

Resistant Gonorrhoea: the end of an{other} era?

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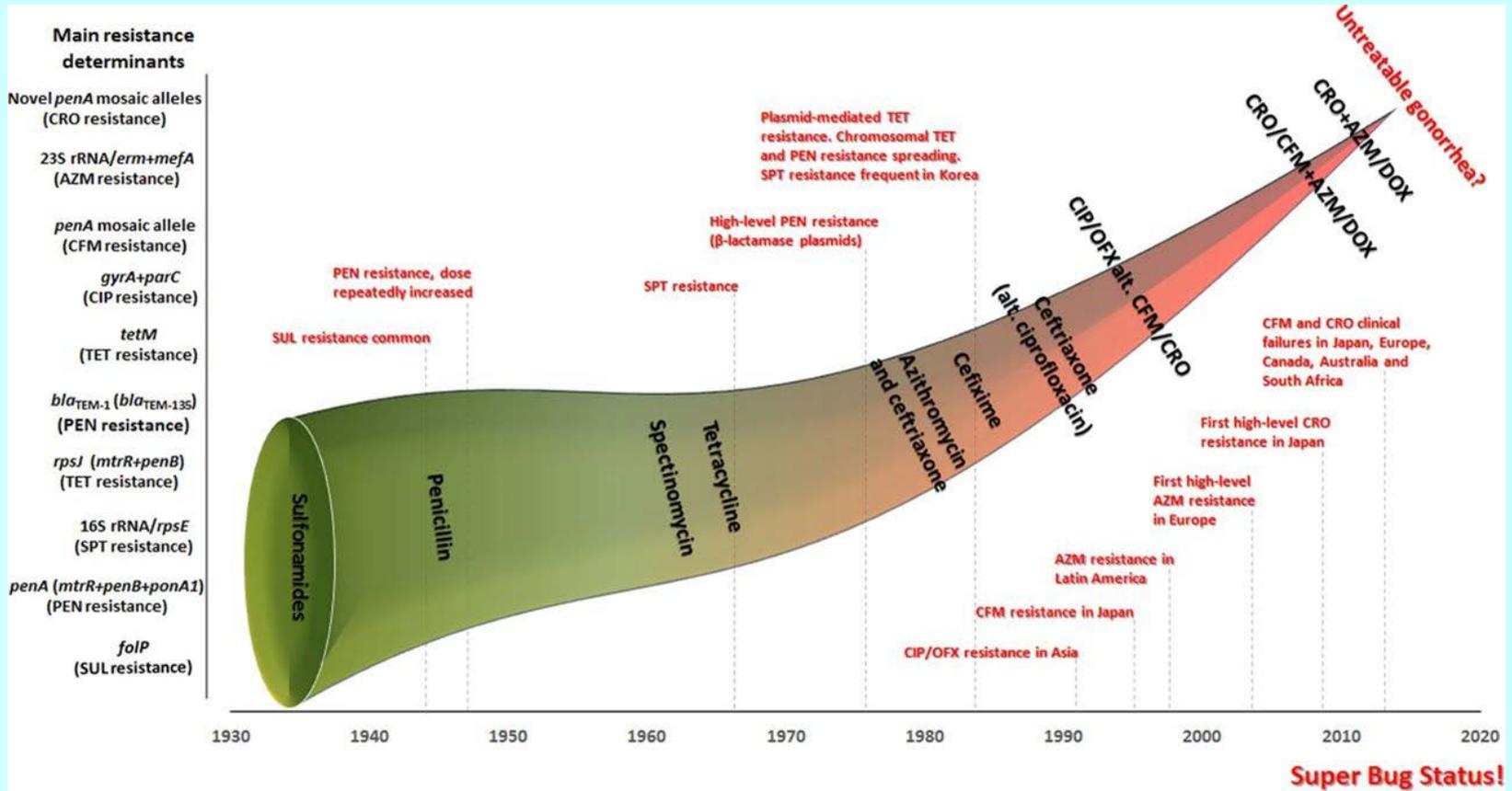
Gonorrhea-Antimicrobial Resistance

- No disclosures
- Thanks to Dr. Jonathan Zenilman, MD, for sharing slides
- Objectives:
 - History & pattern of GC-AMR
 - New options – drugs and vaccines

Antibiotic Resistance in NG-up to 1985

- 1945—Treatment with 50,000 U PCNG
- 1975—Treatment with 4.8 million Units PCN
- 1976-Plasmid mediated penicillin resistance (PPNG)
- 1981- Chromosomally mediated PCN, TET resistance (CMRNG)
- 1985-Plasmid mediated Tetracycline resistance (TRNG)

History of discovered and recommended antimicrobials and evolution of resistance in *Neisseria gonorrhoeae*, including the emergence of genetic resistance determinants, internationally.



Clinical Microbiology Reviews

W.H.O. ACTS TO CURB A NEW STRAIN OF V.D.

By LAWRENCE K. ALTMAN Special to The New York Times
New York Times (1857-Current file), Jan 9, 1977; ProQuest Historical Newspapers The New York Times
pg. 27

W.H.O. ACTS TO CURB A NEW STRAIN OF V.D.

Laboratories Asked to Begin Tests To Detect a Type of Gonorrhea That Resists Penicillin

By **LAWRENCE K. ALTMAN**

Special to The New York Times

GENEVA, Jan. 8—In an urgent step to prevent the development of a major international health problem, the World Health Organization has asked laboratories throughout the world to begin tests to detect a new penicillin-resistant strain of gonorrhea.

Already, the new type of venereal disease has infected Americans in at least 15 states and people in 10 other countries, and it threatens to become the dominant type among the millions of cases of gonorrhea that occur each year throughout the world.

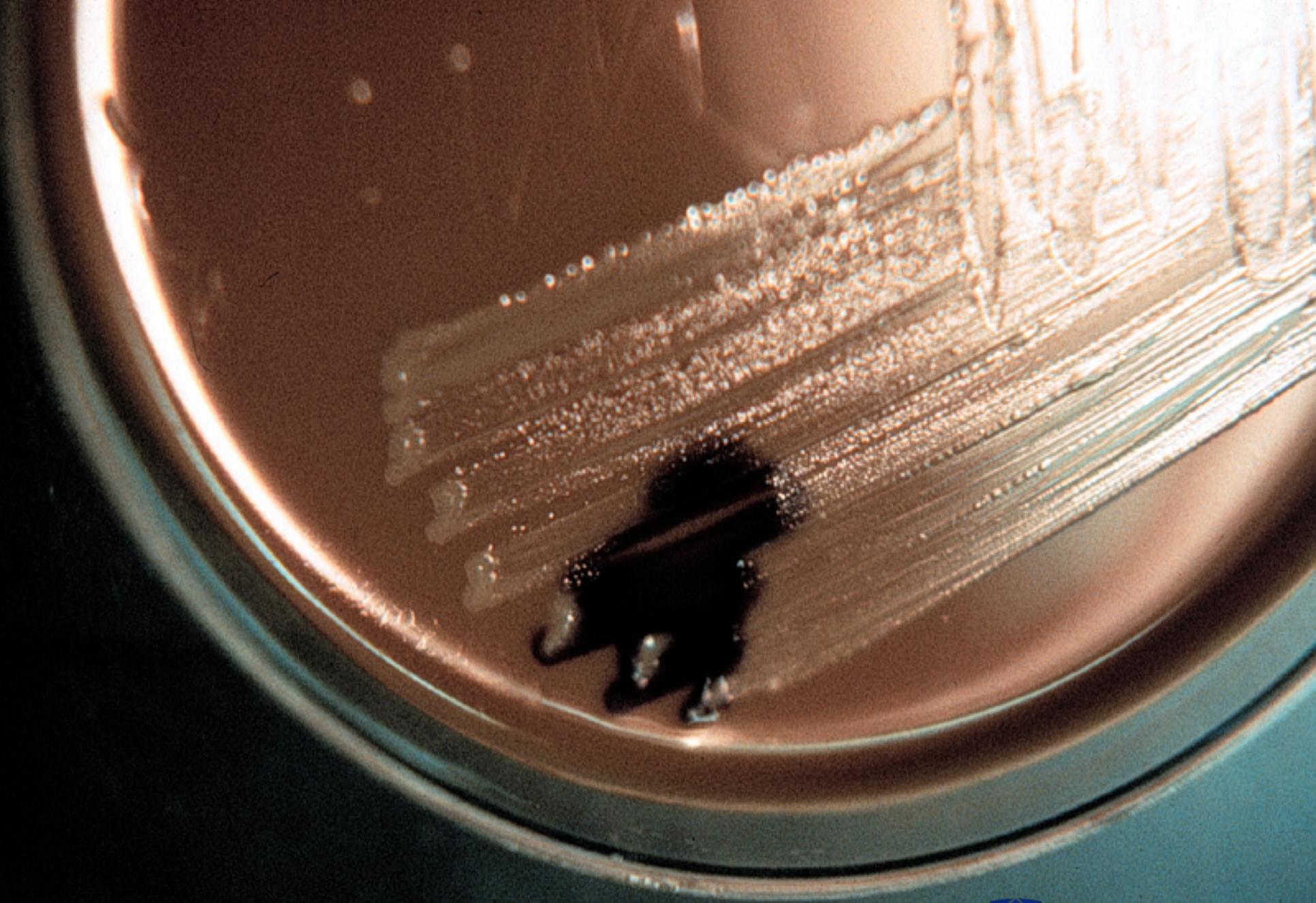
"The volume of air travel throughout the world and the limited surveillance for this organism to date [means] every area of the world must view this as a real or potential problem," the World Health Organization said in a statement sent to health officials in 150 countries that are members of the organization, and to thousands of scientists.

An old story?

NY Times Jan 9, 1977



JOHNS HOPKINS
SCHOOL of MEDICINE



Location of Participating Sentinel Sites and Regional Laboratories, Gonococcal Isolate Surveillance Project (GISP), United States, 2016



NOTE: Austin is a regional laboratory only.

Principles

- Standardized lab procedures including Q/A
- Resistance definitions and clinical action thresholds
- Systematic collection of isolates (first 25 males in participating clinics)

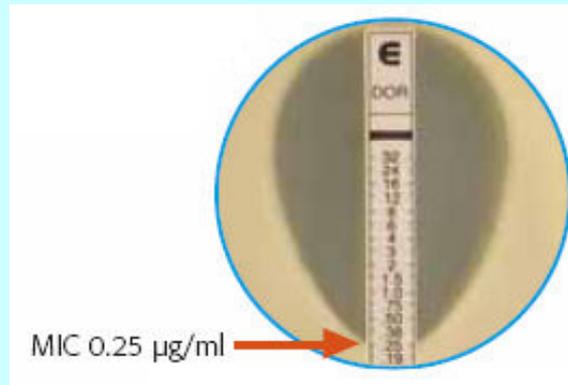
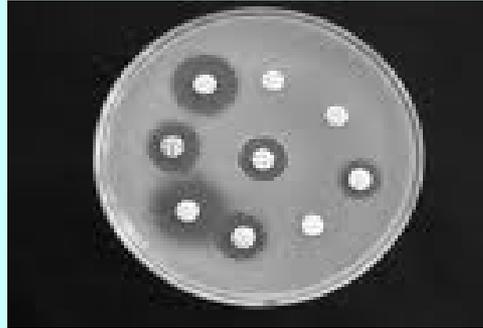
Impact

- Data on over 5,000 isolates/year, >155,000* in database with demographics and Minimum Inhibitory Concentrations (MICs)
- Adoption by Canada, UK, EU, Africa, and Military

* Data estimate provided by Elizabeth Torrone, PhD, CDC

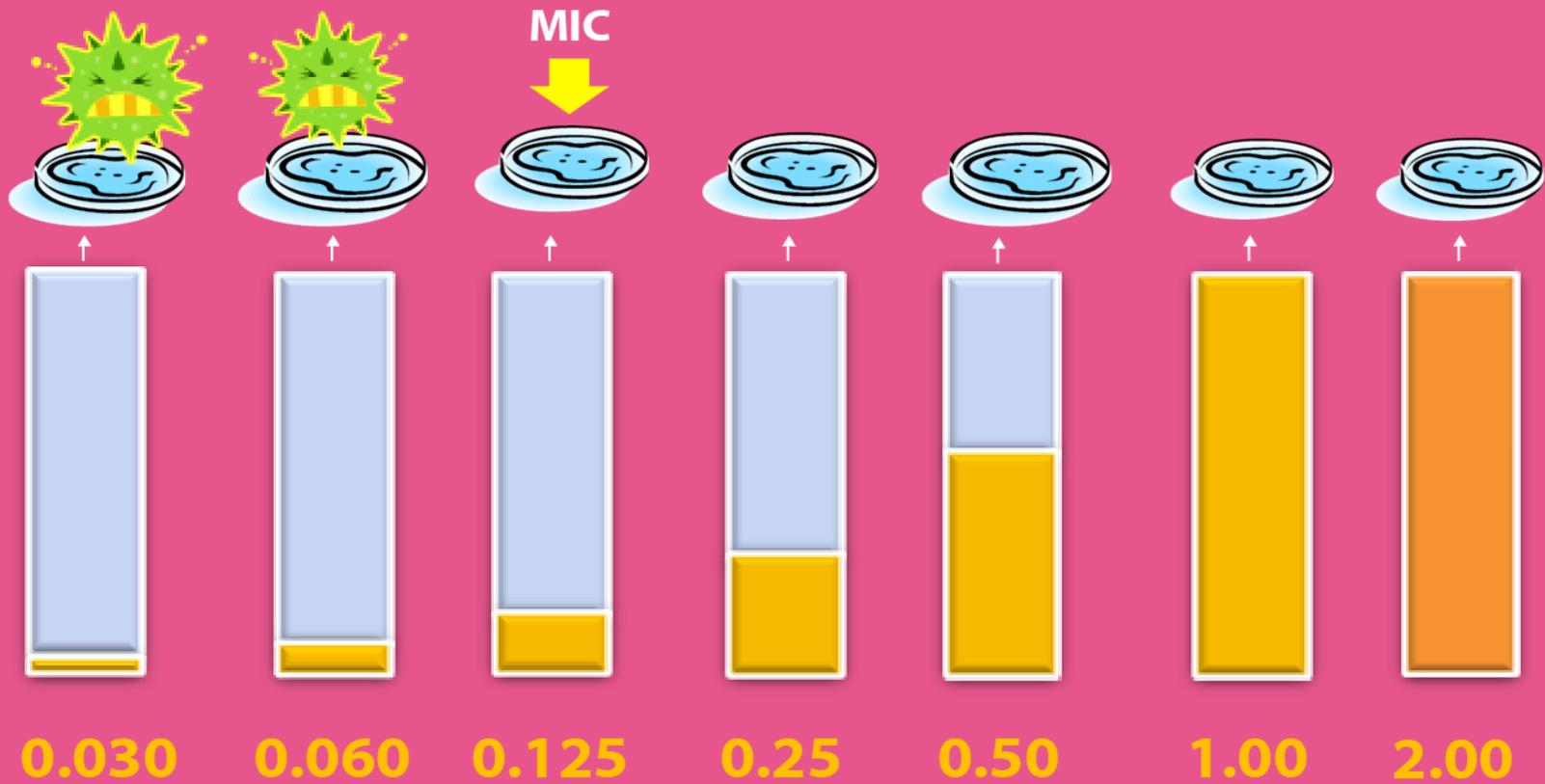
Measuring Antimicrobial Susceptibility

- Disk diffusion
– (Kirby-Bauer)
- E-test*
- Agar dilution*



* Provide minimum inhibitory concentration (MIC): lowest antibiotic concentration that inhibits visible growth

Agar Dilution and MICs



Antimicrobial concentrations

Epidemiology and Program

- Detection of new determinants-quinolones, cefixime, resistant, and rapid assessment
- Document Geographic Dispersal Patterns West→East; Points of Entry; Hawaii
- Behavioral Patterns (MSM)
- Treatment Patterns
- Clear Rx Recommendations-data driven

RESISTANT VD STRAIN ON RISE IN N.Y.

New gonorrhoea fear

UNITED PRESS INTERNATIONAL

ATLANTA—A hard-to-kill gonorrhoea strain is gaining a foothold in New York and in two other areas of the country, forcing doctors to abandon traditional penicillin therapy for more expensive antibiotics, federal health officials said yesterday.

The resistant strain is also on the rise in South Florida

and Los Angeles, said Dr. Jonathan Zenilman, of the national Centers for Disease Control. "In certain parts of the country, penicillin as the drug of choice is becoming a thing of the past," he said.

The resistant strain, PPNG (for penicillinase-producing *Neisseria gonorrhoea*), produces an enzyme that destroys the therapeutic effects of penicillin.

New York City reported 550 cases in the first six months of 1985. About one million cases of all strains are reported each year to the CDC.

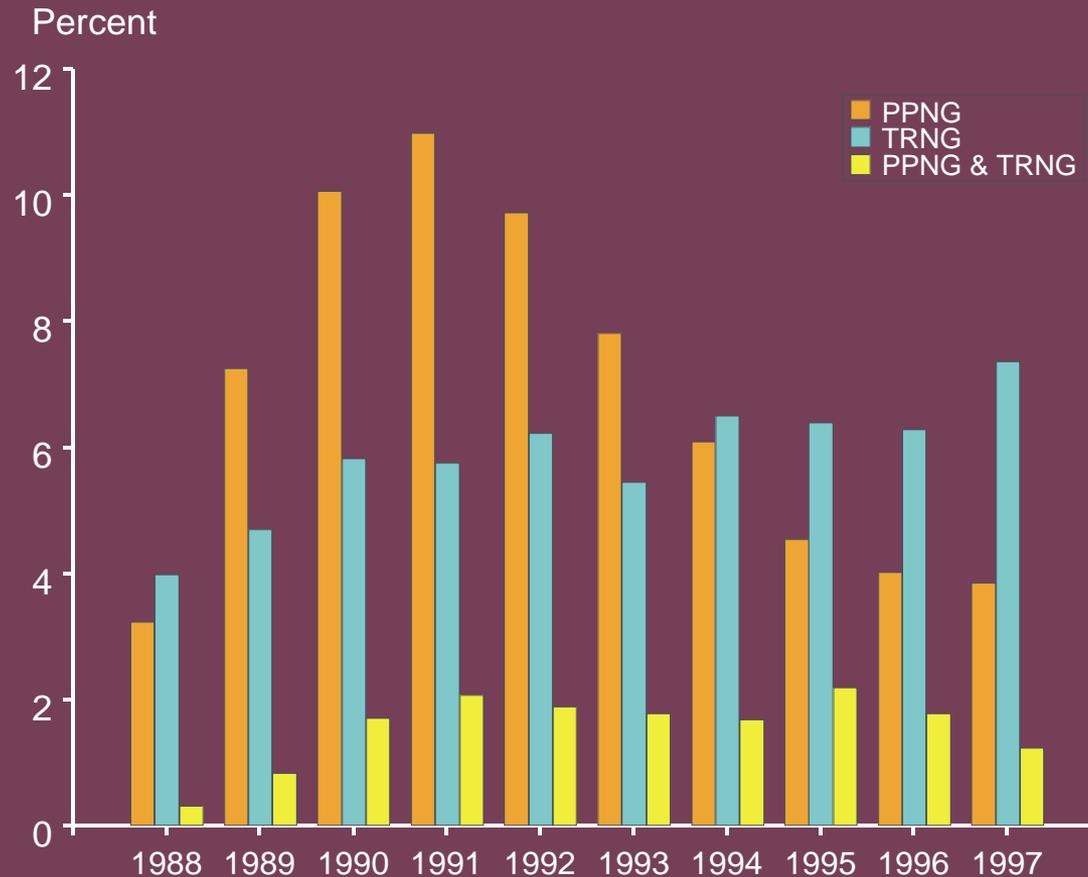
Doctors are treating the new strain with the antibiotic spectinomycin and a newer drug, ceftriaxone, Zenilman said. But the new treatments are "eight times more expensive," he said.

1985

Incurable new VD could strike, say feds

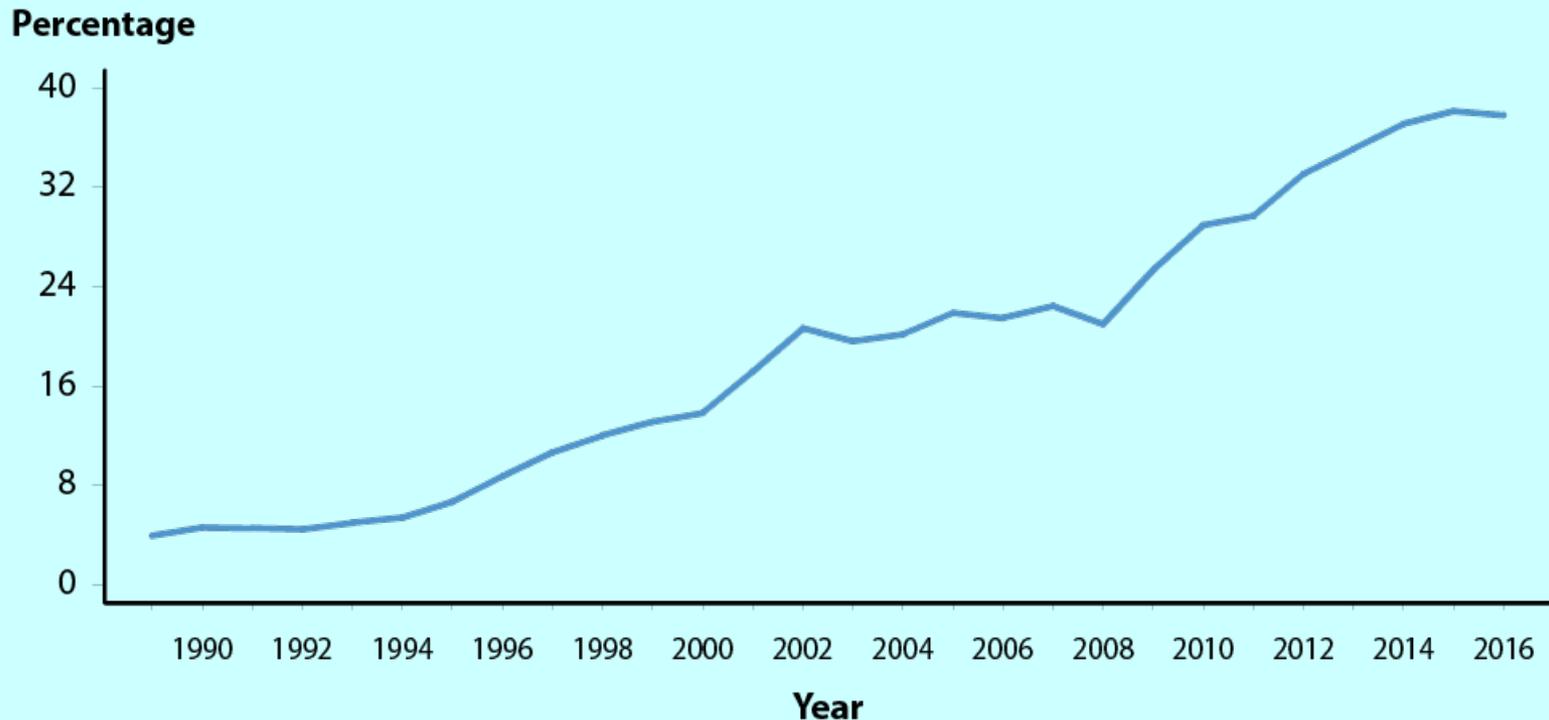
ATLANTA (AP) — A strain of gonorrhoea resistant to every antibiotic on the market could strike in the future, federal health researchers warned yesterday.

Gonococcal Isolate Surveillance Project (GISP) - Trends in plasmid-mediated resistance to penicillin and tetracycline, 1988-1997



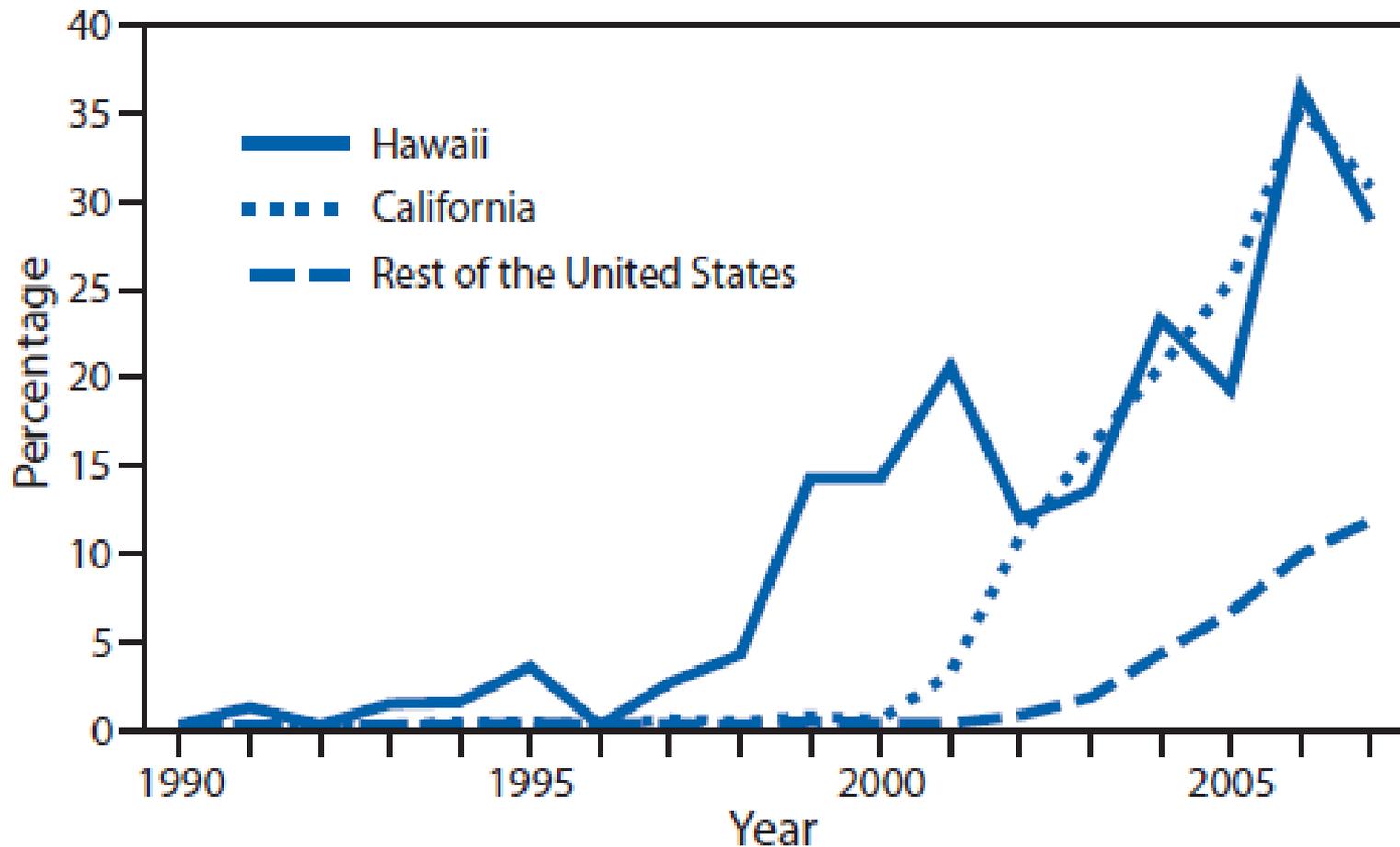
Note: "PPNG" (penicillinase-producing *Neisseria gonorrhoeae*) and "TRNG" (tetracycline-resistant *N. gonorrhoeae*) refer to plasmid-mediated resistance to penicillin and tetracycline, respectively.

Neisseria gonorrhoeae — Percentage of Urethral Isolates Obtained from MSM* Attending STD Clinics, Gonococcal Isolate Surveillance Project (GISP), 1989–2016



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

FIGURE 1. Prevalence of ciprofloxacin resistance* in urethral *Neisseria gonorrhoeae* isolates collected from men in the United States, by location — Gonococcal Isolate Surveillance Project, 1990–2007



* Defined as minimum inhibitory concentrations $\geq 1 \mu\text{g}/\text{mL}$.

Morbidity and Mortality Weekly Report

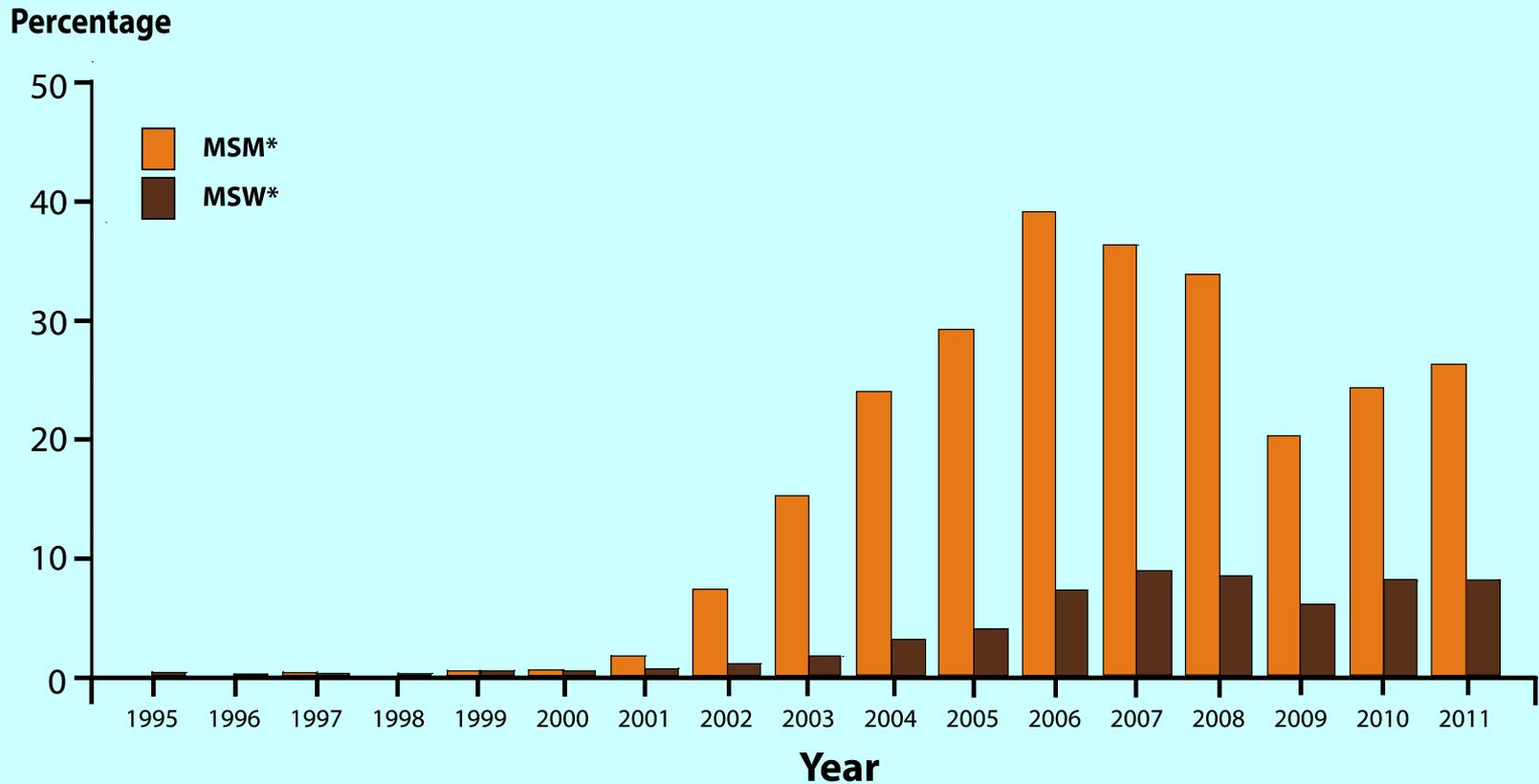
Weekly

April 30, 2004 / Vol. 53 / No. 16

Increases in Fluoroquinolone-Resistant *Neisseria gonorrhoeae* Among Men Who Have Sex with Men — United States, 2003, and Revised Recommendations for Gonorrhea Treatment, 2004

Treatment recommendations were changed on basis of surveillance data BEFORE treatment failures became a problem!

Percentage of *Neisseria gonorrhoea* Isolates that are Ciprofloxacin-Resistant by Sex of Sex Partner, Gonococcal Isolate Surveillance Project (GISP), 1995–2011

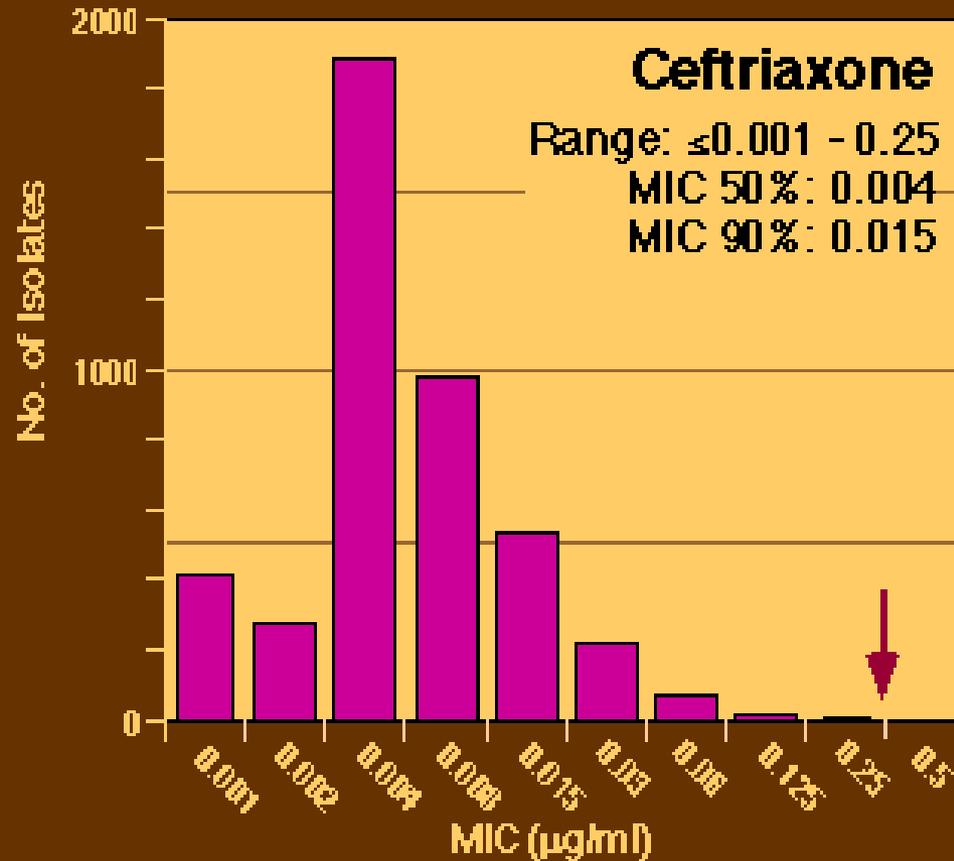


***MSM**=men who have sex with men;

MSW=men who have sex with women only.

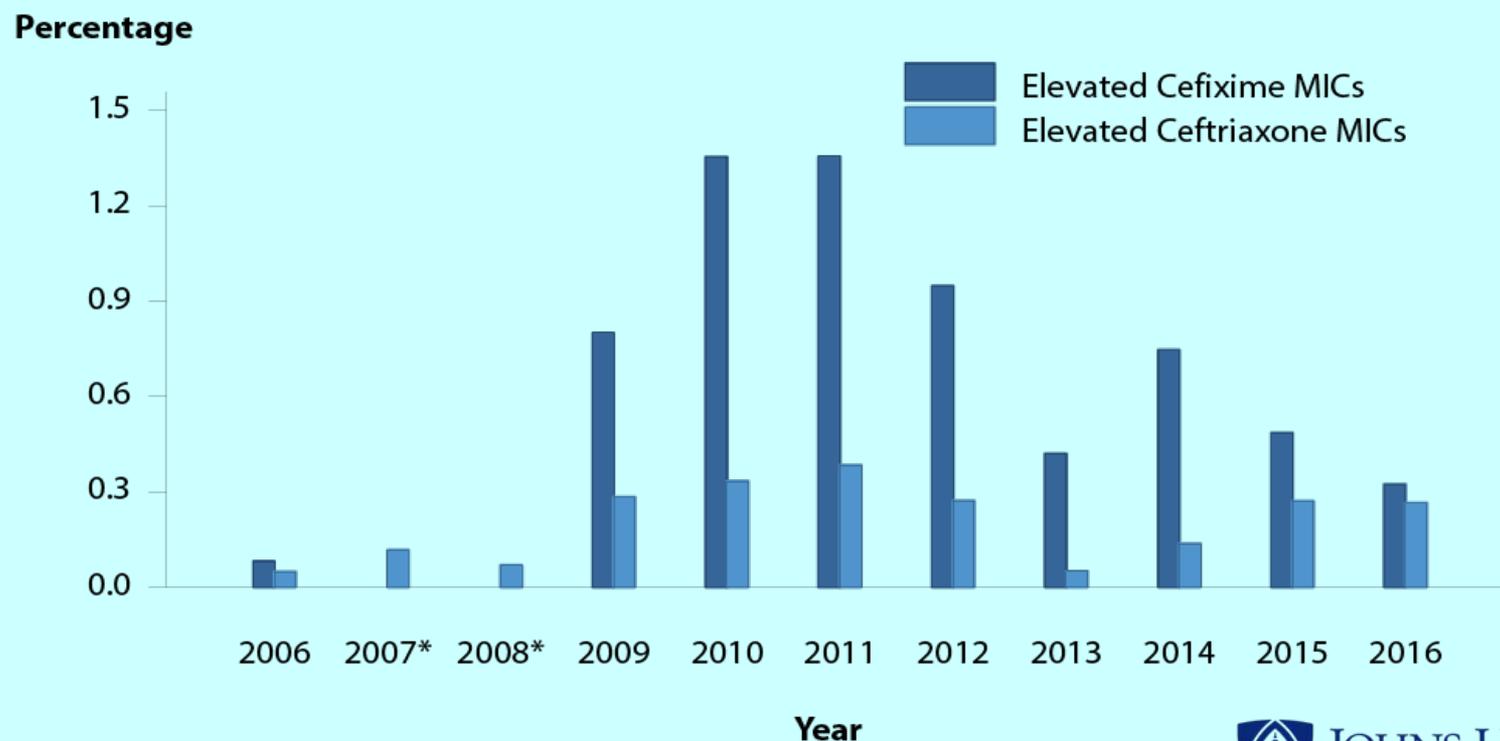
Gonococcal Isolate Surveillance Project (GISP) 1994 - Ceftriaxone

Gonococcal Isolate Surveillance Project - 1994



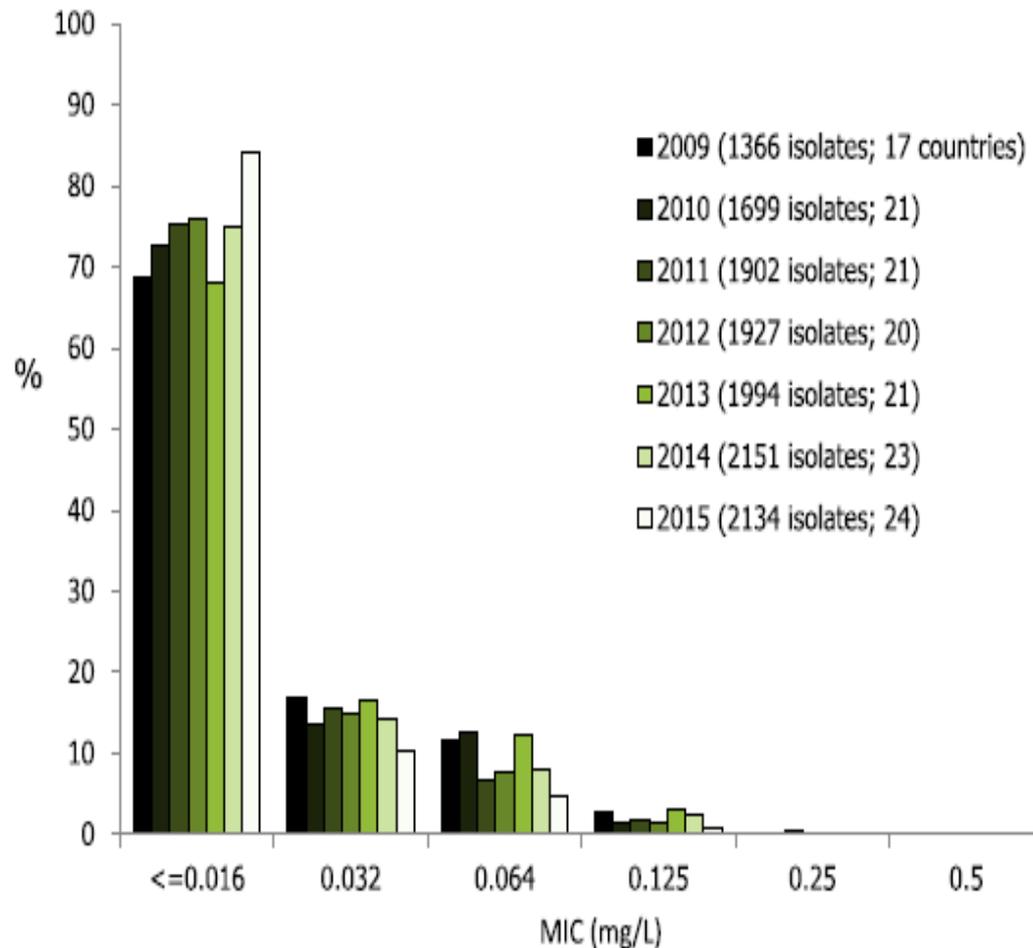
CDC

Neisseria gonorrhoeae — Percentage of Isolates with Elevated Ceftriaxone Minimum Inhibitory Concentrations (MICs) (≥ 0.125 $\mu\text{g/ml}$) and Elevated Cefixime MICs (≥ 0.25 $\mu\text{g/ml}$), Gonococcal Isolate Surveillance Project (GISP), 2006–2016

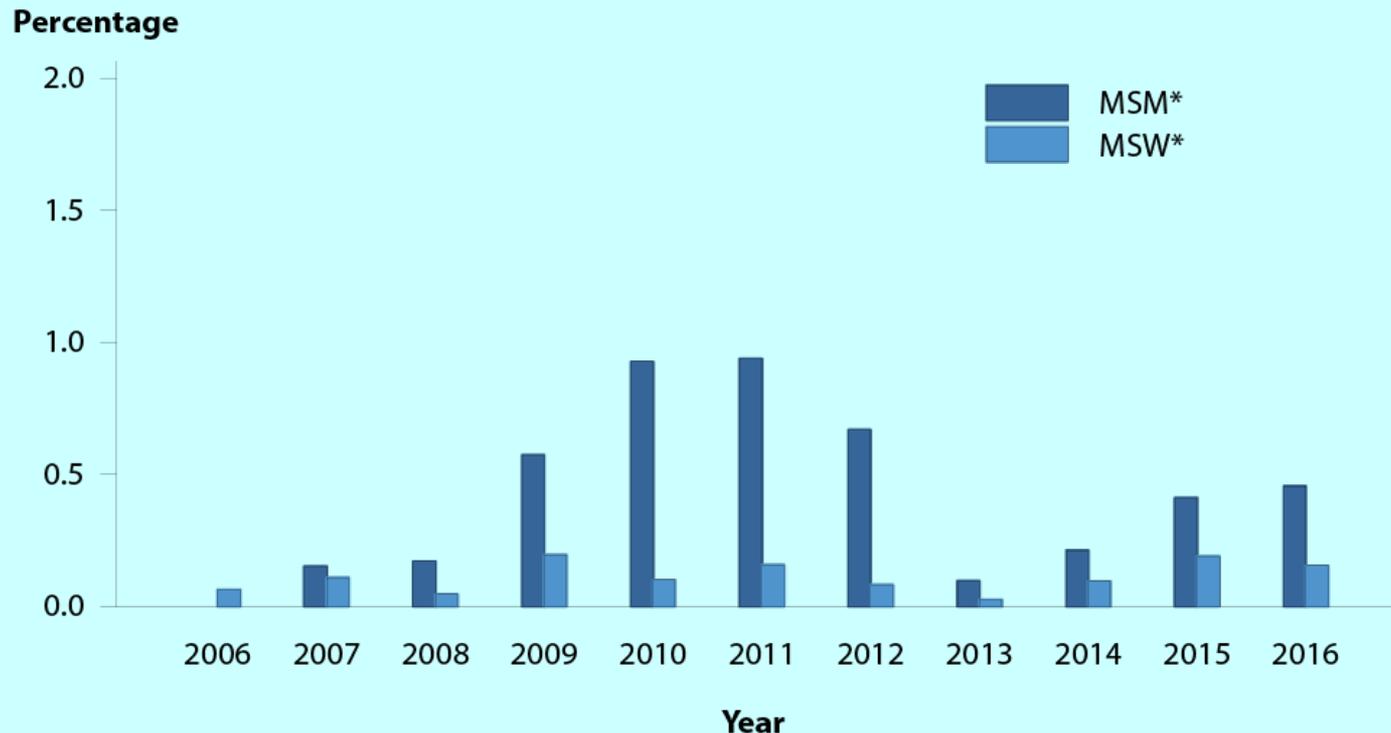


* Isolates not tested for cefixime susceptibility in 2007 and 2008.

Ceftriaxone MIC distribution for *N. gonorrhoeae* isolates in the EU/EEA, 2009-2015

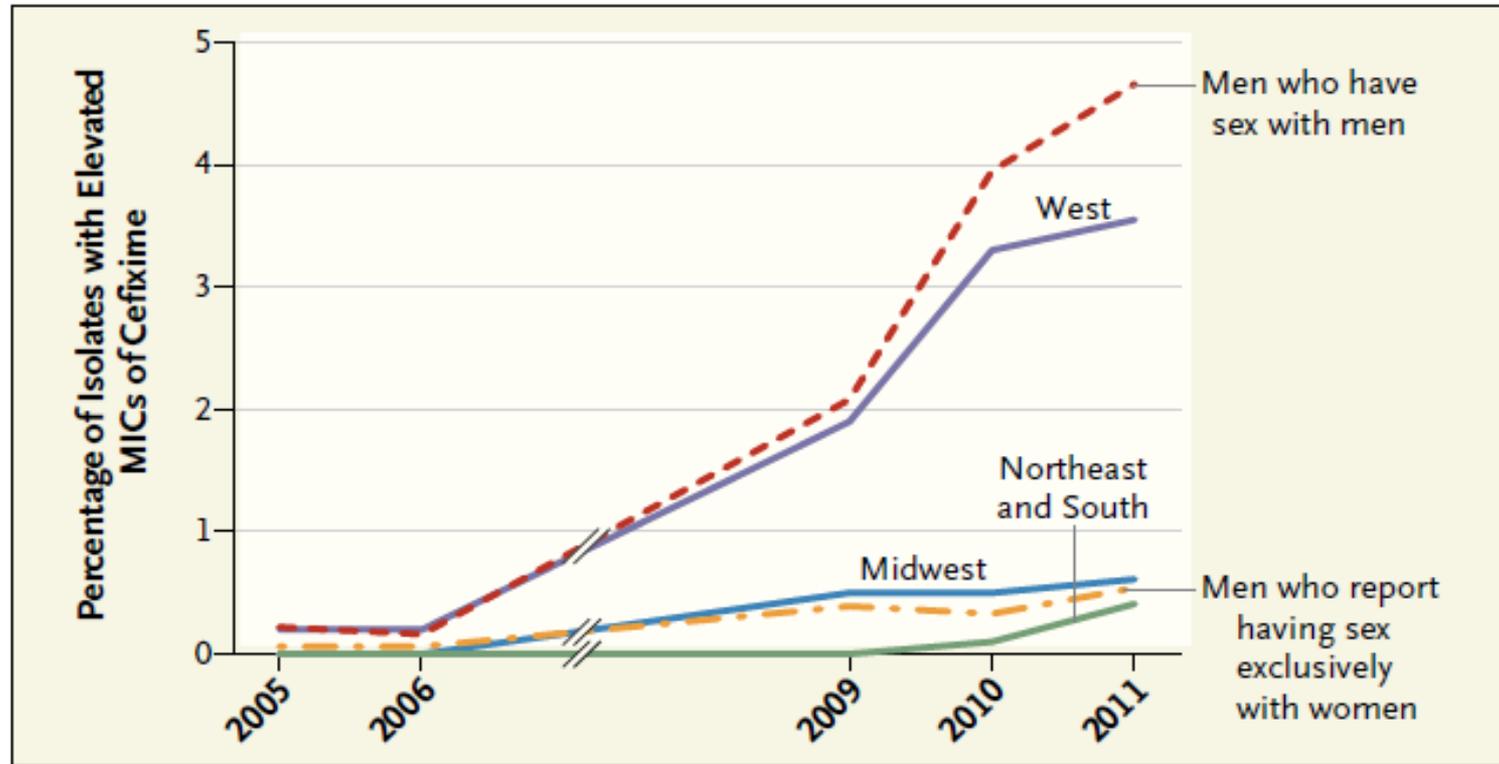


Neisseria gonorrhoea — Percentage of Urethral Isolates with elevated Ceftriaxone Minimum Inhibitory Concentrations (MICs) (≥ 0.125 $\mu\text{g/ml}$) by Reported Sex of Sex Partner, Gonococcal Isolate Surveillance Project (GISP), 2006–2016



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

Percentage of Isolates in which Minimal Inhibitory Concentrations (MICs) of Cefixime Were 0.25 µg per Milliliter or Higher, 2005-2011.



Susceptibility to cefixime was not tested in 2007 or 2008. From the Gonococcal Isolate Surveillance Project.

Neisseria gonorrhoeae Treatment Failure and Susceptibility to Cefixime in Toronto, Canada

Vanessa G. Allen, MD, MPH

Leo Mitterni

Christine Seah, MLT

Anuradha Rebbapragada, PhD

Irene E. Martin, BSc

Colin Lee, MD

Heather Siebert, MLT

Lynn Towns, MLT

Roberto G. Melano, PhD

Donald E. Low, MD

Importance Although cephalosporins are the cornerstone of treatment of *Neisseria gonorrhoeae* infections, cefixime is the only oral antimicrobial option. Increased minimum inhibitory concentrations (MICs) to cefixime have been identified worldwide and have been associated with reports of clinical failure.

Objective To assess the risk of clinical treatment failure of *N gonorrhoeae* infections associated with the use of cefixime.

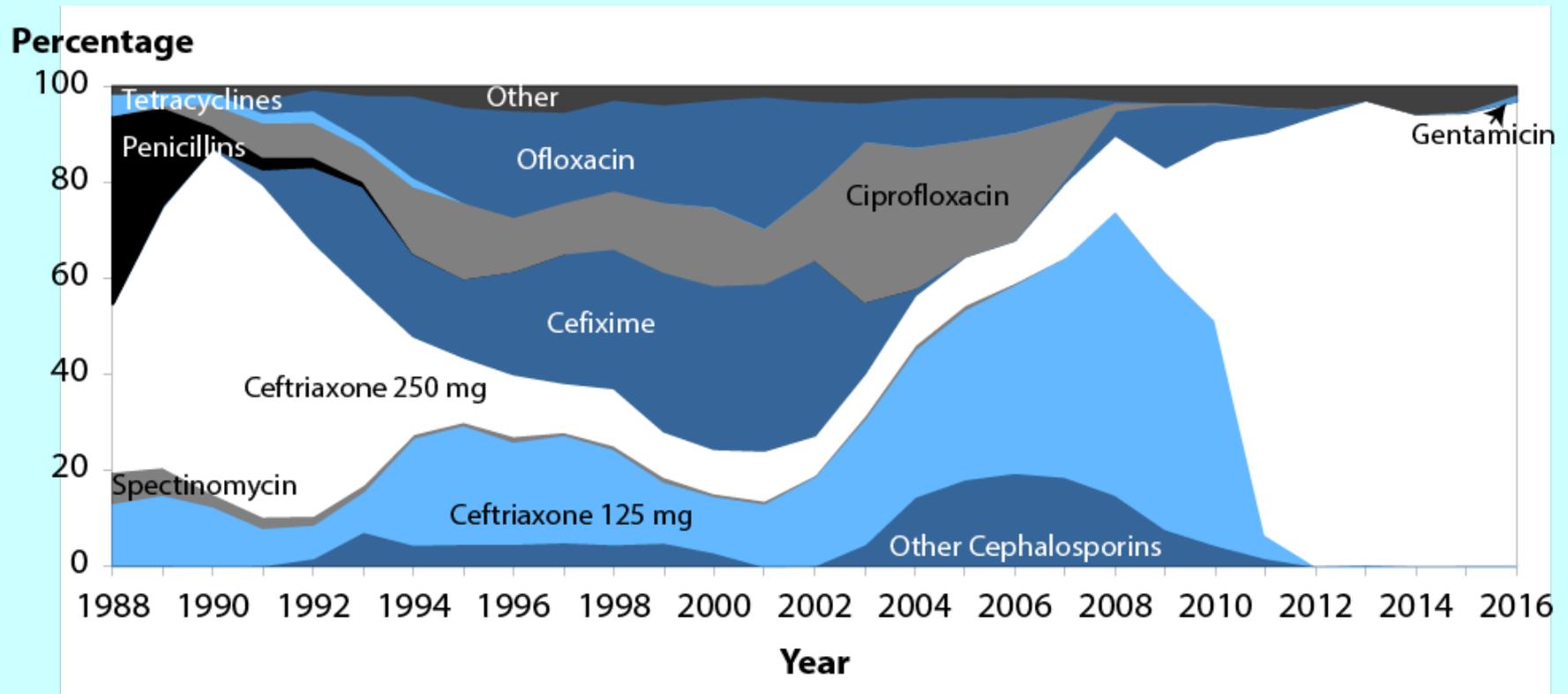
Design, Setting, and Population A retrospective cohort study of culture-positive *N gonorrhoeae* infections at a single sexual health clinic in Toronto, Canada, that routinely performs test of cure. The cohort comprised *N gonorrhoeae* culture-positive individuals identified between May 1, 2010, and April 30, 2011, treated with cefixime as recommended by Public Health Agency of Canada guidelines.

Main Outcome Measures Cefixime treatment failure, defined as the repeat isolation of *N gonorrhoeae* at the test-of-cure visit identical to the pretreatment isolate

JAMA 1/9/13

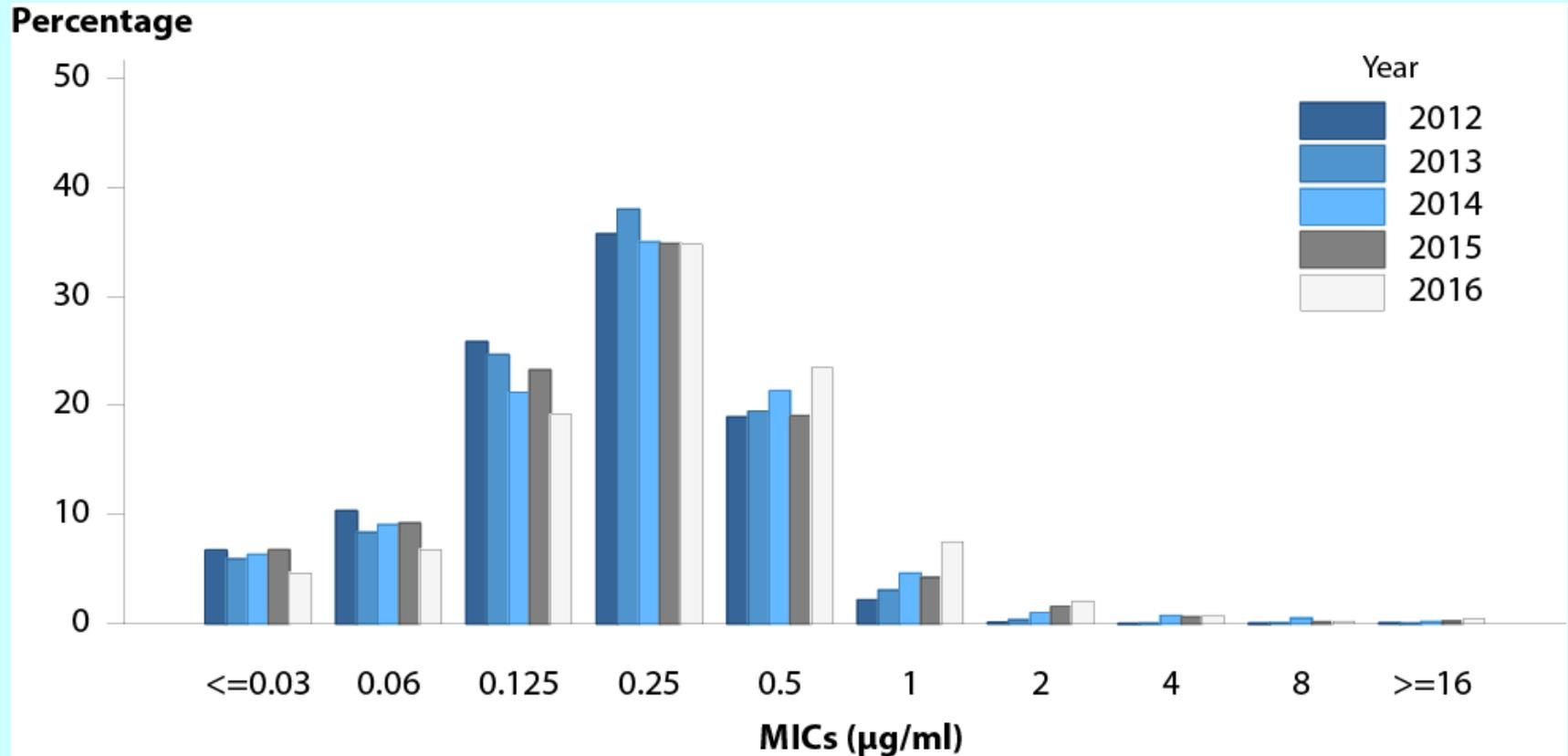
- Cultures 2010-2011
- 291 positives, 133 returned for Test Of Cure
- 13 TOC-positives, 9 cefixime Rx FAIL
- MIC failure for $\geq 0.12\mu\text{g/ml}$ was 25%

Distribution of Primary Antimicrobial Drugs Used to Treat Gonorrhea Among Participants, Gonococcal Isolate Surveillance Project (GISP), 1988–2016



NOTE: For 2016, “Other” includes azithromycin 2g (0.7%), no therapy (0.1%), and other less frequently used drugs (0.8%).

Neisseria gonorrhoea — Distribution of Azithromycin Minimum Inhibitory Concentrations (MICs) by Year, Gonococcal Isolate Surveillance Project (GISP), 2012–2016



RESEARCH ARTICLE

Open Access



Overall Low Extended-Spectrum Cephalosporin Resistance but high Azithromycin Resistance in *Neisseria gonorrhoeae* in 24 European Countries, 2015

Michelle J. Cole^{1*}, Gianfranco Spiteri², Susanne Jacobsson³, Neil Woodford¹, Francesco Tripodo¹, Andrew J. Amato-Gauci², Magnus Unemo³ and Euro-GASP network²

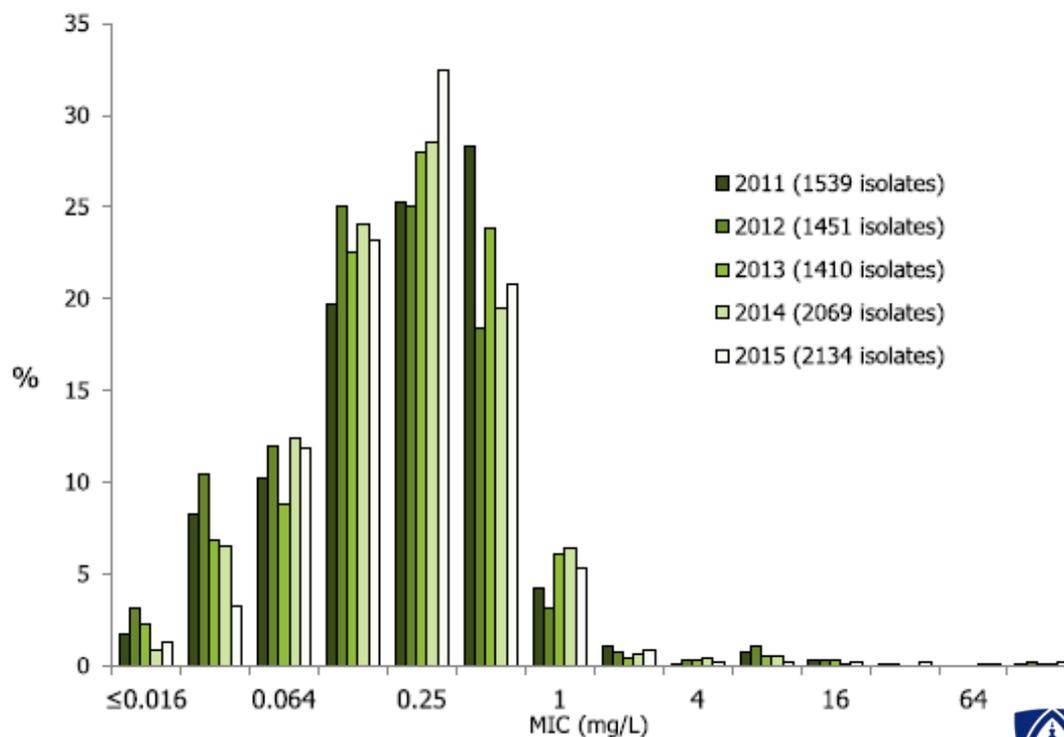


Fig. 3 Azithromycin MIC distribution for *N. gonorrhoeae* isolates in the EU/EEA, 2011–2015

Rationale 2018

- Multiple types of resistance emerging—especially cephalosporin and macrolide
- Culture diagnosis for GC has been replaced by Nucleic acid diagnosis (NAAT)
- Sequencing for resistance detection requires knowledge of specific targets, is time consuming and not practical
- BUT.....

Cluster of *Neisseria gonorrhoeae* Isolates With High-level Azithromycin Resistance and Decreased Ceftriaxone Susceptibility, Hawaii, 2016

Alan R. Katz,^{1,2} Alan Y. Komeya,² Robert D. Kirkcaldy,³ A. Christian Whelen,^{1,4} Olusegun O. Soge,⁵ John R. Papp,³ Ellen N. Kersh,³ Glenn M. Wasserman,^{1,2} Norman P. O'Connor,⁴ Pamela S. O'Brien,⁴ Douglas T. Sato,⁴ Eloisa V. Maningas,⁴ Gail Y. Kunimoto,⁴ and Juval E. Tomas²

¹Department of Public Health Sciences, University of Hawaii, and ²Communicable Diseases Division, Hawaii Department of Health, Honolulu; ³Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, GA; ⁴State Laboratories Division, Hawaii Department of Health, Honolulu; and ⁵Gonococcal Isolate Surveillance Project Regional Laboratory, University of Washington, Seattle

(See the Editorial Commentary by Hook on pages 924–6.)

Resistance to Ceftriaxone and Azithromycin in *Neisseria gonorrhoeae* Isolates From 7 Countries of South America and the Caribbean: 2010–2011

Sidharath Dev Thakur, PhD,*† Pamela Araya, BSc,‡ Graciela Borthagaray, QF,§
Patricia Galarza, MSc, MPH,¶ Alina Llop Hernandez, MD, PhD,|| Daisy Payares, BSc,**
Olga Marina Sanabria Cruz, BSc,†† Maria Elena Trigo Carvallo, BSc,‡‡
Aura Helena Corredor, MSc,† and Jo-Anne R. Dillon, PhD*†



Man has 'world's worst' super-gonorrhoea

By James Gallagher

Health and science correspondent, BBC News

- **Resistant to Ceftriaxone and Azithromycin**
- **Acquired in Thailand**

Culture vs DNA for Resistance

- Culture takes time and resources
- DNA testing would be wonderful—BUT you need to know the target sequence
- Resistant isolates can result from a combination of mutations, and mutations can occur spontaneously
- Therefore, with few exceptions, nucleic acid testing for resistance surveillance is not yet feasible...BUT.....

Cephalosporin Resistance—The Issues

- Since the early 2000s, with development of fluoroquinolone-resistant *N. gonorrhoeae* (QRNG), cefixime has been only oral option
- Increased MICs to cefixime have been developing and are associated with treatment failures
- There are no other first-line current oral options
- We are also seeing increased AZI resistance

Challenges

- Initial studies in Africa, Asia and S America show QRNG rates >80% in many places
- OTC drug availability
- Cefixime RESISTANT isolates found in Japan and SE Asia
- Potential for genetic exchange with other organisms

Neisseria cinerea with High Ceftriaxone MIC Is a Source of Ceftriaxone and Cefixime Resistance-Mediating *penA* Sequences in *Neisseria gonorrhoeae*

Gene Igawa,^a Yuka Yamagishi,^b  Ken-Ichi Lee,^a Misato Dorin,^a Ken Shimuta,^a Hiroyuki Suematsu,^b Shu-Ichi Nakayama,^a Hiroshige Mikamo,^b Magnus Unemo,^c Makoto Ohnishi^{a,d}

^aDepartment of Bacteriology I, National Institute of Infectious Diseases, Tokyo, Japan

Igawa G, Yamagishi Y, Lee K-I, Dorin M, Shimuta K, Suematsu H, Nakayama S-I, Mikamo H, Unemo M, Ohnishi M. 2018. *Neisseria cinerea* with high ceftriaxone MIC is a source of ceftriaxone and cefixime resistance-mediating *penA* sequences in *Neisseria gonorrhoeae*. *Antimicrob Agents Chemother* 62:e02069-17.

Trends--Diagnosis

- GISP networks now being established in sub-Saharan Africa, Asia
- Approaches to nucleic acid based Point-of-Care and rapid testing:
 - Defining “normal” vs abnormal
 - Stable determinants (eg QRNG)
 - Whole genome sequencing

Updated CDC Treatment Recommendations for Gonorrhea

- **First-Line (preferred)**
 - Ceftriaxone 250 mg IM X1 + Azithromycin **1g** PO X 1
 - Even if *C. trachomatis* is ruled out!
 - **Alternate (non-preferred):**
 - Cefixime 400mg IM X1 + Azithromycin **1g** PO X1*
 - Only 92% cure for OP infection
 - Any pt receiving non-1st line for OP needs TOC at 14d by NAAT or culture. If NAAT +ve try to get culture
- * Regimen currently used for EPT

Cephalosporin Treatment Failure

- Sx not resolved after 3d
- +ve Test of Cure (NAAT >7d, culture >72h)
- If a patient experiences **cefixime** treatment failure:
 - Re-treat with 250 mg ceftriaxone intramuscularly and 2g azithromycin orally
 - Return for tests-of-cure within 2 weeks, preferably with culture, or, if culture is not available, with NAAT. If the follow-up NAAT result is positive, a specimen for culture should be obtained

Cephalosporin Treatment failure

- Report to CDC via Health Dept. <24h of diagnosis
- If a patient experiences **ceftriaxone** treatment failure:
 - Re-treat with 250 mg ceftriaxone intramuscularly and 1g azithromycin orally
 - Return for tests-of-cure within 2 weeks, preferably with culture, or, if culture is not available, with NAAT. If the follow-up NAAT result is positive, a specimen for culture should be obtained

Salvage Regimens

- Gemifloxacin 320 mg + AZI 2g (stat PO)
- Gentamicin 240mg IM/+ AZI 2g PO (stat)
- Solithromycin (investigational)

- BUT—there is really not much in the pipeline

AND—think about these other issues

- Patients with penicillin allergy?
- Rectal/Pharyngeal concentrations of drugs—poorly known. However, recent studies show cefixime concentrations in pharynx are negligible



Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Barbara McArdle, Felicity Goodyear-Smith, Steven Black

- Vaccine development against GC has been challenging
 - Only 4 progressed to clinical trials, all before 1990, and all failed to provide any protection
- Observation: Decline in GC cases after introduction of *N. meningitidis* Group B OMV vaccine (MenZB) in NZ where 1 million young adults were vaccinated between 2004 & 2008
- Case Control Study:
 - Estimated adjusted vaccine effectiveness of MeNZB against gonorrhoea 31% (95% CI 21–39)
- MenZB no longer available but the4CMenB contains same antigenic epitope

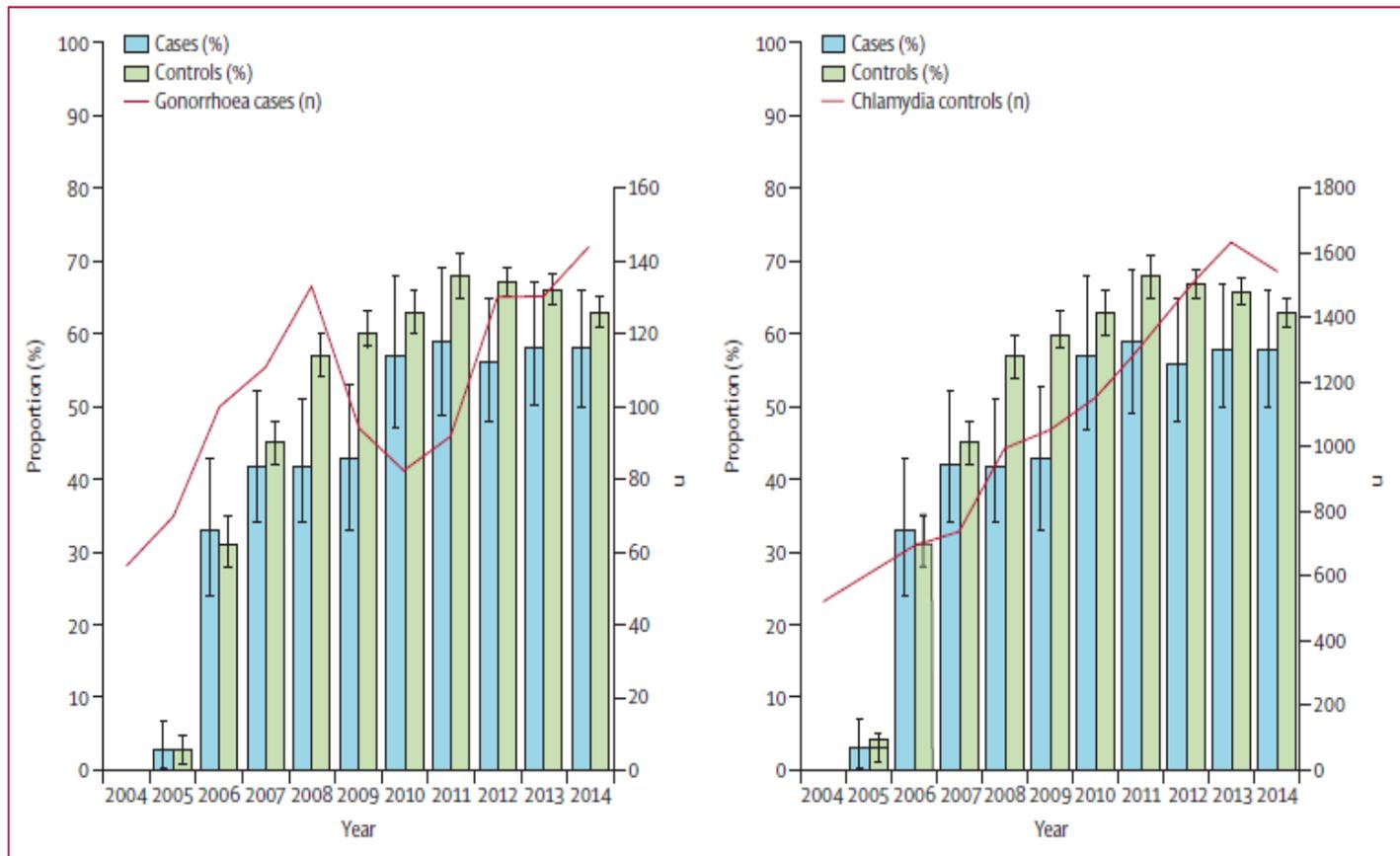


Figure 3: Year-by-year difference in the proportion of cases and controls vaccinated and number of gonorrhoea (A) and chlamydia (B) diagnoses (A) and (B) are identical except for the gonorrhoea and chlamydia counts (note the difference in right axis scales). The difference in height between each pair of columns is the unadjusted estimate of the effect of the vaccine for each year. Error bars show 95% CIs. The number of cases of gonorrhoea and chlamydia gives an indication of the sample size (and by proxy the power) in the estimate for each year. The strongest measured effect occurred in the years immediately after the vaccination programme, then fell over time, suggest a possible waning of the vaccine effect.

Closing Thoughts

- Systematically collected surveillance data can inform treatment policy, and help focus epidemiological efforts on developing issues
- The “data feedback” loop is essential
- Surveillance efforts require continual investment in infrastructure
- The gonococcus will continue to evolve and develop new resistant determinants, underscoring the need for vigilance

DRUG-RESISTANT NEISSERIA GONORRHOEAE



THREAT LEVEL
URGENT

This bacteria is an immediate public health threat that requires urgent and aggressive action.

- GISP viewed as a prototype surveillance network
- CARB initiatives have resulted in major changes and expansion to GISP
- Impact on surveillance program of these changes remains to be seen
- Antimicrobial stewardship / vaccine / POCT

CDC's Antibiotic Resistance (AR) Solutions Initiative

Investing to Defend the United States against Antibiotic Resistance



AND

When the antibiotic well runs dry....

82 Treatment of Gonorrhoea in the Male

meter. This instrument, when introduced into the urethra, can be expanded at will, the degree of expansion being

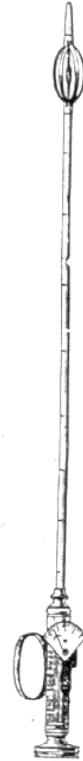


FIG. 18.



FIG. 19.

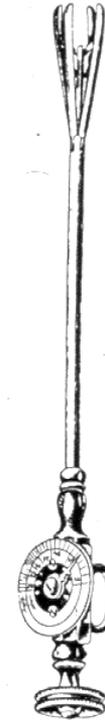
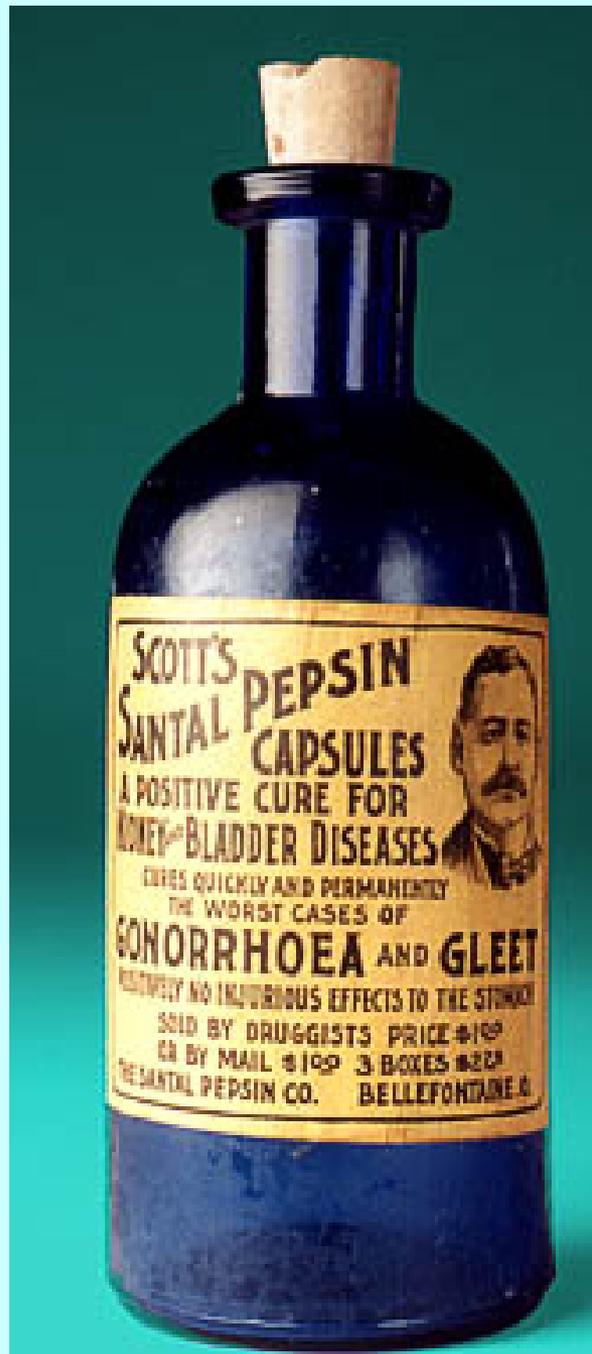


FIG. 20.

indicated by a pointer on a dial. The figures on the dial correspond to the French, or Charrière's, scale for all urethral instruments. In this scale each number represents



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CURES QUICKLY AND PERMANENTLY
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WITHOUT ANY INJURIOUS EFFECTS TO THE STOMACH
SOLD BY DRUGGISTS PRICE \$1.00
OR BY MAIL \$1.00 3 BOXES \$2.00
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Thank you

mhamill6@jhu.edu

Summary

- Antimicrobial resistance in NG is a worldwide problem
- Increases in NG occurring, especially MSM (homosexual men)
- Critical access to effective medications—need new drug development
- Diagnostic issues since few cultures performed—molecular assay development
- Control of antibiotic use (stewardship) –but this will take time