Estimating the Number of Human Cases of Ceftiofur-Resistant *Salmonella enterica* Serovar Heidelberg in Québec and Ontario, Canada

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A stochastic model was used to estimate the number of human cases of ceftiofur-resistant *Salmonella enterica* serovar Heidelberg in Québec and Ontario attributable to chicken consumption and excess cases attributable to human prior antimicrobial consumption. The annual mean incidence of *S.* Heidelberg (Québec/Ontario) decreased from 70/62 cases per 100 000 in 2004 to 29/30 cases per 100 000 in 2007 (Québec)/2008 (Ontario), increasing to 59/45 cases per 100 000 in 2011. The annual mean incidence of ceftiofur-resistant cases from chicken decreased from 8/7 cases per 100 000 in 2004 to 1/1 cases per 100 000 in 2007 (Québec)/2008 (Ontario), increasing to 7/5 cases per 100 000 in 2011. The annual mean total number of excess ceftiofur-resistant cases from chicken attributable to human prior antimicrobial consumption (Québec/Ontario) decreased from 71/123 in 2004 to 6/24 in 2007 (Québec)/2008 (Ontario), but increased to 62/91 in 2011. This model will support future work to determine the increased severity, mortality and healthcare costs for ceftiofur-resistant *Salmonella* Heidelberg infections. These results provide a basis for the evaluation of future public health interventions to address antimicrobial resistance.

Keywords. antimicrobial resistance; ceftiofur; etiologic fraction; *Salmonella* Heidelberg; stochastic model.

Nontyphoidal *Salmonella* is an important global cause of human illness and death [1]. *Salmonella enterica* serovar Heidelberg is one of the top 3 reported serovars in Canada, with a higher frequency of invasive illness (approximately 12%) than other nontyphoidal salmonellae [2]. Between 2003 and 2011, there were 638 human cases of invasive *S.* Heidelberg reported to the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS), with 30% in children <13 years of age.

Case-control studies report links between human *S.* Heidelberg infections and chicken product consumption (meat, nuggets, and eggs) [3–5]. *Salmonella* Heidelberg was one of the most common serovars identified in chicken from retail and slaughter by CIPARS and has been isolated from other animal species such as pigs, turkeys, cattle, and horses, but at lower prevalences [6, 7].

Antimicrobial resistance (AMR) may increase the burden of illness of *Salmonella* by increasing the number of infections, enhancing severity and duration of illness and causing antimicrobial treatment failure [8]. Estimates from the United States suggest that an additional 29 379 *Salmonella* infections occur annually due to AMR, leading to 342 additional hospitalizations and 12 deaths [8]. Although antimicrobial therapy is not indicated for treatment of uncomplicated gastrointestinal illness [1], Danish and US studies found that 36% and 40%, respectively, of patients with salmonellosis received antimicrobial treatment [9, 10].

In assessing the risk to human health from antimicrobial use (AMU) in agriculture, the Institute of Medicine (IOM) in 1989 defined the etiologic fraction for prior AMU and resistant *Salmonella* infection ($EF_{AMU\text{-}R}$) as the proportion of human cases that would not occur "but for the resistance of the infecting

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bacterial strain to the antimicrobial(s) being administered" to the patient prior to infection [11]. The IOM used this to calculate the number of excess cases (ECs) from prior antimicrobial consumption. Human AMU can be a risk factor for salmonellosis by means of 2 possible effects. The competitive effect results from the reduction of competing commensal gastrointestinal flora, whereas the selective effect refers to increasing vulnerability of infection with *Salmonella* strains resistant to the antimicrobial being taken prior to infection for an unrelated reason [8]. Studies consider the combination of these effects by incorporating healthy controls as comparisons.

In humans, the third-generation cephalosporin ceftriaxone is used for the treatment of invasive salmonellosis and salmonellosis in children and pregnant women. Ceftriaxone resistance confers resistance to another third-generation cephalosporin, ceftiofur. In Canada, ceftiofur is approved for use in cattle, swine, horses, sheep, dogs, and cats [12]; however, it is not approved for use in chickens or people. Its extralabel use in ovo for the control of *Escherichia coli* omphalitis in young chicks is legal in Canada. Currently, extralabel drug use is considered a tool for veterinarians within a valid veterinarian–client–patient relationship by Health Canada, although extralabel use of third-generation cephalosporins is not recommended [13]. A hatchery questionnaire conducted in Québec (2003–2004) found that ceftiofur was used in all eggs from 78% of the lots [14]. Québec hatcheries ceased using ceftiofur in 2005 in response to CIPARS results until late 2006 when they reinstituted rotational use. Within Québec, the prevalence of ceftiofur resistance in *S.* Heidelberg (from retail chicken and people) dropped significantly during the withdrawal period, but is rising again [6]. In 2010, Dutil et al [12] reported a significant temporal correlation between the prevalence of ceftiofur-resistant *S.* Heidelberg from retail chicken and humans in Québec.

These temporal correlations raise questions about the direct burden of illness of *S.* Heidelberg. In lieu of Canadian studies that evaluate this direct burden, quantitative risk models can estimate case numbers by incorporating a stochastic process to account for uncertainty in the data [15, 16]. One such example was the US Food and Drug Administration (FDA) report, "Human health impact of fluoroquinolone resistant campylobacter attributed to the consumption of chicken" [17].

The objective of this study was to estimate the annual number of human cases of *S.* Heidelberg in Québec and Ontario, the number of cases of ceftiofur-resistant *S.* Heidelberg attributable to eating chicken, the proportion of these cases attributable to human prior antimicrobial consumption (the $EF_{AMU\text{-}R}$), and the related number of ECs.

MATERIALS AND METHODS

A stochastic model was developed using the framework of the FDA's model for human infection with fluoroquinolone-resistant *Campylobacter* [17]. Separate models were run to estimate case numbers of *S.* Heidelberg for Québec and Ontario for each year from 2003 to 2011. Case incidences were calculated by standardizing these numbers using the provincial populations for each year as reported by Statistics Canada [18].

Estimates from the stochastic models incorporated uncertainty around the input variables. The modeling approach included 4 sections (Figure 1): (1) estimation of the annual reported, laboratory-confirmed *S.* Heidelberg cases for invasive infections and nonbloody and severe diarrhea (bloody or duration >7 days) using annual Canadian surveillance data (2003–2011); (2) estimation of the annual expected cases in the population using Canadian parameters for underascertainment (underreporting and underdiagnosis) [19]; (3) estimation of the annual ceftiofur-resistant cases attributable to eating chicken meat using annual CIPARS surveillance data (2003–2011) and a static Canadian etiologic fraction for chicken ($EF_{chicken}$) [3]; and (4) estimation of the annual ECs attributable to human prior antimicrobial consumption within the past month using the $EF_{AMU\text{-}R}$, and those ECs that were attributable to eating chicken meat. The annual $EF_{AMU\text{-}R}$ was estimated using a static odds ratio for the combined effect (OR_{both}) of the competitive and selective effects of prior antimicrobial consumption and annual Canadian provincial data for antimicrobial prescriptions (2003–2011) to determine the annual prevalence of exposure - the proportion of people taking antimicrobials in the past month (P) in Québec and Ontario. The OR_{both} was estimated using the outputs from a cumulative, random-effects meta-analysis of multiple published studies.

Model parameters, descriptions, and distributions are shown in Table 1. Detailed descriptions of the data sources, model framework, distributions, assumptions, meta-analysis, and references are provided in the Supplementary Data. Key model assumptions included the following:

1. The annual proportions of human ceftiofur-resistant *S.* Heidelberg isolates reported by CIPARS were the same as those in the general population.
2. The estimates used to model the underascertainment of *S.* Heidelberg were the same as Canadian estimates used to model that for nontyphoidal *Salmonella* [19], and these were constant over time.
3. The $EF_{chicken}$ for *S.* Heidelberg cases from eating all chicken meat was equivalent to that for eating chicken nuggets/strips as derived from Currie et al [3], and this was constant over time.
4. The OR_{both} for prior consumption of cephalosporins and infection with ceftiofur-resistant *S.* Heidelberg was the same as that for prior consumption of any antimicrobial and infection with antimicrobial resistant nontyphoidal *Salmonella* as derived from the meta-analysis.
5. The OR_{both} and P to calculate $EF_{AMU\text{-}R}$ for ceftiofur-resistant *S.* Heidelberg were based on consumption of any

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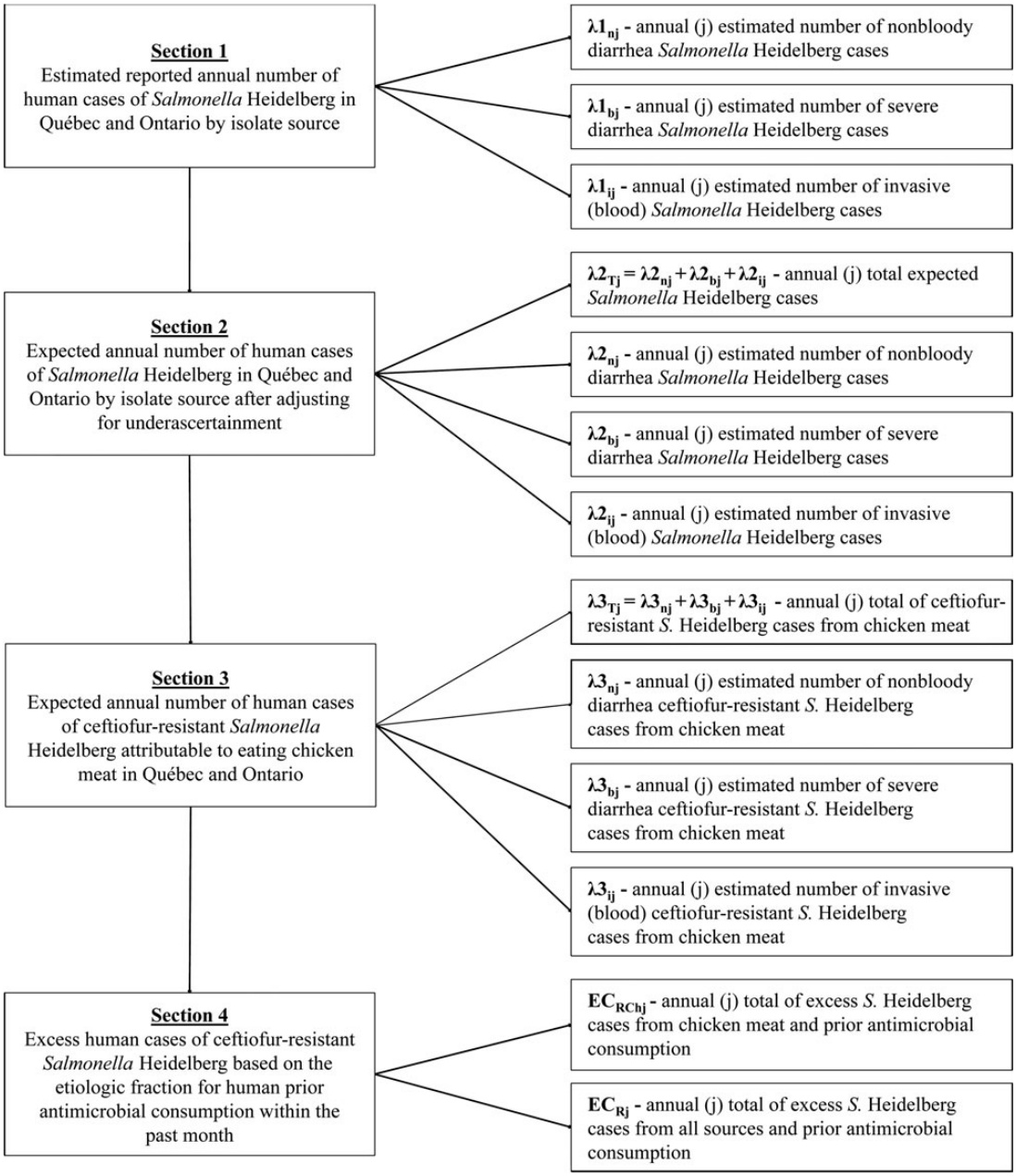

Figure 1. Model and output parameters used to estimate the number of human cases of ceftiofur-resistant *Salmonella* Heidelberg in Québec and Ontario. Parameter definitions for each section are provided in Table 1.

antimicrobial, the OR_{both} was constant over time, and people were taking antimicrobials for reasons unrelated to gastrointestinal illness.

The model was constructed and simulated using @RISK (version 6.0.0, Palisade Corporation, Ithaca, New York) in Excel 2010 (Microsoft Office Professional Edition 2010, Microsoft Corporation, Redmond, Washington). It was run for 100 000 iterations, using Latin hypercube sampling with a Mersenne twister random number generator and a fixed initial seed. The advanced sensitivity analysis function in @RISK was used to identify the relative contributions of input distributions to the model outputs by generating tornado plots of conditional output means for percentiles of the input distributions [20]. Further sensitivity analysis used fixed values for input variables to specify their impact on ceftiofur-resistant cases from chicken and ECs from chicken. Values were fixed independently for inputs that had large contributions to the model outputs as

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Table 1. Parameters, Descriptions, Formulas, and Distributions Used in the Stochastic Model to Estimate the Number of Human Cases of Ceftiofur-Resistant *Salmonella* Heidelberg in Québec and Ontario

Symbol	Description [Reference[a]]	Formulas, Distributions[b] and Input Values	Comparison to the FDA *Campylobacter* Model [17 in Reference List][c]
Section 1: Estimated reported annual number of human cases of *Salmonella* Heidelberg in QC and ON by isolate source			
n	Population of ON and QC based on census data for 2001, 2006 [37] j - year (different surveillance data for each)[d]	Annual fixed values from Canadian data (see model file in Supplementary Data for annual values)	Fixed value from US data
λ_{ij}	Mean number of reported invasive *S.* Heidelberg culture-confirmed cases [8–16, 27] j - year (different surveillance data for each)	Gamma(number of invasive cases, 1) based on annual surveillance data for QC and ON (see model file in Supplementary Data for annual values)	Gamma, US FoodNet data
λ_{ej}	Mean number of reported enteric *S.* Heidelberg culture-confirmed cases [8–16, 27] j - year (different surveillance data for each)	Gamma(number of enteric cases, 1) based on annual surveillance data for QC and ON (see model file in Supplementary Data for annual values)	Gamma, US FoodNet data
p_b	Proportion of enteric infections with severe (bloody [b] and duration >7 d) vs nonbloody [n] (and duration <7 d) diarrhea [39]	Beta(216, 101) based on Canadian data	Normal approximation of Beta-distributed data from multiple US FoodNet catchment sites for bloody diarrhea only (not duration >7 d)
$\lambda1_{nj}$, $\lambda1_{bj}$, $\lambda1_{ij}$	Mean *S.* Heidelberg culture confirmed cases reported (n - nonbloody; b – severe; i - invasive)	$\lambda1_{nj} = \lambda_{ej}(1 - p_b)$ $\lambda1_{bj} = (\lambda_{ej})(p_b)$ $\lambda1_{ij} = \lambda_{ij}$	The same calculations
Section 2: Expected annual number of human cases of *S.* Heidelberg in QC and ON by isolate source after adjusting for underascertainment			
p_{edn}, p_{edb}	Probability that case sought medical care (n - nonbloody; b - severe) [39]	$p_{edn} = \beta(46, 285)$; $p_{edb} = \beta(34, 43)$ based on Canadian data	Beta, US FoodNet data
p_{ln}, p_{lb}	Proportion of cases that submitted a sample for testing (n - nonbloody; b - severe) [39]	$p_{ln} = \beta(10, 37)$; $p_{lb} = \beta(10, 25)$ based on Canadian data	Beta, US FoodNet data
p_{sh}	Proportion of samples that were tested for *Salmonella* [39]	Beta(269, 2) based on Canadian data	Beta, US FoodNet data
p_+	Test sensitivity to detect nontyphoidal *Salmonella* [39]	Pert(0.60, 0.75, 0.90) based on Canadian data	Beta, New Zealand study
p_{lln}	Proportion of cases that were reported by the laboratory to the local health authority [39]	Beta(257, 8) based on Canadian data	FDA model assumed 100%
p_{lp}	Proportion of cases that were reported by the local health authority to provincial authorities [39]	Beta(2966, 96) based on Canadian data	FDA model assumed 100%
p_{pn}	Proportion of cases that were reported by provincial authority to the Canadian National Notifiable Disease Database	Assumed to be 100%	FDA model assumed 100%
p_{id}	Proportion of cases with invasive disease that sought care and is reported to the National Notifiable Disease Database	Assumed to be 100%	The same assumption
$\lambda2_{nj}$, $\lambda2_{bj}$, $\lambda2_{ij}$	Cases in population (n - nonbloody; b - severe; i - invasive)	$\lambda2_{nj} = \lambda1_{nj}$/product ($p_{edn}$, p_{ln}, p_{sh}, p_+, p_{lln}, p_{lp}, p_{pn}) $\lambda2_{bj} = \lambda1_{bj}$/product ($p_{edb}$, p_{lb}, p_{sh}, p_+, p_{lln}, p_{lp}, p_{pn}) $\lambda2_{ij} = (\lambda1_{ij})(p_{id})$	The same calculations
$\lambda2_{Tj}$	Total cases of *S.* Heidelberg (nonbloody + severe + invasive)	$\lambda2_{Tj} = \lambda2_{nj} + \lambda2_{bj} + \lambda2_{ij}$	The same calculations
Section 3: Expected annual number of human cases of ceftiofur-resistant *S.* Heidelberg attributable to eating chicken meat in QC and ON			
p_{ca}	Etiologic fraction for the proportion of *S.* Heidelberg cases attributable to eating chicken meat ($EF_{chicken}$) [3]	Exponentiated Normal ($\ln[1 - EF_{chicken}]$, $[\ln(1 - EF_{chicken\text{-}lower}) - \ln(1 - EF_{chicken\text{-}upper})]/1.96$) $EF_{chicken}$ = 30.6%; lower/upper = 95% confidence interval values (19.8%, 39.9%) based on a Canadian study	Exponentiated Normal ($\ln[1 - EF_{chicken}]$, $[\ln(1 - EF_{chicken\text{-}lower}) - \ln(1 - EF_{chicken\text{-}upper})]/1.96$) using estimates from 2 US studies, then combined as upper and lower bounds

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Table 1 continued.

Symbol	Description [Reference[a]]	Formulas, Distributions[b] and Input Values	Comparison to the FDA *Campylobacter* Model [17 in Reference List][c]
P_{rshj}	Proportion of *S.* Heidelberg infections that are ceftiofur resistant [8–16] j - year (different surveillance data for each)	Beta(a, b) based on annual surveillance data for QC and ON (see model file in Supplementary Data for annual values)	Beta, US data
$\lambda3_{nj}$, $\lambda3_{bj}$, $\lambda3_{ij}$	Number of ceftiofur-resistant *S.* Heidelberg cases from chicken (n - nonbloody; b - severe; i - invasive)	$\lambda3_{nj} = (\lambda2_{nj})(p_{ca})(p_{rshj})$ $\lambda3_{bj} = (\lambda2_{bj})(p_{ca})(p_{rshj})$ $\lambda3_{ij} = (\lambda2_{ij})(p_{ca})(p_{rshj})$	The same calculations
$\lambda3_{nsj}$, $\lambda3_{bsj}$, $\lambda3_{isj}$	Number of ceftiofur-susceptible *S.* Heidelberg cases from chicken	$\lambda3_{nsj} = (\lambda2_{nj})(p_{ca})(1 - p_{rshj})$ $\lambda3_{bsj} = (\lambda2_{bj})(p_{ca})(1 - p_{rshj})$ $\lambda3_{ij} = (\lambda2_{ij})(p_{ca})(1 - p_{rshj})$	The same calculations
$\lambda3_{Tsj}$	Total number of ceftiofur-susceptible *S.* Heidelberg cases from chicken	$\lambda3_{Tsj} = \lambda3_{nsj} + \lambda3_{bsj} + \lambda3_{isj}$	The same calculations
$\lambda3_{Tj}$	Total number of ceftiofur-resistant *S.* Heidelberg cases from chicken	$\lambda3_{Tj} = \lambda3_{nj} + \lambda3_{bj} + \lambda3_{ij}$	The same calculations
Section 4: Excess human cases of ceftiofur-resistant *S.* Heidelberg based on the etiologic fraction for human prior antimicrobial consumption within the past month[e]			
P_j	Proportion of the population taking antimicrobials in the past month [17] j - year (different surveillance data for each)	Number of antimicrobial prescriptions dispensed in QC and ON for a given year/estimated population based on census estimates (and divided by 12 to scale down to 1 mo)	Not part of the FDA model
OR_{both}	Ratio of the odds of exposure (prior antimicrobial consumption within the past month) in people infected with antimicrobial-resistant *Salmonella* vs healthy people. [1, 3, 5–7, 28, 29, 31–36, 41]	Exponentiated Normal (ln[OR], OR SE) OR = 3.76, SE = 0.22 (results of cumulative random-effects meta-analysis)	Not part of the FDA model
$EF_{AMU\text{-}Rj}$	Etiologic fraction: proportion of resistant cases attributable to human prior antimicrobial consumption within the past month to which the bacterium was resistant [30]	$EF_{AMU\text{-}Rj} = [(OR_{both} - 1)P_j]/[1 + (OR_{both} - 1)P_j]$	Not part of the FDA model
EC_{RChj}	Excess human cases of ceftiofur-resistant *S.* Heidelberg attributable to human prior antimicrobial consumption within the past month and consumption of chicken	$EC_{RChj} = (EF_{AMUR\text{-}j})(\lambda3_{Tj})$	Not part of the FDA model
EC_{Rj}	Excess human cases of ceftiofur-resistant *S.* Heidelberg from all sources that are attributable to human prior antimicrobial consumption within the past month	$EC_{Rj} = (EF_{AMUR\text{-}j})(\lambda2_T)(p_{rshj})$	Not part of the FDA model

Abbreviations: FDA, US Food and Drug Administration; FoodNet, Foodborne Diseases Active Surveillance Network; ON, Ontario; OR, odds ratio; QC, Québec; SE, standard error.

[a] References listed in this column refer to those references listed in the Supplementary Data.

[b] Distribution forms: Gamma(shape = number of surveillance events, scale = 1 year); Pert (minimum, most likely, maximum values); Beta(number of successes + 1, number of observations – number of successes + 1) using a Uniform (0,1) prior; Normal (mean, standard deviation).

[c] The FDA model used data and studies pertaining specifically to *Campylobacter* species in the United States. Data inputs for this model were specific to *Salmonella* Heidelberg or nontyphoidal *Salmonella* in Canada.

[d] The subscript "j" denotes variables that have different surveillance input values and resulting output estimates for each year in each province. The parameters n, λ_i, λ_e, and P_{rsh} used annual inputs from yearly surveillance reports, providing annual estimates for $\lambda2_T$, $\lambda3_T$, EC_{RCh}, and EC_R for each province.

[e] Sections 4 and 5 of the FDA *Campylobacter* model differed from this model. Section 4 of the FDA model estimated the quantity of chicken meat contaminated with fluoroquinolone-resistant *Campylobacter*, and section 5 combined sections 4 and 3 to estimate the level of risk based on consumption of contaminated meat. It did not estimate the EF_{AMU} or number of ECs.

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determined from the tornado plots. Fixed values included the minimum, mean, maximum, 5th, 25th, 75th, and 95th percentile results from the main model. An Excel file containing the model, distributions, and data is available in the Supplementary Data. Model outputs are given as mean values with 95% credible intervals (CrIs).

RESULTS

The estimated annual number of *S.* Heidelberg cases (mean per 100 000 population), after accounting for underascertainment, ranged from 29 to 82 in Québec and 30 to 73 in Ontario (Table 2), with similar temporal trends in both provinces. Figure 2 shows how the estimated annual human incidence of ceftiofur-resistant, chicken-attributable *S.* Heidelberg cases (mean per 100 000 population, 95% CrI) decreased from 2004 (Québec, 8 [4–15]; Ontario, 7 [4–13]) to 2007 in Québec (1 [0–2]) and 2008 in Ontario (1 [1–5]), and increased to 2011 levels (Québec, 7 [3–13]; Ontario, 5 [2–9]). The mean estimated $EF_{chicken}$ was 30.4% (95% CrI, 19.8%–39.9%).

Using the meta-analysis estimate for the OR_{both} (3.76 [standard error, 0.22]), the mean estimated OR_{both} was 3.9 (95% CrI, 2.4–5.8). The reported provincial values for (P) ranged from 4.5%–5.1% and 5.6%–6.2% for Québec and Ontario, respectively. Using the OR_{both} and P, the mean $EF_{AMU\text{-}R}$ for Québec over time ranged from 11.4% to 12.5% compared with 13.7% to 14.9% for Ontario. Annual provincial estimates of ECs are presented in Table 3.

An example tornado plot of the conditional mean ECs from chicken in Québec for 2004 over percentiles of the input distributions from the advanced sensitivity analysis in @RISK is shown in Figure 3. This plot ranks the inputs based on their largest impact on the magnitude of the change in mean ECs over the distribution of each input variable. For Québec and Ontario, the inputs with the largest impact on the conditional annual mean of ECs from chicken were (results not shown) the OR_{both}; the $EF_{chicken}$; the annual prevalence of ceftiofur resistance; the probability of stool submission; and the probability of seeking care for cases with nonbloody or severe diarrhea. Results from the sensitivity analysis for $EF_{chicken}$ and OR_{both} are shown in Table 4. As the fixed value for $EF_{chicken}$ increased, the incidence of ceftiofur-resistant cases from chicken increased. Increasing the OR_{both} had the same impact on the ECs from chicken.

Table 2. Total Estimates of All Human *Salmonella* Heidelberg Cases per 100 000 Population and Those Attributable to Chicken Consumption by Year in Québec and Ontario

Province	Year	Estimated Cases per 100 000, Mean (95% Credible Interval)	Estimated Cases per 100 000 Attributable to Chicken Consumption, Mean (95% Credible Interval)
Québec	2003	82 (48–137)	25 (13–45)
	2004	70 (41–118)	21 (11–38)
	2005	53 (31–89)	16 (8–29)
	2006	48 (28–82)	15 (7–27)
	2007	29 (16–50)	9 (4–16)
	2008	33 (19–57)	10 (5–18)
	2009	51 (30–87)	16 (8–28)
	2010	62 (36–104)	19 (9–34)
	2011	59 (34–100)	18 (9–32)
Ontario	2003	73 (43–121)	22 (11–39)
	2004	62 (37–105)	19 (10–34)
	2005	45 (26–75)	14 (7–24)
	2006	43 (25–72)	13 (7–23)
	2007	39 (23–66)	12 (6–21)
	2008	30 (17–51)	9 (5–16)
	2009	37 (22–63)	11 (6–20)
	2010	45 (27–76)	14 (7–25)
	2011	45 (27–76)	14 (7–25)

DISCUSSION

This model provides estimates of the number of human *S.* Heidelberg cases in Québec and Ontario after accounting for underascertainment and uncertainty. The estimates of ceftiofur-resistant *S.* Heidelberg cases attributable to eating chicken and those ECs attributable to human prior antimicrobial consumption and infection with a ceftiofur-resistant strain provide the basis for further work to determine excess costs to the healthcare system and other patient-related burden of illness metrics related to AMR. They can also be used to evaluate the effectiveness of future public health interventions to address AMR.

The number of human cases of ceftiofur-resistant *S.* Heidelberg attributable to eating chicken in Québec and Ontario changed over time relative to changing AMU practices in the Québec poultry industry [12, 14]. In Québec, the mean number of cases dropped from a high of 587 in 2004 to 53 in 2007. This drop in the number of cases alone would create beneficial public health impacts. The number of potentially preventable (excess) cases attributed to chicken consumption, prior antimicrobial consumption, and being infected with a resistant strain was estimated to be 71 in 2004 in Québec and dropped to 6 in 2007. Ontario had similar trends. The preventable cases attributed to prior antimicrobial consumption (from all sources) had a similar drop. This may be due to a decrease in P from 61% (2004) to 54% (2007), but could also be due in part to the decreasing trend of reported *S.* Heidelberg cases over this time period.

Previous analysis of CIPARS surveillance data demonstrated a significant temporal association between the annual prevalence

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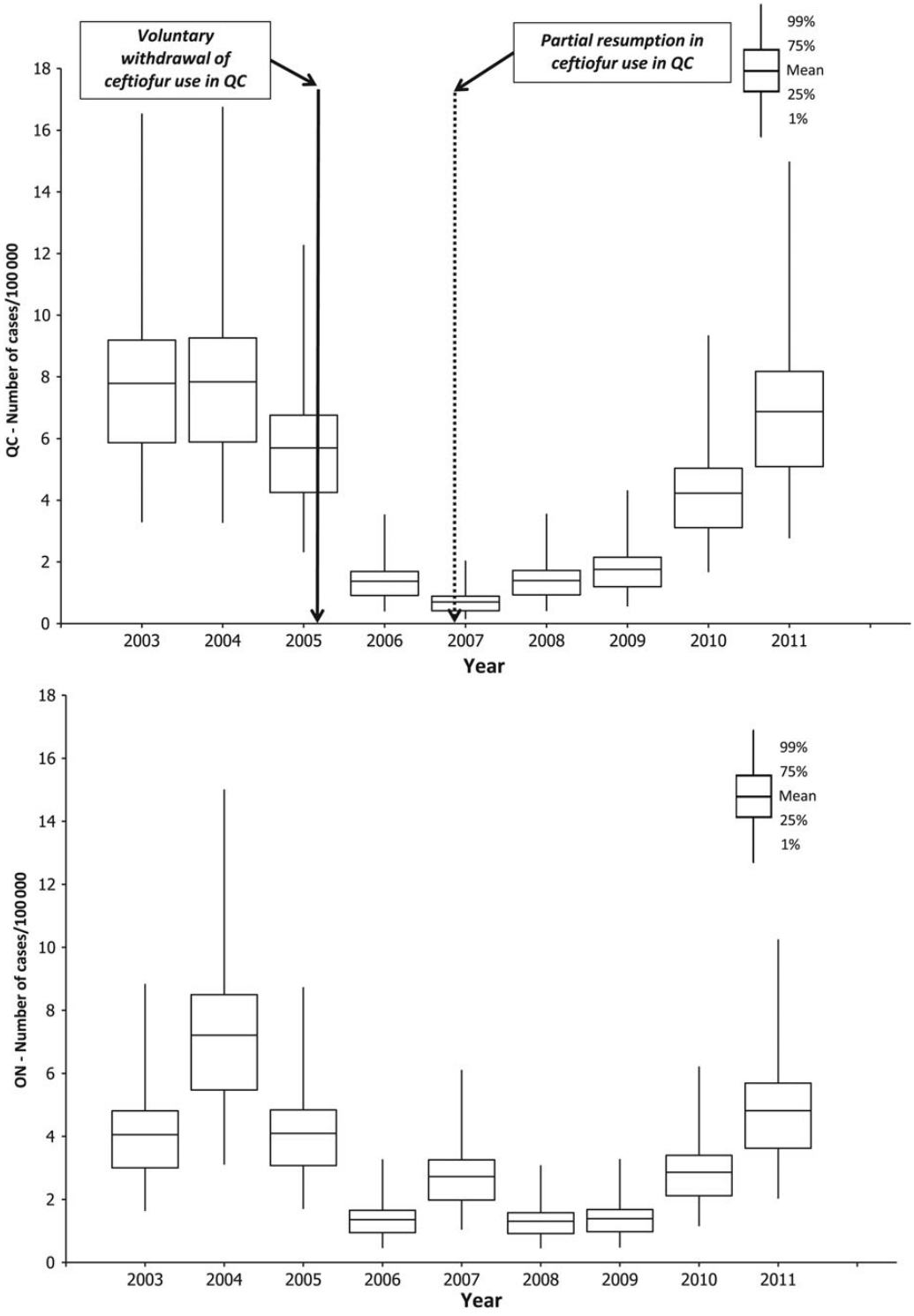

Figure 2. Annual trend in modeled, expected number of human cases per 100 000 population of ceftiofur-resistant *Salmonella* Heidelberg from chicken in Québec (QC) and Ontario (ON).

of ceftiofur-resistant *S.* Heidelberg from retail chicken across Canada and the incidence of ceftiofur-resistant *S.* Heidelberg in people [12]. This model expands this work by providing an estimate of the potential number of cases attributable to chicken consumption and human prior antimicrobial consumption with attendant uncertainty. The drop in the estimated number

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Table 3. Total Number of Excess Human Cases of Ceftiofur-Resistant *Salmonella* Heidelberg Attributable to Human Prior Antimicrobial Consumption (Within the Past Month) in Québec and Ontario

Type of Excess Cases	Province	Year	Mean (95% Credible Interval)
Excess cases from eating chicken	Québec	2003	73 (28–154)
		2004	71 (26–150)
		2005	49 (18–104)
		2006	12 (3–29)
		2007	6 (1–16)
		2008	12 (4–29)
		2009	15 (5–36)
		2010	37 (13–80)
		2011	62 (23–134)
	Ontario	2003	71 (26–152)
		2004	123 (47–254)
		2005	76 (29–161)
		2006	26 (8–59)
		2007	50 (18–110)
		2008	24 (8–55)
		2009	26 (8–58)
		2010	52 (19–111)
		2011	91 (35–192)
Excess cases from any source	Québec	2003	240 (100–483)
		2004	232 (96–468)
		2005	160 (65–327)
		2006	39 (12–91)
		2007	20 (5–51)
		2008	39 (12–91)
		2009	51 (17–115)
		2010	121 (48–252)
		2011	205 (82–422)
	Ontario	2003	233 (95–474)
		2004	403 (172–798)
		2005	251 (105–504)
		2006	85 (30–185)
		2007	166 (65–347)
		2008	80 (29–173)
		2009	84 (30–184)
		2010	171 (69–350)
		2011	301 (126–602)

of ceftiofur-resistant cases in Québec attributable to eating chicken coincides with the 2005 voluntary withdrawal of ceftiofur use in hatcheries by the Québec poultry industry. This information does not in itself provide direct causal evidence that extralabel ceftiofur use by the Québec poultry industry is the reason for human ceftiofur-resistant *S.* Heidelberg infections. Further understanding of these relationships requires detailed information on AMU in the poultry industry and for human cases, as well as source attribution studies.

This study provides a Canadian-specific $EF_{AMU\text{-}R}$ for ceftiofur-resistant *S.* Heidelberg based on Canadian data. The $EF_{AMU\text{-}R}$ for the combined effect ranged from 11% to 15% using the estimated OR_{both} and Canadian provincial antimicrobial prescription data for P. The estimated OR_{both} (3.9) was similar to the IOM's qualitative estimate for AMU and *Salmonella* (5 [range, 2–20]) [11] and to Barza and Travers's estimate for nontyphoidal *Salmonella* (5.3 [95% confidence interval, 1.4–21.0]) [8]. Monthly prescription estimates ranged from 4.5% to 6.2% in both provinces. Barza and Travers used estimates between 6.6% and 15%, based on literature values [8], compared to 0.2%–1.0% used by the IOM [11]. Published estimates for the $EF_{AMU\text{-}R}$ vary widely with inputs for the OR and P. One study reported an $EF_{AMU\text{-}R}$ of 16%–64% based on a review of studies specific to different sources and *Salmonella* serovars [21] compared with the IOM estimate of 2% (range, 0.5%–9%) [11]. However, these studies did not separate out the competitive, selective, or combined effects. The Barza and Travers estimate for the selective $EF_{AMU\text{-}R}$ (13%–26%) [8] is comparable to another study of multidrug-resistant *S. enterica* serovar Typhimurium that reported selective and combined $EF_{AMU\text{-}R}$ of 20% and 17%, respectively [22].

The $EF_{AMU\text{-}R}$ suggests the number of cases that could be prevented by removing human antimicrobial exposure, or "preventable cases," assuming a causal relationship [11]. The data used to estimate the OR_{both} for the $EF_{AMU\text{-}R}$ were based on a meta-analysis of studies relating antimicrobial consumption of any drug class to resistant, nontyphoidal *Salmonella* infection. They were not necessarily specific to ceftiofur-resistant *S.* Heidelberg, and, often, the type of antimicrobial used was not documented in the study. As a result, annual Canadian data for prescriptions for all antimicrobial classes were used to determine P, as opposed to specific cephalosporin use or other drug classes that may have genetically linked resistance mechanisms. At this time, there are no published studies that ascertain the direct causal link between prior cephalosporin consumption and clinical infection with ceftiofur-resistant *S.* Heidelberg.

Further research into Canadian temporal variations for the $EF_{chicken}$ and the OR_{both} for prior antimicrobial consumption, including cephalosporin consumption specific to *S.* Heidelberg cases, would improve the estimated outputs from this model. A small number of studies were used to determine the OR_{both} and not all of these were from Canada, as purely Canadian studies were not available. Both the $EF_{chicken}$ and OR_{both} likely vary over time, but due to lack of temporal data, they were kept constant from year to year. This is comparable to the FDA model for ciprofloxacin-resistant *Campylobacter* that also considered a static $EF_{chicken}$ [17]. Also similar to the FDA model, this model does not account for cross-contamination between chicken and other foods. The $EF_{chicken}$ was based on one Canadian outbreak

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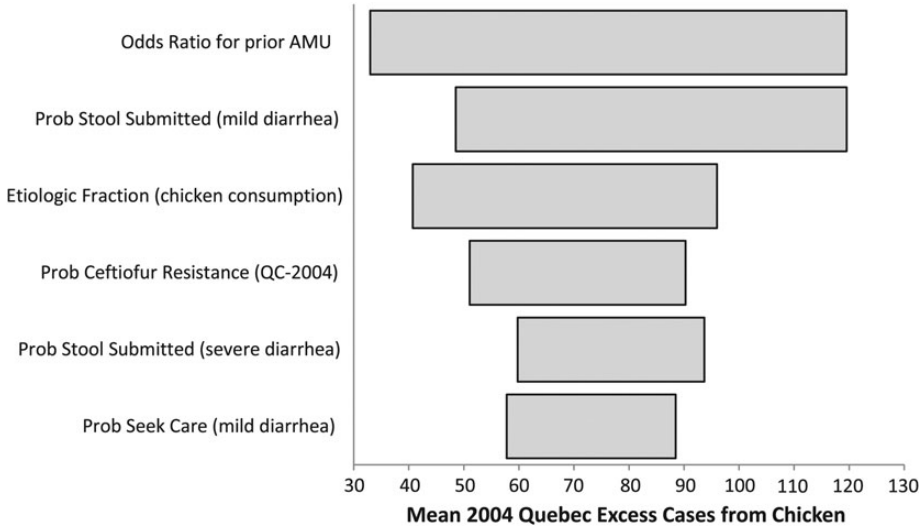

Figure 3. Tornado plot of the conditional mean of excess human cases of ceftiofur-resistant *Salmonella* Heidelberg from chicken that are attributable to human prior antimicrobial consumption and infection with a ceftiofur-resistant strain (for Québec, 2004, cases per 100 000 population) vs percentiles of the distributions for the included model inputs. Abbreviations: AMU, antimicrobial use; Prob, probability of; QC, Québec.

investigation for *S.* Heidelberg, with inputs specific for consumption of chicken nuggets and strips [3]. This was used as a proxy for all chicken consumption due to lack of other Canadian data. The fraction from egg consumption was not included as ceftiofur is not used in the Canadian layer industry (due to the lack of an approved product with a withdrawal time) and as the model results are related to changes in ceftiofur use by the broiler industry [23].

Table 4. Sensitivity Analysis Showing Model Outputs (Human Cases of Ceftiofur-Resistant *Salmonella* Heidelberg) for Québec (2004) Over Fixed Values for $EF_{chicken}$ and OR_{both} While Modeling All Other Inputs

Variable	Fixed Value	Result (Mean, 95% Credible Interval)
$EF_{chicken}$		Resistant cases from chicken
Minimum	2.33	1 (0–1)
5th	21.63	6 (3–10)
25th	27.03	7 (4–12)
Mean	30.38	8 (4–14)
75th	33.93	9 (5–15)
95th	38.49	10 (5–17)
Maximum	51.74	13 (7–23)
Model results	. . .	8 (4–15)
OR_{both}		Excess cases from chicken
Minimum	1.44	12 (6–23)
5th	2.61	42 (20–79)
25th	3.24	57 (28–107)
Mean	3.86	71 (34–132)
75th	4.37	82 (39–153)
95th	5.43	103 (50–192)
Maximum	11.15	193 (93–359)
Model results	. . .	71 (26–150)

Abbreviations: $EF_{chicken}$, etiologic fraction for chicken consumption; OR_{both}, odds ratio for the combined effect of prior antimicrobial consumption within the past month.

Appropriate measures for the burden of illness of antimicrobial resistant pathogens are important for evaluating public health impacts. This is particularly important when assessing potential risk reduction strategies for foodborne AMR, such as reducing or changing veterinary and agricultural AMU. This model provides the first Canadian estimates for annual numbers of human cases of ceftiofur-resistant *S.* Heidelberg and those attributable to chicken consumption. It provides the first Canadian estimate of the excess ceftiofur-resistant cases from chicken that are attributable to human prior antimicrobial consumption and being infected with a ceftiofur-resistant strain. Future work for ceftiofur-resistant *S.* Heidelberg could include incorporation of the impact of increased virulence and severity of infection [8] (eg, prolonged days of diarrhea, increased hospitalization rates, increased length of hospital stay, potential treatment failure, increased mortality, and increased risk of other chronic sequelae). Quantitative AMU information from the broiler chicken sector and human cases would improve the understanding of the relationship between changes in AMU in comparison to changes in resistance. Source attribution through genetic fingerprinting of *S.* Heidelberg isolates from hatchlings, retail chicken, and humans over time would create a clearer picture of the movement of resistance determinants between chickens and people.

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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