Trends in antimicrobial resistance in *Neisseria gonorrhoeae* in the USA: the Gonococcal Isolate Surveillance Project (GISP), January 2006–June 2012

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ABSTRACT

Background *Neisseria gonorrhoeae* has progressively developed resistance to sulfonamides, penicillin, tetracycline and fluoroquinolones, and gonococcal susceptibility to cephalosporins has been declining worldwide.

Methods We described trends in gonococcal antimicrobial susceptibility in the USA from January 2006 through June 2012. Susceptibility data for cefixime, ceftriaxone, azithromycin, penicillin, tetracycline and ciprofloxacin were obtained from the Gonococcal Isolate Surveillance Project (GISP), a sentinel surveillance system that monitors antimicrobial susceptibility in urethral gonococcal isolates collected from symptomatic men at 25–30 sexually transmitted disease clinics throughout the USA.

Results The percentage of isolates with elevated cefixime minimum inhibitory concentrations (MICs) (≥0.25 μg/mL) increased from 0.1% in 2006 to 1.4% in 2010–2011 and was 1.1% in the first 6 months of 2012. The percentage with elevated ceftriaxone MICs (≥0.125 μg/mL) increased from 0.1% in 2006 to 0.3%–0.4% during 2009 through the first 6 months of 2012. There were no temporal trends in the prevalence of elevated azithromycin MICs (≥2 μg/mL) (0.2%–0.5%). The prevalence of resistance remained high for penicillin (11.2%–13.2%), tetracycline (16.7%–22.8%) and ciprofloxacin (9.6%–14.8%).

Conclusions The proportion of gonococcal isolates with elevated cephalosporin MICs increased from 2006 to 2010, but plateaued during 2011 and the first 6 months of 2012. Resistance to previously recommended antimicrobials has persisted. As the number of antimicrobials available for gonorrhoea treatment dwindles, surveillance systems such as GISP will be critical to detect emerging resistance trends and guide treatment decisions.

BACKGROUND

Gonorrhoea is the second most commonly reported notifiable infectious disease in the USA, following chlamydia.[1] In 2011, there were 321 849 cases of gonorrhoea reported to the Centers for Disease Control and Prevention (CDC), yielding a rate of 104.2 cases per 100 000 population.[2] While this case rate represents a 78% decline since reaching a peak of 464.1 cases per 100 000 in 1975, the US gonorrhoea rate has been trending upwards in the last few years.[2] In addition, CDC estimates that fewer than half of all cases are detected and reported, and that over 800 000 cases occur in the USA each year.[3]

Historically, gonorrhoea treatment and control has been complicated by the relative ease with which *Neisseria gonorrhoeae* develops antimicrobial resistance. Since the introduction of antimicrobials to treat gonorrhoea, *N gonorrhoeae* has progressively developed resistance to sulfonamides in the 1940s,[4] penicillin and tetracycline in the 1980s,[5 6] and fluoroquinolones in the 2000s.[7–9] By 2007, cephalosporins (injectable ceftriaxone or oral cefixime) were the only remaining class of drugs recommended by CDC as first line treatment for gonorrhoea.[9] However, gonococcal susceptibility to cephalosporins, particularly cefixime, has been declining worldwide as well as in the USA.[10 11] In 2012, CDC revised its treatment guidelines so that the only recommended first line regimen for gonorrhoea in the USA is dual therapy with ceftriaxone and either azithromycin or doxycycline.[12] The emergence and spread of cephalosporin resistance in *N gonorrhoeae* could severely impair gonorrhoea treatment and control efforts. To prepare for and respond effectively to this threat, robust surveillance of gonococcal susceptibility is critical.

METHODS

The Gonococcal Isolate Surveillance Project

The Gonococcal Isolate Surveillance Project (GISP) is a US-based national sentinel surveillance system that was established in 1986 to monitor trends in antimicrobial susceptibility in *N gonorrhoeae* and to establish a rational basis for the selection of gonococcal therapies in the USA.[13] Sexually transmitted disease (STD) clinics in 25–30 cities throughout the USA participate in GISP as sentinel sites. At each participating STD clinic, urethral *N gonorrhoeae* isolates are collected from the first 25 men presenting with symptomatic gonococcal urethritis each month. Isolates are submitted to regional reference laboratories for antimicrobial susceptibility testing by agar dilution according to a common protocol,[14] and results are sent to CDC. GISP also collects de-identified data on patient characteristics and clinical information (eg, sex of sex partner, age, race/ethnicity, HIV status, previous gonococcal infection in the past 12 months and treatment given) from clinic medical records.

Laboratory methods

Gonococcal isolates collected at each clinic are subcultured at the clinic's local public health laboratory on supplemented chocolate medium and frozen in trypticase soy broth containing 20% glycerol. Isolates are shipped monthly to one of four to five participating regional reference laboratories

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where they are tested for β-lactamase production and susceptibility to azithromycin, penicillin, tetracycline, ciprofloxacin, spectinomycin, cefixime and ceftriaxone using the agar dilution method. Standardised bacterial suspensions are inoculated on Difco GC Medium Base supplemented with 1% IsoVitalex Enrichment (Becton-Dickinson Diagnostic Systems, Sparks, Maryland, USA). Cefixime susceptibility testing was temporarily halted in 2007 due to lack of availability of cefixime in the USA, but was restarted in 2009. Cefpodoxime susceptibility testing was only conducted during 2009–2012.

Minimum inhibitory concentrations (MICs) are interpreted according to criteria for *N gonorrhoeae* recommended by the Clinical and Laboratory Standards Institute (CLSI) when such criteria are available.[15] GISP uses the CLSI definition of resistance to penicillin (MIC≥2 μg/mL), tetracycline (MIC≥2 μg/mL) and ciprofloxacin (MIC≥1 μg/mL). CLSI does not define resistance to ceftriaxone or cefixime, but defines decreased susceptibility to these antimicrobials as an MIC≥0.5 μg/mL. In order to monitor increases in MICs that may predict the emergence of decreased susceptibility or resistance to cephalosporins, GISP uses lower MIC breakpoints, referred to as 'elevated MICs,' to monitor trends in gonococcal susceptibility to cephalosporins: MIC≥0.125 μg/mL for ceftriaxone and MIC≥0.25 μg/mL for cefixime. The breakpoints chosen for the two cephalosporins differ because ceftriaxone MICs in GISP isolates are generally one to two dilutions lower than cefixime MICs.[2] Similarly, as CLSI does not define gonococcal susceptibility or resistance breakpoints for azithromycin, GISP classifies isolates with an azithromycin MIC≥2 μg/mL as having elevated azithromycin MICs. GISP defines penicillinase-producing *N gonorrhoeae* as an isolate with positive results on the nitrocefin β-lactamase test. Isolates resistant to penicillin include isolates with either chromosomal resistance (MIC≥2 μg/mL and β-lactamase negative) or penicillinase-producing strains unless otherwise specified.

To ensure accuracy of antimicrobial susceptibility results at the regional reference laboratories, a set of seven control *N gonorrhoeae* strains with known MICs of various antimicrobials are included with each susceptibility run. In addition, reference laboratories test a CDC-provided panel of 15 unidentified strains twice yearly to compare results and ensure consistency among laboratories. Results obtained from testing of control strains and CDC-provided panels are used for internal quality assurance/quality control only and are not included in antimicrobial susceptibility analysis.

In the antimicrobial susceptibility trend analysis, GISP data from January 2006 through June 2012 are presented. Cochran–Armitage trend tests were performed to assess statistical significance of binary variables over three or more time points. Other proportions were compared using χ^2 tests. Two-sided p values of <0.05 were considered statistically significant. Statistical analyses were conducted using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

From January 2006 through June 2012, a total of 37 233 isolates from men with urethral gonorrhoea were collected through GISP (5467–6089 isolates per year from 2006 to 2011) (table 1). In comparison, 137 819–170 508 male gonorrhoea cases were reported to CDC each year during 2006–2011,[2 16] so that GISP isolates represented 3.6%–4.1% of reported male cases each year. Isolates from the Western USA are overrepresented in GISP compared with the geographic distribution of nationally reported gonococcal infections in men: 36.4% of GISP isolates versus 16.3% of nationally reported male gonorrhoea cases were from the West during 2006–2011.[2 16]

Demographic characteristics

Overall, during 2006–2011, the median age of the men participating in GISP was 26 years. Among GISP participants, 68.5% were non-Hispanic black, 15.8% were non-Hispanic white, and 10.2% were Hispanic or Latino (table 1). Sex with men was reported by 24.6% of men in GISP. HIV infection was reported by 25.5% of men who have sex with men (MSM) and 1.5% of men who have sex with women (MSW) (p<0.001).

Treatment

The percentage of men who have isolates in GISP who were treated with ceftriaxone (either 125 or 250 mg) increased from 48.1% in 2006 to 88.4% in the first half of 2012 (p<0.001) (figure 1). Of 2321 men treated with ceftriaxone in the first half of 2012, 2318 (99.9%) received a dose of 250 mg. Azithromycin was prescribed as an additional treatment to 83.4% of the 2318 men treated with ceftriaxone 250 mg; 16.1% were prescribed doxycycline as a secondary treatment, 0.1% were treated with erythromycin, and 0.4% either were not treated with a second antimicrobial or the data are missing.

Table 1 Demographic and clinical characteristics of men with gonorrhoea: United States Gonococcal Isolate Surveillance Project (GISP), January 2006–June 2012

	GISP, January 2006–June 2012 (n=37 233)	
	n	Per cent
Region		
Northeast	2841	7.6
South	12 482	33.5
Midwest	8355	22.4
West	13 555	36.4
Age (median, IQR)	26	22–34
Race/ethnicity		
AIAN	112	0.3
Asian/PI	650	1.8
Black	25 506	68.5
Hispanic	3790	10.2
White	5878	15.8
Other	643	1.7
Unknown/missing	654	1.8
Sex of sex partners		
Female (MSW)	27 230	73.1
Male (MSM)	9175	24.6
Sex with males only	7707	
Sex with males and females	1468	
Unknown/missing	828	2.2
HIV status (self-report)		
Infected	2278	6.1
Not infected	25 981	69.8
Indeterminate	32	0.1
Unknown/missing	8942	24.0
Previous gonorrhoea (lifetime)		
Yes	17 038	45.8
No	18 258	49.0
Unknown/missing	1937	5.2

AIAN, American Indian or Alaskan Native; MSM, men who have sex with men; MSW men who have sex with women; PI, Pacific Islander.

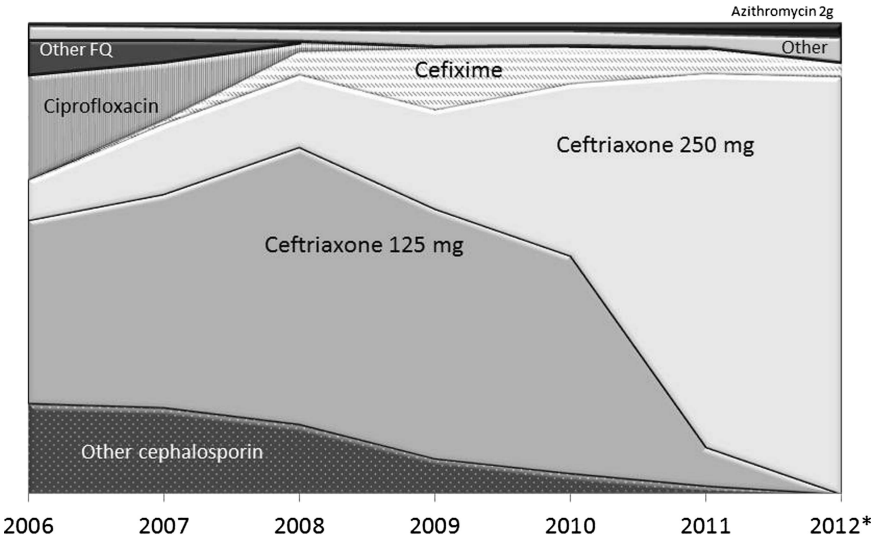

Figure 1 Primary antimicrobials used to treat gonorrhoea, 2006–2012*. *January–June 2012. Other cephalosporin=cefpodixime, ceftizoxime, cefotaxime, ceftibuten or cefdinir; Other FQ=levofloxacin or ofloxacin; Other=none, unknown or missing.

During the first half of 2012, 3.1% of men were treated with cefixime 400 mg as primary treatment and 2.9% were treated with azithromycin 2 g orally as primary treatment (figure 1).

Trends in antimicrobial susceptibilities of GISP isolates and distribution of isolates by characteristics of patients

Cefixime

Overall, the percentage of isolates with elevated cefixime MICs (≥0.25 μg/mL) increased from 0.1% in 2006 to 1.4% in 2010 (p<0.001), but remained stable from 2011 (1.4%) through the first 6 months of 2012 (1.1%, p=0.34) (table 2). Among MSM, the percentage increased from 0.2% in 2006 to 3.9% in 2010 (p<0.001), and then remained stable (3.6% in 2011 and 2.9% during January–June 2012; p=0.19). Among isolates from MSW, the percentage increased slightly from 0.1% in 2006 to 0.4% during the first 6 months of 2012 (p=0.008). Isolates from the Western USA demonstrated an increase from 0.2% in 2006 to 3.3% in 2010 (p<0.001), and then remained stable (3.0% in 2011 and 2.2% during January–June 2012; p=0.15). In the Midwest, the overall percentage of isolates with elevated MICs increased from 0% in 2006 to 0.6% in the first half of 2012 (p=0.042); the percentage also increased in the South from 0.05% in 2006 to 0.4% in the first half of 2012 (p=0.002). There was no significant change in the Northeast (0% in 2006 to 0.4% in the first half of 2012, p=0.15). From January 2006–June 2012, 18 (0.1%) isolates had cefixime MICs of 0.5 μg/mL: nine were collected in 2010, three in 2011 and one in 2012; and 14 (77.8%) were collected from MSM. Only one isolate with a cefixime MIC>0.5 μg/mL has been identified. This isolate was collected in the South from an MSW in 2012 and had a cefixime MIC of 1.0 μg/mL. He was treated with intramuscular ceftriaxone 250 mg and oral doxycycline 100 mg twice daily for 2 weeks, and was lost to follow-up.

Ceftriaxone

The percentage of isolates with elevated ceftriaxone MICs (≥0.125 μg/mL) increased from 0.05% in 2006 to 0.3% in 2009 (p=0.002), but then remained stable (0.3% in 2010, 0.4% in 2011, and 0.3% during January–June 2012) (table 2). Among MSM, the percentage with elevated MICs increased from 0% in 2006 to 0.9% in 2010 (p<0.001), then stabilised; no clear temporal trend in MICs is discernible among MSW.

Azithromycin

There was no temporal trend in the percentage of isolates with elevated azithromycin MICs (≥2.0 μg/mL) (table 2). During January 2006–June 2012, 117 (0.3%) isolates exhibited azithromycin MICs of ≥2 μg/mL: 69 (59.5%) men from whom these isolates were collected were MSM, and 90 (76.9%) were from the West. One isolate, collected from an MSW in Hawaii in 2012, had an azithromycin MIC of ≥256 μg/mL, the highest azithromycin MIC detected in GISP.

Penicillin

During January 2006–June 2012, there was no shift in the prevalence of penicillin resistance (table 2). Of 4545 isolates with penicillin resistance, 3740 (82.3%) exhibited chromosomal penicillin resistance and 805 (17.7%) produced penicillinase.

Tetracycline

The prevalence of tetracycline resistance decreased from 20.6% in 2006 to 16.7% in 2009, and then increased to 22.5% in 2012.

Ciprofloxacin

After reaching a peak in 2007 (14.8%), the prevalence of ciprofloxacin resistance fell to 9.6% in 2009 (p<0.001) (table 2). The prevalence then increased from 2009 to 13.5% during January–June 2012 (p<0.001).

Spectinomycin

All isolates were susceptible to spectinomycin during January 2006–June 2012.

DISCUSSION

The percentage of GISP isolates with elevated cefixime and ceftriaxone MICs significantly increased from 2006 to 2010. The largest increases in the percentage of isolates with elevated cefixime MICs occurred among isolates from the Western USA and among MSM. Following the increase, the percentages remained stable in these populations from 2010 through the first 6 months of 2012. Meanwhile, cefixime MICs gradually increased through June 2012 among isolates collected from men in the Midwest and South.

Higher MICs among isolates from MSM were not limited to cephalosporins. Across antimicrobial classes, isolates from MSM consistently exhibited a higher prevalence of resistance or

Table 2 Percentage of urethral *Neisseria gonorrhoeae* isolates with antimicrobial resistance or elevated MICs, United States Gonococcal Isolate Surveillance Project, January 2006–June 2012

	Total n/N (%)	MSW n/N (%)	MSM n/N (%)	Total n/N (%)	MSW n/N (%)	MSM n/N (%)
	Cefixime (MIC≥0.25 μg/mL)			Ceftriaxone (MIC≥0.125 μg/mL)		
2006	5/6089 (0.1)	3/4681 (0.1)	2/1281 (0.2)	3/6089 (0.05)	3/4681 (0.1)	0/1281 (0)
2007	–	–	–	7/6009 (0.1)	5/4548 (0.1)	2/1316 (0.2)
2008	–	–	–	4/5723 (0.1)	2/4412 (0.05)	2/1173 (0.2)
2009	45/5630 (0.8)	16/4104 (0.4)	29/1393 (2.1)	16/5630 (0.3)	8/4104 (0.2)	8/1393 (0.6)
2010	77/5693 (1.4)	13/3974 (0.3)	64/1619 (3.9)	19/5693 (0.3)	4/3974 (0.1)	15/1619 (0.9)
2011	74/5467 (1.4)	17/3789 (0.5)	57/1599 (3.6)	21/5467 (0.4)	6/3789 (0.2)	15/1599 (0.9)
2012*	29/2622 (1.1)	6/1722 (0.4)	23/794 (2.9)	8/2622 (0.3)	1/1722 (0.1)	7/794 (0.9)
	Azithromycin (MIC≥2.0 μg/mL)			Penicillin (MIC≥2 μg/mL or penicillinase-producing)		
2006	14/6089 (0.2)	4/4681 (0.1)	10/1281 (0.8)	702/6089 (11.5)	315/4681 (6.7)	372/1281 (29.0)
2007	27/6009 (0.5)	15/4548 (0.3)	12/1316 (0.9)	776/6009 (12.9)	365/4548 (8.0)	395/1316 (30.0)
2008	11/5723 (0.2)	8/4412 (0.2)	3/1173 (0.3)	639/5723 (11.2)	307/4412 (6.9)	314/1173 (26.8)
2009	12/5630 (0.2)	3/4104 (0.1)	9/1393 (0.7)	702/5630 (12.5)	377/4014 (9.2)	308/1393 (22.1)
2010	27/5693 (0.5)	7/3974 (0.2)	19/1619 (1.2)	733/5693 (12.9)	405/3974 (10.2)	313/1619 (19.3)
2011	16/5467 (0.3)	6/3789 (0.2)	10/1599 (0.6)	647/5467 (11.8)	364/3789 (9.6)	271/1599 (16.9)
2012*	10/2622 (0.4)	4/1722 (0.2)	6/794 (0.8)	346/2622 (13.2)	159/1722 (9.2)	179/794 (22.5)
	Tetracycline (MIC≥2 μg/mL)			Ciprofloxacin (MIC≥1 μg/mL)		
2006	1256/6089 (20.6)	620/4681 (13.3)	615/1281 (48.0)	843/6089 (13.8)	328/4681 (7.0)	499/1281 (38.9)
2007	1233/6009 (20.5)	642/4548 (14.1)	556/1316 (42.3)	891/6009 (14.8)	397/4548 (8.7)	475/1316 (36.1)
2008	1010/5549 (18.2)	555/4268 (13.0)	438/1145 (38.3)	775/5723 (13.5)	361/4412 (8.2)	394/1173 (33.6)
2009	941/5630 (16.7)	520/4104 (12.7)	404/1393 (29.0)	542/5630 (9.6)	248/4104 (6.0)	280/1393 (20.1)
2010	1149/5693 (20.2)	580/3974 (14.6)	548/1619 (33.9)	709/5693 (12.5)	313/3974 (7.9)	388/1619 (23.9)
2011	1245/5467 (22.8)	655/3789 (17.3)	575/1599 (35.9)	726/5467 (13.3)	302/3789 (7.9)	416/1599 (26.0)
2012*	591/2622 (22.5)	280/1722 (16.3)	287/794 (36.2)	354/2622 (13.5)	134/1722 (7.8)	214/794 (26.9)

*January—June 2012.
MIC, minimum inhibitory concentration; MSM, men who have sex with men; MSW, men who report having sex only with women.

elevated MICs than isolates from MSW. A recent analysis of GISP data found that these differences in susceptibility persisted, even after adjustment for potential confounders.[17]

The prevalence of penicillin and ciprofloxacin resistance has remained high in GISP isolates, even though these agents have not been recommended for treatment for gonorrhoea for years (since 1989 in the case of penicillin[6] and 2007 in the case of fluoroquinolones[9]) and the use of fluoroquinolones as treatment for gonorrhoea has declined.[18] Antimicrobial treatment for other conditions (eg, respiratory tract infections, acne) in the community might contribute to the persistence of gonococcal resistance to these drugs through selection pressure (whereby antibiotic use favours the growth of resistance strains over susceptible strains), but *N gonorrhoeae* may also maintain genetic mutations conferring resistance even after the apparent removal of antimicrobial selection pressure.[19] Kunz *et al*[20] have demonstrated that a mutation associated with ciprofloxacin resistance may increase fitness of the organism, thereby promoting the persistence of ciprofloxacin resistance in the absence of antimicrobial selection pressure. CDC has traditionally used an efficacy threshold of ≥95% (and a resistance threshold of <5%) to recommend antimicrobials for empiric treatment of gonorrhoea.[21] The persistence of high prevalence of resistance to previously recommended antimicrobials, even among isolates from MSW, precludes the re-introduction of these agents as routine empiric therapy.

The recent plateau in the prevalence of isolates with elevated cefixime MICs in the USA is an interesting development. It is too early to determine if this pattern represents simply a brief pause before MICs continue to increase, a true stabilisation or even a decline in prevalence, at least in certain populations. If the increase in prevalence in the West and among MSM has indeed halted, it may be worthwhile to note that it coincided with the publication of the 2010 STD Treatment Guidelines, which recommended dual therapy, a preference for ceftriaxone over cefixime (along with either azithromycin or doxycycline) and a higher (250 mg) dose of ceftriaxone.[9] Although providers in clinics participating in GISP are not representative of all healthcare providers in the USA, the use of ceftriaxone 250 mg as treatment for gonorrhoea in GISP increased after 2010 (figure 1). It is theoretically possible that routine use of dual therapy and a higher dose of ceftriaxone cured infections, particularly pharyngeal infections, more effectively, and slowed the transmission of strains with reduced cefixime susceptibility; however, the explanation for the recent plateau is not yet clear.

As a sentinel surveillance system, GISP has multiple strengths. Although GISP samples a relatively small proportion (approximately 4%) of reported male gonococcal infections each year, GISP has geographic coverage in each region of the USA, and the size of the collected sample (approximately 6000 isolates each year) allows for statistical analysis of trends and for analysis of regional patterns. By design, GISP does not collect a representative sample of male gonococcal morbidity in the USA. To allow for more rapid detection of emerging resistance phenotypes, GISP instead oversamples from the Western USA, where resistance tends to initially emerge.[7 22] to allow for more rapid detection of emerging resistance phenotypes. GISP systematically collects data from consecutively diagnosed men with gonococcal urethritis at participating STD clinics, and has maintained consistent protocols and testing methodologies. Thus,

susceptibility trends observed in GISP are less likely to be confounded by changes in screening or testing practices, populations sampled, or laboratory practice over time.

By conducting surveillance on men with symptomatic gonococcal urethritis, GISP allows surveillance of susceptibility both in MSM and in heterosexual sexual networks. However, a possible limitation of this approach might exist if there were substantial differences in antimicrobial susceptibility between isolates from heterosexual men and those from women, or between isolates from different anatomic sites among MSM. While some data suggest that gonococcal susceptibility differs by anatomic site,[23] these data are likely confounded by sex of sex partner. More data comparing susceptibility of gonococcal isolates from different anatomic sites within heterosexual and within MSM networks are needed. Similarly, surveillance in GISP is conducted exclusively in STD specialty care clinics because of efficiency and cost. Differences in risk behaviours of patients attending different types of healthcare settings have been described previously,[24 25] and it is possible that the antimicrobial susceptibility of *N gonorrhoeae* circulating within the sexual networks captured at GISP STD clinics differs from susceptibilities of infections in other sexual networks. Finally, antimicrobial susceptibility varies by geographic area, and local susceptibility patterns may differ from susceptibility patterns observed at GISP sites. Local data on susceptibility trends and prevalence of resistance outside of GISP remain important and are useful for local health departments and clinicians, particularly in the setting of emerging cephalosporin resistance.

During the past 25 years, data from GISP have directly influenced CDC's STD Treatment Guidelines.[6–9 12 26–30] As the number of antimicrobials available for treatment of gonorrhoea dwindles and resistance continues to emerge, GISP is more important than ever. This sentinel surveillance system, combining an epidemiological approach to sampling with robust laboratory methods, has been highly successful at detecting resistant strains that are circulating in the USA and describing trends in gonococcal susceptibility. To complement GISP, strengthening and maintaining local gonococcal culture capacity outside of GISP are urgently needed. Testing by culture allows for susceptibility testing, particularly when clinicians suspect treatment failure. However, the number of gonococcal cultures performed has declined in the USA due to widespread use of nucleic acid amplification tests,[31–33] and maintenance of culture capacity is an ongoing challenge for local health departments and public health laboratories. The emerging threat of cephalosporin resistance, combined with the lack of new and effective antimicrobial treatments for gonorrhoea, highlights the importance of continued surveillance of *N gonorrhoeae* antimicrobial susceptibility. GISP is a model of a successful, reliable and relatively simple sentinel surveillance system for monitoring susceptibility trends nationwide. GISP, and surveillance of gonococcal susceptibility globally, will be critical to detect emerging resistance trends and guide treatment decisions in the coming years.

Key messages

- The Gonococcal Isolate Surveillance Project (GISP) is a US-based national sentinel surveillance system that monitors gonococcal antimicrobial susceptibilities, using systematic sampling and agar dilution susceptibility testing.
- The percentage of GISP isolates with elevated cefixime MICs increased in 2009 and 2010 and then remained stable through the first 6 months of 2012.
- Isolates collected from men in the western USA and from men who have sex with men tend to have elevated cefixime MICs.
- Continued surveillance of gonococcal antimicrobial susceptibility is critical.

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