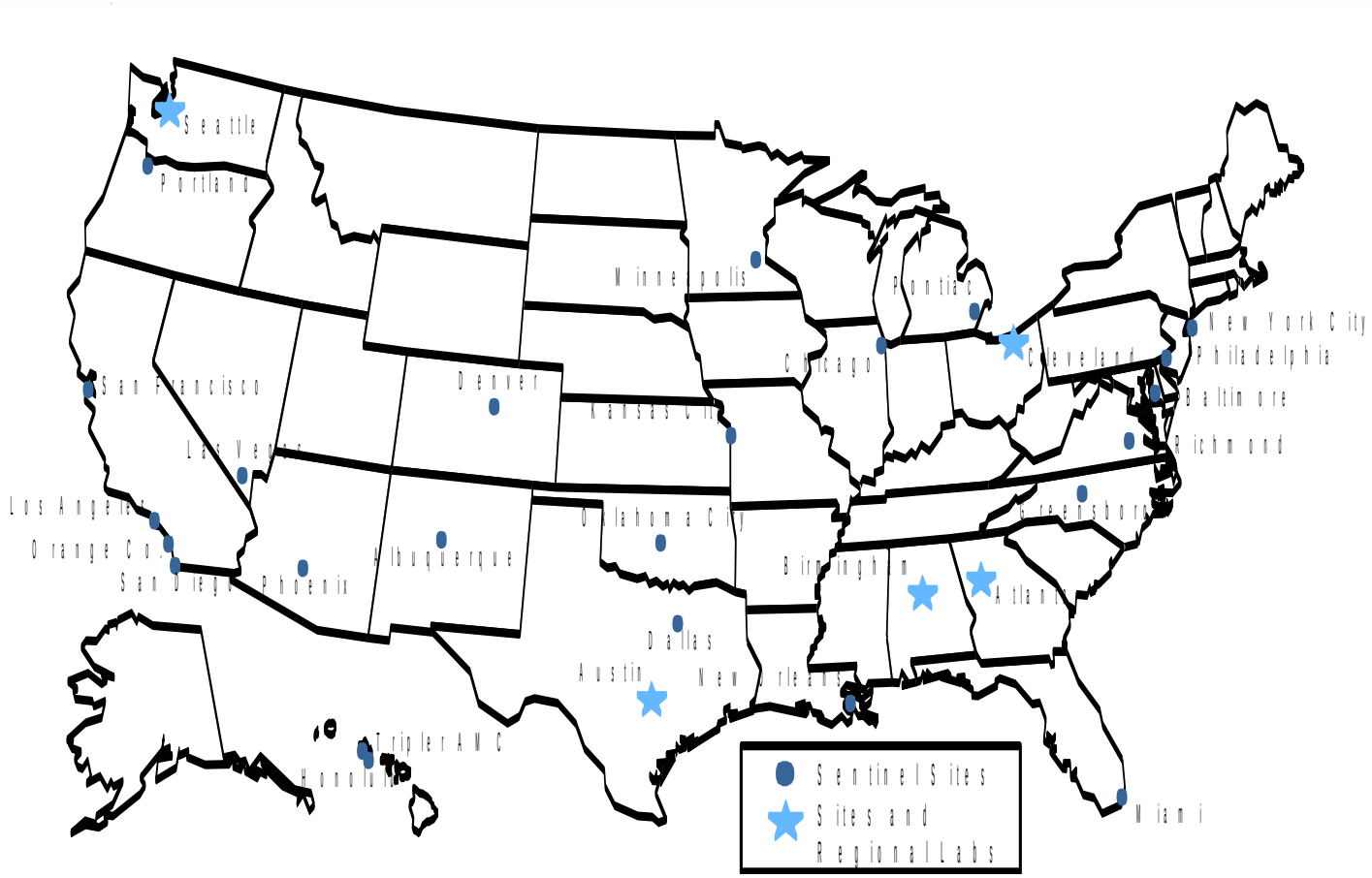
- Macrolides
- Tetracyclines
- Aminoglycosides
- Spectinomycin
- Fluoroquinolones

The Gonococcal Isolate Surveillance Project (GISP)

- **CDC-supported U.S. sentinel surveillance since 1987**
- **Monitors trends in *N. gonorrhoeae* susceptibility to antimicrobials**
- **30 STD clinic sites**
- **Methods**
  - Urethral *N. gonorrhoeae* isolates obtained from the first 25 men per site each month
  - Susceptibility testing conducted by 5 regional laboratories
    - Minimum inhibitory concentrations (MICs) by agar dilution
  - Confirmatory testing by CDC

NG , *Neisseria gonorrhoeae*
STD, Sexually transmitted diseases

GISP Sites and Regional Laboratories 2012



GISP, Gonococcal Isolate Surveillance Project

Antimicrobial Options for Treatment of Gonorrhea in 2006

ONE OF THE FOLLOWING

Ceftriaxone 125 mg IM

Cefixime 400 mg PO

Ciprofloxacin 500 mg PO*

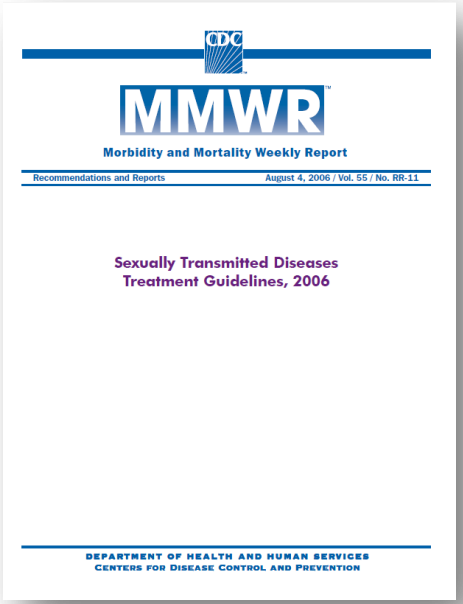
Ofloxacin 400 mg PO*

Levofloxacin 250 mg PO*

AND

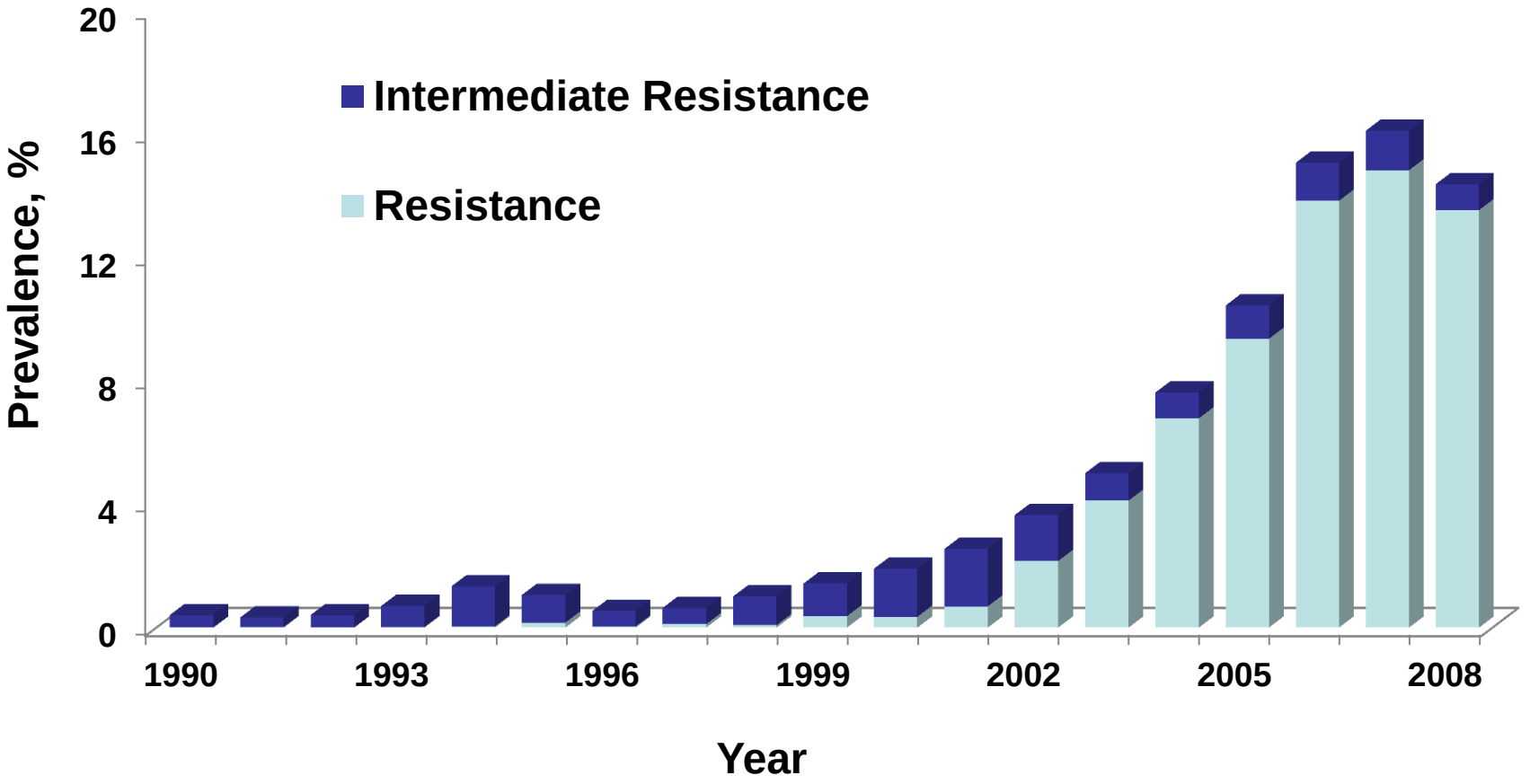
Azithromycin 1 g single dose or doxycycline 100 mg twice a day for 7 days *if chlamydial infection is not ruled out*

* Not for MSM or travelers



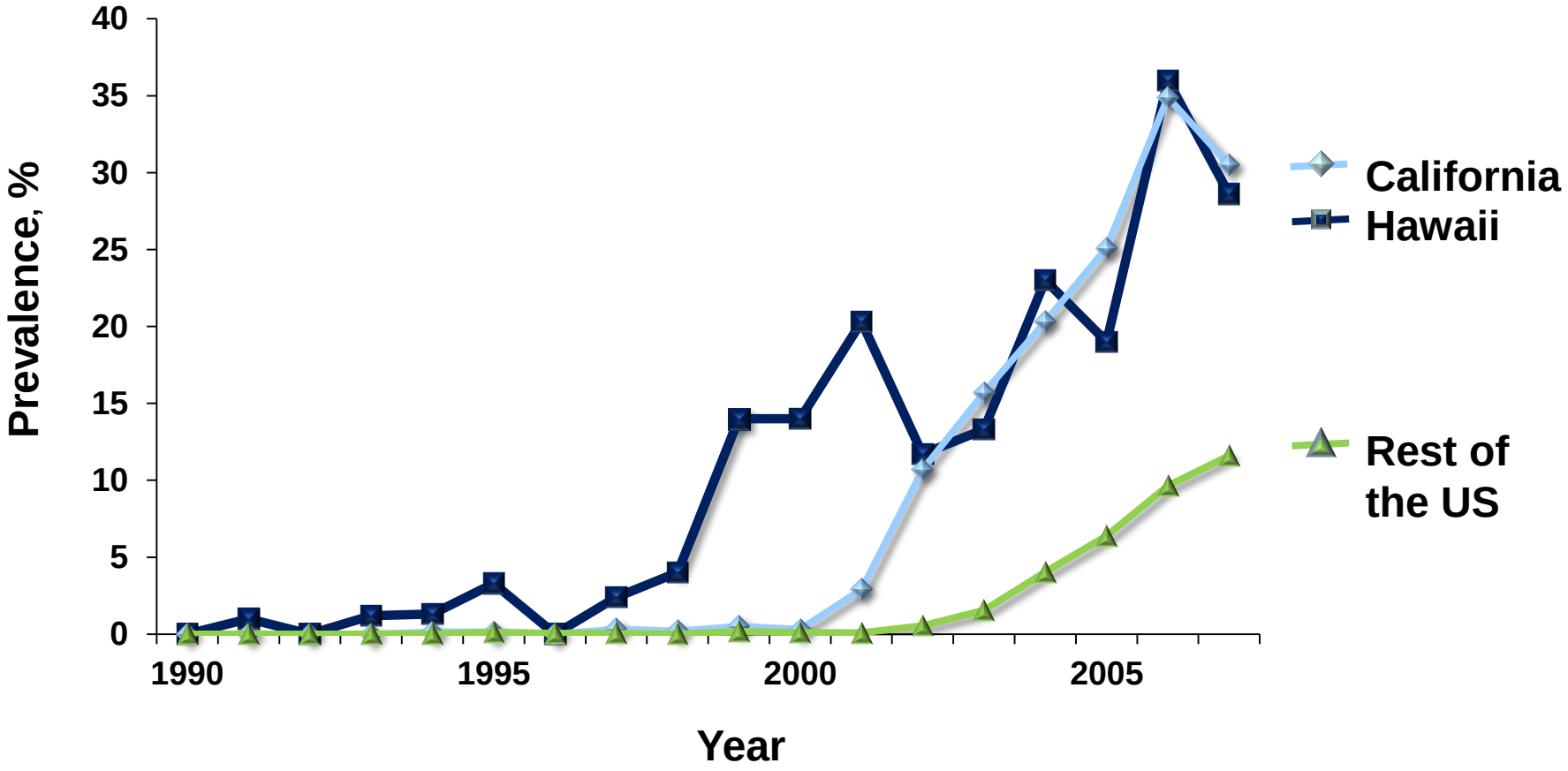
CDC. Sexually Transmitted Disease Treatment Guidelines, 2006. MMWR 2006; Volume 55 (RR-11)
IM, intramuscularly
PO, by mouth
MSM, men who have sex with men

Ciprofloxacin Resistance and Intermediate Resistance in *N. gonorrhoeae*, United States, 1990–2008



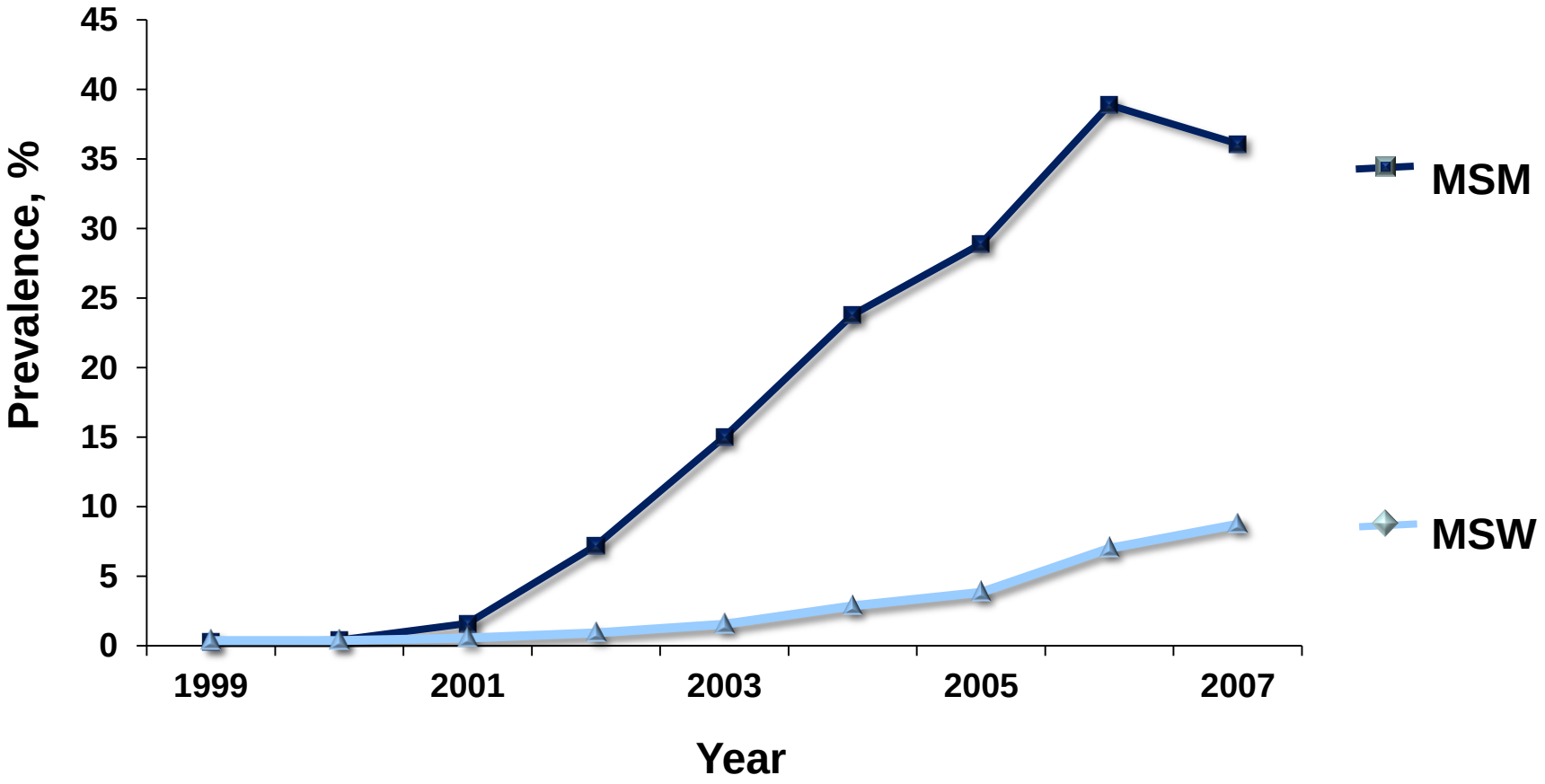
GISP, Gonococcal Isolate Surveillance Project, 1990–2008
Resistant isolates have ciprofloxacin MICs ≥1 µg/ml. Isolates with intermediate resistance have ciprofloxacin MICs of 0.125 - 0.5 µg/ml
Susceptibility to ciprofloxacin was first measured in GISP in 1990

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 Sex 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

Changes in Gonorrhea Treatment, 2007

ONE OF THE FOLLOWING

Ceftriaxone 125 mg IM

Cefixime 400 mg PO

~~**Ciprofloxacin 500 mg PO***~~

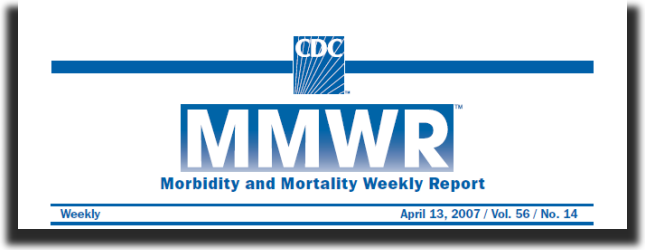
~~**Ofloxacin 400 mg PO***~~

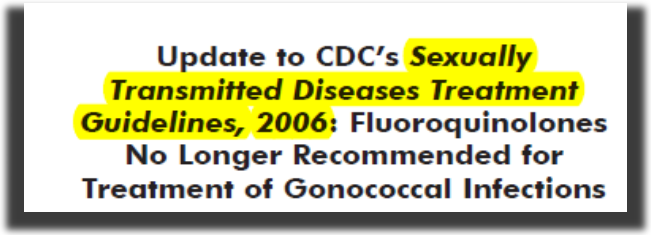
~~**Levofloxacin 250 mg PO***~~

AND

Azithromycin 1 g single dose or doxycycline 100 mg twice a day for 7 days
if chlamydial infection is not ruled out

* Not for MSM or travelers





CDC. Sexually Transmitted Disease Treatment Guidelines, 2006. MMWR 2006; Volume 55 (RR-11)
IM, intramuscularly
PO, by mouth
MSM, men who have sex with men

Antimicrobial Options for Treatment of Gonorrhea, 2010

Ceftriaxone 250 mg IM

OR

Cefixime 400 mg PO

AND

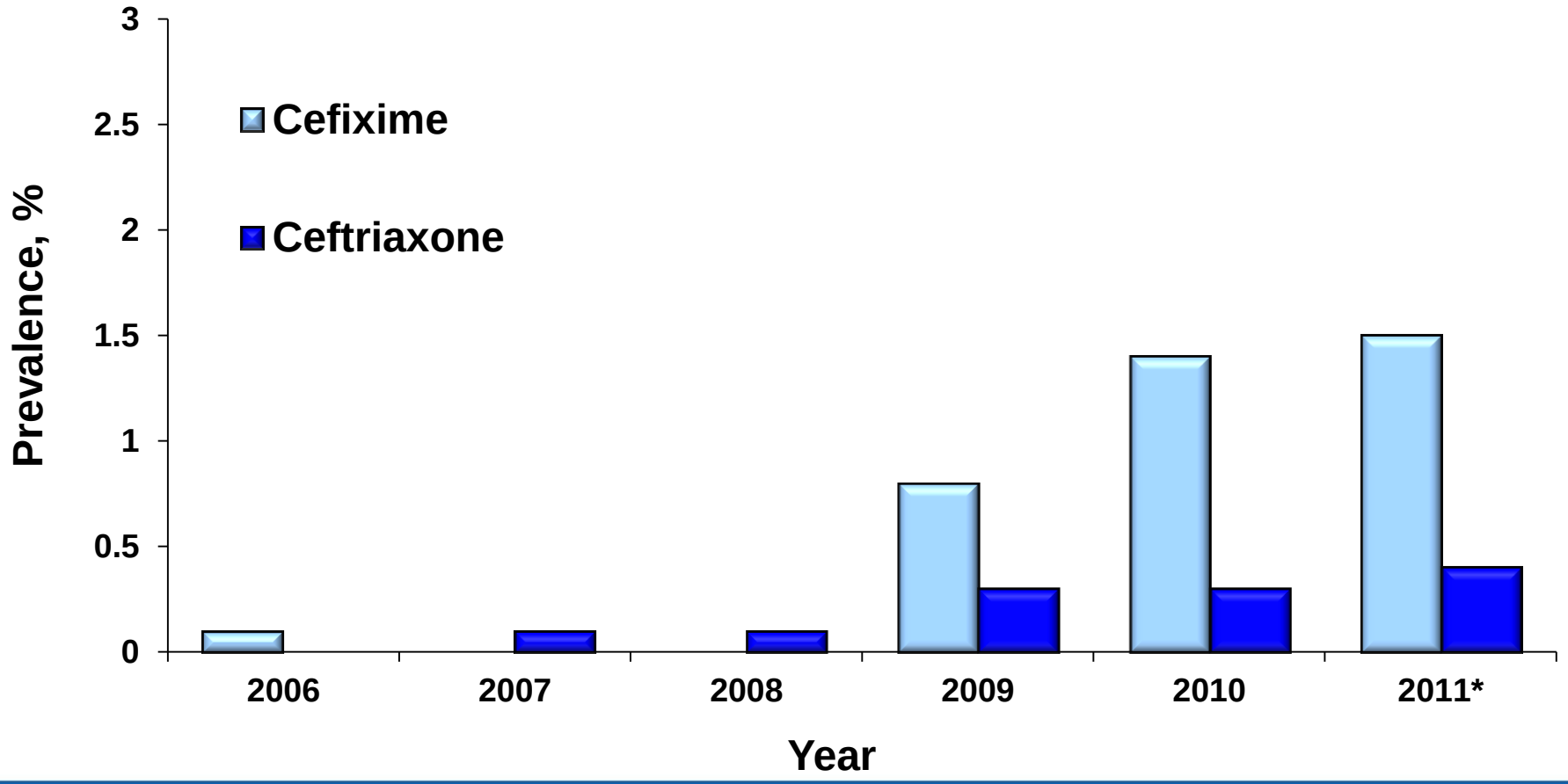
Azithromycin 1 g single dose

OR

Doxycycline 100 mg twice daily for 7 days

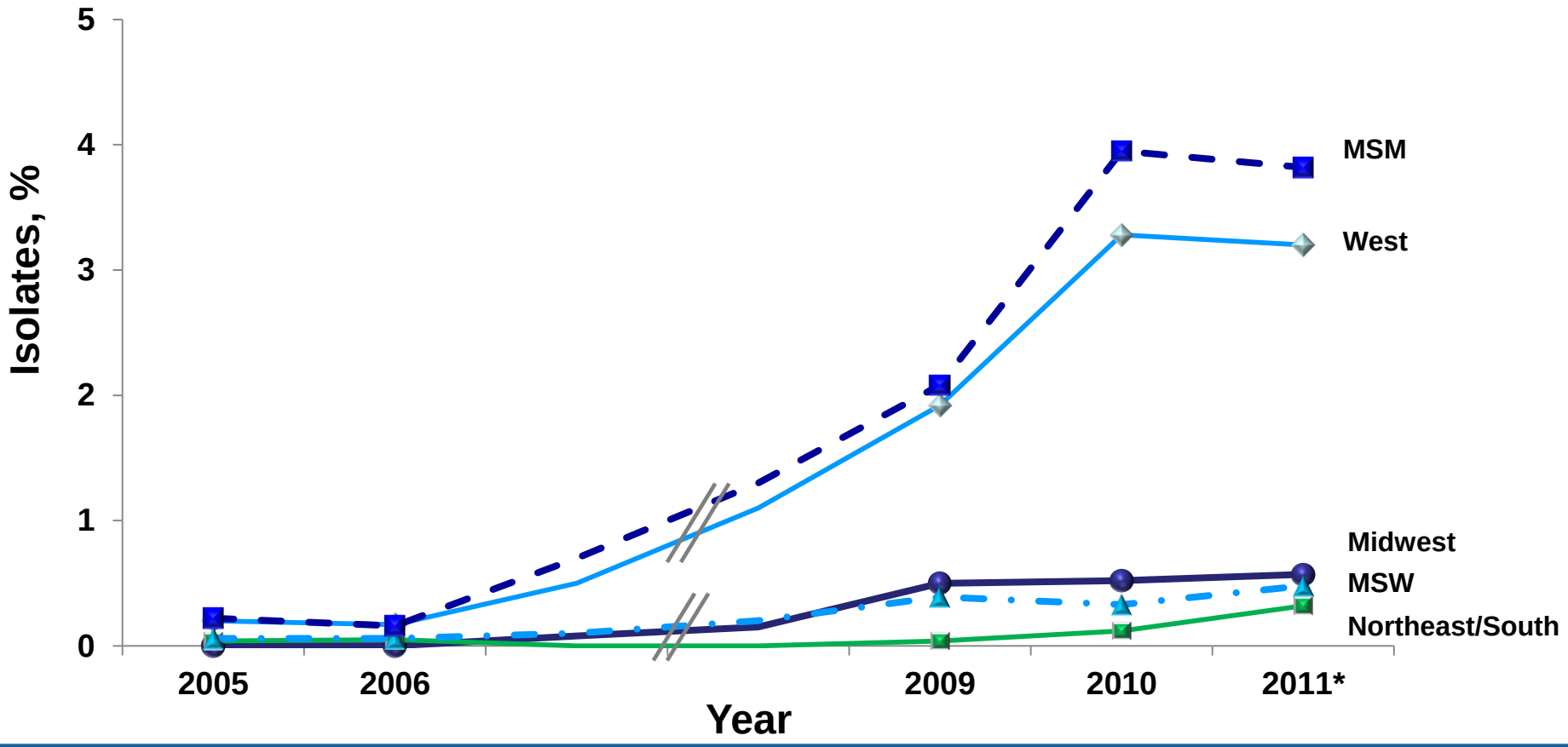
CDC. Sexually Transmitted Disease Treatment Guidelines, 2010. MMWR 2010; Volume 59 (RR-12)
IM, intramuscularly
PO, by mouth

Elevated Cefixime and Ceftriaxone MICs in *N. gonorrhoeae*



GISP, Gonococcal Isolate Surveillance Project
* Cefiixime susceptibility not tested in 2007 and 2008
Elevated cefixime MICs ≥ 0.25 µg/ml; elevated ceftriaxone MICs ≥ 0.125 g/ml
MIC, minimum inhibitory concentration

Percentage of Gonococcal Isolates with Elevated Cefixime MICs (≥0.25 µg/ml), 2005–2011*

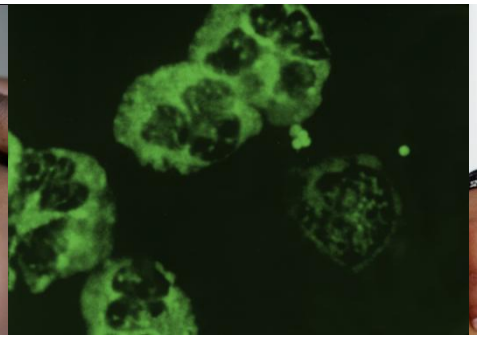


Gonococcal Isolate Surveillance Project, January-August, 2011
Susceptibility to cefixime not tested during 2007–2008
MSM, men who have sex with men; MSW = men who have sex exclusively with women
MIC, minimum inhibitory concentration

Possible Changes in Treatment Recommendations

- **Recommended**
  - Ceftriaxone 250 mg
    PLUS
  - Azithromycin 1 g single dose or doxycycline 100 mg twice a day for 7 days
- **Oral therapy as alternative ("second-line")**

Molecular Basis of *N. gonorrhoeae* Resistance to Antimicrobials

William Shafer, PhD

Professor of Microbiology and Immunology

Emory University

Atlanta, Georgia

Outline

- Resistance mechanisms expressed by the gonococcus
- Culture-based antimicrobial susceptibility testing
- Detection of antimicrobial resistance markers using molecular assays

Genetic Basis of Antimicrobial Resistance of the Gonococcus

- **The gonococcus mutates rapidly**
- **Resistance results from mutations and acquisition of new genes**
- **Resistance is promoted by selection pressure**
  - Antimicrobials kill susceptible strains, but allow resistant strains to survive
  - Resistance genes then spread to other strains of the gonococcus

Resistance of Gonococci to Penicillin and Ciprofloxacin

- **Importance of mechanisms by which the gonococcus developed resistance to penicillin and ciprofloxacin**
  - Persistence of resistance genes
  - Some of the same systems are making the gonococcus less susceptible to ceftriaxone and cefixime, which are the main antimicrobials used to cure gonorrhea today

Genetic Basis of Penicillin Resistance

- **Low level resistance is the result of multiple mutations that**
  - Reduce penicillin influx (entry into the bacterial cell)
  - Increase penicillin efflux (exit from the bacterial cell)
  - Reduce ability of penicillin to bind to enzymes that synthesize the cell wall (penicillin binding proteins 1 and 2: PBP 1 and PBP 2)
- **High level resistance identified in 1976**
  - Acquisition of gene that encodes beta lactamase (enzyme that destroys penicillin)

By 1987, penicillin was discontinued

Genetic Basis of Ciprofloxacin Resistance

- **Ciprofloxacin binds to bacterial enzymes involved in maintaining DNA structures necessary for viability of gonococcus**
  - The genes that code for these enzymes are called *gyrA* and *parC*
- **Early 1990s: Resistance developed first by a mutation in *gyrA* and then *parC***
- **Intermediate resistance: Mutation in *gyrA***
- **High level resistance: Mutations in *gyrA* and *parC***

By 2007, ciprofloxacin was no longer recommended for treatment of gonorrhea

Emergence of Resistance to Cephalosporins

- **1980s: Cephalosporins (ceftriaxone and cefixime) were found to kill gonococci by a mechanism similar to that of penicillin**
- **2007: Cephalosporins became the antimicrobials of choice for empiric treatment of gonorrhea**
- **2009: Gonococcus began showing reduced susceptibility to cephalosporins due to 2 mutations**
  - Acquired a new *penA* gene that encodes PBP-2 from other bacteria
    - Remodeled PBP-2 has a lower affinity for penicillin and cephalosporins
  - Overproduction of an efflux pump that exports antimicrobials, including penicillin and ceftriaxone

PBP, penicillin binding protein

The Importance of the *mtrCDE* Efflux Pump

- Removes hydrophobic molecules from bacterial cell
- Needed for sustained lower genital infection in mice
- Confers bacterial protection against host innate immunity system that consists of antimicrobial peptides and other compounds that bathe mucosal surfaces

Enhanced pump gene expression contributes to penicillin resistance, decreased ceftriaxone susceptibility, and resistance to innate host defenses

Jerse AE, et al. Infect Immun 2003; 71(10):5576-82
Shafer WM et al. PNAS 1998;95(4):1829-33
Veal WL et al J Bact 2002;184(20):5619-24

Increased Expression of the MtrCDE Efflux Pump and Decreased Antibiotic Susceptibility

- **Mutations in genes that normally repress pump genes**
- **High level resistance to antimicrobials**
  - Single nucleotide change near the promoter responsible for pump gene expression
  - Detected in clinical gonococcus isolates with decreased susceptibility to ceftriaxone

Genetic Basis for Persistence of Antimicrobial Resistance in the Gonococcus

- **Resistance persists even after antimicrobial is no longer used for treatment of gonorrhea**
- **Hypothesis**
  - Resistance mutation provides “fitness advantage” even without selection pressure

Conducted experiments with infected female mice to study survival and fitness of gonococci that overexpress the pump or are resistant to ciprofloxacin*

*Collaboration with Dr. A Jerse, Uniformed Services University of the Health Sciences

Antimicrobial Resistance Systems Can Increase Fitness During Infection

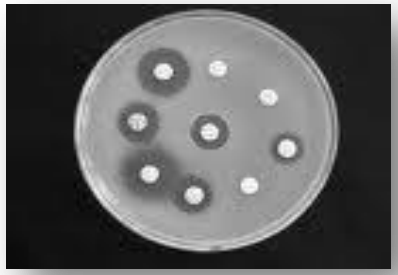
- **Overexpression of the efflux pump**
  - Increased fitness: Competitive Index (CI) of 100-1000
- **Mutation in *gyrA:* Intermediate resistance to ciprofloxacin**
  - Increased fitness: CI of 50
- **Mutations in both *gyrA* and *parC*: High level ciprofloxacin resistance**
  - Slightly decreased fitness: CI of 0.5
- **Mutation that results in overexpression of the efflux pump and mutations in *gyrA* and *parC*:**
  - Increased fitness: CI of 50

Implications of Survival Advantage of Resistant Gonococcus Strains

- Mutations conferring resistance can actually improve survival of bacteria, even without antimicrobial use
- Resistance mutations can persist among bacteria
- Previously recommended antimicrobials cannot be reintroduced for routine use

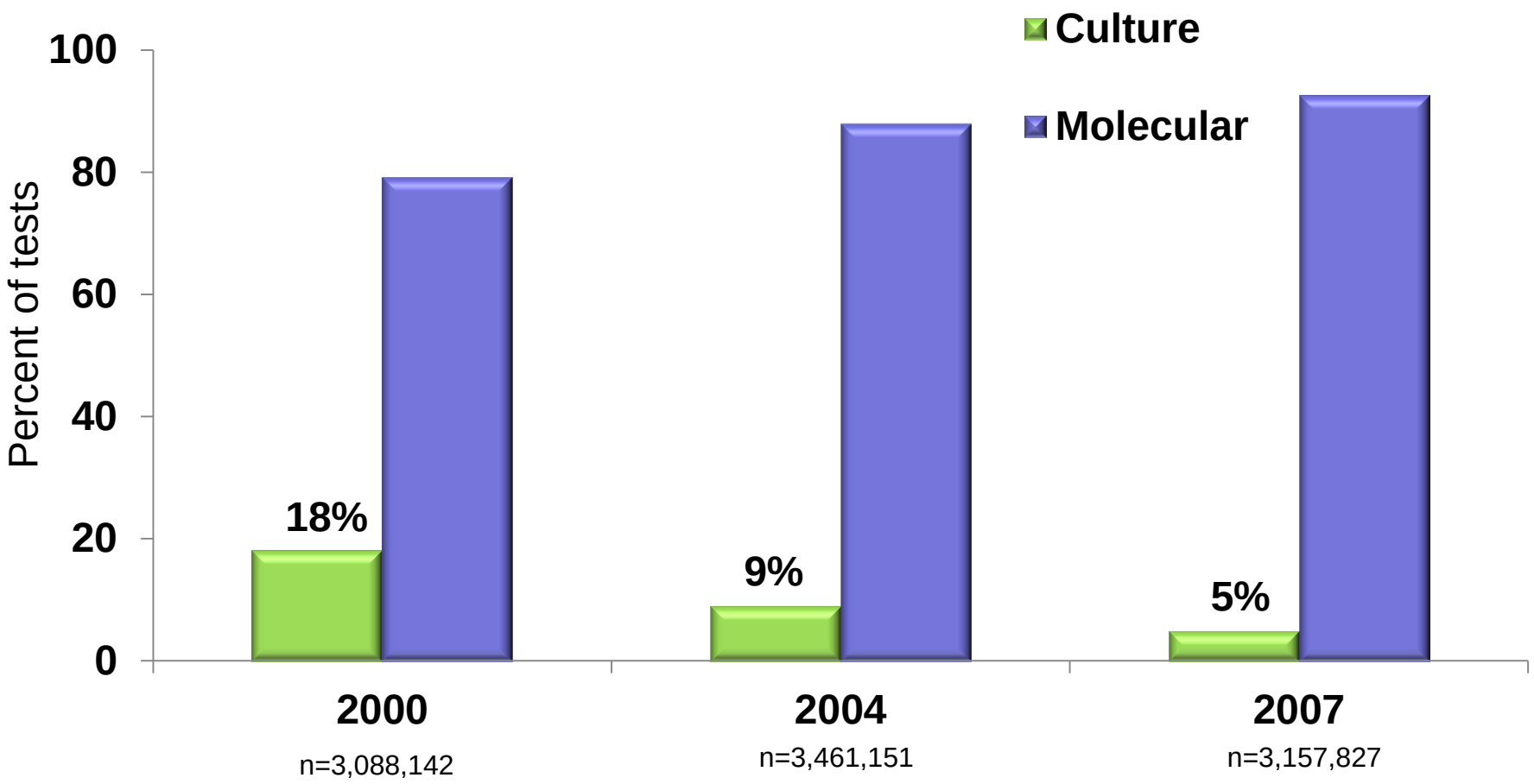
Antimicrobial Susceptibility Testing

- **Laboratory testing to detect whether antimicrobials can kill a certain strain and at what antimicrobial concentration**
  - Disk diffusion, Etest, Agar dilution
- **Requires culturing live organisms**
  - The gonococcus is fragile and difficult to grow
- **Critical for detection and monitoring of resistance**



If a patient fails cephalosporin therapy, culture and antimicrobial susceptibility testing should be done so appropriate antimicrobial therapy can be instituted

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

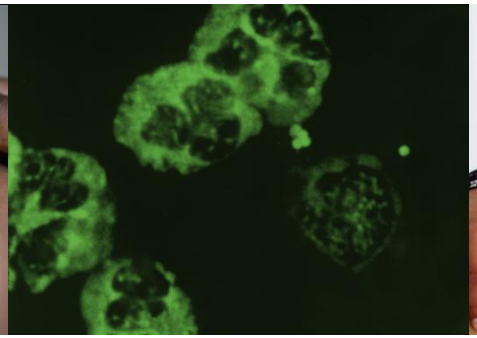
Molecular Assays for Detection of Resistance Markers in Gonococci

- **For clinical diagnosis of gonorrhea**
  - Nucleic Acid Amplification Tests (NAATS) have largely replaced culture
  - Highly sensitive, convenient, and noninvasive
- **For detection of known resistance mutations**
  - Not yet available, but scientists are working to develop them

Summary

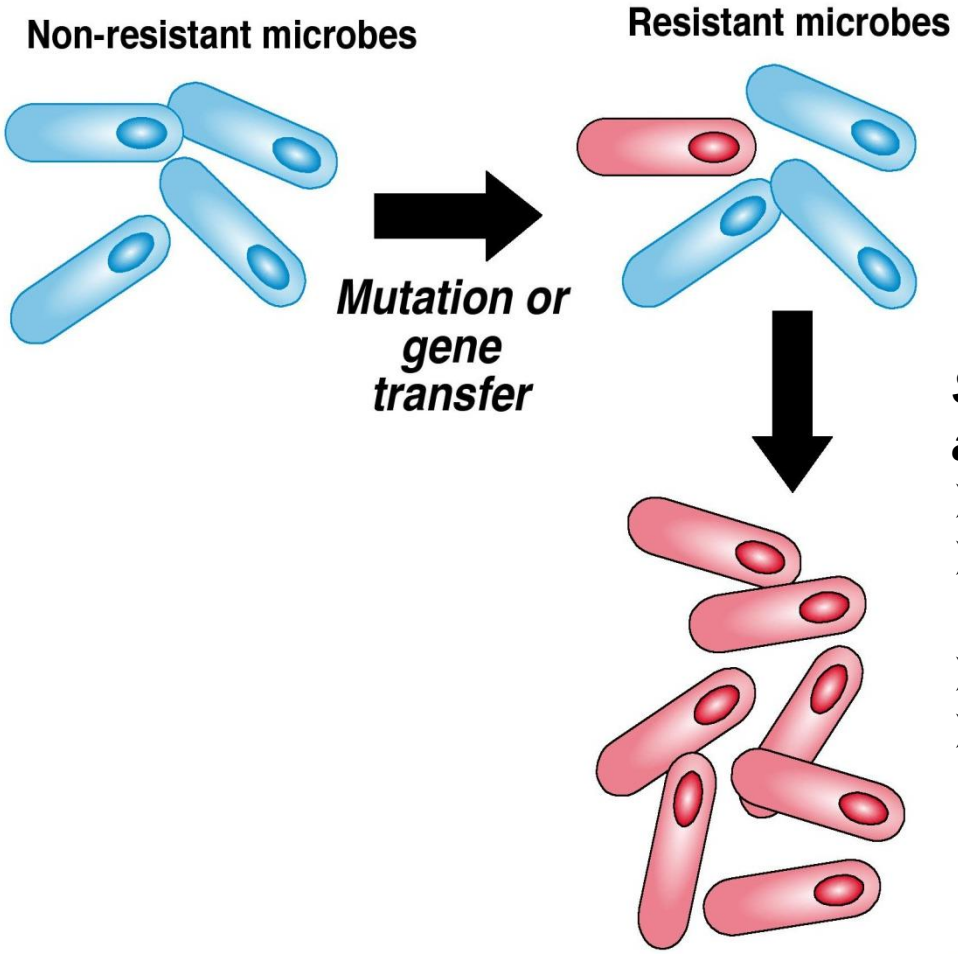
- **The gonococcus mutates rapidly**
  - Can acquire resistance genes from other bacteria
  - Genetic changes can spread among strains of the gonococcus
- **Resistance mutations can persist even when the antimicrobials are no longer routinely prescribed**
- **Declining laboratory capacity to culture gonococci hinder detection and response to cephalosporin resistance and other antimicrobials used in the future**
- **Molecular tests can help in surveillance, but cannot now replace culture-based testing for resistance**

New Tools to Combat Multidrug Resistance

Carolyn Deal, PhD
Chief, Sexually Transmitted Diseases Branch
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Development of Antimicrobial Resistance



Selective pressure by use of antimicrobial drugs

- **Overprescribing by physicians**
- **Use of broad-spectrum vs. narrow-spectrum drugs**
- **Noncompliance by patients**
- **Over-the-counter availability**

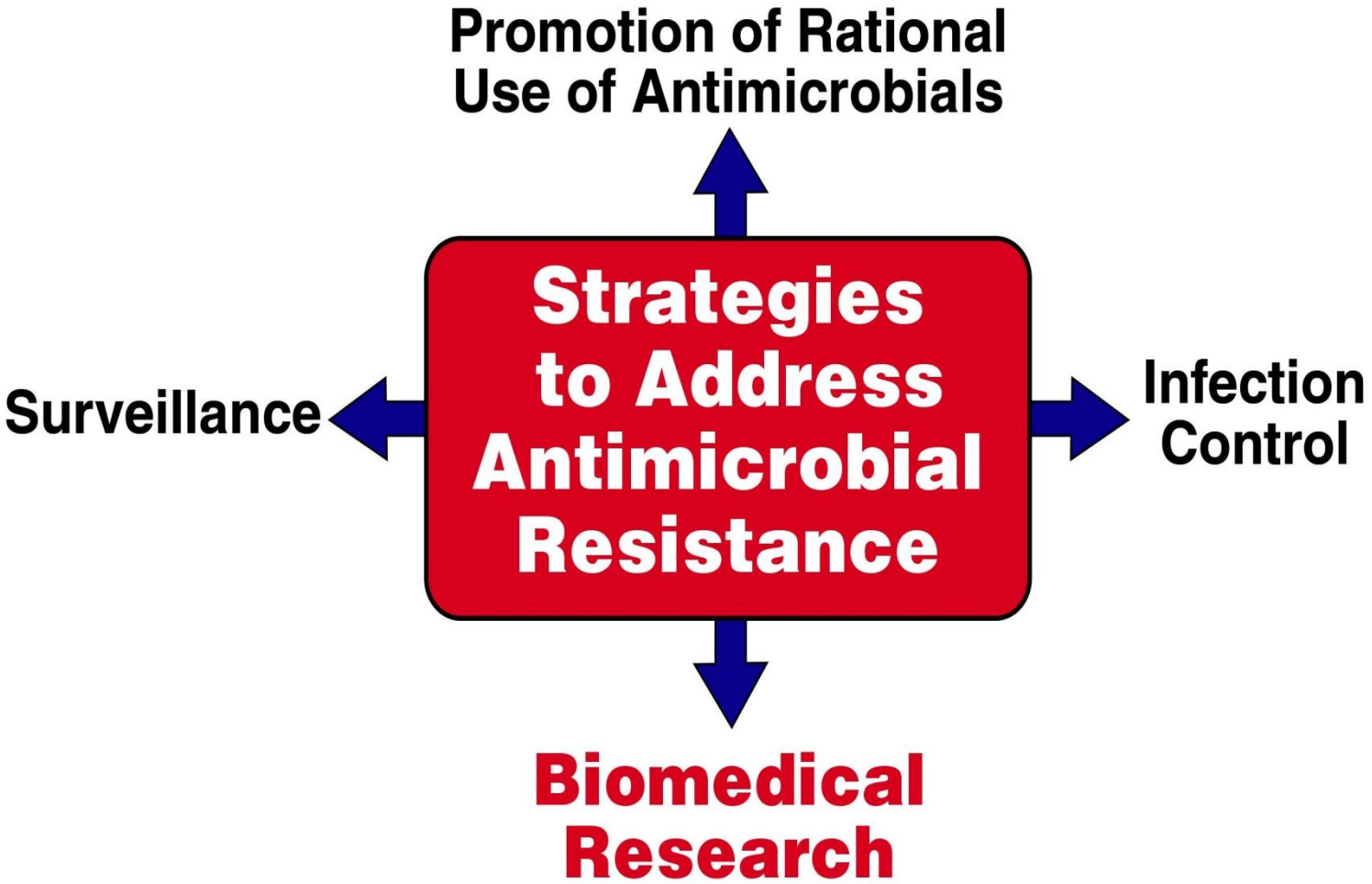
Source: AS Fauci, NIAID Director

Resistant Bacteria: Here and Abroad

- **Hospital pathogens**
  - Vancomycin-Resistant Enterococci (VRE)
  - Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - ESBL-producing *Enterobacteriaceae* (*E. coli*, *Klebsiella, Enterobacter*)
  - *Acinetobacter baumanii*
  - *Pseudomonas aeruginosa*
  - *Clostridium difficile*
- **Respiratory pathogens**
  - *Streptococcus pneumoniae,* MDR/XDR TB
- **Sexually transmitted pathogens**
  - *Neisseria gonorrhoeae*

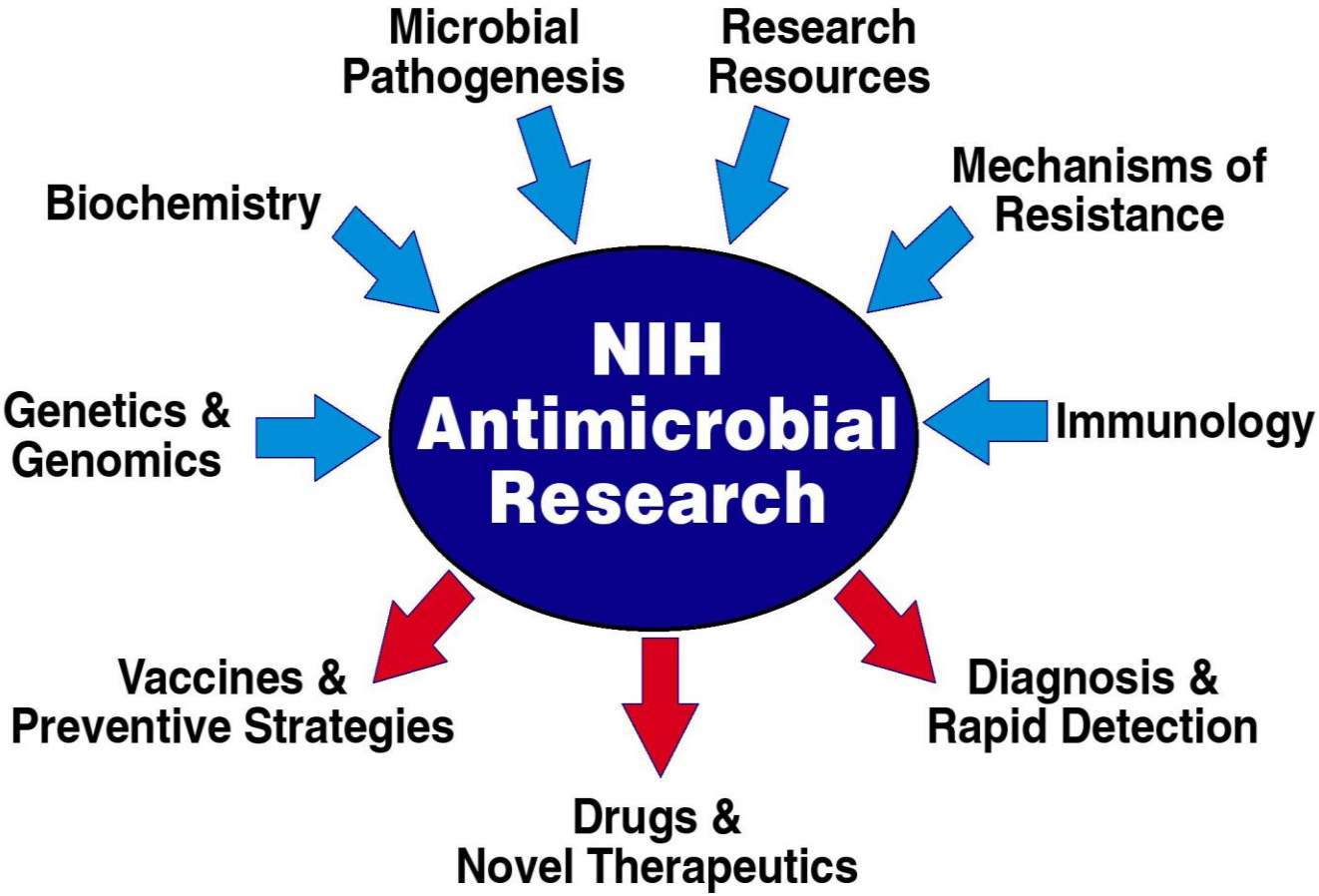
Klevens RM et al. JAMA 2007; 298(15):1733; Schwaber MJ et al. AAC 2006; 50:1257-62
Elemam, et al.. CID 2009; 49; 271-4.; Hidron AI et al. Infectin Control and Hospital Epidemiology. 2008; 29(11)996-1011
Tapsall J. Expert Review of Anti-infective Therapy. 2006; 4(4) 619

National Institute of Allergy and Infectious Diseases Research Agenda



Peters, NK; et al. J Infect Dis. 2008 Apr 15; 197(8): 1087-93

Strategy: Biomedical Research



Source: AS Fauci, NIAID Director

NIAID Sponsored Gonococcal Research

- **Current support for 137 research grants on gonorrhea**
- **Basic research**
  - Bacterial pathogenesis
  - Molecular basis of antigenic variation
  - Immunologic response to infection
- **Translational research**
  - Identifying vaccine candidates
  - Development of new diagnostics
  - Identifying targets for antimicrobial development

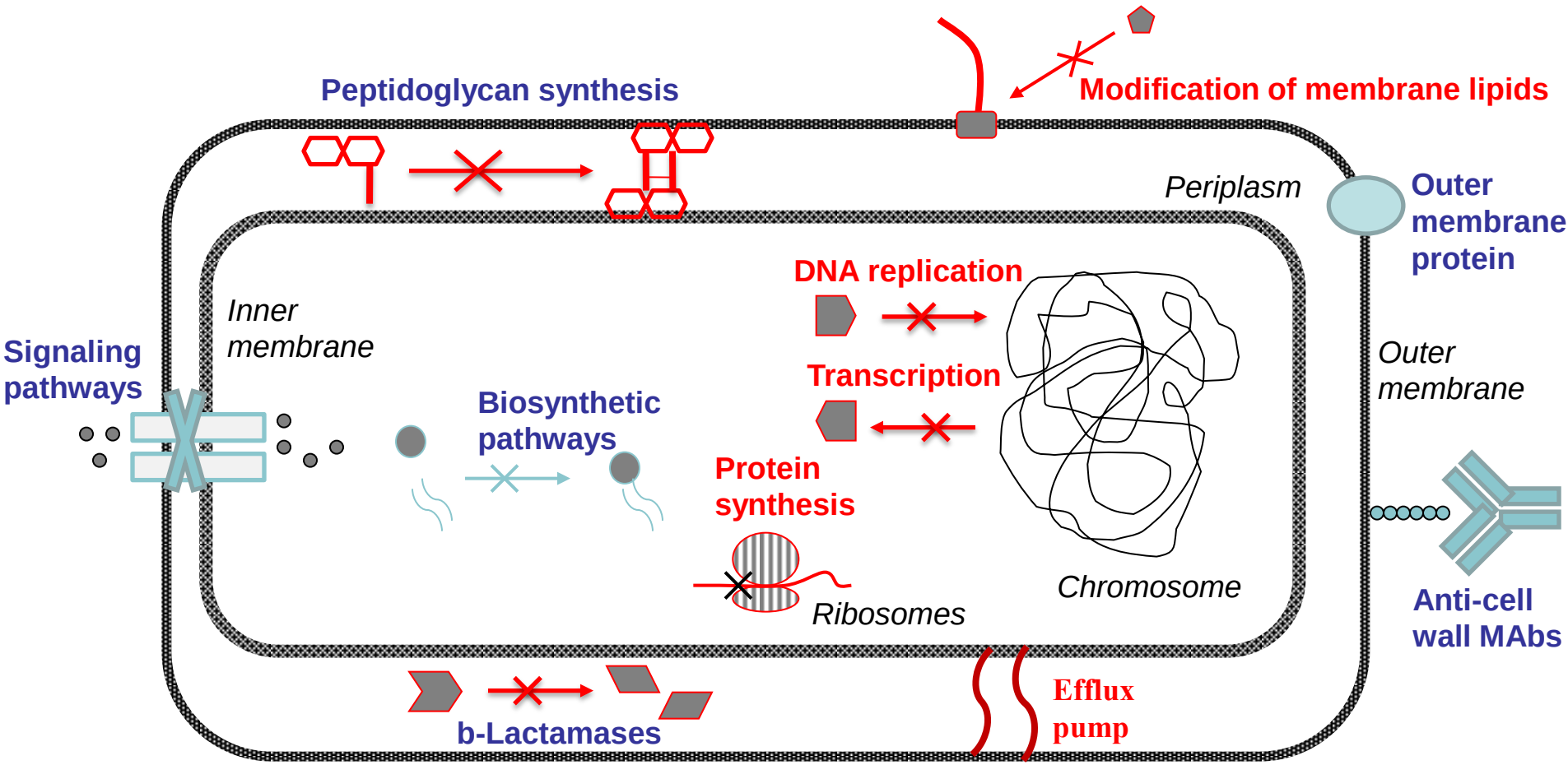
NIAID Sponsored Gonococcal Research

- **Identifying vaccine candidates**
  - Cell surface components
  - Lipooligosaccharides
  - Peptides
- **Development of new diagnostics**
  - Markers specific for the gonococci
  - Reducing the size and cost of instrumentation
  - Increasing the sensitivity and specificity of tests
- **Identifying targets for antimicrobial development**
  - Inhibition of Lipid A biosynthesis, protein synthesis, and DNA replication

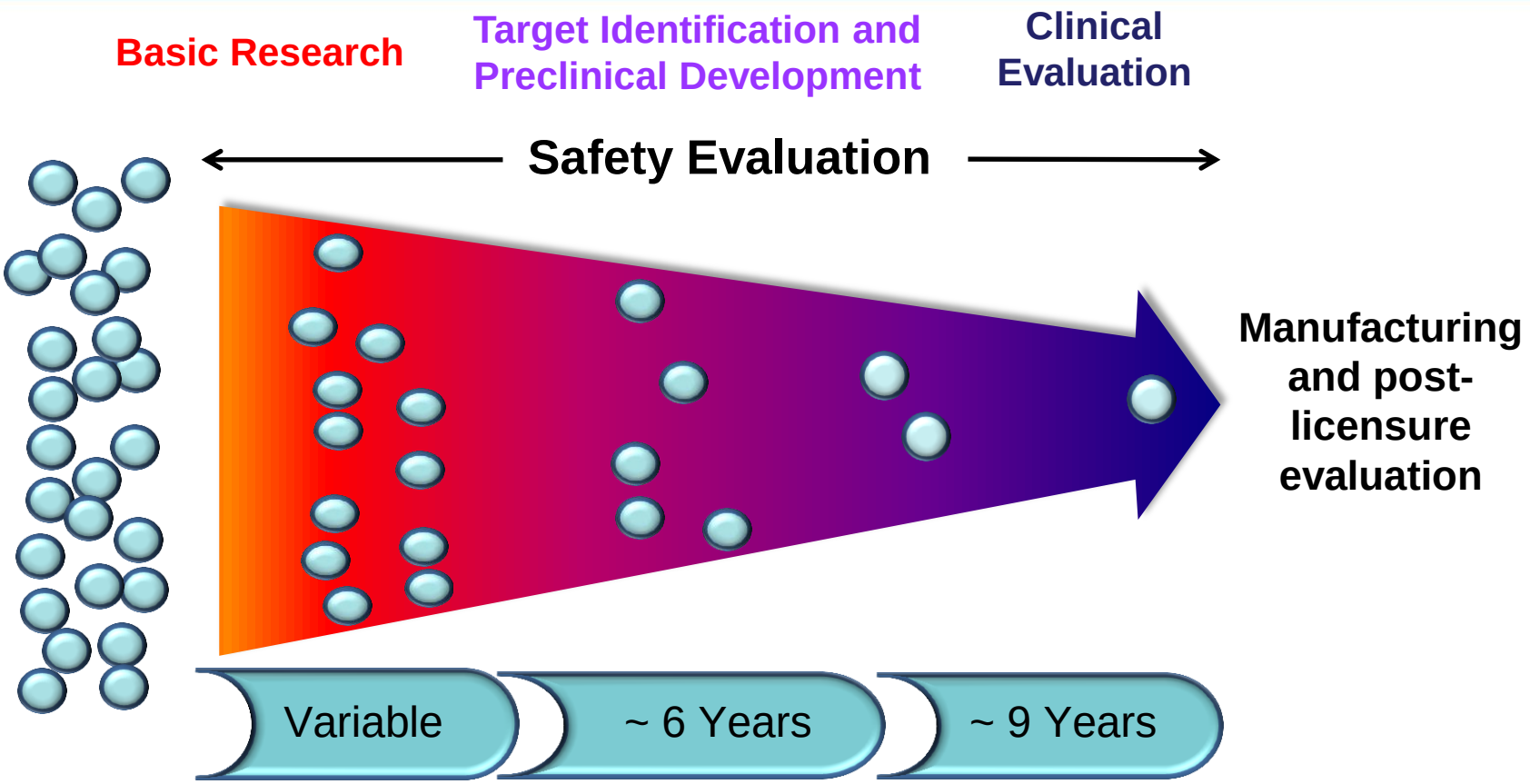
Clinical Research Example

- **Clinical trial to evaluate efficacy**
  - Regimen 1: Gentamicin and azithromycin
  - Regimen 2: Gemifloxacin and azithromycin
- **Outcome: Treatment of uncomplicated urogenital gonorrhea**
- **Principal Investigator: Robert D. Kirkcaldy, CDC**

NIAID Antibacterial Development Exploiting Old and Exploring New Targets

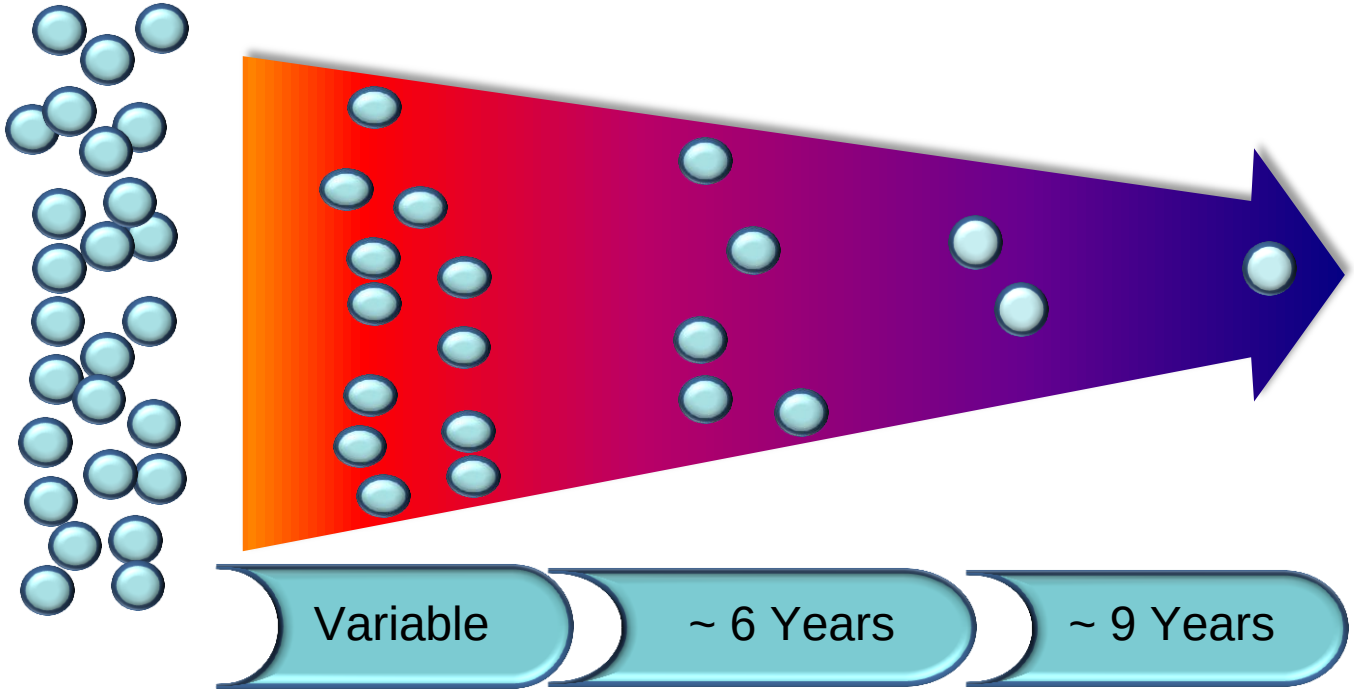


Antimicrobial Pipeline



http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/

Antimicrobial Pipeline



Total cost: $3.7B to $11.8B per new drug

Total time: 15 or more years

http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/

Biomedical Research: Diagnostics

- **Next generation diagnostics**
  - Miniaturization of devices by incorporating new technology
  - Identification of the pathogen in a point-of-care setting
- **New ways to look at the use of diagnostics**
  - Identification of antibiotic resistance markers in the clinical sample
  - Use this knowledge to guide treatment

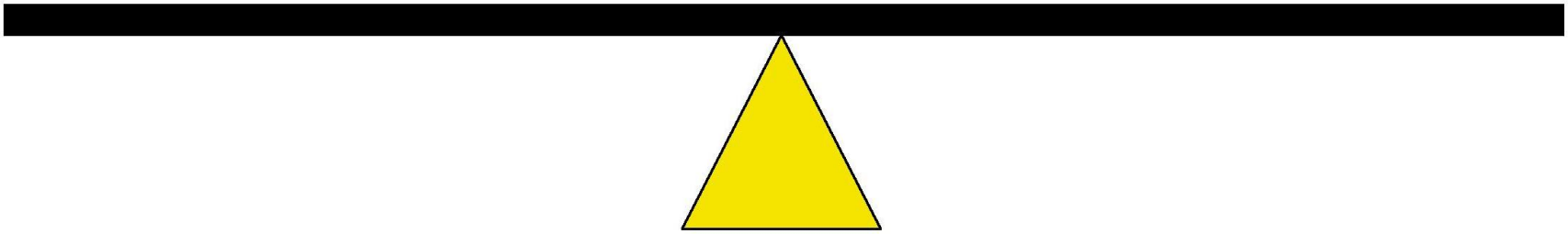
Prevention of Infection by Vaccines or Microbicides

- **Challenges to development of vaccines or antimicrobials**
  - Antigenic variation of bacterial surface components
  - Gonococci can induce antibodies that block the binding of effective antibodies
  - It is unclear what immunological response is protective
- **Candidates that give optimism for the future**
  - Major outer membrane proteins
  - Transferrin (iron) binding proteins
  - Peptide mimics of lipo-oligosaccharide (LOS) antigens
  - Compounds that inhibit attachment to cervical/vaginal cells

A Delicate Balance

Extraordinary capability of microbial pathogens to persist and develop resistance

Public health measures, biomedical research, development of new antimicrobials

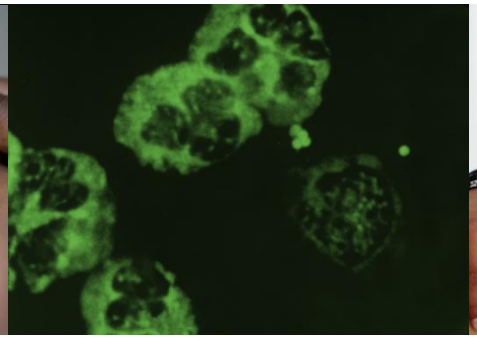


Source: AS Fauci, NIAID Director

Summary

- **Gonococci are one of many organisms with emerging resistance to antimicrobials**
- **Biomedical research**
  - Increases our understanding of the mechanisms of bacterial pathogenesis
  - Identifies prospects for antimicrobials, vaccines, and microbicides
- **Challenges of time scale and economics**
- **Grounds for optimism include promising vaccine and microbicide candidates**

What Public Health Can Do Now and in the Future

Robert D. Kirkcaldy, MD, MPH

Medical Epidemiologist

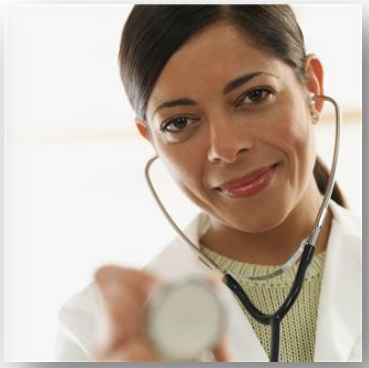
Division of STD Prevention

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

Centers for Disease Control and Prevention

Everyone Can Contribute to the Response

- **Public Health**
  - CDC
  - US Government partners
  - Health departments
- **Clinicians**
- **Laboratories**
- **Sexually active adolescents and adults**



What CDC Can Do Now

- **Continue to closely monitor resistance trends**
  - Use of and investment in GISP
- **Update treatment guidelines based on best available data**
- **Support local surveillance and laboratory capacity**
  - Training and education
  - Reference testing
  - National response plan
- **Study genetic basis for resistance**

GISP, Gonococcal Isolate Surveillance Project

What CDC Can Do Now

- Enhance international collaboration and surveillance of multidrug-resistant gonococci
- Provide scientific basis for need for culture capacity and development of new antimicrobials

What U.S. Government Partners Can Do Now

- Study effectiveness of available antimicrobials
- Support antimicrobial and vaccine development and approval - new antimicrobials are urgently needed

What Local and State Health Departments Can Do Now

- Strengthen local gonorrhea control efforts
- Enhance surveillance for resistant gonococci
- Ensure persons diagnosed with gonorrhea and their partners are treated appropriately
- Remain vigilant for treatment failures
- Promote access to culture and antimicrobial susceptibility testing

What Clinicians Can Do Now

Screen

- **Sexually active women at increased risk**
  - Under 25, prior gonococcal infection, other STDs, new or multiple partners, inconsistent condom use, sex work, or drug use
- **Sexually active MSM at all exposed anatomic sites at least annually**

USPSTF, Screening for Gonorrhea. http://www.uspreventiveservicestaskforce.org/uspstf/uspsgono.htm
CDC. Sexually Transmitted Diseases Treatment Guidelines, 2010
MSM, men who have sex with men

What Clinicians Can Do Now

Screen

- sexually active women at increased risk
- sexually active MSM at all exposed anatomic sites annually

Treat

- **with ceftriaxone 250 mg AND azithromycin 1 g OR doxycycline 100 mg twice daily for a week**
- **patient's partners from prior 2 months**

CDC. Sexually Transmitted Diseases Treatment Guidelines, 2010

What Clinicians Can Do Now

Screen

- sexually active women at increased risk
- sexually active MSM at all exposed anatomic sites annually

Treat

- with ceftriaxone 250 mg AND azithromycin 1 g OR doxycycline 100 mg twice daily for a week
- patient's partners from prior 2 months

Report

- **suspected treatment failures to local or state health department and CDC**

What Laboratories Can Do Now

- Maintain capacity to culture for gonococcus
- Promptly inform clinician and health department of elevated cephalosporin MICs
- Store isolates with elevated cephalosporin MICs or from unsuccessfully treated patients

MIC, minimum inhibitory concentration

What Sexually Active Adolescents and Adults Can Do Now

- **Abstain from sex**
- **Commit to safer sex**
  - Monogamy with uninfected partner
  - Consistent and correct condom use
- **Seek medical care for symptoms**
- **If infected, notify all your partners**
- **Notify your health care provider if symptoms do not resolve**

The Growing Threat of Multidrug-Resistant Gonorrhea: Summary

- **Gonorrhea is a major preventable cause of infertility**
- **Gonococcal antimicrobial resistance threatens treatment and prevention of gonorrhoea**
- **Continued surveillance for gonococcal resistance is vital**
- **Action is needed by public health officials, clinicians, laboratories, and those at risk**
  - Clinicians urged to treat with ceftriaxone and either azithromycin or doxycycline
- **New treatment options are urgently needed**