MAJOR ARTICLE

Increased Burden of Illness Associated with Antimicrobial-Resistant *Salmonella enterica* Serotype Typhimurium Infections

Leah J. Martin,[1,2,a] Murray Fyfe,[6] Kathryn Doré,[2] Jane A. Buxton,[3,a] Franklin Pollari,[2] Bonnie Henry,[3,4,a] Dean Middleton,[4] Rafiq Ahmed,[5] Frances Jamieson,[4] Bruce Ciebin,[4] Scott A. McEwen,[1] Jeffrey B. Wilson,[1,2] and the Multi-Provincial *Salmonella* Typhimurium Case-Control Study Steering Committee[b]

[1]Department of Population Medicine, University of Guelph, and [2]Division of Enteric, Foodborne, and Waterborne Diseases, Health Canada, Guelph, and [3]Field Epidemiology Training Program, Laboratory Centre for Disease Control, Health Canada, Ottawa, and [4]Ontario Ministry of Health and Long-Term Care, Toronto, Ontario, and [5]National Laboratory for Enteric Pathogens, Health Canada, Winnipeg, Manitoba, and [6]British Columbia Centre for Disease Control, Vancouver, British Columbia, Canada

This study investigated the burden of illness associated with 440 cases of *Salmonella enterica* serotype Typhimurium infection identified in Canada between December 1999 and November 2000. We categorized case subjects' infections by definitive phage type 104 (DT104) and antimicrobial-resistance patterns. These variables were then investigated as risk factors for hospitalization. Hospitalization was more likely to occur among case subjects whose infections were resistant to at least ampicillin, chloramphenicol and/or kanamycin, streptomycin, sulphamethoxazole, and tetracycline (R-type AK/CSSuT; odds ratio [OR], 2.3; $P = .003$), compared with case subjects with AK/CSSuT-susceptible infections, and among case subjects with non-DT104 R-type AKSSuT infections (OR, 3.6; $P = .005$), compared with case subjects with non-DT104 AKSSuT-susceptible infections. In contrast, hospitalization rates did not differ between case subjects with DT104 infections and case subjects with non-DT104 infections or between case subjects with DT104 R-type ACSSuT infections and case subjects with DT104 ACSSuT-susceptible infections. We estimated that 57% of the hospitalizations among AK/CSSuT case subjects and 72% of the hospitalizations among non-DT104 AKSSuT case subjects were attributable to the resistance patterns of the infections.

Salmonellosis is a serious public health concern that, in Canada, has been estimated to cause 627,200 cases of infection and cost Can$846.2 million annually [1]. This is more than double the estimated cost for all other foodborne illnesses combined [1].

In 2000, *Salmonella enterica* serotype Typhimurium accounted for 22% of human *Salmonella* isolates reported in Canada (unpublished data, National Enteric Surveillance Program, Health Canada). Definitive phage type 104 (DT104) is a common *Salmonella* Typhimurium phage type that is frequently resistant to ampicillin, chloramphenicol, streptomycin, sulphamethoxazole, and tetracycline (R-type ACSSuT) [2]. Additionally, R-type AKSSuT, which includes resistance to kanamycin rather than to chloramphenicol, has emerged among *Salmonella* Typhimurium non-DT104 isolates [3].

Most individuals infected with *Salmonella* Typhimurium experience mild gastrointestinal illness involving diarrhea, chills, abdominal cramps, fever, head and

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Reprints or correspondence: Leah J. Martin, Foodborne, Waterborne, and Zoonotic Infections Division, Health Canada, 160 Research Lane, Suite 206, Guelph, Ontario N1G 5B2, Canada (leah_martin@hc-sc.gc.ca).

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[a] Present affiliations: Foodborne, Waterborne, and Zoonotic Infections Division, Health Canada, Guelph, Ontario, Canada (L.J.M.); Department of Health Care and Epidemiology, University of British Columbia, Vancouver, British Columbia (J.A.B.); Toronto Public Health, Toronto, Ontario, Canada (B.H.).

[b] Members of the Multi-Provincial *Salmonella* Typhimurium Case-Control Study Steering Committee are listed after the text.

body aches, nausea, and vomiting [4]. Infections are usually self-limiting, and antimicrobial treatment is not recommended for uncomplicated illnesses [5, 6]. However, extraintestinal infection can occur, particularly in very young, elderly, and immunocompromised patients [7, 8]. In these cases, effective antimicrobial treatment is essential [9].

Compared with infections caused by antimicrobial-susceptible bacteria, infections caused by bacteria resistant to ⩾1 antimicrobial have been associated with higher rates of morbidity and mortality [10]. Researchers have hypothesized several mechanisms to account for this increased burden of illness. These include (1) antimicrobial-treatment failures or complications, which become more probable as the number of antimicrobials in the resistance-pattern increases; (2) increased virulence, which is caused by the linkage of virulence determinants with genes encoding for resistance; and (3) diminished colonization resistance of intestinal microflora caused by previous antimicrobial treatment, which facilitates infection with a resistant strain of bacteria [11].

To examine the relationship between increased burden of illness and both DT104 and antimicrobial resistance, we investigated illness severity and rates of hospitalization reported by *Salmonella* Typhimurium case subjects in Canada. Additionally, we estimated the fraction of hospitalizations attributable to the antimicrobial-resistance pattern of the infection and the total costs of hospitalization for case subjects in the present study.

SUBJECTS, MATERIALS, AND METHODS

Sample population. All persons with *Salmonella* Typhimurium infection identified by the provincial public health laboratories in Alberta, British Columbia, and Saskatchewan and every second person with *Salmonella* Typhimurium infection identified in Ontario, between 1 December 1999 and 30 November 2000, were eligible for inclusion in the present study. Every second person in Ontario was chosen because of the higher predicted number of cases of infection in this province. Persons were excluded if they (1) reported that their primary residence was outside the study province, (2) were unable to communicate in English, (3) had no telephone or were unreachable by telephone after 15 attempts, (4) did not report diarrhea, (5) did not know the date of onset of diarrhea, (6) reported the date of onset of diarrhea as being >30 days before the interview date, or (7) were identified as part of an *Salmonella* Typhimurium outbreak. We defined diarrhea as ⩾3 loose stools in a 24-h period. Certification of ethical acceptability for research using human subjects was obtained from the University of Guelph (Guelph, Ontario, Canada), the University of British Columbia (Vancouver, British Columbia, Canada), and the University of Regina (Regina, Saskatchewan, Canada).

Laboratory testing. Provincial public health laboratories performed serotype analysis on all human *Salmonella* species isolated from stool samples and forwarded *Salmonella* Typhimurium study isolates to the National Laboratory for Enteric Pathogens (NLEP, Winnipeg, Manitoba, Canada) for phage type analysis, antimicrobial resistance testing, and confirmatory serotype analysis if the serotype reported to NLEP did not correspond to the phage type.

Study isolates were tested by use of the microtitre dilution method (Sensititre; Trek Diagnostics), with 16 antimicrobials on the drug panel: amikacin, amoxicillin/clavulanic acid, ampicillin, apramycin, ceftriaxone, ceftiofur, cephalothin, chloramphenicol, ciprofloxacin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulphamethoxazole, tetracycline, and trimethoprim-sulphamethoxazole. NLEP followed NCCLS protocols [12] and determined breakpoints by use of NCCLS interpretive standards [13]. Breakpoints for ceftiofur were determined from NCCLS M31-A [14], and those for apramycin were determined from the National Antimicrobial Resistance Monitoring System (NARMS) 1999 Annual Report [3]. MICs were categorized as resistant, sensitive, or intermediate. For analysis, we classified intermediate results as sensitive.

Questionnaire and interview. After providing verbal consent to participate, case subjects were interviewed via telephone by trained interviewers using a detailed questionnaire. For case subjects <12 years old, a parent or guardian was interviewed as a proxy by use of a similar questionnaire. Questions pertained to (1) demographics, (2) general health, (3) medications taken during the 4 weeks before onset of illness, (4) symptoms occurring during the illness, (5) self-perceived illness severity, (6) health care use, and (7) treatments taken for the infection. The questionnaire and case subject recruitment methods were pilot tested, and the study ran from 1 December 1999 to 30 November 2000.

Data management. Data from completed questionnaires were entered into Epi-Info (version 6.04; Centers for Disease Control and Prevention), were verified by double entry, and were linked with laboratory data by a unique study identifier. We analyzed the data using SAS (version 8.0; SAS Institute).

Description of variables. To investigate the relationship between DT104 and burden of illness, we divided case subjects into 2 groups: those infected with *Salmonella* Typhimurium DT104 (DT104 case subjects) and those infected with *Salmonella* Typhimurium phage types other than DT104 (non-DT104 case subjects). To investigate the relationship between antimicrobial resistance and burden of illness, we further classified DT104 case subjects by resistance to at least ampicillin, chloramphenicol, streptomycin, sulphamethoxazole, and tetracycline (DT104 R-type ACSSuT case subjects) and non-DT104 case subjects by resistance to at least ampicillin, kanamycin, streptomycin, sulphamethoxazole, and tetracycline (non-DT104 R-type

AKSSuT case subjects). We classified case subjects as susceptible to ACSSuT or AKSSuT if they were susceptible to ⩾1 of the antimicrobials in the resistance pattern. In addition, to eliminate the effect of DT104 and to focus on antimicrobial resistance, we combined the DT104 case subjects and the non-DT104 case subjects and described them collectively by resistance to at least ampicillin, kanamycin and/or chloramphenicol, streptomycin, sulphamethoxazole, and tetracycline (R-type AK/CSSuT). We classified case subjects as susceptible to AK/CSSuT if they were susceptible to both kanamycin and chloramphenicol or to ⩾1 of the other antimicrobials in the resistance pattern. These classifications resulted in 8 case subject groups: (1) DT104, (2) non-DT104, (3) DT104 R-type ACSSuT, (4) DT104 ACSSuT susceptible, (5) non-DT104 R-type AKSSuT, (6) non-DT104 AKSSuT susceptible, (7) R-type AK/CSSuT, and (8) AK/CSSuT susceptible (figure 1).

We described burden of illness by self-perceived illness severity, health care use, and cost of hospitalization. Case subjects were asked to rate their self-perceived illness severity using a 5-point scale: 1, quite mild (feeling slightly unwell but able to perform all normal activities); 2, fairly mild (feeling quite unwell but able to do most normal activities); 3, moderately severe (having to stay home but able to get out of bed for limited activities); 4, fairly severe (confined to bed at home and unable to do any normal activities); and 5, quite severe (hospitalized). Health care use was described by the number of visits to a family physician, walk-in clinic, and emergency department and/or overnight hospitalization.

Estimating hospitalization costs. In 2000, the average total cost of hospitalization per case of gastroenteritis ranged from Can$1627 to Can$6864 in Ontario [15] and from Can$1784 to Can$9872 in Alberta [16], depending on the level of complexity of the illness. These total costs are the sums of direct costs (those resulting from care of patients) and indirect costs (which include the costs of administration and support services) [15, 16]. By weighting the average cost for each gastroenteritis complexity group, for these 2 provinces, by the total number of case subjects in each complexity group, we estimated the average total hospitalization cost per case of salmonellosis to be Can$2142. We used this value to estimate the total cost of hospitalization overall and the total cost for those case groups that were associated with significantly higher rates of hospi-

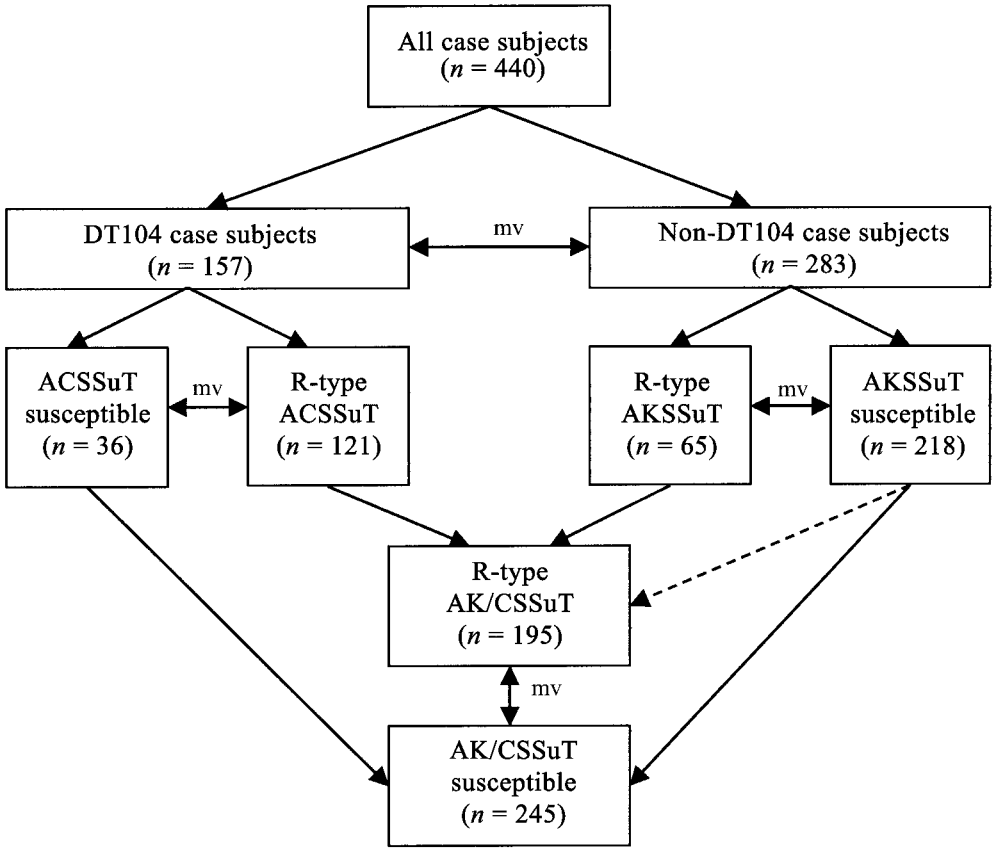

Figure 1. Illustration of *Salmonella* Typhimurium case subject group categorizations and comparisons. The broken arrow indicates a minor contribution to the case group: 9 non–definitive phage type 104 (DT104) case subjects susceptible to ampicillin, kanamycin, streptomycin, sulphamethoxazole, and tetracycline (AKSSuT susceptible) were resistant to ampicillin, chloramphenicol, streptomycin, sulphamethoxazole, and tetracycline (R-type ACSSuT), making them R-type AK/CSSuT; double-ended arrows separate case groups that were compared by multivariate (mv) analysis.

talization. Additionally, for each of these case groups, we estimated the proportion of hospitalizations attributable to DT104 status or to the antimicrobial-resistance pattern by calculating the estimated attributable fraction (AF), using the following formula: estimated AF = (OR − 1)/OR, where OR is the odds ratio [17].

Analysis. Bivariate statistics were computed by use of χ^2 Fisher's Exact test and Student's *t* test, as well as simple logistic regression, where appropriate. $P \leqslant .05$ was defined as significant.

We considered hospitalization an objective burden-of-illness indicator. Using 4 multivariate logistic-regression analyses, we compared the dependent and dichotomous hospitalization variable between the previously described case groups: (1) DT104 versus non-DT104 case subjects, (2) R-type AK/CSSuT versus AK/CSSuT-susceptible case subjects, (3) DT104 R-type ACSSuT versus DT104 ACSSuT-susceptible case subjects, and (4) non-DT104 R-type AKSSuT versus non-DT104 AKSSuT-susceptible case subjects. In addition to these risk factors, we considered all variables that were associated with hospitalization at a significance level of $P < .25$, in simple logistic-regression models. Exceptions were those variables with ambiguous temporal relationships with hospitalization: antimicrobial treatment for salmonellosis and duration of diarrhea. For continuous variables, such as age, that were associated with hospitalization in a nonlinear fashion, we created appropriate categories on the basis of the shape of this relationship. For each of the 4 analyses, we selected a preliminary logistic model by use of a backward-elimination procedure. We individually tested potential confounding variables not selected into this model for their effect on the DT104 risk-factor estimate or the antimicrobial-resistance risk-factor estimate. After accounting for confounding variables, we removed any variables included in the preliminary model that had become insignificant at $P \leqslant .05$ and assessed the fit of the final models by use of the Hosmer-Lemeshow goodness-of-fit test [18].

Controlling for ineffective antimicrobial treatment. We defined antimicrobial treatment as being either ineffective, effective, or of unknown effectiveness on the basis of the first antimicrobial taken by the case subject. Ineffective antimicrobial treatments were those to which the case subject's infection was resistant in vitro, and effective treatments were those to which the case subject's infection was susceptible in vitro. These definitions included only the 16 antimicrobials on the drug panel. We considered case subjects who did not know whether they had taken antimicrobials or did not know the name(s) or the chronological order in which they were prescribed as having taken antimicrobial treatments of unknown effectiveness. From available data, we could not determine whether case subjects took treatments before, during, or after hospitalization. Therefore, to evaluate any effect that antimicrobial-treatment failure had on the association between the antimicrobial-resistance risk factors and hospitalization, we reanalyzed the final logistic model, after having eliminated from the data set case subjects prescribed ineffective antimicrobial treatments and antimicrobial treatments of unknown effectiveness.

RESULTS

Description of the study population. The provincial laboratories identified 640 case subjects eligible for inclusion in the present study. Of these, 536 (84%) were interviewed and 440 (69%) were eligible to participate. Personal interviews were conducted with the 241 case subjects who were ⩾12 years old, and a proxy, usually a parent, was interviewed for the remaining 199 case subjects (<12 years old). Age, education, and income variables (table 1) did not differ significantly between any of the case groups investigated. However, other chronic conditions (table 1) were less commonly reported by DT104 R-type ACSSuT case subjects, compared with DT104 ACSSuT-susceptible case subjects (OR, 0.4; 95% confidence interval [CI], 0.2–1.0; $P = .040$). DT104 case subjects were more likely to have taken antimicrobials during the 4 weeks before onset of illness, compared with non-DT104 case subjects (OR, 2.4; 95% CI, 1.3–4.6; $P = .008$), as were R-type AK/CSSuT case subjects,

Table 1. Demographic information, general health, and medications taken before the onset of diarrhea, reported by all *Salmonella typhimurium* case subjects in the present study.

Variable	No. (%) of case subjects
Demographics	
Female	221 (50)
Attended or completed university/college[a]	218 (50)
Household income >Can$20,000	326 (89)
General health	
Chronic immunosuppressive condition	7 (1.6)
Chronic illness causing diarrhea	10 (2.3)
Surgery removing part of gastrointestinal system	10 (2.3)
Disorder affecting stomach-acid level	20 (4.6)
Other chronic conditions (e.g., asthma, arthritis, hypertension, and diabetes)	78 (18)
Medications taken during 4 weeks before infection	
Antimicrobials	42 (9.9)
Antacids	37 (8.8)
Antidiarrheal medications	12 (2.8)
Laxatives	8 (1.9)
Immunosuppressive medications	3 (0.7)
Radiation/chemotherapy	2 (0.5)

NOTE. The mean (±SD) age for all case subjects was 22 (±22) years.
[a] Or proxy, for case subjects <12 years old.

compared with AK/CSSuT-susceptible case subjects (OR, 2.8; 95% CI, 1.4–5.5; $P = .002$), and non-DT104 R-type AKSSuT case subjects, compared with non-DT104 AKSSuT-susceptible case subjects (OR, 2.7; 95% CI, 1.0–7.0; $P = .037$).

Definitive typing and resistance testing. Of the 440 case subjects in the present study, 157 (36%) were DT104 and 283 (64%) were non-DT104. DT104 was the most prevalent phage type (PT), followed by PT208 (13%) and PT124 (10%). Overall, 44% of the case subjects were R-type AK/CSSuT, 77% of the DT104 case subjects were R-type ACSSuT, and 23% of the non-DT104 case subjects were R-type AKSSuT.

Self-perceived illness severity. Self-perceived illness-severity scores did not differ between DT104 case subjects and non-DT104 case subjects ($P = .482$) or between DT104 R-type ACSSuT case subjects and DT104 ACSSuT-susceptible case subjects ($P = .454$). However, R-type AK/CSSuT case subjects were 1.6 times more likely to perceive their illnesses as "quite severe," compared with AK/CSSuT-susceptible case subjects (95% CI, 1.0–2.5; $P = .035$), and non-DT104 R-type AKSSuT case subjects were 2.8 times more likely to perceive their illnesses as "quite severe," compared with non-DT104 AKSSuT-susceptible case subjects (95% CI, 1.5–5.1; $P = .001$).

Ineffective antimicrobial treatments. Of the 176 case subjects (41%) who took antimicrobials, 145 provided enough information to determine effectiveness of the antimicrobial treatment. Seventeen (12%) of these 145 case subjects were prescribed ineffective treatments: amoxicillin (7 case subjects [41%]), sulphonamides (4 case subjects [24%]), ampicillin (2 case subjects [12%]), first-generation cephalosporin (1 case subject [6.0%]), third-generation cephalosporin (1 case subject [6.0%]), trimethoprim-sulphamethoxazole (1 case subject [6.0%]), and tetracycline (1 case subject [6.0%]). Of these 17 case subjects, 16 (94%) were R-type AK/CSSuT, and 7 (41%), all of whom were R-type AK/CSSuT, were hospitalized. This rate of hospitalization was significantly higher than the rate among case subjects not prescribed antimicrobial treatment (42/257 [16%]; $P = .018$) but was not significantly different from the rate among case subjects prescribed effective antimicrobial treatment (27/119 [23%]; $P = .133$).

Medical care. The 440 case subjects in the present study made 644 visits to their family physicians, 289 visits to emergency departments, and 139 visits to walk-in clinics and accessed other forms of health care 34 times. Overall, 102 case subjects (23%) were admitted to hospital for ⩾1 night. The highest rates of hospitalization were among case subjects <6 months old (5 case subjects [71%]) and those >70 years old (11 case subjects [69%]). Of the 102 hospitalized case subjects, 34 (33%) were DT104, 58 (57%) were R-type AK/CSSuT, 29 (28%) were DT104 R-type ACSSuT, and 28 (27%) were non-DT104 R-type AKSSuT. Hospitalization rates did not differ significantly among the provinces or between DT104 case subjects and non-DT104 case subjects. However, hospitalization was significantly more likely for R-type AK/CSSuT subjects, compared with AK/CSSuT-susceptible case subjects ($P = .004$), and for non-DT104 R-type AKSSuT case subjects, compared with non-DT104 AKSSuT-susceptible case subjects ($P < .001$) (figure 2). Case subjects stayed in hospital for a mean of 4.1 days (SD, 2.3 days; $n = 99$), which did not differ significantly between any of the case groups we compared. We did not identify infection with *Salmonella* Typhimurium as the primary cause of death for any person included in the present study.

Multivariate regression. After controlling for other significant risk factors and confounding variables, R-type AK/CSSuT case subjects were 2.3 times more likely to be hospitalized than AK/CSSuT-susceptible case subjects, and non-DT104 R-type AKSSuT case subjects were 3.6 times more likely to be hospitalized than non-DT104 AKSSuT-susceptible case subjects (table 2). After eliminating case subjects treated with ineffective antimicrobial treatments, these associations remained positive and significant (OR, 2.1 [$P = .026$] and OR, 3.7 [$P = .015$], respectively).

Other factors that increased the risk of hospitalization for *Salmonella* Typhimurium case subjects, regardless of the phage type of their infection, were age <1 year, age >59 years, case subject's (or proxy's) education lower than university or college level, living alone, and presence of an underlying chronic illness. The risk of hospitalization also increased as the maximum number of stools per day increased and if the case subject reported experiencing vomiting or fever. Conversely, the risk of hospitalization was significantly lower for case subjects who took antidiarrheal medications to relieve their symptoms (table 2).

For non-DT104 case subjects, other factors that increased the risk of hospitalization were age >59 years, household income <Can$20,000, household size >4 residents, presence of an underlying chronic illness, and vomiting during the course of the *Salmonella* Typhimurium infection (table 2). In the multivariate analyses, hospitalization rates did not differ significantly between DT104 and non-DT104 case subjects or between DT104 R-type ACSSuT case subjects and DT104 ACSSuT-susceptible case subjects.

Hospitalization: estimated costs and proportion attributable to resistance. The estimated cost of hospitalization for the 102 hospitalized case subjects in the present study was Can$218,484. For the 58 hospitalized R-type AK/CSSuT case subjects, the total estimated cost was Can$124,236. Using the OR of 2.3 from the logistic-regression model, for these case subjects, we estimated that 57% of these 58 hospitalizations were attributable to AK/CSSuT resistance. The total estimated cost for the 28 hospitalized non-DT104 R-type AKSSuT case subjects was Can$59,976. Using the OR of 3.6 from the logistic-regression model, for these case subjects, we estimated that 72%

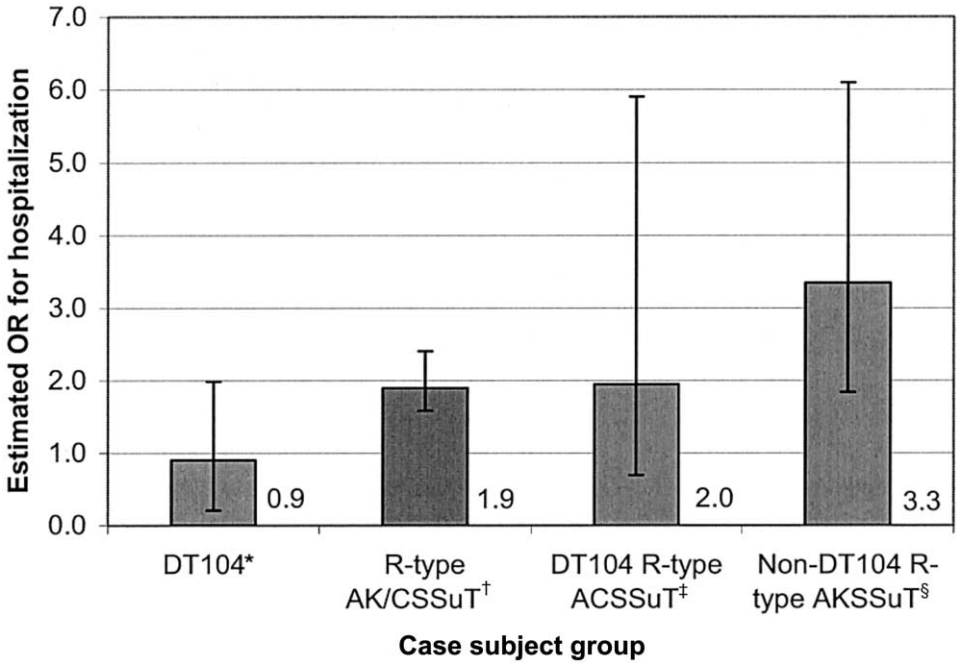

Figure 2. Estimated odds ratios (ORs) for hospitalization, determined by bivariate analyses for *Salmonella* Typhimurium definitive phage type 104 (DT104) vs. non-DT104 case subjects, resistant to ampicillin, kanamycin and/or chloramphenicol, streptomycin, sulphamethoxazole, and tetracycline (R-type AK/CSSuT) versus AK/CSSuT-susceptible case subjects, DT104 R-type ACSSuT vs. DT104 ACSSuT-susceptible case subjects, and non-DT104 R-type AKSSuT vs. non-DT104 AKSSuT-susceptible case subjects. Significance of differences within case subject group: $^{*}P = .559$; $^{\dagger}P = .004$; $^{\ddagger}P = .198$; and $^{\S}P \leqslant .001$.

of these 28 hospitalizations were attributable to non-DT104 AKSSuT resistance.

DISCUSSION

After controlling for other risk factors, we found that R-type AK/CSSuT case subjects were significantly more likely to be hospitalized, compared with AK/CSSuT-susceptible case subjects, and non-DT104 R-type AKSSuT case subjects were significantly more likely to be hospitalized, compared with non-DT104 AKSSuT-susceptible case subjects. Our parallel results for case subjects' self-perceived illness-severity scores corroborate these findings. Furthermore, our results are supported by epidemiological evidence that antimicrobial-resistant infections are associated with increased morbidity, compared with antimicrobial-susceptible infections [10, 19]. After controlling for ineffective antimicrobial treatments, the associations between antimicrobial resistance and hospitalization remained positive and significant. Therefore, it is with greater certainty that one can attribute the increased risk of hospitalization to increased virulence of the pathogen, rather than to antimicrobial-treatment failure. To our knowledge, this is the first study to focus on 1 *Salmonella* serotype, to define specific antimicrobial-resistance patterns, and to control for other risk factors, such as age and ineffective antimicrobial treatment, when assessing the association between antimicrobial resistance and burden of illness.

In the laboratory, the pathogenicity of *Salmonella* is measured by tissue culture invasiveness [20]. However, *Salmonella* Typhimurium isolates resistant to AK/CSSuT are reported to be hypoinvasive in vitro, compared with control strains [20]. This evidence seems to contradict our findings that R-type AK/CSSuT infections appear to be more virulent than other *Salmonella* Typhimurium infections. In vivo laboratory studies of infections with this resistance pattern and molecular testing of virulence determinants may help to improve our understanding of the pathogenicity of these antimicrobial-resistant organisms.

In the present study, hospitalization rates did not differ significantly between DT104 and non-DT104 case subjects or between DT104 R-type ACSSuT and DT104 ACSSuT-susceptible case subjects. These results appear to contradict other studies that show that (1) DT104 R-type ACSSuT infections are associated with higher hospitalization rates, compared with other *Salmonella* infections [21], and (2) R-type ACSSuT infections are associated with higher mortality rates, compared with other *Salmonella* Typhimurium infections, regardless of phage type [22]. However, the comparisons that we made differed somewhat from the case definitions investigated in the previously cited studies. This may account for the discrepancy in results. To better understand whether DT104 isolates are associated

Table 2. Final logistic-regression models describing the relationships between hospitalization and risk factors, for all *Salmonella typhimurium* case subjects and for *Salmonella* Typhimurium non-DT104 case subjects.

Subject, variable	OR (95% CI)	*P*
All case subjects[a]		
R-type AK/CSSuT	2.3 (1.3–4.1)	.003
Age, years		
<1	3.8 (1.3–12)	.019
1–59 (referent)	1.0	
>59	4.1 (1.4–12)	.010
Chronic illness	3.3 (1.6–6.4)	.001
Education level below university or college	2.1 (1.2–3.7)	.009
Lives alone	8.3 (2.1–33)	.003
Maximum number of stools in one day[b]	1.9 (1.4–2.5)	<.001
Vomiting	2.6 (1.5–4.5)	.001
Fever	3.1 (1.2–7.8)	.018
Antidiarrheal medication taken for salmonellosis	0.3 (0.2–0.5)	<.001
Non-DT104 case subjects[c]		
R-type AKSSuT	3.6 (1.5–8.9)	.005
Age, years		
>59	5.5 (1.6–18)	.006
≤59 years (referent)	1.0	
Chronic illness	2.8 (1.2–6.4)	.017
Household income <Can$20,000	2.7 (1.0–7.5)	.053
Household size >4 residents	2.4 (1.1–5.2)	.027
Vomiting	3.1 (1.5–6.4)	.002

NOTE. CI, confidence interval; OR, odds ratio.

[a] $P = .283$, by Hosmer-Lemeshow goodness-of-fit test; $P < .001$, by likelihood ratio test.

[b] Scores were categorized as follows: 1, 3–5 stools; 2, 6–10 stools; 3, 11–20 stools; and 4, >20 stools in one day.

[c] $P = .516$, by Hosmer-Lemeshow goodness-of-fit test; $P < .001$, by likelihood ratio test.

with increased morbidity, a recent laboratory study compared the virulence of *Salmonella* Typhimurium DT104 isolates with that of *Salmonella* Typhimurium ATCC 14028s isolates, by use of in vitro and in vivo assays, but found no significant differences [23]. Therefore, it remains unclear whether DT104 and DT104 R-type ACSSuT infections are associated with increased severity of illness. Laboratory studies using case definitions comparable to those used in epidemiologic studies are required to better understand the virulence of these infections.

Regardless of the phage type or resistance pattern of the infection, hospitalization for gastroenteritis causes economic burdens for the health care system, affected patients, and their families [24, 25]. In addition, hospitalization introduces the risk of nosocomial infections, which can increase these economic burdens [26], complicate the course of recovery, increase the severity of illness, increase mortality, or prolong hospital stay [27]. Therefore, preventing *Salmonella* Typhimurium infections that require hospitalization would not only reduce the severity of illness but would also reduce the cost of treatment.

In the present study, we estimated total hospitalization costs to be Can$218,484. Assuming a cause-effect relationship between the antimicrobial-resistance pattern of the infection and hospitalization, we estimated that 57% of the hospitalizations among R-type AK/CSSuT case subjects and 72% of the hospitalizations among non-DT104 R-type AKSSuT case subjects were attributable to the antimicrobial-resistance pattern of the infecting organism. Therefore, preventing the occurrence of R-type AK/CSSuT and non-DT104 R-type AKSSuT infections would substantially reduce the risk of hospitalization due to *Salmonella* Typhimurium infection in Canada, thereby reducing the costs of treatment.

Most of the people in the present study (86%) characterized their illnesses as "fairly severe" to "quite severe." One therefore needs to interpret our results in this context. Since an estimated 97% of *Salmonella* illnesses go unreported in the United States [24], this Canadian study likely included only a small proportion of *Salmonella* Typhimurium case subjects, and these individuals likely suffered more-severe illnesses.

Several potential limitations existed in the preset study. First, our results relied on self-reported data collected during interviews, which are potentially vulnerable to recall and interviewer biases. We attempted to minimize these biases by eliminating case subjects whose illnesses began >30 days before their interviews and by ensuring that interviewers were unaware of the definitive and resistance type of the case subject's infection. Furthermore, it was unlikely that these biases influenced hospitalization, which was our main outcome.

Second, we could have controlled for ineffective antimicrobial treatments more accurately if we had known the timing of these treatments relative to hospitalization. If ineffective antimicrobial treatments increased the risk of hospitalization, then the strength of association between hospitalization and both R-type AK/CSSuT and non-DT104 R-type AKSSuT would have decreased. However, by eliminating case subjects treated with ineffective antimicrobial treatments from the data set, we adequately controlled for antimicrobial-treatment failure. To control this variable more accurately, future studies should determine the dates of case subjects' hospital stays and relevant treatment regimens.

Third, the hospitalization costs we reported were estimates. They were based on gastroenteritis in general, rather than on salmonellosis specifically, and were restricted to data from Ontario and Alberta. However, case subjects from these provinces made up the majority of our study sample. Therefore, we are confident that these estimates are the best representation of the available data.

The present study has demonstrated that frequently occurring, antimicrobial-resistant *Salmonella* Typhimurium infec-

tions are associated with an important increase in burden and cost of illness. Therefore, preventing the persistence and emergence of antimicrobial-resistant pathogens would likely reduce the risk of severe infections that require hospitalization, thus decreasing treatment costs. This prevention effort requires the prudent use of antimicrobials in agriculture, veterinary medicine, and human medicine.

THE MULTI-PROVINCIAL *SALMONELLA* TYPHIMURIUM CASE-CONTROL STUDY STEERING COMMITTEE

Members of the committee include Murray Fyfe, Jane A. Buxton, Arlene King, and Ana Paccagnella (British Columbia Centre for Disease Control, Vancouver); Karen Grimsrud (Alberta Health and Wellness, Edmonton); Ingrid Zazulak (Capital Health, Edmonton); James Talbot and Robert Rennie (Provincial Laboratory of Public Health for Northern Alberta, Edmonton); Peter Pieroni (Saskatchewan Health, Regina); Rafiq Ahmed and Frank Rodgers (National Laboratory for Enteric Pathogens, Health Canada, Winnipeg); Franklin Pollari, Kathryn Doré, and Jeffrey B. Wilson (Division of Enteric, Foodborne, and Waterborne Diseases, Health Canada, Guelph); Pascal Michel (Laboratory for Foodborne Zoonoses, Health Canada, Saint-Hyacinthe); and Dean Middleton, Monika Naus, Bonnie Henry, Bruce Ciebin, and Frances Jamieson (Ontario Ministry of Health and Long-Term Care, Toronto).

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