Sexually Transmitted Disease Surveillance 2012:

Gonococcal Isolate Surveillance Project (GISP) Supplement & Profiles

Division of STD Prevention
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Web Site
The online version of this report is available at http://www.cdc.gov/std/gisp.

Gonococcal Isolate Surveillance Project (GISP) Supplement and Profiles, 2012

Introduction

Although gonorrhea is an ancient disease that has affected humans for centuries, this sexually transmitted disease remains prevalent: gonorrhea is the second most commonly reported notifiable disease in the United States and 334,826 cases were reported in 2012.[1] As with other STDs, the reporting of gonorrhea is incomplete and the Centers for Disease Control and Prevention (CDC) estimates that approximately 820,000 cases of gonorrhea occur yearly in the US.[2] Infections due to *Neisseria gonorrhoeae* are a major cause of pelvic inflammatory disease (PID) in the United States. PID can lead to serious reproductive outcomes in women, such as tubal infertility, ectopic pregnancy, and chronic pelvic pain.

The cornerstone of public health gonorrhea control is detection and treatment of gonococcal infections, so as to prevent sequelae and limit disease transmission. For decades, gonorrhea has been easily treated with a single dose of a single antimicrobial agent. However, *N. gonorrhoeae* has progressively developed resistance to each antimicrobial used for treatment of gonorrhea. In the last decade, development of fluoroquinolone resistance resulted in the availability of only a single class of antimicrobials that met CDC's efficacy standards – the cephalosporins. Recently, declining susceptibility to cefixime resulted in a change to the CDC treatment guidelines, so that dual therapy with ceftriaxone and azithromycin or doxycycline is the only CDC-recommended treatment regimen for uncomplicated gonorrhea.[3] In 2012, CDC also released the US Cephalosporin-Resistant *Neisseria gonorrhoeae* Public Health Response Plan (http://www.cdc.gov/std/treatment/Ceph-R-ResponsePlanJuly30-2012.pdf). Continued surveillance of *N. gonorrhoeae* antimicrobial susceptibility is critical.

Gonococcal Isolate Surveillance Project (GISP) Overview

The Gonococcal Isolate Surveillance Project (GISP) was established in 1986 to monitor trends in antimicrobial susceptibilities of *N. gonorrhoeae* strains in the United States to establish an evidence-based rationale for selection of gonococcal therapies. GISP is a sentinel surveillance system and collaboration between participating STD clinics and their state or local public health authorities, GISP regional laboratories, and CDC.

N. gonorrhoeae isolates are collected monthly from up to the first 25 men with urethral gonorrhea attending participating STD clinics. Clinical and demographic data are abstracted from medical records. Isolates are shipped from participating clinics to the GISP regional laboratories for agar dilution antimicrobial susceptibility testing. Isolates are tested to determine minimum inhibitory concentrations (MICs) of penicillin, tetracycline, spectinomycin, ceftriaxone, cefixime, ciprofloxacin, and azithromycin. Cefixime susceptibility testing was discontinued in 2007 and re-started in 2009. Cefpodoxime susceptibility testing was conducted during 2009–2012.

Findings from GISP have directly contributed to CDC's STD Treatment Guidelines in 1993, 1998, 2002, 2006, 2010, and updates in 2000, 2004, 2007 and 2012. Data from GISP have also

been presented in multiple scientific papers and conference presentations. Additional information on GISP and links to recent publications can be found on the GISP website: http://www.cdc.gov/std/gisp/.

2012 GISP Sites and Regional Laboratories

STD clinics affiliated with 29 state or city health departments contributed 5,495 gonococcal isolates to GISP in 2012. Of these sites, 13 current sites have participated continuously since 1987: Albuquerque, New Mexico; Atlanta, Georgia; Baltimore, Maryland; Birmingham, Alabama; Denver, Colorado; Honolulu, Hawaii; New Orleans, Louisiana; Philadelphia, Pennsylvania; Phoenix, Arizona; Portland, Oregon; San Diego, California; San Francisco, California; and Seattle, Washington. The other current sites participated during the following years: Chicago, Illinois (1996–2012); Cleveland, Ohio (1991-2012); Columbus, Ohio (2012); Dallas, Texas (2000–2012); Pontiac, Michigan (2012), Greensboro, North Carolina (2002–2012), Kansas City, Missouri (1991–2001, 2007–2012), Los Angeles, California (2003–2012), Las Vegas, Nevada (2002–2012); Miami, Florida (1998–2012), Minneapolis, Minnesota (1992–2012), New York, New York (2006–2012), Oklahoma City, Oklahoma (2003–2012), Orange County, California (1991–2012), Richmond, Virginia (2007–2012), and Tripler Army Medical Center (2001–2012).

Antimicrobial susceptibility testing was conducted by the Cleveland Clinic Foundation (Cleveland, Ohio), Emory University (Atlanta, Georgia), Texas Department of State Health Services (Austin, Texas), University of Alabama at Birmingham (Birmingham, Alabama), and University of Washington (Seattle, Washington).

Susceptibility to Antimicrobial Agents

Susceptibility to cefixime

Susceptibility testing for cefixime began in 1992, was discontinued in GISP in 2007, and was re-started in 2009. The distribution of cefixime MICs each year from 2009-2012 is displayed in Figure 1 and Table 1. Each year, over 70% of isolates exhibited cefixime MICs ≤0.015 μg/ml. The percentage of isolates with elevated cefixime MICs (≥0.25 μg/ml) increased from 0.1% in 2006 to 1.4% in 2010 and 2011, and declined to 1.0% in 2012.

Additional data on susceptibility to cefixime can be found in Sexually Transmitted Disease Surveillance 2012.[1]

Susceptibility to ceftriaxone

Susceptibility testing for ceftriaxone began in 1987. The distribution of ceftriaxone MICs each year from 2008-2012 is displayed in Figure 2 and Table 2. Each year, over 76% of isolates exhibited ceftriaxone MICs ≤0.008 μg/ml. The percentage of GISP isolates that exhibited elevated ceftriaxone minimum inhibitory concentrations (MICs), defined as ≥0.125 μg/ml, increased from 0.1% in 2008 to 0.4% in 2011, and decreased to 0.3% in 2012.

Additional data on susceptibility to ceftriaxone can be found in Sexually Transmitted Disease Surveillance 2012.[1]

Susceptibility to azithromycin

Susceptibility testing for azithromycin began in 1992. The distribution of azithromycin MICs each year from 2008-2012 is displayed in Table 3 and Figure 3. The median azithromycin MIC (MIC50) was 0.25 μg/ml each year. The proportion of GISP isolates with azithromycin MICs of ≥ 2.0 μg/ml increased from 0.2% in 2008 to 0.5% in 2010, and then decreased to 0.3% in 2012.

Additional data on susceptibility to azithromycin can be found in Sexually Transmitted Disease Surveillance 2012.[1]

Susceptibility to ciprofloxacin

Susceptibility testing for ciprofloxacin began in 1990. The proportion of GISP isolates with ciprofloxacin resistance (MIC ≥1 μg/ml) peaked in 2007 at 14.8%. Following a decline in 2008 and 2009, the proportion increased from 9.6% in 2009 to 14.7% in 2012. The prevalence of resistance increased sharply among isolates from men who have sex with men (MSM) during the 2000s, and peaked at 38.9% in 2006 (Figure 4). In 2012, 27.1% of isolates from MSM exhibited ciprofloxacin resistance. The prevalence of ciprofloxacin resistance increased during 2000–2007 among isolates from men who report sex exclusively with women (MSW), decreased during 2008 and 2009, and increased during 2010–2012. In 2012, 8.7% of isolates from MSW exhibited ciprofloxacin resistance.

Susceptibility to other antimicrobials

Data on susceptibility to other antimicrobials can be found in the Site Profiles section of this document and Sexually Transmitted Disease Surveillance 2012.[1]

Site-Specific Profiles

The site-specific profiles consist of figures depicting the demographic and clinical data of the men who submitted specimens for GISP and the antimicrobial susceptibility results of the *N. gonorrhoeae* isolates submitted. Each figure is labeled with the participating site and the number of isolates on which the site's data are based. The maximum number of isolates submitted by each site annually is 300. The number of isolates submitted is lower for some sites located in areas with low gonorrhea morbidity.

Definitions of terms and abbreviations used in the site-specific figures

Figure A: Cases with unknown age were excluded.

Figure B: Cases with unknown race were excluded. The "Asian" category includes Native Hawaiians and the "Other" category includes participants who selected more than one race category. The "Other" category is not used in national gonorrhea reporting; Native Am. = Native Americans

Figure D: Other Cephalo.= cefoxitin, cefpodoxime, ceftizoxime, ceftibuten, cefdinir, and cefotaxime; Other=other less frequently used drugs, including azithromycin

Figure E: Doxy/Tet=doxycycline/tetracycline; Azi/Ery=azithromycin/erythromycin

Figure F: PenR= penicillinase-producing N. gonorrhoeae and chromosomally mediated penicillin-resistant *N. gonorrhoeae*; TetR=chromosomally and plasmid-mediated tetracycline-resistant *N. gonorrhoeae*; QRNG=ciprofloxacin-resistant *N. gonorrhoeae*

GISP Antimicrobial Susceptibility Criteria

Antimicrobial susceptibility criteria used in GISP in 2012 are as follows:

- Ceftriaxone, minimum inhibitory concentration (MIC) ≥0.5 µg/ml (decreased susceptibility)*
- Cefixime, MIC ≥0.5 µg/ml (decreased susceptibility)*
- Azithromycin, MIC ≥2.0 µg/ml (decreased susceptibility)*
- Spectinomycin, MIC ≥128.0 µg/ml (resistance)
- Ciprofloxacin, MIC 0.125–0.5 µg/ml (intermediate resistance)
- Ciprofloxacin, MIC ≥1.0 µg/ml (resistance)
- Penicillin, MIC ≥2.0 µg/ml (resistance)
- Tetracycline, MIC ≥2.0 µg/ml (resistance)

The majority of these criteria are also recommended by the Clinical and Laboratory Standards Institute (CLSI).[4]

* Resistance to cefixime and ceftriaxone, and resistance and susceptibility to azithromycin are not defined by CLSI

Additional resources

Additional information on GISP, as well as useful resources and links, may be found on the CDC Division of STD Prevention Antimicrobial Resistant Gonorrhea website:
http://www.cdc.gov/std/Gonorrhea/arg/default.htm

Other United States surveillance data on *N. gonorrhoeae* and other STDs and additional data from GISP may be found on the CDC DSTDP Surveillance and Statistics website:
http://www.cdc.gov/std/stats/

Data on antimicrobial resistance in *N. gonorrhoeae* and other bacterial pathogens may be found in CDC's report, Antibiotic Resistance Threats in the United States, 2013:
http://www.cdc.gov/drugresistance/threat-report-2013/

Recent publications of GISP data

Kirkcaldy RD, Kidd S, Papp J, Weinstock HS, Bolan GA. Trends in antimicrobial resistance in *Neisseria gonorrhoeae* in the United States—the Gonococcal Isolate Surveillance Project (GISP), January 2006–June 2012. Sexually Transmitted Infections 2013;89(Suppl4):iv5–10.

Kirkcaldy RD, Zaidi A, del Rio C, Hook EW, Holmes KK, Soge OO, Hall G, Papp J, Bolan G, Weinstock HS. *Neisseria gonorrhoeae* antibiotic resistance among men who have sex with men, the Gonococcal Isolate Surveillance Project, 2005–2010. Annals of Internal Medicine 2013;158(5):321–328.

Kirkcaldy RD, Bolan GA, Wasserheit JN. Cephalosporin-resistant gonorrhea in North America. JAMA 2013;309(2):185–187.

CDC. CDC Public Health Grand Rounds: The growing threat of multidrug-resistant gonorrhea. Morbidity and Mortality Weekly Report (*MMWR*) 2013; 62(6):103–106.

Soge OO, Harger D, Schafer S, et al. Emergence of increased azithromycin resistance during unsuccessful treatment of *Neisseria gonorrhoeae* infection with azithromycin (Portland, Oregon, 2011). Sexually Transmitted Diseases 2012;39(11):877-9.

CDC. Update to CDC's sexually transmitted diseases treatment guidelines, 2010: Oral cephalosporins are no longer a recommended treatment for gonococcal infections. Morbidity and Mortality Weekly Report (*MMWR*) 2012; 61(31):590–594.

Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. New England Journal of Medicine 2012;366(6):485–497.

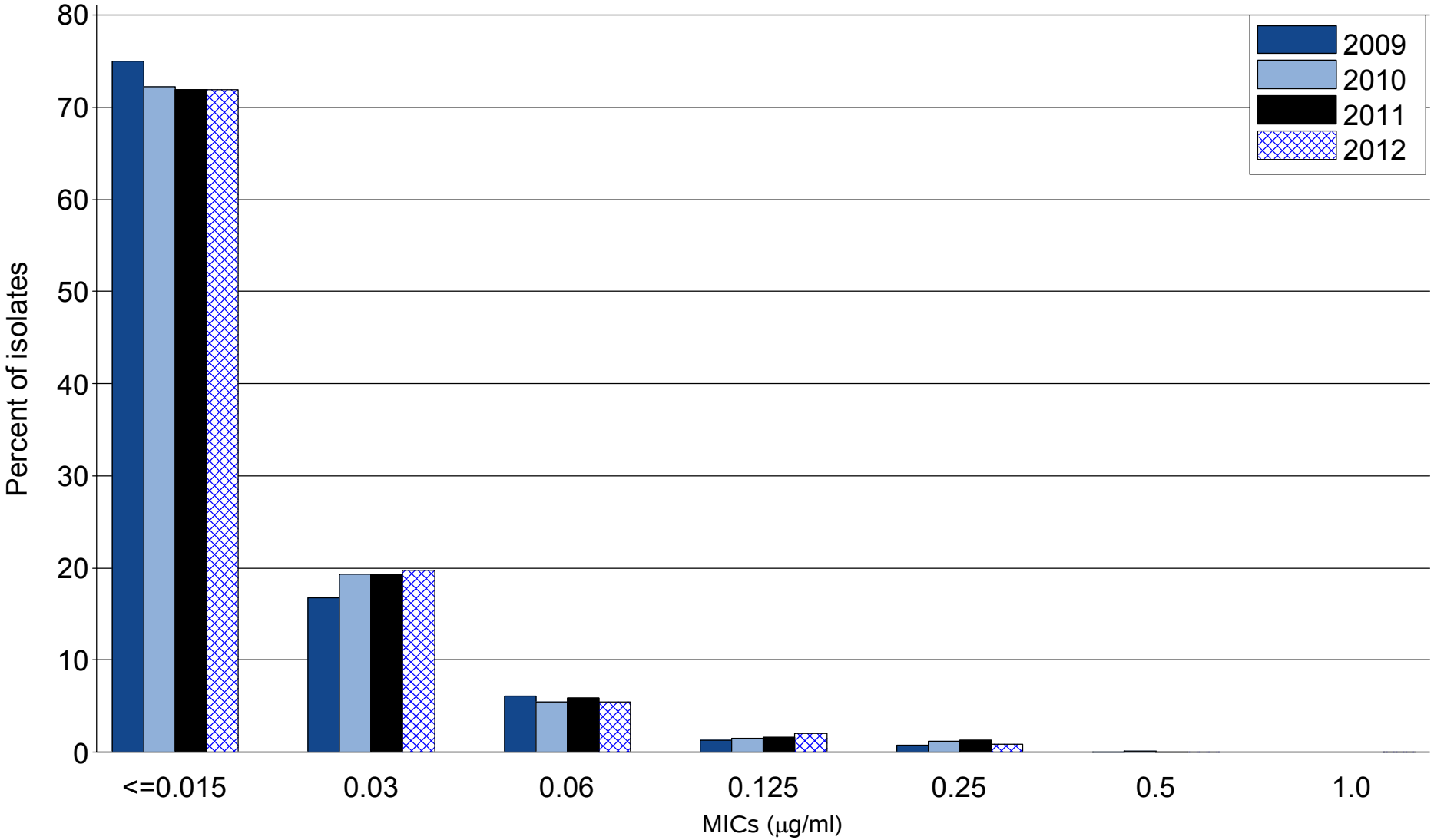
CDC. Trends in cephalosporin susceptibility among *Neisseria gonorrhoeae* isolates – United States, January 2000–June 2010. Morbidity and Mortality Weekly Report (*MMWR*) 2011;60(26): 873–877.

CDC. *Neisseria gonorrhoeae* infections with high minimum inhibitory concentrations to azithromycin-San Diego County, California, 2009. Morbidity and Mortality Weekly Report (*MMWR*) 2011;60(18):579–581.

References

1. CDC. *Sexually Transmitted Diseases Surveillance 2012*. Atlanta: US Department of Health and Human Services; 2013.
2. Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. Sexually Transmitted Diseases 2013; 40(3):187–193.
3. CDC. Update to CDC's sexually transmitted diseases treatment guidelines, 2010: Oral cephalosporins are no longer a recommended treatment for gonococcal infections. Morbidity and Mortality Weekly Report (*MMWR*) 2012; 61(31):590–594.
4. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; Twentieth Informational Supplement, M100-S20. National Committee for Clinical Laboratory Standards, 2010;29(3):84–86.

Figure 1. Distribution of Minimum Inhibitory Concentrations (MICs) of Cefixime Among *Neisseria gonorrhoeae* Isolates, Gonococcal Isolate Surveillance Project (GISP), 2009-2012



NOTE: Isolates were not tested for cefixime susceptibility in 2007 and 2008.

Figure 2. Distribution of Minimum Inhibitory Concentrations (MICs) of Ceftriaxone Among *Neisseria gonorrhoeae* Isolates, Gonococcal Isolate Surveillance Project (GISP), 2008-2012

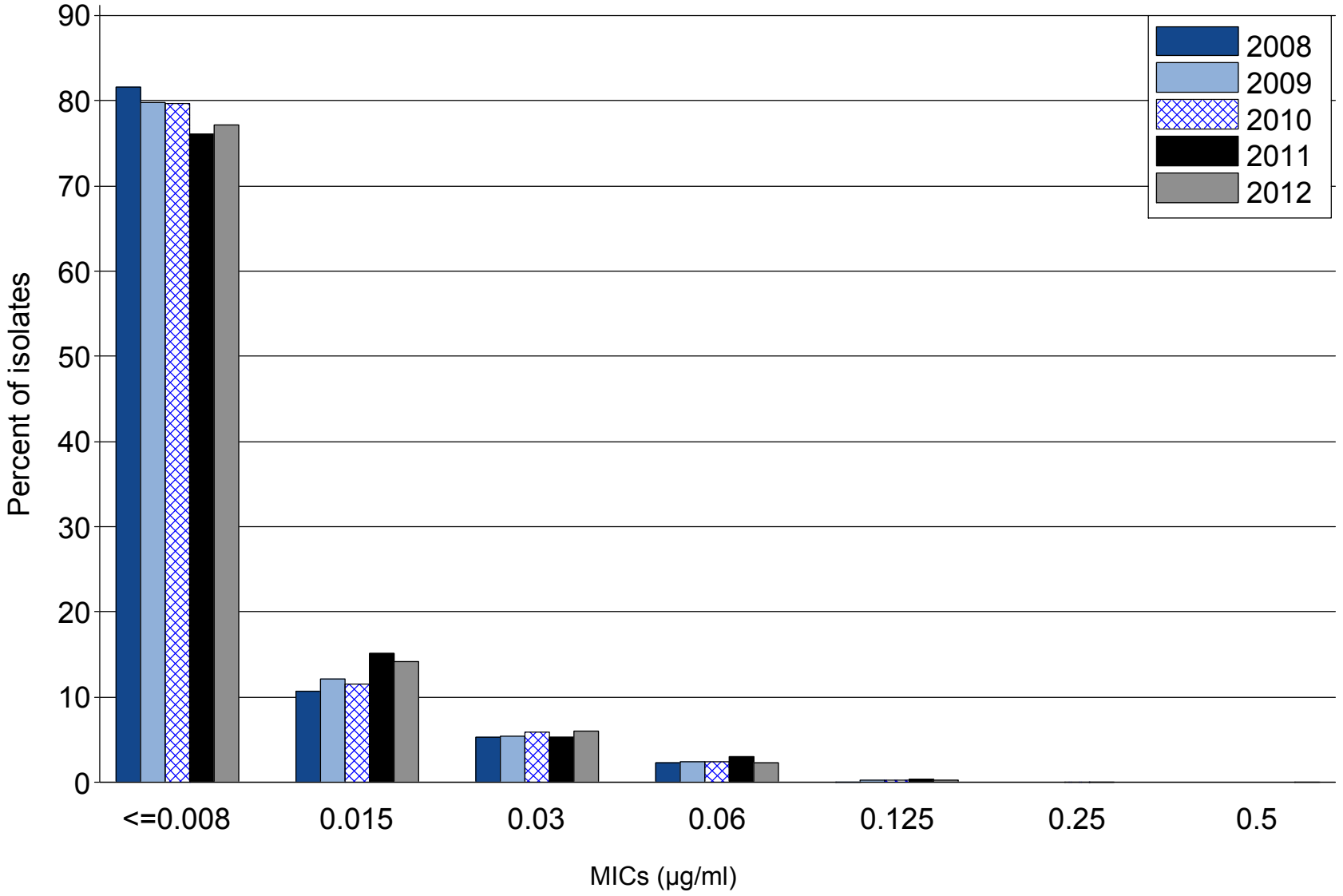


Figure 3. Distribution of Minimum Inhibitory Concentrations (MICs) of Azithromycin Among *Neisseria gonorrhoeae* Isolates, Gonococcal Isolate Surveillance Project (GISP), 2008-2012

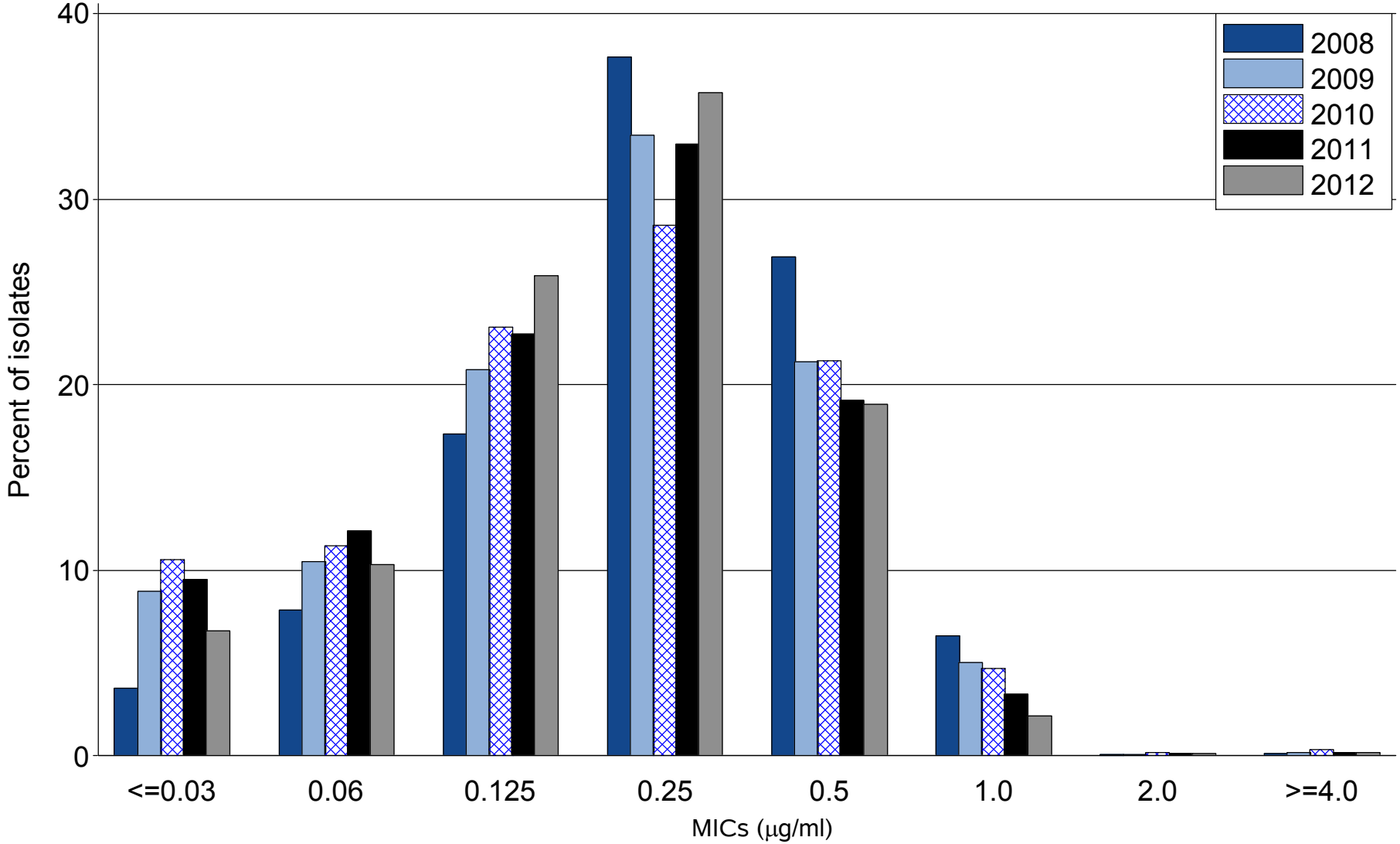
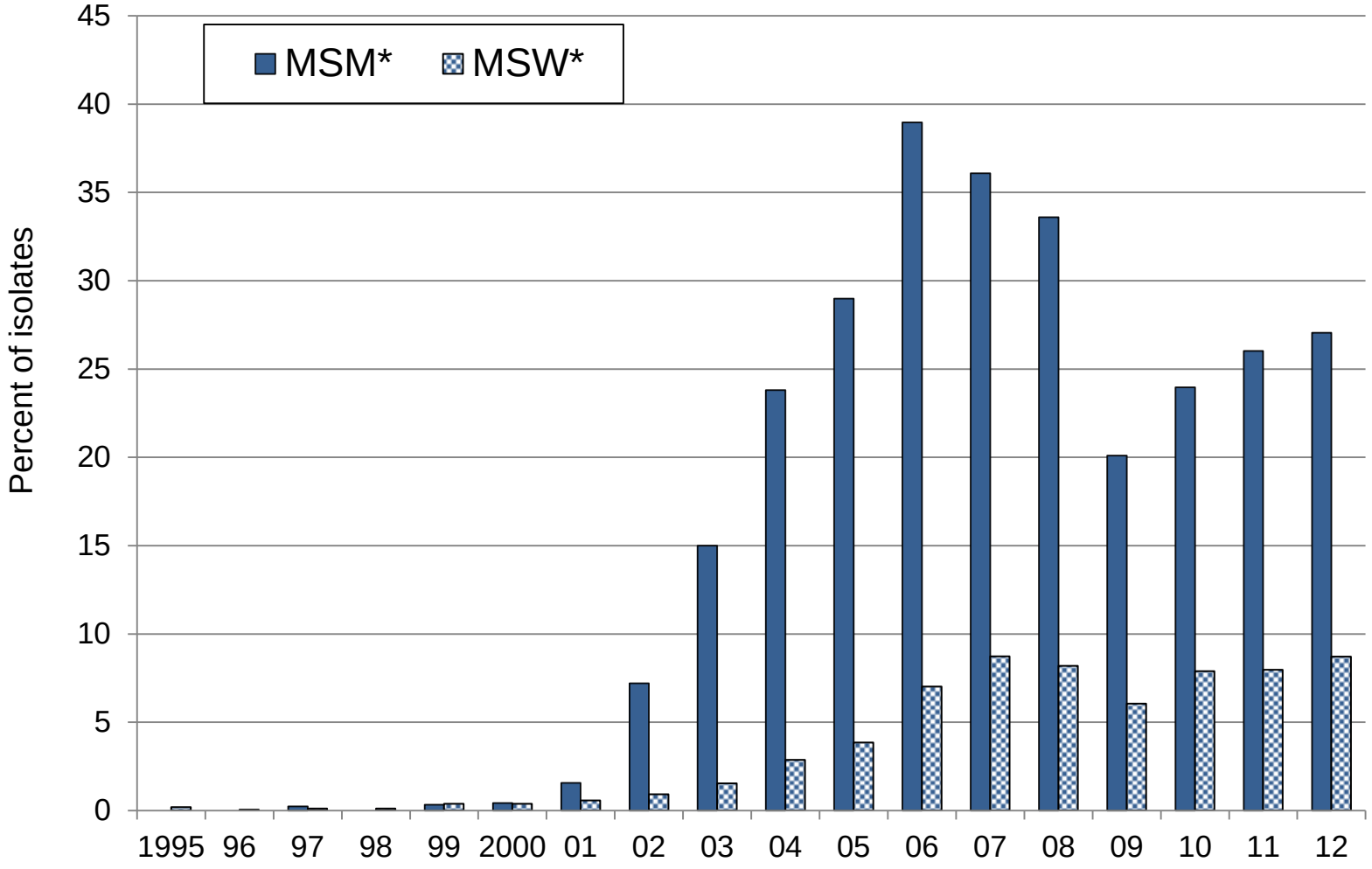


Figure 4. Percentage of *Neisseria gonorrhoeae* Isolates that are Ciprofloxacin-Resistant by Sex of Sex Partner, Gonococcal Isolate Surveillance Project, 1995-2012



*MSM=men who have sex with men; MSW=men who have sex with women only.

Table 1. Distribution of Minimum Inhibitory Concentrations (MICs) of Cefixime among *Neisseria gonorrhoeae* Isolates, Gonococcal Isolate Surveillance Project, 2009–2012

	Minimum Inhibitory Concentrations (µg/ml)							
Year	**≤0.015** **n (%)**	**0.030** **n (%)**	**0.060** **n (%)**	**0.125** **n (%)**	**0.250** **n (%)**	**0.500** **n (%)**	**1.000** **n (%)**	**Total** **n**
2009	4219 (74.9)	946 (16.8)	344 (6.1)	76 (1.4)	41 (0.7)	4 (0.1)	0 (0.0)	5630
2010	4113 (72.3)	1102 (19.4)	313 (5.5)	88 (1.6)	68 (1.2)	9 (0.2)	0 (0.0)	5693
2011	3930 (71.9)	1054 (19.3)	319 (5.8)	90 (1.7)	71 (1.3)	3 (0.1)	0 (0.0)	5467
2012	3951 (71.9)	1083 (19.7)	298 (5.4)	111 (2.0)	49 (0.9)	2 (0.0)	1 (0.0)	5495

Note: Isolates were not tested for cefixime susceptibility in 2007 and 2008.
Percentages represent row percentages.

Table 2. Distribution of Minimum Inhibitory Concentrations (MICs) of Ceftriaxone among *Neisseria gonorrhoeae* Isolates, Gonococcal Isolate Surveillance Project, 2008–2012

	Minimum Inhibitory Concentrations (µg/ml)							
Year	**≤0.008** n (%)	**0.015** n (%)	**0.030** n (%)	**0.060** n (%)	**0.125** n (%)	**0.250** n (%)	**0.500** n (%)	**Total** n
2008	4673 (81.7)	612 (10.7)	305 (5.3)	129 (2.3)	4 (0.1)	0 (0.0)	0 (0.0)	5723
2009	4494 (79.8)	681 (12.1)	303 (5.4)	136 (2.4)	16 (0.3)	0 (0.0)	0 (0.0)	5630
2010	4539 (79.7)	659 (11.6)	338 (5.9)	138 (2.4)	16 (0.3)	3 (0.1)	0 (0.0)	5693
2011	4161 (76.1)	830 (15.2)	289 (5.3)	166 (3.0)	20 (0.4)	1 (0.0)	0 (0.0)	5467
2012	4241 (77.2)	779 (14.2)	331 (6.0)	129 (2.4)	14 (0.3)	0 (0.0)	1 (0.0)	5495

Note: Percentages represent row percentages.

Table 3. Distribution of Minimum Inhibitory Concentrations (MICs) of Azithromycin among *Neisseria gonorrhoeae* Isolates, Gonococcal Isolate Surveillance Project, 2008–2012

	Minimum Inhibitory Concentrations (µg/ml))										
Year	**≤0.030 n (%)**	**0.060 n (%)**	**0.125 n (%)**	**0.250 n (%)**	**0.500 n (%)**	**1.000 n (%)**	**2.000 n (%)**	**4.000 n (%)**	**8.000 n (%)**	**≥16.00 n (%)**	**Total n**
2008	208 (3.6)	449 (7.8)	991 (17.3)	2154 (37.6)	1540 (26.9)	370 (6.5)	3 (0.1)	2 (0.0)	2 (0.0)	4 (0.1)	5723
2009	499 (8.9)	588 (10.4)	1172 (20.8)	1883 (33.4)	1194 (21.2)	282 (5.0)	3 (0.1)	2 (0.0)	5 (0.1)	2 (0.0)	5630
2010	603 (10.6)	643 (11.3)	1314 (23.1)	1627 (28.6)	1211 (21.3)	268 (4.7)	9 (0.2)	1 (0.0)	9 (0.2)	8 (0.1)	5693
2011	518 (9.5)	663 (12.1)	1242 (22.7)	1801 (32.9)	1046 (19.1)	181 (3.3)	7 (0.1)	3 (0.0)	5 (0.1)	1 (0.0)	5467
2012	369 (6.7)	567 (10.3)	1421 (25.9)	1963 (35.7)	1041 (18.9)	119 (2.2)	7 (0.1)	1 (0.0)	2 (0.0)	5 (0.1)	5495

Note: Percentages represent row percentages.