Trends in Neisseria gonorrhoeae Susceptibility to Cephalosporins in the United States, 2006-2014

Gonorrhea is a common sexually transmitted disease that, if untreated, can cause reproductive health complications. Treatments for gonorrhea have been repeatedly jeopardized by antimicrobial resistance. To ensure effective treatment, the US Centers for Disease Control and Prevention (CDC) periodically updates guidelines based on resistance trends. Following declining cephalosporin susceptibility in several countries, the CDC updated its treatment recommendation in 2010 from single-dose cephalosporin (injectable ceftriaxone or oral cefixime) to intensified combination therapy with either ceftriaxone (at a higher dose than previously recommended) or cefixime plus a second antimicrobial.1

The CDC updated the guidelines again in 2012 to recommend ceftriaxone-based combination therapy as the single recommended therapy.1 We describe recent gonococcal cephalosporin susceptibility trends, emphasizing changes following publication of these guidelines.

Methods | We analyzed 2006-2014 data from the CDC’s Gonococcal Isolate Surveillance Project (GISP), a sentinel system that monitors antimicrobial susceptibility in urethral isolates from consecutive men with gonorrhea treated at US public clinics for sexually transmitted disease.2 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 of 0.125 μg/mL or greater or cefixime minimum inhibitory concentrations of 0.25 μg/mL or greater were categorized as exhibiting reduced susceptibility.

Trends were examined overall (and tested for significance [2-sided $P < .05$] by the Cochran-Armitage trend test) and stratified by region and sex of the sex partner. Analyses were conducted using SAS version 9.3 (SAS Institute Inc). 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 the authority to collect and transmit case data to the 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 250 mg of ceftriaxone intramuscularly increased from 8.7% (95% CI, 8.0%-9.5%) in 2006 to 96.6% (95% CI, 96.1%-97.1%) in 2014 ($P < .001$). The percentage of isolates with reduced cefixime susceptibility increased from 0.1% (95% CI, <0.1%-0.2%) in 2006 to 1.4% (95% CI, 1.1%-1.7%) in 2011, and then declined to 0.4% (95% CI, 0.3%-0.6%) in 2013 ($P < .001$) (Figure).

![Figure. Urethral Neisseria gonorrhoeae Isolates With Reduced Cefixime or Ceftriaxone Susceptibility by Year in the Gonococcal Isolate Surveillance Project, 2006-2014](image-url)
In 2014, the percentage of isolates was 0.8% (95% CI, 0.5%-1.0%). Among isolates from men who have sex with men, the percentage with reduced susceptibility peaked at 4.0% (95% CI, 3.1%-5.0%) and was 1.3% (95% CI, 0.8%-1.9%) in 2014 (Table). Among men who reported having sex exclusively with women, the percentage remained low. In regard to ceftriaxone, the annual overall percentage of isolates with reduced susceptibility fluctuated between 0.1% (95% CI, <0.1%-0.1%) and 0.4% (95% CI, 0.2%-0.6%) (Figure).

Discussion | The prevalence of reduced cefixime susceptibility declined nearly 70% between 2011 and 2013, suggesting a halting of drift toward 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. 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 the GISP have been found to reflect trends in other US settings and populations. 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 the CDC’s guidelines.

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Author Contributions: Dr Kirkcaldy had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kirkcaldy, Hook, del Rio, Zenilman.

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### Table. Urethral Neisseria gonorrhoeae Isolates With Reduced Cefixime Susceptibility by Year in the Gonococcal Isolate Surveillance Project, 2006-2014a

<table>
<thead>
<tr>
<th>Year</th>
<th>US Census Region</th>
<th>Sex of Sex Partnerb</th>
<th>No. of Isolates/Total % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>West (n = 14,611)</td>
<td>MSM (n = 11,621)</td>
<td>4/2489 0.2 (0.04-0.4)</td>
</tr>
<tr>
<td>2006</td>
<td>Midwest (n = 9,125)</td>
<td>MSW (n = 27,168)</td>
<td>37/1924 1.9 (1.4-2.6)</td>
</tr>
<tr>
<td>2006</td>
<td>Northeast (n = 3,206)</td>
<td></td>
<td>7/1924 0.4 (0.1-1.4)</td>
</tr>
<tr>
<td>2006</td>
<td>South (n = 12,470)</td>
<td></td>
<td>3/1924 0.2 (0.1-0.4)</td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td></td>
<td>1/1924 0.1 (0-0.3)</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td>12/1924 0.4 (0.2-1.1)</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td>5/1924 0.3 (0.2-1.1)</td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td></td>
<td>5/1924 0.3 (0.2-1.1)</td>
</tr>
<tr>
<td>2013</td>
<td></td>
<td></td>
<td>3/1924 0.3 (0.2-1.1)</td>
</tr>
<tr>
<td>2014</td>
<td></td>
<td></td>
<td>2/1924 0.3 (0.2-1.1)</td>
</tr>
</tbody>
</table>

Abbreviations: MSM, men who have sex with men; MSW, men who reported having sex exclusively with women.

a Reduced cefixime susceptibility defined as minimum inhibitory concentration of 0.25 μg/mL or greater.

b Excludes men with missing sex for sex partner data.
Among a survey of youth aged 12 to 17 years, the majority who self-reported ever experimenting with tobacco started with a flavored product, and most current youth (12-17 years) in the United States. We analyzed youth data from wave 1, collected September 2013 through December 2014 (the survey is available in the eAppendix in the Supplement). Among youth within participating households (weighted household screener rate, 54%), 78.4% participated in an audio computer-assisted interview. Nonresponse analysis showed few differences with referent national surveys.\(^4\) Survey weights were adjusted for nonresponse.

Parents and emancipated youth provided written informed consent, whereas youth assented to participate. Further details regarding the study methods are available.\(^4\) The study was conducted by Westat and approved by the Westat institutional review board.

Youth responded to questions about ever and past 30-day use of tobacco products including cigarettes, e-cigarettes, hookahs, cigars (traditional cigars, cigarillos, filtered cigars), pipe tobacco, all types of smokeless tobacco, dissolvable tobacco, bidis, and kretek. For each product ever used, youth endorsed whether the first product they used was flavored (eg, “Was the first e-cigarette you used flavored to taste like menthol, mint, clove, spice, candy, fruit, chocolate, alcohol [such as wine or cognac], or other sweets?”). Users of noncigarette products reported any past 30-day use of a flavored product. Past 30-day noncigarette tobacco users also reported reasons for product use, including “(It) comes in flavors I like,” for each product. Past 30-day cigarette smokers reported smoking cigarettes flavored to taste like menthol or mint.

We used SAS version 9.3 (SAS Institute Inc) survey procedures to account for weighting and calculated proportions with 95% confidence intervals for all measures. Estimates from denominators of fewer than 50 users are suppressed; estimates with relative standard errors greater than 30% are flagged.

Results | Of the 13 651 youth enrolled and included in this analysis, 51.3% were male, 54.5% non-Hispanic white, 13.7% non-Hispanic black, and 22.5% Hispanic. Mean respondent age was 14.5 (SD, 0.02) years. Table 1 summarizes ever and past 30-day use of flavored tobacco products. The majority of youth ever-users reported that the first product they had used was flavored, including 88.7% of ever hookah users, 81.0% of ever e-cigarette users, 65.4% of ever users of any cigar type, and 50.1% of ever cigarette smokers. For past 30-day youth tobacco use, the overall proportion of flavored product use was 79.8% (95% CI, 77.3%-82.3%) among users of any product and 89.0% among hookah users, 85.3% among e-cigarette users, 71.7% among users of any cigar type, and 59.5% among cigarette smokers.

Table 2 presents leading reasons for use among past 30-day noncigarette tobacco users. Youth consistently reported product flavoring as a reason for use across all product types, including e-cigarettes (81.5%), hookahs (78.9%), cigars (73.8%), smokeless tobacco (69.3%), and snus pouches (67.2%).

Discussion | Among a survey of youth aged 12 to 17 years, the majority who self-reported ever experimenting with tobacco started with a flavored product, and most current youth tobacco users reported use of flavored products. This study extends a recent national report\(^4\) on youth use of flavored tobacco products by examining first use of flavored product among ever users by products and flavorings as a reason for use.