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Effects of vaccination timing and target pathogens on performances and antimicrobial use in long-transported Charolais beef cattle from France to Italy - A retrospective study

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ABSTRACT

Antimicrobial use (AMU) in the livestock sector is a major driver of antimicrobial resistance. Italian beef industry strongly relies on the import of young cattle from France, which are commingled in sorting facilities before transportation to Italy. Both commingling and transportation are stressors for animals and lead to higher risk of bovine respiratory disease (BRD), which in turn increases the risk of AMU. This study aimed to investigate how the timing of first BRD vaccination and the different vaccination target pathogens affect AMU and performance of young Charolais beef cattle imported from France to Italy. Information on animal performance, antimicrobial treatments, and vaccinations was available for 60,726 Charolais cattle belonging to 1449 batches in 33 Italian specialised fattening farms between January 2016 and December 2021. Antimicrobial use was estimated using the treatment incidence 100 adapted for Italy (TI100it). A mixed linear model was used to quantify the effects of the vaccination and the time of first administration on slaughter age, carcase weight, and average daily carcase gain. Similarly, a generalised linear mixed model was used to analyse the TI100it. The vaccination programme was usually applied the first day after the animals' arrival to the Italian fattening farms. Most animals were vaccinated with a polyvalent vaccine against infectious bovine rhinotracheitis (IBR), bovine parainfluenza type 3 virus (PI-3), bovine viral diarrhoea virus type 1 and 2 (BVDV), and bovine respiratory syncytial virus (BRSV). The most used class of antimicrobials to treat BRD were the macrolides, followed by aminoglycosides, amphenicols, tetracyclines, aminopenicillins, and fluoroquinolones. Animals that got vaccinated against any of the considered BRD pathogens upon arrival had significantly lower TI100it, greater average daily carcase gain, and reached slaughter age earlier than animals that got vaccinated later. Animals that received the vaccination against BVDV had lower TI100it and greater average daily carcase gain, and animals that received the vaccination against BRSV were younger at slaughter than unvaccinated animals. The vaccination against *Mannheimia haemolytica* significantly decreased the slaughter age and increased the carcase weight and average daily carcase gain, and the vaccination against PI-3 and *Histophilus somni* significantly increased the slaughter age. Thus, even if the vaccination programme is essential to tackle BRD, this practice is questionable if applied at arrival to the Italian fattening farms and it is advisable that the vaccination programme is planned before the commingling procedure in France.

Abbreviations: BRD, bovine respiratory disease; AMU, antimicrobial use; BHV-1, bovine herpes virus; IBR, infectious bovine rhinotracheitis; BVDV, bovine viral diarrhoea virus type 1 and 2; BRSV, bovine respiratory syncytial virus; PI-3, bovine parainfluenza type 3 virus; BW, body weight; DDDAit, defined daily dose animal for Italy; TI100it, treatment incidence 100 adapted for Italy.

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1. Introduction

Bovine respiratory disease (BRD) is the leading cause of morbidity and mortality in the beef cattle industry worldwide and a common reason for antimicrobial use (AMU) (Urban-Chmiel and Grooms, 2012; Ives and Richeson, 2015; Richeson and Falkner, 2020). Bovine respiratory disease is a complex multifactorial disease which involves several causal viral and bacterial organisms, such as bovine herpes virus-1 (BHV-1), infectious bovine rhinotracheitis virus (IBR), bovine viral diarrhoea virus type 1 and 2 (BVDV), bovine respiratory syncytial virus (BRSV), bovine parainfluenza type 3 virus (PI-3), *Pasteurella multocida*, *Histophilus somni* (formerly *Haemophilus somnus*), *Mannheimia haemolytica* (formerly *Pasteurella haemolytica*), and *Mycoplasma bovis* (Larson and Step, 2012). Particularly in newly received cattle, viruses cause the primary infection and predispose the respiratory tract to the spread of bacterial organisms involved in secondary infection. The latter can result in bronchopneumonia, reduced performance and survival, high treatment costs, and significant economic losses (Stanton et al., 2010; Richeson and Falkner, 2020).

Bovine respiratory disease results in significant negative short-term economic impacts, including veterinary interventions and cattle mortality. Long-term expenses, such as production losses, are challenging to estimate due to subclinical impacts (White and Larson, 2020; Padalino et al., 2021). The primary economic burden of BRD in beef cattle arises from vaccination, veterinary treatments, and monitoring costs for affected animals (Buchanan et al., 2016). According to Buchanan et al. (2016) carcasses from healthy Charolais-sired calves were valued $58.28 more than those treated for BRD at least once. Between 2011 and 2015, BRD in pre-weaned calves cost the US beef cow–calf industry approximately $165 million per year. This amount included expenses related to BRD-affected calf mortality, treatment, and lighter weaning weight which were approximately $126 million, $25 million, and $15 million, respectively. The estimated cost of BRD accounts for up to 20% of farmers income in France and up to 44% in North America (Bareille et al., 2008; Mijar et al., 2023).

Several studies have investigated the risk factors contributing to the development of BRD, categorising three classes of risk factors: pathogen, host, and environment (Louie et al., 2018). In general, lightweight, recently weaned, and highly commingled cattle without known vaccination history that have experienced a long transportation are at high-risk (Edwards, 2010; Ives and Richeson, 2015; Wilson et al., 2017; Louie et al., 2018). Other factors influencing the occurrence of BRD include adaptation to new management and feeding conditions of the fattening farms, climatic variability, seasonality, sex, and breed (Sanderson et al., 2008; Urban-Chmiel and Grooms, 2012; Ives and Richeson, 2015). Bovine respiratory disease mostly occurs during the first few days after animals arrive at the fattening farms (Richeson and Falkner, 2020), likely due to stress-mediated impairment of their immune system. Indeed, stress events can depress the immune system, promoting viral replication and potential secondary bacterial infections in the respiratory tract (Wilson et al., 2017). For instance, the transition from a pasture-based to an indoor intensive system and changes in temperature and humidity conditions act as stressors for animals, increasing the likelihood of developing respiratory diseases (Louie et al., 2018).

Italy ranked as the third-largest beef producer in Europe in 2021, contributing to 11.3% of the total European beef production (EUROSTAT, 2022). The Italian beef sector primarily relies on importing young live animals from France, which are raised at pasture until they reach 11 to 12 months of age and achieve a body weight (BW) of 320–450 kg (~600,000 heads/year; Gallo et al., 2014; Herve et al., 2020). Before transportation to Italy, these animals are typically commingled in French commingling centres to create homogeneous batches based on BW, sex, and breed (Santinello et al., 2022a). Most of the commingling centres in France are in the Auvergne region, resulting in a similar transportation duration for most animals reaching Italian fattening units, traditionally present in the North-Eastern regions of the Po Valley. Upon arrival at the Italian fattening units, the animals undergo an adaptation period to the new farm environment, diet, and management conditions (Santinello et al., 2022a). The temperature and humidity typical of the Po Valley challenge the overall health of the animals. Based on their sex, breed, and production stage animals are fed various diets. As regards the arrival phase (0 to 20–40 days), nutritional strategy involves a diet with low level of energy and protein along with higher fibre content (Galyean et al., 1999). Following this, a transition diet is introduced for a brief period of 10–30 days to ensure a gradual adaptation to the fattening diet, which is characterized by higher energy level and lower fibre content (Dell'Orto and Baldi, 2014). Furthermore, the fattening diet ensures that both heifers and young bulls reach the desired slaughter weight within 6–7 months at an age of 20 to 22 months (Supplementary Table 1). Italian fatteners generally perform two fattening cycles per year. The farms are characterized by closed or open barns with multiple pens. The flooring system, typically either fully slatted or concrete, incorporates straw bedding which is replaced periodically during the fattening cycle (Cozzi et al., 2009). A cross-sectional study by Magrin et al. (2020) reported that the most common flooring type during the finishing phase in Veneto Region (north-east of Italy) is deep litter (60%).

Santinello et al. (2022a) reported that a significant portion of the AMU in Italian fattening farms is directed to tackle BRD. Dehydration and insufficient feed intake during transportation can induce psychological and physical stress, leading to additional immune system suppression (Engen et al., 2018). Barnes et al. (2015) noted that cattle transported for more than 6 h were slightly more prone to developing BRD compared to those transported for less than 6 h. Similarly, Cernicchiaro et al. (2012) observed an increase in BRD morbidity with the distance travelled to reach the feedlot.

Fattening farms used to control BRD morbidity and mortality by performing, after veterinarian approval and justification, single antimicrobial metaphylaxis on newly received cattle upon arrival (Nickell and White, 2010; Abell et al., 2017; Word et al., 2020; Maples et al., 2022; Picault et al., 2022). Although antimicrobial metaphylaxis is an effective strategy to control the negative effects of the BRD, its use is in conflict with judicious antimicrobial application (Abell et al., 2017; Baptiste and Kyvsgaard, 2017; Word et al., 2020), and may contribute to the development of antimicrobial resistance, posing a threat to both animal and human health (Laxminarayan et al., 2013). Consequently, in the European Union, the regulation on the use of antimicrobials in veterinary medicine (Regulation (EU) 2019/6) states that the use of metaphylaxis should be avoided permitting its use only when no alternatives are available. Alternative practices to mitigate the risk of BRD include administering a single or multiple vaccinations upon the animals' arrival and adopting proper on-farm biosecurity measures (Santinello et al., 2022b). The use of BRD vaccination programmes stimulate the individual antibody production (Chase et al., 2008; Stilwell et al., 2008; Richeson and Falkner, 2020).

Nevertheless, numerous factors can interfere with the effective immunisation of the animals, making it difficult to identify the most effective vaccine strategy (Richeson and Falkner, 2020). Stress interferes with the immunisation of the animals and Edwards (2010) suggested to avoid vaccination programmes during the occurrence of any kind of stress (e.g., weaning, adaptation, transportation). Schumaher et al. (2019) found that a double vaccination 15 days before weaning and 15 days before arrival at the feedlot resulted in a greater reduction of disease incidence compared to vaccination at weaning and arrival.

However, it is a good practice to ensure that all calves reach weaning with sufficient serum titers against the BRD pathogens after consuming maternal colostrum (Chase, 2022). Through a meta-analysis, O'Connor et al. (2019) highlighted that the level of protection provided by vaccines is not consistently high. Studies on the efficacy of BVDV and PI-3 vaccines produced unreliable results, while studies on the BRSV vaccine demonstrated unequivocal efficacy without detrimental effects on health (Edwards, 2010). In general, except for BHV-1 and BVDV, there is a lack of evidence regarding the efficacy of vaccination against BRD pathogens, and morbidity among non-vaccinated and vaccinated animals is often similar (Theurer et al., 2015).

To the best of our knowledge, no studies have explored the effect of vaccination against BRD agents on AMU in beef cattle subjected to long transportation. Thus, the present study aimed to investigate the use of BRD vaccination programmes in Charolais cattle transported from France to Italy to detect any effects of vaccination timing and target pathogens on AMU and animal's performance.

2. Materials and methods

2.1. Animals

The data used in this study were retrieved from one of the biggest cooperative of beef producers in north-east of Italy (Associazione Zootecnica Veneta - AZoVe, Cittadella, Italy) and pertain to Charolais bulls and heifers imported from France to Italy between 2016 and 2021. The available information included animal ID, ID of the French farm of origin, date of birth, entry BW (provided as mean BW of the batch, in kg), the ID of the Italian fattening farm, the start and end of the fattening cycle, carcase weight (kg), parenteral antimicrobial treatments administered during the fattening cycle (number, date, reason, and mL of antimicrobial administered), and vaccinations administered at the fattening farm (number, target pathogen, and date of administration).

A given batch, which arrived at the same Italian farm on the same day, consisted of animals with the same average entry BW, sex, and breed. For each batch, the number of animals, number of national French Departments of birth, number of French farms of birth, and number of antimicrobial treatments for BRD per animal were available. France is characterised by a high number of cow-calf medium-size herds that provide animals to sorting facilities. Since France is divided into geographical areas called Departments, a single batch can contain animals from different herds located in different Departments. Thus, batches with less than 10 animals (less than 1% of the total) were removed from the dataset to avoid potential bias due to lack of representativeness of the French procedure of commingling. Batches with average entry BW outside the mean ± 3 standard deviations were also discarded. The age at the beginning of the fattening cycle (days), slaughter age (days), length of the fattening cycle (days), mortality rate per batch (%), average daily carcase gain (kg/day), i.e., the ratio between carcase weight and length of the fattening cycle, and the time between animals' arrival and first vaccination (days) were calculated for each animal. Since the focus of the present study was the occurrence of BRD, only animals with information on vaccinations and antimicrobial treatments related to BRD were retained. Only vaccinations against IBR, BVDV, BRSV, PI-3, *M. haemolytica,* and *H. somni* were considered.

After editing, 60,726 Charolais cattle (20,974 females and 39,752 males) from 1449 batches (555 female and 894 male batches) reared in 33 Italian specialised fattening farms from 2016 to 2021 were available for statistical analysis. Only 3% of the animals were removed during the editing process.

2.2. Quantification of AMU and vaccines

Between 2016 and 2021, 60 veterinary medicinal products containing one or two antimicrobial active ingredients were used to treat BRD in the Italian farms involved in the study. The AMU was estimated using the defined daily doses animal for Italy (DDDAit) established by the Italian Ministry of Health during the development of the ClassyFarm monitoring system (www.classyfarm.it). The DDDAit for beef cattle were described in detail in Diana et al. (2021). Briefly, the DDDAit of a veterinary medicinal product is the dose (mg) of its active ingredient that should be administered per kg of BW per day, according to the summary of product characteristics. The AMU was expressed as the treatment incidence 100 adapted for Italy (TI100it) which was calculated at animal level for each veterinary medicinal product, following the formula (1) adapted from Timmerman et al. (2006) and AACTING (2019):

$$TI100it = \frac{\text{Amount of active ingredient administered per animal (mg)}}{[\text{DDDAit } (\text{mg}/kg/day)\ x\ \ Standard\ \ BW\ \ x\ \ Standard\ \ days\ \ at\ \ risk]}\ \ x\ 100 \tag{1}$$

The 'standard BW' was set at 400 kg and 'standard days at risk' at 230 days (Diana et al., 2021). The TI100it of each veterinary medicinal product were summed up to obtain a total TI100it per animal. Animals that did not receive any treatments were assigned a TI100it of 0.

2.3. Statistical analysis

The experimental unit of the study was the animal. Slaughter age, carcase weight, average daily carcase gain, and TI100it were assessed for normality through visual inspection of their density plots, as well as by skewness and kurtosis. To investigate the effect of the timing of first vaccination on these traits, animals were grouped into two classes: i) VAC1, which included animals vaccinated the day of arrival or the next day and ii) VAC2, which included animals vaccinated from day 2 after arrival. Age at arrival at the fattening farm was grouped into 3 classes for males and 3 classes for females: young (heifers with age at arrival $<$ 289 days and bulls with age at arrival $<$ 282 days), medium (heifers with age at arrival between 289 and 345 days and bulls with age at arrival between 282 and 332 days) and old (heifers with age at arrival $>$ 345 days and bulls with age at arrival $>$ 332 days). The cut-offs for age were determined to obtain an equal number of animals in each class using the relative distribution.

2.4. Models

The statistical analysis was conducted using the SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Model building involved testing each main fixed effect and first-order interactions, retaining only those that significantly explained the variation of the outcome variables. Akaike information criterion, Bayesian information criterion, and Root-

Table 1
Descriptive statistics of number of animals, French Departments of origin, French farms of origin, mortality rate, and body weight at the beginning of the fattening cycle collected on 1449 batches (555 female and 894 male batches).

Trait	Mean	SD	Median	IQR	Minimum	Maximum
N. of animals	54.0	22.0	53.0	34.0 - 64.0	10.0	179.0
N. of French Departments[1]	6.0	2.5	6.0	4.0 - 8.0	1.0	17.0
N. of French farms[2]	22.0	11.2	20.0	15.0 - 27.0	1.0	70.0
Mortality rate (%)[3]	0.34	1.1	0.0	0.0 - 0.0	0.0	14.3
Body weight (kg)	467.9	125.9	422.0	383.0 - 548.0	308.0	790.9

Data are presented as mean and standard deviation (SD), median and interquartile range (IQR), and minimum and maximum.

[1] Number of French Departments of origin where animals of the same batch were born.

[2] Number of French farms of origin where animals of the same batch were born.

[3] Percentage of animals that died per batch during the fattening cycle.

Table 2
Descriptive statistics of animal performances collected on 60,726 Charolais cattle (20,974 females and 39,752 males).

Trait	Mean	SD	Median	IQR	Minimum	Maximum
Age (days)[1]	320.7	61.6	309.0	275.0 - 358.0	180.0	580.0
Length of the fattening cycle (days)	193.7	15.5	192.0	187.0 - 201.0	61.0	240.0
Slaughter age (days)	514.3	61.3	504.0	468.0 - 553.0	283.0	720.0
Carcase weight (kg)	396.7	65.6	414.9	332.6 - 448.0	100.0	998.0
Average daily carcase gain (kg/day)[2]	2.1	0.4	2.1	1.7 - 2.3	1.1	4.0

Data are presented as mean and standard deviation (SD), median and interquartile range (Q1-Q3), minimum and maximum.

[1] Age when the fattening cycle started.

[2] Calculated as the ratio between carcase weight and length of the fattening cycle.

Mean-Square Error were used to assess the goodness-of-fit of each model. Carcase weight and TI100it were investigated using the following linear mixed model:

$$y_{ijklmnopqrstu} = \mu + Timing_i + Sex_j + Year_k + Season_l + Age_m + IBR_n + BVDV_o + BRSV_p + PI3_q + Mh_r + Hs_s$$

$$+ (Sex \times BVDV)_{jo} + (Season \times Age)_{lm} + (Season \times BVDV)_{lo} + (Age \times BVDV)_{mo} + Batch_t(Farm_u) + e_{ijklmnopqrstu},$$

where $y_{ijklmnopqrstu}$ is carcase weight or TI100it; μ is the overall intercept of the model; $Timing_i$ is the fixed effect of the ith class of vaccination timing (i = VAC1, VAC2); Sex_j is the fixed effect of the jth sex of the animal (j = male, female); $Year_k$ is the fixed effect of the kth year of arrival (k = 2016, 2017, 2018, 2019, 2020, 2021); $Season_l$ is the fixed effect of the lth season of arrival (l = autumn – September, October, November; winter – December, January, February; spring – March, April, May; summer – June, July, August); Age_m is the fixed effect of the mth class of age at arrival (m = young, medium, old); IBR_n, $BVDV_o$, $BRSV_p$, $PI3_q$, Mh_r, and Hs_s identify the fixed effect of vaccination status (vaccinated, unvaccinated) against IBR, BVDV, BRSV, PI-3, *M. haemolytica*, and *H. somni*, respectively; $(Sex \times BVDV)_{jo}$ is the fixed interaction effect between sex and BVDV vaccination status; $(Season \times Age)_{lm}$ is the fixed interaction effect between class of age at arrival and season of arrival; $(Season \times BVDV)_{lo}$ is the fixed interaction effect between season of arrival and BVDV vaccination status; $(Age \times BVDV)_{mo}$ is the fixed interaction effect between class of age at arrival and BVDV vaccination status; $Batch_t(Farm_u)$ is the random effect of the tth batch nested within the uth fattening unit of arrival ~N(0, $\sigma^2_{\text{batch(farm)}}$), where $\sigma^2_{\text{batch(farm)}}$ is the batch nested within farm variance; and $e_{ijklmnopqrstu}$ is the random residual ~N(0, σ^2_e), where σ^2_e is the error variance. The effects of departments and fattening cycle were also tested, however, they were not significant and thus were not further considered in the analysis. The TI100it was positive and right-skewed, and thus a generalised linear mixed model with gamma distribution, Laplace method of optimisation, and log-link function in GLIMMIX procedure of SAS was applied (Diana et al., 2021). To address the zero-inflated nature of the TI100it due to the high number of untreated animals (TI100it = 0), a constant of + 3 was added to the TI100it before the analysis. This prevented those animals from being discarded and thus overestimating the AMU (Diana et al., 2021; Santinello et al., 2022a).

Slaughter age and average daily carcase gain were analysed with the same model used for carcase weight but excluding the fixed effect of age at arrival and its interactions with season of arrival and BVDV vaccination.

Results are presented as least squares means ± standard error of the mean. Bonferroni *post-hoc* adjustment was applied for multiple comparisons of least squares means of the fixed effects. The level of statistical significance was set at $P < 0.05$.

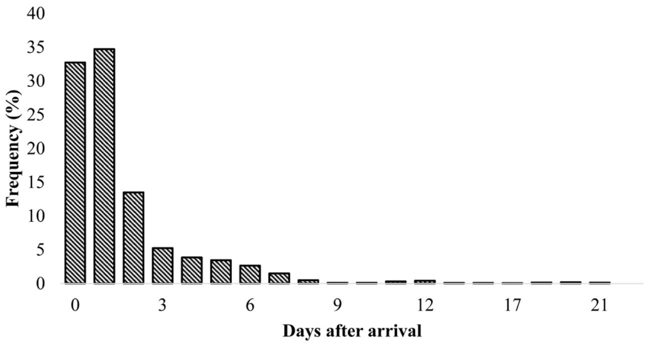

Fig. 1. Frequency of Charolais cattle (n = 60,726) according to the time between the arrival at the fattening farm and the first vaccination.

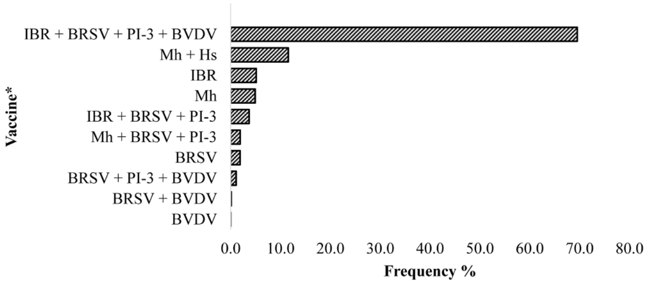

Fig. 2. Frequency of Charolais cattle (n = 60,726) according to the agents against which the animals were vaccinated.*IBR = infectious bovine rhinotracheitis; PI-3 = bovine parainfluenza type 3 virus; BVDV = bovine viral diarrhoea virus type 1 and 2; BRSV = bovine respiratory syncytial virus; *Mh* = *M. haemolytica*; *Hs* = *H. somni.*

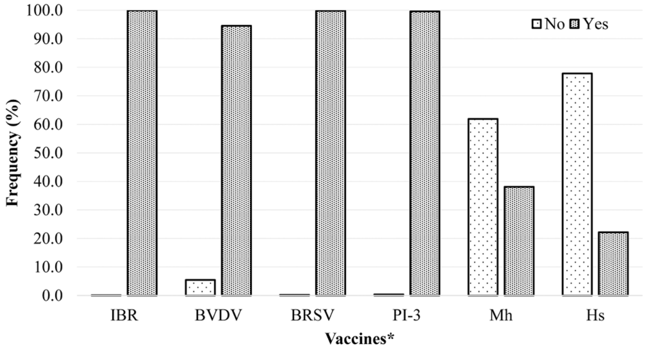

Fig. 3. Frequency of Charolais cattle (n = 60,726) vaccinated for each pathogen target. *IBR = infectious bovine rhinotracheitis; PI-3 = bovine parainfluenza type 3 virus; BVDV = bovine viral diarrhoea virus type 1 and 2; BRSV = bovine respiratory syncytial virus; *Mh* = *M. haemolytica*; *Hs* = *H. somni.*

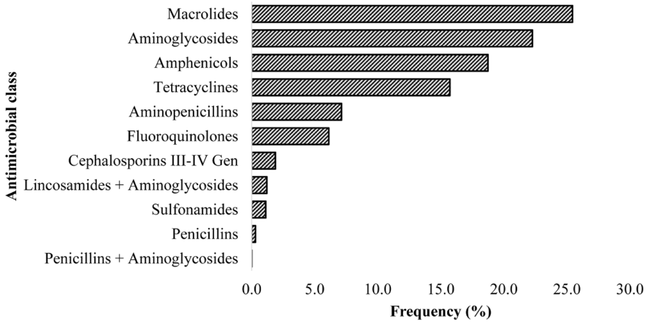

Fig. 4. Frequency of treatments by antimicrobial class received by Charolais cattle (n = 60,726).

3. Results

3.1. Descriptive statistics of batch and animal characteristics

Out of the 1449 batches available for statistical analysis after editing procedure, 234 arrived in 2016 (73 female and 161 male batches), 280 in 2017 (79 female and 201 male batches), 242 in 2018 (68 female and 174 male batches), 188 in 2019 (78 female and 110 male batches), 328 in 2020 (166 female and 162 male batches), and 177 in 2021 (91 female and 86 male batches). Table 1 provides the descriptive statistics for the traits calculated at the batch level.

Descriptive statistics of performances measured at animal level are presented in Table 2. Both males and females underwent a fattening cycle of about 6 months and reached the slaughter weight before 24 months of age.

3.2. Descriptive statistics of AMU and vaccination

Throughout the fattening cycle, each animal was vaccinated on average for 4.5 ± 0.9 (median: 4; IQR: 1) different pathogens selected among IBR, BVDV, BRSV, PI-3, *M. haemolytica,* and *H. somni*, with a minimum of 1 and a maximum of 6. Most of the animals were vaccinated one day after arrival (median: 1 day; IQR: 2 days; Fig. 1) with a polyvalent vaccine against IBR, BRSV, PI-3, and BVDV (Fig. 2). Thus, almost all animals received a vaccination for IBR, BVDV, BRSV, and PI-3 (Fig. 3) and no intranasal vaccine was used. During the fattening cycle, each animal received on average 1.1 ± 1.1 antimicrobial treatments (median: 0.73; IQR: 1.2). The average TI100it was 1.44 (median: 0; IQR: 2.3). On average 49.5 ± 41.7% of the animals that belonged to a batch were treated with at least 1 antimicrobial for BRD (median: 67.9%; IQR: 88.3%). The antimicrobial treatments were mostly administered in the first days after arrival to the fattening farm except for animals that required multiple treatments during the fattening cycle. The class of antimicrobials most frequently used to treat BRD were macrolides, followed by aminoglycosides, amphenicols, tetracyclines, aminopenicillins, and fluoroquinolones (Fig. 4).

3.3. Factors affecting AMU and performance traits

Supplementary Tables 2 and 3 report the estimates of the predictors along with their 95% confidence interval, standard error and the P-value of the respective effects for TI100it, slaughter age, carcase weight, and average daily carcase gain. Additionally, Supplementary Table 4 summarises the least squares means of the traits concerning the effects of sex, age, year, and season, and least squares means for interaction effects are detailed in Supplementary Table 5. The impact of sex was significant in explaining the variation of TI100it, carcase weight, and average daily carcase gain, but not slaughter age. Male animals exhibited significantly higher TI100it than females. The effect of age at arrival was included only in the models of TI100it and carcase weight, and it was always significant. Younger animals at arrival had higher TI100it and lighter carcase weight compared to those categorised as medium or old. Particularly for young animals arriving in autumn, TI100it was higher and carcase weight lighter compared to other combinations. The effect of year of arrival was always significant except for carcase weight. Notably, the TI100it decreased from 2017 to 2019 and increased thereafter. Animals arriving in autumn had lower carcase weight and higher TI100it than those arriving in spring and summer. Least squares means of individual performance traits and TI100it for the effects of the first vaccination and the type of pathogen targeted by the vaccination are presented in Table 3. The timing of the first vaccination significantly influenced the variability of TI100it, slaughter age, and average daily carcase gain. The results showed that VAC1 animals had lower TI100it and reached the slaughter weight earlier with greater average daily carcase gain than VAC2 animals. Animals vaccinated against BVDV had significantly lower TI100it and greater average daily carcase gain, while those vaccinated against BRSV and *M. haemolytica* had lower slaughter age. Vaccination against *M. haemolytica* significantly increased carcase weight and average daily carcase gain. The PI-3 and *H. somni* vaccination significantly increased the slaughter age. The BVDV vaccination significantly reduced TI100it in all seasons, except for spring.

4. Discussion

Young beef cattle are usually not vaccinated for BRD pathogens in French collection centers before transportation to Italy or in the French farms of origin. According to Poizat et al. (2022), French farmers perceive BRD vaccination as an additional cost and a challenging practice in a pasture-based cow-calf system. Consequently, cattle are vaccinated against BRD pathogens upon arrival at the Italian fattening

Table 3

Least squares means (LSM) and standard error of the mean (SEM) of individual treatment incidence 100 adapted for Italy (TI100it), slaughter age (days), carcase weight (kg), and average daily carcase gain (kg/day) for the effects of time between the arrival of animals to the fattening farm and the first vaccination and the type of pathogen targeted by the vaccination.

Effect		TI100it[1]		Slaughter age (days)		Carcase weight (kg)		Average daily carcase gain[2] (kg/day)	
		LSM	SEM	LSM	SEM	LSM	SEM	LSM	SEM
First vaccination[3]	VAC1	1.37^{b}	0.04	516.0^{b}	5.9	383.4	3.2	1.96^{a}	0.03
	VAC2	1.41^{a}	0.04	521.3^{a}	5.9	382.6	3.2	1.94^{b}	0.03
IBR	Yes	1.51	0.08	532.5	10.6	379.1	4.4	1.97	0.06
	No	1.26	0.11	504.8	15.3	386.8	7.6	1.94	0.08
BVDV	Yes	1.31^{b}	0.05	518.6	6.4	383.3	3.4	1.97^{a}	0.03
	No	1.46^{a}	0.04	518.7	5.9	382.6	3.3	1.93^{b}	0.03
BRSV	Yes	1.26	0.12	486.0^{b}	15.0	381.4	6.3	2.00	0.08
	No	1.51	0.13	551.3^{a}	15.9	384.5	6.8	1.90	0.09
PI-3	Yes	1.48	0.1	538.2^{a}	11.5	384.2	5.0	1.88	0.06
	No	1.29	0.09	499.1^{b}	11.0	381.8	4.7	2.02	0.06
M. haemolytica	Yes	1.40	0.04	514.7^{b}	5.9	384.2^{a}	3.2	1.98^{a}	0.03
	No	1.37	0.04	522.6^{a}	6.2	381.7^{b}	3.3	1.92^{b}	0.03
H. somni	Yes	1.38	0.04	522.8^{a}	6.2	383.5	3.3	1.94	0.03
	No	1.39	0.04	514.5^{b}	5.8	382.4	3.2	1.97	0.03

[a,b] Means with different superscripts within trait and effect differ significantly ($P < 0.05$).

[1] Calculated by using the defined daily dose animal for Italy based on Italian guidelines of dosage obtained from the Italian database (www.classyfarm.it).

[2] Ratio between carcase weight and the length of the fattening cycle.

[3] Time to first vaccination: VAC1 = animals vaccinated the day of arrival or the next day (n = 25,942); VAC2 = animals vaccinated from day 2 after arrival (n = 34,784).

units. Although this is not a mandatory practice, Italian fatteners prefer vaccinating cattle against BRD pathogens to prevent the potential spread of diseases in their fattening units. Delabouglise et al. (2017) suggested a strategy to adjust prices of French weaned calves sold to the fatteners based on their vaccination status and recommended the introduction of vaccines at an affordable price to promote early-life vaccination of beef calves and in turn long-lasting immunity with potential benefits during the fattening period.

The present study highlighted that beef cattle entering Italian fattening units are usually vaccinated during the first week after arrival against an average of 4 different pathogens among IBR, BVDV, BRSV, PI-3, *M. haemolytica,* and *H. somni*. Indeed, most of the animals received a polyvalent vaccine instead of monovalent vaccines because the former is less time consuming for the farmers.

The substantial number of French Departments and farms of origin attests to the extensive commingling during batch formation in France. While the mixing of animals may heighten the transmission of various BRD pathogens, it remains an inherent aspect of the French-Italian production system. Indeed, France is characterised by small cow-calf farms, which supply young cattle to specific sorting facilities to produce homogeneous batches of animals destined for the Italian fatteners (Santinello et al., 2022a). Santinello et al. (2022a) reported that young Charolais bulls subjected to a high degree of commingling exhibited increased AMU and decreased performance compared to their low-commingled counterparts. In general, the higher the number of cow-calf farms contributing calves to a batch, the greater the risk of developing BRD (Sanderson et al., 2008; Poizat et al., 2022).

In this study, only antimicrobial treatments for BRD were considered. A mean TI100it of 1.4 suggests that, on average, 1.4% of animals underwent treatment for BRD at any given time during the fattening cycle, indicating a potential for reducing AMU. Unfortunately, the lack of information about specific causes of mortality prevented us from including its consideration in relation to vaccination. Consistently with previous findings (Brault et al., 2019; Santinello et al., 2022b), macrolides emerged as the primary class of antimicrobials used to treat the BRD. Baptiste and Kyvsgaard (2017) highlighted the efficacy of macrolides in reducing BRD mortality. However, caution is advised in their administration, as they have been categorized as highest priority or critically important antimicrobials for human medicine by the World Health Organization (WHO, 2018). The incidence of BRD can be mitigated through various strategies such as preconditioning the animals, vaccinating them prior to the occurrence of the risk, developing new vaccines, and increasing biosecurity (Urban-Chmiel and Grooms, 2012). Preconditioning programmes encompass actions like weaning, vaccination against infectious agents, anthelmintic treatment, castration, dehorning, and acclimation to feeding and watering facilities before transporting animals to feedlots (Duff and Galyean, 2007). Diana et al. (2020a) reported that improving biosecurity measures contributes to significantly reduce AMU and the number of antimicrobial treatments for BRD. For instance, implementation of quarantine and the separation of sick animals from the rest of the batch can reduce the risk of cross-contaminations with BRD pathogens, and can thus reduce AMU and improve performance (Santinello et al., 2022b). However, the implementation of these solutions incurs costs, and the absence of premium prices for preconditioned animals provides no economic incentive for cow-calf producers to enhance the quality of their weaned calves through vaccination (Poizat et al., 2022).

In the present study, it was demonstrated that administering a vaccine against BRD as soon as possible after the animals' arrival not only leads to a reduction in AMU but also contributes to a generally improved performance. Indeed, animals that received their first vaccination within 24 h upon arrival concluded their fattening cycle earlier and exhibited a greater average daily carcase gain. However, determining the optimal timing for the first vaccination in newly received cattle is challenging due to various factors such as the potential occurrence of an infection and the varying levels of stress. Schumaher et al. (2019) reported that serum titers against most of BRD viruses were higher for animals that received an early vaccination 15 days before feedlot entry. In their review, Richeson and Falkner (2020) reported that experimental studies conducted on the efficiency of vaccinations often lack a negative control treatment which leads to poor confidence in the interpretation and control of confounding factors. The ideal scenario would be to vaccinate animals before their arrival to Italian fattening units and prior to stress exposure during the commingling procedure at French sorting facilities.

Additionally, in the present study some vaccinations were shown to be more relevant than others in improving animals' performances. The vaccination against BVDV led to both a reduction in AMU and an increase in average daily carcase gain. In terms of preventing clinical disease, current BVDV vaccines have been demonstrated to induce a rapid onset of immunity (Newcomer et al., 2017), and this could have improved the performances of vaccinated animals. In the meta-analysis of Theurer et al. (2015), 6 out of the 11 trials considered for BVDV vaccination through multiple virus vaccines revealed a significantly lower morbidity risk for vaccinated animals compared to controls. The same meta-analysis reported a significant decrease in morbidity in animals that were vaccinated against BRSV using a multiple virus vaccine. Although high vaccination rates are thought to improve the immune response against BRD agents, a recent systematic review (O'Connor et al., 2019) pointed out that there is scarce evidence on the efficacy of commercial BRD vaccines administered to newly received cattle. Our study showed that the BRSV vaccination only led to a sensible reduction in slaughter age and to a numeric increase in average daily carcase gain. Kirkpatrick and Dougals (2008) found no variation in the performance of animals vaccinated with a multiple virus vaccine compared to the control group. Other studies highlighted that vaccinating calves at arrival was associated with increased BRD morbidity, mortality, and lower final weights and average daily gain (Richeson et al., 2008; Griffin et al., 2018). In the present study, animals vaccinated against *M. haemolytica* exhibited younger age at slaughter and greater carcase weight and average daily carcase gain. Meanwhile, animals vaccinated against *H. somni* and PI-3 were older at slaughter. On the contrary, Arthington et al. (2013) highlighted that vaccination against *M. haemolytica* reduced cattle ADG, and this was explained by considering that within a 2-week period after vaccination, beef calves experience an acute-phase protein response, which may result in reduced ADG and feed efficiency. However, a recent systematic review of vaccine efficacy against *M. haemolytica* and *H. somni* pointed out that too few repeated studies on comparable populations exist to support the efficacy of bacterial vaccine against BRD in North American cattle (Capik et al., 2021). These contrasting findings could be explained by the multitude of factors that affect the efficacy of vaccination in long-transported calves which have been recently exposed to various stressors and are potentially already incubating BRD. In general, the complexity of factors and etiologic agents involved in naturally occurring BRD make the efficacy in field trials harder to determine (Confer and Ayalew, 2019). Indeed, due to the retrospective nature of the present field study, it cannot be excluded that some of these uncontrolled factors and unbalanced data may have influenced the results.

The results of the present study highlighted some of the complexities related to BRD, confirming that sex, age at arrival, year and season of arrival, and timing of vaccination influence AMU. Male animals had greater AMU compared to females, consistently with other studies (Diana et al., 2021). Diana et al. (2021) reported that the average batch size for males was approximately 70% larger than the average batch size for females (69.4 heads vs. 40.1 heads). This could heighten the risk of infectious diseases because of a greater number of animals occupying the same space, thereby increasing the likelihood of pathogen transmission (Hommerich et al., 2019). In the current study, we observed that batches were comprised of an average of 60 animals for males and 48 animals for females. Additionally, both genders exhibited a similar distribution in terms of their farm of origin: on average 22 farms of origin provided the animals for males' batches and 21 for females' batches. Muggli-Cockett et al. (1992) observed that males were at greater risk of BRD than females. Burdick Sanchez et al. (2022) reported differences in the acute phase response following a respiratory disease challenge between heifers and steers. Specifically, body temperature was lower in heifers than steers, as well as the concentrations of neutrophils following vaccination. Animals arriving at fattening farms at a younger age had higher AMU, in agreement with a previous study (Santinello et al., 2022a). As discussed above, stress events such as transportation and commingling may impair the immune response, thus increasing the risk of BRD within 45 days of arrival in lighter and younger feedlot cattle (Avra et al., 2017). The TI100it did not decrease linearly across time, and this was probably due to the nature of the production system which has an intrinsic risk of developing BRD. However, Santinello et al. (2022a) reported a reduction of TI100it by approximately 11% between 2016 and 2018 for Charolais young bulls. This is likely because the study by Santinello et al. (2022a) involved only young bulls and considered also animals treated for other diseases. The season with the highest TI100it was autumn, likely due to the high humidity and low temperature typical of the geographical area (Diana et al., 2021), and to the seasonality of breeding in France that can increase the availability of cattle in that period (Poizat et al., 2022), thus enhancing the risk of high mixing in the commingling centres. Indeed, animals that arrived at younger age during autumn were at a greater risk of being treated with antimicrobials against BRD. Nevertheless, vaccination against BVDV, when applied to young animals or animals that arrived during autumn and winter, facilitates a reduction of AMU. This suggest that vaccination programme applied to animals at greater BRD risk can help them to overcome the illness and thus reduce AMU.

5. Conclusions

This study offers a comprehensive overview of the integrated beef production system between Italy and France, focusing on the Northeast region of Italy. This system is characterized by various stressors, extensive commingling, prolonged transport distances, and changes in management practices and climate conditions. These factors collectively compromise the immune system of the animals, making them susceptible to viral infections that may escalate into bacterial bronchopneumonia, necessitating AMU. An effective strategy to mitigate these challenges could involve implementing a robust vaccination programme. Multiple vaccinations, particularly administered before periods of heightened stress like commingling, transportation, and arrival at a new farm, could serve as a crucial preparatory measure for the immune system. In the context of the French-Italian beef system, a practical approach would be to vaccinate animals promptly after weaning and provide a booster prior to their transfer to French sorting facilities or transportation. This could help to reduce the risk of BRD and the risk of severe lung damage which can lead to economic losses, performance depression, and higher AMU.

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CRediT authorship contribution statement

Penasa Mauro: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Fusi Francesca:** Methodology, Validation, Writing – review & editing. **Alborali Giovanni Loris:** Methodology, Validation, Writing – review & editing. **Santinello Matteo:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Romeo Claudia:** Methodology, Validation, Writing – review & editing. **Lorenzi Valentina:** Methodology, Validation, Writing – review & editing. **Scali Federico:** Methodology, Validation, Writing – review & editing. **De Marchi Massimo:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Declaration of Competing Interest

All authors have approved the manuscript and agree with its submission to Antibiotics. The authors also declare that they have no competing interests.

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Research data

Due to the sensitive nature of the data collected in this study, raw data would remain confidential and would not be shared.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prevetmed.2024.106130.

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