Title

Efficacy of dam vaccination for the prevention of neonatal diarrhea caused by enterotoxigenic *E. coli* in calves: protocol for a systematic review and meta-analysis

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Amendments: This review is not an amendment of a previously published protocol.

The protocol is to be registered with Systematic Reviews for Animals & Food, syreaf.org. and deposited at escholarship.org.

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Introduction:

Diarrhea in calves, also known as scours, is a common disease that negatively affects the cattle production industry. The National Animal Health Monitoring System reports that 57% of calf mortality on dairies (USDA 2010) and 16.3% on cow-calf operations is caused by calf diarrhea (USDA 2020). Scours can affect calves at various ages, between days to months old, often depending on the causative pathogen, and can cause substantial economic loss in cattle production. Enterotoxigenic *Escherichia coli* (*E. coli*) are bacteria that commonly cause diarrhea in young calves less than a week old. Infection happens through oral transmission. Diarrhea caused by this pathogen can be dangerous since it can lead to severe dehydration and electrolyte imbalance in calves (Dubreuil 2016). Prevention of calf diarrhea can be managed by multiple practices, including immunization by vaccination. Vaccinations can target either the calf or the pregnant dam in preventing calf diarrhea.

The proposed meta-analysis will examine published research to determine if vaccinations of pregnant dams against enterotoxigenic *E. coli* can prevent disease and death in neonatal calves due to ETEC. We aim to determine if there is evidence that vaccinated dams will result in lower rates of calf diarrhea, death, and bacterial shedding. The available literature shows mixed results. To our knowledge, there has been no previous meta-analysis done to determine the effectiveness of this approach to prevent calf diarrhea.

Objectives:

The primary objective of this meta-analysis is to examine available data and determine if vaccination efforts described in the literature against enterotoxigenic *E. coli* causing calf diarrhea are effective. We aim to identify the existing literature and compare the outcomes

death from neonatal diarrhea, clinical diarrhea, weight gain, and bacterial shedding in feces to determine if vaccinations given to dams have an effect on these outcomes.

This review defines the methodology with the following PICO question: In calves who are at risk of infection due to enterotoxigenic *E. coli ,* does vaccine intervention of dams lead to favorable outcomes in calves? The specific PICO elements are:

Population: Calves (regardless of commodity, i.e. dairy, beef, or unspecified purpose) up to two weeks of age

Intervention: Any vaccines used to prevent neonatal calf diarrhea due to enterotoxic *E. coli* given to dams to prevent disease in calves

Comparator: placebo or untreated control group

- **O**utcomes: Diarrhea due to ETEC, death from diarrhea due to ETEC, bacterial shedding in feces

Methods:

Search results from a previous scoping review on vaccination for the prevention of neonatal calf diarrhea in cow-calf operations will be complemented with an updated search using the same search criteria. We will eliminate articles that are not focused on enterotoxigenic *E. coli* as the target pathogen for vaccination.

Eligibility criteria

The following studies will be included:

- Original scientific reports
- All study designs except case studies or case series
- Peer Reviewed Articles or conference proceedings >500 words
- Dams vaccinated against enterotoxigenic *E. coli*
- No restriction based on use/commodity
- Published in English
- 1950 and later
- Diagnosis of ETEC through laboratory diagnostics or clinical diagnosis following challenge
- Includes outcome data on one or more: clinical diarrhea, death, bacterial shedding in feces

Information sources: A literature search to update previous results using the following databases and interfaces conducted through the Carlson Health Library at the School of Veterinary Medicine at the University of California Davis with input from other study team members.

Database	Interface
Medline	PubMed
CAB Abstracts	CAB Direct
Biosis	Web of Science

Study Records: Search results will be imported into EndNote™ (Clairvate Analytics, Philadelphia, USA) and duplicate entries removed. Resulting references will be imported into Covidence) where they undergo a second screen for duplicate entries, a 2-level screen for inclusion and data extraction.

Search strategies for the different databases used for original scoping review:

Pubmed

Search	Query
#1	(("Cattle"[Mesh] OR cattle[tiab] OR cow[tiab] OR cows[tiab] OR bos[tiab] OR bovine[tiab] OR bovines[tiab] OR bovinae[tiab] OR heifer[tiab] OR heifers[tiab] OR bullocks[tiab] OR oxen[tiab] OR steer[tiab] OR steers[tiab] OR Angus[tiab] OR Ayrshire[tiab] OR Boran[tiab] OR Brahman[tiab] OR Brangus[tiab] OR Braunvieh[tiab] OR Charolais[tiab] OR Fleckvieh[tiab] OR Friesian[tiab] OR Gelbvieh[tiab] OR Gir[tiab] OR Hereford[tiab] OR Holstein[tiab] OR Jersey[tiab] OR Limousin[tiab] OR Longhorn[tiab] OR Nellore[tiab] OR Ongole[tiab] OR Sahiwal[tiab] OR Sanga[tiab] OR Shorthorn[tiab] OR Simmental[tiab] OR Wagyu[tiab] OR beef[ti] OR herd[ti]) AND (calf[tiab] OR calves[tiab] OR calving[tiab])) OR ((calf[tiab] OR calves[tiab] OR calving[tiab]) AND ("Animals, Newborn"[Mesh] OR "Animals, Suckling"[Mesh] OR neonatal[tiab] OR newborn[tiab] OR newborns[tiab] OR "pre-wean"[tiab] OR prewean[tiab] OR "pre-weaning"[tiab] OR preweaning[tiab] OR "pre-weaned"[tiab] OR preweaned[tiab] OR nursing[tiab] OR suckling[tiab] OR "after birth"[tiab] OR "before weaning"[tiab] OR young[tiab])) OR (calf[ti] OR calf[ot] OR calves[ti] OR calves[ot])
#2	"Bovine Virus Diarrhea-Mucosal Disease"[Mesh] OR "Gastroenteritis/veterinary"[Mesh] OR "Diarrhea"[Mesh] OR diarrhea[tiab] OR diarrheic[tiab] OR diarrheal[tiab] OR diarrhoea[tiab] OR diarrhoeal[tiab] OR scour[tiab] OR scours[tiab] OR scouring[tiab] OR "fecal score"[tiab] OR "faecal score"[tiab] OR "watery feces"[tiab] OR "watery faeces"[tiab]
#3	“Escherichia coli"[Mesh] OR "Escherichia coli"[tiab] OR "E coli"[tiab] OR "Escherichia coli Infections"[Mesh] OR "Salmonella"[Mesh] OR Salmonella[tiab] OR Salmonellosis[tiab] OR Salmonelloses[tiab] OR "Salmonella Infections"[Mesh] OR "Clostridium"[Mesh] OR clostridium[tiab] OR clostridiales[tiab] OR clostridiaceae[tiab] OR clostridia[tiab] OR "Clostridium Infections"[Mesh] OR

	"Shigella"[Mesh] OR shigella[tiab] OR shigellosis[tiab] OR "shiga bacillus"[tiab] OR "Dysentery, Bacillary"[Mesh] OR "Yersinia"[Mesh:NoExp] OR "Yersinia enterocolitica"[Mesh] OR yersinia[tiab] OR yersiniosis[tiab] OR yersinioses[tiab] OR "Yersinia Infections"[Mesh] OR "Coronavirus, Bovine"[Mesh] OR coronavirus[tiab] OR coronaviruses[tiab] OR "Coronaviridae"[Mesh:NoExp] OR "Torovirus"[Mesh] OR "Torovirus Infections"[Mesh] OR toroviridae[tiab] OR torovirus[tiab] OR toroviruses[tiab] OR “Breda Virus”[tiab] OR “Berne Virus”[tiab] OR "Rotavirus"[Mesh] OR rotavirus[tiab] OR rotaviruses[tiab] OR "Rotavirus Infections"[Mesh] OR "Caliciviridae"[Mesh:NoExp] OR nebovirus[tiab] OR Neboviruses[tiab] OR "Norovirus"[Mesh:NoExp] OR norovirus[tiab] OR 599,188 Noroviruses[tiab] OR "Diarrhea Viruses, Bovine Viral"[Mesh] OR "Bovine Viral Diarrhea Virus"[tw] OR "Bovine Viral Diarrhea Viruses"[tiab] OR "Bovine Diarrhea Virus"[tiab] OR "Bovine Diarrhea Viruses"[tiab] OR "Bovine Pestivirus"[tiab] OR "Bovine Pestiviruses"[tiab] OR BVDV[tiab] OR "Cryptosporidium"[Mesh] OR cryptosporidium[tw] OR cryptosporidiums[tiab] OR "Cryptosporidiosis"[Mesh] OR cryptosporidiosis[tiab] OR cryptosporidioses[tiab] OR cryptosporidium[tiab] OR "Giardia"[Mesh] OR giardia[tw] OR giardias[tiab] OR lamblia[tiab] OR lamblias[tiab] OR lambliasis[tiab] OR lambliases[tiab] OR "Giardiasis"[Mesh] OR "fecal pathogens"[tiab] OR "fecal pathogen"[tiab] OR "faecal pathogens"[tiab] OR "faecal pathogen"[tiab]
#4	#1 AND (#2 OR #3)
#5	"Vaccines"[Mesh] OR vaccine[tiab] OR vaccines[tiab] OR "Immunization"[Mesh] OR vaccination[tiab] OR vaccinations[tiab] OR immunization[tiab] OR immunizations[tiab] OR injection[tiab] OR injected[tiab] OR injections[tiab] OR inoculation[tiab] OR inoculations[tiab] OR inoculate[tiab] OR inoculates[tiab] OR inoculated[tiab] OR ScourGuard[tiab] OR ScourBos[tiab] OR Bovilis[tiab] OR Rotavec[tiab] OR Ecolizer[tiab]
#6	#4 AND #5
#7	((calf[tiab] OR calves[tiab] OR calving[tiab]) AND "Diarrhea/prevention and control"[Mesh])
#8	#6 OR #7
#9	#8 AND English[lang]
#10	#9 NOT ("Letter" [Publication Type] OR "Editorial" [Publication Type] OR "Case Reports" [Publication Type]) AND Filters: Publication date from 1950/01/01

CAB Abstracts

Search	Search Term
#1	(od:("Bos") OR up:(bos)) AND (neonatal OR newborn OR newborns OR "pre-wean" OR prewean OR "pre-weaning" OR preweaning OR "pre-weaned" OR preweaned OR nursing OR suckling OR "after birth" OR "before weaning" OR young OR calf OR calves OR calving)
#2	title:((cattle OR cow OR cows OR bos OR bovine OR bovines OR bovinae OR heifer OR heifers OR bullocks OR oxen OR steer OR steers OR Angus OR Ayrshire OR Boran OR Brahman OR Brangus OR Braunvieh OR Charolais OR Fleckvieh OR Friesian OR Gelbvieh OR Gir OR Hereford OR Holstein OR Jersey OR Limousin OR Longhorn OR Nellore OR Ongole OR Sahiwal OR Sanga OR Shorthorn OR Simmental OR Wagyu)) OR ab:((cattle OR cow OR cows OR bos OR bovine OR bovines OR bovinae OR heifer OR heifers OR bullocks OR oxen OR steer OR steers OR Angus OR Ayrshire OR Boran OR Brahman OR Brangus OR Braunvieh OR Charolais OR Fleckvieh OR Friesian OR Gelbvieh OR Gir OR Hereford OR Holstein OR Jersey OR Limousin OR Longhorn OR Nellore OR Ongole OR Sahiwal OR Sanga OR Shorthorn OR Simmental OR Wagyu))
#3	title:((neonatal OR newborn OR newborns OR "pre-wean" OR prewean OR "pre-weaning" OR preweaning OR "pre-weaned" OR preweaned OR nursing OR suckling OR "after birth" OR "before weaning" OR young OR calf OR calves OR calving)) OR ab:((neonatal OR newborn OR newborns OR "pre-wean" OR prewean OR "pre-weaning" OR preweaning OR "pre-weaned" OR preweaned OR nursing OR suckling OR "after birth" OR "before weaning" OR young OR calf OR calves OR calving))
#4	#2 AND #3
#5	#1 OR #4
#6	diarrhea OR diarrheic OR diarrheal OR diarrhoea OR diarrhoeal OR scour OR scours OR scouring OR "fecal score" OR "faecal score" OR "watery feces" OR "watery faeces"
#7	#5 AND #6
#8	"Escherichia coli" OR "E coli" OR Salmonella OR Salmonellosis OR Salmonelloses OR clostridium OR clostridiales OR clostridiaceae OR clostridia OR shigella OR shigellosis OR "shiga bacillus" OR yersinia OR yersiniosis OR yersinioses OR coronavirus OR coronaviruses OR toroviridae OR torovirus OR toroviruses OR "Breda Virus" OR "Berne Virus" OR rotavirus OR rotaviruses OR nebovirus OR Neboviruses OR norovirus OR Noroviruses OR "Bovine Viral Diarrhea Virus" OR "Bovine Viral Diarrhea Viruses" OR "Bovine Diarrhea Virus" OR "Bovine Diarrhea Viruses" OR "Bovine Pestivirus" OR "Bovine Pestiviruses" OR BVDV OR cryptosporidium OR cryptosporidiums OR cryptosporidiosis OR cryptosporidioses OR cryptosporidium OR giardia OR giardias OR lamblia OR lamblias OR lambliasis OR lambliases OR giardiasis OR "fecal pathogens" OR "fecal pathogen" OR "faecal pathogens" OR "faecal pathogen"
#9	#5 AND #8
#10	#7 OR #9
#11	vaccine OR vaccines OR vaccination OR vaccinations OR immunization OR immunizations OR inoculation OR inoculations OR inoculate OR inoculates OR inoculated OR ScourGuard OR ScourBos OR Bovilis OR Rotavec OR Ecolizer
#12	#10 AND #11 AND yr:[1950 TO 2019] AND Language: English
#13	#12 AND Document type: Journal article OR Journal issue OR Conference proceedings OR Conference paper OR Miscellaneous OR Abstract only

BIOSIS

Search	Query
#1	TI=(cattle OR cow OR cows OR bos OR bovine OR bovines OR bovinae OR heifer OR heifers OR bullocks OR oxen OR steer OR steers OR Angus OR Ayrshire OR Boran OR Brahman OR Brangus OR Braunvieh OR Charolais OR Fleckvieh OR Friesian OR Gelbvieh OR Gir OR Hereford OR Holstein OR Jersey OR Limousin OR Longhorn OR Nellore OR Ongole OR Sahiwal OR Sanga OR Shorthorn OR Simmental OR Wagyu) OR TS=(cattle OR cow OR cows OR bos OR bovine OR bovines OR bovinae OR heifer OR heifers OR bullocks OR oxen OR steer OR steers OR Angus OR Ayrshire OR Boran OR Brahman OR Brangus OR Braunvieh OR Charolais OR Fleckvieh OR Friesian OR Gelbvieh OR Gir OR Hereford OR Holstein OR Jersey OR Limousin OR Longhorn OR Nellore OR Ongole OR Sahiwal OR Sanga OR Shorthorn OR Simmental OR Wagyu)
#2	TI=(neonatal OR newborn OR newborns OR "pre-wean" OR prewean OR "pre-weaning" OR preweaning OR "pre-weaned" OR preweaned OR nursing OR suckling OR "after birth" OR "before weaning" OR young OR calf OR calves OR calving) OR TS=(neonatal OR newborn OR newborns OR "pre-wean" OR prewean OR "pre-weaning" OR preweaning OR "pre-weaned" OR preweaned OR nursing OR suckling OR "after birth" OR "before weaning" OR young OR calf OR calves OR calving)
#3	#1 AND #2
#4	TI=(diarrhea OR diarrheic OR diarrheal OR diarrhoea OR diarrhoeal OR scour OR scours OR scouring OR "fecal score" OR "faecal score" OR "watery feces" OR "watery faeces" OR "Escherichia coli" OR "E coli" OR Salmonella OR Salmonellosis OR Salmonelloses OR clostridium OR clostridiales OR clostridiaceae OR clostridia OR shigella OR shigellosis OR "shiga bacillus" OR yersinia OR yersiniosis OR yersinioses OR coronavirus OR coronaviruses OR toroviridae OR torovirus OR toroviruses OR "Breda Virus" OR "Berne Virus" OR rotavirus OR rotaviruses OR nebovirus OR Noboviruses OR norovirus OR Noroviruses OR "Bovine Viral Diarrhea Virus" OR "Bovine Viral Diarrhea Viruses" OR "Bovine Diarrhea Virus" OR "Bovine Diarrhea Viruses" OR "Bovine Pestivirus" OR "Bovine Pestiviruses" OR BVDV OR cryptosporidium OR cryptosporidiums OR cryptosporidiosis OR cryptosporidioses OR cryptosporidium OR giardia OR giardias OR lamblia OR lamblias OR lambliasis OR lambliases OR giardiasis OR "fecal pathogens" OR "fecal pathogen" OR "faecal pathogens" OR "faecal pathogen") OR TS=(diarrhea OR diarrheic OR diarrheal OR diarrhoea OR diarrhoeal OR scour OR scours OR scouring OR "fecal score" OR "faecal score" OR "watery feces" OR "watery faeces" OR "Escherichia coli" OR "E coli" OR Salmonella OR Salmonellosis OR Salmonelloses OR clostridium OR clostridiales OR clostridiaceae OR clostridia OR shigella OR shigellosis OR "shiga bacillus" OR yersinia OR yersiniosis OR yersinioses OR coronavirus OR coronaviruses OR toroviridae OR torovirus OR toroviruses OR "Breda Virus" OR "Berne Virus" OR rotavirus OR rotaviruses OR nebovirus OR Noboviruses OR norovirus OR Noroviruses OR "Bovine Viral Diarrhea Virus" OR "Bovine Viral Diarrhea Viruses" OR "Bovine Diarrhea Virus" OR "Bovine Diarrhea Viruses" OR "Bovine Pestivirus" OR "Bovine Pestiviruses" OR BVDV OR cryptosporidium OR cryptosporidiums OR cryptosporidiosis OR cryptosporidioses OR cryptosporidium OR giardia OR giardias OR lamblia OR lamblias OR lambliasis OR lambliases OR giardiasis OR "fecal pathogens" OR "fecal pathogen" OR "faecal pathogens" OR "faecal pathogen")
#5	#3 AND #4
#6	TI=(vaccine OR vaccines OR vaccination OR vaccinations OR immunization OR immunizations OR inoculation OR inoculations OR inoculate OR inoculates OR inoculated OR ScourGuard OR ScourBos OR Bovilis OR Rotavec OR Ecolizer) OR TS=(vaccine OR vaccines OR vaccination OR vaccinations OR immunization OR immunizations OR inoculation OR inoculations OR inoculate OR

	inoculates OR inoculated OR ScourGuard OR ScourBos OR Bovilis OR Rotavec OR Ecolizer)
#7	#5 AND #6
#8	#7 *AND* **LANGUAGE:** (English) Indexes=BIOSIS Previews Timespan=1950-2019

Selection Process:

We apply a 2-level screen for study inclusion to references identified in the initial search. Level 1 will evaluate the title/abstract for the inclusion and level 2 will be at the full text level. The criteria for passing level 1 at the title/abstract level will consist of the following questions:

- Is the study in English?
- Has the study been published in 1950 or later?
- Does the study compare a vaccination regime administered to dams for the prevention of enterotoxigenic *E. coli* diarrhea or enteritis in calves 2 weeks old or younger?
- Is there a concurrent comparison group?

Two reviewers (CH and GM) will be evaluating the references independently. In order to consider the citations for level 2 review, all the questions for level one should be answered "yes", otherwise the citation will be removed. Studies where no consensus can be reached will be labelled as "unable to decide" and be evaluated at the full text level. Pre-testing of a random sample of 5 studies at level 1 will be completed by reviewer (CH) to validate screening questions and reach consensus on wording and interpretation of criteria.

The criteria to pass level 2 screening at the full text level are the following questions that will be answered with "yes", "no" or "unable to decide":

- Is the full text available in English?
- Is the study an observational or experimental study?
- Does the study compare a vaccination regime for the prevention of enterotoxigenic *E. coli* diarrhea or enteritis in calves 2 weeks old or younger?
- Is there a concurrent comparison group?
- Does the study diagnose the pathogen based on laboratory testing?
- Is the study population calves younger than 1 months old?
- Does the study report one of the defined outcomes, including diarrhea, death, bacterial shedding to evaluate the efficacy?
- Is the study published in a peer-reviewed journal or conference proceedings >500 words?

To be included in the data extraction step, both reviewers must have answered "yes" for all the questions above. Pre-testing for a randomly selected subset of 5 studies will be performed to validate the questions and reach consensus on wording and interpretation criteria.

Data items

Study characteristics:

- Publication year, year of study conduct
- Region and country where study was performed
- Study population:
    - Production system (beef, dairy)
    - Age
    - Breeds
    - Sex
    - Housing
- How has diagnosis of ETEC scours been established?
    - PCR, culture
    - Clinical post challenge
- How often and how long are calves assessed for outcomes
- Publication type:
    - Peer reviewed journal
    - Conference abstract
- Study type
    - Field trial
    - Challenge trial
- Biases/ confounding
    - Was group allocation randomized?
    - Were the researchers blinded?
    - Funding source
- Study Group
    - Intervention (1 or more)
        - Vaccine (type, combination with other pathogens, timing, how many times, route, adjuvant, strain, commercial or experimental), number in group
        - Comparison (1 or more), number in group
            - Placebo
            - No intervention
            - Other
- Exposure
    - Natural
    - Experimental
        - Dose, strain, homologous, heterologous
- Outcomes
    - Clinical diarrhea from ETEC, number with outcome
    - Mortality due to ETEC diarrhea, number with outcome
    - Bacterial Shedding of ETEC in feces, number with outcome

Outcomes and Prioritization

The outcomes of priority we will be looking for are diarrhea from ETEC and death due to diarrhea from ETEC in calves. The secondary outcome we will consider will be fecal bacterial shedding of ETEC.

Risk of Bias

Risk of bias will be assessed by whether blinding of researchers or randomization of animals to study groups was mentioned, what the funding source of the study was, and whether any conflicts of interest could be determined.

Data synthesis

Eligible studies will be summarized in tables according to inclusion criteria and outcomes. Scores from 0 – 7 will be assigned based on description of the following features by authors (Burns and O'Connor, 2008):

- Study population described (breed and age)
- Vaccine regimen described (strain, adjuvant, dose, route, frequency)
- Placebo or adjuvant as control (vs non-vaccination)
- Method of diagnosis described
- Frequency and duration of disease assessment
- Randomization to study groups
- Blinding of researchers to study treatments

Risk ratios will be calculated for the outcomes diarrhea, mortality, and bacterial shedding.

For meta-analysis, individual trials will be weighted by inverse variance. Homogeneity will be assessed via Cochran's Q test. In case of a heterogeneous distribution, random effects models will be fitted.

Publication bias will be assessed via funnel plots.

Subgroup analyses may include experimental versus commercial vaccines and natural exposure versus experimental exposure if the number of studies available allows. Meta-regression may be used if heterogeneity is detected.

Discussion

Limitations:

In this meta-analysis we aim to look at previously published vaccine trials and determine if current vaccines have an effect in reducing diarrhea in calves. Our goal is to provide most of the information available without excluding sources of information based on the quality of research performed, we expect that our review will be limited in the assessment of the quality of studies presented. We will be restricting our search to studies published only in English. There could also be limitations in effectively comparing different vaccines to one another. The conclusions drawn from this review must be considered with this caveat in mind. We will not distinguish between beef and dairy calves although exposures levels for natural infection may be different between the commodities.

This review is focused on vaccination for prevention only, we are not considering other interventions or treatment, which could also provide valuable information for reducing calf scours due to ETEC, such as hygiene.

Conclusions:

This meta-analysis aims to examine if there is evidence to show that current vaccine effort and research shows effectiveness in reducing and eliminating illness and death caused by Enterotoxigenic Escherichia coli in calves. Results can help determine if current vaccine practices could be improved on or further implemented to reduce calf diarrhea.

References:

1.) Cho, Yong-il, and Kyoung-Jin Yoon. "An Overview of Calf Diarrhea - Infectious Etiology, Diagnosis, and Intervention." *Journal of Veterinary Science*, vol. 15, no. 1, 2014, p. 1. *DOI.org (Crossref)*, https://doi.org/10.4142/jvs.2014.15.1.1.

2.) Dubreuil, J. Daniel, et al. "Animal Enterotoxigenic *Escherichia Coli*." *EcoSal Plus*, edited by Michael S. Donnenberg, vol. 7, no. 1, Jan. 2016, p. ecosalplus.ESP-0006-2016. *DOI.org (Crossref)*, https://doi.org/10.1128/ecosalplus.ESP-0006-2016.