Antimicrobial resistance among Salmonella and Shigella isolates in five Canadian provinces (1997 to 2000)

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OBJECTIVE: To describe rates of antimicrobial resistance (AMR) among Salmonella and Shigella isolates reported in five Canadian provinces, focusing on clinically important antimicrobials.

METHODS: The authors retrospectively investigated AMR rates among 6219 Salmonella and 1673 Shigella isolates submitted to provincial public health laboratories in Alberta, Newfoundland and Labrador, Ontario, Prince Edward Island and Saskatchewan from 1997 to 2000; these isolates were estimated to represent 41% of Salmonella cases and 72% of Shigella cases reported by the study provinces.

RESULTS: Among Salmonella isolates, 27% (1704 of 6215) were resistant to ampicillin, 2.2% (135 of 6122) to trimethoprim/sulfamethoxazole, 1.5% (14 of 938) to nalidixic acid, 1.2% (one of 84) to lomafloxacin and 0.08% (five of 6163) to ciprofloxacin. Among Shigella isolates, 70% (1144 of 1643) were resistant to trimethoprim/sulfamethoxazole, 65% (1079 of 1672) to ampicillin, 3.1% (eight of 262) to nalidixic acid, 0.49% (eight of 1636) to ciprofloxacin, 0.14% (one of 700) to ceftriaxone and 0.08% (one of 1292) to ceftazidime.

CONCLUSIONS: Higher rates of resistance to clinically important antimicrobials (including ciprofloxacin) were observed among both Salmonella and Shigella isolates than has previously been reported. Current Canadian data on rates of AMR for these pathogens are required.

Key Words: Canada; Drug resistance; Microbial; Salmonella; Shigella

Salmonella and Shigella are important causes of acute gastrointestinal illness, with a mean of 20 and 4.4 cases per 100,000 population, respectively, reported annually in Canada between 1997 and 2000 (1). In recent years, high rates of antimicrobial resistance (AMR) to multiple antimicrobial classes have been described for these pathogens (2-5); however, little information describing AMR rates for Salmonella and Shigella isolates reported in Canada is available. Comprehensive information on AMR is essential; it enables clinicians to make informed decisions regarding appropriate antimicrobial therapies, improves our knowledge about organisms with emerging resistance, and provides baseline information to evaluate the effectiveness of interventions aimed at minimizing the impact of AMR on human health. The present study describes AMR rates among Salmonella and Shigella isolates tested in five Canadian provinces (Alberta [AB], Newfoundland and Labrador [NL], Ontario [ON], Prince Edward Island [PE] and Saskatchewan [SK]) from 1997 to 2000, emphasizing clinically important antimicrobials to provide baseline data and recommendations for future research activities.

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TABLE 1
Study data and testing methods (1997 to 2000) in a study examining antimicrobial resistance among Salmonella and Shigella isolates in five Canadian provinces

| Province                        | Antimicrobial resistance testing method | Isolates tested, n (%) | Median number of antimicrobials tested (range) | Isolates tested, n (%) | Median number of antimicrobials tested (range) |
|---------------------------------|----------------------------------------|------------------------|-----------------------------------------------|------------------------|-----------------------------------------------|
| Alberta                         | VITEK (GNS 606 cards)*                 | 1559 (25)              | 13 (1–19)                                     | 583 (35)               | 12 (4–20)                                     |
| Newfoundland and Labrador       | Disk diffusion                          | 26 (0.42)              | 9 (8–9)                                       | 0 (0.0)                |                                              |
| Ontario                         | Agar dilution                           | 3959 (64)              | 14 (1–17)                                     | 884 (53)               | 14 (4–17)                                     |
| Prince Edward Island            | Microscan (Panel 12)†                  | 87 (1.4)               | 32 (29–32)                                    | 3 (0.18)               | 32 (32)                                       |
| Saskatchewan                    | Microscan (Panel 5)‡                   | 588 (8.5)              | 12 (6–22)                                     | 203 (12)               | 12 (1–24)                                     |
| Total                           | –                                      | 6219 (100)             | 14 (1–32)                                     | 1673 (100)             | 14 (1–32)                                     |

*bioMérieux Vitek, USA; †No test results for Shigella isolates were provided for Newfoundland and Labrador; ‡Dade International, USA.

METHODS

AB, NL, ON, PE and SK provided available data on human Salmonella and Shigella isolates tested for AMR. Data available differed by province by time span of availability (for NL, data were only available between 1999 and 2000), antimicrobials tested and bacterial typing methods (Table 1). Laboratories used standard methods for identification of Salmonella and Shigella species. The University of Guelph (Guelph, Ontario) provided ethical approval of the study.

Data cleaning

The National Committee for Clinical Laboratory Standards (now the Clinical and Laboratory Standards Institute) guidelines (6) were used to interpret minimum inhibitory concentrations; isolates with minimum inhibitory concentrations in the intermediate range of resistance were classified as resistant. Isolates were eliminated if they were not submitted between 1997 and 2000, not tested for antimicrobial susceptibility or missing susceptibility results, known to be nonhuman in origin (either animal or environmental samples, although some not labelled as such may have remained in the data) or missing genus information. Laboratories may have tested a sample from a single case more than once, creating more than one test result per case. For provinces that provided laboratory or patient numbers, isolates were defined as duplicates if they had the same identification number, were the same organism (at the serotype level for Salmonella and serogroup level for Shigella), had the same antimicrobial resistance pattern, and were collected or received in the same calendar month and year. If the number of antimicrobials tested differed by duplicate isolate, the isolate tested for the greater number of antimicrobials was retained.

Investigating AMR

Resistance was investigated by antimicrobial class (stratified by the most prevalent Salmonella serotypes and Shigella serogroups) and by resistance to antimicrobials of particular clinical importance. Analyses were conducted using SAS version 9.1 (SAS Institute, USA).

RESULTS

Salmonella

After 48 duplicates were removed and exclusion criteria were applied, 6219 Salmonella isolates submitted by the five study provinces were included in the analyses (Table 1). One hundred thirty-one (2.1%) isolates were Salmonella enterica serovar Typhi (S typhi) and 19 (0.31%) were Salmonella paratyphi; the most common non-Typhi serotypes were Salmonella typhimurium (n=2832 [46%]; 151 serovar Copenhagen), Salmonella Heidelberg (n=747 [12%]), Salmonella enteritidis (n=699 [11%]) and Salmonella hadar (n=342 [5.5%]). Genus information alone was available for two isolates. Isolates were most commonly sampled from stool or rectal swabs (n=3864 [62%]), followed by blood (n=131 [2.1%]), urine (n=65 [1.0%]) and other sources (n=30 [0.48%]); specimen source was unknown or not provided for 2129 (34%) isolates. The median age for patients with Salmonella was 22.0 years (age range of less than one to 97 years) (n=5843); 51% of isolates were from female patients (n=6071).

Among the four most common Salmonella serotypes, S typhimurium isolates had the highest rates of resistance in five of antimicrobial classes: extended-spectrum penicillins (50%), chloramphenicol (44%), beta-lactam/beta-lactamase inhibitor combinations (27%), sulfonamides and trimethoprim (15%), and quinolones (0.25%). S hadar isolates showed the highest rates of resistance to tetracyclines (93%), aminoglycosides (25%) and other beta-lactams (23%). S enteritidis showed low rates of resistance (under 7%) in every antimicrobial class except nitrofurantoin, where S enteritidis and S typhimurium were similarly resistant (49% and 47%, respectively).

Among antimicrobials of particular clinical importance, five Salmonella isolates (0.08%) were resistant to ciprofloxacin, two (0.10%) to norfloxacin, six (1.0%) to imipenem, one (1.2%) to lomefloxacin, and 14 (1.5%) to nalidixic acid; no resistance was observed for levofloxacin (n=174) (Table 2). Higher rates of resistance were observed for ampicillin (27%) and trimethoprim/sulfamethoxazole (T/S) (2.2%), and low rates were observed for the third-generation cephalosporins ceftazidime (47 isolates [1.0%]), cefotaxime (29 isolates [0.68%]) and ceftriaxone (10 isolates [0.46%]) (Table 2).

Shigella

After 21 duplicates were removed and exclusion criteria were applied, data on 1673 Shigella isolates, submitted by all provinces except NL, were included in the analyses (Table 1): 1176 (70%) Shigella sonnei isolates, 411 (25%) Shigella flexneri isolates, 57 (3.4%) Shigella boydii isolates, 24 (1.4%) Shigella dysenteriae isolates, and five (0.30%) isolates of unknown serogroup. Isolates originated from stool, anal or rectal swabs (n=1114 [67%]), or from blood samples (n=4 [0.24%]), vaginal samples (n=2 [0.12%]), urine samples (n=1 [0.06%]) or colonic samples (n=1 [0.06%]); 551 (33%) isolates were from
### TABLE 2
Antimicrobial resistance by year for *Salmonella* (1997 to 2000)

| Class and antimicrobial | 1997 | 1998 | 1999 | 2000 | Total |
|-------------------------|------|------|------|------|-------|
| **Amphenicols**         |      |      |      |      |       |
| Chloramphenicol         | 211 (9.4) | 2247 | 286 (26) | 1109 | 360 (30) | 1197 | 1287 (22) | 5915 |
| **Aminoglycosides**     |      |      |      |      |       |
| Amikacin                | 0 (0.0) | 1917 | 0 (0.0) | 605 | 1 (0.12) | 847 | 0 (0.0) | 779 | 1 (0.02) | 4148 |
| Gentamicin              | 104 (5.2) | 2040 | 19 (3.1) | 619 | 26 (2.5) | 1053 | 20 (1.6) | 1245 | 169 (3.4) | 4931 |
| Netilmicin              | 0 (0.0) | 3 | 0 (0.0) | 21 | 0 (0.0) | 33 | 0 (0.0) | 30 | 0 (0.0) | 87 |
| Streptomycin            | 77 (4.0) | 1923 | 11 (1.8) | 619 | 20 (2.3) | 856 | 8 (1.0) | 787 | 116 (2.8) | 4185 |
| Tobramycin              | 0 (0.0) | 1917 | 0 (0.0) | 605 | 1 (0.0) | 847 | 0 (0.0) | 779 | 1 (0.02) | 4148 |
| **Penicillins**         |      |      |      |      |       |
| Extended-spectrum penicillins |      |      |      |      |       |
| Ampicillin              | 359 (16) | 2260 | 340 (29) | 1153 | 521 (37) | 1427 | 484 (35) | 1375 | 1704 (27) | 6215 |
| Carbenicillin           | 21 (9.8) | 215 | 70 (16) | 438 | 64 (15) | 424 | 93 (22) | 432 | 248 (16) | 1509 |
| Mezlocillin             | 1 (33) | 3 | 2 (9.5) | 21 | 4 (12) | 33 | 4 (13) | 30 | 11 (13) | 87 |
| Piperacillin            | 319 (17) | 1926 | 265 (37) | 713 | 431 (44) | 978 | 381 (41) | 926 | 1396 (31) | 4543 |
| Ticarcillin             | 320 (17) | 1919 | 265 (38) | 699 | 428 (45) | 958 | 373 (46) | 811 | 1386 (32) | 4387 |
| **Beta-lactam/beta-lactamase inhibitor combinations** |      |      |      |      |       |
| Amoxicillin/K clavulanate | 31 (9.4) | 330 | 83 (13) | 627 | 75 (13) | 600 | 110 (18) | 617 | 299 (14) | 2174 |
| Ampicillin/sulbactam    | 6 (8.5) | 71 | 2 (9.5) | 21 | 4 (12) | 33 | 18 (14) | 133 | 30 (12) | 258 |
| Piperacillin/tazobactam | – | 0 | 0 (0.0) | 8 | 0 (0.0) | 8 | 6 (1.2) | 487 | 6 (1.2) | 495 |
| Ticarcillin/K clavulanate | 4 (8.9) | 45 | 16 (9.1) | 175 | 15 (9.3) | 161 | 8 (11) | 70 | 43 (9.5) | 451 |
| **Other beta-lactams**  |      |      |      |      |       |
| Cephalosporins and related substances |      |      |      |      |       |
| First generation        |      |      |      |      |       |
| Cefazolin               | 5 (5.1) | 99 | 3 (3.2) | 95 | 3 (5.9) | 51 | 2 (4.6) | 44 | 13 (4.5) | 289 |
| Cefalothin              | 117 (5.3) | 2201 | 46 (4.4) | 1057 | 56 (4.3) | 1295 | 62 (5.0) | 1243 | 281 (4.9) | 5796 |
| Second generation       |      |      |      |      |       |
| Cefamandole             | 3 (7.7) | 39 | 7 (12) | 60 | 3 (100) | 3 | 1 (25) | 4 | 14 (13) | 106 |
| Cefotetan               | 0 (0.0) | 3 | 0 (0.0) | 21 | 0 (0.0) | 33 | 0 (0.0) | 30 | 0 (0.0) | 87 |
| Cefoxolin               | 4 (0.21) | 1918 | 6 (0.97) | 619 | 26 (3.0) | 855 | 20 (2.8) | 785 | 56 (1.3) | 4177 |
| Cefuroxime (oral)       | 1 (11) | 9 | 8 (28) | 29 | 4 (12) | 33 | 6 (20) | 30 | 19 (19) | 101 |
| Cefuroxime (parenteral) | 11 (9.6) | 115 | 3 (4.1) | 74 | 0 (0.0) | 11 | 0 (0.0) | 6 | 14 (6.8) | 206 |
| Cefonicid               | 3 (1.4) | 215 | 23 (5.3) | 438 | 3 (16) | 191 | – | – | 0 | 29 (3.4) | 844 |
| Loracarbef              | 0 (0.0) | 68 | – | – | – | – | 0 | 0 (0.0) | 68 |
| Third generation        |      |      |      |      |       |
| Cefoperazone            | 1 (33) | 3 | 2 (9.5) | 21 | 4 (12) | 33 | 4 (13) | 30 | 11 (13) | 87 |
| Cefotaxime              | 2 (0.10) | 2001 | 1 (1.8) | 559 | 15 (1.8) | 845 | 11 (1.3) | 873 | 29 (0.68) | 4278 |
| Cefpodoxime             | – | 0 | 0 (0.0) | 8 | 0 (0.0) | 40 | 1 (2.5) | 40 | 1 (1.1) | 88 |
| Cefazidime              | 2 (0.10) | 1926 | 2 (0.28) | 713 | 20 (2.0) | 980 | 23 (2.5) | 925 | 47 (1.0) | 4544 |
| Cefizoxime              | 0 (0.0) | 3 | 0 (0.0) | 21 | 0 (0.0) | 33 | 0 (0.0) | 30 | 0 (0.0) | 87 |
| Ceftriaxone             | 1 (0.3) | 329 | 3 (0.48) | 627 | 0 (0.0) | 600 | 6 (0.97) | 617 | 10 (0.46) | 2173 |
| Cefixime                | 2 (2.9) | 68 | – | – | – | – | 0 | 2 (2.9) | 68 |
| Fourth generation       |      |      |      |      |       |
| Cefepime                | – | 0 | – | 0 | – | 0 | 0 (0.0) | 103 | 0 (0.0) | 103 |
| Monobactams             |      |      |      |      |       |
| Aztreonam               | 0 (0.0) | 3 | 0 (0.0) | 21 | 0 (0.0) | 33 | 2 (1.5) | 133 | 2 (1.1) | 190 |
| Carbapenems             |      |      |      |      |       |
| Imipenem                | 1 (1.9) | 52 | 0 (0.0) | 189 | 3 (1.7) | 175 | 2 (1.1) | 185 | 6 (1.0) | 601 |
| Meropenem               | – | 0 | 0 (0.0) | 8 | 0 (0.0) | 33 | 0 (0.0) | 32 | 0 (0.0) | 173 |

*Continued on next page*
unknown sources. The median age for patients with Shigella was 24.0 years (age range of less than one to 88 years) (n=1619); 54% of isolates were from female patients (n=1634).

By antimicrobial class, S. sonnei isolates had the highest rates of resistance to other beta-lactams (26%), sulfonamides and trimethoprim (76%), and quinolones (12 isolates [27%]). S. flexneri isolates had the highest rates of resistance to tetracyclines (90%), extended-spectrum penicillins (73%) and chloramphenicol (71%). Although few S. dysenteriae isolates were tested, this serogroup showed the highest rates of resistance to beta-lactam/beta-lactamase inhibitor combinations (five isolates [63%]) and aminoglycosides (six isolates [27%]); S. sonnei and S. flexneri showed lower rates of resistance to beta-lactam/beta-lactamase inhibitor combinations and aminoglycosides (S. sonnei: 52% and 15%, respectively; S. flexneri: 53% and 16%, respectively). S. boydii isolates had the highest rate of resistance to nitrofurantoin (four isolates [18%]). Sixteen Shigella isolates were resistant to quinolones (12 S. sonnei and four S. flexneri isolates).

Among clinically important antimicrobials, high rates of resistance were observed for T/S (70%) and ampicillin (65%) (Table 3). Most Shigella isolates (n=1636 [98%]) were tested for resistance to ciprofloxacin; eight (0.49%) were resistant (six S. sonnei and two S. flexneri isolates), all of which were additionally resistant to ampicillin and T/S (Table 4). Comparatively few isolates were tested for resistance to nalidixic acid (262 isolates [16%]); of these isolates, eight (3.1%) were resistant (six S. sonnei and two S. flexneri isolates) (Table 3), one of which was also resistant to ciprofloxacin (Table 4). Two S. boydii isolates were resistant to third-generation cephalosporins: one to ceftriaxone (0.14%) and one to cefotaxime (0.08%) (Table 3). The ceftriaxone-resistant isolate originated from a two-year-old patient (sex unknown) with a history of travel to India (Table 5), and the cefotaxime-resistant isolate (also resistant to ampicillin, amoxicillin/K clavulanate, chloramphenicol, cephalexin, imipenem, nitrofurantoin, piperacillin, tetracycline and T/S) originated from a 44-year-old man with no available information on travel history.

Information on travel was available for 17 Shigella cases. Isolates from all 17 cases were tested for resistance to gentamicin, tobramycin, ampicillin, piperacillin, cefazolin, ceftriaxone, imipenem and T/S, and 16 were tested for resistance to ciprofloxacin; none were tested for resistance to nalidixic acid. Fourteen isolates (82%) were resistant to at least one agent, most commonly tetracycline (nine isolates [59%]), ampicillin (10 isolates [59%]), T/S (nine isolates [53%]), amoxicillin/K clavulanate (seven isolates [50%]) and chloramphenicol (five isolates [50%]). India was the most common travel destination reported by cases (five isolates [29%]) (Table 5).

**DISCUSSION**

The present retrospective study describes AMR rates for Salmonella and Shigella isolates passively reported in five Canadian provinces between 1997 and 2000. These data do not include all cases reported in these provinces. A closer estimate, however, can be obtained from the National Notifiable Diseases database (NND). For the provinces and years included in our study (limited to 1999 and 2000 for NL), our data represent 41% (6219 of 14995) of Salmonella isolates (including Typhi and Paratyphi serotypes) and 72% (1673 of 2313) of Shigella isolates reported by the NND (1). Therefore, our results may be more representative for Shigella than for Salmonella.
### TABLE 3
Antimicrobial resistance by year for Shigella (1997 to 2000)

| Class and antimicrobial | 1997 | 1998 | 1999 | 2000 | Total |
|-------------------------|------|------|------|------|-------|
| **Amphenicols**         |      |      |      |      |       |
| Chloramphenicol         | 38 (18) | 211 | 67 (17) | 384 | 94 (27) | 351 | 163 | 262 (21) | 1227 |
| **Aminoglycosides**     |      |      |      |      |       |
| Amikacin                | 0 (0.0) | 165 | 1 (0.45) | 223 | 0 (0.0) | 270 | 1 (0.39) | 255 | 2 (0.22) | 913 |
| Gentamicin              | 1 (0.38) | 282 | 0 (0.0) | 369 | 3 (0.98) | 305 | 0 (0.0) | 339 | 4 (0.31) | 1275 |
| Netilmicin              | –*  | 0 (0.0) | 0 (0.0) | 1 | –  | 0 (0.0) | 0 (0.0) | 2 | 0 (0.0) | 3 |
| Streptomycin            | –  | 0 | 0 | 1 (50) | 2 | 190 (75) | 252 | 191 (75) | 254 |
| Tobramycin              | 0 (0.0) | 223 | 0 (0.0) | 368 | 2 (0.68) | 292 | 3 (1.07) | 280 | 5 (0.43) | 1163 |
| **Penicillins**         |      |      |      |      |       |
| Extended-spectrum penicillins |      |      |      |      |       |
| Ampicillin              | 236 (64) | 370 | 424 (79) | 539 | 243 (59) | 412 | 176 (50) | 351 | 1079 (65) | 1672 |
| Carbenicillin           | 70 (69) | 102 | 92 (78) | 118 | 28 (48) | 58 | 27 (46) | 59 | 217 (64) | 337 |
| Mezlocillin             | –  | 0 | 1 (100) | 1 | –  | 0 | 1 (50) | 2 | 2 (67) | 3 |
| Piperacillin            | 63 (28) | 222 | 231 (55) | 423 | 112 (32) | 351 | 67 (23) | 292 | 473 (37) | 1288 |
| Ticarcillin             | 85 (50) | 170 | 201 (72) | 278 | 191 (58) | 327 | 128 (50) | 257 | 605 (59) | 1032 |
| **Beta-lactam/beta-lactamase inhibitor combinations** |      |      |      |      |       |
| Amoxicillin/K clavulanate | 79 (58) | 137 | 221 (68) | 324 | 43 (32) | 137 | 39 (39) | 99 | 382 (55) | 697 |
| Amoxicillin/sulbactam   | 7 (88) | 8 | 1 (100) | 1 | –  | 0 | 6 (60) | 10 | 14 (74) | 19 |
| Piperacillin/tazobactam | –  | 0 | 0 | 1 (13) | 8 | 0 (0.0) | 116 | 1 (0.8) | 124 |
| Ticarcillin/K clavulanate | 1 (6.7) | 15 | 4 (6.2) | 65 | 2 (3.4) | 59 | 0 (0.0) | 6 | 7 (4.8) | 145 |
| **Other beta-lactams**  |      |      |      |      |       |
| Cephalosporins and related substances |      |      |      |      |       |
| First generation        |      |      |      |      |       |
| Cefazolin               | 0 (0.0) | 106 | 2 (1.2) | 161 | 1 (4.2) | 24 | 0 (0.0) | 27 | 3 (0.94) | 318 |
| Cefalothin              | 76 (26) | 287 | 174 (36) | 483 | 37 (11) | 351 | 34 (10) | 339 | 321 (22) | 1460 |
| Second generation       |      |      |      |      |       |
| Cefamandole             | 7 (54) | 13 | 5 (31) | 16 | 1 (100) | 1 | –  | 0 | 13 (43) | 30 |
| Cefotetan               | –  | 0 | 0 (0.0) | 1 | –  | 0 | 0 (0.0) | 2 | 0 (0.0) | 3 |
| Cefoxitin               | 0 (0.0) | 176 | 0 (0.0) | 369 | 1 (0.35) | 289 | 3 (1.1) | 279 | 4 (0.36) | 1113 |
| Cefuroxime (oral)       | 0 (0.0) | 58 | 0 (0.0) | 32 | –  | 0 | 0 (0.0) | 2 | 0 (0.0) | 92 |
| Cefuroxime (parenteral) | 0 (0.0) | 80 | 1 (0.63) | 160 | 0 (0.0) | 18 | 0 (0.0) | 1 | 1 (0.39) | 259 |
| Cefonicid               | 7 (6.9) | 102 | 59 (52) | 114 | 4 (11) | 35 | –  | 0 | 70 (28) | 251 |
| Loracarbef              | 0 (0.0) | 9 | –  | 0 | –  | 0 | 0 (0.0) | 9 |       |      |
| Third generation        |      |      |      |      |       |
| Cefoperazone            | –  | 0 | 0 (0.0) | 1 | –  | 0 | 0 (0.0) | 2 | 0 (0.0) | 3 |
| Cefotaxime              | 0 (0.0) | 250 | 0 (0.0) | 354 | 0 (0.0) | 283 | 0 (0.0) | 262 | 0 (0.0) | 1149 |
| Cefpodoxime             | –  | 0 | 0 | 0 (0.0) | 7 | 0 (0.0) | 27 | 0 (0.0) | 34 |
| Cefazidime              | 0 (0.0) | 225 | 0 (0.0) | 423 | 1 (0.28) | 352 | 0 (0.0) | 292 | 1 (0.08) | 1292 |
| Cefizoxime              | –  | 0 | 0 (0.0) | 1 | –  | 0 | 0 (0.0) | 2 | 0 (0.0) | 3 |
| Ceftriaxone             | 0 (0.0) | 140 | 1 (0.31) | 325 | 0 (0.0) | 136 | 0 (0.0) | 99 | 1 (0.14) | 700 |
| Cefixime                | 0 (0.0) | 41 | 0 (0.0) | 141 | 0 (0.0) | 51 | 0 (0.0) | 22 | 0 (0.0) | 255 |
| Fourth generation       |      |      |      |      |       |
| Cefepime                | –  | 0 | –  | 0 | 0 (0.0) | 1 | 0 (0.0) | 8 | 0 (0.0) | 9 |
| Monobactams             |      |      |      |      |       |
| Aztreonam               | –  | 0 | 0 (0.0) | 1 | –  | 0 | 0 (0.0) | 10 | 0 (0.0) | 11 |
| Carbenemems             |      |      |      |      |       |
| Imipenem                | 0 (0.0) | 70 | 5 (2.4) | 211 | 2 (2.5) | 81 | 0 (0.0) | 40 | 7 (1.7) | 402 |
| Meropenem               | –  | 0 | –  | 0 | 0 (0.0) | 10 | 0 (0.0) | 10 |       |      |

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TABLE 3 – continued
Antimicrobial resistance by year for *Salmonella* (1997 to 2000)

| Class and antimicrobial | 1997          | 1998          | 1999          | 2000          | Total          |
|-------------------------|---------------|---------------|---------------|---------------|---------------|
|                         | Resistant, n (%) | Tested, n     | Resistant, n (%) | Tested, n     | Resistant, n (%) | Tested, n     | Resistant, n (%) | Tested, n     | Resistant, n (%) | Tested, n     |
| Sulphonamides and trimethoprim |             |               |               |               |               |               |               |               |               |               |
| Sulfamethoxazole | 21 (95)       | 22            | 14 (93)       | 15            | 12 (80)       | 15            | 174 (69)       | 252           | 221 (73)       | 304           |
| Trimethoprim | 8 (89)        | 9             | 1 (100)       | 1             | –             | 0             | 2 (100)        | 2             | 11 (92)        | 12            |
| Trimethoprim/sulfamethoxazole | 255 (69)     | 368           | 403 (76)      | 527           | 275 (68)      | 403           | 211 (62)       | 345           | 1144 (70)      | 1643          |
| Quinolones |  |               |               |               |               |               |               |               |               |               |
| Fluoroquinolones |             |               |               |               |               |               |               |               |               |               |
| Ciprofloxacin | 2 (0.59)      | 341           | 1 (0.19)      | 538           | 4 (0.98)      | 407           | 1 (0.29)       | 350           | 8 (0.49)       | 1636          |
| Levofloxacin | –            | 0             | –             | 0             | –             | 0             | 0 (0.0)        | 10            | 0 (0.0)        | 10            |
| Lomefloxacin | 0 (0.0)       | 9             | 0 (0.0)       | 1             | –             | 0             | –             | 0             | 0 (0.0)        | 10            |
| Norfloxacin | 0 (0.0)       | 143           | 0 (0.0)       | 319           | 0 (0.0)       | 134           | 0 (0.0)        | 88            | 0 (0.0)        | 684           |
| Trovafloxacin | –            | 0             | –             | 0             | –             | 0             | 0 (0.0)        | 8             | 0 (0.0)        | 8             |
| Other quinolones |  |               |               |               |               |               |               |               |               |               |
| Nalidixic acid | 3 (2.7)       | 113           | 3 (2.6)       | 114           | 2 (5.7)       | 35            | –             | 0             | 8 (3.1)        | 262           |
| Ofloxacin | 0 (0.0)       | 9             | 0 (0.0)       | 5             | 0 (0.0)       | 12            | 1 (1.7)        | 59            | 1 (1.2)        | 85            |
| Tetracyclines | 192 (73)      | 263           | 233 (55)      | 426           | 271 (78)      | 346           | 247 (73)       | 335           | 943 (69)       | 1370          |
| Other antibacterials | 2 (1.5)       | 138           | 5 (1.8)       | 275           | 3 (3.8)       | 79            | 3 (3.5)        | 87            | 13 (2.3)       | 579           |

*Not tested

**Salmonella**

When antimicrobial therapy for non-typhoidal *Salmonella* infections is recommended, fluoroquinolones, T/S, ampicillin and third-generation cephalosporins are considered drugs of choice (7). Multidrug-resistant *S. typhi* and *S. paratyphi* infections should be treated with fluoroquinolones, third-generation cephalosporins and azithromycin (8). Among the *Salmonella* isolates in our study, we observed higher rates of resistance to clinically important antimicrobials than previously reported. For example, in a Quebec study of *Salmonella* isolates from patients hospitalized between 1991 and 1995, Gaudreau and Turgeon (9) reported no resistance to ciprofloxacin, 4% of isolates resistant to ampicillin (five isolates) and 0.08% of isolates resistant to T/S (one isolate). In contrast, we observed 0.08% of isolates resistant to ampicillin (five isolates) and 0.08% of isolates resistant to T/S (70%) and ampicillin (65%), drugs that were once commonly used to treat shigellosis (12). Because 98.2% and 99.9% of isolates were tested for resistance to T/S and ampicillin, respectively, these resistance rates are representative of the *Salmonella* isolates included in our study. In comparison, a 1990 study of 598 *Shigella* isolates (11) reported a lower rate of resistance to T/S (26.7% to 37.6%) than our study, as well as rates of resistance to ampicillin ranging from 39.3% to 66.5%. Compared with our study, Gaudreau and Turgeon (9) reported

0.06% (10). However, the methodologies used by CIPARS and the present study were different. In CIPARS, all or a sample of *Salmonella* isolates from the provincial laboratories were systematically tested for resistance to the same antimicrobials. In our study, however, the antimicrobials tested varied among the isolates and provinces. This difference may account for the observed variations.

Based on our results, ampicillin appears to be an inappropriate choice for antimicrobial therapy for a number of *Salmonella* isolates tested in Canada over the study period. Low rates of resistance to T/S, nalidixic acid, ciprofloxacin and third-generation cephalosporins were also observed. In patients with *Salmonella* infections, susceptibility testing should be performed and reported as per current Clinical and Laboratory Standards Institute guidelines. In the present study, only 15% of *Salmonella* isolates were tested for nalidixic acid resistance. However, Crump et al (11) have emphasized the importance of testing for nalidixic acid resistance, citing evidence that inadequate clinical response to fluoroquinolones has occurred among cases infected with fluoroquinolone-susceptible, nalidixic-resistant *Salmonella* isolates.

**Shigella**

Among *Shigella* isolates, we observed high rates of resistance to T/S (70%) and ampicillin (65%), drugs that were once commonly used to treat shigellosis (12). Because 98.2% and 99.9% of isolates were tested for resistance to T/S and ampicillin, respectively, these resistance rates are representative of the *Shigella* isolates included in our study. In comparison, a 1990 study of 598 *Shigella* isolates (11) reported a lower rate of resistance to T/S (26.7% to 37.6%) than our study, as well as rates of resistance to ampicillin ranging from 39.3% to 66.5%. Compared with our study, Gaudreau and Turgeon (9) reported
Antimicrobial resistance among Salmonella and Shigella isolates

| Isolate          | Year | Resistance pattern | Specimen source | Patient age (years) |
|------------------|------|--------------------|-----------------|--------------------|
| Salmonella typhimurium | 1997 | AmCcpPiTeT/S       | Stool           | 28                 |
| Salmonella typhimurium | 1998 | AmCcpPiTeTi        | Stool           | 4                  |
| Salmonella typhimurium | 1999 | AmCcpPiTeTi        | Stool           | <1                 |
| Salmonella typhimurium | 2000 | CpStr              | Stool           | 5                  |
| Salmonella paratyphi A | 2000 | CpTe               | Unknown     | 54                 |

**Shigella**

| Isolate          | Year | Resistance pattern | Specimen source | Patient age (years) |
|------------------|------|--------------------|-----------------|--------------------|
| Shigella sonnei  | 1997 | C/H/Fd/NacidTeT/S  | Not provided    | 49                 |
| Shigella sonnei  | 1997 | AmAugCpTeT/S       | Stool           | 52                 |
| Shigella sonnei  | 1998 | AmCcpPiT/T/S       | Not provided    | 10                 |
| Shigella sonnei  | 1999 | AmC/Cx/Ccp/GmTeTo  | Stool           | 7                  |
| Shigella sonnei  | 1999 | AmCcpPiT/T/S       | Stool           | 63                 |
| Shigella flexneri| 1999 | AmCcpTeTi          | Stool           | 2                  |
| Shigella flexneri| 2000 | AmCcpTeTi          | Vaginal         | 7                  |
| Shigella sonnei  | 2000 | AmC/Cx/Cp/Pix/SrTeT/S | Stool | 2                 |

*Travel information was provided only for the province of Alberta. Am Ampicillin; Aug Amoxicillin/K clavulanate; C Chloramphenicol; C/N Cephalothin; Cfx Cefoxitin; Cip Ciprofloxacin; Fd Furofuranftoin; Gm Gentamicin; Nacid Nalidixic acid; Pi Piperacillin; Sx Sulamethoxazole; T/S Tetracycline; Te Tetracycline; T/S Trimethoprim/Sulfamethoxazole

similar rates of resistance to ampicillin (62.7%) and a lower rate of resistance to T/S (26.3%) among 118 Shigella isolates tested from 1991 to 1995 in Quebec. More recent data from the United States (US) are available for Shigella isolates tested from 1999 to 2002 by the National Antimicrobial Resistance Monitoring System (13), which reported a higher resistance rate for ampicillin (78%) but a lower rate for T/S (46%) than our study. Based on the results of our study, ampicillin and T/S appear to be inappropriate therapeutic choices for most Shigella infections reported in the study provinces.

One S boydii isolate tested in 1998 from a patient with a history of travel to India was resistant to ceftriaxone. Extended-spectrum beta-lactamase-producing S sonnei and S flexneri isolates have been reported in several countries, including France, Argentina, Korea, Turkey, Bangladesh and Taiwan (14-19). However, from 1999 to 2002, no ceftriaxone resistance among Shigella isolates was observed in the US (14), and to our knowledge, this is the first report of ceftriaxone resistance among Shigella isolates in Canada.

Eight (3.1%) Shigella isolates included in our study were resistant to nalidixic acid, which is higher than the numbers reported in a 1990 study (which found no resistance to nalidixic acid [20]) and by the National Antimicrobial Resistance Monitoring System (which found 1% of Shigella isolates resistant between 1999 and 2002 in the US [13]). In contrast, the resistance rate we observed was lower than that reported by a study conducted in England and Wales in 2002 (21), which found 13% of S sonnei isolates, and 10% of S dysenteriae, S flexneri and S boydii isolates resistant to nalidixic acid. Nalidixic acid resistance among Shigella isolates has been associated with decreased susceptibility to ciprofloxacin (19); therefore, it is important to monitor resistance to nalidixic acid to prevent possible fluoroquinolone treatment failures.

Eight (0.49%) Shigella isolates included in our study were resistant to ciprofloxacin, the therapy currently recommended by the World Health Organization to treat shigellosis (12). To our knowledge, few studies have previously reported resistance to ciprofloxacin among Shigella isolates tested in North America. In one example in 2001, a US study (22) reported the uncommon occurrence of an S flexneri isolate resistant to ciprofloxacin from a patient with a history of travel to China. In another example, a Canadian study (23) reported an S dysenteriae type 1 isolate resistant to ciprofloxacin and nalidixic acid from a 56-year-old man from AB in 2004 with a history of travel to India. Unfortunately, travel histories were unavailable for Shigella cases with ciprofloxacin-resistant infections in our study; therefore, we are uncertain whether these organisms were acquired domestically or internationally. Travel histories from Shigella cases should be included with specimens submitted to the laboratory to enable a more comprehensive understanding of the epidemiology of ciprofloxacin-resistant Shigella isolates reported in Canada. This information should indicate whether the case had recently travelled (‘yes or no’), as well as the location. Regardless of the country of origin, Shigella is transmitted via person-to-person contact; thus, there is a potential risk for secondary transmission and infection. If these retrospective resistance rates are predictive of current rates, ciprofloxacin – the currently recommended first-line therapy – may not be effective for a small percentage of Shigella infections occurring in Canada.

**Limitations**

The present study has several limitations. First, we collected data retrospectively; therefore, methods were not uniform
across the provinces or over time, and provincial laboratories may have selectively tested isolates for resistance to certain antimicrobials. These differences could have affected observed rates of resistance; consequently, these data should not be taken as representative of all laboratory-confirmed Salmonella or Shigella isolates reported in the study provinces. Although the culture methods may have varied among the laboratories, each laboratory participated in external proficiency testing programs to maintain high standards for the testing of enteric pathogens. Second, travel histories were available for few cases. Therefore, for isolates from patients without information about travel history, we could not be sure whether the isolates tested originated in Canada or whether they were imported from another country. Third, these data were collected over five years ago; therefore, they should not be considered as characteristic of present Salmonella or Shigella resistance rates. However, these data provide baseline information, and context for future research and surveillance efforts. Despite the limitations of these data, these results represent, to our knowledge, the most comprehensive description of AMR rates for Salmonella during the study period and one of the only multi-provincial descriptions of AMR rates available for Shigella in Canada.

CONCLUSIONS
The rates of resistance we observed among Salmonella and Shigella isolates are concerning; they demonstrate that treatment options are more limited for these infections than previously reported. Current information on AMR rates for these pathogens is needed. CIPARS conducts national surveillance on AMR for Salmonella; however, given that we found Shigella isolates resistant to the recommended first-line therapy, resistance among Shigella isolates should also be monitored by CIPARS, along with the routine collection of patients’ travel histories to differentiate between domestically and internationally acquired infections. Because humans are the key reservoir for Shigella, the resistance observed in these organisms is likely associated with human antimicrobial use. Therefore, prudent antimicrobial drug use is essential to maintain effective antimicrobial therapies for these infections.

ADDENDUM: Aspects of the data found in this study were presented in the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) 2002 Annual Report, which is available online at <http://www.phac-aspc.gc.ca/cipars-picra>.

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REFERENCES
1. Public Health Agency of Canada. National Notifiable Diseases Online: Notifiable disease incidence by year, 1989-2004. <http://dsol-smed.hc-sc.gc.ca/dsol-smed/nlds/c/time_e.html> (Version current at July 24, 2006).
2. Popp E, Ayraud M, Ollis G, et al. Trends in antimicrobial resistance of Salmonella isolated from animals, foods of animal origin, and the environment of animal production in Canada, 1994-1997. Microb Drug Resist 2001;7:197-212.
3. Prats G, Mirella B, Llovet T, Munoz C, Miro E, Navarro F. Antibiotic resistance trends in enteropathogenic bacteria isolated in 1985-1987 and 1995-1998 in Barcelona. Antimicrob Agents Chemother 2000;44:1140-5.
4. Hakken A, Siitonen A, Karttulainen P, Huovinen P. Increasing fluoroquinolone resistance in Salmonella serotypes in Finland during 1995-1997. J Antimicrob Chemother 1999;43:145-8.
5. Askhenazi S, Levy I, Kazarnovski V, Samra Z. Growing antimicrobial resistance of Shigella isolates. J Antimicrob Chemother 2003;51:427-9.
6. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing, 11th informational supplement. NCCLS Document M100-S11. Pennsylvania: National Committee for Clinical Laboratory Standards, 2000.
7. Hohmann EL. Nontyphoidal salmonellosis. Clin Infect Dis 2001;32:263-9.
8. Thaver D, Zaidi AK, Critchley J, Madni SA, Bhutta ZA. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). Cochrane Database Syst Rev 2005;2:CD004130.
9. Gaudreau C, Tarigon P. Antibiotic resistance of Shigella spp., Salmonella spp., and Yersinia spp. isolated in Quebec. Can Commun Dis Rep 1997;23:57-9.
10. Public Health Agency of Canada. Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) 2003 Annual Report. <www.phac-aspc.gc.ca/cipars-picra/2003_e.html> (Version current at July 24, 2006).
11. Crump JA, Barrett TJ, Nelson JT, Angulo FJ. Reevaluating fluoroquinolone breakpoints for Salmonella enterica serotype Typhi and for non-Typhi salmonellae. Clin Infect Dis 2003;37:75-81.
12. Antibiotics in the management of shigellosis. Wkly Epidemiol Rec 2004;79:355-6.
13. Sivapalasingam S, Nelson JM, Joyce K, Hoekstra M, Angulo FJ, Miret ED. High prevalence of antimicrobial resistance among Shigella isolates in the United States tested by the National Antimicrobial Resistance Monitoring System from 1999 to 2002. Antimicrob Agents Chemother 2006;50:49-54.
14. Fortinneau N, Naas T, Guillot O, Nordmann P. SHV-type extended-spectrum beta-lactamase in a Shigella flexneri clinical isolate. J Antimicrob Chemother 2001;47:685-8.
15. Radice M, Gonzalez C, Power P, Vital MC, Gutkind G. Third-generation cephalosporin resistance in Shigella sonnei, Argentina. Emerg Infect Dis 2001;7:442-3.
16. Pai H, Choi EH, Lee HJ, Hong JY, Jacoby GA. Identification of CTX-M-14 extended-spectrum beta-lactamase in clinical isolates of Shigella sonnei, Escherichia coli, and Klebsiella pneumoniae in Korea. J Clin Microbiol 2001;39:757-9.
17. Acikelgi ZC, Gulay Z, Bicmen M, Ozer S, Gamberzade S. CTX-M-3 extended-spectrum beta-lactamase in a Shigella sonnei clinical isolate: First report from Turkey. Scand J Infect Dis 2003;35:503-5.
18. Rahman M, Shoma S, Rashid H, Siddique AK, Nair GB, Sack DA. Extended-spectrum beta-lactamase-mediated third-generation cephalosporin resistance in Shigella isolates in Bangladesh. J Antimicrob Chemother 2004;54:846-7.
19. Huang JF, Chiu CH, Wang MH, Wu CY, Hsieh KS, Chiu CC. Outbreak of dysentery associated with ceftriaxone-resistant Shigella sonnei: First report of plasmid-mediated CMY-2-type AmpC beta-lactamase resistance in S sonnei. J Antimicrob Chemother 2001;48:628-9.
20. Harnett N. High level resistance to trimethoprim, cotrimoxazole and other antimicrobial agents among clinical isolates of Shigella species in Ontario, Canada – An update. Epidemiol Infect 1992;110:463-72.
21. Chewst T, Day M, Threlfall EJ. Increasing incidence of resistance to nalidixic acid in shigellas from humans in England and Wales: Implications for therapy. Clin Microbiol Infect 2004;10:1033-5.
22. Baker NL, Nelson JM, Joyce K, Gay K, Angulo FJ, NARMS Working Group. Quinolone resistance among Shigella: NARMS 1999-2001 (Abst). 2003 Annual Conference on Antimicrobial Resistance [poster P18]. <www.nfsl.org/conferences/resistance03/abstracts.pdf> (Version current at July 24, 2006).
23. Emergence of quinolone-resistant Shigella dysenteriae type I in Canada. Can Commun Dis Rep 2005;31:193-7.