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

La résistance antimicrobienne dans les isolats de salmonelle et de *Shigella* de cinq provinces canadiennes (entre 1997 et 2000)

OBJECTIF : Décrire les taux de résistance antimicrobienne (RAM) dans les isolats de salmonelle et de *Shigella* déclarés dans cinq provinces canadiennes, axés sur les antimicrobiens importants d'un point de vue clinique.

MÉTHODOLOGIE : Les auteurs ont fait l'analyse rétrospective des taux de RAM dans les 6 219 isolats de salmonelle et les 1 673 isolats de *Shigella* soumis aux laboratoires de santé publique provinciaux de l'Alberta, de Terre-Neuve-et-Labrador, de l'Ontario, de l'Île-du-Prince-Édouard et de la Saskatchewan entre 1997 et 2000. On estime que ces isolats représentaient 41 % des cas de salmonelle et 72 % de ceux de *Shigella* déclarés par les provinces à l'étude.

RÉSULTATS : Parmi les isolats de salmonelle, 27 % (1 704 sur 6 215) étaient résistants à l'ampicilline, 2,2 % (135 sur 6 122) au triméthoprim-sulfaméthoxazole, 1,5 % (14 sur 938) à l'acide nalidixique, 1,2 % (un sur 84) à la lomafloxacine et 0,08 % (cinq sur 6 163) à la ciprofloxacine. Parmi les isolats de *Shigella*, 70 % (1 144 sur 1 643) étaient résistants au triméthoprim-sulfaméthoxazole, 65 % (1 079 sur 1 672) à l'ampicilline, 3,1 (huit sur 262) à l'acide nalidixique, 0,49 % (huit cas 1 636) à la ciprofloxacine, 0,14 % (un sur 700) à la ceftriaxone et 0,08 % (un sur 1 292) à la ceftazidime.

CONCLUSIONS : Comme on l'avait déjà déclaré, des taux plus élevés de résistance à des antimicrobiens d'importance d'un point de vue clinique (y compris la ciprofloxacine) s'observaient dans les isolats de salmonelle et de *Shigella*. Des données canadiennes courantes sur les taux de RAM de ces pathogènes s'imposent.

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

		Salmonella		*Shigella*	
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 (9.5)	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 nine 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)

	1997		1998		1999		2000		Total	
Class and antimicrobial	Resistant, n (%)	Tested, n	Resistant, n (%)	Tested, n	Resistant, n (%)	Tested, n	Resistant, n (%)	Tested, n	Resistant, n (%)	Tested, n
Amphenicols										
Chloramphenicol	211 (9.4)	2247	286 (26)	1109	430 (32)	1362	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)	2014	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	–*	0	–	0	0 (0.0)	8	484 (65)	739	484 (65)	747
Tobramycin	77 (4.0)	1923	11 (1.8)	619	20 (2.3)	856	8 (1.0)	787	116 (2.8)	4185
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 (0.0)	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
Cephalothin	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
Cefoxitin	4 (0.21)	1918	6 (0.97)	619	26 (3.0)	855	20 (2.6)	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 (1.6)	191	–	0	29 (3.4)	844
Loracarbef	0 (0.0)	68	–	0	–	0	–	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 (0.18)	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
Ceftazidime	2 (0.10)	1926	2 (0.28)	713	20 (2.0)	980	23 (2.5)	925	47 (1.0)	4544
Ceftizoxime	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	–	0	–	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

TABLE 2 – 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
Sulfonamides and trimethoprim										
Sulfamethoxazole	43 (33)	129	30 (42)	72	23 (62)	37	358 (48)	741	454 (46)	979
Sulfisoxazole	–	0	–	0	7 (78)	9	5 (29)	17	12 (46)	26
Trimethoprim	3 (4.2)	71	0 (0.0)	20	6 (14)	42	1 (2.1)	47	10 (5.6)	180
Trimethoprim/sulfamethoxazole	38 (1.7)	2257	19 (1.7)	1118	34 (2.4)	1407	44 (3.3)	1342	135 (2.2)	6122
Quinolones										
Fluoroquinolones										
Ciprofloxacin	1 (0.04)	2247	1 (0.09)	1153	1 (0.07)	1405	2 (0.15)	1358	5 (0.08)	6163
Levofloxacin	–	0	0 (0.0)	8	0 (0.0)	33	0 (0.0)	133	0 (0.0)	174
Lomefloxacin	1 (1.4)	71	0 (0.0)	13	–	0	–	0	1 (1.2)	84
Norfloxacin	1 (0.27)	368	0 (0.0)	613	0 (0.0)	589	1 (0.19)	523	2 (0.10)	2093
Trovafloxacin	–	0	–	0	–	0	0	103	0 (0.0)	103
Other quinolones										
Nalidixic acid	2 (0.71)	283	7 (1.6)	438	4 (2.0)	200	1 (5.9)	17	14 (1.5)	938
Ofloxacin	1 (1.4)	71	0 (0.0)	13	0 (0.0)	176	1 (0.23)	432	2 (0.29)	692
Tetracyclines										
Tetracycline	515 (24)	2160	389 (40)	984	563 (44)	1273	582 (49)	1199	2049 (36)	5616
Other antibacterials										
Nitrofurantoin	71 (22)	327	127 (24)	533	101 (21)	485	115 (23)	495	414 (23)	1840

*Note that isolates from Newfoundland and Labrador were only available from 1999 to 2000. *Not tested*

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 [1.0%]). *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/or 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 ceftazidime (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 ceftazidime-resistant isolate (also resistant to ampicillin, amoxicillin/K clavulanate, chloramphenicol, cephalothin, 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, ceftazidime, 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 [90%]), 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)

	1997		1998		1999		2000		Total	
Class and antimicrobial	Resistant, n (%)	Tested, n	Resistant, n (%)	Tested, n	Resistant, n (%)	Tested, n	Resistant, n (%)	Tested, n	Resistant, n (%)	Tested, n
Amphenicols										
Chloramphenicol	38 (18)	211	67 (17)	384	94 (27)	351	63 (22)	281	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)	262	0 (0.0)	369	3 (0.98)	305	0 (0.0)	339	4 (0.31)	1275
Netilmicin	–*	0	0 (0.0)	1	–	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
Ampicillin/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
Cephalothin	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 (0.0)	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
Ceftazidime	0 (0.0)	225	0 (0.0)	423	1 (0.28)	352	0 (0.0)	292	1 (0.08)	1292
Ceftizoxime	–	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
Carbapenems										
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 (0.0)	10	0 (0.0)	10

Continued on next page

TABLE 3 – continued
Antimicrobial resistance by year for *Shigella* (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
Sulfonamides 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										
Tetracycline	192 (73)	263	233 (55)	426	271 (78)	346	247 (73)	335	943 (69)	1370
Other antibacterials										
Nitrofurantoin	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 nontyphoidal *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 *Salmonella* isolates resistant to ciprofloxacin, 27% to ampicillin and 2.2% to T/S. This variation could be the result of differences in study design (hospital isolates versus passive provincial laboratory surveillance), differences in study location, or to real increases in AMR rates over time. Our data suggest that resistance to T/S has increased from 1.7% in 1997 to 3.3% in 2000 (Table 2).

More recent Canadian data are available from the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS), which was established to monitor the resistance of enteric pathogens, including *Salmonella*, that are isolated from humans, animals and animal-derived foods across the country (10). Compared with our study results, for *Salmonella* isolates tested in the five study provinces in 2003, CIPARS observed higher rates of resistance to nalidixic acid (1.5% versus 6.8%), similar rates of resistance to T/S (3.3% versus 3.8%) and ciprofloxacin (0.08% versus 0.06%), and lower rates of resistance to ampicillin (27% versus 19%), amoxicillin (14% versus 4.8%) and ceftriaxone (0.46% versus 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

TABLE 4
Description of *Salmonella* and *Shigella* isolates with resistance to ciprofloxacin

Isolate	Year	Resistance pattern	Specimen source	Patient age (years)
Salmonella				
Salmonella typhimurium	1997	AmCCpPiTeTiT/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				
Shigella sonnei	1997	CfCpFdNacidTeT/S	Not provided	49
Shigella sonnei	1997	AmAugCpTeT/S	Stool	52
Shigella sonnei	1998	AmCpPiTiT/S	Not provided	10
Shigella sonnei	1999	AmCCfxCfCpGmTeTo	Stool	7
Shigella sonnei	1999	AmCpPiTiT/S	Stool	63
Shigella flexneri	1999	AmCCpTeTi	Stool	2
Shigella flexneri	1999	AmCCpTeTi	Vaginal	7
Shigella sonnei	2000	AmCfxCpPiSxStrTeTiT/S	Stool	2

Am Ampicillin; Aug Amoxicillin/K clavulanate; C Chloramphenicol; Cf Cephalothin; Cfx Cefoxitin; Cp Ciprofloxacin; Fd Nitrofurantoin; Gm Gentamicin; Nacid Nalidixic acid; Pi Piperacillin; Str Streptomycin; Sx Sulfamethoxazole; Te Tetracycline; Ti Ticarcillin; To Tobramycin; T/S Trimethoprim/sulfamethoxazole

TABLE 5
Antimicrobial resistance patterns for *Shigella* isolates from patients with available travel information* (1997 to 2000)

Year	Isolate	Resistance pattern	Travel destination(s)
1997	*Shigella sonnei*	AmPiT/S	Romania
1997	*Shigella flexneri*	AmT/S	El Salvador
1997	*Shigella flexneri*	Am	Russia
1997	*Shigella flexneri*	T/S	Nepal
1997	*Shigella dysenteriae*	Susceptible	Madagascar
1998	*Shigella sonnei*	Susceptible	Dominican Republic
1998	*Shigella flexneri*	AmAugCPiTeT/S	Nicaragua
1998	*Shigella flexneri*	AmAugCTe	Ethiopia
1998	*Shigella boydii*	AmAugCaxTeT/S	India
1998	*Shigella boydii*	AmAugTeT/S	India
1998	*Shigella boydii*	Fd	Russia
2000	*Shigella flexneri*	AmAugCTeT/S (2 isolates)	Pakistan, Mexico
2000	*Shigella flexneri*	AmAugCTe	Ivory Coast
2000	*Shigella flexneri*	TeT/S	India
2000	*Shigella boydii*	Te	India
2000	*Shigella boydii*	Susceptible	India

**Travel information was provided only for the province of Alberta. Am Ampicillin; Aug Amoxicillin/K clavulanate; C Chloramphenicol; Cax Ceftriaxone; Fd Nitrofurantoin; Pi Piperacillin; 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, then 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 multiprovincial 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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