LETTER TO THE EDITOR

Presence of plasmid-mediated quinolone resistance (PMQR) genes in non-typhoidal Salmonella strains with reduced susceptibility to fluoroquinolones isolated from human salmonellosis in Gyeonggi-do, South Korea from 2016 to 2019

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Abstract

Non-typhoidal salmonellosis remains a pressing public health problem worldwide. Quinolones, particularly fluoroquinolones, are widely used to treat various infections, including non-typhoidal salmonellosis, which can be a serious illness. The emergence of fluoroquinolone-resistant Salmonella has resulted in treatment failure and high mortality rates. In this study, we estimated the presence of plasmid-mediated quinolone resistance (PMQR) genes in Salmonella enterica isolated from human salmonellosis patients in South Korea from 2016 to 2019. We evaluated the association of these genes with fluoroquinolone susceptibility. Antimicrobial susceptibility tests for Salmonella isolates were performed using the Vitek II system, and the minimum inhibitory concentrations (MIC) of ciprofloxacin and levofloxacin were determined using the E-test method. Plasmid-mediated quinolone resistance (PMQR) genes were detected by PCR amplification and quinolone resistance-determining regions (QRDRs) of the gyrA and parC genes were analyzed following Sanger sequencing of the PCR products. Thirty-four Salmonella strains with reduced susceptibility to fluoroquinolones (ciprofloxacin MIC ≥ 0.125 µg/mL and levofloxacin MIC ≥ 0.25 µg/mL) were selected from 208 human clinical Salmonella isolates. Among them, 22 Salmonella strains harbored one PMQR gene (qnrA, qnrB, or qnrS), and three Salmonella strains carried two PMQR genes (qnrS and aac(6′)-Ib-cr or qnrA and qnrB). qnrS was the most common PMQR gene. Serotyping revealed that Salmonella 4,[5],12:i:- (32.4%, 11/34) and Salmonella Typhimurium (29.4%, 10/34) were the two most predominant serovars, and Multilocus sequence typing (MLST) showed that ST19 and ST34 were the most frequent sequence types. In conclusion, qnr gene-positive Salmonella 4,[5],12:i:- and Salmonella Typhimurium were the main serovars responsible for reduced susceptibility to fluoroquinolones. Therefore, our findings suggest that PMQR-positive Salmonella strains, which can be isolated from various samples including human, food, and the environment, should be carefully monitored.

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Background
Salmonellosis is a disease caused by Salmonella that usually produces acute onset of fever, abdominal pain, diarrhea, and vomiting. Antimicrobial therapy is not recommended in healthy individuals with mild or moderate infection [1]. This is due to the use of antimicrobials may not shorten the duration of clinical symptoms, but is rather a risk for prolonged Salmonella infection [2]. However, high-risk groups including infants, the elderly, and immunocompromised patients may require antimicrobial therapy [1]. Quinolones, particularly fluoroquinolones (e.g., ciprofloxacin and levofloxacin), are a critically important antimicrobial class, and invasive Salmonella infections in adults are commonly treated with quinolones. However, because quinolones are frequently used in human and veterinary medicine, resistance to this antimicrobial class has evolved among Salmonella strains [3]. Fluoroquinolone resistance is mostly associated with chromosomal mutations in the bacterial genes encoding targeted enzymes, DNA gyrase and topoisomerase IV (quinolone resistance determining region, QRDR). However, fluoroquinolone resistance can also be acquired by plasmid encoded genes (plasmid-mediated quinolone resistance, PMQR). There are several well-known PMQR gene groups, including qnr families (qnrA, qnrB, qnrC, qnrD, qnrE, qnrS, and qnrVC), antibiotic efflux pump-coding genes (qepA and oqxAB), antibiotic modification enzyme gene (aac(6)Ib-cr), and a newly described phosphorylase gene (crpP) [4]. According to previous studies, the qnr, aac(6′)-Ib-cr, and qepA genes are commonly detected in South Korea; therefore, we chose these genes to investigate in this study [5, 6]. The Qnr is a pentapeptide repeat protein that protects DNA gyrase and topoisomerase IV by inhibiting quinolone [7, 8]. The aac(6′)-Ib-cr gene encodes aminoglycoside acetyltransferase that simultaneously induces resistance against aminoglycoside and fluoroquinolone [9]. PMQR facilitates the spread of quinolone resistance, leading to the emergence of high quinolone resistance, making infections difficult to treat [10]. Therefore, the presence of PMQR genes in Salmonella strains with reduced susceptibility to fluoroquinolones indicates that continuous monitoring and clinical attention are required. Although PMQR genes confer reduced susceptibility of bacteria to fluoroquinolones, their influence on nalidixic acid susceptibility is minor [11]. The United States National Antimicrobial Resistance Monitoring System (NARMS) has indicated the presence of PMQR genes among Salmonella and other enteric bacteria isolated from humans, retail meat, and food animals in the United States. Additionally, NARMS recently reported an increase in the proportion of ciprofloxacin-non-susceptible strains lacking nalidixic acid resistance [12]. In Canada, a relatively high prevalence of PMQR genes has been reported in human isolates of non-typhoidal Salmonella with resistance and reduced susceptibility to fluoroquinolones [13]. Likewise, PMQR gene-positive Salmonella 4,[5],12:i:- were recently isolated from pigs, chickens, humans, geese, and cats in China [14]. In this study, we aim to estimate the presence of the plasmid-mediated quinolone resistance genes and their association with fluoroquinolone susceptibility in non-typhoidal Salmonella isolates from human clinical samples in South Korea from 2016 to 2019.

Methods
Thirty-four nontyphoidal Salmonella strains with intermediate resistance to quinolone or fluoroquinolone were selected and evaluated from 208 human clinical Salmonella strains. The strains were isolated from fecal samples of diarrhea patients in Gyeonggi-do, South Korea, by the Research Institute of Health & Environment from 2016 to 2019 (see Additional file 1). The rectal swab samples were plated on Salmonella–Shigella (SS) agar (Oxoid, Basingstoke, UK) and incubated at 37 °C for 18 to 24 h. Isolates with typical Salmonella phenotypes were confirmed using the Vitek II system with a GN card (bioMerieux Inc., Marcy l’Etoile, France). Salmonella serotyping was done according to the White–Kauffmann–Le Minor scheme using slide agglutination test (O antigen) and tube agglutination test (H antigen) with antisera. The isolates were serotyped using the somatic (O) (provided from Korea Disease Control and Prevention Agency, KDCA) and flagella (H) antisera (Difco, Detroit, MI, USA). The absence of hin gene in the monophasic variant of Salmonella Typhimurium was confirmed by PCR. Antimicrobial susceptibility tests were performed using the Vitek II system with the AST-N169 card (bioMerieux Inc.) according to the manufacturer’s instructions. The minimum inhibitory concentrations (MIC) of ciprofloxacin and levofloxacin were determined using the E-test method (bioMerieux Inc.). Quinolone and fluoroquinolone MIC values were confirmed according to CLSI guidelines [15]. In Salmonella, a ciprofloxacin MIC of 0.12–0.5 µg/mL is defined as intermediate and MIC ≥ 1 µg/mL is defined as resistant, while a levofloxacin MIC of 0.25–1 µg/mL is defined as intermediate and MIC ≥ 2 µg/mL is defined as resistant. Additionally,
a nalidixic acid MIC ≥ 32 µg/mL is defined as resistant, and there is no intermediate category. Total DNA was extracted from overnight cultures of Salmonella isolates using the Nextactor NX-48 system and NX-48 bacterial DNA kits (Genolution Inc., Seoul, Korea). PMQR genes (qnrA, qnrB, qnrS, aac(6′)-Ib-cr, and qepA) were detected by PCR amplification using primers described in previous studies [16–18]. The QRDR region of the gyrA and parC genes was each PCR-amplified using previously described primers [19]. PCR products were purified and Sanger sequenced by Macrogen Inc, Korea. The nucleotide sequences of the QRDRs in gyrA and parC genes were compared with the counterpart sequences of quinolone-susceptible reference strain Salmonella Typhimurium LT2 (GenBank Accession number AE006468) using BLAST. Seven housekeeping genes (aroC, dnaN, hemD, hisD, purE, sucA, and thrA) were amplified using previously reported MLST primers (see Additional file 2). PCR products were sequenced by Macrogen (South Korea).

Each isolate’s sequence type (ST) was assigned according to the PubMLST website. Phylogenetic analyses of the isolates using MLST-based clusters were conducted with BioNumerics software (Applied Maths, Sint-Martens-Latem, Belgium). The correlation between PMQR genes and MIC values was analyzed by Fisher’s exact test using BioNumerics software (Applied Maths, Sint-Martens-Latem, Belgium).

The correlation between PMQR genes and MIC values was statistically insignificant. According to previous studies, the qnr gene family was predominantly detected in Salmonella strains isolated from travelers. Most of the strains carrying the qnrS gene showed reduced susceptibility to ciprofloxacin [21]. The qnrS gene was mostly harbored by Salmonella 4,[5],12:i:- and Salmonella Typhimurium [23, 24]. The qepA gene was not detected in any isolate. According to a study on PMQR gene prevalence in clinical Enterobacteriaceae isolates from South Korea, qnrB was the most frequently observed PMQR gene before 2000, whereas qnrS, aac(6′)-Ib-cr, and qepA emerged after 2000 [25]. Although most PMQR-positive isolates possessed only one gene, two Salmonella Saintpaul isolates were positive for qnrS and aac(6′)-Ib-cr and one Salmonella Carno isolate was positive for qnrA and qnrB. Among the PMQR gene-positive Salmonella isolates from patients and turkey meat, Salmonella Saintpaul carrying one qnrS1 gene was reported in the Netherlands and Denmark [26, 27]. Salmonella Carno is a rare serotype, and this serovar has not been extensively studied.

**Results and discussion**

Thirty-four Salmonella strains with reduced susceptibility to fluoroquinolones were identified from Gyeonggi-do, South Korea, from 2016 to 2019. Salmonella 4,[5],12:i:- (32.4%, 11/34) and Salmonella Typhimurium (29.4%, 10/34) were the predominant serovars. Isolated Salmonella serovars showing intermediate resistance to fluoroquinolones, particularly fluoroquinolones, were presented in Table 1. In the last two decades, Salmonella 4,[5],12:i:- has rapidly emerged worldwide [14]. In South Korea, the first foodborne outbreak of Salmonella 4,[5],12:i:- was reported in 2008 [20]; the same serovar, which exhibits nalidixic acid resistance, was isolated from pigs and chickens in South Korea [21]. Similarly, most Salmonella 4,[5],12:i:- isolates from chickens, geese, and cats in China were resistant to nalidixic acid (52.5%) [14]. Isolates of enrofloxacin-resistant Salmonella 4,[5],12:i:- from swine in the United States have also been reported [22].

All 34 isolates (100%) showed reduced susceptibility to levofloxacin, 32 isolates (94.1%) showed reduced susceptibility to ciprofloxacin, and 27 isolates (79.4%) were also resistant to nalidixic acid. We obtained seven non-typhoidal Salmonella isolates that showed reduced susceptibility to fluoroquinolones and susceptibility to nalidixic acid. Resistance to nalidixic acid could be related to reduced susceptibility to fluoroquinolones because it typically required chromosomal mutations in the quinolone resistance-determining region (QRDR) or acquisitions of PMQR genes (Table 1). Reduced susceptibility to fluoroquinolones without nalidixic acid resistance indicated PMQR presence [10], and the US NARMS has found higher percentages of isolates with reduced susceptibility to ciprofloxacin than nalidixic acid resistance since 2005 [12].

PMQR genes were detected in 25 (73.5%) out of 34 Salmonella isolates, including one (2.9%) isolate positive for qnrA, two (5.9%) isolates positive for qnrB, 23 (67.6%) positive for qnrS, and two (5.9%) positive for aac(6′)-Ib-cr (Table 1). The correlation between PMQR genes and MIC values was statistically insignificant. According to previous studies, the qnr gene family was predominantly detected in Salmonella strains isolated from travelers. Most of the strains carrying the qnrS gene showed reduced susceptibility to ciprofloxacin [21]. The qnrS gene was mostly harbored by Salmonella 4,[5],12:i:- and Salmonella Typhimurium [23, 24]. The qepA gene was not detected in any isolate. According to a study on PMQR gene prevalence in clinical Enterobacteriaceae isolates from South Korea, qnrB was the most frequently observed PMQR gene before 2000, whereas qnrS, aac(6′)-Ib-cr, and qepA emerged after 2000 [25]. Although most PMQR-positive isolates possessed only one gene, two Salmonella Saintpaul isolates were positive for qnrS and aac(6′)-Ib-cr and one Salmonella Carno isolate was positive for qnrA and qnrB. Among the PMQR gene-positive Salmonella isolates from patients and turkey meat, Salmonella Saintpaul carrying one qnrS1 gene was reported in the Netherlands and Denmark [26, 27]. Salmonella Carno is a rare serotype, and this serovar has not been extensively studied.

To estimate genetic correlations, multi-locus sequence typing (MLST) was conducted. Nine isolates of ST19 type (seven Salmonella Typhimurium and two Salmonella 4,[5],12:i:-), 9 isolates of ST34 type (nine Salmonella 4,[5],12:i:-), 2 isolates of ST36 type (two Salmonella Typhimurium), ST27 type (two Salmonella Saintpaul), ST13 type (one Salmonella Agona and one Salmonella Hato) and ST469 type (two Salmonella Rissen) were identified. ST19 and ST34 were the predominant STs in Salmonella Typhimurium and Salmonella 4,[5],12:i:-, which had high genetic diversity but were over 80% similar to each other (Fig. 1). ST19 and ST34 prevalence in Salmonella 4,[5],12:i:- has
significantly increased in Canada, and some of these STs demonstrate quinolone resistance [30]. It has been reported that ST19 is significantly associated with ciprofloxacin resistance in China [31] and that ST34 is linked to the nalidixic acid resistance in Africa [32]. *Salmonella* Agona ST13 was the most prevalent serovar isolated from chicken meat in Sri Lanka [33], and a *Salmonella* Agona strain isolated from chicken meat in China possessed a T57S substitution in ParC and carried *qnrS* [34]. *Salmonella* Rissen ST469 was isolated from ready-to-eat mussels in Spain and pork products in Portugal [35, 36]. Moreover, ST469 was the third most predominant ST isolated from pork samples in China and nearly one-third of the ST469 isolates were resistant to ciprofloxacin [37]. However, the sequence type of one *Salmonella* Derby isolate could not be determined by MLST, suggesting the possibility that a potential novel ST of *Salmonella* Derby has emerged in South Korea.

### Table 1
Isolation and antibiotic resistance information for *Salmonella* isolates evaluated in this study

| # | Serotype     | Year | ST   | AST<sup>a</sup>. | QRDR     | PMQR | MIC<sup>b</sup>. |   |
|---|-------------|------|------|------------------|----------|------|-----------------|---|
|   |             |      |      |                  | Nalidixic acid | Ciprofloxacin | Levofloxacin |
| 29 | Typhimurium | 2016 | 19   | R                | GyrA(D87Y) | –    | 0.125           | 0.25 |
| 43 | Typhimurium | 2017 | 36   | S                | –         | *qnrS1* | 0.125           | 0.38 |
| 44 | Typhimurium | 2017 | 36   | S                | –         | *qnrS1* | 0.125           | 0.38 |
| 48 | Typhimurium | 2017 | 19   | S                | –         | *qnrS1* | 0.125           | 0.25 |
| 63 | Typhimurium | 2017 | 19   | R                | GyrA(D87Y) | –    | 0.125           | 0.25 |
| 53 | Typhimurium | 2018 | 19   | R                | –         | *qnrS1* | 0.19            | 0.38 |
| 17 | Typhimurium | 2018 | 16   | R                | GyrA(S83F) | –    | 0.125           | 0.25 |
| 19 | Typhimurium | 2018 | 19   | R                | GyrA(D87Y) | –    | 0.125           | 0.25 |
| 20 | Typhimurium | 2018 | 19   | R                | –         | *qnrS1* | 0.25            | 0.5  |
| 21 | Typhimurium | 2018 | 19   | R                | GyrA(D87Y) | *qnrS1* | 0.25            | 0.75 |
| 13 | 14,[5],12i- | 2017 | 34   | R                | –         | *qnrS1* | 0.19            | 0.38 |
| 22 | 14,[5],12i- | 2018 | 34   | S                | –         | *qnrS1* | 0.125           | 0.25 |
| 23 | 14,[5],12i- | 2018 | 34   | R                | –         | *qnrS1* | 0.19            | 0.38 |
| 24 | 14,[5],12i- | 2018 | 19   | S                | –         | *qnrS1* | 0.125           | 0.38 |
| 25 | 14,[5],12i- | 2018 | 34   | S                | –         | *qnrS1* | 0.125           | 0.25 |
| 54 | 14,[5],12i- | 2018 | 34   | R                | –         | *qnrS1* | 0.19            | 0.5  |
| 55 | 14,[5],12i- | 2018 | 34   | R                | –         | *qnrS1* | 0.19            | 0.38 |
| 57 | 14,[5],12i- | 2018 | 34   | R                | –         | *qnrS1* | 0.125           | 0.38 |
| 59 | 14,[5],12i- | 2018 | 34   | R                | –         | *qnrS1* | 0.19            | 0.5  |
| 50 | 14,[5],12i- | 2018 | 19   | R                | –         | *qnrS1* | 0.25            | 0.5  |
| 61 | 14,[5],12i- | 2019 | 34   | R                | –         | *qnrS1* | 0.25            | 1    |
| 11 | Rissen      | 2017 | 469  | R                | GyrA(S83Y), ParC(T57S) | – | 0.125           | 0.5  |
| 12 | Rissen      | 2017 | 469  | R                | GyrA(S83Y), ParC(T57S) | – | 0.125           | 0.38 |
| 2  | Saintpaul   | 2017 | 27   | R                | –         | *qnrS1, aac(6')-Ib-cr* | 0.5 | 0.38 |
| 3  | Saintpaul   | 2017 | 27   | R                | –         | *qnrS1, aac(6')-Ib-cr* | 0.5 | 0.38 |
| 8  | Enteritidis | 2017 | 11   | R                | GyrA(D87N) | – | 0.032           | 0.25 |
| 10 | Kentucky    | 2017 | 11   | R                | GyrA(D87G) | – | 0.047           | 0.25 |
| 15 | Carno       | 2017 | 1992 | R                | ParC(T57S) | *qnrA, qnrB* | 0.19 | 0.5  |
| 16 | Agona       | 2017 | 13   | R                | ParC(T57S) | *qnrB* | 0.125           | 0.5  |
| 18 | Hato        | 2018 | 13   | R                | ParC(T57S) | *qnrS1* | 0.125           | 0.5  |
| 32 | Duesseldorf | 2016 | 292  | R                | GyrA(S83F), ParC(T57S) | – | 0.125           | 0.25 |
| 51 | Braenderup  | 2018 | 311  | R                | ParC(T57S) | *qnrS2* | 0.19            | 0.5  |
| 52 | Derby       | 2018 | Undetermined  | S | – | *qnrS1* | 0.125 | 0.38 |
| 62 | Newport     | 2019 | 214  | R                | –         | *qnrS1* | 0.125           | 0.25 |

<sup>a</sup> Vitek II system with AST-N169 card  
<sup>b</sup> E-test method
### Conclusions

We isolated 34 *Salmonella* strains with reduced susceptibility to fluoroquinolones from human salmonellosis. Among them, *Salmonella* 4,[5],12:i:- and *Salmonella Typhimurium* were the most common serovars, and MLST revealed that ST19 and ST34 were the predominant lineages, with a high genetic similarity of over 80%. The spread of plasmid-mediated antibiotic resistance in ST19 and ST34 strains requires careful attention in South Korea. Furthermore, all isolates carried one or two of the PMQR genes, suggesting that various genes associated with quinolone resistance can be transferred horizontally among *Enterobacteriaceae*, causing human infections in South Korea.

#### Fig. 1
Phylogenetic tree based on MLST sequence typing of PMQR-positive *Salmonella* isolates from South Korea. The cluster analysis was performed using the categorical coefficient and the UPGMA in BioNumerics.
Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13099-021-00431-7.

Additional file 1: Table S1. Salmonella serovars isolated from clinical samples in Gyeonggi-do, South Korea. Additional file 2: Table S2. Primer sequences used for this experiment.

Acknowledgements

Not applicable.

Authors’ contributions

SL, NP and SR participated in the conception and design of the study. SL and NP performed the laboratory work. NP and SR analyzed the data and wrote the manuscript. SL, SY, EH, JS, HL and YK contributed to the analysis and helped in writing the manuscript. All authors read and approved the final manuscript.

Funding

This research was supported by a Grant (19162MFD0307) from the Ministry of Food and Drug Safety in 2020.

Availability of data and materials

Data sharing not applicable to this article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 27 January 2021  Accepted: 21 May 2021Published online: 01 June 2021

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