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Considerations for strengthening surveillance of *Neisseria gonorrhoeae* antimicrobial resistance and interpreting surveillance data

Robert D. Kirkcaldy, MD, MPH, **Karen Schlanger, PhD**, **John R. Papp, PhD**, **Elizabeth Torrone, PhD**

Centers for Disease Control and Prevention, National Center of HIV/AIDS, Viral Hepatitis, STD and TB Prevention, Division of STD Prevention, Atlanta, GA

Since the introduction of antimicrobials in the first half of the twentieth century, *Neisseria gonorrhoeae* has repeatedly acquired resistance to the drugs used for treatment. The victims of the bacterium's relentless acquisition of resistance have included sulfonamides, penicillin, tetracycline, and fluoroquinolones. During the past several years, gonococcal resistance has received substantial attention in the United States. Circulating strains of *N. gonorrhoeae* have been found to have reduced susceptibility to recommended treatment options, the antibiotic pipeline remains at a trickle, and STD public health programs are stretched increasingly thin as syphilis, chlamydia, and gonorrhea case rates are increasing.[1] Taking its place among the ranks of *Clostridium difficile* and carbapenem-resistant Enterobacteriaceae, *N. gonorrhoeae* was labeled an "urgent" antibiotic resistance threat by the Centers for Disease Control and Prevention in 2013.[2]

N. gonorrhoeae antimicrobial resistance is a reminder of our global interconnectedness. Penicillinase-producing *N. gonorrhoeae*, fluoroquinolone-resistant *N. gonorrhoeae*, and strains with reduced cephalosporin susceptibility seem to have initially emerged or at least been initially detected in East Asia before being detected in other countries around the world in subsequent years, including the United States.[3–5] In some ways, gonococcal resistance trends and developments in East Asia have served as a canary in a coal mine, allowing us to anticipate possible future developments elsewhere. Thus antimicrobial susceptibility surveillance data from Japan, such as presented in this issue by Yasuda et al, are welcome contributions to our understanding of gonococcal resistance worldwide.[6]

Yasuda et al report antimicrobial susceptibilities of 2,471 gonococcal isolates collected during 2000–2015 by medical facilities in nine regions of Japan. Across the study period, the annual percentages of isolates with resistance to penicillin, tetracycline, or levofloxacin were strikingly high, ranging from 38.6% to 94.3%. Isolates with reduced cephalosporin susceptibility were common in Japan by the early 2000s, nearly a decade before the percentage of isolates with elevated cefixime or ceftriaxone MICs in the United States increased, albeit at much lower percentages.[7] In this Japanese sample, the percentage of

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isolates with cefixime MICs ≥0.5 μg/ml was 19.3% in 2000 and was as high as 42.9% (in 2007); the percentage with 45 ceftriaxone MICs ≥0.25 μg/ml was 6.7% in 2001, and as high as 22.3% (in 2011).

Because of methodologic limitations (discussed below), assessing trends in the Japanese sample is problematic. It is nevertheless intriguing that the percentage of isolates with reduced cephalosporin susceptibility appears to have declined between 2011 and 2012, echoing similar declines in the United States and United Kingdom during approximately the same time period, and also perhaps casting doubt on the speculation that changes in treatment guidelines contributed to the declines in those countries.[7,8]

In the Japanese sample, the percentage of isolates with azithromycin MICs ≥1 μg/ml increased sharply between 2003 and 2004 (from 1.1% to 23.8%) and remained high in subsequent years. A further disquieting finding is the identification of isolates exhibiting reduced susceptibility to both ceftriaxone and azithromycin. Although the percentage of such isolates remains low, and the true resistance breakpoint (i.e., indicating likely treatment failure) for both azithromycin and ceftriaxone is not clearly established, spread of isolates with resistance to both drugs could severely threaten gonorrhea treatment worldwide. This warrants careful monitoring.

Robust high-quality surveillance, which can guide treatment guidelines, policy decisions, and resource allocation, should be a foundational element of national and international responses to gonococcal resistance. The surveillance approach used in this study has limitations that highlight opportunities for strengthening surveillance not only in Japan, but elsewhere in the world. For susceptibility surveillance data to be accurately generalized to a population (and to accurately estimate the prevalence of resistance), persons from whom isolates are collected for surveillance should be representative of the underlying population of persons with gonorrhea (including, for example, the geographic, gender, and gender of sex partner distribution). However, perfect representativeness might not be feasible or even optimal. For example, by design, the Gonococcal Isolate Surveillance Project (GISP), a US-based sentinel surveillance system, is not truly representative of the regional distribution of gonorrhea in the US: GISP oversamples from the West (because resistant strains in the US tend to be initially detected in this region) and under-samples from 69 the South (where gonorrhea rates are highest but the prevalence of resistance tends to be the lowest). Understanding how the surveillance sample compares to the underlying epidemiology of gonorrhea in a population supports a more accurate interpretation of the data and estimation of prevalence. Such an understanding of the epidemiology of gonorrhea may be lacking in many countries. Data on whether the gonococcal isolates analyzed by Yasuda et al are representative of gonococcal infections in Japan are not presented.

A critical element of robust surveillance of susceptibility is systematic sampling. Systematic sampling defines the sampled population, facilitates representativeness, and reduces the likelihood of bias introduced by changes in testing practices or changes in the population sampled. In the US (GISP) and UK (Gonococccal Resistance to Antimicrobials Surveillance), systematic sampling involves collecting specimens from consecutive patients.[7,8] Many countries, seemingly including Japan, rely on convenience samples of specimens

received by a laboratory. Although convenience samples might at times provide reliable estimates, use of convenience samples can result in inaccurate estimates and trends, particularly if some patients, such as those at greater perceived risk of resistance or with persistent symptoms, are more likely than others to have specimens collected for culture and susceptibility testing, or if changes in testing practices result in changes in the patient population tested.

Large isolate sample sizes can further support (but not ensure) representativeness, increase sensitivity for detection of emerging trends and the precision of prevalence estimates, and allow for identification of groups at elevated risk of resistance (by stratification of data). Although the overall sample size in the study by Yasuda et al was somewhat large, the sample sizes for individual years (some as low as 35) are unlikely to be large enough to support accurate trend analyses or provide reliable national estimates.

Standardized collection of epidemiological data associated with each isolate (such as age, race, ethnicity, gender, and gender of sex partners of the patient) can help with the evaluation of representativeness, but more importantly allows for identification of populations at elevated risk of infection with resistant strains. In the United States, gonococcal isolates from men who have sex with men have consistently 93 been more likely to exhibit resistance earlier than isolates from men who report sex only with women; these data have been used to update national treatment guidelines.[9,10] To strengthen international surveillance, the World Health Organization's Gonorrhoea Antimicrobial Surveillance Programme (GASP) and CDC are collaborating to support systematic sampling and standardized collection of associated epidemiologic data in selected countries.

Surveillance can also be strengthened by establishing interpretive criteria for *N. gonorrhoeae* MIC susceptibility breakpoints and harmonizing breakpoints between the US-based Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EU-CAST).[11,12] Readers of the gonococcal susceptibility literature may be perplexed by multiple different MIC breakpoints used and differing resistance categories, such as "resistance", "decreased susceptibility", "reduced susceptibility", "nonsusceptibility", or "elevated MICs." Multiple categories may be used in a single paper depending on whether breakpoints for specific antimicrobials have been established by CLSI or EU-CAST. This complicates comparisons of the prevalence of reduced susceptibility or resistance across countries and regions. Fortunately, efforts are underway to fill gaps in *N. gonorrhoeae* MIC breakpoints and for CLSI and EU-CAST to coordinate on establishment of breakpoints. New data on treatment outcomes stratified by pre-treatment MIC results might enable estimates of the likelihood of treatment response or failure based on resistance categories.

Clearly, gonococcal resistance poses a substantial public health threat. Continued and, in some places, enhanced investment in phenotypic (culture and susceptibility testing-based) surveillance is essential. But what else needs to be done? Effective strategies to prevent or control gonorrhea and gonococcal resistance, particularly strategies relevant to men who have sex with men, need to be identified, implemented, and scaled up. Development of an effective *N. gonorrhoeae* vaccine would be extremely useful. Research into transmission

dynamics and how gonococcal strains spread through populations might help to inform prevention approaches. Although a small number of promising compounds are in various phases of investigation, efforts to develop and identify new antimicrobials remain a critical need. Current efforts to identify genetic determinants of resistance through whole genome sequencing and develop molecular assays for antimicrobial resistance or susceptibility might expand treatment options available to clinicians and reduce the spread of resistant strains. There is much work to be done. Let's get to it.

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