Clinical Infectious Diseases

MAJOR ARTICLE

Increased Severity of Multidrug-Resistant *Shigella sonnei* Infections in People Experiencing Homelessness

Aleksandra Stefanovic,[1,2] Mosaab E. Alam,[3] Nancy Matic,[1,2] Ashley Larnder,[4] Gordon Ritchie,[1,2] Leah Gowland,[2] Samuel D. Chorlton,[5] Elisa Lloyd-Smith,[4,6] Michael Payne,[1,2] Meena Dawar,[4,6] Rohit Vijh,[4,6] Victor Leung,[1,2,3] Mark Hull,[3] Kate S. Baker,[7] Christopher F. Lowe,[1,2] and Marc G. Romney[1,2]

[1]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [2]Division of Medical Microbiology and Virology, St. Paul's Hospital, Vancouver, British Columbia, Canada; [3]Division of Infectious Diseases, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [4]School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada; [5]BugSeq Bioinformatics, Inc, Vancouver, British Columbia, Canada; [6]Vancouver Coastal Health Authority, Vancouver, British Columbia, Canada; and [7]Department of Genetics, University of Cambridge, Cambridge, United Kingdom

Background. *Shigella sonnei* has caused sexually transmitted enteric infections in men who have sex with men (MSM) in Vancouver. We recently observed a high rate of multidrug-resistant (MDR) *S. sonnei* bacteremia among persons experiencing homelessness (PEH). We aimed to describe the wider epidemiology, clinical outcomes, and genomics of *S. sonnei* infections over time.

Methods. A retrospective review of 163 patients with *S. sonnei* infections was undertaken from 2015 to 2022. We collected demographic, clinical, and microbiological data over 2 time periods: historical (2015–2020) and recent (2021–2022). Severe shigellosis definition included hospitalization, bacteremia, or death. Whole-genome sequencing was performed to identify genotype, infer relatedness, and predict antimicrobial resistance.

Results. *S. sonnei* infections increased from 8.3 (historical period) to 56.5 (recent period) cases/year. Over time, the primary population characteristics associated with shigellosis shifted from MSM (45; 98%) to PEH (86; 77%). The population intersection between MSM and PEH historically and recently was similar and occurred in 3 (6%) and 10 (9%) of patients, respectively. Severe shigellosis was significantly higher in the recent versus historical period (69 [61%] vs 7 [14%]; $P < .001$). A dominant clone of MDR *S. sonnei*, 3.6.1.1.2 (CipR.MSM5), emerged with resistance to all first- and second-line agents, yet with susceptibility to ceftriaxone.

Conclusions. We observed a substantial increase in severe shigellosis and shift from sexually transmitted *S. sonnei* infections in MSM to likely environmental transmission among PEH. More severe disease associated with the 3.6.1.1.2 clone of MDR *S. sonnei* in PEH could be a result of underlying vulnerabilities of the affected population.

Keywords. shigellosis; people experiencing homelessness; *S. sonnei*; antimicrobial resistance; severity.

Shigellosis is an acute infectious disease of the gastrointestinal tract with symptoms ranging from mild, self-resolving diarrhea to dysentery, colitis, and sepsis. Disease severity depends on age, nutritional and immune status of the host, and virulence of the *Shigella* species [1–3]. Worldwide, *Shigella* causes significant morbidity and is the second-leading cause of diarrheal mortality. The epidemiology is species-specific, with *Shigella flexneri* being endemic in lower-income and middle-income countries, and *Shigella sonnei* being the dominant species in higher-income countries [2].

Shigella is transmitted by the fecal-oral route, via contaminated fomites, food, or water, or by direct person-to-person contact [2]. Sexual transmission plays an important role among men who have sex with men (MSM) [4]. *Shigella* is highly transmissible due to a low infective dose (10 organisms) needed to infect a host [2]. The risk of shigellosis increases in conditions of overcrowding and inadequate access to hygiene and sanitation. Populations at risk of infection in higher-income countries include children, travelers to endemic regions, MSM, and a more recently recognized group, people experiencing homelessness (PEH) [5].

Dominance of *S. sonnei* in higher-income countries is partly driven by its unique ability to acquire antimicrobial resistance (AMR) genes via horizontal transfer of mobile genetic elements from other bacteria [6]. The last few decades have seen

Received 02 August 2024; editorial decision 12 November 2024; published online 21 November 2024

Correspondence: A. Stefanovic, Department of Pathology and Laboratory Medicine, St Paul's Hospital Microbiology Laboratory, University of British Columbia, 1081 Burrard Street, Vancouver, BC, V6Z 1Y6, Canada (astefanovic@providencehealth.bc.ca).

Clinical Infectious Diseases® 2025;80(2):339–46

https://doi.org/10.1093/cid/ciae575

increasing resistance to fluoroquinolones followed by azithromycin, giving rise to multidrug-resistant (MDR) *S. sonnei* [7, 8]. Concerningly, circulation of MDR—and more recently, extensively drug-resistant (XDR) *S. sonnei*—has been reported throughout Europe, Australia, Canada, and the United States [9–13].

From 2003 to 2012, *S. sonnei* was the most common species isolated in British Columbia, Canada, with the majority of infections occurring in MSM [14]. Recently, however, we observed a high rate of MDR *S. sonnei* bacteremia among PEH [15]. The aim of our study was to characterize the wider epidemiology, clinical outcomes, antimicrobial susceptibility, and genomic epidemiology of *S. sonnei* infections in downtown Vancouver from 2015 through 2022.

METHODS

Study Design and Setting

We conducted a retrospective study of 163 patients with *S. sonnei* recovered from stool or blood cultures by the Microbiology Laboratory at St. Paul's Hospital between 1 January 2015 and 31 December 2022. Based on clinically observed changes in the populations affected and shifts in antimicrobial susceptibility patterns, we stratified study periods into a historical period (2015–2020) and recent period (2021–2022). The Microbiology Laboratory provides diagnostic services to 2 acute care hospitals, specialized sexually transmitted infection (STI) clinics, and general outpatient clinics servicing PEH in downtown Vancouver, Canada. There was no known change in population served and submitting facilities over the study period. We performed chart reviews of hospital electronic medical records and extracted relevant epidemiological and clinical data, including the following: age, sex, date of specimen collection, sexual orientation, housing status, postal code, travel history, substance use disorder (SUD), human immunodeficiency virus (HIV) status, antiretroviral therapy (ART), CD4 count, STI screening, healthcare received, length of hospital stay (LOS), intensive care unit (ICU) admission, specialist referral, colonoscopy, antimicrobial susceptibility testing (AST), and mortality. Severe shigellosis was defined as a positive culture with associated hospitalization, bacteremia, or death [16]. Housing status was separated into housed persons and PEH, which included people having no fixed address, living in single-room occupancy hotels (SROs) or in supportive housing (Supplementary Material). Multidrug resistance was defined as resistance to first-line agents (ampicillin, trimethoprim-sulfamethoxazole, and ciprofloxacin) and azithromycin, while XDR was defined as added resistance to third-generation cephalosporins [17].

Laboratory Procedures

Stool specimens and blood cultures underwent testing using conventional laboratory procedures. Briefly, stool specimens were inoculated onto standard culture media including Hektoen enteric agar for *Shigella* isolation. Blood cultures underwent standard procedures, as previously reported [15]. Suspected colonies were identified by Vitek2 ID (bioMérieux, France) with confirmation by antisera for somatic O antigen (Remel, Lenexa, KS, USA). Over the course of the study, there was no change in the technical methods for the identification of *Shigella* species. Antimicrobial susceptibility testing was performed according to Clinical and Laboratory Standards Institute M100 standards [18]. The number of stool specimens tested remained relatively stable over the study period, except for a 28% decrease in 2020.

Whole-Genome Sequencing and Bioinformatic Analysis

Shigella isolates grown in Cary Blair broth overnight had DNA extracted on the MagNA Pure 24 (Roche Diagnostics, Switzerland). Whole-genome sequencing (WGS) was performed on the GridION with R10.4.1 flow cells using the SQK-NBD114.24 library kit (Oxford Nanopore Technologies, United Kingdom). Guppy (Oxford Nanopore, UK) (v6.4.6) base-called FASTQ files were submitted to BugSeq for bioinformatic analysis, as previously described [19]. Predictors of AMR were detected by searching BugSeq's curated AMR database with BLAST. In addition, Tn7 was downloaded from TnCentral (accession Tn7-NC_002525), and minimap2 (v2.28) was used to search assemblies for the presence of the transposon [20]. The MOB-Suite cluster for pKSR100 was identified by running MOB-typer on National Center for Biotechnology Information (NCBI) accessions NZ_LN624486.1, NZ_CP090162.1, and NZ_LR878367.1 [21]. Reference-based multilocus sequence typing (refMLST) was performed on all isolates using the NCBI RefSeq assembly GCF_013374815.1 *S. sonnei* genome as the reference sequence. The threshold of <20 allele differences by refMLST was previously validated to indicate epidemiological relatedness or clonality and corresponds to <10 alleles by cgMLST [19]. The cladogram was generated by pyCirclize (https://github.com/moshi4/pyCirclize). The genotypic framework by Hawkey et al [22] was used to identify distinct genotypes.

Statistical Methods

Data cleaning and analyses were conducted in R (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). Data were reviewed for errors and inconsistencies, and the amount of missing data for each variable was recorded. Data were described using sample frequency counts for categorical variables and means with SDs (normally distributed) or medians with interquartile ranges (IQRs) (nonnormal distribution) for continuous variables. Comparisons across the periods were conducted using *t* tests (normal) or Mann–Whitney *U* tests (nonnormal) for continuous variables and Pearson's chi-square tests (parametric) or Fisher's tests (nonparametric) for

categorical variables. A P value $\leq .050$ was considered statistically significant across periods.

Ethics approval was obtained from the University of British Columbia/Providence Health Care Research Ethics Board (H22-02183).

RESULTS

Overall, 163 case-patients with *S. sonnei* infections were detected over the study period: 50 in the historical period and 113 in the recent period. A large increase in *S. sonnei* infections was observed over time, from a historical baseline of 8.3 cases/year (IQR: 7.5) to 56.5 cases/year (IQR: 39.5) in the recent period (Figure 1). Patient demographics, clinical characteristics, outcomes, and antimicrobial susceptibilities are summarized in Table 1. A retrospective review of the study patients revealed a significant shift in epidemiology: MSM predominated in the historical period (n = 45; 98%); PEH prevailed in the recent period (n = 86; 77%) (Table 1). MSM status was associated with HIV positivity (26 [58%] of MSM had HIV), while PEH status was associated with SUD (80 [93%] of PEH had SUD). The population in the historical period was composed of 42 (84%) MSM only, 3 (6%) MSM and PEH, and zero (0%) PEH only. Contrastingly, the recent period was composed of 14 (12%) MSM only, 10 (9%) MSM and PEH, and 76 (67%) PEH only. A significant increase in severe shigellosis ($P < .001$) was observed in the recent period compared with the historical period (Figure 1). When comparing the PEH-only and MSM-only groups in the recent period, clinical severity was significantly higher among the PEH-only group (55 [72%] vs 3 [27%]; $P < .001$). More patients required ICU admission (5 [5%] vs 0 [0%]) and had longer LOS (median difference = 1 day) in the recent compared with historical period, although these differences did not reach statistical significance.

Susceptibility of *S. sonnei* to oral antibiotics significantly decreased in the recent period. Multidrug resistance to first-line agents was present in 11 (22%) of historical isolates compared to 109 (96%) of recent isolates. On detection of resistance to all first-line agents, routine azithromycin testing commenced at our center in 2016. Upon initiation of azithromycin testing, an identical MDR susceptibility profile (resistance to first-line agents and azithromycin) was detected in 9 (18%) historical isolates, with 8 (89%) occurring in MSM, and in 108 (96%) recent isolates, with 86 (80%) occurring in PEH. Whole-genome sequencing was performed on 87 (77%) of recent isolates. Only a single blood culture isolate from the historical period was available for analysis, as previously described [19]. The genotypic framework analysis identified 4 distinct genotypes [22]. Genotype 3.6.1.1.2 (CipR.MSM5) was identified in 83 (95%) of the isolates. The remaining genotypes (3.7.18 [Global III], 3.6.1 [CipR parent], and 3.6.3 [Central Asia III]) comprised 2 (2%), 1 (1%), and 1 (1%) of the isolates, respectively. Of the patients with the 3.6.1.1.2 genotype, none had a history of recent travel. Of the 4 isolates with other genotypes, 3 were travel-associated, as previously reported [19]. A single patient, without a recent travel history and no links to MSM or PEH, had infection with the distinct genotype 3.6.3 (Central Asia III) with resistance to ceftriaxone, as previously described [15]. This patient was immunocompromised and hospitalized for treatment with meropenem for 2 weeks prior to being discharged home.

The maximum distance between any two 3.6.1.1.2 isolates in our study was 19 allele differences using refMLST, indicating clonality among these isolates based on a previous validation study [19]. In contrast, the two 3.7.18 isolates had more than 320 allele differences, the 3.6.1 isolate had more than 140, and the 3.6.3 isolate had more than 200 allele differences compared with the 3.6.1.1.2 isolates. All isolates contained transposon (Tn7), which carried trimethoprim resistant dihydrofolate reductase (*dfrA1*) and streptogramin A resistance (*satA2*) in 97.7%, and aminoglycoside resistance (*aadA*) in 2.3% of isolates. Isolates belonging to the 3.6.1.1.2 genotype exhibited conserved plasmid composition and AMR mutations. They all shared ß-lactamase resistance ($bla_{TEM\text{-}1B}$), sulfonamide resistance (*sul1* and *sul2*), trimethoprim resistance (*dfrA1*, and *dfrA17*), as well as triple mutations in Quinolone Resistance Determining Region (QRDR) with mutations in DNA gyrase (*gyr(A)* S83L and *gyr(A)* D87G) and DNA topoisomerase (*parC* S80I). Furthermore, they harbored the plasmid pKSR100-borne *erm(B)* and *mph(A)* genes encoding macrolide resistance (Figure 2). Two isolates with the 3.7.18 genotypes carried *sul2* and *dfrA1*, with 1 of them additionally carrying quinolone resistance (*qnrB19*) gene. A single isolate of 3.6.1 exhibited *gyr(A)* S83L and *dfrA1* mutations. The patient with the distinct genotype 3.6.3, lacking a travel history, carried $bla_{CTX\text{-}M\text{-}15}$, *sul2*, *dfrA1*, and *qnrS1*. The available historical isolate from a 2016 blood culture genotyped as 3.7.18 carried $bla_{TEM\text{-}1B}$ and *dfrA1* [15].

In terms of data quality, some degree of missing data was observed for AST 2 (1%), with higher rates of missing data for ceftriaxone 22 (14%) and azithromycin 36 (22%) AST (due to the antibiotic testing cascade where second-line antibiotics are only tested when resistance is detected to first-line agents). Antibiotic treatment data could not be obtained for outpatients and 33% of emergency department patients, primarily in the historical period. Additional data were missing for STI screening 14 (9%), HIV status 13 (8%), sexual orientation 10 (6%), and travel history 2 (1%).

DISCUSSION

We identified a large increase in laboratory-confirmed *S. sonnei* infections over time, with a concurrent shift in patient demographics and an increase in clinical disease severity among

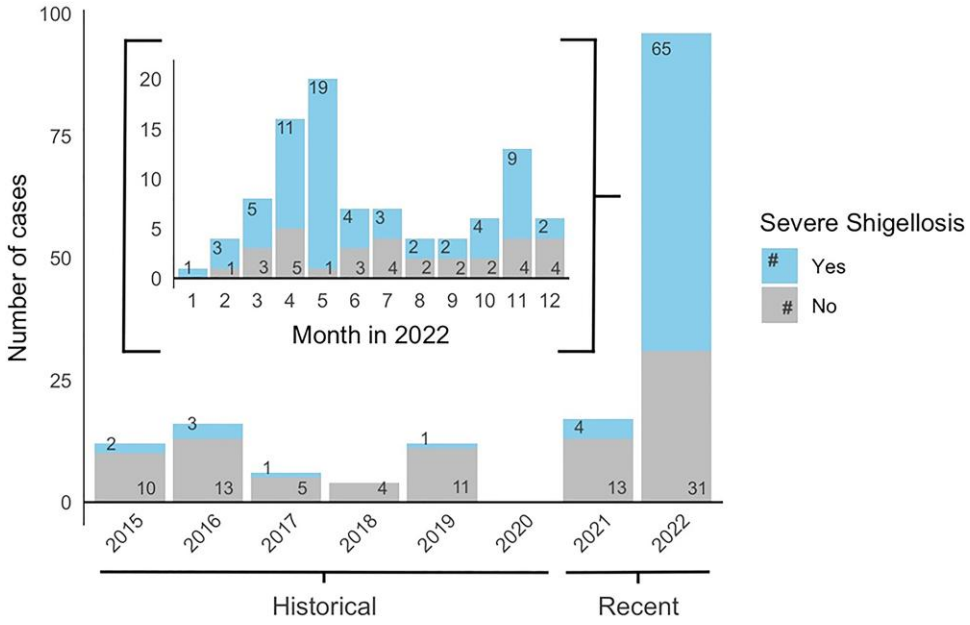

Figure 1. Epidemic curve of patients with *Shigella sonnei* identified from stool or blood cultures by severity, 2015–2022. The distribution of severe (blue) and nonsevere (gray) shigellosis infection are represented by stacked bars. Historical period was defined as 2015–2020 and recent period as 2021–2022. For calendar year 2022, cases distributed by month are shown.

PEH. In 2020, no cases of *S. sonnei* were detected, likely due to a combination of public health measures and reduced healthcare utilization during the coronavirus disease 2019 (COVID-19) pandemic [23]. Similar phenomena were observed in England and the rest of Canada, with a significant decline in *Shigella* cases identified by laboratory surveillance in 2020 [24, 25]. A change in healthcare-seeking behaviors and reduced access to healthcare services likely contributed to the decreased laboratory detection, rather than the true disappearance of infections. Indeed, in our laboratory, stool testing decreased by 28% in 2020. As pandemic measures waned, we observed an increased number of MDR *Shigella* infections, with a particularly dramatic increase in 2022 (Figure 1). Similar increases have been reported in Seattle and King County [13].

We confirmed the epidemiological shift in populations affected over time from predominantly MSM to PEH (Table 1). Before and after 2020, 3 (6%) and 86 (77%) patients were experiencing homelessness, respectively. In the recent cohort, we detected an increase in SUD reflective of the background high rate of addiction among PEH [26]. Classically, *Shigella dysenteriae* type 1 and *S flexneri* are considered the most virulent species of *Shigella*; however, we observed an increase in clinical severity with *S. sonnei* infections in PEH [2, 16]. In addition to increased severity over time, recent infections with the clonal strain of *S. sonnei* exhibited higher severity among PEH than MSM, implicating host factors as likely determinants of severe disease. Host factors, such as malnutrition, high prevalence of SUD, and associated health issues faced by PEH, likely contributed to the increased disease severity in our cohort. Delays in seeking care and nonadherence to therapy have also been implicated as factors leading to high disease severity among PEH [27]. In our PEH cohort, hospitalization was the main contributor to severity. A similar increase in hospitalizations was recently reported from outbreaks among PEH in Seattle, WA, and San Diego County [13, 28]. Although HIV coinfection is an important risk factor for severe shigellosis in adults, we had a greater number of HIV-positive patients in the historical period with, perhaps paradoxically, less severe disease [2, 3]. In a study from South Africa, severe disease was dependent on low CD4 counts, whereas in our historical cohort, most (24; 89%) had well-controlled HIV with CD4 counts greater than 200 cells/μL [29].

In our local context, the AST profiles of historical *S. sonnei* isolates recovered in our laboratory have varied widely, suggesting co-circulation of multiple strains. Once routine azithromycin testing commenced in 2016, we detected MDR *S. sonnei* with azithromycin resistance in 9 (18%) of historical isolates, mostly among MSM. Notable at the time, increasing azithromycin resistance was being reported in MSM-associated *S sonnei* clusters in Canada [10]. Conversely, most (108; 96%) of our recent isolates had identical MDR susceptibility profile (Table 1) and identical genotype 3.6.1.1.2 (CipR.MSM5). Most isolates clustered within 20-allele differences, indicating the presence of a single, clonal expansion (Figure 2). Our genotype belongs to Lineage III, which emerged in South Asia in the early 2000s, and acquired triple fluoroquinolone-resistant

Table 1. Descriptive Characteristics of Patients With *Shigella sonnei* Infections: 2015–2022

Characteristic	Cases of *Shigella sonnei*		*P*
	Historical Period: 2015–2020 (n = 50)	Recent Period: 2021–2022 (n = 113)	
Age, mean (SD), y	41.8 (±13.9)	44.8 (±13.2)	.198
Sex, male, n (%)	50 (100.0)	80 (70.8)	<.001
Sexual orientation, MSM, n (%)	45 (97.8)	24 (22.4)	<.001
Housing status, n (%)			<.001
Housed	47 (94.0)	26 (23.2)	
Persons experiencing homelessness (PEH)	3 (6.0)	86 (76.8)	
Single-room occupancy	1 (2.0)	30 (26.8)	
Supportive housing	1 (2.0)	25 (22.3)	
No fixed address	1 (2.0)	31 (27.7)	
Travel history (last 30 d), yes, n (%)	2 (4.1)	3 (2.7)	.641
Substance use, n (%)			<.001
Substance use disorder	5 (10.2)	91 (82.0)	
Recreational use only	13 (26.5)	0 (0.0)	
None	31 (63.3)	20 (18.0)	
STI screening in 3 m prior, n (%)	30 (69.8)	59 (55.7)	.160
HIV status, positive, n (%)	27 (61.4)	14 (13.2)	<.001
CD4 count (within HIV positive), mean (SD), cells/μL	605.6 (±311.4)	589.3 (±335.5)	.878
Severe shigellosis, n (%)	7 (14.0)	69 (61.1)	<.001
Healthcare received, n (%)			<.001
Inpatient	7 (14.3)	68 (60.2)	
Outpatient	17 (34.7)	22 (19.5)	
Emergency department	25 (51.0)	23 (20.4)	
Length of hospital stay, median (IQR),[a] inpatient days	3.0 (1.5)	4.0 (4.0)	1.000
Referral to specialist,[b] n (%)			.673
Gastroenterology	4 (8.0)	17 (15.0)	
Infectious disease	7 (14.0)	13 (11.5)	
Intensive care unit	0 (0.0)	5 (4.5)	
General surgery	0 (0.0)	3 (2.7)	
Internal medicine	0 (0.0)	1 (0.9)	
None	39 (78.0)	76 (67.3)	
Colonoscopy performed, n (%)	2 (4.0)	3 (2.7)	.088
Bacteremia,[c] n (%)	1 (2.0)	8 (7.1)	1.000
Mortality (30 d), n (%)	0 (0.0)	1 (0.9)	1.000
Antimicrobial susceptibility,[d] n (%)			
Ampicillin	14 (29.2)	3 (2.7)	<.001
TMP/SMX	6 (12.5)	2 (1.8)	.009
Ciprofloxacin	27 (56.2)	2 (1.8)	<.001
Azithromycin	1 (7.1)	3 (2.7)	.448
Ceftriaxone	30 (100.0)	110 (99.1)	1.000

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; STI, sexually transmitted infection; TMP/SMX, trimethoprim/sulfamethoxazole.

[a]Only calculated for hospitalized patients.

[b]Categories are not mutually exclusive, as 2 patients received both intensive care unit and general surgery referrals.

[c]Blood cultures are not part of standardized testing and were only collected from a subset of cases when bacteremia was clinically suspected.

[d]Susceptibility proportions and *P* values were calculated for each antibiotic separately. Note: the "n" for each group differs as susceptibility testing is performed as a cascade, where second-line antibiotics are only tested if resistance is found in the first-line antibiotics. Within the historical period (2015–2020), azithromycin was tested on n = 14 patients and ceftriaxone on n = 30 patients. Within the recent period (2021–2022), ceftriaxone was tested on n = 111 patients.

mutations within QRDR, before spreading globally and giving rise to genotype 3.6.1.1.2 (CipR.MSM5) [22]. Due to the clonal nature of *S sonnei*, we detected the same mutations in the stool isolates as in the strains causing bacteremia (mutations in *gyrA* S83L, *gyrA* D87G, and *parC* S80I encoding ciprofloxacin resistance and plasmid pKSR100-borne *mphA* and *ermB* encoding azithromycin resistance) [15] (Figure 2). Based on the AST profile, MDR *S. sonnei* was circulating among MSM since 2016 and perhaps even earlier. However, the unavailability of historical isolates for WGS precludes us from determining the exact genotype of historically circulating strains. Worldwide, the 3.6.1.1.2 genotype has been associated with MSM in England, France, Belgium, Australia, and the United States [30].

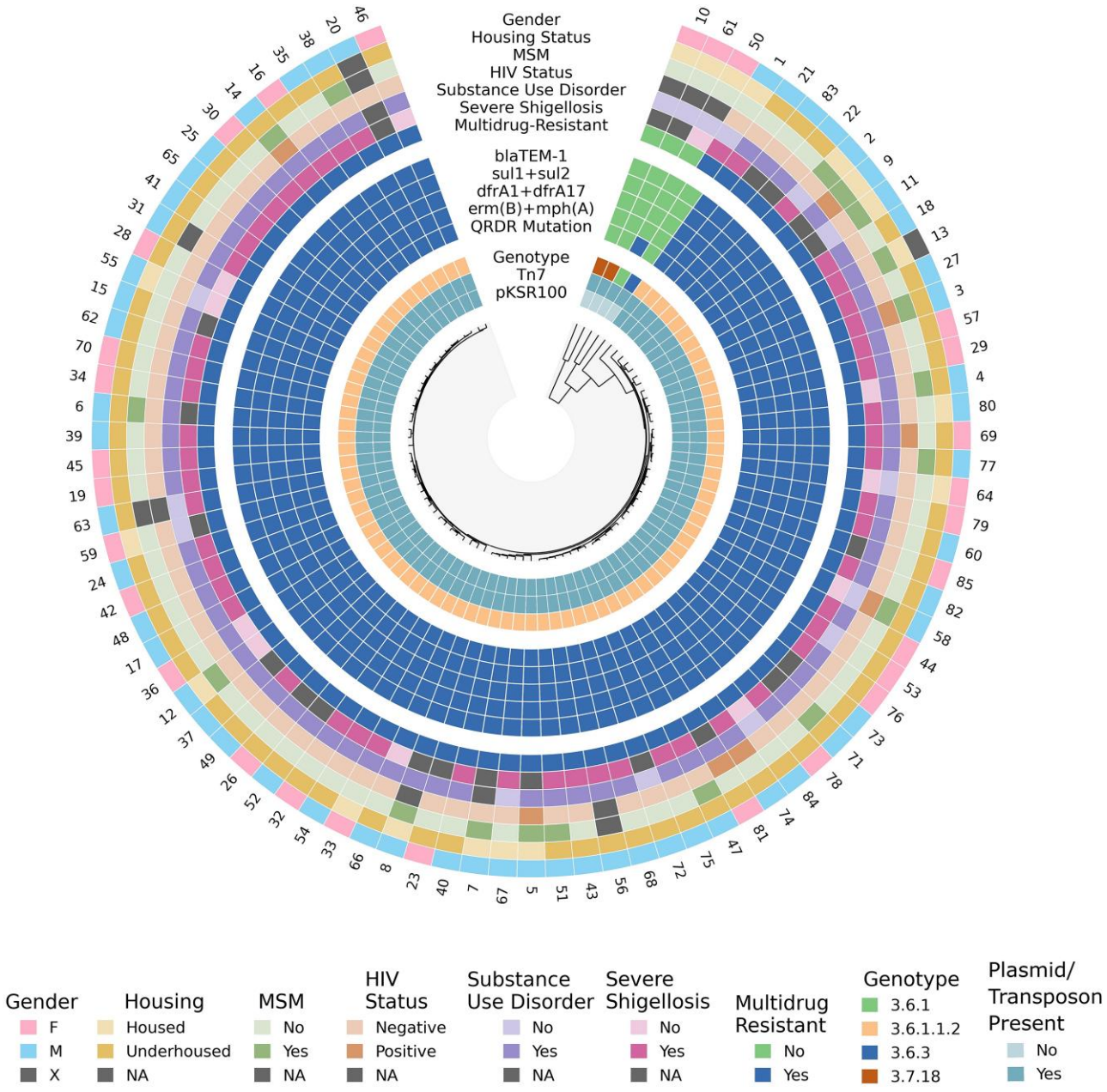

Figure 2. Cladogram illustrating relationships of 87 (77%) of *Shigella sonnei* infections from the recent period. Among variables included are patient demographics and clinical characteristics including severity, multidrug resistance, and genotype. Isolate identification labels are displayed circumferentially in chronological order based on specimen collection date. Genomic features show AMR determinants including genes and mutations with resistance to: ciprofloxacin within QRDR with 3-point mutations (*gyrA*_D87G, *gyrA*_S83L, and *parC*_S80I), azithromycin (*ermB* and *mphA*), trimethoprim (*dfrA1* and *dfrA17*), sulfonamides (*sul1* and *sul2*), and ampicillin (bla_{TEM-1}). Mobile genetic elements included transposon Tn7 (carrying *dfrA1*, *satA2*, or *aadA* resistance genes) and plasmid pKSR100 (carrying *ermB* and *mphA* resistance genes). Abbreviations: AMR, antimicrobial resistance; F, female; HIV, human immunodeficiency virus; M, male; MSM, men who have sex with men; NA, not available; PEH, people experiencing homelessness; QRDR, Quinolone Resistance Determining Region; WGS, whole-genome sequencing; X, unknown.

In 2021, an outbreak of MDR *S flexneri* infections occurred among PEH in downtown Vancouver [31]. While the implicated strain of *S flexneri* was resistant to all first-line agents, azithromycin susceptibility was preserved. At the time, azithromycin was recommended for empirical treatment of shigellosis. In 2022, MDR *S. sonnei* replaced *S flexneri* as the dominant strain causing shigellosis among PEH [32]. We hypothesize that the antibiotic selective pressure from widespread use of azithromycin in PEH may have selected for a clone of azithromycin-resistant *S. sonnei*. Other studies have also shown a shift in species dominance from *S flexneri* to *S sonnei* due, in part, to selective antibiotic pressure and the exceptional ability

of *S. sonnei* to evolve rapidly and acquire resistance determinants [33, 34]. A study from Vietnam described a change in dominance of a successful clone of *S. sonnei* coinciding with a change in antibiotic resistance and increased disease severity [33]. A rising dominance of *S. sonnei* globally is occurring with improvements in sanitation standards and water quality. These improvements have resulted in fewer exposures to *Plesiomonas shigelloides*–contaminated water sources, likely leading to decreased immune cross-protection against *S. sonnei* [6]. Our study illustrates the trajectory of the change in species dominance over a short period, the possible role of antibiotic selective pressure, and increased disease severity when *S. sonnei* is introduced into an area with a vulnerable and susceptible community within a high-income country.

It is difficult to discern precisely how strain 3.6.1.1.2 was initially introduced into the population of PEH and whether it was introduced independently or spread locally. Flanking Vancouver's downtown peninsula are 2 distinct neighborhoods: one known for its large MSM community and another with a significant proportion of PEH. The geographic proximity of the MSM and PEH populations, lack of travel among PEH, population overlap, MSM-associated genotype 3.6.1.1.2 (CipR.MSM5), and the presence of a phenotypically identical MDR strain among MSM historically suggest that this MDR strain was initially circulating among MSM followed by a local spread to PEH. However, the lack of historical strain genotyping precludes us from knowing the exact mode of introduction among PEH as other ways of introduction cannot be excluded. Interestingly, a similar phenomenon occurred in Vancouver in early 2007 with an outbreak of *S. sonnei* among MSM, followed by a separate outbreak later that year among PEH. At the time, the circulating strain was susceptible to ampicillin and ciprofloxacin [35]. A contemporaneous study from Seattle likewise described MDR and XDR *S. sonnei* sequentially circulating among MSM followed by transmission within PEH with a predominant 3.7.29.1.4.1 (Global III VN2·KH1.Aus) genotype, suggesting a separate route of acquisition from our strain [13]. In our study, isolates with distinct genotypes and AST profiles were almost exclusively associated with travel. With the introduction of *Shigella* among PEH, a change in the primary mode of transmission likely occurred. Although sexual transmission is well established among MSM, transmission among PEH is believed to occur following exposure to fecally contaminated environmental surfaces and hands (local public health investigation and M. Dawar, MD, personal communication, 26 February 2024) [5]. High fecal shedding, low infective dose, and susceptibility of population coupled with lack of hygiene and sanitation have been shown to contribute to sustained transmission of *Shigella* in low- and middle-income countries [36]. The introduction of *Shigella* into congregate living settings (shelters, SROs, etc) among PEH with limited access to hygiene and sanitation likely created favorable conditions for its widespread transmission. Similarly, outbreaks of shigellosis among PEH have been described along the West Coast of the United States (Portland, OR; San Diego County, CA; Seattle and King County, WA) [13, 28, 37].

The rapid evolution and increasing detection of MDR and XDR *S. sonnei* strains are resulting in increasingly limited treatment options for managing shigellosis [11]. The World Health Organization has deemed *Shigella* a priority pathogen for urgent new antibiotic development. In the meantime, existing antibiotics with activity against *Shigella* should be reconsidered. With the emergence of XDR *S. sonnei* in Europe, carbapenems have been recommended for severe cases and pivmecillinam and fosfomycin were used for oral step-down therapy [11, 12]. Further studies are needed to assess the activity of potential oral agents for the treatment of drug-resistant shigellosis.

Limitations of our study include the probable underestimation of the true occurrence of shigellosis and the potential for selection bias toward severity, as only patients with more severe infections are likely to seek care or present to a hospital. However, we observed a significant increase in infections and severity compared with our historical cohort also prone to the same selection bias. Although there were no changes in submitting clinics and facilities, unrecognized changes in the population served by our laboratory could have occurred over time, influencing our results. Potential confounding factors, such as psychiatric diagnosis and SUD, may have contributed to hospital admission in PEH [38]. However, most PEH in our cohort were hospitalized for acute shigellosis symptoms, with a high rate of bacteremia pointing toward a true increase in severity. We relied on retrospective chart reviews where some of the variables were not always elicited or documented. Besides HIV diagnosis, we did not collect extensive data on other immunocompromising conditions among PEH, which could have contributed to increased severity. In our bacteremia study and in a large study on systemic shigellosis from South Africa, no immunosuppressive condition was individually associated with invasive shigellosis, except for HIV [15, 29]. Whole-genome sequencing has only recently become available as a clinical tool to assess clonality and genotyping.

CONCLUSION

We observed a large increase in MDR *S. sonnei* infections post–COVID-19 pandemic, including a shift from sexual transmission among MSM to probable environmental transmission among PEH. An increased disease severity and healthcare utilization among PEH was likely driven by host factors. The WGS data provided evidence for a clonal expansion of 3.6.1.1.2 (CipR.MSM5) genotype. Potential interventions to reduce shigellosis in PEH include improved sanitation and handwashing, improved access to hygiene facilities, optimized nutrition, and eventually, vaccination against *Shigella* [39].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. S. and M. G. R. conceptualized and designed the study. A. S. supervised and coordinated the study. M. E. A. collected data. N. M., C. F. L., and M. P. cross-validated data points. L. G. and G. R. performed the laboratory experiments. A. L., E. L.-S., and S. D. C. performed data analysis and interpreted the data. A. S., M. G. R., N. M., C. F. L., and M. P. supported the analysis and interpretation of the data. A. S. drafted the initial manuscript. All authors revised, read, and approved the final draft of the manuscript.

Data sharing. Sequence data have been uploaded to GenBank (BioProject numbers PRJNA1019784 and PRJNA1139194). De-identified clinical metadata can be made available on request. For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising from this submission.

Potential conflicts of interest. S. D. C. is an employee and shareholder in BugSeq Bioinformatics, Inc. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Strauss B, Kurzac C, Embree G, Sevigny R, Paccagnella A, Fyfe M. Clusters of Shigella sonnei in men who have sex with men, British Columbia, 2001. Can Comm Dis Rep **2001**;27:109–12.
2. Kotloff KL, Riddle MS, Platts-Mills JA, Pavlinac P, Zaidi AKM. Shigellosis. Lancet **2018**; 391:801–12.
3. Davies NECG, Karstaedt AS. Shigella bacteraemia over a decade in Soweto, South Africa. Trans R Soc Trop Med Hyg **2008**; 102:1269–73.
4. Aragón TJ, Vugia DJ, Shallow S, et al. Case-control study of shigellosis in San Francisco: the role of sexual transmission and HIV infection. Clin Infect Dis **2007**; 44:327–34.
5. Centers for Disease Control and Prevention. Public health considerations for shigellosis among people experiencing homelessness. Published 2024. Available at: https://www.cdc.gov/shigella/php/public-health-strategy/index.html. Accessed 25 November 2024.
6. Thompson CN, Duy PT, Baker S. The rising dominance of Shigella sonnei: an intercontinental shift in the etiology of bacillary dysentery. PLoS Negl Trop Dis **2015**; 9:e0003708.
7. Gu B, Cao Y, Pan S, et al. Comparison of the prevalence and changing resistance to nalidixic acid and ciprofloxacin of Shigella between Europe-America and Asia-Africa from 1998 to 2009. Int J Antimicrob Agents **2012**; 40:9–17.
8. Boumghar-Bourtchai L, Mariani-Kurkdjian P, Bingen E, et al. Macrolide-resistant Shigella sonnei. Emerg Infect Dis **2008**; 14:1297–9.
9. Ingle DJ, Easton M, Valcanis M, et al. Co-circulation of multidrug-resistant *Shigella* among men who have sex with men in Australia. Clin Infect Dis **2019**; 69:1535–44.
10. Gaudreau C, Barkati S, Leduc JM, Pilon PA, Favreau J, Bekal S. Shigella spp. with reduced azithromycin susceptibility, Quebec, Canada, 2012–2013. Emerg Infect Dis **2014**; 20:854–6.
11. Charles H, Prochazka M, Thorley K, et al. Outbreak of sexually transmitted, extensively drug-resistant Shigella sonnei in the UK, 2021–22: a descriptive epidemiological study. Lancet Infect Dis **2022**; 22:1503–10.
12. Lefèvre S, Njamkepo E, Feldman S, et al. Rapid emergence of extensively drug-resistant Shigella sonnei in France. Nat Commun **2023**; 14:462.
13. Tansarli GS, Long DR, Waalkes A, et al. Genomic reconstruction and directed interventions in a multidrug-resistant Shigellosis outbreak in Seattle, WA, USA: a genomic surveillance study. Lancet Infect Dis **2023**; 23:740–50.
14. Narayan S, Galanis E. Are enteric infections sexually transmitted in British Columbia? Canada Commun Dis Rep **2016**; 42:24–9.
15. Stefanovic A, Matic N, Ritchie G, et al. Multidrug-resistant Shigella sonnei bacteremia among persons experiencing homelessness, Vancouver, British Columbia, Canada. Emerg Infect Dis **2023**; 29:1668–71.
16. McCrickard LS, Crim SM, Kim S, Bowen A. Disparities in severe shigellosis among adults—Foodborne Diseases Active Surveillance Network, 2002–2014. BMC Public Health **2018**; 18:221.
17. Centers for Disease Control and Prevention. Increase in extensively drug-resistant shigellosis in the United States. Health Alert Network. CDCHAN −00486. Published 2023. Available at: https://emergency.cdc.gov/han/2023/han00486.asp. Accessed 9 October 2024.
18. Clinical and Laboratory Standards Institute. CLSI Supplement M100. 32nd ed. Wayne, PA: Clinical and Laboratory Standards Institute, **2022**:34–47.
19. Ritchie G, Chorlton SD, Matic N, et al. WGS of a cluster of MDR Shigella sonnei utilizing Oxford Nanopore R10.4.1 long-read sequencing. J Antimicrob Chemother **2023**; 79:55–60.
20. Li H. Minimap2: pairwise alignment for nucleotide sequences. Bioinformatics **2018**; 34:3094–100.
21. Robertson J, Nash JHE. MOB-suite: software tools for clustering, reconstruction and typing of plasmids from draft assemblies. Microb Genomics **2018**; 4:e000206.
22. Hawkey J, Paranagama K, Baker KS, et al. Global population structure and genotyping framework for genomic surveillance of the major dysentery pathogen, Shigella sonnei. Nat Commun **2021**; 12:2684.
23. Zeitouny S, Cheung DC, Bremner KE, et al. The impact of the early COVID-19 pandemic on healthcare system resource use and costs in two provinces in Canada: an interrupted time series analysis. PLoS One **2023**; 18:e0290646.
24. Public Health England. Sexually transmitted Shigella spp. in England: data up to quarter 2, 2022. Published 2022. Available at: https://www.gov.uk/government/publications/non-travel-associated-shigella-infections/sexually-transmitted-shigella-spp-in-england-data-up-to-quarter-2-2022. Accessed 1 March 2024.
25. Dougherty B, Forrest RO, Smith CR, et al. Impact of the COVID-19 pandemic on the reported incidence of select bacterial enteric diseases in Canada, 2020. Foodborne Pathog Dis **2023**; 20:81–9.
26. Homelessness Services Association of BC. 2023 Homeless count in Greater Vancouver. Greater Vancouver Reaching Home Community Entity. Published 2023. Available at: https://hsa-bc.ca/_Library/2023_HC/2023_Homeless_Count_for_Greater_Vancouver.pdf. Accessed 16 September 2024.
27. Hwang SW. Homelessness and health. CMAJ **2001**; 164:229–33.
28. Ohlsen EC, Angel K, Maroufi A, et al. Shigellosis outbreak among persons experiencing homelessness—San Diego County, California, October–December 2021. Epidemiol Infect **2023**; 152:e61. doi:10.1017/S0950268823001681.
29. Keddy KH, Sooka A, Crowther-Gibson P, et al. Systemic shigellosis in South Africa. Clin Infect Dis **2012**; 54:1448–54.
30. Mason LCE, Greig DR, Cowley LA, et al. The evolution and international spread of extensively drug resistant Shigella sonnei. Nat Commun **2023**; 14:1983.
31. National Collaborating Centre for Infectious Diseases. Shigellosis. Available at: https://nccid.ca/debrief/shigellosis/. Accessed 26 February 2024.
32. Physician and Nurse Practitioner Update. An update on Shigella: change in circulating strain from S. flexneri to S. sonnei. November 3. 2022. Available at: https://www.vch.ca/en/media/15861. Accessed 26 February 2024.
33. Vinh H, Nhu NTK, Nga TVT, et al. A changing picture of shigellosis in southern Vietnam: shifting species dominance, antimicrobial susceptibility and clinical presentation. BMC Infect Dis **2009**; 9:204.
34. Holt KE, Nga TVT, Thanh DP, et al. Tracking the establishment of local endemic populations of an emergent enteric pathogen. Proc Natl Acad Sci USA **2013**; 110: 17522–7.
35. Vancouver Coastal Health. Physicians' update: Shigella outbreak in the downtown Eastside. 2008.
36. Julian TR. Environmental transmission of diarrheal pathogens in low and middle income countries. Environ Sci Process Impacts **2016**; 18:944–55.
37. Hines JZ, Pinsent T, Rees K, et al. Notes from the field: shigellosis outbreak among men who have sex with men and homeless persons—Oregon, 2015–2016. MMWR Morb Mortal Wkly Rep **2016**; 65:812–3.
38. Russolillo A, Moniruzzaman A, Parpouchi M, Currie LB, Somers JM. A 10-year retrospective analysis of hospital admissions and length of stay among a cohort of homeless adults in Vancouver, Canada utilization, expenditure, economics and financing systems. BMC Health Serv Res **2016**; 16:60.
39. Khalil IA, Troeger C, Blacker BF, et al. Morbidity and mortality due to Shigella and enterotoxigenic Escherichia coli diarrhoea: the Global Burden of Disease Study 1990–2016. Lancet Infect Dis **2018**; 18:1229–40.