Government of the District of Columbia
Department of Health

Center for Policy, Planning and Evaluation Administration
Division of Epidemiology – Disease Surveillance and Investigation

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Health Notice for District of Columbia Health Care Providers and Clinical Laboratories
Recommendations for Diagnosing and Managing *Shigella* Strains with Possible Reduced Susceptibility to Ciprofloxacin

Summary
This Health Notice describes the identification of emerging *Shigella* strains with elevated minimum inhibitory concentration (MIC) values for ciprofloxacin and outlines new recommendations for clinical diagnosis, management, and reporting, as well as new recommendations for laboratories. Current interpretive criteria, provided by the Clinical and Laboratory Standards Institute (CLSI), categorizes these strains as susceptible to ciprofloxacin, which is a fluoroquinolone antibiotic and a key agent in the management of *Shigella* infections. However, recent data from the Centers for Disease Control and Prevention (CDC) and state and local public health partners show that these strains often have a quinolone resistance gene that may lead to clinically significant reduced susceptibility. Clinicians treating patients with multidrug-resistant shigellosis for whom antibiotic treatment is indicated should avoid prescribing fluoroquinolones if the ciprofloxacin MIC is 0.12 μg/mL or higher, even if the laboratory report identifies the isolate as susceptible, and should work closely with their clinical microbiology laboratory and infectious disease specialists to determine appropriate antimicrobial therapy.

Background
In the United States (U.S.), there are about 500,000 cases of shigellosis every year, making it the third most common bacterial enteric disease (1). Shigellosis is generally a self-limited infection lasting 5-7 days. Treatment can shorten the duration of some illnesses, though typically only by 1-2 days. CDC has identified an increase in *Shigella* isolates in the U.S. with MIC values of 0.12–1 μg/mL for the fluoroquinolone antibiotic ciprofloxacin. Preliminary data suggest that all *Shigella* isolates with ciprofloxacin MICs in this range for which results are available harbor at least one quinolone resistance gene known to confer reduced susceptibility in enteric bacteria. *Shigella* isolates without a quinolone resistance gene typically have a ciprofloxacin MIC of ≤0.015 μg/mL. Current CLSI criteria categorize *Shigella* isolates with a ciprofloxacin MIC of ≤1 μg/mL as susceptible to ciprofloxacin (2).

CDC does not yet know whether fluoroquinolone treatment of a *Shigella* infection with a ciprofloxacin MIC of 0.12–1 μg/mL is associated with a worse clinical outcome for the patient, or if such treatment increases the risk of transmission to other individuals. In *Salmonella* isolates, ciprofloxacin MICs of 0.12–1 μg/mL have been associated with reduced susceptibility, prolonged clinical illness, and treatment failures and are now categorized by CLSI as intermediate or resistant to ciprofloxacin in *Salmonella* species.

Fluoroquinolone resistance is of particular concern given that data from the National Antimicrobial Resistance Monitoring System indicate that many *Shigella* isolates with a quinolone resistance gene also are resistant to many other commonly used treatment agents, such as azithromycin, trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, and ampicillin. This susceptibility profile may encourage clinicians to prescribe fluoroquinolone antibiotics to patients who require treatment.

Rising fluoroquinolone MIC values among *Shigella* isolates may be related to the emergence of plasmid-mediated quinolone resistance (PMQR) genes in *Shigella* species in the United States. *Shigella* strains harboring PMQR genes were identified earlier this year following whole genome sequencing of isolates from a multistate outbreak of multidrug-resistant *Shigella flexneri* infections predominantly affecting adult men, many of whom identify as men who have sex with men, according to epidemiologic data collected by CDC's *Shigella* program as part of outbreak response. PMQR genes have also been identified in sporadic cases of *Shigella sonnei*. Plasmid-mediated resistance genes are of particular concern because of their ability to spread between bacteria and their ability to promote chromosomal mutations conferring quinolone resistance, potentially resulting in rapid spread of fluoroquinolone resistance within or between populations of bacteria. The prevalence of PMQR genes among all U.S. *Shigella* isolates is currently unknown. Any patient with a *Shigella* infection could carry a strain harboring a quinolone resistance gene with a ciprofloxacin MIC of 0.12–1 μg/mL.

The emergence of *Shigella* species with ciprofloxacin MICs of 0.12–1 μg/mL and their association with quinolone resistance genes raises several concerns related to fluoroquinolone treatment of *Shigella* infection with a strain harboring a quinolone resistance gene:

- Treatment may be less effective and may increase the risk of a more severe clinical course for the individual (e.g., increased duration or severity of symptoms, increased need for hospitalization or admission to an intensive care unit, increased length of hospitalization, or increased risk of death).
- Treatment may increase the risk of secondary cases, if the treatment prolongs the duration or increases the quantity of organisms shed in the stool, given the very low infectious dose required for transmission of *Shigella* bacteria.

Recommendations for Clinicians

Diagnosis

- **Order stool cultures for patients suspected of having a *Shigella* infection to obtain isolates for antimicrobial susceptibility testing.**
    - Culture-independent diagnostic testing does not provide an isolate and therefore cannot be used to assess susceptibility.
- **Order antimicrobial susceptibility testing when ordering stool cultures for *Shigella*.**
    - When antimicrobial susceptibility testing is performed, request ciprofloxacin testing that includes dilutions of 0.12 μg/mL or lower.
    - Even when treatment is not indicated, identifying patients with drug-resistant infections (i.e., ordering susceptibility testing) will help to inform public health management, such as when to return to work, school, and group settings.

Reporting

- All cases of shigellosis must be reported to DC DOH by submitting a Notifiable Disease and Condition Case Report Form.
    - Access the form using our online reporting system **DC Reporting and Surveillance Center** (**DCRC)**: https://doh.dc.gov/service/infectious-diseases.
- Clinicians who identify a patient with shigellosis and a ciprofloxacin MIC of 0.12–1 μg/mL should include this finding along with other information to facilitate further testing of the isolate.

Management

- **Do not routinely prescribe antibiotic therapy for *Shigella* infection. Instead, reserve antibiotic therapy for patients for whom it is clinically indicated or when DC DOH advises treatment in an outbreak setting.**
    - Unnecessary treatment with antibiotics promotes resistance.

- Empiric treatment with an antibiotic to which the organism is resistant may worsen symptoms or prolong the duration of shedding of the organism.
- If empiric treatment is clinically indicated before antimicrobial susceptibility results are available, refer to recent hospital, clinical laboratory, or public health agency antibiograms.
- Antibiotic treatment is recommended for patients who are immunocompromised or who develop severe illness (e.g., patients requiring hospitalization, those with invasive disease, or those with complications).

- **When antibiotic treatment is indicated, tailor antibiotic choice to antimicrobial susceptibility results as soon as possible with special attention given to the MIC for fluoroquinolone antibiotics**
  - Avoid prescribing fluoroquinolones if the ciprofloxacin MIC is 0.12 μg/mL or higher even if the laboratory report identifies the isolate as susceptible.
  - Know the potential risks of fluoroquinolone treatment of *Shigella* infections with *ciprofloxacin MICs in this range, including possible treatment failure and increased risk of secondary transmission*.
  - The interpretation of MIC values varies for the different fluoroquinolone antibiotics; if susceptibility results are reported for a fluoroquinolone other than ciprofloxacin, contact the microbiology laboratory for assistance with interpretation.
  - If MIC values are not reported to the clinician with susceptibility results, consider contacting the microbiology laboratory where the susceptibility testing was performed to determine the ciprofloxacin MIC value before treating a patient with a fluoroquinolone agent. Some susceptibility testing methods do not produce a MIC value; the impact of a quinolone resistance gene on test results by other methods (e.g., disk diffusion) is not yet known.
  - Consult an infectious disease specialist for cases where the *Shigella* isolate is resistant to multiple antibiotics and appropriate treatment is unclear.

- **Obtain follow-up stool cultures in shigellosis patients who have continued or worsening symptoms despite antibiotic therapy.**

- **Consult DC DOH for guidance or support.**
  - DC DOH may advise when patients may return to childcare, school, or occupations that involve handling food.
  - DC DOH may advise antibiotic treatment to mitigate or prevent outbreaks in certain settings (e.g., childcare, food handling).
  - DC DOH can coordinate requesting CDC assistance.

Health Messages for Patients

- **Counsel patients with active diarrhea on how they can prevent spreading the infection to others, regardless of whether antibiotic treatment is prescribed.**
  - Wash hands with soap and water for at least 20 seconds, especially after using the toilet, after handling a soiled diaper, and before eating.
  - Avoid preparing food for others, when possible.
  - Children with active diarrhea should not attend childcare, school, or group activities while they are ill.
  - Wait to have sex (vaginal, anal, and oral) for two weeks after you no longer have diarrhea. Use safe sex practices for several weeks after resuming sex, because *Shigella* bacteria may still be in stool for several weeks.

Recommendations for Laboratories

- Submit all *Shigella* isolates, regardless of susceptibility, to the DC Public Health laboratory (DC PHL). Contact the DC PHL by email at DC.PHL@dc.gov.
- Know that a *Shigella* isolate with a ciprofloxacin MIC of 0.12–1 µg/mL may be associated with the presence of a quinolone resistance gene.
- Test *Shigella* isolates using susceptibility panels that include 0.12, 0.25, and 0.5 µg/mL dilutions for ciprofloxacin, when using a commercially available automated system (such as BD Phoenix, MicroScan, Vitek 2, or similar system) for susceptibility testing.
- Include MIC values for fluoroquinolone agents in the susceptibility testing report for *Shigella* isolates.
- Report all findings of strains of *Shigella* with a ciprofloxacin MIC of 0.12–1 µg/mL to DC DOH (see **Reporting** section above)

Additional Information and Resources

- DC DOH *Shigella* fact sheet for the public: https://doh.dc.gov/page/disease-fact-sheets
- Report a case of shigellosis to DC DOH: https://doh.dc.gov/service/infectious-diseases
- General information about *Shigella* or shigellosis: https://www.cdc.gov/*Shigella*/.
- Technical information about *Shigella* or shigellosis: https://www.cdc.gov/*Shigella*/resources.html.
- Information about prevention and control of shigellosis, including recommendations for men who have sex with men: https://www.cdc.gov/*Shigella*/prevention-control.html.
- Information about the serious public health threat posed by antimicrobial resistant *Shigella*, "Antibiotic Resistance Threats in the United States, 2013": https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.
- Information about ciprofloxacin and azithromycin-nonsusceptible shigellosis in the United States, Health Alert Network Advisory 379: https://emergency.cdc.gov/han/han00379.asp.

Please contact the DC DOH Division of Epidemiology–Disease Surveillance and Investigation for more information:
Phone: 202-442-8141 (8:15am-4:45pm) | 1-844-493-2652 (after-hours calls)
Fax: 202-442-8060 | Email: doh.epi@dc.gov

References

1. Scallan E, Hoekstra RM, Angulo FJ, Tauxe RV, Widdowson MA, Roy SL, Jones JL, Griffin PM. Foodborne illness acquired in the United States--major pathogens. Emerg Infect Dis. 2011;17(1):7-15.
2. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 27th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.