Ciprofloxacin-Resistant Salmonella enterica Serotype Typhi, United States, 1999–2008

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We report 9 ciprofloxacin-resistant Salmonella enterica serotype Typhi isolates submitted to the US National Antimicrobial Resistance Monitoring System during 1999–2008. The first 2 had indistinguishable pulsed-field gel electrophoresis patterns and identical gyrA and parC mutations. Eight of the 9 patients had traveled to India within 30 days before illness onset.

Typhoid fever, caused by Salmonella enterica serotype Typhi, is a systemic bacterial illness that has been rare in the United States in the era of modern sanitation (1,2). However, typhoid fever remains common in many developing countries. In the United States, 72%–81% of patients with typhoid fever report international travel in the month before illness onset (1,3–5). Highest risk has been associated with travel to southern Asia (1–5).

Fluoroquinolones (e.g., ciprofloxacin) are frequently used to treat typhoid fever in adults (4,6). Ciprofloxacin resistance is rare; however, resistance to the quinolone nalidixic acid in the US National Antimicrobial Resistance Monitoring System (NARMS) increased from 19% of isolates tested in 1999 to 59% in 2008 (7). Nalidixic acid resistance in S. enterica serotype Typhi, which has been associated with overseas travel, particularly to southern Asia, correlates with decreased susceptibility to ciprofloxacin (MIC ≥0.12 μg/mL) (4–6,8). Increased risk for fluoroquinolone treatment failure has been demonstrated in Salmonella infections from strains with decreased susceptibility to ciprofloxacin (6,8,9). Chromosomal point mutations in the gyrA and parC topoisomerase genes are mechanisms of quinolone resistance in Salmonella spp. Other resistance mechanisms include efflux pumps, reduced outer membrane permeability, and plasmid-borne genes (e.g., qnr, aac-6’-Ib-cr genes) (6,8,10–12). We report 9 ciprofloxacin-resistant (MIC ≥4 μg/mL) S. enterica serotype Typhi isolates detected in the United States during 1999–2008.

The Cases

State public health laboratories receive Salmonella isolates from clinical diagnostic laboratories as part of routine surveillance. State and local health department officials report demographic, clinical, and travel information about laboratory-confirmed typhoid fever on a standard form to the Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA). Participating states began submitting all S. enterica serotype Typhi isolates to NARMS in 1999; since 2003, all state public health laboratories have participated. Isolates were tested for susceptibility by using broth microdilution (Sensititre: Trek Diagnostics, Westlake, OH, USA). MICs were determined for 15 antimicrobial agents and interpreted by using Clinical and Laboratory Standards Institute (CLSI) criteria when available (Table 1) (7,13). For ciprofloxacin-resistant isolates, subtyping by pulsed-field gel electrophoresis (PFGE) was performed by using the protocol established by the National Molecular Subtyping Network for Foodborne Disease Surveillance (PulseNet) (14). PFGE pattern similarity was assessed by cluster analysis (Dice, UPGMA [unweighted pair group method using arithmetic averages]) and band-matching applications of BioNumerics software (Applied Maths, Sint-Martens-Latem, Belgium) and confirmed by visual comparison (Figure). For ciprofloxacin-resistant isolates detected for 1999–2005, sequencing of the quinolone resistance–determining region (QRDR; defined as amino acids 67–106 for gyrA) was performed according to the methods described by Crump et al. (6), and additional patient information (e.g., antimicrobial drug treatment) was requested by using a questionnaire with institutional review board approval.

During 1999–2005, we detected 2 (0.1%) cases of ciprofloxacin resistance among 1,690 S. enterica serotype Typhi isolates. Case reports follow.

In 2003, a 1-year-old girl had onset of fever 1 day before arriving in the United States from India. A blood specimen collected 3 days after fever onset yielded S. enterica serotype Typhi. Diarrhea or vomiting at time of specimen collection was not reported. Information about
antimicrobial drug treatment was not available. The child was hospitalized for 14 days.

In 2005, a 2-year-old girl had onset of diarrhea, which was treated with ofloxacin, 2 days before she arrived in the United States from India. Seven days later, she continued to have diarrhea, and fever, vomiting, and abdominal cramps developed. She was hospitalized and treated with antimicrobial agents, including ciprofloxacin. Blood and fecal specimens collected 3 weeks after illness onset yielded *S. enterica* serotype Typhi. The patient was discharged after 14 days of hospitalization. She had lived in India for 6 months before traveling to the United States.

The *S. enterica* serotype Typhi isolates were resistant to ciprofloxacin (Tables 1, 2) and had indistinguishable PFGE patterns when restriction enzymes *Xba*I and *Bln*I were used: PulseNet-designated *Xba*I pattern JPPX01.0026 and *Bln*I pattern JPPA26.0110 (Table 2; Figure). QDRR sequencing showed gyrA mutations resulting in a serine to tyrosine substitution at codon 83 and an aspartic acid to asparagine substitution at codon 87, and a parC mutation conferring a serine to isoleucine substitution at codon 80.

Seven (0.6%) ciprofloxacin-resistant infections were detected among patients from whom 1,131 *S. enterica* serotype Typhi isolates were submitted during 2006–2008 (Table 2). The 7 cases occurred in 2006 and 2007. Patients were a median of 22 years of age (range 5–48 years); 5 (71%) were male. All 6 patients with known travel histories reported travel to India in the 30 days before illness onset. In addition to *Xba*I JPPX01.0026 and *Bln*I JPPA26.0110, 3 different *Xba*I and *Bln*I pattern combinations were detected in the 7 isolates (Table 2; Figure).

**Conclusions**

We describe ciprofloxacin-resistant *S. enterica* serotype Typhi isolates from 9 patients in the United States. The first 5 cases were reported previously in aggregated form, without molecular characterization of the isolates (5). The first 2 patients were young children apparently infected in India in 2003 and 2005.
Figure. Pulsed-field gel electrophoresis (PFGE) XbaI (A) and BlnI (B) patterns of 9 ciprofloxacin-resistant Salmonella enterica serotype Typhi isolates detected in the National Antimicrobial Resistance Monitoring System, 1999–2008. PFGE pattern similarity was assessed by cluster analysis (Dice, UPGMA [unweighted pair group method using arithmetic average]) and band-matching applications of BioNumerics software (Applied Maths, Sint-Martens-Latem, Belgium) and confirmed by visual comparison. PulseNet only considers band markings found within the scale of the global standard, which are all bands between 20.5 kb and 1,135 kb. The cluster parameters are Dice coefficient and UPGMA with the tolerance of band position of 1.5% and optimization of 1.5%.

Six additional patients, who were detected in 2006 and 2007, also reported travel to India. Travel to the Indian subcontinent has been associated with nalidixic acid-resistant S. enterica serotype Typhi infection; however, ciprofloxacin-resistant infections are rarely reported by using current CLSI criteria (4,5,11). Other resistance patterns were first described in southern Asia, where the incidence of typhoid fever is high and antimicrobial agents are widely available without prescription, providing the opportunity for the development and selection of resistant strains (8).

Other than reports by 8 patients of travel to India, we have no information about possible shared exposures, such as specific locations visited, sources of food or water, or contact with carriers of S. enterica serotype Typhi. However, the indistinguishable PFGE XbaI and BlnI patterns and identical gyrA and parC mutations of isolates from the first 2 patients suggest that, although typhoid fever occurred nearly 2 years apart, the same ciprofloxacin-resistant strain is likely to have been involved. After 2005, different XbaI and BlnI patterns have been identified in ciprofloxacin-resistant isolates, indicating independent selection of ciprofloxacin resistance in different strains.

The gyrA and parC mutations of isolates from the first 2 patients were reported in ciprofloxacin-resistant S. enterica serotype Typhi in India (11). The 2 gyrA mutations are well characterized and known to be associated with quinolone resistance; 2 point mutations in gyrA and 1 in parC confer fluoroquinolone resistance (8,10–12). Further studies, including characterization of other resistance mechanisms,

Table 2. Patient and isolate description, resistance to other antimicrobial agents, PFGE pattern, and travel reported for 9 ciprofloxacin-resistant Salmonella enterica serotype Typhi infections detected in the National Antimicrobial Resistance Monitoring System, United States, 1999–2008

| Patient no. (isolate) | Age, y/sex | Site | Specimen collection year | Specimen source | Resistance to other agents | PFGE XbaI pattern† | PFGE BlnI pattern‡ | Travel§ |
|-----------------------|------------|------|------------------------|----------------|--------------------------|-------------------|------------------|---------|
| 1 (MA-03)             | 1/F MA     | 2003 | Blood                  | Cot, Fis, Nal, Tet | JPPX01.0026              | JPPA26.0110       | India            |
| 2 (CA-05)             | 2/F CA     | 2005 | Blood                  | Cot, Fis, Nal, Tet | JPPX01.0026              | JPPA26.0110       | India            |
| 3 (CA-06)             | 26/F CA    | 2006 | Blood                  | Nal             | JPPX01.0506              | JPPA26.0187       | India            |
| 4 (TX-06)             | 8/M TX     | 2006 | Blood                  | Amp, Chl, Cot, Fis, Nal Str | JPPX01.0465 | JPPA26.0170       | India, others    |
| 5 (AZ-06)             | 5/M AZ     | 2006 | Stool                  | Cot, Fis, Nal, Tet | JPPX01.0026              | JPPA26.0110       | India            |
| 6 (NY-07)             | 6/M NYC    | 2007 | Stool                  | Nal             | JPPX01.0506              | JPPA26.0187       | India            |
| 7 (CA-07)             | 22/M CA    | 2007 | Stool                  | Cot, Fis, Nal, Tet | JPPX01.0026              | JPPA26.0110       | India            |
| 8 (NJ-07)             | 28/M NJ    | 2007 | Blood                  | Nal             | JPPX01.0026              | JPPA26.0002       | Unknown          |
| 9 (LAC-07)            | 48/F LAC   | 2007 | Blood                  | Nal             | JPPX01.0026              | JPPA26.0187       | Unknown          |

†PFGE, pulsed-field gel electrophoresis. State/local public health laboratories that submitted isolates: MA, Massachusetts; CA, California; TX, Texas; AZ, Arizona; NYC, New York City; NJ, New Jersey; LAC, Los Angeles County, California. Resistance to antimicrobial agents other than ciprofloxacin: Cot, trimethoprim–sulfamethoxazole; Fis, sulfamethoxazole or sulfisoxazole; Nal, nalidixic acid; Tet, tetracycline; Amp, ampicillin; Chl, chloramphenicol; Str, streptomycin.

‡PulseNet-designated PFGE patterns using restriction enzyme BlnI (data as of 2009 Oct 21): JPPX01.0026, the most common BlnI pattern among 409 isolates with reported BlnI pattern in PulseNet, was detected in 61 (14.9%) isolates; JPPA26.0110 was detected in 5 (1.2%), JPPA26.0187 was detected in 3 (0.7%), and JPPA26.0170 was detected in 1 (0.2%).

§Travel outside the United States reported in the 30 d before illness onset; patient 4 also traveled to Bangladesh and the United Arab Emirates.

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are needed to track the evolution of fluoroquinolone-resistant S. enterica serotype Typhi.

Although the ciprofloxacin resistance we detected using current CLSI criteria is rare in S. enterica serotype Typhi, nalidixic acid resistance, which correlates with decreased susceptibility to ciprofloxacin, has increased (7). Clinicians should be aware that infection with Salmonella spp. with decreased susceptibility to ciprofloxacin may not respond satisfactorily to this agent (6,8,9,13,15). In addition, identification of ciprofloxacin-resistant cases has been increasing. In the presence of quinolone resistance, third-generation cephalosporins, such as ceftriaxone, can be used (2,6,8,15). Recent clinical trials suggest that azithromycin might be useful for treating uncomplicated typhoid fever (2,8,9,15). Recommendations for empiric treatment of typhoid fever in the United States are best developed by using information about antimicrobial drug resistance trends in isolates from countries where the infection was acquired.

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