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Laboratory Capacity for Antimicrobial Susceptibility Surveillance of *Neisseria gonorrhoeae*—District of Columbia, 2007–2012

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Abstract

Background: In the District of Columbia (DC), *Neisseria gonorrhoeae* (gonorrhea) infections accounted for more than 25% of 9321 incident sexually transmitted infections reported in 2011; untreated infections can lead to reproductive complications and a higher risk for HIV transmission. In DC, limited capacity to measure the prevalence of antibiotic-resistant *N. gonorrhoeae* is available; culture-based antibiotic susceptibility testing (AST) is needed to monitor antimicrobial resistance. We examined the capacity of laboratories that report to the DC Department of Health to perform AST for ongoing surveillance of antibiotic-resistant *N. gonorrhoeae* and to identify suspected treatment failures.

Methods: We created a survey about diagnostic methods for gonorrhea testing and identified 33 laboratories that reported gonorrhea results to Department of Health in 2007 to 2012. Laboratories were assessed for use of bacterial culture or nucleic acid amplification testing (NAAT) for gonorrhea testing, prevalence of AST on gonorrhea-positive cultures, and types of antibiotics tested during AST. We estimated the prevalence of laboratory practices on the basis of self-report by staff.

Results: Nineteen (58%) laboratories completed the survey, representing 92% of the gonorrhea reporting. Seventeen (89%) of 19 laboratories conducted testing by culture; only 6 (35%) performed AST; 79% performed NAAT. Barriers to AST included longer completion times and limited number of provider requests for AST. Commercial laboratories (32%) were more likely to conduct both culture and NAAT, compared with health care facilities (11%).

Conclusions: We report a low prevalence of laboratories performing AST because of multiple barriers. State-specific strategies addressing these barriers are needed to improve detection of antibiotic-resistant gonorrhea stains circulating among the population.

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Neisseria gonorrhoeae (gonorrhea) infections are the second most commonly reported notifiable disease in the United States; 334,826 cases were reported in 2012, and an estimated of >800,000 cases occur each year.[1,2] Untreated or ineffectively treated gonorrhea infections among women can cause pelvic inflammatory disease leading to infertility and, among both sexes, facilitate transmission of HIV.[3] In 2011, a total of 2572 (28%) of the 9321 incident sexually transmitted infections (STIs) reported in the District of Columbia (DC) were gonorrhea infections, most of which were among adolescents and young adults. When ranked by rate/100,000 persons, DC was eighth of 70 US counties and independent cities in the United States in reported rates of gonorrhea infections at 388.7 infections/ 100,000 persons[2,4]

During the past 50 years, *N. gonorrhoeae* has developed resistance to antibiotics that previously were effective for treatment of gonorrhea, beginning during the 1940s with sulfonamides and during the 1970s with penicillins and tetracyclines. In 2007, increasing rates of *N. gonorrhoeae* resistance to fluoroquinolone antibiotics in the United States led the Centers for Disease Control and Prevention (CDC) to discontinue recommending fluoroquinolones for gonorrhea treatment.[5] Cephalosporins are the only class of antibiotics that meet CDC's efficacy standard and have been recommended for the treatment of gonorrhea infections since 2010.[6] Declining susceptibility to cefixime (an oral cephalosporin) has further reduced effective treatment options.[7] The recommendations of CDC include dual therapy with ceftriaxone (an injectable cephalosporin) and either azithromycin or doxycycline, particularly for uncomplicated gonorrhea of the pharynx, rectum, or urogenital tract.[8] Estimates are that 30% of *N. gonorrhoeae* isolates tested for antimicrobial susceptibility were resistant to any antibiotic.[1] Therefore, the continual threat of cephalosporin resistance highlights the need for continued surveillance of *N. gonorrhoeae* antibiotic susceptibility.

Historically, *N. gonorrhoeae* isolation by culture had been the ultimate standard for gonorrhea screening and diagnosis.[9,10] Culture isolation is low cost and offers the ability to test for *N. gonorrhoeae* among different types of biologic specimens, including the pharynx, urethra, cervix, and rectum.[11] In addition, culture is used for antibiotic susceptibility testing (AST) of *N. gonorrhoeae* isolates. However, since becoming commercially available in 1997, nucleic acid amplification testing (NAAT), a nonculture diagnostic technique that detects and amplifies genetic sequences, has substantially replaced culture to test for *N. gonorrhoeae*.[12,13] Compared with culture, NAAT allows for easier specimen handling, provides faster results, and has higher sensitivity for detecting *N. gonorrhoeae* in invasive and noninvasive specimens (e.g., urine) from both sexes.[11] With the increased use of NAAT, culture isolation and subsequent AST have waned as a routine procedure. Because prevalence of antimicrobial-resistant gonorrhea is increasing, AST is imperative to ensure antibiotics recommended for gonorrhea treatment are effective.

In 1986, CDC established the Gonococcal Isolate Surveillance Project (GISP) to monitor trends in antimicrobial susceptibilities of gonococcal strains in the United States, and this system is the primary source for national- and regional-level susceptibility data.[14] The Gonococcal Isolate Surveillance Project has been established in 28 selected cities and metropolitan areas and annually collects approximately 6000 male patient urethral

gonorrhea samples from sexually transmitted disease clinics nationwide. No GISP clinics are located in the DC metropolitan area; thus, GISP sentinel surveillance has not been conducted in this area. In terms of public health practice, ongoing surveillance of antimicrobial susceptibilities of gonococcal strains being performed in laboratories that report results to the DC Department of Health (DOH) was unknown. Therefore, both the historical trends of antibiotic-resistant *N. gonorrhoeae* in DC and the prevalence were unknown.

In June 2012, to determine the scope of this problem, DOH initiated a study to investigate laboratory practices for diagnosing *N. gonorrhoeae* and to determine the prevalence of antimicrobial susceptibility testing performed by public and commercial laboratories that report STI results to DOH. A piloted survey was used to assess gonorrhea diagnostic methods, including testing *N. gonorrhoeae* for antimicrobial susceptibilities and types of antibiotics tested.

MATERIALS AND METHODS

To identify laboratories that report gonorrhea results obtained from DC residents to DOH, we reviewed incoming laboratory reports in 2007 to 2012. Laboratory identity and contact information, including the name, telephone number, and e-mail address of a laboratory manager or staff, was verified through interviews with DOH personnel. Thirty-three public and commercial laboratories from across the United States were identified. Laboratory managers or staff familiar with gonorrhea testing from all 33 laboratories were contacted, initially by telephone and then by e-mail to participate in the study.

We created a survey with 11 questions about laboratory diagnostic methods for gonorrhea testing. The survey was conducted during the period October 2012 to February 2013. The questions assessed 3 main topics as follows: (1) use of culture or NAAT for gonorrhea diagnosis, (2) prevalence of AST on *N. gonorrhoeae* isolates, and (3) types of antibiotics tested during AST. We specifically inquired about antibiotics that were past or present gonorrhea CDC treatment recommendations, including cephalosporins (ceftriaxone, cefpodoxime, and cefixime), tetracycline, fluoroquinolones (ciprofloxacin), spectinomycin, and azithromyocin; minimal inhibitory concentration (MIC) used for AST was also assessed. We also surveyed location of gonorrhea testing (in-house vs. sent to a reference laboratory), rationale for testing (performed on all *N. gonorrhoeae* isolates or performed only upon provider request), rationale for refusal of testing, and interest in implementing AST for in-house use (if the laboratory did not perform AST). If an interviewed laboratory representative stated that specimens had been routinely sent to a reference laboratory for testing, we asked the name and location of that laboratory. Paper or electronic formats of this survey were based on interviewee preference, and the survey could be completed either by a telephone interview or self-administered by e-mail. Three independent laboratories piloted the survey either by telephone interview or e-mail before the study. The prevalence of culture testing, AST, and NAAT in laboratory practice among laboratories that participated in the survey was calculated. Qualitative data analysis, including proportions, was performed by using STATA 9.0 (StataCorp, LP, College Station, TX). The study was conducted under CDC Human Research Subject (HSR) determination for nonresearch (HSR 2012–00090).

RESULTS

Of the 33 laboratories contacted, 20 (61%) participated and 19 (58%) completed the survey (Table 1). These 19 laboratories accounted for 106,335 (92%) of 115,425 gonorrhea tests performed and reported to DOH in 2007 to 2012. Of those laboratories that completed the survey, 9 (47%) were commercial laboratories, 9 (47%) were health care–associated laboratories, and 1 (5%) was a government-owned laboratory. Of the laboratories surveyed, 31,387 (30%) of gonorrhea reports were from commercial laboratories, 1172 (1%) were from health care laboratories, and 73,776 (69%) were from the government laboratory. Seventeen (89%) laboratories performed bacterial culture for *N. gonorrhoeae* isolation; 14 (74%) of these performed culture in-house, and 3 (16%) sent gonococcal culture to a reference laboratory for diagnostic processing.

Of the 17 laboratories that performed culture for *N. gonorrhoeae* isolation, 6 (35%) tested for antimicrobial susceptibilities of gonococcal strains by using AST. Two (12%) of the 17 laboratories performed AST in-house, whereas 4 (24%) sent specimens to reference laboratories for AST. The most common reason for performing AST on gonorrhea-positive cultures was provider request (4/17 [24%]). Of the 2 laboratories that performed AST in-house, gonorrhea sensitivity was tested for the antibiotics cefixime (n = 1), ciprofloxacin (n = 1), penicillin (n = 1), and ceftriaxone (n = 2). Overall, AST was estimated to have been performed on 10,207 (9%) of 115,425 gonorrhea tests reported to DOH in 2007 to 2012. Of the laboratories that did not perform AST, 2 laboratories expressed interest in implementing AST in-house. The most commonly reported barriers to performing AST in-house were a lack of resources (n = 2); slower completion time for *N. gonorrhoeae* isolation by culture, compared with NAAT (n = 1); and decreased number of provider requests for AST (n = 3).

Fifteen (79%) of the 19 laboratories that completed the survey used NAAT to test for gonorrhea, with 10 (67%) of the 15 laboratories performing NAAT in-house. Eight (42%) of 19 laboratories performed both *N. gonorrhoeae* isolation and NAAT in-house, including 6 (32%) at commercial laboratories and 2 (11%) at health care–associated laboratories. In the clinical setting, most specimens tested with NAAT are from the urogenital area in both males and females; therefore, we did not specify the anatomical source of the specimen in this survey. However, we asked laboratories about validation of NAAT on specimens from extragenital areas such as the pharynx or rectum. Of the 10 laboratories that performed NAAT in-house, 6 (60%) validated NAAT on oropharyngeal and anorectal samples. Only 1 commercial laboratory that reported gonorrhea results to DOH performed all 3 diagnostic methods in-house (*N. gonorrhoeae* isolation, AST, and NAAT).

DISCUSSION

Our findings indicate a limited number of laboratories perform AST on *N. gonorrhoeae* strains because of multiple barriers, including lack of provider request, lack of resources, and longer completion time for results. Sentinel surveillance for *N. gonorrhoeae* infections is needed to monitor the prevalence and trends of antibiotic-resistant infections and assist with the investigation of suspected gonorrhea treatment failures, but is not routinely performed in independent laboratories or health care facilities. Lack of routine surveillance increases the

likelihood for an increase of antibiotic-resistant *N. gonorrhoeae* strains, especially among persons with repeated failures in gonorrhea treatment with standard antibiotic regimens or in communities where gonorrhea infections are highly prevalent. In jurisdictions where routine surveillance is unavailable, missed opportunities to capture the baseline prevalence of antibiotic-resistant *N. gonorrhoeae* strains circulating in the community and to optimize treatment for those affected to prevent infection spread are likely.

Of the barriers mentioned, we found lack of provider request for AST most striking. We do not know why there is a lack of provider requests for AST. We hypothesize that the limited number of provider requests for AST might be attributable to NAAT being a more cost-effective, yet sensitive, method to obtain specimen results in a short turnaround time, making NAAT superior to AST confirm diagnosis and ensure point-of-care treatment was appropriate and sufficient.

Furthermore, the collection and transport of culture specimens to laboratory facilities, especially outside reference laboratories, can introduce a new challenge to AST usage. With these collective challenges, providers might be more likely to determine that AST is only necessary to test for antimicrobial resistance in suspected treatment failures, in patients with persistent symptoms, or in special populations (i.e., pregnant women) when test of cure is recommended. New policy guidelines that outline when culture and AST are recommended for gonorrhea testing in lieu of (or in addition to) NAAT to quickly identify patients with antibiotic-resistant gonorrhea might be necessary, especially for providers that serve communities with a potentially high incidence of antibiotic-resistant gonorrhea.

The Centers for Disease Control and Prevention monitors the emergence of antibiotic-resistant *N. gonorrhoeae* strains through laboratory testing of isolates collected at designated GISP clinics and uses prevalence data to make recommendations about effective treatment regimens.[6,8] However, GISP only collects gonococcal isolates from symptomatic males who attend selected clinics. The Centers for Disease Control and Prevention has provided recommendations to expand surveillance by building capacity at state and local health departments.[15] These recommendations provide evidence that state and local health departments should consider building partnerships with laboratories to increase capacity for culture-based testing to ensure the early detection of antimicrobial-resistant gonococcal isolates and to promote efficient reporting of laboratory results to public health officials and CDC. Although our study indicates that most laboratories that completed this survey performed isolation of *N. gonorrhoeae*, AST was estimated to have been performed on less than 10% of all gonorrhea isolates reported to DOH during the 6-year study period.

Of the 2 laboratories that performed AST in-house, we found that testing of cephalosporin antibiotics was most common, but testing of azithromycin, one of the CDC-recommended antibiotics for gonorrhea cotreatment, was not reported.[8] The ability of *N. gonorrhoeae* to acquire resistance to antimicrobial agents was first identified with sulfonamide antibiotics during the 1940s. During the past 30 years, *N. gonorrhoeae* strains have also developed resistance to penicillins, tetracyclines, fluoroquinolones, and the third-generation cephalosporin antibiotic cefixime.[8,16] Our results indicate that neither laboratory that performed AST in-house included all 3 major antibiotics recommended for gonorrhea

treatment (ceftriaxone, cefixime, azithromycin) for AST testing and, thus, were not in concordance with 2010 CDC guidelines. In addition, the respective MIC thresholds need to be evaluated and should meet recommended standards. Laboratory personnel must remain knowledgeable of current treatment recommendation for *N. gonorrhoeae* and how changes to those guidelines can directly affect both culture and nonculture gonorrheal testing. In addition, laboratory personnel and health care providers must develop relationships to ensure testing protocols are addressing the most current treatment guidelines, and that treatment failures are reported to the provider and the local health department.

Overall, 19 (58%) of 33 invited laboratories completed the survey. The 11-question survey and 2 delivery methods—e-mail and telephone interview—were designed to increase convenience for potential respondents, but nearly 40% of invited laboratories did not participate in the study. Nonparticipation bias in surveys can invalidate results because a differential loss of participants can underestimate the outcome. In this study, potential nonparticipation bias might have led to an underestimation of the proportion of laboratories that perform culture and AST on gonorrhea specimen. However, the 14 nonparticipating laboratories accounted for only 8% of gonorrhea tests reported over the study period, so the magnitude of the effect of nonparticipation bias is relatively small.

The DC study instrument might be used by other state and local health departments without GISP clinics to assess laboratory capacity for identifying emerging antibiotic-resistant gonococcal isolates among residents; the point of contact can be notified for availability. Determining the barriers to routine AST from partner laboratories is needed to enhance gonorrhea surveillance to estimate the prevalence of antimicrobial susceptibility at the local and state levels.

This study has multiple strengths and limitations. It was the first to examine antimicrobial susceptibility testing in the context of practical application for patients treated in a large metropolitan area and reported to a health department. The laboratories surveyed accounted for 92% of gonorrhea cases identified by DC DOH during a 6-year period. Furthermore, we were able to obtain specific information about which antibiotics are tested for gonorrhea sensitivity. A major limitation of this study is that data were self-reported. The laboratories surveyed in this study only represent those that report gonorrhea results to the DC DOH and were not representative of all laboratories that perform gonorrhea testing for any other health department. The survey used in this study specified use of MICs to assess antibiotic resistance using AST, but did not include use of disk diffusion, another common AST method. Therefore, we did not capture data on the use of MIC versus disk diffusion. Lastly, we had limited results regarding the MIC tested for each antibiotic during AST.

N. gonorrhoeae infections are common in DC, but laboratories that report STI results to DOH do not routinely test for antimicrobial resistance of *N. gonorrhoeae* isolates. Similar to other state and local health departments that do not participate in GISP, enhanced surveillance is needed to monitor the prevalence of antibiotic-resistant gonorrhea stains circulating among the population. Identifying barriers to AST and to effective reporting with laboratory partners is needed to develop strategies to identify and prevent the spread of antibiotic-resistant *N. gonorrhoeae* strains, particularly among communities at high risk.

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TABLE 1.

Characteristics of Laboratories Surveyed for *Neisseria Gonorrhoeae* Testing Procedures, 2007–2012

Characteristic	No.	(%)
Gonorrhea test results reported to DC DOH (n = 106,335)		
Type of laboratory		
Commercial	31,387	(30)
Health care	1172	(1)
Government	73,776	(69)
Laboratories with completed surveys (n = 19)		
Type of laboratory		
Commercial	9	(47)
Health care	9	(47)
Government	1	(5)
N. Gonorrhoeae culture performed		
No	2	(11)
In-house	14	(74)
Sent to reference laboratory	3	(16)
AST performed		
No	13	(68)
In-house	2	(11)
Sent to reference laboratory	4	(21)
Reason for AST		
Provider request only	4	(21)
Performed on all *N. Gonorrhoeae* cultures	2	(11)
Not applicable *	13	(68)
NAAT performed		
No	4	(21)
In-house	10	(53)
Sent to reference laboratory	5	(26)

* Not applicable means that question was not relevant, given skip pattern of questions.