

FACTORS ASSOCIATED WITH ANTIMICROBIAL-RESISTANT ENTEROCOCCI IN NORTH AMERICAN BEEF CATTLE: A SCOPING REVIEW PROTOCOL

AUTHORS:

Kayla Strong^{1,2*}, Kaitlin Marasco¹, Jesse Invik¹, Heather Ganshorn³, Richard J. Reid-Smith^{2,4,5}, Cheryl Waldner⁶, Simon J. G. Otto^{2,7}, Brennan Chapman⁵, Sylvia Checkley^{1,2}

¹University of Calgary, Faculty of Veterinary Medicine

²AMR - One Health Consortium

³University of Calgary, Libraries and Cultural Resources

⁴Public Health Agency of Canada, Centre for Food-borne, Environmental and Zoonotic Infectious Diseases

⁵University of Guelph, Department of Population Medicine

⁶University of Saskatchewan, Western College of Veterinary Medicine

⁷University of Alberta, School of Public Health

*Corresponding Author

kayla.strong@ucalgary.ca

The University of Calgary, Faculty of Veterinary Medicine 3280 Hospital Dr. NW Calgary, Alberta T2N 4Z6.

KS will be the primary reviewer and JI will be the second reviewer, blind to the others assessment. SC will be the third reviewer in case of conflict. KS will be the primary author of the article. All co-authors will review and edit the article before submission. SC is the Principle Investigator of the MIF sub-grant and NSERC discovery grant.

ABSTRACT

Introduction: *Enterococcus* spp. is a commensal gram-positive bacterium routinely found in humans and bovines' intestinal tracts; however, it can lead to infection when found outside the intestinal tract.¹ There is increasing difficulty in treating Enterococcal infections due to a rise in resistance, particularly multidrug resistance.² The rise of antimicrobial resistance is a One Health problem resulting from antimicrobial use in human health, animal health, and the environment.³ This research focuses on the connection between animal and human health, and considers the epidemiology of antimicrobial resistance within the North American beef cattle production system. The research will identify factors associated with antimicrobial

resistance in *Enterococcus* spp. from cow-calf operations up to but not including human beef consumption. This project is a component of the broader iAM.AMR initiative.ⁱ

Objectives: The primary objective is to identify what factors increase or decrease the prevalence of antimicrobial resistance in *Enterococcus* spp. within the North American Beef Cattle Industry, from cow-calf operations to the retail setting. The results will populate a component of an integrated assessment model as a component of the Integrated Assessment Model on Antimicrobial Resistance (iAM.AMR) project, built using Analytica software (Educational Professional license, Lumina)

Methods: A double-blinded scoping review following PRISMA guidelines will examine five databases (MEDLINE, BIOSIS Previews, the Web of Science Science Citation Index and Emerging Sources Citation Index, Embase, and CAB Abstracts). The search will consider *Enterococcus* spp., Antimicrobials, Resistance, beef cattle, and search term variants. Articles identified will be screened at three primary stages: bibliography, title and abstract, and full text. The authors will exclude articles published before 1984 (*Enterococcus* spp. was designated a species in 1984), journals specific to a livestock species that is not beef cattle, and non-English articles. Articles that are solely *In vitro*, specific to fermented meat, opinion-based, or not applicable to the North American context will also be excluded. Articles will be included if there is an intervention identified and the AMR impact of the intervention measured. Article information will be charted in an excel spreadsheet.

Following the charting process, authors will identify articles to be included in the iAM.AMR Collection of Epidemiologically Derived Associations with Resistance (CEDARS) database. These articles must have an extractable "factor" associated with AMR *Enterococcus* spp, presented as an odds ratio or prevalence comparison (in text or graph) specific to an "intervention" and "control." The study must use non-selective media and have the total (N) provided for the intervention and control. Relevant data will be collected and coded into an Access (V2103, Microsoft) database. Meta-analysis will occur if two articles examine the same factor and are comparable in the research design and study population.

REVIEW QUESTION

What factors increase or decrease the prevalence of antimicrobial resistance in *Enterococcus* spp. within the North American Beef Cattle Industry, from cow-calf operations to the retail setting.

METHODS

Search Strategy

MEDLINE, BIOSIS Previews, Web of Science's Science Citation Index and Emerging Sources Citation Index, Embase, and CAB Abstracts databases will be searched using controlled vocabulary and text words related to the concepts of enterococcus, beef cattle, and antimicrobial resistance. The CAB Abstracts search is illustrated in Appendix 1. This search will be translated to the other databases.

Study Selection

Authors will begin by removing duplicate articles. Studies will undergo three stages of screening:

Bibliography Screening:

Based on bibliographic information, the authors will exclude the following articles:

- Article published before 1984
 - o *Enterococcus* spp. was designated a species in 1984.
- Journal specific to non-beef cattle
 - o Given the search criteria, we include several general bovine terms which select dairy cattle and beef cattle. Dairy cattle have a different antimicrobial risk profile than beef cattle and are raised in a distinctly different environment. Given the number of differences between the livestock, the authors have chosen to remove dairy cattle-specific journals. Additionally, journals specific to other species (i.e. swine, ovine, and avian sciences) will be removed.
- Articles not in English
 - o The authors will only consider articles in English. The target population is the North American Beef industry, which predominantly publishes in English. There are insufficient research resources within this project to examine articles not published in English.

Title and Abstract Screening

Title and abstract screening will be conducted double-blinded.

- Title or abstract must include Enterococcus*, Antimicrobial* Resistance*, Beef Cattle*
 - o *For each term, different variants of the word will also be accepted. For example, "Beef Cow," "Beef Heifer," "Beef Steer," and "Beef Calf" are all appropriate alternatives to "Beef Cattle."
- Include only field trial articles. If unsure, include the article and assess in the full-text screening.
- Exclude articles specific to fermented meat. If unsure, include the article and assess in the full-text screening.

Full-Text Screening

The full-Text screening will be conducted double-blinded.

- Include only field trial articles.
- Exclude articles specific to fermented meat.
- Conference abstracts are excluded.

- The authors assume that substantial conference abstracts will be later published as an article and collected in the scoping review process. The authors limit the material included in the review to peer-reviewed publications.
- Include articles with an intervention identified and the *Enterococcus* spp. AMR impact of the intervention measured.
 - Examples of measurements may include AMR prevalence, CFU counts, Odds Ratio.
- Include only articles which apply to the Canadian context. If the research was conducted outside of North America, exclude articles which present substantially different cattle rearing practice than those found in the North American market (Cow-Calf (and optional feedlot), Abattoir, Retail), or those who have adopted substantially different antimicrobial stewardship practices.

Data Extraction: EXCEL

Data input will be conducted double-blinded by two reviewers and compared for consistency and error detection at the end. A third reviewer will address conflicts. Authors will extract data into an Excel spreadsheet, supported by Google Forms. A listing of fields to be collected is listed in Appendix 2.

Data Extraction: CEDAR

Following data charting, authors will review included articles and evaluate their suitability to be included in the CEDAR Database.⁴ CEDAR was developed by the iAM.AMR project and is used as the central repository for epidemiological data collected for use in the iAM.AMR project. In addition to the screening criteria used in the scoping review, articles must have an extractable intervention, referred to as a "factor"ⁱⁱ associated with AMR *Enterococcus* spp, presented as an odds ratio or prevalence comparison (in text or graph) specific to the "intervention" and "control." The study must use non-selective media and have the total (N) provided for the intervention and control. Relevant data will be collected and coded into CEDAR, stored as an Access (V2103, Microsoft) database. A listing of fields collected is listed in Appendix 3. Data input will be conducted double-blinded by two reviewers and compared for consistency and error detection at the end. A third reviewer will address conflicts.

ASSESSING CONFIDENCE OF EVIDENCE

Within the iAM.AMR project, meta-analysis will occur if two articles examine the same factor and are comparable in the research design and study population. The authors recognize the risk of bias when conducting a meta-analysis and the differing quality and scale of studies. The initial collection will utilize the checklist developed by the Alberta Heritage Foundation for Medical Research (AHFMR), "Standard quality assessment criteria for evaluating primary research papers from a variety of fields",⁶ when reviewing articles to provide a rating of the quality of evidence. Articles with a low assessment may be either removed or weighted lower within the modelling component.

DATA ANALYSIS AND PRESENTATION

There will be two separate outputs from this review:

- 1) The initial output will be a scoping review of articles summarizing data extracted and identifying interventions associated with increasing or decreasing the prevalence of antimicrobial resistance in *Enterococcus* spp. within the North American Beef Cattle Industry, from cow-calf operations to the retail setting. Authors will use this information to identify knowledge gaps in the literature and determine the range of evidence.
- 2) The secondary output will be the application of factors entered into CEDARS. Authors will process the results from CEDAR using an iAM.AMR developed software package (Sawmill R package⁷) and provide factor-specific odds ratio estimates based on the reported rate table, contingency table, relative risk, or odds ratio. Meta-Analysis will be performed per the iAM.AMR project guidelines.⁴ Findings will be reflected within the integrated assessment model, intended for a secondary publication.

FUNDING

This research is part of the AMR – One Health Consortium, funded by the Major Innovation Fund program of the Ministry of Jobs, Economy and Innovation, Government of Alberta. This project is also funded in part by NSERC and the Genomics Research and Development Initiative Interdepartmental Project on AMR (GRDI-AMR).

ACKNOWLEDGEMENT

We wish to thank Dr. Colleen Murphy and Charly Phillips for their support and guidance in the iAM.AMR project and Dr. Carl Ribble for useful discussions.

REFERENCES

1. Arias, C. A. & Murray, B. E. The rise of the Enterococcus: beyond vancomycin resistance. *Nat. Rev. Microbiol.* **10**, 266–278 (2012).
2. Zaheer, R. *et al.* Surveillance of Enterococcus spp. reveals distinct species and antimicrobial resistance diversity across a One-Health continuum. *Sci. Rep.* **10**, 3937 (2020).
3. McEwen, S. A. & Collignon, P. J. Antimicrobial Resistance: a One Health Perspective. *Microbiol. Spectr.* **6**, (2018).
4. iAM.AMR Team. CEDAR. *iAM.AMR*
https://docs.iam.amr.pub/en/latest/data_extraction/processing_cedar_queries.html (2021).
5. iAM.AMR Team. Literature Search. *iAM.AMR*
https://docs.iam.amr.pub/en/latest/data_extraction/search.html#what-is-a-factor (2021).
6. Kmet, L. M., Lee, R. C. & Cook, L. S. *Standard quality assessment criteria for evaluating primary research papers from a variety of fields.*
<https://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=32004000313&ID=32004000313> (2004).
7. Chapman, B. & Phillips, C. *Sawmill: Process Queries from the CEDAR Database.* (2021).

APPENDIX 1: DATABASE SEARCH STRING SAMPLE

6/4/2021

Print Search History: EBSCOhost

MY



Friday, June 04, 2021 9:42:33 PM

#	Query	Limiters/Expanders	Last Run Via	Results
S1	DE "cattle" OR DE "beef cattle" OR DE "beef herds" OR DE "suckler herds" OR DE "bulls" OR DE "calves" OR DE "cows" OR DE "heifers" OR DE "steers" OR DE "meat production" OR DE "beef production" OR DE "meat and livestock industry"	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	537,103
S2	TI ((beef OR suckler*) AND (cattle OR cow* OR heifer* OR steer* OR stocker* OR bull* OR feeder* OR "cow-calf")) OR AB ((beef OR suckler*) AND (cattle OR cow* OR heifer* OR steer* OR stocker* OR bull* OR feeder* OR "cow-calf"))	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	39,417
S3	TI ((retail OR butcher* OR grocer* OR supermarket*) AND (beef OR meat)) OR AB ((retail OR butcher* OR grocer* OR supermarket*) AND (beef OR meat))	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	6,145
S4	S1 OR S2 OR S3	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	544,879
S5	((DE "drug resistance" OR DE "multiple drug resistance") AND (DE "antibiotics" OR DE	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Advanced	14,088

	"antiinfective agents" OR DE "antibacterial agents"))		Search Database - CAB Abstracts	
S6	TI ((antimicrobial* OR antibiotic* OR "anti biotic*"OR multidrug* or "multidrug" OR microbial* ORdrug* OR antibacterial* OR bacteria* OR "multiple drug*" OR multiclass OR "multi class" OR "multiple class") n3 (resistan* or susceptib*)) OR AB ((antimicrobial* OR antibiotic* OR "anti biotic*"OR multidrug* or "multidrug" OR microbial* ORdrug* OR antibacterial* OR bacteria* OR "multiple drug*" OR multiclass OR "multi class" OR "multiple class") n3 (resistan* or susceptib*))	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	63,604
S7	S5 OR S6	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	65,601
S8	DE "Enterococcus" OR DE "Enterococcus faecalis" OR DE "Enterococcus faecium" OR DE "Enterococcus hirae"	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	17,615
S9	TI (Enterococc* or "e. faecalis" or "e. faecium" or "e. hirae") OR AB ((Enterococc* or "e. faecalis" or "e. faecium" or "e. hirae")	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	17,565
S10	S8 OR S9	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced	20,334

6/4/2021

Print Search History: EBSCOhost

S11	S4 AND S7 AND S10	Search modes - Find all my search terms	Search Database - CAB Abstracts Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CAB Abstracts	338
-----	-------------------	---	--	-----

APPENDIX 2: DATA EXTRACTION: EXCEL

Table 1: Reference Information

Variable	Input Data Structure
Author(s)	String
Year of publication	Numerical
Country and State/Province, City of origin (where the study was published or conducted)	String
Design Type	Predefined List
Aims/purpose	String
Study population	String
Sample size	Numerical
If Applicable, Source of Cattle and Supplementation Background	String
Methodology/methods	String
Enterococcus Spp.	Predefined List
Sample Source	String
Bacteria Isolation Method	String
AMS testing	String
Does the study have Explicit Breakpoints?	Predefined List
Is this breakpoint consistent with the Current CIPARS, NARMS or EUCAST breakpoint?	Predefined List
Does the study have a minimum inhibitory concentration table?	Predefined List
Intervention Type	String
Intervention Case	String
Intervention Control	String
Duration of the intervention (if applicable)	String
AMR Genes	String
AMR Gene Patterns (Multiple Resistance Reported)	String
AMR Phenotypes	String
AMR Phenotypes Patterns (Multiple Resistance Reported)	String
Key findings that relate to the scoping review question/s	String
AHFMR quality assessment value	Numerical
Usable Data for CEDARS	Predefined List
Notes	String

APPENDIX 3: DATA EXTRACTION: CEDARS

Table 2: Factor Information

Variable	Input Data Structure
Title	String
Description	String
Host	Predefined List
Microbe	Predefined List
In Text Location	String
Result Type	Predefined List
Allocated Stage	Predefined List
Observed Stage	Predefined List
Antimicrobial Resistant	Predefined List
Result or Analysis Unit	Predefined List
Odds Ratio	Numerical
Upper Odds Ratio Limit	Numerical
Lower Odds Ratio Limit	Numerical
Odds Ratio Significance	Numerical
Exposed Group Name	String
Reference Group Name	String
Count of AMR units, Exposed Group	Numerical
Count of AMR units, Reference Group	Numerical
Count of AM susceptible units, Exposed Group	Numerical
Count of AM susceptible units, Reference Group	Numerical
Total Units, Exposed Group	Numerical
Total Units, Reference Group	Numerical

Factor information can be collected from a Rate Table, Contingency table, Relative Risk, or Odds Ratio. If the odds ratio is not provided, prevalence or relative risk information will be collected and calculated as an odds ratio. Please note, there is a one-to-many relationship between factors and references. One reference can have multiple unique factors.

ⁱ iAM.AMR is a joint academic and federal initiative that uses integrated assessment models to examine Canadians' exposure to antimicrobial-resistant bacteria arising through the agri-food system. The initiative considers transmission pathways and protective and risk factors influencing the prevalence of antimicrobial resistance within Canadian livestock and aquaculture production systems. For more information, see: <https://docs.iam.amr.pub/en/latest/>

ⁱⁱ The iAM.AMR project adopts a broad definition when discussing factors and does not apply any causal relation to the term. As per project documentation: "In the context of the IAM.AMR project, we have defined a 'factor' as a practice or circumstance which influences the occurrence of AMR. This is an intentionally broad definition that does not consider the concept of causality; we consider any relationship between an exposure and outcome as a factor, whether or not we can elucidate a causal pathway"⁵