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Extended-Spectrum-Beta-Lactamase Production in a *Salmonella enterica* Serotype Typhi Strain from the Philippines▽

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A *Salmonella enterica* serotype Typhi strain was cultured from blood and fecal samples from a 54-year-old man with fever and diarrhea. He had returned from travel to the Philippines a few days earlier. Phenotypic and genotypic analysis confirmed the production of the SHV-12 extended-spectrum beta-lactamase.

Resistance to cephalosporins, due to the production of extended-spectrum β-lactamases (ESBLs), is an ever increasing problem and is a cause of serious concern worldwide. So far, these enzymes have been detected in many species of the family *Enterobacteriaceae*, including different serovars of *Salmonella enterica* (11). To the best of our knowledge, however, ESBL production in *Salmonella enterica* serovar Typhi is as yet unknown. *Salmonella* serovar Typhi is the causative agent of typhoid fever, a severe systemic *Salmonella* infection with high rates of morbidity and mortality, especially in tropical and subtropical countries. Infection occurs by the ingestion of contaminated water or food. Through the use of proper sanitation and hygiene measures and effective antimicrobial chemotherapy, the rates of morbidity and mortality from typhoid fever have been greatly reduced in developed countries, while large outbreaks still occur in developing countries (6). *Salmonella* spp. are usually susceptible to many antimicrobial agents, but a recent increase in the rates of resistance raises are of concern (14). The prevalence of multidrug-resistant *Salmonella* serovar Typhi is also increasing among travelers who have returned from areas where *Salmonella* serovar Typhi is endemic (4). We isolated a strain of *S. enterica* serotype Typhi from blood and fecal samples from a 54-year-old Dutch man who was admitted to the Waterland Hospital in Purmerend, The Netherlands, at the end of November 2007, with signs and symptoms of typhoid fever. These symptoms started 2 weeks after he had returned from a 2-month visit to the Philippines. The patient was successfully treated with ciprofloxacin at 500 mg orally twice daily for 3 weeks. The *Salmonella* serovar Typhi strain was resistant to extended-spectrum cephalosporins but was sensitive to amoxicillin-clavulanate. We investigated whether the resistance to the extended-spectrum cephalosporins was due to the production of an ESBL.

The strain was identified as *S. enterica* serotype Typhi with the Vitek-2 system (BioMerieux, Boxtel, The Netherlands) and by agglutination with *Salmonella* antisera (Remel, United Kingdom). Genomic species determination was confirmed by partial 500-bp sequence analysis of the 16S rRNA gene and by DNA fingerprinting by amplified fragment length polymorphism analysis (12). Antibiotic susceptibilities were determined according to the guidelines of the Clinical Laboratory Standards Institute with the Vitek-2 system (BioMerieux) and Etest (AB Biodisk, Solna, Sweden). ESBL production was detected by a combined disk test (10) and ESBL Etest (AB Biodisk). The ESBL genes were identified by PCR; and subsequent sequence analysis was performed with SHV-, TEM-, and CTX-M-specific primers, which detect the bla_{SHV}, bla_{TEM}, and $bla_{\mathrm{CTX\text{-}M}}$ genes, respectively, as described previously (1, 2).

Phenotypically, the strain was resistant to gentamicin, tobramycin, piperacillin, and trimethoprim-sulfamethoxazole and was sensitive to amoxicillin-clavulanate, ciprofloxacin, meropenem, and piperacillin-tazobactam (Table 1). This strain was also sensitive to chloramphenicol, which is remarkable, as *Salmonella* species are frequently resistant to this antibiotic. PCR and sequence analysis revealed the presence of the genes for SHV-12 and TEM-1. The SHV-12 ESBL enzyme differs from the SHV-1 enzyme by three amino acids substitutions, and it was first described in a *Klebsiella pneumoniae* strain isolated in Switzerland (8). The SHV-12 ESBL is one of the most common non-CTX-M ESBLs and is identified in many gram-negative species, including *Salmonella* species (2, 15). TEM-1 is the most commonly encountered beta-lactamase in the *Enterobacteriaceae*, and it is able to hydrolyze narrow-spectrum penicillins and cephalosporins, such as cephalothin and cephaloridine (10). ESBL production was detected in *Salmonella enterica* strains of different serovars in several countries, like Italy, France, and Nepal; however, to the best of our knowledge, this is the first report to describe an infection caused by an ESBL-producing *S. enterica* serotype Typhi strain.

Typhoid fever is a serious systemic infectious disease with high rates of morbidity and mortality and requires optimal antimicrobial therapy. Multidrug resistance among *S. enterica* serotype Typhi strains is increasing, especially in Southeast Asia (5) and in the Middle East and northeastern Africa (3, 7,

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TABLE 1. MICs for *Salmonella* serovar Typhi

Antibiotic	MIC (mg/liter)
Ampicillin	≥32
Amoxicillin-clavulanic acid	4
Piperacillin	≥128
Piperacillin-tazobactam	≤4
Ceftazidime	48
Cefotaxime	6
Cefpodoxime	≥8
Chloramphenicol	2
Gentamicin	≥16
Tobramycin	8
Ciprofloxacin	≤0.25
Trimethoprim-sulfamethoxazole	80
Cefoxitin	≤4
Meropenem	≤0.25

9). Extended-spectrum cephalosporins, in particular, ceftriaxone, are the drugs of choice for the treatment of infections due to ampicillin- and fluoroquinolone-resistant *Salmonella* serovar Typhi (13). The emergence of an ESBL in *S. enterica* serotype Typhi constitutes a new challenge. This emergence may be explained by the exchange of mobile genetic elements, such as plasmids and transposons, between enteric bacteria and is selected for by the antimicrobial agents used for humans, especially extended-spectrum cephalosporins. Since ESBL genes are nearly always located on mobile genetic elements, further rapid spread among *Salmonella* strains is to be expected.

We provide evidence of the production of an ESBL, SHV-12, in *Salmonella enterica* serotype Typhi due to the presence of a bla_{SHV} gene. This is a worrisome finding with potential serious clinical implications, since the dissemination of this resistance trait will further hamper the therapeutic possibilities for the treatment of typhoid fever.

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