

## Cephalosporin Susceptibility Among *Neisseria gonorrhoeae* Isolates — United States, 2000–2010

*Neisseria gonorrhoeae* is a major cause of pelvic inflammatory disease, ectopic pregnancy, and infertility, and it can facilitate human immunodeficiency virus (HIV) transmission (1). Emergence of gonococcal resistance to penicillin and tetracycline occurred during the 1970s and became widespread during the early 1980s. More recently, resistance to fluoroquinolones developed. Resistance was documented first in Asia, then emerged in the United States in Hawaii followed by other western states. It then became prevalent in all other regions of the United States. In Hawaii, fluoroquinolone resistance was first noted among heterosexuals; however, resistance in the United States initially became prevalent among men who have sex with men (MSM) before generalizing to heterosexuals. This emergence of resistance led CDC, in 2007, to discontinue recommending any fluoroquinolone regimens for the treatment of gonorrhea (2–3). CDC now recommends dual therapy for gonorrhea with a cephalosporin (ceftriaxone 250 mg) plus either azithromycin or doxycycline (4). This report summarizes trends in cephalosporin susceptibility among *N. gonorrhoeae* isolates in the United States during 2000–2010 using data from the Gonococcal Isolate Surveillance Project (GISP). During that period, the percentage of isolates with elevated minimum inhibitory concentrations (MICs) to cephalosporins ( $\geq 0.25$   $\mu\text{g}/\text{mL}$  for cefixime and  $\geq 0.125$   $\mu\text{g}/\text{mL}$  for ceftriaxone) increased from 0.2% in 2000 to 1.4% in 2010 for cefixime and from 0.1% in 2000 to 0.3% in 2010 for ceftriaxone. Although cephalosporins remain an effective treatment for gonococcal infections, health-care providers should be vigilant for treatment failure and are requested to report its occurrence to state and local health departments. State and local public health departments should promote maintenance of laboratory capability to culture *N. gonorrhoeae* to allow testing of isolates for cephalosporin resistance. They also should develop enhanced surveillance and response protocols for gonorrhea treatment failures and report gonococcal treatment failures to CDC.

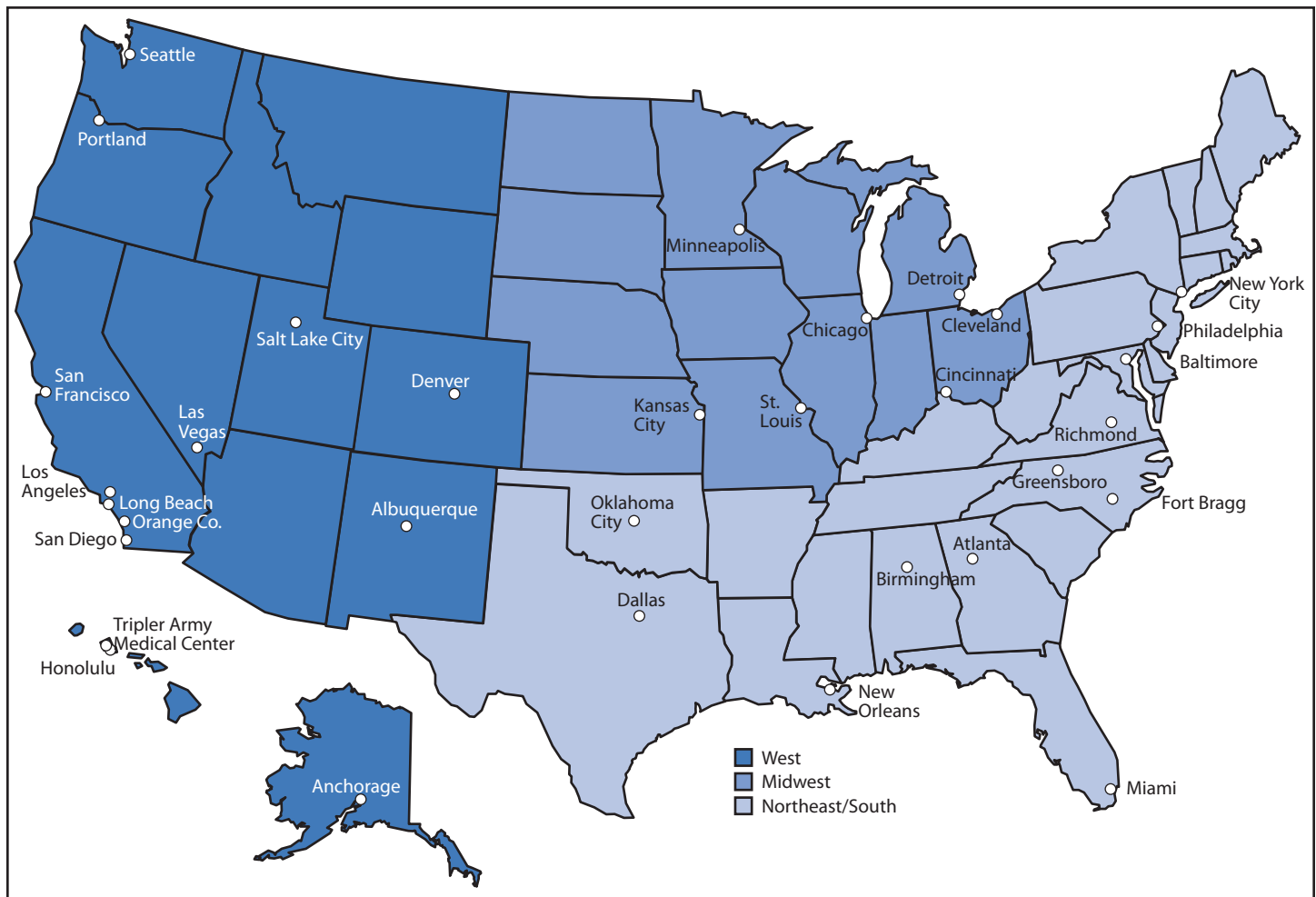
GISP is a CDC-sponsored, sentinel surveillance system that monitors antimicrobial susceptibilities in *N. gonorrhoeae* through ongoing testing of approximately 5,900 male urethral gonococcal isolates obtained annually from consecutive symptomatic men at 25–30 sexually transmitted disease (STD) clinics in the United States; approximately 4% of all reported gonorrhea cases among men are included annually (5). Antibiotic susceptibility is measured by MIC, the lowest concentration of an antibiotic that inhibits visible growth of the bacteria. MICs to cephalosporins (cefixime and ceftriaxone) among gonococcal isolates collected during

2000–2010 were analyzed. Cefixime susceptibilities were not determined during 2007–2008 because cefixime was unavailable in the United States during that period. Decreased antibiotic susceptibility for cefixime or ceftriaxone is defined by the Clinical and Laboratory Standards Institute (CLSI) as MICs  $\geq 0.5$   $\mu\text{g}/\text{mL}$ ; criteria for cefixime and ceftriaxone resistance in *N. gonorrhoeae* have not been defined (6). Because few isolates exhibited decreased susceptibility and increases in MICs can precede the emergence of resistance, the percentage of isolates with elevated MICs ( $\geq 0.25$   $\mu\text{g}/\text{mL}$  for cefixime and  $\geq 0.125$   $\mu\text{g}/\text{mL}$  for ceftriaxone) was assessed to determine if MICs to cephalosporins were increasing with time. These breakpoints were used in GISP for surveillance purposes. The analyses were stratified by U.S. census region and sex of sex partner. The South and Northeast regions were combined because fewer samples are collected in the eastern half of the country compared with the western half (Figure 1). Sex of sex partner was categorized as MSM or men who have sex exclusively with women (MSW). Resistance to penicillin (MIC  $\geq 2.0$   $\mu\text{g}/\text{mL}$ ), tetracycline (MIC  $\geq 2.0$   $\mu\text{g}/\text{mL}$ ), and ciprofloxacin (MIC  $\geq 1.0$   $\mu\text{g}/\text{mL}$ ), a fluoroquinolone, were assessed. Cochran-Armitage trend tests were performed to assess statistical significance ( $p < 0.05$ ).

An average of 5,865 isolates (range: 5,367–6,552) were tested annually during 2000–2010. Overall, the percentage of isolates with cefixime MICs  $\geq 0.25$   $\mu\text{g}/\text{mL}$  increased from 0.2% to 1.4% during 2000–2010 ( $p < 0.001$ ). The percentage of isolates with ceftriaxone MICs  $\geq 0.125$   $\mu\text{g}/\text{mL}$  increased from 0.1% to 0.3% during 2000–2010 ( $p = 0.047$ ). From 2000 to 2010, in the western region, the percentage of isolates with cefixime MICs  $\geq 0.25$   $\mu\text{g}/\text{mL}$  increased from 0% to 3.3% ( $p < 0.001$ ), and the percentage of isolates with ceftriaxone MICs  $\geq 0.125$   $\mu\text{g}/\text{mL}$  increased from 0% to 0.5% ( $p < 0.001$ ) (Table). In the western region, the most prominent increases in cefixime MICs were observed in Honolulu, Hawaii (0% in 2000 and 7.7% in 2010 [ $p < 0.001$ ]), and in California (0% in 2000 and 4.5% in 2010 [ $p < 0.001$ ]). An increase in ceftriaxone MICs also was observed in California (0% in 2000 and 0.6% in 2010 [ $p = 0.001$ ]).

Among MSM, the percentage of isolates with cefixime MICs  $\geq 0.25$   $\mu\text{g}/\text{mL}$  increased from 0% in 2000 to 4.0% during 2010 ( $p < 0.001$ ), and the percentage of isolates with ceftriaxone MICs  $\geq 0.125$   $\mu\text{g}/\text{mL}$  increased from 0% to 0.9% ( $p < 0.001$ ). Overall, no statistically significant increases occurred in cefixime or ceftriaxone MICs among MSW (Figure 2). Regionally, increases in the percentage of isolates with cefixime MICs  $\geq 0.25$   $\mu\text{g}/\text{mL}$

FIGURE 1. Sentinel sites participating in the Gonococcal Isolate Surveillance Project — United States, 2000–2010\*



\* Sites had continuous participation during 2000–2010 with the following exceptions (and years of participation): Anchorage (2000–2003); Detroit (2003–2010); Fort Bragg (2000–2002); Greensboro (2002–2010); Kansas City (2000–2001 and 2007–2010); Los Angeles (2003–2010); Las Vegas (2002–2010); Long Beach (2000–2007); New York City (2006–2010); Oklahoma City (2003–2010); Richmond (2007–2010); Salt Lake City (2003); St. Louis (2000–2004); and Tripler Army Medical Center (2001–2006 and 2009–2010).

among MSM were observed in all regions during 2000–2010 (West: 0% in 2000 and 5.0% in 2010 [ $p < 0.001$ ]; Midwest: 0% in 2000 and 3.4% in 2010 [ $p = 0.001$ ]; Northeast and South: 0% in 2000 and 0.9% in 2010 [ $p = 0.035$ ]). A significant increase among MSW was identified in the West (0% in 2000 and 1.3% in 2010 [ $p < 0.001$ ]); however, no change occurred in the Midwest (0.3% in 2000 and 0.1% in 2010), and a significant decrease occurred in the Northeast and South (0.4% in 2000 and 0% in 2010 [ $p < 0.001$ ]). For isolates with ceftriaxone MICs  $\geq 0.125 \mu\text{g/mL}$ , significant regional increases were observed among MSM in the West (0% in 2000 and 0.8% in 2010 [ $p < 0.001$ ]) and Midwest (0% in 2000 and 2.0% in 2010 [ $p = 0.046$ ]) and among MSW in the West (0% in 2000 and 0.2% in 2010 [ $p = 0.008$ ]); no significant increases were observed among MSM or MSW in other regions.

During 2009–2010, 13 (0.11%) of 11,323 isolates had decreased susceptibility to cefixime (MICs =  $0.5 \mu\text{g/mL}$ ), compared with seven (0.02%) of 41,462 isolates during 2000–2006 ( $p < 0.001$ ) (isolates were not tested for cefixime susceptibility during 2007–2008). All 2009–2010 isolates with decreased susceptibility to cefixime were resistant to tetracycline and ciprofloxacin, all but one were resistant to penicillin, and none exhibited decreased susceptibility to azithromycin ( $\geq 2 \mu\text{g/mL}$ ). Twelve of the men from whom the isolates were obtained were MSM; 10 men resided in the West, and three in the Midwest. No isolates had decreased susceptibility to ceftriaxone during 2000–2010.

TABLE. Number and percentage of gonorrhea isolates with cefixime MICs  $\geq 0.25 \mu\text{g/mL}$  and ceftriaxone MICs  $\geq 0.125 \mu\text{g/mL}$ , by region — Gonococcal Isolate Surveillance Project, United States, 2000–2010

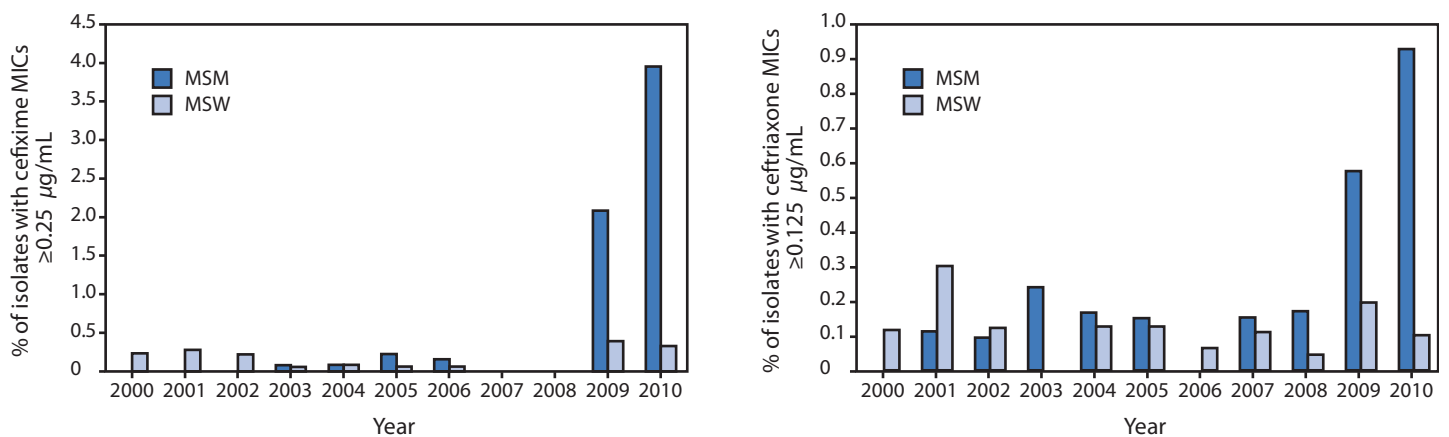
Year	Cefixime											
	West*			Midwest*			Northeast/South*			Total*		
	No.	(%)	No. of specimens tested	No.	(%)	No. of specimens tested	No.	(%)	No. of specimens tested	No.	(%)	No. of specimens tested
2000	0	(0.0)	1,910	3	(0.2)	1,565	7	(0.4)	1,986	10	(0.2)	5,461
2001	4	(0.2)	2,066	1	(0.1)	1,561	7	(0.4)	1,845	12	(0.2)	5,472
2002	0	(0.0)	2,163	1	(0.1)	1,273	8	(0.4)	1,931	9	(0.2)	5,367
2003	1	(0.0)	2,558	0	(0.0)	1,628	3	(0.1)	2,366	4	(0.1)	6,552
2004	2	(0.1)	2,540	2	(0.1)	1,673	2	(0.1)	2,109	6	(0.1)	6,322
2005	5	(0.2)	2,551	0	(0.0)	1,409	1	(0.0)	2,239	6	(0.1)	6,199
2006	4	(0.2)	2,489	0	(0.0)	1,420	1	(0.0)	2,180	5	(0.1)	6,089
2007	—	—	—	—	—	—	—	—	—	—	—	—
2008	—	—	—	—	—	—	—	—	—	—	—	—
2009	37	(1.9)	1,924	7	(0.5)	1,398	1	(0.0)	2,308	45	(0.8)	5,630
2010	68	(3.3)	2,072	6	(0.5)	1,146	3	(0.1)	2,475	77	(1.4)	5,693

Year	Ceftriaxone											
	West*			Midwest			Northeast/South			Total*		
	No.	(%)	No. of specimens tested	No.	(%)	No. of specimens tested	No.	(%)	No. of specimens tested	No.	(%)	No. of specimens tested
2000	0	(0.0)	1,910	5	(0.3)	1,565	0	(0.0)	1,986	5	(0.1)	5,461
2001	4	(0.2)	2,065	5	(0.3)	1,561	7	(0.4)	1,845	16	(0.3)	5,471
2002	0	(0.0)	2,163	1	(0.1)	1,273	6	(0.3)	1,931	7	(0.1)	5,367
2003	3	(0.1)	2,558	0	(0.0)	1,628	0	(0.0)	2,366	3	(0.0)	6,552
2004	3	(0.1)	2,540	3	(0.2)	1,673	3	(0.1)	2,109	9	(0.1)	6,322
2005	0	(0.0)	2,551	1	(0.1)	1,409	7	(0.3)	2,239	8	(0.1)	6,199
2006	1	(0.0)	2,489	0	(0.0)	1,420	2	(0.1)	2,180	3	(0.0)	6,089
2007	1	(0.0)	2,195	5	(0.4)	1,405	1	(0.0)	2,409	7	(0.1)	6,009
2008	4	(0.2)	1,906	0	(0.0)	1,407	0	(0.0)	2,410	4	(0.1)	5,723
2009	11	(0.6)	1,924	5	(0.4)	1,398	0	(0.0)	2,308	16	(0.3)	5,630
2010	11	(0.5)	2,072	4	(0.3)	1,146	4	(0.2)	2,475	19	(0.3)	5,693

Abbreviation: MICs = minimum inhibitory concentrations.

\* Region had a statistically significant ( $p < 0.05$ ) trend (increase or decrease) during 2000–2010, by the Cochran-Armitage test for trend.

FIGURE 2. Percentage of gonorrhea isolates with cefixime MICs  $\geq 0.25 \mu\text{g/mL}$  and ceftriaxone MICs  $\geq 0.125 \mu\text{g/mL}$ , by sex of sex partner — Gonococcal Isolate Surveillance Project, United States, 2000–2010



Abbreviations: MICs = minimum inhibitory concentrations; MSM = men who have sex with men; MSW = men who have sex exclusively with women.

**What is already known on this topic?**

Cephalosporins are a critical component of CDC-recommended gonorrhea treatment; however, declining cephalosporin susceptibility and cephalosporin treatment failures have been reported in Asia and Europe.

**What is added by this report?**

This report describes current trends in cephalosporin susceptibility among *Neisseria gonorrhoeae* isolates in the United States: minimum inhibitory concentrations (MICs) to cephalosporins are increasing, suggesting that susceptibility to cephalosporins might be declining. The prevalence of isolates with elevated MICs remains low overall.

**What are the implications for public health practice?**

Health-care providers should use ceftriaxone and azithromycin for treatment of gonorrhea, remain vigilant for gonorrhea cephalosporin treatment failures, and report treatment failures to their local or state health departments. Local and state health departments should promote the maintenance of local gonococcal culture capacity, establish options for local gonococcal antibiotic susceptibility testing, consider enhancing surveillance for cephalosporin-resistant gonorrhea, and report gonorrhea cases with cephalosporin treatment failure to CDC.

**Reported by**

*Carlos del Rio, MD, Rollins School of Public Health, Emory Univ, Atlanta, Georgia. Geraldine Hall, PhD, Dept of Clinical Pathology, Cleveland Clinic, Cleveland, Ohio. Edward W. Hook, Div of Infectious Disease, MD, Univ of Alabama at Birmingham. William L.H. Whittington, Dept of Medicine, Univ of Washington. Robert D. Kirkcaldy, MD, John R. Papp, PhD, Hillard Weinstock, MD, Div of STD Prevention, National Center for HIV, Hepatitis, STD, and TB Prevention; Erin L. Murray, PhD, EIS Officer, CDC. Corresponding contributor: Robert D. Kirkcaldy, rkirkcaldy@cdc.gov, 404-639-8659.*

**Editorial Note**

The epidemiologic pattern of cephalosporin susceptibility in the West and among MSM during 2009–2010 is similar to that previously observed during the emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the United States (2–3,7). Although the history of fluoroquinolone-resistant *N. gonorrhoeae* might not predict the patterns of decreasing cephalosporin susceptibility, the observed trends are concerning. During 2001–2010, decreased gonococcal susceptibility to cephalosporins and reported treatment failures have been documented in Asia (8). Recently, two cases of gonococcal treatment failure were reported from Norway among heterosexual men with gonococcal urethritis treated with cefixime (9), and a pharyngeal isolate with a ceftriaxone MIC = 2.0 µg/mL was identified from a female commercial sex worker in Japan (10).

The potential emergence of gonococcal cephalosporin resistance is of particular concern because the U.S. gonorrhea control strategy relies upon effective antibiotic therapy. Previously, the emergence and spread of gonococcal antibiotic resistance in the United States was addressed by changing the recommended antibiotics for treatment. No other well-studied and effective antibiotic treatment options or combinations currently are available. The emergence of gonococcal cephalosporin resistance would substantially limit available treatment options.

In light of the diminished resources available to STD control programs and the past inability to prevent emergence of resistance, the eventual emergence of cephalosporin resistance appears likely. Actions undertaken now could delay the spread of cephalosporin-resistant strains and mitigate the public health consequences. Effective treatment of gonorrhea is essential and now requires two antibiotics. The findings in this report suggest that gonococcal resistance to cefixime might emerge in the United States before resistance to ceftriaxone. Ceftriaxone is the most effective cephalosporin for treatment of gonorrhea and should be used for treatment of gonorrhea in combination with azithromycin or doxycycline (4). Azithromycin is preferred over doxycycline for dual therapy with ceftriaxone; of the 2009–2010 isolates with decreased susceptibility to cefixime, none exhibited decreased susceptibility to azithromycin, and all of them exhibited tetracycline resistance. Based on the findings in this report, CDC currently is recommending ceftriaxone 250 mg intramuscularly and azithromycin 1 g orally as the most effective treatment for uncomplicated gonorrhea.

In addition to effective treatment, prompt recognition of cephalosporin-resistant gonorrhea is critical. Although GISP has been successful in identifying important shifts in gonococcal epidemiology and antimicrobial susceptibility, its effectiveness should be complemented through partnerships with local health departments and health-care providers. Clinicians should remain vigilant for treatment failures (evidenced by persistent symptoms or a positive follow-up test despite treatment) among patients treated for gonorrhea with CDC-recommended antibiotics and obtain specimens for gonococcal culture from patients with possible treatment failure. Clinicians caring for patients with gonorrhea, particularly MSM in the western United States, might consider having patients return 1 week after treatment for test-of-cure with culture, preferably, or with nucleic acid amplification tests (NAATs).

If a patient experiences cefixime treatment failure, clinicians should re-treat the patient with 250 mg ceftriaxone intramuscularly and 2 g azithromycin orally (4). If a patient experiences a ceftriaxone treatment failure, clinicians should consult with an infectious disease expert and CDC regarding re-treatment. These patients should return for tests-of-cure

within 1 week, 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. Clinicians also should ensure that the patient's sex partners from the preceding 2 months are tested for gonorrhea (preferably with culture) and empirically treated with ceftriaxone 250 mg intramuscularly and azithromycin 2 g orally. Finally, these treatment failures should be reported to the local or state health department within 24 hours. Laboratorians are requested to report gonococcal isolates with decreased cefixime or ceftriaxone susceptibility ( $\geq 0.5 \mu\text{g/mL}$ ) to their local or state health departments within 24 hours of identification. Local and state health departments are requested to report these cases immediately to CDC ([gispinfo@cdc.gov](mailto:gispinfo@cdc.gov) or 404-639-8659). Isolates can be submitted to CDC's Neisseria Reference Laboratory for confirmation susceptibility testing.\*

Local and state health departments also should promote maintenance of local gonococcal culture capacity, despite the widespread use of NAATs. Gonococcal antibiotic susceptibility testing (AST), necessary for identification of resistant isolates, only can be performed with culture specimens. Health departments should establish options for local availability of gonococcal cultures and AST, and consider enhancing surveillance for cephalosporin-resistant gonorrhea. Options for local culture and AST availability might involve building or enhancing local gonorrhea reference laboratory testing capacity, partnering with regional clinical laboratories or academic institutions, or sending isolates to CDC for susceptibility testing. Enhanced surveillance might include monitoring of multiple cases from the same patient reported within 30–60 days, often discarded as presumed duplicates. Finally, effective alternative antibiotics or antibiotic combinations for the treatment of gonorrhea are needed urgently; thus, the development of novel antibiotics and clinical trials to study combinations of existing antibiotics is necessary.

The findings in this report are subject to at least two limitations. First, data available in GISP only include results from urethral gonococcal isolates from males attending publicly funded STD clinics. Second, the clinical significance of shifts in MICs below CLSI criteria for decreased susceptibility is unclear, and transient increases and decreases in cephalosporin

MICs have been observed previously in GISP. However, in light of similar trends in other regions of the world, the patterns observed in GISP with higher MICs in isolates from the west and MSM, and the ability of *N. gonorrhoeae* to develop resistance, the increasing MICs to cephalosporins in the United States are concerning. Vigilance of clinicians and enhanced surveillance by local and state health departments will be critical for early detection of treatment failures.

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\*Instructions available at [http://www.cdc.gov/std/gonorrhea/arg/specimen\\_shipping\\_instructions1-29-08.pdf](http://www.cdc.gov/std/gonorrhea/arg/specimen_shipping_instructions1-29-08.pdf).