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Individual or collective treatments: how to target antimicrobial use to limit the spread of *Mannheimia haemolytica* among beef cattle?

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Abstract

The overuse of antibiotics has become a major global concern due to its role in diminishing treatment effectiveness and positively selecting antibiotic-resistant bacterial strains. This issue is particularly important in the beef cattle sector, where Bovine Respiratory Diseases (BRD) impose significant economic and welfare burdens. BRD are complex, multifactorial conditions primarily affecting young calves and feedlot cattle, caused by a combination of viral and bacterial pathogens, environmental factors, and stressors. Despite efforts to reduce antimicrobial use (AMU), the cattle production system remains heavily reliant on antibiotics to control BRD, often through the implementation of collective treatments to prevent outbreaks. This study aimed at evaluating the impact of various strategies of collective treatments with antimicrobials on the spread of a BRD pathogen, *Mannheimia haemolytica*, specifically focusing on criteria for implementing collective treatments. Using a mechanistic stochastic model, we simulated the spread of *M. haemolytica* in a multi-pen fattening operation under sixteen different scenarios, considering pen composition, individual risk levels, and treatment strategies. Our findings suggest that an alternative criterion for collective treatments based on the speed of the disease spread, could reduce BRD incidence and AMU more effectively than conventional methods. This research highlights the importance of responsible collective treatment strategies and the potential benefits of novel criteria for collective treatment in improving animal health. Moreover, it emphasizes the need for transparency on the exposure to risk factors along the production chain.

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Introduction

Excessive and inappropriate use of antimicrobials can select resistant bacterial strains, making it harder to treat infections in both animals and humans (Chen et al., 2022; Woolums et al., 2018). However, antimicrobial treatments remain the main control measure for health practitioners to treat bacterial infectious diseases, thus making antimicrobial resistance a global concern (Coetzee et al., 2019; Laxminarayan et al., 2013).

Bovine respiratory diseases (BRD) pose a significant burden on the global livestock industry, causing considerable economic losses and welfare concerns for cattle (Delabougliose et al., 2017). BRD are complex multifactorial respiratory conditions primarily affecting young calves and feedlot cattle (Griffin, 2014). They are caused by a combination of viral and bacterial pathogens, environmental factors, and stressors (Kudirkiene et al., 2021). The bovine respiratory syncytial virus (BRSV) or the parainfluenza-3 (IPV-3) are frequently reported viral agents whereas common bacteria include *Pasteurella multocida*, *Mannheimia haemolytica* or *Mycoplasma* spp. (Caswell et al., 2010; Grissett et al., 2015; Timsit et al., 2013). They lead to reduced feed efficiency, growth rates, and overall productivity, resulting in substantial financial losses for producers (Blakebrough-Hall et al., 2022; Griffin, 2010). Additionally, they cause significant suffering in affected animals, characterized by symptoms such as coughing, fever, and respiratory distress (Hilton, 2014). The prevention and management of BRD are crucial for maintaining animal health, welfare, and sustainable livestock production (Hilton, 2014).

While viral pathogens are typically more infectious, much of the internal damage and clinical signs associated with BRD arise from secondary bacterial infections (Rice et al., 2007). Pasteurellaceae such as *Mannheimia haemolytica* or *Pasteurella multocida* are often associated with severe BRD cases, based upon necropsies of animals presenting severe respiratory symptoms, as well as positive serologies (Booker et al., 2008; Welsh et al., 2004). *M. haemolytica* is particularly recurrent, with seroprevalences up to 80% and incidence risks up to 22.7% (Assié et al., 2009). *M. haemolytica* is commonly reported during BRD episodes in the field (Klima et al., 2014; Sudaryatma et al., 2018). Curative treatments for BRD mostly focus on these secondary infections, as they consist in using antimicrobials (Edwards, 2010). *M. haemolytica*'s response to antimicrobials is well characterized, making it a good candidate for a pathogen specific studies investigating treatment strategies (Noyes et al., 2015).

Despite considerable progress made in the livestock sector to reduce antimicrobial use (AMU) (Bateman et al., 1990; Watts and Sweeney, 2010) the cattle production system is still heavily reliant on this method to control BRD (Abell et al., 2017; O'Connor et al., 2013). Pathogen identification is not done on routine, therefore antimicrobial curative treatment is the baseline response in the event of an outbreak (DeDonder and Apley, 2015). Individual treatment when animals show signs of disease is mostly used to care for affected animals, but collective treatments are also widely embraced to prevent BRD outbreaks and minimize economic losses (Baggott et al., 2011; Nickell and White, 2010; Ollivett, 2020). The latter involves the administration of appropriate medications, such as antibiotics or anti-inflammatory drugs, to affected animals as well as the entire group to prevent additional cases (Ives and Richeson, 2015; Lees and Shojaee Aliabadi, 2002). This solution is motivated by poor sensitivity of current BRD field diagnostic

methods, typical pathogenesis of BRD, and labor issues (Ives and Richeson, 2015). Indeed, the sensitivity for BRD diagnosis was evaluated at around 0.27, making it very unefficient to treat each animal individually upon visual appraisal (Timsit et al., 2016). As a result, a trade-off exists between antimicrobial use and bovine respiratory disease (BRD) occurrence. This trade-off highlights the need for responsible antimicrobial use practices, such as targeted collective treatments with antimicrobials. Yet, to this day, such strategies have not been proposed. Indeed, the relevant criteria and associated threshold to implement collective treatments are still questioned (Edwards, 2010).

Modeling is used to better understand complex infection dynamics and compare scenarios and rank interventions (Ezanno et al., 2020). In the case of BRD, a model ranking treatment strategies at pen level has been published (Picault et al., 2022). It simulates the circulation of an average pathogen in conditions mimicking contrasted farming contexts such as small versus large pens (considered as isolated from other pens) and low versus high risk of contracting BRD at pen level. The authors concluded on a bigger BRD circulation in large pens composed of high risk individuals and discussed which pens could get the highest benefit from collective treatments. A second model compares the impact of farm management practices on the spread of three causal pathogens of BRD in multi-pen farms featuring several individual risk levels of contracting BRD (Sorin-Dupont et al., 2023). This study highlighted that sorting animals in pens in accordance with their individual risk level of developing BRD participates in limiting the spread of the most contagious pathogens. However, no model integrating novel criteria for triggering collective treatments has been proposed so far.

This study aimed at evaluating the impact of collective treatment strategies on the spread of *M. haemolytica* in contrasted farming scenarios. More specifically, the objective was to evaluate criteria for implementing collective treatments in order to identify the best criterion. To that end, we used a mechanistic stochastic model of the spread of *Mannheimia haemolytica* in a multi-pen fattening operation. We investigated sixteen contrasted scenarios reflecting farming practices in fattening operations, based on pen composition, individual risk level distribution, and individual vs. collective treatments based on conventional and original criteria. We compared scenario outputs regarding case occurrence, severity, mortality and AMU.

Material and methods

Model processes and assumptions

We modeled the spread of *M. haemolytica* in a multi-pen fattening farm and the treatment of associated BRD. We extended our stochastic and mechanistic individual-based model previously published (Sorin-Dupont et al., 2023) for studying the circulation of specific pathogens involved in BRD, including *M. haemolytica*, within a fattening farm building, by including the possibility of collective treatments based on conventional and original criteria. Our model monitored 6 individual characteristics, implemented either as input parameters or state machines. First, the model featured the individual risk status of developing BRD as an input parameter, which corresponded to an individual qualitative information (low, medium, high) summarizing the level of stressors predisposing to BRD that the animal had been exposed to prior to its arrival. The model

also featured state machines defining hyperthermia (either due to BRD or unspecific), infection status (susceptible, asymptomatic carrier, infectious), clinical status (asymptomatic, or with mild or severe clinical signs), detection status (detected or not), and treatment status (treated or not treated). Hereafter, we detail how treatments are triggered in this new version of the model. A graphic overview of the model state machines is proposed in Figure 1.

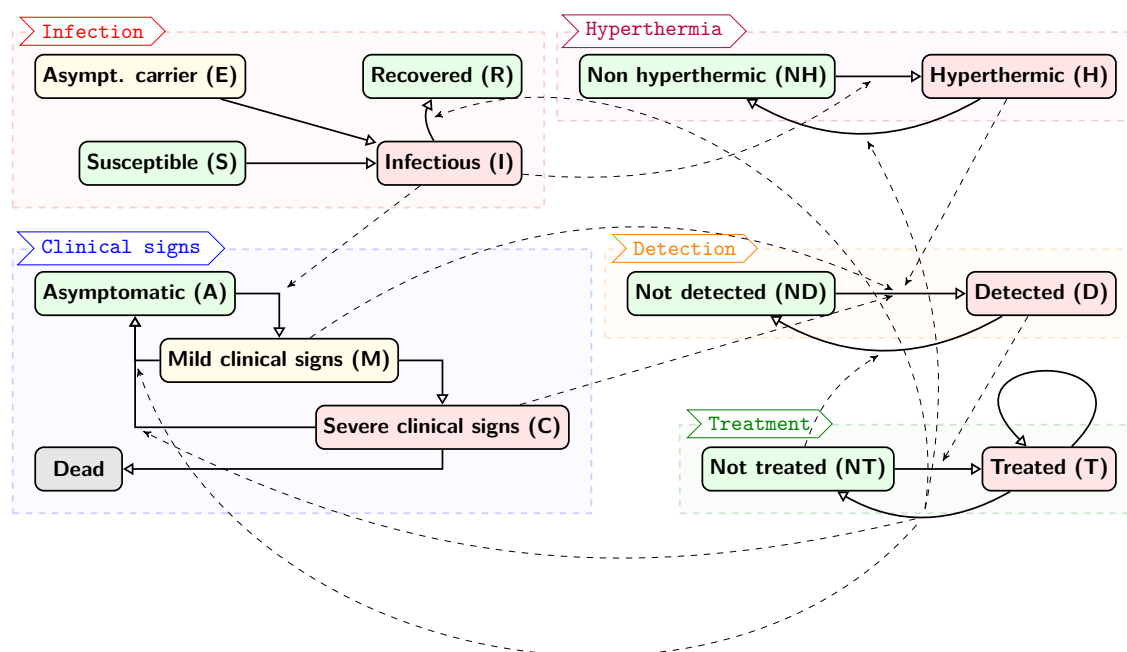


Figure 1 – Graphic overview of the states and transitions in each process of the model. Each animal is defined by its state in each of the 5 state machines included in the model. Full arrows represent a transition from one state to another whereas the dashed lines represent regulatory links. Let X be a regulator (state or transition) of transition T_2 . This will be represented by a dashed arrow starting from X and targeting T_2 . From Sorin-Dupont et al., 2023

Hyperthermia. Hyperthermia was composed of two states: hyperthermic (H) and non-hyperthermic (NH). NH animals could transition to H with probability p_H attributed to non-infectious factors. Once in state H, they remained there for a period τ_H sampled from a Beta distribution adjusted using observed data, before reverting to NH. Additionally, the transitions from NH to H and back could result from the infection process with a 1 probability.

Infection and clinical signs status. Four infection statuses were considered: susceptible (S), asymptomatic carrier (E), infectious (I) and recovered (R) animals. Asymptomatic carriers were modeled as non infectious animals which carry *M.haemolytica* commensally. They could spontaneously turn I with probability p_E and could also be infected by surrounding infectious individuals (I). Three actions were triggered when entering the state I: (1) the individual exhibited mild clinical signs for a duration τ_M drawn from a Beta distribution calibrated from observed data, (2) the

animal changed from NH to H state, (3) a random draw with probability p_C drove whether the individual would display severe clinical signs at the end of its mild clinical signs. The probability p_C is higher if the animal has a high individual risk level. If displaying severe clinical signs, a boolean deciding on the survival of the individual was drawn from a binomial law of probability p_d . Death occurred at the end of the severe clinical signs duration (τ_C). If the individual did not die and was still infectious after τ_C , it transitioned back to MildC. The animal then recovered and became R at the end of the infectious period. Recovery occurred after a duration τ_I drawn from a gamma distribution. Theoretically, τ_I is longer than τ_M . However, $\tau_M + \tau_C$ could exceed τ_I . In that case, the infectious period was $\tau_M + \tau_C$. When transitioning to R state, animals changed from H to NH.

Detection status. Similarly to previous models, animals could be detected upon exhibition of clinical signs or hyperthermia. Severe clinical signs were detected with a sensitivity of 0.6, while the sensitivity for mild clinical signs detection was averaged to 0.3, assuming that lethargy is the main driver for detection of severe clinical signs (Kayser et al., 2019). We assumed a clinical check-up at every time step (12 h, in agreement with farmers' herd monitoring frequency (Terry et al., 2021). After detecting the first case through visual appraisal, all hyperthermic animals were identified using rectal temperature measured at the next feeding time, 12 hours later. (Picault et al., 2022; Sorin-Dupont et al., 2023). False discovery may occur with the temperature check as hyperthermia may be unrelated to infection.

Treatment status. The treatment process represented a standard antimicrobial treatment protocol during the fattening period. Each animal that was detected as affected, either through visual detection or hyperthermia, received one antibiotic dose, assumed to be effective after duration τ_T with a probability p_T , accounting for antimicrobial resistance. Animals still exhibiting clinical signs after this duration were treated again (same duration), the number of treatments per episode being limited (max_T). Transitions from T to NT occurred in three cases: (1) the animal recovered after duration τ_T due to the treatment success with probability p_T ; (2) the end of the infectious period occurred while under treatment but was not caused by it; (3) the animal still expressed clinical signs but was already treated max_T times, thus was not treated again and ignored from further treatments, as per on-field recommendations (Van Boeckel et al., 2017). The values of the parameters as well as their source are summarized in Table 1.

Force of infection

Our model enabled pathogen transmission in a building containing several pens, i.e., groups of animals sharing a same closed indoor space. We assumed that an animal in a given pen was mainly exposed to infectious animals within its pen while also being exposed to the animals in the other pens in the building, albeit to a lesser extent.

The force of infection Φ_i for pen i was frequency-dependent, taking into account the multi-pen nature of our model by accounting for the force of infection within the pen and between pens. Let \mathbb{B} be the set of pens of n individuals each raised simultaneously in a building. In each pen i , the intra pen force of infection was the sum of the individual contribution β_p of each infectious set of individual of risk level ρ ($I_{\rho,i}$). The contribution increased with the individual risk level ρ . Mathematically, this translates to equation (1). In a given pen i , the susceptible individuals experienced an intra pen force of infection with the addition of the contributions of the other

Table 1 – Parameter values used for *M. haemolytica*

Parameter	Symbol	Value	Source
Transmission rate to susceptible for low risk infectious individuals (/h)	β_{Low}	0.005	Picault et al., 2022
Transmission rate to susceptible for medium risk infectious individuals (/h)	β_{Medium}	$1.5 * \beta_{Low}$	Picault et al., 2022
Transmission rate to susceptible for high risk infectious individuals (/h)	β_{High}	$1.5 * \beta_{Medium}$	Picault et al., 2022
Spontaneous shedding probability	p_E	0.14, 0.42 and 0.68 for low, medium and high risk levels respectively	Frank et al., 1986
Initial carrier proportion	E_0/N_0	0.26, 0.48 and 0.72 for low, medium and high risk levels respectively	Timsit et al., 2013
Mild clinical sign duration	τ_M	2-8 (med=6) days	Grissett et al., 2015
Infectious period duration	τ_I	6-10 (med=8) days	Thomas et al., 2019
Asymptomatic period duration	τ_E	1 day	Grissett et al., 2015
Probability of successful treatment	p_T	0.71	DeDonder and Apley, 2015
Probability of severe forms	p_C	0.65	Timsit et al., 2013
Contact rate between pens	c	0.01	Assumed

pens of set \mathbb{B} deprived of i ($\mathbb{B} \setminus \{i\}$) multiplied by a contact rate between pens c defining how isolated the pens were from each other. In our simulations, we set $c = 0.01$. This choice was motivated by the analysis of the effect of this parameter in the previous model (Sorin-Dupont et al., 2023). This value implied a low contact rate between pens, which was compliant to the low airborne transmission of *M. haemolytica* (Timsit et al., 2013). A susceptibility factor σ_ρ increasing with the individual risk level ρ multiplied this total. Mathematically, this translates to equation (2). The force of infection Φ_i was converted to a time-dependent probability p_{Φ_i} using the equation (3), with δt being the current time step.

$$(1) \quad \forall i \in \mathbb{B}, \lambda_i = \sum_{\rho \in \mathbb{P}} \beta_\rho I_{\rho,i}$$

$$(2) \quad \Phi_i = \sigma_\rho \frac{\lambda_i + c \sum_{b \in \mathbb{B} \setminus \{i\}} \lambda_b}{N_i + c(N - N_i)}$$

$$(3) \quad p_{\Phi_i}(\delta t) = 1 - e^{-\Phi_i \delta t}$$

with \mathbb{P} the set of individual risk levels, β_ρ the shedding level of individuals with risk level ρ , $I_{\rho,i}$ the number of infectious individuals with risk level ρ in pen i , N_i the total number of individuals in pen i , N the total population size. This function was proposed for modeling the force of infection as it enables to represent perfectly separated pens ($c = 0$) as well as a unique large pen with homogeneous contacts ($c = 1$) using a single formula.

Collective treatment criteria

In this new model version, in addition to individual treatment of detected animals, we also considered the possibility to trigger a collective treatment at pen scale, based on three different criteria as detailed below. Once one of the criterion was reached, all animals not already under treatment in the pen received an antimicrobial dose, and were then followed individually according to the rules described above.

As a first criterion for triggering a collective treatment (conventional criterion), we tested the cumulative incidence in detected BRD cases in the pen, a collective treatment being performed once this criterion reached a fixed threshold. Such a threshold has been conventionally used for a long time in French fattening operations and continues to be employed in this manner, with values usually around 10% of the pen size (Mornet and Espinasse, 1977), although these values are not backed up by dedicated field or experimental observations.

The second criterion (severity criterion) consisted in triggering a collective treatment based on a severity function. A collective treatment was triggered when this function reached a threshold, which was selected in order to have the best trade-off possible between case incidence and antimicrobial use. The full selection process is defined in SI2. The proposed function is a weighted sum of the number of animals detected as having mild or severe clinical signs in a given pen i . Mathematically, this translates to equation (4):

$$(4) \quad S_i = \alpha D_{Mild,i} + (1 - \alpha) D_{C,i}, \alpha \in [0, 0.5]$$

with $D_{Mild,i}$ the number of animals detected as having mild clinical signs in pen i , and $D_{C,i}$ the number of animals detected as having severe clinical signs. The weight parameter α was smaller than 0.5 to allow an emphasis on severe cases. The process for selecting a relevant value for α is detailed in SI2.

The third criterion (slope criterion) considered to trigger a collective treatment was based on the speed of case appraisal. A collective treatment was triggered when this function reached a threshold, which selection answered to the same logic as the severity criterion. The slope at time t in pen i represented the ratio of the cumulative incidence of detected BRD cases in pen i divided by the time since the beginning of the fattening. To avoid dividing by 0, $P_i(t)$ is only defined for $t > t_0$. This translates to equation (5):

$$(5) \quad P_i(t) = \frac{cumulateD_i}{t - t_0}$$

where $cumulateD_i$ is the cumulative number of individuals detected as affected in pen i , $t_{0,i}$ being the starting time of the simulation, and t the current time. In all these cases, a collective treatment can be performed only once per pen over the simulation time.

Model implementation

To code the model, we used the open-source [EMULSION framework](#) (Picault et al., 2019), which defines models in human-readable structured text files then processed by a simulation engine coded in Python. Such a modeling framework facilitates model co-development and revisions by modelers, clinicians, and epidemiologists all together. EMULSION also supports individual-based stochastic modeling, enabling simulations of small groups characterized by a high variability in biological processes. The framework allows a detailed breakdown of the modeled events and processes. Processes are articulated as finite state machines, a formalism widely employed in computer science to depict states and transitions.

Scenarios and outputs

We investigated sixteen scenarios of BRD treatment in a building of 200 young beef animals, distributed in 10 pens of 20 animals each, during 40 days, as BRD typically occurs in the first few weeks of fattening (Assié et al., 2009; Timsit et al., 2013). These scenarios were defined by one of the four treatment strategies, applied in 2 possible farm-scale proportions of individual risk status of developing BRD and two ways of assigning animals to pens. The four treatment strategies were: (1) individual treatment administered upon detection of clinical signs (Individual); (2) collective treatment triggered when the pen-scale cumulative incidence of BRD cases reached the standard threshold, in addition to individual treatment (Conventional); (3) collective treatment triggered when the weighted severity reached the defined threshold, in addition to individual treatment (Severity); and (4) collective treatment triggered when the slope function reached the defined threshold, in addition to individual treatment (Slope). The two possible individual risk level distributions in the building were: (1) 30%, 40%, and 30% of low, medium, and high risk individuals respectively (HR30); and (2) 10%, 0% and 90% of low, medium and high risk individuals respectively (HR90). We chose these proportions in order to display contrasted situations, one being compliant with previously estimated risk proportion, and the other corresponding to a worst-case scenario (Amrine et al., 2019). Since having a majority of low risk individuals in the building would not feature enough cases to trigger a collective treatment, it was thus left out of this study. Finally, animals could either be assigned into pens randomly (Random) or according to their individual risk level (Sorted).

Each scenario had 200 stochastic replicates. At the building scale (i.e. grouping the 10 pens), we observed the distribution and the median of the cumulative incidence of BRD cases and the average time spent with severe clinical signs per affected animal (in hours) with regards to the total AMU in the building. Moreover, we compared the mortality across the scenarios. We also computed the proportion of treatment misuse for each scenario. This measure corresponds to the ratio of false positives over predicted positives, i.e in our case the ratio between the number of doses given to healthy animals over the total AMU. Furthermore, we observed the delay between the detection of the first BRD case and the collective treatment implementation. We also observed the delay between the infection and the administration of the first dose of antimicrobial on an individual scale. Finally, for the sorted scenario, we counted the proportion of pens of each risk level that triggered a collective treatment. For each of these outputs, all applicable scenarios were compared. As we could neither assume the normality of the distributions or the homogeneity of variances across the scenarios for most of the outputs, non-parametric

tests were used for the analysis. General effects of treatment modalities were assessed with Kruskal-Wallis tests and post-hoc pairwise comparisons were done by using Wilcoxon-Mann-Whitney with Bonferroni correction to reduce the family-wise error rate. The significance levels are indicated throughout the figures are the following:

- "****": p-value < 0.0001
- "***": p-value < 0.001
- "**": p-value < 0.01
- "*": p-value < 0.05
- "ns": p-value ≥ 0.05

Sensitivity analysis

To better understand the behavior of the model and to characterize the impact of parameter uncertainty, we carried out an exploration of the model sensitivity by performing a one-at-a-time sensitivity analysis on six scenarios with a common risk level proportion of 30, 40 and 30% of low risk, medium risk and high risk respectively, as it was the most realistic (Amrine et al., 2019). We simulated our three collective treatment strategies in randomly allocated pens and in sorted pens.

The model was derived from a previous one on which a sensitivity analysis accounting for parameter interaction was performed (Sorin-Dupont et al., 2023). The latter did not provide evidence that parameter interactions contributed to model output variance. Therefore, our analysis was limited to a one-by-one analysis on the thresholds for our two new collective treatment criteria as well as the two key parameters of disease transmission: the transmission rate β and the contact rate between pens c . The thresholds and the transmission rates were used at their nominal values ± 10 and 25%. We used a larger interval for the contact rate, as little effect was observed in the sensitivity analysis of the previous model: we used the nominal value (0.01), multiplied or divided by 0.1, 0.5, 5 and 10. The tested values for each parameter are summarized in Table 2.

Table 2 – Parameter values in the sensitivity analysis.

Parameter	Nominal value	Values
Low risk transmission rate (β_{Low})	0.005	{0.00375, 0.0045, 0.0055, 0.00625}
Contact rate between pens (c)	0.01	{0.001, 0.005, 0.05, 0.1}

Each simulation had 200 stochastic replicates. We recorded the cumulative incidence and AMU. In order to evaluate the impact of a change in value of the transmission rate and the contact rate in each specific scenario, we computed the median of the simulations with the nominal values of the studied parameters. These medians were used as baselines. For each parameter change, we computed the relative variation of the output with regard to its respective baseline in order to evaluate the impact of the parameter change in value. We also compared the distributions of the outputs in the different collective treatment strategies with the tested parameter values in order to test the robustness of our previous conclusions. The distributions of

the outputs were compared using Wilcoxon-Mann-Whitney tests with a Bonferroni correction, as normality could not be assumed.

Results

Outputs

Every scenario using a collective treatment yielded a lower cumulative incidence of BRD cases than their counterpart scenario using individual treatment only (Wilcoxon test, p -value < 0.05). The difference in cumulative incidence of BRD cases between using individual treatments and collective treatments was however lower in HR30 than in HR90 (Figure 2).

In HR30, the cumulative incidence was the lowest in scenarios applying the conventional collective treatment. In the scenario with a random pen allocation, the severity criterion had a lower median incidence than the slope criterion, whereas no significant difference between the two new criteria could be assessed in the scenario with sorted pens.

In HR90, the scenario using the slope criterion and the conventional collective treatment displayed a lower median cumulative incidence of BRD cases than the severity criterion. In the scenario with random pen allocation, no significant difference could be assessed between the conventional collective treatment criterion and the slope-based criterion whereas the latter had a significantly lower median when the pens were sorted by risk levels. Overall, sorting the pens significantly reduced the cumulative incidence in every scenario, except in HR90 for the severity criterion (Wilcoxon test, p -value < 0.05).

Conversely, collective treatment yielded large AMU than individual treatments (Figure 3). In every scenario, the slope criterion yielded the lowest AMU of all the collective treatment criteria, while the conventional criterion yielded the highest.

The treatments appeared to have only a limited impact on the average duration of severe clinical signs (Figure 4). Indeed, in most scenarios, we observed an important overlap of the distributions. However, the conventional criterion for collective treatment was generally associated with the lowest average duration of severe clinical signs.

Collective treatments successfully reduced the occurrence of high mortality in HR90 scenarios when compared to individual treatments (Figure 5). Indeed, in random scenarios, the mortality was higher or equal to 2% in around 28% of scenarios with individual treatment, whereas this mortality was obtained in only 10 to 13% of replicates with collective treatments. In HR30 scenarios, the differences of in high mortality occurrence are less marked, as most of the replicates yielded a mortality lower or equal to 1%, regardless of the applied treatment strategy.

The proportion of treatment misuse was very low when only individual treatments were used and much higher for all collective treatments (Kruskal-Wallis test, p -value < 0.05) (Figure 6). In HR30, the median misuse of antimicrobial for collective treatments was between 50 and 75%. The collective treatment with the lowest misuse appeared to be the one triggered by the slope criterion. Sorting pens appeared to have an effect on treatment misuse when collective treatments were used (Wilcoxon test, p -value < 0.05). In HR90 scenarios, the conventional collective treatment also had a higher misuse than the two new criteria. In scenarios with a random pen

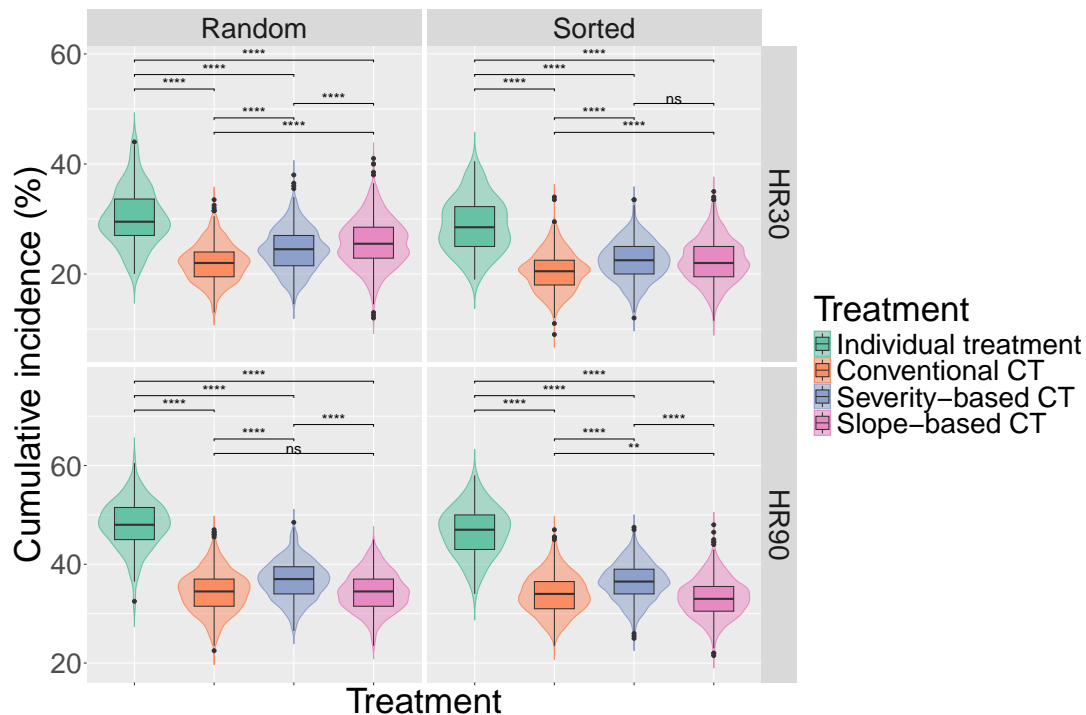


Figure 2 – Distributions of the cumulative incidence of BRD cases in the building population. The boxplots feature the median and quartiles of the distributions. Statistical test: Wilcoxon-Mann-Whitney test with Bonferroni's correction. First column: the animals are allocated randomly in pens. Second column: the animals are allocated in pens according to their individual risk level. Top row : 30, 40 and 30% of low, medium and high risk animals respectively. Bottom row: 10% of low risk animals and 90% of high risk animals.

allocation, the slope criterion was associated with the lowest misuse whereas in scenarios with sorted pens, the two new criteria were not significantly different.

The criterion for triggering a collective treatment affected the delay between the detection of the first BRD case and the collective treatment (Figure 7). Indeed, when collective treatments were triggered with the slope criterion, the delay between the first case and the collective treatment was shorter than a day in the majority of the stochastic replicates, whereas this delay was more often between one and two days for the conventional criterion. Collective treatment triggered by the severity criterion were triggered in less than a day in between 26% and 37% of the replicates with collective treatment. In around 43% of the cases, it was triggered between one and two days after the first case in the pen.

On an individual level, collective treatments shortened the delay between the infection and the treatment (Figure 8). The delay exceeded 2 days in less than 15% of the replicates in scenarios with collective treatments, while delays up to 9 days were observed in scenarios with individual treatments. Among collective treatment criteria, the conventional criterion yielded the biggest proportions of delays shorter than a day (up to 84% in HR90 scenarios), while the other two criteria yielded similar results.

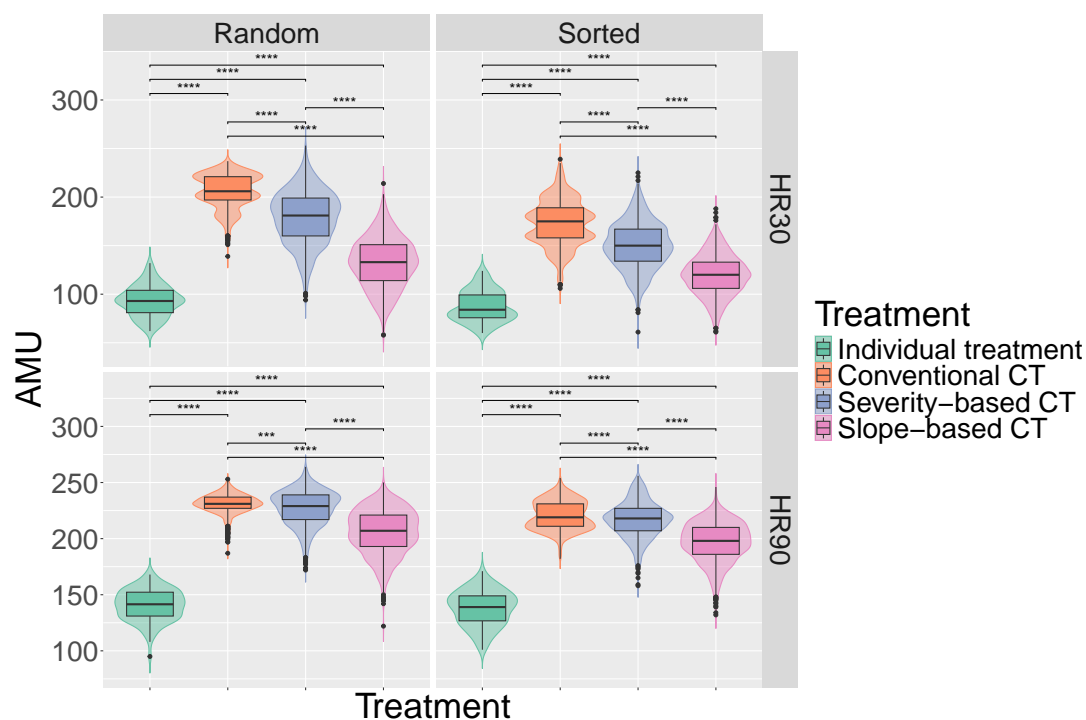


Figure 3 – Distributions of the antimicrobial use (AMU) in the building population. The boxplots feature the median and quartiles of the distributions. Statistical test: Wilcoxon-Mann-Whitney test with Bonferroni’s correction. First column: the animals are allocated randomly in pens. Second column: the animals are allocated in pens according to their individual risk level. Top row : 30, 40 and 30% of low, medium and high risk animals respectively. Bottom row: 10% of low risk animals and 90% of high risk animals

Pens containing animals of the same individual risk level were grouped together across the simulations to observe proportions of triggered collective treatment in each specific group (Table 3). A collective treatment was triggered in most of the pens composed of animals with high risk of respiratory disease, irrespective of the criterion. The conventional criterion had the highest proportion of triggered collective treatments in pens composed of medium risk individuals (83.9%), while the severity criterion triggered a collective treatment in 58.1% of these pens and the slope criterion only triggered a collective treatment in 33.8% of them. In pens composed of low risk individuals, collective treatments triggered by the conventional criterion happened in 35.9% of the pens, while collective treatments based on the severity and slope criteria only happened in 12.6 and 5.5% of the pens respectively.

Table 3 – Proportion of triggered collective treatments in sorted pens.

Treatment strategy	Proportion of pens having triggered a collective treatment (%)		
	Low-risk pens	Medium-risk pens	High-risk pens
Conventional CT	35.9	83.9	99.7
Slope-based CT	5.5	33.8	85.6
Severity-based CT	12.6	58.1	91.8

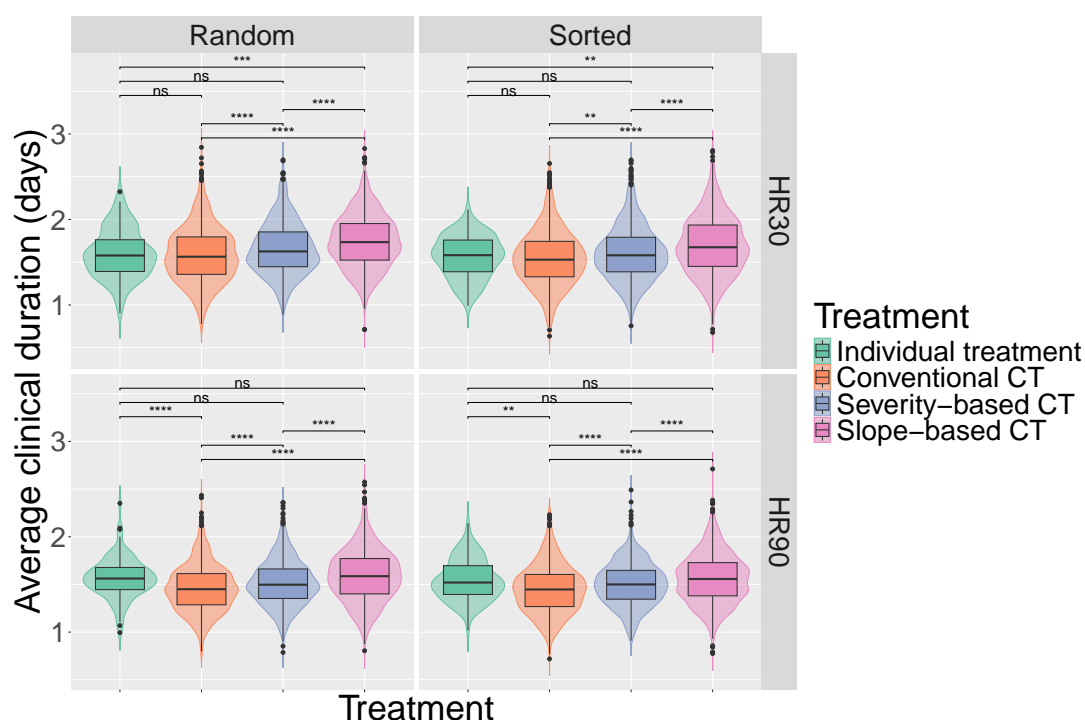


Figure 4 – Distributions of the average duration of severe clinical signs in the building population. The boxplots feature the median and quartiles of the distributions. Statistical test: Wilcoxon-Mann-Whitney test with Bonferroni's correction. First column: the animals are allocated randomly in pens. Second column: the animals are allocated in pens according to their individual risk level. Top row : 30, 40 and 30% of low, medium and high risk animals respectively. Bottom row: 10% of low risk animals and 90% of high risk animals

Sensitivity analysis

The between-pen contact rate had no impact on the outputs when it was lower than its nominal value (Figure 9). In scenarios with a random pen allocation, a contact rate equal to 0.1 was associated with significantly higher AMU and cumulative incidence only when the slope criterion was applied. However, the scenarios with sorted pens were more sensitive to changes in contact rate values: indeed, contact rates higher than the nominal value were associated with significantly higher AMU and cumulative incidences for every collective treatment strategies.

The transmission rate variations yielded a stronger impact on the cumulative incidence than on the AMU (Figure 10). Indeed, the AMU was significantly lower when the transmission rate was equal to 0.00375, with no other clear differences for the other transmission rate values. In particular, the AMU for the slope criterion remained unchanged for every transmission rate value. The cumulative incidence was similarly affected by lower transmission rate values. Additionally, it was also sensitive to transmission rates higher than the nominal value, especially in scenarios with sorted pens. Indeed, in scenarios with sorted pens, the cumulative incidence was significantly higher than the baseline scenario when the transmission rate was equal to 0.00625 for every collective treatment criterion.

Changes in contact rates between pens had little to no impact on the ranking of the collective treatment criterion (Figure 11). Indeed, For every contact rate value, the slope criterion was always associated with the highest cumulative incidence in scenarios with random pens and was

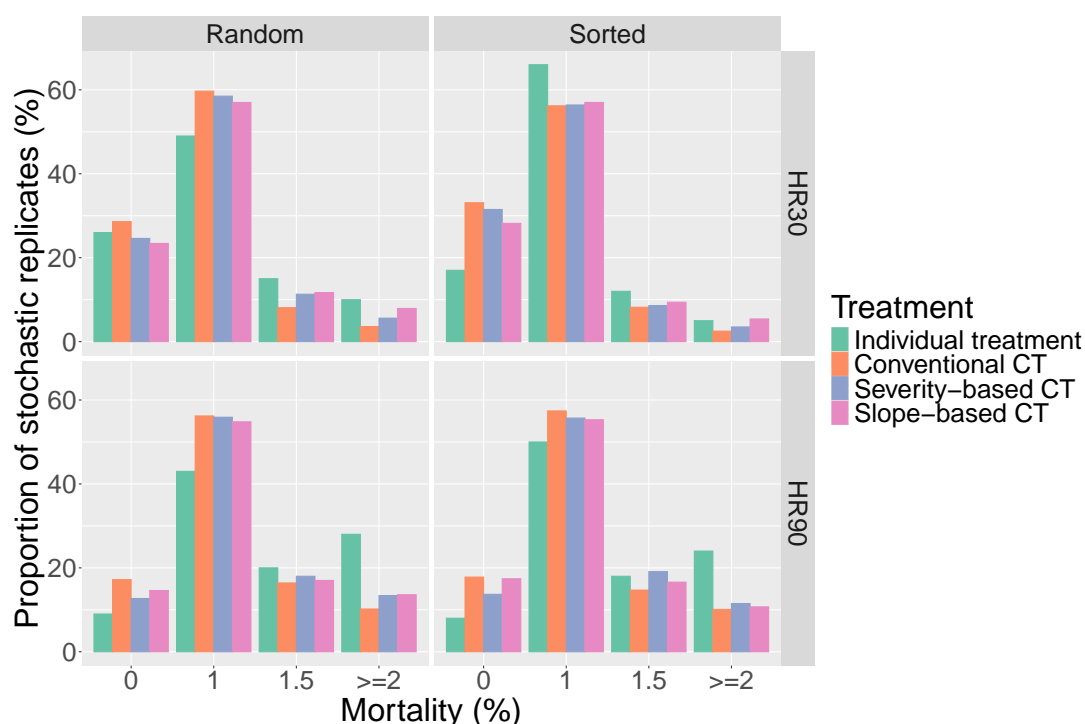


Figure 5 – Barplots of the mortality in the building population. First column: the animals are allocated randomly in pens. Second column: the animals are allocated in pens according to their individual risk level. Top row : 30, 40 and 30% of low, medium and high risk animals respectively. Bottom row: 10% of low risk animals and 90% of high risk animals

associated with the lowest AMU.

Similar results were obtained when comparing the collective treatment criteria under several transmission rates (Figure A.7). Indeed, the slope criterion was still associated with the lowest AMU and the highest incidence in random pen allocation scenarios.

Discussion

This study aimed at modeling the impact of triggering collective antimicrobial treatments according to three different criteria on the spread of *M. haemolytica* in multi-pens fattening systems while accounting for the multi-pen structure, individual risk of being affected by BRD and farming practices in terms of pens composition. We computed the cumulative incidence, the average duration of severe clinical signs and the mortality. We balanced these outputs against the AMU and treatment precision for each scenario. We also computed the delay between the beginning of an episode and the beginning of the treatment and calculated the proportion of pens triggering collective treatments based on each criterion. We proposed that a novel criterion, based on the speed of the spread rather than on a proportion of detected individuals, could yield a better trade-off between BRD case incidence and AMU than the conventional way of implementing collective treatment. This result could have interesting operational implications on the decision-making regarding collective treatment in fattening farms.

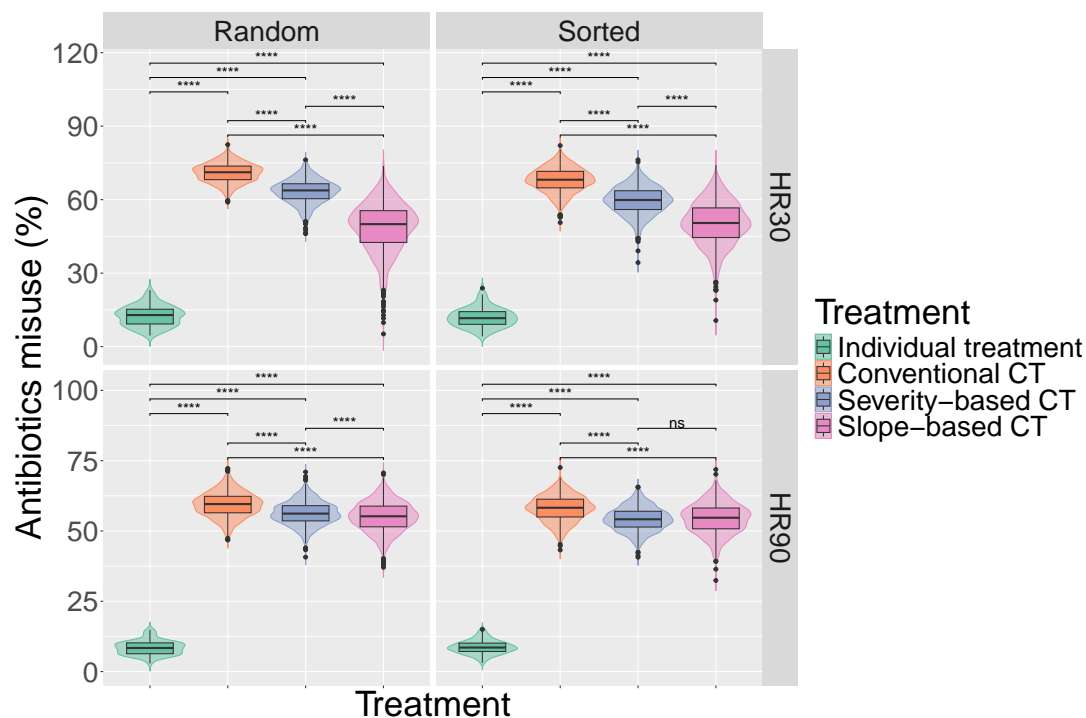


Figure 6 – Distributions of the proportion of treatment misuse. This proportion is the ratio of doses given to healthy individuals on the total AMU. The boxplots feature the median and quartiles of the distributions. Statistical test: Wilcoxon-Mann-Whitney test with Bonferroni’s correction. First column: the animals are allocated randomly in pens. Second column: the animals are allocated in pens according to their individual risk level. Top row : 30, 40 and 30% of low, medium and high risk animals respectively. Bottom row: 10% of low risk animals and 90% of high risk animals

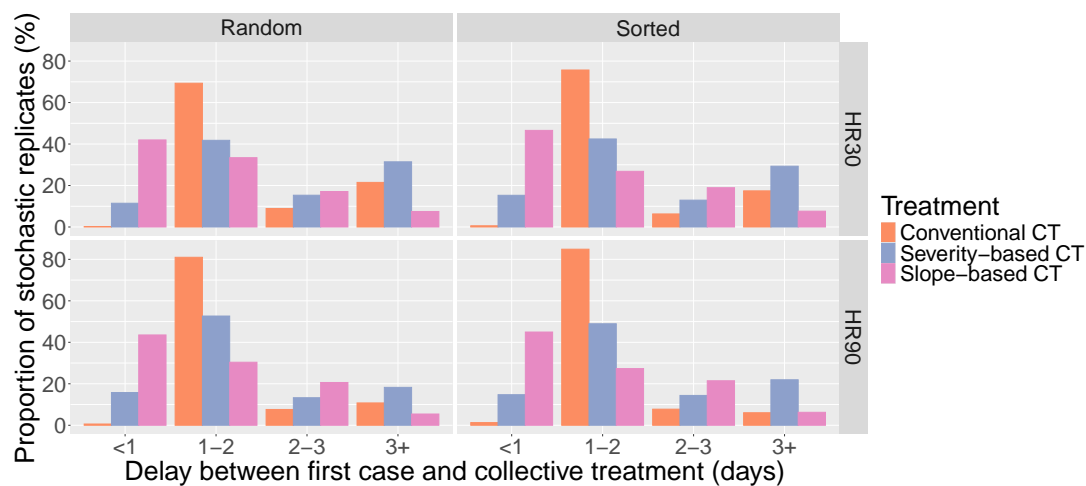


Figure 7 – Delay between the first case in a pen and the collective treatment (in days). First column: the animals are allocated randomly in pens. Second column: the animals are allocated in pens according to their individual risk level. Top row: 30, 40 and 30% of low, medium and high risk animals respectively. Bottom row: 90% of high risk animals. The effect of the treatment modality on the delay is significant according to a χ^2 test.

We showed that collective treatment could efficiently reduce the incidence of bacterial respiratory disease in population with high individual risk of BRD. The positive impact on animal health and welfare balanced the supplementary cost in antimicrobial doses. This compromise

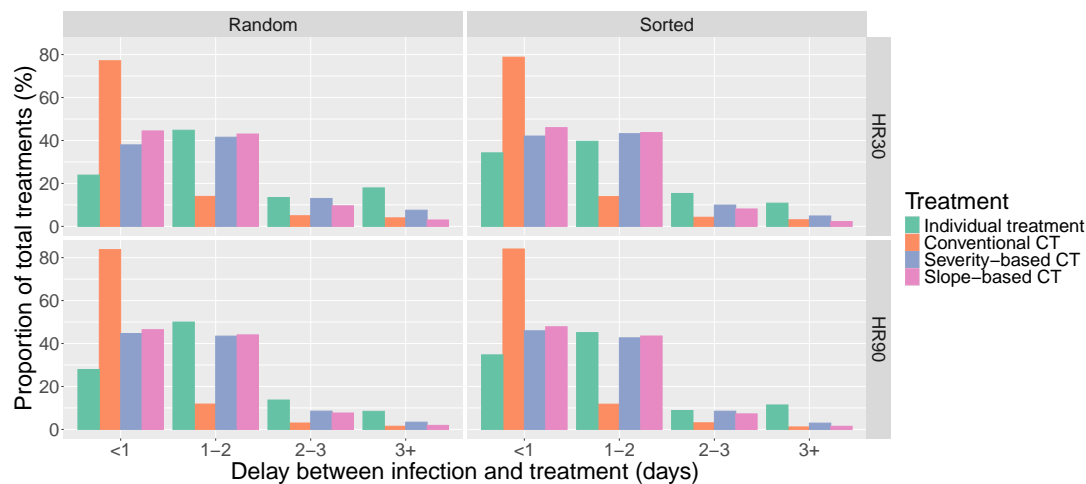


Figure 8 – Delay between infection and treatment (in days). First column: the animals are allocated randomly in pens. Second column: the animals are allocated in pens according to their individual risk level. Top row: the population is composed of 30, 40 and 30% of low, medium and high risk animals respectively. Bottom row: the population is composed of 10% of low risk animals and 90% of high risk animals.

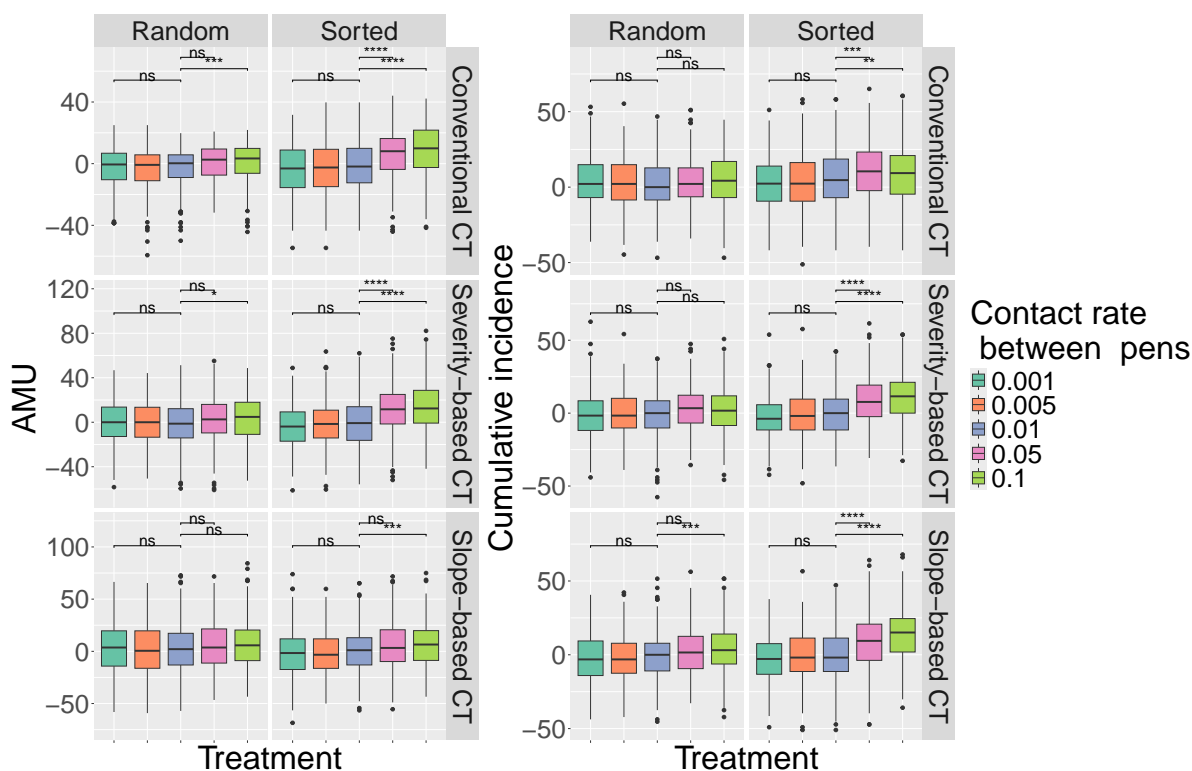


Figure 9 – Analysis of the sensitivity of the outputs to between-pens contact rate values. Top panel: Cumulative incidence variation relative to the median of the baseline scenario – $c = 0.01$ – (in %). Bottom panel: AMU variation relative to the median of the baseline scenario (in %). First row: the animals are allocated randomly in pens. Second row: the animals are allocated in pens according to their individual risk level. CT: Collective treatment. Statistical test: Wilcoxon-Mann-Whitney test with Bonferroni's correction.

in favour of reducing BRD impact was particularly relevant and valuable for high-risk individuals. This finding is consistent with a previous simulation study which implemented collective treatments on an ‘average pathogen’ with less strict thresholds (Picault et al., 2022). In American

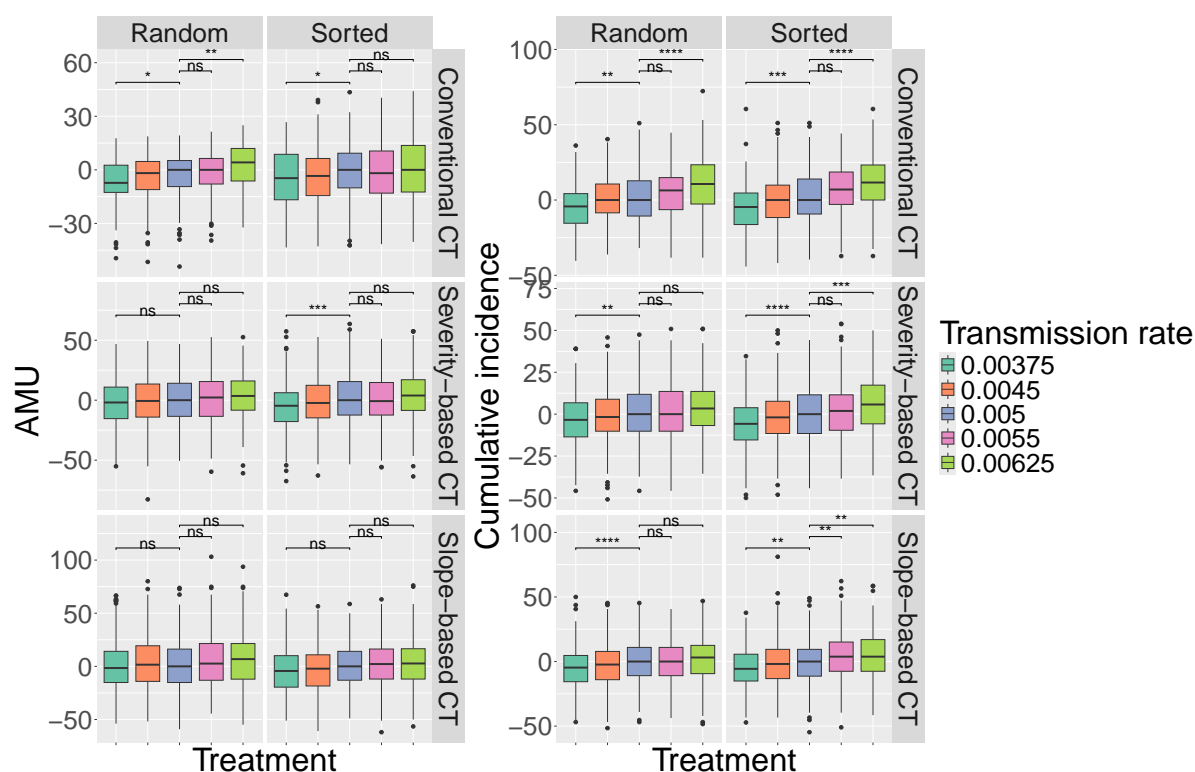


Figure 10 – Analysis of the sensitivity of the outputs to transmission rate values. Top panel: Cumulative incidence variation relative to the median of the baseline scenario – $\beta = 0.005$ – (in %). Bottom panel: AMU variation relative to the median of the baseline scenario (in %). First row: the animals are allocated randomly in pens. Second row: the animals are allocated in pens according to their individual risk level. CT: Collective treatment. Statistical test: Wilcoxon-Mann-Whitney test with Bonferroni's correction.

systems, medication of at-risk cattle is frequent at feedlot entry after their identification and the implementation of preconditioning programs (González-Martín et al., 2011). These programs have been studied in Europe, but the results remained inconclusive regarding their positive impact on animal health and welfare (Vanbergue et al., 2024). The study however concluded that the cattle sector should focus its effort on improving husbandry practices. This suggestion aligns with the use of a selective criterion for the implementation of curative collective treatments.

Our results showcased a positive impact of collective treatments on disease related mortality in the herd in high risk scenarios. However, no criterion was identified as systematically better than the others in reducing the mortality. This can be due to the fact that collective treatments happened rather rapidly after an outbreak, in spite of some differences in delay. This swift reaction did not let time for animals to develop severe clinical signs and to die subsequently to them. Our results aligned with field studies showing reduced mortality in herds where collective treatment was used (O'Connor et al., 2013).

The supplementary cost in antimicrobial was less desirable when the general risk was lower in the population, as the reduction in incidence and severity thanks to collective treatment was

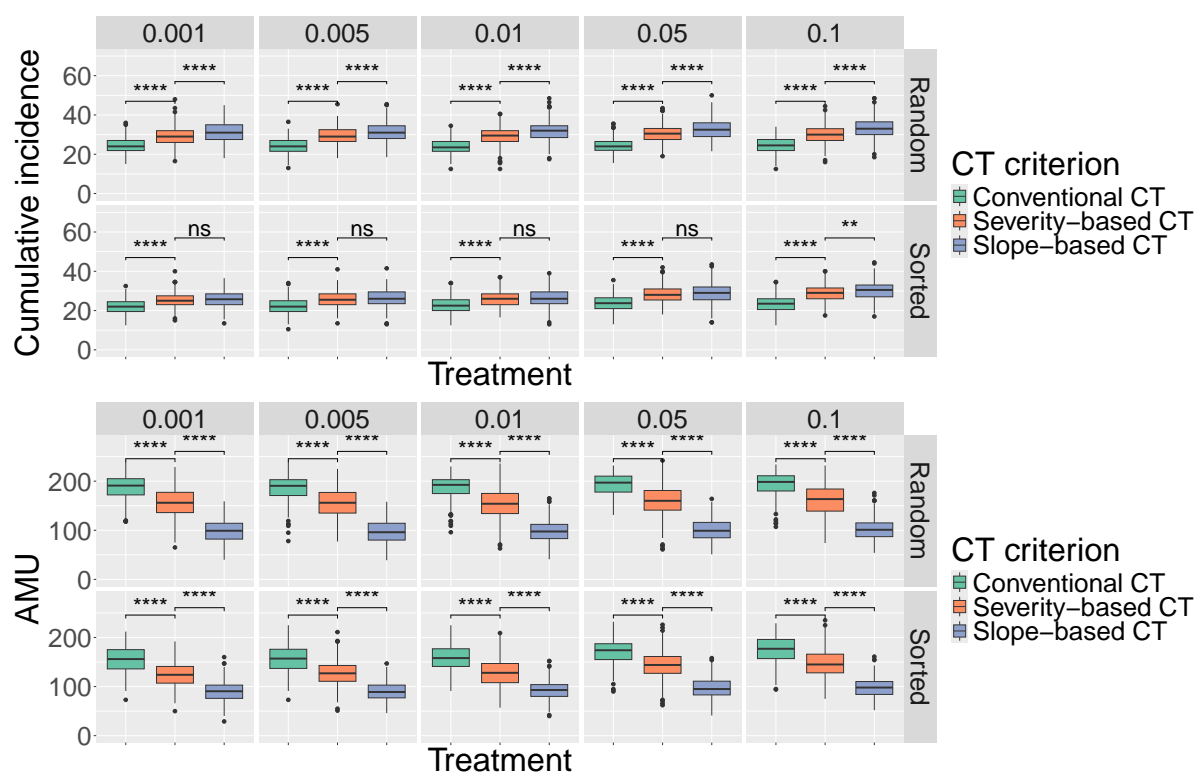


Figure 11 – Impact of the collective treatment strategies on the outputs with the tested between-pen contact rate values. Top panel: Cumulative incidence. Bottom panel: AMU. First row: the animals are allocated randomly in pens. Second row: the animals are allocated in pens according to their individual risk level. Each column represents the tested value for the contact rate. Statistical test: Wilcoxon-Mann-Whitney test with Bonferroni's correction..

less substantial. The overuse of antimicrobial leads to antimicrobial resistance and treatment purchase and administration are costs supported by the farmer (Laxminarayan et al., 2013). Therefore, there appears to be a trade-off between incidence reduction and antimicrobial use which could benefit from a characterization of the risk level of the pens. Such a characterization could guide the farmers in making the best decision regarding treatment and herd management (Edwards, 2010).

Our model allowed us to identify a beneficial novel criterion for collective treatment. Indeed, instead of a threshold of detected animals in a pen, basing a collective treatment decision on the speed of the spread of the disease allowed marginal gains in disease incidence while drastically reducing the AMU and the treatment misuse when compared to the other collective treatment criteria. A field meta-analysis of randomized clinical trials showed that the risk reduction of BRD varied drastically with the criterion for collective treatment (Baptiste and Kyvsgaard, 2017). The routine criterion is 10% of morbidity for two consecutive days, however, there is no evidence based studies proving the relevance of this threshold (Radostits, 2001). Perspectives of this study include the investigation of the novel treatment strategies in broader contexts in order to translate the thresholds used into operative indicators.

Collective treatments based on the speed of the spread of the pathogen proved to be triggered sooner than with the other criteria. This precocity was key for the reduction of the incidence and severity of the disease, especially in high-risk populations. It also showed to target more specifically high-risk groups than the other criteria, as it reduced the proportion of low-risk pens having received collective treatments. On an individual level, the delay between the infection and the administration of the first dose of treatment was also characterized. This delay was shortened by the implementation of collective treatment strategies, particularly for the conventional criterion. These are original findings with clear practical implications, especially with regards to the need for a better knowledge by farmers of individual risk of animals developing BRD, in order to account for this information when constituting pens. However, triggering collective treatments greatly relies on the ability to detect diseased animals in the first place, therefore, increasing the sensitivity via standardized detection procedures may increase the benefit of the subsequent control measures and may modify the most convenient criteria to trigger collective treatment (Kamel et al., 2024).

The novel slope criterion proposed by this study also outperformed the conventional criterion in terms of antimicrobial misuse, especially in moderate risk scenarios. As the animals with a high individual risk of BRD are more prone to develop and to transmit respiratory pathogens, targetting the most at risk pens is a desirable trait for BRD control measures. Our results on collective treatments occurrence in sorted pens highlight the ability of the novel slope criteria to target the most at risk pens, therefore reducing the antimicrobial use in pens with a lesser risk of an outbreak. This also translated to the lowest proportion of treatment misuse at herd level when compared to the other two collective treatment criteria. In scenarios with individual treatments only, the misuse of antimicrobial on healthy animals was even lower than for the slope criterion, as it was solely due to the false discovery of diseased animals via temperature check, as hyperthermia could be non specific to infection.

The conclusions brought up by our model proved to be robust to changes in transmission rates and between-pen contact rates. Furthermore, it also brought evidence that the slope criterion benefited from sorted pens, as this setting allowed the incidence and AMU to be particularly stable. These findings allowed us to prove the robustness of our results and to further emphasize the potential of the new collective treatment criterion we brought forward.

Our model simulated scenarios assuming the circulation of only one bacterial pathogen. BRD is essentially a multi-pathogen disease, and synergies between viruses and bacteria have been reported to change the disease dynamics and severity (Gaudino et al., 2022). Further investigations of the effect of treatment strategies could be conducted in a context with mixed infections. However, quantifying the treatment response in such context is still a pending question (Fulton et al., 2009).

There is clear evidence that antimicrobial resistance is rising among *M.haemolytica* populations (Timsit et al., 2017; Woolums et al., 2018). This rise happens on time scales that are longer than the one we modeled. Therefore, we modeled the existence of resistant strains by calculating a probability of treatment success, which value was set along the span of the simulation. Future work could aim at evaluating the long term effects of collective treatment protocols on

the antimicrobial trends.

The force of infection used in this model assumed an increased pathogen transmission within pens with an additional equal contribution of the surrounding pens. This hypothesis relied on the fact that aerosolization of *M.haemolytica* has been pointed as a contributing factor to rapid disease spread among cattle populations in close quarters (Rice et al., 2007). However, this airborne transmission is not as effective as transmission via close contacts. Adaptions of the model could therefore implement a force of infection based on the farm spatial organization (Ackermann and Brogden, 2000).

Our study advocates for more transparency on the individual risk level for BRD in the cattle production system. Such a characterization could allow mindful investments for the farmers as well as more adequate control measures regarding housing and treatment. Indeed, our novel collective treatment criterion proved to be able to target at-risk pens while not applying collective treatments to lower risk pens.

This model provides a solid basis for testing these new criteria for triggering collective treatments vs. keeping only individual ones on other known respiratory pathogens or a combination thereof, in order to identify potential new operational recommendations on treatment strategies. Future work could also test the inclusion of automated tools for decision making regarding treatment.

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Conflict of interest disclosure

Pauline Ezanno is recommender of PCI Animal Science. The authors declare they comply with the PCI rule of having no financial conflicts of interest.

Data, script and code availability

The complete code for the model can be found on this repository: <https://doi.org/10.5281/zenodo.17090740> (Sorin-Dupont, 2025). The version of the model used for this work is tagged under `pci_animal_science_2024`.

Appendix A. SI1: Model processes

A.1. Implementation and formalism of the model

The model is a stochastic individual based model. In the model, five processes drive the states of individuals: infection, hyperthermia, clinical signs, detection and treatment. They are represented by a formalism broadly used in computer science, finite state machines, which is close to flow diagrams used by epidemiologists, with a higher expressiveness. They represent finite state an individual can find itself in. Their textual description in the YAML format in the model file is easy to read and can be automatically converted in a graphical representation by EMULSION. The model can be found on a git repository, accessible by following this link: <https://forgemia.inra.fr/spicault/brd-withinherd-emulsion.git>. The version of the model used for this work is tagged under `pci_animal_science_2024`.

To help understand the state machine diagrams, we present how the diagram summarising the infection process relates to the state machine specification, extracted from the whole model. More details on how state machines differ from flow diagrams are available in the documentation: https://sourcesup.renater.fr/www/emulsion-public/pages/Modelling_principles.html.

Appendix B. SI2: Threshold selection for the Novel criteria for collective treatment

B.1. Method

In scenarios featuring collective treatment triggered by slope and severity criteria, the collective treatment was implemented when the respective criterion went above a certain threshold. Such a threshold thus had to be defined as a preliminary step of our study.

In order to determine the relevant threshold for intervention, we defined a range of viable threshold values. We thus plotted both criteria on baseline scenarios (without any collective treatments). This baseline scenarios was repeated along 200 stochastic replicates in order to obtain a distribution of values for each time step. For each time step, the median value, the 5th and 95th percentiles were recorded, thus resulting in three time series for each criterion and each scenario (Figures A.1,A.2).

The interval was extracted from the HR30 Random scenario for both criteria. The upper bound was defined as the maximum point of the 95% quantile time series and the lower bound was defined by the maximum point of the median time series. The rationale behind this was to exclude values that would either be too low or too likely while also excluding any values that would be too high or too unlikely. Indeed, HR30 Random represents a baseline scenario and our selection allowed us to select only the higher half of the maximum values in this scenario. Thus, we obtained a credible range of [1, 3] for the severity criterion, discretized with intervals of 0.2. This criterion is also characterized by parameter α , assumed strictly lower than 0.5 to emphasize the number of individuals with severe clinical signs. This parameter was assigned a credible range of [0.1, 0.4] with intervals of 0.1.

We used the same rationale for the selection of a credible range for the slope criterion. We thus selected a range encompassing the maximum value of the median run in the HR30-Random scenario and the maximum of the 95% quantile of this scenario. For the slope criterion, the credible

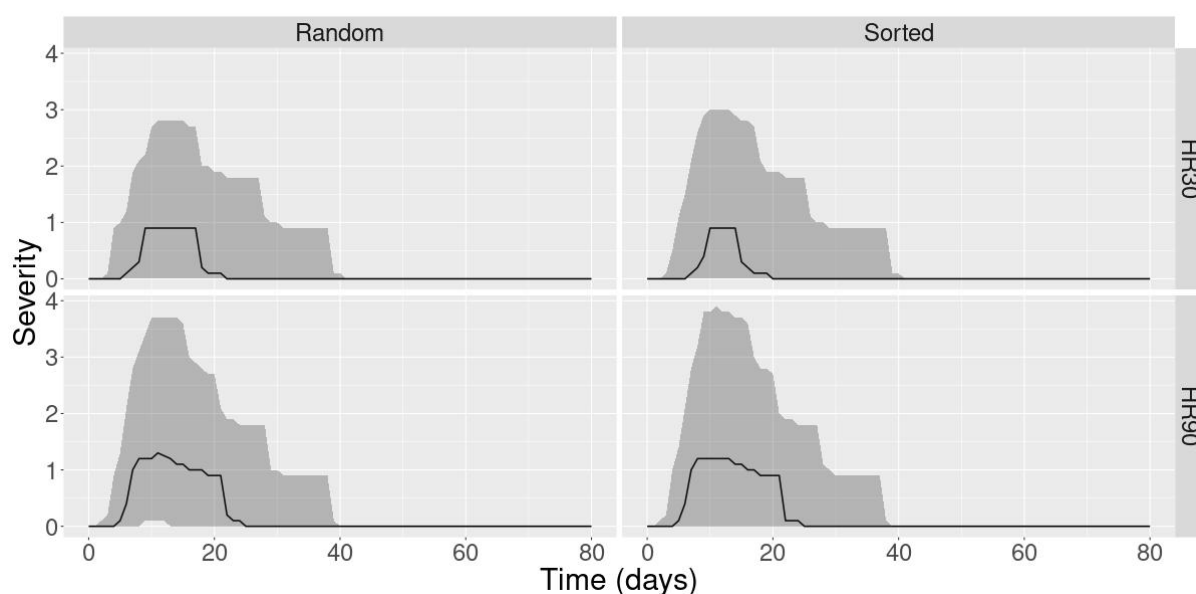


Figure A.1 – Median and 5-95% quantiles of the severity criterion ($\alpha = 0.4$) across scenarios with individual treatments only. The values recorded for the exploration interval were the maxima of the median and 95% quantile in the HR30-Random scenario

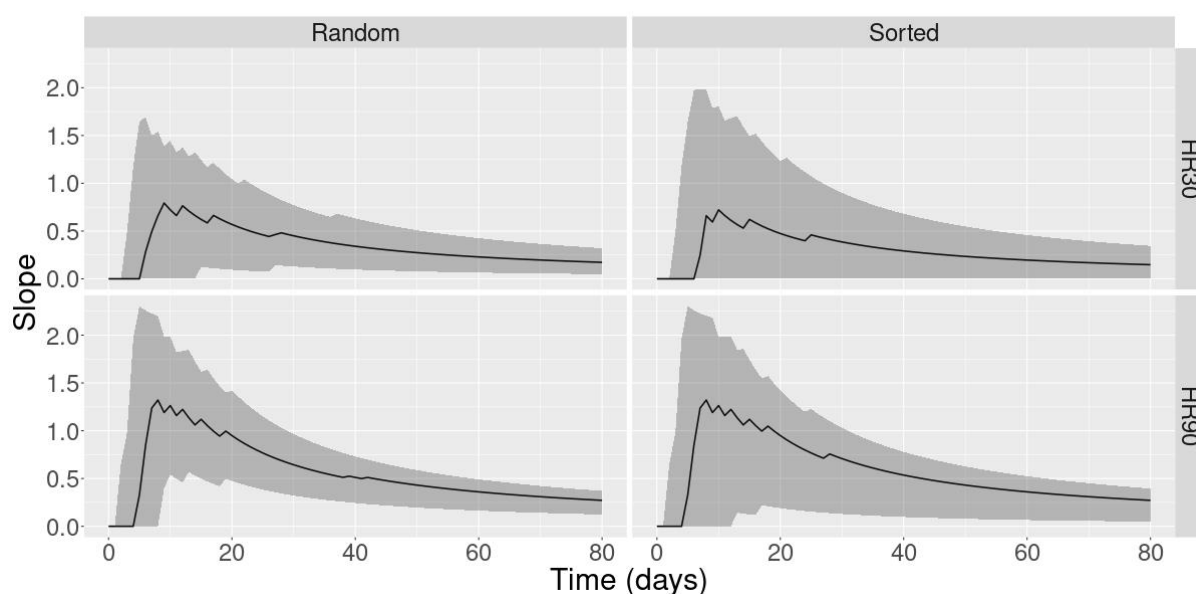


Figure A.2 – Median and 5-95% quantiles of the slope criterion across scenarios with individual treatments only. The values recorded for the exploration interval were the maxima of the median and 95% quantile in the HR30-Random scenario

range was thus $[0.75, 1.7]$, discretized by intervals of 0.05.

We tested each threshold value in scenarios defined by 3 possible farm-scale proportions of individual risk status of developing BRD and two ways of assigning animals to pens.

- 90%, 0% and 10% of low, medium and high risk respectively (HR10). This scenario was used as a 'best case scenario', that should not be triggering collective treatment, thus allowing to discriminate thresholds that would be too sensitive.
- 30%, 40%, and 30% of low, medium, and high risk respectively (HR30)
- 10%, 0% and 90% of low, medium and high risk respectively (HR90)

Additionally, animals could be randomly assigned into pens (Random) or be assigned according to their individual risk level (Sorted).

For each threshold value in each scenario, we computed the median cumulative incidence and AMU in order to identify which threshold value had the best trade-off between case incidence and AMU. We determined the cutoff values of the cumulative incidence and AMU by computing the mean of both of the outputs across the tested thresholds. We then selected the threshold value equal or inferior to the mean of both outputs.

B.2. Results

B.2.1. Severity criterion. In HR10 scenarios, the cumulative incidence was roughly constant across the threshold values (Figure A.3). In HR30 and HR90 scenarios, it increased linearly. The incidence was superior to the cutoff in every scenario when the threshold was higher than 1.5.

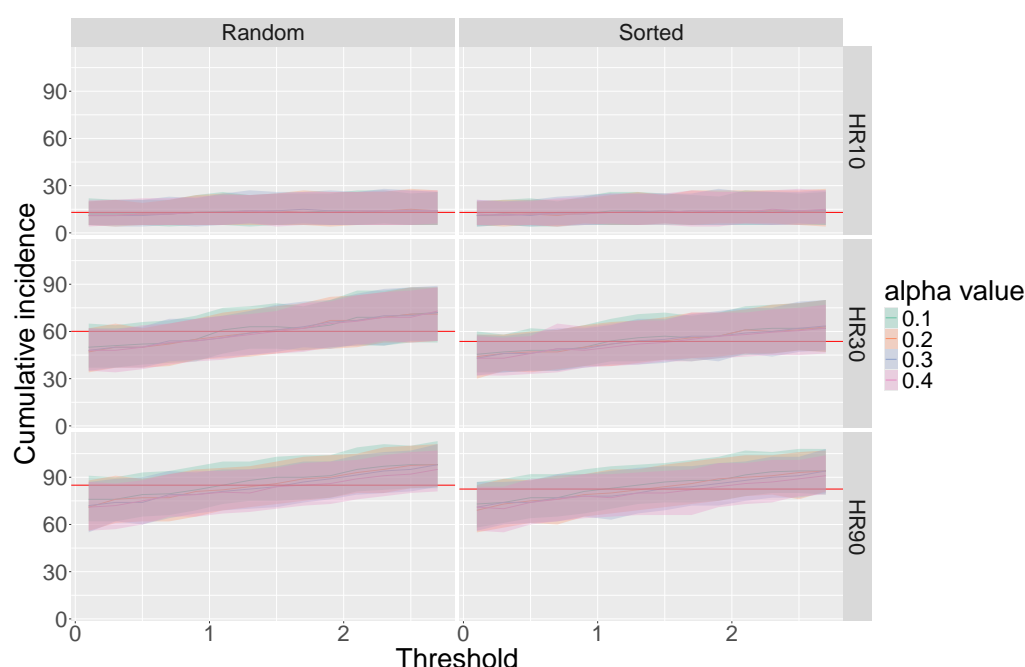


Figure A.3 – Median and 5-95% quantiles of the cumulative incidence across scenarios and threshold values for the severity based criterion. The horizontal red line represents the mean value of the cumulative incidence across the thresholds in the given scenario.

In HR10 scenarios, the AMU had a steady decrease for low threshold values and then plateaued to values lower than the cutoff (Figure A.4). Conversely, we observed a plateau of high AMU with low threshold values in HR30 and HR90 scenarios. Thresholds values lower than 1.5 were either associated with AMU higher than the low plateau in HR10 or entering the high plateau in HR30 and HR90. Therefore, we chose 1.5 as a cutoff value for the severity criterion.

B.2.2. Slope criterion. In HR10 scenarios, the cumulative incidence was also roughly constant across the threshold values (Figure A.5). In HR30 and HR90 scenarios, it increased steadily. The incidence was superior to the cutoff in every scenario when the threshold was higher than 1.15.

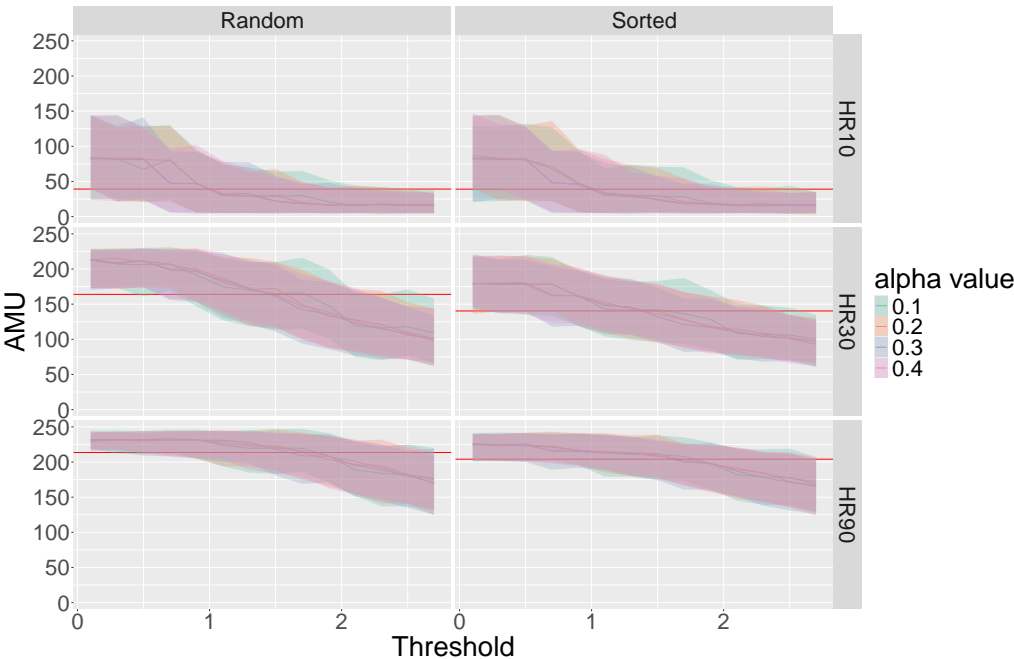


Figure A.4 – Median and 5-95% quantiles of the AMU across scenarios and threshold values for the severity based criterion. The horizontal red line represents the mean value of the AMU across the thresholds in the given scenario.

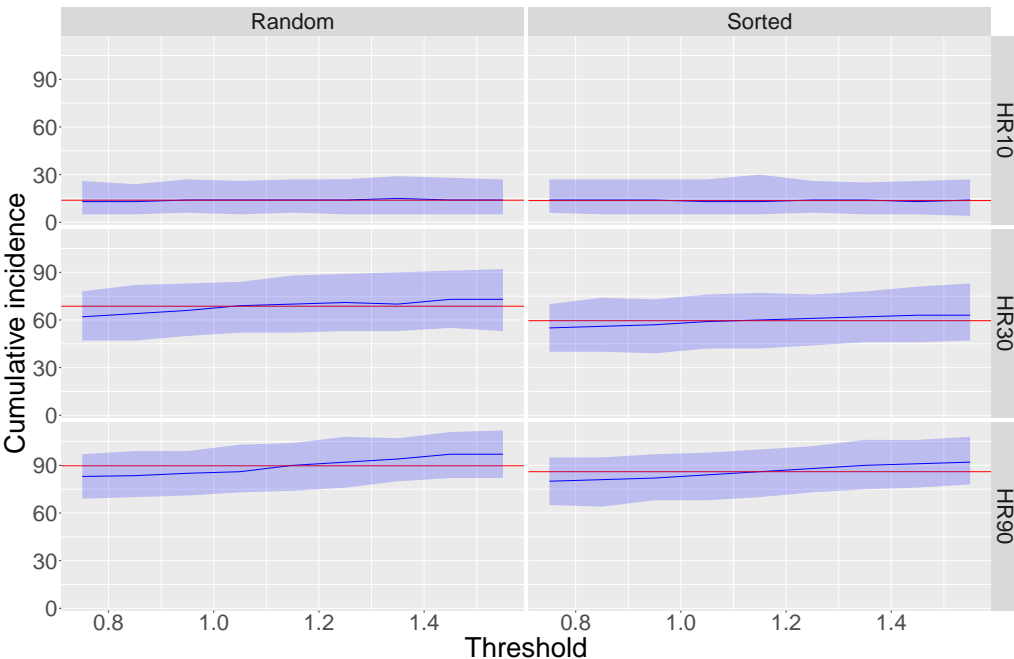


Figure A.5 – Median and 5-95% quantiles of the cumulative incidence across scenarios and threshold values for collective treatment triggered by the slope based criterion. The horizontal red line represents the mean value of the cumulative incidence across the thresholds in the given scenario. First column: the animals are allocated randomly in pens. Second column: the animals are allocated in pens according to their individual risk level. Top row: 90% of low risk animals and 10% of high risk animals respectively. Second row : 30, 40 and 30% of low, medium and high risk animals respectively. Bottom row: 10% of low risk animals and 90% of high risk animals

The AMU was also roughly constant in HR10 scenarios across the threshold values (Figure A.6). It decreased almost linearly in HR30 and HR90 scenarios. The AMU was lower than the cutoff in every scenario when the threshold for the slope criterion was higher than 1.15. We therefore chose this value as threshold for the slope criterion.

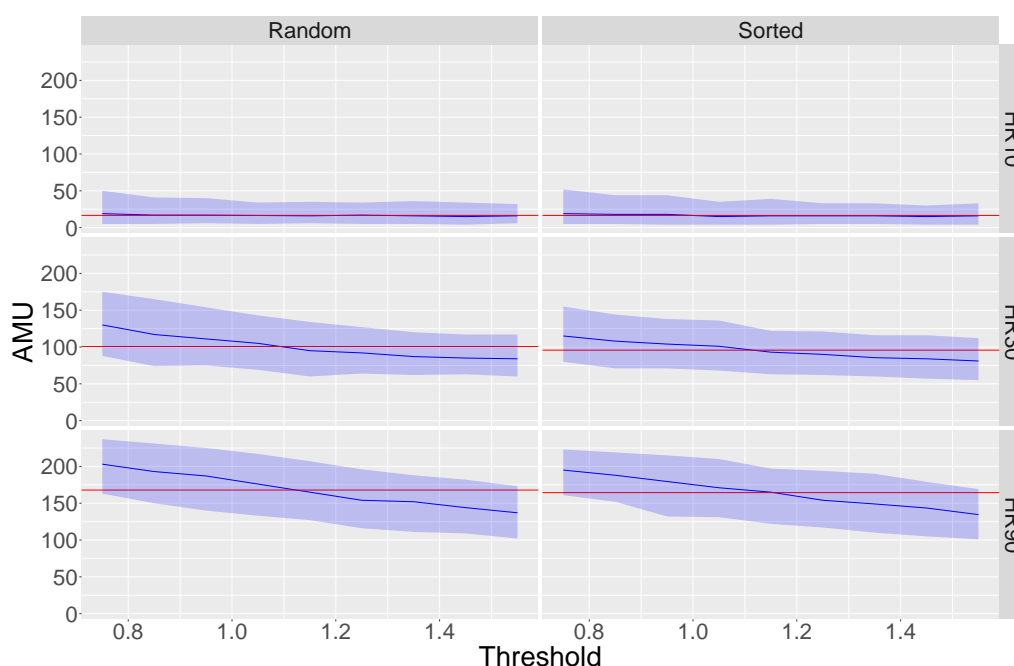


Figure A.6 – Median and 5-95% quantiles of the AMU across scenarios and threshold values for collective treatment triggered by the slope based criterion. The horizontal red line represents the mean value of the AMU accross the thresholds in the given scenario. First column: the animals are allocated randomly in pens. Second column: the animals are allocated in pens according to their individual risk level. Top row: 90% of low risk animals and 10% of high risk animals respectively. Second row : 30, 40 and 30% of low, medium and high risk animals respectively. Bottom row: 10% of low risk animals and 90% of high risk animals

Final threshold values for triggering collective treatments:

- **Threshold for the slope criterion: 1.15**
- **Threshold for the severity criterion: 1.5**

Appendix C. Additional figures

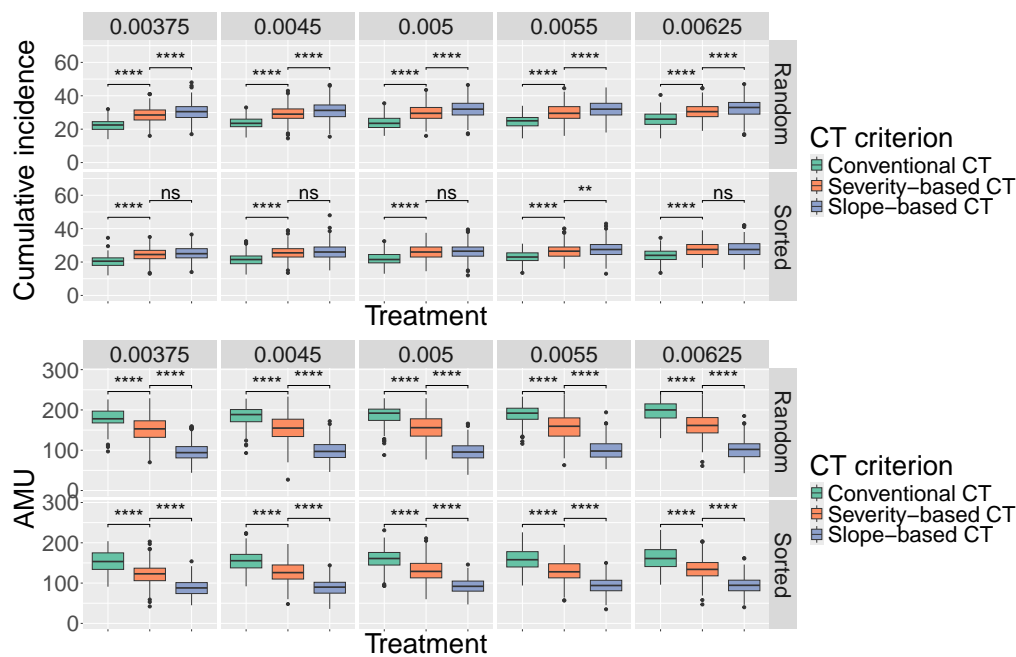


Figure A.7 – Impact of the collective treatment strategies on the outputs with the tested transmission rate values. Top panel: Cumulative incidence. Bottom panel: AMU. First row: the animals are allocated randomly in pens. Second row: the animals are allocated in pens according to their individual risk level. Each column represents the tested value for the transmission rate. Statistical test: Wilcoxon-Mann-Whitney test with Bonferroni's correction.

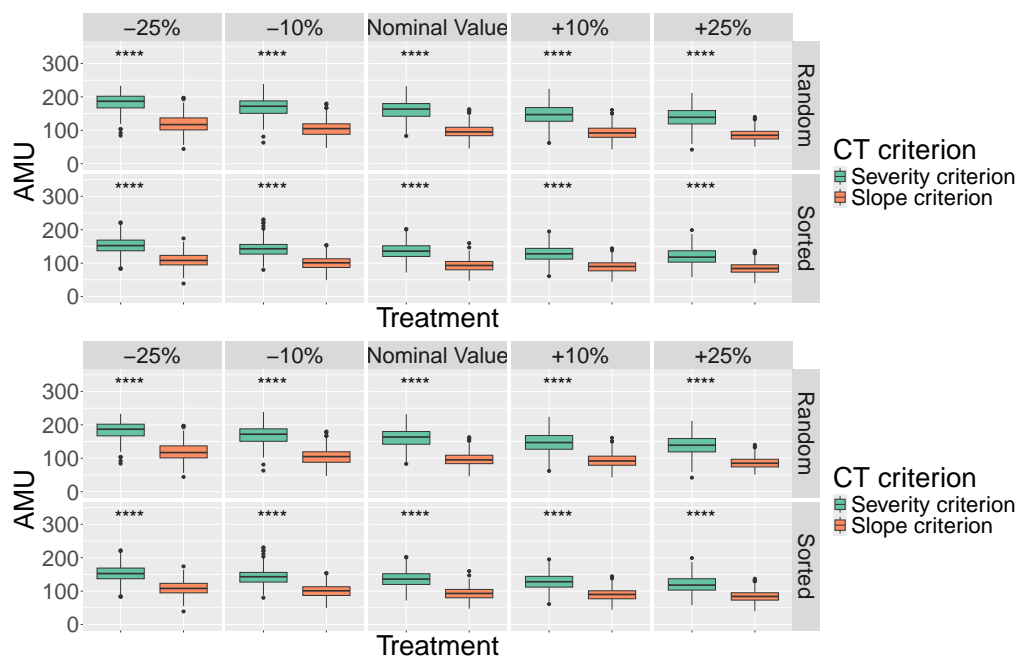


Figure A.8 – Impact of the collective treatment strategies on the outputs with the tested thresholds. Top panel: Cumulative incidence. Bottom panel: AMU. First row: the animals are allocated randomly in pens. Second row: the animals are allocated in pens according to their individual risk level. Each column represents the tested value for the transmission rate. Statistical test: Wilcoxon-Mann-Whitney test with Bonferroni's correction.

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