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## Trends in *Neisseria gonorrhoeae* susceptibility to cephalosporins in the United States, 2006–2014

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### INTRODUCTION

Gonorrhea is a common sexually transmitted disease that, if untreated, can cause reproductive health complications. Gonorrhea treatment has been repeatedly jeopardized by antimicrobial resistance. To ensure effective treatment, the Centers for Disease Control and Prevention (CDC) periodically updates treatment guidelines based on resistance trends. In 2010 and following declining cephalosporin susceptibility in several countries, CDC updated its treatment recommendation from single-dose cephalosporin (injectable ceftriaxone or oral cefixime) to intensified combination therapy of either ceftriaxone (at a higher dose than previously recommended) or cefixime, plus a second antimicrobial.<sup>1</sup> CDC again updated guidelines in 2012 to recommend ceftriaxone-based combination therapy as the single recommended therapy.<sup>1</sup> We describe recent gonococcal cephalosporin susceptibility trends emphasizing changes following publication of these guidelines.

### METHODS

We analyzed 2006–2014 data from CDC's Gonococcal Isolate Surveillance Project (GISP), a sentinel system which monitors antimicrobial susceptibility in urethral isolates from consecutive men with gonorrhea in US public sexually transmitted disease clinics.<sup>2</sup> Jurisdictions competitively apply to participate. GISP is not designed to be nationally representative, but rather to detect emerging changes in susceptibility. Susceptibility is determined by agar dilution. Isolates with ceftriaxone minimum inhibitory concentrations 0.125 µg/mL or cefixime minimum inhibitory concentrations 0.25 µg/mL were

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categorized as exhibiting reduced susceptibility. Trends were examined overall (and tested for significance [two-sided  $P < 0.05$ ] by the Cochran-Armitage trend test) and stratified by region and gender of sex partner. Analyses were conducted using SAS version 9.3 (SAS Institute). GISP was determined by the Office of the Associate Director for Science, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, CDC to be a surveillance activity rather than human subject research; isolates are collected during clinical care and separate consent is not required. Gonorrhea is notifiable; health departments have authority to collect and transmit case data to CDC.

## RESULTS

During 2006–2014, 51,144 isolates were collected in 34 cities. Most isolates were collected in the West (36.6%) or South (32.2%); gay, bisexual or other men who have sex with men contributed 28.1% of isolates. The percentage of participants treated with ceftriaxone 250 mg intramuscularly increased from 8.7% (95% confidence interval [CI] 8.0%–9.5%) in 2006 to 96.6% (96.1%–97.1%) in 2014 ( $p < 0.001$ ). The percentage of isolates with reduced cefixime susceptibility increased from 0.1% ( $< 0.1\%$ –0.2%) in 2006 to 1.4% (1.1%–1.7%) in 2011, and then declined to 0.4% (0.3%–0.6%) in 2013 (Figure). In 2014, the percentage was 0.8% (0.5%–1.0%). Among isolates from men who have sex with men, the percentage with reduced susceptibility peaked at 4.0% (3.1%–5.0%) and was 1.3% (0.8%–1.9%) in 2014 (Table). Among men who report sex exclusively with women, the percentage remained low. In regards to ceftriaxone, the annual overall percentage of isolates with reduced susceptibility fluctuated between 0.1% ( $< 0.1\%$ –0.1%) and 0.4% (0.2%–0.6%) (Figure).

## DISCUSSION

The prevalence of reduced cefixime susceptibility declined nearly 70% between 2011 and 2013, suggesting a halting of a drift towards resistance. Although this improvement in susceptibility appears temporally correlated with treatment guideline changes, we cannot establish a causal relationship. Observed susceptibility trends mirror those in other countries, only some of which changed treatment guidance to ceftriaxone-based dual therapy.<sup>3,4</sup> Other factors, such as mutation fitness costs or faltering transmission of a clone, might have contributed to improved susceptibility. The 2014 data, however, suggest that improvements in susceptibility may be short-lived.

Although sampling is systematic, participants and participating sites are not selected at random. Thus, prevalence data from participating sites are not expected to be nationally representative. However, data from GISP have been found to reflect trends in other U.S. settings and populations.<sup>5,6</sup> Not all jurisdictions participated continuously during 2006–2014. GISP data cannot distinguish incident infections from repeated sampling of the same infection (although this is expected to be rare).

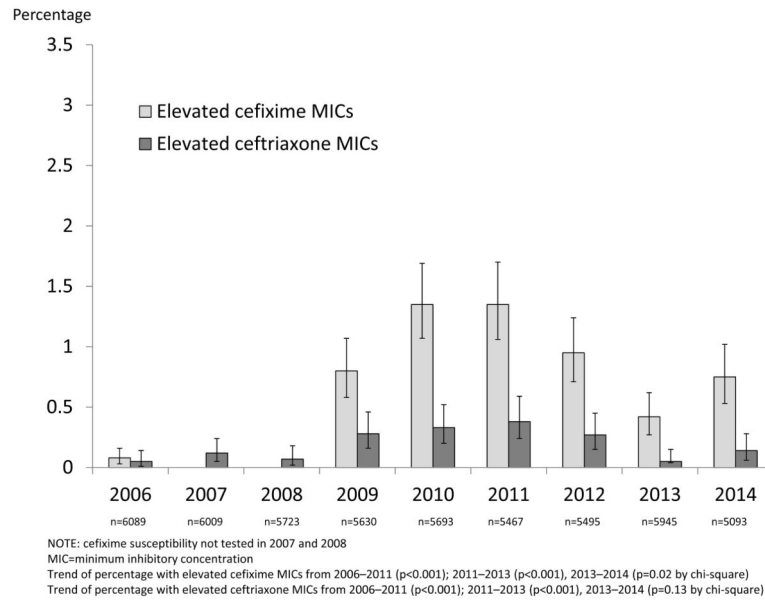
The increased prevalence of reduced cefixime susceptibility in 2014 highlights the need to maintain surveillance, search for new therapeutics, and ensure that gonorrhea is treated according to CDC guidelines.

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## References

1. Centers for Disease Control and Prevention. Update to CDC's sexually transmitted diseases treatment guidelines, 2010: Oral cephalosporins are no longer a recommended treatment for gonococcal infections. *MMWR Morb Mortal Wkly Rep*. 2012; 61:590–594. [PubMed: 22874837]
2. [accessed January 14, 2015] Gonococcal Isolate Surveillance Project (GISP) Protocol. Available at <http://www.cdc.gov/std/gisp/gisp-protocol-oct-2014.pdf>
3. Ison CA, Town K, Obi C, Chisholm S, Hughes G, Livermore DM, et al. Decreased susceptibility to cephalosporins among gonococci: data from the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) in England and Wales, 2007–2011. *Lancet Infect Dis*. 2013; 13:762–768. [PubMed: 23764300]
4. European Centre for Disease Prevention and Control. [accessed May 8, 2015] Gonococcal antimicrobial susceptibility in Europe —2012. Available at: <http://ecdc.europa.eu/en/publications/Publications/gonococcal-antimicrobial-susceptibility-surveillance-Europe-2012.pdf>
5. Kidd S, Lee MV, Maningas E, Komeya A, Kunimoto G, O'Connor N, et al. Gonococcal susceptibility to cephalosporins—Hawaii, 2003 to 2011. *Sex Transm Dis*. 2013; 40(9):756–759. [PubMed: 23949591]
6. Park, K.; Wright, J.; Fuller, S.; Hug, P.; Singh, A.; Steece, R., et al. Fluoroquinolone resistant *Neisseria gonorrhoeae* among women in the United States, 2004. Paper presented at: American Public Health Association 134th Annual Meeting and Exposition, American Public Health Association; November 8, 2006; Boston, MA.

**Figure.**

Percentage of urethral *Neisseria gonorrhoeae* isolates with reduced cefixime susceptibility (minimum inhibitory concentrations 0.25 µg/ml) or reduced ceftriaxone susceptibility (minimum inhibitory concentrations 0.125 µg/ml) by year, Gonococcal Isolate Surveillance Project, 2006–2014.

NOTE: cefixime susceptibility not tested in 2007 and 2008

MIC=minimum inhibitory concentration

Trend of percentage with elevated cefixime MICs from 2006–2011 ( $p<0.001$ ); 2011–2013 ( $p<0.001$ ), 2013–2014 ( $p=0.02$  by chi-square)

Trend of percentage with elevated ceftriaxone MICs from 2006–2011 ( $p<0.001$ ); 2011–2013 ( $p<0.001$ ), 2013–2014 ( $p=0.13$  by chi-square)

Percentage of urethral *Neisseria gonorrhoeae* isolates with reduced cefixime susceptibility (minimum inhibitory concentrations 0.25 µg/ml) by year and census region or gender of sex partner, Gonococcal Isolate Surveillance Project, 2006–2014

Table

Year	Census Region of United States				Gender of Sex Partner*	
	West n=14,611 % (95% CI)	Midwest n=9,125 % (95% CI)	Northeast n=3,206 % (95% CI)	South n=12,470 % (95% CI)	MSM n=11,621 % (95% CI)	MSW n=27,168 % (95% CI)
2006	0.2 (0.04–0.4) n=4/2489	0.0 (0–0.3) n=0/1420	0.0 (0.0–0.1) n=0/353	0.1 (0.0–0.3) n=1/1827	0.2 (0.02–0.6) n=2/1281	0.1 (0.01–0.2) n=3/4681
2007/2008	--	--	--	--	--	--
2009	1.9 (1.4–2.6) n=37/1924	0.5 (0.2–1.0) n=7/1398	0.3 (0.01–1.4) n=1/385	0.0 (0.0–0.2) n=0/1923	2.1 (1.4–3.0) n=29/1393	0.4 (0.2–0.6) n=16/4104
2010	3.3 (2.6–4.1) n=68/2072	0.5 (0.2–1.1) n=6/1146	0.4 (0.1–1.5) n=2/494	0.1 (0.0–0.3) n=1/1981	4.0 (3.1–5.0) n=64/1619	0.3 (0.2–0.6) n=13/3974
2011	3.0 (2.3–3.8) n=60/2031	0.5 (0.2–1.1) n=5/1061	0.8 (0.2–2.0) n=5/504	0.3 (0.1–0.6) n=5/1871	3.6 (2.7–4.6) n=57/1599	0.5 (0.3–0.7) n=17/3789
2012	1.7 (1.2–2.4) n=34/2010	1.0 (0.5–1.7) n=11/1135	0.4 (0.05–1.50) n=2/483	0.3 (0.03–0.5) 5/1867	2.2 (1.6–3.0) n=40/1792	0.3 (0.2–0.6) n=12/3626
2013	0.8 (0.5–1.3) n=17/2057	0.1 (0.01–0.4) n=2/1653	0.7 (0.1–2.0) n=3/441	0.2 (0.03–0.5) n=3/1794	0.8 (0.4–1.3) n=16/2070	0.2 (0.1–0.5) 9/3829
2014	1.3 (0.8–1.9) N=26/2028	0.3 (0.1–0.8) n=4/1312	1.0 (0.3–2.1) n=5/546	0.3 (0.1–0.7) n=3/1207	1.3 (0.8–1.9) n=24/1867	0.4 (0.2–0.7) 14/3165

NOTE: cefixime susceptibility not tested in 2007 and 2008

\* Excludes men with missing gender of sex partner data

CI = Confidence interval, MSM=Men who have sex with men, MSW=Men who report sex exclusively with women