

Comparative human exposure to antimicrobial resistant bacteria from food animals using integrative assessment modelling: A farm to fork approach

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Abstract

There is a need to synthesize existing antimicrobial resistance (AMR) data using a methodology that will help to identify data gaps and research needs, as well as accommodate the integration of new data. An integrated assessment model (IAM) has the capacity to synthesize data from complex systems. Our objective was to build an IAM to comparatively assess human exposure to resistant bacteria from food animals; specifically, the exposure to extended-spectrum cephalosporin resistant *E. coli* (ESC-*E. coli*) from beef cattle, broiler chickens and pigs. A literature search was performed to identify references investigating AMR and antimicrobial use (AMU) for use in the quantitative models. Information at each stage along the food chain was combined in a cumulative manner to account for progression of resistance from farm-to-fork. The individual models were integrated at the point of human consumption and were indexed to assess the relative contribution of each to human exposure to AMR bacteria through retail meat. The models showed that human exposure to ESC-*E. coli* was higher from retail chicken than beef and pork both when considering a conventional management system with AMU and an alternate management system without AMU. Additionally, overall human exposure was lower (when combining broiler chicken, beef cattle and pig models) in an alternate management system without AMU than in a conventional system without AMU. The framework of the IAM provides a foundation for inclusion of additional data to refine the estimates of human exposure and identify potential interventions that will aid decision makers mitigate AMR.

Keywords: *antimicrobial resistance, antimicrobial use, integrative assessment modelling, food animals, human risk*

Introduction

Many groups, organisations and governments have recognized that agricultural AMU may be linked with antimicrobial resistant infections in people (1). In Canada, the number of cases of third-generation cephalosporin resistant *Salmonella* Heidelberg infections in people was strongly correlated with the prevalence of third-generation cephalosporin resistant *S. Heidelberg* in retail chicken (2). Industry actions to reduce and eventually eliminate the preventive use of third-generation cephalosporins within the broiler chicken industry led to a decline in the recovery of third-generation cephalosporin resistant *S. Heidelberg* from both chicken and human sources (3). Consequently, some groups,

organisations and governments have made recommendations to restrict the use of specific antimicrobials. For example, the Canadian poultry industry banned the preventative use of Category I antimicrobials (which includes third-generation cephalosporins) in Canadian poultry flocks in May 2014 (4).

In Canada, AMR is actively investigated with robust surveillance programs and supported research. Synthesizing and integrating this existing data will help to better understand the problem of AMR, to identify and prioritize interventions, as well as to identify knowledge gaps and research needs.

Integrated assessment models have the capacity to synthesize data from complex systems to support decision making or policy development. They are able to integrate data reported on different scales, using different methods of measurement and sources of uncertainty (5-6), including surveillance derived data. They have been used to synthesize data about climate change, water, and agricultural land use (7-8).

Our overall objective was to build a framework to assess human exposure to resistant bacteria from food animals including an integrated assessment model (IAM). We were interested in the relative exposure of humans to selected resistant bacteria (resistance to extended-spectrum cephalosporins, fluoroquinolones, macrolides and tetracycline in *E. coli*, *Salmonella*, *Campylobacter*) from beef cattle, broiler chickens, and pigs. To achieve the overall objective, quantitative models were constructed for multiple scenarios in cattle, chicken or pig populations. Scenarios were a combination of a specific bacterial species, antimicrobial susceptibility and animal population. The specific scenario presented in this paper is a qualitative comparison of human exposure to extended-spectrum cephalosporin resistant *Escherichia coli* (ESC-*E. coli*) from broiler chickens, beef cattle and pigs, and the potential effect of altering practices such as management systems (e.g. conventional, organic, antibiotic free or natural) and AMU, using a quantitative IAM.

Material and methods

Literature review

A comprehensive review of the literature was completed to identify publications investigating (i) the frequency of AMU and AMR, and (ii) factors linked with AMU and/or AMR. Searches included terms for populations (animal and human), antimicrobials, and bacteria of interest (*E. coli*,

Salmonella enterica and *Campylobacter* species). References were retained when they reported (i) data about AMU and AMR in cattle, pig, chicken, or human populations, and (ii) in a Canadian population: frequency data for AMU or AMR for *E. coli*, *Salmonella* or *Campylobacter* species, or (iib) in any geographical location: associations between a factor and AMR or AMU. Full text references that met the inclusion criteria were obtained and reviewed utility for populating quantitative models.

Data extraction and manipulation

Where possible, raw or descriptive data on the relationships between factors and AMR or AMU were extracted from the literature. Otherwise, odds ratios (OR) or risk ratios (RR) were extracted.

Quantitative models

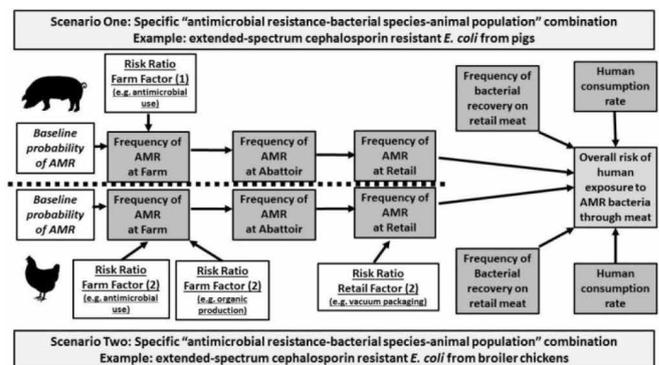
Models were developed using commercial software (Analytica™, Lumina Decision Systems). Prior to construction of the full quantitative models, the research team explored different methods for risk estimation including propagation of probabilities, RR and OR using a simplistic model with two factors (data not presented). Based on the results of the simplistic model, a decision was made to estimate risk through propagation of protective risk ratios ($0 < RR < 1$). The referent groups were defined such that the exposure factor decreased the probability of resistance.

The mathematical structure of the models for each specific animal population (i.e. beef cattle, broiler chicken or pig), bacteria (i.e. *E. coli*) and antimicrobial susceptibility (i.e. extended-spectrum cephalosporin resistance) combination was:

$$\text{Probability of resistance} = \text{baseline probability} * RR_1 * RR_2 * RR_3 \dots * RR_n$$

Where available, the baseline probability was calculated from the intercept reported in the literature. Otherwise, it was estimated using data from the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) (10). Additionally, the baseline probability was taken at the earliest point along the food chain (e.g. chicks at the time of placement on farm). The probability of resistance at each stage along the food chain (farm, abattoir, retail) was calculated by multiplying the probabilities that were calculated using the baseline probability and all risk ratios at the preceding stage (e.g. farm or abattoir) (Figure 1).

Figure 1. Conceptualized framework of the integrated assessment model to assess human exposure to resistant bacteria from food animals using an integrative assessment model (IAM)^a.



^aThis is a conceptual representation of the integrated assessment model. The exemplified factors are not representative of any specific model including the exemplified model.

A beta distribution was selected to account for the uncertainty around the baseline probability estimates and a normal distribution was chosen to represent the uncertainty around the RR (11). Frequencies of AMR at farm, abattoir and retail, and bacterial recovery rates were obtained from CIPARS. Food consumption data were obtained from the Foodbook Report (12). Individual models were integrated at the point of human consumption and the results of the integration were indexed by antimicrobial susceptibility, bacterial species and population to assess the relative contribution of each of these indexes to human exposure to resistant bacteria through retail meat.

Results

The literature searches returned 14,467 abstracts and 1,176 were retained. For the specific quantitative models presented here (ESC-*E. coli* in broiler chickens, beef cattle and pigs), the number of references included in the models ranged between two and seven. With the exception of the model for broiler chickens, modifiable factors were only identified at the farm level. Vacuum packaging of retail chicken was the only off-farm modifiable factor reported. All models included factors about alternate management systems (organic, antibiotic free, natural) and AMU. The broiler chicken model also included other management type factors (number of feed changes, type of litter, breed of bird, hygiene and sanitation and acidification of water).

When considering scenarios in which antimicrobials were used in a conventional management system, human exposure to ESC-*E. coli* was greatest from broiler chickens, followed by pigs and was lowest from beef cattle. In an alternate management system without any AMU, the comparative human exposure remained highest from broiler chickens, followed by beef cattle and was lowest through pigs. Overall, human exposure to ESC-*E. coli* was lower from animals raised in an alternate management systems in which animals were raised without antimicrobials compared to animals raised in conventional systems with AMU.

Discussion

The results presented above describe a qualitative comparison of human exposure to ESC-*E. coli* through major Canadian food animal species. These models will undergo continued refinement including (but are not limited to) use of bidirectional risk ratios ($RR \geq 1$ or ≤ 1) to better reflect current practices in Ontario and Canada, incorporation of measures of frequency that describe the occurrence of a factor, specific and quantifiable AMU metrics (rather than simply use or no use), other metrics describing AMR (e.g. whole genome sequencing) and post-processing factors that may affect exposure (e.g. cooking, cross-contamination). Additionally, temporal and commodity-specific production stage factors (e.g. parent flocks and hatcheries, preweaned livestock, feedlots, grower and finisher pigs), mechanisms to account for data collected over time, human and environmental factors that contribute to human exposure and additional data from future research, stakeholders or other sources (e.g. grey literature) will be considered for incorporation in the IAM model. The framework developed by this project is adaptable to meet additional refinements.

The process of developing the IAM and its framework is helping to identify some of the research gaps and needs. These include the need for specific metrics describing AMU, the identification of potential interventions or factors along the agri-food chain (at farm, abattoir and retail) to (i) reduce the occurrence of resistant bacteria, and (ii) either reduce the bacterial burden or alter the bacterial composition on meat. Other gaps included epidemiological considerations such as the relationships between factors associated with animal illness, AMU and AMR, as well as better understanding of the relationships between measurements along the agri-food chain (e.g. measurement of AMR on farm and its relationship to AMR in retail meats).

The framework of the IAM allows us to better understand human exposure to selected AMR bacteria from different food animal populations. It also has the capacity for additional data to further refine the exposure estimates including quantitative estimates. Lastly, the framework also provides a mechanism to understand data gaps, research needs and the potential impact of interventions to mitigate AMR.

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