A Review of Alternative Practices to Antimicrobial Use for Disease Control in the Commercial Feedlot

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Executive Summary

The purpose of this review was two-fold, to a) give an overview of the modern feedlot industry in North America to provide context, and b) to search the scientific literature in order to identify alternative practices to antimicrobial use for disease control in that same industry. A fundamental assumption of the review was that reducing antimicrobial use would reduce the potential for antimicrobial resistant bacteria to emerge and persist in the feedlot setting. To most effectively reduce antimicrobial use in the feedlot, one needs to find alternative ways to prevent or effectively manage bacterial pneumonia in calves (often the principle reason for antimicrobial use) around the time of their arrival at the feedlot, as well as other diseases caused by bacteria (e.g. liver abscesses). Our key review question, therefore, was: "Are there management practices that do not involve the administration of antimicrobials that reduce the incidence of illness and mortality due to pneumonia, especially in high risk feedlot calves?" We also searched for management practices that reduce the incidence of liver abscesses in feedlot cattle but that do not rely on in-feed or sub-therapeutic antimicrobial use.

Our search strategy included reference to management strategies that *included* antimicrobial use or explored the development of antimicrobial resistance in an attempt to capture *any* papers that could contribute to answering our review questions. We did this because a preliminary search restricted to finding disease management strategies that excluded such references identified very few papers. We used this strategy to search the OVID Medline, CAB, Agricola, EMBASE, and BIOSIS bibliographic databases for studies published from 1988 to April 2009. The strategy produced 2,820 unique abstracts that were then subjected to a series of inclusion and exclusion criteria, which allowed us to classify them according to their relevance to our review questions, the disease or infection control strategy studied, and the strength of the results and conclusions. We then examined the literature cited in key selected papers to identify further papers of relevance to the review. This supplemental search identified 76 additional papers that were also subjected to the inclusion and exclusion criteria.

Research critically evaluating methods to prevent and control disease or the development of antimicrobial resistance (AMR) on feedlots was rare. A significant body of opinion advocated for a comprehensive and multi-method approach to infection control, but **clinical trials or systematic evaluation of the effectiveness of infection control practices was limited almost exclusively to evaluating the effects of vaccinating animals prior to or at the time of arrival at the feedlot, and evaluating the effects of treating animals using different antimicrobial regimes at arrival (metaphylaxis) or after arrival on morbidity, mortality and growth.** Most papers on AMR itself were microbial ecological studies of enteric organisms of public health concern as opposed to cattle pathogens of high concern. These papers dealt to a large degree with *E. coli,* and to a lesser extent with *Salmonella* and *Campylobacter.* Most were cross-sectional in nature and thus did not provide controlled evaluation of management methods to prevent or reduce AMR.

There were 387 papers that had some relevance to our topic, indicating a publication average of

19 papers per year over the past twenty years, or roughly three papers every two months. We classified 142 papers (or 5% of the original 2896 abstracts) as ones that dealt more specifically with management approaches to reduce feedlot disease without antimicrobial use. One quarter (36 or 25%) of these papers dealt with *risk factors* for disease development at the feedlot, while another quarter (33 or 23%) looked at *vaccination upon arrival* at the feedlot. One fifth (28 or 20%) of the papers had *disease management* at the feedlot as their main subject; only nine of these 28 papers presented evidence from new data collected by the authors and none of them provided information that might be useful for designing effective disease management strategies for the large modern feedlot. The remaining papers looked at *nutritional* management of disease (17 or 12%), vaccination or preconditioning (a process involving weaning calves at least three weeks prior to sale, training to eat from a feed bunk, and vaccination) *prior to arrival* at the feedlot (14 or 10%), and miscellaneous issues (14 or 10%).

The papers that dealt with *risk factors* for disease were predominantly observational studies. The majority of these looked at specific pathogens (20 papers or 56%), while some looked at general risk factors (10), and a few examined animal behaviour (3), mixing (2), or transportation. A number of these observational studies are useful for understanding the epidemiology of bacterial diseases in the feedlot and developing hypotheses about alternative disease management strategies. For example, it appears that disease at the feedlot can cluster at the levels of cow-calf sources, feedlots, and pens within feedlots, although this clustering is poorly understood. Time of year animals are purchased, weight of calves purchased (a proxy for age), animal source, distance trucked (in some cases), mixing of calves from different sources, and climatic factors (specifically total precipitation and temperature variability) are variables shown to be potentially important reasons disease clusters at the feedlot. Feedlot managers now use these variables to classify which incoming animals are at high risk of developing disease early during the feeding process to better target metaphylactic antimicrobial use immediately upon arrival. Unfortunately, we did not see much else in the literature in terms of managing high risk animals at arrival, other than to avoid purchasing them, an approach that is only useful for owners of relatively small feedlots. There is much less published on other variables, like pen hygiene, pen sizes or densities, or movement of sick animals within the feedlot, which could be used to help feedlot managers improve their present methods of disease control.

Several of the observational risk factor studies have found that the risk of pneumonia-related morbidity and mortality in calves increases significantly in the fall, when the sale of freshly weaned calves reaches its peak. Furthermore, some have found that this risk can increase significantly as the fall progresses, a phenomenon dubbed the "November effect" by Canadian researchers in the early 1990s. This finding coincides with the observations of some feedlot owners that the effectiveness of their metaphylactic antimicrobial strategies for high risk calves seems to decrease as the fall progresses. Studies are needed that explore how real and widespread this so-called 'November effect' might be across the industry, how much AMR might or might not have to do with the phenomenon, and ultimately, what to do about it. These studies should include comparisons of how different animal management strategies within the feedlot (in terms of pen hygiene, pen densities, nutrition, and animal movement, as well as different antimicrobial use strategies) could effectively decrease the "November effect."

Vaccination on arrival for pneumonia seems to have some effect, although it appears to be less than that for the concurrent strategy of antimicrobial metaphylaxis. This is not surprising given that many calves arrive at the feedlot already harbouring disease, prior to vaccination. However, the true effectiveness of vaccination at arrival has been hampered by design faults present in many papers. Furthermore, given that many vaccine field trials are done where all high risk animals receive metaphylactic antimicrobials at arrival, it is difficult to know how well the vaccines would work in the absence of antimicrobial metaphylaxis. There is also some evidence that vaccination of calves at their source cow-calf farms several weeks prior to being shipped to a feedlot reduces disease at the feedlot, but the consistency and size of the effect has been difficult to establish, at least in part due to design challenges. This, combined with a historical inability of the auction market transfer system to consistently provide cow-calf operators with a premium to vaccinate their calves means that pre-vaccination and preconditioning have not become effective disease management strategies for feedlot owners in North America.

Liver abscesses are one of the most commonly cited reasons for the use of in-feed antimicrobials in feedlots. Only eleven papers dealt specifically with liver abscesses. Attempts at vaccination for this bacterial disease have had, at best, mixed results. In the absence of effective vaccination, and given current feeding protocols that require rapid transition to high energy feeds, medicated feeds remain the most common approach to reducing the prevalence and severity of liver abscesses. There is a lack of studies systematically examining the effect on antimicrobial resistance of feeding antimicrobials under commercial conditions.

We conclude that, with the possible exception of vaccination against some pathogens on or before arrival, there were no intervention studies published in the past 20 years that provide convincing evidence of useful management practices for large modern feedlots that would reduce the incidence of illness and mortality from bacterial pneumonia that do not also involve the administration of antimicrobials. Work from observational studies has provided useful information as to what constitutes a high risk animal on-arrival at the feedlot so that antimicrobial metaphylaxis can be targeted toward this group.

Future observational and intervention studies designed to explore the effectiveness of disease management practices alternative to antimicrobial use should be encouraged. The long-term effects of metaphylactic antimicrobial use in the feedlot on treatment efficacy and AMR should be examined within and across different feedlots. Finally, contact with researchers already exploring antimicrobial cycling or rotation in human hospital settings should be encouraged, as this may provide insights or solutions that have not already been attempted on a commercial feedlot. Design challenges in both settings could be examined to explore how cross-fertilization of ideas could help research to progress in both settings.

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Introduction and Relevant Background Information

The introduction of antimicrobials facilitated the growth and industrialization of feedlot production systems by providing producers with the means to control disease, especially respiratory and enteric diseases, which are common in intensively raised animals (1–3). Nevertheless, morbidity and mortality from infectious diseases continue to be significant impediments to the production of feedlot raised cattle. Antimicrobial use remains important to intensive animal production.

The agriculture industry recognizes growing public concerns regarding the use of antimicrobials in animal production systems. Maintaining consumer confidence is essential to the industry's success. Combating disease also remains essential to economically viable beef production. Key industry managers recognize that relying on "the next new drug" cannot be the foundation of their battle against infections. Alternative treatment and management procedures to reduce the incidence of disease are continuously sought.

For many feedlot managers, problems with morbidity and mortality associated with respiratory disease in high risk calves soon after arrival at the feedlot have increased during the past two decades. This trend has occurred despite the appearance of new and more expensive antimicrobial products. Some have indicated that they perceive a reduction in antimicrobial efficacy as they proceed through the fall season, when the largest volume of calves arrive at the feedlot and weather conditions deteriorate, while respiratory morbidity increases.

Because of this trend, the cattle feedlot industry is well prepared to examine management approaches that decrease the potential for developing antimicrobial resistance (AMR) that could hamper antimicrobial effectiveness in controlling feedlot disease. These approaches include reducing antimicrobial use, exploring different antimicrobial use strategies, and implementing comprehensive infection control practices with the intention of reducing the prevalence of infections on feedlots.

Comprehensive infection control programs are at the foundation of plans to prevent and combat AMR in the human health sector. A top priority of the United States Centers for Disease Control and Prevention report, *The Interagency Task Force on Antimicrobial Resistance and a Public Health Action Plan to Combat Antimicrobial Resistance,* is to, "evaluate the effectiveness…of current and novel infection-control practices for health care and extended care settings and in the community." In contrast, their top priority for dealing with the animal contribution to AMR pathogens focused on the review and approval process for new drugs for agriculture (4). *The WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food* (5) similarly focuses largely on surveillance and prudent drug use as opposed to an integrated program of prevention through comprehensive infection control. There are many papers and opinions regarding the contribution of antimicrobial use to the burden of human resistant pathogens. Yet, there is little documentation of comprehensive and systematic approaches to infection control to prevent antimicrobial drug resistance emergence on farms as a means of primary prevention.

There is evidence in agriculture that when antimicrobial drugs are absent, natural flora compete with AMR pathogens, making proliferation of AMR pathogens less likely (6). Finding ways to reduce the need for antimicrobials, therefore, seems to be a viable strategy and more likely to result in gains in the race against emerging AMR strains than is the continued production of new generation drugs.

Organization of this Report

The purpose of this review was to search the scientific literature in order to identify alternative practices to antimicrobial use for disease control in the North American feedlot industry. A fundamental assumption of the review was that reducing antimicrobial use would reduce the potential for antimicrobial resistant bacteria to emerge and persist in the feedlot setting.

A secondary purpose of the review was to give the reader an overview of key elements of the modern feedlot industry in North America that are relevant to antimicrobial use. To most effectively reduce antimicrobial use in the feedlot, one needs to find alternative ways of preventing or effectively managing bacterial pneumonia in calves (often the principle reason for antimicrobial use) around the time of their arrival at the feedlot, as well as other bacterial diseases such as liver abscesses. We begin this section of the report by providing background about infectious diseases in the feedlot that function as the main stimulus for antimicrobial use. In following sub-sections we briefly explore what is known about antimicrobial resistance in commercial feedlots, present prudent use guidelines that have been developed for antimicrobial use in the North American feedlot, and summarize current antimicrobial use practices in the feedlot.

In Section 3, we return to our specific objectives, focusing in the sections that follow on management techniques that do not involve antimicrobial use. Sections 4 to 6 cover the approach we took to consulting the literature. We present the results of our findings in Section 7, with discussion following in Sections 8 and 9.

For the reader who is new to the feedlot industry and would like more information on how the industry functions in North America, we provide a primer in Appendix 1 entitled "Beef Cattle in North America." Finally, in Appendix 2 we outline standard human infection control guidelines in the health care setting, and compare those to methods of infection control that could potentially be available in beef feedlots.

Infectious Disease in the Feedlot

Bovine respiratory disease (BRD) is the leading cause of morbidity and mortality in the United States feedlots (7). BRD is a complex multifactoral disease in calves that is often precipitated by stressful management or environmental-based events that occur between weaning and the first thirty days on the feedlot (hence the synonym "shipping fever"), and frequently involves one or more viral etiological agents in association with concurrent bacterial infection (7,8). Bovine respiratory syncytial virus (BRS), parainfluenza-3 virus (PI3), infectious bovine rhinotracheitis virus (IBR) and bovine viral diarrhoea virus (BVDV) are often inciting agents, and *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, Arcanobacterium pyogenes, Mycoplasma dispar* and *Mycoplasma bovis* are common bacterial agents in BRD (7–11). The complex pathogenic synergism that results in clinical BRD makes it difficult to accurately diagnose and treat the specific disease-causing agent (9,12); hence calves are typically treated on arrival with a broad spectrum antimicrobial, a procedure called metaphylaxis, as a preventative measure. Unfortunately, BRD-related morbidity and mortality continue to affect newly arrived calves.

Table 1: Most common diseases on feedlots and ranges of prevalence (selected references)

Common Diseases	Disease Rates		Source
	Morbidity	**Mortality**	
Bovine Respiratory Disease Complex (BRD)	15–45%	1–5%	Gallo & Berg (9)
	14–45%	1–5%	Kelly & Janzen (13)
	Can exceed 50%	7.2/1000	Smith (11)
		2.4–5.3%	Ribble, Meek, Jim *et al.* (14)
Liver abscesses	12–32%		Nagaraja & Lechtenberg (15)
Digestive disorders (e.g. bloat)		2.9/1000	Smith (11)
Other		2.5/1000	Smith (11)

In a prevalence study by Gagea *et al.* (16), the primary contributor to death in calves within 60 days of their introduction to Ontario beef feedlots was determined to be fibrino-suppurative bronchopneumonia (49 of 99 calves). Caseonecrotic bronchopneumonia consistent with *Mycoplasma bovis* contributed to 36 of 99 deaths, followed by viral respiratory disease (19/99), Bovine Viral Diarrhoea Disease (BVDV) (21/99), *Haemophilus (Histophilus) somni* myocarditis (8/99), ruminal bloat (2/99) and miscellaneous diseases (8/99). Respiratory problems, from a number of different etiological agents, account for a large proportion of calf mortality. Smith (11) estimated that for every 1000 calves entering a feedlot, 7.2 will die from respiratory problems (primarily bovine respiratory disease, or "shipping fever"), 2.9 will die of digestive tract disorders (such as bloat and coccidiosis), and 2.5 will die from other causes (for example, foot rot, injuries and diphtheria).

Typically, young, recently-weaned calves 6–8 months old from multiple farms that are commingled in auction marts and transport trucks have a much higher risk of respiratory disease (17) and death. There is some evidence that risk is seasonally based, with higher occurrences of fatal fibrinous pneumonia in late October and November (18).

The time bracketing the arrival of a calf on a feedlot is critical for infectious disease control. Major causes of morbidity and mortality in North American feedlots come in two waves (Table 2). The first wave typically occurs within 2–3 weeks after arrival and is associated with the BRD complex (9). The second occurs later in the feedlot cycle and is often attributed to either systemic infection with *Histophilus somni* (9) or Acute Interstitial Pneumonia (AIP) (11). This pattern explains why the majority of antimicrobial use on feedlots is within the first 30 days post arrival (19).

Table 2: Peak times for onset of respiratory disease in feedlot cattle (selected references)

Outcome	Time	Source
Febrile disease classified as BRD	Within 27 days post-arrival on feedlots	Duff & Galyean (7)
Fibrinosuppurative bronchopneumonia or caseonecrotic bronchopneumonia	14.6 ± 2.0 or 15.5 ± 1.5 days	Gagea *et al,* (16)
Mortality rate	Highest by day 16	Ribble *et al.* (20)
Onset of fatal illness	26% of calves that die 1st become ill within 7 days, 22% become fatally ill within 14 days, 48% were ill by day 16	Ribble *et al.* (20)
Seroconversion to bovine coronovirus	58% with 28 days post-arrival (range 20–78%)	Lathrop *et al.* (21)
Majority of cases of respiratory infections	Within the 1st 30 days post-arrival	Alexander *et al.* (22)
Most isolates of the bacterial pathogen P. hemolytica	Within the first 15 days post-arrival	Purdy *et al.* (23)
Most cases of bacterial pneumonia (pasteurellosis)	Within 14 days post-arrival	Griffin (24)

Edwards (17) noted that 70% of the recorded morbidity occurs within the first forty-five days in the feedlot, with 40% of deaths occurring in this same period. Kelly & Janzen (13) reviewed literature published between 1955 and 1984 on morbidity and mortality incidence rates in the first ten weeks after calves arrived at feedlots, relying on papers that used "treatment," "sickness," or "respiratory disease" as case definitions for morbidity. Morbidity incidence ranged from 14 to 45% with an upper limit of 69%. Mortality rates averaged between 1 and 5%, but were reported to be as high as 15%. Biological variability in calves (e.g. immune status, level of stress, pathogen load, nutritional background, amount of mixing with calves from other farms) and management variability between feedlots (e.g. how and where calves are purchased, selection for preconditioning, husbandry practices, staff competence) account for the wide ranges in incidence rates between feedlots, and even on the same feedlot between years and pens.

The first few weeks after arrival on feedlots can also be times of the highest prevalence of AMR bacteria within feedlots. Calves arrive on feedlots with AMR organisms, including organisms resistant to antimicrobials to which the calves have not previously been exposed; the source of calves and environmental stressors seem to affect the proportion of incoming calves with AMR organisms (19,25–28). The odds of calves shedding single and multiple drug resistant *E.coli* increases after only a few days at a feedlot (29). Transmission of AMR organisms between pens and calves seems to be restricted largely to the high stress post-arrival period or for short periods post treatment and does not seem to be widespread (26,30–32). AMR levels can increase after arrival for several weeks, but tend to decrease in the second half of the feeding period, potentially reflecting the effects of post-arrival stressors on shedding (29). Over time, differences in AMR prevalence seen in incoming calves disappears and/or introduced strains fail to persist, presumably due to environmental selection factors (26,27).

Antimicrobial Resistance in Cattle Feedlots

The specific role that agricultural antimicrobial use has in the development of antimicrobial resistance in human pathogens is widely disputed. Antimicrobials are extensively used in human medicine, veterinary medicine, and agriculture for the treatment and prevention of infectious diseases, and in the agriculture sector as feed additives to promote increased growth and meat yield. The development of AMR to cheap and effective first choice antimicrobials is becoming a serious global problem for both human and veterinary medicine (33–36). Concern over this problem has led to action. The Swann report advised in 1969 on precautionary principles that antimicrobials used in human medicine be banned from use as feed additives for livestock in the United Kingdom. Sweden, in 1986, made antibacterial growth promoters available by veterinary prescription only (37), and in July 1989, the European Union implemented a ban on the use of virginiamycin, bacitracin zinc, tylosin and spiramycin as growth promotants, followed in 2006 by a ban on monensin, avilamycin, salinomycin and flavomycin (38).

Resistance emerges when bacterial subpopulations with pre-existing resistance or reduced susceptibility are selected in the face of antimicrobial pressure. This selected subpopulation of microbes can then pass on their resistance genes through replication or conjugation (a process whereby plasmids carrying the resistance genes "jump" from one organism to another related organism) (36), transfection, and transposition. The inappropriate use of antimicrobials – i.e. used for too short a time, at too low a dose, at inadequate potency, or for the wrong disease – is cited as the primary driver in the emergence of antimicrobial resistance (33,36). These basic mechanisms are not under debate. However, the proportional contribution of agriculture to the pool of AMR pathogens to which people are exposed has yet to be established or quantified in a conclusive manner. It is not the intent of this paper to draw definitive conclusions on this issue. Rather, we assume a precautionary approach that favours actions to avoid or reduce AMR organisms in food animals.

In addition to debate about the contribution of use of antimicrobials in cattle to human health risk from AMR, there is also debate about the role of antimicrobial use in the emergence or spread of AMR organisms within feedlots. Numerous studies from geographically distinct beef feedlots have shown that enteric strains of *Escherichia coli, Salmonella, Campylobacter* and *Enterobacter* can carry resistance genes to one or more antimicrobials (28,29,39–42). Some authors have demonstrated an increase in the prevalence of antimicrobial resistance over time spent in a feedlot (29,43). Others have not found any associations between antimicrobial use and antimicrobial resistance on feedlots (39,44,45). Hoyle *et al.* (2006) detected ampicillin-resistant generic *E. coli* on an organic beef farm with no history of antimicrobial use. Dargatz *et al.* (46) found no association between resistance patterns in *Salmonella* on feedlots and drugs being fed to the animals at the time of sampling. These authors, however, warned against making broad generalizations noting that different bacteria react differently to management pressures (46).

These discrepancies prompt some authors to argue that there is currently no clear link between animals being fed antimicrobials and the emergence of AMR pathogens, let alone the transfer of these pathogens to humans (37,47,48). It is cost effective for producers to use antimicrobial feed additives for prophylaxis and growth promotion. Gallo & Berg (37) showed that the inclusion of chlortetracycline and sulfamethazine at concentrations of 250 mg/head/day each in feed for the first fifty-six days after arrival at the feedlot significantly reduced the incidence of acute and chronic respiratory disease and the rate of relapse. A reduction in acute and chronic diseases decreases treatment costs and mortality rates and increases average daily weight gains, which equates to financial gain for the producer.

The effects of antimicrobial use on AMR patterns were not consistent across feedlots, diseases, or pathogens (16,25,49–52). Some research has shown that feedlot antimicrobial use strategies affect the abundance and seasonal distribution of antimicrobial resistance genes (53,54). Others have found no association between antimicrobial use and AMR (39,52,55). The variation between years, feedlots and pens suggest that no single strategy is likely to control AMR; a program of multiple methods that can be applied in an adaptive fashion may be required. However, conflicting results may reflect the approach used to characterize AMR risk (for example, cultivating bacteria versus examining resistance genes) and/or the target organisms studied. Few papers explicitly evaluated the impact of antimicrobial use protocols on AMR outcomes (56). Perhaps most importantly, the research we found on the relationships of antimicrobial exposure and AMR focused largely on the effects of antimicrobials on enteric bacteria (often commensal bacteria for the cattle) that might be of public health concern rather than on the pathogens that result in most feedlot disease (19,25–27,57).

It was not a surprise to find research that showed exposure to antimicrobial drugs increased the prevalence or shedding of resistant bacteria from feedlot cattle. It was also not a surprise to find support for the conclusion that in-feed antimicrobials were more consistently associated with resistance than injectable (individual-animal) medications, as in-feed medications are administered to larger numbers of animals, for longer periods of time, and at lower doses than individual animal treatments (58). There were a number of papers, however, that concluded that the rates of AMR on feedlots was not surprisingly high and, in fact, that rates of multidrug resistance was low and resistance to drugs of high importance for human medicine also was low (29,44,49,55,59–61). A slaughterhouse survey of carcass contamination with enteric bacteria concluded that feedlot animals of high health status posed little public health risk as they carried few *Salmonella* serovars of public health significance and few were broadly resistant to antimicrobials (61).

A number of studies questioned the effects of antimicrobial exposure and AMR patterns, suggesting unspecified environmental selection pressures may play an important role in the presence, type and prevalence of AMR in feedlots (25,26,31,41,49,62). Environmental sources of resistant bacteria, including food and contaminated equipment, may even serve as the source of infection or colonization by AMR organisms on pasture or in the feedlot (25,31,32,63,64).

Studies rarely followed animals through to slaughter to see if resistant clones entered the human food chain. There were data to support the conclusion that resistant clones do not persist and/or significantly decline by the time an animal is slaughtered 26,27,65) and that drug exposure earlier in the feeding period did not result in different resistance patterns than for untreated animals (66). One paper concluded that poor health status and increased hide contamination increased the risk that AMR pathogens of public health importance could enter the food chain at slaughter (61).

Antimicrobial Prudent Use Guidelines for Beef Cattle

Prudent use guidelines for the selection and use of therapeutic antimicrobials are available for a number of livestock species from both the Canadian Veterinary Medical Association (CVMA) and the American Veterinary Medical Association (AVMA). A full summary of these guidelines is presented in Table 3. Guidelines and procedures for antimicrobial use that were identified by the Canadian Cattleman's Association (67) are also presented in Table 3. The Canadian and American veterinary guidelines are more comprehensive than the industry guidelines; this is to be expected given the legal aspects of prescribing and dispensing antimicrobials. Both the CVMA and AVMA prudent use guidelines start with a focus on management issues to decrease the requirements for antimicrobial use. The most recent prudent use guidelines from the CVMA (68) include alternatives to antimicrobials, such as the supportive and symptomatic care of clinical disease. This section was not present in earlier prudent use guidelines (69,70). In the section *Appropriate Selection and Use of Antimicrobials,* emphasis is placed on the judicious use of antimicrobials based on clinical evidence and label recommendations for that product and pathogen/clinical disease. Prophylaxis and metaphylaxis are mentioned fleetingly; however, a carefully designed prophylaxis regimen under veterinary supervision is not prohibited by these prudent use guidelines.

We did not set out to evaluate all available prudent use guidelines for therapeutic antimicrobial use, as this was not intended to be the focus of this report. A large, albeit dated, list of guidelines from mostly North America and Europe were used by the World Health Organization (WHO) (5) to draft a document intended to reduce the overuse and misuse of antimicrobials in food animals. A number of these guidelines are no longer available online through the cited URLs. WHO encouraged national governments to adopt a "proactive approach to reduce the need for antimicrobials in animals and their contribution to antimicrobial resistance and to ensure their prudent use (including reducing overuse and misuse), as elements of a national strategy for the containment of antimicrobial resistance" (5). Routine prophylactic use was strongly discouraged – it "should never be used as a substitute for good animal health management," and efforts to prevent disease should continuously look for ways to reduce the need for prophylactic antimicrobial use (5). In general, however, this publication by the WHO set out to provide guidelines to be followed and modified by individual countries, and is not nearly as comprehensive as the guidelines available through the CVMA and AVMA. Interestingly, the Australian code of practice for prescription and use of antimicrobials states that antimicrobials should only be administered, dispensed or prescribed through a valid veterinary-client relationship following veterinary assessment of confirmed or suspected bacterial disease. Seemingly contrary to the WHO, this document continues to state that it is the responsibility of the veterinarians to "stress to owners the importance of routine prophylaxis to reduce the risk of clinical bacterial disease and the need for antimicrobial therapy (71)." Furthermore, the transmission of AMR pathogens from livestock to humans can be curtailed through proper hygiene and thorough cooking of animal products (71). The reasons behind this statement were not expounded on.

Table 3: Summarized prudent use guidelines for beef cattle, available from the Canadian Veterinary Medical Association (68,70) and the American Association of Bovine Practitioners (69)

Summary: CVMA and AABP Prudent Use Guidelines for Cattle		Industry*
1. Decrease Requirements for Antimicrobials		
Veterinarians should assist clients to design herd management, immunization, housing, and nutrition programs aimed at decreasing the need for antimicrobial use		
a) Management	Husbandry practices, animal housing and farm hygiene to reduce exposure to pathogen	Yes
b) Health status of individuals and the herd	Specific immunity, sources and modes of pathogen transmission, roles of concurrent infections and stressors, impacts of disease on growth, and productivity	
c) Housing	Adequate space, bedding, ventilation, and protection from weather and the environment to reduce stress and maintain health	Yes
d) Nutrition	Adequate water, protein, energy, and micronutrient intake to maintain overall health and productivity	Yes
2. Alternatives to Antimicrobials		
Where scientifically and medically valid, alternative therapeutic options should be considered prior to antimicrobial use, or as an adjunct to antimicrobial use		
a) Supportive care	Electrolyte therapy	
b) Symptomatic care	Anti-inflammatory therapy	
3. Veterinarian-Client Relationship		
Dispensing and prescribing antimicrobials should not be done without a valid veterinary-client relationship		Yes
4. Appropriate Selection and Use of Antimicrobials		
Optimize therapeutic antimicrobial use		
a) Continuing education	Veterinarians knowledgeable as to current antimicrobial use policies and antimicrobial resistance issues	
b) Compounded antimicrobials	Should be avoided whenever possible	
c) Combination antimicrobial therapy	Not recommended unless evidence for increase in efficacy or suppression of resistance in the target pathogen	
d) Knowledge of the antimicrobial	Product choices and regimens based on pharmacokinetics, pharmacodynamics, package insert information, and other literature	

Confine therapeutic antimicrobial use to appropriate clinical indications		
a) Clinical evidence	Antimicrobial prescription based on identification of the pathogen (clinical signs, history, additional diagnostics)	
b) Selection and administration of antimicrobials	Appropriate and justified antimicrobial for the pathogen, and administered at the most effective dose, route, frequency, and duration	
c) Anticipated outcomes	Use antimicrobials with specific clinical outcome(s) in mind	
d) Labelled use	Use antimicrobials labelled for the condition whenever possible at recommended label dose, route, frequency, and duration; special requirements need to be met for extra-label drug use; some extra-label drug use is prohibited	Yes
e) Duration of use	Use antimicrobials for the least amount of time necessary to control the pathogen, reduce pathogen shedding, and minimize carrier state or recurrence of clinical disease	
f) Target the pathogen	Treat for the pathogen appropriately, i.e. do not use an antifungal when the pathogen is bacterial; use antimicrobials with narrow spectrum of activity and known efficacy against the pathogen	
g) Target the affected organ	When appropriate, local therapy is preferred over systemic therapy	
h) Use of human antimicrobials	Avoid when possible, especially when antimicrobials of lesser importance to human medicine are available	
Know when to limit therapeutic antimicrobial use		
a) When not to treat	Chronic cases or animals with poor prognosis should be removed or isolated from the herd	Yes
b) Treat only animals at risk	Treat the fewest animals indicated; treat ill or at-risk animals	
c) Make use of farm history	Morbidity, mortality, and history of therapeutic antimicrobial use on the farm should be used to help decide when to begin treating at the group level	

Minimize the risk of environmental contamination		
a) Avoid spillage and waste	Water medicators and feeders should be properly adjusted to deliver the desired dose	Yes
b) Separation of medicated and non-medicated feeds at the feed mill	Proper and adequate flushing methods at the feed mills following the preparation of medicated feeds	
c) Reduce unintentional feeding of medicated feeds	Feed handling, delivery, and storage practices designed to minimize the risk of cross-contamination between medicated and non-medicated	Yes
Maintain accurate treatment records and outcomes		
a) Accurate animal/ group identification	For trace-back and accountability, e.g. drug residues screening	Yes
b) Monitor compliance	For assessing appropriate antimicrobial use and efficacy of selected therapeutic regimens	Yes
c) Antimicrobial efficacy monitoring	Periodic evaluation of herd pathogen susceptibility and therapeutic response	
Other considerations		
a) Appropriate prophylaxis and metaphylaxis	Based on group, source or production unit evaluation. Do not use as Standard Practice	Yes
b) Cold chain	Protect antimicrobial integrity through proper handling, storage, and observation of the expiration date	Yes

5. Judicious On-Farm Antimicrobial Use		
a) Veterinary oversight	Proper farm use of antimicrobials requires veterinary involvement in decision-making process	
b) Veterinary knowledge	Veterinarians are the primary source of information on the use of antimicrobials	
c) Avoid antimicrobial stockpiling	Dispense appropriate quantities for the production unit size and expected need	
d) Accurate labelling	Labels should be accurate to instruct farm personnel on the correct use of antimicrobials	
e) Training of personnel	Personnel should be adequately trained and competent to accurately diagnose common diseases, and know when and how to store, handle, and dispense antimicrobials	Yes
f) Written guidelines and protocols	Adequately describe conditions and instructions for antimicrobial use; standardized vaccination, parasite, and treatment programs	Yes

* Procedures identified in common between the Feedlot Good Production Practices Manual, June 1996 (67) (originally available from the Canadian Cattleman's Association office) and the AVMA and the CVMA are identified with a "Yes." Blank cells indicate no mention of that particular procedure by industry. Industry procedures not identified by the CVMA or AABP prudent use guidelines include:

- Documentation of previous health and treatment histories should accompany all imported calves
- Use of prophylactic antimicrobials may be warranted to reduce infections during castration and dehorning
- Sorting and mixing of cattle should be minimized to reduce stress and pathogen transmission
- Avoid using ancillary drugs unless prescribed by a veterinarian
- Know and adhere to all withdrawal times
- Do not use outdated antimicrobials, and dispose of them properly
- Preferentially use low volume, long-acting antimicrobials, especially those that can be administered subcutaneously
- Record all drug reactions
- Ensure ongoing education for all feedlot staff, especially as it pertains to antimicrobial use

The most recent CVMA prudent use guidelines (68) include antimicrobial treatment protocols for a number of selected clinical diseases. These antimicrobials were also identified according to the Veterinary Drug Directorate's categorization (VDDC) of antimicrobial drugs based on the importance to human health. Two (tulathromycin and tilmicosin) of the three commonly used antimicrobial products used against bovine pneumonia and undifferentiated respiratory disease are listed as Category II, or of high importance to human medicine (see Table 4). The third drug, Nuflor, is listed as Category III, or medium importance to human medicine. Interestingly, tulathromycin is the newest of the three antimicrobials to become available in the market; it also has the longest duration of effect (ten days). Of the eleven antimicrobials recommended by the CVMA, five are Category I, four are Category II and two are category III. As per the prudent use guidelines (Table 3), Category I antimicrobials are to be avoided whenever possible.

Table 4: Beef cattle antimicrobial treatment guidelines for bacterial pneumonia undifferentiated respiratory disease (68)

Disease	Microbial Agents	Treatment Options	VDDC
Bacterial pneumonia undifferentiated respiratory disease	*Mannheimia haemolytica*	Florfenicol	III
	Pasteurella multocida	Oxytetracycline dihydrate	III
	Histophilus somni	Oxytetracycline hydrochloride	II
	Mycoplasma bovis	Tilmicosin	II
	Mycoplasma spp.	Trimethoprim-sulphadoxine	II
		Tulathromycin	II
		Ceftiofur hydrochloride	I
		Ceftiofur sodium	I
		Ceftiofur crystalline free acid	I
		Danofloxacin	I
		Enrofloxacin	I

VDDC: Veterinary Drug Directorate's Categorization of Antimicrobial Drugs based on the Importance in Human Health.

Category I: Very high importance in human medicine; essential for the treatment of serious bacterial infections; limited or no availability of alternative antimicrobials for effective treatment in case of emergence of resistance to these agents.

Category II: High importance in human medicine; can be used to treat a variety of infections including serious infections and for which alternatives are generally available; bacteria resistant to drugs of this category are generally susceptible to Category I drugs.

Category III: Medium importance in human medicine; used for treatment of bacterial infections for which alternatives are generally available; infections caused by bacteria resistant to these drugs can, in general, be treated by Category II or I antimicrobials.

Category IV: Low importance in human medicine; currently not used in human medicine.

Antimicrobial Use Practices in the Feedlot

The precise quantities of antimicrobials used sub-therapeutically in livestock are unknown. Some authors estimate that 50% in tonnage of all antimicrobials produced are used for prophylaxis, metaphylaxis, and growth promotion in livestock and poultry (33,35,36), but how this translates into public health risk is either unclear or has not been substantiated (37). In Canada, comprehensive antimicrobial consumption data for livestock do not exist (72). Current Canadian legislation allows antimicrobials to be sold as feed additives, with veterinary prescriptions, or over-the-counter (33), making it difficult to track antimicrobial use. Antimicrobial consumption data are available from the United States for 1985: 458 tonnes of antimicrobials were reportedly used therapeutically in cattle, 1,100 tonnes were used sub-therapeutically, and 340 tonnes were used for growth promotion (3). Nothing is known about the cattle population that received these antimicrobials, although 116 million cattle were raised in the United States in 1985 (73). Simply reporting tonnage of antimicrobials is an inadequate way to express risk, as there is no accompanying information on the reasons for use, directions on duration and quantity used, outcomes of treatment, and epidemiological information associated with the animals treated.

Similarities in the use of specific antimicrobial families between human medicine and livestock production have not been well reported. The Government of Canada (72) listed the five most frequently dispensed systemic antimicrobial drug classes in humans in 2005 as: extended-spectrum penicillins (25.71%), macrolides (20.47%); tetracyclines (12.88%), fluoroquinolones (11.66%), and second-generation cephalosporins (5.20%). Such data do not exist for livestock, but Carsen *et al* (74) documented antimicrobial types and quantities reportedly used by 24 Ontario feedlot operators in a year. The most commonly used injectable antimicrobials were penicillin, macrolides, oxytetracycline, florfenicol, and spectinomycin. Monensin, tylosin, lasalocid, and tetracyclines were most commonly used in feed (as calculated according to number of animals exposed, duration, and average dose per day), and lincomycin-spectinomycin, chlortetracycline, and oxytetracycline were dosed in water. Based on estimated weights and measured quantities, however, Carsen *et al* (74) concluded that less than 1% of the antimicrobials reportedly used on the twenty-four Ontario feedlots are considered to be of the highest importance to human medicine in Canada. Caution is warranted, however, because of the ability of certain bacteria to develop resistance to multiple similarly related antimicrobials.

Veterinarians often recommend aggressive antimicrobial therapy for BRD management usually using one or combinations of tilmicosin, florfenicol, ceftiofur, or enrofloxacin (75). The timing of the high risk period, inability of vaccine alone to eliminate key infectious diseases, and the cost of disease to farmers serve as incentives for this approach. As such, well over half of feedlots typically use some form of mass medication on high risk animals on arrival (76).

It is important to note that while more than 50% of feedlots use on-arrival medications for disease control, this may translate to less than 20% of cattle being exposed, as not all arrivals are high risk animals.

There are times during the year when the volume of incoming calves is high and the risk of respiratory disease is increased that mass medicating a truckload of calves at entry is an effective means for reducing the subsequent need for treatment with antimicrobials (7,50,77–80). A number of terms for this approach are used in the literature, including mass medication on arrival, metaphylaxis, and prophylaxis (Table 5). Van Donkersgoed (81) performed a meta-analysis of field trials carried out to evaluate these practices for both parenteral and in-feed use, finding a total of 107 papers published from 1952–1992. Results from the ten trials that evaluated parenteral antimicrobial mass medication and that had a proper control group and randomization of subjects suggested a consistent reduction in subsequent morbidity as measured by treatment and relapse rates. Van Donkersgoed (81) could find no properly controlled and randomized trials examining the efficacy of feed and water mass medication.

Mass medication is also used some time after arrival, usually early during the feeding period, when feedlot personnel decide that pulling and treating animals exhibiting fever is not keeping pace with the daily development of new cases of respiratory disease. A variety of rules govern when such a mass medication occurs, based upon threshold measures of such outcomes as the proportion of the pen treated yesterday, or since arrival, or the steepness of the ascending limb of the epidemic curve. Feedlots develop their own criteria and gather evidence for what mass medication triggers seem to work, but we could find no recent published evidence-based assessment of what might work best across the industry.

Fine tuning the decision rules for which truckloads to mass medicate on arrival or when to mass medicate a pen during the feeding period is an important process for assessing efficacy and reducing expenses related to antimicrobial use. This fine tuning may also be important with respect to the potential effect mass medication has on the development of AMR by respiratory pathogens during the early feeding period. Papers that compare different antimicrobials' effectiveness when used as metaphylactic agents indicate how reduced subsequent antimicrobial treatments are relative to one another or to negative controls that received no antimicrobial on arrival. Of course, the act of mass medicating ensures that all incoming animals receive one injection of a long-acting antimicrobial. If this practice is not targeted towards truly high risk truckloads or pens, there is the potential to significantly increase the amount of antimicrobial use compared to a strategy of "pull, take temperature, and treat those with a fever."

A few papers have included a "pull, take temperature, and treat those with fevers" group along with mass medicated groups in their field trials to see if the approaches were equally effective (82–84). None looked to see if there were AMR differences between the two approaches. It may be, for example, that adhering to a consistent policy of "pull, temp and treat" throughout the high risk period results in less potential problems with reduced antimicrobial effectiveness developing later during the fall. This apparent reduction in antimicrobial effectiveness during the fall is an observation that has been reported by a number of feedlot operators in recent years. Clinical trials that explore using different triggers for applying mass medication, with specific attention paid to which are less likely to increase the prevalence of respiratory pathogens with AMR later in the feeding period, present some design challenges for feedlot disease researchers. If successful, such studies could pay dividends in terms of understanding the importance of targeted mass medication on the prevalence of AMR.

A threat to consistent findings regarding the effectiveness of antimicrobial use on BRD and AMR is the multifactoral nature of BRD and the potential for non-antimicrobial factors affecting AMR patterns. The presence of non-respiratory pathogens such as bovine viral diarrhea virus (85–88) or enteric bacteria (59) can also influence BRD-associated morbidity and/or mortality. Environmental factors such as feedlot design, hygiene, weather, and the source and nature of the cattle population also have been associated with differences in feedlot disease patterns (88).

Table 5: Examples of field trials of antimicrobial mass medication of bovine respiratory disease in calves on commercial or research feedlots since 1990.

Mass Medicated (in-text terminology)	Time of Treatment	Temp & Treat	Pharmaceutical	Randomized	Controlled (presence of untreated cohort)	Health Outcome	Results Summary	References
Prophylaxis	On arrival	No	Florfenicol	Yes	Yes	Morbidity	Prophylaxis (not vaccination) was correlated with decreased incidence of *Mannheimia haemolytica* organisms and delayed onset of bovine respiratory disease	Frank *et al.* (89)
No	After arrival	Yes	Tilmicosin phosphate	No	No	Culture	Tilmicosin treatment eliminated or reduced detectable colonization by *Pasteurella haemolytica* for up to 6 days	Frank *et al.* (84)
Yes (no terminology given)	Half before arrival, half on arrival	No	Tilmicosin phosphate	Yes	Yes	Morbidity	Treatment before or on arrival = lowered incidence of bovine respiratory disease and *Mannheimia haemolytica* colonization compared to controls, but no significant difference between treatment groups	Frank & Duff (90)
Mass medication	On arrival	Yes	Tilmicosin phosphate	Yes	Yes	Morbidity	Treatment based on rectal temp at time of processing was as effective as mass medication	Galyean *et al.* (83)
No	After arrival	Yes	Tilmicosin phosphate	Yes	Yes	Mortality Morbidity	All treatment doses (5, 10 & 20 mg/Kg subcutaneous injection) lowered morbidity and mortality compared to placebo	Gorham *et al.* (82)
Prophylaxis	On arrival and 3 days later	No	Oxytetracycline	Yes	No	Mortality Morbidity	Comparable efficacy between new Oxytet (intramuscular injection and SC routes) and old Oxytet (intramuscular injection routes) for bovine respiratory disease treatment, relapse and mortality rates	Guichon *et al.* (91)
Prophylaxis	On arrival	No	Trimethoprim-sulfadoxine Oxytetracycline	Yes	Yes	Mortality Morbidity	Prophylactic treatment reduced incidence morbidity and mortality due to bovine respiratory disease	Harland *et al.* (92)
Prophylaxis	On arrival	No	Oxytetracycline Tilmicosin	Yes	No	Mortality Morbidity	No significant differences in health outcomes between oxytet and tilmicosin	Schunicht *et al.* (93)
Prophylaxis	On arrival	No	Tilmicosin	Yes	Yes	Morbidity	Average days from arrival to 1st treatment for bovine respiratory disease was 21 d in medicated versus nine days in control group	Schumann *et al.* (94)
Prophylaxis	After arrival	No	Oxytetracycline	Yes	Yes	Serology Morbidity Mortality	Treatment had limited impact on death due to Haemophilus, but did appear to reduce risk of bovine respiratory disease treatment and mortality	Van Donkersgoed *et al,* (50)

Objectives and Policy/ Practice Question Posed

The objective of this report was to consult the literature and to identify validated alternative practices to antimicrobial use for disease control in the feedlot industry. A fundamental assumption of the review was that reducing antimicrobial use would reduce the potential for antimicrobial-resistant bacteria to emerge and persist in the feedlot setting. This is consistent with the suggestion of Gould (95) that the "challenge in antimicrobial stewardship is to reduce total consumption, the only sure way to delay the development of resistance." To most effectively reduce antimicrobial use in the feedlot, one needs to find alternative ways of preventing or effectively managing bacterial pneumonia in calves around the time of their arrival at the feedlot, as well as other diseases caused by bacteria such as liver abscesses.

Our primary specific question, therefore, was to ask: "Are there management practices that do not involve the administration of antimicrobials that reduce the incidence of illness and mortality due to pneumonia, especially in high-risk feedlot calves?" A secondary question was to ask: "Are there management practices that do not involve the administration of antimicrobials that reduce the incidence of liver abscesses in feedlot cattle?"

Materials and Methods

Search Strategy

Our preliminary efforts to identify publications in the literature that reported intervention trials designed specifically to evaluate management practices to reduce feedlot disease without antimicrobial use resulted in very few hits. We decided to ask four much broader questions that also included reference to management strategies that *included* antimicrobial use, and/or explored the development of antimicrobial resistance. We did this in an attempt to capture *any* papers that could have included within them reference to our original primary and secondary questions.

The four questions were as follows:

1. What are the known risk factors for the emergence and maintenance of antimicrobial resistance on feedlots, and have the critical control points been identified?
2. Has the effectiveness, efficiency, and/or acceptability of the application of the various pillars of infection control been assessed in a feedlot setting?
3. How does the metaphylactic use of antimicrobials affect the emergence of resistant bacteria in a feedlot setting?
4. What is the impact of different drug use implementation strategies (including rotation of drugs used within a feedlot) on antimicrobial resistance?

To ensure a high degree of search sensitivity, a combination of subject headings and text-words was used to represent these concepts in the search strategy, which was adapted to the search platform and indexing conventions of each database. The full search strategy is documented in Appendix 3.

The following multi-disciplinary bibliographic databases with international coverage of the literature were searched: OVID Medline, CAB, Agricola, EMBASE, and BIOSIS. Search results for all databases were limited to studies published from 1988 to 2009. No publication type, study design, geographic, or language limits were applied to the search results. The most recent search was performed in April 2009.

Inclusion/Exclusion Criteria

Abstracts for papers identified through our search strategy were reviewed for their relevance and subjected to a preliminary set of inclusion and exclusion criteria that were decided upon prior to the start of the literature search (Table 6). Inclusion and exclusion criteria were re-evaluated after the review team had read approximately 40 abstracts, and some minor modifications were made so as to better capture relevant papers. A primary investigator (PI) and a research assistant (RA) each read the same 75 abstracts for Question 1 (40 abstracts prior to the reevaluation of the inclusion and exclusion criteria, and 35 abstracts after that reevaluation) and 40 abstracts for Question 2. A Kappa test showed 82% and 71% agreement for Question 1, before and after the criteria re-evaluation respectively, and 89% for Question 2. We adjusted the sensitivity of the RA so that no papers in the test section would have been excluded by the RA but included by the PI. The RA was also instructed to follow the policy of including an abstract if there was any doubt about whether or not it should be included in accordance with the preliminary inclusion criteria.

The RA then applied the preliminary inclusion and exclusion criteria to all 2,745 remaining abstracts. The PI then read all of those abstracts not excluded by the RA, applying a secondary set of exclusion criteria (Table 6). Abstracts that were considered not relevant to the primary questions were also removed at this point. This process led to the exclusion of 2,509 papers, leaving 311 papers in the database.

Table 6: Inclusion and exclusion criteria

	Inclusion	Exclusion
	Preliminary Inclusion and Exclusion Criteria	
	Inclusion	**Exclusion**
Language	• English	• Non-English
Time period	• Last twenty years	• Prior to 1988
Agriculture system/ population	• Commercial feedlots • Non-intensive commercial beef production	• Intensive rearing of poultry, fish or swine, sheep, dairy cattle, goats
Study type	• Clinical reports • Clinical trials • Observational research • Economic analyses • Review articles	• General list serves, e-mail distribution lists, chat rooms, electronic versions of textbooks or websites that provide information without a moderator or peer-review process.
Outcomes	• Infectious disease rates • Drug use • Epidemiological patterns of antimicrobial resistant pathogens • Epidemiological patterns of disease on feedlots • Economic effects • Surveillance methods • Microbial ecology	• Does not relate to infectious disease control or drug use in feedlots
	Secondary Inclusion and Exclusion Criteria	
	Inclusion	**Exclusion**
Outcome measures	• Quantitative measures of effects of interventions • Qualitative measures of effects of interventions • Economic analyses	• Reports expressing opinion without supporting data
Data quality	• Meets accepted standards for quality evidence	• Anecdotal • Significant or obvious biases
Location	• Production systems representative of North American beef production systems	• Systems under study are so different from North American practices that the results cannot be confidently generalized

Data Collection and Appraisal Methods

The papers that passed the secondary inclusion criteria were obtained through either the University of Calgary or Vancouver Island University library holdings; papers that were not immediately available at these libraries were requested by inter-library loan. These papers were then read by one of the senior authors of this review (Stephen, Stitt, or Ribble) and classified as to a) their relevance to the specific questions of this literature review, b) the infection control management strategy studied by the paper's authors, and c) the strength of their results and conclusions. The PI then examined the literature cited in key selected papers to identify further papers of relevance to the review. These papers were read by one of the senior authors and incorporated into the full review.

Results

Search Results

The search strategy was applied to each of the four questions independently, working through the five different search engines in succession. This resulted in 5,688 abstracts. Duplicate abstracts across the search engine results were then identified and removed, resulting in 3,183 abstracts. The results of this process are documented in Table 7.

This process insured that there were no duplicates present across the five search engine results for each question. However, there still remained some duplicate abstracts where two or more of the questions produced the same abstract within a search engine. A total of 363 duplicates were identified in this category and removed, leaving 2,820 unique abstracts remaining in the database.

A total of 311 papers passed the secondary inclusion criteria. The PI then identified 76 papers classified as "papers not from searches" that were added to the database to give 387 papers. To gain perspective on the relative volume of papers by general research subject, the full papers were placed in files according to the subject categories shown in Table 8. There were 387 papers that had some relevance to our topic, indicating a publication average of 19 papers per year over the past twenty years, or roughly three papers every two months.

The largest file (#1), entitled "Management to reduce feedlot disease," contained 142 papers that were most relevant to the two primary questions that were the subject of this review: (1) Are there management practices that do not involve the administration of antimicrobials that reduce the incidence of illness and mortality due to pneumonia, especially in high-risk feedlot calves? and (2) Are there management practices that reduce the incidence of liver abscesses in feedlot cattle but do not rely on in-feed or sub-therapeutic antimicrobial use? Our examination of these 142 papers constitutes the subject matter for the rest of the results, found in section 5.2.

Information found in papers in the other files was used to help inform the presentation found in the introduction to this report, or in the background appendices. Information derived from a review of papers in files 3, 5, and 9 was used to construct the introductory section (2.3) on antimicrobial resistance in the feedlot; a review of papers in files 4 and 6–8 were used to help construct the introductory section (2.5) on antimicrobial use practices in the feedlot.

Table 7: Breakdown of total and unique abstracts retrieved by each search engine and by question

Search	OVID Medline Records	CAB Records	Unique CAB Abs Records	Agricola Records	Unique Agricola Records	EM-BASE Records	Unique EMBASE Records	BIOSIS Records	BIOSIS Unique Records
Q. #1	85	103	43	3	Nil	60	17	21	17
Q. #2	1,010	1,845	1,320	2,287	Nil	533	149	520	399
Q. #3	21	25	11	11	Nil	14	Nil	32	24
Q. #4	11	17	12	16	Nil	23	17	51	47
Total	**1,127**	**1,990**	**1,386**	**1,317**	**Nil**	**630**	**183**	**624**	**487**

Table 8: Number of papers found by the search, filed by subject category.

File Number	Subject Category	Number of Papers	Percent of Total
1	Management to reduce feedlot disease	142	37
2	Background and introduction papers	76	20
3	AMR studies involving *E.coli/Salmonella/Campylobacter*	73	19
4	Effect of therapeutic use of antimicrobials in feedlot	34	9
5	Does AMR increase or decrease in the feedlot?	22	6
6	Reducing pathogen load in the feedlot	14	4
7	Management to reduce antimicrobial use	13	3
8	Effect of sub-therapeutic use of antimicrobials in feedlot	7	2
9	AMR causes	6	2
	Total	387	

Management to Reduce Feedlot Disease

We classified 142 papers (or 5% of the original 2,896 abstracts) as ones that dealt more specifically with management approaches to reduce feedlot disease without antimicrobial use. We classified these papers into six categories, as shown in Table 9.

One quarter (36 or 25%) of these papers dealt with *risk factors* for disease development at the feedlot, while another quarter (33 or 23%) looked at *vaccination upon arrival* at the feedlot. One fifth (28 or 20%) of the papers had *disease management* at the feedlot as their main subject. The remaining papers looked at *nutritional* management of disease (17 or 12%), vaccination or preconditioning (a process involving weaning calves at least three weeks prior to sale, training to eat from a feed bunk, and vaccination) *prior to arrival* at the feedlot (14 or 10%), and miscellaneous issues (14 or 10%). In the next five subsections of section 5.2 we present a review of the papers found in each of these categories, in the order that they appear in Table 9.

Table 9: Subcategories of papers in the "Management to reduce feedlot disease" file.

Management to reduce feedlot disease sub-categories	Number of Papers	Percent of Total
Risk factors for disease development at the feedlot	36	25
Vaccination upon arrival at the feedlot	33	23
Disease and infection management at the feedlot	28	20
Nutritional management	17	12
Pre-conditioning and vaccination before the feedlot	14	10
Other	14	10
Total	142	

Risk Factors for Disease Development at the Feedlot

The papers that dealt with *risk factors* for disease were predominantly observational studies. The majority of these looked at specific pathogens, while some looked at general risk factors, and a few examined animal behaviour, mixing, or transportation (Table 10).

A number of these observational studies are useful for understanding the epidemiology of bacterial diseases in the feedlot and developing hypotheses about alternative disease management strategies. Disease (and AMR organisms) at the feedlot can cluster at the levels of cow-calf sources, feedlots, and pens within feedlots, although this clustering is poorly understood (29,30,40,41,96–98). Time of year animals are purchased, mixing of calves from different sources, weight of calves purchased (a proxy for age), animal source, distance trucked (in some cases), and climatic factors (specifically total precipitation and temperature variability) are variables shown to be potentially important reasons disease clusters at the feedlot (18,22).

The risk of pneumonia-related morbidity and mortality in calves increases significantly in the fall, when the sale of freshly weaned calves reaches its peak and larger numbers of animals are managed by an increasingly overworked feedlot crew (18,99,100). This risk may increase significantly as the fall progresses, a phenomenon dubbed the "November effect" by Canadian researchers in the early 1990s (18). This finding coincides with the observations of some feedlot owners that the effectiveness of their metaphylactic antimicrobial strategies for high risk calves seems to decrease as the fall progresses.

Pre-transit mixing of calves at auction markets or in transport trucks is a risk factor for morbidity and mortality at the feedlot (14,100–105). In some cases, there is even a dose-response effect with risk increasing as the housed calves commingle with animals from a larger number of sources (104). The single largest contributor to reduced health may be the commingling effect of calf marketing (105).

Thomson and White (106) argue that purchasing an entire pen of cattle from a single source at one time and/or creating a full pen in the minimum time possible may reduce the impacts of mixing. However, they recognize that this may often not be economically or practically feasible to accomplish. Medium to large-sized feedlots find it difficult to fill their feedlots with animals in a timely and cost-effective manner through sole source acquisition of calves. They rely on the auction market system to supply adequate numbers of feeder animals at appropriate sizes and market prices to fill their pens. Procuring animals in this way results in considerable pre-transit mixing which, for many, would be considered unavoidable.

Table 10: Subcategories of papers in the "Risk factors for disease development at the feedlot" file.

Risk factors for disease development at the feedlot sub-categories	Number of Papers	Percent of Total
Pathogens	20	56
General	10	28
Behaviour	3	8
Mixing	2	6
Transportation	1	3
Total	36	

Feedlot managers now use variables like time of year, weight, source, etc. to classify which incoming animals are at high risk of developing disease early during the feeding process to better target metaphylactic antimicrobial use immediately upon arrival. Unfortunately, we did not see much else in the literature in terms of managing high risk animals at arrival, other than to avoid purchasing them, an approach that is only useful for owners of relatively small feedlots. There is much less published on other variables, like pen hygiene, pen sizes or densities, or movement of sick animals within the feedlot, which could be used to help feedlot managers improve upon their present methods of disease control.

Vaccination Upon Arrival at the Feedlot

Vaccination on arrival for pneumonia seems to have some effect, although it appears to be less than that for the concurrent strategy of antimicrobial metaphylaxis. This is not surprising given that many calves arrive at the feedlot harbouring the causative viral and bacterial agents even before they receive vaccination, not to mention immunological stress from recent weaning and transport. Study design faults present in many of the papers make it difficult to determine the true effectiveness of vaccination at arrival. For example, vaccine field trials are frequently carried out on commercial feedlots where all high risk animals receive metaphylactic antimicrobials on arrival, which possibly confounds the results seen in the vaccine trials.

Many animals arriving at commercial feedlots are bought from auction markets with no known previous immunization history. As a result, a number of "on-arrival" immunization programs have been developed in an attempt to increase antibody titres to targeted bacterial and viral pathogens of feedlot cattle as soon as possible after arrival (107,108). Perino and Hunsaker (109) carried out a comprehensive review of the field efficacy of bovine respiratory vaccines, conducting a literature search of articles published from January 1972 to January 1996. Of the 159 articles that they found relevant to their review, they excluded 137, or fully 86%, for the reasons documented in Table 11.

Almost one-half (47%) of Perino and Hunsaker's reasons for exclusions were due to their wanting to examine only field studies that were carried out under commercial North American feedlot conditions that evaluated morbidity or mortality outcomes. Over 40% (44%) of the reasons were perceived problems in the design or analysis of the research that was carried out. Only 22 papers met their inclusion criteria. After examining these papers, the authors concluded that, "published data supporting BRD vaccination at arrival in North American feedlots is equivocal, at best." They indicated that this finding did not lead them to entirely abandon the concept of vaccinating cattle upon arrival at the feedlot; however, they felt there was an opportunity present for researchers to "critically evaluate vaccination as a management tool."

Table 11: Reasons for exclusion of papers published from 1972–1996 in review of the field efficacy of respiratory vaccines in the feedlot carried out by Perino and Hunsaker (109)

Number Excluded	Reason for Exclusion	Percent of Reasons
55	Used experimental challenge model instead of field or simulated field exposure	27%
25	Blinding of assessors to treatment groups not mentioned	12%
25	Method of assignment of experimental units to treatment groups not mentioned	12%
22	Only reported outcomes such as antibody levels, seroconversion rates, immune function indicators, or product safety instead of clinically relevant outcomes, such as morbidity and mortality	11%
18	Production setting and/or calf type and/or vaccine regimen not practical or applicable to North American beef cattle production	9%
17	No data presented, editorial, or review	8%
13	No statistical analysis of data and insufficient information provided in paper to allow analysis	6%
13	Inadequate statistical power to detect significant differences if they existed	6%
6	No control group or invalid control group	3%
6	Inappropriate definition of experimental unit and pseudoreplication	3%
2	Inappropriate statistical test used to analyze data; p values reported are incorrect	1%
2	Statistical methods not discussed or explained in materials and methods	1%
1	Inadequate follow up of all animals that entered the field trial	0.5%
205[a]	Total reasons for exclusion	

[a] A total of 137 papers out of 159 papers examined were excluded for these reasons; the number of exclusion reasons exceeds the number of papers excluded because 41 papers were excluded for multiple (2 or more) reasons.

Thirty-three of the 142 papers initially filed as "management to reduce feedlot disease" were further categorized as "vaccination upon arrival at the feedlot" (Table 9). Of the 33 papers, seven were excluded because we felt they were not relevant to our question of the effects of on-arrival vaccination against bovine respiratory disease (110–116). We excluded seven papers that were previously reviewed in 1997 by Perino and Hunsaker (20,117–122), three of which they excluded for the reasons listed in Table 12 (20,118,122). We did not include Perino and Hunsaker (1997) in our assessment. Two papers could not be retrieved through University of Calgary and Vancouver Island University digital library subscriptions and inter-library loan services. Of the remaining 17 in our list, 16 were related to BRD vaccines or toxoids, and one towards clostridia.

For our own assessment, we excluded nine of the 17 on our list (89,108,123–129) for the reasons that are documented in Table 12.

Table 12: Reasons for exclusion of papers published from 1988–2009 in our review of the field efficacy of respiratory vaccines in the feedlot.

Number Excluded	Reason for Exclusion	Percent of Reasons
3	Used experimental challenge model instead of field or simulated field exposure	11%
5	Blinding of assessors to treatment groups not mentioned ‡	18%
3	Only reported outcomes such as antibody levels, seroconversion rates, immune function indicators, or product safety instead of clinically relevant outcomes, such as morbidity and mortality	11%
1	Production setting and/or calf type and/or vaccine regimen not practical or applicable to North American beef cattle production	4%
4	No statistical analysis of data and insufficient information provided in paper to allow analysis	14%
8	Inadequate statistical power to detect significant differences if they existed	32%
1	No control group or invalid control group ‡	4%
1	Inappropriate definition of experimental unit and pseudoreplication ‡	4%
1	Inappropriate statistical test used to analyze data; p values reported are incorrect	4%
28[a]	Total Reasons for Exclusion	

[a] A total of 9 papers were excluded for these reasons out of 17 papers examined; the number of exclusion reasons exceeds the number of papers excluded because papers were excluded for multiple (2 or more) reasons.

‡ Used as exclusion reasons by Perino and Hunsaker (109), but not by these authors

Of the 33 papers in the "vaccination upon arrival at the feedlot" file, only 7 (21%) were included for assessment (Table 13). On-arrival vaccination programs for respiratory disease in feedlots can be summarized as follows: (1) the protective effects of vaccines vary with pathogen, animal source, and type of vaccine administered; (2) vaccination generally does not eliminate the target disease, but can sometimes reduce morbidity, mortality, and/or treatment costs; (3) many vaccine trials resulted in inconclusive, marginally significant or no demonstrable benefit and (4) no study was found that evaluated the contribution of vaccination to reducing AMR in feedlots.

Vaccination on arrival at feedlots can have some effect (130–132) on reducing morbidity and mortality, but generally fails to eliminate infections because most feedlot diseases are acquired so soon after arrival that vaccine induced immunity does not have time to be effective (133,134). Despite the practice of routine vaccinations on-arrival, there remains a high incidence of BRD dictating that feedlot veterinarians and cattle farmers continue to rely on the use of antimicrobial agents (135). Reported reasons for vaccine failure include improper use and storage, vaccination occurring too late in the natural history of disease, overwhelming exposures, overwhelming stressors, and variation in vaccine effectiveness (136).

Table 13: Analysis of the methods, materials and results of the 7 papers that were not excluded based on the criteria identified in the text and Table 12 above. All studies dealt specifically with on-arrival vaccination for bovine respiratory disease.

						Sample Size				Statistical Analysis, Control as Numerator				
Study Type	Authors	Intervention	Level of Analysis	Comingling	Study Location	Control (#/pen)	Intervention (#/pen)	Total Pens (Pens/ Intervention)	Total Included in Study	Measured Outcome	RR (95% CI)	P-Value	Conclusions	Notes
Randomized Blinded Field Trial	MacGregor *et al.* (132)	*M haemolytica* bacterin toxoid	Treatment Group	Yes	Commercial Feedlot	1652	1652		3304	Mortality (Crude)	1.5*	0.01	Significant	
										Mortality (BRD)	1.4*	0.08	Not significant	Insufficient Power
										Morbidity	1.1*	0.61	Not significant	Insufficient Power
	Schunicht *et al.* (130)	MLV (control: IBR) vs. MLV (IBR, PI3, BVDV, BRS)	Pen	No	Commercial Feedlot	2582 (<265)	2581 (<265)	20 (10)	5163	Morbidity (Initial UF Tx)	1.30 (1.09 – 1.39)	0.001	Significant	
										Morbidity (First UF Relapse)	1.22 (0.95 – 1.40)	0.065	Not significant	
										Morbidity (Overall Chronicity)	1.12 (0.57 – 2.24)	0.001	Not significant	
										Mortality (BRD)	1.20 (0.72 – 2.05)	0.475	Not significant	
	Bryant *et al.* (131)	Tilmicosin (control) vs. Tilmicosin + *M haemolytica* toxoid	Individual	Yes	Commercial Feedlot	1999	1997	22	3996	Morbidity (BRD)	1.2*	0.0002	Significant	Prophylaxis was a component of the study design
										Mortality (BRD)	1.4*	0.01	Significant	

						Sample Size				Statistical Analysis, Control as Numerator				
Study Type	Authors	Intervention	Level of Analysis	Comingling	Study Location	Control (#/pen)	Intervention (#/pen)	Total Pens (Pens/ Intervention)	Total Included in Study	Measured Outcome	RR (95% CI)	P-Value	Conclusions	Notes
	Perrett *et al.* (107)	*M haemolytica* toxoid (control) vs. *M haemolytica/ P multocida* bacterin-toxoid	Pen	No	Commercial Feedlot	2564 (274)	2564 (274)	10	5128	Mortality (BRD)	0.88 (0.5 – 1.54)	0.669	Not significant	Insufficient Power
										Morbidity (Initial UF Tx)	0.88 (0.76 – 1.02)	0.106	Not significant	
										Morbidity (First UF Relapse)	0.67 (0.46 – 0.99)	0.042	Significant	
										Morbidity (Overall Chronicity)	0.59 (0.40 – 0.88)	0.011	Significant	
	Richeson et al. (134)	MLV (control: IBR, BVDV Type I/II, PI3, BRS) on arrival vs. MLV (IBR, BVDV Type I/II, PI3, BRS) 14 d post-arrival	Pen	No	Research Facility	(10–19)	(10–19)	36 (18)	528	Morbidity (Initial BRD Tx)	1.1*	0.12	Not significant	Prophylaxis in all animals on arrival where rectal temp >40C
										Morbidity (First BRD Relapse)	0.8*	0.17	Not significant	Insufficient Power; Prophylaxis in all animals on arrival where rectal temp >40C
										Mortality (BRD)	2.9*	0.16	Not significant	Insufficient Power; Prophylaxis in all animals on arrival where rectal temp >40C

						Sample Size				Statistical Analysis, Control as Numerator				
Study Type	Authors	Intervention	Level of Analysis	Comingling	Study Location	Control (#/pen)	Intervention (#/pen)	Total Pens (Pens/ Intervention)	Total Included in Study	Measured Outcome	RR (95% CI)	P-Value	Conclusions	Notes
	Wildman et al. (128)	[IBRV, BVDV Type I/II + *M haemolyica/ P multocida* bacterin toxoid (control as per authors)] vs. [IBRV, BVDV Type I, BRSV, PI3 + *M haemolyica* bacterin toxoid]	Pen	No	Commercial Feedlot	1942	1940	12 (6)	3882	Morbidity (Initial UF Tx)	0.78 (0.69 – 0.89)	0.001	Significant	
										Morbidity (First UF Relapse)	0.94 (0.80 – 1.11)	0.498	Not significant	
										Morbidity (Overall Chronicity)	0.61 (0.45 – 0.81)	0.001	Significant	
										Mortality (BRD)	0.56 (0.38 – 0.79)	0.001	Significant	Authors also found significant difference in overall mortality
Randomized Field Trial	Gummow & Mapham (102)	Commercial *P haemolytica* (control) vs. experimental *P haemolytica* biotype A serotype 1 leukotoxin vaccine	Individual	Yes	Commercial Feedlot	1240 (~200)	1241 (~200)		2481	Morbidity	0.8* 1.2 (1.0 – 1.5)	<0.05	Significant	Trend towards higher risk of respiratory disease in vaccinated vs. control and in auction vs. privately bought calves
										Mortality	1* 1.0 (0.4 – 2.9)	?	Not significant	Insufficient Power; Trend towards higher risk of respiratory disease in vaccinated vs. control and in auction vs. privately bought calves

* RR calculated by these authors

Disease and Infection Management at the Feedlot

One fifth (28 or 20%) of the papers in the "Management to reduce feedlot disease" file had *disease and infection management* at the feedlot as their main subject. These 28 papers had the highest likelihood of presenting specific information about management techniques not involving vaccination, nutrition, or antimicrobial use. However, we eliminated 19 of these papers because they were not valid intervention-style assessments of a specific disease or infection management procedure. Among these 19, two were review papers (7,138), 11 were overviews, discussions or informal reviews that presented no new data (105,136,139–147), one was a summary checklist (67), and one was a report of a roundtable discussion (148). Four of the papers were excluded because they were not relevant (149,150), were discussions published in a trade magazine (151), or were not available (152).

Only nine of the 28 papers (32%) presented evidence from new data collected by the authors. Of the nine, five were field trials (50,153–156), two were prospective studies (101,157), and two were cross-sectional surveys (159,160). **Unfortunately, none of these nine papers presented positive evidence that might be useful for designing workable disease management strategies for the large modern feedlot.**

Nutritional Management

We identified 17 papers that dealt with nutritional management. Twelve of these evaluated or discussed the role of trace mineral and roughage on antibody response, health, and growth rates; three focused on liver abscesses and two covered general management considerations for stressed cattle. Specific searches of the 387 relevant papers identified eleven papers on liver abscesses (15,113–115,142,161–166) and three that evaluated the role of feed or feed-bunk contamination on the spread of AMR organisms (63,64,167).

Relatively few papers evaluated feed management on AMR patterns in feedlot cattle. Contaminated water or feed bunks were implicated by some authors as a source of resistant organisms for feedlot pens, or as fomites for the spread of resistant bacteria between pens (63,64). The nature of feed (often the proportion of feed that was grain) sometimes confounded the effects of in-feed antimicrobials on AMR patterns (25,40,167), suggesting that diet may play a confounding role in patterns of AMR prevalence and shedding. These results were not consistent across feeds or experiments (167). The lack of studies systematically examining the effects of feeding on AMR under commercial conditions precludes specific recommendations on feeding practices that would specifically affect AMR patterns.

There was better evidence that feed management could influence patterns of disease. The most striking association between feeding practices, disease, and antimicrobial use involves the prevention of liver abscesses. Even though liver abscesses are one of the most commonly cited reasons for the use of in-feed antimicrobials in feedlots, this condition rarely produces clinical signs in animals and is usually only detected at slaughter. However, their presence in animals can represent a significant economic loss to producers and thus are a target for infection control. Liver abscesses are secondary to acidosis and rumenitis. Rapid dietary energy step-up and poor or inconsistent bunk management characterized by irregular feeding may prompt rumenitis and lead to a higher incidence and severity of liver abscesses (142). The major risk factors for liver abscesses are inadequate roughage in the finishing diet, longer time on feed (both of which are not supportive of the economically required growth rate for feedlot reared animals), grain type and processing, rapid increase in energy, and poor bunk management (15). This creates a management tension between the promotion of high energy diets for maximized growth and the need to use in-feed antimicrobials or other alternatives such as vaccination. Attempts at vaccination for this bacterial disease have not been promising (142), although more recent studies suggest that *Fusobacterium necrophorum* bacterin-toxoids with or without *Arcanobacterium pyogenes* may be beneficial at reducing the prevalence of liver abscess (113–115). Additional studies are warranted to validate these trends. For now, however, the control of liver abscesses in feedlot cattle remains dependent on the use of in-feed antimicrobial compounds (114).

While there was no clinical trial of feeding practices and their effects on AMR, there were a few studies that examined how feeding practices, especially feeding of calves on arrival at feedlots, might or might not reduce other diseases and thus reduce the need for antimicrobials (154,168–170). The careful management of feed rations and trace mineral supplements in the first weeks post-arrival appears to impact subsequent disease effects (131,145,169–174), possibly by moderating antibody responses (175–177) or enteric pathogen shedding (178,179). However, feeding alone does not determine gastrointestinal carriage or shedding of enteric pathogens (63), and trace mineral supplementation has at best limited effects on performance and health, let alone on specific diseases (180).

Gallo & Berg (9) showed a significant reduction in BRD morbidity and mortality as a result of the inclusion of in-feed chlortetracycline and sulfamethazine. The incorporation of prophylactic antimicrobials in feed may have a greater impact on AMR in feedlots than does the therapeutic use of antimicrobials for specific diseases (27,39,40,181). Therapeutic drug use (including metaphylactic use) has little or transient effect on resistance patterns in feedlots (19,26,27,39,40,44,181).

In the absence of effective vaccination against liver abscesses, and the equivocal evidence for feed and feed-bunk management as well as trace mineral supplementation, and given current feeding protocols that require the rapid transition to high energy feeds, medicated feeds will continue to be relied on to reduce the prevalence and severity of liver abscesses.

Unfortunately, there also exists a lack of studies that systematically examine the effects of feeding antimicrobials on AMR under commercial conditions.

Preconditioning or Vaccination Weeks Before Arrival at the Feedlot

Attention has been directed at cow-calf management to reduce feedlot disease largely because the incidence of respiratory tract diseases has been related to farm of origin (120,133) and pre-transport stressors (see below). Kilgore *et al.* (182) suggested that preventive efforts may be, "most effective when directed toward calves at or before their arrival in the feedlot." Several physical and social stressors may come into effect when calves move from pasture with their dam to a feedlot with a group of "strangers." Recovery from physical injury due to castration and dehorning, transition from a milk and grass diet to a high energy diet, and the social stresses of mixing with unfamiliar calves have been linked to immunosuppression, increased shedding of pathogens or commensal bacteria, and/or increased risk for subsequent disease (18,22,99,136,138,154,171,173,183,184). Cusack *et al.* (138) advise that effective BRD control is achieved by "minimizing the stressors responsible for making cattle susceptible to clinical infections with organisms they are inevitably exposed to in the feedlot." This exposure is considered inevitable because many important feedlot diseases are caused by bacteria that can be considered normal flora for calves (184).

Efforts to immunize calves and reduce stressors experienced by them prior to their arrival at the feedlot have been packaged into what are termed "preconditioning" programs. Programs of this nature have been marketed in the industry for years. The programs are not always consistent. The American Academy of Bovine Practitioners defines preconditioning as follows (185):

- Calves weaned at least three weeks prior to sale
- Calves trained to eat from a feed bunk and to drink from a trough
- Calves treated for parasites

- Calves vaccinated for blackleg, malignant edema, parainfluenza-3 virus, infectious bovine rhinotracheitis virus, *Mannheimia,* and sometimes bovine viral diarrhea virus, and *Histophilus somnus*
- Calves castrated and dehorned
- Calves identified with an ear tag
- Calves sold through special auctions

Supporters of preconditioning programs have suggested that they will result in increased on-farm weight gain, reduced market-transit shrink, improved feedlot performance, reduced morbidity and mortality at the feedlot, and increased profits for both the producer and the feedlot owner (185). A review carried out in the early 1980s of the literature evaluating preconditioning programs concluded that the findings were contradictory at best (185). The author noted that, although preconditioning may be a theoretically sound concept, preconditioning programs have "not gained wide acceptance by cow-calf producers or feeders owing to logistics and expense" (185). Our review of papers identified since that time on the topic shows that the situation has not changed significantly.

The effects of preconditioning may be variable and can be affected by factors such as pasture condition, age at weaning, managers' skills, and dam milk production. However, there is a general trend to lower morbidity and mortality rates in preconditioned calves (17,101,144,172,186–189).

Vaccination prior to shipment to feedlots is part of some preconditioning programs. The experience with calf-hood vaccination has been variable. This may in part be due to the multi-factorial nature of BRD and other feedlot infections and the involvement of different pathogens in different settings (136). It may also have to do with differences in the way vaccination or conditioning prior to shipment to the feedlot have been assessed. Calf-hood vaccination has reduced morbidity (172) and mortality rates and treatment costs (112).

"Although preconditioning programs of feedlot calves may represent the most comprehensive tool for prevention of BRD morbidity after arrival in feedlots, the cattle industry has not accepted preconditioning programs as a standard" (182). The reason for this is largely economic. Feedlot operators have not consistently paid the higher cost of preconditioned calves. Preconditioning calves before shipping increases production costs for cow-calf operators, and any premium paid for these calves often fails to compensate for the additional costs (190,191). The economic disincentive to use vaccination is greatest for small scale farmers. In 2004, 80% of United States beef herds had less than forty-nine cows. Small producers with low infrastructure investments have less economic capacity for vaccination purchase. This in part explains why approximately 55% of calves sold in the US are not vaccinated for respiratory diseases (105). Other reasons cow-calf operators do not precondition their calves are weather-related feed shortages and lack of capacity to house calves after weaning (192). Feedlot operators want to maximize the growth potential of younger calves, and thus are reluctant to wait the additional period of rearing on pasture necessary to precondition the calves. Although feedlot operators state the importance of pre-arrival processing of cattle, in fact most still process cattle after arrival to the feedlot (160). Speer *et al.* (144) noted that, "due to decreasing margins for most cow-calf operators, ranchers' efforts to reduce input costs have generally resulted in failure to generate a consistent supply of preconditioned calves, and therefore, support of preconditioning programs within the industry has waned."

We conclude that, while there is some evidence that vaccination or preconditioning of calves at their source cow-calf farms several weeks prior to being shipped to a feedlot reduces disease at the feedlot, the consistency and size of the effect has been difficult to establish, at least in part due to design challenges. This, combined with a historical inability of the auction market transfer system to consistently provide cow-calf operators with a premium to vaccinate their calves means that pre-vaccination and preconditioning have not become effective disease management strategies for feedlot owners in North America.

Mixing, Animal Handling Facilities, and Surveillance

Of the nine papers identified in the "disease and infection management at the feedlot" category (Section 5.2.3) that provided new data, not one presented positive evidence that would be useful for the design of workable disease management strategies on the large modern feedlot. Although we cannot point to specific intervention studies that can be used to provide useful management guidelines, we can look to the literature for a broader discussion of the following issues: mixing after arrival, hygiene and animal movement in the feedlot including traffic flow through hospital pens, and the potential usefulness of feedlot surveillance.

Studies to date have not adequately differentiated between the magnitude of effects of social stressors associated with mixing, and new opportunities for exposure to pathogens. Transport and mixing of calves occurring soon before and after arrival on farms can result in pathogen transmission (183,193). Even though mixing at auction markets appears to be a bigger risk than mixing at feedlots (14), moving and social mixing after arrival can also increase the risk of calves becoming infected (171,194).

Stevenson *et al.* (32) postulate that animal handling facilities serve as a place for transmission, suggesting that both hygiene and animal movement patterns in feedlots could affect disease and AMR spread. Deficits in feedlot biosecurity can result in plenty of opportunity for cross-contamination of equipment, contact between sick and healthy animals, and introduction of pathogens with animals, people, and supplies on feedlots (159). However, widespread transfer of resistant organisms throughout a feedlot seems to be the expectation rather than the rule (32).

The location and number of hospital pens, as well as how best to move animals requiring treatment for a disease condition through the feedlot, have long been topics of discussion for feedlot managers and veterinarians. We found some suggestions in the recent literature about how to manage a hospital pen system (106), **but no papers looked specifically and systematically at health or AMR outcomes for evidence that one system is superior to others.** Some feedlots have adopted strategies that limit the movement of sick animals from their home pens, treating them within the home pen and leaving them there as long as they are not deemed chronically affected. It would be interesting to determine if this practice had some mitigating effect on overall disease or AMR rates. The work of Galland *et al.* (27) might suggest otherwise: they found no difference in the prevalence of resistance in *E. coli* 0157:H7 in four relatively large feedlots over eleven months in home pens versus hospital pens, even though antimicrobial use was higher in the hospital pens.

Ongoing surveillance is essential for adaptive management. Ribble *et al.* (143) commented on the importance ofadequate surveillance in feedlots and prescribed, based on observed disease patterns, components of such surveillance. Many feedlot operators and veterinarians are already creating and applying novel approaches to surveillance. **However, our review failed to recover any papers that systematically evaluated a feedlot-based surveillance system and thus define what is meant by "adequate" surveillance.** Simply asking feedlot staff to spend more time observing animals is not feasible in large feedlot operations (106). Observing all the cattle three times a day and performing a full necropsy on every dead animal would not allow the feedlot crew to get much else done. More efficient and effective means to allocate surveillance efforts to cattle at highest risk for disease are lacking.

Surveillance is also important across the industry with respect to AMR. Several papers have been published that document AMR trends seen in respiratory and/or liver abscess pathogens submitted in swabs from treated or untreated animals to laboratories (75,163,195,196). These studies confirm in general that AMR is higher to antimicrobials that are in use at the time or have been used by feedlot operators for some time. More work needs to be done to interpret how these data can be used to make better treatment choices at the feedlot and pen levels. One can find, for example, instances where feedlot veterinarians use sensitivity data to inform their antimicrobial protocol recommendations, while others claim sensitivity results do not predict clinical efficacy (148). Clarke (197) recommends a surveillance program and antimicrobial treatment protocol based on random culture samples taken from the laryngo-tracheal region of untreated animals with BRD.

Why Has More Management Intervention Research Not Been Published?

There are a number of reasons to explain why more clinical trials have not been published on alternative management strategies to antimicrobial use in the feedlot. A lack of funding sources for non-antimicrobial related management interventions may be an issue. Pharmaceutical companies are understandably motivated to fund research comparing the use of their antimicrobial as a metaphylactic or first-line treatment drug in the feedlot. They may be less motivated to fund research that compares different antimicrobial use or rotational strategies. How often such a proposal has been put forward to a pharmaceutical company for funding is unknown.

Some feedlots employ antimicrobial rotational strategies based upon basic assumptions about the effectiveness of changing antimicrobials that are used serially to treat a non-responding or relapsing patient. For example, calves at high risk of developing pneumonia receive one kind of long-acting antimicrobial as the metaphylactic drug upon arrival. Those that develop pneumonia some time after arrival will be treated with a different, hopefully "unrelated" antimicrobial. So-called "relapses" may receive a third antimicrobial. If the pneumonia recurs or persists, the animals may be declared "chronics" and moved to a pen where they are fed and cared for but no longer treated with antimicrobials. If these "chronics" show signs of suffering they are euthanized.

Unfortunately, proper randomized controlled clinical trial assessments of the relative efficacy of competing rotational antimicrobial strategies in the feedlot have not, to our knowledge, been published. Such an assessment is not as simple as comparing one antimicrobial to another as a metaphylactic treatment drug, especially in the complex environment that a feedlot represents. The authors of a recent review of antimicrobial rotational strategies used in human hospitals were reluctant to recommend this approach in hospitals, given the poor quality of the majority of clinical trials that have been published on the subject (198). They highlighted the design challenges faced by researchers in human hospitals, and concluded that future studies, "will have to be adequately powered in order to overcome confounding variables and will need to employ high-quality epidemiological tools, sophisticated techniques for determining resistance mechanisms and carrying out molecular typing and effective infection control measures." Linking researchers examining rotational and other antimicrobial use strategies in human hospital settings with those working in the feedlot might provide dividends for both parties.

The appearance and success of metaphylactic antimicrobial use at arrival has itself reduced the motivation of the feedlot industry to explore alternatives. It is now standard procedure for feedlots to develop a definition of what constitutes a "high risk" or "ultra high risk" incoming group of calves, using past experiences with such groups, and to use this definition to identify which groups receive parenteral metaphylactic antimicrobials upon arrival. The procedure has been effective enough to industry insiders that they are reluctant to not treat metaphylactically any incoming high risk group of calves. This has made it difficult for researchers to study the epidemiology of pneumonia as it would occur in the absence of antimicrobials at arrival, or to effectively assess alternative management approaches against the metaphylactic approach.

One must also consider that feedlots are in a competitive business. Custom feedlots are, to some extent, competing for clients who are looking for places to feed their cattle. They also compete against one another to buy calves. A feedlot that develops a health management system that enables them to purchase and feed high risk calves with a lower expected death loss will have an advantage. They would be more prepared than their competitors to purchase higher risk calves, which will come at a discount because of lower demand. This discount, and the accompanying increase in profit compared to competitors, may be something that the feedlot with a health management "edge" would be reluctant to share with its neighbours.

We are unsure how much proprietary information of this nature exists within the industry, but the economic motivation to seek an edge creates a competitive environment that might be unfamiliar to researchers working within the Canadian human health care system. This same motivation does present an opportunity for veterinarians and research teams working with individual large-scale feedlots, especially those who are capable of providing research design expertise that allow for effective assessment of new management techniques or technologies in the modern feedlot environment. The longer-term challenge for those researching ways to decrease the potential for AMR to develop across the entire feedlot industry will be how to work with many feedlots without necessarily interfering with the competitive advantage that some have developed on their own.

Future Directions

Much of the clinical trial research on feedlots over the past two decades has focused on the relative efficacy of one antimicrobial to another as either a first-line treatment for respiratory disease or as a metaphylactic injection given to all high risk and ultra high risk calves on arrival. Comparatively little has been published that expands our understanding of the evolving epidemiology of diseases in the feedlot, to study alternative approaches to disease management at the feedlot, or to determine the long-term effects of metaphylaxis on treatment efficacy. Some feedlot owners are concerned that despite the use of newer, more expensive antimicrobials in their treatment protocols, disease problems and death losses equal or exceed levels seen two decades ago. This suggests to us that there is an opportunity on feedlots in North America for researchers and interested funding agencies to support research studies designed to explore (1) the effectiveness of disease management strategies alternative to antimicrobial use, and (2) the effects of different antimicrobial use strategies on AMR development in feedlot disease pathogens. Studies such as these could potentially benefit feedlot owners themselves in their drive to find more effective ways to manage disease, while also reducing antimicrobial use, thereby decreasing the pressure for AMR development in the feedlot.

Several areas of exploration are needed for this to happen. These include the following.

1. Establish a working group of stakeholders that will look for alternative sources of funding for a) intervention studies to test the effectiveness of disease control strategies that do not involve antimicrobial use, b) basic epidemiological studies of the bacterial diseases in the feedlot, and c) research on antimicrobial use strategies. Some of the disease control strategies that might deserve further exploration, listed by category of action and potential control points, are presented in Appendix 4 of this report.
2. Explore a) how real and widespread the observed increase in pneumonia mortality risk in the fall (the so-called "November effect") might be across the industry, b) how much AMR might or might not have to do with the phenomenon and, ultimately, c) what to do about it. These studies should include comparisons of how different animal management strategies within the feedlot, in terms of pen hygiene, pen densities, nutrition, and animal movement, as well as different antimicrobial use strategies, could effectively decrease the "November effect."
3. Examine which triggers for mass medication are most effective while limiting the overall 'load' of mass medication
4. Examine the long-term effects of metaphylactic antimicrobial use in the feedlot on treatment efficacy and the development of AMR in feedlot pathogens
5. Compare feedlots that use metaphylaxis versus those that try a more focussed 'temperature and treat' approach to antimicrobial use
6. Undertake research that explores the differences in health outcomes and AMR development in feedlot animal pathogens across different feedlots, as well as investigate the implementation of feedlot-wide management approaches or interventions that require feedlot-to-feedlot comparisons to determine efficacy
7. Make contact with researchers exploring antimicrobial cycling or rotation in hospital settings to discuss design challenges in both settings and explore how the feedlot may provide opportunities to overcome challenges that face researchers in human hospital settings

Conclusion

We conclude that, with the possible exception of vaccination against some pathogens on or before arrival, no intervention studies published in the past twenty years provide convincing evidence of useful management practices alternative to the administration of antimicrobials that would reduce the incidence of illness and mortality from bacterial pneumonia on large modern feedlots. Work from observational studies has provided useful information as to what constitutes a high risk animal on entrance to the feedlot so that antimicrobial metaphylaxis can be targeted towards this group.

Despite the significant investment in research into antimicrobial strategies and the cost of pharmaceutical use, infectious diseases are still a major problem for feedlots. The mortality rate of feeder calves in the United States has gone from 10.3/1,000 in 1994 to 14.2/1,000 in 1999 to 17.5/1,000 in 2003 (106). This increase is due to multiple factors, but it reflects that new antimicrobials are not able to adequately combat feedlot infections on their own, especially BRD (106,199). Feedlot operators are seeking husbandry means rather than new antimicrobials to combat infections (148) and deal with AMR. Studies that uncovered the many risk factors for feedlot disease have compelled the industry to rethink its disease management strategies (200).

Keeping cattle healthy on feedlots by preventing disease and avoiding the use of antimicrobials is the foundation for reducing disease risks and the need for antimicrobial use (201). If health promotion is used in conjunction with environmental management, it is reasonable to conclude that AMR organisms could be substantially reduced in feedlots. A more comprehensive approach that looks at multiple risk factors rather than targeting pathogens by drugs or vaccines alone is required.

Future observational and intervention studies designed to explore the effectiveness of disease management practices alternative to antimicrobial use should be encouraged. The long-term effects of metaphylactic antimicrobial use in the feedlot on treatment efficacy and AMR should be examined within and across different feedlots. Contact with researchers already exploring antimicrobial cycling or rotation in human hospital settings should be encouraged. Design challenges in both settings could be examined to explore how cross-fertilization of ideas could help research progress in both settings.

There is substantial evidence to show within and between feedlot variation will prevent the application of a generic approach to infection control across the industry. Any disease and infection control recommendations will, for the foreseeable future, remain principle-based rather than specific procedure-based and will be formulated more on opinion and experience than by systematically generated management evidence conducted under commercial conditions.

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Appendix 1: Beef Cattle in North America

The North American Beef Cattle Production Cycle

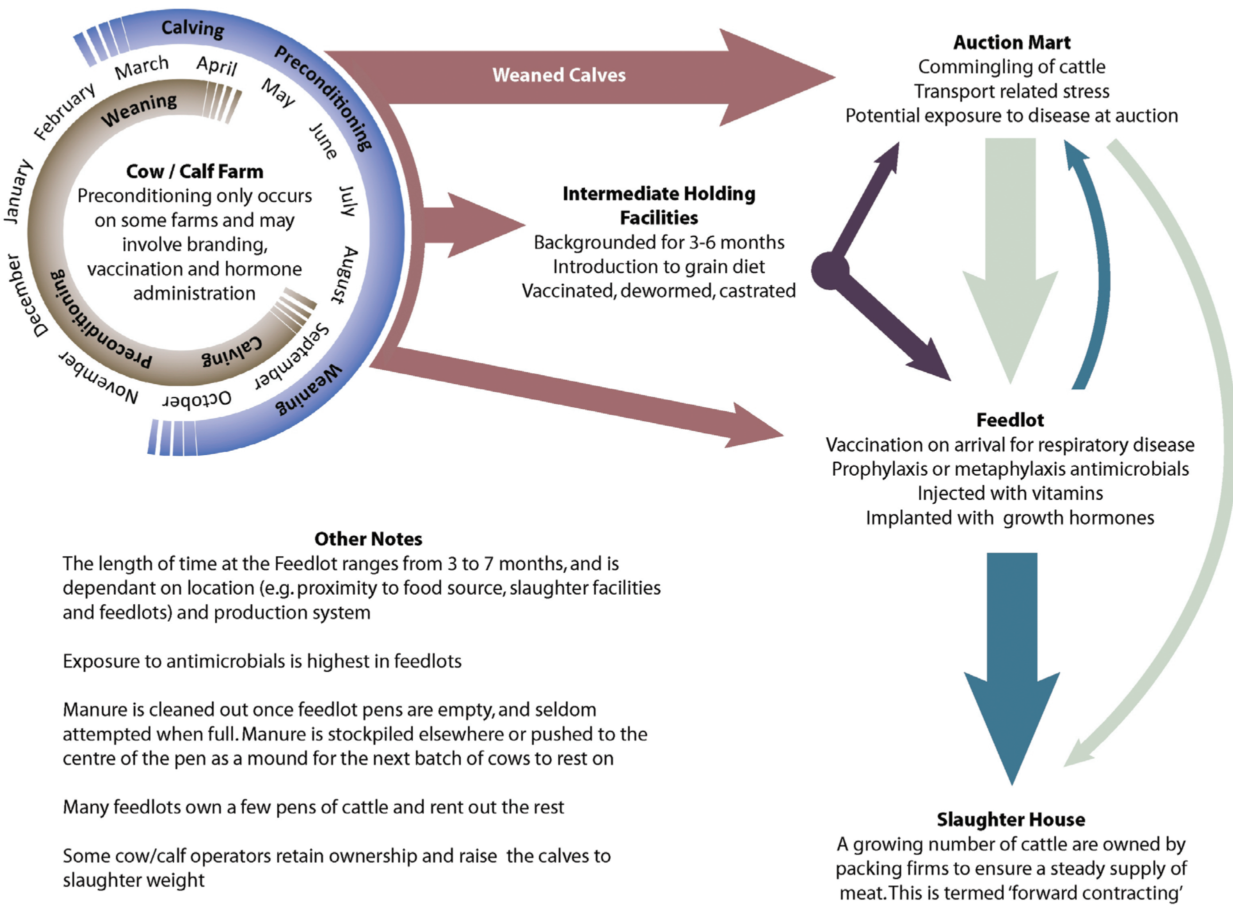
North American beef feedlots specialize in feeding high-energy diets to thousands of young growing cattle to economically produce marketable beef in the shortest time possible. These large capital-intensive enterprises purchase weaned calves six to eight months old, or yearling calves twelve to fourteen months old, and grain feed them for anywhere from sixty days to twelve months depending on the calves' age and weight on arrival (17). Weaned calves are purchased, often through auction marts, from cow-calf operations. Yearling calves are purchased from smaller intermediate feedlots that precondition the calves for grain rations in a process referred to as backgrounding. Regardless of whether calves are recently weaned or backgrounded, they are all obtained and transported overland by truck from a variety of different genetic, nutritional, immunological, and geographical backgrounds to the feedlots. Figure 1 illustrates the typical beef production cycle.

As a result, large numbers of susceptible animals are exposed to respiratory and gastrointestinal diseases in the weeks prior to and just after arrival at the feedlot. Currently, vaccinations and long-acting antimicrobials given on arrival at feedlots, in addition to sub-therapeutic levels in feed, are seen as the most cost effective ways to prevent disease and promote average daily weight gain.

Not all beef cattle destined for human consumption are raised in feedlots. Beef cattle can be raised on pasture in small family and hobby farms, and sold locally through farm-gate sales or to local slaughterhouses and butchers. Small farm feedlots and cow-calf enterprises breed and raise their own heifers and steers, producing between 100 and 1,000 head annually (17). These systems have the option of not introducing animals from other farms or auction marts, thus reducing the risk of bringing disease onto the farm.

Few countries have taken up feedlot operations to the extent of Canada and the United States. Argentina is the world's sixth largest cattle producer with 53.8 million head of cattle (202), the majority of which are raised on pasture. Seven percent of the Argentine cattle are feedlot raised, and only 26,000 of the 250,000 cattle farms have more than 500 head of cattle (203). In one Spanish production system, an "integrator" purchases calves from multiple farms from across Europe and Spain, then distributes these calves in units of 100 to a few hundred animals to farmers that finish the cattle for slaughter (204). The integrator covers all feed, transport, medical, and veterinary related costs associated with raising the cattle. In the United Kingdom and Japan, small numbers of animals are typically finished in individual indoor units (17). Unlike large North American feedlots, other production systems may combine cattle-finishing operations with arable crop farming, dairy enterprises, or other livestock production (204). In these systems, only a few hundred head of cattle will be raised for slaughter each year. Furthermore, the production systems described above have low capital costs and can profitably finish one cohort of cattle annually, whereas the large North American feedlots, which are capital intensive and have low margins of return, will produce up to 2.5 cohorts annually (17). Although feedlots capable of handling 5,000 to 20,000 or more animals are relatively common in certain areas of North America, they are uncommon elsewhere.

Figure 1: Representative beef production flowchart highlighting the primary routes from calving to slaughter, with a proportional representation of cattle numbers that move through each route.



The Canadian Beef Industry: An overview

On July 1, 2008, there was an estimated 15.1 million cattle accounted for in Canada, of which approximately 11.1 million were beef cattle (205). Alberta is the primary producer of beef cattle with 40% of the total Canadian cattle herd (6.0 million out of 15.1 million head) and approximately 44% of the beef herd (4.9 million out of 11.1 million head) 205). Figure 2 illustrates the breakdown of the Canadian cattle inventory by province and stage of production. From 2004 to 2007, an average of 3.47 million head of cattle was fed for slaughter across Canada, with 2.29 million head on feed in Alberta alone (Table 14). MacLachlan (206) claims that in 1990, the 2.6% of Alberta cattle producers who fed for slaughter more than 1,000 cattle annually were responsible for 71.3% of total cattle sales in that province. By 2000, eleven feedlots with capacities of over 20,000 head of cattle per operation could accommodate up to 34.9% (approximately 796,000 head) of all the cattle on feed in Alberta. This represents a significant number of cattle that are intensively raised each year in Canada.

Figure 2: Canadian cattle inventory as of July 1, 2008. The majority of Canada's cattle are located in Alberta and Saskatchewan, and are largely comprised of beef cows and calves followed by steer and beef slaughter heifers. Quebec has the highest number of dairy cows. In Ontario, the number of beef cows to dairy cows is approximately equal. Source: CanFax Statistical Briefer (202)

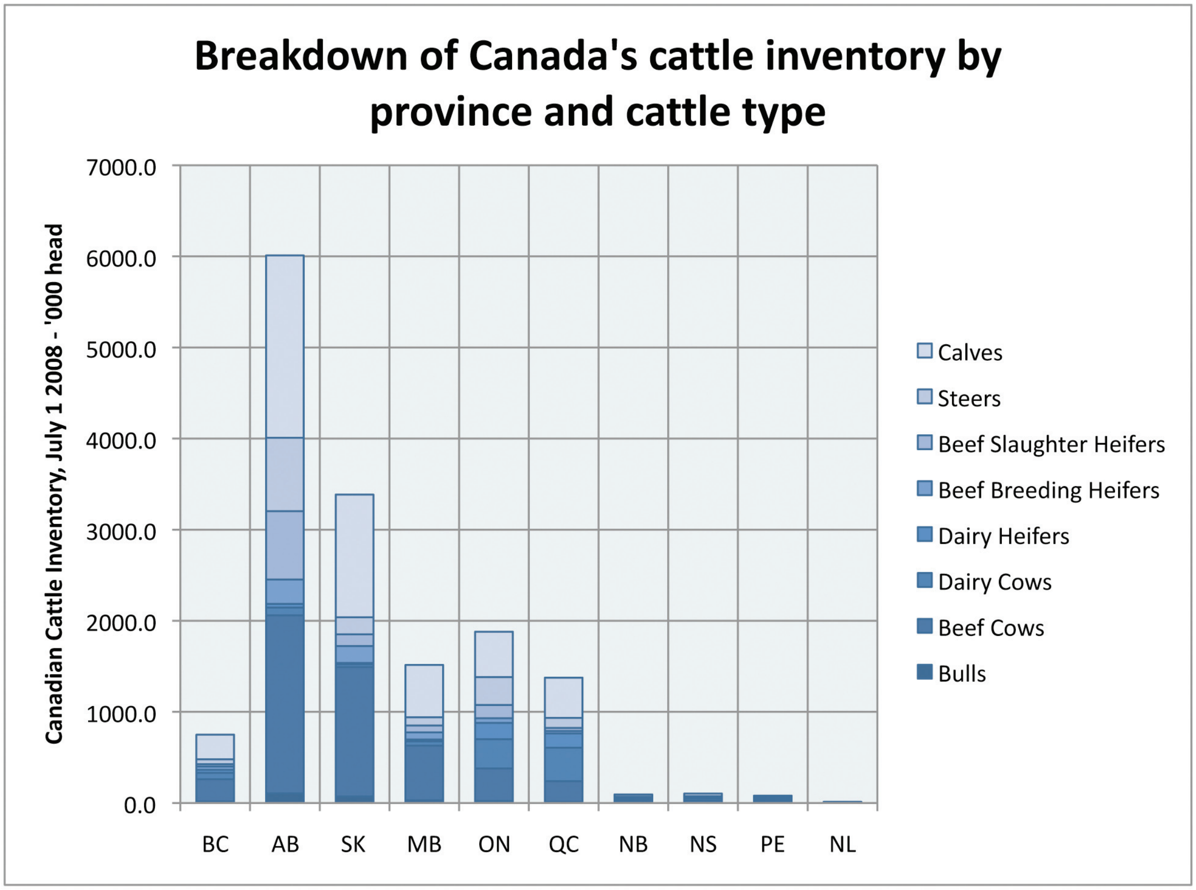


Table 14: Estimates of Canadian beef cattle, by province or geographical region, that were fed for slaughter between 2004 and 2007. Alberta is the primary producer of fed-cattle. Source: Canfax, AAFC, Stats Can (202, 203,205)

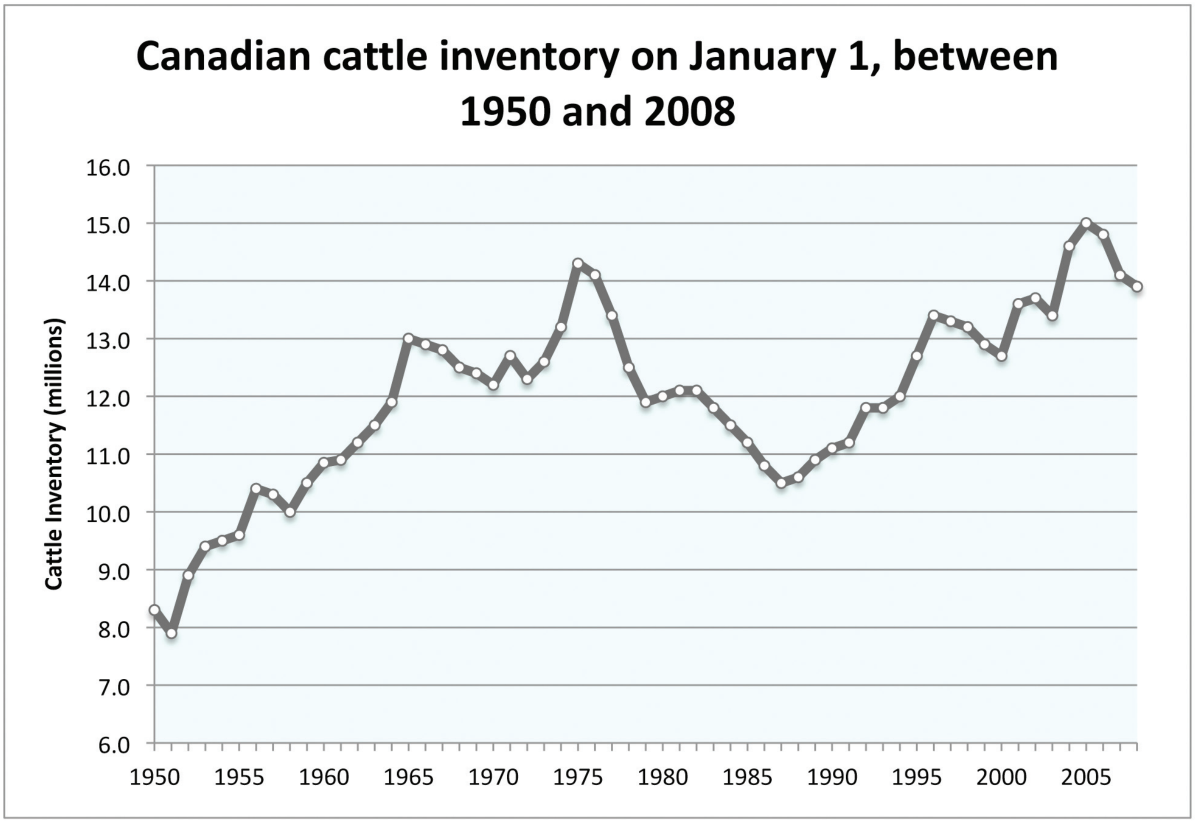
Canadian Fed-cattle Production – '000 head				
	2004	**2005**	**2006**	**2007**
Alberta	2225.4	2370.8	2302.2	2281.3
Ontario	712.9	698.6	685	672.4
Quebec/Atlantic	59.7	80.4	116.3	137.6
British Columbia, Saskatchewan, Manitoba	398.9	402.7	347.9	367.9
Canada	**3396.9**	**3552.5**	**3451.4**	**3459.2**

Canada ranked twelfth for beef cattle production and raised 1.3% of the total world cattle inventory as of January 2008. India, Brazil, China and the United States were the top four cattle producers, with 278, 184, 140 and 98 million head of cattle respectively (202). As thethird largest exporter of cattle behind Brazil and Australia, Canada exported 11% of the world's cattle, of which 95% went to the United States (202).

Cattle inventories are strongly linked to supply and demand, and in North America, tend to follow cattle prices on an approximately ten year cycle (207) (Figure 3).

Fluctuations in grain prices, climatic anomalies (206), and disease outbreaks (e.g. bovine spongiform encephalopathy in Canada and foot and mouth disease in the United Kingdom) affect cattle inventories. There was a decline of 4.3% in the cattle inventory in Canada between July 1, 2007, and July 1, 2008, due in large part to decreases in the beef cow inventory (down 4.7% over the same time period), and a corresponding decrease in the number of calves born (a decline of 4.8%). With cattle for breeding and replacement also down 2% in 2008 from 2007 (205), and the biological constraints of one live calf per viably reproductive female, herd rebuilding will likely be slow in the near future.

Figure 3: Canadian cattle cycles 1 January 1950–2008. Source: Adapted from MacLachlan 2001 (206) and Agriculture and Agri-Canada Red Meat Market Information (208)

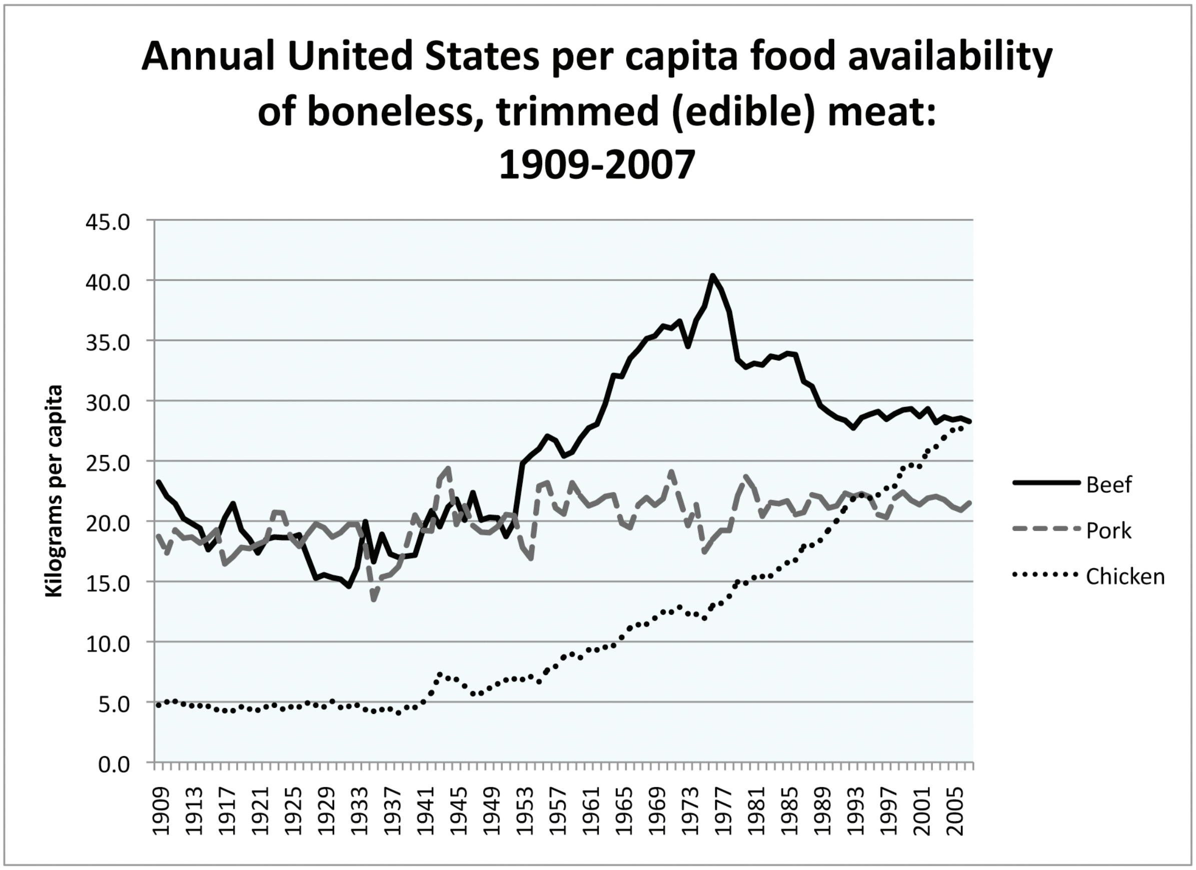


Red Meat Consumption Trends

Seemingly concurrent to increasing national cattle inventories and decreasing beef prices, the United States per capita food availability of boneless, trimmed (edible) red meat (beef) jumped from 20 kg per capita annually in the 1950s to over 40 kg per capita in the mid 1970s, before levelling off at about 27 kg per capita in the 1990s (Figure 4). Total meat consumption has steadily increased since the 1970s in the United States, and similar trends are predicted to occur internationally (209) as low and middle-income countries, primarily China, Brazil, Korea, Malaysia, and Chile, gain more discretionary income (210–212). The observed increase in total meat consumption has been attributed to a dramatic increase in poultry consumption by the United States populace (Figure 4).

Lower relative poultry prices, changing consumer preferences and health concerns toward meats with less cholesterol and saturated animal fats, and reductions in family leisure time – resulting in consumption of meals requiring less preparation time – are all thought to account for this change (209).

Figure 4: Annual U.S. per capita food availability of boneless, raw and edible trimmed meat from 1909 to 2007. Data excludes edible offals, bones, viscera and game consumption. Figure based on un-rounded data (213)



Per capita meat consumption in developing nations, excluding China and Brazil, is currently estimated to be 16 kg, with the potential to double by 2050 (211) even though global meat consumption is unlikely to replicate the dramatic increases observed in China (211). Similar projections have been made for livestock production, with relatively greater increases in production forecasted for developing nations as compared to developed nations (210). With the exception of a few countries (notably Korea, Japan, Malaysia, Kuwait, Saudi Arabia, Mexico, Brazil, Taiwan, and China), the global increase in livestock consumption and production will be primarily as a result of growth in the poultry industry (211). The FAO (211) noted that in the countries where beef consumption has increased, beef production has not (Brazil being the exception), and concluded that this was a result of red meat importation into those countries. Exporting nations, therefore, may see increases in cattle inventories not because of increasing consumer demand within the same country, but because of global trade opportunities.

Summary

With increasing global demands for meat protein and the international trade of beef, intensive cattle production is expected to continue to meet this demand into the foreseeable future. Likewise, antimicrobial resistance as a result of antimicrobial use for disease prevention, disease control, and growth promotion will continue to be an issue for cattle production and public health perception. Fortunately for Canada, the structure of Canada's feedlot industry results in control of the means of production in a relatively small number of producers, most of whom are regionally located in Alberta and Saskatchewan. This provides opportunities for significant impacts on the control of antimicrobial resistance if new best practices for infection control can be identified and implemented. There are anecdotal reports that feedlot managers are open to evaluating and modifying their behaviour to improve health or performance outcomes, especially when there is strong scientific evidence (54) or consumer pressure to support such a change.

Appendix 2: Potential Infection Control Points in A Beef Feedlot

Best practices are those sets of processes and activities that are consistent with values/goals/ethics, theories/beliefs, evidence, and understanding of the environment and that are most likely to achieve goals in a given situation (adapted from Goodstadt & Kahan (214). We identified three steps to identifying candidate best management practices for AMR prevention and control in feedlots: (1) review the current state of infection control on feedlots, (2) identify practices that are of interest to industry and veterinarians to increase the likelihood of their acceptance and adoption, and (3) seek evidence in the literature regarding the possible effectiveness of candidate practices.

To help manage morbidity and mortality on feedlots, many operations have developed health management and production programs based on active surveillance and reliable record keeping. Objectives ideally consist of maximizing feed conversion efficiency to promote growth gains and meat marbling, reducing morbidity and mortality from all causes, optimizing the efficacious use of antimicrobials and vaccines, and meeting federal stipulations on product quality and safety for human consumers (17). Many of these objectives relate to overall herd health, and can be facilitated through disease prevention, for which there are a number of critical control points.

In Table 15, we outline standard human infection control guidelines in the health care setting, and compare them to methods of infection control available to beef feedlots.

Table 15: A comparison of human infection control points in a clinical or health care setting (adapted from Siegel et al. (215) and possible infection control points in a beef feedlot (adapted from Radostits (47).

Human	Beef Feedlot
Adjunctive measures	• Metaphylaxis • Prophylaxis • Chemoprophylaxis • Vaccination • Feed additives (for growth promotion and control of diseases e.g. liver abscesses) • Screen for and restrict movement of sick animals • Culling any animal that is refractory to treatment
Administrative measures	• Infrastructure to guide, support, and monitor infection control strategies • Effective communication between all levels of the feedlot operation • Adequate resources (financial, human, laboratory, infrastructure) • Promoting technologies that encourage infection control
Education	• Education of staff regarding surveillance, disease syndromes, principles and practices of infection control, and treatment protocols • Animal attendants should be knowledgeable and motivated • Written treatment protocols and disease outbreak operating procedures

Human	Beef Feedlot
Environmental measures	• Landscaping to promote good drainage of water and wastes • Insect (vector) control • Wildlife (reservoir) control • Protection from wind, sun, snow, and rain • Pen size and layout to facilitate vehicle access, adequate cleaning of wastes, and efficient movement of animals (healthy, sick and dead) • Pen layout for access by vehicle, separating "dirty" from "clean" movement activity • Cleaning and decontamination of all pens and feed bunks between placement of cohorts • Cleaning and decontamination of transport trucks
Hand hygiene	• Bedding and ground-cover quality & cleanliness
Management of visitors	• Restricted access • Biosecurity protocols (visitor logs, employee reference and criminal background checks, security watchmen, perimeter fencing, access-controlled points-of-entry) • Obtaining history from visitors as to international travel, and refusing access to anyone who may have had contact with foreign animal diseases • Wearing clean clothes/shoes provided and maintained by feedlot management
Patient care equipment and instruments/devices	• Properly clean and disinfect sick pens, quarantine pens, and instruments used on sick or dead animals • Routine maintenance of animal care equipment • Removal of organic debris from animal care equipment prior to disinfection/sterilization • Cleaning and disinfecting equipment used for oral administration of treatments
Patient placement	• Quarantine facilities for observation • Sick pens/treatment areas capable of housing multiple groups of animals • Preferably group animals by source • Minimize commingling of animals from different sources • Isolate animals known or suspected of being diseased (e.g. no fence-line contact with healthy animals)
Personal protective equipment	• Personal protective clothing (e.g. gloves) to avoid transmitting pathogens to healthy animals

Human	Beef Feedlot
Safe work practices	• Limiting extra-label drug use • Adherence to withdrawal times for drug use prior to slaughter • Avoiding unnecessary use of vaccines, prophylactic antimicrobials, and anthelmintics • Proper maintenance of animal chutes and holding facilities
Solid waste	• Manure and waste management
Surveillance	• Daily pen checks • Syndromic surveillance for "sick" animals • Standardized case definitions • Targeted surveillance toward high-risk calves more than one year, and recent arrivals • Diagnostic "rapid tests" (e.g. electronic thermometer) if available to guide treatment plans • Communication of results to pen checkers and health staff • Reliable record keeping
Textiles and laundry	• Not applicable
Transport of patients	• Avoid unnecessary stressors • Proper handling and restraint • Adequate rest • Adequate access to water and food • Protection from the weather
Workflow	• All-in-all-out movement of animal cohorts • Workers move from "clean" to "dirty" zones (i.e. no backflow from hospital pens to feeding pens)
Other	• Surveillance for AMR • Maintaining adequate population densities that maximize production but minimize undue stress and morbidity • Identification and slaughter of infected animals in a herd • Genetic selection for resistance of infectious disease • Eradication under certain conditions, e.g. foreign animal diseases (destruction/disposal of all clinically affected and exposed normal animals in an affected or in-contact herd)

Table 15 provides a hypothetical list of possible target points for infection control in modern feedlots. **Little is known about what proportions of these control points are routinely targeted, or which combination of control targets result in the largest reduction in infection.** A recent study (159) provides cause for a pessimistic assessment. These authors surveyed 106 feedlot personnel in United States feedlots and found that knowledge and application of biosecurity controls was generally low and worse in smaller feedlots. They found plenty of opportunities for cross-contamination between sick and healthy animals as well as many opportunities for pathogens to be introduced into and moved within a feedlot.

While constructing Table 15, we relied heavily on the report by the Healthcare Infection Control Practices Advisory Committee (214), available online at the Centres for Disease Control and Prevention (http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/Isolation2007.pdf). This document was chosen because it was published relatively recently, is comprehensive in scope, and evaluates infection control in a number of settings and circumstances.

Perhaps more importantly and more in line with our goals, Siegal *et al.* (215) emphasizes alternatives to antimicrobial use, which we felt would give time-tested infection control measures from which to compare and contrast standards of practice in the feedlot industry. We broadly classified the human control points based on headings by Siegal *et al.* (215). We then categorized feedlot infection control procedures on the basis of the human categories with the intent to later quantify the number of times certain control points were discussed and evaluated in the literature. After completing our review, it became more or less apparent that the majority of the available scientific literature on feedlot disease control relates to what is considered adjunctive measures in human infection control policies, that is, metaphylaxis, prophylaxis, vaccinations, and culling (isolating or removing) individuals refractory to treatment. Adjunctive measures by human standards are just that, they are used as a last resort. In feedlot infection control, they tend to be used as a first line.

Appendix 3: Search Strategy for Medline (Ovid)

Term Set #1

1. (animal adj1 feed$ adj1 operation$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2. (AFO or CAFO or feedlot$ or feedyard$ or (feed adj1 yard$) or (intensive adj1 feed$) or (intensive$ adj1 fed) or lotfeed$).mp
3. (feeder adj1 (cattle or calf or calves or cow$ or heifer$ or steer$)).mp.
4. 1 or 2 or 3

Term Set #2

5. (backgrounding or stocker).mp.
6. ((source or procure$) adj1 (cattle or calf or calves or cow$ or heifer$ or steer$)).mp.
7. ((hazard adj1 analysis adj1 critical adj1 control adj1 point$) or (movement adj1 control) or mixing or (pen adj1 check$) or (pen adj1 management) or (pen adj1 condition$) or (sick adj1 pen$) or (chronic adj1 pen$)).mp.
8. (biosecurity or haccp or detect$ or monitor$ or prevent$ or disinfection or quarantine or surveillance or vaccination$ or vaccine$ or immunization$ or intervention$).mp.
9. exp Communicable disease control/ or Infection control/ or Disinfection/ or Patient isolation/ or Environmental monitoring/ or Quarantine/ or exp Risk management/ or Animal hospital/ or Population surveillance/ or Sentinel surveillance/ or exp Immunization/ or Vaccination/ or exp Vaccines/ or Hygiene/ or exp Animal feed/ or Housing, Animal/ or Animal husbandry/ or Inservice training/
10. (effluent or feces or faeces or fecal of faecal or groundwater or manure or lagoon$ or sediment$ or sewage or slurry or slurries or (surface adj1 water) or urine or urinary or (waste adj1 management) or wastewater).mp.
11. Feces/ or Manure/ or Sewage/ or Urine/ or Waste management/
12. (indicator$ or predictor$).mp. or exp risk/
13. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

Term Set #3

14. resistan$.mp.
15. drug resistance, microbial/ or drug resistance, bacterial/ or beta-lactam resistance/ or cephalosporin resistance/ or penicillin resistance/ or ampicillin resistance/ or chloramphenicol resistance/ or drug resistance, multiple, bacterial/ or tetracycline resistance/ or drug resistance, multiple/
16. ((antibacterial or anti-bacterial or antibiotic or anti-biotic or antimicrobial or anti-microbial or multidrug or multi-drug) adj2 (resistan$ or susceptib$)).mp.
17. ((bacterial or microbial) adj2 drug adj2 (resistan$ or susceptib$)).mp.
18. (amr or mdr).mp.
19. ((amikacin or ampicillin or apramycin or azithromycin or bacitracin or cephalothin or ceftriaxone or ceftiofur or chloramphenicol or chlortetracycline or ciprofloxacin or coccidiostats or doxycycline or erythromycin or florfenicol or fluoroquinolone or gentamycin or ionophores or monensin or lasalocid or lincomycin or meropenem or nalidixic acid or nalidixic or neomycin or oxytetracycline or spectinomycin or spiramycin or sulphamethoxazole or sulfamethazine or sulfisoxazole or tetracycline or tilmicosin or tylosine phosphate or tylosine or virginiamycin) adj2 (resistan$ or susceptib$)).mp.

20. 14 or 15 or 16 or 17 or 18 or 19
21. (growth adj1 promot$).mp. and 20
22. 20 or 21

Term Set #4

23. Antibiotic prophylaxis/ or (mass adj1 medication$).mp. or metaphylactic.mp. or metaphylaxis.mp. or prevent$.mp. or prophylactic.mp. or prophylaxis.mp. or subtherapeutic.mp. or subinhibitory.mp.

Term Set #5

24. (implementation adj1 strateg$).mp.
25. Drug administration schedule/ or Pulse Therapy, Drug/ or Drug therapy, combination/ or Drug Delivery Systems/
26. ((amikacin or ampicillin or apramycin or azithromycin or bacitracin or cephalothin or ceftriaxone or ceftiofur or chloramphenicol or chlortetracycline or ciprofloxacin or coccidiostats or doxycycline or erythromycin or florfenicol or fluoroquinolone or gentamycin or ionophores or monensin or lasalocid or lincomycin or meropenem or nalidixic acid or nalidixic or neomycin or oxytetracycline or spectinomycin or spiramycin or sulphamethoxazole or sulfamethazine or sulfisoxazole or tetracycline or tilmicosin or tylosine phosphate or tylosine or virginiamycin) adj1 (administration or cycling or cycle$ or dose or dosage or regime$ or rotat$ or protocol$ or strateg$ or "use" or usage)).mp.
27. (((growth adj1 promot$) or treatment$ or therap$ or antibacterial$ or anti-bacterial$ or antibiotic$ or anti-biotic$ or antimicrobial$ or anti-microbial$ or drug$ or medication$) adj1 (administration or cycling or cycle$ or dose or dosage or regime$ or rotat$ or protocol$ or strateg$ or "use" or usage)).mp.
28. 24 or 25 or 26 or 27

Appendix 4: Disease Control Strategies Deserving Further Exploration

These are based upon hypothesized priority control points for a 1,000 plus head North American beef feedlot.

Category of Action	Control points	Strategies
Microbial traffic managed to reduce exposure	Boundaries to entry of pathogens onto the feedlot by ensuring entry of calves of good health status	• Preconditioned programs where cow-calf producers receive a premium for vaccinated calves • Procurement plans to select calves for purchase that are less likely to have disease problems at the feedlot
	Boundaries to within feedlot spread by managing animal traffic flow in the feedlot	• Optimizing sorting, mixing, and movement of healthy animals to meet production goals while reducing stress and opportunities for transmission of sub-clinical pathogens • Creating population management plans in the high risk periods to allow for flexible modification of pen densities in response to changes in morbidity • Controlling the movement and mixing of sick animals within home pens and hospital pens • Operation controls for worker management during high risk periods to ensure prompt tending to low-stress new arrivals at the same time as managing the resident population of sick and healthy cattle
Reduction of antimicrobial use	Rotation of antimicrobials	• Removal of some antimicrobials from use for a period of time for metaphylaxis, prophylaxis, and therapeutic drug use
	Rational use of antimicrobials	• Culture and sensitivity of pathogens to certain antimicrobials prior to use • Appropriate dose and duration of antimicrobials • Single use long-acting versus multiple use short acting antimicrobials
	Remove the feed use of antimicrobials	• Identify high risk periods to allow for limited and strategic use for a reduced portion of the production cycle
	Non-antimicrobial approaches to prevention, treatment, or recovery from pneumonia apart from vaccines	• Nutritional supplements or feeding strategies
Reduced susceptibility to infectious diseases	Reduce stressors at times of high risk for infectious disease	• Behavioural approaches to helping the calves get on feed upon arrival (i.e. train to the feed bin) • Forming the pen cohort at the feedlot – how to optimize the time needed to develop the social hierarchy • Environmental management to cope with adverse stressors
Strategic surveillance	New methods for effective use of surveillance material for infection control	• Necropsy strategies on large feedlots • Improved "real time" information assessment

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