

**CONSULTATION MEETING ON
CEPHALOSPORIN-RESISTANT GONORRHEA
OUTBREAK RESPONSE PLAN**

REPORT OF AN EXTERNAL CONSULTANTS' MEETING CONVENED BY THE
DIVISION OF STD PREVENTION, NATIONAL CENTER FOR HIV, STD, AND TB
PREVENTION, CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

(SEPTEMBER 14 – 15, 2009)

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CEPHALOSPORIN-RESISTANT (CEPH-R) GONORRHEA OUTBREAK RESPONSE PLAN: REPORT OF AN EXTERNAL CONSULTANTS' MEETING

INTRODUCTION

Sexually transmitted diseases (STDs) remain a major public health challenge, contributing to significant morbidity in the United States with CDC estimating approximately 19 million new cases of STDs each year. Gonococcal infection is the second most common notifiable disease in the United States, with 336,742 cases reported in 2008. Over the years, *Neisseria gonorrhoeae* has readily acquired a high level of resistance to a broad spectrum of antimicrobial agents traditionally used for the treatment of the disease. Following the emergence of *N.gonorrhoeae* strains resistant to penicillin and tetracycline, resistance to fluoroquinolone (QRNG) was first identified in 1991. The proportion of such isolates steadily increased during the late 1990s. In 2007, 891(14.8%) isolates tested by the Gonococcal Isolate Surveillance Project (GISP) sites were resistant to ciprofloxacin (MICs $\geq 1.0 \mu\text{g/ml}$), and QRNG isolates were identified from all 29 GISP sites. The proportion of *N.gonorrhoeae* strains resistant to penicillin, tetracycline, ciprofloxacin, or a combination of these antibiotics in 2007 was 27%. As a result, penicillin, tetracycline and the fluoroquinolone antibiotics are no longer recommended as first line treatment for the disease in the United States.

Third generation cephalosporins remain the sole class of antibiotics available which can be used effectively against *N.gonorrhoeae*. This class of antibiotics has been widely used as first-line therapy to treat gonococcal infections in the United States and in many other countries. The recent emergence and spread of gonococcal strains resistant to oral cephalosporins in the Far East is a serious concern. The emergence of multidrug resistant gonococcal strains which are resistant to both oral and injectable cephalosporin drugs could have a catastrophic effect on gonorrhea control activities. The potential emergence and spread of both oral and parenteral cephalosporin-resistance in *N.gonorrhoeae* (Ceph-R NG) needs to be monitored and appropriate action needs to be taken to avoid a major public health problem.

The Centers for Disease Control and Prevention's (CDC) Division of STD Prevention convened an expert consultation to develop recommendations for the national and local public health response to address the potential emergence of Ceph-R *N.gonorrhoeae* in the United States. Fifteen CDC/DSTDP staff and 11 external participants with expertise in epidemiology, modeling, program management and laboratory science attended the 1.5 days meeting held on 14 – 15 September 2009. Participants reviewed and discussed the components of a draft response plan for Ceph-R *N.gonorrhoeae*, specifically on surveillance case definitions, epidemiological triggers, and clinical and public health responses following detection of cases of gonorrhea caused by Ceph-R *N.gonorrhoeae* cases in the U.S. At the opening session, CDC staff members and collaborators presented background information on the emergence of antimicrobial resistant *N.gonorrhoeae*; the potential programmatic challenges following the introduction of Ceph-R *N.gonorrhoeae*; the historical and current perspectives of gonorrhea control activities relevant for preparedness for Ceph-R *N.gonorrhoeae*; and lessons learned from modeling the spread of fluoroquinolone-resistant *N.gonorrhoeae* (QRNG). Following the background presentations, the

meeting facilitator highlighted the four key programmatic questions to be discussed by the participants during the remaining sessions as well as the expected contributions and outcomes of the meeting. The four key programmatic questions were:

1. How do we define “resistance to oral and parenteral cephalosporins in *N.gonorrhoeae*”?
2. What clinical and public health responses are required for patients diagnosed with Ceph-R gonorrhea?
3. What are the public health triggers (or outbreak threshold) for the implementation of the public health response to prevent the persistent transmission of Ceph-R *N.gonorrhoeae* in the U.S?
4. What is the minimum public health surveillance capacity required to enhance early detection of Ceph-R gonorrhea cases?

This report provides a summary of the group discussions on epidemiological, laboratory and programmatic issues that need to be resolved in order to respond to the emergence of multi-drug resistant *N.gonorrhoeae*. Central among these issues is how to craft a response with severely limited alternative treatment options. The group discussion also highlighted the importance of interdisciplinary cooperation and collaboration in responding to such an important public health problem. The recommendations for the above-mentioned key programmatic questions were presented together with the roles and responsibilities of CDC and local health departments. The importance of applying a phased implementation approach was also emphasized in the recommendations. The recommendations also enable the working group at CDC to determine the feasibility of the goals and implementation methods of the proposed activities included in the Ceph-R gonorrhea response plan.

In summary, the discussion and recommendations of the meeting will assist CDC and local health departments to formulate and implement an effective, practical and scalable public health response to the emergence of Ceph-R *N.gonorrhoeae* in the U.S. In conjunction with other gonorrhea prevention and control initiatives, the current attempts to maintain high efficacy anti-gonorrhea therapy would contribute to CDC’s effort to reduce the national gonorrhea rate to the Healthy People 2010 goal of 19 cases per 100,000 population.

SUMMARY OF DISCUSSION AND RECOMMENDATIONS

1) Goal of the Ceph-R gonorrhea response plan

Key Discussion Points

- The initial goal of the Ceph-R gonorrhea response plan is to contain the spread of Ceph-R *N.gonorrhoeae* strains in the U.S. by developing a strategy to vigorously follow all patients fulfilling the case-definition of Ceph-R gonorrhea and to treat both the index patient and their sexual contacts with effective alternative therapy.
- The participants discussed the operational feasibility to achieve such a goal and agreed that containment is NOT programmatically feasible with the limited resources currently available for gonorrhea control.
- The clinical and microbiological criteria required to define Ceph-R gonococcal infection were extensively discussed. The programmatic goal of establishing such case definitions is to assist local health departments with prompt identification of cases of Ceph-R gonorrhea. A multi-level, dynamic and flexible approach is needed to establish a case definition with appropriate sensitivity and specificity to support this objective. Further discussions may be required to establish consensus on several critical issues, notably, addressing the following;
 - variations in pharmacokinetic characteristics of different third generation cephalosporins;
 - the more rapid emergence of resistance to oral when compared to parenteral third generation cephalosporins;
 - differences in treatment efficacy as a result of the anatomical site of infection.

Recommendations

- CDC, in collaboration with state and local health departments, should design and implement a mitigation strategy with the goal to lessen the impact of Ceph-R *N.gonorrhoeae* on gonorrhea control.
- The specific public health objectives should include;
 - implementation of systems to facilitate prompt identification (if present in the community) and maintenance of effective treatment for Ceph-R gonorrhea
 - establishment of a laboratory system to ensure the early detection of Ceph-R *N.gonorrhoeae*
 - early identification of Ceph-R *N.gonorrhoeae* in the community
 - introduction of effective public health measures to treat both index cases and sex partners and limit further spread of infections

- implementation of scalable and reasonable measures to slow the dissemination of Ceph-R *N.gonorrhoeae* into local sexual networks

2) Phased implementation plan and priority issues to consider

Key Discussion Points

- Historically, the approach to the emergence of drug-resistant gonorrhea emphasized two key complementing strategies, namely, (1) routine systematic monitoring of antimicrobial susceptibility patterns (i.e. GISP); and (2) periodic review of national and local antimicrobial resistant patterns of circulating *N.gonorrhoeae* strains to select high efficacy single dose antibiotics for primary recommended treatment.
- The historic approach will be less successful for Ceph-R gonorrhea given the severely limited number of alternative treatment options. Immediate action is needed to develop public health strategies to minimize the negative impact of the emergence of Ceph-R gonorrhea on clinical outcomes and subsequent transmission of resistant strains to other areas of the country.

Recommendations

- CDC and local health departments should establish a phased implementation plan and initiate the activities prior to detection of Ceph-R gonorrhea to the US.

Phase 1 (Preparatory Phase)

- During the initial phase, CDC and local health departments should assess existing capacity and prepare program improvement materials and develop tools to support early detection and mitigation activities.
- Such program improvement materials for successful implementation of mitigation activities should include:
 - Surveillance case definitions for Ceph-R gonorrhea,
 - Standardized operational definitions to differentiate repeat infections, from duplicate notifications in patients with gonorrhea (e.g. analysis of STD Surveillance Network (SSuN) Project data to determine the proportion of GC patients with repeat gonorrhea reported within specified time intervals),
 - Recommendations for local clinical, public health and community responses following detection of Ceph-R *N.gonorrhoeae*,
 - Guidance on alternative therapies for Ceph-R gonorrhea cases and their sexual partners (in consultation with STD treatment guidelines working group),

- Guidance on laboratory diagnostic testing including strengthening of culture and susceptibility testing capacity, training, quality assurance activities in private/commercial and public sector laboratories
 - Laboratory training and support in collaboration with other partners such as APHL and Prevention Training Centers
 - Harmonization with other CDC guideline documents such as STD treatment guidelines, STD laboratory diagnostic guidelines
 - A communication plan to inform clinicians, laboratories and general public including standard templates for advisory letters
- Local health departments, particularly those located in geographical areas with a higher risk of importation of Ceph-R *N.gonorrhoeae* (e.g. West Coast and large metropolitan areas) should prepare to do the following:
 - Assess the local laboratory (commercial and public) capacity to perform gonococcal culture and susceptibility testing
 - Determine the local public and private health services capacity to perform laboratory evaluations in cases of cephalosporin treatment failure. The assessment should include the following:
 - the specific roles and responsibilities of clinic managers, clinicians and laboratorians in the evaluation process,
 - the knowledge/skills gap and training needs for clinic staff on collection, inoculation, storage and transport of specimens to the designated local reference laboratory,
 - the availability of appropriate laboratory supplies at clinics (e.g. specimen collection kits, transport media and candle jars etc.)
 - the procedures to identify and contact local reference laboratories to perform initial culture and susceptibility testing
 - the standard operating procedures for additional laboratory investigations on resistant isolates (if detected) at the national reference laboratory.
 - Establish a plan for clinical management of patients with Ceph-R gonorrhea including possible referral to designated clinics for alternative treatment for persistent infections and follow-up laboratory investigations.
 - Establish and enhance routine reporting of susceptibility testing results from laboratories including potential changes in provider reporting requirements, create routine reminders to providers about reporting requirements (e.g. laboratory notification of resistant organisms on positive results and reminders to clinicians to report and perform culture on patients with persistent symptoms)
 - Facilitate the monitoring and follow-up of Ceph-R gonorrhea patients across different public health jurisdictions by strengthening of the interstate communication control record (ICCR) system which facilitates follow-up of exposed persons across jurisdictions.
 - Develop plans to enhance screening and other prevention efforts in communities where clusters of Ceph-R gonorrhea cases are identified

- CDC and local health departments should work closely together to monitor the progress of the initial preparation of program improvement activities through webinars. Participants should include program consultants, members of the Epidemiology & Surveillance Branch (ESB) and Laboratory Reference & Research Branch (LRRB). Initially, the focus should be to achieve preparedness-ready status on the West Coast and in large metropolitan areas.
- Once the initial preparatory phase (Phase 1) activities have begun, CDC and local authorities should inform health service providers (i.e. clinicians, laboratories) about the issues associated with the emergence of Ceph-R gonorrhea and how to manage identified cases.

Phase 2 (Providers' Awareness and Infrastructure Enhancement Phase)

- After initiation of the Phase 1 activities, CDC should prepare and publish a background paper (preferably in MMWR) describing the threat of Ceph-R gonorrhea and recommended mitigation activities. Local public health authorities should use this publication as guidance to develop local plans and inform health providers in their respective health jurisdictions.
- Local health departments should prepare professional advisory communications and recommended mitigation action for local clinicians and laboratories and identify opportunities to engage and promote awareness among health providers, particularly those who provide treatment and other services for population groups at high risk for gonorrhea.
- Local health departments should also implement alternative treatments according to the national treatment guidelines for Ceph-R gonorrhea, and enhance laboratory infrastructure and capacity. New and innovative approaches should be used to ensure the feasibility and timely implementation of recommendations (e.g. improvement in turn-around-time of gonococcal culture and susceptibility testing, application of appropriate laboratory methods such as disc diffusion for susceptibility testing, and possible molecular detection of appropriate markers associated with Ceph-R *N.gonorrhoeae* such as mosaic *pen A*).
- CDC and local health departments should highlight the urgent need for partner services for probable Ceph-R gonorrhea cases and their sex partners.
- CDC should engage with other partners (e.g. Infectious Diseases Society of America, commercial laboratories, other communicable diseases divisions) to explore the opportunities for advocacy and resource mobilization.

- CDC should take a leadership role in implementation of clinical, laboratory, epidemiological and operational research activities to enhance the current knowledge concerning:
 - mechanisms of resistance to cephalosporins, and molecular markers associated with Ceph-R,
 - alternative effective treatment regimens for Ceph-R gonorrhea,
 - least costly approaches for the expansion of routine culture and susceptibility testing in clinical and public laboratories (e.g. public health pricing on culture plates, analyze the cost of culture and susceptibility testing at different laboratories)
 - feasibility and relevance of routine implementation of test-of-cure for uncomplicated gonococcal infection in the era of Ceph-R *N.gonorrhoeae*
 - appropriate timing for test-of-cure evaluations when using NAATs for diagnosis.
 - inclusion of alternative non-genital anatomical sites for test-of-cure culture and susceptibility testing (e.g. rectal, pharyngeal)

- CDC should assess the strengths and limitations of collecting specimens from rectal and pharyngeal sites on an ongoing basis.

Phase 3 (Monitoring and response phase)

With implementation of program improvements and awareness activities, the probability of early detection Ceph-R gonorrhea cases at the clinics should increase significantly.

- When the local health department has identified the first case of Ceph-R gonorrhea, the recommended clinical and public health responses should be implemented as described in the mitigation plan. (See details in the Ceph-R gonorrhea Response Plan)

- Before and during this phase, CDC and local health departments should enhance general gonorrhea control activities. The successful implementation of defined strategies for gonorrhea control (i.e. targeted/enhanced screening, partner services, active engagement and participation of providers and communities, health education/risk reduction) will contribute by reducing the disease burden and therefore, contribute to achieving the goal of Ceph-R gonorrhea mitigation.

3) Post-consultation follow-up plan

Key Discussion Points

- The CDC working group will prepare the meeting report and a draft of the mitigation plan and distribute it to consultants for their input. In consultation with the consultants, the CDC working group will prepare a timeline for the implementation of Phases 1 and 2.

Recommendations

- In collaboration with national STD program directors, the CDC working group should establish timelines for activities recommended in the different phases.
- The CDC working group should disseminate information on the threat of Ceph-R gonorrhea at the National STD Prevention Meeting in 2010.
- In collaboration with the CDC working group, the National Coalition of STD Directors and APHL should assist in the development and implementation of the laboratory needs assessment.

4) Timelines (Phased Implementation Plan)

Phase 1 (Preparation of program improvement materials)

Activities	Proposed Timelines (2009 - 2010)												Responsible Agency	
	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov		Dec
Development of Ceph-R gonorrhea response plan	X	X	X	X	X									CDC Working Group
Harmonization with other guidelines (i.e. Rx/Laboratory)	X	X	X	X	X									CDC Working Group
Development of Laboratory training & support plan					X	X	X	X						CDC Working Group
Development of communication plan					X	X	X	X						CDC Working Group
Assessment of local laboratory capacity					X	X	X	X						Local Health Dept
Assessment of health services capacity					X	X	X	X						Local Health Dept
Plan for clinical management of Ceph-R gonorrhea cases					X	X	X	X						Local Health Dept
Enhance monitoring, reporting and follow-up of Ceph-R gonorrhea cases							X	X	X	X	X	X	X	Local Health Dept

Phase 2 (Providers' awareness and infrastructure enhancement)

Activities	Proposed Timelines (2009 - 2010)												Responsible Agency	
	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov		Dec
Publication of response plan & specific operational guidance (MMWR/Dear Colleague Letter)					X	X	X							CDC Working Group
Enhance local providers' awareness of mitigation activities							X	X	X	X				Local Health Dept
Enhance treatment services & laboratory infrastructure/capacity							X	X	X	X				Local Health Dept
Enhancement of sexual partners management activities							X	X	X	X				Local Health Dept
Advocacy and resource mobilization for mitigation activities							X	X	X	X				CDC & Local Health Dept
Conduct clinical/laboratory/epidemiological & operations research							X	X	X	X	X	X	X	CDC & Local Health Dept
Monitor susceptibility patterns of gonococcal isolates from non-genital sites (i.e. pharyngeal and rectal specimens)							X	X	X	X	X	X	X	CDC Working Group

Phase 3 (Monitoring and response)

Activities	Proposed Timelines (2009 - 2010)													Responsible Agency
	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
Ongoing surveillance and monitoring of Ceph-R gonorrhoea cases							X	X	X	X	X	X	X	CDC & Local Health Dept
Ongoing response activities for Ceph-R gonorrhoea cases							X	X	X	X	X	X	X	CDC & Local Health Dept
Enhance GC control activities							X	X	X	X	X	X	X	CDC & Local Health Dept