2021

Strengthening the U.S. Response to Resistant Gonorrhea (SURRG) Protocol

This page intentionally left blank

Introduction & Project Summary

Gonorrhea is a sexually transmitted disease (STD) caused by the bacterium *Neisseria gonorrhoeae*. Whereas infections occurring in the urethra are often associated with profuse discharge and painful urination, cervical, pharyngeal, and rectal infections are often asymptomatic. In cisgender women, untreated gonorrhea is a major cause of pelvic inflammatory disease, which can in turn lead to severe reproductive health complications, such as ectopic pregnancy and infertility. Infrequently, gonorrhea can lead to blood-stream infections (disseminated gonococcal infections) and septic arthritis, endocarditis, and meningitis. Gonorrhea increases the risk of sexual transmission of HIV.

Gonorrhea is the second most commonly reported nationally notifiable disease in the United States. in 2018, over 580,000 cases were reported to the Centers for Disease Control and Prevention (CDC). In the United States, rates are highest among adolescents and young adults, among racial and ethnic minorities, and in the Southern US. Rates also appear be increasing among gay, bisexual, and other men who have sex with men (MSM). As a notifiable disease, state and local health departments have authority to conduct surveillance of gonorrhea and collect patient-level data about persons diagnosed with gonorrhea.

Rapid detection and effective treatment of gonorrhea is a cornerstone of public health prevention and control efforts. However, treatment of gonorrhea has been complicated by the ability of *N. gonorrhoeae* to rapidly develop antimicrobial resistance. *Neisseria gonorrhoeae* has developed resistance to each antimicrobial recommended for therapy, including penicillin, tetracycline, and fluoroquinolones, necessitating sequential changes in treatment guidelines. Following the emergence of fluoroquinolone-resistant gonorrhea during the 2000s and declines in cefixime and azithromycin susceptibility, CDC currently recommends a single dose of injectable ceftriaxone. Recent surveillance data suggest that susceptibility to ceftriaxone may be declining. Widespread emergence of ceftriaxone resistance could substantially hinder treatment and control efforts, increase gonorrhea rates and frequency of complications, and contribute to at least $235 million in additional direct medical costs. In the Antibiotic Resistance Threats in the United States, 2019 report, CDC designated *N. gonorrhoeae* as an "urgent" antimicrobial threat facing the United States.

The White House National Strategy and Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) prominently featured the threat posed by resistant *N. gonorrhoeae*. The plans established a goal of slowing the emergence of and preventing the spread of resistant bacteria and set a target of maintenance of the prevalence of ceftriaxone-resistance in *N. gonorrhoeae* at remain below 2% through 2020. Using investments provided by Congress in 2017, CDC established Strengthening U.S. Response to Resistant Gonorrhea (SURRG) is to support the implementation of CARB and the achievement of the Action Plan goals and targets. The objective of SURRG is to prevent the spread of resistant infections by building local laboratory, epidemiological, informatics, and programmatic capacity to rapidly detect and contain emerging *N. gonorrhoeae* resistance threats.

This project supports Healthy People 2020 objectives to reduce gonorrhoea rates of among men and women aged 15–44 (Objectives STD-6.1 and STD-6.2) as well as to strengthen public health laboratory services to support diagnosing and investigating health hazards in the community, support emergency response, disease control and surveillance, and specialized testing (Objectives PHI-11.1-PHI-11.3; PHI-12.2-PHI-12.4; and PHI-12.6-PHI12.7), and to assure comprehensive epidemiology services (Objective PHI-13.4). This project aligns with two of the five goals of the National Strategy for Combating Antibiotic-Resistant Bacteria to slow the emergence of resistant bacteria and prevent the spread of resistant infections (Objective 1.1), and advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria (Objective 3.2).

This document outlines the SURRG protocol and methods for implementing these enhanced programmatic and surveillance activities.

Contents

1.0 Objectives and Justification

1.1 Objectives

To strengthen state and local gonorrhea public health infrastructure and build capacity in high-risk local jurisdictions to support rapid detection of and response to threats of antibiotic-resistant gonorrhea.

The aims of SURRG are to:

- Strengthen local antibiotic-resistant gonorrhea threat coordination, laboratory, and epidemiological capacity and informatics infrastructure
- Enhance timely surveillance for detection of resistant *N. gonorrhoeae* strains
- Enhance local capacity to rapidly conduct gonorrhea case investigations, identify partnership networks and transmission dynamics of gonorrhea, and halt the spread of identified resistant infections.

Lessons learned and data generated from Strengthening U.S. Response for Resistant Gonorrhea (SURRG) will be applied to other jurisdictions and public health efforts to improve United States preparedness and capacity to respond to antibiotic-resistant *Neisseria gonorrhoeae*.

1.2 Justification

Rapid detection and effective treatment of gonorrhea is a cornerstone of public health gonorrhea control and prevention of complications. Monitoring gonorrhea is critical to understand the characteristics of persons and groups affected, trends in infection rates over time, and the geographic extent of affected populations. These data from such efforts can provide necessary insights into the changing landscape of disease and the impact of STD prevention programs.

CDC currently conducts surveillance of gonococcal antibiotic resistance through the Gonococcal Isolate Surveillance Project (GISP), which has effectively monitored long-term trends in antibiotic susceptibility and repeatedly informed changes in national treatment guidelines. However, data from GISP are not sufficiently timely to allow rapid detection and response to antibiotic-resistant gonorrhea and are limited to the susceptibility profile of urethral specimens from men attending participating sexually transmitted diseases (STD) clinics. Outside of established surveillance platforms, detection of resistance is extremely limited because of widespread use of the nucleic acid amplification testing (NAAT) for gonorrhea diagnosis, which has supplanted culture techniques (which are needed for resistance testing). Few clinicians use or have access to gonorrhea resistance testing. Local public health capacity to respond rapidly to antibiotic-resistant gonorrhea is further challenged by increasing STD rates and limited state and local STD public health infrastructure and resources. To support the goals of slowing the emergence of and preventing the spread of resistant *N. gonorrhoeae* articulated in the National Action Plan for Combating Antibiotic Bacteria, strengthening of local and state public health capacity to rapidly detect and respond to emerging antibiotic-resistant gonorrhea is urgently needed.

Partner services — in which potentially infected partners are interviewed, tested, and treated — has traditionally been a foundational element of public health STD control efforts. A critical element of partner services is contact tracing; contact tracing is a core element of public health outbreak investigation and control of other infectious diseases, such as Ebola and COVID-19. However, few health department STD programs have the resources to conduct routine partner services for gonorrhea, much less enhanced investigations to halt the spread of identified resistant strains. SURRG activities focus on building local capacity to respond effectively to and halt the spread of outbreaks of antibiotic-resistant gonorrhea.

The data collected from SURRG will be used to monitor for resistance, advance the understanding of the epidemiology of gonorrhoea and antibiotic-resistant gonorrhea, including identifying populations most at risk, factors contributing to the emergence of resistance, and transmission of resistant gonorrhoea within a population, evaluate the effectiveness of detection and disease control approaches, and support development of public health interventions to prevent the spread of resistance.

2.0 Project Methodology

2.1 Target Population

Each grantee voluntarily applied to participate. All applications underwent a competitive evaluation process for final selection of grantees.

Each funded jurisdiction conducts SURRG activities in at least one STD-specialty clinic and at least one other partnering outpatient healthcare setting or clinic (referred to as a non-STD clinic healthcare facility). Within participating clinics, all persons with symptoms consistent with gonorrhea, deemed at elevated risk for gonorrhea (such as having recently had sex with a person diagnosed with gonorrhea), or who meet U.S. Preventive Services Task Force (USPSTF) or CDC screening criteria and presenting for care will be tested/screened for gonorrhea using culture and nucleic acid amplification tests (NAATs) in accordance with local standards.

Persons found to be infected with an antibiotic-resistant strain or other gonococcal infection of public health significance will be interviewed by health department staff and re-tested to ensure that their infection was cured. Their recent sex partners will be rapidly interviewed, tested, and treated to break the chain of transmission.

2.2 Specimen and Data Collection

SURRG activities will reinforce and enhance existing STD surveillance and public health infrastructure and practices of the funded jurisdictions. Jurisdictions are required to develop local protocols and data collection instruments (paper and/or electronic) for investigators and provide adequate training to health department staff conducting patient and partner contact tracing. While ensuring that data elements for SURRG are collected systematically and consistently, funded jurisdictions can integrate SURRG data collection into established local partner management and treatment assurance protocols.

2.2.1 Specimen collection and testing

Clinicians in participating clinics will screen and test for gonorrhea according to local protocols, USPSTF guidance, and current CDC STD treatment guidelines. Clinicians will collect specimens for NAAT and culture (as described in the Etest protocol from relevant anatomic sites. Performance of NAAT provides excellent sensitivity for *N. gonorrhoeae*, allowing clinicians to diagnose gonorrhea with a high degree of accuracy. Performance of culture provides the opportunity to conduct antibiotic susceptibility testing (AST) for patient care and public health detection of resistance. Persons diagnosed with gonorrhea will be treated according to the most up-to-date CDC STD Treatment Guidelines. Consistent with routine clinical care, epidemiological and clinical data will be collected from patients during the clinical encounter (see below). Partner services will be provided by the local or state public health STD program according to CDC STD Treatment Guidelines as adapted for local or state resources and practices, and when relevant, the SURRG protocol (see laboratory and interview data sections below).

Culture specimens will be transported to the local public health laboratory (PHL) for culture and bacterial isolation. *N. gonorrhoeae* isolates will rapidly undergo AST by Etest.

2.2.2 Interpretation of Antibiotic Susceptibility Testing (AST)

Etest and agar dilution AST methods are used to measure the growth of *N. gonorrhoeae* on a GC base agar medium in presence of the antimicrobial agents at varying concentrations to determine antibiotic susceptibility and provide results as minimum inhibitory concentrations (MICs) (the lowest concentration of antibiotic that inhibits growth of the bacteria in the laboratory). The Clinical Laboratory Standards Institute (CLSI) have established susceptibility breakpoints for cefixime and ceftriaxone (MICs ≤ 0.25 μg/ml)

For surveillance and programmatic purposes, SURRG has set lower breakpoints to identify emerging antibiotic resistance threats. These MIC breakpoints are referred to within SURRG as demonstrating reduced susceptibility (Table 1). The local or state PHL will rapidly communicate AST results demonstrating reduced susceptibility to the site SURRG epidemiological coordinator, who will in turn initiate a SURRG field investigation and notify CDC.

SURRG has also defined MIC breakpoints that may represent an urgent public health concern and for which the AST results should be urgently confirmed. These are referred to within SURRG as "Quick Send" MIC values, reflecting that isolates demonstrating these MICs will be rapidly transported to CDC for confirmatory testing.

Funded jurisdictions may opt to conduct AST on additional antibiotics, but jurisdictions may be limited in use of SURRG funds for such testing.

Table 1: SURRG MIC Interpretive Criteria for Antibiotic Agents

Antimicrobial Agent	Reduced Susceptibility	Quick Send
Ceftriaxone	MIC ≥ 0.125 μg/ml	MIC ≥ 1.0 μg/ml
Cefixime	MIC ≥ 0.25 μg/ml	MIC ≥ 1.0 μg/ml

2.2.3 Assigning Person and Specimen Identifiers

Participating jurisdictions will generate unique numbers for persons from whom specimens for gonorrhea testing were collected. This assigned patient number should be unique within the jurisdiction, remain consistent across visits and the life cycle of SURRG, and not contain personally identifiable information (PII). The site SURRG epidemiological coordinator or designated data manager will be responsible for generating and maintaining the patient numbers.

Participating jurisdictions will generate and assign a unique code to each isolate; each code will have a three-character sentinel site abbreviation followed by a locally-assigned accession number.

The patient number and specimen codes will allow merging of epidemiological and clinical data with AST laboratory results.

Some jurisdictions participating in SURRG also participate in GISP. For those jurisdictions, isolates that are also included in GISP (i.e., the first 25 urethral isolates each month) will have a locally assigned GISP specimen ID consistent with the GISP protocol.

2.2.4 Transport of Isolates to the Antibiotic Resistance Laboratory Network (ARLN) and ARLN testing

N. gonorrhoeae isolates are transported from the local or state PHL to one of the four participating Antibiotic Resistance Laboratory Network (ARLN) regional laboratories using the laboratory transport system.

Consistent with sound laboratory practice, SURRG isolates will be accompanied by a manifest, on which laboratory staff will record a small number of variables, such as sex of the patient, jurisdiction/city, date of specimen collection, and anatomic site of infection, to ensure correct handling and identification of the samples.

Isolates with reduced susceptibility by AST will be sent to the assigned ARLN laboratory within 24 hours of AST. Isolates with MICs meeting "Quick Send" criteria will be sent within 24 hours to both the assigned ARLN and CDC laboratories (Table 1). Isolates with AST results that do not exceed reduced susceptibility alert values presented in Table 1 will be sent to the assigned ARLN laboratory in monthly batches.

The ARLN laboratory will conduct AST by agar dilution. Selected isolates will undergo whole genome sequencing (WGS) for molecular characterization and to support field investigations of persons with resistant infections.

2.2.5 Core Epidemiological, Laboratory, and Interview Data Collection

Clinic-based data

Data managers at each funded jurisdiction will:

- abstract line-listed clinic visit data from participating STD clinics,
- receive line-listed clinic visit data from participating non-STD clinic healthcare facilities, and
- clean and merge data

Data managers at non-STD clinic healthcare facilities will:

- abstract line-listed clinic visit data from their facility, and
- transmit the data to the data manager at the funded jurisdiction.

Laboratory data

Data managers at the participating PHL will:

- manage the results within the laboratory's electronic information system
- abstract relevant results, and
- transmit the data to the data manager at the funded jurisdiction.

Additionally, laboratory staff will quickly communicate reduced susceptibility results to the local SURRG epidemiological coordinator, to facilitate rapid field investigations.

Interview data

Collection of interview data

Once the site epidemiological coordinator is notified by the PHL of an isolate with reduced susceptibility (Table 1), they will initiate a field investigation in collaboration with specially-trained health department staff (referred to as disease investigation specialists or DIS). DIS undergo extensive training to interview patients, elicit names and contact information of recent sexual partners, and locate and interview partners as part of routine and established public health disease control activities. DIS are also extensively trained in maintenance of confidentiality and privacy.

The assigned DIS or health department staff member will interview the patient from whom the isolate was collected to elicit epidemiological data and the names and contact information of recent sexual partners. Recent partners will be interviewed, tested, and treated. If a partner's test results demonstrate an infection, DIS will interview the individual to elicit the names and contact information of their recent sexual partners (who will be interviewed, tested, and treated). DIS may use multiple data sources available to local health department staff to gather contact information for patients and partners, including vital record or government database searches, contact with healthcare providers, and social media (as allowable by local policy). To expand gonorrhoea control efforts, deepen the understanding of gonorrhea epidemiology, and identify possible public health prevention approaches, epidemiological coordinators may also conduct investigations of persons whose gonococcal infection may not demonstrate resistance but is deemed of public health significance.

Data managers at each funded jurisdiction will:

- Receive field investigation data

- Link field investigation data to laboratory results and clinic data using the assigned patient number. As noted above, the assigned patient number will not contain PII or medical record numbers.
- Merge field investigation data with clinic and laboratory data, clean, and structure the data in the request formats
- Transmit the data electronically to CDC using a secure electronic platform.

2.3 Data Transmission to CDC

Site data managers will transmit de-identified epidemiological clinic data, laboratory results (NAAT, culture, and AST), and investigation interview data to CDC using a secure access management service (SAMS). No data containing PII will be transmitted to CDC.

Funded jurisdictions are expected to institute rigorous procedures to assure data quality and validity before submitting data to CDC. CDC will provide data structures with variable names, lengths and types defined for all requested SAS datasets. CDC will also prepare syntax for data validation that will provide for appropriate quality assurance. Local data should be transformed to conform to these data structures and include only the requested data elements properly coded and in appropriate data formats. Datasets failing to comply with pre-determined data structures will be rejected, with notification to jurisdiction. The jurisdiction(s) must re-format, recode or resolve issues, and re-transmit corrected datasets.

Jurisdictions will provide clean and validated datasets to CDC every 2 months with cumulative data starting with records from January 1 of each calendar year. Required datasets will be securely transmitted to CDC each month. Record-level data will only be transmitted to CDC following the Secure Access Management Service (SAMS) protocols. Jurisdictions may also be required to encrypt data using at least 128-bit RSA-compliant strong key-pair encryption (such as PGP).

A final, validated annual SAS dataset will be transmitted each year and archived to become the primary repository of that site's annual reporting. These annual datasets should be preserved at the local level as 'frozen' data for local analytic purposes.

CDC will formally acknowledge all data transmissions and data validation results by e-mail. Datasets received at CDC will be validated and merged into the national SURRG dataset. Project progress will also be measured according to individual program-related guidelines outlined in the Epidemiology and Laboratory Capacity for Infectious Diseases (ELC) Cooperative Agreement Funding opportunity announcement; additional information about the ELC can be found at https://www.cdc.gov/ncezid/dpei/epidemiology-laboratory-capacity.html.

2.4 Confidentiality and Human Subjects Considerations

All SURRG participating jurisdictions are public health departments, not covered entities under HIPAA regulation: "Without individual authorization, a covered entity may disclose protected health information to a public health authority that is legally authorized to collect or receive the information for the purposes of preventing or controlling disease, injury, disability including, but not limited to reporting of disease…and conducting public health surveillance…" (MMWR, 2003). Data sent to CDC will contain no personal identifiers such as name, date of birth, social security number, street address, or medical record number.

SURRG activities are disease control activities, with collected data directly relating to disease control and routine disease surveillance activities, with collected data directly enhancing local and national surveillance of gonorrhoea resistance. The Associate Director for Science (ADS) of the NCHHSTP, CDC, and the Institutional Review Board (IRB) at CDC have reviewed this SURRG protocol and determined that SURRG is a public health activity and not human

subjects research. No incentives are provided to patients or clinic personnel for SURRG activities. Those collaborating health departments should assess their local needs for similar determinations or human subject research reviews.

3.0 Project team and Institutional roles

Eight funded jurisdictions are involved in the concept, design, planning, staff hiring, data collection, analysis, reporting, and data storage. The jurisdictions will ensure coordination of project activities. Data from response activities (case field investigation and contact tracing) will be shared for project purposes. The jurisdiction will hire local staff to conduct epidemiologic, laboratory, and informatics activities for the project.

CDC will provide technical assistance in all project aspects and will lead multisite data cleaning, management, and analyses.

Funded Jurisdictions:

- California Department of Public Health & San Francisco Department of Public Health
- Colorado Department of Public Health and Environment & Denver Public Health
- Indiana State Department of Health & Marion County Public Health Department
- North Carolina Division of Public Health & Guilford County Department of Health and Human Services
- New York City Department of Health & Mental Hygiene
- Pennsylvania Department of Health & Allegheny County Health Department
- Washington State Department of Health & Public Health – Seattle and King County
- Wisconsin Division of Public Health & Milwaukee Health Department

Centers for Disease Control and Prevention staff:

- Karen Schlanger, Project Lead, Epidemiology and Statistics Branch
- Kerry Mauk, Epidemiologist, Epidemiology and Statistics Branch
- Emily Learner, Epidemiologist, Epidemiology and Statistics Branch
- Robert D. Kirkcaldy, Team Lead, Epidemiology and Statistics Branch
- Kyle Bernstein, Branch Chief, Epidemiology and Statistics Branch

- Cau Pham, Laboratory Coordinator, Laboratory Reference and Research Branch
- Evelyn Nash, Co-Laboratory Coordinator, Laboratory Reference and Research Branch
- Brian Raphael, Team Lead, Laboratory Reference and Research Branch
- Ellen Kersh, Branch Chief, Laboratory Reference and Research Branch

- LaZetta B. Grier, Data/IT Specialist, Data Management Team, Surveillance and Data Management Branch
- Melissa Pagaoa, Lead, Data Management Team, Surveillance and Data Management Branch

References

Centers for Disease Control and Prevention. Sexually Transmitted Diseases Surveillance 2018. Atlanta: U.S. Department of Health and Human Services; 2019. DOI: 10.15620/cdc.79370.

Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. MMWR Recomm Rep 2015;64(No. 3): 1-137.

LeFevre M, U.S. Preventive Services Task Force. Screening for Chlamydia and Gonorrhea: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine 2014;161: 902-910.