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A Waterborne Outbreak of *Shigella sonnei* with Resistance to Azithromycin and Third-Generation Cephalosporins in China in 2015

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ABSTRACT Here, we report for the first time a waterborne outbreak of *Shigella sonnei* in China in 2015. Eleven multidrug-resistant (MDR) *S. sonnei* isolates were recovered, showing high resistance to azithromycin and third-generation cephalosporins in particular, due to an *mph*(A)- and $bla_{CTX\text{-}M\text{-}14}$-harboring IncB/O/K/Z group transmissible plasmid of 104,285 kb in size. Our study highlights the potential prevalence of the MDR outbreak of *S. sonnei* in China and its further dissemination worldwide with the development of globalization.

KEYWORDS *Shigella sonnei*, multidrug resistance, outbreak, waterborne

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Shigellosis is one of the most important causes of diarrhea worldwide (1). Shigellosis represents a significant public health burden in developing countries, with more than 160 million cases and 1.1 million deaths annually. Moreover, shigellosis has become one cause of disease-related death in children, particularly in children under 5 years of age (1, 2). Third-generation cephalosporins and fluoroquinolones are an effective treatment for adults. Azithromycin, a macrolide, is recommended by the American Academy of Pediatrics as the first-line empirical antimicrobial treatment for multidrug-resistant ([MDR] resistant to three or more classes of antimicrobials) *Shigella* spp. (3, 4) among children and as a second-line treatment among adults. Here, we report a waterborne outbreak of shigellosis caused by MDR *Shigella sonnei* showing particularly high resistance to azithromycin and third-generation cephalosporins.

On 9 September 2015, an outbreak of shigellosis occurred in a kindergarten class in Guangxi Province, China. We launched an epidemiological field investigation. This study was approved by the ethics committee of the Institute of Disease Control and Prevention, Academy of Military Medical Sciences. Cases were defined as students with two or more of the following symptoms of acute gastroenteritis between 30 August and 28 September 2015: diarrhea (more than 3 times per day), stool abnormalities (watery, mucus, bloody purulent, or bloody stools), nausea and/or vomiting, abdominal pain, and fever (>38°C). The first case was traced to a 5-year-old boy who presented with symptoms, including severe diarrhea (more than 10 watery stools/day), fever, tenesmus, and vomiting on 6 September. From 6 to 11 September, a total of 38 cases were identified among 285 children in the kindergarten class (attack rate, 13.33%). On 9 September, the incidence rate reached a peak (see Fig. S1 in the supplemental material). The male/female ratio was 1.53:1, and the median age was 4 years (range, 2 to 6 years) (see Table S1). Cases were observed from all eight kindergarten classes (see

TABLE 1 MIC results of 23 antibiotics for 11 outbreak *S. sonnei* strains

Isolation no.	MICs (μg/ml)[a]																					
	CAZ	CRO	IMP	NIT	PIP	TET	FEP	CFP	CFZ	FOX	TOB	LVX	GEN	TIC	TIM	ATM	AMP	CHL	SXT	NOR	AMK	AZM	NAL
SH15sh098	<1	>32	<4	<32	>64	>8	<8	>32	>16	<8	>8	<2	>8	>64	64	2	>16	<8	>2	<4	<16	>256	>32
SH15sh099	<1	>32	<4	<32	>64	>8	<8	>32	>16	<8	>8	<2	>8	>64	64	2	>16	<8	>2	<4	<16	>256	>32
SH15sh100	<1	>32	<4	<32	>64	>8	<8	>32	>16	<8	>8	<2	>8	>64	<16	2	>16	<8	>2	<4	<16	>256	>32
SH15sh101	<1	>32	<4	<32	>64	>8	<8	>32	>16	<8	>8	<2	>8	>64	64	2	>16	<8	>2	<4	<16	>256	>32
SH15sh102	<1	>32	<4	<32	>64	>8	<8	>32	>16	<8	>8	<2	>8	>64	<16	2	>16	<8	>2	<4	<16	>256	>32
SH15sh103	<1	>32	<4	<32	>64	>8	<8	>32	>16	<8	>8	<2	>8	>64	64	2	>16	<8	>2	<4	<16	>256	>32
SH15sh104	<1	>32	<4	<32	>64	>8	<8	>32	>16	<8	>8	<2	>8	>64	<16	2	>16	<8	>2	<4	<16	>256	>32
SH15sh105	<1	>32	<4	<32	>64	>8	<8	>32	>16	<8	>8	<2	>8	>64	64	8	>16	<8	>2	<4	<16	>256	>32
SH15sh106	<1	>32	<4	<32	>64	>8	<8	>32	>16	<8	>8	<2	>8	>64	<16	2	>16	<8	>2	<4	<16	>256	>32
SH15sh107	<1	>32	<4	<32	>64	>8	<8	>32	>16	<8	>8	<2	>8	>64	<16	2	>16	<8	>2	<4	<16	>256	>32
SH15sh108	<1	>32	<4	<32	>64	>8	<8	>32	>16	<8	>8	<2	>8	>64	64	2	>16	<8	>2	<4	<16	>256	>32

[a]Cephalosporins: CAZ, ceftazidime; CRO, ceftriaxone; FEP, cefepime; CFP, cefoperazone; CFZ, cefazolin; and FOX, cefoxitin. Fluoroquinolones: LVX, levofloxacin; NOR, norfloxacin; and NAL, nalidixic acid. Penicillins: PIP, piperacillin; TIC, ticarcillin; AMP, ampicillin; TIM, ticarcillin-clavulanic acid; TOB, tobramycin; GEN, gentamicin; and AMK, amikacin. Phenicol: CHL, chloramphenicol. Sulfonamide: SXT, trimethoprim-sulfamethoxazole. Thienamycin: IPM, imipenem. Nitrofuran: NIT, nitrofurantoin. Tetracycline: TET, tetracycline. β-Lactam: ATM, aztreonam. Macrolide: AZM, azithromycin.

Fig. S2). All patients recovered, and no deaths were observed. Based on an environmental epidemiological investigation, we found that the canteen and water supply systems were in poor sanitary condition. After disinfection and other control measures, no new cases occurred.

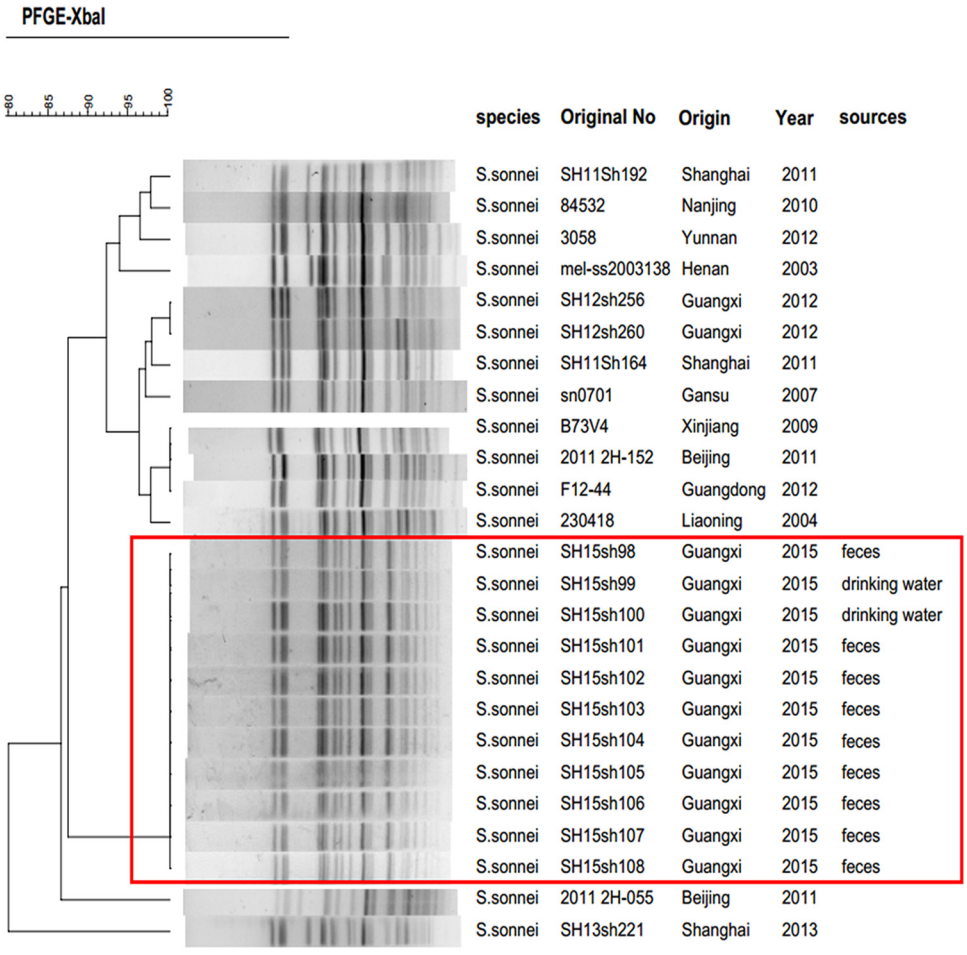
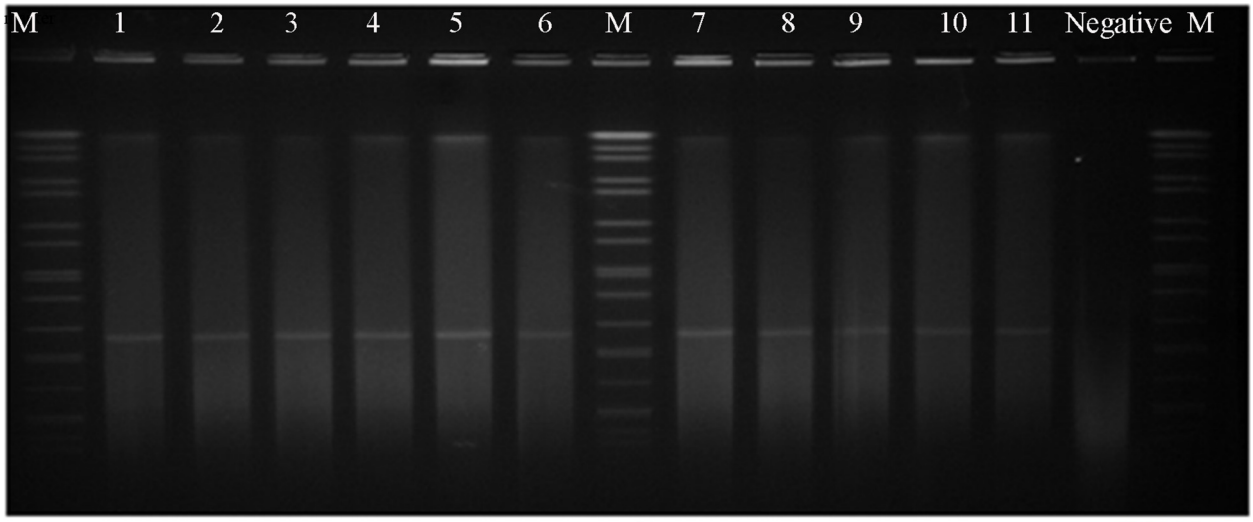


FIG 1 Pulsed-field gel electrophoresis (PFGE) patterns created by digestion with the enzyme XbaI. Dendrogram showing the level of genetic relatedness based on the unweighted pair-group method using average linkages and the Dice coefficient for *S. sonnei* strains. The species, original number, origin, year, and sources of the stains are shown.


M
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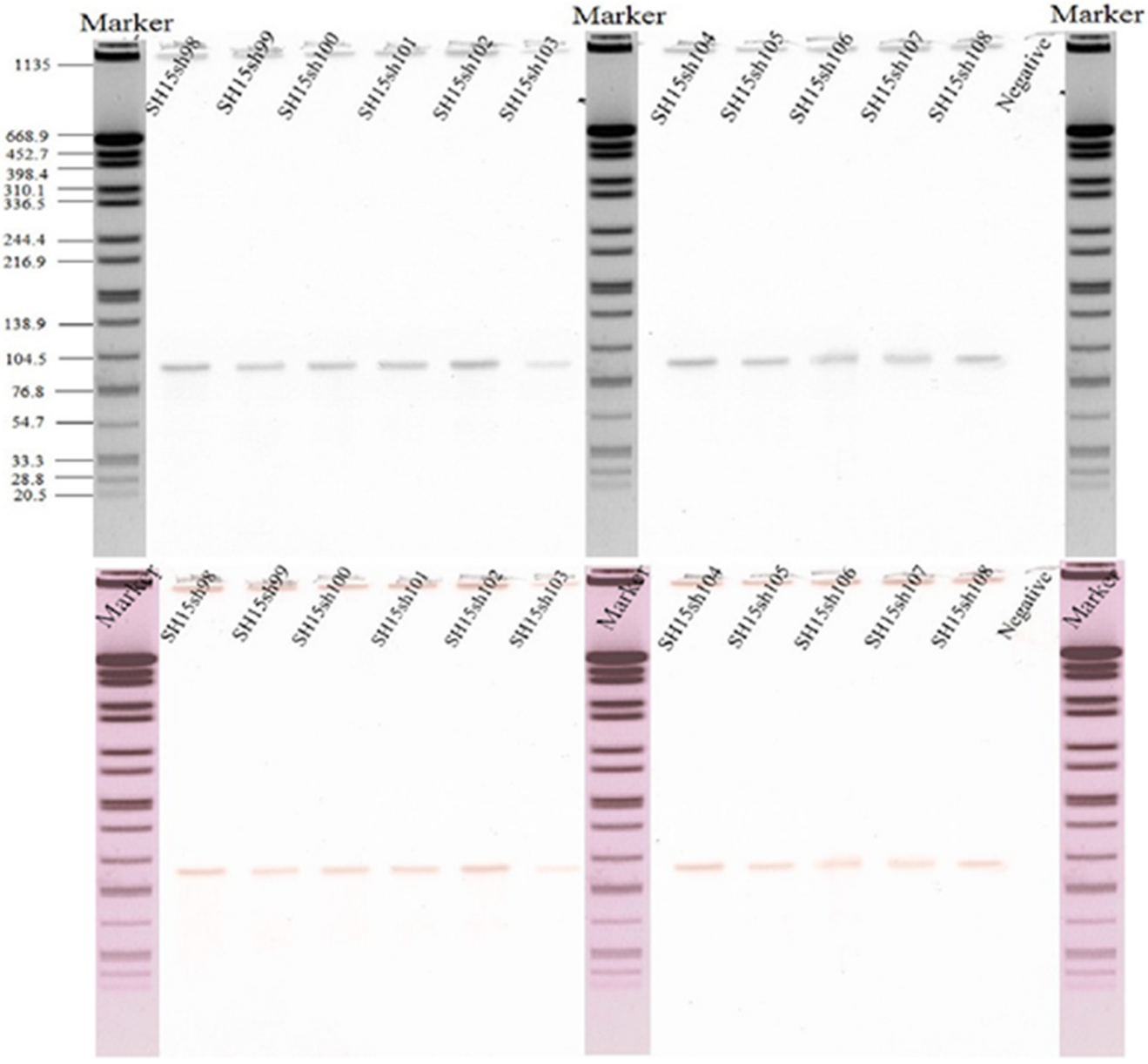
Marker
Marker
Marker
1135
668.9
452.7
398.4
310.1
336.5
244.4
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54.7
33.3
28.8
20.5
SH15sh98
SH15sh99
SH15sh100
SH15sh101
SH15sh102
SH15sh103
SH15sh104
SH15sh105
SH15sh106
SH15sh107
SH15sh108
Negative
Marker
Marker
Marker
SH15sh98
SH15sh99
SH15sh100
SH15sh101
SH15sh102
SH15sh103
SH15sh104
SH15sh105
SH15sh106
SH15sh107
SH15sh108
Negative
Marker

During the outbreak, we collected 35 fresh samples for laboratory identification of enteric pathogens, including 19 rectal swabs and 2 vomitus samples from 19 children with diarrhea, six drinking water samples, and eight suspicious residual foods from the kindergarten. All food and water samples were collected by sterile sampling according to the national food safety standards, such as GB 4789.1-2016, GB 4789.2-2016, GB 4789.3-2016, GB 4789.4-2016, GB 4789.6-2016, and GB 4789.10-2016, and standards for drinking water quality, GB 5749-2006. Suspected isolates recovered from the samples were identified using a commercial biochemical test kit (API 20E system; bioMérieux Vitek, France) according to the manufacturer's recommendations. The serotype of *Shigella* isolates was then determined using a serotyping kit (Denka Seiken, Tokyo, Japan) according to standard methods. We isolated 11 *S. sonnei* strains from the 35 samples, including nine in rectal swabs and two in drinking water. Antimicrobial susceptibility testing was performed by broth microdilution in 96-well microtiter plates (Sensititre, Trek Diagnostic Systems; Thermo Fisher Scientific, Inc., West Sussex, UK) according to the methods of the Clinical and Laboratory Standards Institute (5). The MICs of azithromycin and nalidixic acid were tested with concentrations of 4 to 256 μg/ml and 4 to 32 μg/ml, respectively. All 11 outbreak isolates displayed similar MDR profiles (Table 1). Moreover, high levels of resistance to azithromycin (MIC, $\geq$256 μg/ml) and nalidixic acid (MIC, $>$32 μg/ml) were observed. We used PCR to determine the presence of β-lactamase genes (6–8) and plasmid-mediated quinolone resistance (PMQR) determinants, such as *qnrA*, *qnrB*, *qnrD*, *qnrS*, and *aac*(*6′*)*-Ib-cr* (3, 9–11). The *mph*(A) gene (primers, *mph*A-F [5′-CGAAGACCTCCGAGTCCTGC-3′] and *mph*A-R [5′-CCGCCGATACCTCCCAACT-3′]) encoding macrolide 2-phosphotransferase (12) was also detected. Interestingly, all strains were negative for PMQR determinants but carried $bla_{\text{CTX-M-14}}$ and *mph*(A). An analysis of point mutations in quinolone resistance-determining regions (QRDRs) of *gyrA* and *parC* (13, 14) showed that all isolates contained the *gyr*A(Ser83Leu) point mutation. Pulsed-field gel electrophoresis (PFGE) (15) showed that the outbreak isolates were genetically indistinguishable and were subtyped into one PFGE type, different from that of isolates from other regions of China (Fig. 1). The horizontal-transfer capability of $bla_{\text{CTX-M-14}}$ and *mph*(A) was assessed by broth mating as reported previously (16) (see Table S2). Muller-Hinton agar (BD Biosciences, San Jose, CA, USA) plates containing 200 mg/liter sodium azide and 10 mg/liter cefotaxime were used as a selective medium for *Escherichia coli* J53 transconjugants. Putative transconjugants were confirmed by antimicrobial susceptibility testing and PCR detection of $bla_{\text{CTX-M-14}}$ and *mph*(A) as described above. Plasmid conjugation transfer revealed that $bla_{\text{CTX-M-14}}$ and *mph*(A) were successfully transferred into *Escherichia coli* J53. This result suggested that $bla_{\text{CTX-M-14}}$ and *mph*(A) may be located on one plasmid. Plasmid profiling and Southern blot analysis were performed as reported previously (16) but with differences in switching time from 2.16 s to 29.27 s, as well as with using specific $bla_{\text{CTX-M-14}}$ (probes, $bla_{\text{CTX-M-14}}$-F [5′-AGCCTGCCGATCTG GTTAA-3′] and $bla_{\text{CTX-M-14}}$-R [5′-CCGGTCGTATTGCCTTTG-3′]) and *mph*(A) (probes, *mph*A-F [5′-CGAAGACCTCCGAGTCCTGC-3′] and *mph*A-R [5′-CCGCCGATACCTCCCA ACT-3′]) digoxigenin-labeled probes (Roche). It showed that each of the isolates harbored only one plasmid, with a size of approximately 90 to 100 kb. Notably, the plasmids were positive for both $bla_{\text{CTX-M-14}}$ and *mph*(A) (Fig. 2), which is the primary cause of multidrug resistance in these *S. sonnei* strains. To identify the genes responsible for the multidrug resistance, the DNA of plasmids (pSH15sh99 and pSH15sh104) was extracted and subjected to high-throughput sequencing using Illumina MiSeq (San Diego, CA). The insertion sequences (ISs) were searched by using ISfinder (https://www-is.biotoul.fr/search.php), and the replicons genotypes were searched using PlasmidFinder (https://cge.cbs.dtu.dk/services/PlasmidFinder/). A

FIG 2 Identification of *mph*(A)- and $bla_{\text{CTX-M-14}}$-positive plasmids. (A) S1 nuclease plasmid pulsed-field electrophoresis profiles. (B) Southern blot hybridization for *mph*(A). Lanes: Marker, molecular size marker (strain H9812 digested with XbaI); lane 1 to lane 12 are the *S. sonnei* strains SH15sh98, SH15sh99, SH15sh100, SH15sh101, SH15sh102, SH15sh103, SH15sh104, SH15sh105, SH15sh106, SH15sh107, SH15sh108, and a negative-control strain, respectively. The molecular sizes on the left are in kilobases. (C) Southern blot hybridization for $bla_{\text{CTX-M-14}}$.

TABLE 2 Sequencing characteristics of the two plasmids of outbreak *S. sonnei* strains

Name	Size (bp)	No. of total reads	Inc[a]	No. of copies[b]	IS types
pSH15sh099	104,285	313,326	IncB/O/K/Z	878	IS*Ecp1*, IS*903B*, IS*6100*, IS*26*
pSH15sh104	104,285	366,962	IncB/O/K/Z	965	IS*Ecp1*, IS*903B*, IS*6100*, IS*26*

[a]Inc, plasmid incompatibility group, as determined by PlasmidFinder version 1.2 (10).
[b]Average copy number per cell, normalized to the chromosomal read coverage.

structure analysis showed that the two plasmids were identical and belonged to incompatibility group IncB/O/K/Z with a size of 104,285 bp (Table 2). *mph*(A) and $bla_{CTX\text{-}M\text{-}14}$ were located at 16,000 bp and 80,000 bp positions of the plasmid, respectively. In addition, IS*26* and IS*6100*-IS*26* transposon-like structures flanked *mph*(A) upstream and downstream. $bla_{CTX\text{-}M\text{-}14}$ was found together with an upstream IS*Ecp1* and a downstream IS*903B* (Fig. 3). *aacC3* was also found on the plasmid.

Based on the above epidemiological and laboratory investigations, we concluded that this diarrhea outbreak was probably attributed to contamination of the water supply by MDR *S. sonnei* with high resistance to azithromycin and third-generation cephalosporins. Because of the low infectious dose and environmental persistence, *S. sonnei* can be spread by water (17–20), food (21, 22), and direct person-to-person transmission (23, 24), which can trigger sporadic cases or family outbreaks and may cause more extensive secondary transmission from a common source (25, 26). Therefore, *S. sonnei* outbreaks in childcare centers and schools can typically spread to the community or to other cities.

Concerns regarding *S. sonnei* infections with apparent high-level resistance to azithromycin and third-generation cephalosporins prompted this investigation. Previous outbreaks of *S. sonnei* with resistance to third-generation cephalosporins (27–30) or azithromycin (31–33) alone occurred elsewhere. However, to the best of our knowledge, this is the first report on the outbreak of *S. sonnei* with resistance to both third-generation cephalosporins and azithromycin, attributed to an *mph*(A)- and $bla_{CTX\text{-}M\text{-}14}$-carrying IncB/O/K/Z group transmissible plasmid. In addition, the *gyr*A(Ser83Leu) single point mutation usually results in a high resistance to the narrow spectrum quinolone nalidixic acid and to reduced susceptibility to fluoroquinolones (13, 34). However, fluoroquinolone resistance is always due to multiple point mutations (such as *gry*A[Asp87Asn], *gry*A[Asp87Gly], *gry*A[His211Tyr], and *par*C[Ser80Ile]mutations) or to PMQR.

The *mph*(A) gene has been reported to be located on various plasmids, ranging from 10 to 208 kb (32, 35). Here, we found that the plasmid containing various mobile IS elements that carry multiple resistance determinants was 104,285 kb in size and could be successfully transferred into *E. coli* J53. The potentially widespread dissemination of

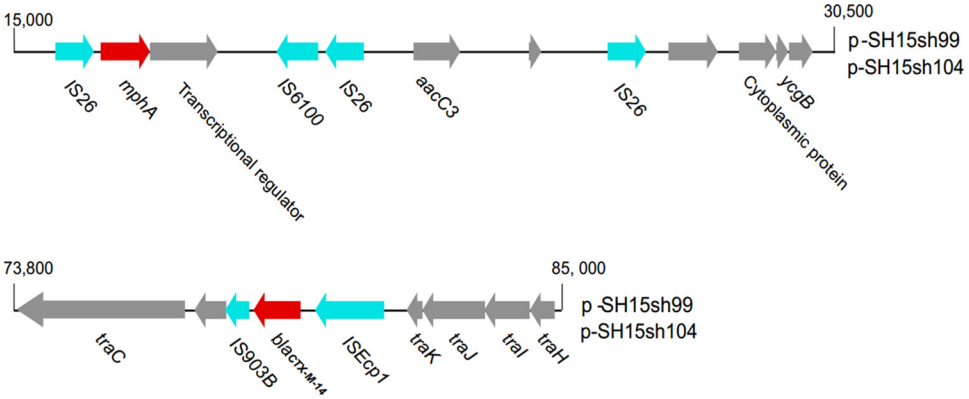

FIG 3 The mosaic region of pSH15sh99 and pSH15sh104 with the surroundings of *mph*(A) and $bla_{CTX\text{-}M\text{-}14}$. The resistance genes are denoted by arrows and colored based on gene function classification. *mph*(A) and $bla_{CTX\text{-}M\text{-}14}$ are colored in red, IS elements are colored in light blue, and others are in gray.

pathogens with plasmid-mediated multidrug resistance, which is expedited by increasing globalization, may represent a major threat to global health.

In conclusion, we described a waterborne outbreak caused by *S. sonnei* with resistance to both azithromycin and third-generation cephalosporin in China, which was attributable to the presence of an IncB/O/K/Z plasmid coharboring *mph*(A) and $bla_{CTX\text{-}M\text{-}14}$. The emergence and spread of MDR *S. sonnei* may necessitate improved strategies for the prevention and control of shigellosis. Moreover, our findings emphasize the importance of continuous surveillance of the prevalence of *Shigella* species and of changes in antibiotic resistance patterns on national and international scales. Whole-genome sequencing data are urgently needed to validate the detailed mechanisms of bacterial resistance, the true relatedness of strains, other resistance genes, and virulence factors.

Accession number(s). The annotated plasmid sequences have been deposited in the GenBank database under accession numbers KY471628 (pSH15sh99) and KY471629 (pSH15sh104).

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.00308-17.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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We have no conflicts of interest to declare.

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