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Extended-Spectrum β -Lactamase *Shigella sonnei* Cluster Among Men Who Have Sex With Men in Chicago, Illinois, July–October 2022

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Abstract

Drug-resistant shigellosis is increasing, particularly among men who have sex with men (MSM). During July–October 2022, an extended-spectrum β -lactamase–producing *Shigella sonnei* cluster of 9 patients was identified in Chicago, of whom 8 were MSM and 6 were festival attendees. The

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Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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cluster also included 4 domestic travelers to Chicago. Sexual health care for MSM should include shigellosis diagnosis and prevention.

Keywords

multidrug resistance; outbreak investigation; molecular epidemiology; extended-spectrum β -lactamase; *Shigella sonnei*

Shigellosis is a gastrointestinal illness that affects approximately 450 000 persons in the United States annually. *Shigella* is easily transmissible and has demonstrated increasing resistance to antibiotics, resulting in few oral treatment options. In 2020, approximately 42% of infections were resistant to azithromycin and 18% were resistant to ciprofloxacin [1]. Resistance to third-generation cephalosporins increased from 5% of isolates reported to the Centers for Disease Control and Prevention (CDC) in 2020 to 12.3% of isolates in 2022 [1, 2].

Drug-resistant *Shigella* infections might result in longer courses of illness because it is more difficult and costly to treat, which increases transmission opportunities. Extended-spectrum β -lactamase (ESBL) production is one of the mechanisms that confers resistance to commonly used antibiotics, including third-generation cephalosporins, amplifying the potential for prolonged illness and transmission opportunities [3]. ESBL resistance genes can be chromosomal or plasmid mediated. Plasmid-mediated resistance is particularly concerning because it can confer resistance to other bacteria [4, 5]. Drug-resistant *Shigella* infections are most common among men who have sex with men (MSM) [6], persons experiencing homelessness, and international travelers [1].

In August 2022, the Chicago Department of Public Health (CDPH) was notified by a local laboratory of 3 cases of infection by ESBL *Shigella sonnei* with indistinguishable antimicrobial resistance patterns. On 21 September 2022, CDPH released a health alert to raise awareness of ESBL *Shigella* and to encourage antibiotic susceptibility testing (AST), especially after treatment failure or recurrence. CDPH investigated the ESBL *S. sonnei* cluster to determine the magnitude and describe the cluster. We also performed whole-genome sequencing (WGS) of ESBL *Shigella* isolates among Chicago residents and travelers to Chicago to characterize resistance patterns expressed, and to guide prevention efforts to minimize spread of ESBL *Shigella* in Chicago. This report describes the cluster, its magnitude, and resistance patterns identified in WGS analysis of associated isolates.

METHODS

Shigellosis is a reportable disease in Illinois. We reviewed surveillance data from the Illinois National Electronic Disease Surveillance System (I-NEDSS) to identify all laboratory-confirmed shigellosis cases among Chicago residents [7]. Because the first case of ESBL *S. sonnei* initially identified in the cluster had a reported illness onset of 8 August 2022, we reviewed all shigellosis cases reported in I-NEDSS starting the month before this date; we followed up cases to the end of the month when the last case was identified. For cluster cases among Chicago residents, we defined cases as laboratory-confirmed ESBL

S. sonnei among Chicago residents during 1 July to 31 October 2022. ESBL *S. sonnei* isolates were identified by (1) intermediate or resistant AST result to third-generation cephalosporins using automated broth microdilution method on the VITEK2 instrument (Biomérieux) followed by ESBL confirmation with disk diffusion method or (2) detection of the *bla*CTX-M gene through WGS [8]. To identify cases among patients residing outside of Chicago, we used the national System for Enteric Disease Response, Investigation, and Coordination (SEDRIC). We defined travel-associated cases as shigellosis cases reported in SEDRIC during 1 July to 31 October 2022, with isolates within 0–9 cgMLST allele differences of the initial 3-case cluster or with genomes containing a *bla*CTX-M gene, and among patients who traveled to Chicago during the 7 days before symptom onset.

We obtained basic demographic and clinical information from the surveillance systems for cluster cases. In addition, we attempted to interview patients using a standardized supplemental survey conducted by telephone. The supplemental survey collected additional information on clinical characteristics, potential exposures, travel, sexual behaviors, patient outcomes, and treatment.

Whole-Genome Sequencing

The Illinois Department of Public Health (IDPH) selectively sequenced submitted *Shigella* isolates before 1 August 2022, and subsequently sequenced all isolates. To understand resistance patterns and genetic relatedness of cluster cases, the Regional Innovative Public Health Laboratory in Chicago performed WGS analysis on isolates obtained through IDPH for Chicago residents and in SEDRIC for travel-associated cases. Contextual US *Shigella* assemblies collected in 2022 were randomly selected from National Center for Biotechnology Information at a ratio of 2 contextual to 1 Chicago isolate to produce the phylogenetic tree for comparison to cluster genomes (Supplementary Material). Assemblies were assessed for quality using the Quality ASsessment Tool (QUAST) and excluded from analysis if L50 > 500, N50 < 5000, or contigs >2000; kSNP3 software was used to generate phylogenetic trees and single nucleotide polymorphism (SNP) distances. Resistance genes and plasmids were investigated using AMRFinderPlus and PlasmidFinder, respectively. We used Prokka and BLASTn to confirm location of resistance genes in plasmids; a resistance gene was considered to be present on a plasmid when the gene and plasmid replicon collocated to a single contig and the contig had 100% coverage to a reference plasmid sequence, or in 1 case, if the gene was located between p0111 phage-associated genes.

Ethics

This study was reviewed by CDC and was conducted consistent with federal law and CDC policy (45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.).

RESULTS

Among 84 Chicago residents with laboratory-confirmed *S. sonnei* during 1 July to 31 October 2022, there were 45 (54%) isolates with resistance information available, including 5 (6%) with AST results only, 18 (21%) with WGS results only, and 22 (26%) with both.

Five isolates were considered ESBL. Three of the 5 had indistinguishable AST profiles. In addition, 4 travel-associated cases were identified through SEDRIC. All 9 isolates were sequenced.

Among the 9 ESBL *S. sonnei* cases, all patients were male, with a median age of 33 years (interquartile range = 31–38 years). All patients were white; 1 of 9 patients was Hispanic or Latino. We interviewed all patients with the supplemental survey. No common food borne exposures were identified. Eight patients reported ever having sexual contact with men, including 5 of 9 patients who reported sexual contact with a man within a week before symptom onset. Six patients reported attending the same festival for lesbian, gay, bisexual, transgender, queer and other (LGBTQ+) community members 4–7 August 2022, presenting exposure opportunities before symptom onset, including 3 out-of-state travelers who attended the event. Of the 5 patients who reported recent sexual contact with men, 4 reported oral-penile contact (4 insertive, 3 receptive), 3 reported anal sex (3 insertive, 2 receptive), and 3 reported oral-anal contact. One patient had a prior *Shigella* infection in the past year and was coinfecting with mpox and non-ESBL *Shigella flexneri* at the time of *S. sonnei* diagnosis. Only 3 patients had heard about *Shigella* before their most recent infection.

We had complete symptom information for 7 of 9 ESBL *Shigella* patients who completed our supplemental survey. Among these 7 patients, all reported diarrhea, 5 reported abdominal cramps, and 4 self-reported fever at the time of their gastrointestinal symptoms. Among all 9 patients, 3 sought medical care in the emergency department, and 2 were hospitalized for dehydration. No patients were immunocompromised. Antibiotic treatment information was available for 5 patients; all had isolates that were resistant to the recommended treatment antibiotics ampicillin, azithromycin, ceftriaxone, ciprofloxacin, and trimethoprim-sulfamethoxazole but susceptible to tetracycline (not a recommended treatment agent). Four of the 5 patients who were treated with antibiotics received an antibiotic to which their isolates were resistant, and 4 patients received tetracycline or doxycycline. One patient received cefixime, despite reduced susceptibility to ceftazidime. No patients reported receiving antibiotics the month before treatment, and there was no reported clinical treatment failure, although we have incomplete follow up for all patients' outcomes.

Whole-Genome Sequencing Results

The phylogenetic tree in Figure 1 shows genetic relatedness of ESBL isolates from Chicago residents relative to travel associated ESBL isolates and other contextual isolates. Isolates from the 8 patients who identified as MSM clustered into a single clade within 7 SNPs (transmission clusters for *Shigella* generally fall ≤ 10 SNPs); 3 genomes from Chicago residents were indistinguishable. All 8 isolates shared a common resistance profile, including the ESBL gene *bla*_{CTX-M-27} and 10 additional resistance genes. The remaining isolate in the cluster was unrelated to those from MSM (median 334 SNP differences), and contained a different ESBL gene, *bla*_{CTX-M-15}, and only 2 additional resistance genes. While ESBL genes in this cluster were not likely plasmid associated, isolates from 9 ESBL *Shigella* cases expressed a different resistance gene (*qnrB19*) that was located

within Co1440I plasmids (indicated in purple on the phylogenetic tree), which could confer resistance to other organisms. Additionally, the ESBL isolate from the patient with no MSM exposure showed *bla*_{CTX-M-15} within the p0111-type phage-plasmid. Analyzed assemblies were generated from short-read sequencing data, so additional plasmid-associated resistance genes might not have been detected and we cannot exclude the possibility that plasmid sequences had integrated into chromosomes. Furthermore, as low-coverage contigs were not filtered in the analysis, we cannot rule out possible sequence contamination of *qnrB19* results for high-copy number plasmids.

DISCUSSION

This cluster is a local example of *S. sonnei* becoming more antibiotic resistant. Overall, there was resistance to multiple classes of antibiotics, including cephalosporins, and 1 resistance gene (*qnrB19*) was located on a plasmid, indicating potential for transmission to other Enterobacterales. Plasmid-mediated ESBL *Shigella* remains a concern. A plasmid-mediated gene (*bla*_{CTX-M-27}) resistant to all first-line antibiotics was found in a similar global cluster first identified in the United Kingdom, predominantly circulating among MSM in early 2022 [9].

MSM are at increased risk of infection from drug-resistant forms of *Shigella*, including ESBL *Shigella* [6]. Eight of 9 ESBL cases in our cluster were MSM; however, we were only able to confirm sexual contact within 1 week before symptom onset for 5 of 8 MSM (56%) patients in the cluster. Given that no common food sources were found, direct transmission through sexual contact is still likely in this cluster, and the LGBTQ+ festival might have led to opportunities for transmission, be it sexual or food borne. While sexual contact is likely the route of transmission for many people in our cluster, we also observed an unrelated isolate among a patient without reported epidemiologic risk factors for sexual transmission, suggesting that resistance is growing among isolates that might have been transmitted through other mechanisms.

Clinicians should perform AST on *Shigella* isolates from patients at higher epidemiologic or clinical risk of shigellosis, including MSM, persons experiencing homelessness, international travelers, and immunocompromised individuals [10]. If AST is not possible due to limitations of the clinical laboratory, close monitoring for signs of treatment failure may be warranted, particularly for patients at high risk for severe illness. During this cluster investigation, AST was conducted for only 27% of all *S. sonnei* isolates among patients in Chicago. AST data are needed to identify drug-resistant shigellosis and ensure appropriate treatments for all at risk groups, including MSM, the immunocompromised and patients with severe shigellosis.

Timely diagnosis of shigellosis and a detailed history of potential exposures and social history is important. Patients experiencing fever or bloody diarrhea should be evaluated for enteropathogens for which antimicrobial agents may confer clinical benefit, including *Shigella*. In an integrated approach, health care providers should provide shigellosis prevention education along with other sexual health prevention measures, such as vaccination for mpox, viral hepatitis, and meningitis, and human immunodeficiency virus

(HIV) preexposure prophylaxis (PrEP) at screenings for sexually transmitted diseases, particularly in treatment settings for patients that face greater risks of sexually transmitted disease, such as HIV PrEP providers. Prior to large events that could present opportunities for new or increased numbers of sexual contacts, it is important to include shigellosis prevention education in activities promoting sexual health. In the event of an outbreak, WGS should be performed for public health intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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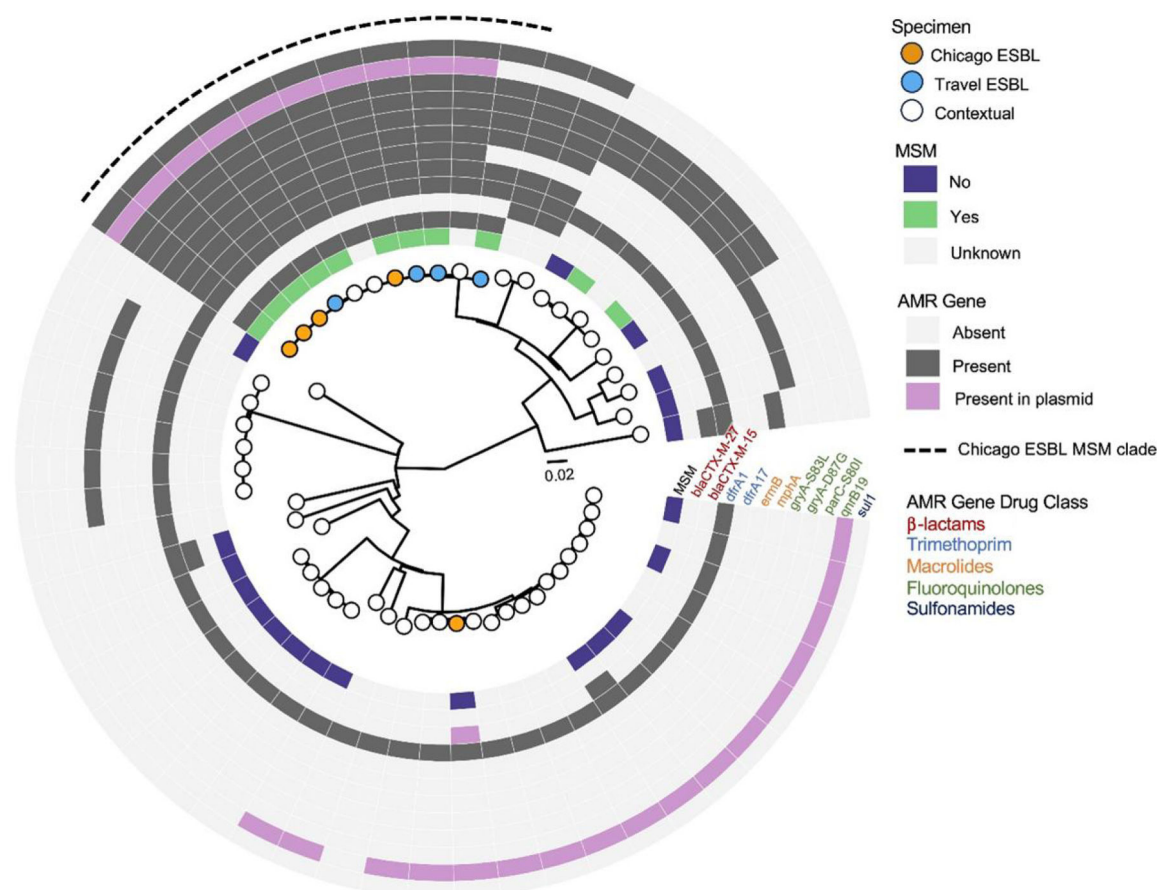


Figure 1. Phylogenetic tree of ESBL: midpoint-rooted core genome SNP-based phylogeny of Chicago (orange tips) and travel-associated (blue tips) ESBL isolates and contextual isolates (white tips) randomly selected from US *Shigella sonnei* isolates collected in 2022. Metadata blocks indicate MSM (green) and non-MSM (indigo) and the presence of selected resistance genes (dark grey). Resistance genes found to be located within plasmids are indicated in lilac. Cases in the Chicago ESBL MSM *Shigella sonnei* clade during July–October 2022 are indicated by a dashed line. Abbreviations: AMR, antimicrobial resistance; ESBL, extended-spectrum β -lactamase; MSM, men who have sex with men; non-MSM, men who did not report having sex with men; SNP, single-nucleotide polymorphism.