The potential for sample testing at the pen level to inform prudent antimicrobial selection for bovine respiratory disease treatment: investigations using a feedlot simulation tool

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Supplementary File S1:
ODD Protocol: Virtual Feedlot Model

A hybrid agent-based and discrete event simulation (ABM-DES) model of AMU and AMR in a western Canadian feedlot

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A hybrid agent-based and discrete event simulation (ABM-DES) model of AMU and AMR in a western Canadian feedlot

A stochastic, continuous-time, agent-based model (ABM) was constructed with AnyLogic® 8 simulation software (version 8.8.6) using Java-based code, with the goal of developing a tool that can be used to explore questions related to antimicrobial stewardship in the management of bovine respiratory disease (BRD) in finishing feedlots [1]. This model description follows the ODD (Overview, Design concepts, Details) protocol for describing agent-based models [2], as updated by Grimm *et al.* [3]. The following description will note where the assumptions and/or model parameters can be modified to customize the output for different feedlot sizes, management practices, and cattle characteristics.

Overview

Purpose

The purpose of the work in [1] was to explore the dynamics of population-level antimicrobial resistance (AMR) emergence in a typical, small to mid-sized Canadian feedlot (6,000 to 10,000 animals) with calves at increased risk for BRD. While the model framework is easily modified for feedlots of any size, this configuration was chosen to provide a balance between the size of many commercial feedlots in Canada and computational efficiency for the ABM. The lighter-weight calves in the baseline model are assumed to represent a moderately high risk of AMR selection and dissemination in the feedlot setting, given the potential for infectious disease spread and exposure to antimicrobials [4].

Hypotheses about how AMR emerges and spreads in the feedlot environment were represented by model variations in the baseline effort in [1]; structural modifications distinguished between 1) a model in which only selection arising from antimicrobial use (AMU) impacted detectable AMR, 2) a model in which only transmission between animals impacted detectable AMR, and 3) a model in which both AMU-linked selection and transmission impacted detectable AMR. A comparison of the relative performances of these models with respect to reproducing empirical trends in AMR was a key component of that work [1], the results of which are reported herein. In brief, the model variants which included the impact of *contagious* acquisition on population-level AMR within the feedlot offered a stronger fit to empirical data than those that relied only on selection associated with AMU [1].

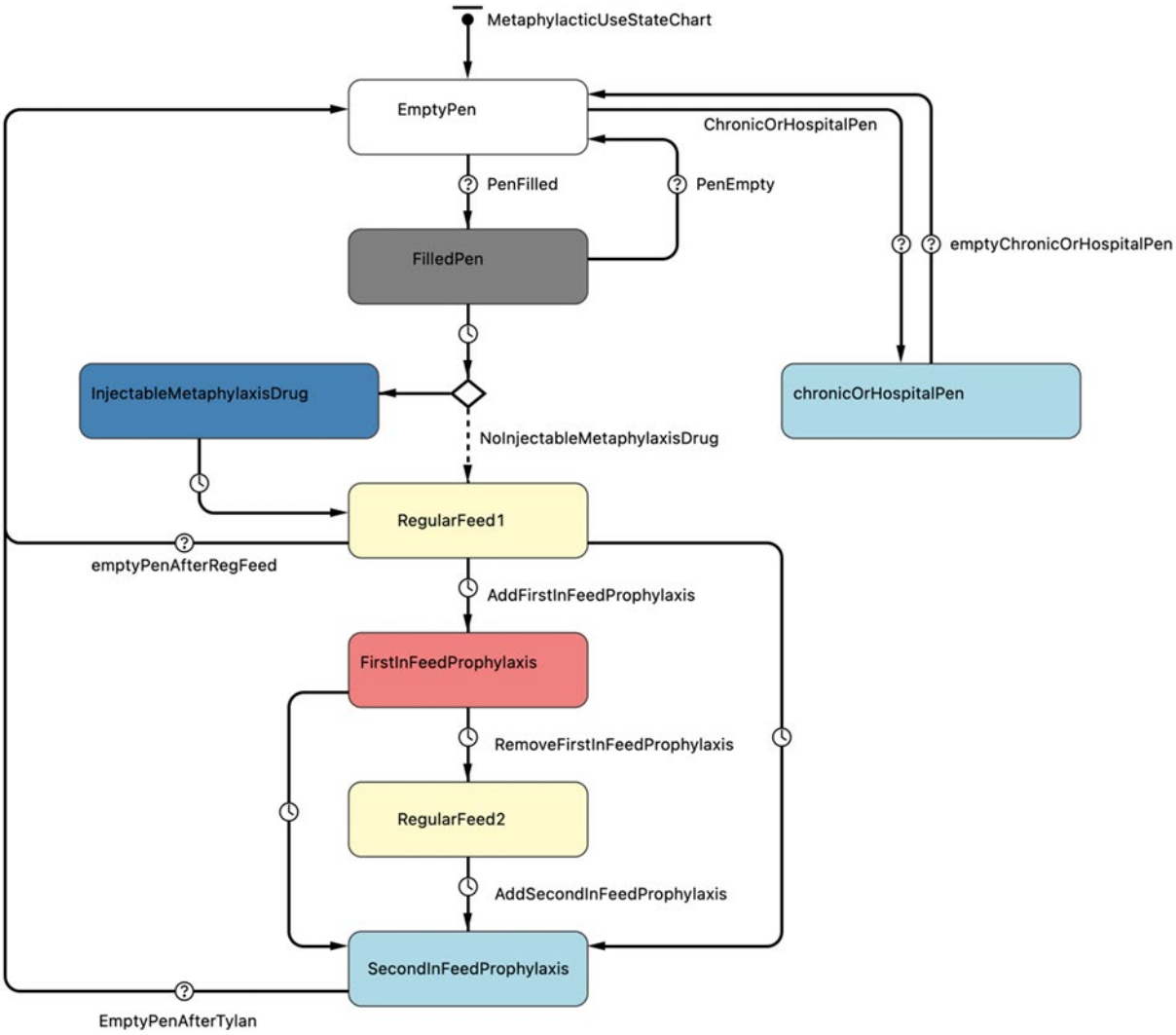
Mannheimia haemolytica is one of several bacterial pathogens implicated in the clinical presentation of BRD, particularly in high-risk calves following feedlot arrival [5, 6]. *M. haemolytica* was selected as the sentinel organism for AMR in respiratory pathogens, given 1) the broad assumption that the resistance status for *M. haemolytica* is representative of clinically relevant AMR in the nasopharyngeal microbiome [5, 7-8], and 2) the availability and reliability of temporal resistance prevalence data for this organism [7-13]. For the purposes of this model, it is assumed that every calf has a population of *M. haemolytica* existing as nasopharyngeal commensals [14]. For each calf in every pen, the resistance status of *M. haemolytica* to select antimicrobial classes (i.e., the presence or absence of detectable AMR in the population of *M. haemolytica*) is monitored over the course of the feeding period. Population-level AMR can evolve due to selection pressure associated with preventative and therapeutic AMU in the model and/or direct transmission of resistant bacteria between calves in the same pen. The model simulates the development and management of select syndromes that most often trigger injectable (i.e., individually-dosed) AMU in the western Canadian feedlot setting, including BRD, bacterial arthritis and infectious pododermatitis (i.e., foot rot) [15-16].

The emergence of resistant BRD pathogens can threaten the therapeutic efficacy of available antimicrobial drugs [17]. Confirmatory diagnostic and susceptibility testing for AMR before treatment offers an opportunity to limit inappropriate AMU and the risks posed by AMR emergence [18]. Modern feedlot operations manage cattle as groups in pens, and recent evidence demonstrates support for the pen-cohort as a prospective target for testing-based interventions [18-20]. The incorporation of sample testing to guide antimicrobial treatment choice at the pen level is hypothesized to reduce BRD relapses, subsequent AMU treatments, total AMU and resultant AMR. The ABM was modified and used in this work to compare the impact of different pen sampling strategies and AMR diagnostic tools on key antimicrobial stewardship metrics and feedlot economics outcomes.

Entities, state Variables, and scales

The system is modeled as a collection of autonomous entities called *agents*. The baseline model describes ten types of agents. The agents in the model are structured hierarchically, with pens filled with cattle. Each calf harbours a resistance agent that represents the detectable susceptibility status of their population of *M. haemolytica* to a set of commonly used antimicrobials. The treatment agent represents specific occurrences of AMU in each calf and has the potential to impact resistance status. The laboratory testing agent represents the potential to test for AMR prior to treatment as a tool to enhance antimicrobial stewardship. Each agent is assigned internal states and behaviours encoded by rules which govern the transitions between states over time. Interactions between agents produce emergent, system-level dynamics.

Figure S1.1. Process of calf management for each home pen in the agent-based model. Transition arrows demarcated by "clock" symbols are processes linked to a particular length of time (e.g., the number of days on a certain feed type). Transition arrows demarcated by "question mark" symbols are processes triggered when a specific condition is met (e.g., the emptying of occupied pens when the average target weight is reached). The branch demarcated by a "diamond" symbol indicates the possibility of two outcomes, where 1) no metaphylaxis (default, dotted line) or 2) injectable metaphylaxis (solid line) as assigned at the feedlot level at model initialization.



Main

The **Main agent** represents the program entry point and top-level agent for most AnyLogic models; it contains all other agents, any sub-models, any parameters that can be varied for scenarios, and live data visualizations. This model is set up to load parameters and other exogenous data tables from externally editable spreadsheet files. All external data files are called within the Main agent.

Feedlot

The **Feedlot agent** governs the processes of calf arrival, the allocation of calves to pens, and the re-sorting of calves among pens later in the feeding period (if enabled through a modifiable parameter). The feedlot consists of individual pens each with a cohort of individual calves. The Feedlot agent is responsible for aggregating pen-level statistics and assigning AMU protocols for disease control (**Figures SA1-SA2**) and treatment (**Figures SA3-SA5**). AMU protocols can be specified by the user or randomized across a range of common alternatives [15-16, 21] developed in consultation with feedlot practitioners. With either option, the selected protocols are applied to the entire feedlot for one realization of the model.

Pen

The **Pen agents** record the filling and emptying of pens by calf agents, and govern the timing and delivery of antimicrobials for disease *control* (i.e., prophylaxis and metaphylaxis, see **Figure S1.1**). Management protocols involving antimicrobials and thus the potential for AMR selection included each of 1) on-arrival injectable metaphylaxis for BRD management; 2) in-feed prophylaxis for histophilosis and liver abscess prevention; and 3) in-feed prophylaxis for foot rot outbreak control, when 10% or more calves in a shared pen were diagnosed with foot rot in a single feeding period. The options and/or likelihoods of available metaphylactic and prophylactic protocols in the model are outlined in **Figures SA1** and **SA2**, respectively. Given that the data available to calibrate the model are largely derived from empirical studies of high-risk calves administered macrolides at feedlot entry [e.g., 12-13], all animals in the baseline scenarios are directed to receive metaphylactic tulathromycin by default.

When the average weight of the animals in a single pen reaches the target finishing weight, calves are assumed to be ready for slaughter. Pens are subsequently de-populated to simulate the shipment of finished calves to a processing plant, and pen summary data are exported. The Pen agent gathers statistics on cattle shipped for processing, including the cumulative incidence of disease and the prevalence of detectable AMR to selected antimicrobial classes at specified time points.

Cattle

Each **Cattle agent** characterizes the health status for a single calf and governs the timing of and response to antimicrobials for disease *treatment*. Healthy calves can become sick with BRD, bacterial arthritis, or foot rot (**Figure S1.2**), syndromes that are most frequently associated with injectable AMU in the western

Canadian feedlot setting [15]. The options and likelihoods of available therapeutic protocols in the model are outlined in **Figures SA3-SA5**. The number of treatments for each calf agent is tracked and reported, as is their health status-dependent average daily gain (ADG) and resultant weight.

Calves become sick at a specified rate per day on feed (i.e., a daily hazard rate dependent on the number of days since feedlot entry) and are administered the prescribed antimicrobial regimen immediately upon their transition to a disease state. The daily hazard rates for the first case of each disease are drawn from empirical distributions reflecting temporal/seasonal and weight-based changes in regional disease risk shared by large private veterinary practices (see **Figure S1.3**). The first-case hazard rate for BRD in high-risk calves is specific to animals who receive metaphylactic tulathromycin at feedlot entry; the rate can be adjusted for other metaphylactic protocols, including "no metaphylaxis", by the risk ratios reported in a recent meta-analysis of injectable antibiotic options for BRD control [22]. Historical on-arrival AMR data are assumed to be reflected in the first-case hazard rate for BRD obtained from feedlot operations and used in the calibrations. In subsequent experiments with the model, the first-case hazard rate for BRD for an individual calf can default to the equivalent of that for "no metaphylaxis" *if* the population of *M. haemolytica* for that calf is resistant to the antimicrobial used for metaphylaxis.

Figure S1.2. Representation of animal health status for each calf in the agent-based model. The "disease" states are mutually exclusive, and an animal can only receive treatment for one disease at any given time. Transition arrows demarcated by "graph" symbols are those governed by daily hazard rates derived from empirical data. Transition arrows demarcated by "envelope" symbols depend on the receipt of an "end treatment" message. The length of treatment refers to the dosing interval (for multi-day regimens) and therapeutic interval (estimated period of selective pressure following dosing interval). Branches demarcated by "diamond" symbols indicate the possibility of two outcomes, including 1) treatment success and return to healthy state (default) or 2) baseline (fixed probability for BRD, arthritis) or resistance-linked (BRD only, when enabled) treatment failure and return to disease state (termed a "relapse" for the purposes of this description).

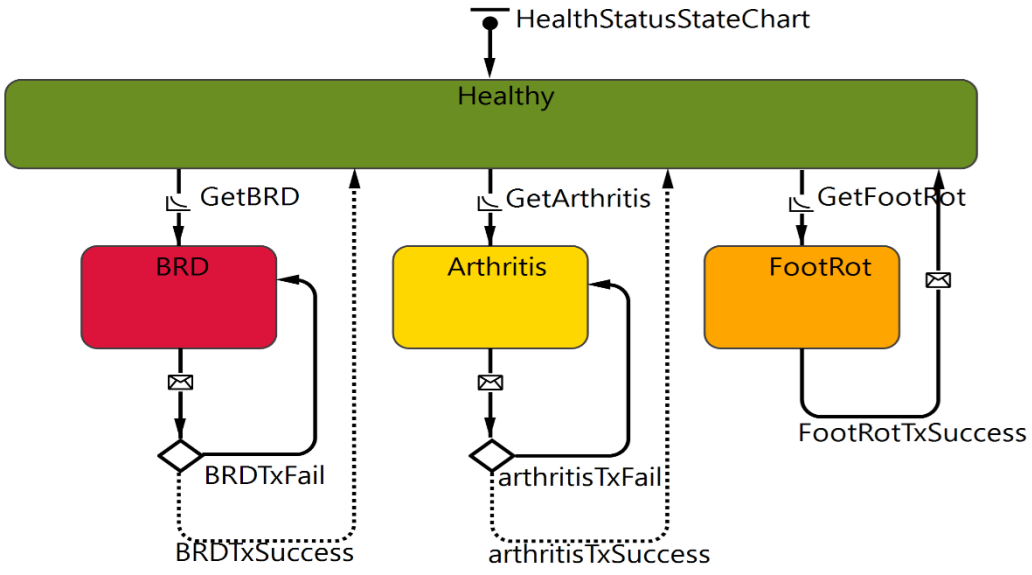
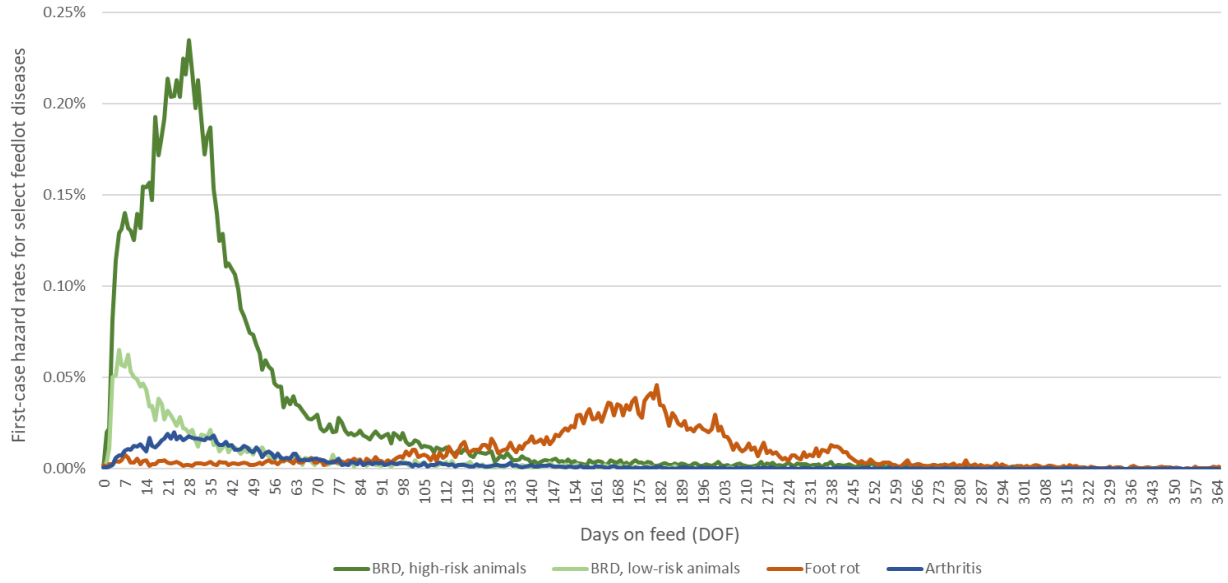


Figure S1.3. Daily hazard rates for first cases of BRD, foot rot and arthritis over the feeding period. Epidemiological curves are derived from empirical data provided by large, private veterinary practices in western Canada. The data for BRD represent approximately 590,000 high-risk, fall-placed animals at feedlot entry over 5 years (2012-2016)1; the data for foot rot and arthritis represent approximately 600,000 fall-placed animals over 13 years (2007-2020) provided as anonymized summaries.



[1]The first-case hazard rate used in the calibration experiments was specific to high-risk calves that received metaphylactic tulathromycin at feedlot arrival; in future experiments, the BRD rate can be adjusted for other metaphylaxis protocols by the risk ratios calculated in O'Connor et al. [11].

BRD- and arthritis-affected calves can experience one or more relapses requiring additional individually-dosed treatments after a first case of either disease (**Figure S1.2**, **Table S1.1**). Calves who received treatment for a first case experience a first relapse with a fixed probability; second and third relapse probabilities are similarly conditional on the calf having had a first and second relapse, respectively. This is possible because the model tracks the individual treatment history of each calf. The probabilities of subsequent relapses for each disease are derived from regional data reflecting temporal/seasonal and weight-based changes in disease risk (see **Table S1.1**).

Calves treated for foot rot in the empirical records available for model parameterization were assumed to have uncomplicated cases of infectious pododermatitis that responded to therapy. However, some of these calves would have been retreated if they were misdiagnosed, treated too late, or if the disease appeared in another foot. The model accounts for this possibility as calves re-enter the total population at risk of infection after receiving individually-dosed treatment (i.e., calves return to a "healthy" state by default after the therapeutic interval had elapsed for the administered antimicrobial, see **Table S1.2**).

Table S1.1. Values and sources for parameters in the operational and calibration versions of the agent-based feedlot model.

Parameter	Condition	Values available for Monte Carlo experiments	Value selected for calibration experiments	Source or rationale, if applicable
Feedlot and pen parameters				
Number of cattle per pen		**200**, user defined	200	Representation of a moderate-sized feedlot; optimization of computational effort
Number of pens across		**10**, user defined	10	
Number of pens high		**5**, user defined	3	
Cattle parameters				
Proportion of high-risk animals entering feedlot		**0-100%**, user defined	100%	
Proportion of steers entering feedlot		**0-100%**, user defined	100%	
Arrival weight for high-risk animals	*Applies to recently weaned and/or lighter-weight calves*	Value selected from uniform distribution, range **500-600 pounds**	Value selected from uniform distribution, range **500-600 pounds**	[23-24]
Arrival weight for low-risk animals	*Applies to backgrounded and/or heavier-weight yearlings*	Value selected from uniform distribution, range **800-900 pounds**	N/A No low-risk, heavyweight animals in calibration	[23-24]
Average daily gain (ADG) for healthy steer calves	*Applies to steers with no BRD or arthritis history who were lighter-weight on arrival*	Value selected from normal distribution with **μ = 3.50** and **σ = 0.44 pounds per day**	See footnote*	Empirical data from 7,685 steer calves with arrival weights ranging from 500-799 pounds (2019-2023)
ADG for healthy yearling steers	*Applies to steers with no BRD or arthritis history who were heavier-weight on arrival*	Value selected from normal distribution with **μ = 3.53** and **σ = 0.59 pounds per day**	N/A No yearling steers in calibration	Empirical data from 440 yearling steers with arrival weights ranging from 800-1099 pounds (2019-2023)
ADG for healthy heifer calves	*Applies to heifers with no BRD or arthritis history who were lighter-weight on arrival*	Value selected from normal distribution with **μ = 3.14** and **σ = 0.47 pounds per day**	N/A No heifer calves in calibration	Empirical data from 19,734 heifer calves with arrival weights ranging from 500-799 pounds (2019-2023)
ADG for healthy yearling heifers	*Applies to heifers with no BRD or arthritis history who were heavier-weight on arrival*	Value selected from normal distribution with **μ = 3.45** and **σ = 0.74 pounds per day**	N/A No yearlings heifers in calibration	Empirical data from 3,736 yearling heifers with arrival weights ranging from 800-1099 pounds (2019-2023)
ADG for animals of either sex being treated in the hospital pen	*Applies to animals temporarily housed in the hospital pen for arthritis treatment*	Fixed value of **0.00 pounds per day**	Fixed value of **0.00 pounds per day**	Model parsimony; consultation with feedlot veterinarians
Absolute change in ADG for animals with first case of BRD	*Applies for remainder of feeding period to animals with single diagnosis (i.e., first case) of BRD*	**0.0453 pounds per day** (relative to healthy animals)	See footnote*	Empirical data from 1,630 steer calves with arrival weights ranging from 500-799 pounds (2019-2023)

Parameter	Condition	Values available for Monte Carlo experiments	Value selected for calibration experiments	Source or rationale, if applicable
Absolute change in ADG for animals with first relapse of BRD	*Applies for remainder of feeding period to animals with first relapse (i.e., second case) of BRD*	**0.1759 pounds per day** (relative to healthy animals)	See footnote*	Empirical data from 366 steer calves with arrival weights ranging from 500-799 pounds (2019-2023)
Absolute change in ADG for animals with second relapse of BRD	*Applies for remainder of feeding period to animals with second or more relapses (i.e., third or subsequent cases) of BRD*	**0.3407 pounds per day** (relative to healthy animals)	See footnote*	Empirical data from 162 steer calves with arrival weights ranging from 500-799 pounds (2019-2023)
Absolute change in ADG for animals with first case of arthritis	*Applies for remainder of feeding period to animals with single diagnosis (i.e., first case) of arthritis*	**0.2538 pounds per day** (relative to healthy animals)	See footnote*	Empirical data from 131 steer calves with arrival weights ranging from 500-799 pounds (2019-2023)
Absolute change in ADG for animals with first relapse of arthritis	*Applies for remainder of feeding period to animals with first relapse (i.e., second case) of arthritis*	**0.4625 pounds per day** (relative to healthy animals)	See footnote*	Empirical data from 32 steer calves with arrival weights ranging from 500-799 pounds (2019-2023)
Absolute change in ADG for animals with second or third relapse of arthritis	*Applies for remainder of feeding period to animals with second or more relapses (i.e., third or subsequent cases) of arthritis*	**0.8778 pounds per day** (relative to healthy animals)	See footnote*	Empirical data from 3 steer calves with arrival weights ranging from 500-799 pounds (2019-2023)
Target market weight for slaughter, healthy animals	*Applies to healthy animals in regular pens; pen is shipped as unit when average weight of animals reaches selected target*	Value selected from uniform distribution, range **1325-1500 pounds**	Value selected from uniform distribution, range **1325-1500 pounds**	[23-25]
High target finishing weight for slaughter, chronic pen animals		**1200 pounds**	**1200 pounds**	Consultation with feedlot veterinarians
Low target finishing weight for slaughter, chronic pen animals		**900 pounds**	**900 pounds**	Consultation with feedlot veterinarians
Disease parameters				
Probability of first BRD relapse in high-risk animals	*Conditional on having had a first case of BRD*	**21.64%**	**21.64%** All animals in calibration are high-risk	Empirical data from approximately 55,000 high-risk calves with first cases of BRD after tulathromycin metaphylaxis (2012-2016)
Probability of second or third BRD relapse in high-risk animals	*Conditional on having had a first or second relapse of BRD, respectively*	**35.80%**	**35.80%** All animals in calibration are high-risk	Empirical data from approximately 12,000 high-risk calves with first relapses of BRD after tulathromycin metaphylaxis (2012-2016)
Probability of first BRD relapse in low-risk animals	*Conditional on having had a first case of BRD*	**26.19%**	N/A	Empirical data from approximately 5600 low-risk calves with first

Parameter	Condition	Values available for Monte Carlo experiments	Value selected for calibration experiments	Source or rationale, if applicable
			No low-risk animals in calibration	cases of BRD after oxytetracycline metaphylaxis (2012-2016)
Probability of second or third BRD relapse in low-risk animals	*Conditional on having had a first or second relapse of BRD, respectively*	**40.45%**	N/A No low-risk animals in calibration	Empirical data from approximately 1450 low-risk calves with first relapses of BRD after oxytetracycline metaphylaxis (2012-2016)
Probability of first arthritis relapse	*Conditional on having had a first case of arthritis*	**11.58%**	**11.58%**	Empirical data from approximately 6000 fall-placed calves with first cases of arthritis (2007-2020)
Probability of second arthritis relapse	*Conditional on having had a first relapse of arthritis*	**20.46%**	**20.46%**	Empirical data from approximately 700 fall-placed calves with first relapses of arthritis (2007-2020)
Probability of third arthritis relapse	*Conditional on having had a second relapse of arthritis*	**19.58%**	**19.58%**	Empirical data from approximately 145 fall-placed calves with second relapses of arthritis (2007-2020)
Chronic pen parameters				
Percentage of animals assigned to "high target finishing weight" group at chronic pen entry		**33.3%**	**33.3%**	Model parsimony
Percentage of animals assigned to "low target finishing weight" group at chronic pen entry		**33.3%**	**33.3%**	Model parsimony
Percentage of animals assigned to "euthanasia" group at chronic pen entry		**33.3%**	**33.3%**	Model parsimony
Number of days between chronic pen weight checks		**7 days**	**7 days**	Model parsimony
Testing parameters				
Number of animals sampled per single pen	*Applies to all home pens in the feedlot (not hospital or chronic pens)*	**20****	N/A Testing module not enabled in calibration	Simulated data from [19]
Time delay for collection of single nasopharyngeal sample	*Delay applies to both diagnostic test types (AST and metagenomic sequencing)*	**1 minute**	N/A Testing module not enabled in calibration	Observations from sample collection step for multi-year research [12] and CFAASP projects [11, 26]
Time delay for transport of nasopharyngeal sample to diagnostic laboratory	*Delay applies to both diagnostic test types (AST and metagenomic sequencing)*	**36 hours**	N/A	Observations from streamlined sample transport step for multi-

Parameter	Condition	Values available for Monte Carlo experiments	Value selected for calibration experiments	Source or rationale, if applicable
			Testing module not enabled in calibration	year CFAASP project [11, 26]
Time delay for nasopharyngeal sample processing and diagnostic testing	*Delay applies to both diagnostic test types (AST and metagenomic sequencing)*	**72 hours**	N/A Testing module not enabled in calibration	Observations from sample processing for multi-year research [12, 27] and CFAASP [11, 26] projects
Time delay for reporting of diagnostic result to feedlot veterinarian	*Delay applies to both diagnostic test types (AST and metagenomic sequencing)*	**0 minutes** (instantaneous)	N/A Testing module not enabled in calibration	Model parsimony
Threshold at which test result for pen-level AMR triggers a change in BRD treatment	*Applies to all antimicrobial classes examined in the model*	**25%****	N/A Testing module not enabled in calibration	Empirical data reported in [1], expert opinion [28]

*****The ADG parameters and change in ADG parameters for disease-affected calves have been updated with stronger empirical data since the model was calibrated in [1]. The values used in the calibration experiments are reported in Table S1.1 in [1], and were derived from performance data in U.S. cattle [29-31]. ******Model assumptions relevant to the Testing agent that are explored in sensitivity analyses in the current study.

To best match empirical data available for calibration, relapses were characterized as the failure of a previous therapy to adequately treat the underlying infection [32], prompting the continuation of symptomatic disease. Historical AMR data were assumed to be reflected in the rates of treatment failure/disease relapse obtained from feedlot operations and used in the calibrations. In subsequent experiments with the model, antimicrobial treatments delivered to BRD-affected calves will fail (i.e., animals will relapse) at a probability equivalent to the pen-level prevalence of AMR, if the pen-level prevalence of resistance to the administered drug exceeds historical rates of retreatments (see BRD treatment failure loop, **Figure S1.2**). Calves with baseline or resistance-linked treatment failure remain in the "disease" state following the therapeutic interval (see **Table S1.2**) and receive the next antimicrobial in the treatment/relapse protocol.

Resistance

The emergent AMR status for the population of *M. haemolytica* in the nasopharynx of each calf is governed at the level of **Resistance agent**. The dynamics of resistance acquisition and loss for each antimicrobial drug are directed by separate and mutually exclusive state charts (described in detail under **Sub-models**). All animals are assumed to have a population of *M. haemolytica* existing as nasopharyngeal commensals [14], acknowledging that this organism is not consistently culturable from all calves [33]. Further, *M. haemolytica* is assumed to be one of the causative agents involved in the progression to clinical BRD [34].

Table S1.2. Pharmacokinetic and initialization parameters for probabilistically selected antimicrobials used for prophylaxis, metaphylaxis or treatment in the feedlot model, and for antimicrobials to which acquired resistance over the feeding period is of interest.

Antimicrobial class	Antimicrobial drug (example of active ingredient)	Antimicrobial drug (example of trade name)	Reason for use in feedlot model[1]	Average probability (%) of detectable resistance at arrival[2]	Withdrawal period (days)[3]	Therapeutic interval (days)[4]
Aminoglycosides	Spectinomycin	N/A	N/A	1.7%	N/A	N/A
Cephalosporins	Ceftiofur CFA	Excede 200	T	0.0%	13	9.2
	Ceftiofur HCl	Excenel RTU EZ	T	0.0%	3	1.1
Fluoroquinolones	Enrofloxacin	Baytril 100	T	0.4%	36	0.7
Macrolides (15-membered ring)	Gamithromycin	Zactran	M, T	2.4%	49	6.9
	Tulathromycin	Draxxin	M, T	2.4%	44	8.3
Macrolides (16-membered ring)	Tildipirosin	Zuprevo	M	4.3%	42	26.3
	Tilmicosin	Micotil	M, T	4.3%	28	3.6
	Tylosin[5]	Tylan 100	P	4.3%	0	0.1
Potentiated sulfonamides	Sulfadoxine	Borgal	T	2.3%	10	1.6
	Trimethoprim			0.3%	10	0.3
Penicillins	Ampicillin	Polyflex	N/A	1.7%	6	0.8
	Penicillin	Procaine Penicillin G	T	1.7%	5	0.1
Phenicols	Florfenicol	Nuflor	T	0.1%	55	3.2
	Florfenicol/ flunixin	Resflor	T	0.1%	60	3.2
Tetracyclines	Chlortetracycline[6]	Chlor 100 Granular	P	4.9%	5-28 (dose dependent)	2.0
	Oxytetracycline	Medicated Premix				
		Liquamycin LA-200	M, T	4.9%	28(IM)-48(SC)	2.6

[1]Abbreviations indicating reason for use in feedlot model: P = prophylaxis, M = metaphylaxis, T = treatment, N/A = not used in model.

[2]Probability of detectable phenotypic resistance on feedlot arrival for each antimicrobial was derived from recent studies of healthy feedlot cattle in western Canada [7-13]. In the calibration experiments, the probability was a weighted average of the extracted prevalence data; in future experiments, the probability will be randomly drawn from a modified PERT distribution where the 95% CIs are the minimum and maximum values, and the average value is the most likely value (mode).

[3]The withdrawal period in days reflects those reported in the Compendium of Veterinary Products – Canada edition [35].

[4]The therapeutic interval is a crude estimate of the effective duration of selective pressure (i.e., period over which the drug is active and selection for resistance is possible). The therapeutic interval for each antimicrobial was estimated from its reported serum elimination half-life in cattle [36-45], multiplied by three.

[5]Prophylactic tylosin use did not co-select for *M. haemolytica* resistance to the other 16-membered ring macrolides in its sub-class, consistent with the observation that "the in-feed levels of tylosin [have] no effect on the prevalence of *M. haemolytica"* [46].

[6]Chlortetracycline at both the "high" and "low" dosages were fully linked to each other and to oxytetracycline. When the "low dose" of chlortetracycline was used, the calibrated "selection probability" for tetracyclines was adjusted by a multiplier (0.2) that reflects the average concentration of that regimen relative to the "high dose" regimen. The multiplier was estimated from AMU data collected by the Canadian Integrated Program for Antimicrobial Resistance Surveillance [referenced in Hannon et al. [47]] and a series of expert interviews with feedlot veterinarians.

Treatment

Each **Treatment agent** governs the delivery of the appropriate prophylactic, metaphylactic or therapeutic AMU protocol to an individual animal (described in detail under **Sub-models**).

Testing

The **Testing agent** is comprised of a discrete event simulation (DES) workflow [48-49] with LabTesting, TestOrder, TestPool and TestSample agents. The laboratory testing process generates information on the pen-level AMR status for the population of *M. haemolytica* with which to make informed treatment decisions for animals that become sick with BRD. The process is described further under **Sub-models**. The testing option was **not** enabled for the development of the baseline model used to test hypotheses about how AMR emerges in the feedlot environment, given that testing for AMR was not a standard part of cattle management in the historical data used for calibration.

Process overview and scheduling

The baseline model describes a typical, small (6,000 animals) to mid-sized (10,000 animals) western Canadian feedlot, populated by auction-sourced beef steer calves arriving in the fall. Calves with this risk profile are most often recently weaned and lighter-weight animals, and are more likely than heavier and older animals to be in the early stages of respiratory disease [4], and to receive metaphylactic antimicrobials at feedlot entry [15]. The model operates on continuous calendar time and the convenience time unit is days. The simulation is run for a period of one year. Events in the model occur at either 1) a fixed time, following the occurrence of another event (e.g., in-feed AMU exposure after a particular number of days on feed (DOF)); or 2) an arbitrary point in time, driven by a daily incidence rate or as a consequence of another event (e.g., receipt of a "transmission" message from a connected calf). In the baseline model, agents are assumed to immediately and perfectly perceive transitions in their health and AMR status that trigger treatment decisions.

The model simulates the arrival by truck of lightweight steers at random intervals starting October 1st (see **Table S1.1** for weight parameters [23-24]). The cattle deliveries increase in frequency from the start of the "fall run" in October and peak in November before slowing again until the feedlot reaches full capacity in December. The size of the feedlot is specified by parameters governing the number of pens and number of cattle per pen. For the calibration experiments, the feedlot consisted of 28 home pens, one chronic sick pen, and one hospital pen arranged in rows (n=30 total pens); the home pens are filled successively from left to right with 200 calves each. For subsequent experiments with the operational version of the model, the number of home pens in the feedlot was increased to n=48 (n=50 total pens). The necessary infrastructure and data are present to incorporate heavier-weight and/or heifer calves in pens and feedlots of different sizes in future experiments with the model. The default model setting fills individual home pens with calves of the same sex and weight (i.e., BRD risk) category. Pen-level variation in other risk factors including origin (auction or ranch-direct) and vaccination status (yes or no) could likewise be integrated as data become available.

All animals in the baseline configurations receive metaphylactic tulathromycin (i.e., Draxxin) by default. However, the choice of metaphylactic antimicrobial (if any) can be probabilistically selected at model initialization if desired (see **Figure SA1**). In subsequent experiments with the model, calves with on-arrival resistance to the antimicrobial drug used for metaphylaxis will be subject to a first-case hazard rate for BRD equivalent to those who receive "no metaphylaxis". This adjustment changes the size but not timing of the peaks in **Figure S1.3**. The probability that the population of *M. haemolytica* in each calf has detectable resistance on arrival is derived from empirical data in the published literature [7-13] (see **Table S1.2**).

Prophylactic antimicrobials to prevent histophilosis and liver abscesses are delivered at the pen level to all calves in the feedlot via medicated feed. The prophylactic regimen (drug choice, start date, duration, and dosage with or without pulse delivery regime) for each indication is probabilistically selected at model initialization (see **Figure SA2**). The selected protocol applies to all home pens in the feedlot for a unique model run (i.e., one replication in a calibration experiment), but can be set to vary across multiple iterations within experiments. The variation described in the literature is expected to best reflect the AMU conditions that generated the AMR data used in calibration experiments.

Calves are assumed to be healthy at feedlot arrival, and are assigned at entry a rate of average daily gain (ADG) drawn from a normal distribution (see **Table S1.1** for weight gain parameters [24, 29-31]). Calves become sick at a daily hazard rate dependent on the number of days since feedlot entry (**Figure S1.3**), and are administered the prescribed antimicrobial regimen immediately upon their transition to a disease state. The therapeutic regimen for each indication is probabilistically selected at model initialization (see **Figures SA3-SA5**) and varies by animal weight at infection (all diseases) and risk at feedlot entry (BRD only). Calves that transition to a "disease" state due to BRD or arthritis are assigned a reduced rate of ADG (i.e., gain weight more slowly) for the duration of their time in the feedlot (see **Table S1.1)**; the reductions in ADG are additive for calves affected by both diseases over the feeding period. Long-term ADG was not substantially affected in calves with foot rot in a previous report [50], and thus the rate of growth does not change for these animals.

Therapy is assumed to be effective for uncomplicated foot rot, and calves return to a "healthy" state by default after the therapeutic interval has elapsed for the administered antimicrobial (see **Table S1.2**). If 10% or more of the calves in a shared pen are diagnosed with foot rot in a single feeding period, a course of in-feed antimicrobials is administered at the pen level as part of a preventative "outbreak protocol" (see **Figure SA5**).

BRD- and arthritis-affected calves can experience one or more relapses requiring additional individually-dosed treatments after a first case of either disease. Calves who received treatment for a first case experience

a first relapse with a fixed probability; second and third relapse probabilities are similarly conditional on the calf having experienced a first and second relapse, respectively. The probabilities of subsequent relapses for each disease are derived from regional data reflecting temporal/seasonal and weight-based changes in disease risk (**see Table S1.1**).

All animals in the same pen are connected to each other via a transmission network or "spatial neighbourhood" configured by the user at model initialization. Networks can be reconfigured by the user in future experiments to include distance-based connections and/or connections between animals in adjacent pens. Calves being treated for first or subsequent cases of arthritis are moved to a specialty pen for acutely sick animals requiring multi-day therapeutic regimens, designated the "hospital pen" (see **Figures SA4, SA6**); the calf's connections are reconfigured to include their temporary pen-mates during their hospital stay. These animals return to their home pens after their final doses are administered, and are the only potential vectors for the inter-pen spread of resistance in the baseline model where both cattle re-sorting and inter-pen connections are disabled. Calves do not gain weight while they are housed in the hospital pen and are temporarily assigned an ADG equal to zero; once they return to their home pens, the animals resume weight gain at the reduced rate described in **Table S1.1**. If the home pen has been depopulated (i.e., sent for slaughter) before the calf returns, the animal is instead transferred to the "chronic pen" as there is no "rail pen" specified in the model.

Chronically sick animals, including a proportion of heavyweight calves with arthritis and/or calves experiencing a third relapse from either BRD or arthritis, are permanently moved to the second specialty pen designated the "chronic pen" (**Figures SA3-SA4, SA6**). Calves housed in this pen do not receive prophylactic (i.e., in-feed) or therapeutic antimicrobials to prevent or treat illness, given that they have not and are not expected to respond to established treatment protocols; these animals continue to gain weight at the reduced rate of ADG in accordance with their diagnosis. As in the hospital pen, the connections of calves in the chronic pen are reconfigured to include their new pen-mates.

At chronic pen entry, calves are probabilistically assigned to one of three ultimate destinations consistent with what might occur for large feedlot operations. One-third of the calves who enter the chronic pen are euthanized, and the remainder are evenly split between 1) those who are eventually shipped to a slaughter plant (as with healthy calves), as they achieve near-to-target weights in a reasonable time frame; and 2) those who are slaughtered at a reduced final weight (see **Table S1.1** for chronic pen parameters). The disposition and/or weight of chronically sick animals was evaluated every seven days. The animals are sent for slaughter when they reach the minimum finishing weights specified in **Table S1.1**. Animals in the

chronic pen which fail to reach their minimum target weight before the end of the feeding period are euthanized.

The market or target animal weight for a unique model run is randomly selected at initialization (see **Table S1.1** for target weight parameters [25]). When the average weight of the animals in a particular pen reaches the selected target, the pen is emptied and the calves are shipped for slaughter and processing. Calves in any pen type can die of disease prior to reaching their target weight, and this is captured in the model by a daily mortality rate dependent on the number of days since feedlot entry (see **Figure SA6**). Daily mortality rates subdivided by cause are drawn from empirical distributions reflecting temporal/seasonal environmental changes in risk (see **Figures S1.4 and S1.5**). For the purposes of the model, it is assumed that death due to BRD is conditional on having experienced at least a first case of BRD requiring treatment with antimicrobials. While it is possible for animals to die from BRD without being diagnosed and treated, empirical data attributing death loss to treated *versus* untreated animals was not available. This assumption does not impact total death losses in the model.

Figure S1.4. Daily mortality rates due to BRD over the feeding period. Epidemiological curve is derived from empirical data provided by a large, private veterinary practice in western Canada. These data represent approximately 700,000 high-risk, fall-placed animals at feedlot entry over 5 years (2012-2016).

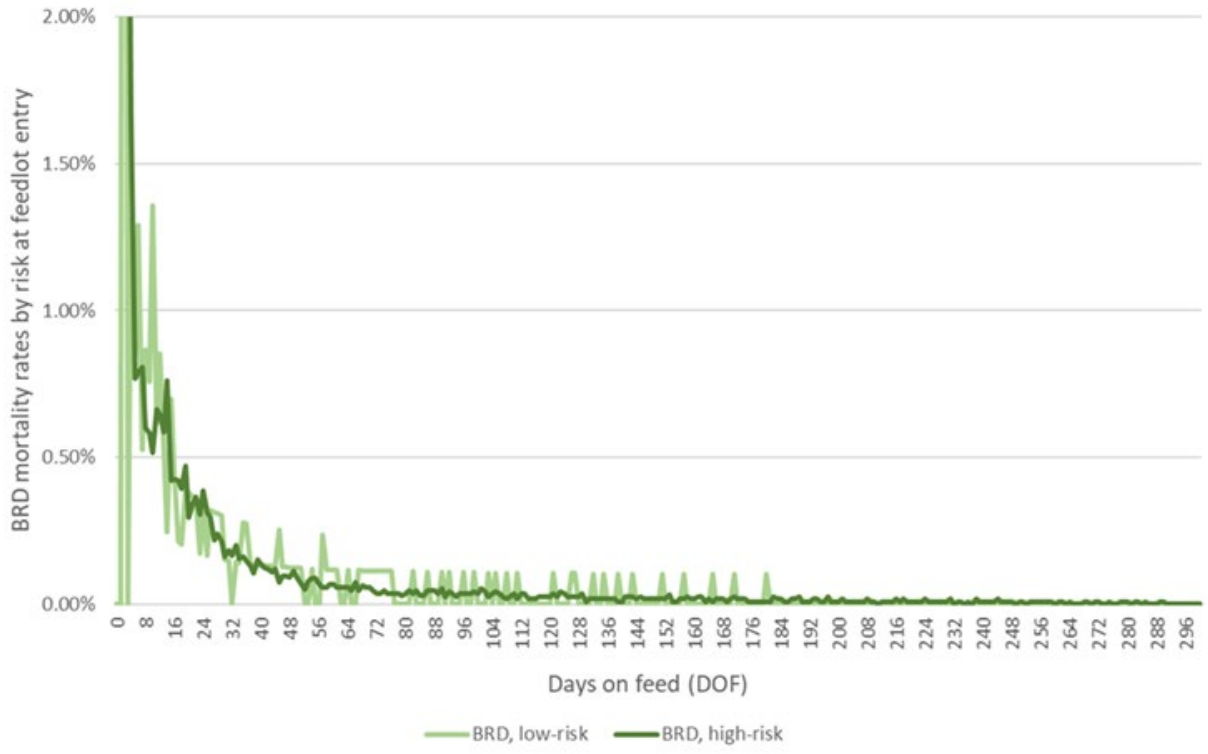
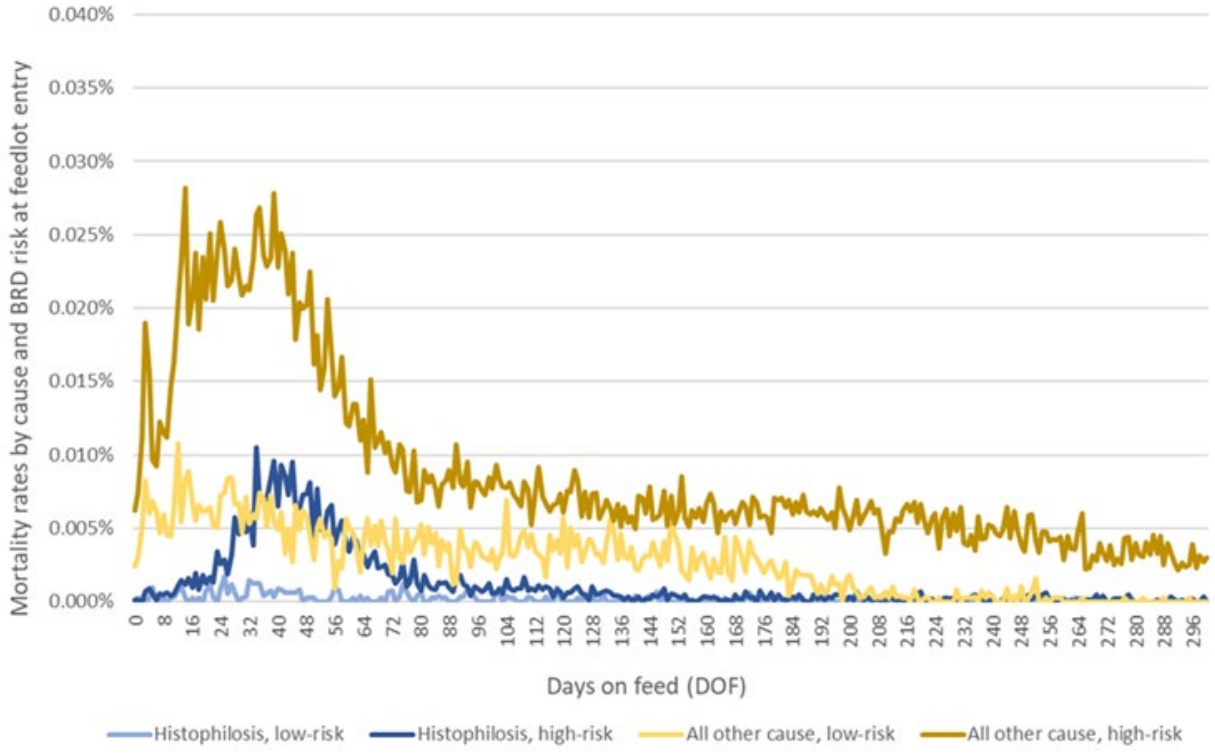


Figure S1.5. Daily mortality rates due to histophilosis and other causes over the feeding period. Epidemiological curves are derived from empirical data provided by a large, private veterinary practice in western Canada. These data represent approximately 700,000 high-risk, fall-placed animals at feedlot entry over 5 years (2012-2016).



Design concepts

Basic Principles

BRD is the most common and costly disease affecting North American beef cattle [511], and is therefore a major determinant of AMU in feedlots [15-16, 21]. AMU exerts a selective pressure on populations of microorganisms, favoring the survival of bacteria that harbor resistance genes. In the absence of selective pressure from AMU, the related fitness costs have the potential to make resistance expression less advantageous. AMR can also disseminate directly between animals via the transfer of resistance genes and/or microorganisms with resistance genes. Antimicrobial drugs from the same class (e.g., tetracyclines) or sub-class (e.g., 15-membered ring macrolides) are assumed to be equally vulnerable to the genetic mechanism(s) conferring resistance to populations of bacteria. The model thus simulates the co-selection, co-waning and co-transmission of detectable resistance for drugs in the same class.

Therapeutic failures linked to AMR (i.e., the failure of a BRD case to respond to a particular therapy due to resistance in the causative organism) are proposed to increase the number of antimicrobial uses and therefore AMR prevalence in response to selective pressure [17, 32]. The availability of AMR information via diagnostic testing to inform antimicrobial drug selection prior to BRD treatment could limit the number of BRD relapses, unnecessary AMU and the risks posed by AMR emergence. An updated version of the feedlot simulation tool [1] was used to examine *if* and *under what conditions* a laboratory testing-informed BRD treatment strategy at the *pen* level could meaningfully impact select antimicrobial stewardship and feedlot economics outcomes.

Emergence

The primary emergent outcomes of the model are the time-varying prevalences of detectable AMR in *M. haemolytica* to select classes of antimicrobial drugs, arising from the combination of initial conditions, temporal trends in feedlot disease, and prophylactic and therapeutic treatment selections. Related outputs emerging from the model *for each antimicrobial class* and at *each time point* included 1) the cumulative number of uses of antimicrobials belonging to that class; 2) the cumulative number of acquired resistance events due to selection and 3) the cumulative number of acquired resistance events due to transmission.

AMR acquisition and loss events are simulated stochastically in response to emergent patterns of prophylactic and therapeutic AMU. Disease occurs stochastically in the model, and therefore the number and timing of antimicrobial uses for therapy is also emergent. The transmission of AMR between calves occurs at a time-dependent stochastic rate specific to each antimicrobial class, and its emergence depended in part on the prevalence of animals with detectable resistance available to transmit to susceptible contacts.

Resistance-linked treatment failure could not be decoupled from other-cause treatment failure in the empirical data available for parameterization, and was therefore externally specified in the calibration version of the model. In the operational version of the model, responsiveness to detectable resistance and the availability of diagnostic information allows for increasingly complex feedback between AMU and AMR. The first-case hazard rate for BRD defaults to the equivalent of that for "no metaphylaxis" if the local population of *M. haemolytica* for a calf is resistant in that calf to the antimicrobial used for metaphylaxis. The resultant higher first-case hazard rate for BRD increases the potential for AMU-associated selection pressure.

Similarly, if the prevalence of pen-level AMR for the antimicrobial used to treat a first or second BRD relapse exceeds the baseline failure rate, then treatment failure occurs at the higher rate equivalent to the pen-level prevalence of AMR. While not all treatment failures will be due to AMR, the exact probability is unknown and as such this assumption that AMR above the baseline will result in additional treatment failure is a worst-case scenario assumption. The decreasing success of treatment can result in additional BRD

cases, emergent patterns of AMU that apply selective pressure, and the associated potential for additional emergent AMR.

The responsiveness of the model to AMR is extended further when the laboratory testing process is enabled. In these scenarios, the pen-level prevalence of resistance to the first-line antimicrobial drug in the treatment protocol can be determined in advance of the need to treat for BRD. If the pen-level prevalence of resistance to the default (i.e., first-line) drug meets a prescribed threshold at the time of sample, the calves in that pen that develop a first or subsequent case of BRD will be directed to receive a pre-specified alternative option at the time of treatment. The availability of testing information to inform treatment can result in fewer BRD relapses and deaths, shifts in the patterns of AMU across the feeding period, and the associated potential for additional emergent AMR.

The number and timing of animals moving to the chronic pen are other emergent outcomes. A proportion of heavyweight calves with arthritis and/or calves experiencing a third relapse from either BRD or arthritis are deemed "chronically ill" and moved to this specialty pen.

Adaptation

In the current version of the model, results from the laboratory testing of samples are allowed to inform the selection of antimicrobial treatments for BRD. The various sampling and testing conditions in different combinations will or will not trigger the decision rule (i.e., "switch to the alternative drug for treatment if resistance to the first-line option meets the treatment change threshold"), which is a form of adaptation.

Objectives

No goal-seeking on the part of agents is applied in the model.

Learning

No learning on the part of agents is applied in the model.

Prediction

The prediction is that the time-varying prevalence of population-level AMR to select classes of antimicrobials will be an emergent pattern of the model, given the assumptions about on-arrival AMR prevalence, disease incidence and timing, and AMU exposures. The extent to which AMU-linked selective acquisition of resistance *versus* contagious acquisition of resistance is responsible for emergence is likewise predicted to impact the primary emergent outcome.

Sensing

In the baseline version of the model, agents are assumed to immediately and perfectly perceive transitions in their health and AMR states that trigger treatment decisions. In the current version of the model, parameters defining the accuracy of the diagnostic test (i.e., the sensitivity and specificity of the test to detect resistance to antimicrobial drugs) can be specified in the laboratory testing agent. An imperfect

diagnostic test allows for the possibility of false positive and false negative results (i.e., testing information that does not capture the true prevalence of pen-level resistance) which are used to inform treatment decisions. Further, testing in the model occurs in advance of the need to treat for BRD, and the tested AMR prevalence at the time of sampling does not necessarily reflect the real-time prevalence of AMR at the time of treatment.

Interaction

Cattle in the same pen interact with each other and can transmit AMR to the populations of *M. haemolytica* local to each animal. Transmission messages are sent from animals with detectable AMR to a randomly selected pen-mate at the calibrated contact rate. The per-day contact rate is adjusted by the calibrated stress multiplier to reflect the increased likelihood of transmission when animals are physiologically stressed. When a transmission message is received by a susceptible calf, the contact is considered to be "effective" (i.e., results in contagious transmission). Dependent on their health status, animals might be moved to the hospital or chronic sick pens, thereby modifying their contact networks.

The use of antimicrobials applies selection pressure to the *M. haemolytica* population within an animal. Resistance acquired selectively or contagiously does not wane in the model if the animal is being actively exposed (i.e., within the therapeutic interval of) to the relevant drug class. In the absence of selection pressure to the *M. haemolytica* population within an animal, the potential exists for resistance to wane at a specified rate. Immediately after waning, an animal is once again at risk of acquiring resistance if subjected to selective pressure due to AMU or if exposed via contact with pen-mates (i.e., a calf cannot become "immune" to resistance).

Stochasticity

Cattle arrive at the feedlot as part of a stochastic process, with a variable number of animals arriving and filling each pen within two days at varying intervals between October to December. The random assignment of 1) arrival weight (from a uniform distribution); 2) rate of ADG (from a normal distribution); and 3) probability of detectable resistance to each antimicrobial class (from a PERT distribution) to incoming lightweight steers at model initialization. The target market weight for healthy animals was also randomly selected from a uniform distribution at model startup. The prophylactic and therapeutic AMU protocols for a single realization of the model were randomized across a range of plausible alternatives at the start of the simulation.

The calves in the model become sick with first occurrences of select diseases at stochastic rates drawn from exponential distributions informed by the empirical data summarized in **Figure S1.3**. Treatment failures and associated relapses of BRD and arthritis were likewise random events that occurred with fixed probabilities. When AMR responsive mechanisms are initialized in the model, BRD treatment failures in

excess of the baseline probability are responsive to emergent pen-level AMR and are therefore stochastic processes (**Table S1.1**). When the laboratory testing process is enabled, the number and type of antimicrobial uses (i.e., BRD treatment choices) are responsive to the tested pen-level prevalence of AMR and are likewise stochastic processes.

AMR acquisition and loss events were simulated stochastically per the calibrated selection and waning rates, respectively, and depended in part on emergent patterns of prophylactic and therapeutic AMU. Contagious transmission events were stochastic processes arising from both 1) the calibrated contact rates and 2) random contacts between calves in the same pen with discordant resistance status.

Collectives

The model's architecture reflects the hierarchical structure of a typical western Canadian feedlot. Agents that represent the phenotypic resistance status of respiratory bacteria to select antimicrobial classes are collected within cattle; cattle are collected into pens, which are collected into a feedlot. Animal-level delivery of *therapeutic* antimicrobials impact the resistance phenotypes nested within individual calves. Pen-level delivery of *prophylactic* and *metaphylactic* antimicrobials apply to all calves within that pen and impact the resistance phenotypes nested within those calves. Feedlot management decisions, including decisions about AMU regimens, calf allocations and re-sorting, apply to all pens in the feedlot for a single model realization.

Within the laboratory testing module, a test order represents a collection of diagnostic tests for AMR in *M. haemolytica* populations in animals sampled from a single pen. A single test sample corresponds to one animal. Within a particular test order, samples can be tested individually (as in the current experiments) or be grouped ("batched") into sample pools for pooled testing. Test results from single samples are collected or summarized at the pen level, and the tested pen-level prevalence of AMR is used to inform the selection of *therapeutic* antimicrobials for all calves within that pen that become sick with BRD.

Observation

In single-run configuration, the model opens a graphical representation of the feedlot with colours and patterns that indicate the state of the pen- and calf-level agents. These depictions enable the user to visually confirm that the code results in the intended agent behaviors during the simulation. The model likewise displays dynamic graphs for single runs that update each model day and permit the real-time observation of resistance prevalence for each antimicrobial class, disease and mortality incidence, resistance acquisition incidence by route (i.e., selection or transmission), and chronic sick and hospital pen usage.

Further, detailed model results are output to a Microsoft Excel workbook at the end of the model run. These results include a complete readout of parameter settings for the unique simulation. Feedlot-level summaries of disease incidence and resistance prevalence by antimicrobial class are generated each model day, and

pen-level summaries of the same are generated every model month. If the laboratory testing agent is enabled, the results also include records for every test order and single-sample or pooled-sample test, as appropriate; the result includes the true AMR status of the samples in addition to the result generated by the diagnostic test. A summary of each pen at its market date is recorded and includes case counts for each disease and resistance prevalence by antimicrobial drug. Finally, every chronically sick calf and its ultimate destination (high finishing weight, low finishing weight, or euthanasia) is listed.

For multi-run configurations, including calibration experiments, graphics are not displayed and the detailed file output is suppressed. Instead, a multi-run summary table with a reduced set of outputs is generated in Excel for both the pen and feedlot levels. Depending on the unit of analysis, each row in the summary table represents a single pen or feedlot from one model realization. Summaries of animal growth (e.g., mean arrival and finishing weights), AMU (e.g., counts of regimen applications, total amounts of drugs used), disease and mortality (e.g., counts of first and subsequent instances of disease), and specialty pen use (e.g., calf-days in hospital pen, chronic pen destination) are listed in this file. Additional outputs related to the testing component include the count of single tests performed, the count of tests that were positive for resistance by antimicrobial class, and the count of pens where the number of positive tests met the threshold for treatment change.

Details

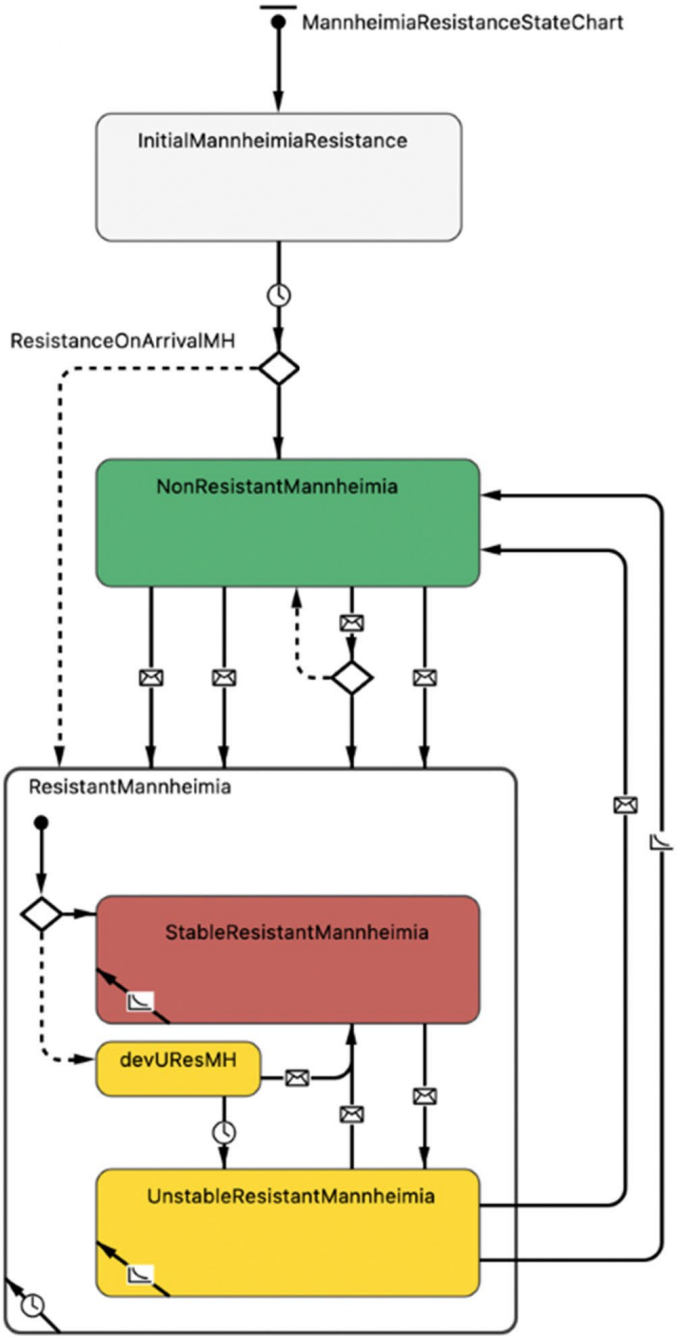
Initialization

The model is initialised as an empty feedlot at the beginning of a one-year cycle. Each production cycle starts on the 1st of October. A single one-year cycle is used for all scenarios examining AMR in *M. haemolytica.* The feedlot size and cattle arrival parameters are described in **Table S1.1**, and the simulation initialization settings are reported in **Table S1.3.**

Input data and parameters

Model inputs relevant to each of the feedlot, pens, cattle, disease, and optional laboratory testing are displayed in **Table S1.1.** Parameter values are informed in part by the peer-reviewed literature, empirical data from private feedlot operations, market analyses, and expert opinion via consultations with feedlot veterinarians. In the absence of a relevant source, inputs deriving from simplifying assumptions are favoured for the calibration experiments (identified as "model parsimony" in **Table S1.1**). The inputs in **Table S1.1** are organized by subheading to better highlight the agent or state chart where the value is used; the condition(s) precipitating the use of particular values are likewise detailed in the table.

Figure S1.6. Representation of AMR status for the population of *M. haemolytica* in the nasopharynx of each calf in the agent-based model. The first branch demarcated by a "diamond" symbol indicates the possibility of two outcomes, where 1) resistance is present on arrival (default, dotted line, to a composite "resistant" state with sub-states) or 2) resistance is not present on arrival (solid line, to a "non-resistant" state) as derived from empirical data. Two of the transition arrows demarcated by "envelope" symbols depend on the receipt of a "selection" or "transmission" message. Other transition arrows demarcated by "envelope" symbols reflect "co-selection", "co-transmission" or "co-waning" messages from linked antimicrobial drugs belonging to the same class or sub-class and undergoing the same transition (see **Figure A8**). Transition arrows with envelopes within the resistant agent reflect messages related to the status of antimicrobial exposure impacting whether resistance within the bacterial population has the potential to wane.



The antimicrobial drugs listed in **Table S1.2** include those available for use in the model and those to which acquired resistance might be of particular interest. Where relevant, the table notes if the drug is used for prophylaxis, metaphylaxis or therapy in the model, applications which are fully detailed in **Figures SA1-SA5**. The AMU options are common in western Canadian feedlot medicine and were developed in consultation with feedlot experts that included the teams which provided the model's morbidity data. A "variation" option in the **Main agent** allows the user to select the default treatment option, or alternatively directs the model to probabilistically select a regimen from a defined list of commonly used protocols. For example, one of two antimicrobial drugs (ceftiofur and enrofloxacin) is randomly selected as the treatment option for first relapses of BRD in high risk calves under 1200 pounds (see **Figure SA3**).

Peer-reviewed or other reliable data are not available to estimate the duration of selective pressure following treatment with an antimicrobial (i.e., the "therapeutic interval" in **Table S1.2**). Elimination half-lives were therefore used to estimate the time required for the drug's activity to be limited by its decreasing concentration [36-45]. Three half-lives (i.e., the time when 88% of the drug is expected to be eliminated from the animal) was used as a crude estimate of the therapeutic interval. For example, the interval used for tulathromycin in the baseline model (8.3 days), corresponds to the midpoint of the plausible values proposed as that drug's duration of effect (DOE) by Brault et al. [52]. These values can be modified on an accessible spreadsheet external to the model to account for alternative hypotheses or updated data as they become available.

Incidence timeseries for first treatment for BRD, arthritis and foot rot (**Figure S1.3**), as well as for mortality due to BRD (**Figure S1.4**), histophilosis and all other causes (**Figure S1.5**), are also loaded from an external file. These are represented as a daily time series for a single 1-year feeding cycle.

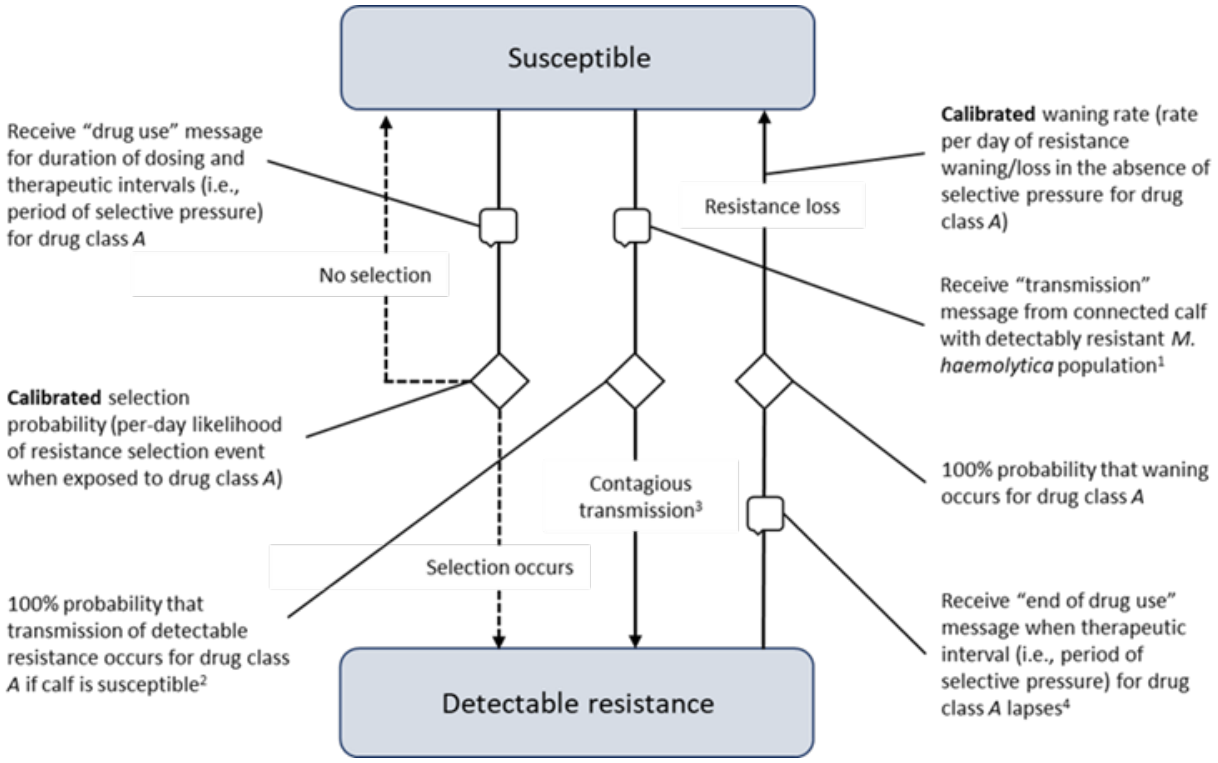
Sub-models

Resistance

The emergent AMR status for the population of *M. haemolytica* in the nasopharynx of each calf is governed at the level of **Resistance agent**; each Resistance agent is associated with one of the 17 antimicrobials represented in the model (**Figure S1.6**). Antimicrobial drugs from the same class (e.g., tetracyclines) or sub-class (e.g., 15-membered ring macrolides) are assumed to be equally vulnerable to the relevant resistance mechanism. The model thus simulates the co-selection, co-waning and co-transmission of detectable resistance for drugs in the same class, with the following exception. In-feed tylosin use (see **Figure SA2**) is assumed *not* to co-select for *M. haemolytica* resistance to injecTable S1.16-membered ring

macrolides in its sub-class, consistent with the finding in Zaheer et al. [46] that subtherapeutic tylosin had no effect on the prevalence of resistant *M. haemolytica.* The probability that the population of *M. haemolytica* in each calf has detectable resistance to each antimicrobial class at feedlot arrival is derived from empirical data in the published literature [7-13].

Figure S1.7. Processes underlying the acquisition and waning of phenotypic resistance for the sentinel nasopharyngeal organisms unique to each calf. Transitions demarcated by "speech bubble" symbols are triggered by the receipt of a message from another agent in the model (i.e., the calf's home pen or a connected calf in the same pen).



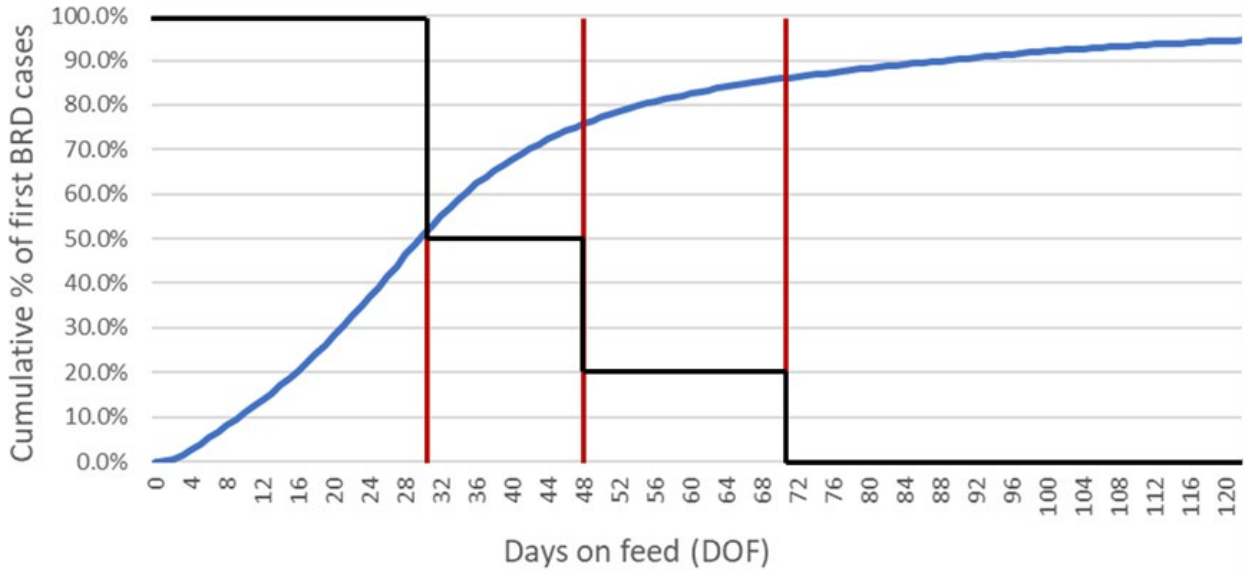
[1]Transmission messages are sent from animals with detectable resistance to a randomly selected pen-mate at the calibrated contact rate, and the baseline contact rate is adjusted by the calibrated stress multiplier. There is a 48-hour delay before on-arrival resistance can be transmitted to pen-mates to establish the appropriate population-level resistance at simulation start.
[2]When a transmission message is received by a calf with a susceptible M. haemolytica population, the contact is always "effective" (i.e., results in contagious transmission).
[3]There is a 48-hour delay before contagiously acquired resistance can wane and/or be transmitted to pen-mates, to permit the resistant population to become established in the affected animal.
[4]Resistance acquired selectively or contagiously cannot wane if the animal is being actively exposed to (i.e., within the therapeutic interval of) the drug class of relevance; further, there is a 48-hour delay before on-arrival resistance can wane to establish the appropriate population-level resistance at simulation start.

M. haemolytica populations within calves acquire detectable resistance at the calibrated "selection probability", the per-day likelihood of developing a resistant phenotype in response to antimicrobial drug exposure (**Figure S1.7**). The selection probability is active during therapy (i.e., the dosing period) and for the period of selective pressure following the final -- and often only -- dose (i.e., the therapeutic interval, see **Table S1.2**). During active exposure to the relevant drug, resistant *M. haemolytica* is considered "stable" and cannot wane. After the therapeutic interval has elapsed and in the absence of selective pressure for a particular antimicrobial, the population of *M. haemolytica* can lose its detectable resistance at the calibrated "waning rate" (i.e., is "unstably" resistant). Resistance present on arrival is assumed to be temporarily stable in a 48-hour "delay" state, such that it cannot transmit or wane *even in the absence of* selective AMU pressure. This lag is included to establish expected probabilities of population-level resistance during the period the pen is filling.

In addition to selection, a local population of *M. haemolytica* can acquire detectable resistance at the calibrated "contact rate" by way of contagious spread from a connected calf in a shared pen (see **Figure S1.7**). The calibrated contact rate parameter is the rate per day that an animal with detectable resistance sends a "transmission" message to a randomly selected pen-mate. When the message is received by a calf with a susceptible *M. haemolytica* population, it is assumed to be an effective (i.e., transmitting) contact. This simplifying strategy was chosen to minimize the number of messages associated with transmission and the associated computational burden. As with on-arrival resistance, detectable resistance acquired contagiously (i.e., via transmission) is subject to a 48-hour lag before it can 1) wane at the calibrated rate, given the absence of selective pressure for the relevant drug; or 2) transmit at the calibrated contact rate to unaffected pen-mates. This lag is included to permit the resistant population to establish and facilitate the estimation of calibrated parameters. Similar lags between initial colonization, bacterial reproduction, and successful transmission would be expected in a true biological infection.

The potential for transmission over the feeding period is mediated by a calibrated "stress multiplier", a dynamic parameter responsive to the temporal distribution of BRD events at the population level. The per-day contact rate is adjusted to reflect the increased likelihood of contagious transmission when animals are physiologically stressed and shedding higher numbers of respiratory pathogens [53]. The multiplier's effect is governed by a step function derived from cumulative incidence data (see **Figure S1.8**) and the cluster analysis in Babcock et al. [54]. The combined impact of the calibrated stress multiplier and step function can vary from zero (i.e., no incremental effect on the per-day contact rate) to some positive increment corresponding to the product of the stress multiplier and DOF-determined step function value, added to the per-day contact rate.

Figure S1.8. Cumulative incidence of first-case BRD diagnoses in high-risk calves through 120 DOF. The epidemiological curve (blue) is derived from empirical data provided by a large, private veterinary practice in western Canada. These data represent approximately 590,000 fall-placed animals over 5 years (2012-2016). A step function (black) is superimposed over the cumulative incidence curve; the red vertical lines delimit where unique regions of the curve (i.e., distinct periods of physiological stress/pathogen shedding) correspond to DOF[1]. The stress effect multiplier adjusts the baseline contact rate to account for changing transmission potential over the feeding period as determined by the step function (e.g., after 70 DOF when the step function reduces to zero, the multiplier has no impact on the baseline contact rate)[2].



[1]By 30 DOF, 50% of the high-risk animals who will get sick have a first case of BRD; by 48 DOF, 75% will have a first case of BRD; by 70 DOF, 85% will have a first case of BRD.

[2]The impact of the calibrated stress multiplier on the contact rate in the **baseline** scenario is reduced by half (from 10 to 5) between 30 and 48 DOF, reduced to 2 between 48 and 70 DOF, and reduced to 0 after 70 DOF.

Treatment

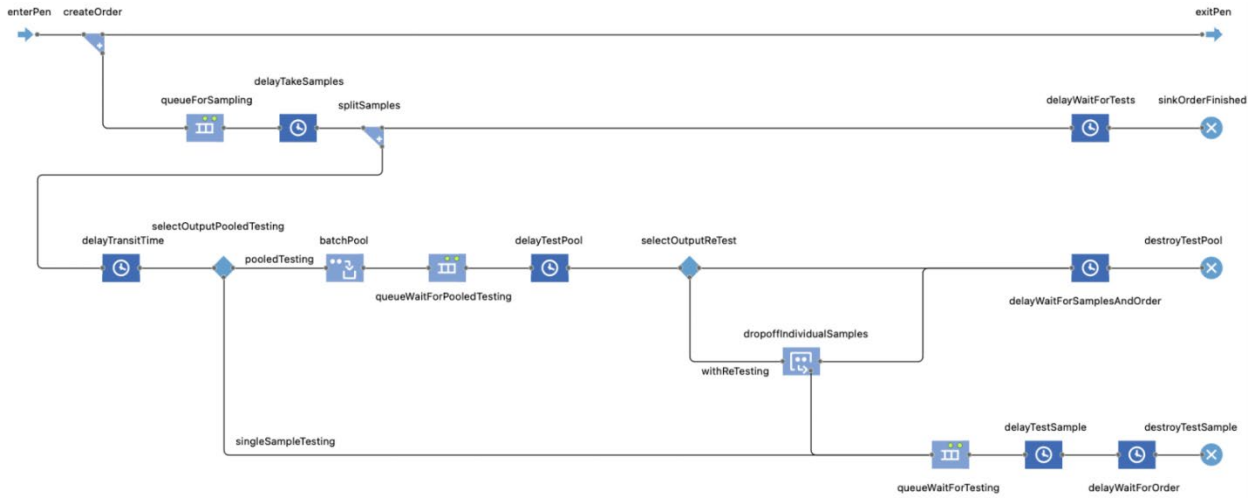
Each **Treatment agent** governs the delivery of the appropriate AMU protocol to an individual animal (**Figure SA7**). For all metaphylactic and most therapeutic indications, the antimicrobial is administered in a single injectable dose. For all prophylactic (i.e., in-feed) indications and treatments for arthritis, the antimicrobial is administered in a multi-day regimen (**Figures SA2, SA4**). During therapy (i.e., the "dosing period") and the subsequent therapeutic interval (see **Table S1.2**), the selection probability is active and can lead to detectable resistance in the population of *M. haemolytica* for the treated animal. After the therapeutic interval has elapsed following a final dose in a regimen, an "end treatment" message is sent to the resistance agent for the treated calf. The message triggers the transition from "stable" to "unstable" resistance (see **Resistance agent**), such that detectable resistance is eligible to wane. Some AMU regimens

(e.g., the pulse application of chlortetracycline in feed) are represented by multiple treatment agents. Treatment agents are deleted after the withdrawal period [35] for the associated antimicrobial has expired for that animal (**Table S1.2**).

Testing

In this study, a **Testing agent** was added to the model's infrastructure to facilitate the comparison of different pen sampling strategies and AMR diagnostic tools. The agent contains a DES workflow [48-49] that governs the sampling and testing process (**Figure S1.9**). As part of this process, a Pen agent symbolically enters the system and has a "test order" created for it; the order dictates that a specified number (n = 20) of randomly selected animals in the home pen (see **Table S1.1**) be sampled and tested to determine the pen's AMR status. The time at sampling and number of samples can be varied as desired through modifiable parameters. The DES workflow likewise allows the user to incorporate and vary time delays for sample collection, sample transit, and sample processing as required [11-12, 26-27] (**Table S1.1**). It is assumed that the time required to ship and process the nasopharyngeal samples delays the availability of test results with which to make informed treatment decisions [55-56]. Before the test is performed and/or before the results are available from the diagnostic laboratory, the alternative treatment options are not used by the model. Instead, treatment for BRD fails at a probability equivalent to the real-time pen-level prevalence of AMR as described in the Cattle agent section.

Figure S1.9. Discrete event simulation (DES) component of the hybrid agent-based model, detailing the process[1] of sampling and diagnostic AMR testing of samples from calves in home pens.



[1]A Pen agent enters the system and has a "test order" created for it; the default setting dictates that 20 randomly selected animals in the "home pen" be sampled and tested to determine the pen's AMR status. The workflow follows the samples through the event-driven testing process, which incorporates modifiable time delays for collection, transit and processing. The time required to ship and process the nasopharyngeal samples delays the availability of test results with which to make informed treatment decisions.

The Testing agent also contains information on diagnostic test performance (i.e., test sensitivity and test specificity). Results from a theoretically "perfect" test would report the true prevalence of AMR in the *M. haemolytica* population at the time of sampling; the information from tests with imperfect sensitivity and specificity may be impacted by false positive and false negative results. The threshold at which the tested pen-level prevalence of resistance to the first-line drug triggers a change to that pen's treatment protocol is set to 25% (i.e., 5 positive tests of 20 tested animals) by default (**Table S1.1**). The default "treatment change" threshold was intentionally selected to marginally exceed that probability of all-cause treatment failure in the baseline model, and reflects the suggestion of Lubbers and Turnidge in [28]. The ability to modify the relevant threshold is available for future experiments. When the pen-level prevalence of resistance to the default (i.e., first-line) drug meets the prescribed threshold at the time of sample, the calves in that pen that develop a first or subsequent case of BRD will be directed to receive a pre-specified alternative option at the time of treatment.

Samples are tested individually by default, but the option exists to pool samples before testing. If pooled testing is enabled, tests are grouped ("batched") according to the pool size, which is specified in a parameter. The tested prevalence of resistance in this scenario is impacted by the sensitivity and specificity of the test for pooled samples. If the pool tests negative, the results are reported; if the pool tests positive, the option exists to test each sample from that pool individually. Test results are reported to the Pen agent, which retains them for summary output; if the "testing-informed treatment" setting is enabled, the test information is used to inform BRD treatment decisions for animals in that pen.

Model calibration

Calibration refers to the systematic estimation of static input values that minimize the dissimilarity between the model's emergent behaviour (i.e., the time-varying prevalence of AMR across the feeding period) and the observed or empirical data that serve as calibration "targets" [57]. Automated calibration experiments using the widely implemented OptQuest global optimization routine were created in the commercial software program [58-60]. Key parameters linked to the emergence and inter-animal spread of resistance on feedlots (i.e., resistance selection probabilities, resistance waning rates, baseline contact rates, and stress multipliers) were unknown values that were expected to differ by drug class (see **Figure S1.7**). The unknown parameters were estimated in [1] for distinct configurations of the baseline model by calibrating the model to previously reported resistance data for each antimicrobial class.

The automated procedure used in this instance offered substantial advantages over manual calibration exercises in its optimization algorithms and capacity to manage stochastics and uncertainty in other model inputs. While the authors of this model [61-65] and others [66-69] have contributed sophisticated computational statistics and machine learning techniques that excel in supporting automated parameter estimation via sampling in higher dimensional parameter spaces, the results in [1] are well supported by the optimization-based approach used in that work.

Reference data set

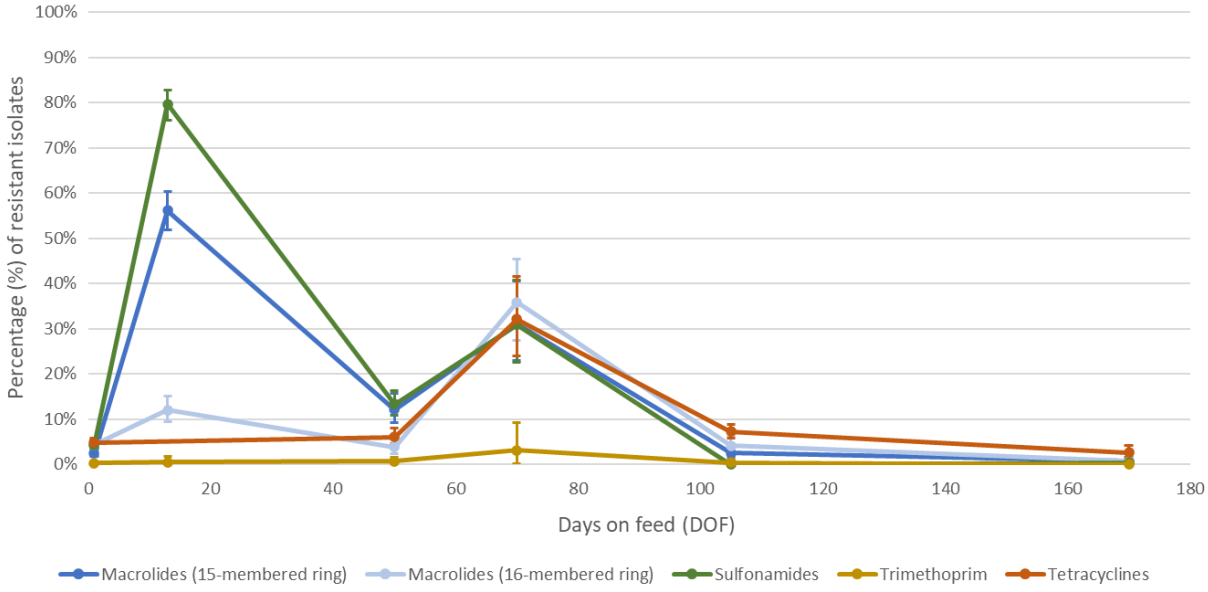
A rapid search of the literature was performed to identify relevant sources of resistance prevalence data for *M. haemolytica* isolates from healthy feedlot calves at various points across the feeding period. Studies concerning samples from primarily sick or dead cattle were excluded, given that these animals were more likely to have been treated with multiple classes or courses of antimicrobials and were not representative of the general feedlot population. Raw data from pertinent studies of western Canadian feedlot cattle [7-13] were extracted to a spreadsheet in MS Excel, and included the average DOF at time of sample, the total number of tested isolates, and the percentage of phenotypically resistant isolates for each antimicrobial of interest.

Data points clustered closely in time were grouped together into DOF ranges that best defined the unique phases of the feeding period. Prevalence data from isolates collected at feedlot arrival were classified as occurring at 1 DOF; the DOF for subsequent time points were selected to 1) coincide with a historical reference dataset [9] and DOF relevant to management events in the feeding period; *or* 2) reflect the midpoint of the DOF range in the reported data. The authors in [9] supplied additional data and details to permit the calculation of resistance prevalence for specific DOF (P. Morley, personal communication, 2018).

A custom longitudinal dataset with updated phenotypic resistance prevalence values was synthesized from the extracted data from all sources for *M. haemolytica* (see **Figure S1.10**). Because antimicrobial drugs from the same class or sub-class were assumed to be equally vulnerable to the relevant resistance mechanism (see the drug linkage matrix in **Figure SA8**)), the drug with the most complete data set (i.e., one or more data points for each time point) was selected to represent all others in its class. Prevalence and exact 95% confidence intervals were estimated using an intercept-only (or null) generalized estimating equations model in SAS version 9.4 with a binary outcome, binomial distribution and logit link function for each antimicrobial class of interest at each time point (1, 13, 50, 70, 105 and 170 DOF), accounting for clustering by study with a repeated term and exchangeable covariance structure. If the model did not converge, exact confidence intervals were determined using the Clopper-Pearson estimation method. The

percentage of resistant isolates at each time point was therefore an average of the raw data values available for that range, weighted by the total number of isolates tested. A prevalence estimate was unavailable for the tetracycline class at 13 DOF; in-feed chlortetracycline was not provided to the animals in the only study with data from that time point [12], and the level of detectable tetracycline resistance (<1%) was an outlier among comparable studies.

Figure S1.10. Percentage of *Mannheimia haemolytica* isolates with detectable phenotypic resistance to select antimicrobial classes[1] over the feeding period. The custom longitudinal dataset was synthesized from recent empirical studies of antimicrobial resistance prevalence in western Canadian feedlot cattle from mixed origins[2] and used as external targets against which to calibrate the model.



[1]Antimicrobial classes were selected for calibration if the prevalence of detectable resistance was >1% at any time point **and** the class was relevant for antimicrobial use in feedlot medicine [70]. Each class was represented by AMR to one drug (see **Table S1.4**) with the most complete reference data set.
[2]Percentage of resistant isolates at each time point is a weighted average of prevalence values extracted from recent studies of healthy feedlot cattle in western Canada [7-13].

Table S1.3. Simulation parameters used to perform individual calibration experiments for each of the selected antimicrobial class and configuration combinations.

	Value for model calibrations	Possible alternative settings	Implication
Initialization parameters			
Number of pens in feedlot	30	User selection	Modifiable setting based on feedlot size or desired balance of population size and computational efficiency
Number of animals per pen	200	User selection	Modifiable setting based on pen size or desired balance of pen density and computational efficiency
Proportion of high-risk animals in simulation	100%	0-100%	Modifiable setting based on risk level of incoming animals
Proportion of steers in simulation	100%	0-100%	Modifiable setting based on sex of incoming animals
Default metaphylactic drug selection	Tulathromycin (i.e., Draxxin)	Probability table, **see Figure SA1**	Probability of metaphylactic drug selection can be fixed or vary by BRD risk level per empirical data
Simulation parameters			
Number of iterations (i.e., model runs with unique combinations of target parameters)	2500	User selection	Modifiable setting based on desired balance of adequate exploration of parameter space (i.e., methodological rigour) and computational efficiency
Number of realizations per iteration (i.e., model runs with identical combinations of target parameters but different "random seeds")	30	1	Modifiable setting based on desired balance of adequate exploration of stochastic variation within parameter set and computational efficiency
Optimization (objective) **criterion**	Minimize	Not applicable	The calibrated parameters are optimized (i.e., the best fit is achieved) when the objective function returns its smallest non-negative value
Optimization (objective) **function**	Compound function comprised of two components: 1) **curve fitness**, which quantifies the difference between linear datasets; and 2) **point fitness**, which quantifies the weighted difference between particular points in the datasets (1, 13, 70 and 170 DOF)	Not applicable	Function is the sum of the 1) average absolute difference between simulated and empirical datasets; and 2) the exponentiated absolute difference between specific reference points with stronger empirical data. The point fitness weighting scheme can be modified to reflect variable user confidence in the empirical data points.

Antimicrobial classes were selected for the calibration experiments if 1) the prevalence of detectable resistance was >1% at any of the time points, *and* 2) the class was relevant to products used for feedlot medicine (e.g., tetracyclines) [70]. The 1% threshold was used to distinguish antimicrobial classes where the change in detectable resistance over time was sufficient to model an association with AMU or contagious transmission. The 15- and 16-membered ring macrolides were treated as distinct/independent sub-classes given that their reference data sets were sufficiently dissimilar. Resistance breakpoints approved by the Clinical & Laboratory Standards Institute do not exist for two of the representative drugs selected for calibration, trimethoprim and sulfadimethoxine [71]; "resistance" as defined for these drugs refers to the percentage of isolates that grow at (i.e., are not inhibited by or are not susceptible to) the only tested concentrations (2 µg/mL and 256µg/ml, respectively) on the commercially available Bovine BOPO7F AST plate (ThermoFisher Scientific™). Based on their detectable prevalence in the reference data (>1%) (**Figure S1.10**), the antimicrobial classes chosen for the initial calibration experiments were macrolides (15- and 16-membered ring), sulfonamides, trimethoprim and tetracyclines.

Configurations and settings

Three model variants with unique structural configurations were each calibrated to the reference data for *M. haemolytica* and subsequently compared. In the first "antimicrobial use only" configuration, the potential for transmission between animals was disabled and could not affect the spread of detectable resistance; selection pressure from AMU was therefore the only driver for AMR in this scenario. The selection probability and waning rate parameters were varied in this configuration to find the best fit to the reference data.

In the second "transmission only" configuration, the potential for selection due to AMU was disabled and could not affect the emergence of detectable resistance; contagious transmission was therefore the only driver for AMR in this scenario. The waning rate, contact rate and stress effect multiplier parameters were varied in this configuration to find the best fit.

In the final "both antimicrobial use and transmission" configuration, both drivers were enabled and could jointly affect the emergence of detectable resistance. All of the selection probability, waning rate, contact rate and stress effect multiplier parameters were varied in this configuration to find the best fit.

The initialization and simulation settings for each calibration are detailed in **Table S1.3.** Automated calibration experiments using OptQuest's optimization tool were run in AnyLogic® 8 for n=2500 iterations (model runs with unique combinations of target parameters) with n=30 replications (model runs that explore the extent of stochastic variation within each parameter set) per iteration. The number of iterations and

replications per iteration were selected to balance the competing priorities of methodological rigour (i.e., adequate assessment of stochastic variation for a specific vector of parameters) and computational efficiency to allow adequate exploration of the parameter space.

Objective function

Each calibration experiment (n=15 initial combinations of 5 antimicrobial classes by 3 configurations) searched the parameter space defined by the minimum and maximum values in **Table S1.4** for the set of inputs that best reproduced the reference data. The best fit was achieved when the average of the objective functions across the realizations within an iteration returned its lowest non-negative value (i.e., when the difference between the simulated and empirical data was minimized by the optimizer). The compound objective function employed in this calibration was comprised of two components: 1) the curve fitness component, and 2) the point fitness component, which assigns greater weight or importance to reference points with stronger empirical data.

The components are summed as follows to calculate the objective value:

root.getCurveFitness() + root.getPointPrevelanceFitness(**1.0**, 1.0) +
root.getPointPrevelanceFitness(**13.0**, 1.0) + root.getPointPrevelanceFitness(**70.0**, 1.0) +
root.getPointPrevelanceFitness(**170.0**, 1.0)

The curve fitness component applies the difference function in AnyLogic, which returns the square root of the average of the square of difference between linearly interpolated data sets, *R* (reference/empirical) and *M* (model/simulated). The point fitness component returns $\mathbf{e}^{(|r-m|*w)}$ comparing two points in the *R* and *M* datasets (values *r* and *m,* respectively) with weight *w.* The resulting fit at day 1, 13 (if available), 70 and 170 DOF is assigned additional weight ($w = 1.0$) relative to 50 or 105 DOF given the recency and relevance of the data informing reference estimates for those time points.

Table S1.4. Best objective and calibrated parameter values from individual calibration experiments for each of the antimicrobial class and configuration combinations.

Antimicrobial class	Reference drug belonging to class[1]	Configuration	Best objective value[2]	Selection probability, if applicable (Mean probability per day)	Waning rate (Mean rate per day)	Contact rate, if applicable (Mean rate per day)	Stress effect multiplier, if applicable (Unitless)
15-membered ring macrolides	Tulathromycin	Drug use only	0.213	0.593	0.008	--	--
		Transmission only	**0.157**	**--**	**0.173**	**0.130**	**0.438**
		Both drug use/ transmission	0.186	0.625	1.118	1.163	0.119
16-membered ring macrolides	Tilmicosin	Drug use only	0.592	0.763	0.001	--	--
		Transmission only	0.391	--	1.449	1.600	0.026
		Both drug use/ transmission	**0.382**	**1.000**	**0.825**	**0.915**	**0.026**
Sulfonamides	Sulfadimethoxine	Drug use only	1.725	0.955	0.001	--	--
		Transmission only	0.154	--	2.113	1.299	0.685
		Both drug use/ transmission	**0.153**	**0.452**	**3.393**	**1.982**	**0.741**
Trimethoprim	Trimethoprim	Drug use only	0.039	1	0.013	--	--
		Transmission only	0.018	--	0.035	0.004	3.150
		Both drug use/ transmission	**0.017**	**0.829**	**0.058**	**0.026**	**0.459**
Tetracyclines	Oxytetracycline	Drug use only	0.337	0.134	0.005	--	--
		Transmission only	**0.291**	**--**	**0.011**	**0.005**	**0.623**
		Both drug use/ transmission	0.299	0.011	0.007	0.002	0.940
Cephalosporins	Ceftiofur	Both drug use/ transmission	0.001	0.001	2.763	0.379	0.667
Fluoroquinolones	Enrofloxacin	Both drug use/ transmission	0.002	0.025	0.610	0.001	0.046
Phenicols	Florfenicol	Both drug use/ transmission	0.007	0.002	0.014	0.001	3.038
Fixed minimum value for the calibration search function				0.001	0.001/day	0.001/day	0
Fixed maximum value for the calibration search function				1	5/day	2/day	10

[1]The antimicrobial drug with the most complete dataset (i.e., one or more raw data points for each time point) was selected to represent the entire class.
[2]The best (i.e., smallest) objective value was an average of the objective values from each realization (n=30) in the best iteration.

Model output and evaluation

The objective value for each iteration is an average of the objective values from each realization in the iteration (n=30). The calibrated parameters associated with the best iteration (i.e., the iteration with the smallest objective value) for each configuration/drug class combination are reported in **Table S1.4.** A systematic comparison of model "fit" for different configurations was critical for examining our hypotheses about how detectable resistance emerges and spreads in the feedlot environment. The relative fits of candidate configurations (antimicrobial use only *vs.* transmission only *vs.* both antimicrobial use and transmission) for each antimicrobial class were evaluated by dividing the absolute differences between the objective values for each pair by the average for each pair. Percentage differences in excess of 20% indicated a substantial difference in model fit per the assessment criteria [72]; a cutoff of 20% is frequently used as the change-in-estimate criterion for identifying confounders in epidemiological studies and was adopted here. The results are reported in a difference matrix in **Table S1.5**.

For each of the antimicrobial classes, the "transmission only" and "both" configurations offer a substantially better fit to the empirical data than the "antimicrobial use only" variation. The percentage differences >20% in almost every case, with few exceptions; differences for "both" *vs.* "drug use only" for 15-membered ring macrolides and for "both" and "transmission only" *vs.* "drug use only" for tetracyclines do not reach the 20% threshold. The differences between best objective values for the "transmission only" and "both" configurations were less than substantial (<20%) for all classes.

Based on these findings, single calibration experiments for the "both" configuration were performed to estimate unknown parameters for antimicrobial classes with prevalences of resistance that did not exceed 1% in the empirical data (**Figure SA9**), but are nevertheless important in feedlot medicine and specified as treatment options in the model [70]. Parameters for cephalosporins (ceftiofur), (enrofloxacin), and phenicols (florfenicol) are reported in **Table S1.4**.

Table S1.5. Pairwise comparisons of best objective values from candidate scenarios for each antimicrobial class. The absolute difference between two objective values is divided by the average of those values to compare the ability of candidate scenarios to reproduce the reference data. Percentage differences exceeding 20% (shaded blue) indicate a substantial difference in model fit.

Antimicrobial class		15-membered ring macrolides			16-membered ring macrolides			Sulfonamides			Trimethoprim			Tetracyclines		
	Scenario	Drug use	Transmission	Both	Drug use	Transmission	Both	Drug use	Transmission	Both	Drug use	Transmission	Both	Drug use	Transmission	Both
15-membered ring macrolides	Drug use		**30.3%**	13.5%												
	Transmission	**-30.3%**		-16.9%												
	Both	-13.5%	16.9%													
16-membered ring macrolides	Drug use					**40.9%**	**43.1%**									
	Transmission				**-40.9%**		2.3%									
	Both				**-43.1%**	-2.3%										
Sulfonamides	Drug use								**167%**	**167%**						
	Transmission							**-167%**		0.6%						
	Both							**-167%**	-0.6%							
Trimethoprim	Drug use											**72.4%**	**78.6%**			
	Transmission										**-72.4%**		5.6%			
	Both										**-78.6%**	-5.6%				
Tetracyclines	Drug use														14.6%	11.9%
	Transmission													-14.6%		-2.7%
	Both													-11.9%	2.7%	

Testing-informed treatment scenarios

The laboratory testing sub-model (**Figure S1.9**) was enabled in the series of experiments explored in this work. This sub-model operates in two modes: 1) the test-only (TO) control mode, where no treatment changes are made based on test results; and 2) the testing-informed treatment (TI) mode, where testing information is used to inform the choice of antimicrobial treatment for BRD in sick calves. In the TI intervention experiments, calves that develop a first or subsequent case of BRD are directed to receive a pre-specified alternative option at the time of treatment *if* the pen-level prevalence of resistance to the default (i.e., first-line) drug meets the prescribed "treatment change" threshold at the time of sample. Because testing for AMR was not a standard part of cattle management in the historical data used to calibrate the model, the testing sub-model was **not** enabled for the construction of the model in [1].

Table S1.6. Fixed treatment protocols for non-BRD prophylactic and therapeutic indications in this series of experiments. Protocols were selected probabilistically from the options detailed in **Figures SA2-SA4** and held constant across the experiments in this study.

Antimicrobial use type	Indication	Condition, if applicable	Case description	Default antimicrobial selection(s)	Regimen
Prophylaxis (in-feed at *pen* level)	Histophilosis	--	--	Chlortetracycline	2 x 5-day courses of high-dose CTC[1] (18-23 DOF, 25-30 DOF)
	Liver abscesses	--	--	Chlortetracycline Tylosin	Low-dose CTC starts at 42 DOF; switch to TYL[2] 28 days before end of feeding period
	Foot rot	Detected in 10% of animals in same pen (cumulative)	--	Chlortetracycline	7-day course of high-dose CTC
Treatment (injectable at *calf* level)	Arthritis	Lightweight at time of detection (<1000 lbs)	First case/pull	Oxytetracycline	3 doses (single dose every 3 days)
			First relapse (second case/pull)	Trimethoprim-sulfadoxine	5 doses (single dose per day x 5 days)
			Second relapse (third case/pull)	Ceftiofur CFA[3]	2 doses (single dose every 4 days)
		Heavyweight at time of detection (>1000 lbs); **and** selected for treatment (50%)	First or subsequent case/pull	Ceftiofur HCl[3]	Single dose
	Foot rot	Lightweight at time of detection (<1200 lbs)	First or subsequent case/pull	Penicillin G	Single dose
		Heavyweight at time of detection (>1200 lbs)	First or subsequent case/pull	Ceftiofur HCl	Single dose

[1]CTC is the abbreviation for chlortetracycline.
[2]TYL is the abbreviation for tylosin.
[3]Ceftiofur is not expected to be effective against uncomplicated *Mycoplasma bovis*-associated arthritis [73]. However, arthritis diagnosed late in the feeding period in fall-placed calves can be confounded by other infectious agents, and some cases are likely sequelae of chronic and unresponsive foot rot.

Treatment protocols

For the purposes of these experiments, the AMU protocol for each indication was held constant across experiments (i.e., the parameter permitting variation in AMU protocols across unique runs in a single experiment was disabled). This choice ensured that relative changes in the median values for outputs of interest (e.g., number of antimicrobial uses by class) could be attributed to the experimental conditions rather than stochastic variation across iterations. The metaphylaxis and first line options for first and subsequent cases of BRD in the baseline treatment protocol scenarios were developed by experts and are reported in **Figure SA10a** (TO controls); the alternative options reported in **Figure SA10b** (TI experiments) were licensed antimicrobials purposively selected to better distinguish between the impacts of the intervention on successive BRD treatments in the simulated data.

In a different subset of experiments, the baseline BRD treatment protocol was replaced with a theoretical "extreme 15-membered ring macrolide use" protocol to create scenarios with very high selection pressure for AMR. Tulathromycin was used for metaphylaxis and first-line therapy for all BRD cases in the extreme protocol (**Figure SA11a**); for ease of comparison, the alternative options (**Figure SA11b**) remained the same as in the baseline protocol. The fixed treatment protocols used in these experiments for non-BRD prophylactic and therapeutic indications are reported in **Table S1.6**.

AMR in *M. haemolytica* at feedlot arrival

The probabilities of phenotypic resistance to each antimicrobial class in *M. haemolytica* isolates at feedlot arrival are summarized in **Table S1.7**. In the experiments with baseline on-arrival resistance, the estimated probabilities were equal to the values used in the calibration experiments in [1]. The probabilities of incoming resistance were increased in a subset of "worst-case" scenario experiments designed to simulate higher levels of AMR to the first-line therapeutic options. In the "high on-arrival resistance" experiments, the values were set to the upper confidence intervals of the population-averaged prevalence estimates for *M. haemolytica* isolates (n = 70) from calves sampled in 2022 as part of the Canadian Feedlot Antimicrobial Use and Antimicrobial Resistance Surveillance Program (CFAASP) [74].

Diagnostic paradigms for AMR

There were two AMR diagnostic paradigms explored in this study. The "phenotypic" approach concerns the susceptibility of the sentinel pathogen to a particular antimicrobial class as determined by culture-dependent antimicrobial susceptibility testing (AST) [20]. The "genotypic" approach concerns the presence or absence of a particular antimicrobial resistance gene (ARG) in the sentinel pathogen as determined by long-read metagenomic sequencing (MS) [27]. The model was calibrated to the time-varying proportion of resistant *M. haemolytica* isolates across the feeding period in [1] (**Figure S1.10**); given the lack of published data, a similar longitudinal dataset could not be generated for the proportion of *M. haemolytica* isolates

with known ARGs. The calibrated AMR selection, waning and transmission parameters from [1] were therefore assumed to be reasonable proxies for the acquisition and loss of genes that confer resistance to the associated antimicrobial class in this work. It follows that for the purposes of this study, we made the conservative assumption that the pathogen's resistance genotype and phenotype were perfectly concordant (i.e., the presence of a known ARG always confers clinical resistance to the associated antimicrobial class).

Diagnostic test accuracy

The diagnostic test parameters (i.e., empirical estimates for test sensitivity and specificity) for both AST and MS are reported in **Table S1.8.** Within the phenotypic paradigm, the test parameters define the ability of AST to detect phenotypic resistance to targeted antimicrobial classes (macrolides, tetracyclines) in *M. haemolytica* isolates from nasopharyngeal samples. Within the genotypic paradigm, the test parameters define the ability of MS to detect the presence representative ARGs (*msrE-mphE*, *estT*, *tetH*) in *M. haemolytica* reads from nasopharyngeal samples. The low, median, and high estimates for sensitivity and specificity in **Table S1.8** were obtained from latent class analyses (LCA) of field data from over 900 feedlot calves sampled at least three times as part of a multi-year research project [75]. Specifically, the estimates were derived from two-test, three- or five-population Bayesian latent class models (BLCMs) in the absence of a "gold standard" [76] for detecting resistant *M. haemolytica* from deep nasopharyngeal swabs of feedlot cattle.

Table S1.7. Values used in the experiments for the on-arrival prevalence of resistance to select antimicrobial drugs in *Mannheimia haemolytica* isolates in the (a) baseline and (b) high on-arrival AMR scenarios.

		Probability of resistance at arrival (CI)	
Antimicrobial class	**Reference drug[1]**	**Baseline scenarios[2]**	**High (worst-case) scenarios[3]**
Cephalosporins	Ceftiofur	0% (0%, 100%)	5.1% (0%, 5.1%)
Fluoroquinolones	Enrofloxacin	0.4% (0.2%, 0.9%)	5.1% (0.2%, 5.1%)
15-membered ring macrolides	Tulathromycin	2.4% (1.8%, 3.3%)	9.3% (1.8%, 9.3%)
16-membered ring macrolides	Tilmicosin	4.3% (3.4%, 5.4%)	5.1% (3.4%, 5.1%)
Potentiated sulfonamides	Trimethoprim	0.3% (0.1%, 0.6%)	5.1% (0.1%, 5.1%)
	Sulfadimethoxine	4.3% (3.5%, 5.3%)	74.8% (3.5%, 74.8%)
Phenicols	Florfenicol	0.1% (0.03%, 0.5%)	5.1% (0.03%, 5.1%)
Tetracyclines	Oxytetracycline	4.9% (4.1%, 5.7%)	9.3% (4.1%, 9.3%)

[1]The antimicrobial drug with the most complete dataset (i.e., one or more raw data points for each time point) was selected to represent all others in its class in the calibration experiments in [1].
[2]In the experiments with **baseline on-arrival resistance,** the estimated probability of phenotypic resistance to each antimicrobial at arrival was equal to the values used in the calibration and Monte Carlo experiments in [1].
[3]In the experiments with **high (worst-case) on-arrival resistance,** the probability of phenotypic resistance to each antimicrobial at arrival was equal to the *upper confidence interval* of the estimated prevalence for feedlot calves sampled in 2022 as part of CFAASP [74, 77].

Table S1.8. Diagnostic test sensitivity and specificity values used in the experiments for (a) the detection of phenotypic resistance to select antimicrobial drugs and (b) the detection of select antimicrobial resistance genes in *Mannheimia haemolytica* isolates from nasopharyngeal samples.

			Diagnostic test characteristics					
			Sensitivity estimate (%)			Specificity estimate (%)		
Antimicrobial class	**Diagnostic test type**	**Reference drug[1] or gene[2]**	**Low**	**Median**	**High**	**Low**	**Median**	**High**
Classes with BLCM-derived estimates[3]								
15-membered ring macrolides	*AST*	Tulathromycin	73%	80%	86%	99%	100%	100%
	Metagenomics	*msrE-mphE*	56%	62%	69%	96%	98%	99%
16-membered ring macrolides	*AST*	Tilmicosin	10%	23%	38%	99%	100%	100%
	Metagenomics	*estT*	22%	43%	65%	98%	99%	100%
Sulfonamides	*AST*	Sulfadimethoxine	83%	90%	98%	98%	99%	100%
	Metagenomics	*sul2*	57%	63%	69%	90%	92%	95%
Tetracyclines	*AST*	Oxytetracycline	11%	18%	25%	99%	100%	100%
	Metagenomics	*tetH*	66%	82%	95%	94%	97%	99%
Classes without BLCM-derived estimates[4]								
Diaminopyrimidines	*AST*	Trimethoprim	10%	18%	25%	98%	99%	100%
	Metagenomics	*dfrA14*	22%	43%	65%	90%	92%	95%
Cephalosporins	*AST*	Ceftiofur	10%	18%	25%	98%	99%	100%
	Metagenomics	*blaROB-2*	22%	43%	65%	90%	92%	95%
Fluoroquinolones	*AST*	Enrofloxacin	10%	18%	25%	98%	99%	100%
	Metagenomics	*gyrA mutation*	22%	43%	65%	90%	92%	95%
Phenicols	*AST*	Florfenicol	10%	18%	25%	98%	99%	100%
	Metagenomics	*floR*	22%	43%	65%	90%	92%	95%

[1]The antimicrobial drug with the most complete dataset (i.e., one or more raw data points for each time point) was selected to represent all others in its class in the calibration experiments in [1].
[2]The antimicrobial resistance gene detected most frequently by metagenomic sequencing in [27, 78-79] and known to confer resistance to the reference drug was selected for Bayesian latent class analysis in [75] and/or these Monte Carlo experiments.
[3]Bayesian latent-class model (BLCM)-derived estimates for sensitivity and specificity were available for select reference drugs and resistance genes only [75]. The low and high estimates for each test characteristic are equal to the lower and upper limits of the 95% credible interval for the estimate, respectively.
[4]Bayesian latent-class model (BLCM)-derived estimates for sensitivity and specificity were not available for select reference drugs and resistance genes with low prevalences of phenotypic and/or genotypic resistance in [75]; for these classes, the low, median, and high values for sensitivity and specificity were conservatively set to equal that of the reference drug (for AST) or gene (for metagenomic sequencing) with the **lowest** BLCM-derived estimate.

Time of sample

The experiments reported here involve one of two sampling time points selected for distinct reasons, including 1) the ease and feasibility of sampling (i.e., at the time of animal processing on feedlot arrival, referred to in this work as 0 DOF), and 2) the likelihood of resistance at sampling (i.e., at 13 DOF, after the highest impact of tulathromycin metaphylaxis on the respiratory bacteria [80] but before the peak of first BRD cases expected for fall-placed calves [1, 81]). Notably, the time at sampling can be varied as desired

in future experiments with the model. In the absence of resistance data to inform treatment (i.e., before the test is performed and/or before the results are available from the diagnostic laboratory), the alternative options (**Figures SA10b and SA11b**) are not used by the model and treatment for BRD will continue to fail at a probability equivalent to the real-time pen-level prevalence of AMR.

Summary of Monte Carlo experiments

A summary of the sampling and testing scenarios examined with the model is provided in **Figure S1.11**. Many of the experiments were designed to simulate the conditions for maximum responsiveness to AMR in one of two ways: 1) the on-arrival prevalences of resistance to the therapeutic options were increased to empirical "worst-case" levels for a subset of experiments using the baseline (expert-developed) treatment protocol for BRD; *or* 2) the baseline BRD treatment protocol was replaced with a theoretical "extreme 15-membered ring macrolide use" protocol that maximized selection pressure for AMR when on-arrival resistance was held at baseline. The high responsiveness scenarios allowed us to better examine the impact of imperfect diagnostic tests on the expected outcomes, given that the changes to key outputs were otherwise negligible under baseline conditions.

The chart in **Figure S1.11** highlights the variations across scenarios in terms of treatment protocol (baseline *vs.* extreme), on-arrival AMR prevalence (baseline *vs.* high), diagnostic paradigm (phenotype *vs.* genotype), diagnostic test accuracy (perfect *vs.* empirical) and time of test (feedlot arrival *vs*. 13 DOF). Note that when test accuracy was perfect, the choice of diagnostic paradigm did not functionally change the model; perfect tests were thus only completed for phenotype and not genotype scenarios. Each scenario was simulated for both the TO and TI settings (n = 52 total experiments, including sensitivity analyses). Experiments were run for n = 5,000 iterations over a one-year model time horizon. Simulated outputs were generated for both the pen and feedlot levels and summarized in an MS Excel workbook with the medians, interquartile range (IQR), and 95% prediction intervals (2.5^{th} and 97.5^{th} percentiles).

Sensitivity analyses

Additional scenarios were examined as part of a sensitivity analysis to evaluate the impact of changes to key testing parameters on the outputs for select experiments that used the baseline BRD treatment protocol (see final column in **Figure S1.11**). To assess the impact of sample number on the diagnostic test positivity rate, the first experiment doubled (from 20 to 40) the number of sampled cattle per pen at both testing times (0 and 13 DOF). In a second experiment, we assessed the impact of lowering the threshold of pen-level resistance that triggered a treatment change (from 25% to 10%, or 2 of 20 sampled calves) at both time points. The sensitivity experiments were run for n = 5,000 iterations over 1 year, and the outputs (medians, IQRs and 95% prediction intervals) were extracted to the data repository in MS Excel for comparison.

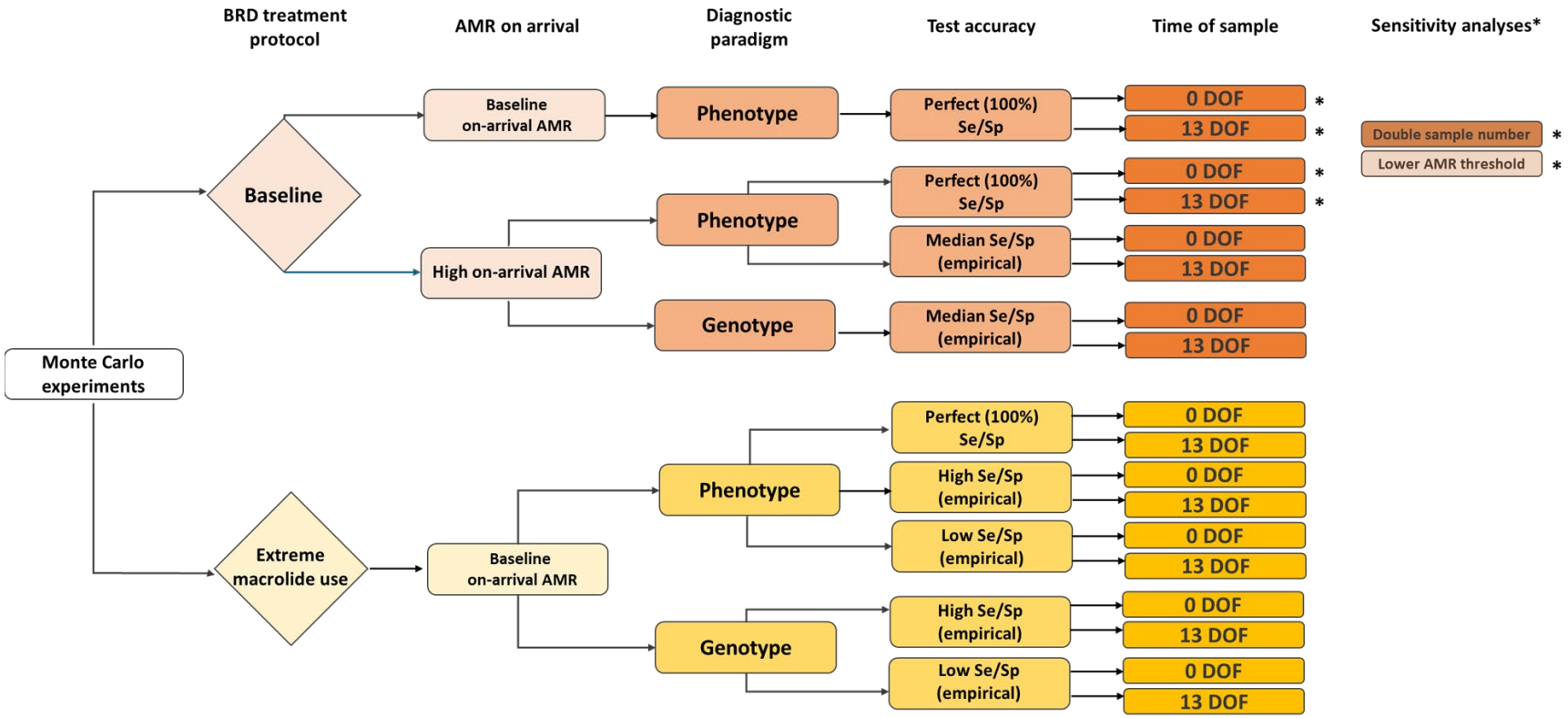


Figure S1.11. Summary of cattle sampling and AMR testing scenarios analyzed in this series of Monte Carlo experiments; each scenario is simulated for both a test-only (i.e., no treatment changes based on test results) and a testing-informed treatment setting (n = 52 total experiments). Scenarios were purposively selected to highlight changes to key outputs, and feature variations in BRD treatment protocol (baseline vs. extreme), on-arrival AMR prevalence (baseline vs. high), diagnostic test type and accuracy, and time of test (feedlot arrival vs. 13 DOF). Sensitivity analyses were only performed for scenarios which used the baseline BRD treatment protocol and a perfect AMR test (marked with a *).

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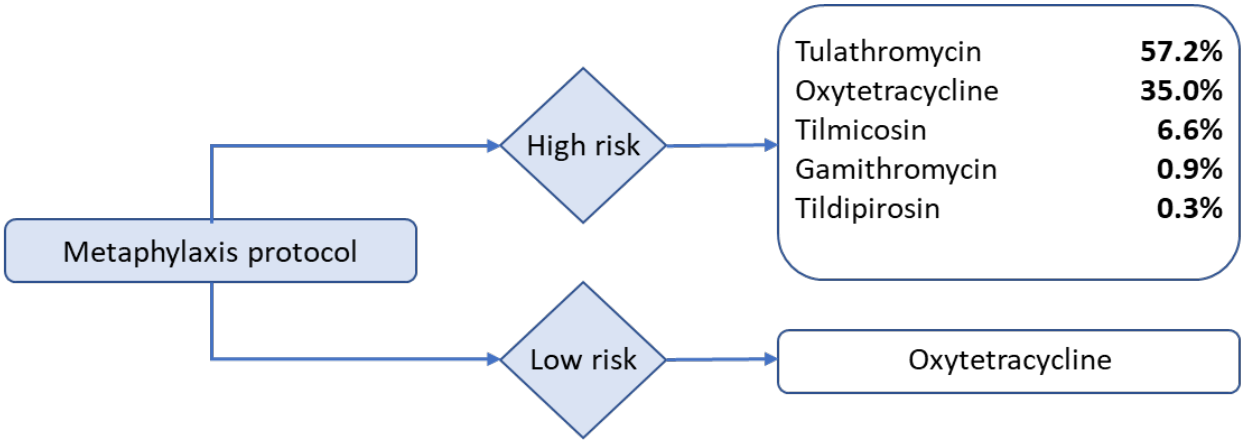
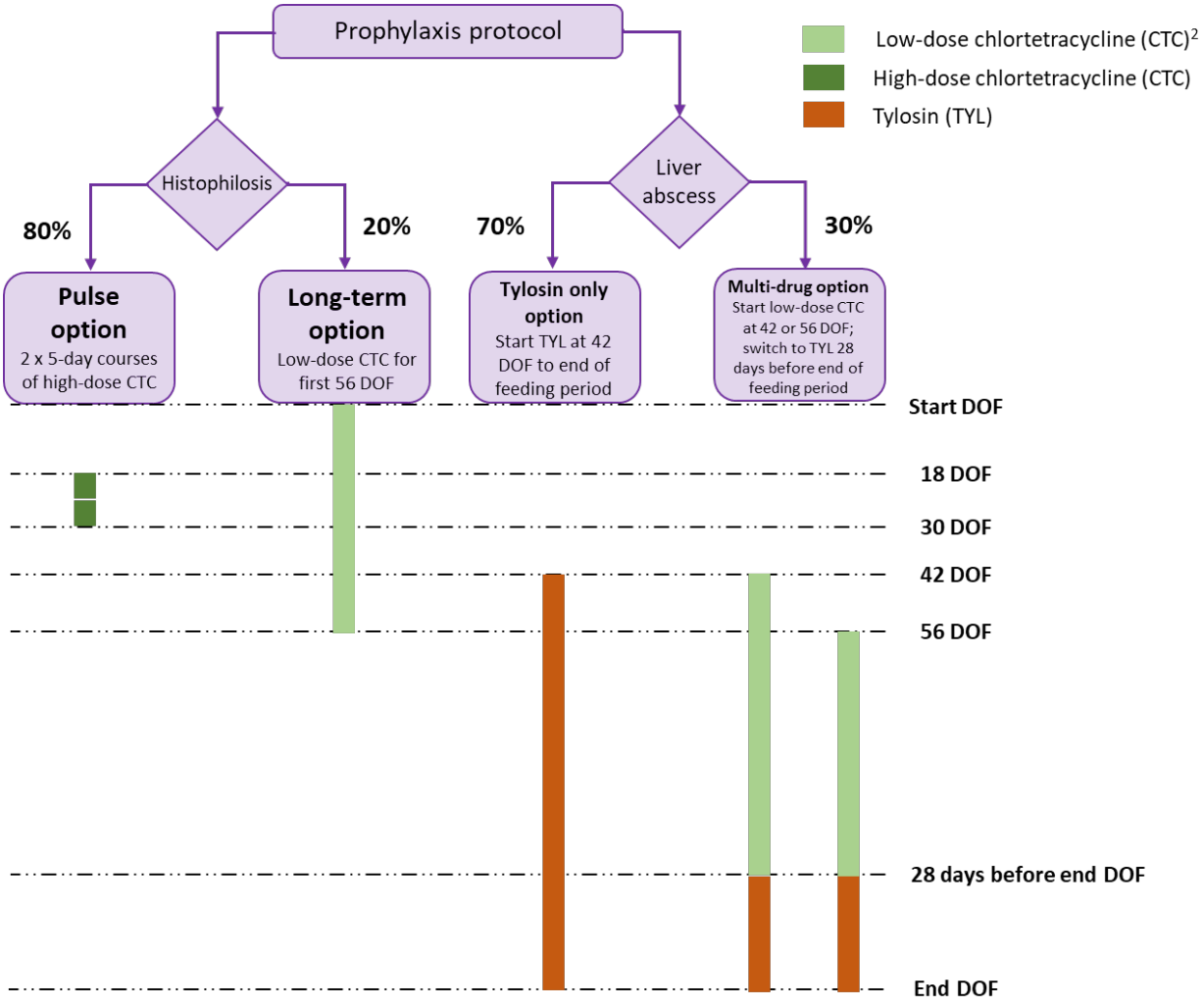
Appendix with additional figures

Figure SA1. Probability of metaphylactic drug choice based on level of BRD risk at feedlot entry[1]. Protocol by risk group[2] can be probabilistically selected at model initialization and applies to all animals of that type in the feedlot for a unique model run.



[1]Probabilities were derived from a sub-analysis of antimicrobial use trends on western Canadian feedlots [15]. Historical use data were assembled from the literature to correspond with the timing of antimicrobial resistance data used in the model calibration experiments and are not an endorsement of any particular regimen. Gamithromycin is no longer available in Canada.
[2]BRD risk is determined by animal weight at feedlot arrival [23-24]; in future experiments with the model, the infrastructure exists to incorporate a mixture of risks based on factors including animal sex, origin, and vaccination status.

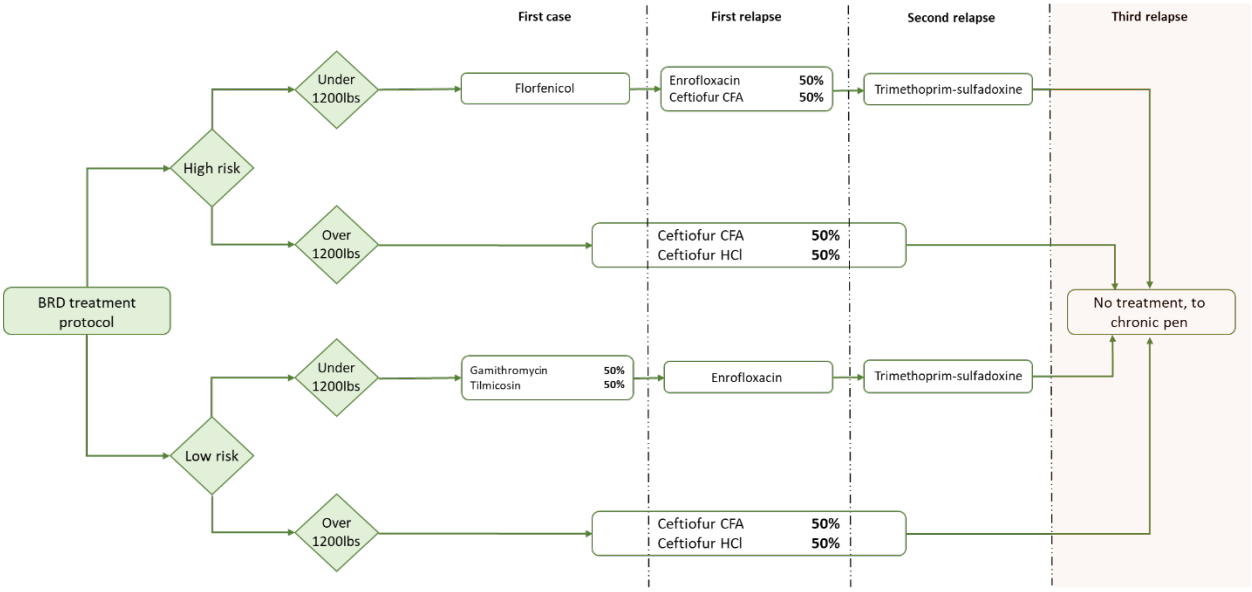
Figure SA2. Probability and duration of prophylactic (i.e., in-feed) protocols for the prevention of histophilosis and liver abscesses[1]. Protocol for each indication can be probabilistically selected at model initialization and applies to all pens in the feedlot for a unique model run.



[1]Probabilities were estimated from sub-analyses of antimicrobial use trends on western Canadian feedlots [15], antimicrobial use data collected by the Canadian Integrated Program for Antimicrobial Resistance Surveillance [referenced in Hannon et al. [47]], and a series of expert interviews with feedlot veterinarians. Historical use data were assembled from the literature to correspond with the timing of antimicrobial resistance data used in the model calibration experiments, and are not an endorsement of any particular regimen.

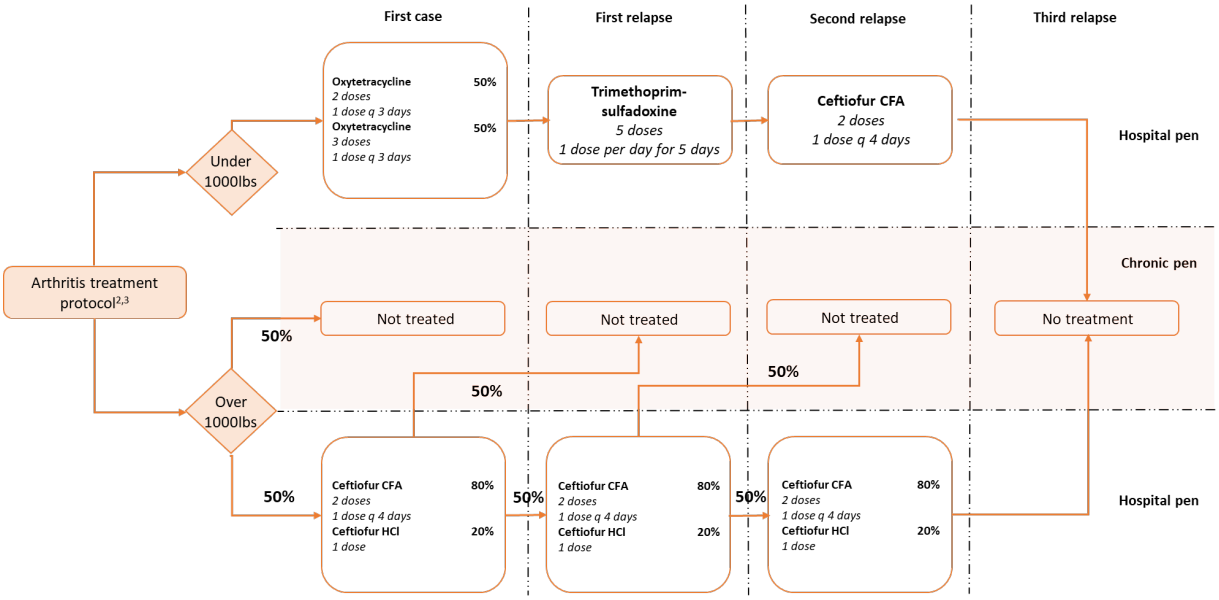
[2]Chlortetracycline (CTC) are administered prophylactically at both "low" and "high" dosages (indicated above with the light and dark green bars, respectively). When the "low dose" of CTC is used, the calibrated "selection probability" for tetracyclines is adjusted by a multiplier (0.2) that reflects the average concentration of that regimen relative to the "high dose" regimen.

Figure SA3. Probability of therapeutic drug choice for first and subsequent BRD diagnoses based on level of BRD risk at feedlot entry[1] and animal weight at time of infection. Protocol by risk[2] and weight group can be probabilistically selected at model initialization and applies to all animals in the feedlot for a unique model run.



[1]BRD risk is determined by animal weight at feedlot arrival [23-24]; in future experiments with the model, the infrastructure exists to incorporate a mixture of risks based on factors including animal sex, origin, and vaccination status.
[2]BRD treatment protocols were developed following a series of expert interviews with feedlot veterinarians. Historical use data were assembled from the literature to correspond with the timing of antimicrobial resistance data used in the model calibration experiments and are not an endorsement of any particular regimen. Gamithromycin is no longer available in Canada.

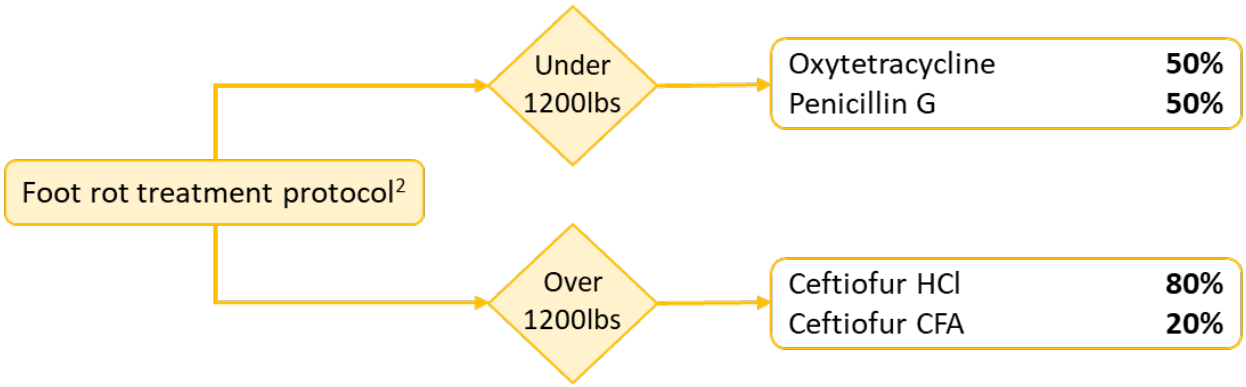
Figure SA4. Probability of therapeutic drug choice and location of therapy for first and subsequent arthritis diagnoses based on animal weight at time of diagnosis[1]. Protocol by weight group can be probabilistically selected at model initialization and applies to all animals in the feedlot for a unique model run.



"q" = "every" in the above figure

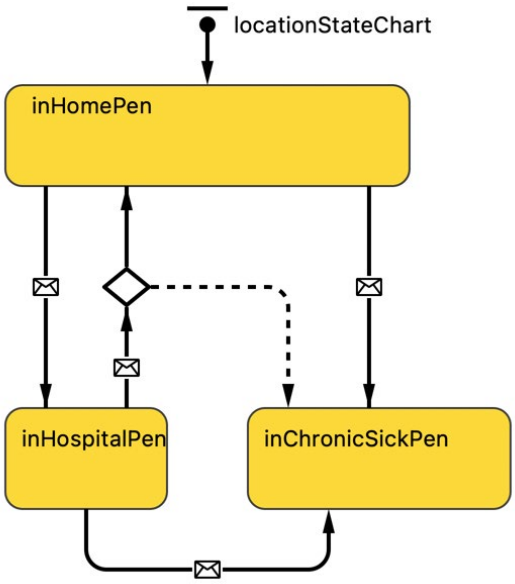
[1]Arthritis treatment protocols were developed following a series of expert interviews with feedlot veterinarians. Historical use data were assembled from literature to correspond with the timing of antimicrobial resistance data used in the model calibration experiments and are not an endorsement of any particular regimen. Gamithromycin is no longer available in Canada.
[2]Animals that are probabilistically selected for arthritis treatment are relocated to the hospital pen and administered antimicrobials as part of multi-day regimens rather than single exposures; calves in the hospital pen are temporarily assigned an ADG equal to zero.
[3]Ceftiofur is not expected to be effective against uncomplicated *Mycoplasma bovis*-associated arthritis [73]. However, arthritis diagnosed late in the feeding period in fall-placed calves can be confounded by other infectious agents, and some cases are likely sequelae of chronic and unresponsive foot rot.

Figure SA5. **Probability of therapeutic drug choice for foot rot diagnosis based on animal weight at time of infection[1].** Protocol by weight group can be probabilistically selected at model initialization and applies to all animals in the feedlot for a unique model run.

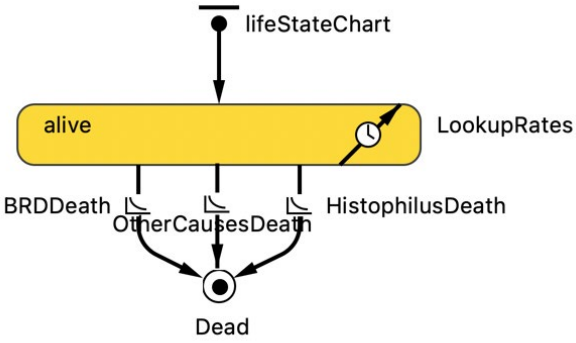


[1]Foot rot treatment protocols were developed following a series of expert interviews with feedlot veterinarians. Historical use data were assembled from literature to correspond with the timing of antimicrobial resistance data used in the model calibration experiments and are not an endorsement of any particular regimen.
[2]An "outbreak protocol" is triggered if 10% or more of the animals in a shared pen are diagnosed with foot rot in a single feeding period; in this scenario, a 7-day course of high-dose chlortetracycline (CTC) is administered at the pen-level (i.e., in-feed) to control the outbreak/prevent additional cases.

Figure SA6. State charts for location (A) and mortality (B) in the Cattle agent. A: Calves being treated for arthritis are moved to the hospital pen for the duration of their treatment; calves that are not expected to respond to further treatment are moved to the chronic pen. Transition arrows demarcated by "envelope" symbols depend on the receipt of a "move to pen" message. **B:** Calves can die from BRD, histophilosis or other causes in the model. Transition arrows demarcated by "graph" symbols are those governed by daily mortality rates derived from empirical data. Living calves periodically update their hazard rates according to the days on feed (DOF) and their condition.



A



B

Figure SA7. State chart for Treatment agent. The treatment agent administers a specific antimicrobial to a particular animal as outlined in the AMU protocols (**Figures SA1-SA5**). Treatments transition to the withdrawal state in one of two ways: 1) a prescribed amount of time has elapsed (arrow demarcated by a "clock" symbol), or 2) the animal reaches a threshold weight (arrow demarcated by a "question mark" symbol).

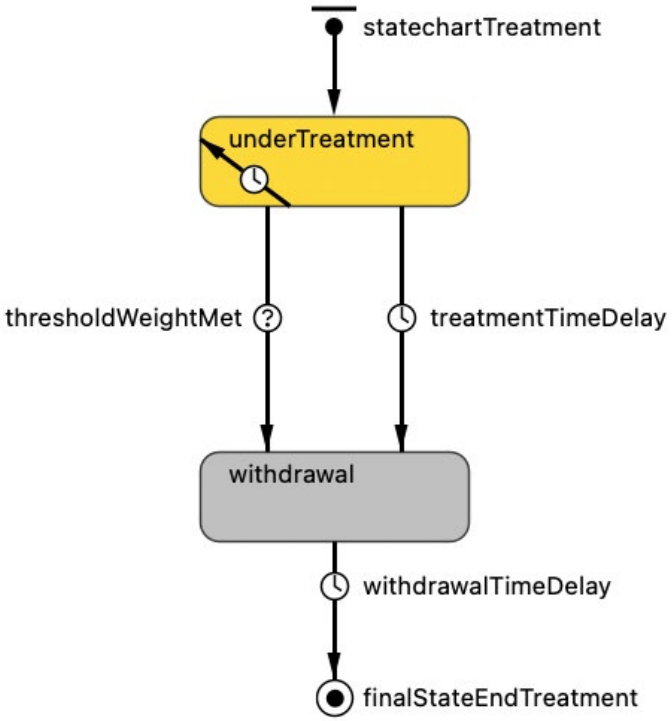


Figure SA8. Matrix describing the linkages between drugs belonging to the same antimicrobial class or sub-class. Drugs from the same class were assumed to be equally vulnerable to the relevant resistance mechanism; co-selection, co-waning and co-transmission of detectable resistance was thus observed for fully linked (=1) drugs (**Figure S1.7**). Drugs from different classes were assumed to be selected and transmitted independently of each other.

Antimicrobial drug (active ingredient)	Ceftiofur CFA	Ceftiofur HCl	Enrofloxacin	Tulathromycin	Gamithromycin	Tilmicosin	Tildipirosin	Tylosin	Sulfadoxine	Trimethoprim	Ampicillin	Penicillin	Spectinomycin	Florfenicol	Florfenicol/ flunixin	Oxytetracycline	Chlortetracycline (high dose)	Chlortetracycline (low dose)
Ceftiofur CFA	**1.00**	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ceftiofur HCl	**1.00**	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Enrofloxacin	0.00	0.00	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Tulathromycin[1]	0.00	0.00	0.00	**1.00**	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Gamithromycin[1]	0.00	0.00	0.00	**1.00**	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Tilmicosin[1]	0.00	0.00	0.00	0.00	0.00	**1.00**	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Tildipirosin[1]	0.00	0.00	0.00	0.00	0.00	**1.00**	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Tylosin (in-feed)[2]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Sulfadoxine[3]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Trimethoprim[3]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Ampicillin	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**1.00**	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00
Penicillin G	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**1.00**	**1.00**	0.00	0.00	0.00	0.00	0.00	0.00
Spectinomycin	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**1.00**	0.00	0.00	0.00	0.00	0.00
Florfenicol	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**1.00**	**1.00**	0.00	0.00	0.00
Florfenicol/flunixin	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**1.00**	**1.00**	0.00	0.00	0.00
Oxytetracycline	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**1.00**	**1.00**	**1.00**
Chlortetracycline (high dose)[4]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**1.00**	**1.00**	**1.00**
Chlortetracycline (low dose)[4]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**1.00**	**1.00**	**1.00**

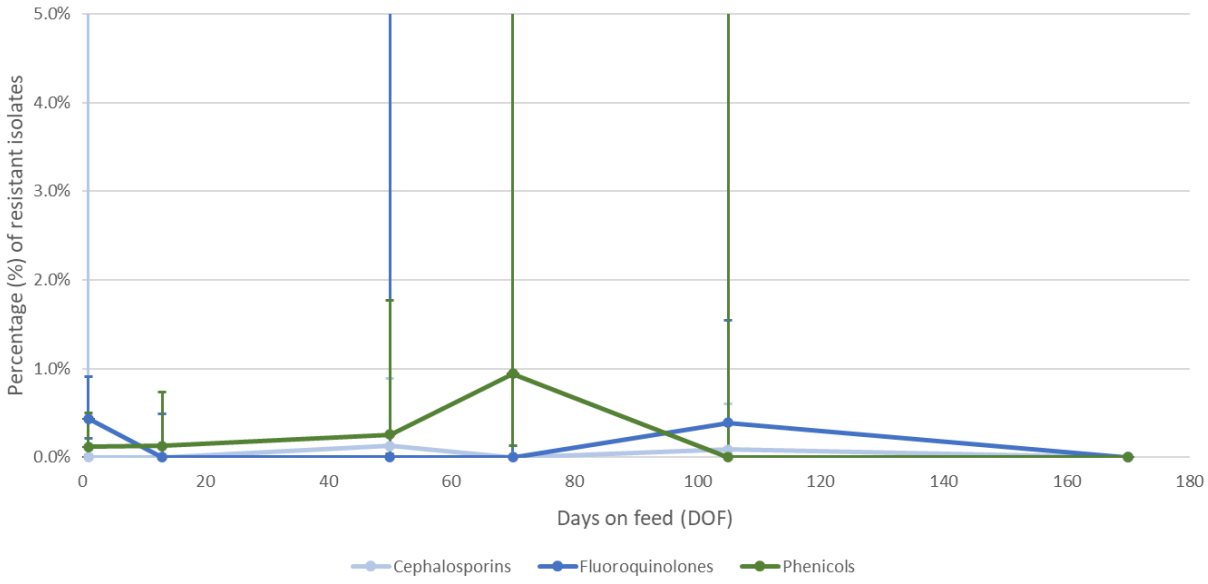
[1]15-membered ring macrolides tulathromycin and gamithromycin were independent from 16-membered ring macrolides tilmicosin and tildipirosin (=0) in the initial calibration experiments.

[2]Prophylactic (i.e., in-feed) tylosin use does not co-select for resistance to injecTable S1.16-membered ring macrolides in its sub-class (=0), consistent with the observation that "the in-feed levels of tylosin [have] no effect on the prevalence of *M. haemolytica"* [46].

[3]The use of potentiated sulfonamide Trivetrin (see **Table S1.2**) in the model triggered the individual "selection probabilities" per day for both trimethoprim and sulfonamides, but resistances to these classes are independent and do not co-select, co-wane or co-transmit (=0).

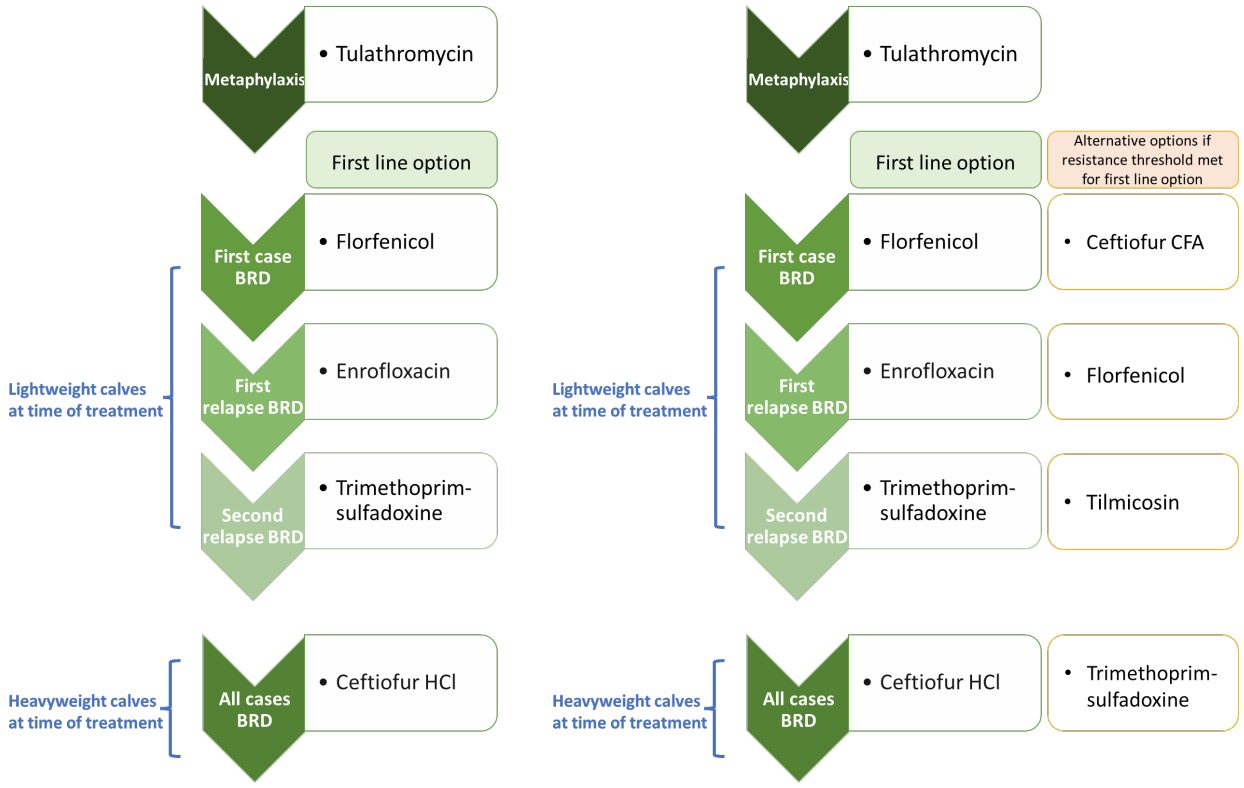
[4]Chlortetracycline at both the "high" (i.e., therapeutic) and "low" (i.e., prophylactic) dosages were fully linked to each other and to oxytetracycline (=1). When the "low dose" of chlortetracycline was used, the calibrated "selection probability" for tetracyclines was adjusted by a multiplier (0.2) that reflected the average concentration of that regimen relative to the "high dose" regimen. The multiplier was estimated from AMU data collected by the Canadian Integrated Program for Antimicrobial Resistance Surveillance [referenced in Hannon et al. [47]] and a series of expert interviews with feedlot veterinarians.

Figure SA9. Percentage of *Mannheimia haemolytica* isolates with detectable phenotypic resistance to antimicrobial classes of interest *not selected for calibration*[1] over the feeding period. The custom longitudinal dataset was synthesized from recent empirical studies of antimicrobial resistance prevalence in western Canadian feedlot cattle from mixed origins[2].



[1]Antimicrobial classes were selected for calibration if the prevalence of detectable resistance was >1% at any time point **and** the class was relevant for antimicrobial use in feedlot medicine [70]. Each class was represented by AMR to one drug (see **Table S1.4**) with the most complete reference data set.
[2]Percentage of resistant isolates at each time point is a weighted average of prevalence values extracted from recent studies of healthy feedlot cattle in western Canada [7-13].

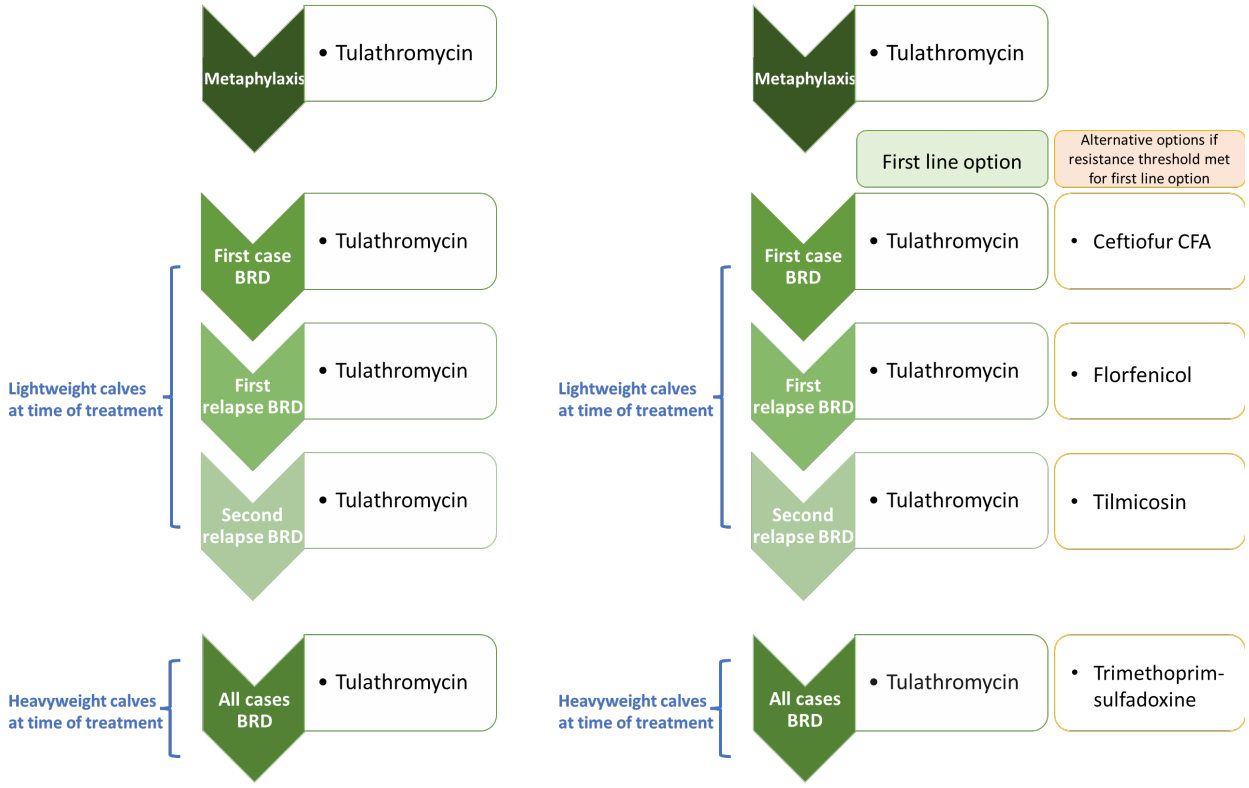
Figure SA10. Metaphylaxis and BRD treatment protocol in the baseline scenarios for high-risk feedlot calves in the (a) test-only experiments[1], left and (b) testing-informed treatment experiments[2], right.



[1]The first-line BRD control and treatment protocol for the baseline scenarios was developed in consultation with feedlot experts [1]. Where there were multiple treatment options for an indication in [1] (e.g., first BRD relapses), we selected only *one* option that remained constant across experiments for the purposes of this study (the parameter permitting variation in AMU protocols across unique runs in a single experiment was disabled). This ensured that relative changes in the median values for outputs of interest could be attributed to the experimental conditions rather than stochastic variation across iterations.

[2]The alternative BRD treatment protocol in the testing-informed treatment experiments included licensed antimicrobials purposively selected to better distinguish between the impacts of the intervention on successive BRD therapies (i.e., changes in the number of antimicrobial uses by class) in the simulated data. The alternative drugs were **not** necessarily selected for the purpose of good antimicrobial stewardship.

Figure SA11. Metaphylaxis and BRD treatment protocol in the theoretical "extreme macrolide use" scenarios for high-risk feedlot calves in the (a) test-only experiments[1], left and (b) testing-informed treatment experiments[2], right.



[1]The first-line BRD control and treatment protocol for the "extreme macrolide use" scenarios was designed to maximize selection pressure for AMR, and mirrors the conditions for the thought experiment investigated in [1].

[2]For ease of comparison, the alternative BRD treatment protocol in the testing-informed treatment experiments for the "extreme macrolide use" scenarios was the same as in the baseline scenarios (**Figure SA10b**).