Salmonella enterica serovars associated with bacteremia in Canada, 2006–2019

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Abstract

Background: Members of the bacterial genus *Salmonella* cause salmonellosis, a disease with a spectrum of clinical presentations from a self-limiting gastroenteritis to more severe bacteremia, organ failure and sepsis. The genus consists of over 2,600 serological variants (serovars). Important differences in the pathogenesis of *Salmonella* serovars have been noted.

Objective: The purpose of this study was to determine which *Salmonella* serovars were more likely to be associated with bacteremia in Canada.

Methods: Information on the total number of *Salmonella* infections and blood isolations reported to the National Enteric Surveillance Program (NESP) from 2006 to 2019 was extracted for each serovar. The risk (proportion) and likelihood (odds) of bacteremia were calculated for all serovars.

Results: Of the 96,082 *Salmonella* cases reported to the NESP during the 14-year study period, 4.4% (95% CI: 4.3%–4.6%) were bacteremic. Twenty nontyphoidal *Salmonella* (NTS) serovars were associated with lower rates of bacteremia compared to all NTS serovars, and 19 NTS serovars were identified as having higher rates. Heidelberg, Oranienburg, Schwarzengrund, Virchow, Panama and Poona among the top 25 most commonly reported serovars in Canada during the study period.

Conclusion: The identification of serovars associated with *Salmonella* bacteremia in Canada is a first step towards understanding differences in pathogenesis and disease presentation.

Introduction

Salmonella bacteria are an important cause of human illness with a variety of clinical presentations (1). The genus consists of two species, six subspecies and over 2,600 serological variants (serovars). Although all species and subspecies have been reported to cause illness, most human infections are caused by *S. enterica* spp. *enterica* (subspecies I) (2). Subspecies I include typhoidal and nontyphoidal serovars. Typhoidal serovars cause typhoid (enteric) fever, a serious invasive infection that can lead to multiorgan failure, bacteremia and sepsis (3). Nontyphoidal salmonellosis (NTS) mainly results in an acute self-limiting gastroenteritis, although more severe infection can occur (3). In Canada, the majority of reported salmonellosis cases—including about 925 hospitalizations and 17 deaths per year—are due to NTS (4).

One of the defining features of *Salmonella* is the presence of virulence genes encoded on sections of the genome called *Salmonella* pathogenicity islands (SPIs). All 2,659 *Salmonella* serovars possess SPIs and therefore encode the ability to cause infections (5). Nevertheless, only a small proportion of serovars are responsible for the majority of reported human infections, with over 80% of reported salmonellosis cases attributed to 20 serovars despite that over 200 serovars are reported annually in Canada (6). Although some frequently reported serovars are associated with greater exposure risks because they are more prevalent in the environment, the presence of several highly prevalent but rarely reported serovars suggests differences in virulence between serovars (7). This hypothesis is supported by studies on the pathogenesis of the typhoidal serovars and NTS serovars such as Choleraesuis, Dublin, Typhimurium and Enteritidis (1,7). The pathogenesis of most NTS serovars, however, is understudied and therefore poorly understood.

Examining the rates of *Salmonella* bacteremia in humans is one way to compare the relative virulence of serovars. Globally, about 2%–8% of reported NTS infections lead to bacteremia, and in some cases, bacteremia is not preceded by gastroenteritis (8–11). Patients with bacteremia are more likely to experience severe outcomes, including hospitalization and death, unless treated promptly with antibiotics (12,13). Therefore, the early identification of high-risk patients can improve the prognosis of *Salmonella* bacteremia (9,14). Human risk factors for bacterial dissemination from the gut include compromised immunity, underlying medical conditions and extremes of age. Bacterial virulence factors involved in this process include adhesion proteins, immune evasion proteins and other secreted effectors (3,10,15,16).

The objective of this study was to compare bacteremia rates of different *Salmonella* subspecies and serovars to gain a better understanding of the differences in virulence. Identification of *Salmonella* serovars that are more or less likely to be associated with bacteremia is a key step towards the development of better predictors of *Salmonella* bacteremia and, eventually, better standards of care.

Methods

Data sources

The research team obtained data from the National Enteric Surveillance Program (NESP), which is administered by the Public Health Agency of Canada (6). The data are a summary of laboratory data submitted weekly by provincial/territorial public health microbiology labs to the NESP. We extracted data from 2006 to 2019 for this analysis, including the number of *Salmonella* infections by subspecies, serovar and specimen source for extraintestinal isolations. Each reported isolation represents one clinical case. Blood isolates were recovered from blood and taken as a proxy for the number of bacteremia cases caused by *Salmonella* (*Salmonella* bacteremia). Total isolates were those recovered from all specimen sources.

Data analysis

Information on the reporting frequency and distribution of *Salmonella* subspecies and serovars was tabulated using Microsoft Excel 2016 and visualized using GraphPad Prism 8.0.2.

We calculated rates of *Salmonella* bacteremia over time by dividing the number of blood isolates reported every year by the number of total *Salmonella* reports for that year. The chi-square/Cochran–Armitage test for trend was used to determine if there was a linear trend in bacteremia rates over time. This temporal analysis was conducted at the genus level as well as at the level of individual NTS serovars.

Bacteremia proportions (BP) of individual *Salmonella* serovars or groups were calculated by dividing the number of blood isolates of a given serovar/group by the number of total isolates of the

same serovar/group for all years combined. The 95% confidence intervals (CI) for BP were calculated using the following formula:

$$BP \pm \frac{1.96\sqrt{BP(1 - BP)}}{n}$$

For some analyses, we grouped serovars according to their subspecies designation (I–VI) and disease presentation (typhoidal or NTS). Significantly higher or lower rates of bacteremia in individual serovars or groups of *Salmonella* were assessed using Fisher exact test. To identify subspecies and serovars with higher rates of blood isolations, we compared the following groups: subspecies I versus all other subspecies (II, IIIa, IIIb, IV and II–VI); typhoidal serovars versus NTS serovars; and individual NTS serovar versus all NTS serovars.

Odds ratios were calculated by comparing the odds of a given serovar to infect the blood (*a/b*) to the odds of any NTS strain infecting the blood (*c/d*); where *a* and *b* are the respective number of blood and non-blood isolates for each serovar and *c* and *d* are the corresponding numbers for all NTS strains. We used the following formula to calculate the 95% CI for the odds ratio:

$$e^{\left(\left[ln(OR) \pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{d}\right)}\right]\right)}$$

We conducted all calculations and statistical tests using Microsoft Excel 2016 and GraphPad Prism 8.0.2. A *p*-value of less than 0.05 was considered significant for all statistical tests.

Results

From 2006 to 2019, 96,082 *Salmonella* isolations were reported to the NESP. During this period, 4,252 bloodstream isolations were reported, that is, an overall bacteremia rate of 4.4% (95% CI: 4.3%–4.6%). Investigation of annual rates of bacteremia showed an increasing trend over the 14-year period, with an average annual rate of increase of 0.2% (95% CI: −0.4% to 0.7%) and a range of 2.7% in 2007 (95% CI: 2.4%–3.2%) to 5.9% (95% CI: 5.4%–6.5%) in 2017 (*P*<0.0001, **Figure 1** and **Figure 2**).

Figure 1: Number of total reports and blood isolations of *Salmonella* bacteremia as reported to the NESP, 2006–2019[a]
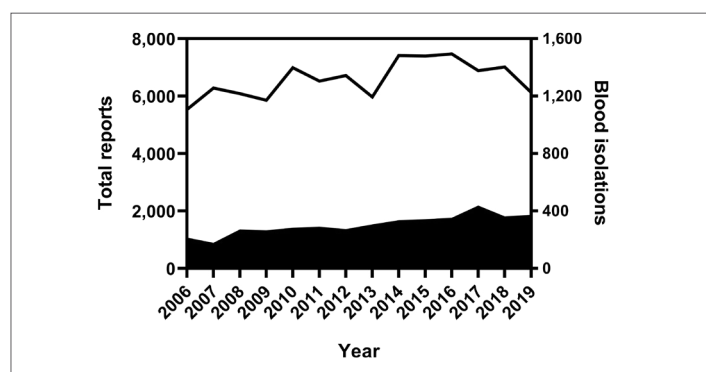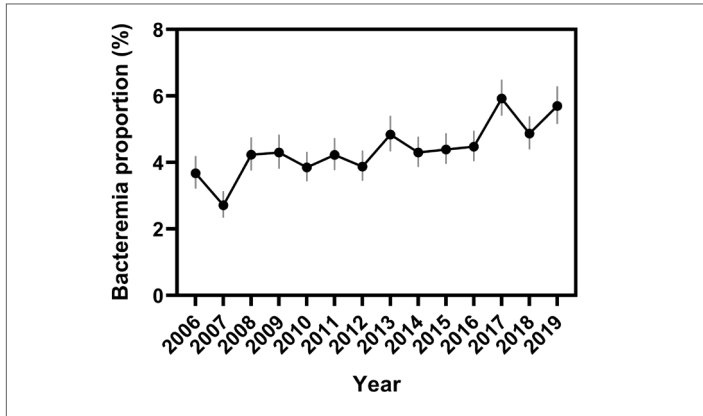

Abbreviation: NESP, National Enteric Surveillance Program
[a] Total (line) and blood (solid shape) isolations reported to the NESP

**Figure 2: Change in *Salmonella* bacteremia proportions over time, based on reports to the NESP, 2006–2019[a]**

Abbreviation: NESP, National Enteric Surveillance Program
[a] Vertical lines indicate 95% confidence intervals
Note: *P*<0.0001

Of the 96,082 reported *Salmonella* isolates, 95,385 (99.3%) were typed to the serovar level, 258 (0.3%) to the subspecies level and 439 (0.5%) to the genus level. The genus group was excluded from further analysis. Of the 4,252 blood isolates, seven were excluded from further analysis because they were only typed to the genus level.

Table 1 lists the subspecies distribution of the reported typed isolates. There were only two reports of *S. bongori* during the reporting period; both were isolated from stool. The remaining isolates were *S. enterica*, with 99.3% of the total isolates and 99.5% of blood isolates typed as subspecies I.

The bacteremia rate of subspecies I was 4.4% (95% CI: 4.3%–4.6%). With the exception of subspecies IIIb, this rate did not differ significantly from those of the other subspecies even when they were analyzed as an aggregate group to reduce the imprecision associated with low numbers of isolates (*P*=0.0728, **Figure 3**). The bacteremia rate of subspecies IIIb, 1.4% (95% CI: 0.5%–3.5%), was significantly lower than that of other subspecies I (*P*=0.0087).

Figure 3: Comparison of bacteremia proportions of *Salmonella enterica* subspecies, based on reports to the NESP, 2006–2019[a,b,c]
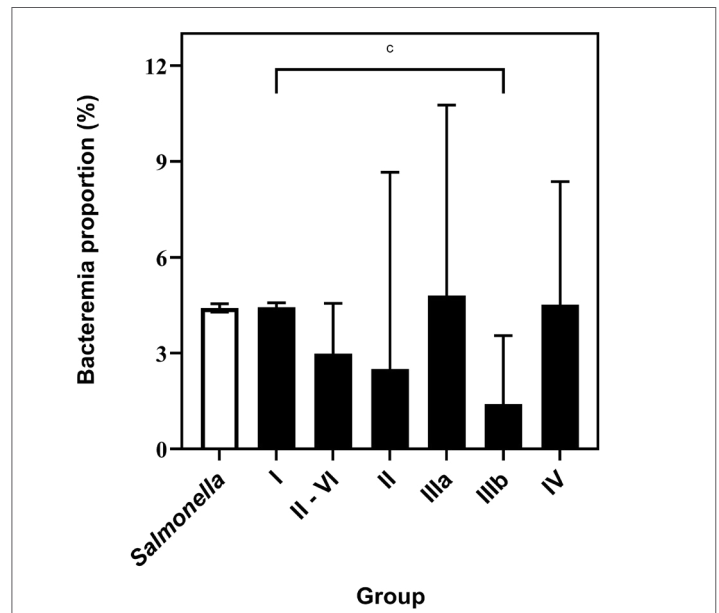
Abbreviation: NESP, National Enteric Surveillance Program
[a] White bar depicts the overall bacteremia proportion of the genus *Salmonella*
[b] Vertical lines indicate 95% confidence intervals
[c] *P*=0.0087

Of the isolates in subspecies I, there were 3,678 total isolations of typhoidal strains (2,350 Typhi, 1,198 Paratyphi A, 124 Paratyphi B and 6 Paratyphi C) and 1,295 blood isolations (794 Typhi, 485 Paratyphi A, 16 Paratyphi B and 0 Paratyphi C). The bacteremia rate of typhoidal strains was 35.2% (95% CI: 33.7%–36.8%), significantly higher than the rate calculated for nontyphoidal strains (3.2%, 95% CI: 3.1%–3.3%, *P*<0.0001, **Figure 4**).

Of the 570 NTS serovars reported to the NESP from 2006 to 2019, 136 were associated with bacteremia. Enteritidis was the most frequently associated with bacteremia, with over 1,000 reports. With Heidelberg, these two serovars accounted for 60% of the blood reports (**Figure 5**). Typhimurium, Dublin and

Table 1: Frequency of *Salmonella* species and subspecies reported to the NESP, 2006–2019

Species	Subspecies	Total reports		Blood reports	
		Number of serovars	Number of isolates	Number of serovars	Number of isolates
Salmonella enterica	*enterica (I)*	574	94,972	139	4,218
	salamae (II)	40	80	2	2
	arizoniae (IIIa)	19	104	4	5
	diarizonae (IIIb)	95	285	4	4
	houtenae (IV)	24	199	4	9
	indica (VI)	1	1	0	0
Salmonella bongori	NA	1	1	0	0

Abbreviations: NA, not applicable; NESP, National Enteric Surveillance Program

Figure 4: Comparison of proportions of bacteremia of typhoidal and nontyphoidal strains of *Salmonella enterica* subspecies, based on reports to the NESP, 2006–2019[a,b,c]
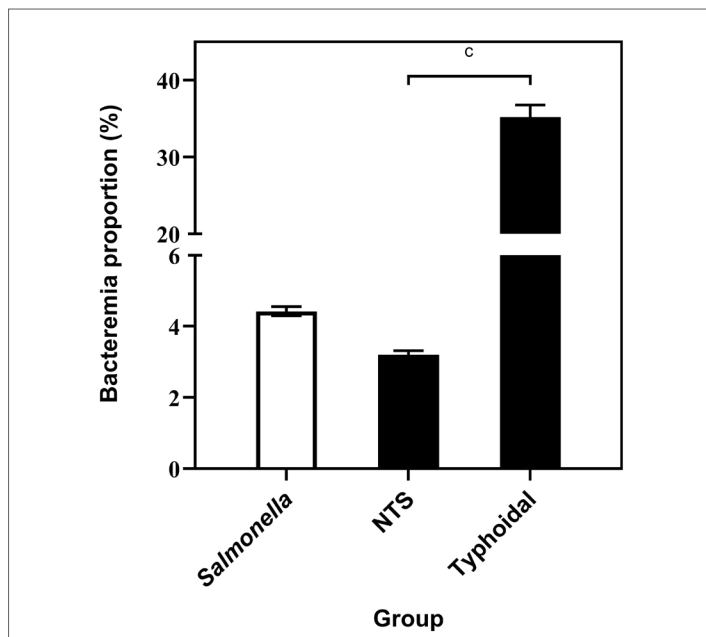
Abbreviations: NESP, National Enteric Surveillance Program; NTS, nontyphoidal
[a] White bar depicts the overall bacteremia proportion of the genus *Salmonella*
[b] Vertical lines indicate 95% confidence intervals
[c] *P*<0.0001

Oranienburg were, respectively, the third, fourth and fifth most frequently serovars reported in blood (Figure 5).

Figure 5: Frequency distribution of the top five *Salmonella enterica* nontyphoidal serovars isolated from blood as reported to the NESP, 2006–2019[a]
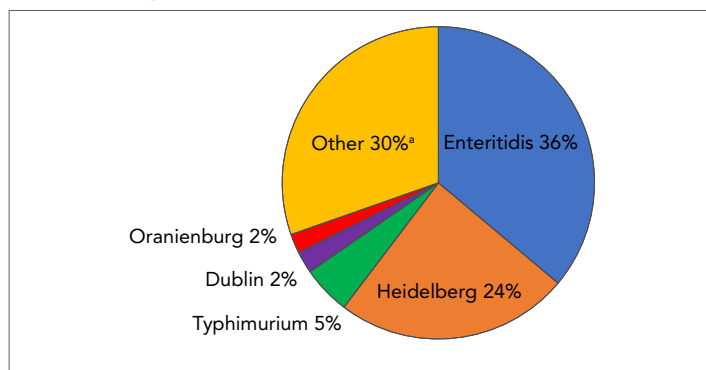
Abbreviation: NESP, National Enteric Surveillance Program
[a] Number of serovars represented by "Other"=131

Sixty-three serovars were associated with only one blood report during the 14-year reporting period. As a comparison, the top two NTS serovars from all specimen sources were Enteritidis and Typhimurium, accounting for 50% of the total reports. Serovars Heidelberg, I 4,[5],12:i:- and Infantis rounded out the top 5 (**Figure 6**).

Figure 6: Frequency distribution of the top five *Salmonella enterica* nontyphoidal isolated from all specimen sources as reported to the NESP, 2006–2019[a]
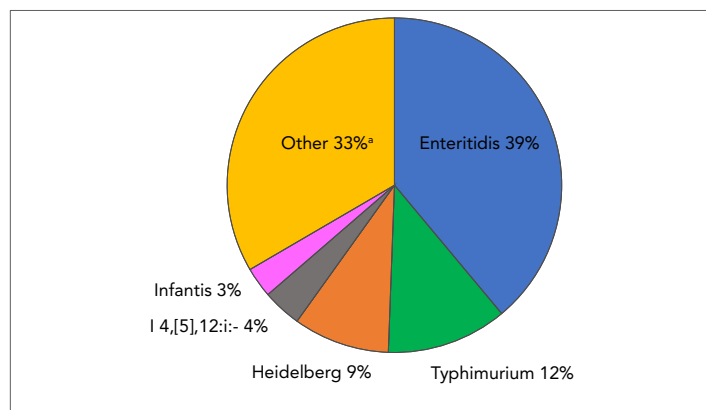
Abbreviation: NESP, National Enteric Surveillance Program
[a] Number of serovars represented by "Other"=565

Bacteremia proportions for individual NTS serovars associated with at least 10 infections are listed in **Table 2** in descending order of frequency.

Nineteen serovars had bacteremia rates significantly higher than that of the NTS group. In terms of frequency, these serovars varied from the third most reported (Heidelberg) to the 85th (I 6.7:c:-). The serovars with the highest rates of bacteremia were Choleraesuis (33 reports, bacteremia rate 36.4%, 95% CI: 22.2%–53.3%); Dublin (187 reports, bacteremia rate 35.3%, 95% CI: 28.8%–42.4%); and I 6,7:c:- (30 reports, bacteremia rate 30.0%, 95% CI: 16.7%–47.9%).

Table 3 lists the NTS serovars with at least 10 reports and no reposted blood isolations. Of these, 20 had significantly lower rates of bacteremia compared to the group of all NTS serovars. Included in this group were Enteritidis and Typhimurium. In addition, 48 serovars reported at least 10 times between 2006 and 2019 were not associated with any blood isolations.

The reporting trends of the three most frequently reported serovars, Enteritidis, Typhimurium and Heidelberg, are shown in **Figure 7**. From 2006 to 2019, the number of blood reports for serovar Enteritidis increased from 15 to 97 and the number of total reports increased from 1,338 to 2,254, a bacteremia rate that increased from 1.1% (95% CI: 0.7%–1.8%) to 4.1% (95% CI: 3.4%–5.0%, *P*<0.0001). The bacteremia rate of Typhimurium also appeared to increase during the reporting period, from 0.4% (95% CI: 0.2%–1.0%) to 2.3% (95% CI: 1.3%–3.9%, *P*=0.0031). The number of blood reports remained relatively stable, with four in 2006 and 13 in 2019, but the number of total reports decreased from 998 in 2006 to 557 in 2019.

Table 2: Bacteremia proportions of nontyphoidal *Salmonella* serovars with at least 10 reports to the NESP, 2006–2019

Serovar[a]	Number of blood isolates	Total number of isolates	Bacteremia rate (%)[b]	95% CI (%)	*p*-value[c]	Odds ratio[d]	95% CI
NTS	2,917	91,088	3.2	3.1–3.3	NA	NA	NA
Enteritidis[e]	1,053[e]	35,459[e]	3.0[e]	2.8–3.2[e]	0.0326[e]	0.9[e]	0.9–1.0[e]
Typhimurium[e]	147[e]	10,617[e]	1.4[e]	1.2–1.6[e]	<0.0001[e]	0.4[e]	0.4–0.5[e]
Heidelberg[f]	707[f]	8,482[f]	8.3[f]	7.8–8.9[f]	<0.0001[f]	2.7[f]	2.5–3.0[f]
I 4,[5],12:i:-[e]	52[e]	3,430[e]	1.5[e]	1.2–2.0[e]	<0.0001[e]	0.5[e]	0.4–0.6[e]
Infantis[e]	28[e]	2,672[e]	1.0[e]	0.7–1.5[e]	<0.0001[e]	0.3[e]	0.2–0.5[e]
Thompson[e]	46[e]	2,582[e]	1.8[e]	1.3–2.4[e]	<0.0001[e]	0.6[e]	0.4–0.7[e]
Newport[e]	38[e]	2,474[e]	1.5[e]	1.1–2.1[e]	<0.0001[e]	0.5[e]	0.3–0.7[e]
Saintpaul	47	1,466[e]	3.2	2.4–4.2	0.9405	1.0	0.7–1.3
Javiana	45	1,384[e]	3.3	2.4–4.3	0.8778	1.0	0.8–1.4
Agona[e]	15[e]	1,255[e]	1.2[e]	0.7–2.0[e]	<0.0001[e]	0.4[e]	0.2–0.6[e]
Braenderup[e]	6[e]	1,208[e]	0.5[e]	0.2–1.1[e]	<0.0001[e]	0.2[e]	0.1–0.3[e]
Hadar[e]	13[e]	1,077[e]	1.2[e]	0.7–2.0[e]	<0.0001[e]	0.4[e]	0.2–0.6[e]
Oranienburg[f]	58[f]	1,063[f]	5.5[f]	4.2–7.0[f]	0.0002[f]	1.7[f]	1.3–2.3[f]
Stanley[e]	19[e]	981[e]	1.9[e]	1.2–3.0[e]	0.0221[e]	0.6[e]	0.4–0.9[e]
Muenchen[e]	11[e]	884[e]	1.2[e]	0.7–2.2[e]	0.0003[e]	0.4[e]	0.2–0.7[e]
I 4,[5],12:b:-	24	880	2.7	1.8–4.0	0.4998	0.9	0.6–1.3
Paratyphi B var. Java[f]	41[f]	874[f]	4.7[f]	3.5–6.3[f]	0.0201[f]	1.5[f]	1.1–2.0[f]
Montevideo	12	544	2.2	1.3–3.8	0.2207	0.7	0.4–1.2
Mbandaka[e]	6[e]	474[e]	1.3[e]	0.6–2.7[e]	0.0122[e]	0.4[e]	0.2–0.9[e]
Virchow[f]	28[f]	425[f]	6.6[f]	4.6–9.4[f]	0.0004[f]	2.1[f]	1.5–3.1[f]
Schwarzengrund[f]	30[f]	422[f]	7.1[f]	5.0–10.0[f]	<0.0001[f]	2.3[f]	1.6–3.4[f]
Panama[f]	47[f]	414[f]	11.3[f]	8.6–14.8[f]	<0.0001[f]	3.9[f]	2.8–5.3[f]
Poona[f]	35[f]	396[f]	8.8[f]	6.4–12.0[f]	<0.0001[f]	2.9[f]	2.1–4.2[f]
Kentucky[e]	1[e]	395[e]	0.3[e]	0.01–1.4[e]	<0.0001[e]	0.1[e]	0.01–0.6[e]
Anatum[e]	3[e]	378[e]	0.8[e]	0.2–2.3[e]	0.0046[e]	0.2[e]	0.1–0.8[e]
Brandenburg[f]	27[f]	346[f]	7.8[f]	5.4–11.1[f]	<0.0001[f]	2.6[f]	1.7–3.8[f]
Derby	5	342	1.5	0.6–3.4	0.0868	0.5	0.2–1.1
Uganda	13	328	4.0	2.3–6.7	0.4292	1.2	0.7–2.2
Litchfield[e]	2[e]	317[e]	0.6[e]	0.1–2.2[e]	0.0055[e]	0.2[e]	0.1–0.8[e]
Bareilly[e]	3[e]	308[e]	1.0[e]	0.3–2.8[e]	0.0216[e]	0.3[e]	0.1–0.9[e]
Reading[f]	28[f]	304[f]	9.2[f]	6.4–13.0[f]	<0.0001[f]	3.1[f]	2.1–4.5[f]
Hartford	6	297	2.0	0.9–4.3	0.3200	0.6	0.3–1.4
Sandiego[f]	32[f]	290[f]	11.0[f]	7.9–15.2[f]	<0.0001[f]	3.7[f]	2.6–5.4[f]
Kiambu	4	275	1.5	0.6–3.7	0.1197	0.5	0.2–1.2
Bovismorbificans	8	255	3.1	1.6–6.1	>0.9999	1.0	0.5–2.0
Berta[e]	2[e]	248[e]	0.8[e]	0.1–2.9[e]	0.0278[e]	0.3[e]	0.1–1.0[e]
Chester[f]	14[f]	198[f]	7.1[f]	4.3–11.5[f]	0.0066[f]	2.3[f]	1.3–4.0[f]
Dublin[f]	66[f]	187[f]	35.3[f]	28.8–42.4[f]	<0.0001[f]	16.5[f]	12.2–22.3[f]
Corvallis	3	185	1.6	0.4–4.7	0.2948	0.5	0.2–1.6
Manhattan	3	182	1.6	0.4–4.7	0.2944	0.5	0.2–1.6
Mississippi	1	170	0.6	0.03–3.3	0.0478	0.2	0.02–1.3
Tennessee	2	160	1.3	0.2–4..4	0.2534	0.4	0.1–1.5
Give	4	150	2.7	1. 0–6.7	>0.9999	0.8	0.3–2.2
Muenster	8	149	5.4	2.7–10.2	0.1536	1.7	0.8–3.5
Hvittingfoss	1	137	0.7	0.04–4.0	0.1379	0.2	0.03–1.6
Rissen	2	134	1.5	0.3–5.3	0.4533	0.5	0.1–2.1
Eastbourne	6	129	4.7	2.1–9.8	0.3125	1.5	0.7–3.3
Havana	2	116	1.7	0.3–6.1	0.5927	0.5	0.1–2.1

Table 2: Bacteremia proportions of nontyphoidal *Salmonella* serovars with at least 10 reports to the NESP, 2006–2019 (*continued*)

Serovar[a]	Number of blood isolates	Total number of isolates	Bacteremia rate (%)[b]	95% CI (%)	*p*-value[c]	Odds ratio[d]	95% CI
I Rough-O:-:-	1	116	0.9	0.04–4.7	0.1905	0.3	0.04–1.9
Oslo	2	106	1.9	0.3–6.6	0.7781	0.6	0.1–2.4
Haifa	4	94	4.3	1.7–10.4	0.5478	1.3	0.5–3.7
London	3	91	3.3	0.9–9.2	0.7681	1.0	0.3–3.3
Indiana	2	91	2.2	0.4–7.7	>0.9999	0.7	0.2–2.8
I 9,12-:-	3	88	3.4	0.9–9.6	0.7610	1.1	0.3–3.4
Ohio	2	85	2.4	0.4–8.2	>0.9999	0.7	0.2–3.0
Durban[f]	8[f]	84[f]	9.5[f]	4.9–17.7[f]	0.0056[f]	3.2[f]	1.5–6.6[f]
Telelkebir[f]	6[f]	75[f]	8.0[f]	3.7–16.4[f]	0.0334[f]	2.6[f]	1.1–6.1[f]
Bredeney	4	71	5.6	2.2–13.6	0.2921	1.8	0.7–4.9
Pomona	2	65	3.1	0.6–10.5	>0.9999	1.0	0.2–3.9
Minnesota	1	57	1.8	0.09–9.3	>0.9999	0.5	0.1–3.9
Carrau	3	54	5.6	1.5–15.1	0.2495	1.8	0.6–5.7
Cubana	1	53	1.9	0.1–9.9	>0.9999	0.6	0.1–4.2
Bonariensis	4	52	7.7	3.0–18.2	0.0487	2.5	0.9–7.0
Aberdeen	2	51	3.9	0.7–13.2	0.6792	1.2	0.3–5.1
Rubislaw	2	51	3.9	0.7–13.2	0.6792	1.2	0.3–5.1
Gaminara	1	51	2.0	0.1–10.3	>0.9999	0.6	0.1–4.4
Cerro	1	49	4.1	0.7–13.7	0.6710	1.2	0.3–5.3
Gatuni	1	46	2.2	0.1–11.3	>0.9999	0.7	0.1–4.9
Worthington	1	45	2.2	0.1–11.6	>0.9999	1.0	0.1–5.0
Urbana[f]	4[f]	42[f]	9.5[f]	3.8–22.1[f]	0.0450[f]	3.2[f]	1.1–8.9[f]
I 6,7:r:-	1	41	2.4	0.1–12.6	>0.9999	0.8	0.1–5.5
Arechavaleta	2	39	5.1	0.9–16.9	0.3566	1.6	0.4–6.8
Agbeni	1	39	2.6	0.1–13.2	>0.9999	0.8	0.1–5.8
Nessziona	2	38	5.3	0.9–17.3	0.3449	1.7	0.4–7.0
Lomalinda[f]	5[f]	35[f]	14.3[f]	6.3–29.4[f]	0.0049[f]	5.0[f]	2.0–13.0[f]
Johannesburg	3	34	8.8	3.0–23.0	0.0944	2.9	0.9–9.6
Choleraesuis[f]	12[f]	33[f]	36.4[f]	22.2–53.3[f]	<0.0001[f]	17.2[f]	8.5–351[f]
Stanleyville[f]	7[f]	33[f]	21.2[f]	10.7–37.8[f]	<0.0001[f]	8.1[f]	3.5–18.7[f]
Ebrie	1	33	3.0	0.2–15.3	>0.9999	1.0	0.1–6.9
Kottbus	1	32	3.1	0.2–15.7	>0.9999	1.0	0.1–7.1
Livingstone	1	32	3.1	0.2–15.7	>0.9999	1.0	0.1–7.1
I 6,7:c:-[f]	9[f]	30[f]	30.0[f]	16.7–47.9[f]	<0.0001[f]	12.9[f]	5.9–28.3[f]
Nima	1	28	3.6	0.2–17.7	0.5981	1.1	0.2–8.2
Chailey	2	26	7.7	1.4–24.1	0.2021	2.5	0.6–10.6
I 6,7:k:-	1	26	3.8	0.2–18.9	0.5710	1.2	0.2–8.9
Daytona	1	25	4.0	0.2–19.5	0.5569	1.3	0.2–9.3
Meleagridis	1	25	4.0	0.2–19.5	0.5569	1.3	0.2–9.3
Colindale	1	24	4.2	0.2–20.2	0.5422	1.3	0.2–9.7
I Rough-O:g,m:-	2	23	8.7	1.6–27.8	0.1671	2.9	0.7–12.3
Monschaui	1	23	4.3	0.2–21.0	0.5270	1.4	0.2–10.2
Baildon	1	22	4.5	0.2–21.8	0.5114	1.4	0.2–10.7
Coeln	1	22	4.5	0.2–21.8	0.5114	1.4	0.2–10.7
Emek	1	22	4.5	0.2–21.8	0.5114	1.4	0.2–10.7
Kintambo	1	20	5.0	0.3–23.6	0.4785	1.6	0.2–11.9
Praha	1	17	5.9	0.3–27.0	0.4250	1.9	0.3–14.2
Michigan	1	16	6.3	0.3–28.3	0.4060	2.0	0.3–15.2
Wandsworth	1	16	6.3	0.3–28.3	0.4060	2.0	0.3–15.2

Table 2: Bacteremia proportions of nontyphoidal *Salmonella* serovars with at least 10 reports to the NESP, 2006–2019 (*continued*)

Serovar[a]	Number of blood isolates	Total number of isolates	Bacteremia rate (%)[b]	95% CI (%)	*p*-value[c]	Odds ratio[d]	95% CI
I Rough-O:r:1,2	1	15	6.7	0.3–29.8	0.3864	2.2	0.3–16.4
Glostrup	1	14	7.1	0.4–31.5	0.3661	2.3	0.3–17.7
I 4,[5],12:e,h:-	1	14	7.1	0.4–31.5	0.3661	2.3	0.3–17.7
Takoradi	1	13	7.6	0.4–33.3	0.3451	2.5	0.3–19.3
Napoli	1	12	8.3	0.4–35.4	0.3234	2.7	0.4–21.3
Nottingham	1	10	10.0	0.5–40.4	>0.9999	3.4	0.4–26.5

Abbreviations: CI, confidence interval; NESP, National Enteric Surveillance Program
[a] Serovars with at least 10 reports are listed in descending order of reported frequency
[b] Bacteremia proportions were calculated as the number of blood isolates as a proportion of total isolates
[c] *p*-values were calculated by comparing bacteremia proportions of each serovar with that of the group of all nontyphoidal serovars
[d] Odds ratios were calculated relative to all nontyphoidal serovars
[e] Serovars associated with significant lower rates of bacteremia in comparison to all nontyphoidal serovars (green)
[f] Serovars associated with significant higher rates of bacteremia in comparison to all nontyphoidal serovars (red)

Table 3: *Salmonella* serovars reported to the NESP in 2006–2019 that were not associated with bacteremia

Serovar	Total isolates	*p*-value[a]
Weltevreden	382	<0.0001
Senftenberg	313	<0.0001
Mississippi	170	0.0478
Blockley	117	0.0568
Miami	105	0.0847
I 9,12:-:1,5	100	0.0804
Adelaide	86	0.1188
Albany	86	0.1188
Alachua	54	0.4216
Concord	53	0.4187
Cotham	46	0.4059
Norwich	46	0.4059
Ealing	45	0.4053
Singapore	44	0.4050
Richmond	38	0.6349
I 4,[5],12:-:1,2	36	0.6309
I 6,7:-:-	31	0.6260
Altona	27	>0.9999
I 4,[5],12:d:-	27	>0.9999
Potsdam	25	>0.9999
I Rough-O:HNM	25	>0.9999
Ago	24	>0.9999
Bardo	24	>0.9999
Irumu	23	>0.9999
Liverpool	23	>0.9999
Othmarschen	23	>0.9999
Istanbul	21	>0.9999
Fluntern	20	>0.9999
Putten	20	>0.9999
I 6,8:e,h:-	20	>0.9999

Table 3: *Salmonella* serovars reported to the NESP in 2006–2019 that were not associated with bacteremia (*continued*)

Serovar	Total isolates	*p*-value[a]
Kedougou	19	>0.9999
Larochelle	19	>0.9999
I 6,7:e,h:-	19	>0.9999
Isangi	16	>0.9999
Goettingen	15	>0.9999
Lexington	15	>0.9999
Amsterdam	14	>0.9999
Apapa	14	>0.9999
Kingabwa	13	>0.9999
I 13,23:b:-	13	>0.9999
Abony	12	>0.9999
I Rough-O:i:1,2	12	>0.9999
Kisarawe	11	>0.9999
Saphra	10	>0.9999
I 6,8:-:-	10	>0.9999

Abbreviation: NESP, National Enteric Surveillance Program
[a] *p*-values were calculated by comparing bacteremia proportions of each serovar with that of the group of all nontyphoidal serovars

The reporting frequencies of serovar Heidelberg fluctuated nonlinearly during the reporting period, from a low of 19 blood reports in 2019 to a high of 99 in 2017. The number of total reports varied from a low of 267 in 2019 to a high of 1,071 in 2012. The corresponding bacteremia rate also fluctuated from a low of 5.4% (95% CI: 3.9%–7.5%) in 2007 to a high of 18.2% (95% CI: 15.2%–21.7%) in 2017.

Figure 7: Bacteremia rates of individual nontyphoidal *Salmonella* serovars, 2006–2019[a,b,c]
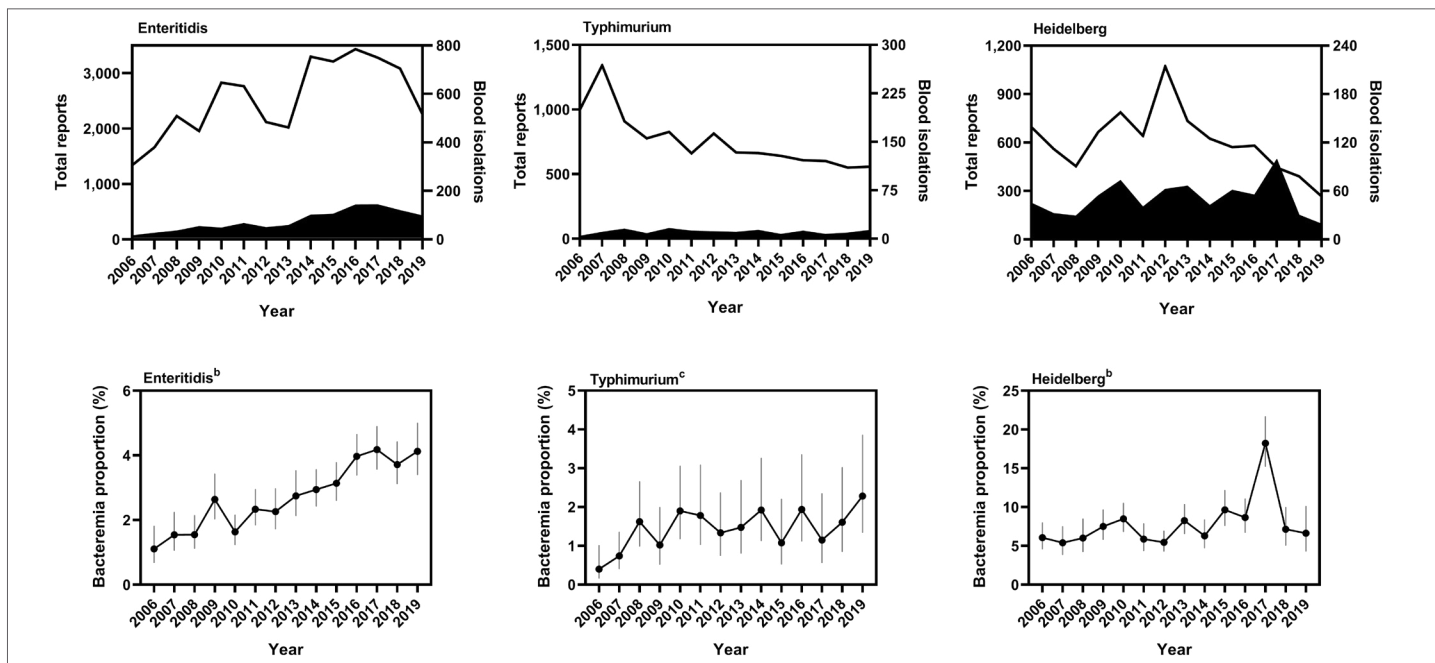
[a] Top row shows total (line) and blood (solid shape) isolations reported to the National Enteric Surveillance Program (NESP). Bottom row shows the bacteremia proportions. Vertical lines indicate 95% confidence intervals
[b] $P<0.0001$
[c] $P=0.0031$

Discussion

Based on data submitted to the NESP, the overall rate of *Salmonella* bacteremia in Canada was 4.4% (95% CI: 4.3%–4.6%) from 2006 to 2019. Annual rates varied from 2.7% to 5.9% and increased on average by 0.2% per year during the reporting period. Analysis of the bacteremia rate for individual serovars showed that it shifted over time with the number of total and blood reports. The overall rate for the genus then, is expected to reflect changes in the reporting patterns of all *Salmonella* serovars in Canada. The underlying reasons for these changes warrant further study, but could reflect changes in exposure pathways, changes in serovar prevalence, demographic or other changes in the patient population, or a combination of these factors (14,15).

The rate of bacteremia for typhoid isolates was 35.2% (95% CI: 33.7%–36.8%), over the 14-year reporting period. Bacteremia is often a consequence of typhoid fever and the rate reported here is in line with published values (17). The bacteremia rate of NTS isolates was 3.2% (95% CI: 3.1%–3.3%). This rate was slightly lower than estimates from the United States (US; 5%) (18,19) and higher than the 2.1% reported for England (14).

These differences could be due to differences in the reporting periods of the three studies (US: 1996–2006, England: 2004–2015) and differences in serovar prevalence (14,19). The top five serovars reported in the American study were Typhimurium, Enteritidis, Newport, Heidelberg and Javiana (19). In England, the top five serovars were Enteritidis, Typhimurium,

Virchow, Newport and Infantis (14). There was considerable overlap in the serovars most commonly associated with bacteremia in Canada, the US and England (14,19). Of the 19 serovars identified as having high bacteremia rates in this study, eight were also identified as having high bacteremia rates in England and the US: Heidelberg, Oranienburg, Virchow, Schwarzengrund, Panama, Poona, Brandenburg and Dublin. Canada shared four additional serovars with the US (Reading, Sandiego, Urbana and Choleraesuis) and two with England (Chester and Paratyphi B var. Java) (14,19).

Geographic variations in serovars were also noted between the three studies. Serovars Durban, Telelkebir, Lomalinda, Stanleyville and I 6,7:c:- were all identified in this study as having higher rates of bacteremia. Collectively, these five serovars are rare and accounted for 257 lab-confirmed cases from 2006 to 2019 (or 0.3% of all NTS reports). These serovars were not listed in the English and American reports, suggesting that exposures are travel related or unique to Canada.

Continued study on the pathogenesis of NTS serovars associated and not associated with bacteremia will provide knowledge on the relative risks of *Salmonella* serovars. Understanding these differences will inform methods to improve patient care through the early identification and treatment of salmonellosis cases that are at a high risk of developing bacteremia.

Strengths and limitations
The rates of bacteremia presented above are estimates of the true rate based on data submitted to the NESP. Data submission

to the NESP is voluntary. The values in this report only represent the isolates submitted by provincial and territorial laboratories, and understate the number of salmonellosis cases in Canada (20).

Data on the isolate source are captured by the NESP based on details collected by the submitting laboratories. As this information is not always available, data on extraintestinal *Salmonella* infections may also be underreported. Although every effort is made to prevent duplications, the limited source data precludes identification of duplicate isolations from different sources from the same patient. In addition, the data include travel-related cases, which does not reflect the true representation of strains endemic to Canada.

The strength of studies such as this rely on the quality and quantity of surveillance data available. Fewer reported isolates lead to greater degrees of imprecision. The numbers presented here are likely to be skewed higher towards bacteremia since patients with more severe symptoms are more likely to seek medical attention than those with a self-limiting form of the disease. With the absence of clinical data, it is assumed that the cases from which *Salmonella* blood isolates were recovered were more severe than those that had positive stool cultures.

Conclusion

Based on data submitted to the NESP, an estimated 4.4% of the cases of salmonellosis that occurred between 2006 and 2019 resulted in bacteremia. Specific *Salmonella* groups and serovars that were associated with higher and lower rates of bacteremia compared to the larger group of *Salmonella* strains were identified. The results of this study will inform future research aimed at predicting and improving the outcomes of *Salmonella* bacteremia in Canada.

Authors' statement

ST — Conceptualization, methodology, formal analysis, writing–original draft, writing–review and editing
BD — Writing–review and editing
KN — Data curation, writing–review and editing

Competing interests

None.

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