

Identifying Research Gaps for the Role of the Environment in transmission of Antimicrobial-Resistant *Escherichia coli* in Cow-Calf Operations in North America: A Scoping Review Protocol.

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Introduction

Background

Escherichia coli (*E.coli*) is a gram negative rod-shaped bacteria which is found in the intestines of people, animals and in the environment. *E.coli* is also found in food and untreated water. Antimicrobial use in animal production against bacteria such as *E. coli* is essential for maintaining animal health. However, increased antimicrobial use poses the risk of contributing to the problem of antimicrobial resistance. Antimicrobial resistance occurs when microorganisms selectively develop mechanisms to protect themselves from the effects of antimicrobial compounds. Antimicrobial resistance is a One Health concern as it impacts animal, human and ecosystem health.

In North America, the term cow-calf production refers to cattle raised exclusively or largely on pasture, having a grass- or hay-based diet, and which may consume a low amount of concentrate diet, producing an annual crop of calves. The calves are intended for beef production and are usually backgrounded on pasture or backgrounding lots and then finished with a high concentrate diet in feedlots. Although

this literature review is not restricted to North America, information retrieved will be discussed in relation to cow-calf operations in North America. For the purpose of this scoping review, the term “environment” will refer to environmental features such as: manure, wildlife, soil, insects, and water sources. By including these search terms, the scoping review will identify environmental reservoirs that have been shown to impact the transmission of antimicrobial-resistant *E. coli* in cow-calf operations.

Our aim is to conduct a scoping review of the evidence regarding the role of the environment in the transmission and maintenance of antimicrobial-resistant *E. coli* within cow-calf operations. This study will identify gaps in knowledge regarding the reservoirs and transmission of antimicrobial-resistant *E. coli* in cow-calf operations (2). Because the mechanisms of maintenance and transmission of antimicrobial resistance in the environment are obscure, this scoping review will aid in determining the quantity and nature of information that presently exists in this field, and aid in identifying directions for future research (3). The review will be conducted between July 1, 2021 and August 31, 2021.

Objectives

The objective of this study is to conduct a scoping review to determine the extent of current research in the field, to identify gaps in knowledge and to inform future research studies on the role of the environment in the maintenance and transmission of antimicrobial-resistant *E. coli* in cow calf operations in the North American context.

Review questions

What is the evidence that the production environment as represented by: manure, soil, wildlife, water, plays a role in the maintenance and transmission of antimicrobial-resistant *E. coli* or genes in cow-calf production systems?

Sub-questions:

- What environmental samples provide evidence for transmission of *E. coli* in cow-calf production?
- What is the molecular biology, epidemiology or statistical modelling evidence of transmission of *E. coli* in cow-calf production?

Methods

The study will be conducted using the scoping review framework as outlined by Arksey and O'Malley (1). The research question was developed using the population, concept, context (PCC) framework. To investigate the research question a multi-disciplinary team which included a librarian (HG), an epidemiologist (SC), and a veterinary microbiologist (KL) designed this scoping review according to the PRISMA-ScR extension for scoping reviews (4). The guidelines in the JBI Reviewer Manual were followed (5). This protocol will be registered through open-access deposition in the University of Calgary's Digital Repository PRISM. Amendments to the protocol will be recorded in PRISM and reported in the scoping review manuscript.

A comprehensive literature search will be performed using the following databases: CAB Abstracts, MEDLINE, Embase, BIOSIS Previews, and the Web of Science Core Collection (Science Citation Index and Emerging Sources Citation Index). Primary studies in peer-reviewed journals and grey literature such as data published on government websites will be included. Grey literature including conference abstracts, theses and dissertations will be excluded. Database records of articles retrieved for this study will be imported into the Covidence online platform (Veritas Health Innovation, Melbourne, Australia). The Covidence Extraction tool 2.0 will be used for data extraction and data will be exported into Excel. Abstract and full article screening will be recorded in Covidence. One reviewer will conduct the literature search and import of results into Covidence (HG). Two independent primary reviewers will perform title, abstract, and full article screening in parallel (PM, SL). Two other independent reviewers will conduct secondary screening of the extracted results (SC, KL). The concordance among reviewers will be evaluated by random selection of citations at the title and abstract stages of the process as measured by Covidence. The preferred reporting items for systematic reviews and meta-analysis extension for scoping review (PRISMA-ScR) will be used to present the study results. The results will be discussed in a North American context.

Search strategy

The population, concept, context (PCC) framework was used to develop the research question and the search strategy.

- Population: Antimicrobial-resistant *Escherichia coli* isolated from beef cattle, wildlife, soil, water, feed, insects
- Context: Cow-calf operations
- Concept: Evidence of transmission of antimicrobial-resistant *E. coli* through use of whole-genome sequencing, MLST, strain typing methods, plasmid analysis, plasmid transfer, other molecular biology or epidemiological methods

Search

The CAB Abstracts search strategy is outlined in Appendix 1. This strategy will be translated to the syntax of the other databases.

The search strategy will incorporate controlled vocabulary and keywords related to the following concepts:

- Beef cattle
- *E. coli*
- Antimicrobial resistance
- Transmission
- Environmental factors such as agriculture, manure, feed, water, soil and wildlife

Environmental factors are often studied independently of beef cattle and may also examine antimicrobial-resistant genes that are not specific to *E. coli*. For this

reason, our search strategy contains two separate searches, combined with OR at the end:

- The first search is a combination of the concepts of beef cattle OR environmental factors (soil, water, manure, animals) OR farming/agriculture AND E. coli AND antibiotic/antimicrobial resistance AND transmission. This ensures we capture the broadest set of articles related to AMR-resistant E. coli in contexts that may not be specifically agricultural but may affect beef cow-calf operations.
- The second search is a combination of the concepts of beef cattle OR environmental factors (soil, water, manure, animals) AND antibiotic/antimicrobial resistance AND transmission AND agriculture or farming or farmland (without the concept of e. coli, as many of the papers we found on the spread of resistant genes in agriculture did not mention e. coli.). We ANDed agriculture in this case because we are interested specifically in this context, and with the removal of the concept of E. coli, the search was impossibly broad.

Inclusion Criteria

- Full text available in English
- Publication date is after 1985
- Article relevant to cow-calf production
- Article describes E. coli from environmental samples
- Article describes data relevant to transmission of *E.coli*

Exclusion Criteria

- Full text is not available in English
- Articles was published prior to 1985
- Article relates to feedlot cattle alone
- Article relates to Dairy cattle alone
- Cattle are not raised on pasture or grass-fed
- Article is not relevant to cow-calf production
- Article does not describe data relevant to transmission
- Article does not describe *E. coli*

Data Extraction

Data obtained will be extracted using COVIDENCE and exported into EXCEL. Two independent reviewers will conduct data extraction. Disagreements will be resolved by another independent reviewer.

Table 1.0: Variables for data extraction; Covidence tags

Variable	Input Data Structure
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Location of study	Country
Cow-calf production	Descriptive terms
Bacteria type E. coli	yes/no
Sample type environmental	Manure, soil, water, feed, insect, wildlife, bird, other
Antimicrobial susceptibility testing (AST) method	Estrip, microbroth dilution, disc diffusion
Molecular strain-typing method	MLST, WGS, PFGE, PCR, Genomics, other
WGS platform type	Illumina, MiSeq, other
Statistical analysis performed	Association, correlation, ANOVA, modeling, other
Resistant E. coli transmission assessment method	Strain-typing, PFGE, WGS, metagenomics, PCR, statistical modeling, plasmid typing, plasmid transfer, other
Laboratory methods for evidence for transmission	Molecular biology, PFGE, strain-typing, WGS, metagenomics, statistical modeling, plasmid typing, plasmid transfer, other
Stated key findings of study	Evidence for transmission of resistant E. coli, evidence for transmission of resistance plasmids in E. coli, evidence for role of environment in transmission of E. coli, evidence for role of environment in maintenance of resistant E. coli

Data Analysis and Presentation

The Arksey and O'Malley scoping review framework will be used for charting the data, and for collating, summarizing, and reporting the results of the study. Quality assessment of the articles included in the review will be conducted as per GRADE criteria.

References

1. Arksey, H., & O'Malley, L. (2005). Scoping studies: Towards a methodological framework. *International Journal of Social Research Methodology*, 8(1), 19-32.
2. Sucharew, H., Macaluso, M. (2019). Methods for research evidence synthesis: The scoping review Approach. *J. Hosp. Med.* 14(7), 416-418.
3. Larsson, D., Andremont, A., Bengtsson-Palme, J., Koefoed Brant, K., et al. (2018). Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance. *Environ. Int.*, 117, 132-138.

4. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med.* (2018) 169:467–73. doi: 10.7326/M18-0850
5. Aromataris E, Munn Z. *Joanna Briggs Institute Reviewer's Manual*. Adelaide, SA: Joanna Briggs Institute (2017).

Appendix 1. Scoping review search strategy.

#	Query	Limiters/Expanders	Last Run Via	Results
S20	S18 OR S19	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	5,577
S19	S5 AND S8 AND S14 AND S17	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	2,897
S18	(S5 or S8) AND (S11 AND S14 AND S17)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	3,425
S17	S15 OR S16	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	2,417,835
S16	TI (transmi* or transfer* or spread* or disseminat* or dispers* or infect* or environment* or exposure* or "gen* relat*" or "gene spread") OR AB (transmi* or transfer* or spread* or disseminat* or dispers* or infect* or environment* or exposure* or "gen* relat*" or "gene spread")	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	2,405,018
S15	DE "disease transmission" OR DE "infection"	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced	90,934

			Search Database - CAB Abstracts	
S14	S12 OR S13	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	56,076
S13	TI ((antibiotic* or antimicrobial*) N3 (resistan* OR toleran*) OR AB ((antibiotic* or antimicrobial*) N3 (resistan* OR toleran*))	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	35,599
S12	(DE "drug resistance" OR DE "multiple drug resistance") AND (DE "antiinfective agents" OR DE "antibacterial agents" OR DE "antibiotics")	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	41,465
S11	S9 OR S10	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	132,552
S10	TI ("escherichia coli" OR "e. coli") OR AB ("escherichia coli" OR "e. coli")	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	123,779
S9	DE "Escherichia coli" OR DE "Escherichia coli infections"	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	106,397
S8	S6 OR S7	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	982,816
S7	TI (agricultur* OR farm*) OR AB (agricultur* OR farm*)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced	974,461

			Search Database - CAB Abstracts	
S6	(DE "farms" OR DE "agricultural land") OR (DE "agriculture")	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	70,042
S5	S1 OR S2 OR S3 OR S4	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	3,693,251
S4	TI (manure or environment or feed or feedstuff* or water or soil or wildlife or deer or bird* or goose or geese or duck* or gull* or rodent* or mouse or mice or rat or rats or fly or flies or insect*) OR AB (manure or environment or feed or feedstuff* or water or soil or wildlife or deer or bird* or goose or geese or duck* or gull* or rodent* or mouse or mice or rat or rats or fly or flies or insect*)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	3,296,807
S3	(DE "farmyard manure" OR DE "animal manures" OR "cattle manure" OR DE "poultry manure" OR DE "sheep manure" OR DE "feeds")	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	131,417
S2	TI ((beef OR suckler* OR cattle OR cow* OR heifer* OR steer* OR stocker* OR bull* OR "cow-calf") OR AB (beef OR suckler* OR cattle OR cow* OR heifer* OR steer* OR	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	506,139

stocker* OR bull* OR
"cow-calf"))

S1

(DE "beef cattle" OR DE
"beef herds" OR DE
"suckler herds")

Search modes - Find all
my search terms

Interface - EBSCOhost
Research Databases
Search Screen - Advanced
Search
Database - CAB Abstracts

26,269