Increasing clinical resistance rate of *Shigella sonnei* to cefotaxime in Jiangsu Province, China, between 2012 and 2015

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Background: The objective of this study is to evaluate the prevalence of *Shigella sonnei* (*S. sonnei*) and characterize the mechanism of its increasing resistance to cefotaxime, a third-generation cephalosporin agent between 2012 and 2015.

Methods: We investigated the drug resistance in 95 isolates of *S. sonnei* by K-B dilution method and isolates with the extended-spectrum beta-lactamases (ESBLs)-producing genes were detected by polymerase chain reaction (PCR) and sequencing.

Results: Over a 4-year period, the resistance rate of *S. sonnei* to cefotaxime increased from 31.6% to 64.3%, between 2012 and 2015. Molecular characterization of the ESBL genes, comprising 28 strains of *CTX-M-1* group: bla*CTX-M-55* (n=22), bla*CTX-M-3* (n=3) and bla*CTX-M-15* (n=3); 11 strains of *CTX-M-9* group: bla*CTX-M-14* (n=9) and bla*CTX-M-65* (n=2), and 36 strains with bla*TEM-1* gene. None of *S. sonnei* isolates carried bla*CTX-M-2* group and *SHV*-type.

Conclusions: The antimicrobial resistance rate of *S. sonnei* to cefotaxime significantly increased. Accordingly, regular surveillance of the cephalosporin-resistant *S. sonnei* should be emphasized. Moreover, exploration of the mechanism underlying the resistance of *S. sonnei* to cefotaxime contributes to the prophylaxis of further emergence of drug resistance.

Keywords: *Shigella sonnei* (*S. sonnei*); resistance; extended-spectrum beta-lactamases (ESBLs)

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Introduction

Shigellosis is the most common communicable disorder of the gastrointestinal tract, mainly spread by fecal-to-oral transmission (1). There is an estimated annual prevalence of 165 million cases of shigellosis worldwide, with 163.2 million in the developing world and the remaining 1.5 million in industrialized countries (2). So far shigellosis has been a peril to public health, particularly in developing countries. *Shigella*, comprising four serotypes: *S. flexneri*, *S. sonnei*, *S. boydii*, and *S. dysenteriae*, is one of the most dominant etiological agents of bacillary dysentery. Statistical analyses demonstrated that most *S. sonnei* strains were detected in high-income regions, with a percentage of 77% in industrialized countries and 15%

in developing countries, respectively (2-4). The proportional increase of *S. sonnei* infections in developing countries is becoming a global concern (5).

Cefotaxime, a third-generation cephalosporin, was initially approved for a variety of clinical bacterial pathogens such as *Shigella* (6) in EU and North America. Thereafter the widespread use of cefotaxime for *Shigella*, especially *S. sonnei*, inevitably resulted in bacterial resistance, as illustrated in the contrast between a null prevalence rate of resistant *S. sonnei* in Santiago, Chile and 88.9% in Iran (7,8), thus exacerbating the dilemma in antibiotic prescribing. Herein, our study investigated the drug-resistant patterns of *S. sonnei* to cefotaxime in the Jiangsu Province, China.

The emergence of cefotaxime-resistant *S. sonnei* was attributed to extended-spectrum beta-lactamases (ESBLs)-producing genes, encoded by plasmids which are responsible for the spread of drug resistance between bacteria, from resistant to susceptible strains via a series of procedures, i.e., conjugation, transformation, and transduction. Ever since the first description of ESBLs in Germany in 1983 (9), ESBLs-resistant genes in *Shigella* were identified in South Korea (10), Iran (8), Vietnam, etc. (11). Continuous emergence of ESBLs gene alerts us to the severity of expanded-spectrum cephalosporins.

In this study, we investigated and evaluated the resistance rate to cefotaxime as well as the resistance mechanism, spreading pathway of ESBL-producing clinical *S. sonnei* strains isolated between 2012 and 2015 in Jiangsu Province, China, which would provide the reference directing clinical prophylaxis and therapeutics.

Methods

Isolation and identification of Shigella strains

Clinical *Shigella* strains, collected from stools of patients from hospitals in major cities in Jiangsu Province, China. For stool testing, fresh feces with pus, blood and mucous should be collected and cultured, with each sample about 1–5 g. In the case of infants or incontinence, rectum swab was applied. Fecal samples were identified by API 20E test strips (bioMérieuxVitek, Marcy l'Étoile, France) and serotyped by slide agglutination with a commercial antiserum kit (Tianrun Bio-Pharmaceutical Co. Ltd., China).

Antimicrobial susceptibility test

Antimicrobial susceptibility tests to *S. sonnei* were performed by the Kirby-Bauer disk diffusion method with the following antimicrobials: cefalotin, cefotaxime, ampicillin, amoxicillin/clavulanic acid, gentamycin, nalidixic acid, norfloxacin, tetracycline, sulfamethoxazole according to the Clinical and Laboratory Standards Institute (CLSI) standards (12). The control strains were *E. coli* ATCC 25922 and *E. coli* ATCC 35218.

Detection of ESBLs genes

Genomic DNA of each *S. sonnei* isolate was extracted using an extraction kit (Biospin plasmid extraction, Bioflux), with genes bla*TEM*, bla*SHV*, bla*CTX-M-1*, bla*CTX-M-2*, bla*CTX-M-9*, and bla*OXA* detected using two pairs of primes as previously reported (13). Amplification of the antibiotic-resistant genes was performed at following temperature conditions: pre-denaturation at 95 ℃ for 5 min, followed by 30 cycles at 95 ℃ for 30 s, annealing for 30 s and at 72 ℃ for 1 min, with a final extension procedure at 72 ℃ for 5 min. Polymerase chain reaction (PCR) products were analyzed by electrophoresis with 2.0% agarose.

DNA sequence analysis

PCR products with positive results for electrophoresis were sequenced and compared with the sequences of GenBank database to further identify the subtypes of the β-lactamase genes. Similarity and alignment searches for the nucleotide sequences were analyzed using BLAST (http://www.ncbi.nlm.nih.gov/BLAST).

Results

Distribution of pathogen

A total of 95 strains of *S. sonnei* were isolated from hospitals in various regions in Jiangsu Province between 2012 and 2015. There were 41 strains of *S. sonnei* between 2012 and 2013, and 54 isolates during 2014 and 2015. Of the strains, 49 isolates were from male patients and 46 in females. In addition, 31 (32.6%) of patients with dysentery were aged 1–10, 26 (27.4%) aged 11–30, 24 (25.3%) aged 31–50 and 14 (14.7%) aged >50. With respect to cities in Jiangsu Province, Zhenjiang (24.2%, n=23) contributed to the largest proportion of *S. sonnei* collected, followed by Wuxi (13.7%, n=13), Changzhou (12.6%, n=12), Suzhou (9.5%, n=9), Nantong (9.5%, n=9), Nanjing (8.4%, n=8), Xuzhou (7.4%, n=7), and Yancheng (7.4%, n=7), with other cities

Table 1 Resistance of *S. sonnei* from 2012 to 2015

Antimicrobial agent	2012, n (%)	2013, n (%)	2014, n (%)	2015, n (%)	Average resistant rate, n (%)
Number	19	22	26	28	95
Ampicillin	13 (68.4)	17 (77.3)	20 (76.9)	21 (75.0)	71 (74.7)
Amoxicillin/clavulanic acid	0 (0.0)	1 (4.5)	4 (15.4)	0 (0.0)	5 (5.3)
Cefalotin	11 (57.9)	10 (45.5)	7 (26.9)	18 (64.3)	46 (48.4)
Cefotaxime	6 (31.6)	10 (45.5)	7 (26.9)	18 (64.3)	41 (43.2)
Gentamicin	7 (36.8)	11 (50.0)	13 (50.0)	3 (10.7)	34 (35.8)
Nalidixic acid	19 (100.0)	18 (81.8)	24 (92.3)	22 (78.6)	83 (87.4)
Norfloxacin	7 (36.8)	0 (0.0)	1 (3.8)	0 (0.0)	8 (8.4)
Tetracycline	16 (84.2)	15 (68.2)	18 (69.2)	20 (71.4)	69 (72.6)
Cotrimoxazole	17 (89.5)	16 (72.7)	22 (84.6)	21 (75.0)	76 (80.0)

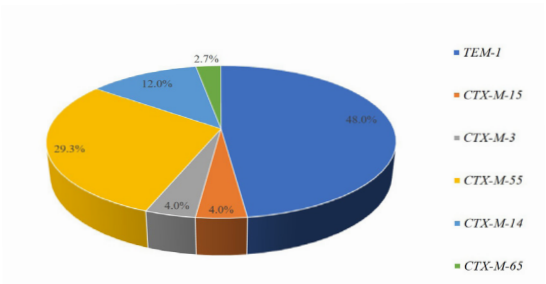

Figure 1 Genotypes of ESBLs in *S. sonnei* from 2012 to 2015. *S. sonnei*, *Shigella sonnei*; ESBLs, extended-spectrum beta-lactamases.

having less than 5 strains in toto.

Antimicrobial resistance of S. sonnei

Our research validated an increasing resistance of *S. sonnei* to cefotaxime, with its resistance rate of 31.6% in 2012, significantly increasing to 64.3% in 2015, two times over that of 2012. During the four years, there was a rising tendency of resistance of *S. sonnei* to ampicillin, nalidixic acid, tetracycline and cotrimoxazole, with the mean rates of resistance to each agent all exceeding 70%. A significant decline in resistance to gentamicin was observed, with 31.6% in 2012 and 10.7% in 2015. Moreover, *S. sonnei* isolates retained high susceptibility of 5.3% and 8.4% to amoxicillin/clavulanic acid and norfloxacin, respectively.

Cefotaxime-resistant *S. sonnei* exhibited a regional diversity, with Suzhou contributing to the highest resistance rate (77.8%), followed by Nanjing and Yancheng (75.0% and 57.1%, respectively) in contrast to the null drug resistance in Xuzhou, Lianyungang and Suqian (*Table 1*).

Molecular characterization

Of 95 clinical *S. sonnei* isolates, 66 strains were confirmed to have ESBLs-producing resistance genes by PCR amplification and DNA sequence analysis. 75 genotypes were detected in 66 *S. sonnei* isolates, with bla*TEM-1* gene in 36 (48.0%) strains, and bla*CTX-M-1* group in 28 (37.7%) strains, comprising 3 species of genotypes: bla*CTX-M-55* (n=22), bla*CTX-M-3* (n=3) and bla*CTX-M-15* (n=3). There were 11 (14.7%) strains harboring bla*CTX-M-9* group, encompassing bla*CTX-M-14* (n=9) and bla*CTX-M-65* (n=2). Both bla*CTX-M-2* and bla*SHV* was negative in the amplification of these *S. sonnei* strains (*Figure 1*).

In addition, bla*TEM-1* and bla*CTX-M-55* were highly detectable in *S. sonnei* between 2012 and 2015, and the bla*CTX-M-14* between 2013 and 2015, with the remainders less frequent (*Table 2*). In addition, with respect to cities in Jiangsu Province, bla*TEM-1* (10 cities) was highly detectable, and bla*CTX-M-55* (6 cities) and bla*CTX-M-14* (5 cities) were moderate, whereas the remnants of genotypes were only detected in one city each.

Discussion

In China, shigellosis remains a common infectious disease, due to *Shigella*, a gram-negative, non-lactose-fermenting, and non-motile bacillus of the family *Enterobacteriaceae*. In the human body, *Shigella* specifically invades and colonizes the

Table 2 Distribution of genotypes of ESBLs in 95 *S. sonnei* from 2012 to 2015

Gene type	2012 (n=19), n (%)	2013 (n=22), n (%)	2014 (n=26), n (%)	2015 (n=28), n (%)
TEM-1	7 (36.9)	12 (54.5)	12 (46.2)	5 (17.9)
CTX-M-15	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.7)
CTX-M-3	0 (0.0)	3 (13.6)	0 (0.0)	0 (0.0)
CTX-M-55	3 (15.8)	3 (13.6)	5 (19.2)	11 (39.3)
CTX-M-14	0 (0.0)	2 (9.1)	1 (3.8)	6 (21.4)
CTX-M-65	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)

colonic mucosa, resulting in colonic disruption (4). As per the structure of the lipopolysaccharide O-antigen, *Shigella* is categorized into four species: *S. flexneri*, *S. dysenteriae*, *S. boydii*, and *S. sonnei*, with the most prevalent serotype being *S. flexneri*, followed by *S. sonnei*. Since the first collection and characterization by Sonne *et al.*, *S. sonnei* was predominantly prevalent in developed countries, and global epidemiological studies showed a significant tendency in increasing prevalence, especially in developing countries. For instance, in China, the proportion of *S. sonnei* was 17.4% between 2003 and 2004, and reached 58.2% between 2011 and 2013, and was mainly distributed in the central and southeastern regions of China compared with *S. flexneri* (14). Therefore, our study was designed to investigate the prevalence and resistance pattern of *S. sonnei* in Jiangsu Province, China between 2012 and 2015 as well as the characterization of its molecular mechanisms, which might new light to the prophylaxis and clinical therapeutics for shigellosis.

A 10-year surveillance of antimicrobial susceptibility patterns among *Shigella* species isolated in China showed that *Shigella* strains resistant to cefotaxime increased from 7.87% in 2005 to 29.94% in 2014 (15). The resistance of *S. sonnei* to third-generation cephalosporin, particularly cefotaxime, significantly increased, has piqued our concern over resistance. Our data revealed a median resistance rate (43.2%) to cefotaxime in the *S. sonnei* from 2012 to 2015, well beyond that of *S. sonnei* (17.9%) monitored in Jiangsu Province between 2006 and 2011 (16). In addition, our findings also authenticated a rising tendency in resistance pattern, from 31.6% in 2012 to 64.3% in 2015, at a rate more than twice as that in 2012. Furthermore, in terms of provincial scales, the drug resistance rate of *S. sonnei* to cefotaxime was 30.8% in Zhejiang (17), 62.5% in Anhui (18), and 100% in Shanghai (19), far exceeding that in Jiangsu. Internationally, in Esfahān, Iran, *S. sonnei* showed a very high resistance pattern to cefotaxime, reaching 47.1% from 2010 to 2015 (20), with results similar to Jiangsu, China. In contrast, Nepal and Bangladesh, resistance rates to *S. sonnei* were relatively lower, accounting only 18.0% and 0%, respectively (21,22). Therefore, the continuous emergence of *S. sonnei* in Jiangsu Province and other developed provinces as well as the persistent elevation in drug resistance to cefotaxime might be attributed to the rapidity in economic development and the resultant modification of living styles and food diversity, wherefrom shigellosis cases inevitably occur and wherefore medication increased in these areas.

β-lactamase is the most indicated antimicrobial agent for *Shigella*, and plasmid-borne ESBLs, with the enzyme active against the expanded spectrum β-lactam antibiotics, consisting of four families, i.e., TEM, SHV, CTX-M and OXA and were produced by several members of the *Enterobacteriaceae* family. Our experimental data revealed that ESBL-encoding genes were mainly concentrated on the bla*TEM-1*, bla*CTX-M-1* and bla*CTX-M-9* group, whereas neither the bla*CTX-M-2* or bla*SHV*-type was detectable. Moreover, bla*TEM-1* (n=36, 48.0%) and bla*CTX-M-55* (n=22, 29.3%) accounted for the largest proportion of ESBLs genotypes, indicating that the two subtypes were predominant types in Jiangsu Province, whereas the main epidemic ESBL-encoding genes were bla*CTX-M-14* and bla*CTX-M-15* in Zhejiang and Shanghai (17,19), and bla*TEM-1* and bla*CTX-M-14* in Anhui (23). In countries like Iran (24,25), Lebanon (26) and Turkey (27), bla*CTX-M-15* has been the most prevalent ESBLs variant, thus posing a threat to human health (28).

bla*TEM-1*, described in 1965, was the first plasmid-mediated and the most commonly encountered β-lactamase in gram-negative bacteria. Amino acid substitutions of the TEM enzyme may possess the ability to hydrolyze cefotaxime, which may serve to explicate the production of TEM-1 β-lactamases in cefotaxime-resistant *S. sonnei* (29-31). Despite its slight proportion, TEM-1 β-lactamase

in *S. sonnei* has been reported in several countries or regions, e.g., South Korea (32), Lebanon, Spain (33), Turkey as well as Anhui, China. In our study, 36 strains of *S. sonnei* harbor bla*TEM-1*, accounting for 37.9%, the largest proportion. By contrast to its modest proportions in other countries as well as other regions in China, bla*TEM-1* detection rate increased at an alarming speed in Jiangsu, which requires vigilance against bla*TEM-1* and countermeasures to avoid its sustained increase.

bla*CTX-M-55*, which is similar to bla*CTX-M-15* and possesses only a single amino acid substitution, Ala-77-Val, was initially reported in ESBL-producing *E. coli* or *K. pneumonia* in Thailand (34). Subsequently, the bla*CTX-M-55* gene was also detected in other gram-negative bacteria, such as *Salmonella* and *Shigella* (35,36). CTX-M-55 ESBLs are categorized under CTX-M-type β-lactamase, one of the most common β-lactamase-resistant ESBLs in China (37), for which CTX-M-55-type β-lactamase has been proposed to have hydrolytic activity and an increasing catalytic efficiency to cefotaxime (38). Our results show that of the 22 strains of *S. sonnei* harboring the bla*CTX-M-55* gene, 21 strains presented resistance to cefotaxime, which was in conformance with the pre-conjecture mentioned afore. Not only bla*CTX-M-55* constituted a large proportion in detection rate, but also exhibited a wide range of regional distribution, with its emergence in six cities in Jiangsu, validating its rapidity in dissemination in Jiangsu Province and awaiting meticulous surveillance.

Similar to the genes bla*TEM-1* and bla*CTX-M-55*, *CTX-M-14*, is also a common ESBL subtype in Jiangsu Province, whereas other genotypes of ESBLs: bla*CTX-M-3*, bla*CTX-M-15*, and bla*CTX-M-65*, were detected in 3, 3 and 2 strains of *S. sonnei*, with each genotype detected in individual cities in this experiment. Despite their low detection rates, surveillance of these subtypes should be emphasized as well so as to prevent the dissemination of the resistance-producing genes between cities. In particular, two ESBL subtypes were coexistent in 10 strains of *S. sonnei*: 7 isolates were carriers of both bla*TEM-1* and bla*CTX-M-1* group genes, 2 isolates carried both bla*TEM-1* and bla*CTX-M-1* group genes, 1 strain harbored both bla*CTX-M-1* and bla*CTX-M-9* group genes, all of which affirmed the complexity and diversity of ESBLs-producing resistant genes of *S. sonnei* at the gene level.

Conclusions

Due to the increasing proportion of *S. sonnei*, in parallel with the rising resistance rate to cefotaxime, bla*TEM-1* and bla*CTX-M-55* of *S. sonnei* has become regional prevalent genotypes of ESBLs in Jiangsu Province. It is high time for each local healthcare and disease-control authority to implement surveillance of cefotaxime-resistant *S. sonnei* and *bla* genes and reduce the abuse of antibiotics with urgency, velocity and accuracy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Ethics Committee of Jiangsu Provincial Center for Disease Control and Prevention (IRB number: 2017018).

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