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Rising to Meet the Programmatic Public Health Challenges of Emerging *Neisseria gonorrhoeae* Antimicrobial Resistance: Strengthening the United States Response to Resistant Gonorrhea

Karen Schlanger, PhD, MPH,

Robert D. Kirkcaldy, MD, MPH

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

The challenges of preventing and controlling *Neisseria gonorrhoeae* are compounded by the bacteria's alarming ability to develop antimicrobial resistance (AR) that can undermine effective treatment. *N. gonorrhoeae* first unveiled its prowess in rapidly developing resistance when confronted with sulfonamide antibiotics in the 1930s.[1] Over the next 90 years, the bacterium successively developed AR to each antimicrobial recommended for treatment, prompting efforts by public health officials to keep pace through repeated changes to treatment guidelines.[2] As a summary of recent examples, in 2010 and in light of growing concern about emerging cephalosporin resistance in *N. gonorrhoeae*, the Centers for Disease control and Prevention (CDC) updated treatment guidelines to both increase the recommended dose of ceftriaxone and recommend dual therapy for gonorrhea with a cephalosporin (cefixime or ceftriaxone) plus either azithromycin or doxycycline.[3] By 2015, the only remaining treatment recommendation was the combination of ceftriaxone 250 mg as a single intramuscular dose and a single gram of oral azithromycin.[4] Yet by then, azithromycin susceptibility was declining in the United States, and a small but growing number of ceftriaxone-resistant infections were reported across the world.[5,6] As of December 2020, recommended therapy was modified to a single 500-mg dose of injectable ceftriaxone.[5] Meanwhile, the number of new antimicrobial agents that have become commercially available through the "antibiotic pipeline" has slowed to a trickle in the past several decades.[7] With resistance continuing to emerge and few new antimicrobials in the pipeline, experts have warned of the prospects of untreatable gonorrhea.[8] Adding further complexity, detection of AR relies on antimicrobial susceptibility testing (AST) of culture-based gonococcal isolates. However, in many health care settings apart from sexually transmitted disease (STD) clinics, such as those participating in CDC's long-standing Gonococcal Isolate Surveillance Project, culture for *N. gonorrhoeae* has become a relic of a bygone era, supplanted by the widespread use of nucleic acid amplification testing. Lack of timely access to culture and AST in most health care settings may allow for widespread transmission of resistant strains before resistance is even detected.

Correspondence: Karen Schlanger, PhD, MPH, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop US12-2, Atlanta, GA 30329-4027. Khs4@cdc.gov.

Currently, approximately 1.6 million gonococcal infections occur per year in the United States, contributing to chronic pelvic pain, ectopic pregnancy, tubal factor infertility, and HIV transmission and estimated total lifetime costs of $271 million.[9,10] Because of structural determinants of health, including poor access to health care, unacceptably high gonorrhea case rates are observed in some populations.[11] The impact of widespread transmission of highly resistant or untreatable gonorrhea would be dire. Widespread resistance would likely increase case counts, the frequency of sequelae, the complexity of patient management, and health care costs, and exacerbate existing disparities.

In the first Antimicrobial Resistance Threats in the United States report (2013), the CDC designated drug-resistant *N. gonorrhoeae* as one of three urgent AR threats facing the United States.[12] The report informed the subsequently released of the National Strategy for Combating Antibiotic-Resistant Bacteria (2014) and National Action Plan for Combating Antibiotic-Resistant Bacteria (2015).[13,14] To address gonococcal resistance, the National Action Plan identified urgent needs for new antimicrobials, new diagnostics, and new prevention approaches such as a vaccine, in addition to outlining a public health approach to slow the emergence of resistant bacteria and prevent the spread of resistant infections. Notably, the National Action Plan established a national target to maintain the prevalence of ceftriaxone-resistant *N. gonorrhoeae* less than 2% by 2020 and a milestone for state health departments to maintain advanced capacity for rapid response to drug-resistant gonorrhea, including capacity to detect, diagnose, and investigate suspected resistant cases within their state or region and assist health care providers in providing an appropriate treatment for infected patients.[14]

To support these elements of the National Action Plan, the CDC established *Strengthening the United States Response to Resistant Gonorrhea* (SURRG) to fund state-, city-, and county-level health departments to enhance capacity in participating jurisdictions to detect and respond to gonococcal infections with reduced azithromycin, cefixime, or ceftriaxone susceptibility. To boost capacity for detection, participating jurisdictions implemented or expanded specimen collection for *N. gonorrhoeae* culture from patients of all genders attending STD clinics and other participating (non-STD clinic) health care settings, and from genital, rectal, and pharyngeal anatomic sites. Participating jurisdictions also established and performed local rapid AST by Etest on all gonococcal isolates to rapidly detect reduced antimicrobial susceptibility and facilitate public health responses.

SURRG provided resources to funded jurisdiction for data system modernization to facilitate rapid local exchange of information between laboratories, STD program staff, epidemiologists, and clinicians about any identified reduced susceptibility. Participating jurisdictions also were able to upgrade surveillance data systems, laboratory information management systems, and clinic electronic health record systems; enhance interoperability of data systems; and strengthen local data management and analysis capacity with personnel and training. In addition, to enhance response capacity, jurisdictions invested in field investigation personnel and training and implemented a SURRG-enhanced investigation model. Once isolates with reduced susceptibility were identified, disease investigation specialists (DISs) in participating jurisdictions sought to rapidly contact the patient from whom the isolate was collected, encourage the patient to return to the clinic for a test

of cure to ensure treatment success, conduct partner services, and collect epidemiological data. Recognizing that partner services and detection of new cases through partner services are often limited by a patient not knowing or providing locating information about their sexual partners, DISs (using the SURRG enhanced investigation model) attempted to circumvent this barrier by leveraging the interconnectedness of a sexual network and reach more deeply into a network than is done with traditional partner services. Specifically, when conducting investigations of persons identified as having infections with reduced susceptibility, investigative staff attempted to elicit not only contact information for recent sexual partners (the strategy used for traditional partner services) but also social contacts (nonsexual contact who might benefit from STI testing). DISs would then attempt to contact and refer all named contacts for testing and any needed treatment. In addition, DISs would attempt to gather locating information from the index patient's sexual partners about *their* sexual partners even if that index patient's sexual partner(s) tested negative for gonorrhea. This model would continue until 2 generations of sexual partners to any index case or to any new investigation identified cases of gonorrhea tested negative.

On a broader scale, SURRG has provided an opportunity to pilot and evaluate these and other innovative approaches for rapid detection (i.e., enhanced local surveillance) and response to emerging resistance and, importantly, to build toward an evidence base of effective practices to address gonococcal ceftriaxone resistance when it appears. Ideally, these practices would be translatable to other jurisdictions not participating in SURRG. There are surprisingly few published data on effective programmatic public health response approaches to emergent or present gonococcal resistance, despite prior experience responding to the emergence of penicillinase-producing *N. gonorrhoeae* and fluoroquinolone-resistant *N. gonorrhoeae* in the United States during the past 4 decades. Other gaps in knowledge exist. For example, despite CDC recommendations for (1) test of cure, (2) specimen collection for culture, and (3) AST in the setting of suspected treatment failures,[4,5] knowledge of the feasibility of, or optimal approaches to, tests of cure, collection of culture specimens outside of traditional STD clinics, and local AST implementation has been incomplete. Furthermore, with rapid recent advances in genome sequencing technology, little is known about how best to apply genomic epidemiology and to integrate genomic data with case and case investigation data to inform programmatic action. Quantitative and qualitative information gleaned through SURRG—including pragmatic programmatic lessons learned—may fill such critical knowledge gaps.

In this supplement of *Sexually Transmitted Diseases*, we are excited to share findings and lessons learned from the first 5-year cycle of SURRG (with a focus on activities between 2018 and 2019). These findings and the growing evidence base from SURRG are anticipated to inform national, state, and local preparedness efforts and responses to outbreaks of gonococcal resistance in the United States. The committed efforts of the jurisdictions participating in SURRG, in conjunction with national and international efforts to develop new therapeutics, diagnostics, and a gonococcal vaccine, are advancing the United States capacity to meet the challenges of emerging gonococcal resistance.

Disclaimer:

The findings and conclusions in this publication are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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