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Revised ESVAC reflection paper on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals[1]

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1. Summary

In response to the request from the European Commission, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project is preparing the collection of data on the consumption of veterinary antimicrobials by animal species.

The main aim of this reflection paper is to discuss how to establish systems for the collection of reliable and standardised data on consumption of antimicrobial agents by animal species for the ESVAC database and to report the data taking into account the differences in dosing between the various antimicrobial agents as well as the animal population at risk for treatment.

It is acknowledged that the various Member States (MSs) have/will establish different systems for the collection of data at national level, including which data are collected. However, it is vital that the data provided to ESVAC are standardised in order to obtain harmonised data across the EU; this includes which data on consumption of antimicrobial agents are provided and furthermore which animal species, weight groups and production type should be included.

As a first step a protocol should be developed on how to collect data by species and a template on which data is to be provided to ESVAC. In order to gain experience, it is suggested to run a pilot project to test the protocol and the template in a limited number of MSs that are willing to participate and subsequently to collect and analyse these data by ESVAC.

Taking into account the limited resources available at the Agency and MSs, it is recommended that after the above mentioned pilot project, a baseline study collecting data for one species per year is performed with the following order: pigs, poultry and cattle.

Ideally, data should be collected continuously from e.g. farmers' or veterinarians' records in order to get the most accurate estimates. As this requires automated collection of standardised data that are electronically stored and can afterwards be electronically transferred to ESVAC this is at present feasible only in a few countries. For those that cannot collect such data, the suggested option is to collect data from e.g. farmers' or veterinarians' records by use of cross sectional studies or prospective longitudinal studies. The representativeness of the sample of the farms from which the data are collected is vital to assure accurate estimates and to allow extrapolation of the results to express estimates of the consumption by the actual species, weight group, and production type for the whole country and year.

Another option is to estimate the consumption of antimicrobial veterinary medicinal products by species by stratification of national sales of the products marketed for more than one species. However, it has to be noted that this method does not allow obtaining data by weight class (e.g. weaning pigs and finishers). Furthermore, this method is only applicable for those countries that obtain their overall sales data from marketing authorisation holders (MAHs) (about 7 MSs) as wholesalers do not collect such data.

The data to be provided to the ESVAC will be the prescribed or estimated amounts used, in weight of active ingredient, by country and year for each product (name and pharmaceutical form or administered route) per defined animal species and weight group/production type.

In order to correct for the differences in daily dose between the different antimicrobial agents, pharmaceutical forms and animal species, it is recommended to use defined daily dose animals (DDDA) for the analysis of the data provided to ESVAC (in tonnes) across the EU. A similar unit (DDD) has long been used as a technical unit of measurement in human medicine (e.g. ESAC–Net data) and by

implementing DDDA it would facilitate analysing the consumption data in the animal sector together with the consumption data in the human sector. Furthermore, it is suggested to use the defined course dose animal (DCDA) as an additional technical unit of measurement in order to also take into account differences in treatment duration. Since data will be collected and reported for a variety of animal weight classes, the DDDAs and the DCDAs for the various antimicrobial agents should be assigned by kg bodyweight and animal species; these values can then be calculated to express the values for the DDDAs and the DCDAs for the actual weight group and species, e.g. weaning pigs.

In principle all food producing species (e.g. poultry, pigs, cattle, other ruminants, horses, fish and rabbits) and companion animals should be included in the surveillance, but since collection of harmonised and valid data on consumption at animal species level is resource-demanding, at this stage some prioritisation of species is needed.

As a first priority ESVAC should assign European-wide DDDA and DCDA for the various antimicrobial agents and pharmaceutical forms for pigs, poultry (broilers and turkey) and cattle because this is also the prioritised animal species for the collection of consumption of antimicrobial agents.

Animal population data used as the denominator is suggested to be obtained from Eurostat (Eurostat, 2013) (slaughter and livestock) and TRAde Control and Expert System (TRACES, 2013) (animals transported for fattening or slaughter in another MS). For the reporting of data by species three different indicators will be used:

- Weight of active ingredient consumed per 1000 animals by species, weight group/production type per year (mg/1000 animals produced per year) by country.
- Number of DDDA consumed per 1000 animals by species, weight group/production type per year (number of DDDAs/1000 animals produced or livestock per year).
- Number of DCDA consumed per 1000 animals produced by species, weight group/production type per year (number of DCDAs/1000 animals produced or livestock per year).

In order to obtain harmonised and appropriate data across the MSs, it is suggested that it should clearly be legally defined which data should be recorded and stored in the records by the veterinarians and animal owners and that these data should be made available to the ESVAC national contact point in a standardised manner.

2. Introduction

All use of antimicrobial agents – in humans, animals and plants – promotes the selection and dissemination of antimicrobial resistant bacteria and resistance genes, as well as the emergence of new resistant bacteria through genetic mutations and gene movements. Therefore, use of antimicrobial agents in animals - for treatment and disease prevention - may give rise to treatment failures in veterinary medicine as well as being a potential food safety problem. Furthermore, it may cause contamination as resistant bacteria and resistance genes can spread from food animals or food derived thereof to humans through the food-chain, through direct contact from animals to animal keepers but also to the environment. As genetic mutations, gene selection and movements in bacteria are associated with the use of antimicrobial agents, efforts to contain antimicrobial resistance must focus on avoiding unnecessary use of antimicrobial agents and promoting their responsible use. Prevention and containment of antimicrobial resistance requires a holistic, multifaceted and inter-sectorial approach.

One of the key elements to establish a strategy for the containment of antimicrobial resistance in the animal sector is the availability of data on antimicrobial resistance and on the consumption of antimicrobial agents. Such data are important for risk profiling and risk assessment. Furthermore, at national/regional level such data are vital for assessing the effect of responsible use campaigns, implementation of targeted intervention measures such as legislative restrictions of use, setting targets for reduction of the consumption and implementation of animal health prevention measures. It is therefore important to establish a baseline against which the effectiveness of risk management measures can be evaluated. Knowing the consumption of antimicrobial agents may also support risk communication.

In recognition of this, the European Commission requested the European Medicines Agency in 2008 to develop a harmonised approach for the collection and reporting of data on antimicrobial veterinary medicinal products based on national sales figures and combined with estimations of consumption in at least the major groups of species (poultry, pigs, veal, other ruminants, pets and fish). The Commission, through the *Communication from the Commission to the European Parliament and the Council: Action plan against the rising threats from antimicrobial resistance* (European Commission, 2011) emphasised the importance of strengthening the surveillance systems on AMR and on consumption of antimicrobial agents in veterinary medicine by recommending: "*Promotion and extension of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) with the collaboration of EMA to obtain harmonised data on the usage per animal species and production categories as well as for different indications from all Member States"*.

In response to the request from the Commission (2008) the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project was launched by the Agency in September 2009. As a first step existing data from nine European countries (2005-2009) were collected and published in a harmonised manner (EMA/238630/2011) (ESVAC, 2011). Furthermore, ESVAC has implemented a system for the collection of harmonised and valid data on national sales figures of veterinary antimicrobial agents from 19 EU/EEA countries from 2010 detailed at package level and at least 5 more EU countries will provide 2011 data (EMA/88728/2012) (ESVAC, 2012). These data provide information on overall sales, sales by antimicrobial class and by pharmaceutical form. Based on information from the EU MSs and on experience from human medicine, the Agency foresees that within 2015 a baseline on the overall sales of veterinary antimicrobial agents are established for most of the MSs.

The next step of the ESVAC project is to develop a system for collecting harmonised and valid data on consumption of antimicrobial agents by animal species at EU-level and to develop technical unit(s) of measurement in order to take into account differences in dosing when reporting the consumption data.

It should be noted that information such as daily dose used and duration of treatment, group or individual treatment, curative, methaphylactic or prophylactic, indication or diagnosis, can also be very useful at national level but will not be collected from the MSs by the ESVAC project.

Data obtained through surveillance of antimicrobial consumption by animal species will increase the understanding of the development and occurrence of resistance and the impact of interventions. Such data can be used to estimate the number of animals exposed to a specific antimicrobial class within a given time period. Such estimates may either refer to all animals at risk, regardless of when the treatment with antimicrobial agents was initiated, or focus on animals that were given antimicrobial agents within a defined period. The collection of data is most meaningful when part of a continuous evaluation system, i.e. when the patterns are followed over time and comparison over e.g. consecutive livestock production cycles or companion animal years, is possible.

Studying and ultimately understanding the link between consumption of antimicrobial products and bacterial resistance in animals is of high importance to be able to provide advice on responsible use as well as enabling sustainable availability of efficacious antimicrobial agents. However, the detailed analysis and description of the link between animal species, antimicrobial class and bacterial level is usually complex and requires accurate and detailed data both on antimicrobial resistance as well as on antimicrobial consumption. Detailed data by species are needed to, e.g. determine whether differences in antimicrobial resistance amongst animal species can be related to differences in consumption patterns of antimicrobial agents. Data acquisition at species level is of high importance to fulfil all these purposes efficiently and accurately. It is also important to take the production stages into consideration because intervention measures, such as restriction or ban of use of particular antimicrobial classes, may concern only particular production stages. To achieve these objectives, it is crucial that the data are both accurate and representative.

This reflection paper is divided into three parts; the first part addresses current systems in place in Europe for the collection of data by species; the second part addresses the collection of data by species by describing how such data should be collected in order to quantify the overall consumption of antimicrobial agents by species, including weight group and production type, by country, taking into account harmonisation across the MSs, minimum level of accuracy and reproducibility, practical feasibility and sustainability, including cost, of the data collection process. The third part addresses which technical units of measurement, animal population data (denominator) and indicators are applicable for the analysis and reporting of the data to best suit the intended purpose.

3. Terms of reference

Terms of reference on collecting data per animal species:

Describe what data is needed on overall use of antimicrobial agents by species and country, including criteria for acceptance for ESVAC such as the comparability, minimum level of precision (e.g. confidence limit of estimate), reproducibility etc.

Describe and discuss the applicability of:

- *Cross-sectional or point prevalence studies (farm level, veterinary practices).*
- *Prospective longitudinal studies (farm level, veterinary practices).*
- *Models for repartition of totals sales based on e.g. Periodic Safety Update Report (PSUR) from pharmacovigilance or Marketing Authorisation Holder declarations.*

to obtain estimates of the needed data.

Emphasis should be placed on sustainability, possibilities for validation of the data and potential for improvement of the respective methods as well as comparability of results obtained with the different methods.

In principle all food producing species (e.g. poultry, pigs, cattle, other ruminants, horses, fish, and rabbits) and companion animals should be included in the surveillance, but since collection of harmonised and valid data on consumption at animal species level is resource-demanding, at this stage some prioritisation of species is needed.

Terms of reference on establishing technical units of measurement:

Develop a reflection paper suggesting which technical units of measurement could be applicable.

- *in order to standardise reporting and interpretation of the data on use of veterinary antimicrobial agents in the ESVAC project,*

- *taking into account the various purpose of the surveillance of the consumption of veterinary antimicrobial agents.*

The technical unit(s) of measurement selected should be applicable independently of the data source for the collection of data on use of antimicrobial agents by animal species; however, limitation for reporting should be addressed. It should be explored whether the technical unit(s) can be used for integrated analysis of resistance in animals and humans and consumption in human medicine.

A standardised terminology should be suggested.

4. Existing data collection and reporting of consumption of antimicrobial agents per animal species

4.1. Legal basis in the European Union for collecting data per animal species

Directive 2001/82/EC as amended, articles 11, 69 and 70 and Directive 96/23 as amended, article 10 requires veterinarians and animal owners to keep detailed records of veterinary medicinal products use. The legislation indicates:

"In particular, Member States may require the maintenance of a record giving at least the following information:
(a) Date;
(b) Name of the veterinary medicinal product;
(c) Quantity;
(d) Name and address of the supplier of the medicinal product;
(e) Identification of the animals treated."

4.2. Data collection systems currently in use in Europe

When comparing the different available data collection systems for consumption of veterinary antimicrobial agents a general distinction can be made between data collected at national level with the purpose to describe overall national sales patterns by antimicrobial class and pharmaceutical form across time on the one hand and data collected at farm (or practice) level to describe and quantify the consumption of antimicrobial agents in full detail at animal species level on the other hand. Table 1 shows the various types of data collection systems currently in use by MSs. These approaches have advantages and disadvantages and are used for different purposes. Hybrid data collection systems combining characteristics of national and farm level systems also exist.

Table 1. Overview of type of data on consumption of veterinary antimicrobial agents collected in the different European countries**.**

Country	National overall sales		Animal or herd level data collection system	
	MSs provided data to ESVAC for 2010	Additional MSs provided/to provide data to ESVAC for 2011	Continuous surveillance data	Single or multiple time studies/ research data
Austria	X			X
Belgium	X		X[1]	X
Bulgaria		X		
Czech Republic	X			
Cyprus		X		
Denmark	X		X	
Estonia	X			
Finland	X		X[1]	X
France	X			X
Germany		X		X
Hungary	X			
Iceland	X			
Ireland	X			
Italy	X[2]			X
Latvia	X			
Lithuania	X			
Netherlands	X		X	X
Norway	X		X[1]	X
Poland		X		
Portugal	X			
Slovakia		X		
Slovenia	X			
Spain	X			X
Sweden	X		X	
United Kingdom	X			X
Switzerland	X			X

[1]Under development; [2]Delivered but not in ESVAC 2010 report

4.2.1. Collection of overall national sales data

In many of the EU MSs, data on sales of veterinary antimicrobial agents have since 2010 (or earlier) been collected at package level from wholesalers or MAHs but also from feed mills and pharmacies. Based on these data, the total sales of veterinary antimicrobial agents, subdivided by different classes and formulations, are calculated and give thus an overview of the overall sales by veterinary antimicrobial classes in the MSs. Data from these sources are usually relatively easy to obtain since they are provided by a limited number of data providers and allow for analysis of trends on the overall sales of veterinary antimicrobial agents. A limitation of overall sales data is the lack of information they provide on the distribution of consumption in the different animal species, weight groups or

production type; however, overall national sales data, when obtained at package level are important for crosschecking the data collected by species.

4.2.2. Collection of consumption data by species

Several study types are used to collect data on the consumption of antimicrobial agents by species. An overview of the different types of studies applied and their characteristics is provided in Table 2.

Table 2. Different types of studies on consumption of antimicrobial agents by animal species applied and their characteristics.

	Stratification of overall national sales	Cross-sectional studies	Prospective studies	Continuous automated data collection
Definition	Stratification between species of sales data according to MAH or external sources (e.g. PSURs, studies)	Estimation of the consumption of antimicrobial agents in a sample of animals/flocks/ batches/herds treated on a given time/period	Herds/farms/ batches studied over time, with data being collected at multiple intervals	Data collected continuously from e.g. farmers or veterinarians records
Data collected	Sales repartition	Administrations of antimicrobial agents (date/weight group, nature, indication) from logbook, on-farm documents, etc.	Administrations of antimicrobial agents (date/weight group, nature, indication) from logbook, on-farm documents, etc.	Administrations, prescriptions or delivery of antimicrobial agents
Amount per unit (herd, flock, animal)	No	Yes	Yes	Yes
Daily dose, duration	Yes	Yes	Yes	Yes
Indication of use of antimicrobial agent	No	Depends on how the system is set up	Depends on how the system is set up	Depends on how the system is set up
Production type	No	Yes	Yes	Yes
Proportion of animals, flocks, batches treated	National statistics	Yes	Yes	Yes
Variability between herds, flocks, batches	No	Yes	Yes	Yes
Extrapolation - comparison with national	No	Yes if representative	Yes if representative	Yes

	Stratification of overall national sales	Cross-sectional studies	Prospective studies	Continuous automated data collection
sales				
Time trends	Yes	Through repeated surveys	Through repeated surveys	Yes
Comparison with resistance data	+/- (depends on specification of sales by species and antimicrobial class)	Yes	Yes	Yes
Representativeness	Not applicable (exhaustive)	+/-	+/-	Yes if mandatory
Precision Accuracy	+/- (depends on the MAHs declaration or external source and magnitude of unknown off-label use)	+/- (confidence interval can be calculated, depends on sample size achieved)	+/- (confidence interval can be calculated, depends on sample size achieved)	Yes if the system is exhaustive
Species exhaustive coverage	Yes	Possible by stratified sampling and extrapolation to national level	Possible by stratified sampling and extrapolation to national level	Yes
Sustainability	Yes	No (can be regularly repeated)	No (can be regularly repeated)	Yes
Feasibility	Depends on MAH data or external source availability	Time and labour consuming	Time and labour consuming	Depends on automated recording and connection with servers
Advantages	Major species are covered. Low cost	A large amount of detailed data can be acquired.	A large amount of detailed data can be acquired.	Permanent and continuous data collection.
Limitations	No information at the herd, flock level, weight group and on indications. Data difficult to obtain per production type	Representative-ness of the data, sample size and frequency can be impaired and limited by the workload required. Relatively low cost	Representative-ness of the data, sample size and frequency of realisation can be impaired and limited by the workload required. At relatively modest cost	Require specific infrastructure. Relatively costly in collecting and analysing

4.2.2.1. Collecting data on herd or animal level

Existing automated data collection systems

Automated data collection systems are already implemented in a few EU MSs (e.g. Denmark and the Netherlands) (Jensen et al., 2012) and are currently under development in some others (e.g. Belgium, Finland and Norway). These systems are characterised by using electronically stored data from

pharmacies and/or veterinary practices on administrations and prescriptions, respectively, and on data from farmers on administrations. They are usually based on the integration of two types of data that are linked to each other. The first type of data is used to calculate the consumption (numerator). It generally originates from farmers, veterinarians, pharmacies and feed mills or combinations of these sources, and, depending of the data source includes the data on the prescribed or administered antimicrobial agents such as product (name, form and strength), quantity used (number of packages). For prescription data this may also include information on dosage, treatment duration, number of treated animals and their body weight or weight group. The second type of data is used to calculate the population at risk of being treated (denominator) and involves farm data such as type and numbers of animals present as well as length of production cycles. These farm data are obtained from national databases and can be verified and refined with data entered by the farmer, or can completely be entered by the farmer.

Existing systems for manual collection of data

In many countries single or repeated data collections occur in the framework of scientific research (Table 2) where consumption of antimicrobial agents is described and quantified in detail in only a (limited) sample of herds. In these studies, the collected data are generally related to other herd characteristics or presence of resistance (Callens et al., 2012; Chauvin et al., 2005b; Dunlop et al., 1998; Pardon et al., 2012; Timmerman et al., 2006). To calculate the consumption, either treatments administered (product name, form and strength, daily dosage and treatment duration), number of treated animals, their body weight or antimicrobial agents acquired (product name, form and strength, number of packages, animal weight group) are collected for a defined period of time from e.g. farmer's log-book or bills. Population at risk for treatment present during the same period of time (denominator) is also collected in the same way. The advantages of this type of studies are the possibility of collecting detailed data on the consumption by animal species including specific production and weight groups as well as the indication for treatment (Chevance and Moulin, 2011). Also, the variation in the consumption and consumption patterns of antimicrobial agents between herds within the same animal species and weight group can be studied, and changes over time can be detected.

However, such studies are usually expensive and time consuming and as a result information is only obtained on a sample of the herds. Sampled herds are often selected based on the willingness of the farmer to cooperate and inherently include the risk of bias. As a result, extrapolation of the obtained data to the entire population should be done cautiously. In the ideal circumstances of a true random sample from all herds, the extrapolation towards the whole population is feasible.

4.2.3. Stratification of overall national sales data by species

In the ESVAC project, the data on overall sales are split into tablets that are almost solely used in pets (cats and dogs) and all other pharmaceuticals forms that are used mainly in food producing animals. For antimicrobial veterinary medicinal products marketed for food producing animals, further stratification of the overall sales data currently available in the ESVAC database is not possible as most products are authorized for several species.

However, MAHs may collect information on which species their products are used. Such data have been collected by France since 2009 requesting MAHs to provide an estimated distribution of the sales of antimicrobial agents by target species (Chevance A., 2009), enabling an estimation of the amounts of antimicrobial agents sold per species (Mevius et al., 1999). These estimates are regularly compared to results obtained through periodic on-farm studies to check for consistency. However, these data do

not include information on weight group and production type. Data on sales by species can be obtained from MAHs (PSUR) but these data are not always collected for a calendar year. Data on consumption by species can also be obtained from manufacturers of medicated feeds for those countries that have such production in place. However, again these data do not give information on sales by weight group or production type.

Since the wholesalers do not collect data on sales by species this approach is limited to those countries (about 7 MSs) obtaining their overall sales data from MAHs.

4.3. Existing technical units of measurement and indicators for reporting of consumption

4.3.1. Human medicine

In human medicine defined daily doses (DDD) have been assigned to antimicrobial agents at international level allowing for standardised reporting of the consumption of antimicrobial agents by classes, time periods and countries. The DDDs are assigned by the WHO International Working Group for Drug Statistics Methodology (WHO Collaborating Centre for Drug Statistics Methodology, 2011) and the unit is defined as follows: "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults".

In human medicine, the most used indicator to present the consumption of antimicrobial agents is the number of DDDs per inhabitant per day (DDDs/1000 inhabitants/day). This may provide a rough estimate of the proportion of the population treated daily with a particular antimicrobial agent or class. The number of DDDs sold is calculated from sales of each active ingredient and administration form. Since the DDD does not take into account differences in the treatment duration of the various antimicrobial agents this technical unit of measurement cannot be used to calculate the number of inhabitants treated with a course of an antimicrobial agent and thus the incidence of treatment cannot be calculated without making assumptions regarding average treatment duration.

4.3.2. Veterinary medicine

A similar standardised unit of measurement to the DDD has not yet been developed for veterinary antimicrobial agents either at global or regional level. However, some countries have already established national units of measurement in veterinary medicine but those are not harmonised across these countries – i.e. different units of measurement have been applied by different countries.

In addition to weight of active ingredient two groups of technical units of measurement have been identified:

Units taking into account the differences in the daily dose for the individual ingredients, e.g.:

- Defined daily dose for animal (DDDA): is a technical unit of measurement similar to DDD usually based on recommendation from the Summary of Product Characteristics (SPC) and in some cases based on information from the scientific literature. DDDA is assigned per kg animal in a given species for its main indication.
- Prescribed daily dose for animal (PDDA): is a unit estimated from prescription data and is mainly used when data is collected based upon prescriptions (rather than what is truly administered).
- Used daily dose for animal (UDDA): is the truly administered daily dose obtained by specific studies. UDDA directly reflects the truly administered daily dose in the observed animals.

Units taking into account the daily dose and the duration of treatment, e.g.:

- Defined course dose animal (DCDA): is a technical unit of measurement usually based on recommendations as described in summary of product characteristics and in some cases on information from or scientific literature.

4.4. Denominators applied in existing national data collection systems

To allow comparison between time periods and countries, the population at risk of being treated should be taken into account. Therefore the data have to be reported together with the population at risk. This allows correction for changes in the population according to time and to estimate the proportion of subpopulation treated in comparison to the total animal population at risk. It is crucial to establish a denominator that is stable in order to compare across time periods and countries.

Example of denominators:

- In national reports, some countries use the total body weight of the animal population slaughtered or present in the country (including or not companion animals) as the denominator when reporting overall sales
- The denominator used when expressing consumption data obtained at farm level is the number of animals present in a certain weight group or production type and the time present.

5. Collection and reporting of consumption of antimicrobial agents by species applicable across EU Member States in the ESVAC framework

In the framework of the ESVAC project it is important to define how and which data should be collected and which data is to be reported to obtain valid and reliable data in a standardised manner and to allow comparison between animal species, weight classes, production types and countries. This reflection paper describes how data can be collected from farmers and veterinarians.

In order to obtain harmonised and appropriate data across the MSs, it is suggested that it should be clearly defined in the legislation which data should be recorded and stored in the records by the veterinarians and animal owners and that these data should be made available to the ESVAC national contact point in a standardised manner.

5.1. Types of data collection applicable for monitoring consumption data by species

The required data to be provided to such a system can be collected in different manner depending on the specific MS situation and the systems already established.

5.1.1. Continuous and automated data-collection

Whenever a country has established a continuous and automated data collection system for data on antimicrobial consumption, this system may serve as the data source for ESVAC for those animal species that are included in the system and provided that the system collects the minimal required information as listed in Table 6. The characteristics of such an automated data collection system are described above (4.2.2.1). In brief they combine data on consumption (nominator) originating from the veterinarians through the digital record of a prescription or an administration / delivery or from

other distributors of medicines such as pharmacies or feed-mills, and on the number of animals in the weight group in question present at the herd (denominator). All data sheets are transferred electronically via interfaces between the personal computer or the electronic administration system from the veterinarian, feed mill, pharmacy or farmer and a central server. The whole system should make use of internet portals or internet based connections between peripheral computers and a central storage server.

Based on such a database a complete analysis of all farms becomes possible. As the data collected in such a system is already digitally stored in a database, exporting the data and providing it to ESVAC in the required format should be easily feasible. These automated data collection systems have the advantage that there is no need for additional specifically designed data collection efforts. Moreover, if the system is collecting census data originating from all herds rather than from a representative selection of herds, then the risk of selection bias is totally removed. Given the major advantages these systems of continuous electronic data collection are highly advised to all MS for the future. Yet, it need to be emphasized that given the difference between countries on topics such as the use of medicated feed, the legislation regarding the administration and delivery (selling) of drugs by veterinarians, every country needs to develop tailor made systems that fits to the country specific situation regarding the distribution system for antimicrobial agents, including distribution of medicated feed.

5.1.2. Cross-sectional studies

Cross-sectional studies on the consumption of antimicrobial agents can be based on a single data collection event per study unit (e.g. herd) during which retrospective information on the consumption of veterinary antimicrobial agents is collected for a given time period (e.g. past production cycle) such as lactation or the last batch(es) reared. The data can be collected from e.g. records kept at the farm by use of a questionnaire which can be self-administered by the farmer or preferentially by a trained person that fills in the questionnaire together with the farmer during a herd visit. Based on the collected information, estimates of the amount of antimicrobial agents used by species and weight group, including production type if applicable, and year can be calculated (see example of calculations in section 5.5).

The accuracy of the collected data in such a system strongly depends on the knowledge of the animal keeper on the performed treatments or the availability of herd documentation of such treatments. If the information is only based on the farmers' recollection of the use of the products it is prone to recall bias. Especially individual treatments of rare diseases or infrequently applied treatments are likely to be overlooked. In animal species for which individual treatments contribute to the major part of the consumption of antimicrobial agents (e.g. cattle), collecting this type of data may be problematic. In contrast to individual treatments, group treatments are generally well known by the farmer because they are performed regularly and are expected to be more easily reproduced from recollection. In animal species such as poultry and, to a lesser extent, veal calves and pigs where group treatments are applied regularly for the major proportion of the consumption of antimicrobial agents (Callens et al., 2012), the number of unrecorded treatments is likely to account for negligible amounts of antimicrobial agents consumed. When available, on-farm documents mandatory to keep, such as health-records (Chauvin et al., 2005b), invoices (Chauvin et al., 2005a; Mevius et al., 2009) prescriptions or treatment log books can be consulted to collect the necessary information; these are a very valuable source of information that should be used for this purpose. An advantage of this type of studies is that they are relatively easy to organize and conduct and that with one herd visit a significant amount of data can be collected.

5.1.3. Prospective longitudinal studies

In a prospective longitudinal study herds are monitored or investigated repeatedly over a certain time period (e.g. production cycle). During this period all treatments with antimicrobial products are recorded in predesigned sheets or electronic data recording systems either by the farmer or by the veterinarian. Alternatively the data may also originate from veterinary prescriptions or delivery data from a specific period of time, provided that they contain sufficiently detailed information to assign the products to a specific species and weight group. The advantage of this study type is that data can be collected in a more complete and standardised manner and by doing so the problem of recall bias is avoided. On the other hand compliance with voluntary record keeping may be difficult to maintain. In continuous data collection systems, data sources are generally veterinarians or pharmacies records that are electronically transmitted to a central database.

Unless the data are collected continuously, prospective longitudinal studies should usually be conducted in a selected number of study farms that are representative for the study region in order to minimise the workload.

5.2. Representativeness, accuracy, validation and repetition over time

Automated data collection systems as well as cross-sectional or prospective longitudinal studies, when properly conducted, will provide accurate and detailed data regarding number of animals treated, dosages, treatment durations as well as the weight groups of the treated animals. These data allow for estimation of consumption of veterinary antimicrobial agents by species, weight group and production type by country and year that can be provided to ESVAC.

As described above, nationwide automated data collection systems are optimal from the point of view of representativeness.

To enhance representativeness in the cross-sectional and prospective longitudinal studies, herds should ideally be selected on a random basis and in sufficiently large number to provide reasonably accurate estimates of the consumption. Sometimes stratified sampling may be more efficient, but the sample has to be weighted back to the source population to obtain unbiased estimates of average consumption. Whenever selection criteria such as herd size, geographical location and willingness to cooperate are applied they may impair the representativeness and reduce the external validity of the collected data; therefore these selection criteria should be avoided as much as possible. Especially in prospective longitudinal studies this might be problematic as farm selection is generally made on a voluntary basis and based on willingness to participate.

Unless automated data collection systems are implemented, data will have to be collected manually, which is time and labour consuming. If manual data entry by the farmer or veterinarian is requested, the quality of the data (accuracy, completeness) has to be evaluated very carefully. The confidentiality of the individual farm data should be assured.

In all types of data collection, whether they are collected manually or electronically, a thorough data validation step is of great importance. Data on consumption of antimicrobial agents are highly prone to data errors such as simple wrong data entries or the use of wrong units (e.g., grams instead of milligrams). The data need to be cross-checked against other available data such as sales data - e.g. for specific products and antimicrobial classes.

Independently of the study type selected, in order to evaluate changes over time, the study needs to be repeated regularly on farms selected by using the same selection criteria.

5.3. Animal species for which data should be collected

The priority list of animal species to be included in the data collection should be based on the relative size of the species populations, general information on occurrence of infection diseases and on "heavy users" among the species, weight groups and production categories. Based on this and since the data on consumption are among others intended for integrated analysis with data on antimicrobial resistance, the priority should be given to species currently addressed in the EFSA reports on occurrence of antimicrobial resistance (EFSA/ECDC, 2012) being cattle *(bovine animals)*, pigs and poultry (broilers and turkey*)*.

Consumption data from other food producing species, including horses, and companion animals are also important. Yet, generally there are good reasons to start with the three mentioned species and once these systems are implemented gradually enlarge the scope with the other relevant animal species. In some countries food producing animals other than cattle, pigs and poultry are of importance, such as rabbits in France and farmed fish in Norway. In such countries it is highly advised to include these species into the national data collection systems on consumption of antimicrobial agents from the beginning. The animal categories to be included in ESVAC are shown in Table 4.

In order to obtain comparable data across times and MSs and to analyse and report the data by use of DDDA and DCDA the weight group has to be defined for all the animal categories for which the data are to be provided to ESVAC (Table 4). Data on average weight at treatment is available only for a few MSs (ESVAC, 2013) and these weights varies considerably; therefore standard weight classes have been assigned for the various categories and this is unavoidably a compromise.

For the three selected animal species and production category (Table 4) the age group to be included in the studies have to be defined in order to obtain comparable data across times and MSs.

Table 4. Animal species and weight groups/production type for which data should be provided to ESVAC

Species	Weight group/Production type	Weight group
Pigs	Suckling piglets	4 kg
	Weaners	12kg
	Sows/boars	220 kg
	Finishers	50 kg
Cattle	Veal calves	80 kg
	Dairy cattle	500 kg
	Meat cattle (beef)	500 kg
Poultry	Broilers	1 kg
	Turkeys	6 kg

5.4. Groups of antimicrobial agents to be included in the monitoring

In principle data on prescribing and administration of all pharmaceutical forms and medicated feed should be collected; however, some pharmaceutical forms (e.g. dermatological preparations, those for eye and ear and cutaneous spray) are suggested to be excluded as the consumption is low and because it is difficult to establish the DDDA and DCDA for such products. Furthermore, these forms are not included in the data on consumption of human antimicrobial agents (ESAC-Net). In the context of the ESVAC project it is recommended that the antimicrobial groups as described in the ATCvet system

(Anatomical, therapeutic and chemical veterinary classification) detailed in Table 5 should be reported by the MSs.

Table 5. Groups of veterinary antimicrobial agents to be included in the monitoring by animal species as applicable (ATCvet = Anatomical, therapeutic and chemical veterinary classification)

Groups of antimicrobial agents	ATCvet codes
Antimicrobial agents for intestinal use	QA07AA; QA07AB
Antimicrobial agents for intrauterine use	QG01AA; QG01AE; QG01BA; QG01BE QG51AA; QG51AG
Antimicrobial agents for systemic use	QJ01
Antimicrobial agents for intramammary use	QJ51
Antimicrobial agents used as antiparasitic agents	QP51AG

5.5. Data to be collected. Extrapolation from farm-level data to national-level data

For the ESVAC project the data should be provided as the true or estimated overall consumption, in tonnes, for the actual antimicrobial agent by species and weight groups. These data will be analysed and reported by use of DDDA and DCDA values harmonised across EU and the appropriate denominator. In contrast to data obtained through continuous data collection with 100% coverage of the data, e.g. administered or prescribed, throughout the whole year, data collected from a representative number of farms or veterinarians have to be extrapolated in order to provide estimates on sales for the actual species and weight group.

5.5.1. Data to be collected

The minimum set of variables to be collected/recorded for each administration, acquired packages of antimicrobial agents or volume of medicated feed delivered in order to be able to calculate the consumption by the defined weight groups under surveillance is shown in Table 6. Type I data are usually obtained from prescriptions or records or by interview while Type II data are obtained from e.g. invoices and pharmacies.

Table 6. Minimum set of variables to be collected/recorded on each prescription (veterinarians), administered treatment (farm data) or packages acquired (invoices and pharmacies) of antimicrobial agents for each treatment in the sampled farm

Item	Data to collect on consumption of antimicrobial agents on each farm	Type I data from e.g. prescriptions, records or interview Treatments administered	Type II data from e.g. invoices and pharmacies Packages of antimicrobial agents acquired
1	Number of days of observation period	X	X
2	Medicinal product (name /form/strength/active ingredient/ prodrug) if	X	X

Item	Data to collect on consumption of antimicrobial agents on each farm	Type I data from e.g. prescriptions, records or interview Treatments administered	Type II data from e.g. invoices and pharmacies Packages of antimicrobial agents acquired
	applicable[1]		
3	Content of each active ingredient in package[2]		X
4	Form or route of administration	X	X
5	Number of packages bought and/or distributed		X
	Volume of medicated feed bought of delivered		
6	Animal species and weight group/production type	X	X
7	Number of animals administered/prescribed for	X	
8	Animals weight at treatment	X	
9	Daily dose of each active ingredient in mg/kg body weight	X	
10	Number of days treated for each treatment/prescribed treatment	X	
11	Total number of animals per species and weight group/production type in sampled farm	X	X

[1]See comment on prodrug in Table 7 on variables to be provided to ESVAC; [2]Usually not collected at farm level or prescriptions but variable needed to calculate consumption;

In addition, information on the total number of animals produced or livestock per species for the year of data collection is required. Preferably data from Eurostat (slaughtered and livestock) and TRACES (net import or export of animals for fastening and slaughter in another MS) should be used but if the deviation from national statistics is more than 5% national statistics could be used.

Information such as daily dose used and duration of treatment, group or individual treatment, curative, methaphylactic or prophylactic, indication or diagnosis, can also be very useful at national level but will not be collected from the MSs by the ESVAC project.

5.5.2. Example on extrapolation to national level

For data based on nation-wide continuous data collection systems extrapolation to national level is not applicable since it aims at 100% data coverage. When data are collected from a representative sample of farms or veterinarians these will have to be extrapolated in order to provide an estimate on the national consumption of veterinary antimicrobial agents by animal species and weight group. The following stepwise approach can be applied (see Table 6 and Figure 1).

- Step 1. Calculation of amounts used for each record/event (numbers refers to item numbers in Table 6)

  Data Type I (7)x(8)x(9)x(10) = prescribed/administered amount in weight of active ingredient (a)

  Data Type II (3)x(5) = prescribed/administered amount in weight of active ingredient (a)

- Step 2. Calculation of total consumption (weight of active ingredient) in sampled farms

  For both data type I and II

  A = $a_1 + a_2 + a_3$…..

- Step 3. Calculation of ratio of number of animals in sampled farms/total number of animals in country

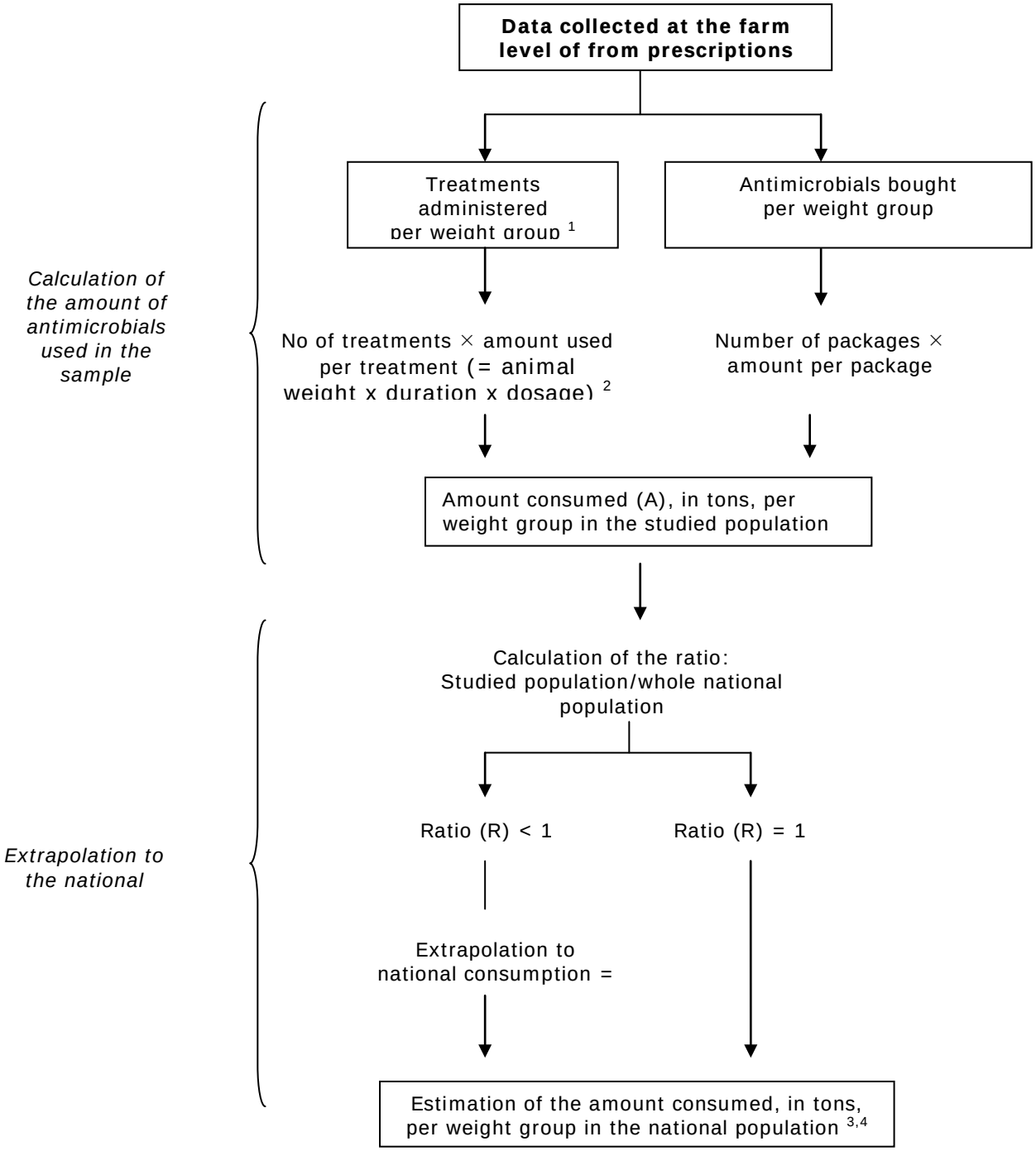
  R = Σ(11)/total number of animals per species and weight group including production stage, if applicable, at national level a year

- Step 4. Calculation of consumption per species and weight group/production stage by country

  Estimated consumption = (A) x (1/R)

If the farm sample studied is issued from a stratified random process, calculations are to be performed per stratum first and extrapolations made at the stratum level are secondly summed to express the national consumption. Technical explanations on extrapolation from a sample of farms or veterinarians to national level data should be given in the protocol tested through a pilot.

Figure 1. Calculation and extrapolation of data on consumption of veterinary antimicrobial agents collected from a representative sample of farms and veterinarians covering a representative sample of farms or by continuous data collection from all farms in the reporting year.



[1] Treatments could be recorded from prospective or cross-sectional studies.
[2] Depending on the study type and data recorded, parameters used could be exact dosages and duration administered/prescribed or recommended (according to SPC) ones, animal weight treated can be an estimated.
[3] Confidence intervals can also be estimated from simple or stratified samples.
[4] Guidance for extrapolation should be given in the protocol

5.6. Data to be provided to ESVAC

For the ESVAC data base the data should be provided as overall annual consumption, in tonnes, for each antimicrobial agent/product for each species and weight class, including production type if applicable (Table 7) by year.

Table 7. List of variables to be provided to ESVAC for the estimated annual consumption of each veterinary antimicrobial product by animal species and weight group, including production type if applicable.

Variable	Description of variable	Comments	Variable format
COUNTRY	ISO Code	To identify place of collected sales data	CHARACTER
YEAR		To identify time period for collected sales data	NUMBER
DATA SOURCE	Farmers (F); Veterinarians (V); Pharmacies (P); Stratified data (S)		
DATA COLLECTION METHOD	Continuous data collection all farms (C-TOTAL); Continuous data collection selection farms (C); Prospective longitudinal study in sample of herds (P); Cross-sectional study in sample of herds (CS); Stratification of overall national sales (S)		CHARACTER
SPECIES	Cattle (CA); Pig (PIG); Poultry (POU)	To identify species concerned	CHARACTER
ANIMAL SPECIES AND WEIGHT GROUP/PRODUCTION TYPETYPE	**type** Sows/boars/suckling piglets/weaners/finishers Veal calves/dairy cattle/meat cattle Broilers/turkeys	To identify weight group and production type	CHARACTER
NUMBER OF ANIMALS ADMINISTERED/PRESCRIBED THE ANTIMIROBIAL AGENT			NUMBER
TOTAL NUMBER OF ANIMALS PRESENT IN FARMS SAMPLED		To identify proportion of animals treated when data represent a sample	NUMBER
NAME	**Medicinal Product Name** (in national language)		CHARACTER
INGR	**Active Ingredient Name** (ATCvet name)	In order to analyze and report data by antimicrobial class DDDA/DCDA	CHARACTER
ATCvet CODE		To allow cross checking the quality of the data	CHARACTER

Variable	Description of variable	Comments	Variable format
PRODRUG[1]		When dosing is based on the strength of the prodrug - in order to calculate number of DDDA/DCDA consumed	CHARACTER
FORM	**Pharmaceutical Form** Bolus (BOLUS), Injection (INJ), Injection long acting (INJ-LA), Intramammary (INTRAMAM), Intramammary dry cow treatment (INTRAMAM-DC), Oral solution individual treatment (ORAL SOLU-IND), Oral solution herd treatment (ORAL SOLU-HERD), Oral pasta (ORAL PASTA), Oral powder individual treatment (ORAL POWD-IND), Oral powder herd treatment (ORAL POWD-HERD), Premix (PREMIX), Tablets (TABL), Intrauterine preparation (INTRAUT)	In order to have harmonized terms for forms. Important to avoid misinterpretation of pharmaceutical form if given in other language than English	CHARACTER
TONS USED	Total tons consumed of Active Ingredient per year		NUMBER

[1] ESVAC will calculate consumed tons of prodrug from consumed active ingredient by use of standardised conversion factor for prodrug

The data to be provided have to be standardised/harmonised across EU in order to obtain comparable data. As an initial step a data providing form (in Excel) should be developed by the ESVAC project and be subjected to a pilot study before implemented in the Member States.

5.7. Technical units of measurement and indicators for reporting of consumption

In this paper the number of “technical units of measurement” consumed refers to the amount of the antimicrobial agent consumed (numerator), whereas an “indicator” refers to the number of technical units of measurements consumed normalized by the animal population at risk of being treated in a defined period.

Usually, data obtained through monitoring of antimicrobial agents are reported by antimicrobial class. A technical unit to report consumption of veterinary antimicrobial agents aggregated by classes for each animal species and weight group could be weight of active ingredient (e.g. tonnes). However, this summarizes the consumption of different antimicrobial agents with different daily doses and treatment duration. Therefore, the species data on consumption (numerator) of an antimicrobial agent and pharmaceutical form should also be presented taking into account factors such as the daily dose administered and the duration of the treatment for each veterinary antimicrobial product. This also allows comparison of consumption between species and weight groups, route of administration and antimicrobial classes across time and countries. It facilitates analysis of the data together with consumption data from the human sector. Furthermore, when reporting the data in terms of exposure to antimicrobial classes animal demographics have to be taken into account.

Data obtained through monitoring of consumption of veterinary antimicrobial agents may be expressed by application of different indicators. Since the population at risk in the various countries or regions

under monitoring differ substantially this should be taken into account when reporting of the consumption data.

Assessment of the selection pressure is aiming to characterize the level of exposure and how long the microbial flora is exposed to a specific antimicrobial agent. To describe this, the following information is needed:

- Which antimicrobial agents were administered?
- Which daily dose was given and how long did they receive the veterinary antimicrobial medicinal product?
- How many animals were administered the veterinary antimicrobial medicinal product?
- How many animals were at risk of receiving the veterinary antimicrobial medicinal product?

5.7.1. Technical units of measurement and indicators applicable for reporting by species data in the ESVAC project

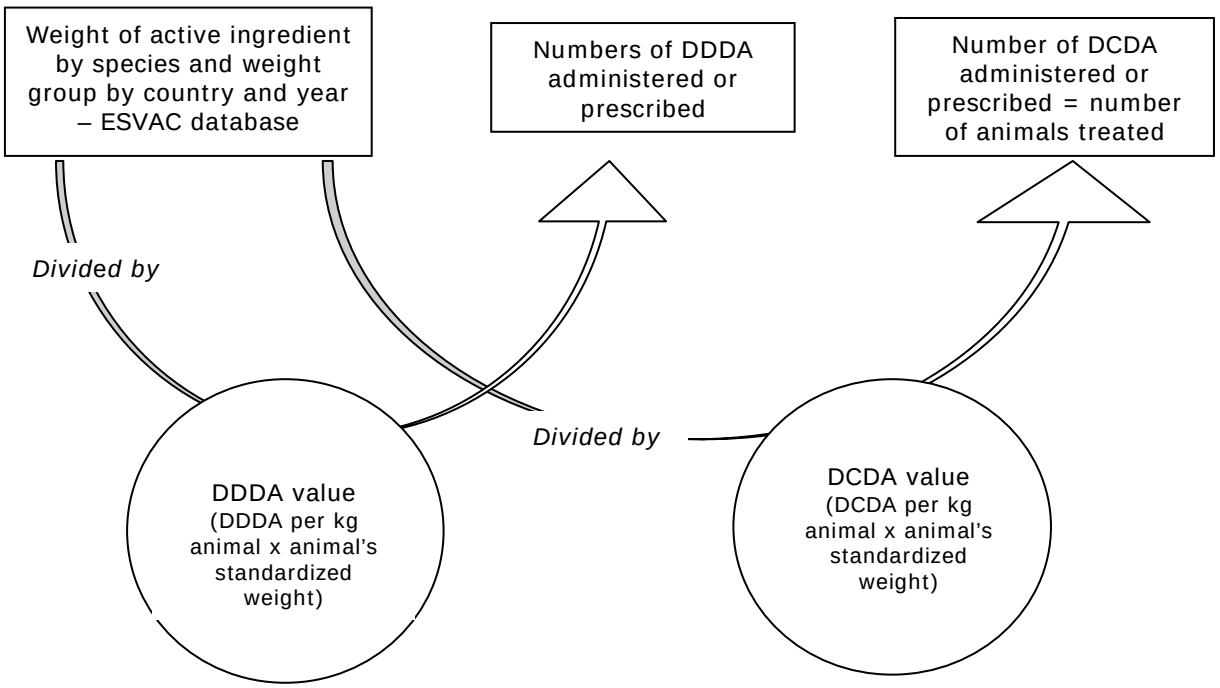
Since used daily dose animal (UDDA) is a unit to express the real dose administered to each herd/individual it would be in conflict with the nature of this unit to standardise it across EU. This is also the case for prescribed daily dose animal (PDDA). To report data on the consumption of veterinary antimicrobial agents in EU in a harmonised manner by species, it is suggested to apply defined daily dose animal (DDDA) and defined course dose (DCDA) in the ESVAC project. Since data from summary of product characteristics (SPC) are easily available for all Member States and are a transparent system SPCs should be used as the basis for establishing the same DDDA and DCDA for similar products – i.e. active ingredient and formulation. Furthermore, this allows for harmonization of the reporting of ESVAC data with human medicine (ESAC-Net).

In the ESVAC project, the indicators for consumption of veterinary antimicrobial agents should be numbers of DDDA or DCDA consumed by weight group divided by the number of animals species produced or as livestock (e.g. dairy cattle) by country and year.

The consumption given as numbers of DDDA and DCDA per year is obtained by dividing the estimated consumption per year (in weight of active substance) by the assigned DDDA and DCDA value (Figure 2). This also gives an estimate of the number of animals treated.

The number of DDDAs per year for a certain weight group expresses the number of standardized daily doses consumed for an animal species of a specific weight group in a year by country. The number of DCDAs per year for a certain weight group expresses the number of standardized courses dose (full treatments with a standardised treatment dose and duration) consumed for an animal species and weight class in a year and country (Figure 2).

Figure 2. Analysis of the data on consumption of veterinary antimicrobial agents by animal species and weight group/production type by country and year by ESVAC



5.8. Denominators applicable for the ESVAC project by species data

For consumption data by species, the number of animals, either produced or livestock (e.g. dairy cattle) by species and weight group by country and year, should be used as the denominator. If data from Eurostat and if applicable also TRACES are available, these should be used, else the denominator data have to be based on national statistics.

5.9. Indicators for reporting the data

In the ESVAC project, the indicators for consumption of veterinary antimicrobial agents should be numbers of DDDA or DCDA consumed/ 1000 animals produced or as livestock for each weight group/production type by country and year. Furthermore, it is suggested to use mg active ingredient consumed/1000 animals produced or as livestock for each weight group/production type per year and country as one of the indicators to express the consumption data of veterinary antimicrobial agents by class.

6. Assignment of DDDA and DCDA values

SPC data on dose and duration of treatment for the species decided to be prioritised in the ESVAC project – i.e. cattle, pigs and poultry (broilers, turkey), should be collected in a standardised manner from MSs. These data should be used for the assignment of common values for the DDDA and DCDA for the various antimicrobial agents and formulations across EU. It has to be noted that DDDAs and DCDAs based upon SPC assume that products are usually administered according to the SPC despite being known from the field that this is not always the case (Callens et al., 2012).

DDDA and DCDA should be assigned by kg animal species in order to enable calculation of number of for each animal species and weight group included in the ESVAC data.

Detailed protocol on how to standardise the assignment of DDDA and DCDA should be developed following the consultation of this reflection paper.

6.1. Products with one active ingredient

For veterinary antimicrobial products containing only one active ingredient a similar approach as that used for human antimicrobial products can be applied.

6.2. Combination products of antimicrobial agents

For human drugs the DDDs assigned for combination products are based on the main active ingredient with some exceptions counting the combination as one daily dose, regardless of the number of active ingredients included in the combination. However, the DDD were not developed to express the selection pressure but to measure development in treatment with medicines. Furthermore, the consumption in DDDs in human medicine is commonly reported with the corresponding ATC code which enables the identification on combination products.

When using data consumption of antimicrobials agents for the purpose of risk management or to follow trends in prescriptions, antimicrobial combinations need to be considered. However, in the context of antimicrobial resistance it is difficult to state that one active ingredient is the main component of a combination of antimicrobial agents. Also this will not allow for estimating the consumption of the other antimicrobial agents that can be more important in terms of selection pressure than the most important therapeutic ingredient. For intramammary and intrauterine preparations this can be solved by using the daily number of applicators and numbers of applicators per treatment as the DDDA and DCDA, respectively.

When using data on consumption of antimicrobials agents for the purpose of risk assessment or for the purpose of comparison with antimicrobial resistance data it is important to consider individual antimicrobial agents in such a product. The selection pressure to be evaluated is related to the use of a specific antimicrobial agent or class (whether or not it is administered in combination).

The problem with identifying the various components in combination products can be overcome in a database by linking ATCvet codes of the single active ingredients to the ATCvet combination code.

6.3. Long acting products

Long acting products administered by parenteral route are commonly used in veterinary medicine; for such products only one dose is typically administered.

For these products, the doses do not adequately represent the duration of action and therefore the selection pressure.

As a part of assignment of DDDAs for these long acting products a harmonised duration of action should be taken into account.

7. Recommendations applicable for the ESVAC project

Collecting data by animal species

The recommended methods are ranked in order of preference:

- Continuous automated data collection including all prescriptions/administrations/delivery in a country per year.
- Cross-sectional or prospective longitudinal studies in a representative number of farms in order to estimate national consumption, in tonnes of active ingredient, by species, weight group and production type, if applicable.
- Stratification by species based on overall sales data.

Technical units of measurement

The proposed technical units of measurement for reporting of the data in ESVAC by animal species are

- Weight of active ingredient
- DDDA
- DCDA

DDDA and DCDC should be assigned for the species suggested to be prioritised in the ESVAC project – i.e. pigs, poultry (broilers and turkey) and cattle.

Indicators

The proposed indicators to be used for reporting of the consumption of antimicrobial agents by species the proposed indicators are:

- Weight of active ingredient consumed by weight group/1000 animals produced or livestock/year.
- Number of DDDA or DCDA consumed by weight group/1000 animals produced or livestock/year.

8. Suggestions for implementation

As a first step a protocol on how to collect data by species and a template on data to be provided to ESVAC should be developed. In order to gain experience, it is suggested to run a pilot project to test the protocol and the template in a limited number of MSs that are willing to participate and to collect and analyse these data by ESVAC.

Taking into account the limited resources available at the Agency and the MSs, it is recommended that following the pilot project, a baseline study collecting data for one species per year is performed with the following order: pig, poultry and cattle.

In parallel it is suggested to develop guidelines on how to assign DDDA and DCDA values for pigs, poultry and cattle across EU and to subsequently establish EU DDDA and DCDA values for these species.

9. List of abbreviations

DCDA	Defined Course Dose Animal
DDDA	Defined Daily Dose Animal
ESAC-Net	European Surveillance of Antimicrobial Consumption
EMA	European Medicines Agency
MAH	Marketing Authorisation Holder
MS	Member State
OIE	World Organisation for Animal Health
PSUR	Periodic Safety Update Report
SPC	Summary of Product Characteristics
WHO	World Health Organisation

10. Definition of terms

Daily dose: The dose given daily of an antimicrobial agent.

Duration of treatment: The number of days of an antimicrobial treatment.

Defined Daily Dose animals (DDDA): The assumed average maintenance dose per day per kg body weight for the main indication in a specified species.

Defined Course Dose animals (DCDA): The assumed average maintenance dose per day per kg body weight for the main indication in a specified species (DDDA) multiplied with the assumed duration of treatment.

Indicator: Express consumption using both the numerator and the denominator. Applied by WHO (http://apps.who.int/medicinedocs/pdf/s4876e/s4876e.pdf).

Technical unit of measurement: Unit to express consumption of antimicrobial agents. Applied by WHO as a term for units correcting for differences in doses or doses and length of treatment of various medicines in drug utilization studies (http://www.whocc.no/atc_ddd_methodology/history/).

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