Original Paper

Sources of variation of antimicrobial use in Charolaise and Limousine beef breeds in Veneto region (Italy)

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The development of antimicrobial resistance is a growing problem which jeopardises both human and animal health. Livestock sector is generally blamed as principal contributor due to the over-use of antimicrobials to treat animals. Hence, new strategies to reduce antimicrobial use (AMU) are necessary. Little is still known on potential factors affecting AMU in beef production. Therefore, the objective of this study was to explore the impact of farm, breed, sex and season on AMU in Charolaise and Limousine breeds. Data on body weight, breed, sex and AMU were collected from 10 specialized beef farms (543 batches) located in Veneto region (Italy). Average daily gain (ADG) was calculated and AMU data were used to calculate a treatment incidence (TI100it) through the Defined Daily Dose Animal based on Italian dosage. An ANOVA was performed to investigate sources of variation of ADG and TI100it. Overall, farms differed significantly for both ADG and TI100it. The ADG was greater for Charolaise than Limousine breed (P <0.05). Limousine had greater TI100it than Charolaise (P <0.05), and males had greater TI100it than females (P <0.05), likely due to their higher susceptibility to respiratory diseases. Differences among seasons were also observed, with the coldest periods of the year having greater TI100it compared to summer and spring (P <0.05). Findings of the present study shed a light on potential risk factors of AMU in beef cattle, which will be useful to develop new strategies for the reduction of antimicrobials.

Keywords: antimicrobial, beef cattle, treatment incidence

1   Introduction

Improved livestock production has benefited from the discovery of antimicrobials, which are now part of the general farm management for disease care (Van Boeckel et al., 2015). However, the wide use of antimicrobials, estimated to increase by 67% within 2030 (Van Boeckel et al., 2015), is recognized as the main contributor to the emergence of antimicrobial resistance (AMR) (Noyes et al., 2016a, EMA, 2019), a global issue that threatens human and animal health alike (Murphy et al., 2018). Thus, there is need to set up guidelines for a more prudent antimicrobials stewardship through the identification of potential risk factors that may be responsible for greater usage (Vieira et al., 2011) and develop new strategies to reduce anticmicrobial use (AMU). An efficient system to enhance preventive and/or corrective measures is the on-farm monitoring of AMU (Speksnijder et al., 2015). The European Medicines Agency (EMA) and the European Food Safety Authority are the main authorities involved in the quantification of AMU in livestock sectors, and in the identification of reliable metrics to compare AMU data among countries. In particular, EMA has proposed the Defined Daily Dose Animal (DDD) as the most accredited metric for the calculation of AMU, thus allowing for a more standardized measurement system between human and animal medicine (EMA, 2014). Livestock species are generally blamed for their large AMU (EMA, 2018, Tarakdjian et al., 2020). However, there is lack of information on AMU in beef production, whereby major knowledge on factors affecting AMU in this sector may be crucial for the reduction of AMR (Noyes et al., 2016b). Italy is the second EU country in terms of antimicrobial sales in livestock species (EMA, 2019), and beef herds are mostly located in the

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north of the country, specifically in Veneto region (Gallo et al., 2014). The major beef breeds farmed in this area are Charolaise and Limousine (Cozzi, 2007), which are mainly purchased from France and recognized as cosmopolitan breeds with good meat quality traits (ANACLI, 2019, Fabbri et al., 2019). Hence, the aim of this study was to investigate the effect of farm, sex, breed and season on AMU in Charolaise and Limousine beef breeds.

2   Material and methods

2.1   Data collection and editing procedure

Data were provided by AZoVe (Cittadella, Italy), a cooperative of beef producers located in Veneto region (north-east of Italy), and were collected from 2016 to April 2019. Only farmers that recorded performances and AMU data were included in the study. Moreover, only farms constituted by batches of Charolaise and Limousine breeds were considered for the analysis, meaning that farms had both breeds. A batch was defined as a group of young animals of the same breed and sex that arrived together at the farm and that were bred similarly for the entire fattening period (Herve et al., 2020). After editing procedure, the final dataset included 543 batches from 10 farms, for a total of 35,820 animals (Charolaise = 20,531 and Limousine = 15,289) of whom 4,074 were females and 31,746 were males. The following information was available per batch: date of start and end of the fattening cycle, number of deaths, number of animals treated and body weight (BW) at start and end of the fattening cycle. For each batch, duration of the fattening cycle (days), ADG, mortality rate, percentage of animals treated and starting season of the fattening cycle were calculated. Details on data and editing procedure are available in Diana et al. (2020).

2.2   AMU data and calculation of the treatment incidence

Information on the veterinary medicinal products (VMP, n = 33) used, quantity of the product (ml) and reason of its administration was available. Reasons of administration of antimicrobials were grouped in 5 categories: respiratory disease, lameness, gastrointestinal disease, general prophylaxis and other (e.g. dysmetabolic disease, injuries, dermatitis). The DDD, which represents the dose of active ingredient administered per kg of BW per day (mg/kg) (EMA, 2016), was assigned to each active ingredient with antimicrobial activity of those 33 VMP, by using the Summaries of Product Characteristic as for EMA guidelines (EMA, 2016). Nevertheless, DDD based on EMA's dosages was not available for 4 active ingredients of the 33 VMP included in the study and thus DDD were estimated based on Italian Summaries of Product Characteristics which were established during the development of the ClassyFarm integrated monitoring system (www.classyfarm.it) of the Italian Ministry of Health. These DDD provide a more reliable information of the Italian beef scenario. The DDD were used to calculate the treatment incidence (TI100it) which quantifies the frequency of antimicrobial treatments. In particular, the TI100it was calculated for each of the 33 VMP, then all TI100it values were summed to obtain a total TI100it per batch. The following formula (modified from Timmerman et al., 2006) was used:

$$\text{TI100it} = \frac{\text{amount of AI used per batch (mg)}}{\text{DDD (mg/kg/day)} \times \text{animals at risk} \times \text{standard weight (kg)} \times \text{standard days at risk}} \times 100,$$

where animal at risk identifies the number of animals per batch, standard weight is the average BW (400 kg) of animals at treatment and standard days at risk is the duration of the breeding cycle (230 days). Assuming to have a TI100it of 10, this can be interpreted as 10 animals out of 100 that were under treatment (AACTING, 2019). Finally, another index, named HPCIA TI100it, was calculated in a similar manner, but using only the VMP classified as Highest Priority Critically Important Antimicrobials (HPCIA) by the World Health Organization, in order to gain more knowledge about those antimicrobials that are considered main contributors for the development of AMR (WHO, 2017).

2.3   Statistical analysis

The dataset was checked for normality before analysis with batch as experimental unit. Descriptive statistics of number of animals, mortality rate, number and percentage of animals treated, performance traits, TI100 indexes and number of batches per farm and breed were calculated using the MEANS procedure of SAS 9.4 (SAS Institute Inc., Cary, NC, USA). An ANOVA was performed on AMU with the GLM procedure of SAS according to the following linear model:

$$y_{ijkl} = \mu + \text{farm}_i + \text{breed}_j + \text{sex}_k + \text{season}_l + e_{ijkl},$$

where y_{ijkl} is the dependent variable (TI100it or HPCIA TI100it); μ is the overall mean, farm_i is the fixed effect of the ith farm (i = 1 to 10); breed_j is the fixed effect of the jth breed (j = Charolaise, Limousine); sex_k is the fixed effect of the kth sex (k = male, female); season_l is the fixed effect of the lth starting season of the fattening cycle (l = spring, summer, autumn, winter); and e_{ijkl} is the random residual $\sim N(0,\sigma^2_e)$, where σ^2_e is the error variance. The same model with the addition of the fixed effect of TI100it was used to investigate sources of variation of ADG. For this purpose, the TI100it was categorized into 3 classes according to mean ± 1 SD: low, which included TI100it values <0.89, medium, which included TI100it values between 0.89 and 4.46 and high, which included TI100it values >4.46. Data are presented as least squares means and standard error, and a multiple comparison of least squares means was performed using Bonferroni *post hoc* test (P <0.05).

3   Results and discussion

3.1   *Descriptive statistics of number of animals, animals treated, mortality rate, performance traits and reasons of administration of antimicrobials*

Descriptive statistics are presented in Table 1. The mean batch size was 53.46 and 79.89 for Limousine and Charolaise, respectively, and the percentage of animals treated per batch was 90.53 vs. 67.54%. The initial and final BW were 288.13 and 554.67 kg for Limousine and 396.55 and 703.64 kg for Charolaise. Finally, the TI100it averaged 3.06 and 2.24 for Limousine and Charolaise, respectively. Frequency of the number of batches per farm and breed is presented in Table 2.

Table 1 Descriptive statistics of number of animals, mortality rate, number and percentage of animals treated, performance traits and treatment incidence (TI100) indexes per batch for Charolaise and Limousine breeds

Item	Charolaise (257 batches)				Limousine (286 batches)			
	Mean	SD	Min	Max	Mean	SD	Min	Max
Animals per batch (n)	79.89	42.18	15.00	220.00	53.46	29.66	15.00	144.00
Mortality rate (%)	0.54	1.05	0	5.55	0.84	1.94	0	15.56
Animals treated (n)	54.71	41.68	1.00	219.00	49.16	30.68	1.00	144.00
Animals treated (%)	67.54	35.74	2.50	100.00	90.53	23.96	2.80	100.00
Fattening cycle (days)	193.51	17.23	134.98	287.06	197.66	13.99	143.65	261.20
Initial body weight (kg)	396.55	41.02	275.49	535.00	288.13	11.49	233.20	345.03
Final body weight (kg)	703.64	59.87	522.97	778.87	554.67	44.49	395.08	668.29
Average daily gain (kg/day)	1.57	0.19	0.83	1.89	1.34	0.23	0.39	2.00
TI100it[1]	2.24	1.58	0.05	11.02	3.06	1.88	0.06	11.11
HPCIA TI100it[2]	1.63	1.53	0.00	8.67	2.33	1.69	0.00	11.11

[1] TI100it - treatment incidence 100 for Italy, calculated by using the Defined Daily Dose Animal for Italy (DDD) based on Italian guidelines of dosage (www.classyfarm.it)

[2] HPCIA TI100it - treatment incidence 100 for Italy, calculated by using the DDD based on Italian guidelines of dosage but only of those veterinary medicinal products classified as Highest Priority Critically Important Antimicrobials; SD – standard deviation; Min – minimum; Max – maximum

Table 2 Number of batches per farm and breed

Farm	Limousine	Charolaise	Total
1	35	10	45
2	13	26	39
3	19	7	26
4	91	35	126
5	29	32	61
6	16	29	45
7	21	38	59
8	17	39	56
9	23	35	58
10	22	6	28
Mean	28.6	25.7	54.3

The higher percentage of animals treated and TI100it for Limousine than Charolaise may be partially explained by considering the reason of administration of antimicrobial (Figure 1). Indeed, although the most common reason of treatment in both breeds was respiratory disease, a higher proportion of batches were treated for respiratory disease in Limousine (89.86%) than Charolaise (73.15%), followed by general prophylaxis (11.19%) for Limousine and lameness (25.29%) for Charolaise. This is in accordance with other studies that identified respiratory disease as the most common health issue in beef cattle (Edwards, 2010, Caucci et al., 2018, Herve et al., 2020). Specifically, the bovine respiratory disease (BRD) is known for its negative impact on ADG (Edwards, 2010). Also, beef breeds with low BW are more susceptibile to diseases (Sanderson et al., 2008; Taylor et al., 2010) as they may have a weaker immune system (Herve et al., 2020). This in turn can reduce their adaptability to a new farming environment and increase their likelihood to be treated. The lower initial BW for Limousine than Charolaise support our assumption. Our results also showed that a high proportion of Charolaise batches was treated for lameness likely due to the higher BW of this breed compared to Limousine or inadequate flooring system as reported in other studies (Gallo et al., 2014, Magrin et al., 2019). Further research is needed to confirm our results, also taking into account the different management systems of the farms.
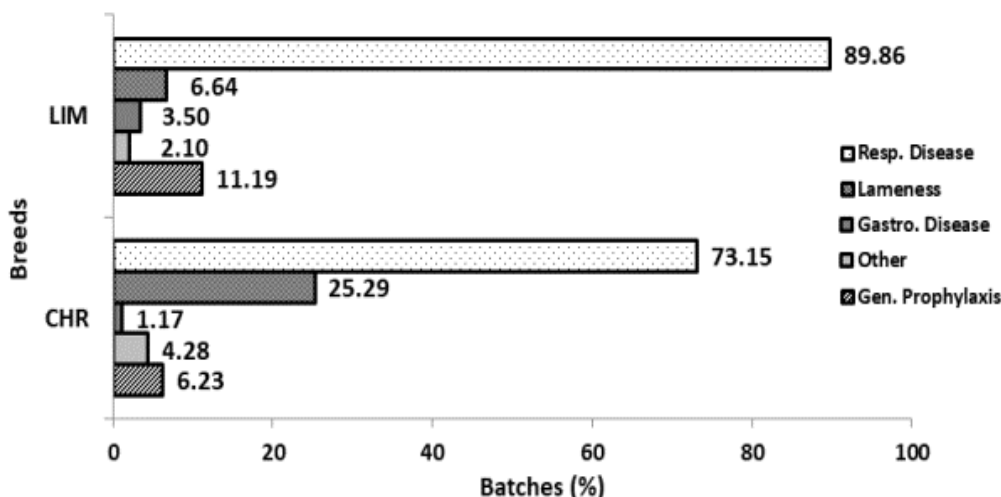

Figure 1 Prevalence of Charolaise (CHR, n=257) and Limousine (LIM, n=286) batches that were treated at least once with antimicrobials for different reasons

3.2 Effects of farm, breed, sex, season and TI100it on average daily gain

Farms differed significantly for ADG (P <0.05; Figure 2), likely due to different management applied on farm such as feeding strategies (Gallo et al., 2014). Other variables may help to explain the variation among farms such as different environmental conditions and animal welfare standards. If

environmental mitigation strategies are not properly applied to minimize animal discomfort, performance can be affected (Mader, 2014). Keane et al. (2017) reported that beef heifers accommodated on a flooring system with straw had greater ADG than heifers on concrete slats. In their study on Charolaise bulls, Herve et al. (2020) observed that batches less mixed at weaning and heterogeneous in terms of BW had better perfomance than batches with animals having similar BW. In fact, procedures such as sorting at weaning according to animals BW or re-mixing may affect the establishment of the hierarchy leading to aggressive behaviour (Mounier et al., 2006). This in turn impairs their growth performance (Bøe & Færevik, 2003). Also, Cernicchiaro et al. (2012b) highlighted the stressful effect of transportation on ADG, showing that long distances may reduce animals ADG.
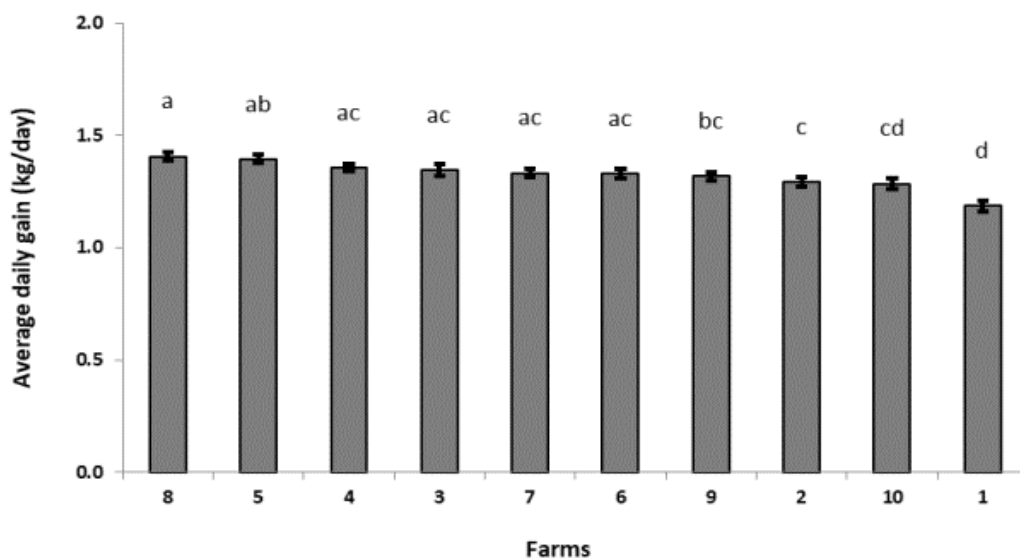

Figure 2 Least squares means (with standard error) of average daily gain for the farm effect

[a,b,c,d]*Means with different superscript letters indicate significant differences* (P <0.05)

Average daily gain was greater for Charolaise than Limousine (1.42 vs. 1.24 kg/day, respectively; P <0.05, Table 3), which agrees with previous studies (Gallo et al., 2014, Magrin et al., 2019). As expected, ADG was greater in males than females (1.51 vs. 1.14 kg/day, respectively; P <0.05) which is in line with results of Simčič et al. (2006). Average daily gain differed among seasons with batches purchased during summer and spring having higher growth performance than those purchased in autumn (P <0.05; Table 3). This result may be due to differences in mean temperatures experienced during each season (Cernicchiaro et al., 2012a). Indeed, a cold weather, which is typical of autumn and winter, may increase the risk of BRD (Cernicchiaro et al., 2012b, Herve et al., 2020). This is in contrast with findings of Sturaro et al. (2005) who suggested the high temperatures experienced during summer as main factor to explain the reduced ADG in beef cattle. Although, there was no effect of TI100it on ADG (P = 0.318), an increase of ADG was observed as TI100it decreased. This suggests that AMU can be reduced without jeopardising the overall animal performance, but further research is needed to confirm our results.

Table 3 Least squares means (LSM) of average daily gain (kg/day) for breed, sex, season and TI100it effects

Effect		LSM	SE
Breed			
	Charolaise	1.41[a]	0.01
	Limousine	1.24[b]	0.01
Sex			
	Male	1.51[a]	0.01
	Female	1.14[b]	0.02
Season			
	Autumn	1.29[a]	0.01
	Winter	1.32[a,b]	0.01
	Spring	1.34[b]	0.01
	Summer	1.35[b]	0.01
TI100it			
	Low	1.34[a]	0.01
	Medium	1.33[a]	0.01
	High	1.31[a]	0.02

TI100it – treatment incidence 100 for Italy, calculated by using the Defined Daily Dose Animal for Italy based on Italian guidelines of dosage (www.classyfarm.it); SE – standard error; [a,b]Means with different superscript letters within the same effect indicate significant differences (P <0.05)

3.3   Effects of farm, breed, sex and season on AMU

Large variability among farms for both TI100it and HPCIA TI100it (P <0.05) was reported in the current study (Figure 3), suggesting that differences in distinctive farm-factors such as environmental conditions, management practices and biosecurity strategies may play a role in the overall AMU (Wierup, 2000, Herve et al., 2020). It is important to highlight that each Italian fattening farm can purchase its animals from different locations in France, where calves have undergone an initial mixing (Sanderson, 2008, Herve et al., 2020). Calves are then re-mixed according to their BW to create homogeneous batches. This is a common practice applied on-farm at the beginning of the fattening cycle to facilitate the general management (Herve et al., 2020). All these practices combined with transportation from one country to another are recognised as stressors for the animals, thus affecting their health and welfare (Sanderson, 2008, Cernicchiaro et al., 2012a). In fact, an impaired immune system may increase the likelihood to diseases of young animals (Stanger et al., 2005, Herve et al., 2020) and the consequent higher AMU. In addition, we also observed that farms with higher TI100it had also higher HPCIA TI100it (Figure 3). This result suggests that farms that usually have high AMU are also more prone to use high amount of HPCIA in their batches. The role of vets may be crucial to potentially explain the variability observed among farms on AMU. Indeed, vets should be considered like guides who both promote alternative strategies to reduce AMU and encourage a more responsible use of antimicrobials that are essential to maintain a good animal and human health (Visschers et al., 2014, Bokma et al., 2018, Scherpenzeel et al., 2018). In fact, a study on dairy farmers reported that the most important source of information on AMU, which was considered trusthworthy by farmers, was the category of vets (Jones et al., 2015). Whereas, Visschers et al. (2014) reported an association between lower AMU and vet consultation in pig farmers. Finally, it is likely that farms variability on AMU may also be linked to farmers' belief and awareness about AMU and the associated risk of AMR. For instance, Marvin et al. (2010) reported that pig farmers were in general less worried of the risk of AMR than vets (20% vs. 60% of the participants, respectively). In their study on dairy farmers, Jones et al. (2015) showed that only 15% of participants thought that reduction of antimicrobials is a positive thing to apply because would reduce AMR while the majority of them (64%) identified cost-reduction as the most important reason to decrease AMU. Nevertheless, further studies are needed to provide a more in-depth explanation to the variability of AMU observed among farms.
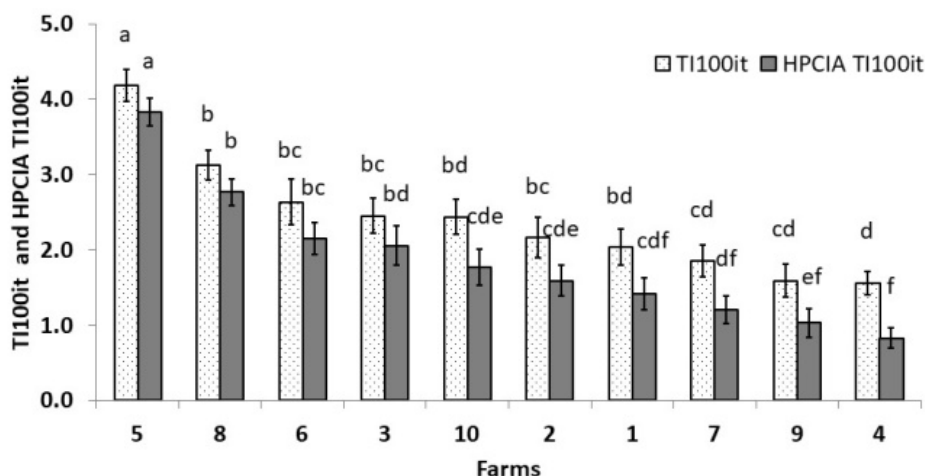
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Figure 3 Least squares means of antimicrobial use for the farm effect. TI100it - treatment incidence 100 for Italy, calculated by using the Defined Daily Dose Animal for Italy (DDD) based on Italian guidelines of dosage (www.classyfarm.it)

HPCIA TI100it - treatment incidence 100 for Italy, calculated by using the DDD based on Italian guidelines of dosage but only of those veterinary medicinal products classified as Highest Priority Critically Important Antimicrobials. [a,b,c,d,e,f]Means with different superscript letters within treatment incidence index indicate significant differences (*P* <0.05)

Table 4 Least squares means (LSM) of antimicrobial use for breed, sex and season effects

		TI100it[1]		HPCIA TI100it[2]	
Effect		LSM	SE	LSM	SE
Breed					
	Charolaise	1.83[b]	0.12	1.34[b]	0.10
	Limousine	2.98[a]	0.12	2.38[a]	0.10
Sex					
	Male	2.93[a]	0.08	2.21[a]	0.07
	Female	1.87[b]	0.19	1.52[b]	0.17
Season					
	Autumn	2.76[a]	0.14	2.19[a]	0.12
	Winter	2.94[a]	0.15	2.30[a]	0.13
	Spring	2.06[b]	0.14	1.48[b]	0.12
	Summer	1.85[b]	0.14	1,48[b]	0.12

[1] TI100it – treatment incidence 100 for Italy, calculated by using the Defined Daily Dose Animal for Italy (DDD) based on Italian guidelines of dosage (www.classyfarm.it);

[2] HPCIA TI100it – treatment incidence 100 for Italy, calculated by using the DDD based on Italian guidelines of dosage but only of those veterinary medicinal products classified as Highest Priority Critically Important Antimicrobials. [a,b]Means with different superscript letters within effect and trait indicate significant differences (*P* <0.05)

Both TI100it and HPCIA TI100it were significantly higher in Limousine than Charolaise (*P* <0.05; Table 4). As previously discussed, this may be explained by the results observed for the proportion of batches treated for respiratory disease which was higher in Limousine than Charolaise. Indeed, respiratory disease is the main health issue reported for beef cattle (Edwards, 2010, Caucci et al.,

2018), thus justifying, at least partly, the differences of AMU between the two breeds. Data showed that AMU was higher in males than females (P <0.05; Table 4), likely due to males being at greater risk of BRD than females. Similar results were also observed by Muggli-Cockett et al. (1992) who reported that males were at major risk of BRD than females, and by Alexander et al. (1989), who investigated the same risk of BRD after the arrival of the animals to the feedlot. The TI100it and HPCIA indexes differed also among seasons with winter and autumn having higher values compared with spring and summer (P <0.05; Table 4). This may suggest a link between season and AMU. Indeed, cold seasons are usually associated with an increase of respiratory diseases (Cernicchiaro et al., 2012ba, Herve et al., 2020), which helps to justify the higher AMU found during these periods of the year.

4   Conclusions

In conclusion, this study was important to identify potential sources of variation of AMU in Charolaise and Limousine beef cattle because knowledges on this topic are still poorly availble. Our findings can be useful to provide preliminary guidelines for a more responsible AMU in beef production. For instance, we suggest major focus on animals purchased during winter or an improvement of management measures towards Limousine cattle and males which are both at greater risk of AMU. Finally, due to the wide variability of AMU observed among farms, further research is required to investigate specific farm-factors that may affect the general antimicrobials consumption like for instance management practices and farmers' treatment strategy.

Acknowledgments

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