Evaluating a selective therapy approach to antimicrobial treatment of high-risk calves at arrival to a male dairy calf rearing facility on future health, growth and antimicrobial use: A group randomized controlled trial

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Abstract

The objective of this group randomized controlled trial was to compare a selective therapy strategy to a conventional group antimicrobial strategy at the time of arrival on mortality, morbidity, average daily gain and antimicrobial use. Data were collected from 1,032 calves in 19 rooms over an 84-day study period between January 15 and August 7, 2018. All calves were randomly assigned to rooms and subject to a standardized screening risk assessment upon arrival at the facility. Rooms were randomly assigned to receive either conventional group oral antimicrobials; or, selective therapy based on risk assignment (long-acting parenteral antimicrobials, oral electrolytes, or both). Cox proportional hazards models were built for calf health outcomes, while mixed linear regression models were constructed for calf growth and antimicrobial use outcomes. There was no difference between interventions for morbidity over the entire study period. However, lightweight calves assigned to the conventional group antimicrobial therapy had higher total and group treatment incidence. Calves assigned to the selective therapy strategy that had rectal temperatures below 103.1 °F (39.5 °C) at the time of arrival were more likely to be treated with antimicrobials. The selective therapy strategy had an increased hazard of mortality. Growth was lower in calves assigned to the selective therapy strategy in the winter as compared to calves assigned to conventional group metaphylaxis. This study demonstrates that a selective therapy strategy at the time of arrival may not be appropriate for all facilities or in all seasons despite the overall reduction in antimicrobial use.

Key words: antimicrobial use, calf, risk assessment, arrival strategies

Introduction

Neonatal calves require careful management early in life, while their immune and physiological systems are maturing, to ensure future health and productivity. Male dairy calves often face challenges within the first few weeks of life, such as the stress of transportation, variable periods of fasting, comingling, new housing and a new diet. These challenges have been shown to contribute to the high levels of morbidity and mortality seen in veal and dairy beef operations.[1,2] To mitigate this risk, group metaphylaxis at the time of arrival has been a common practice.[3-5]

Growing concerns about the development of antimicrobial resistance and potential human health consequences are driving initiatives to reduce antimicrobial use in food producing animals through improved antimicrobial stewardship.[6] In response to these concerns, some countries in the European Union have either banned or restricted the use of prophylaxis or metaphylaxis.[7] Since group level metaphylaxis has been a commonly employed strategy to address the health challenges seen soon after arrival to veal or dairy beef facilities, veal industry stakeholders have concerns that large reductions in antimicrobial use in this high risk group of animals could lead to negative consequences on calf health, welfare and the economic viability of veal production.[8]

A potential solution to reducing antimicrobial use, while addressing animal health and welfare concerns, is the use of a selective antimicrobial therapy strategy targeting the calves at highest risk of disease at the time of arrival.[2,9-11] The challenge of this approach lies in identifying which calves are high-risk, as calves are often sourced from multiple locations and auction barns and arrive without information about their age, previous management, or medical history. In addition to this challenge, risk identification should yield results in a quick time frame so that management decisions can be made soon after the calves arrive at the facility. Previous work has identified a number of observable risk factors at the time of arrival such as the inspection of a calf's hydration status, flank, navel health and attempt to elicit a cough.[1]

The objective of this randomized controlled trial (RCT) was to determine the effect of a selective therapy strategy based on an individual calf risk assessment conducted at the time of arrival on morbidity, mortality, average daily gain, and antimicrobial use as compared to a positive control, conventional group oral antimicrobial strategy. It was hypothesized that: 1) there would be an improvement in morbidity, average daily gain, and, the primary outcome, mortality, in the selective therapy treatment group; and, 2) there would be reduced antimicrobial use in the calves assigned to the selective therapy strategy. This manuscript is reported following the RCT for livestock and food safety (REFLECT) guidelines.[12]

Materials and methods

Study design

This RCT was conducted in 1 of 3 barns located on a single commercial grain-fed veal operation in Ontario, Canada. The operation and barn were selected based on convenience, with the cooperation of the producer/owner. This study was approved by the Animal Care Committee of the University of Guelph (Animal Use Protocol # 3850).

Sample size calculation

Sample size was calculated based on the desire to detect a difference in the proportion of mortality events between interventions within the first 21 days at the facility. Higher mortality rates have been linked to higher antimicrobial use and providing oral antimicrobials upon arrival has been associated with increased morbidity and gains in the first few weeks.[18,19] Based on previous work by Winder et al. (2016) and Renaud et al. (2018), mortality within the 21 days was estimated to be 3.5%.[1,3] A 70% reduction in mortality from 3.5% to 1% was used to estimate the sample size using a proportion estimation calculation. The desired confidence interval was 95% and the power was 80%. The sample size estimate was 552 calves at high risk for mortality per intervention group for a total of 1,104 high-risk calves in the study. A large proportion of calves enter calf rearing facilities with at least one health abnormality that increases their mortality risk.[1] Using an estimate of 50% for calves at high risk for mortality arriving to the facility would suggest that enrollment of 2,208 calves would achieve our desired sample size.

Intervention

The intervention consisted of 2 strategies for administering metaphylaxis to calves at the time of arrival: conventional group oral antimicrobial strategy (COA); or, selective therapy strategy (STS) based on an individual calf risk assessment conducted at the time of arrival. Block randomization was applied at the level of the room by the lead investigator prior to the start of the study in order to assign rooms between the 2 interventions. See **https://hdl.handle.net/1813/116210** for supplemental Figure S1. Room assignment was concealed from facility staff until the day that rooms were filled. Rooms were filled sequentially. If multiple rooms were filled within a week, calves were systematically moved in groups of 2 to 3 into each room in sequence as they were unloaded so that an equal number of calves from each truck were allocated between each room. If an odd number of calves arrived at the facility, the last calf was assigned to the room by coin toss. Facility staff were blinded to the individual calf risk assignment in both STS and COA rooms. A sealed envelope containing the treatment administered to calves upon arrival was provided for STS rooms to be opened only if calves were to be selected for antimicrobial treatment by facility staff earlier than 3 days from the time of arrival at the facility.

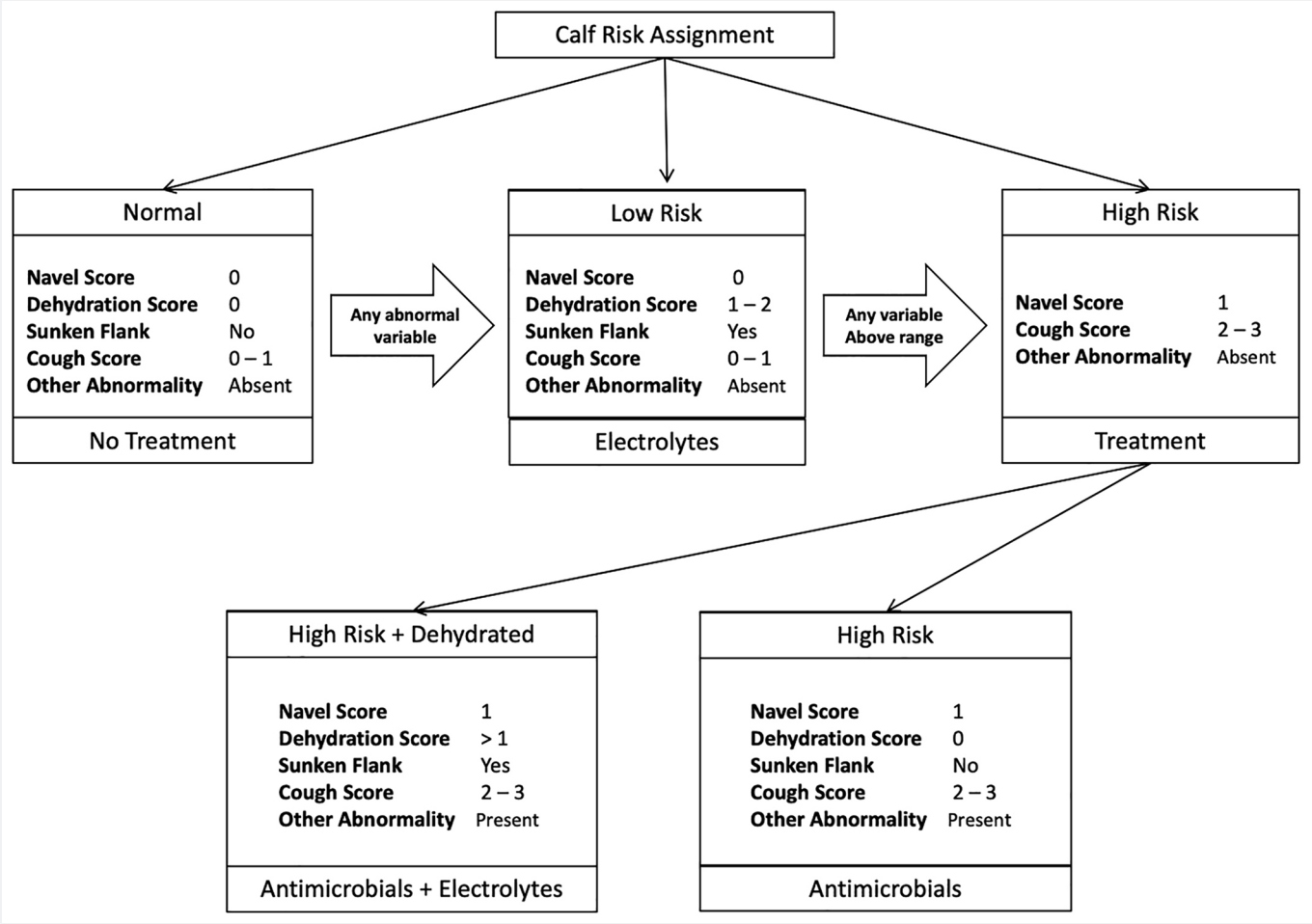
The COA strategy was provided by the facility to all calves assigned to the COA intervention rooms as per the facility protocol of administering milk replacer medicated with neomycin sulfate[a] (NEO) and trimethoprim sulfadiazine[b] (UNI) for the first 7 days after arrival (0.01 lb/calf/d [4.8 g/calf/d] NEO; 0.01 lb/calf/d [2.64 g/calf/d] UNI). The STS strategy was provided by the researchers to all calves assigned to STS intervention rooms at the time of arrival. Calves were administered antimicrobial therapy, rehydration therapy, both antimicrobial and rehydration therapy, or no therapy based on the results of their individual risk assessment according to the algorithm illustrated in Figure 1. Antimicrobial therapy was administered to calves that were considered high risk with a health score suggestive of infection (Figure 1). The antimicrobial therapy was administered in the form of a single subcutaneous injection of tulathromycin[c] at 1.13 mg/lb (2.5mg/kg) of body weight at the time of arrival. Electrolyte therapy was administered to calves that were considered either low risk or high risk and dehydrated (Figure 1). The electrolyte therapy consisted of a single feeding of oral electrolytes[d] 0.17 lb (76g) dissolved in 0.53 gal (2 L) of warm water administered by esophageal tube feeder[e]. Esophageal tube feeders were washed and rinsed with hot water between uses with a detergent[f] designed for calf feeding equipment. No therapy was provided to calves that were considered normal based on individually assigned risk as defined in the protocol provided in Figure 1.

Animal enrollment and management

Calves were enrolled in this study between January 15, 2018 and May 15, 2018. In the initial trial design, we aimed to enroll calves over the period of one year to assess the effect of season. The barn contained 16 rooms with 54 individual slatted floor pens with solid siding per room, and 54 to 56 calves allocated per room at the time of arrival. Rooms were organized with 27 pens facing each other in 2 rows with a central feeding aisle. Direct contact between calves was possible between adjacent pens via a shared water pipe and calves within a room shared airspace. Calves remained in individual pens for the duration of the 84-day feeding period at the facility. During the enrollment period, 16 rooms were used with 22 total groups of calves (rooms were filled more than once during the study period). Of these 22 rooms, 19 were enrolled in the trial, comprising 1,037 calves. The 3 rooms excluded from the study were due to an inability to fill the room with calves within 2 weeks (n = 1); at the request of the facility manager (n = 1); and, if there were insufficient research staff available to evaluate all calves entering the room (n = 1). Each room was filled with calves within 1 to 9 days based on the normal purchasing behavior of the operation. The operation strived to fill rooms within 1 to 3 days; however, purchasing decisions were made based on calf prices, calf quality and calf availability. Calves were sourced from drovers and auction barns within Ontario and Quebec, Canada.

All calves had ad libitum free access to water upon arrival through a pressure sensing water pipe shared between pairs of pens. Calves were bucket fed a 21% protein and 19% fat milk replacer[g] using the following schedule: 0.51 lb in 0.53 gal (230 g in 2 L) twice daily from day 1 to 3; 0.53 lb in 0.53 gal (240 g in 2 L) twice daily from day 4 and 5; 0.60 lb in 0.59 gal (270 g in 2.25 L) twice daily for day 6; 0.62 lb in 0.59 gal (280 g in 2.25 L) twice daily for day 7 and 8; 0.69 lb in 0.66 gal (313 g in 2.5 L) twice daily for day 9 to 12; 0.76 lb in 0.73 gal (344 g in 2.75 L) twice daily for day 13 to 15; 0.83 lb in 0.79 gal (375 g in 3 L) twice daily for day 16 to 29; 0.55 lb in 0.53 gal (250 g in 2 L) twice daily for day 30 to 38; and, 0.41 lb in 0.40 gal (188 g in 1.5 L) once daily for day 39 to 45 when calves were weaned. Calves were offered a texturized calf starter (17% CP) using the following schedule: 0.002 lb (0.7 kg) for week 1; 0.004 lb (1.7 kg) for week 2; 0.007 lb (3.2 kg) for week 3; 0.01 lb (5.4 kg) for week 4; 0.02 lb (8.5 kg) for week 5; and, 0.03 lb (11.4 kg) for week 6.

Figure 1: Algorithm for the selective therapy strategy (STS) protocol based on individual calf risk assessment performed at the time of arrival.



Calves were then transitioned to a finishing ration (13% CP) using the following schedule: 38.6 lb (17.5 kg) of 50/50 starter and finishing ration for week 7; 41.4 lb (18.8 kg) of the finishing ration for week 8; 45.2 lb (20.5 kg) for week 9; 46.3 lb (21.0 kg) for week 10; 53.8 lb (24.4 kg) for week 11; and, 50.9 lb (23.1 kg) for week 12. Calves were shipped to a separate location for finishing after the 84-day growing period at this facility.

Data collection

Baseline health parameters

All calves enrolled were evaluated using a standardized health scoring system (adapted from Renaud et al. [2018])[1] upon arrival. Laminated reference sheets with definitions and images for each health score were available at all times during scoring and are available at **https://hdl.handle.net/1813/116210.** Navel score, cough score, hydration score, sunken flank evaluation and "other" detectable health abnormalities (such as heavy ocular discharge equivalent to respiratory score 3 developed by McGuirk and Peek [2014];[13] or, an infected wound) were assigned by one of 2 observers. Observer 1 was a practicing large animal veterinarian and observer 2 was a trained research assistant. Inter- and intra-observer evaluation of health scores were evaluated and are reported in von Konigslow et al. (2020)[14] as ≥ 90% agreement between and within observers for all health score except for hydration that had 75% agreement between observers. The risk assessment protocol did not include rectal temperature since it has not been associated with increased mortality at the time of arrival.[1] Temperatures were measured at the time of arrival using a digital rectal thermometer[h]. Although rectal temperature was not included in the risk assignment algorithm, it was included in the study since temperatures are often a part of facility health monitoring and treatment protocols. All health data were recorded electronically using Qualtrics[i] on an iPad[j].

Average daily gain

Calves were weighed using a digital scale[k] at the time of arrival by researchers and a second time 7 to 9 weeks post-arrival by farm staff. The digital scale and calf chute were washed with soap and hot water between rooms. The average daily gain (ADG) was calculated by subtracting the arrival weight by the second weight measured and dividing by the number of days at the facility between measurements.

Treatment and mortality records

Treatment and mortality data were collected between January 15, 2018 and August 7, 2018. Calf health monitoring was performed by experienced facility staff twice daily after feeding according to barn protocols. Facility staff were blinded

to all calf health scores and to STS calf individual treatment records. Individual and group antimicrobial therapy was provided to calves according to facility protocols that were developed with veterinary oversight. The facility received routine herd health visits by the third-party herd veterinarian. Calves within STS rooms were only eligible to receive individual antimicrobial therapy within the first 3 days at the facility if they had not received an antimicrobial at the time of arrival. An STS room was not eligible to receive group antimicrobial therapy within the first 7 days of arrival unless more than 15% of calves that did not receive treatment at the time of arrival were identified as having the same illness within a 24-hour period. After the first week at the facility, both COA and STS rooms were managed in the same manner as per facility protocol. All treatment and mortality events were recorded by facility staff both on paper as well as in their electronic system Trax-It[l]. Post-mortem examinations were performed on all calves that died to determine cause of death as per farm protocol by the third-party herd veterinarian employed by the operation. Treatment and mortality records were provided to researchers after calves were shipped in a Microsoft Excel spreadsheet and subsequently uploaded into a Microsoft Access[m] database.

Individual and group antimicrobial use for treatment of disease throughout the growing period was recorded both on paper and in the facility electronic system[l]. Individual antimicrobial use consisted of parenteral administration of one of the following antibiotics according to an existing facility protocol developed under veterinary oversight: lincomycin and spectinomycin[n] (LS); tulathromycin[c] (TU); penicillin G procaine[o] (PENG); trimethoprim sulfadoxine[p] (TMS); or, florfenicol[q] (FF). Individual antimicrobial therapy was most commonly administered for respiratory disease in calves exhibiting a combination of elevated respiratory rate, nasal or ocular discharge, presence of a cough, or an elevated rectal temperature using LS and reserving FF for refractory cases. At the onset of diarrhea, oral electrolytes were provided reserving injectable antimicrobial use with TMS for calves that became dull or depressed. During the study, TU was administered to calves individually according to the study protocol within STS rooms on the day of arrival (Figure 1). All other individual antimicrobial therapy was used on a case-by-case basis. Group antimicrobial use consisted of oral administration of both of the following antibiotics according to facility protocols developed under veterinary oversight: oxytetracycline HCL[r] (OTC); and, erythromycin thiocyanate[s] (ET). Group antimicrobial therapy was most commonly administered for respiratory disease outbreaks. To quantify antimicrobial use in terms of treatment frequency adjusted by standard dose, treatment incidence (TI) was reported using defined daily dose information according to the following formula (adapted).[15,16] Defined daily dose was selected as the standard dose as it has been used for reporting on antimicrobial use in cattle.[17] Both the standard dose and equation for TI (1) were selected to improve comparability in research reporting on antimicrobial use.

In this equation the numerator is the amount of active antimicrobial administered expressed in mg. The denominator is calculated using the defined daily dose of an antibiotic in mg/kg based on published work or the prescribed dose if defined daily dose was not available.[15,17] The denominator was also calculated using the days at risk at the time of treatment (from the time of arrival or the time of last treatment) and the estimated body weight of the calf in kg at the time of treatment. The estimated individual body weight was determined using the arrival weight of the calf and estimated weight gain at the time of treatment using the mean ADG of all calves enrolled in the study. Treatment indices were calculated for each calf and each antimicrobial therapy event. A calf's total TI was comprised of the sum of every TI event including all individual and group antimicrobial therapy. A calf's individual TI was calculated as the sum of all individual antimicrobial therapy events; and, a calf's group TI was calculated as the sum of all group antimicrobial therapy events administered to the room in which a calf was managed. The antimicrobial use in the STS intervention was included within the individual TI, while the antimicrobial use in the COA intervention was included within the group TI.

Analysis

Statistical analyses were performed using Stata 15[t] and data were imported from a Microsoft Excel[m] spreadsheet. Calves that had missing outcome data (morbidity, mortality, ADG or TI) were excluded from that outcome's analysis (Figure 2).

Descriptive statistics were generated for health parameter measured on the day of arrival. A Pearson Chi Square test was used to determine if the health parameter scores were statistically different between interventions (Table 1). The Shapiro-Wilks test was applied to the TI, arrival weight and rectal temperature data to determine normality. To establish if TI, arrival weight or rectal temperature were significantly different between interventions groups a Wilcoxon rank-sum test (non-parametric) or a t-test (parametric) was performed (Table 2).

The hypothesized causal diagram between outcomes (morbidity, mortality, ADG or TI) and explanatory variables (arrival weight, season, rectal temperature and intervention) that was used to guide model building is illustrated in Figure 2. Spearman's rank coefficient was used to assess collinearity among explanatory variables. Collinear variables (coefficients > 0.6) were examined and the most reliable or biologically relevant explanatory variable were retained in model building. Locally weighted regression (lowess) of the outcome on the explanatory variable was assessed for all outcomes of interest. Variables that did not exhibit a linear relationship with the outcome were categorized.

Figure 2: Casual diagram used to illustrate the hypothesized relationship between measured variables to the outcomes of interest morbidity, mortality, average daily gain and treatment incidence.

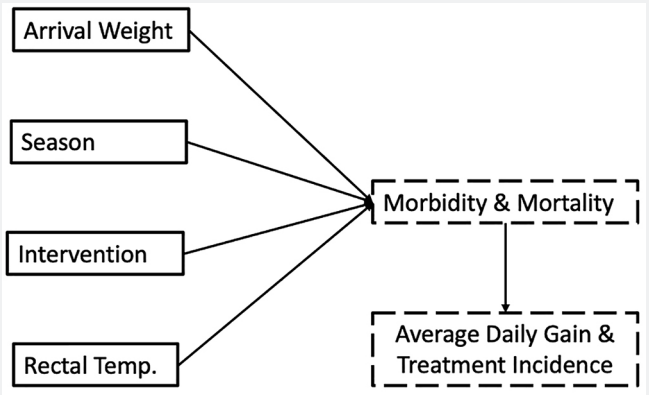


Table 1: Distribution of baseline health parameter scores evaluated on the day of arrival in 1,032 calves randomly allocated into selective therapy strategy (STS) rooms (n = 488) and conventional group oral antimicrobial strategy (COA) rooms (n = 544) groups at a grain-fed veal calf facility.

Health parameter		Description	STS (n = 488) [Prevalence % (no.)]	COA (n = 544) [Prevalence % (no.)]	*P*-value
Dehydration score	0	Skin tent returns to normal < 2 sec, bright alert responsive, strong suckle reflex, < 5% dehydrated	85.3 (416)	71.8 (391)	< 0.01
	1	Skin tent returns to normal in 2 sec, good suckle reflex, bright alert responsive, 6-8% dehydrated	13.9 (68)	26.7 (145)	
	2	Skin tent returns to normal in 2-4 sec, slightly sunken eyes, dull, good suckle reflex, 9-10% dehydrated	0.8 (4)	1.5 (8)	
	3	Skin tent returns to normal in 4-8 sec, depressed, sternal recumbence moderate sunken eyes, poor suckle reflex, > 10% dehydrated	0 (0)	0 (0)	
Cough score	0	No cough	94.5 (461)	95.4 (519)	0.60
	1	Single cough induced	4.3 (21)	2.9 (16)	
	2	Occasional spontaneous or repeated induced coughs	0.8 (4)	1.3 (7)	
	3	Repeated spontaneous coughs	0.4 (2)	0.4 (2)	
Flank score	0	Normal	71.5 (349)	59.0 (321)	< 0.01
	1	Paralumbar fossa is visibly depressed	28.5 (139)	41.0 (223)	
Navel score	0	No pain, heat, swelling, and navel is < 20mm dowel	73.2 (357)	67.8 (369)	0.07
	1	Pain, heat, swelling, discharge, or navel is > 20mm dowel	26.8 (131)	32.2 (175)	
Other score	0	No evidence of health abnormality other than those assessed	95.1 (464)	95.0 (517)	0.97

Table 2: Descriptive statistics of the treatment incidence (TI) for specific antimicrobials evaluated in 1,0291 calves randomly allocated into selective therapy strategy (STS) rooms (n = 488) and conventional group oral antimicrobial strategy (COA) rooms (n = 541) at a grain-fed veal calf facility.

Active antimicrobial ingredients	STS				COA				Wilcoxon rank-sum	Defined daily dose (mg/kg/d) mg/lb/d	Source
	Mean	SD	Min	Max	Mean	SD	Min	Max	*P*-Value		
Total TI	0.18	0.34	0.00	6.94	0.54	0.47	0.26	8.35	< 0.01		
Individual TI	0.10	0.33	0.00	6.94	0.04	0.09	0.00	0.60	< 0.01		
Florfenicol TI	0.10	0.02	0.06	0.16	0.14	0.05	0.08	0.25	0.01	4.54 (10)	Lardé et al., 2020
Penicillin G Procaine TI	0.46	0.02	0.45	0.47	0.43	0.11	0.27	0.60	0.56	3.99 (8.8)	Lardé et al., 2020
Lincomycin/ Spectinomycin TI	0.13	0.07	0.00	0.41	0.12	0.05	0.07	0.31	0.44	6.80 (15)	Pardon et al., 2012
Tulathromycin TI	0.15	0.54	0.08	6.94	–	–	–	–	–	0.16 (0.36)	Lardé et al., 2020
Group TI	0.08	0.06	0	0.68	0.50	0.47	0.26	8.35	< 0.01		
Oxytetracycline HCL TI	0.05	0.04	0.01	0.30	0.04	0.02	0.01	0.15	0.03	5.58 (12.3)	Lardé et al., 2020
										18.14 (40)	As prescribed with erythromycin
Neomycin with sulfonamides TI	–	–	–	–	0.30	0.33	0.16	5.88	–	6.40 (14.1)	Lardé et al., 2020
Trimethoprim/ sulfonamides TI	–	–	–	–	0.13	0.14	0.07	2.47	–	13.61 (30)	Pardon et al., 2012
Erythromycin thiocyanate	0.11	0.06	0.07	0.60	0.10	0.01	0.07	0.11	0.01	18.14 (40)	As prescribed with oxytetracycline HCL
Tulathromycin TI	–	–	–	–	0.06	0.01	0.04	0.10	–	0.16 (0.36)	Lardé et al., 2020

Cox proportional hazard models were constructed to assess the relationship between the time to morbidity or mortality in the first 14 days and over the entire 84-day study period. The first 14 days of the study were analyzed to interpret outcomes prior to group treatment of respiratory disease outbreaks in some rooms at the facility prior to 21 days on feed. Mixed linear regression models were constructed to assess the relationship between the ADG and TI outcome data over the entire 84-day study period. Each model accounted for clustering by including room as a random effect. Initial screening of all explanatory variables was performed by constructing univariable models using a *P* value of 0.2. Manual backward stepwise selection was used in model construction with statistical significance set to $P \leq 0.05$. Biologically plausible two-way interactions were assessed and variables were retained in the model if they were part of a two-way interaction with an important explanatory variable. A variable was determined to have a confounding effect and retained in the model if its removal changed the coefficient of an important variable by ≥ 20%. Model fit and model assumptions were examined in each model. Influential observations were investigated and retained if data records were complete and biologically plausible. Deviance, Martingale residuals, Cox-Snell residuals, Schoenfeld residuals as well as the test for proportional hazards, were examined for Cox proportional hazards models. The normality and homoscedasticity of residuals as well as the best linear unbiased predictions for the random effect to account for clustering by room were evaluated for the mixed linear regression models.

Results

Animal population

Calf age was unknown; however, age is estimated to be between 3 to 7 days as less than one-fifth of male calves from dairy farms are kept for longer than 7 days.[20] Figure 3 presents a flow chart of the number of calves enrolled and the reason for exclusion from analysis for each outcome modelled. Of the 1,037 enrolled calves, 5 were removed to non-trial rooms the day after arrival leaving 1,032 calves eligible for analysis of which 642 were considered high-risk.

Baseline health parameters

Table 1 describes the prevalence of health parameter scores recorded for calves allocated into both STS and COA rooms at the time of arrival. Despite the random allocation of calves to rooms, the percentage of calves exhibiting signs of dehydration differed between interventions with 14.7% of calves in STS rooms exhibiting signs of dehydration compared to 28.2% of calves in COA rooms showing some level of dehydration ($P < 0.01$). Additionally, the percentage of calves observed with a depressed paralumbar fossa differed between interventions with 28.5% of calves in STS rooms exhibiting this trait and 41% of calves in COA rooms ($P < 0.01$). The percentage of calves observed with an enlarged navel, elicitation of a cough on tracheal palpation or other health scores were not statistically different between groups at arrival. The mean (± standard deviation) rectal temperature measured was 102.0 °F ± 32.9 °F (38.9 °C ± 0.5 °C) in the COA calves and 102.4 °F ± 32.9 °F (39.1 °C ± 0.5 °C) in the STS calves at the time of arrival with only 11.6% of calves arriving with a temperature > 103.1 °F (39.5 °C). Mean rectal temperature was statistically significant between groups at arrival ($P < 0.01$). From the calves that arrived with a rectal temperature > 103.1 °F (39.5 °C), 62% were designated as high risk according the assignment protocol (Figure 1). Of those calves assigned to the STS intervention, 38% that arrived with a temperature > 103.1 °F (39.5 °C) received antimicrobial therapy at the time of arrival. The mean arrival weight measured was 109.8 lb ± 12.3 lb (49.8 kg ± 5.6 kg) in the COA calves and 111.1 lb ± 11.9 lb (50.4 kg ± 5.4 kg) in the STS calves at the time of arrival. Arrival weight was statistically significant between groups at arrival ($P = 0.03$).

Morbidity models

The time post-arrival until a calf received its first individual treatment with an antimicrobial was used as a proxy for onset of morbidity. During the 84-day study period, 25% of calves received at least one individual antibiotic treatment and 31% of those treated received the antimicrobials within the first 2 weeks at the facility. The time to first individual antimicrobial treatment for both STS and COA calves is illustrated in Figure 4B. Farm staff recorded the reason for individual antimicrobial therapy as follows: 97% respiratory disease; and, 3% omphalitis. Due to challenges with poor ventilation at the facility, use of antimicrobials for the treatment of respiratory disease was common. The prompt use of oral electrolytes resulted in very rare use of injectable antimicrobials for diarrhea therapy. Of the calves that received individual antimicrobial therapy, 28% received more than one individual treatment and 93% of these calves received the additional treatments for the same reason.

None of the explanatory variables assessed for hazard of morbidity over the first 14 days at the facility remained statistically significant. Thus, there was no association found between intervention and hazard of morbidity in the first two weeks at the facility ($P = 0.21$). When assessing morbidity over the entire 84-day study period, season was found to be associated with the hazard of morbidity (Table 3). Calves that arrived in spring had a 28% reduced hazard of morbidity as compared to those that arrived in winter (HR = 0.72; 95% CI 0.53 – 0.97; $P = 0.03$). No association was found between intervention and hazard of morbidity in the model ($P = 0.11$). Clustering by the room in which calves were housed was statistically significant in the model ($P < 0.01$).

Figure 3: Diagram illustrating subject flow through the study in both the conventional group oral antimicrobial strategy (COA) and selective therapy strategy (STS) groups, with reasons for missing data by outcome by intervention group.

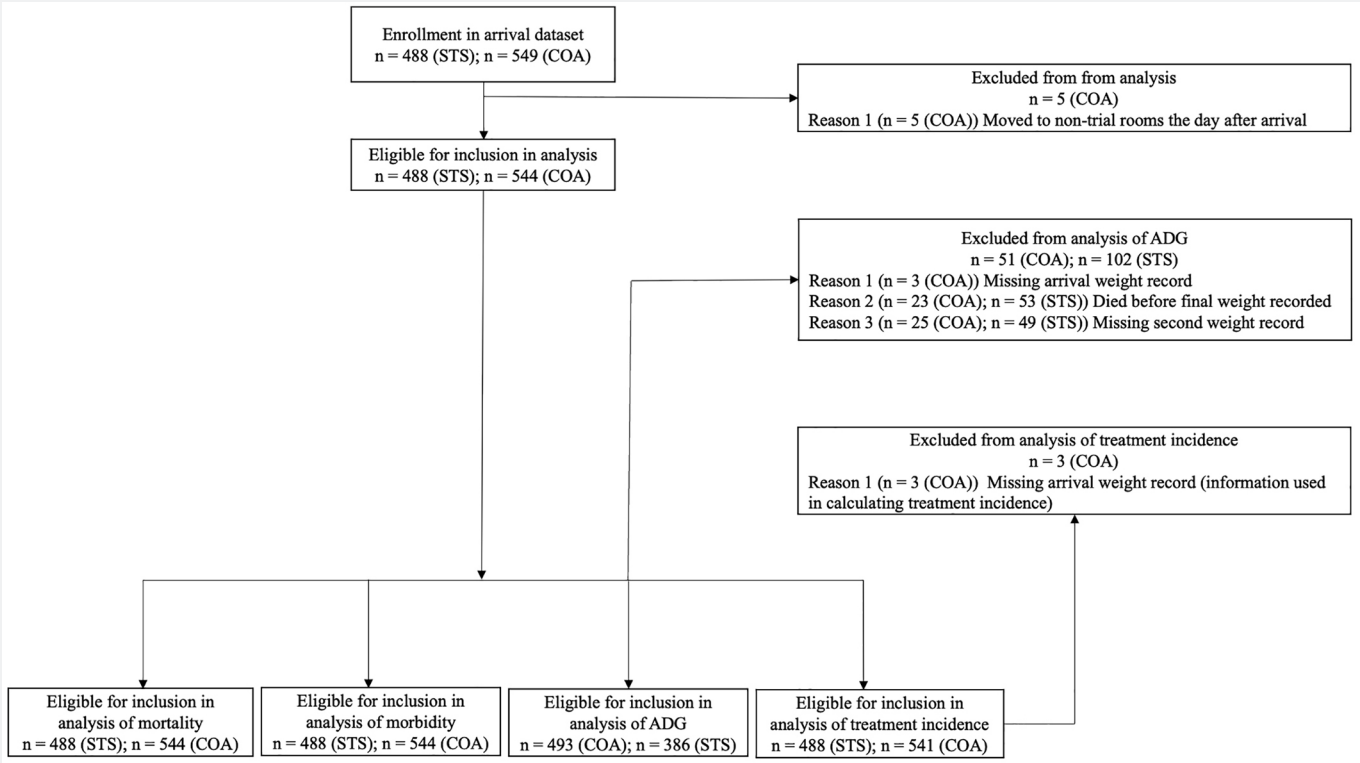
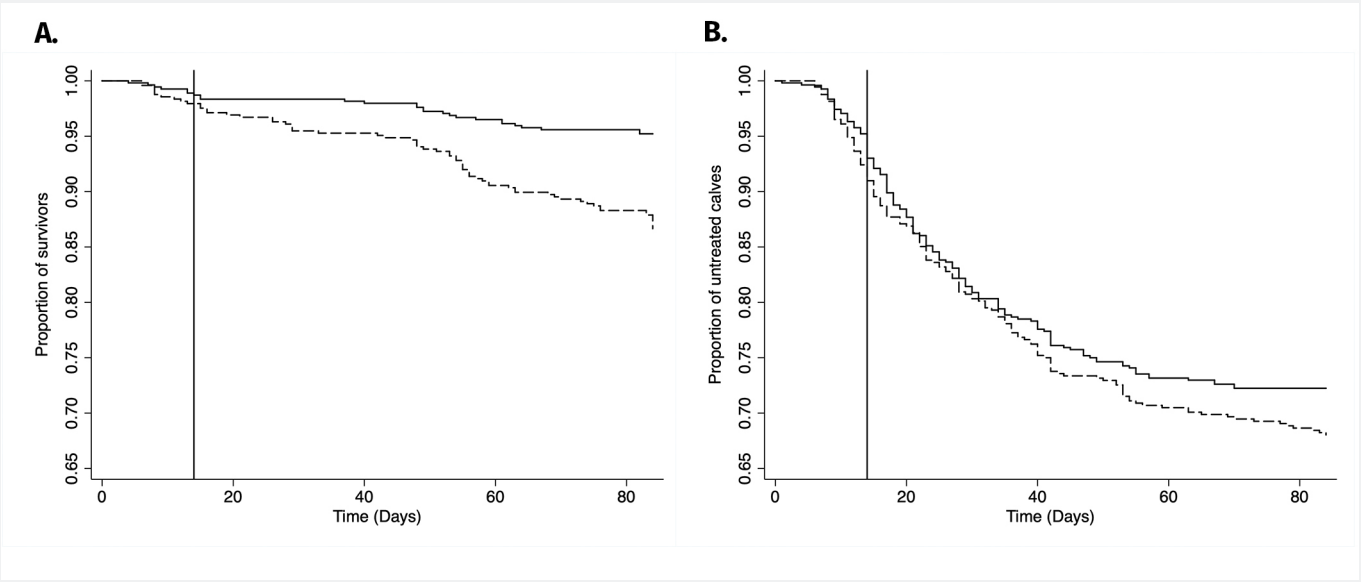


Table 3: Results of the Cox-Proportional Hazard model assessing the significance of the explanatory variables measured from 1,032 calves randomly allocated into selective therapy strategy (STS) rooms (n = 488) and conventional group oral antimicrobial strategy (COA) rooms (n = 544) at the time of arrival for predicting the hazard of morbidity over the entire 84-day growing period.[1]

Variable	Description	n (no. calves)	Morbidity (no. calves)	Hazard Ratio	95% CI	*P*-value
Intervention	COA	544	151	Referent		
	STS	488	156	1.28	0.95 to 1.72	0.11
Season	Winter	623	202	Referent		
	Spring	409	105	0.72	0.53 to 0.97	0.03

[1] Random effect for clustering by the room in which calves were managed *P*-value = 0.001

Figure 4: A) Kaplan-Meier survivor curve of the proportion of calves that have survived over time. The vertical line marks the second week post-arrival. The solid line represents calves in the conventional group oral antimicrobial strategy (COA) group and the dashed line represents calves in the selective therapy strategy (STS) group.; **B)** Kaplan-Meier curve of the proportion of calves remaining untreated over time. The vertical line marks the second week post-arrival. The solid line represents calves in the conventional group oral antimicrobial strategy (COA) group and the dashed line represents calves in the selective therapy strategy (STS) group.



Mortality models

Mortality over the 84-day study period was 8.9 % with 1.7 % occurring within the first 2 weeks at the facility. This is illustrated for both STS and COA rooms in Fig 4A. Post-mortem examinations determined cause of death as follows: 55% respiratory disease; 14% emaciation; 10% bloat; 8% undiagnosed; 3% culled; 2% injury; 2% septicemia; and, 1% for each of omphalitis, diarrhea, lameness, congenital defect and perforated ulcer. In the first 2 weeks at the facility, 50% of mortality was from emaciation; 17% due to bloat; 11% was unreported; and, 6% each for diarrhea, septicemia and perforated ulcer. Approximately 90% of the mortality due to respiratory disease occurred > 30 days post-arrival.

There were too few mortality events within the first 14 days at the facility to assess hazard models in this time frame. When assessing mortality over the entire 84-day study period, the intervention was associated with the hazard of mortality. None of the other explanatory variables assessed for hazard of mortality remained statistically significant in the model. Calves within an STS room had a 2.8 times (95% CI: 1.47 – 5.19; $P < 0.01$) greater hazard of mortality over calves in a COA room. Clustering by the room in which calves were housed was statistically significant in the model ($P < 0.01$).

Average daily gain models

The mean ADG was 1.5 lb/d ± 0.7 lb/d (0.7 kg/d ± 0.3 kg/d). Season, intervention, and arrival weight were associated with ADG over the study period (Table 4). Calves that arrived with a body weight between 102.3 to 108.2 lb (46.4 to 49.1 kg) gained 0.11 lb/d (0.05 kg/d) (95% CI: 0.002 to 0.22 lb/d (0.001 to 0.1 kg/d); $P = 0.05$) more than calves that weighed between 80.2 to 102.1 lb (36.4 to 46.3 kg); and, calves that weighed between 116.4 to 171.3 lb (52.8 to 77.7 kg) gained 0.13 lb/d (0.06 kg/d) (95% CI: 0.04 to 0.24 lb/d (0.02 to 0.11 kg/d); $P = 0.01$) more than calves that weighed between 80.2 to 102.1 lb (36.4 to 46.3 kg). Season

Table 4: Results of the mixed linear model assessing the relationship between explanatory variables measured from 879 calves randomly allocated into selective therapy strategy (STS) rooms (n = 488) and conventional group oral antimicrobial strategy (COA) rooms (n = 544) at the time of arrival and the ADG lb /d (kg/d) over the entire 84-day growing period.[1]

Variable	Description	n (no. calves)	Coefficient lb/d (kg/d)	Std. Err.	95% CI	*P*-value
Intervention	COA	493	Referent			
	STS	386	-1.46 (-0.66)	0.08	-0.81 to -0.51	< 0.01
Season	Winter	551	Referent			
	Spring	328	-0.31 (-0.14)	0.06	-0.26 to -0.01	0.03
Season * intervention	Interaction	1029	2.67 (1.21)	0.30	0.62 to 1.80	< 0.01
Arrival weight lb (kg)	Quartiles					
	80.2 to 102.1 (36.4 to 46.3 kg)	Referent				
	102.3 to 108.2 lb (46.4 to 49.1 kg)	0.11 (0.05)	0.05	0.001 to 0.10	0.05	
	108.5 to 116.2 lb (49.2 to 52.7 kg)	0.02 (0.01)	0.63	-0.04 to 0.06	0.63	
	116.4 to 171.3 lb (52.8 to 77.7 kg)	0.13 (0.06)	0.01	0.02 to 0.11	0.01	

[1] Random effect for clustering by the room in which calves were managed *P*-value < 0.001; intra-class correlation coefficient = 54.4%.

and intervention were part of a significant interaction ($P < 0.01$) that is illustrated in Figure 5. Calves that were assigned to an STS rooms gained significantly less in the winter than calves that were assigned to COA rooms ($P < 0.05$). In the spring, there was no statistical difference in gain between STS and COA rooms. Clustering by the room in which calves were housed was statistically significant in the model and accounted for 54% of the variance observed in the model ($P < 0.01$; Intra-class correlation coefficient = 54.4%).

Treatment incidence models

Table 2 describes the treatment incidence (TI) in defined daily dose for calves allocated into both STS and COA rooms at the time of arrival. The total TI differed between interventions ($P < 0.01$), with COA rooms having a higher total TI. Group TI differed between interventions ($P < 0.01$), with COA rooms having a higher group TI. When considering the antimicrobials used in group therapy, STS rooms had higher TI for OTC ($P = 0.03$) and ET ($P = 0.01$) while COA rooms had higher TI for TU, NEO and UNI. All rooms received at least one group treatment for a respiratory disease outbreak during the study period. Individual TI also differed between interventions ($P < 0.01$), with STS rooms having a higher TI. Looking at the different antimicrobials chosen for individual therapy, there was no difference between interventions in the use of PENG ($P = 0.56$) or LS ($P = 0.44$). Interventions differed in their use of FF ($P = 0.01$), with COA having a higher TI for FF. Only STS rooms used TU for individual therapies at the time of arrival. Within STS rooms, none of the calves required individual therapy before 3 days at the facility or group antimicrobial therapy before 7 days at the facility.

Arrival weight and intervention were associated with the total TI over the entire 84-day study period (Table 5). Arrival weight and intervention were involved in a significant interaction ($P = 0.01$) that is illustrated in Fig 6A. Calves that were assigned to STS rooms had relatively constant total TI over all arrival weights. However, calves that were assigned to COA rooms with lighter arrival weights had greater total TI than calves that arrived with heavier arrival weights. Clustering by the room in which calves were housed was statistically significant in the model but only accounted for 1% of the variance observed in the model ($P = 0.05$; intra-class correlation coefficient = 1.0%).

Arrival weight and intervention were associated with group TI over the entire 84-day study period (Table 6). Arrival weight and intervention were involved in an important interaction ($P < 0.01$) that is illustrated in Figure 6B. Calves that were assigned to STS rooms had relatively constant group TI over all arrival weights. However, calves that were assigned to COA rooms with lighter arrival weights had greater group TI than calves that arrived with heavier arrival weights. Clustering by the room in which calves were housed was statistically significant in the model but only accounted for 1% of the variance observed in the model ($P = 0.04$; intra-class correlation coefficient = 1.0%).

Rectal temperature measured at the time of arrival and intervention were associated with individual TI over the entire 84-day study period (Table 7). Rectal temperature at arrival and intervention were involved in an important interaction ($P = 0.04$) that is illustrated in Fig 6C. Calves that were assigned to COA rooms had relatively constant individual TI over all rectal temperatures measured at the time of arrival. Individual TI in STS rooms was greater than in COA rooms at rectal temperatures that were < 103.1 °F (39.5 °C) at the time of arrival.

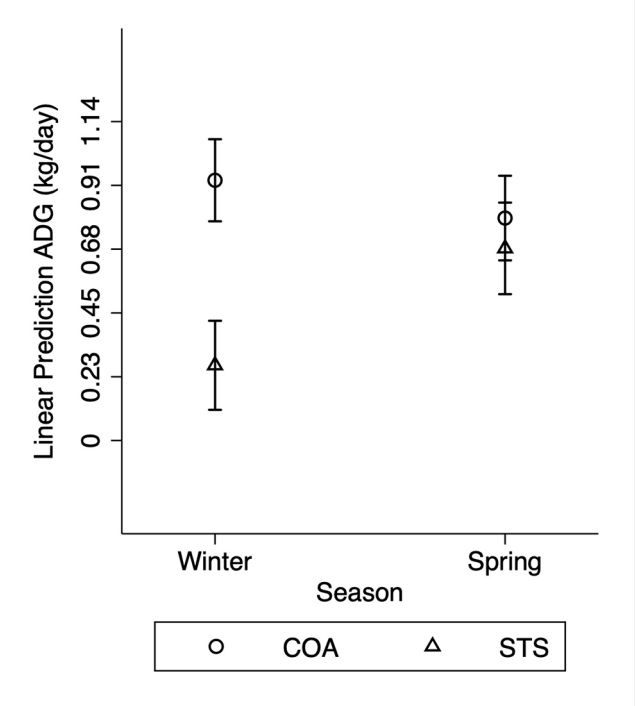
Adverse events

Although there were no adverse events directly associated with STS or COA assignment, the trial was halted prematurely by request of the facility. This was due to an outbreak of *Salmonella enterica* (serovar Dublin).

Discussion

This study demonstrates that a selective therapy strategy based on individual calf risk assessment used at the time of arrival was associated with important differences in mortality, growth and antimicrobial use in calves raised at a grain-fed veal facility. An improvement in health and growth outcomes was not observed in calves assigned to STS as anticipated. Although no difference was found between interventions on the hazard of morbidity, calves assigned to STS at the time of arrival exhibited an increased hazard of mortality over the entire study period. These results may be related to an outbreak of *Salmonella enterica* (serovar Dublin) which is associated with a high level of mortality.[21] Season and intervention were involved in an important interaction with calves assigned to STS during the winter exhibiting reduced growth as compared to calves assigned to COA during the same season. A reduction in the total amount of antimicrobial used was observed in calves assigned to STS as compared to COA as anticipated. This finding was linked to an important interaction with arrival weight where lightweight calves assigned to COA had higher total and group treatment incidence over the entire study period. Further study is needed to determine if this reduction in antimicrobial use is still observed when group antimicrobial therapy can be tailored to individual body weight.

Figure 5: Margins plot of the linear prediction of the ADG (kg/d) for the interaction between season and intervention (conventional group oral antimicrobial strategy [COA]; or, selective therapy strategy [STS]) from the mixed linear model assessing the relationship between explanatory variables measured from 879 calves at the time of arrival and the ADG (kg/d) over the entire 84-day growing period (Table 4).



The COA strategy at the time of arrival had a reduced hazard of mortality over the entire growing period compared to the STS strategy. One explanation for this finding would be that the current risk assessment protocol was not sensitive enough to detect a high enough proportion of calves arriving at high risk of morbidity and mortality to have a protective effect. Given the importance of arrival weight in this study and its association with morbidity and mortality in previous work, it should be incorporated into future screening protocols for risk assessment.[3,10,22] Additional work to refine assessment protocols via the addition of clinically measurable biomarkers show promise so long as results can be obtained in a timeframe that can be used to make management decisions on farm.[2,9,14]

In previous work assessing the use of oral antimicrobials provided at the time of arrival in neonatal male dairy calves, no statistical difference in mortality was detected over 28 days between calves provided oral antimicrobials and those that were not provided oral antimicrobials.[23] However, those calves that were provided oral antimicrobials were found to gain more and had a lower hazard of morbidity.[23] In a similar study conducted on a large dairy farm that raised both male and female calves, providing oral antimicrobials was associated with increased neonatal diarrhea, lowered weight gain and lowered grain consumption.[19] In both studies, calves were

Table 5: Results of the mixed linear model assessing the relationship between explanatory variables measured from 1,029 calves randomly allocated into selective therapy strategy (STS) rooms (n = 488) and conventional group oral antimicrobial strategy (COA) rooms (n = 541) at the time of arrival and the total treatment incidence (defined daily dose [DDD]) over the entire 84-day growing period.[1]

Variable	Description	n (no. calves)	Coefficient (DDD)	Std. Err.	95% CI	*P*-value
Intervention	COA	541	Referent			
	STS	488	-0.98	0.24	-1.44 to -0.51	< 0.01
Arrival weight	Kg	1029	-0.01	0.001	-0.01 to -0.002	< 0.01
Intervention *	Interaction	1029	0.01	0.002	0.001 to 0.01	0.01
Arrival weight						

[1] Random effect for clustering by the room in which calves were managed *P*-value = 0.047; intra-class correlation coefficient = 1.0%

Table 6: Results of the mixed linear model assessing the relationship between explanatory variables measured from 1,029 calves randomly allocated into selective therapy strategy (STS) rooms (n = 488) and conventional group oral antimicrobial strategy (COA) rooms (n = 541) at the time of arrival and the group treatment incidence (defined daily dose [DDD]) over the entire 84-day growing period.[1]

Variable	Description	n (no. calves)	Coefficient (DDD)	Std. Err.	95% CI	*P*-value
Intervention	COA	541	Referent			
	STS	488	-0.88	0.19	-1.26 to -0.50	< 0.01
Arrival weight	Kg	1029	-0.01	0.003	-0.02 to -0.01	< 0.01
Intervention *	Interaction	1029	0.01	0.004	0.002 to 0.02	0.02
Arrival weight						

[1] Random effect for clustering by the room in which calves were managed *P*-value = 0.036; intra-class correlation coefficient = 1.0%.

Figure 6: Margins plots of the linear predictions for interactions from the mixed linear regression models assessing the relationship between explanatory variables measured from 1,029 calves at the time of arrival over the entire 84-day growing period and intervention (conventional group oral antimicrobial strategy [COA]; or, selective therapy strategy [STS]): **A)** total treatment incidence (Defined Daily Dose) outcome interaction between arrival weight and intervention (Table 5); **B)** group treatment incidence (Defined Daily Dose) outcome interaction between arrival weight and intervention (Table 6); **C)** individual treatment incidence (Defined Daily Dose) outcome interaction between rectal temperature and intervention (Table 7).

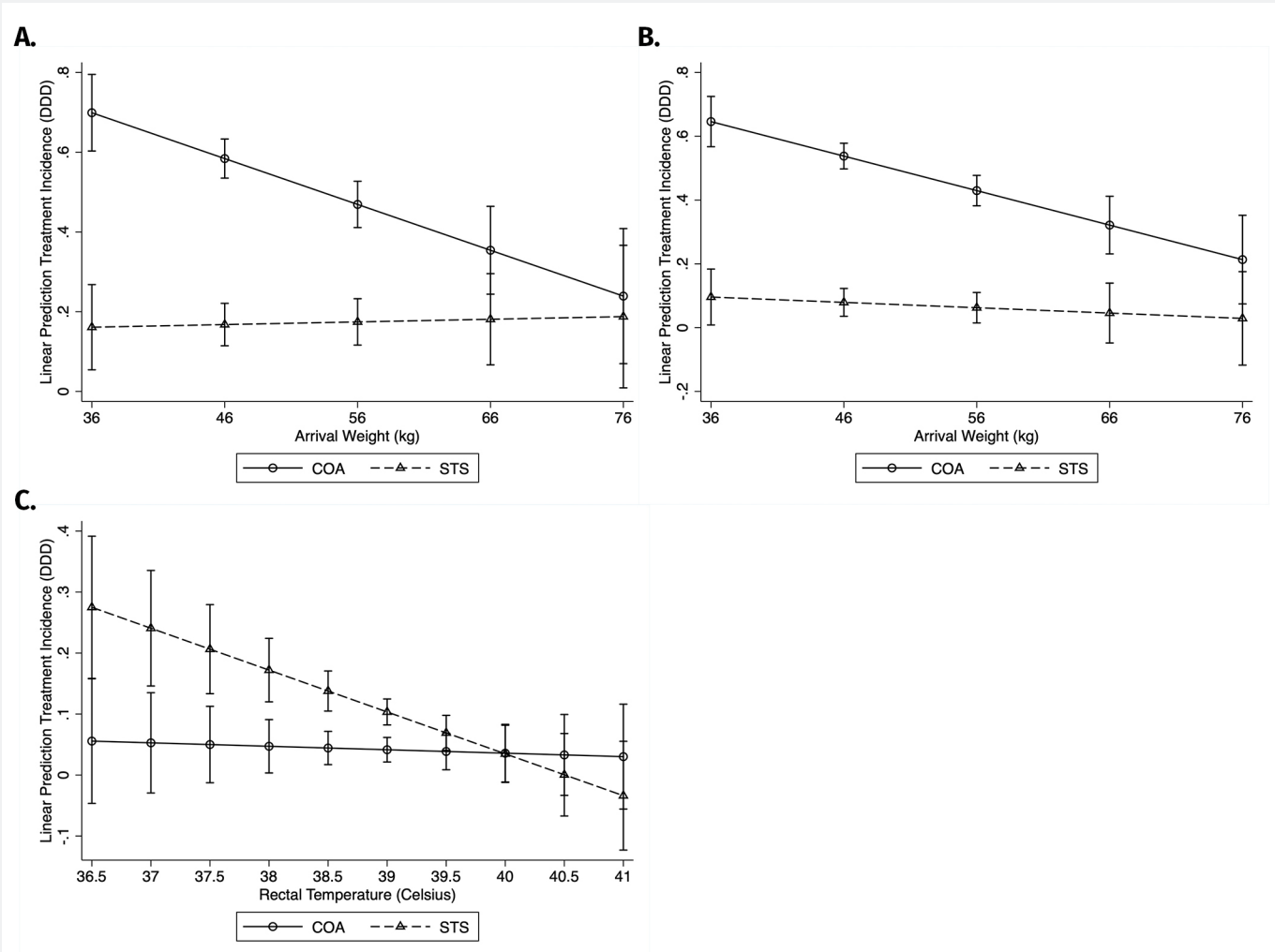


Table 7: Results of the mixed linear model assessing the relationship between explanatory variables measured from 1,029 calves randomly allocated into selective therapy strategy (STS) rooms (n = 488) and conventional group oral antimicrobial strategy (COA) rooms (n = 541) at the time of arrival and the individual treatment incidence (defined daily dose [DDD]) over the entire 84-day growing period.[1]

Variable	Description	n (no. calves)	Coefficient (DDD)	Std. Err.	95% CI	*P*-value
Intervention	COA	541	Referent			
	STS	488	2.52	1.21	0.15 to 4.88	0.04
Rectal temperature	Celsius	1029	-0.01	0.02	-0.05 to 0.04	0.79
Intervention * Rectal temperature	Interaction	1029	-0.06	0.03	-0.12 to -0.002	0.04

[1] Random effect for clustering by the room in which calves were managed *P*-value > 0.05.

only followed for 28 days after intervention assignment. However, in the current study, calves were followed for 84 days after initial intervention assignment with differences in mortality between intervention groups becoming more pronounced later in the study period. It is possible that the full impact of group antimicrobial use early in life has longer reaching effects; however, in a recent observational study oral antimicrobials administered for the first week of life were not found to be associated with morbidity or mortality when calves were followed over a 77-day study period.[24] It is unclear what the overall impact of antimicrobial use on mortality is, with reports of decreased mortality, no association with mortality, and increased mortality.[18,24-26] However, it is of note that in all of these studies, the conditions under which calves were acquired and reared differed, lending support to the notion that factors beyond simple antimicrobial use behaviours may explain the difference in mortality observed.[26]

Selective therapy strategy was found to not be as effective when calves are received in the winter. Specifically, calves that were assigned to STS during the winter experienced decreased growth as compared to calves that were assigned to COA. This seasonal difference may be due directly to environmental stressors, such as exposure to cold weather on the source farm or during transportation, or due to seasonal variations in other management factors such as ventilation, bedding, nutrition, and infection pressure.[3] Additionally, calves that are transported in the winter experience variable periods of fasting in cold weather which is a time when they would require additional energy for thermoregulation.[27] The seasonal difference in growth observed between interventions may be due to the prevention and control of disease provided with the employment of the metaphylactic strategy when disease pressures are higher.

Arrival weight may be an important addition to further refine risk assessment protocols. In this study, calves that arrived at the facility with a greater arrival weight had better growth over the study period. This was also reported in a recent study by Renaud et al. (2018).[1] Higher arrival weights may reflect better nutrition early in life, which has been shown to improve future productivity.[28] Although age is not known, greater arrival weights may also correlate to calves that are an older age making them better prepared to cope with the stress of transportation, comingling, and a new environment.[2] Arrival weight has also been linked to morbidity and mortality in veal calves.[3,22] Since disease and congenital defects can affect calf growth, it is possible that heavier calves represent healthier calves upon arrival. Many facilities are not set up to weigh calves as they arrive. To design a risk assignment algorithm that was achievable for most producers, individual arrival weight was not included in this study. However, given its importance in predicting future health and growth, careful consideration and further study should focus on determining how arrival weight would best inform risk assignment and prophylactic antimicrobial use decisions.

Rectal temperature was measured upon arrival but was not used in the risk assessment protocol as it was not found to be associated with increased mortality when measured at the time of arrival.[1] In this study, calves with a rectal temperature below 103.1 °F (39.5 °C) at the time of arrival that were assigned to STS were at greater risk of receiving individual antimicrobial therapy during the study period than those with a higher rectal temperature. Less than 12% of calves arriving had a rectal temperature measuring over 103.1 °F (39.5 °C). The intervention provided to calves with high temperature that exhibited other clinical signs of disease may have put them at lower risk for individual antimicrobial therapy later in the production cycle. Calves that arrived with elevated temperatures could also have been exhibiting transient pyrexia due to acute stress, whereas calves that did not exhibit an increase in rectal temperature were responding to more chronic stress or longer transportation times.[2] In addition, calves that were not exhibiting higher temperatures could have been hypoglycemic, dehydrated, or unable able to thermoregulate thus putting them at higher risk of individual therapy.[2] This finding was not seen in the conventional group therapy calves, which may be a result of all calves in this group being treated at the time of arrival mitigating increased susceptibility to disease early in the study period that might results from conditions affecting rectal temperature such as dehydration or hypoglycemia.[2] Although no difference was found between interventions when considering treatment as a proxy for morbidity, it is possible that staff relied on the protective effect of group treatment resulting in some bias in individual treatment decisions masking the relationship between rectal temperature and individual antimicrobial therapy in these rooms.

Stakeholders in male dairy calf industries are concerned by the animal health, welfare and economic impacts of restrictions to antimicrobial use.[8] Bokma et al. (2019)[26] found that herd size and factors unassociated with antimicrobial use had a larger impact on mortality and animal welfare. This is in line with stakeholder perceptions that substantial changes to farm size and management practices are required throughout the veal supply chain to successfully reduce antimicrobial use, preserve calf health, and protect the economic viability of this industry.[8] In this study, the room in which calves were managed was important in the models of health, growth and antimicrobial use. This difference could be due to room specifics such as microenvironment. However, given that the management of rooms within the barn would be similar under facility protocols with the same staff, this importance could have been driven by external factors such as time (e.g. season, weather, calf availability/quality/price at auction), management prior to arrival (e.g. length of time in transit, management on source farm, age at transport), and room specific outbreaks of disease (e.g. one or multiple respiratory disease outbreak events, *Salmonella enterica* (serovar Dublin)). Although some of these factors can be managed with modifications to calf procurement practices and changes to facility biosecurity protocols, others (such as the management of calves on source farms) are outside of facility influence.

Limitations

The antibiotic used and method of administration for the antibiotics was different between the COA and STS strategies. The rationale for this decision was that the commercial facility preferred for COA animals to receive their typical arrival metaphylactic treatment of neomycin and trimethoprim/sulfadiazine. Due to the nature and method that medicated feed is mixed and fed at the facility, it was not possible or practical to selectively provide calves with the medicated milk replacer over the period of 7 days within STS rooms. The use of medicated milk with neomycin and sulfonamides in pre-weaned dairy breed animals is common in Canada and the use of neomycin on its own or in combination with other antimicrobials is common in the U.S.[17,23,29] In response to regulatory changes in both countries focusing on responsible antimicrobial use and increased veterinary oversight, however, these in feed medication practices may become less commonly used.[30,31] As researchers were only involved with calves at the time they were received by the facility, a commonly used long acting parenteral, tulathromycin, was selected to have a similar duration of action as the oral COA protocol.[17,23] The use of an injectable antibiotic would have created an additional calf handling and restraint event as compared to oral antibiotic use; however, it could also have provided more accurate dosing.[32] It also allowed for blinding to the risk assessment and treatment of calves at the time of arrival to facility staff who would be feeding and managing the calves post arrival. Both the oral and parenteral antimicrobials administered at the time of arrival represent Category II products that have label claims for respiratory pathogens, however the oral antimicrobials also have a label claim for pathogens responsible for enteritis. Since STS rooms were not treated with medicated milk replacer, it was not possible to blind facility staff as to the therapy strategy used in each room. It is therefore possible that the facility staff could be biased to their treatment of the rooms. For instance, if facility staff were to place calves within the STS rooms under additional scrutiny during routine health monitoring, they may identify and treat more health events. This would bias morbidity and TI models away from the null, meaning that the actual difference between groups might be less than estimated.

Calves were randomly allocated into STS and COA rooms by the researchers prior to risk assignment at the time of arrival. Despite randomization, there were more calves that exhibited some level of dehydration or had a visibly sunken flank assigned to COA rooms. A visibly sunken flank and dehydration measured at the time of arrival in milk-fed veal calves has been associated with a higher hazard of mortality early in the production period.[1] Additionally, hydration status at the time of arrival has been found to be associated with future growth.[14,20] This suggests that healthier calves were allocated to STS rooms. Therefore, the true difference between interventions may be even greater than observed.

The trial was halted prematurely by request of the facility due to an outbreak of *Salmonella enterica* (serovar Dublin) and the greater amount of mortality observed in STS rooms. Consequently, only 2 seasons were represented in the data collected as opposed to the 4 seasons that were desired. Additionally, this reduced the power of the study by preventing the enrollment of the number of calves within both the STS and COA intervention groups estimated during pre-trial sample size calculations. However, the study had adequate power to detect a difference between interventions in mortality, growth, and antimicrobial use models. One of the consequences of a low powered study is that it increases the chance of a Type II error, the probability of retaining the null hypothesis when it should in fact be rejected. In other words, a much greater effect size is required in low powered studies to detect statistically significant differences, which may result in a bias favouring the null hypothesis.[33,34] When the null hypothesis is not rejected in a low powered study this can either mean the null hypothesis reflects reality or that the results are inconclusive because the study was underpowered. In this study, the difference in mortality, ADG and TI observed may be biased towards the null meaning that the true effect size of the differences detected may be even greater than observed. No difference was detected between interventions in the morbidity models observed which may be a reflection of the power of the study.

Conclusions

This study demonstrates that the selective therapy strategy used at the time of arrival was associated with an increased hazard of mortality, despite there being no difference between interventions for morbidity over the study period at this facility. Further study is required to determine the nature of the association. On average, calves receiving selective therapy in the winter did not grow as well as those receiving group metaphylaxis. Overall antimicrobial use was greater in rooms that received group metaphylaxis at the time of arrival.

Selective therapy strategy at the time of arrival may not be appropriate for all facilities in all seasons. Further refinement to arrival risk assessment algorithms may be required to successfully employ a selective therapy strategy at the time of arrival such as the addition of arrival weight and biomarkers data. Additionally, factors associated with the facility such as housing, management, and calf procurement; as well as external factors such as season, calf age and length of time calves are in transit may play a role in determining whether a selective therapy strategy should be employed. Further study should focus on determining if external and facility level factors should be considered when deciding if a selective therapy strategy is appropriate at the level of the facility.

Acknowledgements

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Endnotes

[a] NeoMed 325 (DIN 01981390, Bio Agri Mix, ON, Canada)

[b] Uniprim (DIN 02241375, Neogen, Michigan, USA)

[c] Draxxin (DIN 02285452, Zoetis Canada Inc., QC, Canada)

[d] Calf Lyte II (DIN 02242113, Vetoquinol, QC, Canada)

[e] Flexi Tuber (Antahi, Cambridge, New Zealand)

[f] Liquipfan (GEA Westfaliasurge, Bönen, Germany)

[g] Grober VG (Grober Nutrition, Cambridge, ON)

[h] MC-343F-E (Omron Healthcare, Ontario, Canada)

[i] Qualtrics XM, Utah, USA

[j] Apple Inc., Cupertino, CA

[k] Tru-Test, Texas, USA

[l] Merit-Trax Technologies, Quebec, Canada

[m] Microsoft Corporation, Redmond, WA

[n] Linco-Spectin 100 (DIN 00813818, Zoetis Canada Inc., QC, Canada)

[o] Procillin (DIN 02245714, Bimeda Canada, ON, Canada)

[p] Borgal (DIN 00555657, Merck Animal Health, QC, Canada)

[q] Nuflor (DIN 02216558, Merck Animal Health, QC, Canada)

[r] Oxytetracycline HCL Soluble Powder 1000 (DIN 02256983, Bio Agri Mix, ON, Canada)

[s] Gallimycin (DIN 00531960, Vetoquinol, QC, Canada)

[t] StataCorp LP, College Station, TX

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