Non-antibiotic approaches for disease prevention and control in beef and veal production: a scoping review

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Abstract
Livestock producers are encouraged to reduce the use of antibiotics belonging to classes of medical importance to humans. We conducted a scoping review on non-antibiotic interventions in the form of products or management practices that could potentially reduce the need for antibiotics in beef and veal animals living under intensive production conditions. Our objectives were to systematically describe the research on this broad topic, identify specific topics that could feasibly support systematic reviews, and identify knowledge gaps. Multiple databases were searched. Two reviewers independently screened and charted the data. From the 13,598 articles screened, 722 relevant articles were charted. The number of relevant articles increased steadily from 1990. The Western European research was dominated by veal production studies whereas the North American research was dominated by beef production studies. The interventions and outcomes measured were diverse. The four most frequent interventions included non-antibiotic feed additives, vaccinations, breed type, and feed type. The four most frequent outcomes were indices of immunity, non-specific morbidity, respiratory disease, and mortality. There were seven topic areas evaluated in clinical trials that may share enough commonality to support systemic reviews. There was a dearth of studies in which interventions were compared to antibiotic comparison groups.

Introduction
Antimicrobial resistance (AMR) poses a threat to the health and wellbeing of humans and livestock (Laxminarayan et al., 2014). The World Health Organization (WHO), the World Organization for Animal Health (OIE), and the Food and Agriculture Organization of the United Nations (FAO) have all published statements identifying antimicrobial use in humans and animals as the main driver of AMR, and have called for a worldwide effort to reduce inappropriate and unnecessary antimicrobial use in all sectors (WHO, 2012; FAO, 2016; OIE, 2016).

The consequences of AMR in humans with serious infections are more severe when pathogens are resistant to antimicrobials of medical importance, particularly those of critical importance, because there exist limited or no alternative treatment options (WHO, 2018). Antibiotic classes have been categorized according to their importance for human health by the WHO (2018) and importance for animal health by the OIE (2015). These categorizations can be used to prioritize strategies to contain AMR, such as improved antibiotic stewardship. For example, WHO has developed guidelines that recommend certain restrictions on use of medically important antibiotics in non-human sectors (WHO, 2017). Antibiotics belonging to classes of medical importance to humans are used in livestock to treat ill animals, individually or in groups, or to prevent infections in vulnerable animals (Cameron and McAllister, 2016; CDDEP, 2015; WHO, 2018).

Individual nations are responding to the call for reduced antibiotic use in livestock through various regulations and industry guidelines. For example, in Canada, regulations imposed in December 2018 require veterinary oversight for administration by injection or by addition to feed or water all antibiotics belonging to classes of medical importance to humans, thereby eliminating their ‘over-the-counter’ use (Government of Canada, 2018). The US Food and Drug Administration Center for Veterinary Medicine promotes the prudent use of antibiotics belonging to classes of medical importance to humans in livestock by requiring their use be limited to purposes for assuring animal health and be administered with veterinary oversight. The use of medically important antibiotics in healthy animals for production purposes was prohibited by 2017 in the USA (US FDA, 2017).
In beef production, antibiotics belonging to classes of medical importance to humans are most commonly used inveal calves to prevent and treat diarrhea, in beef calves or stocker cattle newly arrived to feedlots to prevent and treat respiratory infections, and in finishing feedlot cattle to prevent liver abscesses (Ribble et al., 2010; Reinhardt and Hubbert, 2015; Sneeringer et al., 2015; Amachawadi and Nagaraja, 2016; Cameron and McAllister, 2016). The rationale for the use of antibiotics in beef cattle andveal calves to treat or prevent infections caused by bacteria and other microbes stems from the complex polymicrobial nature of bovine infections (Hodgins et al., 2002; Hässig and Kretschmar, 2016). For example, in cases of bovine respiratory disease (BRD), the upper respiratory tract may first be infected and immune-compromised by a viral infection followed by a pulmonary infection of bacteria normally carried in the nasopharynx (Hodgins et al., 2002). A reduction in the use of antibiotics without compromising production efficiencies requires a comprehensive approach to the multiple modifiable risk factors that lead to beef andveal cattle infections that are currently prevented or treated with medically important antibiotics (Ribble et al., 2010). Management practices can potentially reduce the need for antibiotic therapy through several pathways, including ensuring passive immunoglobulin transfer to calves via adequate good quality colostrum intake; reducing stress at weaning, during transportation and immediately after relocation; and reducing exposure to viral and bacterial pathogens by limiting the mixing of animals from different sources (Sanderson et al., 2008; Pardon et al., 2015). Products in the form of vaccines, non-antibiotic feed additives, or non-antibiotic medications may enhance health and potentially the need for antibiotics. Further, the prevalence and severity of liver abscesses is generally inversely proportional to the level of dietary roughage or neutral detergent fiber content in beef cattle diets, and so dietary alterations could also reduce the need for antibiotic use (Nagaraja and Lechtenberg, 2007; Hernández et al., 2014; Amachawadi and Nagaraja, 2016).

Scoping reviews in the agriculture and agri-food sector are a relatively new method of knowledge synthesis (Pham et al., 2014). In a scoping review of scoping reviews, Pham et al. (2014) reported that 1.2% of the 344 scoping reviews identified were on agriculture and agri-food topics. The purpose of scoping reviews is to systematically map the literature with regard to the extent, range, and nature of the existing research in a particular topic area (Arksey and O’Malley, 2005; Levac et al., 2010). In addition, scoping reviews are useful as preliminary ‘reconnaissance’ to investigate the feasibility of undertaking a full systematic review and to identify gaps in existing research (Arksey and O’Malley, 2005; Levac et al., 2010). In contrast, systematic reviews aim to address a specific research question by collating all of the evidence that fits pre-specified eligibility criteria while minimizing bias by using explicit, systematic methods (Higgins and Green, 2011). Scoping reviews are descriptive and broader in nature than systematic reviews (Arksey and O’Malley, 2005). A scoping review of non-antibiotic approaches to beef andveal production at this time of increased attention to antibiotic stewardship may help researchers interested in advancing knowledge of alternative approaches by indicating research areas that could be subject to formal systematic reviews or merit further research. In addition, such a scoping review could illuminate current gaps in the research on non-antibiotic approaches to production for beef industry professionals, beef researchers, and research funding agencies.

The objectives of this scoping review were 3-fold: first, to examine and describe the range and nature of research on non-antibiotic approaches that may ultimately reduce the need for medically important antibiotics to prevent, control, or treat illnesses in beef andveal production; second, to identify areas where the available literature may support systematic reviews that could summarize the effect of specific non-antibiotic approaches within the broader topic area; and third, to identify knowledge gaps where additional primary research might provide valuable insight into the effectiveness of different specific non-antibiotic approaches.

Methods

Our methods followed the scoping review framework as described by Arksey and O’Malley with some modifications (Arksey and O’Malley, 2005). A protocol was not registered for this scoping review and its reporting follows the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines for the reporting of scoping reviews (Tricco et al., 2018).

Our review question was as follows: What is the nature of the primary research literature published since 1990 that measures a health outcome and evaluates non-antibiotic interventions (i.e. products and management practices) to prevent or control bacterial and viral illnesses, which therefore might reduce the need for medically important antibiotics to be used in beef andveal production in North America and other regions and countries with similar production conditions? We included viral illnesses, based on the proposition that preventing viral infections may reduce the need to treat secondary bacterial infections. We make the assumption that some non-antibiotic interventions have the potential to improve animal health in the face of infectious disease challenges thereby ultimately reducing the need for antibiotics. However, our objective was to describe the literature, and summarizing or otherwise indicating the reported efficacy of various interventions therefore was beyond the scope of this review. An assessment of the quality or risk of bias in the included studies was also beyond our scope. In this paper, we followed the definitions for disease prevention and control as given by the American Veterinary Medical Association (AVMA) (2019) and the United States Government Accountability Office (US GAO-11-801 report) in which prevention of disease at the population level is the administration of an intervention to a group of animals, none of which have evidence of infection or disease, in situations where disease is likely to occur without the intervention. Whereas, disease control refers to the administration of the intervention to a group of animals containing some individuals that exhibit clinical disease or infection with the intention of reducing the risk of further disease in the group.

Expert stakeholder engagement

The amount of literature worldwide on this broad topic was potentially very extensive. Consequently, we sought to focus this scoping review on the body of literature pertaining to non-antibiotic approaches most relevant to intensive beef production. The goal of the expert stakeholder engagement process was to inform the scope of this review. The stakeholder engagement included five specific objectives: first, to identify the countries or regions with similar intensive beef industries to those of Canada; second, to rate the importance of various antimicrobial types to antimicrobial stewardship in the beef industry (e.g. antibiotics belonging to medically important classes, ionophores,
Table 1. Data platform and database information sources used in the scoping review search on non-antibiotic approaches for disease prevention and control in beef and veal production

| Data platform | Databases |
|---------------|-----------|
| ProQuest      | AGRICOLA  |
| ProQuest      | MEDLINE, Published (not MEDLINE) |
| Web of Science| Core Collection |
| Web of Science| MEDLINE |
| Web of Science| Current Contents Connect |

The primary reviewer (LW) conducted the scoping review database search from 14 to 18 October 2016, using two data platforms, ProQuest and Web of Science, which incorporate multiple databases (Table 1). The data platform CAB Direct was originally targeted for inclusion, but was not used due to technical difficulties. Additional unpublished articles were identified through the Google search engine in a search conducted from 31 March to 7 April 2017. Beyond our contact with stakeholders regarding additional sources of articles, we did not attempt to contact authors to identify further sources.

Full texts of journal articles, theses, proceedings, or technical reports were obtained for relevant citations through the University of Guelph library resources, through Google, or using author requests via the researcher social networking site ResearchGate.

Search

The search was filtered by language (English), date of publication (from 1990), and by location filters for eligible countries if available. Additional filters were applied as available through the data platform and included source and document type (i.e. article, proceedings paper, meeting abstract, thesis, and review), subject or research areas and MeSH headings or qualifiers. No limits were applied as to where the search terms appeared (i.e. title, abstract, or full text). Citations were imported into the reference manager software EndNote (Clarivate Analytics, Philadelphia, USA). Removal of exact match duplicates was conducted in EndNote. Further deduplication based on close matches was conducted using the systematic review software DistillerSR (Evidence Partners, Ottawa, Canada).

The search included terms related to the specific cattle populations of interest (i.e. veal calves, dairy calves, beef cows, beef calves, stockers, and feedlot cattle), as well as intervention terms in the form of products (e.g. vaccines, feed additives including the addition of specific dietary components, and medications) or in the form of management practices (e.g. biosecurity, housing,
and feed types) (Table 2). Search terms were combined using the Boolean operator ‘OR’ and grouped according to population terms and intervention terms. These two search term groupings were connected by the Boolean operator ‘AND’ in a search string. The search was conducted by the first author in consultation with a librarian. A single reviewer (LW) conducted the gray literature search in Google and screened the results for relevance. Because the Google platform cannot interpret long search strings, the search terms were presented to Google in short strings with approximately 100 hits examined for each search string; each small group of population terms were combined with each small group of intervention terms.

Selection of sources of evidence

The review team consisted of veterinary epidemiologists, one of whom acted as the primary reviewer, and two trained epidemiologists who served as second reviewers. Pre-testing for relevance screening was conducted on 500 articles based on the title and abstract. The data charting form was pre-tested on 60 full text articles. Two independent reviewers performed the screening and data extraction using forms created in DistillerSR. Disagreements were resolved by consensus or by a third reviewer. After pre-testing, the relevance screening and data charting questions did not change throughout the review, except on one occasion to simplify an ambiguous question distinguishing between experiments versus field trials. For purposes of this scoping review, field trials and experiments were combined into one category called clinical trials.

Study selection and data charting were conducted as separate steps. Each citation was initially screened for relevance based on information in the title and abstract. If sufficient information was lacking in the title and abstract alone, the citation was screened for relevance based on the full text.

Data charting process

Data charting was conducted in duplicate by the primary reviewer and a second reviewer working independently using a form in DistillerSR. Disagreements were resolved by consensus or by a third reviewer. The form to determine which variables to extract was developed, piloted, and updated iteratively by the veterinary epidemiologists. The form is available upon request. Data were charted from each article similarly; if more than one study was described, the data were collated so that all data charting was conducted at the article level. Data charting was conducted using the full text, and consequently data were only charted from citations for which the full text could be obtained. For purposes of reporting in this review ‘article’ refers to journal article, thesis, proceeding, or technical report.

Data items

We charted data on the study characteristics (e.g. study design, population settings, study location, study size, and year of publication) and trial characteristics (e.g. population type, intervention, comparison groups, and outcome(s) measured) (Table 3). The data charting was conducted using pre-selected response fields for all questions with an added text box for additional responses or clarification for the intervention type and outcomes measured. With one exception, we did not chart data that pertained to a common intervention among all the treatment group(s) (i.e. all
and in other studies was evaluated as a risk factor (e.g. beef calves for disease resistance and survivability) (Williams et al., 2008). Some studies was treated as a modifiable intervention (e.g. genetics were treated similarly. Examples included breed, which in general study characteristics

| Variable | Description of items |
|----------|----------------------|
| Study design | Clinical trial (i.e. experimental or field-based trial under conditions of natural exposure), challenge trial (i.e. deliberate exposure to a pathogen or immune agent under the control of the investigator), observational study, case report/case series, outbreak report |
| Population settings during the study | Population settings (i.e. experimental research settings, commercial farm, or unclear) |
| Study location | Country and region where the study was conducted as stated in the article or first author address if not stated |
| Year of publication | Year of publication of article |

Table 3. Description of data charting items for relevant journal articles, technical reports, proceedings, or theses

| Variable | Description of items |
|----------|----------------------|
| Specific beef animal population type in which the intervention was given and/or outcome measured | Veal calves (i.e. male veal calves or mixed sex dairy calves), cow-calf (i.e. beef cows and their calves), beef calves only living under cow-calf conditions, beef cows or heifers only, stocker cattle (i.e. weaned beef calves fed pasture or mostly forage), feedlot cattle (i.e. weaned calves housed in feedlots and fed mostly concentrates after initial adaptation period), cattle (i.e. unspecified cattle populations or beef cattle combined with dairy cattle) |
| Interventions in the form of a product or management practice | Breed or genetic characteristics, feeding regime (e.g. amount or schedule), diet type or format; non-antibiotic feed additives including the addition of specific dietary components, colostrum or milk replacer additive, maternal antibody as a measure of colostrum intake, non-antibiotic medication (e.g. any medication, vitamin, mineral, or antibodies administered directly to an individual), vaccination to treatment group only, vaccine given to all groups and another intervention given to the treatment group(s) for the purpose of comparing the intervention effect on the vaccine immune response, maternal vaccination, weaning method, castration method, biosecurity (e.g. comingling, mixing, introductions, contact with wildlife), comorbidities/coinfections, environmental conditions (e.g. season, ambient temperature, rainfall), housing or flooring (e.g. animal density, feed bunk and water supply factors, shade, flooring), transportation factors, unspecified pre-conditioning |
| Comparison group | No treatment or conventional practice control, placebo or sham, antibiotic, different level of treatment or exposure level, breed type |
| Health outcomes of interest | Mortality, non-specific morbidity such as fever or generally ill appearance, diarrhea (i.e. non-specific diarrhea), respiratory disease (i.e. non-specific respiratory disease), other clinical disease (i.e. non-diarrhea, non-respiratory clinical disease such as otitis, infectious bovine keratitis, and omphalitis), pathology (i.e. post mortem findings other than liver abscesses), rumen or omasum development, total tract barrier function, acidosis (i.e. specifically stated as acidic, or not) liver abscesses, lameness or foot lesions, surrogate measures of disease and susceptibility (i.e. pathogen detection or indices of specific immunity such as serology and cell mediated immunity), indices of nonspecific immunity (i.e. immunoglobulins to non-infectious agents, immune markers: acute-phase proteins, tumor necrosis factor), ‘treatments for illness’ as the number of treatments given to individual sick animals, injection site lesions, gene expression (e.g. immune resistance or susceptibility), abortion, treatment costs, total farm-level antibiotic use |
| Levels at which the outcome was measured | Individual, pen, herd |
| Study size | Number of study subjects in the analysis of each relevant study reported within the article |

There was no attempt to distinguish between non-antibiotic interventions that were intended to prevent disease from those that were intended to treat or control disease because the distinction is often unclear in research reports. We defined the intervention type ‘medication’ to include any non-antibiotic medication, vitamin, mineral, antibody, or other treatment that was administered directly via injection or oral bolus to individual animals. The same medication given to the entire group of animals via their feed was charted as a feed additive.

Some studies reported the outcome ‘treatment rate’ referring to the number of treatment(s) given to individual sick animals, but since a measure of time was not included in the denominator, the measure of disease frequency most were referring to was a risk frequency among these groups, the data for the intervention type and the comparison groups were charted as ‘different levels of treatment’ (e.g. an article described the effects of various dietary levels of wet corn gluten feed on liver abscesses) (Hussein and Berger, 1995).
rather than a rate. For purposes of this review, we referred to the term as ‘treatments for illness.’ For purposes of this review, surrogate measures of disease and susceptibility included detection of infection and indices of specific immunity.

To meet our second objective of identifying feasible future systematic reviews, we identified topic areas for which there was commonality among clinical trials with regard to the population, intervention, and clinically important outcomes measured. Observational study designs, non-randomized clinical trials or randomized clinical trial (RCT) designs can be used in systematic reviews of interventions. However, the RCT is considered to have the best evidentiary value (Sargeant et al., 2014). For this reason, we chose to focus our second objective on clinical trials. Clinically important outcomes were defined after data charting and included mortality, non-specific morbidity, respiratory disease, diarrhea, liver abscesses, acidosis, and treatments for illness. Thus, not all outcomes of interest were considered clinically important outcomes. For example, infections with specific pathogens and indices of specific or non-specific immunity may not reliably predict clinical outcomes; consequently these outcomes were not included as clinically important outcomes (Fleming and Powers, 2012). Study results were not extracted, and no attempt was made to determine the direction of the effect of the outcome (e.g. if the intervention showed a favorable outcome), as that was beyond the scope of this review. The topic areas identified as potentially extensive enough for systematic review were those with a minimum of five clinical trials reporting similar interventions or types of intervention (e.g. specific respiratory disease vaccines, probiotics, medications, minerals, and feed types such as roughage content) and the same specific population in which the outcome was measured (e.g. veal calves and feedlot cattle) and at least one, but not necessarily the same, reported clinically important outcome.

Synthesis of results

The charted data were entered into a database in Stata 15.1 (College Station, Texas, USA). Descriptive statistics were compiled according to our stated data charting scheme for all study designs and were presented in the form of tables and figures. We presented detailed results for articles that reported clinical trials or observational studies so as to emphasize the literature with the greatest evidentiary value (Sargeant et al., 2014). For challenge trials, we presented details only for the types of challenges studied.

Results

Expert stakeholder engagement

Seventy-four experts received an invitation to the survey, of which 38 (51%) responded. The stakeholder engagement process helped to inform the search strategy and the data charting items. No publications were suggested by the stakeholders that had not been captured in the search.

Selection of sources of evidence

There were 13,598 unique citations identified by the search that underwent relevance screening and 1110 (8%) were assessed for relevance based on the full text. There were 722 full text articles considered eligible for data charting (Fig. 1). The majority of sources of evidence were full text published articles identified through the database searches. Theses, proceedings, and technical reports from the database sources represented 6% of the relevant evidence (Fig. 1). Interestingly, 11 of the 15 full text theses were identified through the Google search.

Characteristics of sources of evidence

Sixty-eight articles (9%) described more than one study of the same design or different design within the same article. Among the 722 included articles, there were 752 studies described which comprised clinical trials (n = 439, 61%), observational studies (n = 162, 22%), and challenge trials (n = 151, 21%).

The clinical trials and challenge trials were conducted largely using animals living under experimental farm settings (n = 365, 83%) and (n = 148, 98%) respectively, whereas the observational studies were conducted largely in animals living under commercial farm settings (n = 128, 79%). Some articles included experimental and commercial settings and in 11 articles it was unclear if the farm settings were commercial or experimental. Among the articles in which the settings were clearly identified, the majority of the explicitly described beef populations (e.g. stockers, veal calves, feedlot cattle, beef calves, cow–calf pairs, and cow/heifers) were animals living under experimental settings (83, 81, 75, 73, 62, and 51%) respectively whereas, the unspecified cattle populations were largely animals living under commercial settings (80%).

The majority of articles described clinical trials, challenge trials, and observational studies conducted in USA and Canada (74%). The cattle populations most commonly studied in USA, Canada, and Australia/New Zealand were feedlot cattle, whereas in Western and Eastern Europe the cattle populations most often studied were veal calves (Table 4). In South American countries and Mexico, there were relatively few English articles (n = 29) and they included nearly equal numbers of veal calf and cow–calf population types. In Canada, the majority of the studies (n = 130), occurred in Alberta (n = 60), Saskatchewan (n = 47), and Ontario (n = 23), where the majority of the country’s feedlot and cow–calf operations are located (Statistics Canada, 2018). In the USA, the majority of the studies (n = 405), occurred in Texas (n = 50), Kansas (n = 45), Nebraska (n = 33), Oklahoma (n = 30), Florida (n = 27), and California (n = 23). In addition, in North America, 13 and 6% of the studies spanned multiple provinces or states in Canada and the USA, respectively. In Western Europe (n = 119), the two countries with the largest proportion of studies were Ireland (n = 27, 23%) and Spain (n = 14, 12%).

The number of articles published per year increased in an approximately linear trend over the decades since 1990. There were 6–18 articles per year from 1990 to 1999, 13–48 from 2000 to 2009, and 41–55 from January 2010 to October 2016 (Fig. 2).

Synthesis of results for challenge trials

Challenge trials (n = 151) were used extensively for studies of vaccinations (n = 49), non-antibiotic feed additives (n = 43), and non-antibiotic medications (n = 19) (Fig. 3). These trials described challenges with infectious agents or their toxins (n = 89) and immune stimulants (n = 52) administered to detect a measurable immune response in conjunction with another intervention. The infectious agents or toxins included Haemophilus somnus, Bovine herpes virus 1 (BoHV-1), Pasteurella spp., Mannheimia haemolytica, Bovine respiratory syncytial virus (BRSV), Bovine parainfluenza virus 3 (PI-3), Bovine rotavirus, Mycoplasma bovis,
Salmonella spp., Salmonella toxins, *Fusobacterium necrophorum*, Bovine viral diarrhea virus (BVDV), Bovine leukemia virus, *Mycobacterium bovis*, *Leptospira* spp., *Ureaplasma diversum*, *Mycobacterium avium* (MAP), *Brucella abortus*, *Histophilus somni*, lipopolysaccharide, *Escherichia coli* strain K99+, and *Fasciola hepatica*. The immune stimulants included ovalbumin, porcine red blood cells (RBC), human RBC, keyhole limpet hemocyanin (KLH), antigens (hen egg white lysozyme with DTH-inducing antigen *Candida albicans*), intradermal phytohemagglutinin (PHA). Other types of challenges (*n* = 10) included acidosis challenge, ACTH challenge, amphotericin-induced lameness, and induced wounds.

Outcomes most commonly reported in challenge trials included surrogate measures of disease and susceptibility (*n* = 112), morbidity (*n* = 91), respiratory disease (*n* = 48), and non-specific immunity (*n* = 47) (Fig. 4).

**Synthesis of results for clinical trials and observational studies**

**Non-antibiotic interventions**

The interventions evaluated in clinical trials and observational studies varied widely (Table 5). The most frequent interventions studied were feed additives, followed by breed type and then vaccines (Fig. 3). Clinical trials were the most frequent study design for the evaluation of feed additives, vaccinations, feed types, maternal antibody, medications, milk replacer additives, weaning, transportation, feeding regimes, and non-specific pre-conditioning. Observational studies were the most common study design for evaluation of breed type, biosecurity, environment, and housing.

We charted data for 15 categories of non-antibiotic interventions, which are presented in decreasing order of frequency in Table 5. Details of the specific vaccine interventions studied in clinical trials are given in Supplementary Appendix 3, and details of the specific non-vaccine, non-antibiotic interventions studied in clinical trials are given in Supplementary Appendix 4.

**Comparison groups**

Among the 601 clinical trials and observational studies, the most commonly reported comparison group was a control group that received a different form or level of the intervention or exposure (*n* = 487). The next most commonly reported comparison group was the ‘no treatment control or conventional practice’ category (*n* = 235). A placebo or sham treatment group (*n* = 61) was utilized largely for vaccination trials (*n* = 39). Direct breed-to-breed comparisons for specific breeds were reported in 15 studies. Among the 167 clinical trials that investigated a non-antibiotic feed additive or medication, only 17 included an antibiotic comparison group (Supplementary Appendix 5). These 17 studies all evaluated the non-antibiotic approach for disease prevention or control, none for treatment in animals known to be clinically ill.

**Outcomes measured**

We extracted data for 18 categories of health outcomes. It was common for studies to report results for multiple outcomes. The 10 most frequently reported categories are presented in...
Fig. 4. Surrogate measures of disease and susceptibility was the most commonly reported outcome category among clinical trials (20%) whereas, surrogate measures of disease and susceptibility and mortality were equally the most commonly reported outcome categories among observational studies (29% each) (Fig. 4). Details of the outcomes measured in the vaccine and non-vaccine clinical trials of non-antibiotic interventions are presented in Supplementary Appendices 3 and 4, respectively.

Among clinical trials and observational studies, the outcome ‘treatments for illness’ \( (n = 83) \) was most commonly reported in veal calves \( (n = 48) \) followed by veal calves \( (n = 22) \). The outcome diarrhea \( (n = 77) \) was more frequently reported in veal calves \( (n = 57) \) than other populations. Other clinical disease (i.e. non-respiratory and non-diarrheal infections) specifically identified by clinical disease \( (n = 23) \) such as infectious bovine keratitis, omphalitis, and otitis were reported in observational studies \( (n = 11) \) typically evaluating breed factors, and in clinical trials \( (n = 12) \) typically evaluating vaccines. Most studies reporting treatment cost \( (n = 26) \) were clinical trials \( (n = 23) \).

Of the 27 vaccine clinical trials conducted in feedlot cattle, there were eight that did not measure a clinically important outcome but did measure indices of immunity. These eight studies ranged in size from 8 to 179 individuals and were all conducted under experimental farm settings. Similarly, of the 11 vaccine clinical trials conducted in veal calves, there were three that did not measure a clinically important outcome. These three trials ranged in size from 10 to 200 calves with the largest being conducted on a commercial farm (Soehnlen et al., 2011).

### Study size

Most studies reported the results and analyses at the individual level \( (n = 568) \) as opposed to the group \( (n = 28) \) or herd level \( (n = 66) \). Study sizes varied widely from 4 to 8,904,965 animals. The size of clinical trials in experimental settings varied from 4 to 12,617 animals, whereas the size of clinical trials in commercial settings varied from 10 to 79,171 animals. The smallest studies \( (n = 4–6) \) were typically clinical trials that evaluated feed type or a non-antibiotic feed additive in feedlot cattle housed under experimental settings with or without fistulae measuring acidosis, performance, digestion, and bio-mechanisms. The two largest studies \( (n = 2,542,266) \) and \( (n = 8,904,965) \) were observational studies of commercial cattle. The study with 2,542,266 animals evaluated the association of breed or genetics and the environment (i.e. season or year) on calf mortality and fertility.

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### Table 4. Numbers of studies involving specific beef populations\(^a\) by country or region where challenge trials, clinical trials, and observational studies were conducted

| Specific population | Canada \((n = 141)\) | USA \((n = 485)\) | Western Europe \((n = 124)\) | Australia or New Zealand \((n = 29)\) | South America\(^b\) or Mexico \((n = 29)\) | Eastern Europe or Russia \((n = 12)\) | Total \((n = 820)\) |
|--------------------|---------------------|----------------|----------------------|-----------------|-----------------|-----------------|----------------|
| Veal calves        | 14                  | 77             | 50                    | 0               | 10              | 7              | 158            |
| Beef calves        | 13                  | 43             | 7                     | 3               | 1               | 0              | 67             |
| Beef cows/heifers  | 5                   | 14             | 7                     | 3               | 4               | 1              | 34             |
| Cow-calf           | 21                  | 74             | 13                    | 6               | 9               | 1              | 124            |
| Stockers           | 12                  | 80             | 2                     | 1               | 1               | 0              | 96             |
| Feedlot            | 74                  | 186            | 22                    | 13              | 2               | 3              | 300            |
| Cattle (mixed or unspecified populations) | 2   | 11             | 23                    | 3               | 2               | 0              | 41             |

\(^a\)Some articles included more than one study and more than one specific population.

\(^b\)South American countries included Brazil, Argentina, and Uruguay.
of the British National herd (Gates, 2013), whereas the largest study evaluated the association between cohort level risk factors such as arrival month, sex, and cohort mean arrival weight on the mortality rate and culling risk in 16 US feedlots over multiple years (Babcock et al., 2013).

Material for potential systematic review questions

To meet our objective of assessing the feasibility of conducting systematic reviews, we explored the clinical trial data for all potential topic areas that shared some commonality of intervention, population, and a clinically important outcome. We found seven topic areas that may feasibly lead to systematic review questions assessing non-antibiotic interventions to reduce the need for medically important antibiotics in beef or veal production (Table 6 and Supplementary Appendix 6). Within these seven topic areas, there was some variation of specific interventions used and outcomes measured (Table 6). The full range of the specific interventions used within the identified topic areas are listed in Supplementary Appendix 6. Though we identified material for seven potential systematic review questions, only the material for BRD vaccines and feed type roughage for the prevention of liver abscesses in feedlot cattle included more than one study in commercial settings (Table 6).
Table 5. Description of non-antibiotic interventions* in beef or veal animals evaluated in clinical trials and observational studies from January 1990 to October 2016 presented in decreasing order of frequency

| Non-antibiotic interventions that may reduce or prevent disease | Description of interventions or risk factors in clinical trials and observational studies |
|---------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Feed additive including the addition of specific dietary components (non-antibiotic) | Vitamins (A, E, thiamine), cysteine-rich feather meal, trace minerals, maternal mineral supplementation, hormones, crude protein, fatty acids, organic acids, molasses, high fructose corn syrup, urea, rumen modifier, bicarbonate, anion-cation buffer, wet breeder’s grains, fibrinolytic enzyme, wet breeder’s or distillers’ grains, ground flax, seaweed or plant extracts, essential oils, fish oil, yeast or yeast extracts, bicarbonate, probiotics, prebiotics, yeast fermentation extract, supplemental fat from safflower seed or cottonseed hulls, wheat straw versus beet pulp, anti-phospholipase antibody, polyclonal antibody, Actigen®, ractopamine or zilpaterol |
| Total (n = 129) Clinical trial (n = 121, 94%) Observational (n = 8, 6%) | | |
| Breed | Breed or breed combination comparisons, heterosis versus purebred, sire and dam breed and heterosis, generations of rotational breeding, genome association with disease, breed type as risk factor for diseases, single-nucleotide polymorphisms, BoLA type and sire effects, heritabilities of pre-weaning mortality, heritability for disease susceptibility, haplotypes, familial associations |
| Total (n = 114) Clinical trial (n = 32, 28%) Observational (n = 82, 72%) | | |
| Vaccinations (treatment group received vaccination, comparison group (s) received different vaccinations or vaccine protocol or no vaccination) | Timing of vaccination, live versus inactivated vaccines, booster vaccination, various adjuvants, novel combinations of vaccines, methods and routes of administration, season of vaccination, efficacy of needle-free vaccination under cold and warm conditions. Vaccine efficacy for specific infections including: BRD, IBVD, Moraxella bovis, S. typhimurium, S. choleraesuis, S. Newport, S. dublin, Mycoplasma bovis, M. bovis cytotoxin, Rota viruses, corona virus, bovine herpes virus-1, Brucella bovis, Infectious bovine rhinotracheitis virus, parainfluenza-3 virus, bovine respiratory syncytial virus, Haemophilus somnus, Mannheimia haemolytica, Pasturella spp., E. coli, Clostridial spp., Leptospira spp., Fusobacterium necrophorum bacterin or leukotoxin, Arcanobacterium pyogenes polysyn |
| Total (n = 108) Clinical trial (n = 82, 76%) Observational (n = 26, 24%) | | |
| Feed type | Forage sources, chop length, silage, and forage level in diet, grain types, brewers or distillers grains as wet or dry, with or without solubles, corn gluten, by-product pellets, grain processing methods, feedlot diet, calf starter format, pasture mix, crude protein concentration, dietary starch and energy concentration, molasses, waste milk, alkaline hydrogen peroxide treated wheat straw, summer versus winter feeding strategies, self-selection of dietary ingredients versus total mixed ration |
| Total (n = 107) Clinical trial (n = 94, 88%) Observational (n = 13, 12%) | | |
| Environment | Housed indoors versus outdoors in high ambient temperature, shade provided, rain shelters, extended summer and winter feeding strategies, efficacy of needle-free vaccination under cold and warm conditions, environmental conditions and spatial allowances during transportation, ambient temperature at birth, birthing seasons, vaccination season spring versus fall, exposure to sour gas sulfur dioxide, hydrogen sulfide, and volatile organic compounds (VOCs), high altitudes, geographic regions, climactic conditions upon feedlot entry |
| Total (n = 65) Clinical trial (n = 13, 20%) Observational (n = 52, 80%) | | |
| Biosecurity | Regrouping and relocation, multiple sources versus single source, source of calves, infection control, disinfection and housing types, presence of other animals on the farm (wildlife, game farms, poultry, sheep, goats, dogs), animal movements, production systems, feedlot management practices, sick calf management, calving management, replacement heifers born on farm versus purchased, community and rental pastures, bovine TB management, badger activity, paraTB previously diagnosed on farm, movement of pregnant cows with persistently infected BVD calves, Johne’s test and control practices, application of producer knowledge regarding biosecurity |
| Total (n = 56) Clinical trial (n = 8, 14%) Observational (n = 48, 86%) | | |
| Maternal antibody | Access to and quality of maternal IgG Colostrum Antibody. In some studies it was measured to indicate immune response to another intervention such as a feed additive |
| Total (n = 52) Clinical trial (n = 41, 79%) Observational (n = 11, 21%) | | |
| Non-antibiotic medication or supplement administered directly by injection, implant, or bolus | Trace minerals, yeast, hormones, recombinant bST, growth implant, beta-adrenergic agonists, non-steroidal anti-inflammatory drugs (NSAIDs), vitamins B, A, D, E, and C, zinc, selenium yeast, parapox ovis-based immunomodulator, insulin, botanical extracts, DNA immunostimulant (Zelnate), mycobacterium cell wall fraction (Immunoboost®), nitric oxide, brown seaweed extract, probiotic, homeopathic treatment, Convert calf gel® mix, Tween 80®, non-pathogenic E. coli strain Nissle 1917 |
| Total (n = 51) Clinical trial (n = 46, 90%) Observational (n = 5, 10%) | | |
| Housing | Single versus group pen, grouping by age, animal pen density, presence of a sick bay, tie stall versus free stall, calving facilities and protocols, winter housing, post weaning housing, bunk manger space and management, flooring and bedding, days on pasture |
| Total (n = 42) Clinical trial (n = 16, 38%) Observational (n = 26, 62%) | | |

(Continued)
Table 5. (Continued.)

| Non-antibiotic interventions that may reduce or prevent disease | Description of interventions or risk factors in clinical trials and observational studies |
|---------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Milk or colostrum replacer additive                            | Prebiotic, probiotic, symbiotic, whey protein, Vit A and E levels, lactoferrin, trace minerals (source and type), chromium, selenium, yeast or yeast extract, fermentation product, fatty acids, clinoptilolite (zeolite), milk-free versus milk-based, commercial lacteal-derived colostrum replacer, spray-dried animal plasma, clenbuterol, plane of nutrition, roughage supplement, essential oils |
| Weaning                                                        | Weaning protocols (e.g. 2-stage weaning with nose flaps, levels of contact with dam, yard weaning with or without feed-bunk training, weaned with or without trainer cow, early versus late weaning, organic versus conventional versus intensive beef system), concentrate dependent weaning, milk versus concentrate, creep feeding, time from weaning to shipping, dam age, weaned and housed versus returned to pasture, weaned concurrently or consecutively with castration, length of weaning period and timing of vaccination before weaning or on arrival at feedlot, regular weaning protocol versus Michigan State University protocol |
| Feeding regime                                                 | Feed, energy, protein, or nutrient restriction, beef cow grain supplementation schedule, ad libitum versus limit fed, rangeland protocols for supplementary forage and other nutrients, grain adaption protocol, amount of roughage fed, milk replacer delivery system or allowances, starter diet/creep feeding protocols at weaning, feed amounts at various periods of gestation and lactation, self-selection of dietary ingredients versus total mixed ration |
| Maternal vaccination                                           | Vaccine timing, evaluation of specific disease agent vaccines |
| Pre-conditioning (general or unspecified)                     | Certified preconditioning program versus Kentucky Gold Tag program, vaccinated or conditioned calves sold through special auction types, timing of vaccination before or after shipment, number of vaccines prior to shipment, preconditioning program type, preconditioning nutrition, branding method, preconditioning and length of transportation |

Total number of clinical trials and observational studies described \( n = 890 \).
Study designs: clinical trials \( n = 583, 66\% \) and observational studies \( n = 293, 33\% \).
*Some articles describing non-antibiotic interventions reported multiple studies and some studies reported multiple interventions.

Discussion

This scoping review of the research evaluating non-antibiotic approaches that may reduce the need to use medically important antibiotics in beef and veal production relevant in the North American context identified a large body of diverse literature. The diversity of this research pertained not only to the specific interventions and specific populations studied but also to the comparison groups and outcomes measured. Though there was a large volume of research evaluating a considerable variety of interventions, there was relatively little replication of studies. Our findings that this body of literature had breadth but limited depth reflected those of Murphy et al. (2016) as reported in their scoping review of non-antibiotic factors or interventions to reduce AMR in North American cattle. Because the findings of a single trial can be the result of a random event, clinical and policy decisions are best guided by the findings among multiple relevant studies (Garg et al., 2008). Clinicians and policy decision makers can benefit from a credible summary of the primary research for a particular topic, particularly in the form of a systematic review (Garg et al., 2008). However, replication of research is a prerequisite for combining and summarizing the research on a specific topic.

We charted data regarding the farm settings of the animals in the study in terms of experimental versus commercial farms. The majority of clinical trials occurred on experimental farms. Some experimental farms are as large as some commercial farms, and so may closely mimic commercial settings. However, it is unknown to what extent the experimental versus commercial farm settings impact external validity in beef cattle and veal calf research.

We chose to focus our reporting on clinical trials rather than challenge trials as challenge trials have a tendency to report more favorable outcomes compared to clinical trials of the same intervention (Wisener et al., 2014; Theurer et al., 2015). Nevertheless, challenge trials serve an important purpose in the research continuum, providing proof of concept prior to field trials under natural exposure conditions (Sargeant et al., 2014).

Consistent with Ribble et al. (2010) we found that there was a dearth of clinical trials evaluating feedlot management interventions such as biosecurity, infection control, animal mixing and animal movement, and pen densities. These types of interventions may be difficult to study under clinical trial conditions; moreover, it may be difficult to source funding for trials of non-antibiotic management interventions (Ribble et al., 2010). These types of interventions were more frequently studied though observational approaches, which can provide a high level of evidentiary value about an intervention and can be used in systematic reviews (O’Connor and Sargeant, 2014). However, even among the

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observational study designs that can be used for hypothesis testing, the inherent selection and confounding biases that can result from the lack of randomization must be carefully considered in the decision to base a systematic review on these studies (O’Connor and Sargeant, 2014).

Had we focused exclusively on studies that compared a specific alternative intervention group to a preventive antibiotic group, our scoping review would have been very limited: first, because the studies in which a specific non-antibiotic alternative intervention group was compared to an antibiotic treatment group were limited to feed additive and medication interventions; and second, because there were relatively few feed additive or medication intervention studies with a preventive antibiotic comparison group. In the literature that described non-antibiotic approaches to improve the health of beef or veal animals and thereby reduce the need for antibiotics, this lack of direct comparison to a preventive antibiotic comparison group may represent a knowledge gap for decision-making regarding non-antibiotic alternatives.

The comparison group(s) did not always include a ‘no treatment or conventional practice’ control group, but more commonly consisted of animals receiving different levels of the same treatment or a variation of the treatment. In some cases, including a no treatment control group would have resulted in an unacceptable standard of care for that group. For many studies, we found it difficult to determine what may have been considered the ‘no treatment or conventional practice’ control in the context of the study, and thus we may have misclassified these comparison groups. For example, one study evaluated the effect of late son groups. For example, one study evaluated the effect of late

Table 6. Articles describing similar specific non-antibiotic interventions, specific populations, and clinically important outcomes in beef or veal animals evaluated from among the clinical trials (n = 439) from January 1990 to October 2016 that may feasibly support systematic reviews

| Intervention | Intervention specifics | Population | Clinically important health outcomes |
|--------------|-----------------------|------------|-------------------------------------|
| Vaccinations (BRD) (n = 24) | Vaccine types (n = 12) | Feedlot cattle | Respiratory disease (n = 16) |
| | Vaccination–revaccination and vaccination schedules (n = 10) | Exp. (n = 15) | Morbidity (n = 22) |
| | Novel vaccine routes and novel combinations of viral-bacterial respiratory vaccines (n = 1) | Comm. (n = 8) | Mortality (n = 15) |
| | Vaccination site on animal (n = 1) | Unclear (n = 1) | Treatments for Illness (n = 10) |
| Feed additive (probiotics) (n = 5) | Yeast culture live (n = 2), yeast (live or cell wall extract) (n = 1), DFM product (Bovamine Defend®) (n = 1), commercial feed additives containing probiotics and/or feed enzymes (n = 1) | Feedlot cattle | Respiratory disease (n = 3) |
| | | Exp. (n = 5) | Morbidity (n = 5) |
| | | Comm. (n = 0) | Mortality (n = 4) |
| | | | Treatments for Illness (n = 3) |
| Feed additive supplement (daily vitamin E) (n = 5) | Vit. E levels (n = 1), Vit E 550 IU or cysteine-rich feather meal (n = 1), Vit E 2000 IU (n = 1), Vitamin E with either flaxseed oil or safflower oil or alone (n = 1), Vit E (2000 IU) supplement for various lengths of time (n = 1) | Feedlot cattle | Respiratory disease (n = 1) |
| | | Exp. (n = 4) | Morbidity (n = 4) |
| | | Comm. (n = 1) | Mortality (n = 2) |
| | | | Treatments for Illness (n = 3) |
| Feed additive supplement (chromium supplementation) (n = 6) | Organic versus inorganic chromium (n = 3), chelated chromium (n = 2), unspecified chromium (n = 1) | Feedlot cattle | Respiratory disease (n = 1) |
| | | Exp. (n = 6) | Morbidity (n = 6) |
| | | Comm. (n = 0) | Mortality (n = 1) |
| | | | Treatments for Illness (n = 1) |
| Medications NSAID ¹ (n = 5) | Flunixin meglumine as ancillary treatment for BRD (n = 2), flunixin, ketoprofen and carprofen tested as ancillary treatment for respiratory disease (n = 1), meloxicam at castration (n = 2) | Feedlot cattle | Respiratory disease (n = 4) |
| | | Exp. (n = 3) | Morbidity (n = 5) |
| | | Comm. (n = 1) | Mortality (n = 2) |
| | | Unclear (n = 1) | Treatments for Illness (n = 2) |
| Feed type (roughage and grains) (n = 41) | Roughage type, processing methods, and roughage levels (n = 14), forage feeding protocols (n = 3), grain feeding protocols (n = 3), grain processing methods (n = 3), grain type (n = 6), replacing barley grain (n = 6) | Feedlot cattle | Liver abscesses (n = 26) |
| | | Exp. (n = 36) | Acidosis (n = 21) |
| | | Comm. (n = 5) | |
| | | Unclear (n = 1) | |
| Milk replacer additive (probiotics) (n = 14) | Probiotics including yeasts (n = 6), prebiotics (n = 4), combination probiotic and/or prebiotic (n = 4) | Veal calves | Diarrhea (n = 14) |
| | | Exp. (n = 14) | |
| | | Comm. (n = 0) | Mortality (n = 2) |
| | | | Morbidity (n = 5) |

¹Clinically important health outcomes (i.e. mortality, non-specific morbidity, respiratory disease, treatments for illness, liver abscesses, and acidosis).
²Exp. (i.e. populations living under experimental settings).
³Comm. (i.e. populations living under commercial settings).
⁴Morbidity (i.e. non-specific illness or pyrexia).
⁵Treatments for illness (i.e. sequential antibiotic treatments administered to sick animals).
⁶NSAID (nonsteroidal anti-inflammatory medication).
lower quality of evidence than patient-important or animal-
important outcomes, as determined by guidelines or the clinician,
researcher, or patient perspectives (Guyatt et al., 2011a, 2011b). In
the human medical literature, the assumption that the intervention
effect on a biomarker reflects the intervention effect on a patient-
important outcome can be false (Fleming and Powers, 2012).
However, indices can serve as useful outcomes to provide insights
for ‘proof of concept’ trials (Fleming and Powers, 2012).

This scoping review described the literature on the broad
topic of non-antibiotic interventions without attempting to demon-
strate if these interventions could actually reduce the need for
antibiotics. Summarizing the efficacy of various interventions and
assessing the methodological quality or risk of bias of the
included articles was beyond the scope of this review. However,
in addition to mapping the broader intervention literature, we
attempted to identify areas where the available literature may sup-
sport systematic reviews that could summarize the effect of par-
ticular non-antibiotic approaches within the broader topic area.
Systematic reviews of interventions combine similar studies
together to summarize the overall effectiveness of particular inter-
ventions. The purpose of the systematic review determines the
scope of the review question as broad versus narrow (Higgins
and Green, 2011). The scope then informs the degree of similarity
among each of the study PICO components: specific population,
treatment, comparison group, and outcome measured. We
found relatively few similar studies for any specific intervention.
Theurer et al. (2015) also reported finding limited published evi-
dence to support a systematic review and meta-analysis of the
effectiveness of commercially available vaccines against BRDs, a
topic area of great importance for the reduction in the use of med-
ically important antibiotics in the beef industry (Cameron and
McAllister, 2016). Ribble et al. (2010) reported finding few non-
vaccine intervention studies published in the last 20 years that did
not involve the use of antibiotics in their review of alternative
practices to antimicrobial use for disease control in commercial
feedlots. Among the studies we identified with similar specific
interventions we found a considerable range of outcomes
reported. In systematic reviews, studies with disparate outcomes
may not be meaningfully synthesized (i.e. combined). A lack of
commonality in measured outcomes can result in some studies
being excluded from a systematic review, resulting in an overall
loss of research information needed to answer specific research
questions about a summary effect size or to understand factors
that affect that effect size. The outcome(s) selected for a systematic
review of an intervention should be important to the end-user
(O’Connor et al., 2014). Despite the availability of multiple studies
evaluating a specific intervention in a specific population, a lack of
a common outcome restricts the number of studies that can con-
tribute to the systematic review.

We used an arbitrary minimum of five clinical trials with some
commonality of the intervention, population, and measured out-
comes to identify potentially feasible topics for a systematic review
and meta-analysis. Technically, a minimum of two studies is suf-
cient to conduct a meta-analysis if those studies are similar
enough to combine in a meaningful way (Borenstein et al.,
2009). However, an insufficient number of studies limits the
opportunity to assess between-study variability, which in turn
impacts the interpretation and meaning of the meta-analysis
(Borenstein et al., 2009). Depending on the systematic review
question, there may be good reasons to combine studies that are
somewhat dissimilar – for example, to explore the reasons for dif-
ferent results among the studies (Ioannidis et al., 2008).

In this scoping review, we identified seven topic areas for
which it may be feasible to conduct a systematic review to answer
a specific question about a specific intervention in a specific
population measuring a specific outcome. The topic area with the
most clinical trials was vaccines for BRD. Theurer et al. (2015)
reported a systematic review and two meta-analyses for
commercial BRD viral antigen vaccines in beef calves and in
dairy calves in which two trials in beef calves and three trials in
dairy calves with unspecified sex were included. We found more
trials than Theurer et al. (2015) but we did not restrict BRD vac-
cines to commercially available vaccines. Larson and Step (2012)
reported a meta-analysis for commercial BRD bacterial antigen
vaccine effectiveness in feedlot cattle that included six clinical
trials published since 1990. Though some knowledge synthesis
has been conducted on the topic of commercial BRD vaccines,
updated systematic reviews into commercial BRD vaccines could
explore factors that impact the summary effect of different
vaccines.

Within the identified seven topic areas, we observed some vari-
ination in the specifics of the interventions and the outcomes mea-
sured. Future primary research could focus on these seven specific
area topics with an emphasis on building a body of research on
specific interventions with more depth. These primary studies
could be further assessed using systematic review and
meta-analysis methods to answer specific questions about the
overall effectiveness of that intervention and to explore sources of
variation among the studies.

This scoping review had several potential limitations. First, we
included a wide variety of interventions in our search terms, but
may have failed to include all possible search terms for specific
interventions, thereby potentially missing articles. Systematic
reviews of specific interventions should include a more compre-
prehensive search. Second, we may have overlooked some non-
antibiotic interventions or health outcomes if they were not listed
in the article title or abstract. Third, we accessed only publically
available sources through data platforms available via the
University of Guelph, and so we may have missed additional arti-
cles such as unpublished studies generated by companies testing
products. We attempted to overcome this potential deficit using a
Google search, but we recognize that any Google search is nei-
ther repeatable nor transparent. Google is a search engine and not
data platform, and so Google was unable to deliver meaningful
results for our extensive number of search terms in a Boolean
string (Grindlay et al., 2012). Nevertheless, we obtained the
majority of the theses, for which there were no subsequent pub-
lished articles, through the Google search. Fourth, we were unable
to search the CAB Direct platform due to technical difficulties and
without the addition of studies identified through that platform
we may not have achieved as comprehensive a search as intended.
Grindlay et al. (2012) compared the coverage of veterinary jour-
nals by nine databases and found that CAB Abstracts had excel-
lent coverage, and so it is possible that the CAB platform
contained relevant articles that our search did not identify.
Fifth, our data charting process would have been more accurate
had we charted the data at the individual study level rather than at
the article level. However, with only 9% of our relevant articles
describing more than one study we do not think that
charting the data at the article level substantially impacted our
findings. Finally, we did not chart data regarding inherent bias in
the included studies such as randomization of clinical trials,
lack of concealment or blinding, loss to follow-up, or selective
outcome reporting. Any systematic review utilizing the results of

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this scoping review should include a risk of bias assessment (Higgins and Green, 2011).

**Conclusion**

In this scoping review, we described the literature on non-antibiotic approaches for disease prevention and control in beef and veal production. Although there was considerable volume and breadth of research within this body of literature, there was limited depth. The research diversity pertained not only to specific interventions and populations but also to the comparison groups and outcomes measured. Despite a large volume of research evaluating a huge variety of interventions there was relatively little replication of studies. There were relatively few clinical trials utilizing a preventive antibiotic comparison group. No studies evaluated a non-antibiotic treatment compared to an antibiotic treatment in ill animals. Some clinical trials did not report clinically important outcomes.

Systematic reviews and meta-analyses, if not already done, could be conducted for the seven topic areas identified as having sufficient literature with enough commonality to combine. These could potentially answer questions about the summary effectiveness of specific interventions and explore sources of variation among studies (i.e. what factors influence different results found among similar studies). Future primary research could focus on these seven topic areas, with the inclusion of clinically important outcomes, thereby enhancing the depth of this research and provide opportunities for exploration of variation among similar studies. Future primary research could also include preventive antibiotic use comparison groups where appropriate to enhance the evidence for antibiotic alternatives in beef and veal production.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S1466252319000252.

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