The Economic Impact of Alternative Antimicrobial Management Strategies in Western Beef Feedlots: An Agent-based Model

by

Yunxuan Chen

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Department of Resource Economics and Environmental Sociology
University of Alberta

Abstract

There is growing evidence that antimicrobial use (AMU) in animal agriculture contributes to antimicrobial resistance (AMR), which has created global public threats that adversely affect health and welfare in society. This thesis explores the economic impact of antimicrobial use management strategies addressing Bovine Respiratory Disease (BRD) in the beef feedlot sector in western Canada. The research mainly examines the cost-effectiveness of alternative disease management strategies including an early diagnostic test compared to the currently used mass medication strategies as a common practice of feedlot managers. Externality costs of AMU, variability of frequency and expenditures of early diagnostic tests, and increasing impacts of AMR are further analyzed to compare the advantages and disadvantages of those strategies.

A framework that integrates an agent-based model (ABM) and a modified susceptible-infected-recovered (SIR) model is developed to simulate the BRD disease dynamics and disease management strategies in a representative pen of cattle in a feedlot in western Canada. This integrated framework can incorporate individual heterogeneity which is important when modelling disease spread but is ignored by most of the studies that employ the population-based compartment models. An economic model of a feedlot manager who is assumed to maximize expected profits after finishing is constructed to assess the economic impacts of the different disease management strategies. Based on applying a single or combinations of these strategies over time, we designed nine representative disease management scenarios in this study.

We find that the expected profits in the scenarios containing metaphylaxis strategy are higher than other disease management scenarios; however, the costs of required antimicrobial drugs are also higher. An early diagnostic test as a more accurate and rapid strategy could help to control

BRD spread at an early stage and therefore reduce the unnecessary antimicrobials for those healthy calves that do not require AMU. Even though its expected profit is $8.61 per head lower than that under the "business as usual" scenario of arrival metaphylaxis, the total costs of antimicrobials are significantly reduced by $20.44 per head. Moreover, the advantages of early diagnostic tests are more evident when we consider the externality costs of antimicrobial use, the variability of early diagnostic tests, and the increased impacts of AMR in long-run practice. Findings from this study have implications not only for feedlot managers in advancing their antimicrobial management, but also for policymakers to choose appropriate mechanisms, such as providing subsidies to support the use of potential early diagnostic strategies or other regulations.

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Table of Contents

List of Tables

List of Figures

Chapter 1 Introduction to the Thesis

1.1 Introduction

The emergence and spread of antimicrobial resistance (AMR) have created a global public threat, and if not addressed, will have devastating impacts on the health and welfare of the planet that may be hard to reverse (Council of Canadian Academies 2019). AMR is generally due to disease-causing bacteria that are increasingly able to resist antimicrobials for treatment, and the main cause of AMR is antimicrobial use (AMU). Antimicrobial drugs are widely used to support agriculture animals' health and maintain livestock productivity. With AMR increasingly occurring in emerging economies where the demand for livestock products is growing faster than in developed countries, global consumption of antimicrobials in food-producing animals is projected to rise by two-thirds by 2030 (Laxminarayan et al. 2015). Noticing the importance and in order to preserve the effectiveness of antimicrobial drugs critical for human medicine, the Word Health Organization (WHO) has published guidance about AMU in food animals and defined human-used antimicrobial classes as "medically important antimicrobials (MIAs)" (Brault et al. 2019). According to Infection Prevention and Control Canada (2018), approximately 80% of MIAs sold in Canada are used in livestock. There is concern that routine AMU in livestock is leading to antimicrobial-resistant pathogens, with repercussions for human and animal health. To cope with this threat, in 2017, Health Canada amended food and drug regulations and stated that starting from December 2018, all MIAs for veterinary use in Canada are to be sold by prescription only (Government of Canada 2019). Both the European Union (EU) and the United States had imposed similar AMU regulations earlier than Canada. Some EU counties (e.g., the United Kingdom, the Netherlands, and Denmark) imposed more restrictive regulations for a quicker AMU reduction (Lhermie et al., 2019). For this series of changes and questions regarding AMR and AMU, the livestock industry is facing challenges from many sectors including government, consumers, and major retailers to select and use antimicrobials more prudently. Producers should not only be better at noticing and understanding the deficiencies of existing antimicrobial management as well as their relations with AMR in the long term, but also need to learn the tradeoffs between reducing AMU and the resulting potential economic losses if there are new restrictions on the use of antimicrobial drugs.

This thesis chooses a research focus of the feedlot industry, where antimicrobials are widely administered to control many infectious diseases. Bovine Respiratory Disease (BRD) is the most economically important infectious disease of beef cattle in North America and the most common reason for AMU in feedlots. Currently, the beef feedlot industry relies on antimicrobial metaphylaxis, which is a practice of group treatment of high-risk animals upon feedlot arrival, to minimize the risk of BRD. This preventative use of antimicrobials is due to several important reasons, particularly the lack of effective and economic early diagnostic tools. Infected calves in the incubation period that lack obvious symptoms are hard to detect and very likely to be neglected if the diagnosis of BRD is solely based on pen checkers' inspections and experience. In addition, the segmented infrastructure of feedlot and cow-calf industries is also an important reason contributing to the preventative use of antimicrobials, since the credibility of source of arriving cattle upon feedlot regarding health status is often ambiguous (Baptiste and Kyvsgaard 2017). A lack of trust in terms of use of vaccinations might be another issue. Several early diagnostic methods have been developed and proposed to reduce ambiguous preventative AMU due to BRD, such as biosensors, rapid blood tests, and global positioning systems (Richeson et al. 2018). These methods may help identify the calves at an early infection stage, and therefore reduce unnecessary AMU; however, they have not been mass adopted due to economic and other reasons (e.g., practical training of farmers) (Richeson et al. 2018).

In order to change the current intensity of AMU and assess the economic viability of alternative antimicrobial management strategies, the cost-effectiveness associated with AMU levels and resulting profits from different levels of presence of the disease are evaluated and compared under both current and alternative strategies. The outcomes can provide beef feedlot producers with better information regarding the economic implications of current and future restrictions on antimicrobial drug use. The magnitude of the economic impacts of alternative AMU substitution strategies can help regulatory agencies adjust policies/regulations to support the development and sustainability of the Canadian beef feedlot industry.

1.2 Background of Canadian Beef Feedlot Industry

The Canadian beef cattle industry plays a significant role in animal agriculture and makes a large contribution to the national economy. Statistics Canada (2020) reported that each year there are over 70,000 farms reporting cattle with an average of over 150 head per farm from 2016 to 2020. The cash receipts from cattle are totaling $9.4 billion on average annually, which made the Canadian beef industry the second-largest single source of farm cash receipts from 2014 to 2018 (The Canadian Cattlemen's Association 2020). The premium quality of the meat has built a great reputation, which not only has incentivized domestic beef consumption (around 25.4 kilograms per capita), but also has increased international exports of red meat and livestock. These exports have occurred to 56 countries and nations including the U.S. (largest importer and accounts for 74% of all beef export), Japan, mainland China & Hong Kong, Mexico, Southeast Asia, and South Korea (The Canadian Cattlemen's Association 2020).

1.2.1 Beef Cattle Production Cycle

The Canadian cattle business is similar to that of the U.S. in North America, which is broken down into various segments and each segment generally sells to the next in line. The Canadian beef cattle system includes three main stages in beef production: cow-calf farming/ranching operations, stocker production/backgrounding operations, and feedlot operations. Producers in cow-calf operations maintain herds of mature cows and mate them to produce calves. These calves are raised and eventually sold after weaning (about six to eight months), with a typical weight range of between 450 and 600 pounds. Based on different feeding and production systems, some weaned calves from cow-calf operations would not be shipped to feedlots; instead, they would be transferred to an intermediate holding facility, also called backgrounder farms. Calves in this preconditioning stage are growing with a grain diet based on an appropriate forage-pasture ration for a further six to twelve months; therefore, their ages are often greater than one year and they are older than those originally shipped to feedlots from the cow-calf operation. Preconditioned calves in this stage are vaccinated, dewormed, and/or castrated so that their immune systems are not overwhelmed. Many studies have indicated that although preconditioned calves increase additional purchasing costs, they might still be profitable for feedlots. They have lower costs of gain due to improved feed efficiency and lower medical costs due to decreased treatment rates and fatality rates (Canfax Research Service 2015). However, not many cow-calf producers choose backgrounding as a normal practice and the related adoption rate is only 9% in western Canada (Canfax Research Service 2015). The last stage of the beef production cycle is feedlot operations. They are places which receive cattle either from the cow-calf operation or from the backgrounding operations. They are continually feeding calves with a substantial proportion of cereal grain or alternative high-energy sources to quickly gain weight until calves meet the market target and then ship them to the slaughterhouse.

1.2.2 Risk Exposure of Infectious Diseases in Feedlots

Feedlot operations represent 60% of total energy use during the beef production process, of which more than 80% is allocated for feed production (Smith et al. 2001). In other words, most calves gain weight, mostly at feedlots. The inherent segmentation between cow-calf operation and feedlots creates problems for the individual to see a bigger picture of beef industries and sometimes limits the available alternative opportunities (University of California Cooperative Extension 1996). As a result, the large capital-intensive enterprises usually purchase weaned calves through auction marts, which are facilities that cattle producers bring their cattle to be sold via auction (Griffith 2019). It has been the most common method of marketing cattle because auction marts collect and provide sufficient demand information for both sellers (cow-calf operations and backgrounding operations) and buyers (feedlots) to complete successful transactions. Therefore, calves arriving at feedlots might have a high variety of ages, genetic, nutritional, immunological, and geographic backgrounds based on their original farms. In North America, regardless of whether calves are recently weaned or backgrounded, usually they have to be obtained and transferred overland by trucks (Ribble 2010). The mixed backgrounds and characteristics of calves in the transportation and/or arrival of the feedlots can lead to a great number of susceptible animals exposed to infectious diseases (e.g., respiratory diseases and gastrointestinal diseases). Those processes of clustering and shipping increase the risk for disease transmissions due to close contacts between susceptible calves and infective calves in a squeezed space. Even though some arriving calves are originally shipped from backgrounding operations or small cow-calf farms with a lower risk of getting exposure to the diseases, many studies indicated that the stressful shipping environment might cause increased anxiety and contribute to decreasing calf immunity that accelerating the disease infections. Once the outbreak of one or more infectious diseases is out of control, the cattle's health status and weight gain might be rapidly and severely influenced, and the following losses of production as well as costs of treatment would increase dramatically. Therefore, in order to control infectious diseases and avoid those unexpected outcomes, feedlot personnel take measures to treat, prevent, and control infectious diseases after cattle arrival until final finishing in the feedlot.

1.3 BRD and AMU in Western Canada

1.3.1 Bovine Respiratory Disease (BRD)

Bovine Respiratory Disease (BRD), also referred to as "shipping fever", is the most important disease of beef cattle in North America and the most common reason for AMU. The U.S. Department of Agriculture, Animal and Plant Health Inspection Service, and Veterinary Services (2001) stated that nearly all feedlots have at least one animal that develops BRD. There is 14.4 percent of placements affected by BRD at feedlots, approximately five times the percentages of placements with the next most reported disease, acute interstitial pneumonia (U.S. Department of Agriculture, Animal and Plant Health Inspection Service, and Veterinary Services 2001). BRD is a general name which refers to any disease of the upper or lower respiratory tract. It is commonly associated with infections of the lungs causing pneumonia in calves that have recently been weaned or recently arrived at the feedlot (Beef Cattle Research Council 2019). Bacterial agents are the direct causative pathogens, which include *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis.* Viral agents may also produce a clinical syndrome similar to BRD without bacterial co-infection; however, they generally involve the process that is antecedent to or concurrent with the bacterial infection, rather than primarily contributing to the infection (Taylor et al. 2010). Risk factors such as host heterogeneity and environmental factors may increase the incidence rate or risk of infection for a susceptible individual exposed to infective agents.

BRD usually starts infection when calves arrive at the feedlot with outbreaks occurring several weeks after they settle in. Usually, the peak morbidity occurs in ranch-delivered feedlot cattle 7 to 14 days after arrival, but the outbreak could have occurred much earlier if the affected cattle are auction-mart derived, with the peak occurrence as early as 4 to 6 days after arrival (Smith et al. 2001). An epidemiologic study of fatal fibrinous pneumonia in auction-market-derived feedlot calves in western Canada stated that peak mortality happened approximately 16 days after arrival at the feedlot (Patterson et al. 2017). Similarly, Snowder et al. (2016) recorded the BRD epidemic pattern over 10,000 calves from multiple sources in 200 feeding days in the U.S. and indicated that there is a dramatic increase in incidence after 5 days in the feedlot which peaked within 14 days on feed and remained high until approximately 80 days on feed. After 110 days the number of infected calves was negligible.

The clinical signs of BRD are often associated with fever of over 40°C, difficulty breathing, nasal discharge, depression, rapid and shallow breathing, coughing, and so on (Beef Cattle Research Council (BCRC) 2019; Alberta Agriculture and Food 2008). However, only based on the regular inspection of those symptoms is not sufficient to diagnose and isolate all the infected calves. This is because some infectious agents do not produce toxins which can cause depression or other typical clinical signs for the hosts; as a result, these cattle may hide the signs of disease until they feel overwhelmed (U.S. Department of Agriculture, Animal and Plant Health Inspection Service, and Veterinary Services 2016). The subclinical BRD infection in cattle creates more difficulties of diagnosis for feedlot personnel.

1.3.2 Antimicrobial Use (AMU)

Since it is not likely to completely eradicate infectious pathogens of many livestock diseases (like pneumonia and diarrhea) from the feeding environment, antimicrobial interventions are nearly unavoidable, and they play significant roles in decreasing pathogen transmission and controlling disease incidence rate of animals to a reasonable level (Snowder et al. 2006). Similar to the published guidelines of the WHO on preserving the antimicrobial drugs relevant to human medicine, Health Canada also classifies antimicrobial drugs in category I to IV based, on their importance to human health. Specifically, category I is very high importance, category II is high importance, category III is medium importance, and category IV is low importance to human health (Health Canada 2002).

The major types of antimicrobial drugs used in food animals in Canada are used to include therapy to treat disease, control and prevent infection and growth promotion (Health Canada 2002). However, in order to preserve the effectiveness and minimize the development and spread of AMR, Health Canada has removed the growth promotion claims from MIA drug labels in early 2018 and restricted the use of MIAs in food-producing animals only to treat or prevent diseases (Health Canada 2019). The medication can be administered to animals either by injection or by putting medicine into feed or drinking water (Table 1.1). Therapeutic treatment is the most common and effective approach to treat clinical observed infected animals, commonly referred to as "pull and treat". Almost all (99.8%) feedlots in the U.S. use injectable antimicrobials as part of therapeutic treatment (U.S. Department of Agriculture, Animal and Plant Health Inspection Service, and Veterinary Services 2001). Therapeutic treatments have the benefits of isolating and medicating targeted individual animals. However, as the number of times an animal is pulled and treated increases, medication costs rise, carcass and offal quality decline, and mortality and culling rates increase (Dennies et al. 2018). Therefore, it is often more feasible and efficient to treat an entire group of high-risk animals. According to Health Canada (2002), mass medication of groups of animals at therapeutic level (also called Metaphylaxis) is the treatment of an entire group of animals after the diagnosis of infection and/or some clinical cases in part of the group, with the aim of not only treating clinical animals but also preventing the infectious diseases further spreading to others at high risk. Prophylaxis is another mass medication of groups of animals (often used during a general high-risk infection period but before diagnosing clinical signs, such as after weaning or transport of animals (Health Canada 2002). The purpose is always to prevent the occurrence of disease or infection, and most prophylactic AMUs are administered via animals' feed and water in a relatively long-acting term of one to two weeks. In order to highlight the purposes of preventing or treating diseases, all in-feed and in-water MIAs are now labelled with responsible use statements from early 2018 (Health Canada 2019). In general, mass medications and pull-and-treat are commonly used jointly to manage high health risk animals.

Brault et al. (2019) studied the usage of antimicrobials in western Canada and reported that usage based on the data about mixed-breed cattle placed in 36 western Canadian feedlots from 2008 to 2012 (representing about 21.5% of fed cattle in Canada during that time period). BRD and liver abscesses are the two main diseases that contribute to the largest amount of antimicrobial usage. Most feedlot calves are generally mediated antimicrobials through injection at a group level to treat and control BRD, with category III to category II antimicrobial drugs (medium to high importance to human medicine as categorized by Health Canada Veterinary Drugs Directorate) used most frequently. Tetracyclines and Macrolides are the two most representative and most used drugs in these two categories. Besides the medically important AMUs, ionophore-use antimicrobial is added with routinely fed rations to promote growth and prevent the disease as well (Brault et al. 2019).

Table 1.1 Types of Antimicrobial Use in Food Animals

Type of Antimicrobial Use	Purpose	Route or Vehicle of Administration	Administration to Individuals or Groups	Diseased Animals
Therapeutic	Therapy	Injection, feed, water	Individual or Group	Diseased individuals or some of the individuals in groups
Metaphylactic	Disease Prophylaxis/therapy	Injection, feed, water	Group	Some
Prophylactic	Disease Prevention	Feed	Group	None-evident although some infections may be subclinical
Growth Promoter (No longer allowed)	Growth Promotion/Feed efficiency	Feed	Group	None

1.3.3 Diagnostic Strategies

1.3.3.1 Shortcomings of Current Diagnostic Strategy

Successful controlling BRD depends on early diagnosis, the isolation of infective calves and prompt treatment with antimicrobials (Alberta Agriculture and Food 2008). Current diagnostic strategies in feedlots mostly rely on pen checkers' subjective diagnosis of visual signs of illness, often accompanied by some physical testing like rectal temperature or lung auscultation to inform AMU protocols (Blakebrough-Hall et al. 2020). These diagnosis methods have varying accuracy and highly depend on the pen checkers' experiences. According to White and Renter (2009), the sensitivity and specificity of traditional clinical assessment of BRD are very poor, with both rates of just over 60%. Some more reliable diagnostic methods like laboratory blood testing also could help with controlling disease. However, there is usually a lag between the collection of samples and results of such laboratory tests (Owen et al. 2017). As pen checkers are distressing to accurately identify all the animals that require treatment, greater emphasis must be placed on the prevention of BRD (Griffin, 1997). Mass medications are often administered to cover the treatment with undiagnosed cattle to lower the risk of outbreaks in the entire group. From the feedlot managers' perspectives, instead of taking greater risks of disease transmission and economic losses, mass medications have lower operating difficulties of control, even though they may cause extra medical costs.

In addition, as AMR grows there will continue to be fewer and fewer antimicrobials available for use in animals and humans. The changes in antimicrobial availability and possible future AMU regulations are likely to have economic repercussions in animal agriculture. Producers may need to seek out alternatives to antimicrobials.

1.3.3.2 Early Diagnostic Strategies

Having an accurate and rapid diagnostic approach is a precondition of effective treatments and reducing the risk of disease outbreaks. Several decades ago, people started to introduce and integrate electronic technologies in animal agriculture to achieve early diagnosis and prevention of infectious diseases. Electronic identification (EID) of cattle based on the radio frequency

(RFID) was first emerged in the 1970s (Eradus and Janasen 1999), and more recently, RFID combined with multiple sensors used to monitor behavioral patterns of livestock is back to the public attention again (Richeson et al. 2018). For example, accelerometers or pedometers could be useful devices affixed to animals via ear tag to quantify step count, standing and lying time, and other physical individual activities. Besides, transponders affixed to collars can monitor feeding and watering behaviors like duration and frequency of animals visiting to feed bunks or water bunks. Moreover, a real-time location system (RTLS) or global positioning system could monitor the cattle throughout the housing area and their locations inside the pen (Richeson et al. 2018). Rapid blood tests are another advanced diagnostic method that has great potential power as health management tools in the beef feedlot. For instance, one of the rapid blood tests could indicate stress, dehydration and immune challenges based on measures of blood leukocyte differentials (BLD) in a very short time; as a result, the accuracy and timeliness of disease detection are improved (Maday 2018). Instead of metaphylactic AMU, it may determine the need for antimicrobial intervention and predict outcomes for fed cattle tested on arrival. More importantly, they may help identify the calves in the incubation period and inform individual-based AMU for targeted calves, and therefore reduce preventative AMU (Al-Alawneh et al. 2015; Richeson et al. 2018; National Academies of Sciences, Engineering, and Medicine 2019). However, these early diagnostic methods are not adopted due to economic and other reasons (Al-Alawneh et al. 2015; Richeson et al. 2018).

1.4 Research Objectives

The overall goal of the thesis is to develop a bioeconomic framework to study the cost-effectiveness of alternative disease management strategies addressing BRD in the beef feedlot sector in western Canada. Findings from this study not only have implications for feedlot managers to advance their judicious use of AMUs and for policymakers to decide appropriate mechanisms, such as subsidies for early diagnostic strategies or other regulations.

There are three specific objectives to achieve this goal:

1. Develop an agent-based bioeconomic framework to model the spread of BRD with the different disease management strategies, identifying the corresponding economic consequences within the framework.
2. Evaluate the cost-effectiveness of alternative disease management strategies in terms of the levels of AMU and the resulting profit, compared with the current commonly used strategies.
3. Evaluate the possible changes in cost-effectiveness of alternative control strategies when taking into account externalities associated with AMU, variability and expenditures of early diagnostic tests, and increasing AMR in the simulation.

To pursue the first objective, we propose a new framework that integrates an agent-based model (ABM) and a modified susceptible-infected-recovered (SIR) model to simulate the BRD disease dynamics at a representative feedlot in western Canada. After that, we overlay the epidemiological transmission with a process in which current and alternative disease management strategies can be imposed on the individuals. The consequences of BRD prevalence and corresponding economic results under different disease management strategies are generated.

For pursing the second objective, a feedlot manager’s profit-maximizing economic model is used to assess the cost-effectiveness of alternative disease management strategies for disease control.

The relevant economic and AMU information are obtained from the agent-based bioeconomic framework, along with BRD prevalence consequences.

The third objective aims to investigate the changes in outcomes and deal with three critical questions. First, would the profit rankings of management strategies change if we consider the externality costs of antimicrobials? Second, what are the other possible options regarding the frequency of early diagnostic tests and what are their breakeven costs compared to testing cost? Thirdly, would the early diagnostic test strategies become more cost-effective when there is declining efficacy of current mass medications caused by the increasing effect of AMR in a long-run application? The answers to these questions are not only beneficial for feedlot managers and policymakers, but also useful to guide the research efforts of disease ecologists, animal pathologists, and animal scientists involved in BRD and AMU research.

1.5 Organization of Thesis

The remainder of the thesis is divided into five chapters. Chapter 2 firstly provides a literature review of the economic analyses related to AMU and AMR in animal agriculture. Next, it presents classic epidemiological frameworks and the applications in bioeconomic models for livestock disease management. In addition, a review of the agent-based modeling method and its advantages addressing the problems of current bioeconomic models for livestock diseases is also discussed in chapter 2.

Chapter 3 includes the explanation of the overall model scope and logic as well as two main models of the study. Firstly, an agent-based disease model including BRD infection and disease management strategies built at calf level presents each individual's disease status, weight status, life status, diagnostic status, AMU status, as well as their relationships. The associated model parameters and calibrations are presented and discussed subsequently. Secondly, this chapter introduced a constructed economic model of a feedlot manager assumed to maximize expected profits after finishing.

Chapter 4 presents the experiment design for nine disease management scenarios associated with the single or combinations of current and alternative disease management strategies including early diagnostic test informed AMU. The bioeconomic measures and economic information relevant to the designed scenarios are provided. After that, this chapter presents the initial states distribution, repeated number, and process of simulations.

Chapter 5 provides the results of the simulated result. The main results of the cost-effectiveness of alternative disease management scenarios are first provided in this chapter. The tradeoffs in terms of profitability and AMU levels of these management scenarios are presented. In addition, the outcomes related to animal health and weight gain in these scenarios are also discussed. After that, the impacts of externality costs of antimicrobials are analyzed, and the changes of cost-effectiveness for the listed disease management scenarios are highlighted. Moreover, the results of frequency and expenditure of early diagnostic tests are discussed. Lastly, this chapter provides a sensitivity analysis of AMR impacts on the profitability and AMU costs in the listed disease management scenarios.

Finally, Chapter 6 presents conclusions and implications of the study results, a summary of the study's limitations, and possible extensions for future studies.

Chapter 2 Literature Review

This chapter summarizes the literature that is relevant to this study's research objectives. It first summarizes the current economic analyses of AMU and AMR in animal agriculture. After that, an introduction of a classic disease modeling and its various derived forms are presented. Based on those disease modeling frameworks, an investigation of the current bioeconomic models used in managing livestock diseases and corresponding economic analyses will be conducted, as well as their advantages and disadvantages will be discussed. Next, addressing the drawbacks in current methodologies, a literature review of the agent-based modeling is presented, which emphasizes its merits for disease modeling when incorporating with epidemiological conceptual framework compared to previous studies. By the end of the chapter, it is clear why the model choice is the best fit for our study objectives.

2.1 Economic Analyses of AMU and AMR in Animal Agriculture

From realizing the negative impacts of AMR on human and animals' health and welfare, wider economic tools have been used to measure the economic impacts of AMR and create the interventions to stem AMR development (Roope et al. 2009). Similar to the problem of "climate change", the broader social costs of AMR and benefits of interventions are always hard to estimate because it involves complex problems including identification of diffuse impacts, comparing the current and future impacts, and uncertainty and difficulties in measurement and valuation (Coast et al. 2002; Wernli et al. 2017). For the animal agriculture sectors, the suggested solutions to decrease AMR is making improvements in AMU such as reducing the unnecessary routine use of antimicrobial drugs. The assessments of the feasibilities of these proposed changes require corresponding economic analyses to evaluate and make suggestions for both producers and policy makers.

Most recent economic analyses related to AMU and AMR in animal agriculture and their relations with humans focused on the health and economic burden of AMR in humans, the impact of AMU in animal agriculture on AMR in animals, the fraction of AMR in humans attribute to animal agriculture, and AMU in animals (Innes et al. 2020). Among them, AMU management in animals is the most studied topic. Specifically, the studies are more concentrated on evaluating the potential economic consequences if food animals are raised completely without antimicrobials or with reduced antimicrobial use.

The ideas of "Raised Without Antimicrobials" are proposed in many livestock industries (such as beef industry and poultry industry), which eliminates any preventive antimicrobial use (MIAs or ionophore) in injection and/or in feed for animals at high risk of developing the diseases (Bowman et al. 2016; Bowman 2018). However, given the current reliability of AMU used to prevent and treat several diseases, there is a huge challenge in changing the current management structures (Bowman 2018). For example, in the beef industry, this program requires not only an elimination of any preventative AMU used in feed in calves, but also the animals that are treated with antimicrobials to be identified and separated at sale. All these changes require substituting other inputs and management practices to raise healthy animals and will lead to increased production costs (Bowman 2018). In addition, the cost-effectiveness of the "Raised Without Antimicrobials" in terms of the economic problems of higher morbidity and mortality, lower feed efficiency, and the increased costs of separation and tracing is uncertain and variable in different stages of production. On the other hand, there are other studies emphasizing the demand side of the economic evaluation of voluntary labeling of "Raised Without Antimicrobials" not understanding whether this improves efficiency in the market (Bowman et al. 2016); however, lack of information on premiums for this approach, particularly at the retail level, provides a challenge to study economic benefits to producers of raising animals without antimicrobials (Bowman 2018).

Another aspect of the economic analysis of AMU in animal agriculture sectors addresses some economic consequences under reduced AMU regulations as well as opportunities for reducing AMU. Following the WHO recommendation to ban AMU for growth promotion, many countries and regions have introduced new regulations or laws to restrict the AMUs. Many studies have examined the economic effects and output variability resulting from the restricted AMU in different production sectors (Graham et al. 2007; Key and McBride 2014; Laxminarayan et al. 2015). Other policy instruments like economic incentives, taxes, subsidies and tradeable permits, and voluntary agreements are also discussed in some studies with the aim of reducing the AMU level in animal agriculture sectors (Lhermie et al. 2019).

From the perspectives of food-producing industries, the economic evaluations of potential opportunities to reduce the level of AMU are also the objectives of many studies. For example, in the feedlot industry, economic evaluations revolve around alternative approaches including vaccination protocols, disease prevention with improved management practices, early detection and treatment of infection, the credibility of sources, and balancing feed efficiency and AMU. The goal of these approaches is to maximize the AMU reduction without decreasing the profitability of producers (Bowman 2018).

2.2 Classical Disease Modeling

One of the most widely used epidemic frameworks for infectious disease modeling is the typical compartmental structure of Susceptible-Infectious-Recovered (SIR), which was introduced by Kermack and McKendrick in 1927 (Kermack and McKendrick 1927) to present the population-level dynamic of disease transmission (Blackwood and Childs 2018). Individuals are aggregated into homogeneous groups based on disease status and track the corresponding population sizes through time. The transitions between compartments are modeled through differential or difference equations, often parameterized stochastically. Susceptible (S) individuals become infected through contact with infectious individuals (I), and infectious individuals recover (R) at a fixed rate and confer lifelong immunity. The fixed rate is interpreted as the average time an individual spent in the infectious class. Although there is a time lag for almost every disease between infection and becoming infectious, this duration is not considered in this basic form, as an assumption. The reason is that when the time lag is short (hours or days) on a timeline of long-term dynamics (years), it is reasonable the effect of this lag duration is negligent (Blackwood and Childs 2018). Another important assumption for this basic SIR framework is that it only fits for simulating the feature of disease-pathogens that infection is thought to confer life-long immunity; in other words, a recovered individual would never be infected again. Many other similar models are derived from this basic form, and these two assumptions could be relaxed based on the modified model structures. The following table (Table 2.1) summarizes the various derivative models.

Table 2.1 Summary of Derivatives of Epidemiological Model from Basic SIR Model

Model	Description	Assumptions	Examples
SIS	Susceptible ↔ Infectious	Do not confer any long-lasting immunity. Do not give immunity upon recovery from infection, and individuals become susceptible again	Common cold, influenza
SIRD	Maternally derived immunity → Susceptible → Infectious → Recovered	Passive immunity for babies that not born into the susceptible compartment but are immune to the disease for the first few months of life due to protection from maternal antibodies	Measles
SIR with Carrier state	Susceptible ↔ Infectious ↔ Carrier →Recovered	Some people never completely recover and continue to carry the infection, whilst not suffering the disease themselves. They may then move back into the infectious compartment and suffer symptoms, or they may continue to infect others in their carrier state, while not suffering symptoms	Tuberculo sis, Typhoid fever
SEIR	Susceptible → Exposed → Infectious → Recovered	A significant incubation period during which individuals have been infected but are not yet infectious themselves	COVID-19
SEIS	Susceptible → Exposed → Infectious → Susceptible	Like the SEIR model except that no immunity is acquired at the end	N/A
MSEIR	Maternally derived immunity → Susceptible → Exposed → Infectious → Recovered	Including the factor of passive immunity, and a latency period	N/A
MSEIRS	Maternally derived immunity → Susceptible → Exposed → Infectious → Recovered → Susceptible	Similar to the MSEIR, but the immunity in the R class would be temporary, so that individuals would regain their susceptibility when the temporary immunity ended	N/A

2.3 Bioeconomic Models of Livestock Disease Management

The recent bioeconomic models in managing infectious animal diseases in livestock are mostly used to analyze productivity losses from diseased animals, human health concerns, and threats of costly trade sanctions designed to prevent disease spread (Horan et al. 2010). Mathematical models play a significant role in solving problems with a complex system of disease transmissions, management strategies, and host heterogeneities over space and time. Most of the studies on economic evaluations of animal agricultural diseases and control strategies are integrating the compartment SIR-type epidemiological models and the corresponding economic consequences within the models. The trade-offs between economics and disease spread would provide an ex-ante evaluation of control strategies for their cost-effectiveness through estimating potential losses resulting from different levels of presence of diseases. Some typical examples are listed as follows: Rossi et al. (2017) built and analyzed a stochastic farm-to-farm SIS spread model through both direct and indirect contact to evaluate the role of fomites on transmission, Reeves et al. (2005) from the U.S. Department of Agriculture developed a stochastic, herd-based compartment model to simulate the spread and control of highly contagious diseases in a population of susceptible animals, Cho et al. (2011) developed a compartment framework implemented with a discrete optimal control to evaluate the economic and epidemiological consequences of various control strategies for Johne's disease (JD). Further, Cho et al. (2012) investigated the epidemiological effect and economic values of vaccines for JD in various stages of development.

Most epidemiological frameworks used in livestock to simulate infectious diseases are developed from the classic epidemiological models for human diseases. However, some defined classes may be different from the examples mentioned in section 2.2. Since there is always a link between disease status and production in livestock, many studies have divided the levels of infection to separately analyze their impacts on production. Therefore, livestock diseases that can be artificially interfered within a complex system have better fit with such a model application. As a comprehensive disease-specific epidemiological framework is built to represent the disease transmission, the cost-effectiveness of different management strategies and their corresponding economic feedbacks could be analyzed by a dynamic optimization approach. This combination has solved the shortcomings of the previous model that 1) only considering the reduction of farm-level economic losses while disregarding the infection dynamics or 2) ignore cost-effectiveness analysis or only conduct the cases of the eradication of the diseases (Cho et al. 2011; Negassa et al. 2015).

In spite of the benefits of the compartmentalized model in analyzing disease transmission and economic components at the same time, the limitations in such models should also be considered. All animals within a compartment are assumed to exist in the same disease state or age state, which is actually limiting in disease modeling, especially in our case of BRD for two reasons. Firstly, calves are heterogeneous in disease transmission. For example, a susceptible calf could be exposed to the disease from infectives at any time during the feeding period, but the probability of infection and the probability of showing symptoms may depend on its sex, age, and weight at that time. Secondly, since there is a mixing of healthy, symptomatic, and asymptomatic calves, they are heterogeneous in being detected by diagnostic strategies over time. Compartment models cannot account for decisions made at the animal level for such problems. For example, a feedlot pen checkers' inspection is a disease-status dependent strategy that they only can diagnose observed clinical calves. As a result, for asymptomatic infected calves, the pathogens may not be detected before they transmit the disease to other calves, causing the outbreak to be out of control and irreparable losses in production.

2.4 Agent-based Models

Addressing the issues mentioned in the previous sections, computational modeling approaches like cellular automata (CA) and agent-based modeling (ABM) have been used in diverse fields as a "bottom-up" approach to study complex systems. The rapid development of CA and ABM benefits from the advancements of computational and information-processing techniques in the fields including computing science, physics, game theory, and evolutionary science during the twentieth century (Tracy et al. 2018). Cellular automata theory has been introduced early to model dynamic processes with characteristics of discrete space and time of susceptible population, as well as embedding stochastic parameters to capture the probabilistic nature of transmitted diseases. However, the representation of individuals' movements and interactions over space was not captured (Perez and Dragicevic 2009). Since they are important factors for simulating transmitted diseases, an emerging and improved approach, ABMs were created and applied to a broader field of studies. The history of the ABMs dates back to the 1970s with John Conway's Game of Life that first created simple rules in a virtual world in the form of 2D checkerboard (Gardner 1970) and Thomas Schelling's segregation model that represented the autonomous agents iterating in a shared environment (Schelling 1971). ABMs, also known as individual-based models, have been well established to study the epidemiology of complex infectious diseases in public health (e.g., influenza, HIV, tuberculosis, foot and mouth disease) (Willem et al. 2017). In these models, autonomous agents (which can be anything from a pathogen or an animal to an organization and a nation-state), governed by a set of coded rules, interact with each other and their environment (Hunter et al. 2018). Nowadays, with the generalization of the computational technologies and reduction of associated costs, ABMs using simulation methodology have gained more attention in human and animal health and economics.

There are three potential improvements of ABM relative to the compartment model when studying livestock disease transmission and control. Firstly, unlike compartment models, ABMs account for decisions made at the individual level but analyze the results from a global level. In ABM, one overall model embodies the behaviors of the system's units (agent) and their interactions, which captures the emergent phenomena from the bottom up when the simulation is run (Bonabeau 2002). Explicitly modeling each agent in a population allows ABM to capture population heterogeneity (Bradhurst et al. 2016). Secondly, ABMs collect data of each animal's attributes (e.g., disease status, age status, weight status), which would more closely mimic the natural behaviors of individual animals and real decisions of managers made on farms (Chiu et al. 2018). Thirdly, an ABM is highly flexible from many dimensions. For example, one of the dimensions is that it has the feature of building agents at multi-levels, which makes the networks happen in separated space. It is allowed to code different behaviors, degree of rationality, ability to learn and evolve, and rules of interaction at a lower agent level, but also there is the ability to collect and aggregate single agent or subgroup of agents at a higher level (Bonabeau 2002). This feature is beneficial for modeling animals' behaviors in livestock industries, since animals are always grouped for feeding or transporting between operations. For instance in our study, an individual calf could be an agent and a feedlot pen could be another higher-level agent which containing calves.

Although ABMs have been extensively studied in human disease-transmission dynamics, their use to solve livestock economics is rare. A few applications include estimation of benefit and costs of control strategies associated with Johne's disease in a commercial dairy herd (Chiu et al.

2018) and evaluation of the effect of producer specialization on the epidemiological resilience of the U.S. hog production networks (Wiltshire 2018). Other similar examples of ABMs are used in plant diseases, such as trade-offs between pest control and pollination service provision in the case of neonicotinoid insecticides (Wu and Atallah 2019) and diffusion and control of grapevine leafroll disease (Atallah et al. 2015). In beef production sectors, previous ABMs have focused on disease-transmission dynamics (Ross et al. 2011; Nepomuceno et al. 2018); however, they did not access the trade-offs between profitability and AMUs related to control strategies for the diseases. To the best of our knowledge, there have not been studies on the economic impact of early diagnostic methods on AMU in livestock production.

2.5 Model Choice for BRD

The unique characteristics of certain livestock-transmitted diseases like BRD restrict the choice of approaches to model disease transmission and control strategies. Regarding our research objective of modeling Bovine Respiratory Disease, the first characteristic of this disease is that it is simultaneously driven by integrated dynamic and stochastic forces. For example, a susceptible calf in a pen of a feedlot might be infected with BRD when exposed to other sick calves, but the infection probability might be changing depending on its weight and other factors over time.

Second, the treatment of BRD for diagnosed calves in the feedlot involves isolation and switching of feeding environment. Specifically, a diagnosed individual calf will be moved to a hospital pen for isolation and treated with antimicrobials for a period of time. This means there are at least two collections of pen-level agents containing populations of calves.

Calf heterogeneity is the third characteristic of certain diseases. Individual calves are heterogeneous in the time to and the likelihood of being infected by other infective calves or diagnosed by various diagnostic strategies. The infection probability of a healthy calf is own weight-dependent, and the diagnostic process is disease-state dependent for different diagnostic strategies. These three above mentioned characteristics call for agent-based and stochastic-dynamic models of disease transmission and control for BRD.

Chapter 3 Model

3.1 Overall Model Scope

This BRD bioeconomic modeling project contains two main models: a disease model and an economic model. All the model components are built in a java-based software AnyLogic. The disease model includes the BRD transmission process and the disease management strategies. An adjusted Susceptible-Infectious-Recovered (SIR) epidemiological infection framework is built at the calf-level representing an individual calf's infection status and the disease transmission with others. Next, we overlay the epidemiological infection framework with a process in which various BRD management strategies can be imposed on the population, including the diagnostic tests and AMUs.

The economic model is used to evaluate the cost-effectiveness among alternative BRD management strategies, which mainly focus on the trade-offs between expected profit and required AMU level among different scenarios that could be generated by the disease model. The expected profits are determined by total revenue and total costs after finishing. The total revenue after finishing is dependent on calves' finishing weights that are influenced by their status (disease status, weight status, life status, diagnostic status, and AMU status) during the feeding period. Feed costs, testing costs, and AMU costs are strategy-based, but other required costs are fixed for all individuals.

3.2 Disease Model

We first propose a disease model that integrates an agent-based model (ABM) and an adjusted susceptible-infected-recovered (SIR) model to simulate the BRD disease dynamics at a representative feedlot in western Canada. The model components for different disease management strategies including diagnostic tests and AMUs are also built at the agent-level and interact with the disease transmissions.

There are two state variables and two control variables defined in the disease model. The first state variable is the disease infection state $S_{i,t}$, which describes calf i's infection state at time t. We assume that at a particular time t, a calf can only be at one of the four mutually exclusive infection states: *Susceptible, Subclinical, Clinical* and *Treated.* The second state variable is the weight of a calf $W_{i,t}$. It interacts with the disease infection state and the transition rules among different states.

The first control variable is *Diagnostic Test*, denoted as $\tau_{i,t}$. At time t, a feedlot manager can choose to apply to calf i with one of the three diagnostic test methods: Conventional Lab Test, Early Diagnostic Test, and Pen Checkers' Simple Inspection (No Test) for BRD diagnosis. *AMU Administration*, denoted as $A_{i,t}$, is the other control variable. We assume there are three AMU administration methods: Individually Dosed AMU, Metaphylaxis, and Prophylaxis for BRD treatment. Individually Dosed AMU only applies to diagnosed calves in hospital pen, while all the calves in the home pen receive AMU treatment under Metaphylaxis and Prophylaxis. The changes in infection states and weight states are affected by *Diagnostic Test* and *AMU Administration* of feedlot managers. The details of their relationships and state transition rules will be introduced in the following sections of infection components (section 3.2.1) and disease management components (section 3.2.2).

The spatial geometry of cattle feeding and disease transmission and control is represented in Figure 3.1. A single agent in the model is defined as an individual calf, and its color indicates the infection states overtime during the simulation. There are two rectangles which represent a typical home pen for cattle normal feeding and a hospital pen for isolation and individual treatment for infective calves with antimicrobial drugs. The home pen contains a randomly distributed population of individual calves at the beginning of the simulation while the hospital pen is initially empty. There is a network (the lines connecting individuals in Figure 3.1) that an individual calf is randomly connected with other calves within the home pen. During the feeding period, a susceptible calf could only be infected by the connected calves that at the infective states. We assume the contact rate between calves with connections in the home pen is λ per day. Diagnosed calves from the home pen would be moved to the hospital pen to receive antimicrobial treatment and moved back to the home pen once they are recovered. The two environments are separated so that disease cannot be spread between pens. One overall model factor is the time t in simulation, which is set in days. Each calf's position, either in the home pen or the hospital pen, is updated daily.

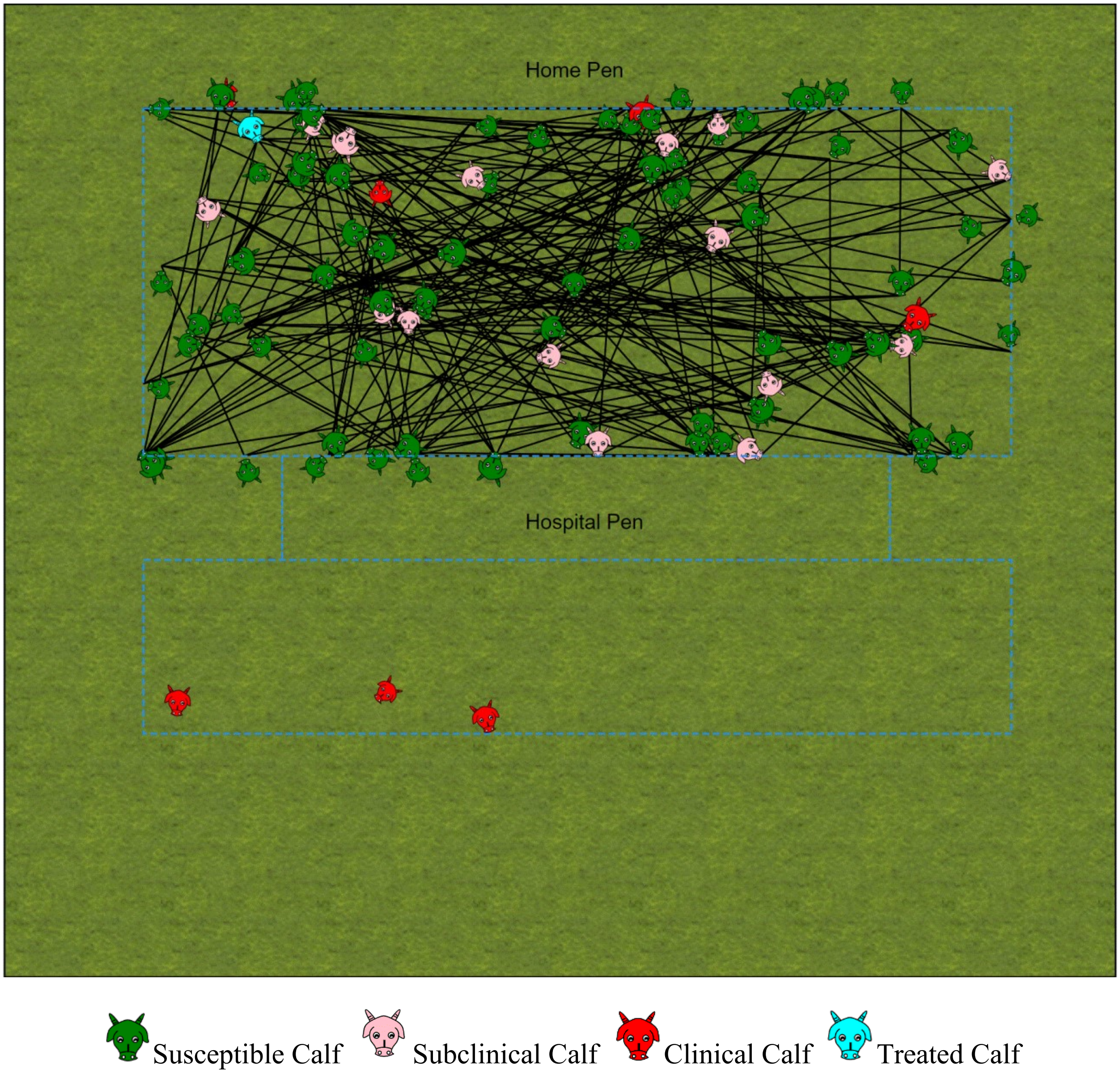

Figure 3.1 A Snapshot Representation of Interactive Cattle with Different Infection States in Home Pen and Hospital Pen

3.2.1 Infection Components of the Disease Model

Since there is a typical incubation period for an infected calf with BRD, an Infection Statechart built in this project is derived from the classic Susceptible-Infectious-Recovered (SIR) model, with slightly modified states to fit BRD context (Figure 3.2).

This framework is built as a hierarchical statechart and consists of four basic states: *Susceptible, Subclinical, Clinical,* and *Treated.* The *Subclinical* and *Clinical* states are built within a "hierarchical structure" that both of them belong to the *Infective* state. Separating the two states allows us to model the different impacts of diagnostic approaches as BRD symptoms are heterogeneous among infective individuals over time. These states are defined as follows:

- ***Susceptible****:* A healthy calf in a **s**usceptible state. When a susceptible individual and an infective (subclinical or clinical) individual come into "infectious contact", the susceptible individual receives a message of "Exposed" to change state.
- ***Subclinical (within Infective)****:* An infective calf in a subclinical state. This is an individual who has been infected but has not shown any symptoms. Calf in this state could send a message "Exposed" to randomly connected calves in the environment with a defined contact rate.
- ***Clinical (within Infective)****:* An infective calf in a clinical state. This is an individual who has been infected and has shown some symptoms. The calf in this state could send a message of "Exposed" to randomly connected calves in the environment with a defined contact rate.
- ***Treated****:* A recovered calf in a treated state. This is an individual who has been infected but has been treated from antimicrobials by any AMU interventions. Calf in this state has developed an antimicrobial induced immunity to BRD.

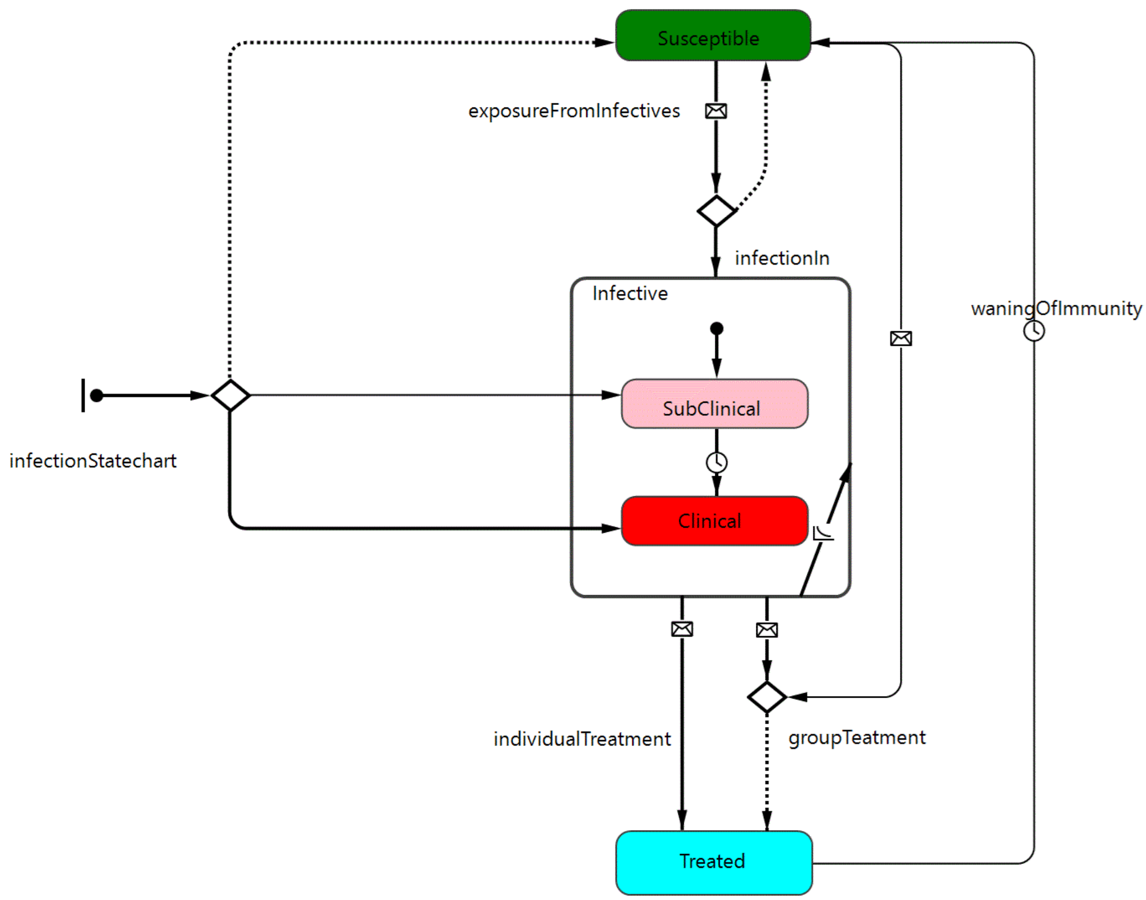

Figure 3.2 Infection Statechart and Transition Rules

Given each calf's infection state $S_{i,t}$ at time t and an infection state transition matrix P, its infection state $S_{i,t+1}$ at time $t+1$ is computed according to the following infection-state transition equation:

$$E\left(S_{i,t+1}\right) = P^T \cdot S_{i,t}$$
$$\text{for } t = 0, 1, 2, \ldots, 229 \tag{1}$$

where E is the expectation operator and P^T is the transpose of matrix P. $E(S_{i,t+1})$ is a *4 × 1* vector that represents the new infection state at next time point after applying with P. The infection state transition probability matrix P governs disease transmissions. Mathematically, P can be express as follows:

$$P = \begin{bmatrix} 1-a-b & a & 0 & b \\ 0 & 1-c-d & c & d \\ 0 & 0 & 1-e & e \\ f & 0 & 0 & 1-f \end{bmatrix} \quad (2)$$

We now describe how the infection state transition probability matrix *P* governs disease transmissions. As the Infection Statechart showed in Figure 3.2, at the start of the Infection Statechart, a calf can be in one of the three states, namely *Susceptible, Subclinical, Clinical.* After initialization, a healthy calf starts in the *Susceptible* state, and it could get exposed to other infective calves within the home pen. This is controlled by a message-triggered transition between a sender (infective calf) and a receiver (susceptible calf) that is connected with each other. A weight-dependent probability a determines whether it will get infected by other infectives. If it is true, it will enter the *Infective* state in which the disease can now spread to others. The *subclinical* state is the prior substate that it enters and then transits to the *Clinical* substate subsequently with a probability c. It is a timeout triggered transition that becomes enabled after *X* days elapses. After that, there is a *Treated* state which could be reached through two types of message-triggered transitions: *individual treatment* and *group treatment* from *Infective* state (either *Subclinical* or *Clinical* substates). The triggers of these two transitions are different. If a *subclinical* calf is diagnosed by a testing strategy (Conventional Lab Test or Early Diagnostic Test) and then treated with Individually Dosed AMU, it will transit through *individual treatment* transition with a probability d to the *Treated* state. Differently, apart from a testing strategy, a *Clinical* calf could also be diagnosed by Pen Checkers' Inspection. After an individual antimicrobial treatment, it will transit to the *Treated* state through *individual treatment* transition with probability e. Another transition between the *Infective* state and the *Treated* state is occurring when there is a mass medication event (*Metaphylaxis Event* or *Prophylaxis Event*) applying to the entire pen. An *Infective* calf will transit through *group treatment* transition with a probability b. It is important to note that all other calves including the healthy ones in the home pen receive the antimicrobials as well. As a result, a *susceptible* calf will simultaneously jump to the *Treated* state with the same probability b. Finally, after a period of waning of immunity, given as M in the model, a treated calf will transit back to the *Susceptible* state with a probability e.

As mentioned above, probability a controlling the *Susceptible* to *Subclinical* transition not only conditional on previous own infection state and all connected calves' infection states, but also it is weight dependent. A calf's weight range is defined as small, medium, and large as growing during the simulation. The weight state $W_{i,t}$ falling in each weight range has interactions with Infection Statechart to give the heterogeneity of individuals' response as exposed to BRD. Specifically, a small weight calf is defined under m_1 pounds with α_1 probability of infection; a medium weight calf is between m_1 pounds and m_2 pounds with α_2 probability of infection; and a large weight calf is greater than m_2 pounds with α_3 probability of infection.

Culling rate is another factor that affects the weights of calves. A culled calf will be deleted from the system and its weight is fixed at the time t that it was culled (The relevant definitions and process will be introduced in section 3.2.2 of Disease Management Components). The weight of each calf is updated daily, and it is calculated by cumulatively adding up the live daily gain, given as $LDG_{i,t}$, to the arrival weight from the beginning. The $LDG_{i,t}$ of a calf is dependent on its current weight, infection state, and whether it receives AMU administration at time t. Given each calf's weight state $W_{i,t}$, its weight state $W_{i,t+1}$ at time $t+1$ is computed according to the following weight-state transition equation:

$$W_{i,t+1} = W_{i,t} + \left(1 - Cull_{i,t}\right)LDG_{i,t}\left(W_{i,t}, S_{i,t}, A_{i,t}\right)$$
$$\text{for } t = 0, 1, 2, \ldots, 229 \qquad (3)$$

where $Cull_{i,t}$ is a dummy variable that $Cull_{i,t} = 1$ if the calf is culled at time t. Live Daily Gain ($LDG_{i,t}$) is a function of Weight state ($W_{i,t}$), Infection state ($S_{i,t}$) and AMU administration ($A_{i,t}$) at time t. The arrival weight ($W_{i,0}$) is following the weight distribution of the auction-mart derived cattle: $W_{i,0} \sim uniform(450, 600)$.

Live daily gain information is derived from Beef Cattle Research Council (2019), and Figure 3.3 below shows the relationship between $LDG_{i,t}$ and the $W_{i,t}$.

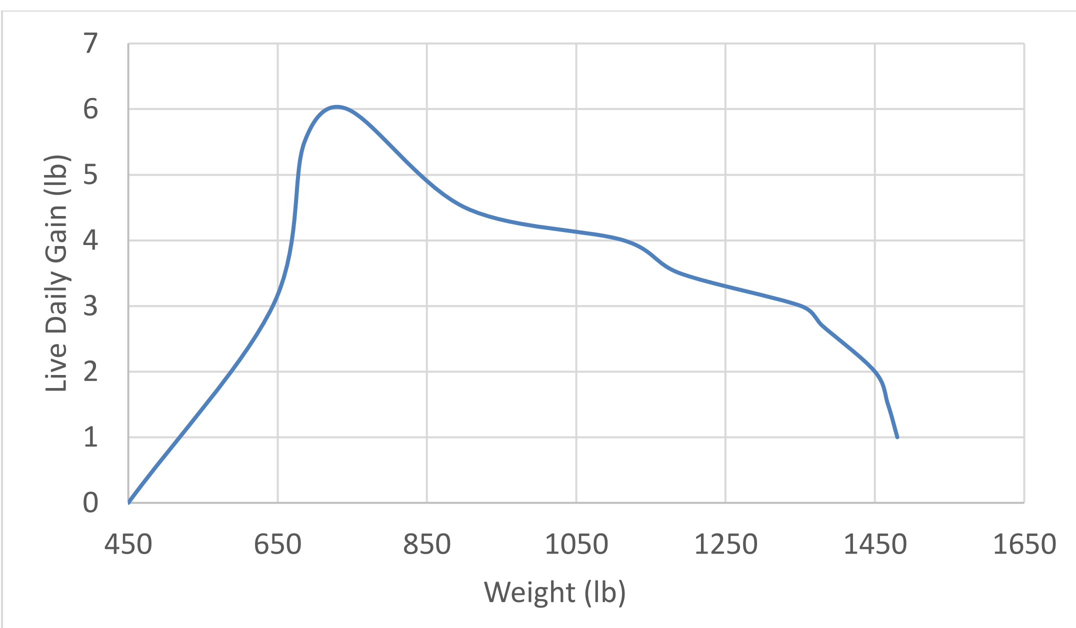

Figure 3.3 The Relationship between Live Daily Gain and Weight of a Susceptible Calf

Infection states and AMU administrations are two main factors that affect the above trend of weight gain of a calf. Specifically. There is a daily loss of $LDG_{i,t}$ for a calf that is staying in *Subclinical* state or *Clinical* state, given as W_l. However, there is a daily improvement in $LDG_{i,t}$ when an antimicrobial treatment for a calf staying *Susceptible* state, given as W_g.

3.2.2 Disease Management Components of the Disease Model

Disease Management components are used to simulate the process of diagnosis and antimicrobial treatment of calves infected with BRD. For the diagnostic process, the model components mainly cover the strategies of Conventional Lab Test, Early Diagnostic Test, and Pen Checkers' Inspection Only *(*No Test*)*. Conventional Lab Test and Early Diagnostic Test can detect the *Subclinical* and *Clinical* states while Pen Checkers' Inspection Only can only diagnose *Clinical* state. For the treatment process, they are simulating the AMUs, which include Individually Dosed AMU for a diagnosed calf in hospital pen, and Metaphylaxis and Prophylaxis as mass medications for all the calves in home pen. Individually Dosed AMU is followed by the diagnostic results for a specific calf. The scheduled starting time and duration of the Metaphylaxis and Prophylaxis administrations are modeled by separated events in the model. These events are interacted with the Infection Statechart and call for the infection state transitions.

3.2.2.1 Testing Statechart and Transition Rules

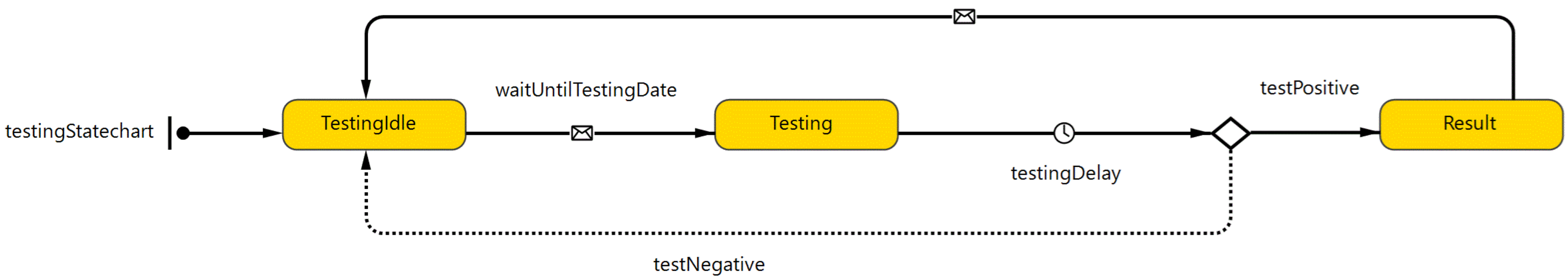

Figure 3.4 Testing Statechart and Transition Rules for Conventional Lab Test and Early Diagnostic Test

Testing Statechart is used for providing a simple representative framework of a testing process. It covers the Conventional Lab Test and Early Diagnostic Test strategies for BRD (Figure 3.4). There are three main states in this statechart, which are *Testing Idle* state, *Testing* state, and *Result* state. *Testing Idle* state is a state which a calf resides in while it has not been tested. Once there is a call on starting a diagnostic test, the testing state of all the calves within the home pen will transit to the *Testing* state. The *Testing* state takes into account testing sensitivity (given as SE) and specificity (given as SP) conditional on different infection states at the testing period. An action chart is developed in the model to represent the details of the testing process (Appendix 1). After that, there is a delaying time to get the results after the testing, which leads to the main difference between Conventional Lab Test and Early Diagnostic Test. Respectively, the delaying time is controlled by two different parameters of D_c and D_e for these two tests in the model. It is important to note that disease transmission is still running so that there could be changes of infection states for many calves during this lag period. Once the lag period is finished, the diagnostic result is clear for an individual. If it is BRD positive, the calf will be sent to the hospital pen and treated with Individually Dosed AMU. If it is BRD negative, the calf will be staying in the home pen and wait for the next testing date.

3.2.2.2 Simple Inspection Statechart and Transition Rules

Simple Inspection Statechart only contains one state that every calf within the home pen will be daily inspected by the pen checkers (Figure 3.5). It always serves as a background operation to detect the diseased animal. The accuracy of this type of diagnosis is relatively low, and we define the average diagnostic rate as θ in the model. Another limitation of this method is that it only diagnoses calves staying in the *Clinical* infection state. Similar to a testing strategy mentioned before, when a calf is diagnosed by this approach, it will be sent to the hospital pen and treated with Individually Dosed AMU.

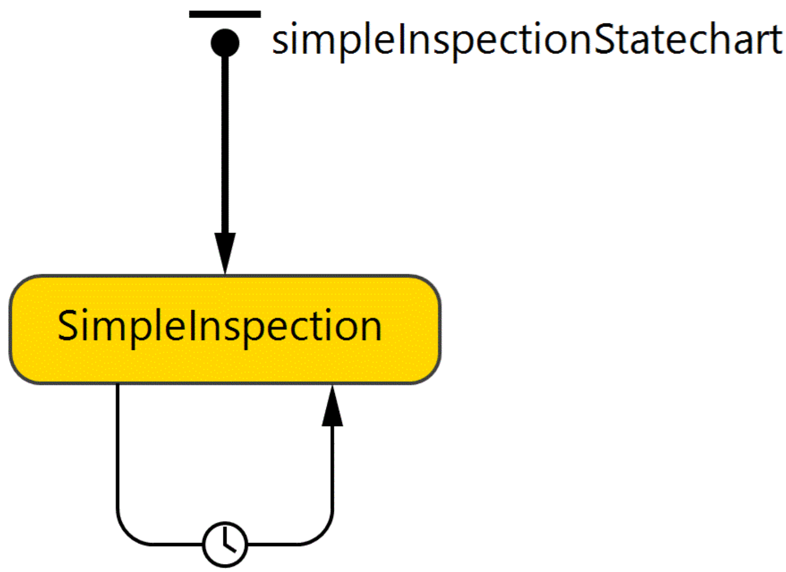

Figure 3.5 Simple Inspection Statechart and Transition Rules

3.2.2.3 Diagnostic Statechart and Transition Rules

The Diagnostic Statechart is used for indicating a calf's diagnostic status (Figure 3.6). There are two states including *ReadyForDiagnosis* and *Diagnosed.* Every calf resides in the *ReadyForDiagnosis* state until it is diagnosed by the three diagnostic strategies mentioned above.

The transition is triggered by messages sent from either Testing Statechart or Simple Inspection Statechart. Once it transits to the *Diagnosed* state, a message would call for the location changes of the calf from home pen to hospital pen, and then the individual antimicrobial treatment gets started. After the treatment complete, the diagnosis state of this calf will transit back to the *ReadyForDiagnosis*.

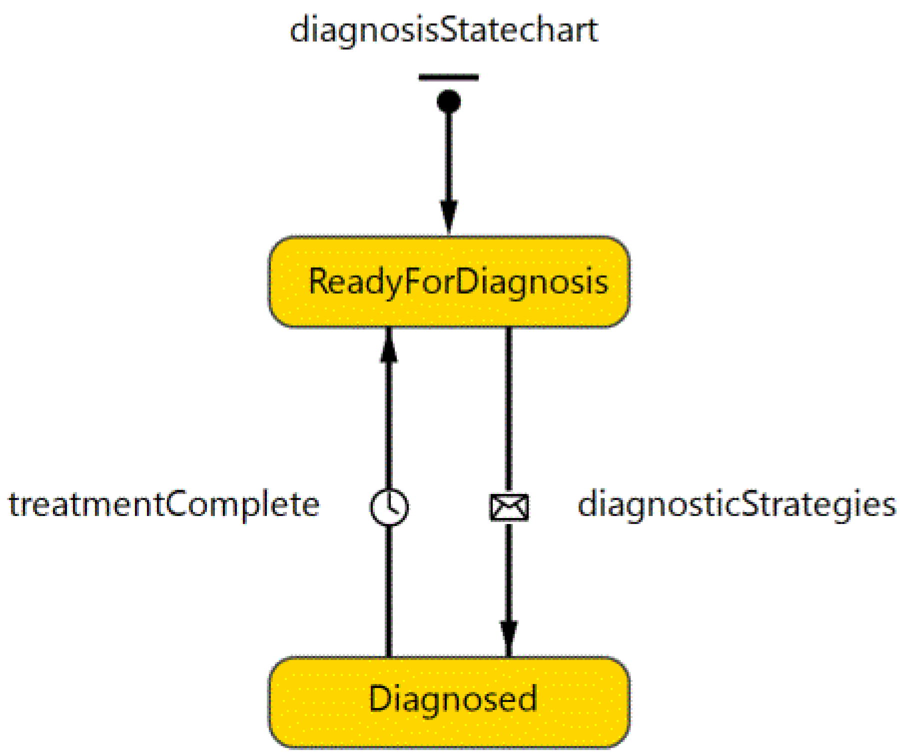

Figure 3.6 Diagnosis Statechart and Transition Rules

3.2.2.4 AMU Treatment: Process Flowchart and Dynamic Events

We define Individually Dosed AMU as a single antimicrobial treatment applying to a diagnosed calf in the hospital pen. After a period of treatment, if it is recovered, it will be moved back to the home pen and continue the normal feeding with other cohorts. This period is given as K in the model. However, in the hospital pen, an infective calf also has a chance of being culled. An average culling rate is given as μ for a diagnosed clinical calf. A process flowchart is used to support the above transitions of calves between the home pen and the hospital pen (Figure 3.7)

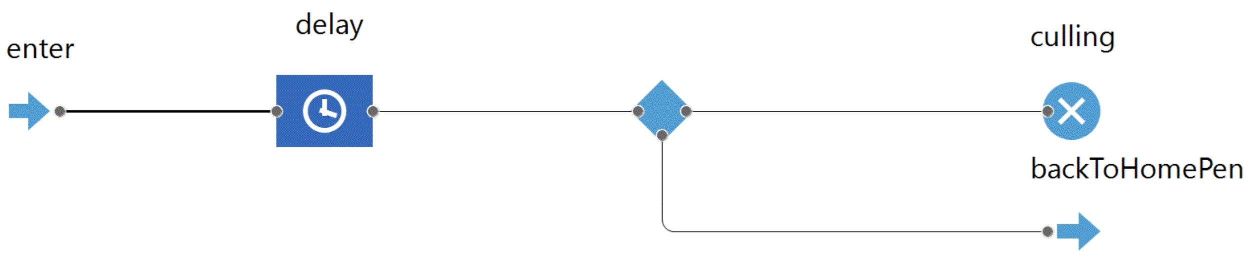

Figure 3.7 Process Flowchart for Diagnosed Calves in Hospital Pen.

In addition to the introduced modeling components for the Individually Dosed AMU, *Metaphylaxis Dynamic Event* and *Prophylaxis Dynamic Event* are used to control the number of administrations, scheduled starting time, and duration of mass medications strategies in the model. Respectively, T_m represents the time spent for a Metaphylaxis administration and T_p represents the time spent for a Prophylaxis administration.

When these two scheduled dynamic events are finished, they are sending messages to the Infection statechart and call for the changes of infection states of the individual calves in the home pen. However, not all the calves are jumping from the current infection state to the *Treated* state. The efficacy of Metaphylaxis is defined as β_M and the efficacy of Prophylaxis is defined as β_P in the model.

3.3 Parameterization and Calibration for Disease Model

In our disease model, there are many parameters used for simulations due to the complex nature of interactions between agents and other agents, agents and statecharts, and agents and environments. We organized the parameters into groups, which are Infection Parameters, Diagnosis and Treatment Parameters, and Cattle Parameters (Table 3.1). Most of the values of parameters are directly chosen from relevant literature, but some of them are manually calibrated relying on important time points selected from representative prevalence trends from other studies. The explanations of the calibrations will be provided as well.

Table 3.1 Infection Parameters, Diagnosis and Treatment Parameters, and Cattle Parameters in the Disease Model

Symbol	Descriptions	Formula/value in model	Unit	Sources
Infection Parameters				
λ	Contact rate of an infective calf to a randomly chosen calf from connections within home pen	2	day^{-1}	Calibration experiment based on Snowder et al. (2016), Timsit et al. (2011), and Smith (2001)
M	Period of waning of treatment induced immunity	uniform_discr (2, 7)	$days$	Campbell (2015)
X	Period spent in *Subclinical* state before a calf transition to *Clinical* state	uniform_discr (2, 10)	$days$	Campbell (2015)
α_1	Probability of infection for a small-weight *Susceptible* calf	0.15		Ackernann (2010)
α_2	Probability of infection for a medium-weight *Susceptible* calf	0.07		Calibration experiment based on Snowder et al. (2016),Timsit et al. (2011), and Smith (2001)
α_3	Probability of infection for a large-weight *Susceptible* calf	0.03		Calibration experiment based on Snowder et al. (2016),Timsit et al. (2011), and Smith (2001)

Symbol	Descriptions	Formula/value in model	Unit	Sources
Diagnosis and Treatment Parameters				
θ	Probability of a *Clinical* calf diagnosed by pen checkers' simple inspection	0.618		Patterson et al. (2017)
SE	Test sensitivity for both *Subclinical* and *Clinical* calf	0.9		Patterson et al. (2017)
SP	Test specificity for both *Subclinical* and *Clinical* calf	0.9		
μ	Average culling rate for a diagnosed *Clinical* calf in hospital pen	0.06		Smith (2001)
K	Period spent in hospital pen to for a diagnosed calf	uniform_discr (1, 3)	$days$	Ackernann (2010)
β_M	Efficacy of Metaphylaxis Administration	0.75		Smith (2001)
β_P	Efficacy of Prophylaxis Administration	0.237		Agga er al. (2016)

Symbol	Descriptions	Formula/value in model	Unit	Sources
T_m	Time spent for a Metaphylaxis Administration	3	$days$	Brault et al. (2019)
T_p	Time spent for a Prophylaxis Administration	uniform_discr (5, 10)	$days$	Patterson et al. (2017)
D_c	Delay in getting results from Conventional Lab Test	5	$days$	Owen et al. (2017) and Conrad et al. (2020)
D_e	Delay in getting results from Early Diagnostic Test	1	$days$	Advanced Animal Diagnostics (2019)
Cattle Parameters				
m_1	Weight boundary between small weight and medium weight of a calf	500	lb	Sanderson et al. (2008)
m_2	Weight boundary between medium weight and large weight of a calf	700	lb	Sanderson et al. (2008)

Symbol	Descriptions	Formula/value in model	Unit	Sources
W_l	Loss of live daily gain for an *Infective* calf	uniform (0.3, 0.5)	lb/day	Snowder et al. (2006)
W_g	Improvement percentage of live daily gain when a *Susceptible* calf is given an antimicrobial treatment	uniform (1, 15)	%	Health Canada (2002)

The diversity of guidelines of drug use, disease management strategies, and source of animals in different regions may lead to different BRD epidemic patterns in feedlot cattle. Generally, in western Canada, cattle placements from the auction market are believed to have a high health risk. A "business as usual" practice of BRD control is administering metaphylactic antimicrobials upon arrival accompanied with pen checkers' regular inspection for any observable symptom of calves throughout the rest of feeding time (Checkley et al. 2010).

We performed manual calibrations for the contact rate for an infective calf with others (λ in Table 3.1) and infection probabilities ($\alpha_1, \alpha_2, and\ \alpha_3$ in Table 3.1) for the "business as usual" practices. These two factors are the most important to determining the epidemic pattern (prevalence versus days on feed) of BRD in the feedlot. Relying on the two trend graphs (Appendix 2) drawn from real surveillance data performed by two studies (Timsit et al. 2011; Snowder et al. 2016), and the descriptions about prevalence changes on the critical feeding time points after arrival in Patterson et al. (2017), we mainly calibrate these parameters by matching prevalence at two time points. The first one is that on average, the cumulative infective cases reach 30% of the population between 7 to 21 days after arrival. The second is that the prevalence should be close to zero around 110 days. We manually vary the values of the contact rate of an infective calf to others and infection probabilities in the calibrated model to match the above two points as much as possible.

3.4 Economic Model

The feedlot managers decide whether to apply disease management strategies including the diagnostic tests and AMUs to control the spread of BRD during the feeding period in the feedlot. The mentioned disease management strategies could be singly chosen or used in combinations.

The expected profit after finishing is an important factor evaluating different management strategies, which is calculated by total revenue of a representative pen subtracting all the required costs after finishing.

The objective of a risk-neutral feedlot manager is to maximize the total profit of a pen by choosing an optimal BRD control scenario from a discrete set of diagnostic strategies and AMUs, δ^*. Each scenario translates into two decisions for each calf i. The first decision a manager faces is choosing which tests ($\tau_{i,t}$) for BRD diagnosis, and the second is choosing AMU administrations ($A_{i,t}$) for the treatment. Letting Π be the final pen-level profit which is the summation of the calf-level profit $\pi_{i,t}$ after 230 days in the feedlot. The objective of a feedlot manager is to maximize Π as follows:

$$\begin{aligned} \max_{\delta} \Pi &= \sum_{i} \pi_{i,T} \\ &= \sum_{i} \left\{ R_{i,T} - C_{feed_{i,T}} - \left(C_{test_{i,T}} + C_{AMU_{i,T}} \right) - FC \right\} \end{aligned} \tag{4}$$

subject to the infection state transition equation (equation 1) and the weight state transition equation (equation 3).

The $R_{i,T}$ in equation (4) represents the revenue of an individual calf. It depends on the total finishing weight of the calf and the selling price at time T. If a calf is culled due to BRD during the feeding period, the T is set equal to the culling time t, where $t \in \{0,1,2\ldots,229\}$. Note that its culling weight is also included in the total pen-level weights. In addition, the selling price at the finishing is fixed, given as p. The revenue $R_{i,T}$ can be expressed as follows:

$$R_{i,T} = pW_{i,T} \tag{5}$$

The $C_{feed_{i,T}}$ in equation (4) represents the total costs of feed for an individual calf. It depends on the unit feed cost and the weight of a calf at time T. We assume all the individual calves placed in a pen after arrival at the same time $t = 0$, and the arriving weight of a calf is following the representative weight distribution of a feedlot in western Canada that derived from auction mart. The weight of a calf is cumulatively adding up the live daily gain ($LDG_{i,t}$) to the arrival weight defined in the weight transition equation (Equation 3) until the finishing. The finishing weight is given as $W_{i,T}$. Feed costs are continuous and conditional on the calf's life as well, so a calf will no longer be fed if it is culled. The unit cost of feed is given as r. The $C_{feed_{i,T}}$ can be expressed as follows:

$$C_{feed_{i,T}} = r\left(W_{i,T} - W_{i,0}\right) \tag{6}$$

The $C_{test_{i,T}}$ in equation (4) represents the total testing costs for an individual calf. It depends on the chosen types of testing strategies and their associated testing costs during the overall feeding period ($T = 229$). A set of testing strategies is given as a *3 × 1* vector $\tau_{i,t}$, containing Conventional Lab Test, Early Diagnostic Test, and Pen checkers' inspection (No Test). The unit costs of these three diagnostic strategies are defined in a *1 × 3* vector $\boldsymbol{c_{\tau}}$. Note that testing cost is discrete and only counted when a specific test is utilized for an individual calf at time t. The total testing cost for an individual calf is the sum of all the required testing costs during the entire feeding period. $C_{test_{i,T}}$ can be expressed as follows:

$$C_{test_{i,T}} = \sum_{t=0}^{T} \left(\tau_{i,t} \cdot c_{\tau}\right) \tag{7}$$

The $C_{AMU_{i,T}}$ in equation (4) represents the total cost of antimicrobial drugs for an individual calf. It depends on the chosen types of AMUs and their associated costs of antimicrobial drugs during the overall feeding period ($T = 229$). A set of AMU administrations is denoted as a *3* × *1* vector $\mathrm{A}_{i,t}$, containing Individually Dosed AMU, Metaphylaxis, and Prophylaxis. The corresponding unit cost of these three AMU administrations for an individual calf is defined in a *1* × *3* vector c_{A}. Similar to the diagnostic costs, costs of antimicrobial drugs are also discrete and only counted when a specific AMU administration is applied on an individual calf at time t. The total costs of antimicrobial drugs for an individual calf are the sum of all the required AMU costs during the entire feeding period. $C_{AMU_{i,T}}$ can be expressed as follows:

$$C_{AMU_{i,T}} = \sum_{t=0}^{T} \left(\mathrm{A}_{i,t} \cdot c_{\mathrm{A}}\right) \tag{8}$$

Lastly, the FC in equation (4) represents other costs that occurred during the entire feeding period, such as interest cost and yardage costs. They are assumed to be fixed for each calf.

In summary, the economic model describes the objective of a feedlot manager to maximize the total profits of a representative pen of cattle after 230 feeding days, by choosing an optimal BRD control scenario δ^* from a set of diagnostic strategies and AMUs, subject to the infection state transitions and the weight state transitions of calves. The complete mathematical model is included in Appendix 3. Based on the disease model and economic model in this chapter, we will introduce the experiment design and relevant economic parameters in the next chapter. These steps will serve as the basis of simulations for different BRD management scenarios.

Chapter 4 Experiment Design

4.1 Disease Management Scenarios

Disease management strategies (including diagnostic strategies and AMUs) introduced in Chapter 3 could be used at a specific time point. A disease management scenario is to use single or combinations of disease management strategies one or more times over the entire feeding period. We design nine different representative disease management scenarios. Most of the scenarios are designed as adding extra strategies over the base of a pen checkers' inspection strategy. Scenario (1) is defined as the "business as usual" practice. Scenarios (1) to (5) are designed for mass medication strategies while Scenarios (6) to (8) are designed for test-informed Individually Dosed AMU. The detailed definitions are shown in Table 4.1.

Table 4.1 Definitions of Disease Management Scenarios

Disease Management Scenarios		
1	Arrival Metaphylaxis	Administration of injectable AMU to the entire pen of calves after arrival in the feedlot, with pen checkers' inspection run through the rest of time
2	Metaphylaxis Twice	Administration of injectable AMU to the entire pen of calves after arrival and at day 21, with pen checkers' inspection run through the rest of time
3	Arrival Prophylaxis	Administration of infeed AMU to the entire pen of calves after arrival in the feedlot, with pen checkers' inspection run through the rest of time
4	Prophylaxis Twice	Administration of infeed AMU to the entire pen of calves after arrival and at day 21, with pen checkers' inspection run through the rest of time
5	Metaphylaxis and Prophylaxis Combination	Administration of injectable AMU after arrival and infeed AMU at day 21 to the entire pen of calves, with pen checkers' inspection run through the rest of time
6	Conventional Lab Test	Conventional lab tests to the entire pen of calves after arrival and at day 21, with pen checkers' inspection run through the rest of time
7	Early Diagnostic Test	Early diagnostic tests to the entire pen of calves after arrival and at day 21, with pen checkers' inspection run through the rest of time
8	Simple Inspection Only	Pen checkers regularly inspect calves to detect any BRD symptoms through the entire of time
9	No Infection	Assume no BRD case and no antimicrobial application from the beginning to end

Notes: Scenario (1) to Scenario (7) is applying combinations of the strategy of Pen Checkers' Inspection and other disease management strategies throughout the entire simulation. Scenario (8) and Scenario (9) contain only the strategy of Pen Checkers' Inspection.

4.2 Bioeconomic Outcomes Measures

We use the objective function (Equation 4 in Chapter 3) to rank the feedlot manager's expected "close-out" total profit under the listed disease management scenarios. For each scenario, antimicrobial doses are collected during the simulations and total doses are calculated at the end of simulations. The trade-offs between expected profits and the AMU levels are the main factors for evaluating the cost-effectiveness of those alternative disease management scenarios.

The diversities of types and dosages of antimicrobial drugs across many feedlots located in different regions or even within a single feedlot with different control strategies post a challenge for the measurement of AMU levels. To cope with this challenge, we choose Tetracyclines, which is the most commonly used antimicrobial drug through both channels of injection and infeed (Brault et al. 2019) as a representative drug and calculate the total required doses under each disease management scenario. The economic parameters and AMU parameters with descriptions are listed in Table 4.2. Note that there may exist a nonlinear relationship between dose of AMUs and the resulting antimicrobial costs, since the costs of AMUs are measured based on the average costs of one or more drugs for an individual calf during a treatment.

Table 4.2 Economic Parameters and AMU Dose Parameters

AMU Dose and Economic Parameters	Values	Unit	Sources
Cost of Individually Dosed AMU	31.5	$\$/case$	U.S. Department of Agriculture, Animal and Plant Health Inspection Service, and Veterinary Services (2013)
Metaphylaxis Cost	30.9	$\$/head/admin$	Dennis et al. (2018)
Prophylaxis Cost	9.76	$\$/head/admin$	Calculations from Brault et al. (2019)
Feeder Cost	1.9	$\$/lb$	Manitoba Agriculture (2019)
Selling Price	1.54	$\$/lb$	Manitoba Agriculture (2019)
Testing Price	10	$\$/case$	Assumed
Individually Dosed AMU	8.001	$g/head/admin$	Calculations from Brault et al. (2019)
Dose of Metaphylaxis	8.001	$g/head/admin$	Calculations from Brault et al. (2019)
Dose of Prophylaxis	3.174	$g/head/admin$	Calculations from Brault et al. (2019)

Note: All values in Canadian dollars

4.3 Model Simulation

At the beginning of a simulation, a population of 100 calves in the home pen are randomly distributed as follows: 85% are susceptible, 10% are subclinical, 5% are clinical. Even though there is no information that describes a specific distribution associated with BRD states at cattle arrival, most studies stated that auction-mart derived calves always have higher infection risks and more latent cases among the population. We set the initial disease infection distribution as mentioned above based on the observed occurrence of BRD treatment in a feedlot in western Canada for five years reported in Hendrick and Abeysekara (2009), and on the rate of positive isolates of BRD pathogens in auction market raised calves in Wennekamp (2020). The arrival weight of each calf is uniformly randomly selected from a weight range of 450 to 600 pounds (Alberta Cattle Feeder's Association 2020).

We implement the Monte Carlo Experiment to collect simulation outputs for our bioeconomic model that was developed with stochastically varied parameters in this project. Each experiment that differs in disease management strategies consists of a set of 10,000 simulation runs over 230 days on feed for a representative 100-cattle pen in western Canada. Each run within an experiment is set by a random seed so that the outcome realizations are different. Data collected over simulation runs are the expected values of the bioeconomic outcomes under each disease management scenario. We simulate these experiments in AnyLogic Cloud Computing Service.

Chapter 5 Results and Discussion

This chapter provides the results of the economic viability of alternative disease management scenarios outlined in chapter 4. The main results of the cost-effectiveness in terms of producers' profitability and the required AMU of those scenarios are first presented and discussed. The two additional important outcomes about animal health and weight gain would further explain the cost-effectiveness of these alternative disease management scenarios.

Next, the results aiming at answering the three critical questions are provided. They address the outcome changes of those scenarios by embedding extra information into the model. Respectively, the three questions are: 1) would the profit rankings of management strategies change if we consider the externality costs of antimicrobials? 2) what are the other possible options regarding the frequency of Early Diagnostic Tests, and what are their breakeven costs compared to testing cost? 3) would the early diagnostic test strategy become more cost-effective when there is declining efficacy of current mass medication caused by the increasing effect of AMR in a long-run application? Along with the presentation of the changes in results, discussions of important findings are also provided.

5.1 Cost-effectiveness of Alternative Disease Management Scenarios

5.1.1 Profitability and AMU Costs

Table 5.1 Simulated Results of Profits and Antimicrobial Costs in Different Disease Management Scenarios

Scenario Number	Scenario Name	Profits ($/head)	Antimicrobial Costs ($/head)
1	Arrival Metaphylaxis	18.77	49.75
		(29.15)	(15.75)
2	Metaphylaxis Twice	17.71	67.55
		(13.34)	(4.57)
3	Arrival Prophylaxis	-11.04	48.84
		(28.97)	(12.50)
4	Prophylaxis Twice	-1.50	50.24
		(27.75)	(11.47)
5	Metaphylaxis and Prophylaxis Combination	32.37	49.89
		(22.88)	(7.93)
6	Conventional Lab Test	-36.45	48.10
		(29.47)	(10.82)
7	Early Diagnostic Test	10.16	29.31
		(25.79)	(7.97)
8	Simple Inspection Only	-14.18	43.97
		(29.00)	(11.77)
9	No Infection	99.17	0.00
		(17.67)	(0.00)

Note: Standard deviations in parentheses.

The expected profits of an individual calf with the associated antimicrobial costs in each disease management scenario are listed in table 5.1. Antimicrobial costs, feed costs, and other costs are included in the profit calculations. The profit per head within a pen that has no BRD infection from beginning to end is estimated to be $99.17. The estimated profit for the Simple Inspection Only scenario is -$14.18, with an antimicrobial cost of $43.97.

Overall, we find that the scenarios containing Metaphylaxis strategy (scenarios 1, 2, and 5) tend to have higher profit than the other scenarios, but the AMU costs associated with these scenarios are also higher. Arrival Metaphylaxis, the "business as usual" scenario, shows a profit of $18.77 per head and antimicrobial costs of $49.75 per head. Metaphylaxis Twice scenario shows that an additional Metaphylaxis administration on the 21st day after arrival may not improve the profits; on the contrary, its profit is about $1 per head lower than the Arrival Metaphylaxis scenario. However, the antimicrobials cost increases by about $17.8 per head over the treatment and disease control.

The other two mass medication scenarios are Arrival Prophylaxis and Prophylaxis Twice, which only implement the infeed prophylactic antimicrobials to control and prevent the disease transmission. The results show that their performances are not satisfactory due to negative profits for both of them, but the antimicrobial costs are only slightly lower than the Arrival Metaphylaxis scenario.

Thus, if only one type of mass medication is considered to interfere with the disease transmission, the expected profits for feedlot managers with metaphylactic AMU are higher than those with prophylactic AMU. The results of a combination of metaphylactic AMU and prophylactic AMU show the synergy between the two types of mass medication strategies. It has a similar input cost of antimicrobials as other mass medication scenarios, but its profit is the highest among all scenarios. This suggests that a mix of metaphylactic AMU and prophylactic AMU may be more cost-effective in managing BRD, because it provides opportunities for feedlot managers to apply more flexible responding measures to target different prevalence levels at different feeding periods.

Apart from the mass medication as an intervention applying to all individuals regardless of their disease states, the two diagnostic strategies of Conventional Lab Test and Early Diagnostic Test are enhancing the diagnostic process on the basis of the pen checkers' inspection. The testing results could tell the positive cases even when a calf is in the subclinical state. It is important to note that these two testing strategies incur extra testing costs, which are accounted for in the corresponding profits in Table 5.1. For the Conventional Lab Test scenario, the estimated profit is negative and even lower than that of the Simple Inspection Only (No Test) scenario. This suggests that a feedlot manager should not consider replacing the Metaphylaxis involved scenarios with a Conventional Lab Test scenario. The Early Diagnostic Test scenario performs better than the scenario of Conventional Lab Test in both the profit and the AMU level. The estimated profit per head is $10.16, and the antimicrobial cost is $29.31. In addition, if we compare it with the "business as usual" (Arrival Metaphylaxis) scenario, we find that in spite of the lower expected profit under the Early Diagnostic Test scenario, the antimicrobial costs for disease management are also reduced. Specifically, the estimated profit under the Early Diagnostic Test scenario is $8.61 lower than that under the Arrival Metaphylaxis scenario; however, the antimicrobial costs decrease by $20.44. Since it increases diagnostic efficiency and accuracy at the early stage of the disease transmission, the required antimicrobials are only used on the targeted diseased calves. As a result, the prevalence is decreased dramatically after the testing on the population, and there are almost no unnecessary antimicrobials wasted on the healthy calves.

5.1.2 Animal Health

This section analyzes the cost-effectiveness associated with animal health. The results of expected total infective cases and expected total number of cattle culled under the different disease management scenarios over the 230-day feeding period are provided in Figure 5.1.

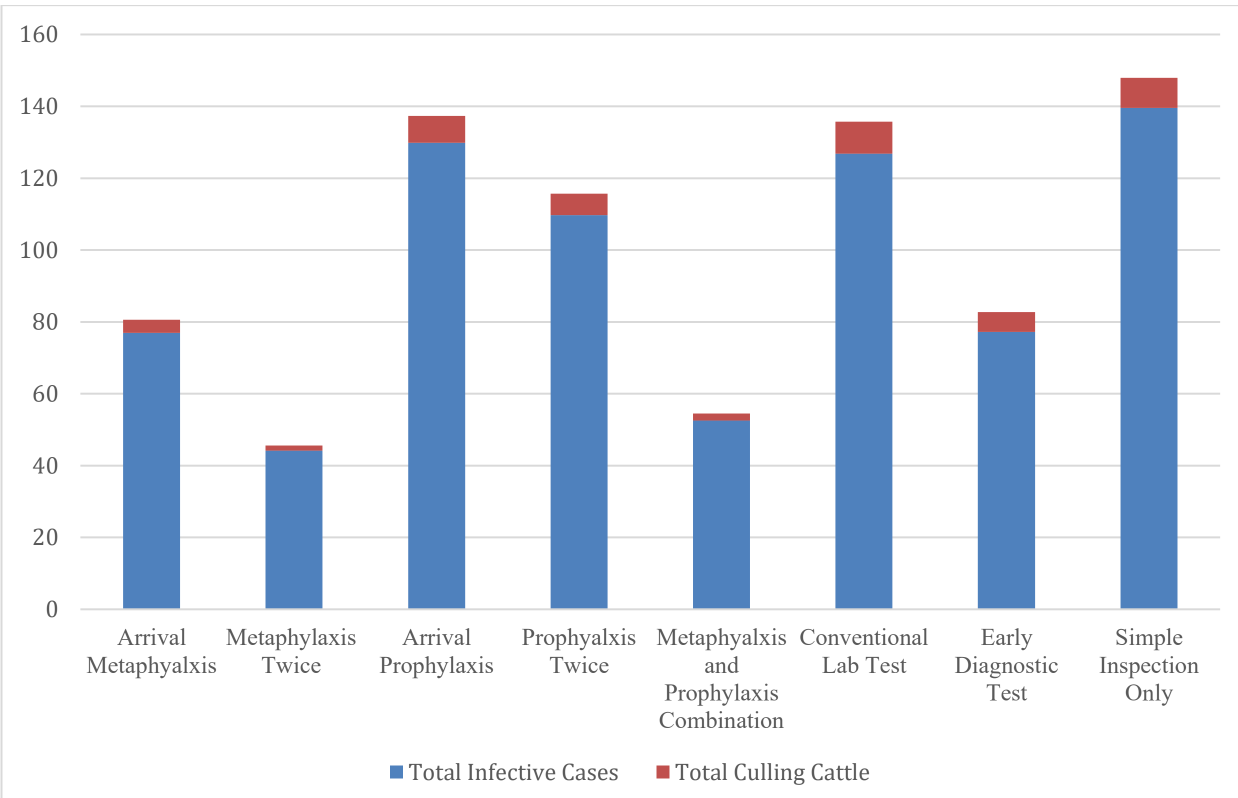

Figure 5.1 Simulated Results of Total Infective Cases and Culling Cases under Different Disease Management Scenarios

The results of total infective cases show the real incidence in the defined transmission networks among the population in the system, so they include all infective cases as long as the calves have entered either in *Subclinical* state or *Clinical* state regardless of how long they spend in those states. Some of the treated calves may be exposed to the disease again after the first infection but are past the period of protection of antibodies obtained from the first antimicrobial treatment, so the second infection may occur. As a result, the counted total infective cases during the entire feeding period might be greater than the total population. Some of the total infective cases under the listed disease management scenarios are above a hundred cases, which indicates that most calves are infected at least once, which is consistent with the results from Timsit et al. (2011).

From our simulated epidemic results (Figure 5.1), four scenarios of Arrival Metaphylaxis, Metaphylaxis Twice, Metaphylaxis and Prophylaxis Combination, and Early Diagnostic Test have the average incidence rate below one infection per head. Among them, the scenario of Metaphylaxis Twice has the lowest incidence rate. The other four scenarios have the average infection rate greater than one infection per head, with the highest incidence rate in the scenario that only relies on the simple inspection of pen checkers.

The culling rate in a feedlot is approximately the same as the annual mortality rate, but usually a feedlot manager may cull the calves early before the fattening period was complete due to the inferior performance, in order to reduce economic losses (Smith et al. 2001). The rankings of the number of total culled cattle among the scenarios listed above are similar to the rankings of incidence rates, with the scenario of Metaphylaxis Twice having the lowest culled cattle and the scenarios of Conventional Lab Test and Simple Inspection Only having the highest culled ones.

Now we focus on the prevalence associated with days on feed to explain the impacts of AMU in different disease management scenarios on animal health. The daily prevalence for each scenario is presented in Figure 5.2. Although most cases of BRD tend to occur in the first 50 days after arrival, the time of peak prevalence within a pen can be highly influenced by disease management strategies and the feature of the disease complex. For the current management strategies involving mass medications, we find that injectable metaphylactic AMU plays a significant role in controlling the prevalence at a reasonable level. By comparing the epidemiological trends in the scenarios of Arrival Metaphylaxis and Metaphylaxis Twice (Figure 5.2, scenario 1 and scenario 2) to that in Simple Inspection Only scenario (Figure 5.2, scenario 8), we find that the injectable metaphylactic AMU at arrival is able to control the prevalence to below 5% shortly after administration, but there might be a second wave of the disease occurring about one month later. This epidemic pattern is similar to the results in the study of Nickell and White (2010), which indicated that metaphylaxis at arrival might be a valuable tool to decrease the number of infective cases occurring early in the feed phase, but there is a risk that prevalence could spike up again over time.

Usually, the second metaphylaxis is administered at the considered high-risk period of outbreaks, but some subjective factors such as feedlot managers' experience and management approaches may lead to large differences associated with the time of application (Patterson et al. 2017). The simulations of this study provide an example of applying a second metaphylactic AMU at 21st days after arrival (Figure 5.2, scenario 2), and the epidemic trend shows that it reduces the risk of a second wave infection and keeps the prevalence at a very low level for the rest of feeding period. Therefore, having applications of scenarios of Arrival Metaphylaxis or Metaphylaxis Twice could reduce the prevalence to a relatively low level, but whether these methods are cost-effective associated with profits and the level of inputs of antimicrobials needs to be considered carefully.

Compared with the injectable Metaphylaxis strategy, the infeed Prophylaxis strategy has a weaker effect on reducing the live prevalence after the administrations. This is not only reflected in the magnitude of reduction in prevalence but also in the time it takes to decline (Figure 5.2 scenario 3 and scenario 4). As mentioned in Health Canada (2002), prophylaxis is often used as disease prevention; therefore, only relying on this infeed Prophylaxis strategy accompanied with pen checker's inspection may not be sufficient to control the disease at a target level, and economic losses would increase.

However, according to Patterson et al. (2017), the Prophylaxis strategy might be more appropriate to use when the considered incidence is low, which might be reflected in the scenario of Arrival Metaphylaxis and Prophylaxis Combination in which we set injectable metaphylactic AMU at arrival and infeed prophylactic AMU at the 21st day on feed. Its epidemic curve (Figure 5.2 scenario 5) shows that the prophylactic AMU on day 21 is still effective in decreasing the prevalence level and stem the outbreak at the second wave when there are not so many infective cases in the pen. One of the possible reasons is that it could improve immunity level to some extent for the susceptible population due to adoption of infeed mass medications despite the lower efficacy for treatment. Healthy calves passively receive antimicrobials even if they are not infected.

Besides relying on mass medication strategies to maintain an acceptable level of prevalence, testing strategies could promote more prudent use of antimicrobials. Unlike the mass medication for the entire feeding pen, antimicrobial drugs are informed by the testing results to give to the targeted calves. However, these testing strategies, on the other hand, may have other problems like lag time in collecting samples and results. Conventional laboratory testing may help detect the asymptomatic cases, but there is an approximate five-day lag in getting results which is sufficient to cause the failure of disease control and prevention. The infectious pathogens can spread quickly while the feedlot managers are waiting for the results to have the next actions

(Owen er al. 2017). Its higher incidence rate (Figure 5.1) compared with other scenarios shows that the Conventional Lab Test management scenario is not competitive, and its effect on disease control is much lower than that of metaphylactic AMU involved scenarios.

To address the defect of the delay in getting the results, the Early Diagnostic Test scenario integrated the advanced technologies to speed up the diagnostic process and keep the accuracy of diagnosis. Instead of relying on the metaphylactic AMU, the Early Diagnostic Test strategy is implemented for all the calves staying in a pen at arrival and 21 days later. The result (Figure 5.1) shows that the number of total infective cases under this scenario is similar to that under the scenario of Arrival Metaphylaxis, but the costs on antimicrobials are reduced by over 40% (Table 5.1). By comparing the particular epidemic trends between these two scenarios associated with days on feed (Figure 5.2, scenario 1 and scenario 7), we find that even though the scenarios of Arrival Metaphylaxis and Early Diagnostic Test had a similar effect on reducing the infective cases, the epidemic curve of the latter has a faster rebound after the first drop in prevalence. This could be explained by our model capturing the effects of antimicrobial induced immunity for the treated calves after having the antimicrobials treatment, so the population within a pen receiving the mass medications would slow down the spread of the disease. The early diagnostic tests only diagnose and isolate the infective calves, but the rest of the calves staying in the original pen are not treated with any antimicrobial and are still susceptible to the infectious pathogens.

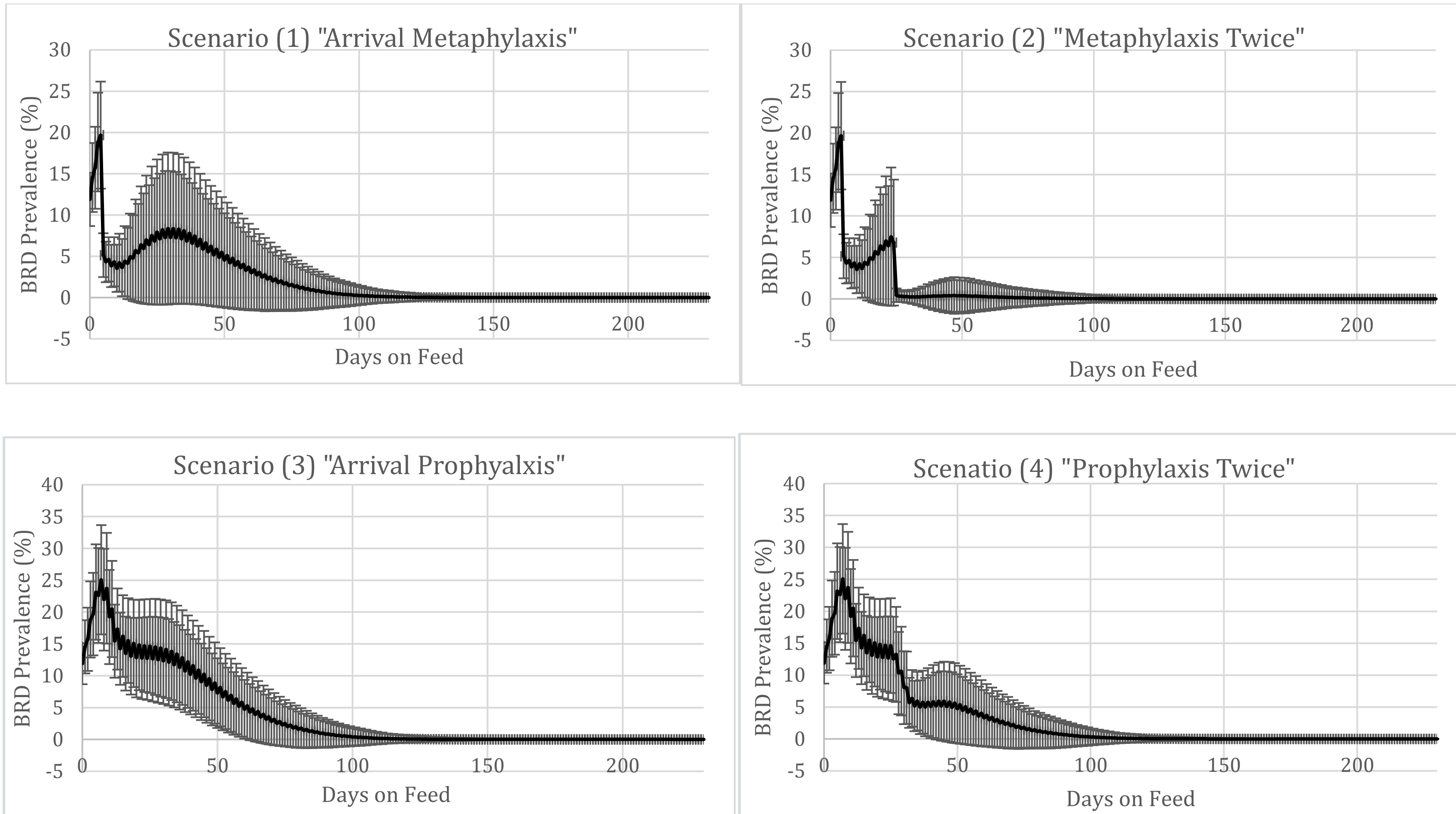

Figure 5.2 Simulated Results of BRD Daily Prevalence Associated with Days on Feed in Different Disease Management Scenarios

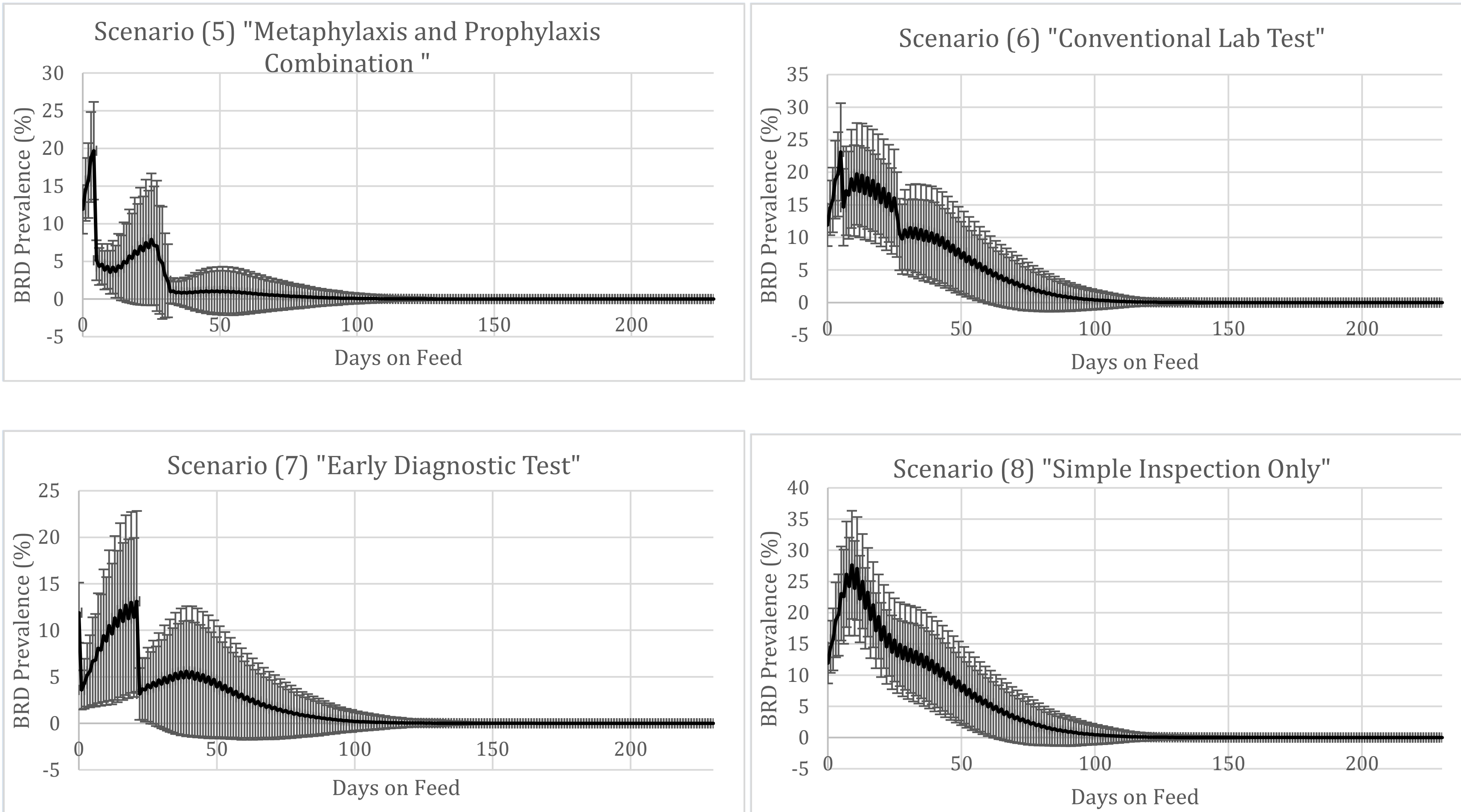

Figure 5.2 Cont.

5.1.3 Weight Gain

Unlike the studies about human diseases that focus on human health, such as the number of lives saved or life-years, research on livestock diseases is more concerned with the relationships between the health states of the animals and their livestock outputs. The purpose of feedlots is to feed cattle to grow and gain important body fat and muscle over a period to meet the finishing requirements. During this period, a calf's weight gain could be affected by many factors. As mentioned in Chapter 3, in our model, disease state and antimicrobial applications are two main factors that affect the rate of weight gain.

The expected finishing weight, ADG, totaling culling weight, and average culling weight are provided in Table 5.2. The expected finishing weight per head within a pen that has no infection during the 230 days on feed is 1263.45 lb, with an ADG of 3.22 lb. However, under the scenario of Simple Inspection Only, the expected finishing weight is 1,190.65 lb, and the ADG is 3.14 lb. For all the mass medications scenarios, calves managed under scenarios of Arrival Metaphylaxis, Metaphylaxis twice, and Metaphylaxis and Prophylaxis Combination to control the disease have higher finishing weights and ADG. This is consistent with the epidemic results that fewer infective cases are occurring in these scenarios, so the impacts of the disease on the weight gain are smaller than those in the other scenarios. In addition, because there are more calves that receive antimicrobials from the metaphylaxis administration, the improvements in feed efficiency in these scenarios are greater as well. By contrast, even though the long-acting antimicrobials are put into the feed or water which also provide the growth promotion, the results of the scenarios of Arrival Prophylaxis and Prophylaxis Twice show that the finishing weight and ADG are not higher compared with other mass medication scenarios. The reason could be that these two scenarios are not able to effectively mitigate the disease transmission so that the infection status of calves is still the main driver of their lower rates of weight gain.

The scenarios of the Conventional Lab Test and Early Diagnostic Test are only relying on Individually Dosed AMU to the targeted animals, so there are no hidden influences of growth promotion from the mass medications. The weight gain of calves might be lower than those with mass medication scenarios. However, taking together with the epidemic results, the high incidence rate is still the main reason for the low weight gain rate in the scenario of Conventional Lab Test.

The method of the Early Diagnostic Test is more effective in diagnosing the infective cases and use antimicrobials to the targeted animals at the early stage. As a result, there are fewer impacts of disease on the animals' weight gain. For the Early Diagnostic Test scenario, although the expected finishing weight is 13.2 lb less than that of the "business as usual" scenario of Arrival Metaphylaxis, the trade-offs associated with the largely reduced antimicrobial drugs and associated costs should be considered.

Total culling weight under each scenario is consistent with the number of culled calves during the feeding period. As the infection is under control with the Metaphylaxis involved strategies, the culled calves are also fewer in the scenarios of Arrival Metaphylaxis, Metaphylaxis Twice, and Metaphylaxis and Prophylaxis Combination. The estimated total culling weight under the Early Diagnostic Test scenario is 3,090.39 lb, which is slightly higher than the three scenarios mentioned earlier. The average weights of those culled calves are around 550 pounds. In all the scenarios, which happen around the period of peak prevalence after arrival.

Table 5.2 Simulated Results of Finishing Weight, ADG, Total Culling Weight and Average Culling Weight under Different Disease Management Scenarios

Scenario Number	Scenario Name	Finishing Weight (lb/head)	ADG (lb/head)	Total Culling Weight (lb)	Average Culling Weight (lb/head)
1	Arrival Metaphylaxis	1231.26 (37.55)	3.18 (0.09)	2101.50	565.83
2	Metaphylaxis Twice	1249.82 (26.49)	3.20 (0.09)	737.11	536.47
3	Arrival Prophylaxis	1198.94 (37.62)	3.15 (0.10)	4169.65	561.12
4	Prophylaxis Twice	1211.02 (35.94)	3.16 (0.10)	3284.35	554.60
5	Metaphylaxis and Prophylaxis Combination	1246.13 (29.42)	3.20 (0.09)	1038.92	546.80
6	Conventional Lab Test	1188.89 (38.51)	3.15 (0.10)	4947.95	556.58
7	Early Diagnostic Test	1218.06 (33.30)	3.18 (0.09)	3090.39	552.84
8	Simple Inspection Only	1190.65 (37.69)	3.14 (0.10)	4665.70	558.43
9	No Infection	1263.45 (22.37)	3.22 (0.08)	0.00	0.00

Note: Standard deviations in parentheses.

5.2 Externality Costs of AMU

In economics, an externality is referring to the cost or benefit that is imposed by one or several parties on a third party who did not agree to incur that cost or benefit. As we notice that the threat of antimicrobial use in animal agriculture may contribute to the antimicrobial resistance in humans, the external costs associated with health and economics on society are inevitable. However, these externality costs are usually positive and not properly reflected in market prices. Innes et al. (2020) estimated an externality cost of about US$1,500 per kilogram of fluoroquinolone administration in the poultry industry, which provides important evidence for the later calculations of externality costs of antimicrobials that serve to treat, prevent and control BRD within a pen in our simulations. Fluoroquinolones fall into category I of antimicrobial drugs that have very high importance to human medicine under the categorization of Health Canada Veterinary Drug Directorate (Brault et al. 2019), so the frequency of use of this drug in addressing BRD in feedlots is relatively low. By accessing the data on dosage of fluoroquinolones used in beef feedlots in western Canada (Brault et al. 2019), we change values of the baseline parameters and recalculate the total antimicrobial doses, externality costs, and the net benefits under each scenario of disease management strategies (Table 5.3). Externality costs are included in the net benefits. The detailed conversions and calculations of antimicrobial doses and externality costs are provided in Appendix 4.

Table 5.3 Simulated Results of Net Benefits, Antimicrobial Doses, and Externality Costs under Different Disease Management Scenarios

Scenario Number	Scenario Name	Net Benefits ($/head)	Antimicrobial Doses (g/head)	Externality Costs ($/head)
1	Arrival Metaphylaxis	7.98	5.54	10.80
2	Metaphylaxis Twice	2.97	7.56	14.74
3	Arrival Prophylaxis	-21.58	5.40	10.53
4	Prophylaxis Twice	-12.40	5.59	10.90
5	Metaphylaxis and Prophylaxis Combination	21.48	5.58	10.88
6	Conventional Lab Test	-46.76	5.29	10.32
7	Early Diagnostic Test	3.88	3.22	6.28
8	Simple Inspection Only	-23.61	4.84	9.44
9	No Infection	99.17	0.00	0.00

Note: $Net\ Benefit = Profit - Externality\ Cost$

We find that most of the calculated externality costs under listed disease management scenarios are higher than $10 per head. Due to the applications of mass medications on the population of calves in a pen, all the scenarios involving metaphylaxis or prophylaxis have higher externality costs than those only containing the individual treatment addressing BRD. The estimated externality costs of the "business as usual" scenario that applying metaphylactic AMU at arrival is $10.80 per head. If adding another metaphylactic application on day 21st, the externality costs will increase by $3.94 per head. Since the scenario of the Early Diagnostic Test has the smallest dose of antimicrobial of 3.22 gram per head, the corresponding estimated externality costs of $6.28 per head is the smallest among all the listed disease management scenarios. Comparing to the scenarios of Arrival Metaphylaxis, Metaphylaxis Twice, and Metaphylaxis and Prophylaxis Combination, the Early Diagnostic Test scenario reduces the externality costs of $4.51, $8.46, and $4.6, separately (Figure 5.3).

Table 5.3 represents the results of the expected net benefits of production of an individual calf after finishing in the feedlot, calculated by taking the difference between estimated feedlot managers' profits and associated externality costs of antimicrobials. Comparing to the situation that does not consider externality, the rankings of net benefits under different scenarios are changed. The main difference is that the net benefit generated in the scenario of Metaphylaxis Twice changes to become lower than that generated by the scenario of Early Diagnostic Test, due to the greater externality costs included.

For the mass medication scenarios, Arrival Metaphylaxis, Metaphylaxis Twice, and Metaphylaxis and Prophylaxis Combination could generate positive profits for feedlot managers. If they decide to implement the early diagnostic test informed AMU to replace these three scenarios, the trade-offs between profits reduction and the externality costs reduction are presented in Figure 5.3. It suggests that feedlot managers should be more encouraged to adopt the Early Diagnostic Test scenario if currently using the Metaphylaxis Twice scenario to manage BRD, since the externality cost reduction is higher than the profit reduction by the substitution. However, for the other two scenarios involved with metaphylaxis, government should consider providing financial compensations or other instruments to incentivize the adoption of Early Diagnostic Test strategies.

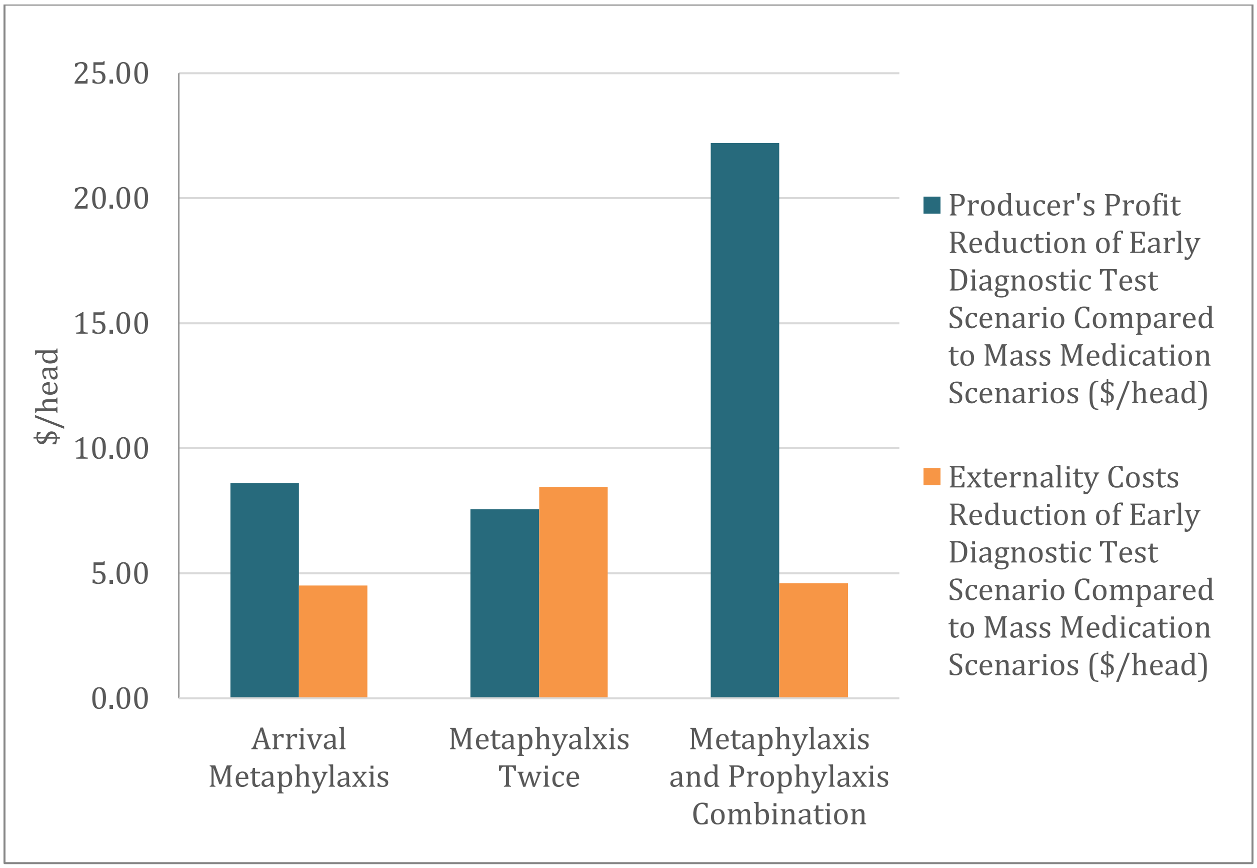

Figure 5.3 Producer's Profit Reduction and Externality Costs Reduction of Early Diagnostic Test Scenario Compared to Mass Medication Scenarios

5.3 Early Diagnostic Tests and Expenditures

5.3.1 Variability of Early Diagnostic Tests

As mentioned earlier that the Early Diagnostic Test strategy may improve the prudence of antimicrobials use, a proper frequency of testing is crucial to determine the epidemic level and the resulting profits. A low frequency of testing may not effectively control the disease prevalence and lead to the higher costs of required antimicrobial inputs as well as lower weight gain of calves. On the other hand, a high frequency of testing may lead to overdiagnosis and unnecessary costs on testing, and therefore, decreased profits.

We choose the same interval of 21 days between testing applications to the entire pen of calves as scheduled in mass medication scenarios, and then adjust the application times along with the days on feed in the model to simulate the impact of different frequencies of Early Diagnostic Test strategies. The feedlot managers' profits, incidences, and the total required antimicrobial doses for different frequencies of Early Diagnostic Test scenarios are summarized in Figure 5.4. If we keep the $10 testing cost per case, all the profits under various Early Diagnostic Tests scenarios are lower than the profit under Arrival Metaphylaxis scenario. A single application of Early Diagnostic Test on arrival, twice applications at arrival and on day 21, and three applications at arrival, on day 21 and day 42 will generate positive profits, but an additional testing on day 63 will lead to negative profit. The profit is the highest for the scenario of testing twice.

The level of antimicrobial use in the two-testing scenario is the lowest as well, with approximately 42% lower than the level under the Arrival Metaphylaxis scenario. Although a third testing may provide a higher diagnostic power to detect the more infective cases in the later feeding time, the AMU dosage is almost the same compared with the two-testing scenario. This suggests that the diagnostic power of two testings is sufficient to control disease transmission. The total infective cases in these scenarios show a consistent trend with the AMU level, which shows a small marginal decline after the third testing. A significant drop in the total infective cases occurs at the transition between once and twice of testing applications. Therefore, considering the cost-effectiveness among profits, incidence rate and AMU level, testing twice might be the optimal testing frequency.

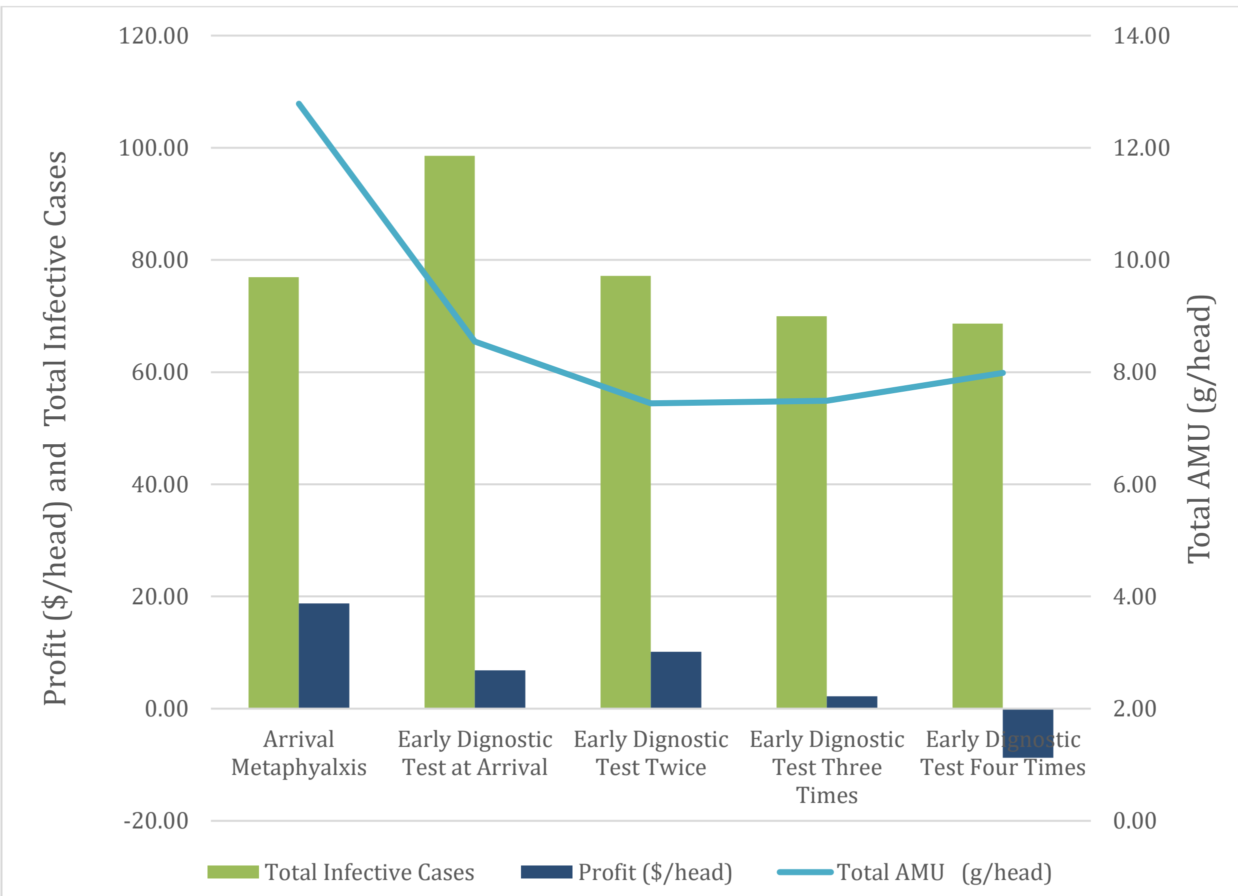

Figure 5.4 Comparison of Simulated Results of Profit, Incidence and AMU level between Different Early Diagnostic Test Scenarios and Arrival Metaphylaxis Scenario

5.3.2 Expenditures on Early Diagnostic Tests

The adoption of the Early Diagnostic Test scenarios by feedlot managers is most likely dependent on the resulting profit level, which is significantly affected by the testing costs. Through the sensitivity analyses, we find that a break-even unit cost of $5.34 per case for a two-application frequency equalizes the profit levels of the Early Diagnostic Test and the Arrival Metaphylaxis scenarios. If the unit testing cost is lower than $5.34, the profit under two applications is not only higher than the resulting profits under Arrival Metaphylaxis but also higher than that under other testing frequencies (Table 5.4).

The excess profits under Early Diagnostic Test scenario over Arrival Metaphylaxis scenario along with the changes of testing price are shown in Figure 5.5. As an extreme case, the zero-testing cost leads to an excess profit of $9.85 for Early Diagnostic Tests. If the unit testing cost is higher than $5.34, all the profits under various Early Diagnostic Test scenarios are lower than the profits under the Arrival Metaphylaxis scenario. In addition, the unit testing cost of $13.8 is the cut-off price between using a single application and two applications of testing. Therefore, if the feedlot managers are forced to adopt an early diagnostic test strategy and the unit price is higher than $13.8, they may prefer to testing once at arrival to get higher benefits, but the required AMU level is also high (Table 5.4). As the price increase further, a testing price of $15.5 will lead to zero profit under twice applications, and a price of $17.00 will lead to zero profit under application once at arrival.

Table 5.4 Optimal Number of Early Diagnostic Administrations in Different Testing Price Ranges

	Testing Price Range ($/case)	Optimal Testing Administrations
Free selection	(0, 5.34]	2
	(5.34, ∞)	0
Force to adopt Early Diagnostic Test strategy	(0, 13.8]	2
	(13.8, ∞)	1

If we add the externality considerations and regenerate the relationships between the profits and testing price, we find that the advantages of the Early Diagnostic Tests over the Arrival Metaphylaxis are more significant (Figure 5.5). At the same level of testing price, the net benefits are larger than before because there is a reduction of externality costs on society. If the testing price is higher than $5.34 but lower than $7.78, there is an actual benefit to society despite the negative profits for producers.

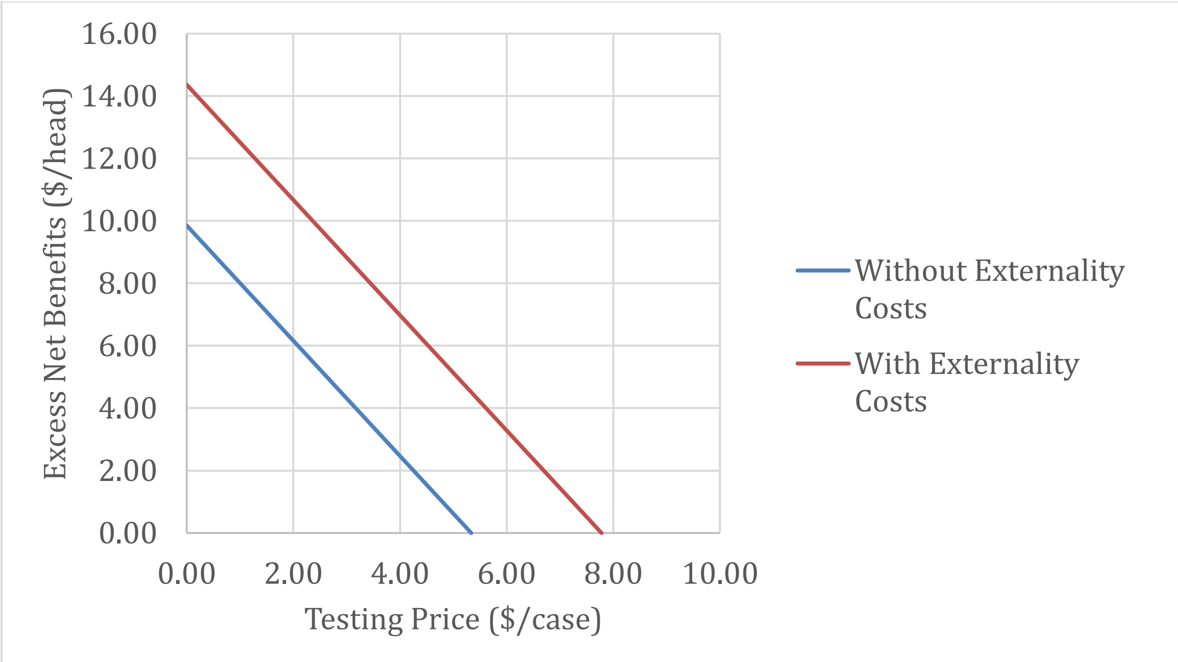

Figure 5.5 Relationships between Excess Net Benefit of Early Diagnostic Test over Arrival Metaphylaxis and Testing Price

5.4 AMR Sensitivity Analysis

Our current model is appropriate for simulating one feeding season for calves in a feedlot, during which the contribution of AMR to the disease control is likely very small. In our simulations, we assume the efficacy of the antimicrobials used in the control strategies is the same throughout the entire feeding period.

However, from a long-term perspective, increasing AMR is considered to be an unavoidable consequence, particularly scenarios involved with mass medications. According to Health Canada (2002), increasing AMR causes a decreased ability to treat infections and illness in people, animals, and plants. Therefore, we did a sensitivity analysis to assess the potential negative impacts of AMR on the producers' profits and AMU level by reducing the efficacies of antimicrobials used in mass medications. It is important to note that we assume the efficacies of the Individually Dosed AMUs in our model keep the same. The reason is that a diagnosed calf in the hospital pen usually receives a strictly controlled dosage of antimicrobials under the veterinary guidance (Patterson 2017). As a result, individual treatment with a rotation of drugs has a relatively low probability of AMR development. By contrast, the methods with mass medications are often relying on the same type of antimicrobial applied to the entire pen, so the likelihood of building AMR is high.

As we decrease the efficacies of mass medication by 25%, 50%, and 75%, respectively, the trends of resulting profits and antimicrobial costs for the three profitable mass medication scenarios of Arrival Metaphylaxis, Metaphylaxis Twice, and Metaphylaxis and Prophylaxis Combination are shown in Figure 5.6 and Figure 5.7.

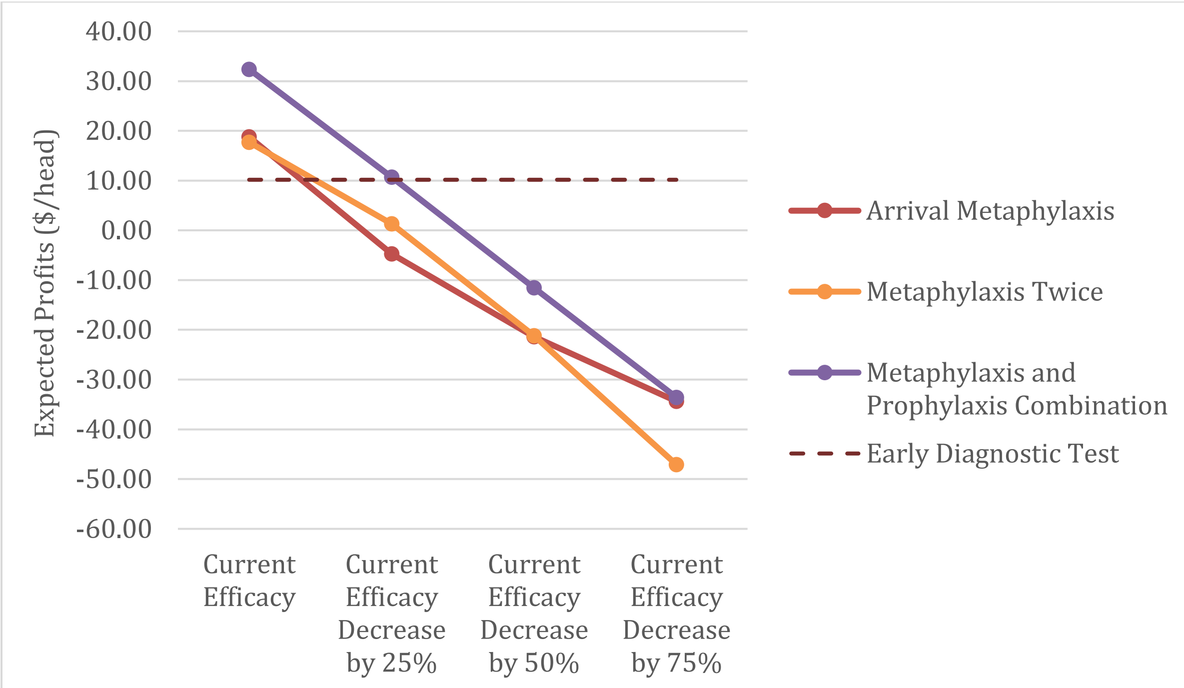

Figure 5.6 Simulated Results of Profits under Three Metaphylaxis Involved Scenarios with Declined Levels of Efficacy of Mass Medications by 25%, 50%, and 75%

We find that the profits are declining dramatically for all three mass medication strategies as the efficacies decrease. On average, an additional 25% decrease in efficacy will lead to expected profit reductions of $17.71, $21.98, and $21.60 under scenarios of Arrival Metaphylaxis, Metaphylaxis Twice, and Metaphylaxis and Prophylaxis Combination. When the current efficacy in mass medication decreases by 25%, the profit under the Arrival Metaphylaxis scenario becomes negative. Even though the profits could be higher if the feedlot managers put a second-time administration showed in the other two mass medication scenarios, all these three scenarios have profit levels similar to or below the level under the Early Diagnostic Test scenario. As the efficacies further decrease by 50% and 75%, the profits of the three mass medication scenarios are all negative. If the efficacy decreases by 100%, the prevalence level will be the same as those in the scenario of Simple Inspection Only. However, the costs of antimicrobials spent in the administrations of mass medications will not reduce at all.

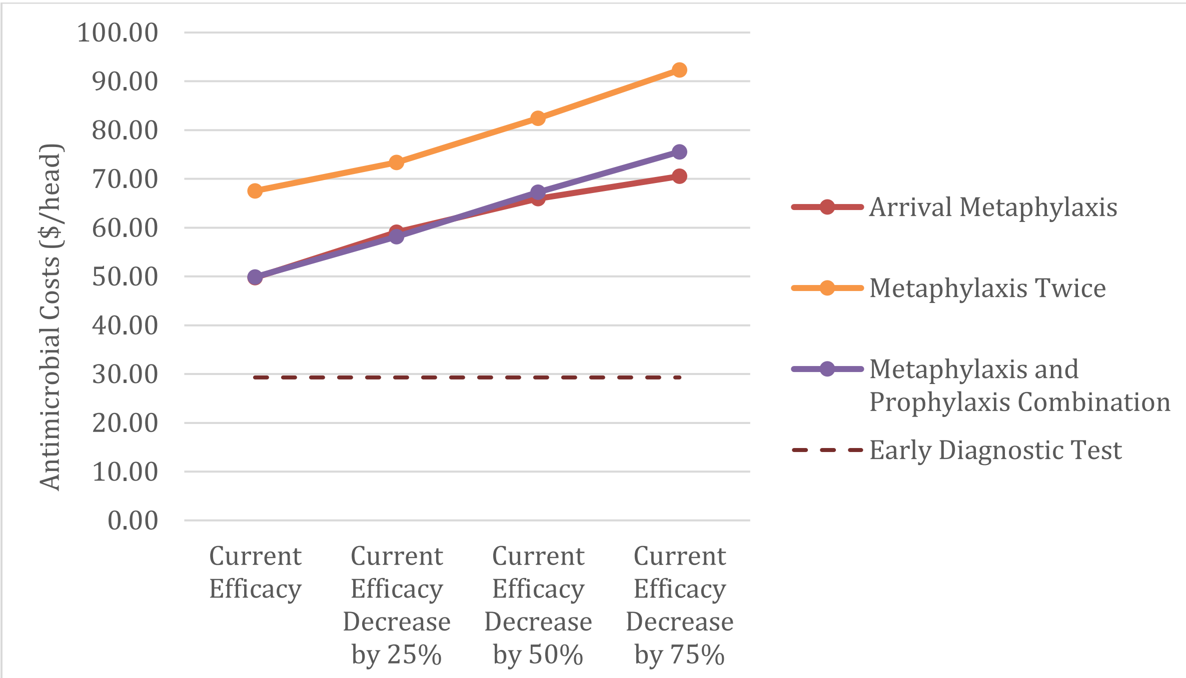

Figure 5.7 Simulated Results of Antimicrobial Costs under Three Metaphylaxis Involved Scenarios with Declined Levels of Efficacy of Mass Medications by 25%, 50%, and 75%

The expenditures on required antimicrobial inputs increased significantly as the efficacies decease. On average, an additional 25% decrease in efficacy will lead to an increase in antimicrobial cost of $6.93, $8.55, and $8.25 under scenarios of Arrival Metaphylaxis, Metaphylaxis Twice, and Metaphylaxis and Prophylaxis Combination. The extra costs of antimicrobials are mainly from the increased individual treatments in the hospital pen. As the effectiveness of mass medications decreases, the spread of the disease could be out of control and there would be more infective cases occurring. Therefore, more calves would be diagnosed and isolated to the hospital pen, and the required antimicrobials used for the individual treatment will increase as well.

Overall, the levels of profits and costs of antimicrobial inputs under decreased efficacies of mass medications highlight the potential advantages of the adoption of the Early Diagnostic Test scenario. In spite of the relatively lower benefits of the Early Diagnostic Test scenario at the current efficacies of mass medications, this strategy may provide more benefits to producers in the long term.

Chapter 6 Conclusions and Future Research

6.1 Conclusions

There is growing evidence that AMR has created a global public threat that adversely impacts the health and welfare of human and animals. The large contribution to antimicrobial use from animal agriculture, where they are used to control infectious diseases, has attracted great attention in the world.

This thesis aims to develop a bioeconomic framework to study the economic impact of alternative disease management strategies addressing BRD in the beef feedlot sector in western Canada. We develop a new framework that integrates an agent-based model (ABM) and a modified susceptible-infected-recovered (SIR) model to simulate the BRD disease dynamics and disease management strategies in a representative feeding pen in a feedlot in western Canada. This integrated framework can incorporate individual heterogeneity which is important when modelling disease spread but is ignored by most of the studies that employ the population-based compartment models. Besides, we develop an economic model to assess the cost-effectiveness of alternative disease management strategies.

The results show the nine representative disease management scenarios incorporate single or combination of strategies to control BRD over time. The commonly implemented mass medication strategies result in different incidence rates, with the metaphylactic AMU strategies performing better than prophylactic AMU strategies in general. The three most profitable disease management scenarios are Arrival Metaphylaxis, Metaphylaxis Twice, and Metaphylaxis and Prophylaxis Combination. Arrival Metaphylaxis, the "business as usual" scenario for managing the disease among the auction-mart derived calves as is done currently, generates an expected profit of $18.77 per animal after 230 days on feed, with $49.75 of antimicrobial costs. The scenarios of Arrival Prophylaxis and Prophylaxis Twice that relying on infeed mass medications are not recommended because both of them generate negative profits for producers. The scenario of Conventional Lab Test has a higher incidence rate and a lower profit relative to other disease management scenarios due to the long lag time between the collection of sample and results.

The Early Diagnostic Test scenario, which controls disease spread at an early stage and reduces unnecessary antimicrobials, can potentially replace the mass medication scenarios. Even though the expected profit might be lower than that under metaphylactic AMU scenarios, the total doses and associated costs of antimicrobials are significantly lower. The profit per animal managed by Early Diagnostic Test scenario is $8.61, $7.55, and $22.21 lower than that under the three most profitable disease management scenarios of Arrival Metaphylaxis, Metaphylaxis Twice, and Metaphylaxis and Prophylaxis Combination, but the costs of antimicrobials are also reduced by $20.44, $38.24, and $20.58, respectively.

Externality considerations, variabilities of frequencies and expenditures of Early Diagnostic Test, and increased impacts of AMR are proposed for further evaluation of various disease management scenarios in this study. After taking into account the externality costs of AMU, the difference in profit between the Early Diagnostic Test scenario and the three most profitable scenarios of Arrival Metaphylaxis, Metaphylaxis Twice, and Metaphylaxis and Prophylaxis Combination decreased. The net benefits of the Early Diagnostic Test scenario are even higher than that of the Metaphylaxis Twice scenario. These net benefits under different scenarios include the benefits to society, other than only for the group of feedlot owners, which suggest the potential for government support for strategies that reduce AMU.

Regarding the variability of Early Diagnostic Tests, the optimal testing frequency is two applications, which has the highest profit and the lowest level of AMU among all the frequencies. A break-even cost of $5.34 per case leads to the same profits for the Early Diagnostic Test and the Arrival Metaphylaxis scenarios.

For the studies related to AMR, the results of sensitivity analysis on antimicrobial efficacies show that the expected profits of the mass medication scenarios will decline dramatically if the efficacy of mass medications are reduced due to AMR developments. When the current efficacy decreases by 25%, the estimated profits under Arrival Metaphylaxis scenario will become negative, and the profits of these scenarios are the same or below the profit level under the Early Diagnostic Test scenario.

6.2 Implications

The findings from this study can help inform feedlot managers and policymakers to identify the trade-offs between current mass medication strategies versus several alternative disease management strategies that incorporate different early diagnostic methods. It provides an ex-ante evaluation for their cost-effectiveness by estimating AMU levels and resulting benefits after finishing. Feedlot managers could adjust the values of model parameters based on their own input data to get the regional or feedlot specific estimations.

These outcomes are also useful for policymakers. Our results suggest that the Early Diagnostic Test strategy, although not the most profitable strategy, has the potential to generate positive profit under an appropriate testing price. Moreover, the level of antimicrobial use is significantly reduced under the Early Diagnostic Test strategies, compared with other disease management strategies included in the study. Our estimation of the break-even testing cost can help policymakers in providing incentive compensations to encourage the uptake of Early Diagnostic Test strategies.

Moreover, the results related to the externality of AMU, variabilities of frequencies and expenditures of Early Diagnostic Tests, and increasing impacts of AMR developments provide more suggestions on the evaluation of disease management strategies. They are not only beneficial for producers and policymakers when making decisions but also useful to guide the research efforts of disease ecologists, animal pathologists, and animal scientists involved in BRD and AMU research.

Finally, the model developed in this study can be generalized to study the management of other similar livestock infectious diseases, with adjustment of disease-specific parameters. The characteristics of the agent-based modeling and the SIR-type framework provide an alternative to study the economic impact of complex disease transmission in livestock production.

6.3 Limitations

Four limitations are discussed in this section. First, the model developed in this study is still over-simplified as compared to reality. BRD has a multifactorial etiology that involves complex interactions between environmental factors, host factors, and pathogens. A framework of four disease states of an individual animal and the simple transmission process among the population within a pen are still insufficient to simulate the true epidemiology of BRD in a feedlot. Many factors are ignored or with simplified assumptions. Besides, it needs to be recognized that the results are specific to the designed scenarios and representative characteristics, including the epidemiological characteristic among the cattle population and the disease management approaches of feedlot managers. In reality, a feedlot manager’s disease management strategies and detailed steps are possibly more flexible and more complex. For example, based on the evaluation of health conditions and source of arrival calves, only the sorted high-risk ones would be applied with mass medications; however, the criteria of sorting are very subjective to the management styles and experience of feedlot managers in different regions. Moreover, there could be other management strategies that are currently used by feedlot managers but are not included in this study.

The second limitation is that the results from simulation rely on the credibility of correct parameter values. Most of the parameters used in the simulation are from literature, which are not directly estimated from actual feedlot data/experiment. For example, the daily gain information is derived from Beef Cattle Research Council (BCRC), but weight gain in a particular feedlot could be quite different from our setting. Feedlots are rather reluctant to disclose such sensitive information. The impact of AMU on weight gain and therefore the finishing weight and the final profits might subject to the changes. In addition, although we sought to find the parameter values that best fit the management of BRD in a western Canada feedlot, our model might not represent the feedlot management perfectly. Since some parameters used in our model do not exist, we used parameter values from U.S. studies. If future studies in a Canadian context can provide a better estimate of the parameter values, the results from this study should be updated.

That the model only allows one type of antimicrobial drug is the third limitation. There is an assumption that the type of drug used in all disease management strategies is the same. However, when managing BRD in reality, feedlot managers may use multiple types of drugs in multiple rounds to treat the disease. For example, the drugs used in individual treatments are not likely to be the same as those used in mass medications. Multiple drugs with rotations are used to treat the targeted calves based on the assessment of levels of infection severity. This study only chooses the values from the most representative drug that is commonly used to address BRD in the feedlots in western Canada. The results of estimated AMU levels do not capture the variation of drugs used in different types of disease management strategies.

The fourth limitation is the lack of a comprehensive study on the externality costs of antimicrobial use in the feedlot industry, which is mainly reflected in two aspects. First, the model in this study is only designed for a one-year simulation of calves in the feedlot, so the model did not take into account the buildup of AMR due to AMU overuse. Second, we only have the information from the literature that describes the externality costs of a specific type of antimicrobial fluoroquinolones used in the poultry industry. However, this type of drug is categorized as of higher importance to human and has a relatively low application rate in feedlot cattle. Therefore, only relying on this type of drug as an aggregated AMU level in the model to measure the overall externality costs of antimicrobials in the feedlot may under-estimate the results.

6.4 Future Research

As stated above, this study develops a new framework integrating ABM and SIR models to assess the trade-offs associated with AMU level and resulting profits between the current mass medication strategies and various alternative disease management strategies in a representative feedlot pen in western Canada. There are some opportunities to extend the framework.

Firstly, the overall model could be extended to a "Hierarchical Metapopulation" agent-based model. The current model only considered the cattle interactions within a representative pen, and there is only one defined pen-level population for all the calves. However, feedlots in reality, especially the large commercial ones, usually contain multiple pens, and the calves in those pens are fed simultaneously. These pens are often categorized by risk of infections, and the arrival calves would be placed in different pens based on the assessment of their health conditions. The management strategies for controlling the disease might be different for high-risk pens and low-risk pens. The “Hierarchical Metapopulation” model structure could capture those pen-to-pen variabilities and simulate the possible interactions between multiple pens.

Another extension would incorporate the temporal price dynamic. The model in this study assumes all the prices (such as feeder price, selling price, and drug price) are constant, so the results are limited to the set of the parameters of prices in the model. If one or more of these prices change, the effectiveness of listed control strategies might be different than the ones currently identified in this study. For example, if the drug prices are substantially higher than the defined current price due to new policies of government on restrictions of antimicrobial use, the Early Diagnostic Test strategy could be more likely to be accepted by the feedlot managers.

Last but not least, this study can be extended to add more detailed steps in Early Diagnostic Test strategies. Regarding the testing process built in this model, there are two possible aspects that further studies could address. The first one is that different sampling strategies can be incorporated into the testing structure in the model. Large feedlots with more calves may not need the tests to be applied to all the calves. Instead, a selected sample of the population could be used to estimate the prevalence level at a specific period, and further actions such as whether to increase the sampling rate may be required as appropriate. The second aspect is related to the analysis of lag time between the collection of samples and results. The unit simulation time defined in this model is set to be days, so the shortest possible delaying time after testing to get results is a single day. There might be other early diagnostic methods which are able to detect the infectious pathogens in less than one day, so further model development could address the smaller units of time (such as hourly) to match those potential diagnostic strategies.

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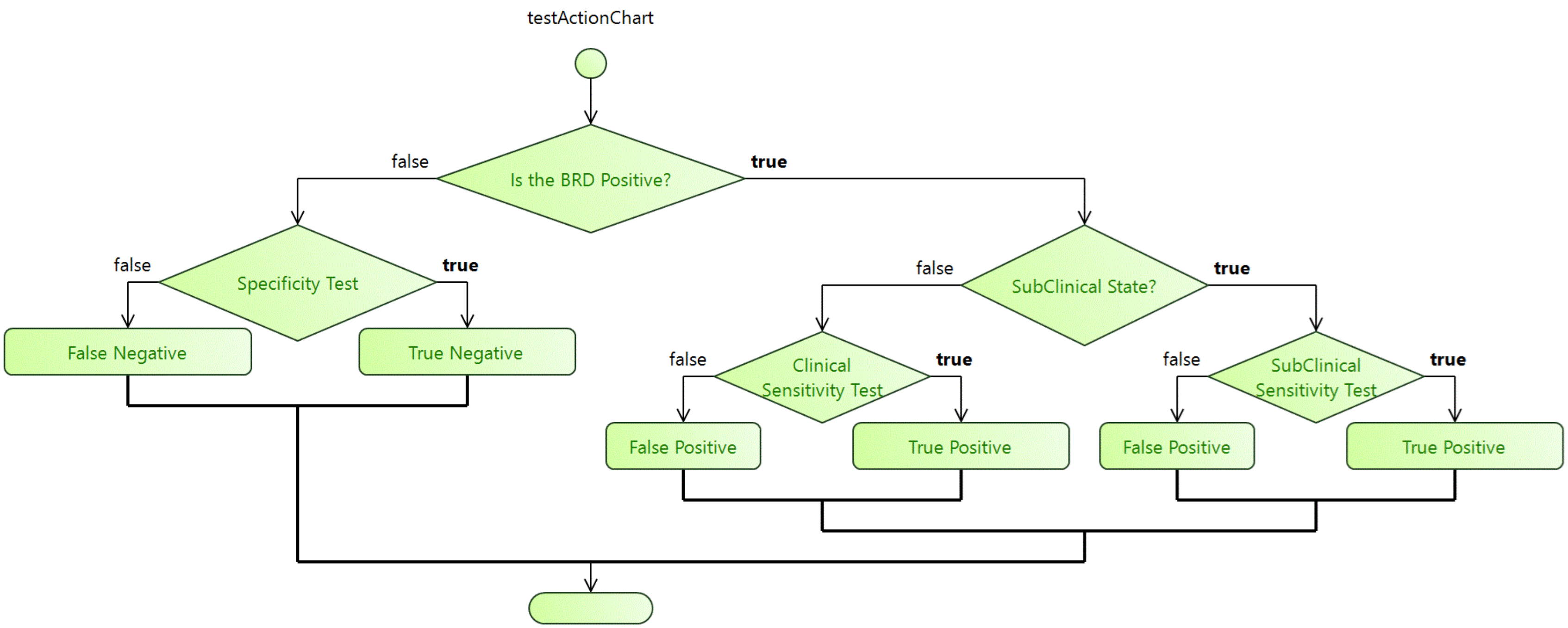
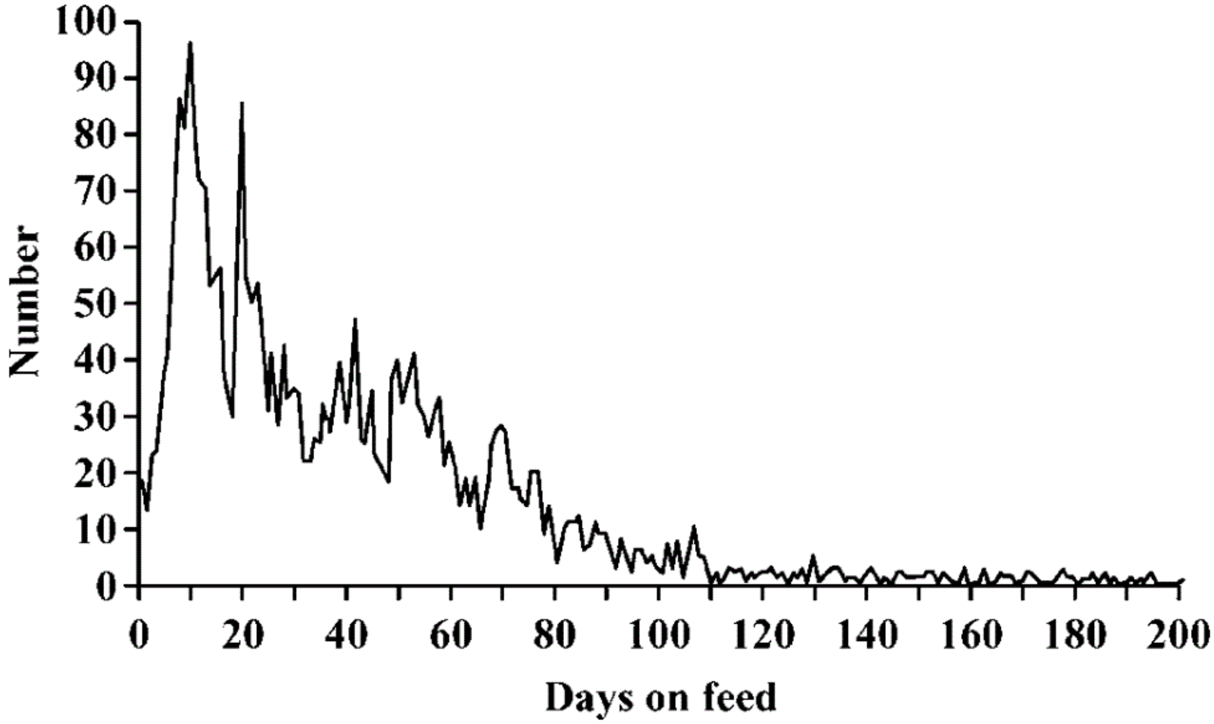
Appendix 1 Details of Testing Process



Testing Action chat Representing the Details of Testing Process for an Individual Calf at a Testing Date

Appendix 2 Two Trend Graphs Drawn from Real Surveillance Data Performed by Two Studies

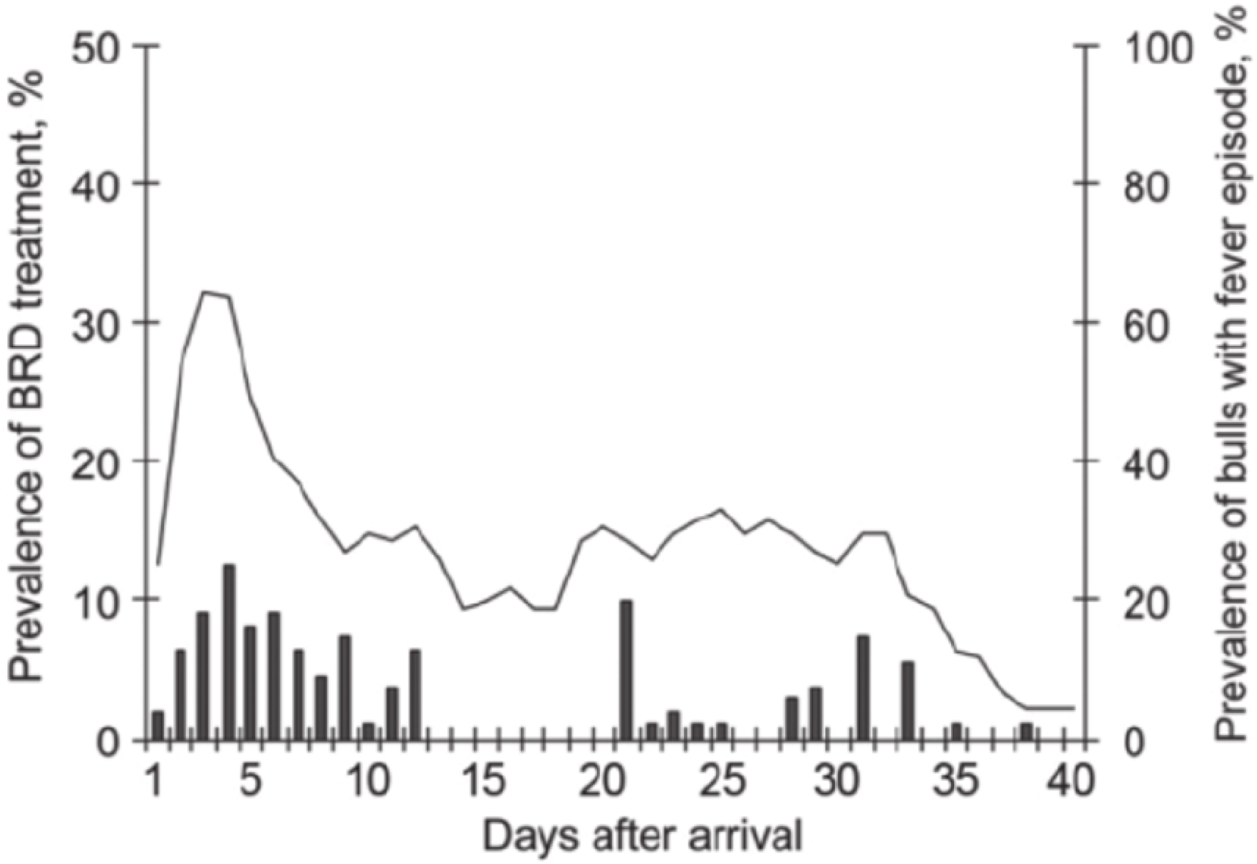
Study 1



The Number of Calves with BRD Treated Per Day Across 15 Years Associated with Days on Feed for 11,182 Calves in a U.S. Feedlot.

Source: Snowder, G.D., L.D. Van Vleck, L.V. Cundiff, and G.L. Bennett. 2006. "Bovine respiratory disease in feedlot cattle: environmental, genetic, and economic factors." *Journal of animal science* 84(8):1999-2008.

Study 2



The Prevalence of BRD Treatment and the Prevalence of Bulls with Fever Episode over 40 Days after Arrival of Newly Received 120 Beef Bulls at 3 French Fattening Operations.

Source: Timsit, E., N. Bareille, H. Seegers, A. Lehébel, and S. Assie. 2011. "Visually undetected fever episodes in newly received beef bulls at a fattening operation: occurrence, duration, and impact on performance." *Journal of animal science* 89(12):4272-4280.

Appendix 3 The Complete Economic Model

$$\max_{\delta} \Pi = \sum_{i} \pi_{i,T}$$

$$= \sum_{i} \left\{ R_{i,T} - C_{feed_{i,T}} - \left(C_{test_{i,T}} + C_{AMU_{i,T}} \right) - FC \right\}$$

$$= \sum_{i} \left\{ pW_{i,T} - r\left(W_{i,T} - W_{i,0}\right) - \sum_{t=0}^{T} \left(\tau_{i,t} \cdot c_{\tau} + \mathrm{A}_{i,t} \cdot c_{\mathrm{A}}\right) - FC \right\}$$

s.t.

$$E\left(S_{i,t+1}\right) = P^{T} \cdot S_{i,t} \text{ for } t = 0, 1, 2, \dots, 229$$

$$W_{i,t+1} = W_{i,t} + \left(1 - Cull_{i,t}\right) LDG_{i,t}\left(W_{i,t}, S_{i,t}, A_{i,t}\right) \text{ for } t = 0, 1, 2, \dots, 229$$

$$S_{i,0}, W_{i,0} \text{ given}$$

where

$$P = \begin{bmatrix} 1-a-b & a & 0 & b \\ 0 & 1-c-d & c & d \\ 0 & 0 & 1-e & e \\ f & 0 & 0 & 1-f \end{bmatrix}$$

Appendix 4 Doses of Three Antimicrobial Drugs

	Tetracycline	Macrolide	Enrofloxacin
Average Individually Dosed AMU (g/head/admin)	8.001	2.531	3.465
Average Dose of Metaphylaxis (g/head/admin)	8.001	2.531	3.465
Average Dose of Prophylaxis Dose (g/head/admin)	3.174	0.743	1.094

Tetracycline is used as a representative drug for baseline simulation to determine the required antimicrobial doses for different disease management scenarios. The estimations of externality costs of AMUs are based on the simulation results that by switching the values of parameters related to the drug of Enrofloxacin in the model.

By converting the units of AMU doses and currency, the total externality costs of antimicrobials for an individual calf under disease management scenarios in Canadian dollars are calculated as follows:

$$Externality\ Costs = Antimicrobial\ Doses \times 1.95$$