JOURNAL OF CLINICAL MICROBIOLOGY, July 2011, p. 2671–2675 Vol. 49, No. 7
0095-1137/11/$12.00 doi:10.1128/JCM.00754-11

Emergence of Extended-Spectrum β-Lactamase (CTX-M-15 and CTX-M-14)-Producing Nontyphoid *Salmonella* with Reduced Susceptibility to Ciprofloxacin among Food Animals and Humans in Korea▽

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Received 15 April 2011/Accepted 13 May 2011

Twenty of 1,279 nontyphoid *Salmonella* strains isolated from food animals and humans produced CTX-M-type extended-spectrum β-lactamase. All expressed CTX-M-15, except two which coexpressed CTX-M-14 and TEM-1. Insertion sequence IS*Ecp1* was identified upstream of $bla_{\text{CTX-M}}$ genes. The $bla_{\text{CTX-M-15}}$ and $bla_{\text{CTX-M-14}}$ genes were disseminated by large conjugative IncFIIs and IncI1-Iγ plasmids, respectively.

Extended-spectrum cephalosporin (ESC) and fluoroquinolone are the drugs of choice for invasive *Salmonella* infections (14). Unfortunately, resistance to both drug classes has emerged among the *Salmonella* species worldwide, causing a serious problem in both human and veterinary medicine (2, 4). Similarly, reduced susceptibility to fluoroquinolones in *Salmonella* has been associated with clinical treatment failure, causing significant therapeutic problems in the clinical setting (1). During the past couple of decades, CTX-M-type extended-spectrum β-lactamases (ESBLs) or cefotaximases have been increasingly reported in many countries of the world (23). Currently, the CTX-M β-lactamase family consists of at least 92 different CTX-M β-lactamases that are clustered into five groups based on their amino acid identities, including CTX-M-1, -2, -8, -9, and -25 groups. ESBL production in *Salmonella* was first identified in 1988 (13). Since then, the number of studies reporting ESBL-mediated resistance in nontyphoid *Salmonella* (NTS) has been increasing (2, 4, 23), including from the Republic of Korea (20, 32), which has become a cause of concern. Thus, in the present study the phenotypic and genotypic characteristics of cefotaxime-resistant NTS strains isolated from food animals and humans in South Korea were investigated.

A total of 1,279 NTS isolates were obtained from food animals ($n = 692$) and human patients between January 1995 and December 2009. Animal isolates of NTS were recovered from various samples of food animals collected from all the nine provinces of South Korea and were isolated from pigs ($n = 455$), pork ($n = 5$), poultry ($n = 54$), chicken meat ($n = 171$), and cattle ($n = 7$). The human NTS strains were received from the Gwangju Research Institute of Public Health and Environment, South Korea. Identification and serotyping of *Salmonella* isolates were done as described previously (22). Overall, 20 NTS strains were resistant to cefotaxime. Except one isolate of *Salmonella enterica* serovar Essen, all of them belonged to serotype Enteritidis. Screening of these isolates by double disk synergy test (9) demonstrated production of ESBL, which was subsequently confirmed by the Epsilometer test (Etest) (AB Biodisk, Sweden). The geographical, temporal, and serotype distributions and origins of these 20 isolates are shown in Table 1. The MICs for selected antimicrobial agents were determined using the Etest strips according to Clinical and Laboratory Standards Institute (CLSI) guidelines (9). All of them were resistant to ampicillin (MIC, >256 mg/liter) and cefotaxime (MIC, >16 mg/liter). The presence of clavulanic acid reduced the MICs of cefotaxime for all the isolates by ≥128-fold (Table 2).

The PCR amplification and sequencing of entire bla_{TEM} and bla_{SHV} genes were done as described previously (26). The presence of the $bla_{\text{CTX-M}}$ gene was screened for using CTX-M universal primer sets as described previously (3). All 20 cefotaxime-resistant NTS strains carried $bla_{\text{CTX-M}}$ genes. These were confirmed by a second PCR using group-specific primers for CTX-M-1, CTX-M-2, CTX-M-8, and CTX-M-9 groups as described previously (5). Finally, combinations of CTX-M group-specific and ISECP1-U1 primers (27) were employed to amplify and sequence the complete $bla_{\text{CTX-M}}$ genes. Among them, 18 strains harbored the $bla_{\text{CTX-M-15}}$ gene only whereas two remaining strains isolated from human patients coharbored $bla_{\text{CTX-M-14}}$ and $bla_{\text{TEM-1}}$ genes. Since $bla_{\text{CTX-M-15}}$ was first identified in *Enterobacteriaceae* in 2003 in South Korea (18), $bla_{\text{CTX-M}}$ genes have been increasingly reported in *Enterobacteriaceae* either singly or in combination with other resistance determinants (21, 29). However, until recently, reports on CTX-M-type β-lactamase in *Salmonella* were limited to human isolates, particularly those causing salmonellosis in pediatric patients (19, 32). Thus, to our knowledge, cefotaximase has never been reported in *Salmonella* strains of animal origin from South Korea.

Additionally, all the 20 NTS strains exhibited high-level re-

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▽ Published ahead of print on 25 May 2011.

TABLE 1. Phenotypic and molecular characteristics of nontyphoid *Salmonella* strains isolated from food animals and humans carrying bla_{CTX-M} genes[a]

Strain	Serotype	Origin	Farm	Province	Isolation date (yr.mo.day)	bla_{CTX-M} gene	Other *bla* gene	Self-transfer[b]	Phage type	PFGE profile	
										XbaI	AvrII
09-V06-15	*S.* Enteritidis	Chicken meat	C1	Jeonbuk	2009.01.28	CTX-M-15	−	Yes	PT21	X4	A3
09-V06-16	*S.* Enteritidis	Chicken meat	C1	Jeonbuk	2009.01.28	CTX-M-15	−	Yes	PT21	X5	A1
09-V06-20	*S.* Enteritidis	Diseased chicken	C2	Jeonbuk	2009.03.12	CTX-M-15	−	Yes	RDNC	X4	A3
09-V06-21	*S.* Enteritidis	Diseased chicken	C2	Jeonbuk	2009.03.12	CTX-M-15	−	Yes	PT21	X4	A3
09-V06-22	*S.* Enteritidis	Diseased chicken	C2	Jeonbuk	2009.03.12	CTX-M-15	−	Yes	RDNC	X3	A2
09-V06-23	*S.* Enteritidis	Diseased chicken	C2	Jeonbuk	2009.03.12	CTX-M-15	−	Yes	RDNC	X4	A1
09-V06-25	*S.* Essen	Diseased chicken	C3	Jeonbuk	2009.03.27	CTX-M-15	−	No	ND	ND	ND
09-V06-28	*S.* Enteritidis	Diseased chicken	C4	Jeonbuk	2009.04.22	CTX-M-15	−	Yes	RDNC	X2	A1
09-V05-54	*S.* Enteritidis	Chicken meat	C6	Chungnam	2009.04.13	CTX-M-15	−	No	PT21	X6	A4
09-V05-56	*S.* Enteritidis	Chicken feces	C6	Chungnam	2009.04.13	CTX-M-15	−	No	PT21	X6	A4
09-V05-57	*S.* Enteritidis	Chicken feces	C6	Chungnam	2009.04.13	CTX-M-15	−	No	PT1	X6	A4
09-V05-58	*S.* Enteritidis	Chicken feces	C7	Chungnam	2009.05.18	CTX-M-15	−	Yes	PT21	X1	A3
09-V05-59	*S.* Enteritidis	Chicken feces	C6	Chungnam	2009.04.13	CTX-M-15	−	No	PT1	X6	A4
09-G-022	*S.* Enteritidis	Human stool		Gwangju	2009.06.01	CTX-M-15	−	No	PT1	X8	A6
09-G-081	*S.* Enteritidis	Human stool		Gwangju	2009.10.05	CTX-M-15	−	No	PT21	X6	A5
09-G-004	*S.* Enteritidis	Human stool		Gwangju	2009.02.02	CTX-M-15	−	Yes	PT1	X4	A3
09-G-097	*S.* Enteritidis	Human stool		Gwangju	2009.11.23	CTX-M-15	−	Yes	PT21	X4	A3
09-G-063	*S.* Enteritidis	Human stool		Gwangju	2009.08.17	CTX-M-15	−	Yes	PT21	X4	A3
09-G-069	*S.* Enteritidis	Human stool		Gwangju	2009.09.07	CTX-M-14	TEM-1	Yes	PT6a	X7	A4
09-G-076	*S.* Enteritidis	Human stool		Gwangju	2009.09.14	CTX-M-14	TEM-1	Yes	PT6a	X7	A6

[a] Abbreviations: PFGE, pulsed-field gel electrophoresis; RDNC, reacted but did not conform to any recognized phage types; ND, phage or PFGE typing not done; −, negative.
[b] Self-transfer of plasmid carrying bla_{CTX-M} gene in conjugation experiments.

sistance to nalidixic acid (MICs, 128 to 512 mg/liter) and reduced susceptibility to ciprofloxacin (MICs, 0.125 to 0.25 mg/liter). Screening of plasmid-mediated quinolone resistance determinants using the primer sets and conditions as described previously (16, 17, 24) revealed that none of them carried the *qnr*, *aac(6′)-Ib-cr*, or *qepA* gene. Thus, PCR amplification and sequencing of the quinolone resistance-determining regions (QRDRs) of *gyrA* and *parC* genes were carried out as described previously (12). It was found that all of them contained a single mutation within the QRDR of *gyrA* at codon 87 (Table 2). Although fluoroquinolones are important alternative antimicrobials for treatment of invasive salmonellosis in adults, there are increasing reports of treatment failures for *Salmonella* infections caused by strains with decreased susceptibility

TABLE 2. Antimicrobial susceptibility and point mutation in DNA topoisomerase of nontyphoid *Salmonella* strains isolated from food animals and humans carrying bla_{CTX-M} gene[a]

Strain	DDT	Etest MIC (mg/liter)[b]										Point mutation within QRDR of:	
		AMP	CTX	CTX + CA	CAZ	CAZ + CA	FEP	ATM	FOX	NAL	CIP	*gyrA*	*parC*
09-V06-15	+	>256	>16	0.064	<0.5	0.125	16	24	1.5	256	0.125	Asp87→Asn	Wild type
09-V06-16	+	>256	>16	0.094	<0.5	0.19	16	24	1.5	512	0.25	Asp87→Asn	Wild type
09-V06-20	+	>256	>16	0.094	<0.5	0.25	24	24	2	512	0.25	Asp87→Asn	Wild type
09-V06-21	+	>256	>16	0.064	<0.5	0.19	16	32	1.5	256	0.125	Asp87→Asn	Wild type
09-V06-22	+	>256	>16	0.094	<0.5	0.25	16	24	2	512	0.25	Asp87→Asn	Wild type
09-V06-23	+	>256	>16	0.125	<0.5	0.25	24	24	1.5	512	0.25	Asp87→Asn	Wild type
09-V06-25	+	>256	>16	0.125	<0.5	0.25	16	24	2	512	0.25	Asp87→Tyr	Wild type
09-V06-28	+	>256	>16	0.064	24	0.125	12	16	1.5	128	0.125	Asp87→Asn	Wild type
09-V05-54	+	>256	>16	0.094	<0.5	0.19	12	24	1.5	256	0.125	Asp87→Asn	Wild type
09-V05-56	+	>256	>16	0.094	<0.5	0.19	16	24	1.5	512	0.25	Asp87→Asn	Wild type
09-V05-57	+	>256	>16	0.094	<0.5	0.19	12	24	1.5	512	0.25	Asp87→Asn	Wild type
09-V05-58	+	>256	>16	0.094	<0.5	0.19	16	24	1.5	512	0.25	Asp87→Asn	Wild type
09-V05-59	+	>256	>16	0.094	<0.5	0.19	16	24	1.5	512	0.125	Asp87→Asn	Wild type
09-G-022	+	>256	>16	0.064	<0.5	0.19	16	24	1.5	256	0.125	Asp87→Asn	Wild type
09-G-081	+	>256	>16	0.094	<0.5	0.19	16	24	1.5	512	0.25	Asp87→Asn	Wild type
09-G-004	+	>256	>16	0.094	<0.5	0.19	16	24	1.5	256	0.125	Asp87→Asn	Wild type
09-G-097	+	>256	>16	0.094	<0.5	0.19	16	24	1.5	512	0.25	Asp87→Asn	Wild type
09-G-063	+	>256	>16	0.094	<0.5	0.19	12	24	1.5	512	0.25	Asp87→Asn	Wild type
09-G-069	+	>256	>16	0.094	1.5	0.19	6	3	1.5	256	0.125	Asp87→Gly	Wild type
09-G-076	+	>256	>16	0.094	1.5	0.19	6	3	1.5	256	0.125	Asp87→Gly	Wild type

[a] Abbreviations: DDT, double disk diffusion test; Etest, Epsilometer test; QRDR, quinolone resistance-determining region; AMP, ampicillin; CTX, cefotaxime; CAZ, ceftazidime; ATM, aztreonam; FEP, cefepime; FOX, cefoxitin; CA, clavulanic acid; NAL, nalidixic acid; CIP, ciprofloxacin.
[b] MICs of ciprofloxacin and nalidixic acid were determined by agar dilution method following the CLSI guidelines.

TABLE 3. Characteristics of *E. coli* J53 transconjugants carrying bla_{CTX-M} genes described in this study[a]

Transconjugant	Donor strain	*bla* gene transferred	Approximate plasmid size (kb)	Replicon type by PCR	IS*Ecp1* upstream of bla_{CTX-M}	IS*903* downstream of bla_{CTX-M}	Resistance transferred
p9V0615-1J	09-V06-15	CTX-M-15	95	FIIs	+	−	AMP CEP XNL CTX ATM GEN STR TET SUL
p9V0616-1J	09-V06-16	CTX-M-15	95	FIIs	+	−	AMP CEP XNL CTX ATM GEN STR TET SUL
p9V0620-1J	09-V06-20	CTX-M-15	95	FIIs	+	−	AMP CEP XNL CTX ATM GEN STR TET SUL
p9V0621-1J	09-V06-21	CTX-M-15	95	FIIs	+	−	AMP CEP XNL CTX ATM GEN STR TET SUL
p9V0622-1J	09-V06-22	CTX-M-15	95	FIIs	+	−	AMP CEP XNL CTX ATM GEN STR TET SUL
p9V0623-1J	09-V06-23	CTX-M-15	95	FIIs	+	−	AMP CEP XNL CTX ATM GEN STR TET SUL
p9V0628-1J	09-V06-28	CTX-M-15	95	FIIs	+	−	AMP CEP XNL CTX ATM GEN STR TET SUL
p9V0558-1J	09-V05-58	CTX-M-15	95	FIIs	+	−	AMP CEP XNL CTX ATM GEN STR TET SUL
p9G004-1J	09-G-004	CTX-M-15	95	FIIs	+	−	AMP CEP XNL CTX ATM GEN STR TET SUL
p9G097-1J	09-G-097	CTX-M-15	95	FIIs	+	−	AMP CEP XNL CTX ATM GEN STR TET SUL
p9G063-1J	09-G-063	CTX-M-15	95	FIIs	+	−	AMP CEP XNL CTX ATM GEN STR TET SUL
p9G069-1J	09-G-069	CTX-M-14	95	I1-Iγ	+	+	AMP CEP XNL CTX
p9G076-1J	09-G-076	CTX-M-14	95	I1-Iγ	+	+	AMP CEP XNL CTX

[a] Abbreviations: AMP, ampicillin; CEP, cephalothin; XNL, ceftiofur; CTX, cefotaxime; ATM, aztreonam; GEN, gentamicin; STR, streptomycin; TET, tetracycline; SUL, sulfamethoxazole; IS*Ecp1*, insertion sequence IS*Ecp1*; IS*903*, insertion sequence IS*903*; +, positive; −, negative.

to fluoroquinolones (1). Thus, it is worrisome to find the reduced susceptibility to fluoroquinolones among the ESBL-producing NTS strains, which would further exacerbate the complexity of the problem.

Conjugation experiments performed as described previously (28) demonstrated the transfer of the ESC resistance phenotype from 13 bla_{CTX-M}-positive *S. enterica* serovar Enteritidis isolates to the sodium azide-resistant *Escherichia coli* J53 recipients. PCR analysis showed the presence of respective bla_{CTX-M} genes in all the transconjugants. However, the bla_{TEM-1} gene did not transfer and was not amplified in the corresponding transconjugants. In addition to cephalosporin resistance, resistance to non-β-lactams also cotransferred along with the $bla_{CTX-M-15}$ gene (Table 3). In contrast, no additional non-β-lactam resistance cotransferred along with the $bla_{CTX-M-14}$ gene from the isolates that expressed them. These findings strongly suggest the association between $bla_{CTX-M-15}$ and multidrug resistance (MDR), in contrast to $bla_{CTX-M-14}$.

The plasmid DNA preparation using the QuickGene plasmid kit S II plasmid isolation system (Fujifilm Corporation, Japan) from the transconjugants revealed a large conjugative plasmid of approximately 95 kb, whereas the donor strains demonstrated at least one large plasmid of ~95 kb common to all strains. A PCR-based Inc/replicon typing was done using plasmid DNA from both donors and transconjugants, as described previously (7). The results of replicon typing of plasmids from the transconjugants showed that the IncFIIs plasmid was involved in the dissemination of the $bla_{CTX-M-15}$ gene in association with multidrug resistance (MDR) in both animal and human populations, whereas the IncI1-Iγ plasmid was involved in the dissemination of $bla_{CTX-M-14}$ genes with no connection to MDR phenotype, suggesting a possible relationship among specific replicon type, CTX-M type, and MDR. These results are in agreement with those of a previous study in which the association of $bla_{CTX-M-15}$ and $bla_{CTX-M-14}$ genes with plasmids of IncFII and IncI1 replicon types, respectively, has been reported in two different clinical *S.* Enteritidis isolates in addition to a number of *E. coli* isolates (15). In fact, the dissemination of $bla_{CTX-M-15}$ genes by IncFII plasmids or of $bla_{CTX-M-14}$ genes by IncI1 in the members of the *Enterobacteriaceae* has been well documented in several reports (6).

PCR amplification and sequencing of the regions surrounding bla_{CTX-M} genes using various CTX-M and insertion sequence primer sets as described previously (10, 27) identified insertion sequence IS*Ecp1* upstream of all the bla_{CTX-M} genes in both the wild NTS strains and their transconjugants. Furthermore, insertion sequence IS*903* was detected downstream of the $bla_{CTX-M-14}$ gene in the two human NTS strains and their transconjugants. The identification of the bla_{CTX-M} gene in *Salmonella* in association with insertion sequence IS*Ecp1* or IS*903* is a serious concern because these insertion sequences play an important role in the capture, expression, and continuous spread of these genes to other susceptible bacteria in the environment (25).

Among the 20 animal and human NTS strains carrying bla_{CTX-M} genes, phage typing of 19 *S. enterica* serovar Enteritidis isolates as described previously (31) identified three different phage types, and four of them did not react with any of the standard typing phages used (Table 1). In order to compare the genetic relatedness of NTS strains isolated from food animals and humans, molecular typing of all the 19 bla_{CTX-M}-positive *S.* Enteritidis isolates was done by pulsed-field gel electrophoresis (PFGE) using XbaI (Takara Bio Inc., Japan)- or AvrII (New England BioLabs)-digested genomic DNA according to the Centers for Disease Control and Prevention pulseNet standardized procedure as described previously (11). The XbaI-PFGE showed eight (X1 to X8) and the AvrII-PFGE revealed six (A1 to A6) arbitrary profiles among the 19 isolates. Identical PFGE profiles were found for strains from both animal and human sources by either XbaI- or AvrII-PFGE (Fig. 1).

For further discrimination, XbaI- and AvrII-PFGE profiles were combined to produce 11 different arbitrary combination profiles. The most predominant XbaI-AvrII combined profile was X4A3, followed by X6A4. Finally, we combined the results of phage typing and molecular typing to produce arbitrary phage-genotype profiles. The combination of phage type and XbaI-AvrII genotype showed that certain common identical profiles were present among NTS strains from food animals as

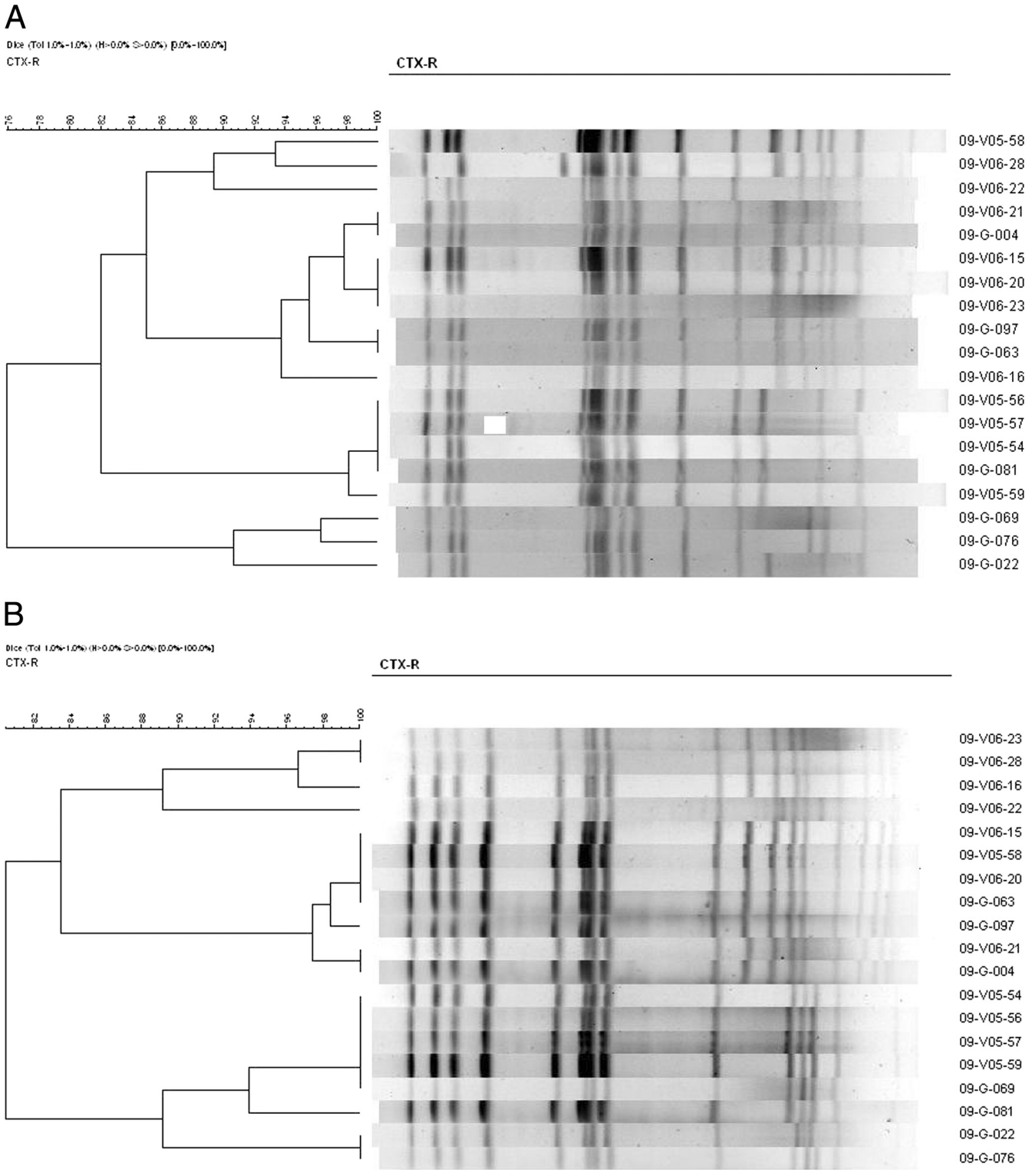

FIG. 1. Dendrogram generated by Bionumerics software showing the cluster analysis of XbaI- (A) and AvrII-PFGE (B) patterns of cefotaxime-resistant *Salmonella* serovar Enteritidis strains isolated from animals and humans. A cutoff similarity value of 95% was used to define clones. Similarity analysis was performed by using the Dice coefficient, and clustering was done by the unweighted-pair group method with arithmetic averages (UPGMA).

well as humans, suggesting a clonal relationship between $bla_{CTX\text{-}M\text{-}15}$-positive *S.* Enteritidis isolates of animal and human sources, although the human isolates did not seem to have any epidemiological link with the animal isolates. Our result is in agreement with a previous study done in South Korea which showed a clonal relationship between human and broiler chicken NTS strains and suggested the transmission of specific clones of NTS from livestock to humans (8). A similar study carried out in Taiwan also reported the transmission of certain common clones of NTS between human and animal sources and reported that these remained in circulation between humans and animals as epidemic strains for years (30). Furthermore, clonal relationships between the food animal and human isolates of NTS producing CTX-M-type ESBL or plasmid-mediated AmpC β-lactamase and the transmission of these organisms to humans through the food chain have been reported from Europe (4) and North America (33), respectively.

In conclusion, our results suggest that a combination of clonal and horizontal transmission is spreading $bla_{CTX\text{-}M}$ genes among NTS strains in South Korea. To the best of our knowledge, this represents the first report of a $bla_{CTX\text{-}M}$ gene in *S. enterica* serotype Essen and the first report of CTX-M-14 and CTX-M-15 β-lactamases among NTS strains of animal origin with decreased susceptibility to ciprofloxacin in South Korea. The emergence of cefotaximase-producing NTS strains with reduced susceptibility to fluoroquinolones among food animals and humans is of great public health concern and should be carefully monitored.

This work was supported by a grant from the National Veterinary Research and Quarantine Service, Ministry of Food, Agriculture, Forestry, and Fisheries, Republic of Korea.

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