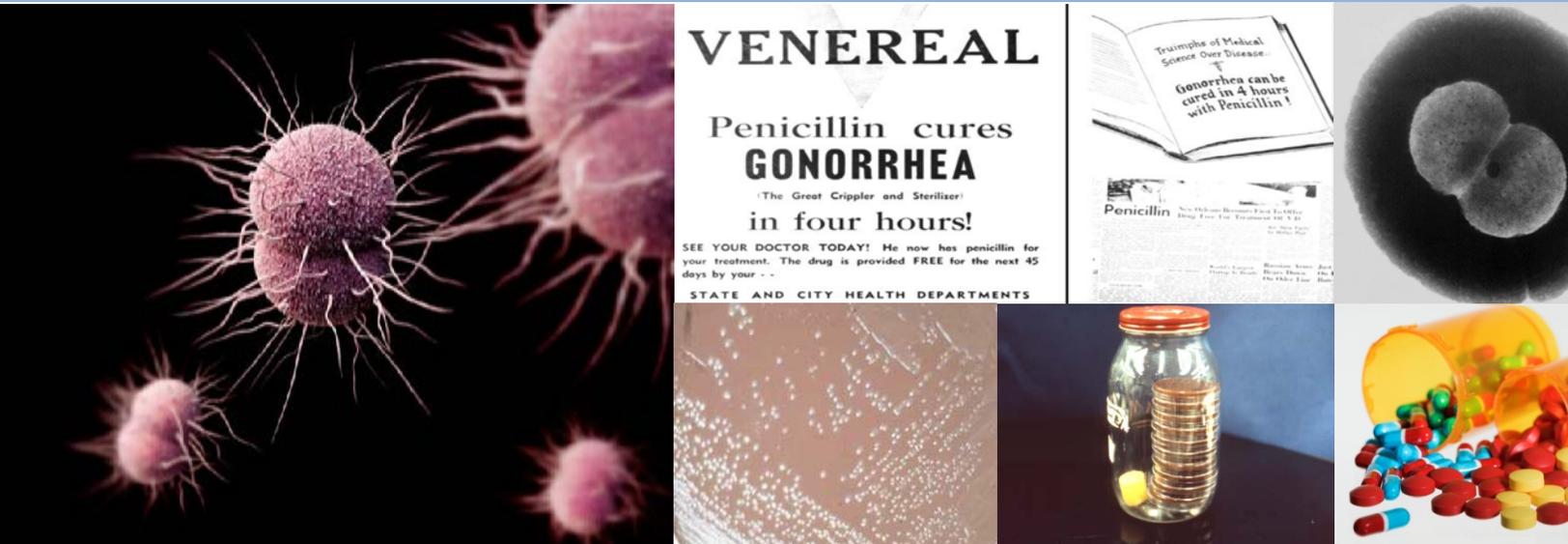


Gonococcal Isolate Surveillance Project (GISP)



Protocol

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1. Introduction

1.1. Background

The treatment and control of *Neisseria gonorrhoeae* infections have been complicated by the organism's ability to acquire antimicrobial resistance. The increasing prevalence of strains with plasmid-mediated resistance to penicillin (PPNG) prompted the abandonment of penicillins as single-dose therapies for gonorrhea in 1987. The development of plasmid-mediated resistance to tetracycline, i.e., TetM, caused the Centers for Disease Control and Prevention (CDC) to recommend, in 1985, that tetracycline not be used for the treatment of gonococcal infections. The prevalence of chromosomally-mediated resistance to fluoroquinolones reached levels in the United States at which fluoroquinolones were no longer recommended for gonorrhea treatment by 2007. Occasional chromosomal-mediated resistance to spectinomycin has also been reported. Minimum inhibitory concentrations (MICs) of oral cephalosporins, such as cefixime, have increased in many regions of the world, including the United States. Isolates with high azithromycin minimal inhibitory concentrations have been detected sporadically.

The Gonococcal Isolate Surveillance Project (GISP) was established in 1986 to monitor antimicrobial susceptibility trends in *N. gonorrhoeae* strains in the United States and to establish a rational basis for the selection of gonococcal therapies. Data from this project have been reported and used to revise the CDC's STD treatment recommendations in 1989, 1993, 1998, 2002, 2006, 2010, and 2014. This protocol supersedes all previous protocols for the project.

1.2. Objectives

1. To monitor trends in antimicrobial susceptibilities in *N. gonorrhoeae*.
2. To characterize male patients with gonorrhea, particularly those infected with *N. gonorrhoeae* that are not susceptible to recommended antimicrobials.
3. To phenotypically characterize antimicrobial-resistant isolates to describe the diversity of antimicrobial resistance in *N. gonorrhoeae*.

2. Methods

The Gonococcal Isolate Surveillance Project is a collaboration between: the CDC Division of STD Prevention (DSTDP) Surveillance & Data Management Branch (SDMB) and the Laboratory Reference & Research Branch (LRRB), with support from the Program Development and Quality Improvement Branch (PDQIB); five regional laboratories; and selected public health STD program and associated STD specialty care clinics in the United States. The responsibilities of each group of participants are detailed in this protocol.

GISP analyses are based on (a) demographic and clinical data from the first 25-30 male patients attending the sentinel clinics each month who have been identified to have a positive urethral culture for *N. gonorrhoeae*, and (b) antimicrobial susceptibility data from these urethral isolates.

3. Collaborator Activities and Responsibilities

3.1. Sentinel Sites

3.1.1. Overview

A GISP Sentinel Site is responsible for the monthly submission of (a) male urethral gonococcal isolates to its assigned GISP Regional Laboratory, and (b) clinical/demographic data on GISP patients to CDC.

To participate in GISP, the sentinel STD specialty care clinics will routinely use gonococcal culture in lieu of or in addition to non-culture testing on all or a subset of male patients with urethritis. Culture provides useful data (i.e., data on antimicrobial susceptibility) that can benefit patients directly and is important for local disease control efforts.

At each Sentinel Site, an individual will be assigned to be responsible for data collection and appropriate gonococcal isolate collection, and to ensure that the isolates are sent to the Regional Laboratories and the epidemiologic data are sent to CDC.

3.1.2. Sentinel Site Laboratory Collection, Handling, and Shipping of Isolates

1. Urethral isolates of *N. gonorrhoeae* (based on a presumptive* or confirmed identification) will be collected from the first 25 men with urethral gonococcal infection (regardless of symptom status) each month. Usually, the isolates will be collected starting on the Monday of the first full week each month.

Because there may be occasional month-to-month variability in the number of isolates submitted, a sentinel site may provide >25 isolates in any given month to make up for providing <25 isolates in other months; the overall goal is for each sentinel site to provide at least 300 isolates per year. Most isolates will be pre-treatment isolates; however, post-treatment isolates may be included in the sample.

*A presumptive identification of *N. gonorrhoeae* will be based on the following criteria: (i) growth of typical appearing colonies on a selective medium such as Thayer-Martin at 35° C to 36.5° C in 5% CO₂, (ii) a positive oxidase test, and (iii) the observation of gram-negative, oxidase-positive diplococci in stained smears.

2. Gonococcal isolates will be subcultured from the selective primary medium to a non-inhibitory medium, e.g., chocolate agar with 1% IsoVitaleX to obtain a pure culture of the isolate. If the subcultured isolate is not pure, serial subcultures of individual colonies must be performed until a pure culture is obtained. After 18 to 20 hours of incubation, growth from the pure culture is suspended heavily in trypticase soy broth containing 20% (v/v) glycerol; duplicate frozen cultures of each isolate are prepared.
3. Isolates will be assigned sequential identifiers for each month. Each identifier will be composed of a three-letter designation for the Sentinel Site (see Appendix 1), followed by a six-digit number indicating the year and month of isolate collection (yyyymm), and a two digit number in the sequence from 01 through 25 or higher. For example, the 20th isolate selected in January 2014 in Atlanta will be given the number ATL-201401-20.

Each Sentinel Site laboratory should maintain a monthly log of GISP identification numbers and the

corresponding patient name or identification number. This log is for local use only and is not to be shared with the Regional Laboratory or CDC. This information must be routinely shared with the Sentinel Site staff person who is responsible for abstracting demographic and clinical data on GISP patients. So that data can be properly merged at CDC, the GISP identification number of individual isolate must match the GISP identification number of the demographic and clinical data for the patient who submitted the isolate.

4. Isolates will be frozen to -70° C if possible. If a -70° C freezer is not available, isolates may be frozen to -20° C (freezer/dry ice chest) until shipped to the Regional Laboratory; isolates to be shipped must be placed in the coldest sections of the -20° C freezer (not in the door or at the front of a shelf) and should be stored in containers separate from any other frozen gonococcal cultures (including separate from duplicate frozen specimens). GISP isolates should not be subjected to changes in temperature as they may result in loss of viability during storage. A frost-free freezer should not be used.
5. Isolates should be shipped each month to the Regional Laboratory on Monday of the week immediately following completion of collection of the isolates but no later than the first Monday of the month following the month of isolate collection. Duplicate isolates must be kept until the Regional Laboratory confirms that viable isolates have been received.

*Please e-mail or telephone the Regional Laboratory **prior** to shipping the strains to confirm when the strains will be shipped and to ensure that someone in the Regional Laboratory will be available to receive the strains. Ideally, isolates should be shipped no later than Wednesday in any week in which they are shipped to ensure that they are received at the Regional Laboratory before close of business on Friday.

Isolates must be packed in two leak-proof containers, one inside the other. The package containing the isolates should be packed in insulated styrofoam containers (to be provided by CDC) with dry ice (at least 10 lb.); dry ice should be packed on each side of the package of isolates. Ship the container by overnight express, charging the shipping costs to the FedEx account number provided by CDC. The container will be returned to the Sentinel Site by FedEx Express Saver 3-day delivery for future shipments. Sites should ship GISP isolates **each month**; isolates should not accumulate for several months and then be shipped together because this prevents the Regional Laboratories from completing the susceptibility testing on schedule.

3.1.3. Sentinel Site Clinic or Program Activities

3.1.3.1. Reporting Demographic and Clinical Data

Demographic and clinical data should be submitted for each patient from whom a GISP isolate is submitted. A unique GISP number will be assigned to each patient (see Section 3.1.2, item 3 above). Data may be obtained through review of medical records by clinic staff. Data will be submitted electronically using Form 1 (CDC 73.60 A) of the secure GISP web-based application and maintained locally in the clinic files (see Appendix 1 for description of requested data elements). Data may also be submitted electronically as comma-delimited (.csv) files. Demographic and clinical data reports should be received at CDC *no more than four weeks* after the end of the month in which the corresponding isolates were collected.

Appendix 1 provides detailed descriptions of the requested data elements. The GISP Coding Guide (available at: www.cdc.gov/std/gisp) provides instructions on correct coding of responses. The following is a concise list of the requested demographic and clinical data elements:

- Sentinel site code
- Specimen collection (YYYY/MM)
- Sequential patient number (01- 25 or higher)
- Clinic code (for those sentinel sites submitting GISP isolates from more than one clinic)
- Sex
- Ethnicity
- Race (census categories)
- Date of clinic visit
- Age
- Sex of sex partner
- Presence of symptoms
- Previous history of gonorrhea
- Number of previous confirmed episodes of gonorrhea in past year
- Most recent known HIV status at clinic visit for gonorrhea
- Travel outside the United States during the previous 60 days
- History of giving or receiving drugs / money for sex in the previous 12 months
- Any antibiotic use during the previous 60 days
- History of injection drug use in the previous 12 months
- History of non-injection recreational drug use (excluding alcohol) in the previous 12 months
- Primary treatment for gonorrhea
- Secondary treatment for gonorrhea (co-treatment for presumed chlamydia, if present)

3.1.3.2. Annual Process Measure Reporting

As described in the STD AAPPS Funding Opportunity Announcement (CDC-RFA-PS14-1402), sentinel sites are expected to monitor and report on process measures to document progress towards achieving GISP project outcomes. The data should be submitted to CDC as part of the annually-submitted Interim Progress Report (IPR).

At a minimum, awardees are expected to monitor and report on the following measures:

- Number of cases of gonococcal urethritis diagnosed in men attending the STD clinic

- Number of isolates submitted to the GISP regional laboratory
- Percentage of submitted isolates that were found by the GISP regional laboratory to be non-viable or contaminated
- Percentage of monthly isolate batches shipped to the GISP regional laboratory within one week after the end of monthly collection
- Percentage of monthly data transmissions that were submitted to CDC within 4 weeks after the end of the month in which the corresponding isolates were collected
- Percentage of collected isolates for which the following data elements were reported: (a) age, (b) race/ethnicity, (c) sex of sex partner/sexual orientation, (d) HIV status, (e) antibiotic use, and (f) treatment

In addition, awardees should describe their plans to address challenges faced in enrollment, specimen quality and viability, timeliness of specimen or data transmission, and data completeness.

3.2. Regional Laboratories

The Regional Laboratories in Atlanta, Baltimore, Birmingham, Seattle, and Austin are responsible for determining β -lactamase production and antimicrobial susceptibilities of GISP isolates received from the Sentinel Sites.

3.2.1. Receipt of Isolates

The isolates will be cataloged and frozen at -70° C until tested. Any problems with the isolates such as improper shipping, non-viability, or contamination should be reported as soon as possible to the Sentinel Site and to CDC. The insulated containers will be returned to the Sentinel Sites for future shipments by FedEx Express Saver charging the shipping costs to the FedEx account number provided by CDC.

3.2.2. Confirmatory Testing

The Regional Laboratories are not required to perform confirmatory tests on all isolates although it is recommended that confirmatory tests be performed on any isolate that exhibits atypical colonial morphologic characteristics or aberrant susceptibility patterns. Because we are testing only urethral isolates, we do not anticipate a significant problem with the inclusion of nongonococcal isolates in the sample. However, occasionally, urethral *N. meningitidis* isolates may be isolated, rather than *N. gonorrhoeae*. Because gonococcal serologic reagents may cross-react with nongonococcal *Neisseria* and related species, we recommend that strains be identified with tests that detect acid production from carbohydrates and/or enzyme substrate tests or with a probe culture confirmation test.

3.2.3. β -lactamase Tests

All isolates will be tested for β -lactamase by the Nitrocefin test (Appendix 2).

3.2.4. Antimicrobial Susceptibility Testing

Antimicrobial susceptibilities (minimal inhibitory concentrations, MICs) to penicillin G, tetracycline, spectinomycin, cefixime, ceftriaxone, ciprofloxacin, and azithromycin will be determined by the agar-dilution procedure on Difco GC medium base (Becton Dickinson, Cockeysville, MD) inoculated with 10^4 colony forming units (CFU). Appendix 3 describes the current GISP testing ranges and details for preparation of antibiotic-containing media. Regional Laboratories should include a set of control strains (F-18 [ATCC 49226; quality control isolate mandated by the Clinical and Laboratory Standards Institute (CLSI) F-28, P681E, CDC 10328, CDC 10329, SPJ-15, and SPL-4) with each run and should report control strain MIC data on Form 3 (CDC 73.60C) each month (see Appendix 4, CDC Reference Strains of *N. gonorrhoeae*). The results of Form 3 should be entered into the GISP web-based application and the receipt copy should be maintained in laboratory files (see Appendix 1 for description of Data Elements, Form 3 or CDC 73.60C). It is expected that susceptibility testing will be completed within one month of receipt of isolates from a Sentinel Site, and reported to CDC on a monthly basis within one week of completion.

If isolates meeting Alert Value MIC criteria as listed below are identified, it is the responsibility of the Regional Laboratory to retest these isolates to confirm the MICs. Regional Laboratory personnel may retest these isolates with the next batch of isolates, provided this is no longer than one month after the initial test.

3.2.4.1. Isolates with Alert Value MICs

Isolates with MICs defined as “alerts” require confirmation by retesting and prompt reporting.

Alert MIC Criteria

Ceftriaxone MIC ≥ 0.125 $\mu\text{g/ml}^*$

Cefixime MIC ≥ 0.25 $\mu\text{g/ml}^*$

Azithromycin MIC ≥ 2.0 $\mu\text{g/ml}^{}$**

Spectinomycin MIC > 128 $\mu\text{g/ml}^\dagger$

* For ceftriaxone and cefixime, isolates should be tested for growth on medium containing the antibiotics at concentrations ranging from two dilutions below the initial MIC to sufficient concentrations above the initial MIC to obtain an endpoint MIC.

** For azithromycin, isolates should be tested for growth on medium containing azithromycin at concentrations ranging from two dilutions below the initial MIC to sufficient concentrations above the initial MIC to obtain an endpoint MIC.

† For spectinomycin, isolates should be retested for growth on 128.0 $\mu\text{g/ml}$ of spectinomycin.

The GISP Project Officer at CDC, sentinel site, and the pertinent local and/or state STD programs should be notified **within one working day** by telephone or by e-mail of any isolate(s) identified to demonstrate an alert MIC. If the alert isolate(s) is re-tested, the GISP Coordinator and Project Officer at CDC, sentinel site, and the pertinent local and/or state STD programs should be notified **within one working day** after the alert value(s) has been confirmed.

Alert isolates must be stored and shipped in *triplicate* to the CDC & ATSDR Specimen Packaging, Inventory and Repository (CASPIR) Facility on a quarterly basis (4 times per year). Ship alert isolates on dry ice by priority overnight delivery, charging the shipping costs to the FedEx account number provided by CDC. A sheet marked “Alert Value Isolate Packing Form” that contains the original and the retest MIC values for each isolate should be included with the isolate shipment; a copy of this same sheet should **also** be sent separately to the GISP Project Coordinator.

The GISP Project Officer may occasionally request that selected alert isolates (critical values) be sent rapidly to CDC (CASPIR) for confirmatory testing or further evaluation/characterization by LRRB. These isolates may have susceptibility results that might warrant public health action (see below).

Ceftriaxone MIC ≥ 0.5 $\mu\text{g/ml}$

Cefixime MIC ≥ 1.0 $\mu\text{g/ml}$

Azithromycin MIC ≥ 8.0 $\mu\text{g/ml}$

3.2.4.3. Archive isolates

On an annual basis, CDC will request that regional laboratories ship additional GISP isolates (“archive” isolates) to CDC/CASPIR for long-term storage. These isolates may be of phenotypic interest or may be a random sample of isolates submitted to the reference lab. These isolates will contribute to the GISP isolate bank, which is one of the few remaining large collections of gonococcal cultures.

Based on current archive isolate criteria, CDC will generate the list of requested isolates and send the list to each regional laboratory. This list will usually be generated in the Autumn of the year following specimen collection: the list of 2014 archive isolates will be generated and sent to labs in late 2015.

Duplicate copies of each requested archive isolate should be shipped to CASPIR, CDC by priority overnight delivery, charging the shipping costs to the FedEx account number provided by CDC.

3.2.5. Isolate Preservation

All isolates should be suspended in trypticase soy broth containing 20% (v/v) glycerol and frozen at -70° C in duplicate at the Regional Laboratories. When isolates are requested by CDC, **triplicate** (in the case of alert and critical isolates) or **duplicate** (archive isolates) copies of each requested isolate should be shipped to CASPIR, CDC. A copy of each shipped isolate must be maintained at the Regional Laboratory until notified by the GISP Coordinator or GISP Manager that the isolates have been received. This will generally require maintenance of isolates from the current year and the previous year.

3.2.6. Shipping isolates to CASPIR

When preparing GISP specimens for shipment to CDC and ATSDR Specimen Packaging, Inventory and Repository (CASPIR), please put specimens into **liquid nitrogen suitable cryotubes with screwcaps** (no snapcaps).

GISP isolates should be shipped to:

Robert J. Davidson
CDC CASPIR™ Facility
602 Webb Gin House Rd., Bldg. C
Lawrenceville, GA 30045
Office: 770-339-5950
Fax: 770-339-5943
E-mail: rum8@cdc.gov

GISP isolates should be shipped on Mondays or Tuesdays using FedEx. At the time that a GISP shipment is sent, Robert Davidson should be e-mailed with the date of shipment and the FedEx tracking number so that he can expect and monitor the shipment.

3.2.7. Data reporting

Upon completion of laboratory testing, the antimicrobial susceptibilities for isolates submitted from each Sentinel Site will be entered in the GISP web-based application. See Appendix 1 for data elements for Form 2, CDC 73.60 B). Instructions for coding are found in the GISP Coding Guide (available at: www.cdc.gov/std/gisp). The results of Form 2 should be entered into the GISP web-based application and

the receipt copy of Form 2 should be maintained in the laboratory files. A copy of the results of Form 2 should also be sent back to their respective sentinel sites.

3.2.8. External Quality Assessment (EQA)

Twice each year, a set of 15 coded cultures will be provided to the Regional Laboratories by CDC (LRRB) for antimicrobial susceptibility testing. These cultures will include strains selected to represent susceptible and resistant isolates of *N. gonorrhoeae* and may include more than one copy of some strains. With the isolate shipment, LRRB will include the date by which results are requested to be returned by the regional laboratories to LRRB. LRRB will report back to each Regional Laboratory within 30 days of receiving results from each site with a preliminary discussion of results to allow the Regional Laboratory to assess its intra-laboratory reproducibility. Some assessment of overall performance may be based on previously determined modal MICs for strains. Each preliminary report will indicate individual MICs that are ≥ 2 dilutions greater or less than the previously determined modal MIC for that strain and antimicrobial agent. If the EQA results suggest problems in MIC testing, the Regional Laboratory should identify and address these problems, and report to CDC (LRRB) on corrections made. This report should be made within 30 days of notification by CDC that corrective actions are necessary. Depending upon the extent of testing problems, a second set of EQA cultures may then be provided for testing, with another 60 days for completion. Customized testing procedures may be used to address specific testing difficulties. Finally, if proficiency problems cannot be solved, testing may have to be shifted to an alternate laboratory.

EQA Testing Range

<u>Antimicrobial agents</u>	<u>Range ($\mu\text{g/ml}$)</u>
penicillin	0.008 – 64.0
tetracycline	0.06 – 64.0
spectinomycin	32.0 – 256.0
ceftriaxone	0.001 – 1.0
cefixime	0.002 – 1.0
ciprofloxacin	0.001 – 32.0
azithromycin	0.008 – 16.0

3.2.9. Training and Consultation for Sentinel Sites

The Regional Laboratories may need to perform training of Sentinel Site personnel or provide technical assistance consultation to Sentinel Sites to improve or optimize the quality of GISP isolates submitted. If a problem with non-viability or contamination is recognized by the Regional Laboratory, this should be brought to the attention of the Sentinel Site quickly, as these problems may indicate problems with sentinel site laboratory isolate collection, handling, storage, or shipping.

So that sentinel sites can monitor and report accurately on non-viability and contamination as part of their annual reporting process, regional laboratories are asked to develop systems to record and track non-viability and gross contamination of isolates and share these data with the sentinel sites.

3.2.10. Regional Laboratory Annual Process Measure Reporting for Annual Funding

As required by STD Laboratory-based Surveillance & Gonococcal Isolate Surveillance Project (FOA PS14-1401), Regional Laboratories are required submit an Interim Progress Report (IPR) annually. The IPR functions as both a mechanism for reporting progress towards project objectives and for requesting continued funding for the following fiscal year.

For monitoring of progress towards project objectives, laboratories are asked to report the following items:

- Number of isolates received
- Number (and percentage) of isolates received from each sentinel site that were non-viable
- Number (and percentage) of received isolates from each sentinel site that were contaminated
- Number of isolates tested for antimicrobial susceptibility
- Percentage of monthly batches of isolates that were tested within 1 month of receipt of isolates
- Whether the laboratory achieved a passing grade of $\geq 80\%$ agreement with the modal MIC ± 1 dilution of each EQA assessment for which results are available

3.3. Centers for Disease Control and Prevention

The administrative duties and technical assistance responsibilities relating to GISP will be performed by DSTDP SDMB and LRRB, with support from PDQIB.

3.3.1. Description of SDMB and PDQIB activities

1. Perform site visits, as needed, to Sentinel Sites and Regional Laboratories.
2. Implement data collection protocols, including modification of data collection forms when necessary and complying with Office of Management and Budget requirements. Perform data management. Provide annual report to each Sentinel Site describing the percentage of the Sentinel Site data that are incomplete or missing.
3. Perform review and analysis of demographic, clinical, and antimicrobial susceptibility data. Communicate important clinical findings to STD programs.
4. Prepare and distribute regional and site-specific data in electronic format to sites participating in GISP on a per request basis.
5. Prepare and distribute annual report summarizing project findings.
6. Request GISP isolates from Regional Laboratories for archival storage in CASPIR.
7. Evaluate IPRs, Annual Progress Reports (APRs) and budget requests from Sentinel Sites and Regional Laboratories.
8. Recruit new sites as needed.
9. Address human subject research issues for the project.
10. Update the protocol, coding guide, data collection forms, and GISP website, as needed.

3.3.2. Description of LRRB Activities

1. Perform site visits to Regional Laboratories as needed.
2. Train Regional Laboratory personnel when necessary.
3. Select, quality control, evaluate, and distribute to Regional Laboratories (a) Difco GC medium base for antimicrobial susceptibility testing, (b) antimicrobial powders that do not require Material Transfer Agreements (e.g., penicillin, spectinomycin, etc.), and (c) control strains.
4. Confirm antimicrobial susceptibility results for isolates with Critical Value MICs, and other isolates as needed, and provide MICs to GISP Coordinator within 4 weeks of receipt of isolates in LRRB.
5. In consultation with the GISP Coordinator, distribute External Quality Assessment (EQA) cultures twice annually. Prepare and distribute biennial EQA reports.
6. Perform molecular epidemiologic characterization of selected isolates (e.g. isolates with cefixime MICs ≥ 0.25 $\mu\text{g/ml}$, ceftriaxone MICs ≥ 0.125 $\mu\text{g/ml}$, or azithromycin MICs ≥ 2.0 $\mu\text{g/ml}$, and others as deemed appropriate). Molecular characterization of isolates collected under this protocol may include genome sequencing and other advanced molecular detection approaches.

7. Perform identification of novel antimicrobial susceptibility patterns among isolates that require further investigation.
8. Assist with analysis of antimicrobial susceptibility data.
9. Conduct Etest[®] (bioMérieux, Durham, NC) and agar dilution confirmatory testing for endpoints of isolates exhibiting azithromycin MICs ≥ 16 $\mu\text{g/ml}$ by agar dilution and cefixime MICs of ≥ 0.5 $\mu\text{g/ml}$

4. General Project Issues

4.1. Quality Assurance

It is expected that Sentinel Sites, Regional Laboratories, and CDC will perform the tasks described in this protocol in a timely and efficient manner within the prescribed deadlines. A summary of the GISP timelines for project participants may be found in Appendix 5. Difficulties in adhering to the protocol with regards to isolate collection at the Sentinel Sites should be reported to the Regional Laboratories; difficulties in adhering to the protocol with regards to clinical/demographic data collection at the Sentinel Sites and difficulties in adhering to the protocol at the Regional Laboratories should be referred to the GISP Coordinator at CDC.

The duties listed in this protocol for the various GISP participants may overlap in many areas. Frequent communications among GISP participants are to be conducted to monitor the day-to-day activities of the project. On an annual basis, a meeting of the Principal Investigators will take place. Additional meetings are to be scheduled as required.

4.2. Human Subjects

The GISP protocol was reviewed by the Office of the Associate Director for Science (ADS), NCHHSTP, CDC, (most recently in May 2014) and was determined not to require CDC Institutional Review Board (IRB) review or oversight because the project activity is considered a surveillance and disease control activity, and not human subjects research.

4.3. Office of Management & Budget

The GISP protocol has been reviewed and approved by the Office of Management and Budget (most recent OMB Decision date 8/21/2013).

4.4. Publication of GISP Data

In order to make GISP data widely available, CDC will publish GISP data in the annual STD Surveillance Report, annual GISP profiles, and other GISP reports and peer-reviewed manuscripts as needed.

Reports of analyses of overall GISP susceptibility trends and prevalence of resistance will include CDC and one principal investigator from each regional laboratory as collaborators and co-authors.

Papers describing analyses of data from an individual sentinel site or an outbreak investigation at a specific sentinel site should involve staff from the relevant sentinel site.

Local use of GISP data is encouraged. Sentinel sites can develop abstracts and manuscripts for peer-reviewed publication based on local GISP data. In such cases, sentinel sites should acknowledge GISP as the source of data in the Methods Section, and if appropriate, sentinel sites are encouraged to collaborate with the regional laboratory that conducted the susceptibility data. Sentinel sites are asked to provide the GISP Project Officer at CDC with courtesy copies of accepted abstracts and manuscripts.

For papers that combine GISP data with other data sources or for which the described analyses expand substantially beyond GISP susceptibility data, GISP and the regional laboratories should at least be acknowledged. Authorship will be decided on a case-by-case basis.

4.5. Use of GISP Isolates and GISP Data

GISP isolates are collected primarily for surveillance of *N. gonorrhoeae* susceptibility, but some uses of GISP isolates and GISP data not described in this protocol may be desirable and may enhance the public health usefulness of this project.

To ensure adequate communication and address any human subjects issues which may arise with the use of isolates or data collected for public health surveillance, proposals by external parties for use of GISP isolates or GISP data not described in this protocol should be initiated through the following process: 1) a brief (i.e., 1-2 page) written proposal should be provided to the GISP Project Officer for CDC review, 2) if appropriate, consent and/or collaboration of the relevant Sentinel Site state or local STD programs that provided the isolates should be sought (and appropriateness can be determined by the CDC GISP team based on the nature of the project), and 3) Institutional Review Board (IRB) review should be sought as appropriate. Submission of the proposal to the GISP Project Officer at CDC is requested as a first step to ensure that projects do not overlap with work already in progress and to allow an assessment of whether the proposed project fits within the non-human subject research determination at CDC or requires IRB review.

An exception to this process is when isolates are already collected dually under GISP and another ongoing protocol. In that case, appropriate consents and/or collaborations of the persons collecting and processing the isolates should already have been obtained. Local IRB review should be sought as appropriate.

Sentinel sites and regional laboratories are asked to notify the CDC GISP Project Officer of proposed local uses of isolates collected through GISP.

4.6. Selection Criteria for Project Expansion

Sentinel sites and regional laboratories were chosen through a competitive application and objective review panel process (Funding Opportunity Announcements [FOAs] 14-1402 for the sentinel sites and 14-1401 for the laboratories). Both of these FOAs cover a five year cycle. Potential sites and laboratories that are not part of GISP will be able to apply for participation in the next funding cycle (that will begin in 2019).

Appendix 1

GISP Data Elements

Demographic/Clinical Data (Form1 or CDC 73.60A)

Variable Name	Type/Length	Description	Values
CLINIC	[Char, 3]	Sentinel site code	ALB=Albuquerque, ATL=Atlanta, BOS=Boston, BUF=Buffalo, BHM=Birmingham, CHI=Chicago, COL=Columbus, CLE=Cleveland, DAL=Dallas, GRB=Greensboro, HON=Honolulu, IND=Indianapolis, KCY=Kansas City; LAX=Los Angeles, LVG=Las Vegas, MIN=Minneapolis, NOR=New Orleans, NYC=New York City, ORA=Orange County, PHI=Philadelphia, PHX=Phoenix, PON=Pontiac, POR=Portland, SDG=San Diego, SEA=Seattle, SFO=San Francisco, TRP=Tripler Army Medical Center
YRMO	[Char, 6]	Year/Month of patient's visit	YYYYMM
ID	[Char, 2]	Patient of isolate number	01, 02, 03, 04...50
CLINID	[Char, 1]	Clinic identifier number	1, 2, 3...9
SEX	[Char, 1]	Sex	1=male, 2=female, 9=unknown
ETHNIC	[Char, 1]	Hispanic	1=Hispanic or Latino, 2=not Hispanic or Latino, 9=unknown
AMIND	[Char, 1]	American Indian/Alaskan Native	1=yes, 2=no, 9=unknown
ASIAN	[Char, 1]	Asian	1=yes, 2=no, 9=unknown
BLACK	[Char, 1]	Black	1=yes, 2=no, 9=unknown
NAHAW	[Char, 1]	Native Hawaiian/Pacific Islander	1=yes, 2=no, 9=unknown
WHITE	[Char, 1]	White	1=yes, 2=no, 9=unknown
ORACE	[Char, 1]	Other race	1=yes, 2=no, 9=unknown
DATEVIS	[Char, 10]	Date of clinic visit	MM/DD/YYYY
AGE	[Num, 2]	Age in years	99= unknown
SEXOR	[Char, 1]	Sexual orientation	1=women only (heterosexual) 2=men only (homosexual) 3=women and men (bisexual) 9=unknown
SYMP	[Char, 1]	Symptoms of gonorrhea	1=discharge and/or pain, 2=no discharge and no pain, 9=unknown
HISTORY	[Char, 1]	Previous history of gonorrhea (ever)	1=yes, 2=no, 9=unknown
EPSDS	[Num, 2]	Number of previous episodes within the past 12 months	0=no documented episodes 99=unknown
HIVSTAT	[Char, 1]	Most recent known HIV status known at time of clinic visit for gonorrhea	1=positive, 2=negative, 3=indeterminate, 9=unknown
TRAVEL	[Char, 1]	Travel outside of US in past	1=yes, 2=no, 9=unknown

60 days

Variable Name	Type/Length	Description	Values
SEXWK	[Char, 1]	History of giving or receiving drugs/money in the past 12 months	1=yes, 2=no, 9=unknown
ANTIBIOT	[Char, 1]	Antibiotic use in the past 60 days	1=yes, 2=no, 9=unknown
IDU	[Char, 1]	History of injection drug use in the past 12 months	1=yes, 2=no, 9=unknown
NONIDU	[Char, 1]	History of non-injection drug use in the past 12 months	1=yes, 2=no, 9=unknown
TRMT1	[Char, 2]	Primary treatment for gonorrhea	00=none 03=spectinomycin (Trobicin) 2 gm 04=ceftriaxone (Rocephin) 250 mg 05=ceftriaxone (Rocephin) 125 mg 06=ciprofloxacin (Cipro) 500 mg 07=cefoxitin (Mefoxin) 2 gm 12=cefixime (Suprax) 400 mg 14=cefpodoxime proxetil (Vantin) 200 mg 15=ofloxacin (Floxin) 400 mg 17=ceftizoxime (Cefizox) 500 mg 18=cefotaxime (Claforan) 500 mg 21=azithromycin (Zithromax) 2 gm 22=levofloxacin (Levaquin) 250 mg 23=cefpodoxime proxetil (Vantin) 400 mg 24=ceftibuten (Cedax) 400 mg 25=cefdinir (Omnicef) 300 mg 26=cefdinir (Omnicef) 600 mg 27= gemifloxacin 320 mg 28= gentamicin 240 mg (or weight-based dosage) 88=other (please indicate in Other Treatment 1) 99=unknown
OTHTRMT1	[Char, 15]	Other treatment not listed as code for TRMT1	If code "88" was entered for Treatment 1, please type in the name and dosage of the drug used for primary treatment of gonorrhea.
TRMT2	[Char, 2]	Second antibiotic used as part of dual therapy for gonorrhea (and treatment of chlamydia)	00=none 01=ampicillin/amoxicillin 09=doxycycline (Vibramycin)/tetracycline 10=erythromycin 11=azithromycin (Zithromax) 1 gm 15=ofloxacin 21=azithromycin (Zithromax) 2 gm 22=levofloxacin 88=other 99=unknown

Antimicrobial Susceptibility Testing (Form 2 or CDC 73.60B)

Variable Name	Type/Length	Description	Values
CLINIC	[Char, 3]	Sentinel site code	ALB=Albuquerque, ATL=Atlanta, BOS=Boston, BUF=Buffalo, BHM=Birmingham, CHI=Chicago, COL=Columbus, CLE=Cleveland, DAL=Dallas, GRB=Greensboro, HON=Honolulu, IND=Indianapolis, KCY=Kansas City, LAX=Los Angeles, LVG=Las Vegas, MIN=Minneapolis, NOR=New Orleans, NYC=New York City, ORA=Orange County, PHI=Philadelphia, PHX=Phoenix, PON=Pontiac, POR=Portland, SDG=San Diego, SEA=Seattle, SFO=San Francisco, TRP=Tripler Army Medical Center
YRMO	[Char, 6]	Year/Month of patient's visit	YYYYMM
ID	[Char, 2]	Patient of isolate number	01, 02, 03, 04...50
B_LAC	[Char, 1]	Beta-lactamase test	1=positive, 2=negative
PEN	[Num, 6]	Penicillin MIC	0.008, 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, 64.0
TETRACY	[Num, 6]	Tetracycline MIC	0.06, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, 64.0
SPCTINO	[Char, 1]	Spectinomycin sensitivity	1=sensitive, 2=resistant
CFX	[Num, 6]	Cefixime MIC	0.002, 0.004, 0.008, 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2.0
CRO	[Num, 6]	Ceftriaxone MIC	0.001, 0.002, 0.004, 0.008, 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2.0
CIPRO	[Num, 6]	Ciprofloxacin MIC	0.001, 0.002, 0.004, 0.008, 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0
AZI	[Num, 6]	Azithromycin MIC	0.008, 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, 64.0
DATETEST	[Date, 10]	Date isolate tested	MM/DD/YYYY
CONTROL	[Char, 1]	Control ID	A, B, C, D

NOTE: MIC values listed as possible responses may include values that are no longer included in the current recommended testing ranges.

Control Strain Susceptibility Testing (Form 3 or CDC 73.60C)

Variable Name	Type/Length	Description	Values
LAB	[Char, 3]	Regional laboratory	AUS=Austin regional laboratory EMO=Atlanta regional laboratory JHU=Baltimore regional laboratory UAB=Birmingham regional laboratory UWA=Seattle regional laboratory
CONTROL	[Char, 1]	Control ID	A, B, C, D
STRAIN	[Char, 9]	Strain number	F-18 F-28 SPL-4 P681E CDC 10328 CDC 10329 SPJ-15
B_LAC	[Char, 1]	Beta-lactamase test	1=positive, 2=negative
PEN	[Num, 6]	Penicillin MIC	0.008, 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, 64.0
TETRACY	[Num, 6]	Tetracycline MIC	0.06, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, 64.0
SPCTINO	[Char, 1]	Spectinomycin sensitivity	1=sensitive, 2=resistant
CFX	[Num, 6]	Cefixime MIC	0.002, 0.004, 0.008, 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2.0
CRO	[Num, 6]	Ceftriaxone MIC	0.001, 0.002, 0.004, 0.008, 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2.0
CIPRO	[Num, 6]	Ciprofloxacin MIC	0.001, 0.002, 0.004, 0.008, 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0
AZI	[Num, 6]	Azithromycin MIC	0.008, 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, 64.0
DATETEST	[Date, 10]	Date isolate tested	MM/DD/YYYY

NOTE: MIC values listed as possible responses may include values that are no longer included in the current recommended testing ranges.

Appendix 2

β -lactamase Testing

β -lactamase may be detected with a chromogenic cephalosporin test, the Nitrocefin test.

Methods for detection of β -lactamase may be obtained under Application Notes: Techniques for the Rapid Detection of β -Lactamase Using Nitrocefin, at <http://www.millipore.com/catalogue/item/484400-5MG>

The following is an extract of that resource:

Preparing a Nitrocefin (500 μ g/mL) solution

- Dissolve 1 mg Nitrocefin in 100 μ l dimethylsulfoxide (DMSO) and vortex.
- Add 1.9 ml phosphate buffer (100mM, pH 7.0) to produce 2 ml total volume.
- This yields a working Nitrocefin solution of 500 mg/L (approx. 1 mM), which is suitable for most applications.

Nitrocefin, particularly in solution, is very sensitive to light. PROTECT FROM LIGHT.

The stock solution may be stored at -20°C for up to two weeks.

Techniques for the rapid detection of β -lactamase using Nitrocefin

Direct plate method: Add one drop of the Nitrocefin working solution on to the surface of the colony. If the isolate is a high β -lactamase producer then the colony and the surrounding area will turn red quickly.

Additional methods (a slide method, a broth method, and a paper disc spot method) are also provided on the webpage.

β -lactamase-positive and -negative control strains should be tested with each testing of unknown isolates.

Please note that DMSO is a hazardous chemical; a Material Safety Data Sheet may be obtained at

http://www.emdmillipore.com/life-science-research/nitrocefin/EMD_BIO-484400/p_fOKb.s1LIJgAAAEWfVhTm;sid=Hw5DsI4yJBd5sNzHE-kv5ybyml1RQOSVJyBd5j2fPXr90wC8M-4gGogMCFXODaVLn31TrI3r4jZqtwf7vYr2WyF4Pvpa9ELiLJT7kTYrm5_WDO2YGTBhxDBR?attachments=MSDS

Appendix 3

Methods for Antimicrobial Susceptibility Testing

Antimicrobial Agents and Range of dilutions ($\mu\text{g/ml}$) (last revised February 2009)

Standard panel:	Penicillin G: 0.25 to 16.0
	Tetracycline: 0.25 to 16.0
	Spectinomycin: 128.0
	Cefixime: 0.015 to 0.5
	Ceftriaxone: 0.008 to 0.5
	Ciprofloxacin: 0.015 to 16.0
	Azithromycin: 0.03 to 16.0
	β -lactamase: positive or negative

Retest criteria for isolates with alert value MICs:

If the MICs of strains are not determined at the highest concentration of agent tested, the MIC should be retested for susceptibility to a higher range of two-fold dilutions. An endpoint should be determined. For specific repeat testing criteria, see page 10.

Preparation of Antibiotic-Containing Media

Difco GC medium base (Becton Dickinson, Cockeysville, MD) supplemented with 1% IsoVitaleX (or an equivalent supplement) is used.

1. Prepare the required volume of GC base medium in single strength according to the manufacturer's directions.
2. Autoclave the medium at 121 C for 15 min. Cool to 50 C in a waterbath.
3. Reconstitute the dehydrated IsoVitaleX with the provided diluent according to the manufacturer's directions.
4. Add 10 ml of supplement per liter of base medium, i.e., 1% (v/v); mix thoroughly. This medium is GCS medium.
5. Dispense the required volume of medium into individual containers for the addition of antimicrobial solutions. Maintain media at 50 C in a waterbath.
6. Prepare the working solutions and dilutions of antimicrobial agents from the stock solutions or standard powder.

Note: *It is important that no longer than 1-hour elapse between the time that the stock solution is thawed, the dilutions are prepared and added to the base medium and the plates are poured.*

7. Add the required volumes of the prepared working solutions and dilutions of the antimicrobial agents to the respective bottles of GCS medium, mix thoroughly and dispense into *clearly labeled* plates. Thorough mixing of the antibiotics in the medium can be accomplished by swirling the contents three times in a clockwise and counterclockwise motion followed by inverting the bottle three times, minimizing bubble formation.
8. Allow the plates to cool. *Invert the plates and store them in sealed plastic bags at 4 C to 8 C for no longer than two weeks prior to use.*

Agar-Dilution Susceptibility Test Procedure

1. Grow pure cultures of isolates to be tested on chocolate agar at 35 C to 36.5 C in a CO₂-enriched (5%) atmosphere for 16 to 18 h. Use pure cultures on chocolate agar to prepare the inoculum. *Do not use the first subculture from a frozen culture; subculture these isolates again before using to prepare the inoculum. Do not use isolates grown on antibiotic-containing media to prepare the inoculum.* The complete set of control strains provided by the CDC should be included in each run. If two or more sets of plates (prepared in the same batch) are being inoculated on the same day, it is not necessary to inoculate the complete set of control strains on each set of plates. Two or three control strains may be inoculated on each set of plates, but all control strains should be included in each day's test runs.
2. Use a cotton applicator or a bacteriologic loop to suspend isolated colonies (or cells from less dense areas of growth on the plate) in approximately 2 ml of Mueller-Hinton (MH) broth. (The exact volume of broth required will depend on the method for measuring the turbidity of the suspension. If a spectrophotometer is used, the volume of broth must be sufficient to completely cover the light path and will vary according to the type of spectrophotometer).
3. Adjust the density of the suspension to contain 10⁸ colony forming units (CFU)/ml by comparison with a 0.5 McFarland BaSO₄ turbidity standard. (If a spectrophotometer is used to measure the optical density of the suspensions, set the wavelength at 450 nm. Adjust the turbidity to approximately 0.15. It may be necessary to dilute this suspension further than indicated in step #4. Determine the viable count for the suspension and either adjust the initial optical density to which the suspension is prepared or the dilution to give a final viable count of 10⁷ CFU/ml as indicated in step #4.)
4. Dilute this suspension 1:10 in MH (or equivalent) broth to give 10⁷ CFU/ml.
5. Dispense an equal volume of each suspension into wells of a replicating device, e.g., Steer's or Cathra replicators. These replicating devices deliver 0.001 - 0.005 ml of the bacterial suspension to the surface of the medium, i.e., 10⁴ CFU.
6. Inoculate each plate of the set of antibiotic containing media plus a plate of chocolate agar or GCS medium (as a control to determine that all isolates grew). You may also wish to inoculate a GCS plate between each set of antibiotic-containing medium to ensure against carry-over of antimicrobial agents from one medium to another; these plates also allow for monitoring for contamination of the inocula during the inoculation process.

Note. *The time elapsing between the preparation of the strain suspensions and inoculation of the plates should not exceed 1 h.*

7. Allow the inoculated plates to air-dry at room temperature for approximately 15 min. Invert the plates and incubate at 35 C to 36.5 C in a CO₂-enriched (5%) atmosphere for 20–24 hours.
8. Examine the plates for growth. Use a separate sheet to record the results for each antibiotic tested and record the growth for each isolate on each antibiotic concentration tested. Record the growth as good (+), poor (±), or no growth (-). By using this scheme, the results can be reviewed at a later date for transcription errors and, when isolates grow on the highest concentration tested, the degree of growth will indicate whether the isolate is growing strongly or is partially inhibited.

Appendix 4

Agar Dilution Susceptibility of CDC *Neisseria gonorrhoeae* Reference Strains

Strain #	Resistance phenotype ^a	MIC Range (µg/ml)							
		β-lac	Pen	Tet	Spc	Cro	Cfx	Cip	Azi
F-18	Susc	-	0.25–2.0	0.25–2.0	8.0–32	0.004–0.03	0.008–0.06	0.001–0.008	0.25–1.0
F-28	Susc, SpcR	-	0.015–0.6	0.125–0.5	>256.0	≤0.001–0.004	0.001–0.008	0.001–0.004	0.03–0.25
P681E	PP/TR	+	1.0–≥64.0	8.0–32.0	8.0–32.0	0.002–0.008	0.008–0.03	0.002–0.008	0.03–0.25
10328	PPNG, CipI	+	4.0–≥32.0	0.25–1.0	8.0–32.0	0.002–0.015	0.004–0.03	0.125–1.0	0.015–0.125
10329	PPNG, TetR, CipR	+	16.0–≥64.0	2.0–4.0	8.0–32.0	0.004–0.03	0.008–0.06	1.0–2.0	0.125–1.0
SPJ-15	Susc, Azi RS	-	0.25–1.0	1.0–4.0	8.0–32.0	0.004–0.015	0.008–0.06	0.002–0.008	1.0–8.0
SPL-4	CMRNG, CipR, Cfx DS	-	4.0–16.0	2.0–8.0	8.0–32.0	0.03–0.25	0.25–0.5	8.0–32.0	0.125–1.0

Abbreviations

Antimicrobials: Azi=azithromycin; β-lac=β-lactamase; Cfx=cefixime; Cip=ciprofloxacin; Cro=ceftriaxone; Pen=penicillin; Spc=spectinomycin; Tet=tetracycline;

Phenotypes: Azi RS=isolate exhibiting reduced susceptibility (MIC ≥2.0 µg/ml) to azithromycin; Cfx DS=isolate exhibiting decreased susceptibility (MIC ≥0.5 µg/ml) to cefixime; CipI=isolate with MIC 0.125-0.5 µg/ml of ciprofloxacin; CipR=isolate with MIC ≥1.0 µg/ml of ciprofloxacin; CMRNG= β-lactamase-negative and MIC >2.0 µg/ml of penicillin and MIC ≥2.0 to 8.0 µg/ml of tetracycline; PPNG=penicillinase (β-lactamase)-producing *N. gonorrhoeae*; PP/TR, β-lactamase-positive strains with MICs ≥2.0 µg/ml of tetracycline; SpcR=spectinomycin-resistant (MIC >128.0 µg/ml); Susc=susceptible to penicillin and tetracycline (MICs <2.0 µg/ml); TetR=MIC <2.0 µg/ml of penicillin and MIC ≥2.0 µg/ml of tetracycline.

^aResistance phenotypes are composed of resistance phenotypes for ciprofloxacin, penicillin, spectinomycin, and tetracycline according to Clinical Laboratory Standards Institute breakpoints, supplemented with designations for penicillin resistance mechanisms and values for azithromycin and cefixime.

Appendix 5. Summary of GISP Timelines for Project Participants

Sentinel Sites

1. **Demographic and clinical data** (i.e., Form 1) - Due monthly to CDC, no more than 4 weeks after the end of the month in which the corresponding isolates were collected.
2. **Isolates** - Due monthly to assigned Regional Laboratory, shipping out on Monday or Tuesday of the week immediately following completion of isolate collection but no later than the first Monday of the following month.
3. **AAPPS (14-1402) grant application reporting** - Due annually, when AAPPS (14-1402) grant applications are due in late summer or early fall.

Regional Laboratory

1. **Testing of isolates** - Should be completed within one month of receipt of isolates.
2. **Susceptibility test data** (i.e., Form 2) - Due monthly to CDC and to Sentinel Sites, within one week of completion of testing.
3. **Control strain susceptibility test data** (i.e., Form 3) - Due monthly to CDC, within one week of completion of testing (together with the Sentinel Site Form 2 susceptibility data obtained from the same run).
4. **Notification of Alert Value Isolates** - Reporting of the identification of Alert Value Isolates to CDC should take place within one working day of when the test results are read. Confirmatory testing should be done within a month of first test.
5. **Shipping of batched alert value isolates** – quarterly
6. **Shipping of selected alert value isolates to CDC** – ad hoc
7. **Interim Progress Reports and funding applications reporting** - Due annually, usually due in late summer or early fall.
8. **Annual Progress Reports** – due annually as per the Notices of Award
9. **Shipping of archive isolates** - yearly

CDC:

1. **Final date for receiving corrections or updates to previous year's GISP data from Sentinel Sites and Regional Laboratories** - Mid-March
2. **Electronic GISP data files for Sentinel Sites** - Available by August upon request to GISP Data Manager.
3. **Publish annual GISP Report** - By Fall/Winter of the year following the year of isolate collection.
4. **Notification of Alert Value Isolates** - Will ensure that appropriate Sentinel Site(s) and the local and/or state STD Program(s) are notified

Appendix 6. Project Personnel

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