Received: 28 March 2018 | Revised: 3 July 2018 | Accepted: 23 July 2018

DOI: 10.1111/zph.12515

ORIGINAL ARTICLE

WILEY

Factors potentially linked with the occurrence of antimicrobial resistance in selected bacteria from cattle, chickens and pigs: A scoping review of publications for use in modelling of antimicrobial resistance (IAM.AMR Project)

Colleen P. Murphy[1,2] | Carolee Carson[2] | Ben A. Smith[3] | Brennan Chapman[3,4] | Jayme Marrotte[2,4] | Maggie McCann[2,4] | Courtney Primeau[2,4] | Parth Sharma[2,4] | E. Jane Parmley[2]

[1]Natural Sciences and Engineering Research Council Visiting Fellow, Centre for Food-borne, Environmental and Zoonotic Infectious Disease, Public Health Agency of Canada, Guelph, Ontario, Canada

[2]Centre for Food-borne, Environmental and Zoonotic Infectious Disease, Public Health Agency of Canada, Guelph, Ontario, Canada

[3]Public Health Risk Sciences Division, National Microbiology Laboratory, Public Health Agency of Canada, Guelph, Ontario, Canada

[4]Department of Population Medicine, University of Guelph, Guelph, Ontario, Canada

Correspondence
C. P. Murphy, 269 Bronk Road, Corbyville ON K0K 1V0, Canada.
Email: colleen.p.murph@gmail.com

Funding information
This work was supported by the Ontario Ministry of Agriculture, Food and Rural Affairs – New Directions Funding Program. Project ND2013-1967: Characterizing the relationship between livestock antimicrobial use and antimicrobial resistance in people in Ontario

Abstract

Antimicrobial resistance is a complex issue with a large volume of published literature, and there is a need for synthesis of primary studies for an integrated understanding of this topic. Our research team aimed to have a more complete understanding of antimicrobial resistance in Canada (IAM.AMR Project) using multiple methods including the literature reviews and quantitative modelling. To accomplish this goal, qualitative features of publications (e.g., geographical location, study population) describing potential relationships between the occurrence of antimicrobial resistance and factors (e.g., antimicrobial use; management system) were of particular interest. The objectives of this review were to (a) describe the available peer-reviewed literature reporting potential relationships between factors and antimicrobial resistance; and (b) to highlight data gaps. A comprehensive literature search and screening were performed to identify studies investigating factors potentially linked with antimicrobial resistance in *Campylobacter* species, *Escherichia coli* and *Salmonella enterica* along the farm-to-fork pathway (farm, abattoir (slaughter houses) and retail meats) for the major Canadian livestock species (beef cattle, broiler chicken and pigs). The literature search returned 14,966 potentially relevant titles and abstracts. Following screening of titles, abstracts and full-text articles, the qualitative features of retained studies ($n = 28$) were extracted. The most common factors identified were antimicrobial use ($n = 13$ studies) and type of farm management system (e.g., antibiotic-free, organic; $n = 8$). Most studies were conducted outside of Canada and involved investigations at the farm level. Identified data gaps included the effect of vaccination, industry-specific factors (e.g., livestock density) and factors at sites other than farm along the agri-food chain. Further investigation of these factors and other relevant industry activities are needed for the development of quantitative models that aim to identify effective interventions to mitigate the occurrence of antimicrobial resistance along the agri-food chain.

KEYWORDS
bacterial, *Campylobacter*, drug resistance, *Escherichia coli*, *Salmonella enterica*

1 | INTRODUCTION

Antimicrobial resistance is global issue that threatens the health of humans and animals. There is general agreement that widespread antimicrobial use creates conditions that can select for the expression and exchange of resistance genes in pathogenic and commensal bacteria. Yet, the relative contributions of antimicrobial use in veterinary and human medicine to the emergence of resistant infections in people are not fully understood (Government of Canada, 2015; Helke et al., 2017; Hoelzer et al, 2017; WHO, 2018). Globally, fluoroquinolone use in broiler chickens was linked with fluoroquinolone-resistant *Campylobacter* infections in people (Cheng et al., 2012; Endtz et al., 1991; Gupta et al., 2004). In the European Union, the emergence of vancomycin-resistant enterococci in people was linked with avoparcin use in pigs and chickens (Cogliani, Goossens, & Greko, 2011). In Canada, changes in the use of ceftiofur, a third-generation cephalosporin, in broiler chickens mirrored changes in the incidence of ceftriaxone-resistant *Salmonella* Heidelberg infections in people (Dutil et al., 2010). However, some studies have reported that resistance patterns in livestock do not always correlate with antimicrobial resistance trends observed in humans (ECDC/EFSA/EMA, 2017; Mather et al., 2012; Threlfall, Day, de Pinna, Charlett, & Goodyear, 2006).

Impact

- There are numerous studies published about antimicrobial resistance; however, fewer studies report on factors that may alter the occurrence of antimicrobial-resistant *Campylobacter* species, *Escherichia coli* and *Salmonella enterica* in specific food animal populations (e.g., beef cattle, broiler chickens or pigs).
- The most common factor reported in the literature that potentially affected antimicrobial resistance in *Campylobacter* species, *Escherichia coli* and *Salmonella enterica* was antimicrobial use. There was a substantial data gap regarding other factors, including interventions that may reduce the occurrence of antimicrobial resistance.
- Most of the retained studies were performed in the United States. There is a need to study factors that may reduce antimicrobial resistance in other geographic regions, including Canada.

Quantitative models have been used to explore some of these observations, particularly. the relationships between antimicrobial use and antimicrobial-resistant infections in livestock and humans. However, these often investigate a single exposure (e.g., use of fluoroquinolones) and its association with resistance to a single antimicrobial agent in a particular bacteria (i.e., hazard) in a single population (e.g., fluoroquinolone-resistant *Campylobacter* in broiler chicken) (Hao et al., 2016; Horigan, Kosmider, Horton, Randall, & Simons, 2016; Hurd, Vaughn, Holtkamp, Dickson, & Warnick, 2010; Lewis et al., 2016; McEwen, 2012), and not the over-all contribution of antimicrobial use, or the complexity of the epidemiology on the occurrence of resistance (e.g., multiple antimicrobials, bacteria, genes, host population, levels of aggregation, metrics of measurement and pathways of exposure).

Stemming from the considerable public health concerns about antimicrobial resistance (Government of Canada, 2015; WHO, 2018), the complexity of the topic and the volume of published literature, there is a need to better understand what data currently exist and for synthesis of this information. Furthermore, to support evidence-based decision-making, there is a demand for an integrated understanding of the epidemiology of antimicrobial resistance (Barber, Miller, & McNamara, 2003; Garner et al., 2015; Laxminarayan et al., 2013; Newell et al., 2010; So, Shah, Roach, Chee, & Nachman, 2015). This approach should incorporate data from the major agricultural species, human sources, the natural environment (e.g., soil, water), other sites with antimicrobial resistance genetic determinants (e.g., hospital environments) and transmission of genetic determinants or bacteria between sites and populations.

External validity of available data is an important consideration when using integrated methods to develop a better understanding of the epidemiology of antimicrobial resistance (Sargeant & O'Connor, 2014a). The data collected may be from diverse sources including other populations, settings or time frames. Describing, and reviewing qualitative features including geographical location, outcome measured, production stage, study population and type of interventions are critical components of any synthesis approach, including quantitative modelling.

To inform future efforts to quantitatively model antimicrobial resistance along the agri-food chain using integrated assessment models for the major food animal species in Canada (beef cattle, broiler chicken, and pigs), our research team conducted a scoping literature review to identify and describe factors potentially linked with the occurrence of antimicrobial resistance. A factor was defined as a measured observation whose relationship with antimicrobial resistance was investigated (e.g., antimicrobial use; management system). Taking a pragmatic approach, the research team targeted selected "scenarios" (Figure 1). A scenario was defined by resistance to an antimicrobial or antimicrobial class in a specific bacterial genus/species in a defined host population (e.g., fluoroquinolone resistance in *Campylobacter jejuni* from broiler chickens). Results of the scoping review are presented herein, whereas results of other components (e.g., integrated assessment models) of the larger Integrated Assessment Modelling of Antimicrobial Resistance (IAM.AMR) project, including quantitative aspects, will be published separately.

Therefore, the objectives of this study were (a) to qualitatively describe the available peer-reviewed literature reporting potential relationships between factors and antimicrobial resistance in selected scenarios and (b) to identify and highlight data gaps. The selected scenarios were as follows: resistance to extended-spectrum cephalosporins in *Escherichia coli* and *Salmonella enterica* from beef

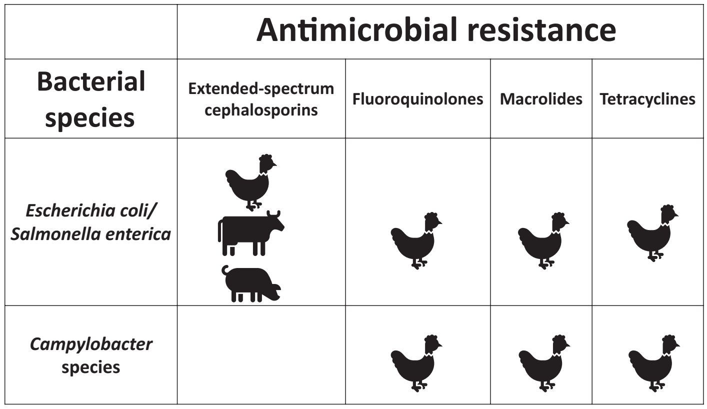

FIGURE 1 The "antimicrobial-bacteria-host population" resistance combinations (scenarios) selected for identification of factors potentially linked with antimicrobial resistance. *Note*. A factor was defined as a measured observation whose potential relationship with antimicrobial resistance was investigated (e.g., antimicrobial use; type of management system)

cattle, broiler chickens and pigs; resistance to fluoroquinolones, macrolides or tetracyclines in *Campylobacter* species, *E. coli* or *S. enterica* from broiler chickens.

2 | METHODS

2.1 | Literature search terms and strategy

A goal of the literature search and screening was to identify sources of data for all components of the larger IAM.AMR project. Consequently, the search strings and screening of references were broader than what was needed to meet the objective of this scoping review; yet comprehensive enough to capture the references targeted for this review. Comprehensive literature search strings were developed and pretested in Medline to return records for both human and animal populations of (a) the frequency of antimicrobial use or resistance (results not presented) and (b) the factors potentially associated with antimicrobial use or resistance (results presented herein; Appendix 1). The characterization of associations was broad and was not limited to interpretations of statistical significance, but included nonsignificant, causal and correlative relationships, or possible spurious findings. The searches included multiple broad and specific search terms for antimicrobial susceptibility, antimicrobial use, and population (animal or human), and specific search terms for *Campylobacter* species, *E. coli*, and *S. enterica*, and searches were not limited to a particular study design (e.g., observational, experimental, field trials, mathematical models). Following the pretest, Medline and three other databases were searched as follows: Agricola, Centre for Agriculture and Bioscience, and Cumulative Index to Nursing and Allied Health Literature, using database-specific search strings adapted from the initial pretested Medline search string. The initial search was conducted in May 2015 and was updated in June 2016. All citations were exported and deduplicated (electronically and manually) in a web-based bibliographic database manager (Mendeley Ltd).

2.2 | Scenario selection

Antimicrobial resistance is a very broad topic and the research team targeted selected "scenarios" (Figure 1) to represent common bacteria studied or under surveillance in Canada where resistance maybe concerning to permit data integration (a) across host populations (beef cattle, broiler chicken and pigs) and (b) across bacterial species within a host population (e.g., resistance to fluoroquinolones, macrolides and tetracyclines in *Campylobacter* species from broiler chickens). A scenario was defined by resistance to an antimicrobial or antimicrobial class in a specific bacterial genus/species in a defined host (animal or human) population (e.g., fluoroquinolone resistance in *Campylobacter jejuni* from broiler chickens). Nine scenarios were selected (resistance to extended-spectrum cephalosporins in *Escherichia coli* and *Salmonella enterica* from beef cattle, broiler chickens, and pigs; resistance to fluoroquinolones, macrolides, or tetracyclines in *E. coli*, *S. enterica*, or *Campylobacter* species from broiler chickens). These scenarios were selected after the literature search was conducted and prior to data extraction to streamline the multitude of potential antimicrobial-bacteria-host population combinations possible.

2.3 | Relevance screening of abstracts and full-text citations

Initially, each abstract (or title, where no abstract was available) and full-text articles were screened independently by two reviewers (Figure 2). Studies were included for the scoping review, excluded or reserved for the larger IAM.AMR with agreement by two reviewers. In the case of disagreement, the decision to include, exclude or reserve was based on review by a third member of the research team. The purpose of the screening was to identify studies for all components of the IAM.AMR project, including studies from any geographical region reporting factors potentially linked with antimicrobial resistance from the major Canadian food-animal species for the nine selected scenarios (results presented herein).

2.4 | Qualitative data extraction

Primary data extraction focused on the initial nine scenarios. Information including data about humans, other animal species, other bacterial species, other antimicrobial resistance data, and other sources (e.g., mathematical modelling, reviews, in vitro) was reserved for future work and are not discussed here (Figure 3).

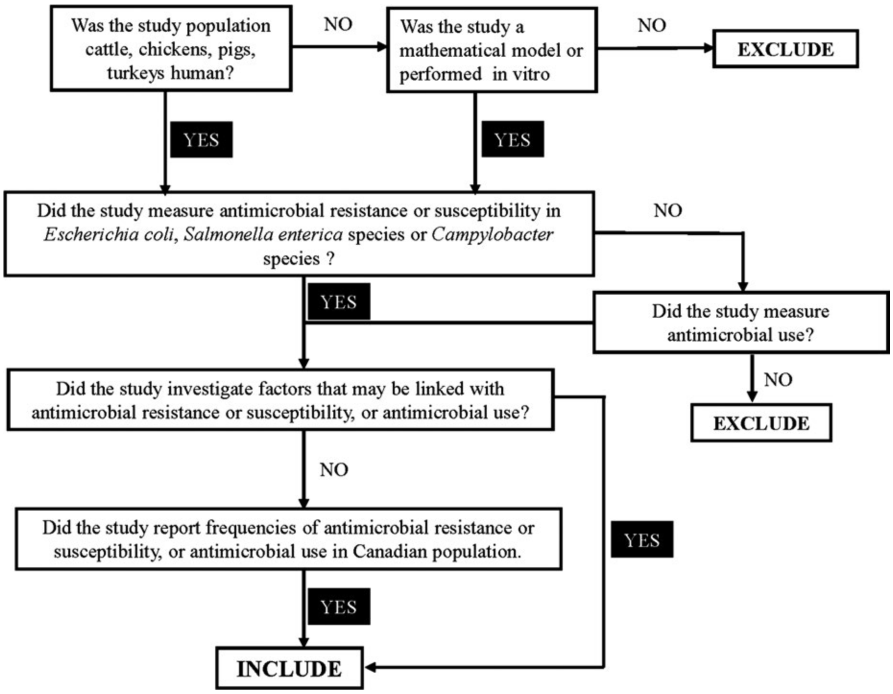

FIGURE 2 Decision-tree screening tool for identification of studies with factors potentially linked with antimicrobial resistance for qualitative review. See Figure 1 note

The qualitative data extracted included animal population (e.g., beef cattle), antimicrobial susceptibility/resistance tested (antimicrobial class and specific antimicrobial; for example, extended-spectrum cephalosporin resistance, ceftiofur resistance), bacterial population (e.g., *E. coli*), bibliographic information, and geographical region. Other data extracted were description of factor(s) investigated (e.g., antibiotic-free production, antimicrobial use, organic), location along the agri-food chain (i.e., farm, abattoir, retail), production stage of animals (e.g., feedlot cattle, nursery pigs) and type of study (e.g., controlled trial, observational). Qualitative data were extracted from each study by a small group of trained research assistants (single entry per study) and managed using a pretested electronic spreadsheet program (Microsoft Excel 2016) with oversight by senior members of the research team.

3 | RESULTS

3.1 | Features of references (overall)

There were 14,966 records (deduplicated and updated search) screened and reviewed for relevancy (Figure 3); 28 references reported potential relationships between factors and antimicrobial resistance for the nine selected scenarios (beef cattle *n* = 4, broiler chickens *n* = 18, and pigs *n* = 6; Figure 3). The majority (57%) of the studies were conducted in the United States (*n* = 16) with two studies conducted in Canada. The remaining studies were conducted in Belgium (*n* = 2), France (*n* = 2), United Kingdom (*n* = 2), Denmark (*n* = 1), Japan (*n* = 1), Portugal (*n* = 1) and Spain (*n* = 1; Tables 1–4). Factors potentially related to antimicrobial resistance in *E. coli* were reported by 17 references, *S. enterica* by six references (broiler chickens: *S.* Kentucky (*n* = 1) and unspecified serovars (*n* = 3); pigs: *S.* Agona and *S.* Orion (*n* = 1) and unspecified serovar (*n* = 1)), and *C. jejuni* by eight references (Tables 1–4). Most of the studies analysed antimicrobial resistance data at the bacterial isolate level (*n* = 25). The other levels of aggregation reported were animal (*n* = 1), farm (*n* = 1), flock (*n* = 1), package (retail meat) (*n* = 1) and sample (*n* = 1). Only two studies reported factors at locations other than the farm: chilling methods at abattoir and packaging type at retail for broiler chickens. The most commonly evaluated factor was antimicrobial use, followed by farm production system (e.g., antibiotic-free, organic; Table 5).

3.2 | Features of references for specific scenarios

3.2.1 | Extended-spectrum cephalosporin resistance in *Escherichia coli* and *Salmonella enterica* from beef cattle, broiler chickens and pigs

Seventeen studies reported data on factors potentially linked with resistance to extended-spectrum cephalosporins in *E. coli* (*n* = 14) and *S. enterica* (*n* = 5) (Table 1) (beef cattle *n* = 4, broiler chickens *n* = 7, pigs=6).

For beef cattle (*n* = 4), all studies examined antimicrobial resistance in *E. coli* and evaluated antimicrobial use with controlled trials in feedlot cattle (antimicrobial use was the only evaluated factor). No studies reported antimicrobial resistance for *S. enterica*. One study was conducted in Canada, and the remaining studies were conducted in the United States (*n* = 3). Antimicrobial resistance results for *E. coli* were reported for the following: ceftiofur (*n* = 2), ceftazidime (*n* = 1) and ceftriaxone (*n* = 1).

For broiler chickens (*n* = 7), five studies investigated antimicrobial resistance in *E. coli* and three studies in *S. enterica*. Most of the studies were observational (*n* = 6), and one study was a controlled trial in an experimental unit. One study was Canadian, and the remaining

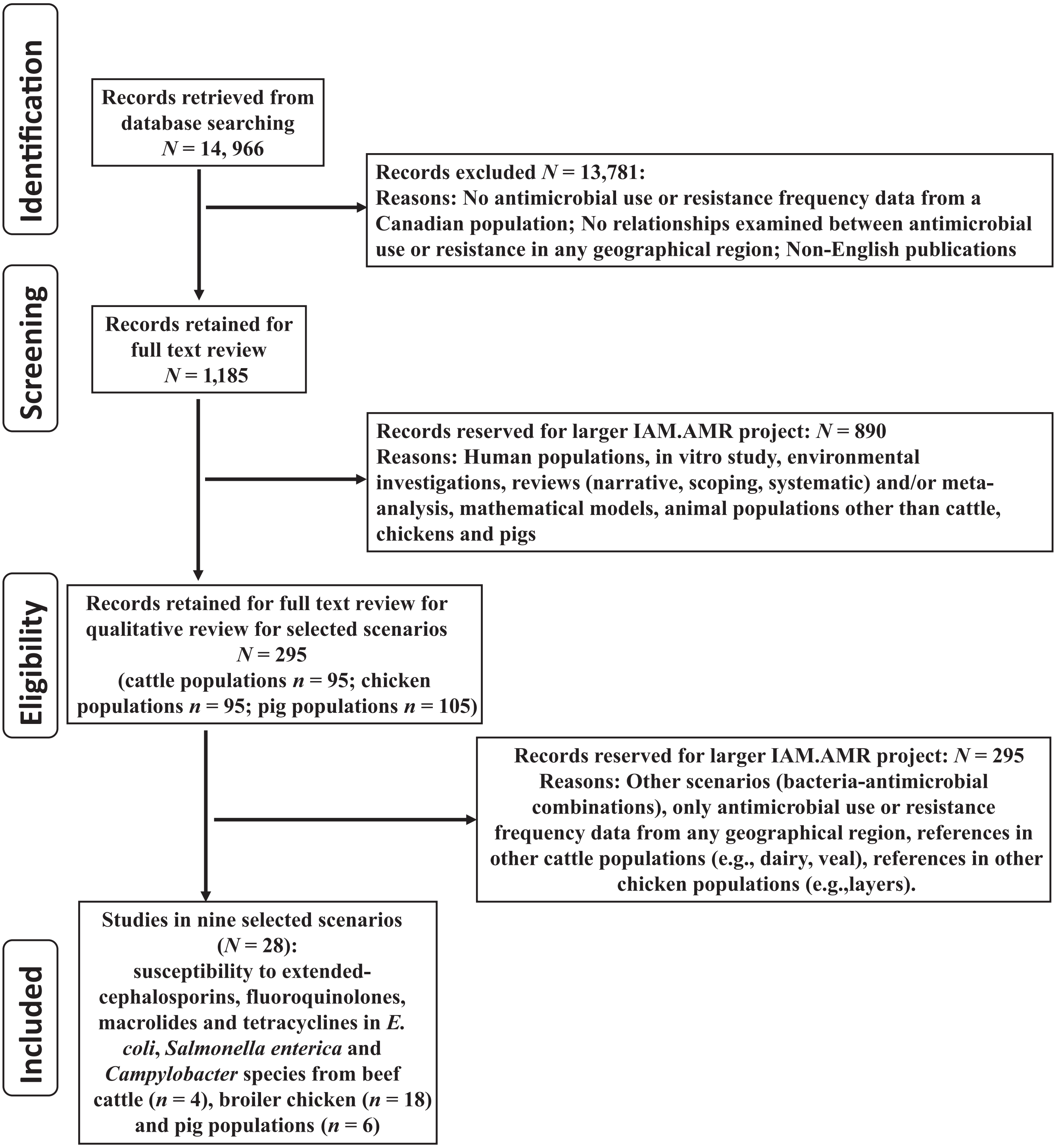

FIGURE 3 The literature retrieval and screening to identify studies with factors[a] potentially linked with antimicrobial resistance for scoping qualitative review. See Figure 1 note

studies were conducted in Belgium (*n* = 1), Denmark (*n* = 1) and the United States (*n* = 4). Susceptibility to ceftriaxone (*n* = 1) and ceftiofur (*n* = 5) was reported, and one reference reported identification of CMY-2 and CTX-M genes. Factors reported were antimicrobial use (*n* = 3), type of production system (organic, conventional) (*n* = 2), farm management factors (acidification of water, hygiene, number of feed changes, type of litter) (*n* = 1) and the type of retail packaging (*n* = 1).

Six studies reported data about resistance to extended-spectrum cephalosporins in pigs on farms (*E. coli n* = 5, *S. enterica n* = 2). Four were controlled trials (weaned piglets *n* = 1, finisher pigs *n* = 3) on farms and two studies were observational (preweaned piglets *n* = 1, finisher pigs *n* = 1). No studies were conducted in Canada. Studies were conducted in the United States (*n* = 4), Belgium (*n* = 1) and Spain (*n* = 1). Susceptibility to ceftiofur (*n* = 5), cefoxitin (*n* = 1),

TABLE 1 Qualitative features of studies with factors[a] potentially linked with extended-spectrum cephalosporin resistance in beef, broiler chicken, and pigs

Bacteria	Population	Specific antimicrobial	Region	Site sampled in the food chain	Production stage (where applicable)	Sample	Study type	Factors[a]	References
Escherichia coli (*E. coli*)	Beef cattle	Ceftazidime	Alberta, Canada	Abattoir	Feedlot	Multiple aggregated samples from the same study population: rectal faecal pre-slaughter, hides, carcass, ground meat, abattoir environment	Controlled trial	Antimicrobial use. Group 1: Chlortetracycline and sulfamethazine in feed, 440 ppm each; Group 2: No antimicrobial treatment	Alexander et al. (2010)
		Ceftiofur	United States	Farm	Feedlot	Rectal faecal	Controlled trial	Antimicrobial use: Group 1: Ceftiofur crystalline free acid (CCFA) 6.6 mg/kg BW SQ on day 0 to all animals in the pen, followed by chlortetracycline (22 mg.kg BW) top-dress on days 4–8, 10–14, 16–20; Group 2: CCFA as described in Group 1 administered to one animal in a pen, followed by chlorotetracycline as described in Group 1	Kanwar et al. (2013)
		Ceftriaxone	United States	Farm	Feedlot	Rectal faecal	Controlled trial	Antimicrobial use. Group 1: Cefttiofur (crystalline free acid) (CCFA) 6.6.mg/kg BW SQ, single dose; Group 2: CCFA 4.4 mg/kg BW SQ, single dose; Group 3: CCFA 6.6 mg/kg BW SQ, 3 doses on days 0, 6 and 13; Group 4: No antimicrobial treatment	Lowrance et al. (2007)
		Ceftiofur	United States	Farm	Feedlot	Faecal pats	Controlled trial	Antimicrobial use Group 1: In-feed tylosin and ionophores in accordance with the U.S. and Drug administration regulations for in-feed medications; Group 2: No in-feed tylosin and ionophores	Morley et al. (2011)
	Broiler chicken	Ceftriaxone	Denmark	Abattoir	Commercial flock	Cloacal swab	Observational	Antimicrobial use. Group 1: Exposure to aminopenicillins within 6 months of slaughter; Group 2: No exposure to aminopenicillins within 6 months of slaughter	Agersø, Jensen, Hasman, and Pedersen (2014)
		Ceftiofur	Canada	Experimental unit	Commercial flock	Caecal contents, cloacal swab	Controlled trial	Antimicrobial use. Group 1:Bambermycin 2 mg/kg feed;Group 2: Penicillin 2.2 mg/kg feed; Group 3: Salinomycin 60 mg/kg feed; Group 4: Bacitracin 4.4 mg/kg feed; Group 5: Bactracin (3.3 mg/kg feed) and salinomycin (1.1. mg/kg feed); Group 6: No antimicrobial treatment .	Diarra et al. (2007)
		Ceftiofur	Belgium	Farm	Commercial flock	Cloacal swabs	Observational	Multiple factors investigated: Hygenic condition of the treatment reservoir, acidification of the water, type of litter material and number of feed changes per cycle	Persoons et al. (2011)
		Ceftoifur	United States	Farm	Commercial flock	Litter sample	Observational	Antimicrobial use. Group 1: On farm oxytetracycline use; Group 2: On farm sarafloxacin use; Group 3: No on farm antimicrobial use	Smith et al. (2007)

TABLE 1 (*Contiuned*)

Bacteria	Population	Specific antimicrobial	Region	Site sampled in the food chain	Production stage (where applicable)	Sample	Study type	Factors[a]	References
E. coli; Salmonella enterica (*S. enterica*)	Broiler chicken	CMY−2 gene; CTX-M gene	United States	Retail	Commercial flock	Boneless chicken breast	Observational	Retail packaging; Management system. Factor 1: Vacuum packaged; Factor 2: Not vacummed packaged; Factor 3: Organic management; Factor 4: Antibiotic- free; Factor 5: Conventional management.	Mollenkopf et al. (2014)
S. enterica	Broiler chicken	Ceftiofur	United States	Farm	Commercial flock	Litter samples	Observational	Management system. Group 1: Organic production system; Group 2: Conventional production system	Alali, Thakur, Berghaus, Martin, and Gebreyes (2010)
		Ceftiofur	United States	Farm	Commercial flock	Litter samples	Observational	Management system. Group 1: Organic system; Group 2: Conventional system	Sapkota et al. (2014)
E. coli	Pig	Ceftiofur, Ceftriaxone	United States	Farm	Weaned	Rectal faecal	Controlled trial	Group 1: Copper sulphate 16.5 ppm; Group 2: Copper sulphate 125 mg/kg feed; Group 3: In-feed chlortetracycline 550 mg/kg feed; Group 4: Copper sulphate 125 mg/kg feed and chlorotetracycline 550 mg/kg feed	Agga et al. (2014)
		Ceftiofur, Ceftriaxone	United States	Farm	Finisher	Faecal (pen)	Observational	Management system Group 1: Antibiotic-free system; Group 2: Conventional system	Bunner et al. (2007)
		Ceftiofur	Belgium	Farm	Pre-weaned piglets	Rectal swab	Observational	Antimicrobial use. Group 1: Treatment with enrofloxacin; Group 2: No treatment with enrofloxacin	Callens et al. (2015)
		Cephalosporins	Spain	Farm	Finisher	Rectal faecal	Controlled trial	Antimicrobial use: Group 1: Ceftiofur 5 mg/kg BW IM; Group 2: Tulathromycin 2.5 mg/kg BW IM	Cameron-Veas, Moreno, Fraile, and Migura-Garcia (2016)
E. coli; *S enterica*	Pig	Ceftiofur	United States	Farm	Finisher	Faecal (pen)	Controlled trial	Antimicrobial use. Group 1: In-feed chlortetracycline 100 g/ton throughout the finishing period except for the 2 weeks prior to marketing; Group 2: In-feed tylosin 40 g/ton throughout the finishing period; Group 3: In-feed chlorotetracycline 400 g/ton pulse administration of 1 week treatment/2 weeks no treatment throughout the finishing period; Group 4: In-feed tylosin 100 g/ton pulse administration of 1 week treatment/2 weeks no treatment throughout the finishing period; Group 5: No antimicrobial treatment.	Wagner, Straw, Fedorka-Cray, and Dargatz (2008)
S. enterica	Pig	Ceftiofur, Cefoxitin, Ceftriaxone	United States	Farm	Finisher	Rectal faecal	Controlled trial	Antimicrobial use. Group 1:50 grams of chlortetracycline per ton of feed in finisher ration; Group 2: No in feed antimicrobial use	Funk, Lejeune, Wittum, and Rajala-Schultz (2006)

[a]A factor was defined as a measured observation whose potential relationship with either antimicrobial resistance was investigated.

TABLE 2 Qualitative features of studies with factors[a] potentially linked with fluoroquinolone resistance in broiler chickens

Bacteria	Specific antimicrobial susceptibility	Region	Site sampled in the food chain	Production stage (where applicable)	Sample
Campylobacter jejuni	Enrofloxacin	Japan	Farm	Commercial flock	Faecal sample
	Enrofloxacin	France	Abattoir	Commercial flock	Caecal and skin samples
	Ciprofloxacin	United States	Retail	Commercial flock	Whole carcass
	Ciprofloxacin	United States	Abattoir	Commercial flock	Whole carcass
	Ciprofloxacin	United States	Retail	Commercial Flock	"Bone-in" and "skin-on" retail meat
	Ciprofloxacin	United States	Retail	Commercial Flock	"Bone-in" and "skin-on" retail meat
	Ciprofloxacin	United Kingdom	Retail	Commercial flock	Retail meat
	Enrofloxacin	United Kingdom	Farm	Commercial flock	Retail meat
Escherichia coli	Enrofloxacin	Portugal	Experimental unit	Commercial flock	Litter sample
	Enrofloxacin	See data under extended-spectrum cephalosporin resistance in broiler chicken			
	QRDR gene	See data under extended-spectrum cephalosporin resistance in broiler chicken			
	Ciprofloxacin	Vietnam	Farm	Commercial flock	Faecal samples from boot swabs
	Enrofloxacin	See data under extended-spectrum cephalosporin resistance in broiler chicken			
Salmonella enterica	Ciprofloxacin	See data under extended-spectrum cephalosporin resistance in broiler chicken			
	Ciprofloxacin	See data under extended-spectrum cephalosporin resistance in broiler chicken			

[a]A factor was defined as a measured observation whose potential relationship with either antimicrobial resistance was investigated.

ceftriaxone (*n* = 1) and cephalosporins (*n* = 1) was reported. Factors reported were antimicrobial use (*n* = 4), antimicrobial use with copper (*n* = 1) and type of production system (antibiotic-free, conventional) (*n* = 1).

3.2.2 | Resistance to extended-spectrum cephalosporins, fluoroquinolones, macrolides and tetracyclines in *Escherichia coli*, *Salmonella enterica* and *Campylobacter* from broiler chickens

Ten studies reported data about factors potentially linked with resistance to extended-spectrum cephalosporins, fluoroquinolones, macrolides and/or tetracyclines in *E. coli* (*n* = 7) and *S. enterica* (*n* = 4) from broiler chicken(s) (Tables 2–4). Seven studies investigated antimicrobial resistance to fluoroquinolones (*E. coli* *n* = 5, *S. enterica* *n* = 3), one study investigated macrolide resistance in *S. enterica*, and six studies investigated tetracycline resistance in *E. coli* (*n* = 3) and *S. enterica* (*n* = 3).

Most of the studies were observational (*n* = 8), and two studies were controlled trials. One study was Canadian in origin, and the remaining studies were conducted in the United States (*n* = 5), and Belgium, Denmark, Portugal and Vietnam (*n* = 1 each). Factors reported were antimicrobial use (*n* = 5), farm management factors (boot changes, intensity of management) (*n* = 2), type of production system (conventional, organic) (*n* = 2), method of chilling at abattoir (*n* = 1) and the type of retail packaging (*n* = 1).

Eight studies reported data on factors potentially linked with resistance to fluoroquinolones, macrolides and tetracyclines in *Campylobacter* species from broiler chicken(s) (Tables 2–4). Seven studies investigated resistance to fluoroquinolones, five studies investigated tetracycline resistance and four studies investigated macrolide resistance. Most of the studies were observational (*n* = 7), and

Study type	Factors[a]	References
Observational	Antimicrobial use. Group 1: On-farm tetracycline use within the preceding 6 months. Group 2: No on-farm antimicrobial use	Asai et al. (2007)
Observational	Growth promotor ban (virginiamycin, tylosin, spiramycin, bacitracin) and management system. Group 1: Samples collected between 1992–1996 prior to the ban on growth promoter; conventional management; Group 2: Samples collected between 1992–1996 prior to the ban on growth promoter; free-range management. Group 3: Samples collected between 2001–2002 following the ban of growth promoters; conventional management; Group 4: Samples collected between 1992–1996 prior to the ban on growth promoter; free-range management.	Desmonts, Dufour-Gesbert, Avrain, and Kempf (2004)
Observational	Management system. Group 1: Organic labelling; Group 2: Conventionally raised	Han, Lestari, Pu, and Ge (2009)
Observational	Chilling method. Group 1: Immersion chilled; Group 2: Air chilled	Sánchez et al. (2002)
Observational	Management system. Group 1: Antibiotic-free; Group 2: Conventional	Price, Johnson, Vailes, and Silbergeld (2005)
Observational	Management system. Group 1: Antibiotic-free; Group 2: Conventional	Price, Lackey, Vailes, and Silbergeld (2007)
Observational	Management system; Point of purchase. Group 1: Organic management; Group 2: Intensive management; Group 3: Intensively raised, purchased at a supermarket Group 4: Intensively raised, purchased at butchers	Soonthornchaikul et al. (2006)
Experimental	Antimicrobial use. Experiment 1-In water enrofloxacin: Group 1:50 ppm for 5 days; Group 2:125 ppm for 3 days; Group 3:250 ppm for 1 day. Experiment 2-In water enrofloxacin for 3 days at: Group 1:12 ppm; Group 2:25 ppm; Group 3:50 ppm; Group 4:125 ppm; Group 5:250 ppm; Group 6:500 ppm.	Stapleton et al. (2010)
Controlled trial	Antimicrobial use. Group 1: In water enrofloxacin on days 1–3 after hatch at 23.8. mg/kg BW; Group 2: No antimicrobial exposure	Costa, Belo, Goncalves, and Bernardo (2009)
		Diarra et al. (2007)
		Mollenkopf et al. (2014)
Observational	Management factors and antimicrobial use. Group 1 & 2: Boot change compared to no boot changes; Group 2: On-farm quinolone; Group 3 On-farm tetracycline use; Group 4: No antimicrobial use/	Nguyen et al. (2015)
		Smith et al. (2007)
		Alali et al. (2010)
		Sapkota et al. (2014)

one study was a controlled trial. There were no Canadian studies. Three studies were conducted in the United States, and the remaining studies were conducted in France (n = 2), the United Kingdom (n = 2) and Japan (n = 1). Factors reported were antimicrobial use (n = 4), type of production system (organic, conventional) (n = 3) and method of chilling at abattoir (n = 1).

4 | DISCUSSION

Antimicrobial resistance has been studied for decades and has a vast and diverse body of peer-reviewed literature. However, when investigating risk factors or potential interventions to alter the occurrence of antimicrobial resistance in a specific antimicrobial-bacteria-host population, there is little breadth or depth in the published literature; this finding has been observed in previous work (Murphy et al., 2016). In the present study, antimicrobial use (particularly therapeutic use) was the most commonly reported factor investigated for the selected scenarios. This is not unexpected and is an important finding, as there is widespread recognition that antimicrobial use is an important contributor to the occurrence of antimicrobial resistance.

However, despite the important role of antimicrobial use on the occurrence of resistance, there are other potential factors occurring at various points along the agri-food chain that may impact the occurrence of antimicrobial resistance (Singer, Ward, & Maldonado, 2006). The most common nonantimicrobial use factor identified in this study was type of management system (e.g., antibiotic-free, conventional, organic). Although identified as a single factor, it is a global variable that could encompass many practices (e.g., antimicrobial use, feed, housing, intensity of production, stocking density). Further work is needed to characterize the contribution of specific practices within the various management systems on the occurrence

TABLE 3 Qualitative features of studies with factors[a] potentially linked with macrolide resistance in broiler chickens

Bacteria	Specific antimicrobial susceptibility	Region	Site sampled in the food chain	Production stage (where applicable)	Sample	Study type	Factors[a]	References
Campylobacter jejuni	Erythromycin	See data under fluoroquinolone resistance in broiler chicken						Desmonts et al. (2004)
	Erythromycin	See data under fluoroquinolone resistance in broiler chicken						Han et al. (2009)
	Erythromycin	See data under fluoroquinolone resistance in broiler chicken						Sánchez et al. (2002)
	Erythromycin	See data under fluoroquinolone resistance in broiler chicken						Soonthornchaikul et al. (2006)
Salmonella enterica	Erythromycin	See data under fluoroquinolone resistance in broiler chicken						Sánchez et al. (2002)

[a]A factor was defined as a measured observation whose potential relationship with either antimicrobial resistance was investigated.

TABLE 4 Qualitative features of studies with factors[a] potentially linked with tetracycline resistance in Canadian broiler chickens

Bacteria	Region	Site sampled in the food chain	Production stage (where applicable)	Sample	Study type	Factors[a]	References
Campylobacter jejuni	See data under fluoroquinolone resistance in broiler chicken						Asai et al. (2007)
	France	Abattoir	Commercial flock	Caecal sample	Observational	Antimicrobial use. Group 1: On farm avilamycin use; Group 2: No on-farm antimicrobial use	Avrain et al. (2003)
	See data under fluoroquinolone resistance in broiler chicken						Desmonts et al. (2004)
	See data under fluoroquinolone resistance in broiler chicken						Han et al. (2009)
	See data under tetracycline resistance *E. coli* in broiler chicken.						Sánchez et al. (2002)
Escherichia coli	See data under fluoroquinolone resistance in broiler chicken						Costa et al. (2009)
	See data under extended-spectrum cephalosporin resistance in broiler chicken						Diarra et al. (2007)
	See data under extended-spectrum cephalosporin resistance in broiler chicken						Smith et al. (2007)
Salmonella enterica	United States	Farm	Commercial flock	Litter samples	Observational	Management system. Group 1: Organic production; Group 2: Conventional	Alali et al. (2010)
	See data under fluoroquinolone resistance in broiler chicken						Sánchez et al. (2002)
	See data under extended-spectrum cephalosporin resistance in broiler chicken						Sapkota et al. (2014)

[a]A factor was defined as a measured observation whose potential relationship with either antimicrobial resistance was investigated.

of antimicrobial resistance, and to identify specific practices that have the potential for widespread adoption across farming industries. This may be a practical alternative to the costly modifications of an entire management system.

The other evaluated factors were mainly farm-level factors (e.g., addition of copper to feed, litter-type, number of feed changes). Most of these identified factors were from retrospective observational studies that incorporated survey data. Although the identification

TABLE 5 General classification of factors[a] potentially linked with antimicrobial resistance in selected scenarios[b]

Population	Factors[a]: general (number of references)
Beef cattle	Antimicrobial use (n = 4)
Broiler Chicken	Antimicrobial use (n = 9)
	Non-conventional management systems (e.g., organic) (n = 7)
	Farm management factors (e.g., boot changes, hygiene, litter) (n = 2)
	Retail packaging (vacuum packaging) (n = 1)
	Chilling (e.g., air, water) (n = 1)
	Point of purchase (e.g., butcher, supermarket) (n = 1)
Pig	Antimicrobial use (n = 4)
	Non-conventional Management (n = 1)
	Other compounds (e.g., copper) (n = 1)

[a]A factor was defined as a measured observation whose potential relationship with either antimicrobial resistance was investigated. [b]Resistance to extended-spectrum cephalosporins in *E. coli* and *S. enterica* from beef cattle, broiler chickens and pigs; resistance to fluoroquinolones, macrolides or tetracyclines in *E. coli*, *S. enterica* or *Campylobacter* species from broiler chickens.

of these factors was important, it is difficult without repeated studies to understand their relationship, particularly causal, with the occurrence of antimicrobial resistance and their application in the Canadian context.

Investigation of nonantimicrobial use factors that may alter the occurrence of antimicrobial resistance is important and a data gap that needs to be addressed. However, identification of these factors may be challenging. Some factors may not have a direct relationship with antimicrobial resistance but may be associated with the occurrence of illness (and subsequent antimicrobial use) or antimicrobial use alone, and thus, indirectly impact the occurrence of antimicrobial resistance. These include factors not identified in this review such as animal density, biosecurity measures, farm density, housing, microbial burdens on carcasses and vaccination. In Denmark, vaccination was the most commonly reported action used by surveyed swine veterinarians and farmers to reduce antimicrobial use in response to the national antimicrobial use initiative, “Yellow-card Scheme” (Dupont, Diness, Fertner, Kristensen, & Stege, 2017), implemented to reduce the occurrence of antimicrobial resistance. In Canada, vaccines are routinely recommended and applied in livestock production systems (Codes of Practice for the care and handling of farm animals [n.d.]; https://www.nfacc.ca/codes-of-practice). Studies have reported the relationship between vaccination and antimicrobial use (Del Pozo Sacristán, Michiels, Martens, Haesebrouck, & Maes, 2014; Fertner, Toft, Martin, & Boklund, 2016; Lava, Schüpbach-Regula, Steiner, & Meylan, 2016); however, an assessment of these combined actions on the occurrence of resistance has not been published to our knowledge. The absence of vaccination and other nonantimicrobial use factors at the farm level of the agri-food chain in this review represents an important data gap in the literature.

However, there were other data gaps identified further along the agri-food chain. There is a wide body of the literature investigating the impact of factors at the abattoir that reduce microbial load on a carcass (Argeullo, Álvarez-ordoñez, Carvajal, Rubio, & Prieto, 2013; Hermans et al., 2011; Lassok & Tenhagen, 2013; Sahin et al., 2015; Soon, Chadd, & Baines, 2011; Umaraw, Prajapati, Verma, Pathak, & Singh, 2017). Our literature search and screening focused on factors associated with antimicrobial-resistant bacteria. Consequently, factors that were associated with reducing microbial burden or contamination (without investigations of susceptibility) at abattoir or retail were outside the scope of this project and hence not captured. It has been reported that abattoir interventions may be the most effective at reducing human exposure to potential food-borne pathogens (Hill et al., 2016) and by extension antimicrobial-resistant bacteria arising from the consumption of food. Additionally, it is plausible that abattoir interventions may have varying effects on different antimicrobial-resistant bacteria. Further study to understand the impact of interventions at abattoir on the occurrence of antimicrobial-resistant bacteria, particularly on antimicrobial-resistant bacteria of public health importance, is needed.

Another key finding from the review was the geographic locations of the study populations. Only two of the retained studies were performed in Canadian populations. Agricultural and husbandry practices can vary substantially between countries (Sargeant & O’Connor, 2014b), and these differences in practices can impact the types of factors investigated and the relationships observed between the measured factors and antimicrobial resistance. This is an important consideration as our research team is strongly interested in a comprehensive understanding of antimicrobial resistance in Canada. It is understood that agricultural practices differ regionally within Canada (e.g., distance between farms, farm size, intensity of management, source of animals) and that data obtained in one region may not be generalizable nationally. This underscores the need for research to be performed on a scale targeted to the specific region of interest.

Although a comprehensive literature review was performed, there are still some limitations to the presented approach. Resources limited the review to English language publications. However, as many of the publications on antimicrobial resistance are published in English, this likely has a negligible effect on the findings (Jüni, Holenstein, Sterne, Bartlett, & Egger, 2002; Moher, Pham, Lawson, & Klassen, 2003; Young et al., 2014). At this time, a structured review of grey literature has not been performed. Consultations with Canadian agricultural industry representatives did not identify any additional grey literature sources, in particular about production system or stage-specific factors. There are grey literature publications, particularly from surveillance systems with data captured at large regional scales that investigate links between antimicrobial use and antimicrobial resistance (ECDC/EFSA/EMA, 2017). The quantitative data reported from these studies need to be reviewed prior to their use in modelling because the scales of aggregation (large regional scale) were different from the references obtained in the literature searches (mostly isolate level). This could lead to possible false inferences of interpretations because of the scale differences (ecological fallacy; Blakely & Woodward, 2000).

A comprehensive literature search of this nature is resource intensive. However, these are necessary for developing and/or curating a data resource to support synthesis research and to guide future research and surveillance. This review identified references investigating factors possibly linked with antimicrobial resistance. Antimicrobial use was the most commonly identified factor. There were other factors identified; however, their potential relationships with antimicrobial resistance remains incompletely understood and require further research. There were also gaps in knowledge on the impact of common actions such as vaccination and abattoir interventions on the occurrence of antimicrobial resistance. Investigation of these factors and other widespread industry activities in Canadian populations will aid in further understanding the aggregated effects of actions throughout the Canadian agri-food chain on the occurrence of antimicrobial resistance and potential exposure to humans. Addressing data gaps in the literature requires communication and collaboration between stakeholders such as farm commodity groups and researchers to so that practical and effective interventions can be identified and implemented to mitigate the threat of antimicrobial resistance.

ACKNOWLEDGEMENTS

We would very much like to thank Aamir Fazil, Antoinette Ludwig, Scott McEwen, Laura Pullum, and Richard Reid-Smith for their assistance, guidance and insight. We would also like to thank, Dakota Barnes, Christopher Burnie, Lucie Collineau, Dana Ramsey, Ruby Wong for their assistance.

CONFLICT OF INTEREST

None.

ORCID

Colleen P. Murphy http://orcid.org/0000-0003-3294-5028

REFERENCES

Agersø, Y., Jensen, J. D., Hasman, H., & Pedersen, K. (2014). Spread of extended spectrum cephalosporinase-producing *Escherichia coli* clones and plasmids from parent animals to broilers and to broiler meat in a production without use of cephalosporins. *Foodborne Pathogens and Disease*, *11*, 740–746. https://doi.org/10.1089/fpd.2014.1742

Agga, G. E., Scott, H. M., Amachawadi, R. G., Nagaraja, T. G., Vinasco, J., Bai, J., … Tokach, M. D. (2014). Effects of chlortetracycline and copper supplementation on antimicrobial resistance of fecal *Escherichia coli* from weaned pigs. *Preventive Veterinary Medicine*, *114*, 231–246. https://doi.org/10.1016/j.prevetmed.2014.02.010

Alali, W. Q., Thakur, S., Berghaus, R. D., Martin, M. P., & Gebreyes, W. A. (2010). Prevalence and distribution of *Salmonella* in organic and conventional broiler poultry farms. *Foodborne Pathogens & Disease*, *7*, 1363–1371. https://doi.org/10.1089/fpd.2010.0566

Alexander, T. W., Inglis, G. D., Yanke, L. J., Topp, E., Read, R. R., Reuter, T., & McAllister, T. A. (2010). Farm-to-fork characterization of *Escherichia coli* associated with feedlot cattle with a known history of antimicrobial use. *International Journal of Food Microbiology*, *137*, 40–48. https://doi.org/10.1016/j.ijfoodmicro.2009.11.008

Argeullo, H., Álvarez-ordoñez, A., Carvajal, A., Rubio, P., & Prieto, M. (2013). Role of Slaughtering in *Salmonella* spreading and control in pork production. *Journal of Food Protection*, *76*, 899–911. https://doi.org/10.4315/0362-028X.JFP-12-404

Asai, T., Harada, K., Ishihara, K., Kojima, A., Sameshima, T., Tamura, Y., & Takahashi, T. (2007). Association of antimicrobial resistance in *Campylobacter* isolated from food-producing animals with antimicrobial use on farms. *Japanese Journal of Infectious Diseases*, *60*, 290–294. https://doi.org/10.1111/j.1574-695X.2006.00085.x

Avrain, L., Humbert, F., L'Hospitalier, R., Sanders, P., Vernozy-Rozand, C., & Kempf, I. (2003). Antimicrobial resistance in *Campylobacter* from broilers: Association with production type and antimicrobial use. *Veterinary Microbiology*, *96*(3), 267–276. https://doi.org/10.1016/j.vetmic.2003.07.001

Barber, D. A., Miller, G. Y., & McNamara, P. E. (2003). Models of antimicrobial resistance and foodborne illness: Examining assumptions and practical applications. *Journal of Food Protection*, *66*(4), 700–709. https://doi.org/10.4315/0362-028X-66.4.700

Blakely, T. A., & Woodward, A. J. (2000). Ecological effects in multi-level studies. *Journal of Epidemiology and Community Health*, *54*, 367–374. https://doi.org/10.1136/jech.54.5.367

Bunner, C. A., Norby, B., Bartlett, P. C., Erskine, R. J., Downes, F. P., & Kaneene, J. B. (2007). Prevalence and pattern of antimicrobial susceptibility in *Escherichia coli* isolated from pigs reared under antimicrobial-free and conventional production methods. *Journal of the American Veterinary Medical Association*, *231*, 275–283. https://doi.org/10.2460/javma.231.2.275

Callens, B., Faes, C., Maes, D., Catry, B., Boyen, F., Francoys, D., … Dewulf, J. (2015). Presence of antimicrobial resistance and antimicrobial use in sows are risk factors for antimicrobial resistance in their offspring. *Microbial Drug Resistance*, *21*, 50–58. https://doi.org/10.1089/mdr.2014.0037

Cameron-Veas, K., Moreno, M. A., Fraile, L., & Migura-Garcia, L. (2016). Shedding of cephalosporin resistant *Escherichia coli* in pigs from conventional farms after early treatment with antimicrobials. *Veterinary Journal*, *211*, 21–25. https://doi.org/10.1016/j.tvjl.2016.02.017

Cheng, A. C., Turnidge, J., Collignon, P., Looke, D., Barton, M., & Gottlieb, T. (2012). Control of fluoroquinolone resistance through successful regulation, Australia. *Emerging Infectious Diseases*, *18*, 1453–1460. https://doi.org/10.3201/eid1809.111515

Codes of Practice for the care and handling of farm animals (n.d.). Retrieved January 29, 2018, from https://www.nfacc.ca/codes-of-practice

Cogliani, C., Goossens, H., & Greko, C. (2011). Restricting antimicrobial use in food animals: Lessons from europe banning nonessential antibiotic uses in food animals is intended to reduce pools of resistance genes. *Microbobe*, *6*, 274–297. https://doi.org/10.1128/microbe.6.274.1

da Costa, P. M., Belo, A., Goncalves, J., & Bernardo, F. (2009). Field trial evaluating changes in prevalence and patterns of antimicrobial resistance among *Escherichia coli* and *Enterococcus spp.* isolated from growing broilers medicated with enrofloxacin, apramycin and amoxicillin. *Veterinary Microbiology*, *139*, 284–292. https://doi.org/10.1016/j.vetmic.2009.06.006

Del Pozo Sacristán, R., Michiels, A., Martens, M., Haesebrouck, F., & Maes, D. (2014). Efficacy of vaccination against *Actinobacillus pleuropneumoniae* in two Belgian farrow-to-finish pig herds with a history of chronic pleurisy. *Veterinary Record*, *174*, 302–302. https://doi.org/10.1136/vr.101961

Desmonts, M.-H.-H., Dufour-Gesbert, F., Avrain, L., & Kempf, I. (2004). Antimicrobial resistance in *Campylobacter* strains isolated from French broilers before and after antimicrobial growth promoter bans. *The Journal of Antimicrobial Chemotherapy*, *54*, 1025–1030. https://doi.org/10.1093/jac/dkh473

Diarra, M. S., Silversides, F. G., Diarrassouba, F., Pritchard, J., Masson, L., Brousseau, R., … Topp, E. (2007). Impact of feed supplementation with antimicrobial agents on growth performance of broiler chickens, *Clostridium perfringens* and enterococcus counts, and antibiotic resistance phenotypes and distribution of antimicrobial resistance determinants in *Escherichia coli* isolates. *Applied & Environmental Microbiology*, *73*, 6566–6576. https://doi.org/10.1128/AEM.01086-07

Dupont, N., Diness, L. H., Fertner, M., Kristensen, C. S., & Stege, H. (2017). Antimicrobial reduction measures applied in Danish pig herds following the introduction of the "Yellow Card" antimicrobial scheme. *Preventive Veterinary Medicine*, *138*, 9–16. https://doi.org/10.1016/j.prevetmed.2016.12.019

Dutil, L., Irwin, R., Finley, R., Ng, L. K., Avery, B., Boerlin, P., … Pillai, D. R. (2010). Ceftiofur resistance in *Salmonella enterica* serovar Heidelberg from chicken meat and humans, Canada. *Emerging Infectious Diseases*, *16*, 48–54. https://doi.org/10.3201/eid1601.090729

ECDC (European Centre for Disease Prevention and Control), EFSA (European Food Safety Authority) & EMA (European Medicines Agency) (2017). ECDC/EFSA/EMA second joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals-Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report. *EFSA Journal*, *15*, 4872–5007. https://doi.org/10.2903/j.efsa.2017.4872

Endtz, H. P., Ruijs, G. J., van Klingeren, B., Jansen, W. H., van der Reyden, T., & Mouton, R. P. (1991). Quinolone resistance in *Campylobacter* isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. *The Journal of Antimicrobial Chemotherapy*, *27*, 199–208. https://doi.org/10.1093/jac/27.2.199

Fertner, M., Toft, N., Martin, H. L., & Boklund, A. (2016). A register-based study of the antimicrobial usage in Danish veal calves and young bulls. *Preventive Veterinary Medicine*, *131*, 41–47. https://doi.org/10.1016/j.prevetmed.2016.07.004

Funk, J. A., Lejeune, J. T., Wittum, T. E., & Rajala-Schultz, P. J. (2006). The effect of subtherapeutic chlortetracycline on antimicrobial resistance in the fecal flora of swine. *Microbial Drug Resistance-Mechanisms Epidemiology & Disease*, *12*, 210–218. https://doi.org/10.1089/mdr.2006.12.210

Garner, M. J., Carson, C., Lingohr, E. J., Fazil, A., Edge, V. L., & Trumble Waddell, J. (2015). An assessment of antimicrobial resistant disease threats in Canada. *PLoS One*, *10*(4), e0125155. https://doi.org/10.1371/journal.pone.0125155

Government of Canada (2015). Federal action plan on antimicrobial resistance and use in Canada. Building on the federal framework for action. Retrieved January 29, 2018 from https://publications.gc.ca/collections/collection_2016/aspc-phac/HP40-141-2015-eng.pdf

Gupta, A., Nelson, J. M., Barrett, T. J., Tauxe, R. V., Rossiter, S. P., Friedman, C. R. … NARMS Working Group. (2004). Antimicrobial resistance among *Campylobacter* strains, United States, 1997–2001. *Emerging Infectious Diseases*, *10*, 1102–1109. https://doi.org/10.3201/eid1006.030635

Han, F. F., Lestari, S. I., Pu, S. H., & Ge, B. L. (2009). Prevalence and antimicrobial resistance among *Campylobacter* spp. in Louisiana retail chickens after the enrofloxacin ban. *Foodborne Pathogens and Disease*, *6*, 163–171. https://doi.org/10.1089/fpd.2008.0171

Hao, H., Sander, P., Iqbal, Z., Wang, Y., Cheng, G., & Yuan, Z. (2016). The risk of some veterinary antimicrobial agents on public health associated with antimicrobial resistance and their molecular basis. *Frontiers in Microbiology*, *7*, 1626. https://doi.org/10.3389/fmicb.2016.01626

Helke, K. L., McCrackin, M. A., Galloway, A. M., Poole, A. Z., Salgado, C. D., & Marriott, B. P. (2017). Effects of antimicrobial use in agricultural animals on drug-resistant foodborne salmonellosis in humans: A systematic literature review. *Critical Reviews in Food Science and Nutrition*, *57*, 472–488. https://doi.org/10.1080/10408398.2016.1230088

Hermans, D., Van Deun, K., Messens, W., Martel, A., Van Immerseel, F., Haesebrouck, F., … Pasmans, F. (2011). *Campylobacter* control in poultry by current intervention measures ineffective: Urgent need for intensified fundamental research. *Veterinary Microbiology*, *152*(3–4), 219–228. https://doi.org/10.1016/j.vetmic.2011.03.010

Hill, A. A., Simons, R. L., Swart, A. N., Kelly, L., Hald, T., & Snary, E. L. (2016). Assessing the effectiveness of on-farm and abattoir interventions in reducing pig meat-borne salmonellosis within E.U. member states. *Risk Analysis*, *36*, 546–560. https://doi.org/10.1111/risa.12568

Hoelzer, K., Wong, N., Thomas, J., Talkington, K., Jungman, E., & Coukell, A. (2017). Antimicrobial drug use in food-producing animals and associated human health risks: What, and how strong, is the evidence? *BMC Veterinary Research*, *13*, 1–38. https://doi.org/10.1186/s12917-017-1131-3

Horigan, V., Kosmider, R. D., Horton, R. A., Randall, L., & Simons, R. R. L. (2016). An assessment of evidence data gaps in the investigation of possible transmission routes of extended spectrum β-lactamase producing *Escherichia coli* from livestock to humans in the UK. *Preventive Veterinary Medicine*, *124*, 1–8. https://doi.org/10.1016/j.prevetmed.2015.12.020

Hurd, H. S., Vaughn, M. B., Holtkamp, D., Dickson, J., & Warnick, L. (2010). Quantitative risk from fluoroquinolone-resistant *Salmonella* and *Campylobacter* due to treatment of dairy heifers with enrofloxacin for bovine respiratory disease. *Foodborne Pathogens and Disease*, *7*, 1305–1322. https://doi.org/10.1089/fpd.2010.0550

Jüni, P., Holenstein, F., Sterne, J., Bartlett, C., & Egger, M. (2002). Direction and impact of language bias in meta-analyses of controlled trials: Empirical study. *International Journal of Epidemiology*, *31*, 115–123. https://doi.org/10.1093/ije/31.1.115

Kanwar, N., Scott, H. M., Norby, B., Loneragan, G. H., Vinasco, J., McGowan, M., … Boerlin, P. (2013). Effects of ceftiofur and chlortetracycline treatment strategies on antimicrobial susceptibility and on *tet*(A), *tet*(B), and bla_{CMY-2} resistance genes among *E. coli* isolated from the feces of feedlot cattle. *PLoS One*, *8*, e80575. https://doi.org/10.1371/journal.pone.0080575

Lassok, B., & Tenhagen, B. A. (2013). From pig to pork: Methicillin-resistant *Staphylococcus aureus* in the pork production chain. *Journal of Food Protection*, *76*, 1095–1108. https://doi.org/10.4315/0362-028X.JFP-12-341

Lava, M., Schüpbach-Regula, G., Steiner, A., & Meylan, M. (2016). Antimicrobial drug use and risk factors associated with treatment incidence and mortality in Swiss veal calves reared under improved welfare conditions. *Preventive Veterinary Medicine*, *126*, 121–130. https://doi.org/10.1016/j.prevetmed.2016.02.002

Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A., Wertheim, H., Sumpradit, N., … Goossens, H. (2013). Antibiotic resistance - the need for global solutions. *The Lancet*, *13*, 1057–1098. https://doi.org/10.1016/S1473-3099(13)70318-9

Lewis, C., Kathe Bjork, C., Carolee Carson, C., Hungerford, L., Beth Karp, C., Cristina Lanzas, O., … Gröhn, Y. T. (2016). A proposed analytic framework for determining the impact of an antimicrobial resistance intervention at the National level. A report from the NIMBioS working group on modeling antimicrobial resistance intervention. Retrieved January 28 from https://www.nimbios.org/ifiles/WG_amr_report.pdf

Lowrance, T. C., Loneragan, G. H., Kunze, D. J., Platt, T. M., Ives, S. E., Scott, H. M., … Brashears, M. M. (2007). Changes in antimicrobial susceptibility in a population of *Escherichia coli* isolated from feedlot cattle administered ceftiofur crystalline-free acid. *American Journal of Veterinary Research*, *68*, 501–507. https://doi.org/10.2460/avjr.68.5.501

Mather, A. E., Matthews, L., Mellor, D. J., Reeve, R., Denwood, M. J., Boerlin, P., … Reid, S. W. J. (2012). An ecological approach to assessing the epidemiology of antimicrobial resistance in animal and human populations. *Proceedings of the Royal Society B: Biological Sciences*, *279*, 1630–1639. https://doi.org/10.1098/rspb.2011.1975

McEwen, S. A. (2012). Quantitative human health risk assessments of antimicrobial use in animals and selection of resistance: A review of publicly available reports. *Revue Scientifique Et Technique (International Office of Epizootics)*, *31*, 261–276. https://doi.org/10.20506/rst.31.1.2116

Moher, D., Pham, B., Lawson, M. L., & Klassen, T. P. (2003). The inclusion of reports of randomised trials published in languages other than English in systematic reviews. *Health Technology Assessment (Winchester, England)*, *7*, 1–90. https://doi.org/10.3310/hta47410

Mollenkopf, D. F., Cenera, J. K., Bryant, E. M., King, C. A., Kashoma, I., Kumar, A., … Wittum, T. E. (2014). Organic or antibiotic-free labeling does not impact the recovery of enteric pathogens and antimicrobial-resistant *Escherichia coli* from fresh retail chicken. *Foodborne Pathogens and Disease*, *11*, 920–929. https://doi.org/10.1089/fpd.2014.1808

Morley, P. S., Dargatz, D. A., Hyatt, D. R., Dewell, G. A., Patterson, J. G., Burgess, B. A., & Wittum, T. E. (2011). Effects of restricted antimicrobial exposure on antimicrobial resistance in fecal *Escherichia coli* from feedlot cattle. *Foodborne Pathogens & Disease*, *8*(1), 87–98. https://doi.org/10.1089/fpd.2010.0632

Murphy, C. P., Fajt, V. R., Scott, H. M., Foster, M. J., Wickwire, P., & McEwen, S. A. (2016). Scoping review to identify potential non-antimicrobial interventions to mitigate antimicrobial resistance in commensal enteric bacteria in North American cattle production systems. *Epidemiology and Infection*, *144*, 1–18. https://doi.org/10.1017/S0950268815000722

Newell, D. G., Koopmans, M., Verhoef, L., Duizer, E., Aidara-Kane, A., Sprong, H., … Kruse, H. (2010). Food-borne diseases - The challenges of 20 years ago still persist while new ones continue to emerge. *International Journal of Food Microbiology*, *139*, S3–S15. https://doi.org/10.1016/j.ijfoodmicro.2010.01.021

Nguyen, V. T., Carrique-Mas, J. J., Ngo, T. H., Ho, H. M., Ha, T. T., Campbell, J. I., … Schultsz, C. (2015). Prevalence and risk factors for carriage of antimicrobial-resistant Escherichia coli on household and small-scale chicken farms in the Mekong Delta of Vietnam. *The Journal of Antimicrobial Chemotherapy*, *70*, 2144–2152. https://doi.org/10.1093/jac/dkv053

Persoons, D., Haesebrouck, F., Smet, A., Herman, L., Heyndrickx, M., Martel, A., … Dewulf, J. (2011). Risk factors for ceftiofur resistance in *Escherichia coli* from Belgian broilers. *Epidemiology & Infection*, *139*, 765–771. https://doi.org/10.1017/s0950268810001524

Price, L. B., Johnson, E., Vailes, R., & Silbergeld, E. (2005). Fluoroquinolone-resistant *Campylobacter* isolates from conventional and antibiotic-free chicken products. *Environmental Health Perspectives*, *113*, 557–560. https://doi.org/10.1289/ehp.7647

Price, L. B., Lackey, L. G., Vailes, R., & Silbergeld, E. (2007). The persistence of fluoroquinolone-resistant *Campylobacter* in poultry production. *Environmental Health Perspectives*, *115*(7), 1035–1039. https://doi.org/10.1289/ehp.10050

Sahin, O., Kassem, I. I., Shen, Z., Lin, J., Rajashekara, G., & Zhang, Q. (2015). *Campylobacter* in poultry: Ecology and potential interventions. *Avian Diseases*, *59*, 185–200. https://doi.org/10.1637/11072-032315-review

Sánchez, M. X., Fluckey, W. M., Brashears, M. M., McKee, S. R., Sanchez, M. X., Fluckey, W. M., … McKee, S. R. (2002). Microbial profile and antibiotic susceptibility of *Campylobacter spp*. and *Salmonella spp*. in broilers processed in air-chilled and immersion-chilled environments. *Journal of Food Protection*, *65*, 948–956. https://doi.org/10.4315/0362-028x-65.6.948

Sapkota, A. R., Kinney, E. L., George, A., Hulet, R. M., Cruz-Cano, R., Schwab, K. J., … Joseph, S. W. (2014). Lower prevalence of antibiotic-resistant *Salmonella* on large-scale U.S. conventional poultry farms that transitioned to organic practices. *The Science of the Total Environment*, *476–477*, 387–392. https://doi.org/10.1016/j.scitotenv.2013.12.005

Sargeant, J. M., & O'Connor, A. M. (2014a). Study designs and systematic reviews of interventions: Building the evidence across study designs. *Zoonoses and Public Health*, *61*, 10–17. https://doi.org/10.1111/zph.12127

Sargeant, J. M., & O'Connor, A. M. (2014b). Introduction to systematic reviews in animal agriculture and veterinary medicine. *Zoonoses and Public Health*, *61*, 3–9. https://doi.org/10.1111/zph.12128

Singer, R. S., Ward, M. P., & Maldonado, G. (2006). Can landscape ecology untangle the complexity of antibiotic resistance? *Nature Reviews Microbiology*, *4*, 943–952. https://doi.org/10.1038/nrmicro1553

Smith, J. L., Drum, D. J. V., Dai, Y., Kim, J. M., Sanchez, S., Maurer, J. J., … Lee, M. D. (2007). Impact of antimicrobial usage on antimicrobial resistance in commensal *Escherichia coli* strains colonizing broiler chickens. *Applied & Environmental Microbiology*, *73*, 1404–1414. https://doi.org/10.1128/AEM.01193-06

So, A. D., Shah, T. A., Roach, S., Chee, Y. L., & Nachman, K. E. (2015). An integrated systems approach is needed to ensure the sustainability of antibiotic effectiveness for both humans and animals. *Journal of Law, Medicine and Ethics*, *43*, 38–45. https://doi.org/10.1111/jlme.12273

Soon, J. M., Chadd, S. A., & Baines, R. N. (2011). *Escherichia coli* O157:H7 in beef cattle: On farm contamination and pre-slaughter control methods. *Animal Health Research Reviews*, *12*, 197–211. https://doi.org/10.1017/S1466252311000132

Soonthornchaikul, N., Garelick, H., Jones, H., Jacobs, J., Ball, D., & Choudhury, M. (2006). Resistance to three antimicrobial agents of *Campylobacter* isolated from organically- and intensively-reared chickens purchased from retail outlets. *International Journal of Antimicrobial Agents*, *27*, 125–130. https://doi.org/10.1016/j.ijantimicag.2005.09.020

Stapleton, K., Cawthraw, S. A., Cooles, S. W., Coldham, N. G., la Ragione, R. M., Newell, D. G., & Ridley, A. M. (2010). Selecting for development of fluoroquinolone resistance in a *Campylobacter jejuni* strain 81116 in chickens using various enrofloxacin treatment protocols. *Journal of Applied Microbiology*, *109*, 1132–1138. https://doi.org/10.1111/j.1365-2672.2010.04734.x

Threlfall, E. J., Day, M., de Pinna, E., Charlett, A., & Goodyear, K. L. (2006). Assessment of factors contributing to changes in the incidence of antimicrobial drug resistance in *Salmonella* enterica serotypes Enteritidis and Typhimurium from humans in England and Wales in 2000, 2002 and 2004. *International Journal of Antimicrobial Agents*, *28*, 389–395. https://doi.org/10.1016/j.ijantimicag.2006.07.009

Umaraw, P., Prajapati, A., Verma, A. K., Pathak, V., & Singh, V. P. (2017). Control of *Campylobacter* in poultry industry from farm to poultry processing unit: A review. *Critical Reviews in Food Science and Nutrition*, *57*, 659–665. https://doi.org/10.1080/10408398.2014.935847

Wagner, B. A., Straw, B. E., Fedorka-Cray, P. J., & Dargatz, D. A. (2008). Effect of antimicrobial dosage regimen on *Salmonella* and

Escherichia coli isolates from feeder swine. *Applied & Environmental Microbiology*, *74*, 1731–1739. https://doi.org/10.1128/aem.01132-07

WHO Antimicrobial resistance. Fact Sheet (2018). Retrieved January 30, 2018 from https://www.who.int/mediacentre/factsheets/fs194/en/

Young, I., Waddell, L., Sanchez, J., Wilhelm, B., McEwen, S. A., & Rajić, A. (2014). The application of knowledge synthesis methods in agri-food public health: Recent advancements, challenges and opportunities. *Preventive Veterinary Medicine*, *113*, 339–355. https://doi.org/10.1016/j.prevetmed.2013.11.009

How to cite this article: Murphy CP, Carson C, Smith BA, et al. Factors potentially linked with the occurrence of antimicrobial resistance in selected bacteria from cattle, chickens and pigs: A scoping review of publications for use in modelling of antimicrobial resistance (IAM.AMR Project). *Zoonoses Public Health*. 2018;65:957–971. https://doi.org/10.1111/zph.12515

Appendix 1

Search terms to return references for screening to identify records reporting (1) the frequency of antimicrobial resistance, and (2) the factors linked with antimicrobial resistance

((((Antimicrobial[Title/Abstract] OR Antibiotic[Title/Abstract]) AND (Resistance[Title/Abstract] OR Susceptibility[Title/Abstract])) AND (B-lactam$[All Fields] OR ("cephalosporins"[MeSH Terms] OR "cephalosporins"[All Fields] OR "cephalosporin"[All Fields]) OR ("tetracycline"[MeSH Terms] OR "tetracycline"[All Fields]) OR ("quinolones"[MeSH Terms] OR "quinolones"[All Fields] OR "quinolone"[All Fields]) OR ("fluoroquinolones"[MeSH Terms] OR "fluoroquinolones"[All Fields] OR "fluoroquinolone"[All Fields]) OR ("macrolides"[MeSH Terms] OR "macrolides"[All Fields] OR "macrolide"[All Fields]) OR ("nalidixic acid"[MeSH Terms] OR ("nalidixic"[All Fields] AND "acid"[All Fields]) OR "nalidixic acid"[All Fields]) OR ("ciprofloxacin"[MeSH Terms] OR "ciprofloxacin"[All Fields] OR ("enrofloxacin" [MeSH Terms] OR "enrofloxacin" [All Fields])))) AND (cow$[Title/Abstract] OR cattle[Title/Abstract] OR beef[Title/Abstract] OR dairy[Title/Abstract] OR pig$[Title/Abstract] OR sow$[Title/Abstract] OR piglet$[Title/Abstract] OR pork[Title/Abstract] OR chicken$[Title/Abstract] OR broiler$[Title/Abstract] OR chick$[Title/Abstract] OR horse$[Title/Abstract] OR turkey$ss[Title/Abstract] OR human$[Title/Abstract] OR foal$[Title/Abstract] OR cat$[Title/Abstract] OR dog$[Title/Abstract] OR sheep[Title/Abstract] OR lamb$[Title/Abstract] OR goat$[Title/Abstract] OR fish[Title/Abstract] OR rabbit$[Title/Abstract] OR people[Title/Abstract] OR adult$[Title/Abstract] OR children[Title/Abstract] OR kid$[Title/Abstract])) AND (E. coli[Title/Abstract] OR Escherichia coli [Title/Abstract] OR Salmonella[Title/Abstract] OR Campylobacter[Title/Abstract])