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Original Article

Trends in ESBLs and PABLs among enteric *Salmonella* isolates from children in Gwangju, Korea: 2014—2018

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Abstract *Objectives:* Non-typhoid *Salmonella* infection is a major agent of food-borne outbreaks as well as individual cases worldwide. However, few studies on drug-resistant *Salmonella* strains, especially those recovered from young children, are available. Therefore, we determined the prevalence and characteristics of cephalosporin-resistant *Salmonella* isolates in the south-west region of Korea over a five-year period.
Methods: Non-duplicate *Salmonella* clinical isolates were recovered from diarrhoeagenic patient specimens at 12 hospitals in Gwangju, Korea between January 2014 and December 2018. Antimicrobial susceptibility testing and molecular features of cephalosporin-resistant isolates were determined.
Results: A total of 652 *Salmonella* isolates were collected and 48 cefotaxime-resistant *Salmonella* isolates (7.4%), that belonged to nine *Salmonella* serovars, were identified. These were *S.* Enteritidis, *S.* Typhimurium, *S.* I 4,[5],12:i:-, *S.* Virchow, *S.* Agona, *S.* Bareilly, *S.* Infantis, *S.* Newport, and *S.* Schleissheim. The prevalence rate increased from 5.3% in 2014 to 10.3% in 2018. *S.* Virchow (44.4%) showed significantly high resistant rate compared to the other serovars. PGFE genotyping revealed high genetic homogeneities among each *Salmonella* serovars, suggesting clonal dissemination of cephalosporin-resistant strains.

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Conclusions: Progressive increases in carriage rates and the possibility of community outbreaks by cephalosporin-resistant *Salmonella* in young children may pose tangible public health threats.

Introduction

Salmonella is one of the major etiologic agents of water and foodborne diseases, which are known to cause gastroenteritis and bacteremia in both human and animals.[1,2] Around 2600 serovars have been identified based on the criteria regarding the somatic and flagella antigen. *Salmonella* is predominantly found in poultry, eggs and dairy products.[1,2] Other food sources that are involved in the transmission of *Salmonella* include fresh fruit and vegetables.[3] *Salmonella* strains are divided into Typhoid *Salmonella* and Non-typhoid *Salmonella* (NTS) according to the clinical features in human.[1] NTS infection is one of the major causes of foodborne outbreaks as well as individual case worldwide. For example, the incidences of *Salmonella* collected from 10 US sites were over 9000 cases in 2018 according to the Food-net report.[4] Likewise, *Salmonella* infection has been consistently reported in Korea. For instance, more than 13 outbreak cases (202 persons) were reported in 2015 and over 19 cases (3516 persons) in 2018.[5] In most cases, its origin and transmission route has remained unknown. Recommended antibiotics for severe acute gastroenteritis in Korea are azithromycin, ciprofloxacin, ceftriaxone, ampicillin, trimethoprim-sulfamethoxazole, doxycycline, and aminoglycoside. The use of antibiotics should consider the distribution of pathogens and its antibiotic sensitivity in local communities or traveler's area.[6] Yet, antibiotics are frequently prescribed for young children with severe acute gastroenteritis in spite of the regulation on antibiotic therapy before/without laboratory testing of pathogens.

Extended-spectrum cephalosporins are general therapeutic option for invasive salmonellosis in children.[7] However, the emergence and spread of antimicrobial-resistant bacteria carrying β-lactamases, such as extended spectrum β-lactamases (ESBLs) and plasmid-determined AmpC-type β-lactamases (PABLs), has been continuously reported.[8,9] Above all, the prevalence of CTX-M β-lactamases has increased since its first appearance in Korea. The CTX-M-14 and CTX-M-15 have been the dominant types in clinical isolates of Enterobacteriaceae since 2000.[10,11] However, these studies on drug-resistant bacteria have focused on tertiary hospital setting, adult patients and Enterobacteriaceae (e.g., *Escherichia coli* and *Klebsiella pneumoniae*) other than *Salmonella* isolates.[12,13] Young children are occasionally suspected to be major carriers for drug-resistant bacteria. Yet, few data on intestinal carriage of resistant organisms, especially those recovered from children with acute diarrhoea, are available.[14] Therefore, we characterized the prevalence and molecular features of ESBLs- and PABLs-producing *Salmonella* isolates from diarrhoetic children in 12 community-based hospitals in Gwangju, Korea, over a 5-year period.

Materials and methods

Bacterial isolates and antimicrobial susceptibility testing

Non-duplicate *Salmonella* isolates were recovered from patient specimens at 12 hospitals in Gwangju, Korea, between January 2014 and December 2018. These bacterial isolates were all collected from stool or rectal swab specimens of children with gastro-intestinal (GI) symptoms, such as diarrhoea, abdominal pain, vomiting, etc. The isolates were identified using the VITEK II system (bioMérieux, France) and serotyped by the Kauffmann—White scheme based on surface antigens. *E. coli* ATCC 25922 was used as a quality control organism for antimicrobial susceptibility tests. *Salmonella enterica* serotype Braenderup (H9812, ATCC BAA-664) was used as a standard universal size marker for PFGE. Bacterial isolates were assessed for antimicrobial susceptibility using VITEK II AST-N169 cards (bioMérieux, France) and were confirmed by a broth microdilution method using Sensititre ESB1F plates (Trek Diagnostic Systems, USA) for all isolates showing resistance to cefotaxime. Additionally, Sensititre KORN plates (Trek Diagnostic Systems, USA) were used to detect resistance to carbapenems. The antibiotic susceptibility testing results were interpreted in accordance with the CLSI guidelines.[15]

Genetic characterization

Multiplex PCR was used to detect *bla* genes of the TEM, SHV, CMY, OXA, DHA and CTX-M types for cefotaxime resistant *Salmonella* isolates. Further PCR and nucleotide sequencing analyses were performed to confirm the types of β-lactamases using the BLAST search tool. Previously described PCR conditions and specific primers were used.[16] Plasmid replicons were determined for the ESBLs- and PABLs-producing strains using PCR-based method described by Carattoli*et al.*[17]

Clonal relationships among *Salmonella* isolates were identified by PFGE analysis. The PFGE patterns of chromosomal DNA restriction fragments obtained with the *Xba*I enzyme (Roche Diagnostic GmbH, Germany) were generated according to the highly standardized PulseNet PFGE protocols of CDC (http://www.pulsenetinternational.org), using a CHEF-Mapper system (Bio-Rad Laboratories, USA). The restriction fragment patterns were analyzed with

BioNumerics software (Applied Maths, Belgium) using the Dice similarity coefficient and Unweighted Pair Group Mean Average (UPGMA) clustering method with a 1.5% position tolerance and 1.5% optimization. Isolates with ≥80% similarity were considered to be genetically related.

Statistical analysis

All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL), and the chi-squared test was applied to assess any statistically significant ($P < 0.05$) differences in this study.

Results

Distribution of ESBLs and PABLs-producing *Salmonella* isolates

A total of 652 *Salmonella* isolates were identified from clinical specimens of children with GI symptoms. Of these, 48 *Salmonella* (7.4% of 652 total *Salmonella*, gender; 30 male and 18 female patients, mean ± SD age; 4.1 ± 3.8 years) showed resistance to cefotaxime (n = 48) and cefoxitin (n = 8) (Fig. 1), that belonged to nine serovars of *S. enterica* subspecies *enterica*. These were *Salmonella* Enteritidis (n = 14/95), *S.* Typhimurium (n = 10/62), *S.* I 4,[5],12:i:- (n = 9/183), *S.* Virchow (n = 4/9), *S.* Agona (n = 3/22), *S.* Bareilly (n = 3/62), *S.* Infantis (n = 3/52), *S.* Newport (n = 1/7), and *S.* Schleissheim (n = 1/5) (Fig. 2). *Salmonella* Virchow (44.4%) showed significantly high resistant rate compared to the other *Salmonella* serovars (9.7%), P-value was <0.001, OR (95% CI values) were 8.07 (2.09–31.16), which refer to comparisons between *S.* Virchow and the other serovars. Some of the *Salmonella* isolates were also resistant to gentamicin (31.3%, n = 15/48), nalidixic acid (39.6%, n = 19/48) and tetracycline (81.3%, n = 39/48). Fortunately, all isolates showing cefotaxime -resistance we studied here were susceptible to amikacin, cefotetan, ciprofloxacin and imipenem (data not shown for cefotetan and amikacin). In sum, the prevalence of cefotaxime-resistant *Salmonella* increased from 5.3% in 2014 to 10.3% in 2018 as depicted in Fig. 3.

ESBLs, PABLs characterization, plasmid replicons and PFGE

All 48 isolates with ESBLs/PABLs phenotype were subjected to PCR to detect β-lactamase genes. PCR of β-lactamase genes detected members of the CTX-M-1 and CTX-M-9 clusters in 35 and 6 isolates, respectively. According to the subsequent sequence analysis, the most common type of CTX-M was $bla_{CTX\text{-}M\text{-}15}$ (n = 20). $bla_{CTX\text{-}M\text{-}1}$ (n = 9), $bla_{CTX\text{-}M\text{-}55}$ (n = 6) and $bla_{CTX\text{-}M\text{-}14}$ (n = 6) were also detected. TEM-1 (n = 9) and PABLs such as CMY-2 (n = 1) and DHA-1 (n = 5) were also identified (Table 1). CTX-M-2, CTX-M-25 group, SHV, OXA-1 and carbapenemase were not detected in this study. Six isolates with resistance to second-generation cephalosporins (cefoxitin) harbored DHA or CMY type β-lactamase and showed high-level resistance for cefotaxime (or ceftazidime) - clavulanic acid combinations (MIC = 4/4–16/4 and 32/4–64/4, respectively). The remaining two cefoxitin-resistant isolates were negative for PCR primers we selected in this study.

We determined the plasmid replicon types for the ESBLs- and PABLs-producing strains using PCR-based method. Seven types of replicons were detected, namely IncI1 (n = 17) in three out of nine *S.* I 4,[5],12:i:-, all three *S.* Infantis, all *S.* Typhimurium (n = 10) and in one *S.* Newport; IncFIIS (n = 15) in all 14 *S.* Enteritidis and one of all *S.*

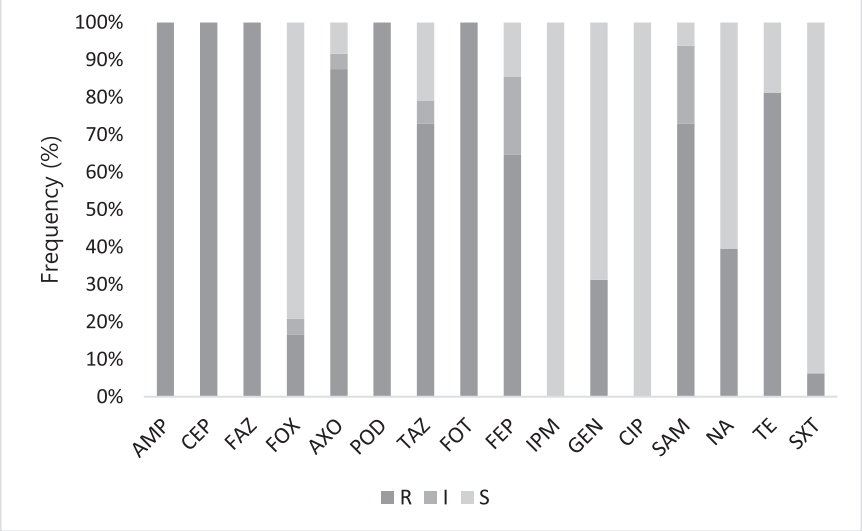


Figure 1. Results of antimicrobial susceptibilities for 48 cephalosporin-resistant *Salmonella* isolates from patients with GI symptoms in Gwangju, Korea, during 2014–18. AMP, ampicillin; CEP, cephalothin; FAZ,cefazolin; FOX, cefoxitin; AXO, ceftriaxone; POD, cefpodoxime; TAZ, ceftazidime; FOT, cefotaxime; FEP, cefepime; IPM, imipenem; GEN, gentamicin; CIP, Ciprofloxacin; SAM, Ampicillin/Sulbatam; NA, nalidixic acid; TE, tetracycline; SXT,Trimethoprim/sulfamethoxazole; R, resistant; I, intermediate-resistant; S, susceptible.

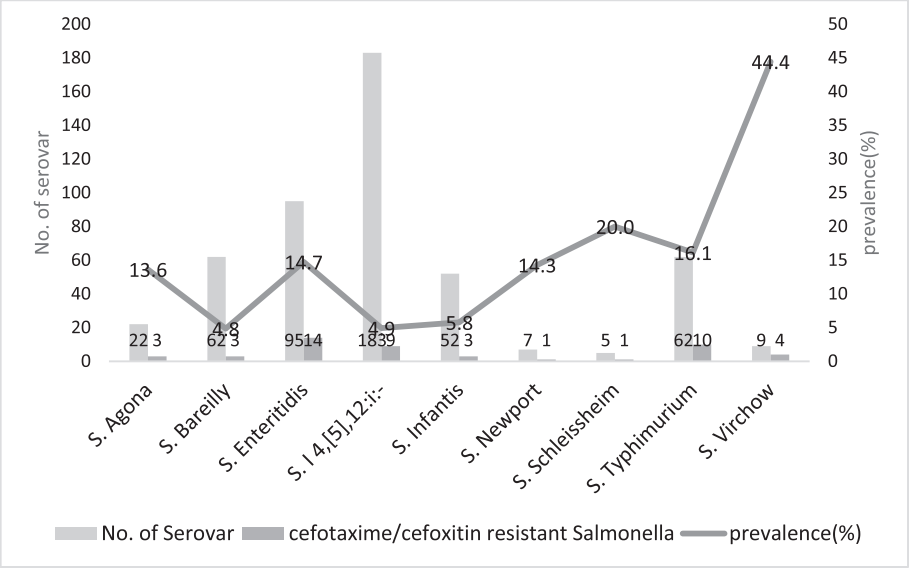


Figure 2. Prevalence of cephalosporin-resistant *Salmonella* isolates collected from patients with GI symptoms in Gwangju, Korea, during 2014—18.

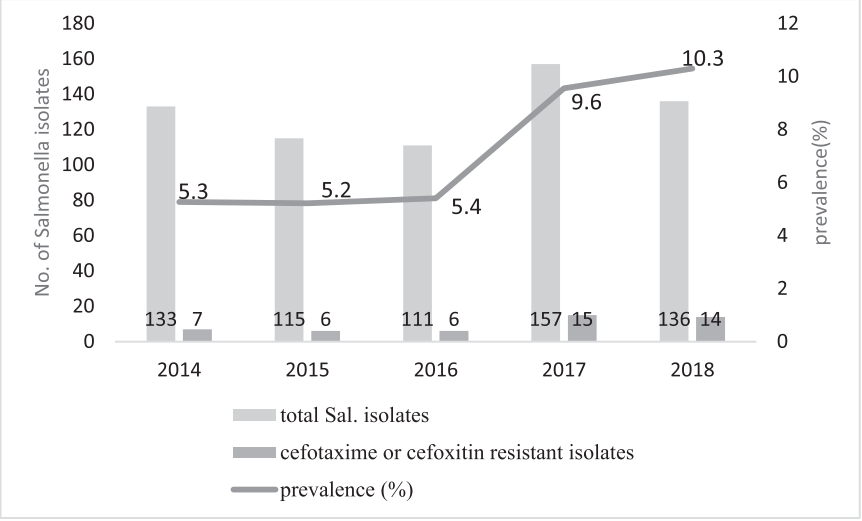


Figure 3. Prevalence of 9 cephalosporin-resistant *Salmonella* serovars collected from patients with GI symptoms in Gwangju, Korea, during 2014—18. These were S. Enteritidis, S. Typhimurium, S. I 4,[5],12:i:-, S. Virchow, S. Agona, S. Bareilly, S. Infantis, S. Newport, and S. Schleissheim. S. Virchow showed significantly high resistant rate compared to the other serovars. P-value was <0.001, OR (95% CI values) were 8.07 (2.09—31.16), which refer to comparisons between S. Virchow and the other serovars.

Typhimurium; IncFIB (n = 4) in four out of nine S. I 4,[5],12:i:-, IncA/C (n = 3) in all three S. Agona; IncHI1 (n = 3) in three of four S. Virchow; IncK/B (n = 1) in S. Schleissheim and IncN (n = 1) in one of nine S. I 4,[5],12:i:-. The remaining five *Salmonella* serovars; three S. Bareilly, one S. I 4,[5],12:i:- and one S. Virchow, were negative for replicon typing (Fig. 4).

PFGE genotyping was performed to determine whether the clonal dissemination of β-lactamase-producing *Salmonella* was responsible for the 48 isolates in this study. The results indicated that strains belonging to the same serovars were either identical or very closely related to each other, showing similar band patterns irrelevant to the isolation time, which demonstrates considerable genetic homogeneity, i.e.S. Enteritidis (n = 13/14) except one isolate with additional CMY-2 and S. Typhimurium (n = 9/10) except one isolate with $bla_{CTX\text{-}M\text{-}15}$ made one or two cluster with 80% pattern similarity, respectively. Three S. Agona, three S. Infantis, and four S. Virchow were also closely related with unique PFGE profiles among same serovars. Interestingly, six S. I 4,[5],12:i:- isolates (total N = 9) harboring various β-lactamases such as $bla_{CTX\text{-}M\text{-}14}$, $bla_{CTX\text{-}M\text{-}55}$ and TEM-1 were assigned to one group. Two S. Bareilly harboring DHA-1 were identical over 98% similarity, yet genetic distance of one with $bla_{CTX\text{-}M\text{-}14}$ was far from this cluster (Fig. 4).

Table 1 Occurrence of cephalosporin-resistant and ESBLs-, PABLs-, and carbapenemases-producing *Salmonella* during 2014—18.

Phenotype/genotype	Number by year/period						*P* [OR (95% CI)][a]
	2014	2015	2016	2017	2018	2014—18	
Cefotaxime-resistant	7	6	6	15	14	48	0.124 [0.484 (0.19—1.24)]
Prevalence (%)	5.3	5.2	5.4	9.6	10.3	7.4	—
TEM-1	1		1	3	4	9	—
ESBL producer							
CTX-M	5	6	5	14	10	40	0.199 [0.492]0.16—1.48)]
CTX-M-1		3		6		9	—
CTX-M-15	5	3	2	5	5	20	—
CTX-M-55				2	4	6	—
CTX-M-14			3	1	1	5	—
PABL producer	2	1	0	0	3	6	0.670 [0.677 (0.11—4.12)]
CMY-2		1				1	—
DHA-1	2				3	5	—
Total isolates	133	115	111	157	136	652	—

[a] *P* value were calculated by chi-squared test; p-value < 0.05 were considered statistically significant. OR and 95% CI values refer to comparisons between the years 2014 and 2018.

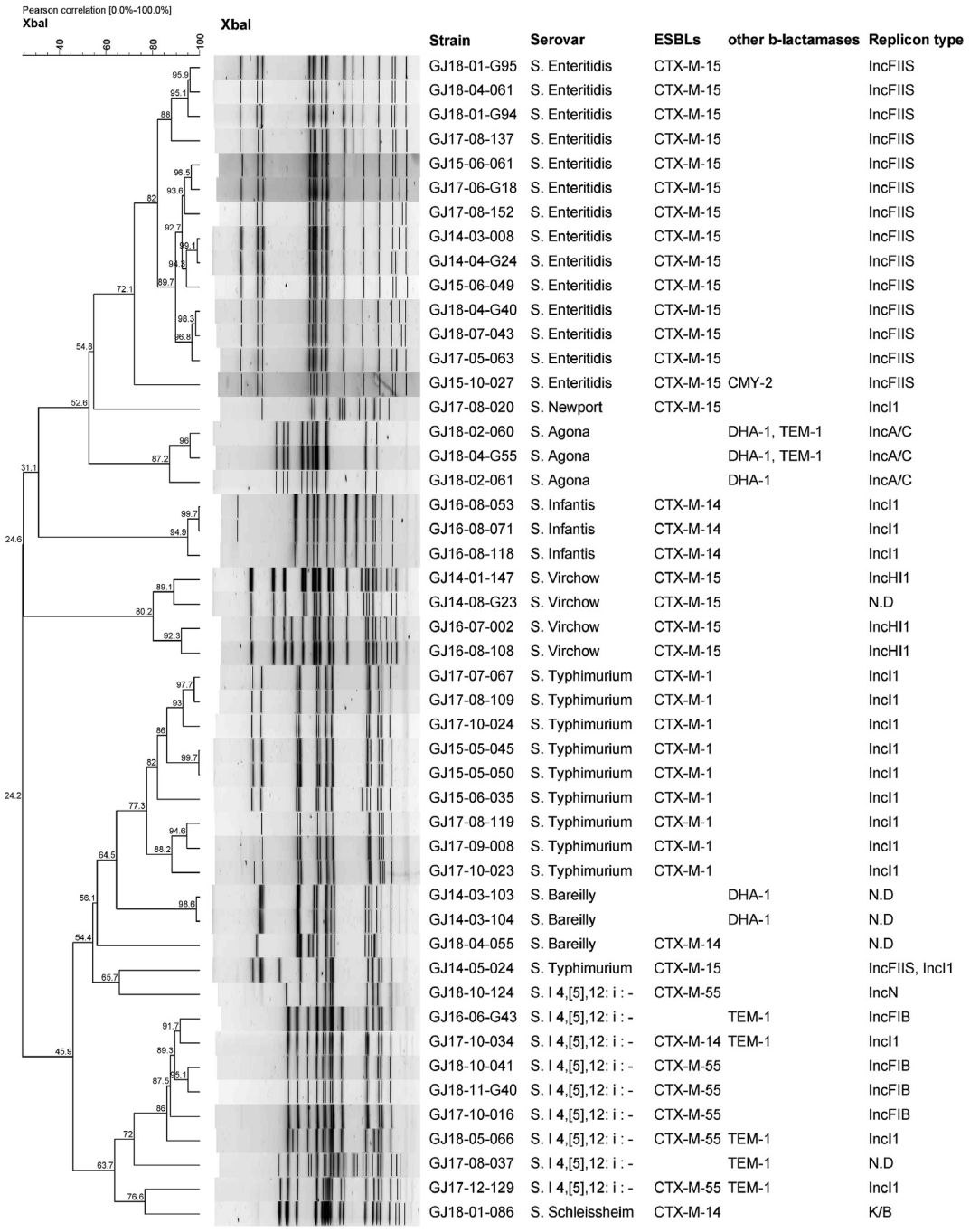
Discussion

A total of 652 *Salmonella* isolates were obtained from diarrhoeal patients during a period of 5 years. The phenotypic and genotypic characteristics of cefotaxime-resistant *Salmonella* strains were demonstrated. Overall, 48 isolates (7.4%) of 652 *Salmonella* showed resistance to cefotaxime or cefoxitin, suggesting the possible production of ESBLs and PABLs. ESFA/ECDC reported that 1.4% of 11,286 NTS from all over the European countries were resistant to cefotaxime, varying from 0.3% in Slovenia to 4.2% in Slovakia and only few isolates (0.2%) exhibited resistance to both ciprofloxacin and cefotaxime.[18] According to the ESFA/ECDC report, the proportions differed between regions, with 2.8% in Asia and 1.9% in Africa. A study from China reported that the resistance rates were 3.4%, 7.6% for ceftriaxone and ceftiofur, respectively.[19] In Ghana, 4.5% and 2.7% of *Salmonella* isolates were resisted to cefotaxime and cefoxitin, respectively.[20] Notably, our data in the 5-year period is alarming because the prevalence (7.4%) is the highest compared to those reports and the proportions have increased steadily as time went by, reaching 10.3% in 2018. There are a number of factors that might have influenced on our results. For instance, the rate of antibiotics consumption in Korea was 31.7 defined daily doses per 1000 inhabitants/day (DID), while the rate of average use in the Organisation for Economic Co-operation and Development (OECD) countries was 20.5 DID. The study revealed the prescription rate of extended-spectrum cephalosporins showed an increasing trend in Korea. The antibiotic resistance rates for third-generation cephalosporins for *E. coli* and *K. pneumoniae* was also at the higher end, compared to OECD countries.[21] Regarding these factors, the fact that few studies on drug-resistant Salmonella strains from young children are available highlights the scientific merit of our research.

Salmonella Typhimurium and monophasic *S.* Typhimurium (*S.* I 4, [5], 12:i:-) have emerged as important clinically problematic serovars as 1) *Salmonella* itself have extremely high survival rates in environment by forming biofilm,[22] 2) they have presented multiple antimicrobial resistances[18] partly due to phage type 104 epidemic clone worldwide, which are resistant to ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline,[20] and 3) they were the most common serovars associated with food or animal-borne outbreaks.[4,23] In the present study, *S.* I 4, [5], 12:i:- was the predominant serovar accounting for 28.1% (n = 183/652), while *S.* Typhimurium (9.5%) ranked third following *S.* Enteritidis. It is noteworthy that 16.1% of *S.* Typhimurium we studied possessed cephalosporin resistance, which is in accordance with ESFA data.[18] Here, *S.* Typhimurium have possessed $bla_{\text{CTX-M-1}}$ (n = 9/10) and-$bla_{\text{CTX-M-15}}$ (n = 1/10). On the other hand, $bla_{\text{TEM-1}}$(n = 6), $bla_{\text{CTX-M-55}}$ (n = 6), and $bla_{\text{CTX-M-14}}$ (n = 1) were detected from *S.* I 4, [5], 12:i:-. Two isolates expressing cefoxitin resistance were negative for ESBLs and PABLs encoding gene PCR we targeted in this study; this may be due to the other sort of PABLs such as FOX, ACC, MOX, LAT, etc., which were not screened here.

All 14 *S.* Enteritidis isolates harboring $bla_{\text{CTX-M-15}}$ were resistant to nalidixic acid (NA). As our results pointed out the extremely high resistance to NA by these bacteria, a study showed high nalidixic acid resistance (81.0%) pattern of *S.* Enteritidis collected from Jeollanam-do province during 2004—14, where geographically surrounding Gwangju, Korea.[24] In addition, our results pointed out that 44.4% of *S.* Virchow showed third-generation cephalosporin resistance. In accordance with our data, the Korea National Institute of Health (KNIH) reported that clonally connected CTX-M-15-producing *S.* Virchow has dramatically increased since the first isolation in 2011, of which the rate has marked 82.3% in 2014 in South Korea.[25] All four *S.* Virchow we studied also harbored $bla_{\text{CTX-M-15}}$.

Among eight *Salmonella* isolates resistant to cefoxitin were *S.* Agona (n = 3/3), *S.* Bareilly (n = 2/3) with DHA,



Strain	Serovar	ESBLs	other b-lactamases	Replicon type
GJ18-01-G95	S. Enteritidis	CTX-M-15		IncFIIS
GJ18-04-061	S. Enteritidis	CTX-M-15		IncFIIS
GJ18-01-G94	S. Enteritidis	CTX-M-15		IncFIIS
GJ17-08-137	S. Enteritidis	CTX-M-15		IncFIIS
GJ15-06-061	S. Enteritidis	CTX-M-15		IncFIIS
GJ17-06-G18	S. Enteritidis	CTX-M-15		IncFIIS
GJ17-08-152	S. Enteritidis	CTX-M-15		IncFIIS
GJ14-03-008	S. Enteritidis	CTX-M-15		IncFIIS
GJ14-04-G24	S. Enteritidis	CTX-M-15		IncFIIS
GJ15-06-049	S. Enteritidis	CTX-M-15		IncFIIS
GJ18-04-G40	S. Enteritidis	CTX-M-15		IncFIIS
GJ18-07-043	S. Enteritidis	CTX-M-15		IncFIIS
GJ17-05-063	S. Enteritidis	CTX-M-15		IncFIIS
GJ15-10-027	S. Enteritidis	CTX-M-15	CMY-2	IncFIIS
GJ17-08-020	S. Newport	CTX-M-15		IncI1
GJ18-02-060	S. Agona		DHA-1, TEM-1	IncA/C
GJ18-04-G55	S. Agona		DHA-1, TEM-1	IncA/C
GJ18-02-061	S. Agona		DHA-1	IncA/C
GJ16-08-053	S. Infantis	CTX-M-14		IncI1
GJ16-08-071	S. Infantis	CTX-M-14		IncI1
GJ16-08-118	S. Infantis	CTX-M-14		IncI1
GJ14-01-147	S. Virchow	CTX-M-15		IncHI1
GJ14-08-G23	S. Virchow	CTX-M-15		N.D
GJ16-07-002	S. Virchow	CTX-M-15		IncHI1
GJ16-08-108	S. Virchow	CTX-M-15		IncHI1
GJ17-07-067	S. Typhimurium	CTX-M-1		IncI1
GJ17-08-109	S. Typhimurium	CTX-M-1		IncI1
GJ17-10-024	S. Typhimurium	CTX-M-1		IncI1
GJ15-05-045	S. Typhimurium	CTX-M-1		IncI1
GJ15-05-050	S. Typhimurium	CTX-M-1		IncI1
GJ15-06-035	S. Typhimurium	CTX-M-1		IncI1
GJ17-08-119	S. Typhimurium	CTX-M-1		IncI1
GJ17-09-008	S. Typhimurium	CTX-M-1		IncI1
GJ17-10-023	S. Typhimurium	CTX-M-1		IncI1
GJ14-03-103	S. Bareilly		DHA-1	N.D
GJ14-03-104	S. Bareilly		DHA-1	N.D
GJ18-04-055	S. Bareilly	CTX-M-14		N.D
GJ14-05-024	S. Typhimurium	CTX-M-15		IncFIIS, IncI1
GJ18-10-124	S. I 4,[5],12: i : -	CTX-M-55		IncN
GJ16-06-G43	S. I 4,[5],12: i : -		TEM-1	IncFIB
GJ17-10-034	S. I 4,[5],12: i : -	CTX-M-14	TEM-1	IncI1
GJ18-10-041	S. I 4,[5],12: i : -	CTX-M-55		IncFIB
GJ18-11-G40	S. I 4,[5],12: i : -	CTX-M-55		IncFIB
GJ17-10-016	S. I 4,[5],12: i : -	CTX-M-55		IncFIB
GJ18-05-066	S. I 4,[5],12: i : -	CTX-M-55	TEM-1	IncI1
GJ17-08-037	S. I 4,[5],12: i : -		TEM-1	N.D
GJ17-12-129	S. I 4,[5],12: i : -	CTX-M-55	TEM-1	IncI1
GJ18-01-086	S. Schleissheim	CTX-M-14		K/B

Figure 4. Dendrogram showing the cluster analysis of *xba*I PFGE patterns of 48 β-lactamase-producing *Salmonella* isolates from patients with GI symptoms in Gwangju, Korea, during 2014—18. The restriction patterns were analyzed by using the Dice similarity coefficient and UPGMA with a 1.5% position tolerance and 1.5% optimization.

and one *S*. Enteritidis possessing both CMY-2 and CTX-M-15. The rest two *S*. I 4, [5], 12:i:-, which resistant to cefoxitin, were found to have no related genes we studied here. These eight isolates also showed high MICs for cefotaxime and ceftazidime - clavulanic acid combinations, which is in accordance with previous study revealing that PABLs are not affected by β-lactamase inhibitors.[26]

Previous molecular epidemiological studies on plasmid and CTX-M genes have revealed that the IncFIA, IncFIB and IncFII are frequently associated with $bla_{CTX\text{-}M\text{-}15}$ while IncF, IncK and IncI1 are related to $bla_{CTX\text{-}M\text{-}14}$ gene, $bla_{CTX\text{-}M\text{-}1}$ gene to IncN, and IncI1.[27] In the present study, IncI1 plasmid were detected in CTX-M-1-harboring *S*. Typhimurium; FIIS in *S*. Entertidis with CTX-M-15; IncI1 from CTX-M-14-possessing isolates. Note that three *S*. Agona with DHA-1 were positive for IncA/C type (Fig. 4).

Interestingly, the molecular profiles suggested that the transmission of resistance determinants among *Salmonella* isolates we studied here could be the results of clonal expansion, considering PFGE genotyping showing great

homogeneity among serovars and same β-lactamases among same serovars, rather than horizontally transferable genetic elements. However, we should pay heed to jumping conclusion bias as the Korea National Institute of Health (KNIH) reported that genetically close *S.* Virchow were harboring transferable CTX-M-15,[24] which poses a significant public health threat in view of the contribution of horizontal gene transfer to the spread of drug-resistant determinants between bacteria in soil, water environments, animal, and human.[28] Moreover, *S.* I 4, [5], 12:i:- harboring different sort of β-lactamases yielded PFGE patterns that fell into one cluster. This provides a reasonable evidence for the horizontal transmission of β-lactamase among *S.* I 4, [5], 12:i:-.

Although there were evidences of clonal dissemination in our study, given our previous study on dissemination of cephalosporin-resistant *E. coli*, which demonstrated horizontal gene transfer rather than clonal expansion,[29] the fact that transferability of resistant genes was not investigated is a major limitation. Also, we did not evaluate the underlying causes, such as additional clinical signs, drug history and travel history, for the yearly increase of cephalosporin-resistant *Salmonella*. So, further studies are required to better define the prevalence and dissemination mechanisms of these resistant organisms. Nonetheless, our data provide meaningful information on changes in the pattern of resistant genes and clinical evidence of clonal expansion of cephalosporin-resistant *Salmonella* species. The latter strongly differs with conventional dissemination mechanisms of resistant determinants among *Enterobacteriace*.

In conclusion, we have conducted a comprehensive study on dissemination of ESBLs- and PABLs-producing *Salmonella* strains isolated from patients with GI symptoms in Gwangju, Korea. Among 652 isolates collected during 2014—18, 48 were resistant to cefotaxime and/or cefoxitin. Our findings suggest that the cephalosporin-resistant *Salmonella* are genetically very close and harbor a sort of β-lactamases among same serovars. Though there are additional risk factors that need to be considered, such as foods, farm animals, and environment, progressive increase in prevalence and the possibility of community outbreaks by clonally disseminated cephalosporin-resistant *Salmonella* may pose a major health problem.

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Declaration of competing interest

All authors have no conflict of interest.

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Appendix A. Supplementary data

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