



Relatório Final de Estágio
Mestrado Integrado em Medicina Veterinária

**Development and testing of an information system for monitoring
and analyzing consumption of veterinary antimicrobial drugs in
dairy cattle, compatible with the European Surveillance of
Veterinary Antimicrobial Consumption (ESVAC) directives**

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Eng. José Paulo Lobo Araújo dos Santos,
Mestre Inês Filipa Martins de Almeida (DGAV) e
Dr. João Fernandes Fagundes da Silva (UNICOL)

Porto, 2021



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com as diretivas do sistema European Surveillance of Veterinary
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ABSTRACT

The urgency of preventing the development of antimicrobial resistance has been addressed by international authorities, such as EMA and WHO, monitoring systems capable of reporting usage of antimicrobial drugs are regarded as one of the main pillars of this fight.

In line with the European and Portuguese action plans against the development of antimicrobial resistance, our main goal was to develop an information network sustained by a system capable of collecting and analysing veterinary antimicrobial drug consumption data, within Portuguese dairy farms. Created according to EMA's guidelines, it will be utilized by the Portuguese veterinary authority (DGAV) to generate information, to contribute to the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project. In addition, the information can be used by partner associations and veterinarians to advise farmers, as adapted antimicrobial consumption metrics were created along with costs and milk production analysis.

The Vet-AMNet project started as a conjoint initiative of the Faculty of Biomedical Sciences Abel Salazar- Porto University (ICBAS-UP), the Portuguese veterinary authority (DGAV) and the Portuguese Dairy Farmers Association (ANABLE). There is also a collaboration protocol with the dairy farmers cooperatives UNICOL and PROLEITE. Farmers' participation operated on a voluntary basis. The information system was created using Business Intelligence solutions, to facilitate production and sharing of restricted and customizable dashboards.

A questionnaire to gather information that improves the analysis on antimicrobial use, at farm level, was created and validated. The main metrics created will be presented and applied to a Case Study, together with the Dashboards designed for DGAV, veterinarians and farmers. Main findings and challenges will be discussed, along with the implications and limitations of the information generated. The high heterogeneity found between farms suggests there is a long way before optimisation is achieved. The use of critically important antimicrobials needs to be addressed in future studies.

Key Words: Antimicrobial resistance; One-health; Surveillance, Public health; Stewardship

RESUMO

A urgência do combate ao desenvolvimento de resistências antimicrobianas (RAM) tem sido expressa por autoridades internacionais como a OMS e a EMA, sendo a criação de sistemas de monitorização capazes de reportar o consumo de medicamentos antimicrobianos (AM) tida como um dos pilares essenciais desta luta.

Em linha com os Planos de Ação Europeu e Nacional de combate ao desenvolvimento de RAM, o principal objetivo deste trabalho foi desenvolver um sistema de recolha de dados, análise e partilha de informação sobre consumos de AM em explorações de bovinos leiteiros, em Portugal. Criado seguindo as diretivas da EMA, será utilizado pela DGAV para gerar informação a enviar ao sistema European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). Complementarmente, associações e médicos veterinários poderão usar a informação gerada para aconselhar produtores, pois foram criadas métricas de análise de consumos de AM adaptadas, de análise de custos e de produção de leite.

A rede Vet-AMNet arrancou com uma parceria entre o ICBAS, a Associação Nacional para o Melhoramento dos Bovinos Leiteiros (ANABLE) e a DGAV. Foi depois alargada às cooperativas UNICOL e PROLEITE. A participação dos produtores envolvidos é voluntária. A rede é suportada por um sistema de informação desenvolvido recorrendo a soluções de *Business Intelligence*, o que facilita a criação e disponibilização de relatórios dinâmicos, personalizados e restritos.

Foi também criado e validado um questionário para recolha informação que expande a análise dos dados de utilização de AM, ao nível das explorações. As principais métricas criadas serão apresentadas e aplicadas num *Case study*, assim como os *Dashboards* desenhados para a DGAV, veterinários e produtores. Discutem-se implicações e limitações da informação gerada. A heterogeneidade verificada quanto aos consumos de AM, mostra que há espaço para reduções. A utilização de AM de alta importância para a saúde pública levanta questões quanto ao seu uso sistemático.

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ABBREVIATIONS

AMEG Antimicrobial Advice Ad Hoc Expert Group

AMR Antimicrobial resistance

AMU Antimicrobial Usage

ANABLE Portuguese Dairy Farmers Association

APCU Adapted population correction unit

BI Business intelligence

Bovinfo web-based farm-management system managed by ANABLE

DAX Data Analysis Expressions

DGAV Direção Geral de Alimentação e Veterinária, Portuguese Veterinary Authority

ECDC European Centre for Disease Prevention and Control

EFSA European Food Safety Authority

EMA European Medicines Agency

ESVAC European Surveillance of Veterinary Antimicrobial Consumption

EU European Union

EU European Union

EEA European Economic Area

Eurostat European Statistical Office

HIV human immunodeficiency virus

ICBAS Instituto de Ciencias Biomédicas Abel Salazar

JIACRA Joint Interagency Antimicrobial Consumption and Resistance Analysis

MS Member state of the European Union

PCU population correction unit

SQL Structured Query Language

UNICOL Terceira Island Dairy Cooperative

Proleite Oliveira de Azeméis Dairy Cooperative

US United States

USD United States Dollar

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1 – INTRODUCTION

1.1 - Emergence of antimicrobial resistance and its connection with animal production

Historically, antimicrobial usage in animals is thought to have started after World War II, beginning by accident due to the contamination of an experimental feeding alternative to vitamin B12 with chlortetracycline. This led to the start of antimicrobial usage (AMU) for growth-promoting purposes, and consequently to big market changes. (Guardabassi, 2013) Afterwards, when disease outbreaks became intolerable due to the intensification of livestock production, sub-therapeutic administration of various AM drugs became a common practice (Da Costa et al., 2013).

According to WHO: “Antimicrobial resistance (AMR) occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines, making infections harder to treat and increasing the risk of disease spread, severe illness and death” (World Health Organization, 2020a).

Salmonella and Campylobacter are traditionally responsible for most of the registered cases associated with zoonotic transmission of AMR. Fortunately, infections by these agents are generally self-limiting. On the other hand, there are bacteria as livestock-associated methicillin resistant *Staphylococcus aureus* (LA-MRSA), which pose a bigger threat to public health due to their resistance to first-line therapeutic drugs such as cephalosporins (Guardabassi, 2013).

The pressure exerted by AM usage triggers the process of evolutionary selection of the most adapted bacteria, which through obtaining and expressing the appropriate resistance genes (Kahn, 2017) become more prevalent. This happens each time AM are utilized. However, excessive usage both in human and veterinary medicine has been intensifying this process. Genetic modifications can occur by spontaneous mutations or by acquisition of other bacteria's genetic material (Da Costa et al., 2013).

As most AM classes are used both in human and veterinary medicine, the generated pressure is subsequently cumulative, and their effectiveness is reduced in both sectors (Palma et al., 2020). In hindsight, restricting the most important substances to exclusive human medicine use could have been wise (Guardabassi, 2013).

“The environment is the melting pot of AMR” (Da Costa et al., 2013). Not only do acquired resistance genes originate from environmental microbiota, but also, for many bacteria, the environment in which they have become resistant should be considered an essential element of the selective pressure exerted (Da Costa et al., 2013). Effluents from

urban areas and animal production units can often be contaminated both with resistant bacteria and AM substances, even when treated in wastewater treatment plants, meaning the development of AMR can happen in a very distant place and time from where and when these drugs were administered. (Da Costa et al., 2013) Additionally, the dissemination of resistant bacteria into the environment is perpetuated by the agricultural use of slurry and manure as soil fertilizers. (Da Costa et al., 2013) (Magouras et al., 2017) . Livestock trade and wild animals, due to their contact with contaminated environments, also play a major role in the establishment of complex resistant pathogen dissemination networks (Magouras et al., 2017).

Transmission of AMR from food animals to humans can happen directly as farm and slaughterhouse workers can pick up resistant strains by having direct contact with infected animals. (Graham et al., 2019). Across the food chain, contaminated foods can function as vectors, carrying AM resistant bacteria and/or AM resistance genes, that can originate directly from agricultural production, be added intentionally during food processing and/or by cross-contamination. Therefore, in food production, good hygienic and manufacturing practices are imperative (Verraes et al., 2013).

AMR is causing a significant impact on health systems. The combined burden of AMR infections is already similar to the effects of Influenza, tuberculosis and HIV combined (Cassini et al., 2019). It was estimated that in the European Economic Area, in 2015, there have been 671 689 infections with antibiotic resistant bacteria, which caused 33 110 attributable human deaths and the loss of 874 541 disability-adjusted life-years (Cassini et al., 2019). The ECDC has even compared these figures to the loss of 100 medium-sized planes. (European Centre for Disease Prevention and Control, 2020) In Portugal, in the same year, there have been a total of 24 021 infections leading to 1 158 deaths (Cassini et al., 2019). It was also estimated, in 2013, that AMR was costing the US Health Care service about 20 billion USD, and that the country was losing 35 billion USD in productivity, per year (Smith & Coast, 2013)

Given the fact that AMR genes can circulate in any direction within and between a global and complex system composed by the environment, humans, and animals; a coordinate multisectoral approach appears to be fundamental to comprehend the problem in its broad spectrum (Palma et al., 2020). Therefore, a One-health approach, being “the collaborative effort of multiple health science professions to attain optimal health for people, domestic animals, wildlife, plants, and our environment.” appears to be the logical framework to approach it. (Kahn, 2017)

1.2 – Policies and actions against the of emergence antimicrobial resistance– legal framework

The WHO has recognized the fight against AM resistance as one of the most important challenges that humanity will have to face in the present decade (World Health Organization, 2020b). Since the prohibition of the use of AM as growth promoters, in 2006, the European Union is recognized as the region with the best practices regarding AMR preventive measures (Ferreira & Staerk, 2017). In 2017, with the establishment of the European One Health Action Plan against Antimicrobial Resistance (AMR), the necessity of a multisectoral agenda, boosting research, development, and innovation on AMR actions to maintain the EU as an example to rest of the world, was widely recognized, together with the need of implementing systems to measure its success (European Commission, 2017). The 2020 Farm to Fork strategy is a cornerstone of the European Green Deal, and aims to make food systems fair, healthy, and environmentally friendly. According to this strategy, reducing AM consumption in animal production up to 50% is to be achieved by 2030(European Commission, 2020b). To support this, three new EU regulations were released and will come into force from January 2022; some of their major key point are:

(EU) 2019/4 – medicated feed: Ban on the preventive use of medicated feed in animal groups (European Parliament and the Council of the European Union, 2019a).

(EU) 2019/5 – adapting the responsibilities of the European Medicines Agency: establishing as one the EMAs' key tasks, the obligation of continuing contributing to the Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) reports. (European Parliament and the Council of the European Union, 2019b)

(EU) 2019/6 – veterinary medicinal products: a Ban on the preventive use of AM, in animal groups; Restrictions on AM metaphylactic use; Reinforcement of the ban on the use of AM as growth promoters and increase yield; Reservation of certain AM for human use only; Concerning imported animals and products from outside the EU, a ban on AM as growth promoters and restrictions on AM's reserved for human use; and, more relevant to this work, "Member States shall collect relevant and comparable data on the volume of sales and on the use of antimicrobial medicinal products used in animals, to enable in particular the direct or indirect evaluation of the use of such products in food-producing animals at farm level"(European Parliament and the Council of the European Union, 2019c). The execution of this regulation was delegated to EMA, who determined that, as of January 2024, MS are obliged to report AM sales and usage data, together with animal population data for cattle, pigs, chickens, and turkeys. At least one year before, in January 2023, reporting systems must be operational(European Medicines Agency, 2019a).

In EMA's network strategy to 2025, one defined strategic goal is to: "Provide high quality information on antimicrobial consumption and surveillance data on antimicrobial resistance in animals and humans in support of policy development and by ensuring proper implementation of Regulation (EU) 2019/6 on the ground"(European Medicines Agency, 2020a). The creation of a system of this nature also relates to objectives 3 and 5 of the Portuguese National Plan Against Antimicrobial Resistance "Plano Nacional de Combate à Resistência aos antimicrobianos": Strengthen the knowledge and the evidence through epidemiological surveillance, and Ambiental monitorization and investigation, and optimization of antimicrobial use, respectively (Direção Geral de Saúde, 2019).

Two fundamental articles on the collection of AM usage data in animals have been announced: Article 57(3) on data requirements, which has already been adopted, following EMA's scientific recommendation (European Commission, 2018), and Article 57(4) on the format of the data to be collected, which has not been released yet.

1.3 - Objectives of antimicrobial consumption surveillance

The main drivers behind the emergence of AMR appear to be the excessive/inconsiderate AM usage, both in animal and human health as well as in the environment, together with the complex global dissemination patterns of resistance genes (Kahn, 2017). In order to control the emergence of this issue, monitoring the use of Antimicrobials and the development of resistances is essential(Ferreira & Staerk, 2017). The main objectives of monitoring AM consumption are: facilitating the interpretation of patterns and tendencies related to the emergence of AMR, as a basis for risk evaluation and management ; establishing a foundation for evaluating the effectiveness of implemented control measures; identifying emergent use of certain AM substances, critically important AM to human health, as an example of a necessary differentiation; allowing the comparison of AM usage at a national and international level, and in a given time frame; evaluating the transmission and the effect of environmental AM pollution; and highlighting areas where research and development are needed (European Medicines Agency, 2015).

1.4 - ESVAC project and Portugal's reported values

EMA started the ESVAC project in September 2009, with the objective of collecting data on AM usage in animals, to inform policy makers. Currently, ESVAC collects and publishes data on AM sales in 31 European countries 30 EU/EEA countries and Switzerland(European Medicines Agency, 2021). National participation has been working on a voluntary basis. However, in the future, reporting AM sales and consumption to ESVAC

(or to another system based on this project) will be a legal obligation, as predicted in the stepwise approach described in regulation (EU) 2019/06 (European Parliament and the Council of the European Union, 2019c).

AM sales data, to be published in the ESVAC report, are presented in the form of mg/PCU, which can be taught as milligrams of active ingredient per biomass kilogram (European Medicines Agency, 2019c). In Portugal, DGAV is the entity responsible for collecting and transmitting AM sales data to ESVAC, provided by the pharmaceutical companies (European Medicines Agency, 2020b).

The European Commission's goal of reducing AM consumption in animal production, stated in the Farm to Fork strategy, established the tenth ESVAC report, published in 2020, as a reference. The overall average consumptions for the 27 EU member states was 118,3 mg/PCU, which results in a target value of 59.2 mg/PCU. Portugal registered 186.6 mg/PCU, so the goal is to reach 93,3 mg/PCU (European Commission, 2020a).

When making country sales data comparisons using ESVAC data, it is important to consider that differences might be partially due to discrepancies in the incidence of bacterial diseases, animal population, production schemes, daily doses administered and duration of treatments. In addition, it could be the case that some countries are underreporting. However, it's worth noting that Portugal has systematically reported consumptions above the European median for overall AM consumption and, particularly, for Category B AM substances, as specified in Table 1 (European Medicines Agency, 2020b). According to EMA's AMEG classification, which was elaborated in relation to the risk which the use of a specific molecule might bring to the development of AMR, as well as its importance in human medicine, considering the existence of alternative substances. Category B substances should be of "Restricted" use in veterinary medicine, as these molecules are critically important substances to human medicine. Other categories are as follows: Category A "Avoid" - AM which are not authorised for use in animal production; Category C "Caution" - AM for which there are reliable alternatives in human medicine, but few veterinary alternatives; Category D "Prudence" - for use, in a prudent way, as a first line of treatment, whenever possible (European Medicines Agency, 2019b).

Table 1: AM sales data from 2018, published in the Tenth ESVAC report (European Medicines Agency, 2020b)

AM classes	Portugal	Europe's (31 reporting countries) Median values
3rd- and 4th-generation cephalosporins	0,4 mg/PCU	0,2 mg/PCU
Quinolones, specifying the quantity of fluoroquinolones	fluoroquinolones 7,6 mg/PCU; <0,01 mg/PCU other quinolones	Fluoroquinolones 1,2 mg/PCU; other quinolones <0,01 mg/PCU;
polymyxins	12,6 mg/PCU	1,6 mg/PCU
Overall	186.6 mg/PCU	57,0 mg/PCU

It should also be mentioned that, in 2018, more than 60% of Portugal's registered veterinary AM (mg/PCU) sales were in the Premix form and 30% oral pharmaceutical forms. ESVAC also states that it is safe to assume that only a small fraction of oral forms is used in individual animal treatments (European Medicines Agency, 2020b). This means that, with the implementation of regulation (EU) 2019/4 imposing a ban on the preventive use of medicated feed in animal groups, this value should decrease considerably, and production systems will have to adapt to new schemes.

1.5 - Measurement of AM sales/consumption

To publish national AM sales data in mg/PCU units, total active ingredients milligrams are calculated by multiplying the national sales amount, in metric tons, by 10^9 . Animal biomass at risk of being treated with AM, represented by PCU (population correction unit), is based on national statistics multiplied by standardized average weights per animal class (European Medicines Agency, 2019c). For dairy cattle, that is assessed by multiplying the number of individuals older than 24 months, registered in the Eurostat database, by 425 kilograms, the weight attributed by EMA to an adult dairy cow (European Medicines Agency, 2019c). EMA recommends the use of PCU's (expressed in kilograms) as a denominator to normalize AM consumption analysis (European Medicines Agency, 2018).

Participating countries have manifested their disagreement about the denominator PCU, defending its review and the establishment of more precise animal weights and categories within species (European Medicines Agency, 2018). This is currently in discussion and could result in a PCU denominator that brings the population at risk of being treated closer to the actual population treated (European Medicines Agency, 2021).

In order to calculate AM usage per animal species, EMA recommends using 3 metrics: (1) milligrams of active substance adjusted to PCU; (2) number of “Defined Daily Doses” (DDDvet’s) adjusted to PCU; (3) Number of “Defined Course Dose” (DCDvet’s) adjusted to PCU (European Medicines Agency, 2019a).

1.6 - DDDvet/DCDvet units and the need to report more granular data

Similarly, to what happens in human medicine, in order to strengthen AM consumption data analysis, EMA has created the “defined daily dose” (DDDvet) and “defined course dose” (DCDvet), which represent standardized treatment units. These respectively correspond to the average daily dose per kilogram, and to the average full course dose per kilogram (European Medicines Agency, 2015). They have been established per active ingredient, with administration form differences, based on dose related data found in product characteristics form 9 European countries that represented approximately 65% of the European production, in 2012, and have been established for chickens, cattle, and pigs (European Medicines Agency, 2015).

In dairy cattle, dosing values have been distinguished by each active ingredient for oral and parenteral pharmacological formulations. For intrauterine and intramammary AM, constant values have been attributed to the formulation groups. They have been defined per animal kilogram for oral and injectable products; by animal for intrauterines; and by single teat and udder for intramammary products for lactating and dry cows, respectively. Topic pharmaceutical formulations have not been assigned DDDvet and DCDvet values because establishing a dosage for these treatments is too complex. In the future, these constants should also be assigned for sheep, goats, rabbits, fish, horses, dogs, cats, and fur animals (European Medicines Agency, 2019a).

The need to establish standardized reporting units has been evidenced by the discrepancy showed in the average dosing between animal species. Using oral fluoroquinolones as an example, the DCDvet values can fluctuate from 10 to 40 mg/kg. Even within AM classes, different active ingredients can have very distinct values, for example, the dose for oxytetracycline is about four times that of doxycycline (European Medicines Agency, 2020b). Therefore, reporting in a standardized way allows for comparison between different species and populations.

1.7 - Relating antimicrobial consumption to antimicrobial resistance – JIACRA report

ECDC, EFSA and EMA have already published two joint reports (JIACRA), with a third one due to be released this year, on the integrated analysis of AMC and the occurrence of AMR in bacteria from humans and food-producing animals. Overall, these reports confirm a positive association between them, while also recognizing the complexity of this analysis, due to the influence of unaccountable external factors. These reports use data collected by multiple surveillance/monitoring systems, with different goals and other primary purposes, making the integrated analysis of such data inherently hindered, which inevitably affects direct comparisons between countries. (European Centre for Disease Prevention and Control (ECDC), 2017)

A list of harmonized outcome indicators to assist EU Member States in assessing their progress in reducing AMC and occurrence of AMR both in humans and food-producing animals has been established by these official entities. For food-producing animals, the proposed indicators for AMC include overall sales of veterinary AM and sales for EMA's AMEG category B classes, measured in mg/PCU, collected from the ESVAC reports (as shown in the Table 1). AMR data is collected using commensal bacteria found in food producing animals. These can be used as indicators for AM selective pressure, and thus for the potential development of resistance genes, as they naturally inhabit the hosts' microflora. (ECDC (European Centre for Disease Prevention and Control), 2017)

The availability of more detailed and comprehensive data would increase the possible scope of analyses, as well as the robustness of corresponding outputs. Reporting AMC data by DDDvet/DCDvet units and by animal species, including production type, and collection of AMR data from all countries, will help address this. (European Centre for Disease Prevention and Control (ECDC), 2017)

1.8 – Objectives of this work and dissertation structure

1.8.1 – Objectives of this work

Reporting more granular AM consumption data, enhancing its precision, proved to be crucial to provide a better understanding of AMR development. Doing it in a standardized way is essential, so countries can be compared and more effective policy actions can be implemented (European Centre for Disease Prevention and Control (ECDC), 2017), (European Medicines Agency, 2015).

The main goal of this work was to design and test a system capable of collecting Portuguese dairy farms' AM usage data to generate standardized information to be used

by DGAV to contribute to the ESVAC report. The system's functionalities have meanwhile been expanded to include customized metrics that relate AM consumption to production levels and costs, creating an analysis tool to assist AMU related decision making, to be used by veterinarians and farmers in their daily activities.

The following characteristics were identified as essential to the systems' success: **flexibility** - the tool should allow adaptations to be made to different output requirements and data processing alterations; **universal** - it should be compatible with most data input formats, from different data sources, so collaborations are not restricted by input norms; **real time response** - after establishing the systems' architecture, it should be able to produce outputs in a time efficient way, once standardized inputs are submitted; **customization** - as the need to orient decision in an efficient way was identified, the tool was designed to be able to provide farmers, veterinarians and the veterinary authorities with information that is relevant to their needs, so their decision making requirements are efficiently met.

1.8.2 – Dissertation structure

This dissertation has been structured in the following way:

- Introduction.
- Chapter 2 is a main component of this work. In it, the conception, development, and testing of a system created to respond to the objectives set above, with the essential characteristics identified, will be detailed.
- Chapter 3 presents the main results of this work, which include the dashboards created for farmers, veterinarians, and DGAV, as well as the validation of the questionnaire that complements AMU analysis.
- Chapter 4 refers, in a summarized manner, to an expanded version of a paper submitted to the Portuguese Buiatrics Association (in Annex C) , which is presented as one possibility of scientific exploitation of the system developed.
- Chapter 5 is a discussion of this work.
- Annex A contains the projects agenda, until the time of writing.
- Annex B includes the two questionnaires that were developed.
- Annex C includes the article mentioned in Chapter 4.

2 – CONCEPTION, DEVELOPMENT, AND TESTING OF AN ANTIMICROBIAL CONSUMPTION SURVEILLANCE SYSTEM PROTOTYPE

2.1 – Main stakeholders and agenda

The project started in 2019 as a conjoint initiative between ICBAS, DGAV and ANABLE. Collaboration lines have been, and are being, extended to Portuguese dairy farmers cooperatives. UNICOL and Proleite were the first partners. With this expansion, from a system to a network, the project was renamed Vet-AMNet, and the logo in Figure 1 was designed by me, and adopted. In table A1, the projects' main meetings, held until the writing of this document, are registered, together with the main objectives of each one.



Figure 1: VetAMNet logo

2.2 –Data collection

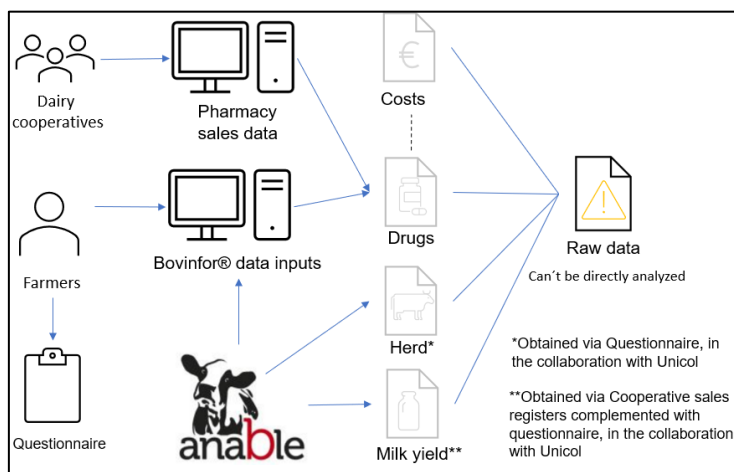


Figure 2: Vet-AMNet's Raw data collection scheme

EMA's Advice on implementing measures under Article 57(3) on data requirements, mentioned at the end of chapter 1.2, were considered in the design of the system. Raw data collection dynamics operated as schematized in Figure 2, and are described below:

ANABLE: AM purchase data were extracted from the “treatments book” tool in the BOVINFOR platform, which is filled in manually by farmers or, alternatively, via the cooperatives' pharmacies with BOVINFOR's direct web service. Milk production originated from ANABLE's milk yield database. Animal population present in the farm was taken from BOVINFOR and iDigital/SNIRA (Sistema Nacional de Informação e Registo Animal), Portugal's national animal registry. UNICOL: AM purchase data was extracted from the cooperative's pharmacy database. Animal

population data was collected by UNICOL's clinical team through the filling of a questionnaire; milk production data was taken from official cooperative sales documents and complemented via the same questionnaire, inquiring producers about the number of litres fed to each calf and if they sold milk production quotas to other farmers. The questionnaires were developed by me and filled in via mobile. They can be found in Annex B, under the name "UNICOL – farms' information". All the farmers signed a contract allowing ICBAS's Department of Population Studies to use their data for scientific reporting purposes, with anonymity.

2.3 – Sample

The prototype of the system developed was implemented using data from 46 farms, 22 associated with ANABLE, and 24 associated with UNICOL. A total of 17300 cows, 8109 heifers, and 3452 calves, from at least three years of production were included. The main selection criteria were as follows: farms from UNICOL all guaranteed they acquired most of the AM they used at the farmers' cooperative pharmacy, while ANABLE selected farms that were committed to the BOVINFOR informatic management system. At the time of writing, PROLEITE's data was not treated, because their veterinary team are in the process of recruiting up to 150 farms of their associated farms, following the same selection criteria as UNICOL, for reasons that will be further addressed in "5.1 - VetAMNet's system as a tool".

2.4 – Data Pre-processing: Cleansing and editing

All the raw data gathered was submitted to pre-processing, which involved data cleansing and editing. Data cleansing is the process of removing all the corrupt entries found; data editing was mainly done by aggregating entries from the original sources, which are presented with a blue header, in Figure 3, and by shaping data to the desired structure, presented in grey, that was designed in order to harmonize all inputs.

Herd data inputs were aggregated by farm and by year. An algorithm was created to differentiate the animals by age and sex, and to multiply the generated numbers according to the weight classes as described in chapter "2.9 - Creation of an adapted denominator (APCU)".

Annual milk yield by farm was assessed by calculating each cows' monthly test day milk yield values which were later multiplied by the number of days in each year and summed by herd.

Drug and costs inputs were aggregated by year, farm and active ingredient. Their pre-processing is further detailed in chapter "2.5 - Official documents data merge", as it also involved this technique.

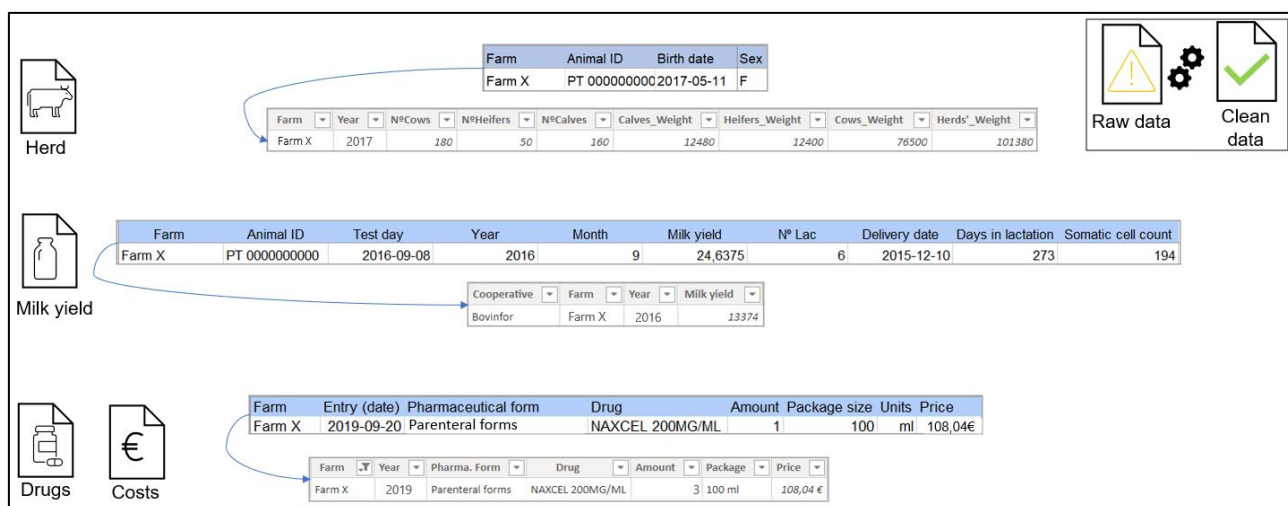


Figure 3: Vet-AMNet's steps taken in data pre-processing illustration.

2.5 - Official documents and data merge

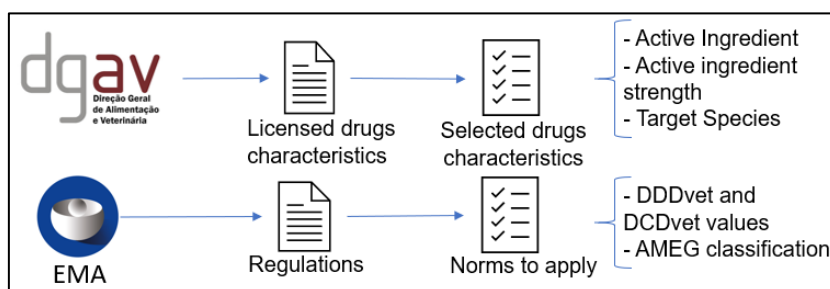


Figure 4: Vet-AMNet's official documents input.

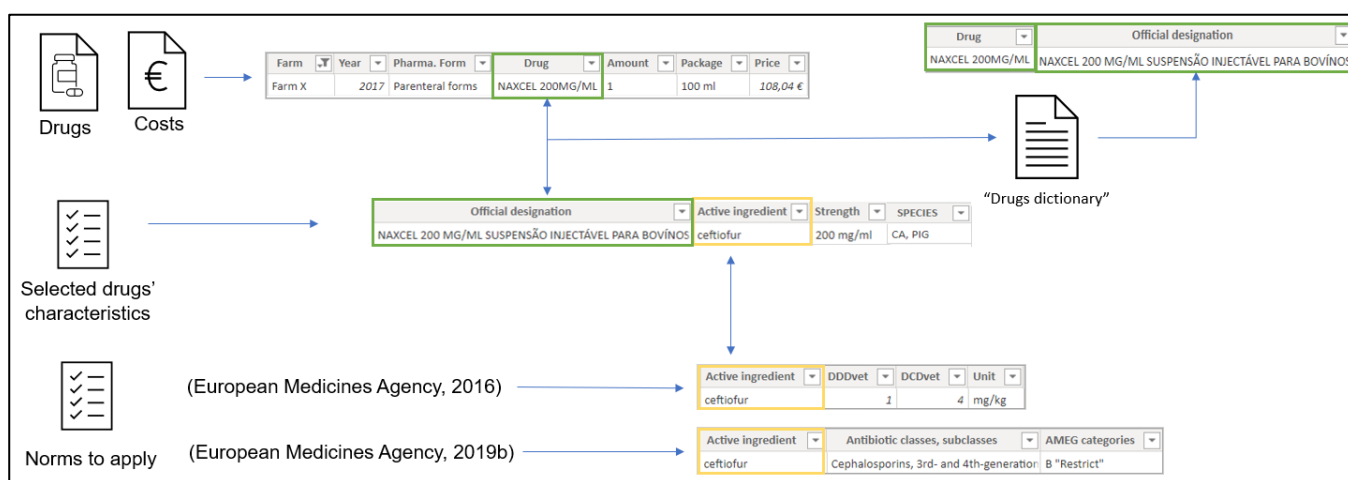


Figure 5: Vet-AMNet's merging tables illustration.

As represented in Figure 4, official documents, from both EMA and DGAV, were essential tools to perform the desired analysis. The commercial names of the drugs recognized by the partners' pharmacy informatic systems, or manually input by

farmers/associates via BOVINFOR informatic system, were associated to the correspondent designations, present in the official list of licenced AM drugs and respective characteristics, provided by DGAV, allowing the merge of the Active ingredient, Strength and Target species fields. This association could only be done by using a “Drugs dictionary”, customized for every partner, which established the right correspondence between the two designations. Creating this dictionary was the most time-consuming step of building the system, as it demanded a careful analysis, specific to each data source, of all data entries. This will be further addressed in chapter “5.1 - VetAMNet’s system as a tool”. Drugs which had no specified registered use in cattle, in DGAV’s official documentation, were removed from the analysis. The quantity of active ingredient, in milligrams, used by each farm was calculated by multiplying the yearly purchased amount of drugs, by package volumes, by the respective active substance strength. All the measurement units were converted to milligrams, according to EMA’s conversion tables used for ESVAC (European Medicines Agency, 2019c), and active ingredient quantities and associated costs were aggregated by year.

Each active ingredient was directly merged with its correspondent DDDvet and DCDvet value taken from EMA’s official lists (European Medicines Agency, 2016), as represented in Figure 5. The same process, also shown in Figure 5, was applied to group active ingredients according to their AMEG categorization (European Medicines Agency, 2019b).

2.6 - Choosing Power BI as a data management and output tool

Business intelligence (BI) can be defined as “a combination of processes, policies, culture, and technologies for gathering, manipulating, storing, and analysing data collected from internal and external sources, in order to communicate information, create knowledge, and inform decision making”(Foley & Guillemette, 2011). Adopting BI methods in the architecture of the desired system was elected as this appeared to be the most efficient approach to transform raw data from farmers and pharmacies into significative information, as detailed in chapters “2.4 – Data Pre-processing: Cleansing and editing”, “2.5 - Official documents data merge” and “2.7 - Data architecture”. Aiming to create a versatile and long-lasting tool, which could use very different data structures incoming from different partners and be readily accessible from mobile devices, and adaptable to each users’ demands, the system was developed using Microsoft Power BI®.

Power BI® Desktop is an application that enables the connection, transformation, and visualization of data. It allows the connection of data from different sources, its transformation/cleaning, and its combination by relating tables to each other (data

modelling). Data models originate fields that can be combined and used to construct visual representations (visuals), such as graphics and tables, which can be grouped and shared as reports and dashboards. The developed data model was optimized to make these connections in the most time-efficient way.

To facilitate the management of large quantities of data, from multiple information sources and in different storage formats, Power BI® was also a good solution, as it is very versatile in what concerns data source connections, because it can be connected to Excel®, .csv files and SQL servers, among many others (Microsoft, 2021b), providing the necessary universal compatibility mentioned in chapter “1.8 – Objectives of this work”.

Power Query Editor is the part of Power BI® where data is sculpted to the intended shape, by cleaning and transforming it through actions such as merging columns and multiple calculations. Each step applied to the data is recorded, so that whenever a different source of data is connected, these steps will be automatically applied, and new incoming data is always treated in the same specified method (Microsoft, 2021c). The processes described in chapter “2.4 – Data Pre-processing: Cleansing and editing” and “2.5 - Official documents data merge” have been optimized using this tool.

In the building process of this system, two different programming languages were used: Power Query Formula language ‘M’, during data import, to clean-up data and to create costume columns, and DAX language, after the data was imported into the data model, to create costume columns and measures.

A dashboard is a group of selected visuals that are fixed in a single canvas, only selecting metrics that matter to whom it is intended. The main objective of this solution is to show all information needed to make decisions (Microsoft, 2021a), in this case, allowing the monitorization of AM consumption and associated costs, or the benchmarking of farmers. Among VetAMNet’s collaborators, this proved to be a low cost and popular solution to gather data and present information. Some of the dashboards created can be found in in chapters “3.1 - Dashboard and visuals’ design” and “5.3 – Antimicrobial stewardship as a marathon”. The paper in Annex C was crafted using visuals designed in the system, using its data base, at the time.

2.7 - Data architecture

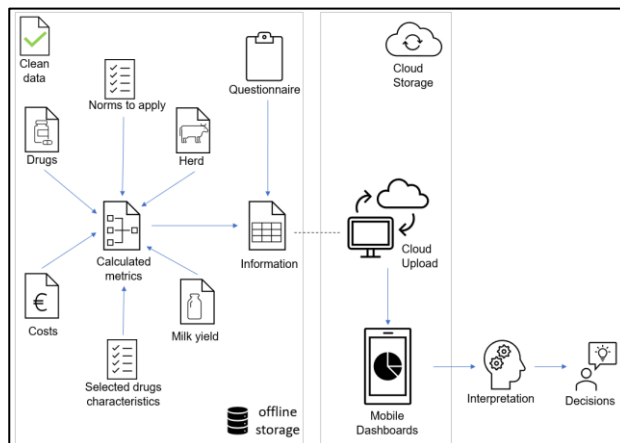


Figure 6: Vet-AMNet's data architecture

After pre-processing all data inputs, these were modelled by establishing farm and year relations between the tables, and the metrics detailed in “2.10 - Main algorithm and metrics description” were calculated and will be related to the results of a questionnaire, described in “2.8 - Creation and validation of a complementary questionnaire”. The information generated will be uploaded to the Cloud, and transformed into Dashboards, as described in “3.1– Dashboard and visuals’ design” to be further interpreted by collaborators, and hopefully used to make informed decisions. Figure 6 illustrates the processes described above.

2.8 - Creation of a complementary questionnaire

A questionnaire, aimed to be used in the near future, was created with the intention of establishing a general profile of the farms collaborating in the project. It can be regarded as a data collection tool that complements the analysis produced by VetAMNet by guiding the interpretation of each farm's registered AMU, as it can be seen in Figures 2 and 6. It is composed by 4 sections, with the main objectives behind each one being:

- 1) Animal health problems within the farm: understand the main health issues affecting the herd, how they are handled, if and how they are registered, in order to investigate the possibility of relating these occurrences to AMU.
- 2) Farmers' perception of AMR as problem: evaluate the general attitude of the producer regarding AM consumption, its relation to AMR, and his opinions on the impact that current and future restrictions in AMU can have on his business.
- 3) AM usage practices: understand how AM are introduced in the farm; where they are purchased. To assess to what extent dairy cooperative pharmacy sales data can be

utilized as a AM sales data source; how pharmaceutical formulations are applied in the herd, to validate the adapted PCU approach, as will be described in chapter 2.9; if there are any easily identifiable incorrect practices based in the European commission's Guidelines for the prudent use of antimicrobials in veterinary medicine (European Commission, 2015); how, by whom, and when AM treatments are registered; what happens to the purchased AM after they expire, and whether they are correctly eliminated

- 4) AM consumption reduction: understand if/how common health promoting measures are already being applied; and to evaluate if active and easy to apply reduction measures are already in place.

The questionnaire can be found under the name “VetAMNet complementary analysis”, in the Annex B, and the logic behind the distribution of the questions in the different sections is explained in the flowchart below:

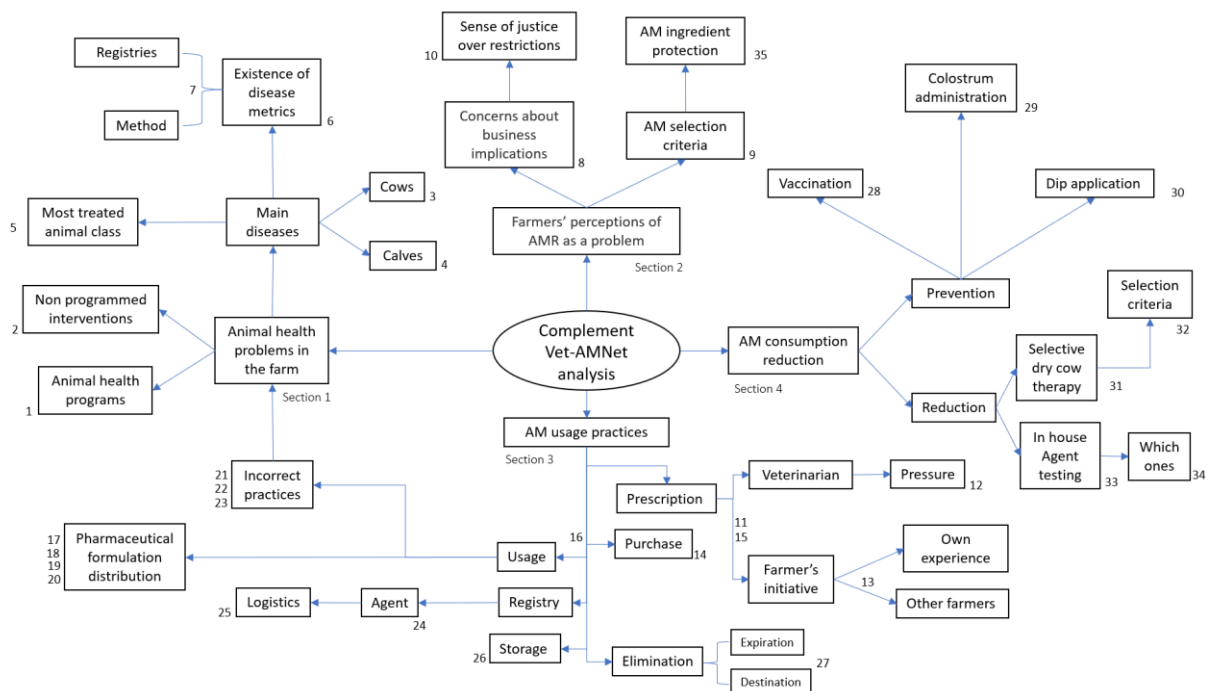


Figure 7: VetAMNet complementary analysis questionnaire Mind Map. The numbers in the figure correspond to the questions that can be found in this questionnaire.

2.9 - Creation of an adapted denominator (APCU)

Aiming to approximate the theoretical DDD's and DCD's calculated values to the Portuguese dairy production panorama, a customized denominator was crafted, adapting the live weights used in calculations to internal statistical data from the ICBAS's Department of Population Studies, and to the target animals of the different AM drugs. By dividing 425

(the weight designated by EMA for a 24-month-old cow, or older, who has calved at least once) by 600, which is an estimate of the live weight of an adult cow, a conversion ratio of 0,71 was obtained. That was used to index the weight of the other three age classes considered: Heifers aged between 12 and 24 months: 319,5 kilograms; Heifers aged between 6 and 12 months: 177,5 kilograms; calves until 6 months of age: 78,1 kilograms.

The following target populations were established for each AM pharmacological formulation group analysed, based on the most commonly occurring diseases that require AM treatments, and clinical principle that the animals contained in these classes are more likely to be subjected to treatment with the correspondent pharmacological AM groups: Oral antimicrobial forms are expected to be used in calves up to 6 months of age; Parenteral AM's - all herd; Intramammary AM's for dry / lactating cows - adult cows; Intrauterine AM - Adult cows(Guardabassi et al., 2009). This approach was later confirmed by questionnaire.

2.10 - Main algorithm and metrics Description

The flowchart bellow represents the main algorithm of the created system. All the metrics are explained in detail, in Tables 2,3,4 and 5. With the purpose of making the interpretation of the created metrics more intuitive, the designation “standard cow” was attributed to all metrics calculated using the PCU denominator recommended by EMA, and “standard animals” was attributed to the ones calculated using the adapted PCU.

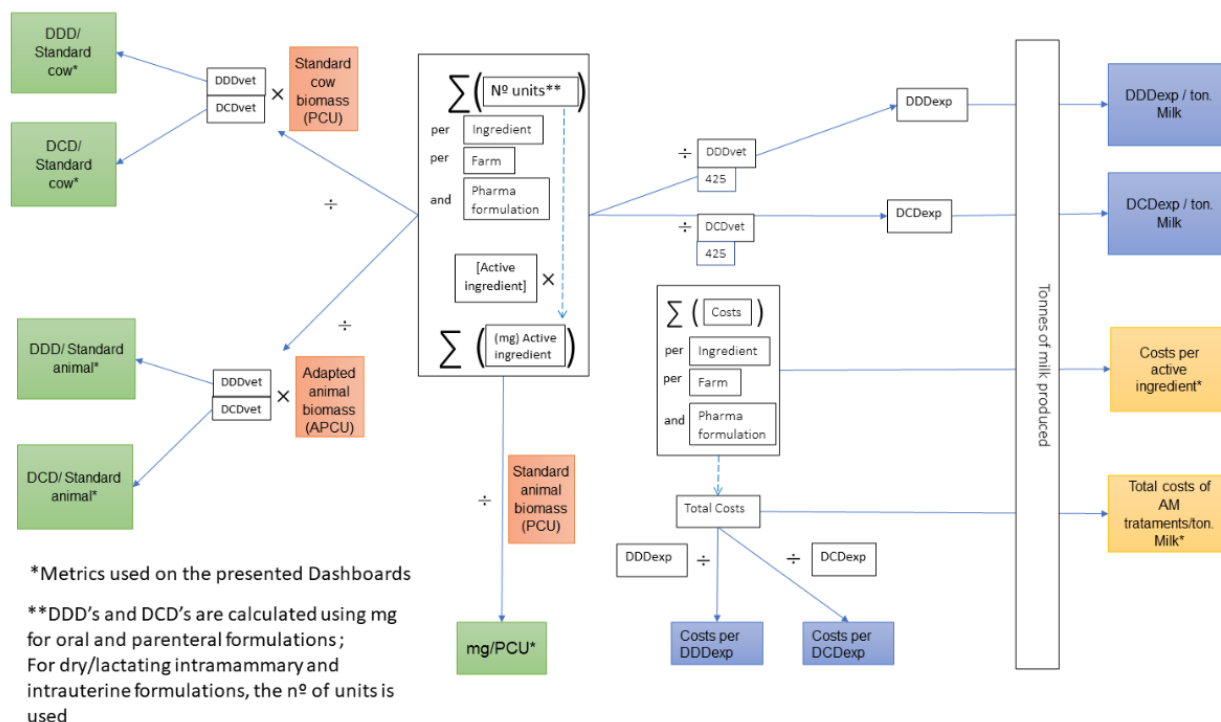


Figure 8: VetAMNet's main algorithm, based on “Figure 1” found in (Collineau et al., 2017)

Table 2: Animal Biomass denominators (Orange boxes, in Figure 8)

Metric	Description	Formula	Commentary
PCU: population correction unit	Standard animal biomass that, at a given year period, might be subjected to treatment with AM substances	n° of adult cows x 425*	*standard weight attributed by EMA to an adult cow that's maintained for milk producing purposes (European Medicines Agency, 2019c)
Adapted PCU (APCU): Adapted Population correction unit	Adapted animal biomass that, at a given year period, is more likely to be subjected to treatment with specific AM pharmaceutical formulations	(a), (b) n° Calves (up to 6 months) x 78,1 (b) n° Heifers (6 to 12 months) x 177,5; (b) n° Heifers (12 to 24 months) x 319,5; (b), (c), (d) n° Adult Cows (from 24 months) x 425	Assumed Target population for the different AM pharmaceutical formulations: Oral forms: (a) Parenteral: (b) Intramammary dry / lactating cows: (c) Intrauterines: (d)

Table 3: Animal level AMU metrics (Green boxes, in Figure 8)

Metric	Description	Formula	Commentary
mg/PCU	Milligrams of active substance available for treatments, per animal biomass kilogram	$\frac{\text{mg of active substance}}{\text{PCU}}$	Official EMA units to report sales data
DDD's: "Defined Daily Doses" and DCD's: "Defined Course Doses" (DDD's are obtained by using the constant DDDvet, and DCD's by using the constant DCDvet)	DDD: n° of standard treatment days DCD: n° of completed standard treatments Hypothetically applied per standard cow if PCU is used, or standard animal if APCU is used	$\frac{\text{mg of active substance}}{\text{DDDvet} \times \text{PCU}}$	For oral and parenteral AM pharmaceutical formulations
		$\frac{\text{mg of active substance}}{\text{DCDvet} \times \text{PCU}}$	
		or $\frac{\text{mg of active substance}}{\text{DDDvet} \times \text{APCU}}$ $\frac{\text{mg of active substance}}{\text{DDDvet} \times \text{APCU}}$	
		$\frac{\text{n° of units}}{\text{DDDvet} \times \text{n° adut cows}}$ $\frac{\text{n° of units}}{\text{DCDvet} \times \text{n° adut cows}}$	For intrauterine and intramammary pharmaceutical formulations

Table 4: Costs metrics (Yellow boxes, in Figure 8)

Metric	Description	Formula	Commentary
Costs per active ingredient	Registered costs in AM treatments, in euros	$\sum (\text{costs}), \text{ per active ingredient, farm, and pharmaceutical formulation}$	Financial analysis metrics, created for economic advisory purposes

Costs/ ton. of milk	Registered costs in AM treatments, in euros, per ton of milk produced	$\frac{\sum \text{costs}}{\text{Tonne of milk produced}}$	The main metric to establish AM cost comparisons, because herd sizes can differ a lot, so direct costs should not be used for comparisons
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Table 5: Farm based AMU/costs metrics (Blue boxes, in Figure 8)

Metric	Description	Formula	Commentary
DDDexp and DCDexp (DDDexp's are obtained by using the constant DDDvet and DCDexp's by using the constant DCDvet)	Number of possible treatment days (DDDexp), or	$\frac{\text{mg of active substance}}{\text{DDDvet} \times 425}$	For oral and parenteral AM pharmaceutical formulations
	Number of possible complete treatments (DCDexp), acquired by the farm	$\frac{\text{mg of active substance}}{\text{DCDvet} \times 425}$	For intrauterine and intramammary pharmaceutical formulations
DDDexp / ton. Milk and DCDexp / ton. Milk	Number of treatments acquired by the farm, divided by milk production	$\frac{\frac{\sum \text{DDDexp's}}{\text{Tonne of milk produced}}}{\frac{\sum \text{DCDexp's}}{\text{Tonne of milk produced}}}$	per active ingredient, farm and pharmaceutical formulation
Cost/DDDexp and Cost/DCDexp	Cost per treatment acquired by the farm	$\frac{\frac{\sum \text{costs}}{\sum \text{DDDexp's}}}{\frac{\sum \text{costs}}{\sum \text{DCDexp's}}}$	per active ingredient, farm and pharmaceutical formulation

3 – RESULTS

3.1 Dashboards and visuals

To create relevant outputs, the dashboards presented in this chapter have been developed in collaboration with the intended end users, by presenting and discussing these outputs with several collaborating farmers, veterinarians, and members of DGAV.

Dashboards can be designed specifically to meet a single user's requirements. However, the ones presented in this chapter were built to be standard models that can respond to the most frequent data output demands. All the visuals presented are dynamic in nature, meaning they can be interacted with by using the Filters and units of measure selection panel, presented in Figure 9, or by clicking other connected visuals found in the same dashboard. All the ones that show data per pharmacological group have a built-in hierarchy so they can also show data by active ingredient, and vice-versa.



Figure 9: Farms geographic distribution, and regional selection dashboard

Figure 9 presents a regional descriptive dashboard. By selecting one region of Portugal in the selection panel where “Azores” is highlighted, collaborating farms will appear as dots, in the map, together with a regional farm count, and the average herd

description by animal classes. The aim of this dashboard is to monitor the achievement of national-wide representation, as this is a clear target for the future, that will be further discussed in chapter “5.4 - VetAMNet’s next steps”.

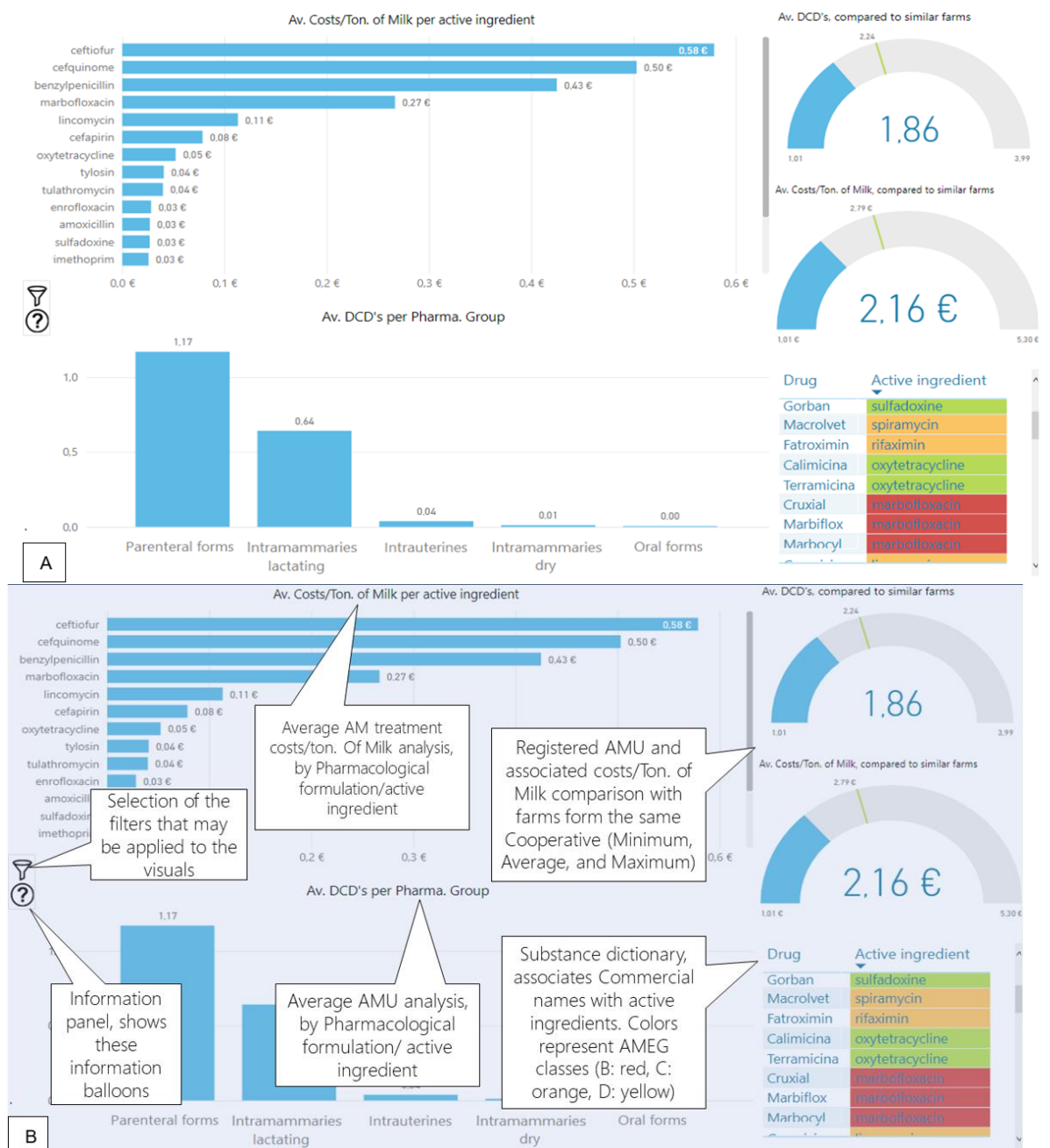
Figure 10: Filters and units of measure selection panel

Figure 10 introduces a built-in feature that can be found in all three of the main user’s dashboards, shown in figures 11, 12 and 13. By selecting the desired filters, users can control the visuals which compose their Dashboards. This allows the manager of the system to restrict the information to be shared with the different users, and after this process, it allows users to focus their analysis in their specific needs by, as an example, displaying data on category B “Restrict” drugs only. Costs and AMU metrics can also be selected according to the desired analysis. As

information is intended to be shared with different classes of users, in a selective way, maintaining its relevance and confidentiality levels, and given that the filters are used to select the data that can be visualized, user’s information access restrictions are translated into the filters they can apply to the visuals.

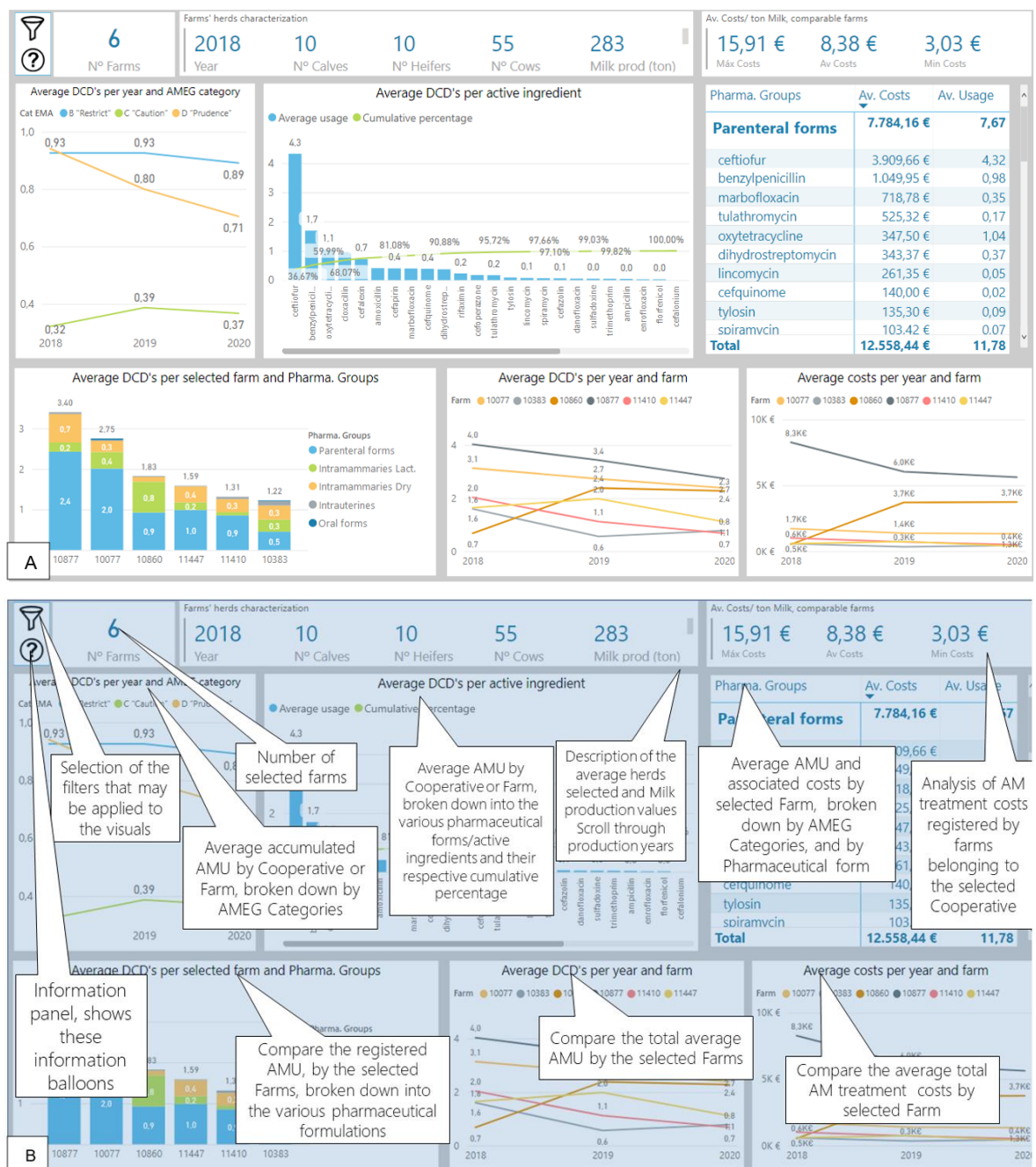
The dashboard developed for farmers (Figure 11) focuses on a single farm level. The main demands at this level were related to the comparison of the farm's AMU values, and costs associated, with other farms. An intuitive guide to raise awareness about AM restriction categories has also been designed. Farmers have expressed their concern about the possibility that learning how to use the created tool could be too time consuming. Therefore, when designing this Dashboard, simplicity was priority.

Figure 11: Farmer's dashboard overview (A) and visuals functionalities guide (B)



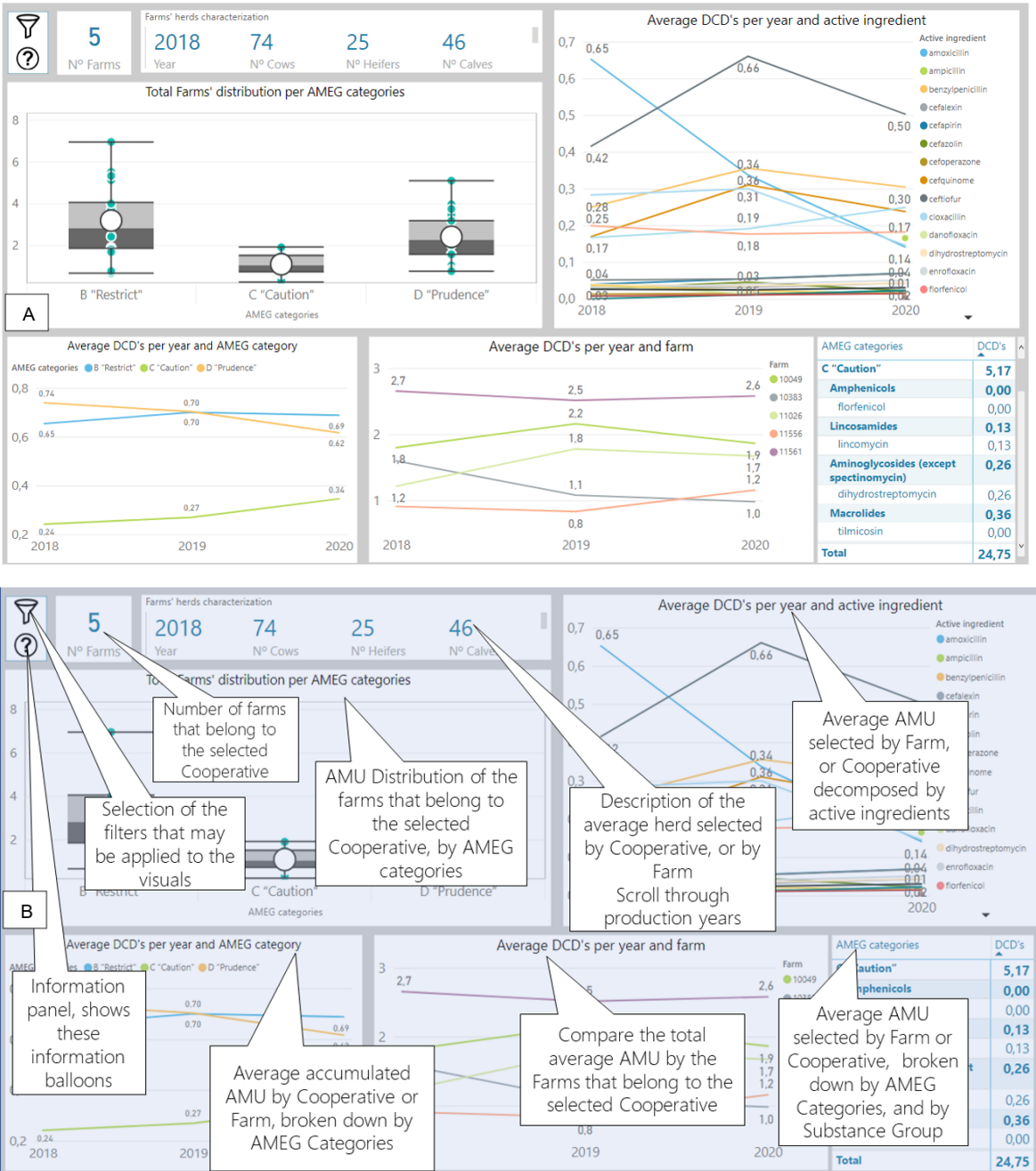
The veterinarians' dashboard (Figure 12) focuses on AM consumption at farmers' cooperative level. The main requirements expressed by collaborators, included the possibility of establishing direct comparisons between similar farms, AMU time trends, herd and milk production yearly overview, costs analysis and detailed active ingredient categorization and usage. By knowing the more common pathologies at each farm, veterinarians can play an important role as advisors and prioritize disease prevention programs.

Figure 12 Veterinarians' dashboard overview (A) and visuals functionalities guide (B)



The dashboard designed for DGAV (Figure 13), targets AM consumption at a national level, compiling data from all partners and stakeholders. The main information requirements identified, during the several meetings held, included the establishment of temporal AMU trends, up to an active ingredient level, the distinction of Category B AM substances to report to the ESVAC system, as presented in chapter “1.4 - ESVAC project and Portugal’s reported values”, and the distribution of farms according to their consumption of restricted molecules.

Figure 9: DGAV’s dashboard overview (A) visuals functionalities guide (B)



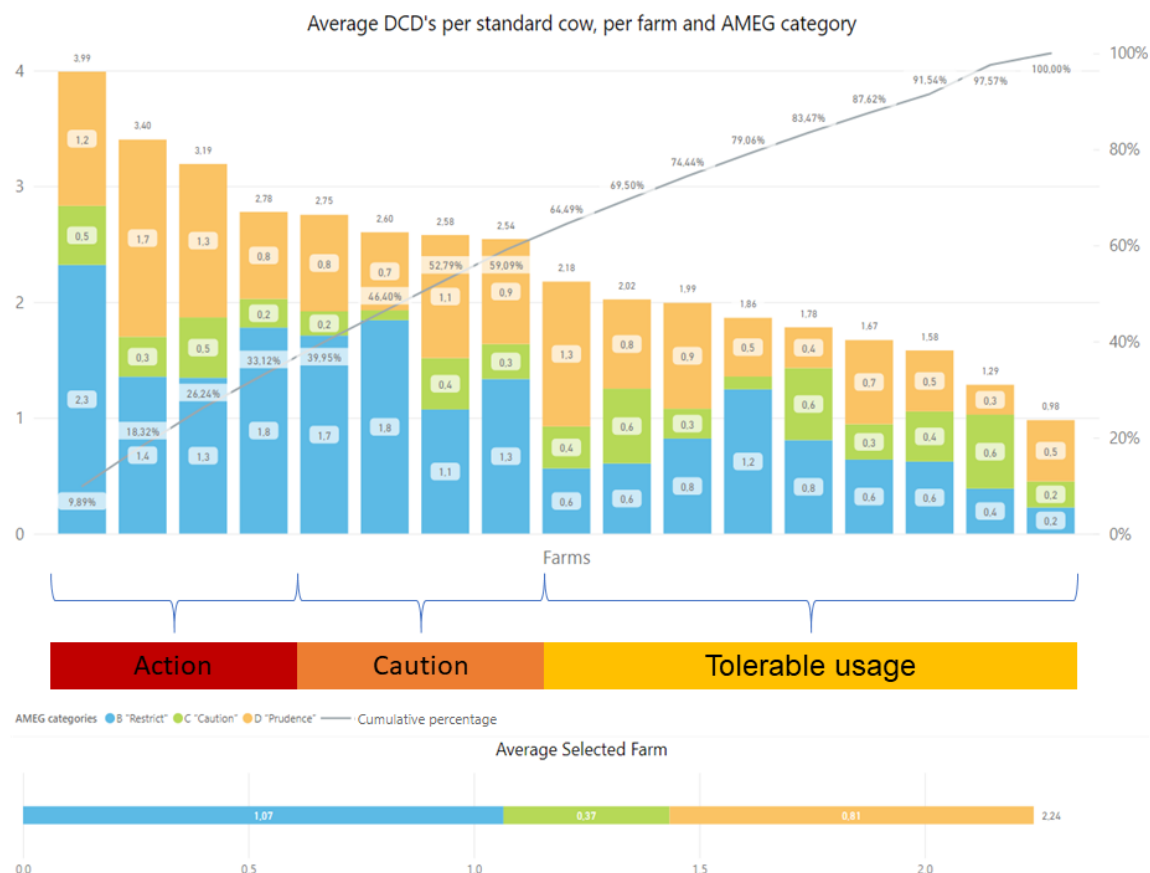


Figure 14 Farm benchmarking visual, AMU decomposed by AMEG categories.

Figure 14 demonstrates how the system can be used to apply benchmarking methods. In this case 17 farms associated with UNICOL are presented and compared. Benchmarking methods will be further detailed in chapter “5.3 – Antimicrobial stewardship as a marathon”. This type of visual must be driven by DGAV to better achieve progress in AMU consumption reduction but is ultimately intended to be shared with all the parts involved.

3.2 Validation of the questionnaire

Beyond the scope of this dissertation’s main objectives, a questionnaire was created and validated in the field, by visiting five of the farms that collaborate with Vet-AMNet, in the North region. Due to the COVID-19 pandemic, it was not possible to visit all the collaborating farms to apply it, so that it could be connected to the analysis made. However, syntax changes were made accordingly to the responses given, making the questionnaire more time efficient and easy to understand.

4 –Terceira Islands’ Case study

A detailed AMU analytic study using the database was performed on Terceira Islands’ farms. The results obtained constitute a good representation of the systems current analytical possibilities. This study was submitted to the Portuguese Buiatrics Association journal, and it is currently under revision. An extended version of the submitted paper can be found the ANNEX C and will be further analysed in chapter “5.1 - VetAMNet’s system as a tool”.

5 - DISCUSSION

5.1 - VetAMNet’s system as a tool

All data analysis systems are subject to failure, mainly related to the inconsistency of data inputs quality. Additionally, when it comes to analysing information generated by voluntary participation, one needs to be careful in the interpretation and extrapolation of the results to a wider level, as collaborating farmers may be more conscious than the average, meaning the sample presented may not be representative of the general population. Very low and/or other out of production-context values need to be validated, as they may not have been correctly reported. It should be made clear to farmers that the main objective of implementing a system of this kind is having a management tool that supports the adoption of prudent practices on use of AM. This is best achieved if it mimics reality as close as possible (Sanders et al., 2020).

From the partnerships established, it was possible to conclude that the data sent directly by pharmacies was easier to work than data coming directly from farmer’s registries, as it was already noticed before by Sanders et al. (2020), due to the lack of standardization in manual farmers’ data inputs. As a consequence, for ongoing and forthcoming partnerships with other dairy cooperatives pharmacy data inputs should be preferred.

It is important to point out that the metrics used to express AM consumption data result from a standardization, to allow comparison between farms, regions, and countries. In this way, the standard PCU (standard cow) metrics can be used to establish international comparisons. The APCU (standard animal) metrics, created for the purpose of our analysis, can only be used in national comparisons, between farms that collaborate with Vet-AMNet. However, the weights attributed to animals and the assumption that every drug purchased was administered in the year of the registry are estimates done to make the analysis possible. Thus, the information derived from these inferences, should be carefully interpreted and not translated directly. The current lack of rigorous treatment records and

protocols, make it difficult to connect AMU data to the health problems that caused the registered AM treatments. In the future, producers should receive training on how to fill in treatment forms, so that these data inputs are more harmonized and can be treated to generate more precise and detailed. For now, the outputs generated from this type of data need to be linked and interpreted to the farms' health status by producers and the assistant veterinarians.

Through several meetings held during the development of this project, it became clear that collaboration lines needed to be established with Portuguese dairy farmers cooperatives, to reach national-wide representative coverage.

Our system can become an important tool to provide farmers and veterinarians with relevant information, to promote a more responsible AM use, and to answer future AM consumption restriction policies in an efficient way. In the present case study, the potential advantages of analysing AM consumption, together with costs and production values, at a farm level, have partially been demonstrated by: the analysis of AM treatment costs estimations; the highlight of the farms' potentially problematic areas, which might need priority interventions to improve animal welfare to reduce disease incidence, and, consequently, AM consumption; the identification of active ingredients usage trends, differentiated by AMEG's categorization groups.

5.2 - A One-health approach to dairy farming

In dairy farms, most AM are used in response to disease. However, to prevent mastitis, wide-spectrum AB can sometimes be systematically used once cows enter the dry period. As mentioned earlier, a good part of the farms that collaborate with the system have implemented selective dry cow therapy, using teat sealers in alternative to AB. This is regarded as an effective and safe alternative to reduce AMU (Crispie et al. 2004), and can be promoted by veterinarians, using our data outputs to present AMU reduction figures to producers. Prophylactic use of AM via feed is mainly used as prevention of the development of respiratory disease and liver abscesses, mainly in sucklers, and is more associated with beef cattle (Palma et al., 2020)(Economou & Gousia, 2015).

The One Health concept should be adopted in livestock management, aiming for more sustainable and safer animal-based foods. Dairy farmers must be aware about both the impact which the products that enter their farms (particularly water and feed) can have in their animal's health, and the impact that the products they put on the market could have on the general population, if they are not safe. (Garcia et al., 2019). Prophylactic measures should always be a concern throughout the various stages of production, as these were acknowledged as the most important factors in AM reduction by an international group of

veterinarians connected with different fields livestock production (Carmo et al., 2018), and better sanitary practices should be put in place in order to prevent both the dissemination of AM residues and of resistant bacteria from the places where AM drugs are administered (Da Costa et al., 2013). It is important to note that these improvements, need the consumers' support as ultimately, they have the power to sustain livestock market changes (Patel et al., 2020).

5.3 - Antimicrobial stewardship as a marathon

Antimicrobial stewardship can be defined as “A coherent set of actions which promote using antimicrobials responsibly” (Dyar et al., 2017), with its primary goal being “to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use” (Dellit et al., 2007).

The successful cases of countries that undertook drastic measures to reduce AM consumption proves that implementation of farm level AM surveillance systems tends to be a more success-defining factor than active reduction measures (Sanders et al., 2020).

Benchmarking, by establishing points of reference against which farms may be compared, makes it possible to identify the most problematic farmers of AM that should be targeted by controlling measures. It can be done, as an example, after the distribution of the reference population by AM usage, by defining static targets like the median and the percentile 75, thus allowing the establishment of zones with 3 categories in between the defined targets: zone one of “Tolerable usage”, with usage below the lowest target; a “Caution” zone with usage between the lowest and the highest marks, and an “Action” zone, with a usage above the superior target (Sanders et al., 2020). Figure 14 has been designed to illustrate this benchmarking method. The success achieved by countries like The Netherlands and Denmark can be partly explained by this kind of approach, therefore, it should be regarded an important success factor in AM stewardship programs (Magouras et al., 2017).

Mandatory benchmarking interventions, such as the Danish “Yellow Card” initiative, or legislation implementing biosecurity measures might have to be included in national AM usage reduction strategies, as these have proven to be the most efficient measures in the reduction of AM consumption both at national overall and species level (Magouras et al., 2017), whereas exclusively volunteer approaches to reduce AM consumption in animal production have rarely been successful (Speksnijder & Wagenaar, 2018). When certain limits are exceeded, countries may activate different risk management norms or intervention actions, such as: mandatory elaboration of action plans to reduce AM consumption, detailing additional actions to reduce the incidence of diseases; additional veterinary visits

and/or farm inspections; mandatory external advice; fines; or exclusion from quality certification programs (Sanders et al., 2020).

On behalf of the MINAPIG consortium, two detailed studies were conducted in four different European countries. These are good examples on how AM consumption in livestock production should be assessed and optimized.

The first one aimed to evaluate potential connections between herd management specificities, production parameters, biosecurity status and AMU in farrow-to-finish pig farms; those first three factors were assessed using the Biocheck.UGent™ risk-based tool (which previously proved to be a comprehensive and repeatable scoring system with predictive and discriminating validity) and were related to farm level-AMU data. It made it possible to associate a younger weaning age with higher AMU, and better external biosecurity with lower AMU, among other factors that could be causing an indirect impact on AMU. Identifying these links is fundamental to help producers, health advisors and policy makers understand which farm practices can and should be optimized and which need to be abandoned in favour of other alternatives (Postma et al., 2016). Biocheck.UGent™ biosecurity questionnaires have already been applied in 151 farms located in the North and Centre of Portugal (MIL-HOMENS, 2020) and are currently being applied to farms associated with Proleite, one of Vet-AMNets' associate cooperatives. This kind of initiatives, when complemented with AMU analysis, should produce valuable information on the most relevant risk factors associated with an increase in AMC in Portuguese dairy farms.

The second publication assessed the effect that herd specific AM reduction measures can have in the AMU of farrow-to-finish farms, and the effects that this reduction could have in herd health. Tailor-made plans that included improvements on vaccination, feed, and water quality, among others, were designed and implemented in 68 farms. Following this, AMU and disease metrics were evaluated and compared to values registered in the year before the adoption of the plan. Through this approach, AMU was reduced considerably - a 54% reduction was registered on weaned pigs and a 69% reduction in the use of polymyxins, an AMEG class B "Restrict" AM, and this was achieved without noticeable occurrence of more diseases. In this work, Raasch et al. stated that an identical approach cannot be adopted by every farm, because to achieve results of this scale on other farms, evidence needs to be gathered on the risk factors connected to an increase in AMU, herds need to be benchmarked on AMU, and herd-specific AM reduction strategies need to be carefully designed (Raasch et al., 2020).

Health status and production context disparities are not the only factors that influence AMU. Human behaviour also plays a significant role, as Veterinarians' expertise and working methods are primordial while advising farmers on animal husbandry practices

and prescribing AM drugs, making social sciences relevant in the planning of better interventions. (Magouras et al., 2017) Currently, it is widely acknowledged that a veterinarian's role should be one of active animal health management advisor, abandoning the old traditional practices of prescribing AM instead of mitigating the causes of health problems. However, clinical decisions can be influenced by fear of losing the farmers' trust, fear of appearing too invasive when giving management advice, and even by eventual specific treatment requests by farmers (Speksnijder & Wagenaar, 2018). The monitorization and analysis of AM consumption and the benchmarking of farmers can be useful tools to support unbiased veterinary advice.

The behaviour change required in what concerns AM usage will not be easy, or immediate. According to the Transtheoretical model of change, developed by Prochaska and DiClemente, for an individual to alter his behaviour, first it is necessary that he recognizes the need to change, so that the idea of doing so, grows in him. These plans should translate into action, that should afterwards be maintained. In this phase, relapses into wrong patterns should be prevented. To sustain a behaviour shift, individuals should receive support adjusted to the phase in which they can be placed. Therefore, at the start of the process, it is necessary to develop the intention of changing and to educate farmers on how to do it. After changes are implemented, positive behaviours should be reinforced, to prevent relapses into bad practices. It is also important that the veterinarian does not deprive the producers of a sense of choice over the recommendation, and that recommendations are discussed with producers, because this type of sensitivity is appreciated and leads to more openness in implementing suggestions (Speksnijder & Wagenaar, 2018).

5.4 – Publication of our work

Vet-AMNet has been expanding rapidly. The paper submission mentioned in “4 – Terceira Islands' Case study” was elaborated with the aim of introducing the network to Portuguese dairy cooperatives and veterinarians, as an attempt to reach a more significant nation-wide voluntary coverage. An abstract describing the Vet-AMNet project was submitted for presentation at the 2021 AACTING international conference, however, due to the pandemic situation, this event was postponed. The major objective of this network is to provide practical advice on the setting up of AMU data collection systems to guide AM stewardship (AACTING, 2020).

5.5 - VetAMNet's next steps

Portugal still has a long way to go to achieve the 50% AMU reduction target defined by the Farm 2 Fork Strategy. For government authorities, it is advisable to stimulate and allow new initiatives with the aim of lowering AM consumption (Speksnijder & Wagenaar, 2018), together with other actions as a multisectoral approach to the problem requires. The system presented after this work can potentially become a tool to generate data and information to be reported by DGAV to the ESVAC system, according to EMAs' current Guidelines. Additionally, it can also provide farmers and veterinarians with relevant information to promote a more responsible AMU, and be used as a basis to establish, and monitor future AMU policy targets in an efficient way. As a first attempt to create a system of this nature in Portugal, we have generated important intelligence, mainly related to data quality and data management practices that should be taken into consideration when planning the implementation of similar systems to be used for reporting farm-level AMC in other animal species.

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ANEX A. Meetings calendar

Table A 1: Vet-AMNet's agenda

Date	Participants	Objectives
17/09/2020	Eng. Samuel Pinto, Eng. António Martins, Eng. António Ferreira (ANABLE)	Introduction to stakeholders; Strategic Outlining
04/11/2020	Eng. Samuel Pinto, Eng. António Martins, Eng. António Ferreira (ANABLE)	Algorithm presentation; Metrics discussion
11/12/2020	UNICOL	Project presentation; Collaboration proposal
07/01/2021	Eng. Paulo Lobo	Business Intelligence consultancy (general)
23/01/2021	Eng. Paulo Lobo	Business Intelligence consultancy (data modelling)
27/01/2021	(DGAV) Director of Veterinary Drugs Authorization and Management Division: Dr. Inês Almeida; Veterinary Drugs Management and Authorization Division: Dr. Xavier Canavilhas	System prototype presentation; DGAV's new digital drugs platform presentation
04/03/2021	Eng. Paulo Lobo	Business Intelligence consultancy (model optimization)
14/04/2021	Prolete	Project presentation; Collaboration proposal
21/04/2021	(DGAV) Director of Veterinary Drugs Authorization and Management Division: Dr. Inês Almeida	DGAV's Data outputs requirements discussion
22/04/2021	Eng. Paulo Lobo	Business Intelligence consultancy (dashboard design)
13/05/2021	(DGAV) Director of the Department of Animal Protection Services: Dr Alexandra Fernandes; Director of the Department of Food Safety Services: Maria Manuel Mendes; Director of Veterinary Drugs Authorization and Management Division: Dr. Inês Almeida (ANABLE) Eng. Samuel Pinto, Eng. António Martins, Eng. António Ferreira	Vet-AMNet presentation; main findings discussion; future collaboration lines discussion

ANEX B. Questionnaires

UNICOL – farms' information

Open questions

- 1) Doctors' ID
- 2) Farms' ID
- 3) Farms' Localization
- 4) Average number of cows 2018
- 5) Average number of cows 2019
- 6) Average number of cows 2020
- 7) Average number of Heifers 2018
- 8) Average number of Heifers 2019
- 9) Average number of Heifers 2020
- 10) Average number of Calves 2018
- 11) Average number of Calves 2019
- 12) Average number of Calves 2020
- 13) Number of litters of milk spent in the nursery, for each calf.
- 14) Milk quota sales transitions
- 15) Are the medicines purchased intended only for dairy herds? If not, specify which species.
- 16) What is the herd vaccinated for?
- 17) Additional notes

VetAMNet complementary analysis (for more details, the full questionnaire can be found on the link: <https://forms.gle/YaivrA6KdWm8BMRh8>)

Section 1 Animal health problems in the farm

- 1) For which animal health areas do you have a veterinary assistance contract?
- 2) How often do you request veterinary assistance, to treat animals, extra assistance contract?
- 3) What kind of problems happen more frequently, in adult cows?
- 4) What kind of problems happen more frequently, in calves?
- 5) What animal class do you treat the most?
- 6) Do you register the occurrence of diseases, at your farm?
- 7) If you register disease occurrences, what kind of occurrences do you register, and how do you do it?

Section 2: Farmers' perception of AMR as a public health problem

- 8) Do you consider it possible that some AB's have lost effectiveness with their excessive use, in your exploration? If yes, indicate commercial name of the drug(s)
- 9) When selecting an AB to be used in your farm, wish of the following options do you consider most important.
- 10) Do you consider it fair that certain antibiotics that might be cheaper, or more effective for treatment of diseases are withdrawn from use in cattle?

Section 3: AM usage practices

- 11) In 10 treatments that you apply to your animals, how many of them are prescribed by the veterinarian (being the rest of them decided by you) ?
- 12) If you request veterinary assistance to treat a sick animal, do you consider that it is more likely to recover if the treatment includes the administration of AB?

- 13) In 10 treatments that you decide to apply to your animals, how often do you request another producer's advice?
- 14) Do you buy all the drugs that you use to treat your animals the pharmacy of the farmers' cooperative you are associated with?
- 15) Your farm's pharmacy was set up mostly based on:
- 16) The purchased drugs are only intended for dairy cows?
- 17) In which animal classes do you administer more injectable AB's?
- 18) In which animal classes do you administer more Oral AB's?
- 19) In which animal classes do you administer more intramammary AB's?
- 20) In which animal classes do you administer more intrauterine AB's?
- 21) Do you administer AB to calves when they are born, or enter the farm?
- 22) After calving, do you administer AB to cows?
- 23) Do you Reuse milk from cows undergoing AB treatments to feed calves?
- 24) After a veterinary intervention, who fills in the treatment book?
- 25) When is the treatment book filled in?
- 26) When you acquire a larger quantity than what you need to carry out the prescribed treatments, do you store what is leftover?
- 27) After the expiry date, do you eliminate the drug? (Yes/No) What destination do you give it?

Section 4: AMC reduction

- 28) What is the herd vaccinated for?
- 29) How many litters of colostrum do you administer to calves in their first 6 hours of life?
- 30) Do you apply Pre and/or Post dips to milked cows?
- 31) Apply teat sealers in the dry period, as an alternative to AB ?
- 32) What criteria do you use to decide whether or not to apply teat sealers to a cow ?
- 33) Do you use rapid testing to identify the causative microbial agents of Mastitis ?
- 34) What rapid tests do you use?

Section 2: Farmers' perception of AMR as a public health problem

- 35) What is your level of agreement, regarding the following sentence: "ABs that are essential for human health should also be used in animal production" (1 to 10)
- 36) Comment the previous statemen.

ANEX C. Terceira islands' case study

C1 - Study material

Terceira islands' dairy farming system is primarily based on natural pasture and pasture rotation, most of the herds comprise 20-100 animals, predominantly of Holstein-Friesian cattle, and farms are typically constituted by different parcels of land that are rarely connected (de Almeida et al., 2021).

By intention, five farms were selected for generic analysis of AM consumption and costs analysis. The values presented are an average of the last 3 years of production (2018-2020). Each farm represents an approximation of the extremes and percentiles 25, 50 and 75 regarding registered AM consumption, present in the current system database.

The active substances tildipirosin and gamitromicin, which belong to the macrolides class, were removed of consumption analysis, because, up until the writing of this dissertation, they have no attributed DDDvet or DCDvet constant values, and therefore these substances were only accounted for cost analysis. Drugs which use is not licensed for cattle, in the official documentation provided by DGAV, were excluded from the analysis.

C2 - Results

C2.1 - Section I Consumption

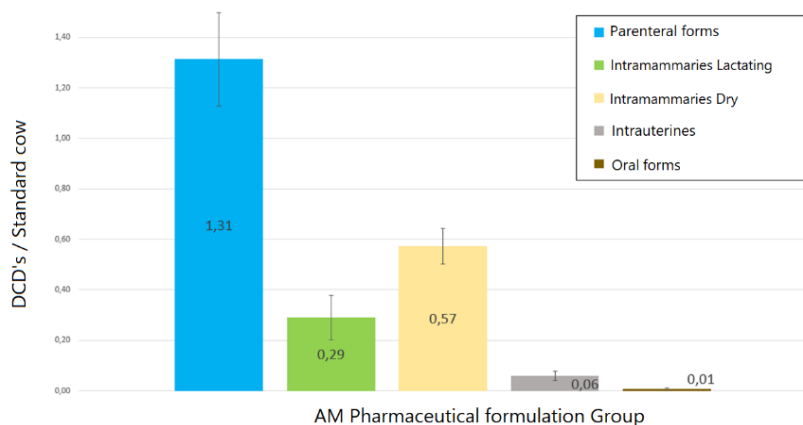


Figure C 1: Annual average (last 3 years); DCD per standard EMA cow, distributed by the different AM pharmaceutical formulations, with a 95% confidence interval.

Figure C 1 shows that in a universe of a few dozen farms, associated with BOVINFOR and UNICOL, parenteral AM are the most utilized pharmaceutical formulation group, averaging 1,31 full course treatments, per year, per standard cow, followed by dry cow intramammary, averaging 0,57 treatments per standard cow. This value is less than 1 due to selective dry cow therapy practiced in a many of the analysed farms, along with natural reproductive inefficiency. There is also a big discrepancy in the usage of lactating cow intramammary AM, which might be linked to the variable incidence of mastitis between farms, and the various therapeutic options to respond to this problem. The usage of oral AM formulations is practically residual, because this calculation's denominator corresponds to the standard adult population, and usually only calves are eligible for this route of treatment.

Farms	n°Cows	n°Heifers	n°Calves	ton. milk produced (annually)	ton. milk/cow
Farm A	110,0	50,0	60,0	914,90	8,32
Farm B	96,7	40,0	30,0	634,44	6,56
Farm C	68,0	17,7	14,7	476,52	7,01
Farm D	29,3	9,3	8,0	295,45	10,07
Farm E	30,0	7,3	17,3	209,58	6,99

Table C 1: Farms that represent the sample extremes and percentiles 25, 50 and 75. The values present an arithmetic average of the herds' animal classes, from the last 3 years of production (in tons of milk), ranked from the highest milk production to the lowest.

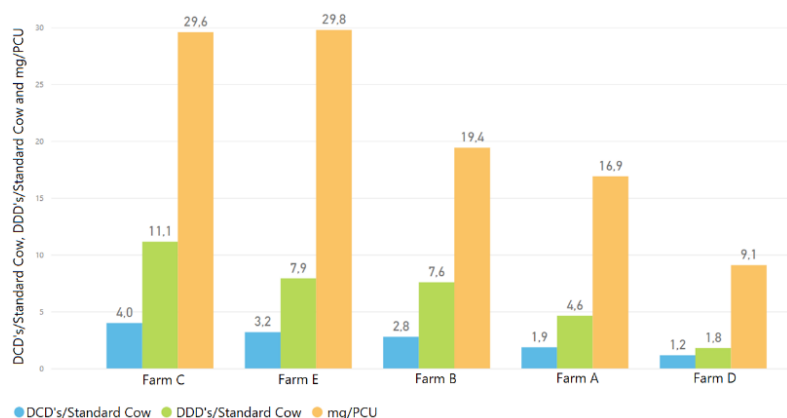


Figure C 2: Comparison between the average annual consumptions registered, in the five selected farms, within the last 3 years, represented by the 3 metrics recommended by EMA to report AM consumption.

Comparing Figure C 2 and table C 1, which differentiates the production data of the selected farms, it is possible to conclude that Farm A, the one that produced, in average, more milk, is the second smallest AM consumer, per standard cow. This is an interesting finding as it highlights the potential for animal health progress. Farm C, median in production, has the largest treatment days (DDD's) and complete treatments (DCD's) per standard animal. However, it presents a lower mg/PCU value than Farm E, which confirms the importance of reporting AM consumption using DDD's and DCD units, for it allows the distinction between dosages of the different active ingredients. As an example, comparing farms C and E, which have similar mg/PCU values, in Farm C each cow is treated 11 days per year, whereas in farm E, each cow is only treated 8 (7,9) days per year. On the other hand, Farm B, with 60% less mg/PCU, presents very similar values in days of treatment to farm E. The difference presented from Farm B to Farm A should also be pointed, as this is around - 13% in mg/PCU and - 40% in DDD's/Standard cow.

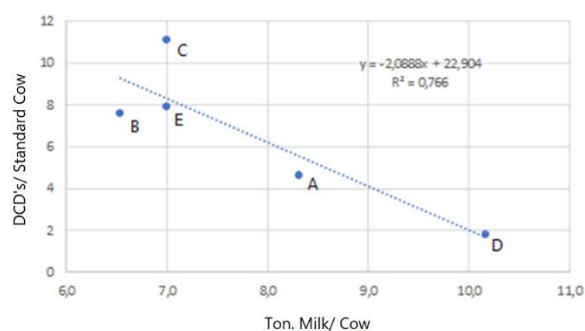


Figure C 3: Relation between the average production per cow and the number of DCD's reported per standard cow.

Even though disease is not the only determinant factor in milk production, (Looper, 2010) there is a negative linear regression between the consumption of AM and the average yearly milk yield per standard cow, this relation may justify improvements in animal health, in order to make some farm businesses more profitable, as the monetary investments in disease prevention appear to be returned both in savings related to AM treatments and in milk production.

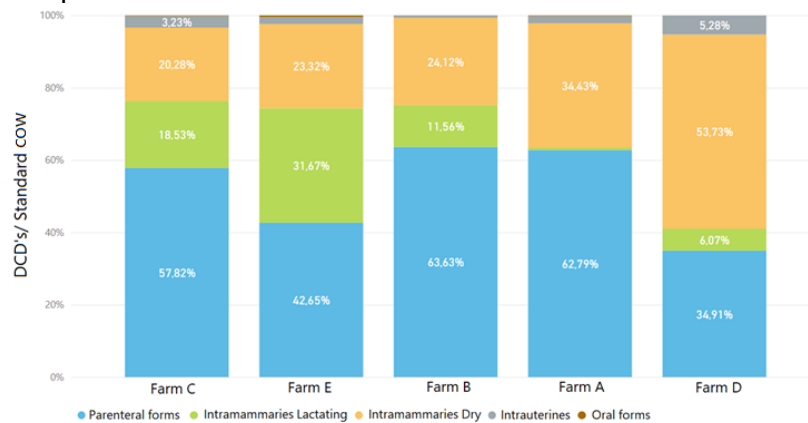


Figure C 4: Average percentual annual AM consumption (within the last 3 years) between the different groups of AM pharmaceutical formulations using DCD's per standard cow.

Figure C 4 allows the comparison of the consumption of different AM pharmaceutical formulations in each farm. The analysis of the percentual distribution of the number of complete treatments shows that Farm D is the only one in which parenteral AM treatments is not the dominant group. This farm is also the one that registered less general consumption, with dry cow therapy being the most significant, which might be explained by general better herd management, and possibly udder health problems. In farm E, we can notice larger use of intramammary AM for dry cows rather than for lactating ones. Additionally, this is also the farm with the biggest percentual consumption of this pharmaceutical form. The usage of oral forms is residual in every farm.

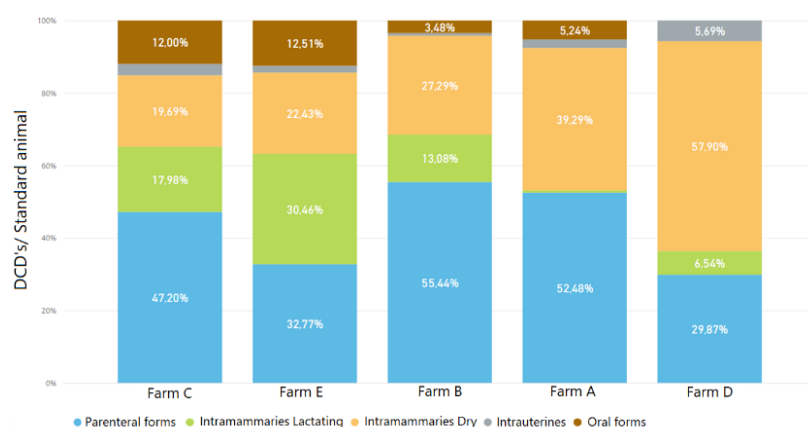


Figure C 5: Annual average distribution (within the last 3 years) of treatments applied in the selected farms, distributed by the five groups of AM formulations, using adapted PCU units (standard animals)

In figure C 5, the metrics presented were calculated using the APCU, so the proportion was established in DCD's per standard animal, allowing the allocation of oral treatments to calves, and of other pharmacological groups as it was described in chapter "2.9 - Creation of an adapted denominator (APCU)". With this approach we can anticipate

that Farms C and E may have more calves related problems than the other farms, due to their more significative oral forms usage. By comparing Figures 4 C and 5 C, we can notice that the standard animals (APCU) approach makes oral AM usage more explicit, by increasing its relevance while maintaining the remaining proportions approximately constant. With this approach it is possible to have a better understanding of which areas in the farm require more urgent intervention.

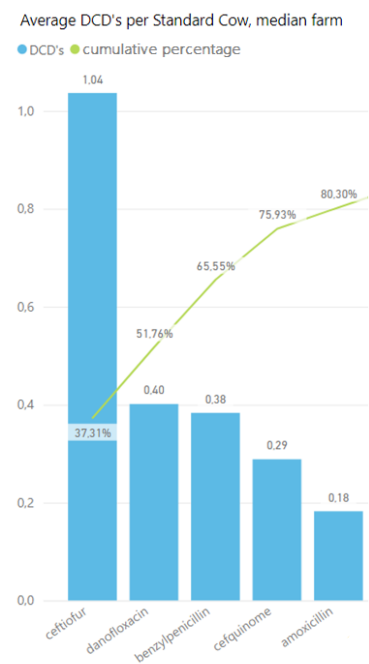
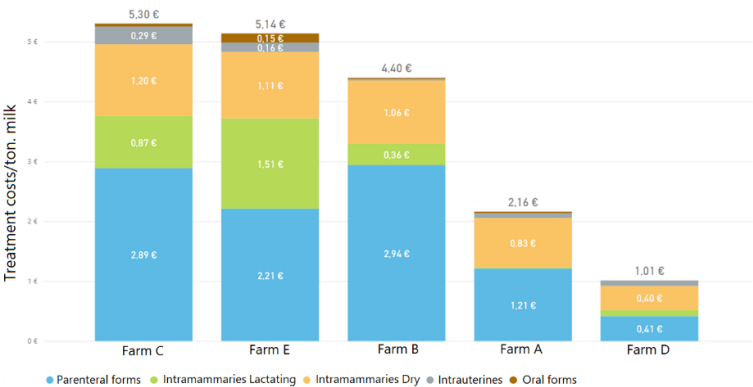


Figure C 6: Average active ingredient consumption analysis (within the last 3 years) in standard cow DCD's, median farm

By examining the average annual AMU values, presented in DCD's, registered by the median farm in terms of overall consumption, it is possible to notice that ceftiofur (third-generation cephalosporin) is, by a large margin, the most consumed active ingredient, accounting for 37,31% of the completed standard treatments. This might be explained by the fact that this molecule, in its various official commercial forms, can be used to treat several frequent diseases such as bovine respiratory disease, foot rot and metritis and that, in Portugal, its use has no withdrawal period associated with milk production, which means that milk does not need to be discarded from commercialization following its use (DGAV, 2010, 2013, 2019). However, it is worth mentioning that macrolides AMU data was removed from consumption analysis, as described in “C1 - Study material”, and they are second in line for the treatment of respiratory diseases, with 3rd generation cephalosporins being the third one. (Economou & Gousia, 2015). Veterinarians that provide assistance to the collaborating frams, examined the consumptions presented in Figure 14, and argued that the use of Ceftiofur in the Terceira Islands' farms is mainly related to the treatment of foot rot, caused the long distances that cows need to travel in order to move between land parcels, and that farmers preferred this molecule because of the reason stated above.



C2.2 - Section II: Costs

Figure C 7: Average annual expenses (within the last 3 years) with AM treatments, per ton of milk produced, among the five analysed AM groups.

By analysing the costs associated with AM treatments, represented in Figure C 7, expressed in Euros per ton of milk produced, for the different AM pharmaceutical forms, it is possible to notice visibly that

the proportion between costs and consumption stays approximately the same. Parenteral forms are, for every farm, the group on which more money is spent.

It was possible to conclude that there is a fivefold difference (4 euros per ton of milk) from the farm's spectrum extremes. Farm E spends approximately two times more money than Farm C in intramammary AM for lactating cows and that Farms B and C have high relative costs with parenteral forms.

C2.3 - Section III – Consumption categorization

The analysis of the distribution of the registered expenses in AM treatments per milk tone produced shows that the farms are spending more money in category B "Restrict" AM (the most restricted category allowed in veterinary medicine), followed by category D "Prudence", and in the last place lastly category C "Caution". The latest is also the least used category, as it is possible to verify in Figure C 8. Within category B, 3rd and 4th generation cephalosporines are the most commonly used; within category C 1st and 2nd generation cephalosporins are the most used, and in category D, the use of penicillins is the most prominent.

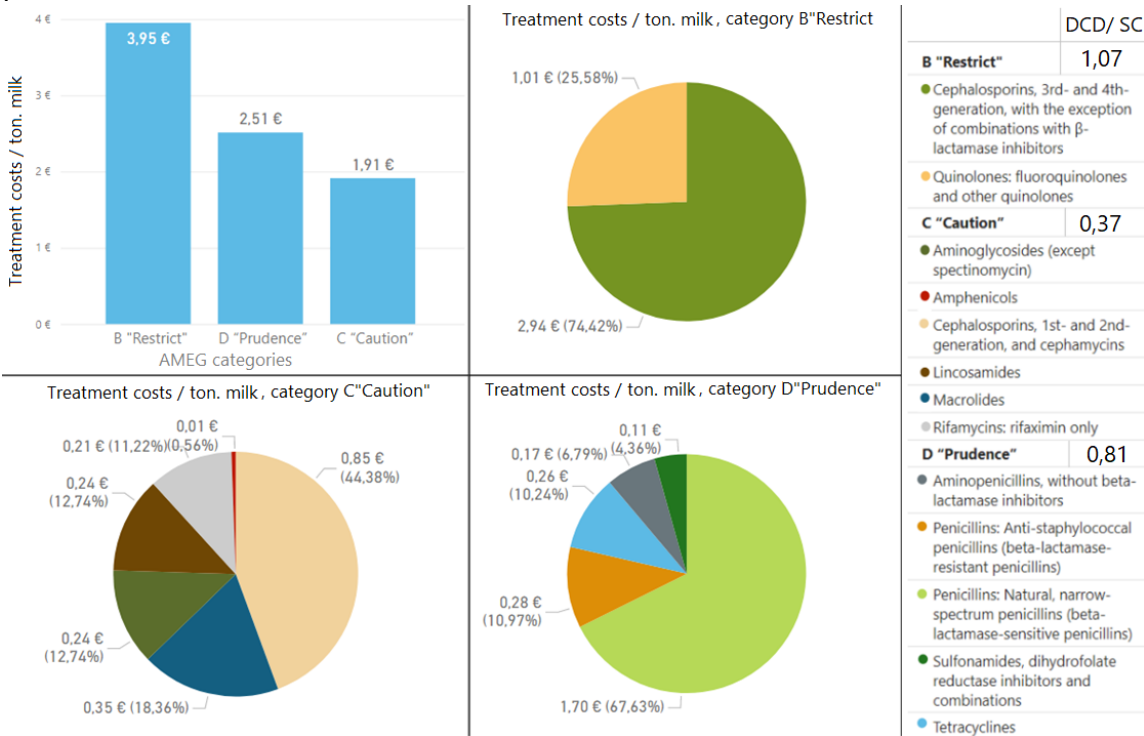


Figure C 8: Analysis of the average annual expenses of the last 3 years, in applied AM treatments, per ton of milk, distributed by the AMEG categories and within these, by the different groups of substances recognized by EMA.