Monitoring and benchmarking antibiotic usage of italian beef farms: a pilot study

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SUMMARY
Beef production in Italy represents an important economic sector. Antimicrobials are administered to cattle to treat various pathological disorders such as respiratory diseases. The One Health approach promotes the rational use of antimicrobial drugs to contrast the antimicrobial resistance (AMR). The present study constitutes the first attempt to analyse antibiotic consumption of the beef cattle sector in the region of Piedmont (North-West of Italy).
The goal of our study was to assess the antibiotic use, in both quantitative and qualitative terms, of a sample of beef farms with a software that would then enable us to set benchmark levels for the considered sample.
To this aim, the antibiotic usage of ten intensive beef farms in the two-year period was recorded and analysed. For each farm that is part of the panel analysed, data about its annual antibiotic usage in 2017 and 2018, subdivided between the various antibiotic commercial products utilised, was recorded directly by the veterinarians that manage the selected farm. These data was then used as an input for the specific software, developed by the Italian Society of Veterinarians operating in the Livestock Sector (Sivar), to measure the antibiotic consumption of each selected beef farm and calculate the DDD/y (Defined Daily Dose per year), in mg/kg/day, of a singular farm.
The results of data elaboration were discussed considering a DDD/y benchmark system, specifically designed for the considered farm's panel, based as close as possible to the one already use by the Netherlands Veterinary Medicines Institute (SDa). The DDD/y benchmark levels, at the basis of the considered one, were developed to fit the specific farming conditions of the intensive Piedmontese beef cattle sector, in accordance with the veterinarians that manage the selected farms. The main results showed an average DDD/y value of the considered panel of farms equal to 2.876 considering the two-years period. The DDD/y ranged from 0.150 to 7.409 for the singular farm in one year. Differences about the relative use of different classes of antibiotics were detected between farms. Furthermore, three farms out of ten fell out of the highest set benchmark level in at least one year of the biennium analysed.
Further studies will be needed to assess whether the benchmark levels set in the current pilot study can be extended to all the Piedmontese beef farming sector.

KEY WORDS
Beef, antibiotic, antimicrobial, Defined Daily Dose (DDD), Piedmont.

INTRODUCTION

The rational use of antibiotics in the livestock sector is a major concern in nowadays health management. Furthermore, this approach has a direct positive impact on the antibiotic resistant bacteria selection risk. It has been proven that bacteria traits resistant to antibiotics can be selected in livestock farms thus setting a starting point to work on to reduce the risk in question[1].
The beef cattle sector is usually less interested in measuring antibiotic consumption than the dairy one. This is probably due to the antibiotic usage in the meat supply chain does not have a direct negative effect on the income of beef farmers, as instead happens on milk production. In fact, the antibiotic con-

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sumption on dairy cows ordinarily results directly in higher quantities of milk not sellable. In this context, reference levels of antibiotic consumption in beef cattle farms should be set to reduce their use. To achieve this, the first step is to measure the actual use of antibiotics at farm level. This is important, primarily, for two reasons: to promote a more rational use of antibiotics in general and, more specifically, to reduce to the minimum the use of those classes of antibiotics which are of primary importance in human care (cephalosporins of 3rd and 4th generation and fluoroquinolones)[2]. The antibiotic classes in question are used in the farming sector because they work in livestock health management as well as in human medicine[2,3]. The rational use of antibiotics at farm level, by enabling farms to achieve a more accurate usage that can result in limiting their overall consumption, could reduce the selective pressure on pathogens in the farming environment. This must be done to try to avoid the development of antibiotic-resistant traits which, in the worst case scenario, may transmit their new resistance to human pathogens. To this end it is necessary to achieve a rational level of antibiotic consumption as close to zero as possible. Since the selective pressure on bacteria resulting from the use of antibiotics cannot be completely avoided, the effectiveness of life-saving antibiotics must be preserved to ensure human safety. The problem arising from the selection of antibiotic-resistant bacteria is perceived as such not only by the medical sector, but also by the agricultural sector. Indeed, many stakeholders recognise the need to reduce the overall use of antibiotics at farm level as a priority[2].

In the current study a software designed to measure antibiotic consumption as DDD/y (Defined Daily Dose per year), which was developed by the Italian Society of Veterinarians operating in the Livestock Sector (Sivar), was used to analyse antibiotic consumption at farm level. The software in question is available to all Veterinarians that are Sivar members. Studies of antibiotic consumption in the Italian livestock sector that use DDD indexes are quite recent in Italy[4,5,6]. The DDD/y index, which considers the posology of each commercial antibiotic product, does not only give us primarily a measure of antibiotic consumption, but a risk index of selecting antibiotic resistant bacteria at farm level. For the dairy sector, however, many veterinarians have already used this tool to assess the level of antibiotic consumption at farm level.

The key to approach the problem of antibiotic resistance remains the One Health concept[7,8]. At this purpose, this work has been conducted to investigate the consumption of antibiotics at farm level, as this is one of the levels at which antibiotic-resistant microorganisms can develop and subsequently spread to other health care sectors[8].

This research represents the first pilot study to analyse the consumption of antibiotics on cattle farms in Piedmont. Currently, no standard has been set to assess the consumption of antibiotics in the cattle breeding sector by Italian regulators.

MATERIALS AND METHODS

Ten intensive beef farms specialised in the only fattening of beef bulls and located in the Po plain area between the cities of Turin and Cuneo (Piedmont, Italy) were involved in the research for data collection. The low number of farms included in the study is strictly related to farmers' availability to take part in the research. The panel consistency is however adequate to achieve the objectives of the current pilot study. The selected farms have been chosen to be representative of the Piedmontese intensive beef farming production system in terms of number of animals fattened (on average 294 beef bulls, ranging from 43 to 572 animals per farm), of production cycle and of animals characteristics (breed and final weight at slaughter). The Piedmontese beef farming sector is based on a high degree of intensity, a long fattening cycle and a relevant incidence of animal imports. In the Italian Po plain, due to the high pressure of the livestock sector on a limited agricultural area, animals are not ordinarily raised extensively on pasture and beef cattle are sold to the slaughterhouse usually aging between sixteen and eighteen months. Furthermore, a relevant percentage of beef animals farmed in Piedmont are bought, just after weaning, directly from France. In 2017, according to statistical data provided by the national Italian livestock Register (Anagrafe Nazionale Zootecnica), 212,898 bovines were imported in Piedmont from other countries and the nearly 96% from France. For each analysed farm, antibiotic usage data was collected relatively to the two-year period 2017-2018 in order to compare the difference in consumption between different years. The list of all antibiotic administrations of the biennium under analysis, together with the number of medicine packages used and the corresponding actual dosages of each administration, were recorded, directly by veterinarians, for each considered farm. This data was employed by the Sivar software to calculate the DDD/y values of each farm. The first step in the software calculation process consisted in obtaining the partial DDD/y value of every commercial antibiotic (named $(DDD/y)_p$) by applying the formula (a):

(a) $$(DDD/y)_p = \frac{Active\ Ingredient}{DDDA} \times \frac{1}{\Sigma\ (Number\ of\ Animals \times Standard\ Weight)}$$

where:

- **Active Ingredient** refers to the total amount of active ingredient in milligrams;
- **DDDA** is the reference dosage calculated for every commercial antibiotic, measured as mg/kg/day, DDDA values are based on the corresponding EMA ones[9];
- **Number of Animals** is the actual herd consistency in the year under analysis
- **Standard Weight** is the standard weight of the animal category under analysis.

All the values of the partial $(DDD/y)_p$ (expressed in mg/kg/day) calculated for each commercial antibiotic for each farm were summed by the software to obtain the overall DDD/y value of the singular farm. Consequently, at the end of the calculation process, the DDD/y value is expressed in milligrams of antibiotic administered on average in a single day of the year to one average kilogram of body weight of all the animals farmed in one year (mg/kg/day).

The Sivar software groups all beef cattle into just one category of animals, all weighting 600 kg. Rearing farms are not included into the Sivar software.

In order to obtain the farm DDD/y value relative to a singular antibiotic class, the $(DDD/y)_p$ values of all commercial antibiotics that contains the same active ingredient, that have been used in one year, are summed together. If commercial antibiotic formulations with more than one active ingredient are present, the software calculates each antibiotic class separately. Different antibiotic classes are grouped as follows: beta-lactams, macrolides, tetracyclines, quinolones, phenicols, aminoglycosides, lincosamides, sulfonamides, cephalosporins of 1st & 2nd generation, cephalosporins of 3rd & 4th generation, pleuromutilis, rifaximins and glycopeptides.

The classification of critically important antibiotics that was considered in the present study is the one utilised by the Netherlands Veterinary Medicines Institute (SDa) in its annual reports, the most recent of which was released in 2018[10]. This was done to enable us to set our benchmarking system as close as possible to the SDa one. Our choice is also linked to the fact that when the Sivar software was developed in 2014, it was set as close as possible to the antibiotic management system in place in the Netherlands.

The Dutch equivalent of the DDD/y index (incorporated into the Sivar software) is the $DDDA_{NAT}$ (Defined Daily Dose Animal) which is calculated with the same formula (a) and on a year base as well.

Despite the Sivar system has been set as close as possible to the Dutch one (by adopting the same index calculated as shown in (a)), the reference weights of the two systems are different: the Sivar software attributes an average weight of 600 kg to one average fattening bull, while the Dutch system only of 500 kg. This choice is probably linked to the average final weight of bulls of specialized beef breeds typically fattened in Italy, which is considerably higher than the average one of beef breeds reared in Northern Europe. Consequently, 600 kg probably represents a good estimate of the average weight of a single animal during the fattening process in Italy, especially since this data is in accordance with the statistics provided by the Italian Institute of Statistics (ISTAT-Istituto Nazionale di Statistica).

Since our benchmark system was set as close as possible to the Dutch SDa one, it was necessary to determine the following thresholds: the upper limit of the Target zone, under which the DDD/y values of farms should be; the bottom limit of the Action zone above which a DDD/y value by a beef farm is automatically followed by sanctions, if there are no overt medical justifications for it. The DDD/y values scored by farms, that fall between the upper limit of the Target zone and the bottom limit of the Action zone are included into the Signalling zone. By falling into the Signalling zone a farm is not necessarily exposed to sanctions.

Benchmark levels for dairy farms used by the Dutch SDa were proved to be applicable to the Sivar software calculation to benchmark Piedmontese dairy farms[11].

Since the Sivar software and the Dutch SDa adopt the same formula to calculate the DDD/y value of one beef farm, the benchmark levels for Piedmontese beef farms were set lower than the Dutch ones for dairy farms (Dutch benchmark levels for dairy farms are set at a DDD/y value equal to 4 and 6). This is due to there is no medical reason to justify a higher level of antibiotic use, on average per one kilogram of live weight, for fattening beef bulls higher than the level of antibiotic used, always on average per one kilogram of live weight, for dairy cows and lactating calves. This is so because, due to milking management of dairy cows and sanitary problems connected with lactating calves, these animal categories are more prone to infections and diseases than fattening beef bulls reared in the modern and up to date farms of the Nord of Italy. In the calculation process of the DDD/y value of one farm, which is the same for the Dutch SDa and the Sivar software, for dairy farms are considered the antibiotic usage of dairy cows, heifers and lactating calves wile for beef farms is considered only the antibiotic usage of fattening beef bulls.

The actual benchmark levels set at a DDD/y value equal to 3 and 5 were determined empirically with the help of the veterinary practitioners that manage the beef farms that make up the panel. The upper limit of the target zone was set at a DDD/y value of 3 as veterinarians have stated that it is impossible for them to bring this value below 3 for all cattle farms they manage, especially with the tools at their disposal. For example, the use of antimicrobial resistance testing is not a viable option as the available laboratories take too many days to provide the results of these tests. This means that waiting for the results before prescribing appropriate antibiotics can lead to the death of sick animals. The lower limit of the zone of action is set at a DDD/y of 5 because the causes that lead farms to exceed this limit have always been declared solvable with the diagnostic tools available to them by farm veterinarians. If the DDD/y value of one farm in between 3 and 5 it falls into the Signalling zone, which requires further analyses of the singular farm antibiotic management strategy.

It is also important to underline whether differences in antibiotic usage are present between beef farms with higher antibiotic usage and those with a lower one. To achieve this, the average DDD/y values of the antibiotic classes considered by the Sivar software, of the three farms with higher antibiotic usage and of the three with a lower one, were analysed.

RESULTS

In Figure 1 the overall DDD/y values of every beef farm under analysis are reported. The comparison between the two considered years and set benchmark levels are included.

Five farms out of ten fall out of the estimated Target zone in 2017. In the same year only one beef farm has a DDD/y value higher than five (DDD/y = 5.034).

In 2018 three of the five farms that exceeded the DDD/y = 3 benchmark in 2017, are well under the same level. Curiously, the two farms with the highest DDD/y value of the panel in 2017, increased their antibiotic usage consistently. The farm F08 underwent an even higher increase in antibiotic usage in 2018, than the other two beef farms in question (F09 and F10).

In 2017 only half of the farms of the panel managed to keep their DDD/y value under three. In 2018 however, it can be detected a reduction in antibiotic consumption that brings a total of seven farms under the benchmark level in question. However, the three farms which scored higher DDD/y values (as average DDD/y values of the biennium under analysis), used more antibiotics in 2018 than in 2017.

In Figure 2 the average DDD/y values of the different classes of antibiotics used by farms are reported.

Beta-lactams antibiotic was the antibiotic class most used in 2017, followed by macrolides, tetracyclines and quinolones. The four classes of antibiotic mentioned, as an all, amount to 80% of total antibiotic usage in the same year. In 2018, beta-lactams alone, represent on average 48% of the total DDD/y of the average beef farm of the panel. Beta lactams usage increases consistently in 2018 while the use of macrolides, tetracyclines and quinolones decreased.

Figure 3 represents the antibiotic usage, in 2017, of the three beef farms with lower DDD/y values and of the three farms with higher ones, respectively.

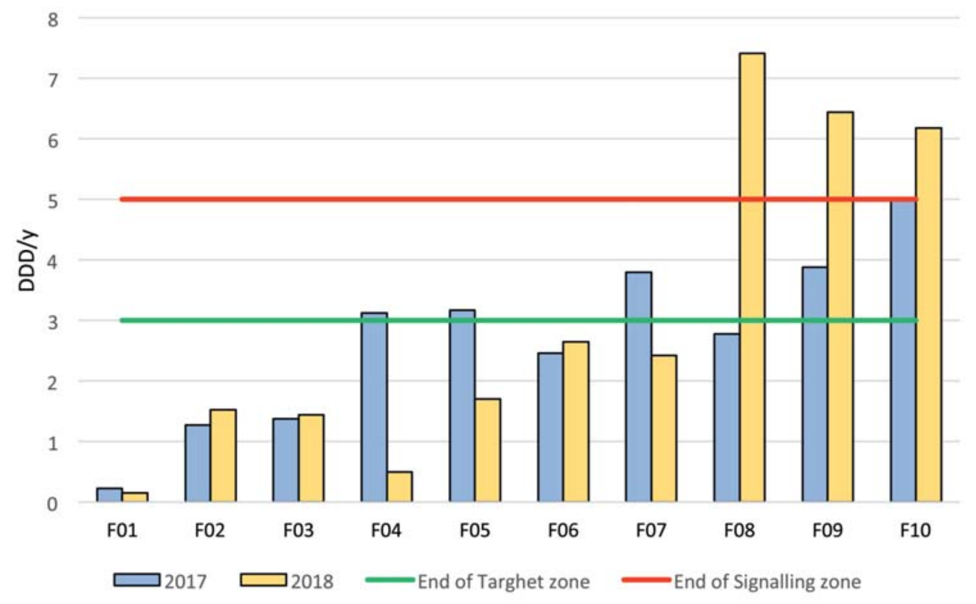

Figure 1 - DDD/y values of the panel in 2017 and 2018, with benchmark levels.

Figure 4 represents the average antibiotic usage in 2018 of the three beef farms with the lowest DDD/y value and of the three farms with the highest, respectively.

In both groups, beta-lactams and macrolides were the classes of antibiotics which are more used in 2017 as well as in 2018. In farms with lower DDD/y values, however, macrolides are more used than beta-lactams. Beef farms with higher DDD/y values utilise more beta-lactams than macrolides but it is important to underline that their average DDD/y value for macrolides is actually higher than the one of farms, which scored a lower total DDD/y value.

No relevant differences between the usages of different classes of antibiotics are detected between the two years. When overall antibiotic consumption increases, the use of every antibiotic class typically increases, even if not always of the same relative amount.

DISCUSSION

In this research, the semaphore structure, utilised in the Netherlands since 2012, was adopted to reduce in an efficient way the pressure on selecting antibiotic resistant bacteria at farm level. The upper limit of the Target zone (green) was set at DDD/y=3, while the border that separates the Signalling zone (yellow) and the Action zone (red) were set at DDD/y=5. To maintain the effectiveness of a benchmark system on the long run it should be periodically adapted[12]. Under the current conditions, the benchmark levels set in this work seem to guarantee the highest reduction in overall antibiotic usage, as a result of a more rational use, in the Piedmontese beef farming sector. No beef farm that makes up the panel analysed used any cephalosporins of 1st & 2nd generation, cephalosporins of 3rd & 4th generations, pleuromutilins, rifaximins or glycopeptides, in

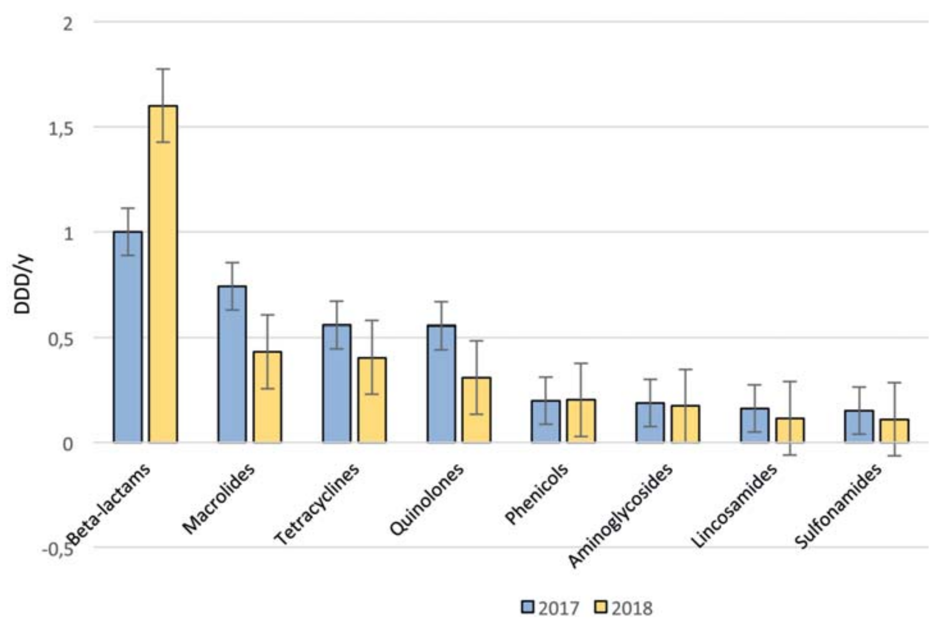

Figure 2 - Average DDD/y values of the panel for every antibiotic class: 2017 and 2018.

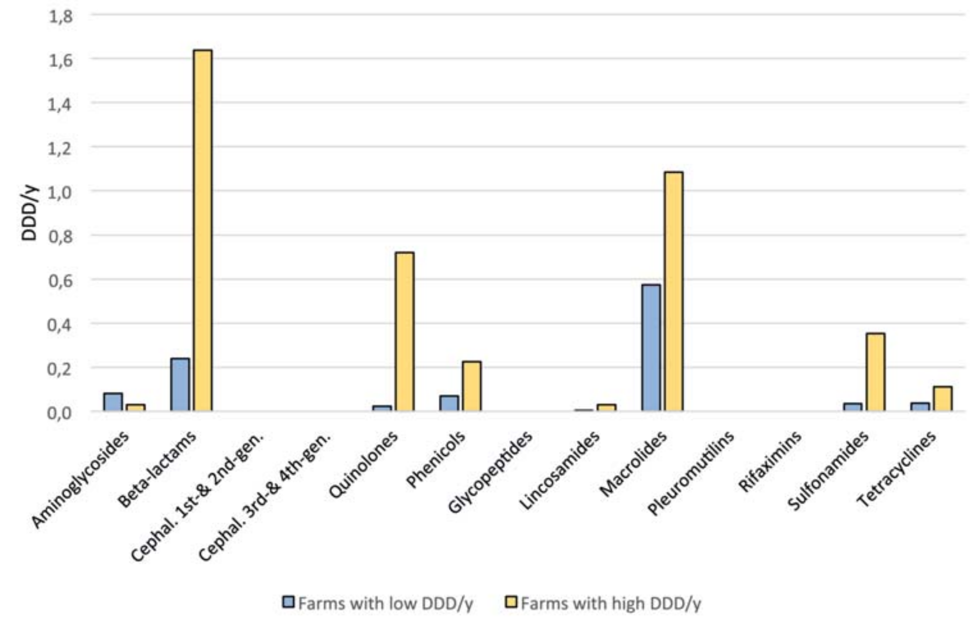

Figure 3 - Antibiotic usage of farms with lower and higher DDD/y value: 2017.

the biennium 2017-2018. They also utilised a very low amount of quinolones (fluoroquinolones are included), the use of which underwent a reduction amounting at -44.3% in 2018 with respect to 2017.
Such a low usage of the antibiotics of the classes in question is the result of the voluntary work, of the veterinarians that manage the beef farms analysed. They dedicate their efforts to rationalise the use of antibiotic classes of primary importance to human health: this enabled the farms of the panel to reach consumption levels, of the classes of antibiotics in question, equal to zero in both the analysed years.
Veterinarians are often aware of the pivotal role they play in reducing the risk of selecting bacteria resistant at farm level[14,15]. Even if dedicated protocols, specifically designed by veterinarians, result in an increase in the workload for farmers, the benefits they provide have been proved to outnumber the inevitable increase in complexity of the resulting farm management[15].

If the number of veterinarians working in the livestock sector who decide to voluntarily undertake the discussed approach were to increase, then the risk of selecting antibiotic-resistant bacteria could be significantly reduced by a more rational use of antibiotics. This would be achievable with the approach analysed even in the absence of specific regulations. Indeed, in the United States, for example, despite the lack of national policies on antimicrobials, a consistent spread of a voluntary approach has helped the legislator to start tackling the problem[16]. Another potential driver that can help spreading the use of the DDD/y Sivar system are animal welfare certifications, which were proved to be high valued by consumers[17]. If a DDD/y system like the Sivar one, were to be incorporated into the assessment process of animal welfare certifications, it can also become a stimulus to lower antibiotic usage levels despite the lack of specific regulations on a national level[18,19]. However, as all historic data from European countries, that have dealt with the

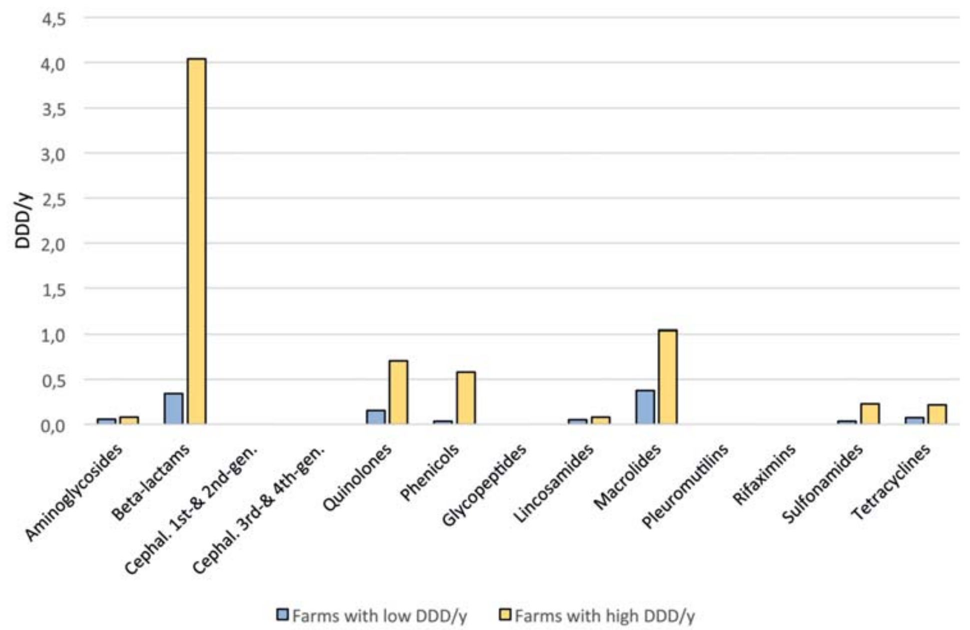

Figure 4 - Antibiotic usage of farms with lower and higher DDD/y value: 2018.

same problem in the past (such as Sweden, Denmark, Germany and the Netherlands), have shown, no great result on the rational usage of antibiotics can be expected without a dedicated regulation system put into place by central authorities[20,21,22].

CONCLUSIONS

The developed system for antibiotic usage management and control, which was based on the Sivar software designed to calculate the DDD/y value, seems to be able to guarantee the maximum reduction in the overall use of antibiotics on the selected panel of cattle farms, which is possible under current conditions. Being set as close as possible to the one officially in force in the Netherlands, it can also help to build a common antibiotic resistance prevention system. In Italy no mandatory system to decrease antibiotic consumption at farm level is currently adopted. However, veterinarians that are Sivar members can decrease the risk of developing antibiotic resistant bacteria, in the beef farms in which they operate, by utilizing the DDD/y based Sivar software on a voluntary basis.

Since the current work constitutes the first attempt to study antibiotic usage of Piedmontese intensive beef farms, further studies will be needed to analyse antibiotic consumption considering an higher number of beef farms. This would make it possible to assess the changes to the developed benchmark system that may be needed to ensure its effectiveness in different contexts, regional and national. Reducing the risk of selecting antibiotic resistant bacteria is an ongoing process that plays a key role in the application of the One Health approach. By promoting a more rational use of antibiotics, the agricultural sector can do its part to ensure global health.

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