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Short Report: Increasing Fluoroquinolone Resistance in *Salmonella typhi* in Ontario, 2002–2007

Shaun K. Morris,* Susan E. Richardson, Laura J. Sauve, E. Lee Ford-Jones, and Frances Jamieson

Division of Infectious Diseases, Hospital for Sick Children and The University of Toronto, Toronto, Canada; Department of Microbiology, Hospital for Sick Children, The University of Toronto, and Ontario Agency for Health Protection and Promotion, Toronto, Canada; Division of Infectious and Immunologic Diseases, British Columbia Children's Hospital and The University of British Columbia, Vancouver, Canada; Division of Social Pediatrics, Hospital of Sick Children and The University of Toronto, Toronto, Canada; Department of Laboratory Medicine and Pathobiology, The University of Toronto and Ontario Agency for Health Protection and Promotion, Toronto, Canada

Abstract. We reviewed the antibiotic susceptibility patterns of all isolates of *Salmonella typhi* in Ontario, Canada from January 2002 to December 2007. We identified a total of 381 unique cases over the 5-year period (50–73 cases per year). Of the 381 cases, 171 were female, 164 were male, and no gender was identified for 33 cases. Age of the patients ranged from less than 1 to 102 years of age (median age of 20 years). Although resistance patterns for ampicillin, trimethoprim-sulfamethoxazole, third generation cephalosporins (cefotaxime until May 2005 and ceftriaxone from June 2005 to present), and chloramphenicol remained stable, nalidixic acid resistance rose sharply between 2003 and 2005 and has remained at approximately 80% of isolates since 2005. The significant and sustained increase in nalidixic acid-resistant *S. typhi* suggests that ciprofloxacin should no longer be used as the drug of choice for the empiric treatment of typhoid fever in Ontario.

Typhoid fever, caused by *Salmonella typhi*, remains an important global public health issue. Although the risk of acquiring the disease in developed countries is low, imported cases are not uncommon, reflecting travel from endemic areas, especially the Indian subcontinent. According to the 2006 Canadian census, between 2001 and 2006, 64.6% of immigrants to Ontario (2006 census population of 12.16 million) came from Asia. India is the leading country of origin for Asian immigrants, with Pakistan third, and Sri Lanka the fifth most common.[1] Until the early 1990s, the treatment of choice for typhoid fever was ampicillin, choloramphenicol, or trimethoprim-sulfamethoxazole. However, because of increasing resistance to these drugs, ciprofloxacin replaced them as the drug of choice in the early 1990s, with good clinical efficacy.[2] Reduced susceptibility and *in-vitro* resistance to ciprofloxacin followed shortly thereafter, accompanied by clinical treatment failures.[3,4]

Reduced susceptibility to fluoroquinolones in *Salmonella* spp. most often arises from point mutations in the quinolone resistance determinant (QRDR) of the *gyrA* gene encoding the A subunit of DNA gyrase. In the microbiology laboratory, this is detected by resistance to nalidixic acid and increased minimum inhibitory concentration (MIC) to ciprofloxacin, though ciprofloxacin usually remains within the susceptible range for *Enterobactireaceae*.[5] In 2003, the Clinical Laboratory Standards Institute (CLSI) included testing for resistance to nalidixic acid (nalidixic acid-resistant *S. typhi*, or NARST) as an indicator of reduced fluoroquinolone susceptibility in *Salmonella* spp.[6,7] *Salmonella typhi* is considered to be resistant to naladixic acid at an MIC equal to or greater than 32 mg/L. It is considered to be intermediate to ciprofloxacin at an MIC equal to 2 mg/L and resistant at an MIC equal to or greater than 4 mg/L.

We reviewed the antibiotic susceptibility patterns of all unique isolates of *S. typhi* in Ontario, Canada from January 2002 to December 2007. In Ontario, all isolates of *S. typhi* are sent to the Central Public Health Laboratory (CPHL) for confirmatory identification and antibiotic susceptibility testing (AST). The AST was performed by agar dilution according to CLSI recommendations.[8] In June of 2003, nalidixic acid was added to the AST protocol for *S. typhi.* Isolates susceptible to ciprofloxacin, but resistant to nalidixic acid were reported as susceptible to ciprofloxacin with the following comment: "This strain is resistant to nalidixic acid. Fluoroquinolone-susceptible strains of *Salmonella* that test resistant to nalidixic acid may be associated with clinical failure or delayed response in fluoroquinolone-treated patients with extra-intestinal salmonellosis."

We identified a total of 381 unique cases over the 5-year period (50–73 cases per year, Figure 1). Of the 381 cases, 171 were female, 164 were male, and no gender was identified for 33 cases (Figure 2). Age of the patients ranged from less than 1 to 102 years of age (median age 20 years). During this period of time, there were no documented outbreaks of infection in Ontario. All cases were travel-related or linked to someone who had traveled. Figure 3 shows antibiotic resistance patterns for ampicillin, trimethoprim-sulfamethoxazole, third generation cephalosporins (cefotaxime until May 2005 and ceftriaxone from June 2005 to present), chloramphenicol, ciprofloxacin, and nalidixic acid. Although resistance to other antimicrobials remained stable, nalidixic acid resistance rose sharply between 2003 and 2005, and has remained at approximately 80% of isolates since 2005.

The significant and sustained increase in nalidixic acid-resistant *S. typhi* suggests that ciprofloxacin should no longer be used as the drug of choice for the empiric treatment of typhoid fever in Ontario. Similar recommendations hold true for other settings including the United States, in which the majority of imported cases originate in travelers and immigrants from the Indian subcontinent, or where the prevalence of NARST in isolates of *S. typhi* is known to be high.[9] All individuals arriving from South Asia with typhoid fever should be considered at high risk for having a fluoroquinolone resistant strain of *S. typhi*. A recent prospective population-based study in five Asian countries confirmed that

* Address correspondence to Shaun K. Morris, Division of Infectious Diseases, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada, M5G 1X8. E-mail: shaun.morris@utoronto.ca

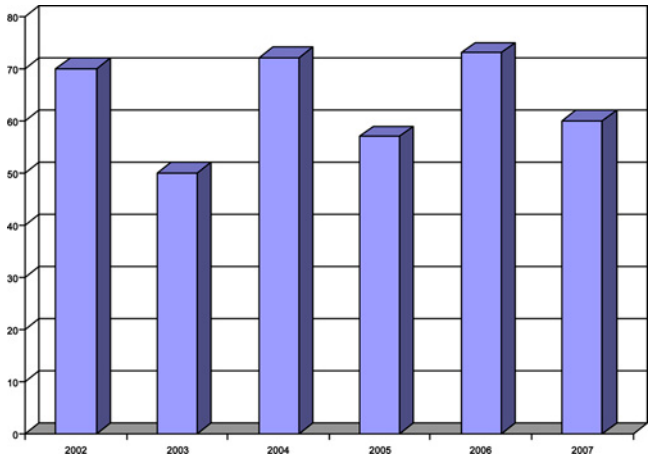

FIGURE 1. *Salmonella typhi* cases per year in Ontario, 2002–2007. This figure appears in color at www.ajtmh.org.

S. typhi resistance to naladixic acid is greater than 50% in both India and Pakistan.[10] In cases of fluoroquinolone resistance, therapeutic alternatives include a third generation cephalosporin, or azithromycin for those with a beta lactam allergy. It will be important to establish standardized interpretive criteria for AST of azithromycin with respect to *Salmonella* spp. Although azithromycin is recommended for the treatment of *S. typhi* infections, no AST guidelines exist at present.

Enteric fever caused by *S. typhi* remains an important clinical and public health problem which, as a result of travel and immigration, is not rare in the developed world. Given the documented ability of *S. typhi* to develop resistance to various antibiotics, it is important for clinicians to remain aware of changing trends in antimicrobial resistance of *S. typhi* to ensure appropriate therapy for this potentially fatal disease.

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Authors' addresses: Shaun K. Morris, Division of Infectious Diseases, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada, M5G 1X8, and the University of Toronto, Tel: 416-813-7807, Fax: 416-813-5032, E-mail: shaun.morris@utoronto.ca. Susan E. Richardson, Division of Microbiology, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada, M5G 1X8, the University of Toronto, and Ontario Agency for Health Protection and Promotion, E-mail: susan.richardson@sickkids.ca. Laura J. Sauve, Division of Infectious Diseases, British Columbia Children's Hospital, 4480 Oak Street, Vancouver, British Columbia, Canada, V6H 3N1, and the University of British Columbia, E-mail: lsauve@cw.bc.ca. E. Lee Ford-Jones, Division of Social Pediatrics, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada, M5G 1X8, and the University of Toronto, E-mail: lee.ford-jones@sickkids.ca. Frances Jamieson, Public Health Laboratories – Toronto, Ontario Agency for Health Protection and Promotion, 81 Resources Rd., Toronto, Ontario, Canada, M9P 3T1, Ontario Agency for Health Protection and Promotion, and Department of Laboratory Medicine and Pathobiology, University of Toronto, E-mail: frances.jamieson@oahpp.ca.

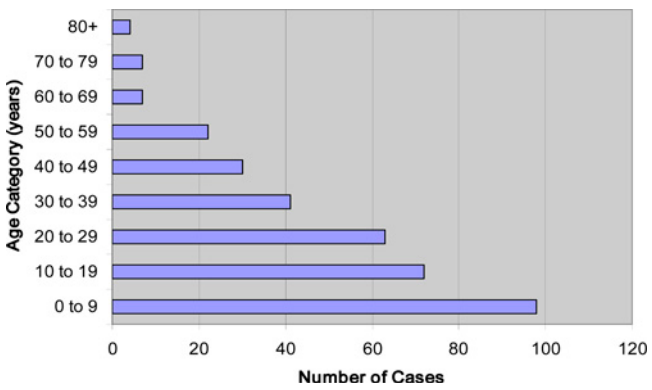

FIGURE 2. Cumulative age breakdown of cases. This figure appears in color at www.ajtmh.org.

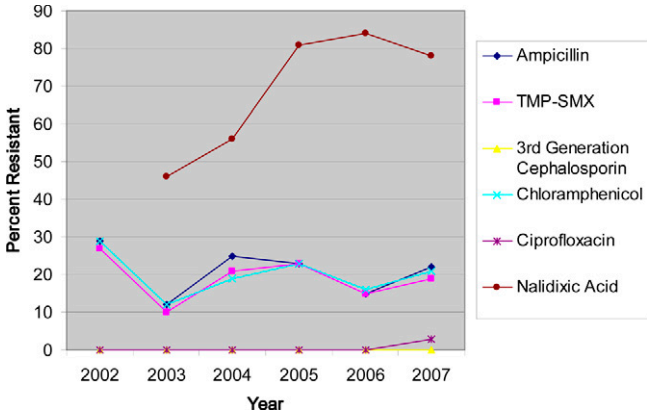

FIGURE 3. Changes in *Salmonella typhi* antibiotic resistance. This figure appears in color at www.ajtmh.org.

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