Characterization of *Salmonella* serotypes prevalent in asymptomatic people and patients

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**Abstract**

**Background:** Infection with *Salmonella enterica* usually results in diarrhea, fever, and abdominal cramps, but some people become asymptomatic or chronic carrier as a source of infection for others. This study aimed to analyze the difference in serotype, antimicrobial resistance, and genetic profiles between *Salmonella* strains isolated from patients and those from asymptomatic people in Nantong city, China.

**Methods:** A total of 88 *Salmonella* strains were collected from patients and asymptomatic people from 2017 to 2018. Serotyping, antimicrobial susceptibility testing, and PFGE analysis were performed to analyze the characteristics of these strains.

**Results:** Twenty serotypes belonging to 8 serogroups were identified in the 88 *Salmonella* strains. *S. Typhimurium* remained to be the predominant serotype in strains from both patients and asymptomatic people. Among the 27 strains from patients, *S. Enteritidis* and *S. Rissen* were shown as the other two major serotypes, while *S. London*, *S. Derby*, and *S. Meleagridis* were demonstrated as the other significant serotypes among the 61 strains from asymptomatic people. Antimicrobial resistance testing revealed that 84.1% of strains from both resources were multi-drug resistant. PFGE displayed a highly discriminative ability to differentiate strains belonging to *S. Derby*, *S. Typhimurium*, etc., but could not efficiently differentiate serotypes like *S. Enteritidis*.

**Conclusions:** This study’s results demonstrated that *S. Typhimurium* could cause human infection in both symptomatic and asymptomatic state; *S. London*, *S. Derby*, and *S. Meleagridis* usually cause asymptomatic infection, while *S. Enteritidis* infection mainly results in human diseases. The high multi-drug resistance rate detected in the antimicrobial resistance and diverse PFGE profiles of these strains implied that the strains were isolated from different sources, and the increased surveillance of *Salmonella* from both patients and asymptomatic people should be taken to control the disease.

**Keywords:** *Salmonella*, Asymptomatic infection, PFGE, Antimicrobial susceptibility
Background
Salmonellosis is an infection with bacteria called Salmonella. Human salmonellosis generally manifests two kinds of disorders: typhoid fever caused by typhoidal Salmonella enterica serotypes S. Typhi, S. Paratyphi A, S. Paratyphi B, and S. Paratyphi C, and another is gastroenteritis caused by nontyphoidal Salmonella (NTS) serotypes such as S. Enteritidis and S. Typhimurium [1]. Salmonella can cause symptomatic infections, which is defined as the occurrence of any number of watery stools during 24 h period accompanied by fever, vomiting or abdominal cramps [2]. Besides, some people can get a Salmonella infection without any symptoms and clear the infection within a few days, or become persisting or abdominal cramps [2].

A bacterial load of $10^6–10^8$ CFU of NTS organisms is needed to cause symptomatic disease in healthy adults [4]. It is estimated that approximately 93.8 million gastroenteritis cases and 155,000 deaths are attributed to NTS worldwide annually [5]. According to the United States and European Food Safety Authority (EFSA) data, S. Enteritidis and S. Typhimurium have remained the top serotypes causing clinical human salmonellosis [6, 7]. Both serotypes were predominantly contributed to human gastroenteritis due to Salmonella infection in hospitals from different provinces or cities of China [8–11]. With difference to the serotypes identified in patients, S. Derby, S. London, and S. Senftenberg have been demonstrated to be the major Salmonella serotypes in asymptomatic food handlers as well as S. Typhimurium and S. Enteritidis [12]. Therefore, it is necessary to characterize the difference in Salmonella serotypes between patients and asymptomatic people.

Phenotypic and genotypic methods allow the identification and characterization of bacterial strains with different sources [13]. Salmonella serovars’ appearance with multidrug-resistant (MDR) patterns has increased rapidly and become a heavy burden on the clinical treatment of salmonellosis [4, 14]. A report of 1826 NTS isolates from human patients in Guangdong province of China revealed that 46% of the isolates were MDR, and 72% showed resistance to at least one antimicrobial [8]. Among 109 Salmonella isolates from diarrheagenic children in Beijing, 50% of the strains showed resistance to at least three antimicrobials, and 12.8% were resistant to six [15]. In Malaysia, seven Salmonella strains were isolated from a total of 317 asymptomatic food handlers, and these strains showed multidrug-resistance to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, sulfonamides, streptomycin, and tetracycline [16]. Since the bacteria have evolved to be resistant to various antimicrobials, constant antibiotic surveillance is warranted, and the genotyping techniques are essential to tracing the source of the bacteria. The pulsed-field gel electrophoresis (PFGE) was considered as the golden standard genotyping technique for differentiation of Salmonella isolates [17, 18]. Furthermore, it can also be used to trace the source of infections and the transmission route of the strains [18].

This study investigated the serotypes distribution, antimicrobial resistance, and PFGE profiles of S. enterica isolated from patients and asymptomatic people in Nantong, China. By comparing the characteristics of Salmonella strains from two different kinds of sources, we could develop effective strategies to control Salmonella infection in humans.

Methods

Serotyping of Salmonella isolates from human
A total of 88 Salmonella isolates were obtained from patients and asymptomatic people by the Center for Disease Control and Prevention, Nantong, China. Among the 88 strains, 61 was isolated from people on physical examination without any symptoms, while 27 was isolated from patients with diarrhea. This study received ethical approval from the Ethics Committees of Center for Disease Control and Prevention of Nantong city. Serotyping of the isolates was performed using slide agglutination test according to the instructions of Salmonella antisera kit (Tianrun Bio-Pharmaceutical Co. Ltd., Ningbo, China) based on somatic O, as well as phase 1 and phase 2 flagella antigens. The serotype identification of each strain was based on the Kauffmann-White scheme [19].

Antimicrobial susceptibility testing
Susceptibility testing of the 88 Salmonella isolates with the Sensititre National Antimicrobial Resistance Monitoring System Gram-negative susceptibility plates (Customized version, Sensititre; Trek Diagnostic Systems, Inc., Westlake, OH) was performed according to the manufacturer’s instructions. Twenty-six antimicrobial agents (antimicrobial abbreviations and dilution concentration ranges are given in parentheses, in micrograms per milliliter) were used as follows: ampicillin (AMP, 2–64); ampicillin-sulbactam (AMS, 2–64 and 1–32); amoxicillin-clavulanic acid (AMC, 2–64 and 1–32); aztreonam (AZM, 1–32); cefazolin (CFZ, 0.5–16); cefotaxime (CTX, 0.25–8); ceftazidime (CAZ, 0.5–16); cefoxitin (CFX, 2–64); cefepine (FEP, 0.25–16); gentamicin (GEN, 1–32); amikacin (AMI, 1–32); imipenem (IMI, 0.25–8); meropenem (MEM, 0.06–4); chloramphenicol (CHL, 2–64); trimethoprim/sulfamethoxazole (SXT, 0.25–8 and 4.75–152); sulfisoxazole (SUL, 32–512); tetracycline (TET, 1–32); minocycline (MIN, 1–32); nalidixic acid (NAL, 4–64); ciprofloxacin (CIP, 0.03–32); levofloxacin (LEV, 0.125–8); doxycycline (DOX, 0.5–16); kanamycin

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(KAN, 8–64); streptomycin (STR, 4–32); colistin sulphate (CT, 0.5–16); polymyxin B (PB, 0.5–16); The Clinical and Laboratory Standards Institute (CLSI, 2018) on Antimicrobial Susceptibility Testing breakpoints were used to assess the results [20]. *Escherichia coli* ATCC25922 with known antimicrobial resistance profiles was used as a quality control organism.

**PFGE**

PFGE was conducted to reveal the clonal-relatedness of *Salmonella* strains following the standardized laboratory protocol for molecular subtyping of *Salmonella* by PFGE [17]. The *S. Braenderup H9812* was used as a marker strain. Briefly, agarose-embedded genomic DNA samples were digested with *XbaI* (Takara, Japan) at 37 °C for 2 h. The Chef Mapper electrophoresis system was then used to separate restriction fragments in 0.5X Tris-borate-ethylenediaminetetraacetic acid (EDTA; TBE) extended-range buffer (Bio-Rad, United States) with recirculation at 14 °C for 18–20 h. The gel was stained with GelRed and visualized under UV light to record the gel results with TIFF images. The genetic patterns for each of the strains were compared and analyzed using the BioNumerics version 7.5 software (Applied Maths, Belgium). A dendrogram was produced using the Dice coefficient correlation and unweighted pair group method using the arithmetic mean algorithm (UPGMA) with 1.5% optimization and a band position tolerance.

**Results**

**Prevalence and distribution of serotypes for *Salmonella* isolates from humans**

A total of 88 *Salmonella* strains were isolated, 49 (55.7%) from males and 39 (44.7%) from females in Nantong city (Table 1). Nearly 69.3% (61/88) of strains were isolated from asymptomatic people, while 30.7% (27/88) were from patients (Table 1). Among the 27 strains from patients, 8 (29.6%) were isolated from children. All of the strains with their information, including the age, sex, and samples, were listed in Table S1. Among the identified 88 *Salmonella* isolates, 20 serotypes distributed in 8 serogroups were identified, with B (38.6%) and E (26.1%) as the top 2 predominant serogroups (Table 2). The *S. Typhimurium* serotype was detected in 21.6% of the 88 isolates, followed by 12.5% of *S. London*, 11.4% of *S. Derby*, 10.2% of *S. Enteritidis*, and 7.5% of both *S. Rissen* and *S. Meleagris* (Table 2, Fig. 1a). However, compared to 19 serotypes identified in 61 isolates from asymptomatic people, 8 serotypes were detected in 27 isolates from patients (Table 2, Fig. 1b). Only 1 out of 11 *S. London* isolates was obtained from a patient, while 77.8% (7/9) of *S. Enteritidis* can cause human disease, and all of the 3 *S. Paratyphi A* strains were isolated from patients (Table 2, Fig. 1c). *S. Typhimurium* (16.4%) and *S. London* (16.4%) was the predominant serotype in the isolates from asymptomatic people, followed by *S. Derby* (14.8%) and *S. Meleagris* (11.5%) (Fig. 1b). In contrast, *S. Typhimurium* (33.3%) and *S. Enteritidis* (25.9%) were the top 2 serotypes causing symptoms in patients, followed by *S. Rissen* (14.8%) (Fig. 1c).

**Table 1** The sampling information of *Salmonella* from humans

| Variable          | Value |
|-------------------|-------|
| Sex               | n (%) |
| Male              | 49 (55.7%) |
| Female            | 39 (44.3%) |
| Age               | median (range) |
| 37 (1–77)         |
| Place             | n (%) |
| Nantong CDC       | 61 (69.3%) |
| Chongchuan district | 23 (26.1%) |
| Other counties    | 4 (4.6%) |
| Source            | n (%) |
| Asymptomatic people | 61 (69.3%) |
| Patient           | 27 (30.7%) |

*n represents the number of strains

**Table 2** Distribution of serotypes for 88 *Salmonella* isolates from patients and asymptomatic people

| O group (no) | Serotype (no, percentage)* | NO. | Percentage (%) |
|--------------|-----------------------------|-----|----------------|
| A (3)        | Paratyphi A (3, 100%)       | 3   | 3.4            |
| B (34)       | Indiana (1, 50%)            | 2   | 2.3            |
|              | Agona                       | 3   | 3.4            |
|              | Derby (1, 10%)              | 10  | 11.4           |
|              | Typhimurium (9, 47.4%)      | 19  | 21.6           |
| C1 (14)      | Singapore                   | 1   | 1.1            |
|              | Infantis                    | 1   | 1.1            |
|              | Mbandaka                    | 2   | 2.3            |
|              | Thompson (1, 33.3%)         | 3   | 3.4            |
|              | Rissen (4, 57.1%)           | 7   | 8.0            |
| C2-C3 (4)    | Corvallis                   | 1   | 1.1            |
|              | Manhattan                   | 1   | 1.1            |
|              | Newport                     | 2   | 2.3            |
| D1 (9)       | Enteritidis (7, 77.8%)      | 9   | 10.2           |
| E1 (19)      | Uganda                      | 1   | 1.1            |
|              | Meleagris (1, 12.5%)        | 8   | 9.1            |
|              | London                      | 10  | 11.4           |
| E4 (4)       | Liverpool                   | 1   | 1.1            |
|              | Senftenberg                 | 3   | 3.4            |
| H (1)        | Poano                       | 1   | 1.1            |

*represents the number of strains isolated from patients with diarrhea, fever, or abdominal cramps in hospitals and the percentage of these strains among the same serotype
Antimicrobial resistance

A total of 8 (8/88, 9.1%) strains were susceptible to all the 26 antimicrobials, and all of the 88 isolates showed susceptibility to meropenem, a type of carbapenems used to treat symptomatic *Salmonella* infection (Fig. 2). *S.* Derby showed a high rate of multi-drug resistance to these antimicrobials (90%, 9/10), followed by *S.* Enteritidis (88.9%, 8/9), *S.* Meleagridis (85.7%, 6/7), *S.* Typhimurium (84.2%, 16/19), *S.* London (81.8%, 9/11), and *S.* Rissen (71.4%, 5/7). Besides, 85.2% (52/61) of the isolates from asymptomatic humans and 85.2% (23/27) of those from patients were identified to be MDR (Fig. 2).

Among the 26 antimicrobial agents belonging to 8 classes (β-Lactamases, aminoglycosides, carbapenems, polymyxins, phenicols, sulfonamides, tetracyclines, fluoroquinolones), resistance to sulfisoxazole, tetracycline, and ampicillin was found in 81.8, 80.7, 77.3% of isolates, respectively (Fig. 2). These top three antimicrobials were also seen in the 61 isolates from asymptomatic people. Besides, 73.8% (45/61) of these isolates showed resistance to the three antimicrobials (Fig. 2). However, ampicillin (81.5%), tetracycline (70.4%), and nalidixic acid (66.8%) were the top three antimicrobials found in 27 isolates from patients. Resistance to all of the three antimicrobials was seen in 51.9% (14/27) of these isolates.

Among the 88 isolates, the *S.* Meleagridis F2–6 and *S.* Rissen F5–5 strain showed resistance to amikacin and imipenem, respectively (Fig. 2). Four isolates belonging to three serotypes (*S.* Parytyphi A, *S.* Enteritidis, *S.* Typhimurium) were resistant against polymyxin E, an antibiotic medication used as a last-resort treatment for MDR gram-negative infections, and all four strains were isolated from patients. The *S.* Enteritidis F6–1 strain displayed resistance to both polymyxin E and polymyxin B.

PFGE analysis

The 88 strains were then subjected to the PFGE analysis with the restriction enzyme *XbaI* for inter-serotype differentiation to reveal their genetic relationship. Among
the 16 strains belonging to 8 serotypes in C1 and C2-C3 groups, 10 profiles (X01 to X10) were identified with X04 shared by all of the 8 S. Rissen strains isolated from both patients and asymptomatic people (Fig. 3a). Among the 23 strains belonging to E1 and E4 groups, 8 genetic profiles (designated X01 to X08) were presented to show the genetic difference of 6 serotypes (Fig. 3b). The X01 and X03 represented 3 S. Senftenberg and 8 S. Meleagridis strains, respectively (Fig. 3b). Except for one strain of S. London without clear DNA bands, the other 9 strains were distributed in 4 different profiles, which were X02, X05, X06, and X07 (Fig. 3b).

Among the 34 strains belonging to the B group, S. Typhimurium and S. Derby took up 85.3% with diverse PFGE profiles (Fig. 3c, d). Twelve profiles (X01 to X12) were identified in 19 S. Typhimurium strains (Fig. 3d). The X01, X02, X04, X05, X07, X019, and X12 profiles were detected in strains isolated from patients, while the X03, X08, X10, and X11 profiles were found in strains isolated from asymptomatic people (Fig. 3d). The X06 profile consists of five strains from both sources, but 80% (4/5) of them in this profile were from asymptomatic people (Fig. 3d). Except for one strain of S. Derby with smear patterns, the other 9 strains displayed 5 PFGE profiles (X01 to X05) with X01 and X04 as predominant profiles, each of which are shared by 3 strains (Fig. 3c). The only one strain F10–3 isolated from the patient belonged to the X04 genetic profile (Fig. 3c).

In our study, S. Enteritidis is the only detected serotype in the D group. Three profiles (X01, X02, and X03) were presented for 8 out of 9 S. Enteritidis strains. Four strains (F6–1, F10–1, F10–2, and F4–1) belonging to the X03 were obtained from patients, and X03 was identified as the predominant PFGE profile (6/8, 75%) for the 8 strains (Fig. 3e).

**Discussion**

**Distribution of Salmonella spp. in patients and asymptomatic people**

_Salmonella_ is one of the major pathogens causing human diarrhea, which is closely related to the consumption of bacterially contaminated foods. Therefore, _Salmonella_ reports have been published every year by the US National Enteric Disease Surveillance system, the European Food Safety Authority (EFSA), and the European Centre for Disease Prevention and Control (ECDC). According to the US and EU reports, _S. Enteritidis_ and _S. Typhimurium_ (including _S. Typhimurium_ monophasic variants) have been the top 2 serotypes causing human salmonellosis [6, 7]. Our study showed
that *S. Typhimurium* is the predominant serotype from diarrhea patients in Nantong city, followed by *S. Enteritidis*, correspondent to the previous reports in China [8]. However, in asymptomatic people, *S. London* became the predominant serotype as well as *S. Typhimurium*, followed by *S. Derby* and *S. Meleagridis*. The difference in serotype distribution in patients and asymptomatic people reflected that many NTS serotypes could infect humans without any symptom, but these serotypes were underestimated in the existing surveillance system for mostly patients. Additionally, these NTS serotypes have frequently been isolated from pig, chicken, and their associated meat products [14, 21], implying the potential transmission of *Salmonella* from animal foods to humans. Except for *S. Typhimurium* causing disease or no symptoms, *S. Rissen* displayed a similar characteristic to *S. Typhimurium* in human infection (Table 2). In 2009, *S. Rissen* caused >80 people infection in over 4 different states of the USA, and the cases for human infection by *S. Rissen* were also reported in Denmark, Thailand, UK, and China [22–24]. Among 208 *S. Rissen* isolates from human samples, 108 out of the isolates were from patients, 100 isolates were from the asymptomatic carriers [22], reflecting that nearly 50% of the people infected with *S. Rissen* were in the asymptomatic state as well as in our study (Table 2). However, some serotypes have been mainly isolated from patients, such as the typhoidal *S. Paratyphi A* (100%) obtained from blood samples, and nontyphoidal *S. Enteritidis* (77.8%) collected from diarrheagenic patients.

**Multidrug-resistance of *Salmonella* spp.**

Among the used 26 antimicrobial agents belonging to 8 different types, 84.1% (74/88) of *Salmonella* isolates showed resistance to at least three types of antimicrobials, which is dramatically higher than the reported 46 and 50% of *Salmonella* isolates from patients were MDR in Guangdong and Beijing, respectively [8, 15]. Among the 61 *Salmonella* isolates from asymptomatic people, 49.2% (30/61) of the strains showed resistance to 6 out of 8 types of antimicrobial agents, while 73.8% showed resistance to 5 types of antimicrobials. This
demonstrated that the NTS organisms from asymptomatic people showed strong resistance to antimicrobials as well as the human diarrheal or bloodborne isolates, which is similar to the report that 81.8% of *Salmonella* isolates from asymptomatic food handlers were MDR [25]. However, the result was different from the recently reported fewer MDR NTS isolates in asymptomatic children than in symptomatic individuals in Vietnamese [26]. Twenty-three out of 88 *Salmonella* isolates showed resistance to one or more antimicrobial agents belonging to extended-spectrum β-lactamases (ESBLs). One ESBL S. Thompson strain displayed resistance to all of the detected β-lactamases, including aztreonam, cefepime, cefazolin, ceftazidime, and amoxicillin/clavulanic acid. The emergence of ESBL-producing *Salmonella* may cause a substantial increase in treatment costs and prolonged treatment periodicity [27].

**PFGE differentiation of *Salmonella* strains**

Although the whole-genome sequencing (WGS)-based typing methods have been considered highly discriminating epidemiological tools, PFGE has a relatively high concordance with epidemiological relatedness [28]. The PFGE profiles not only showed perfect correspondence to serotypes belonging to C1, C2–3 or E1, E4 serogroups (Fig. 3a, b), but also displayed a highly discriminative ability to different strains of serotypes like *S. London*, *S. Newport*, and *S. Mbandaka*, which is potentially caused by the integration of new genetic elements for adaption to adverse conditions [29].

*S. Derby* is another frequently reported serotype isolated from both human and animal or animal foods. Most isolates were obtained from asymptomatic people, revealing that it is not the predominant serotype causing severe infections in humans. In this study, the 9*S. Derby* strains were divided into 5 profiles by PFGE analysis, which has been confirmed as a molecular subtyping method used to differentiate *S. Derby* strains (Fig. 3c). Ten PFGE profiles were obtained in 16 *S. Derby* strains of human origin with 9 antimicrobial resistance patterns [30]. With difference to *S. Derby*, *S. Typhimurium* is the predominant serotype causing either human diarrhea or asymptomatic infection [30]. Four clusters were identified in 19*S. Typhimurium* strains, most of which are distributed in cluster III, including 7 and 4 strains from asymptomatic people and patients, respectively (Fig. 3d). This is the reason for considering *S. Typhimurium* as one of the most important serotypes in the *National Salmonella* surveillance system [6]. Another serotype, *S. Enteritidis* has been confirmed as the predominant serotype causing human diarrhea, and it could not be efficiently differentiated by PFGE (Fig. 3e). Other molecular typing methods, such as CRISPR typing and whole-genome sequencing (WGS) based typing, can be further used to study the evolutionary relationship of these isolates [31, 32].

Although PFGE has been considered as the “gold standard” for bacterial typing, the WGS has superior resolution to PFGE, and it can differentiate isolates which were indistinguishable by PFGE. WGS can distinguish strains with difference at only a single nucleotide and provide higher resolution than the other molecular typing methods [33]. In this study, the PFGE showed high discriminatory power in some serotypes, such as *S. Typhimurium*, but it could not efficiently distinguish *S. Enteritidis* isolates. Further analysis will be performed to reveal the relationship of the isolates belonging to the same serotype from different sources.

**Conclusion**

This study compared the serotypes, antimicrobial resistance phenotypes, and genetic profiles of *Salmonella* strains between asymptomatic people and patients. The results revealed that *S. Typhimurium* is the predominant serotype causing human infection in both symptomatic and asymptomatic state. The other NTS including *S. London*, *S. Derby*, and *S. Meleagridis* mainly cause asymptomatic infection, while *S. Enteritidis* infection commonly results in human diseases. The high multi-drug resistance rate detected in these strains and diverse PFGE profiles showed no significant difference in strains between symptomatic and asymptomatic individuals, implying that all human-related *Salmonella* strains can induce both human salmonellosis and asymptomatic infection. Therefore, increased surveillance of *Salmonella* from both patients and asymptomatic people should be taken to control the transmission of the pathogen.

**Abbreviations**

NTS: Nontyphoidal Salmonella; MDR: Multidrug-resistant; EFSA: European Food Safety Authority; PFGE: Pulsed-field gel electrophoresis; CFU: Colony-forming unit; AMP: Ampicillin; AMS: Amoxicillin-clavulanic acid; ATCC: American Type Culture Collection; CRISPR: Clustered regularly interspaced short palindromic repeats; WGS: The Whole-genome sequencing; ESBLs: Extended-spectrum β-lactamases; UPGMA: The arithmetic mean algorithm; UV: Ultraviolet

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12879-021-06340-z.

**Additional file 1:** Supplementary Table 1. The information and antimicrobial resistance phenotype of human *Salmonella* isolates.
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Authors’ contributions

HX and QL conceived the design of this study. HX, WBZ, and WZ collected the bacteria strains and performed the experiments. KZ, YZ, and ZW facilitated the data collection and performed the analysis. HX drafted the manuscript. KZ, YL, and QL revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Declarations

Ethics approval and consent to participate

This study received ethical approval by the Human Research Ethics Committee of Nantong Center for Disease Control and Prevention (38–2017–1701). All the bacterial isolates were provided with written consents for the research in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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