Monitoring Antimicrobial Drug Usage in Animals: Methods and Applications

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ABSTRACT Monitoring antimicrobial drug usage in animals at the national and international levels is important for identification and tracking if and how often quantities are used. This information can be used for many purposes, including raising awareness, comparing use patterns across countries, identifying trends over time, integrating with antimicrobial resistance data, conducting risk assessment, and evaluating the effectiveness of measures to manage antimicrobial usage. The goal of this article is to describe how monitoring systems for antimicrobial drug usage in animals are set up and conducted, using examples from specific countries as well as international efforts. Several key figures and variables are used to describe and evaluate antimicrobial consumption in animals, including the amount in kilograms of active ingredient, standardized units (e.g., number of defined daily dose animals, DDDAs) and number of treatments (e.g., number of used daily doses, UDDA). Data can be collected from a variety of sources including pharmaceutical sales, pharmacy dispensing, veterinary prescriptions, and farm records. In many countries, data analysis and reporting at the national level provide statistics on overall quantities used in animals, in some cases by animal species. Antimicrobial consumption data should be contrasted to the respective animal population, for example, the weight of different categories of livestock and slaughtered animals. Several countries have established antimicrobial usage monitoring systems. Most report overall sales data, but some provide usage data to the levels of animal species and production type. At the international level, several organizations (e.g., European Union, World Organization for Animal Health, World Health Organization) have initiatives to support the development of antimicrobial consumption data collection and reporting. However, these initiatives are ongoing and so far lack harmonization, which will be the biggest challenge for the future.

INTRODUCTION

To show relationships between the use of antimicrobial agents and the selection and spread of bacteria with resistance characteristics, it is necessary to have access to information about prescription and consumption of antimicrobial drugs in the population to be studied. This requires suitable methods, but also the establishment of figures which adequately describe the use of antimicrobial agents on the level of the enterprise, the veterinarian or the farmer individually, as well as in a cumulative form for countries, regions, or special production forms. The overarching goal of this article, therefore, is to describe the way monitoring systems for antimicrobial drug usage in animals are set up.

Each country applies different systems, and therefore, different calculations for the analysis of data on antimicrobial use are available. As a consequence, the results

are not always directly comparable. This article provides an overview of the national and international terminology and variables, summarizes definitions, and identifies those variables that are most suitable for particular objectives.

KEY FIGURES AND VARIABLES TO DESCRIBE ANTIMICROBIAL DRUG USAGE IN ANIMALS

The key figures and variables that are used to describe and evaluate antimicrobial consumption in animals can be divided into categories. Here, the terms and definitions describing antimicrobial consumption are divided into two main categories, following van Rennings et al. ([1]). The first group defines variables based on quantity. These are terms describing the amount of an active substance administered in grams or kilograms per animal or animal group or per kilogram of body weight of the target animal species. The second group includes variables based on application, defining, for example, the frequency of treatment of a single animal or an animal group with an active substance or drug. To give a better overview of these figures, the glossary (see the Appendix) comprises all given terms.

Key Figures and Variables Based on Quantity

As the first step in characterizing antimicrobial use, we describe variables and measures related to quantity in the broadest sense, in which "dose" and "dosage" are the basic terms.

The dose is the amount of an active substance administered to a single animal in a single application, whereas the dosage corresponds to the amount of active substance applied per kilogram of bodyweight. Based on these terms, the following additional values are defined.

Amount

When analyzing antimicrobial consumption, it is reasonable to first calculate the overall amount applied in the target animal population for every active substance. The (overall) amount is the sum of all doses of one active substance administered to all animals in the target population (e.g., herd, population of a defined region or a country) in kilograms or tons.

The amount is the variable used most often to describe consumption ([2]), but it does not give detailed information regarding the specific treatment ([3], [4]). In particular, drugs applied in large doses, such as tetracyclines, may be overrated in their importance, while drugs applied in small doses may be underrated. Because particularly potent substances such as fluoroquinolones are applied in smaller doses, the presentation of the amount alone might lead to an unintended underrating of their importance ([5], [6]).

However, taking a look at the amount provides a first overview of the consumption of active substances in different farms, regions, or countries ([2]). The amount does not give any information about the number or category of animals treated or the route or indication for treatment. Therefore, the interpretation of this variable is limited, and a comparison between animal species and categories is not possible.

Defined daily dose animal (DDDA)

This variable is widely used and was first described as "animal daily dose" in the Danish National Monitoring System for Consumption of Veterinary Drugs (VETSTAT) ([7]). The term DDDA was recommended by the European Medicines Agency ([8]). The DDDA describes the average recommended daily dose of an active substance per animal and should be defined for every target animal species, age group, and productive livestock group. The definition is established using specialized information (from drugs containing the same active substance) and expert opinions regarding the main indication for administration of the active substance. It should correspond to the daily dose, which is the assumed average maintenance dose per day for a drug used for a certain indication and animal species. The dose is defined for animals with a standardized body weight that differs depending on the literature source. It has to be kept in mind that the DDDA is a theoretical variable representing an equivalent of application.

The definitions for standardizing the dose are borrowed from the defined daily dose (DDD), which is used in human medicine. According to the WHO, the DDD is "the assumed average maintenance dose per day for a drug used for its main indication in adults" ([9]). In human medicine, the DDD as a technical measure includes the consumption of all drugs independently from formulation and compound of the single drug, its package size, or from sales data. The DDD is used to compare drug consumption between regions and time periods. It can be applied individually or for trans-boundary comparisons ([5], [10]).

Some authors use a different definition for DDDA, associating it with the overall amount and the population, thus describing the number of applied doses per animal or person. This can cause confusion and lead to misunderstanding. Therefore, to clearly distinguish between the DDDA and the variable describing the number of applied doses per animal, for the latter, the term

"nDDDA$_{population}$" is recommended (see paragraph on key figures and variables based on application).

Given the lack in veterinary medicine of a variable comparable to the DDD in human medicine, VETSTAT defined the DDDA for every active substance, every animal species, and every age group (11). The DDDA can also be used for comparison of drug consumption between animal groups, veterinary practices, or regions, and it allows for division into animal species, production type, method of application, or indication. In Scandinavia, the DDDA is used regularly to describe amounts of drug consumption.

The Dutch and Belgian counterpart of the DDDA is the DDD (12, 13). Here, it is defined as the daily dose of active substance per animal. In the Dutch monitoring system, there are only data available on the overall amount of active substances used, and no information on the number of treated animals. Using the above-mentioned definition of DDD, the daily dose per animal can be estimated as a mean value per year, i.e., how many kilograms of body weight (kilograms of animal) could be treated with the used amount of active substance by applying the DDD (14).

It is important to note that the DDDA is also an equivalent of application and that it has to be adapted in case of use under practical conditions and known indications. Therefore, calculations based on this measure can only yield estimated values, because the actual dose applied does not always correspond to the recommended one. In the glossary, this is expressed by adding "est" for "estimated" to the term in question.

In addition, it has to be noted that in combination preparations, the DDDA always corresponds exclusively with the main active substance (15), and other active substances of the drug are not considered.

Used daily dose (UDD)

Because the DDDA is a recommended or theoretical variable, Timmerman et al. introduced the UDD (15). This variable was first established in Belgium and displays the actually administered daily dose of one active substance per animal. The UDD can be calculated only from an indicated amount if the number of treated animals and the days of treatment are recorded. The UDD can be estimated for a whole livestock population as an average value per animal by dividing the amount of active substance administered per treatment by the product of the animal count and days of treatment. If the same active substance is used several times in different dosages on a farm, an average dose can be calculated for this farm (15). The UDD is particularly useful for evaluating antimicrobial consumption on the farm level.

Because the DDDA is calculated with an average treatment scenario that may not always reflect the actual field situation, deviations from the UDD are expected. The ratio of UDD and DDDA or UDD and DDD, respectively, described by Timmerman et al. (15) and Persoons et al. (13), compares the actually administered amount with the recommended dosage. By definition, this ratio is not an indicator to establish the correctness of the dosage. Nevertheless, the range of this ratio from 0.8 to 1.25 may be assumed as plausible.

Prescribed daily dose (PDD)

In addition to the DDD and the actually administered UDD, the PDD is the third measure of dose adopted from human medicine, where it is used to describe prescription patterns and offers insights into the habits of individual physicians (10). Because compliance is crucial in the administration of drugs, the ratio between PDD and DDD (physician compliance) and between UDD and PDD (patient compliance) are important measures of consumption.

Arnold et al. (5) used the concept of PDD to evaluate the amount of drug consumption in veterinary medicine. They described PDD as the amount of active substance per prescription divided by the product of average weight, number of treated animals, and days of treatment (in combination preparations every active substance is observed separately). This value has a particular importance in veterinary practice, because depending on the diagnosis of the veterinarian, the active substance can also be dosed individually. In contrast to human medicine (practitioner-patient relation), the definition in veterinary medicine has an additional dimension (veterinarian-farmer-animal relation) and therefore may be used in different settings.

Key Figures and Variables Based on the Course of Application

As a second category, variables indicating whether and how often an antimicrobial drug was used are described here.

Treatment and number of treatments

In the following, as the term is used in Europe, a treatment is the handing over of a drug from the veterinarian to the farmer for its application to the population under study for a defined number of days. The treatment does not consider the number of active substances in the preparation or the number of treatment days. The number of

treatments within a certain time period may represent the number of diseases treated in the population within this time period and is therefore an indicator of animal health in the population.

Single application, sum of single applications, and number of UDDs

The single application can be seen as a basic variable to describe antimicrobial use. It defines the treatment of one animal with one active substance on one day and allows for comparison of applications independently from the prescribed dosage (16). If a drug is applied more often than once a day, this is still seen as only a single application. Hence, if the drug is applied by feed or water, the whole daily ration for one animal represents one single application.

The sum of single applications in a population under study for a given time period is the product of the number of animals treated, the number of days of treatment, and the number of active substances applied. Based on expert consultations at the European Medicines Agency (EMA), this is also described as the number of used daily doses (nUDD) (17).

Regarding preparations with a long-lasting effect, the single application is a variable that requires particular interpretation, because the single application (correlated with duration of effect of one day) is small in comparison to the effect (longer than one day). In such cases, the number of days of treatment may be adjusted with the help of a preparation-specific factor. To evaluate drug consumption, it is more suitable to choose the number of single applications than the amount of used drug in kilograms, because the latter depends on the dosage.

Treatment frequency (TF) and nUDD$_{population}$

The TF indicates for how many days, on average, an animal in the study population is treated within the observation period, e.g., how many single applications were administered to one animal on average (6, 18). Formally, it can also be described as the number of administered UDDs per animal in the study population.

The TF corresponds to cumulative incidence in epidemiology (19). It is independent from the applied amounts and considers the days when an active substance is used. Within the calculation, any observation period can be considered. As a classical ratio, the denominator, i.e., the definition of the population at risk, is of basic importance. Here, several definitions can be used, e.g., the number of places in a farm or the average number of animals present, also taking into account the time present (20).

TF is well suited for comparisons of antimicrobial consumption in the sense of a benchmarking. Because it takes into account the number of active substances in the drug and the days of treatment, it is a value to describe the possibilities in the study population to select resistant bacteria.

Treatment incidence/treatment density

The treatment incidence (TI) described by Timmerman et al. (15) also quantifies the frequency of treatments. Following Persoons et al. (13), the TI is calculated by dividing the overall amount of used active substance by the product of UDDs per kilogram, the overall weight of the treated animals, and the length of the production cycle. Thus, the TI corresponds with the quotient of the product of the number of treated animals and days of treatment, on the one hand, and the product of animals on the farm and the duration of the production cycle on the other hand.

This is an equivalent to the time-at-risk approach in epidemiology, which takes the dynamics within a population into account, and may therefore be denoted as treatment density (21). By definition, the TI is a rate; i.e., it measures consumption per time-at-risk. This time-at-risk displays the sum of all times during which animals were really kept on the farm. When calculating the TI, idle times and periods with different occupancy in a population are included completely. Therefore, the TI shows a more precise picture of the situation within a population under study. But it is important to note that to facilitate the calculation of the TI, much more detailed data have to be collected at the farm level.

If all animals in a population are treated, as is commonly the case for poultry, the TI describes the portion of a production cycle when treatment with the observed active substance takes place.

Sales Data

Sales data are available in many countries and have been widely used since their first application in drug utilization studies (22). These data were first used by the pharmaceutical industry and are still in use for economic purposes. Sales data can be easily obtained from wholesalers, pharmacies, and feed mills, but contain only information on the amount of a product sold (e.g., in tons or kilograms or number of packages) and do not say anything about the species and the number of animals treated or the duration of treatment. Sales data therefore are not appropriate for evaluation of veterinary medical aspects or the relation to antimicrobial resistance. Therefore, it is not recommended to use sales data to

evaluate antimicrobial consumption if the purpose is to analyze the impact on selection of antimicrobial resistance. However, as a general measure, sales data give an overview of the consumption within a population under study.

Nevertheless, sales data can also be used for an overall estimation of the amount of antimicrobial agents that have been consumed in livestock husbandry or in the veterinary sector. In this case, data should always be contrasted to the respective animal population. Because animals differ considerably in their weight, it is not useful to take the number of animals as the value for the animal population. Therefore, standard population figures such as livestock units are usually used (see Glossary).

In Europe, the amounts of veterinary antimicrobial agents sold in different countries are, among others, linked to the animal demographics in each country. The annual sales figures in each country are divided by the estimated weight at treatment of livestock and of slaughtered animals in the corresponding year, taking into account the import and export of animals for fattening or slaughter in another member state. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project introduced a population correction unit (PCU) and expresses sales data in milligrams of active substance/PCU. The PCU is used as the term for the estimated weight, and it is purely a technical unit of measurement, used only to estimate sales corrected by the animal population in individual countries and across countries. In the ESVAC report, 1 PCU = 1 kg of different categories of livestock and slaughtered animals. The data sources used and the methodology for the calculation of PCU are described comprehensively in Appendix 2 of the first report of the EMA (23).

To compare antimicrobial consumption in humans and animals, some countries estimate the biomass of the national human population and use the sales data in milligrams of active substance/kilograms of human and animal biomass/PCU, respectively (for example, the United Kingdom [24] and Sweden [25]).

MONITORING OF ANTIMICROBIAL DRUG USAGE IN FOOD-PRODUCING ANIMALS: SELECTED EXAMPLES
Monitoring Systems in the European Union
Since 2006, the use of antimicrobial substances as growth promoters has been prohibited in the European Union by Regulation (EC) No 1831/2003 on additives for use in animal nutrition (26). The consumption of antimicrobial drugs in livestock is monitored in most European coun-

tries, and some countries apply certain measures if the usage of antimicrobial drugs seems inappropriate. Unfortunately, monitoring and surveillance of antimicrobial consumption is not harmonized throughout the European region and not even within the European Union, hampering the comparison of data between countries.

The ESVAC project aims at harmonizing the monitoring of antimicrobial consumption in animals on the European Union level (see passages on "Sales data" and "The ESVAC project"). Some European countries, such as Austria (27), Denmark (28), the Netherlands (29), Norway (30), and Sweden (25), established active monitoring programs years ago, which have been continuously carried out and extended to date. Other countries just started recently. At least information on sales of antimicrobial drugs is collected in most countries, but some countries record more data, enabling in-depth analysis, for example, of target animal species. The variables used and calculated differ in the various systems. Results are usually published in annual reports, mostly together with results from antimicrobial resistance monitoring.

In addition to that, there are also private monitoring systems, such as quality assurance systems, which communicate their data only to the participating farmers and/or veterinarians.

Belgium
The Belgian Veterinary Surveillance of Antibacterial Consumption consortium, founded under the wings of the Belgian Antimicrobial Policy Coordinating Committee, set up surveillance of veterinary antimicrobial consumption in Belgium and started to publish the national consumption report for data from the year 2007. Sales data for all products in all pharmaceutical formulations registered on the Belgian market that contain antimicrobial agents are aggregated. These data are collected from all wholesaler-distributors registered for supplying veterinarians and pharmacies in Belgium with veterinary medicines during the observation period. Reporting is done electronically and is consistent with the Anatomical Therapeutic Chemical (ATC) system for classification of veterinary medicines according to the WHO Collaborating Centre for Drug Statistics Methodology (Norwegian Institute of Public Health). In Belgium, antimicrobial agents are only available by prescription or by delivery from a veterinarian. Information on animal feed containing antimicrobial agents sold to Belgian farms is collected from feed mills, using the same Web-based system. All additional product information in accordance with the ESVAC recommendations is added to the reported data in a database, and

this allows the number of packages sold to be converted to the amount of active substance used. Annual consumption figures with biomass as a yearly adjusted denominator are calculated according to the methodology described by Grave et al. ([31](#)). The animal species included are based on the vast majority of the biomass present (estimated to be 92% of the total biomass present in Belgium). This does not include other animal species such as horses, rabbits, small ruminants, and companion animals.

Currently in Belgium, both private (AB register) and governmental (SANITEL MED) herd-level data collection systems are set up that allow for reporting of usage data at the animal species level. For antibacterial premixes, data on animal species are known, and only pigs, poultry, and rabbits receive medicated feed.

Animal population data are taken from Eurostat, and biomass (in kilograms) is calculated, according to the method of Grave et al. ([31](#)), as the sum of the amount of beef, pork, and poultry meat produced that year in Belgium plus the number of dairy cattle present in Belgium times 500 kg of metabolic weight per head ([32](#)). The Center of Expertise on Antimicrobial Consumption and Resistance in Animals was recently founded in Belgium and became operational on January 2012 (http://www.amcra.be).

Denmark

The Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP) has monitored antimicrobial resistance and consumption of antimicrobial agents in food animals and in humans in Denmark since 1995. At the beginning, DANMAP published trends on the consumption of antimicrobial agents in production animals based on reports from pharmaceutical companies on their annual sales of veterinary antimicrobial agents to wholesalers without any information on target species ([33](#)).

In 2000, VETSTAT was implemented as a second-generation monitoring system based on information on antimicrobial agent consumption at the herd level. Data are entered electronically, and monthly reporting is mandatory for pigs, poultry, cattle, sheep, goats, fish, and mink. Information on pets can be provided on a voluntary basis. Reporters are pharmacies, veterinarians, and feed mills. Information is collected on the reporter, receiver of the antimicrobial agents (e.g., Central Husbandry Register number), ID number of the veterinarian, product number according to the ATCvet list, amount used, animal species, age group, and diagnosis. The overall amount of antimicrobial agent is measured in kilograms of active compound. The VETSTAT system was developed and is maintained by a private contractor ([33](#)). From 2003, a national system of animal DDDs for each age group and species determined by VETSTAT was used to measure antimicrobial consumption. The usage was further standardized, taking into account the number of animals in the target population ([7](#)).

In 2012, DANMAP introduced new metrics to follow trends in antimicrobial consumption, to ensure the robustness of the analyses over time, and to facilitate comparisons between animal species, as well as comparisons between the veterinary and human sectors by using defined or prescribed animal daily doses. In the context of DANMAP, comparison is based on dosages to keep in focus the newer, potent antimicrobial agents such as fluoroquinolones and cephalosporins that are critically important in the treatment of human infections. Furthermore, the biomass of the live population is used as the denominator to allow for comparisons of selection pressure between animal populations. This follows the concept of nDDDA per biomass, which may be converted to the TF (see Glossary).

In 2010, the Danish Veterinary and Food Administration established the so-called Yellow Card Initiative, a benchmarking system for farmers which was designed to target the highest consumers of antimicrobial agents in pig production. Within this system, thresholds for use of antimicrobial agents were formulated for pig and cattle herds. The threshold is given in Animal Daily Dose per 100 animals per day. When the consumption of antimicrobial agents in a herd exceeds the threshold, the number of annual advisory inspections by a veterinary practitioner increases, and the farmer gets a warning, i.e. a yellow card.

In July 2016, the Differentiated Yellow Card was implemented to also promote responsible use of antimicrobial agents. All classes of antimicrobial agents are assigned a factor, resulting into a so-called Weighted Animal Daily Dose (Weighted ADD). Antimicrobial agents critically important for human medicine, e.g. fluoroquinolones, are assigned factor 10, while simple penicillin is assigned factor 1. Thus, the use of antimicrobial agents with a higher factor accelerates exceeding the threshold for the particular herd (https://www.foede varestyrelsen.dk/english/Animal/AnimalHealth/Pages /The-Yellow-Card-Initiative-on-Antibiotics.aspx).

France

France has been collecting data on the annual sales of veterinary antimicrobial agents since 1999, and the French Agency for Food Environmental and Occupa-

tional Health Safety (ANSES) publishes the results in annual reports. Data are collected in collaboration with the French Union for the Veterinary Medicinal Product and Reagent Industry, based on annual reporting of antimicrobial sales. These companies also provide an estimated breakdown by target species of the drugs sold. The information collected from the companies covers 100% of authorized drugs. Antimicrobial sales data are compared with other sources of information such as reported turnover from the companies marketing veterinary drugs and data from epidemiological surveys of antimicrobial consumption.

To assess animal exposure to antimicrobial agents, ANSES considers the dosage and duration of administration as well as changes in the animal population over time. As usual in sales data systems, DDDAs per PCU are calculated as well as overall sales figures. By relating the estimates of body weight treated to the mass of the animal population potentially treated with antimicrobial agents, ANSES obtains an estimate of the so-called level of exposure (animal level of exposure to antimicrobial agents, ALEA). This indicator is related to the percentage of animals treated relative to the total population. Data are analyzed for livestock animals, domestic carnivores, horses, and rabbits. In the report, additional indicators are calculated (34) (www.anses.fr).

Germany

In Germany, several systems exist to monitor antimicrobial consumption in livestock animals. Two monitoring systems are official and compulsory, and these include sales data on the one hand and use of antimicrobial agents data on the other hand. Reliable data on total antimicrobial sales were collected for the first time in 2011, based on a legal requirement for the pharmaceutical industry and wholesalers to report total sales data to the German Institute for Medical Documentation and Information (35). Reporting includes information on the annual total sales of veterinary drugs (in tons) containing antimicrobial agents as active substances.

In Germany, veterinarians have the right to dispense and are allowed to obtain drugs from wholesalers and pharmaceutical companies, to deliver drugs to animal owners, and to compound and keep drugs. This activity has to be documented formally by means of the German Medicinal Products Act (in German, Arzneimittelgesetz). Obligatory monitoring of antimicrobial usage was adopted by the 16th amendment of the German Medicinal Products Act in 2014, and reporting started in mid-2014 (36). The variable used to describe antimicrobial consumption is TF. Veterinarians are required to report treatments of animals and the delivery of veterinary drugs to animal owners on specific forms (treatment and delivery forms). With these forms, each application and dispensing of medicine to food-producing animals by the veterinarian is documented for farms with a given minimum number of animals. The farmer has to ensure that twice-a-year reporting is done on time and may designate the veterinarian as the reporter. Reporting is done electronically using the central system HI-Tier (www.hi-tier.de), and data are collected at the farm level on fattening animals (poultry, cattle, and pigs).

The aim of this system is to reduce the usage of antimicrobial agents in fattening animals, and thus the system is used to benchmark the farms. Twice a year, the Federal Office of Consumer Protection and Food Safety calculates two index numbers of the entire distribution of individual farm therapy frequencies, namely, the median and the 75% percentile (www.bvl.bund.de). These index numbers are used to benchmark the farms, and certain measures have to be undertaken if index number 1 or 2 is exceeded. Information on antimicrobial consumption is also summarized in the German report on antimicrobial consumption and antimicrobial resistance in human and veterinary medicine in Germany, GERMAP (37).

The private food quality assurance system, QS Qualität und Sicherheit GmbH, covers all trade levels of meat and meat products from farms to retailers (38). Part of this system involves antimicrobial monitoring for QS members following rules similar to those laid down by legislation and by scientific studies, and with which benchmarking of the participating farms is implemented. The antimicrobial monitoring system has been in place since 2012, and the farmer is responsible for the reporting. The system includes fattening pigs and poultry, and the treatment therapy is registered quarterly. Results are communicated to QS members only.

As a scientific project, the Veterinary Consumption of Antimicrobial Agents (VetCAb) program has collected data from the whole of Germany since 2007 (6, 39). Within this system, participating farmers and veterinarians report the antimicrobial classes used, and this information is collected through the treatment and delivery forms as well.

The Netherlands

The Monitoring of Antimicrobial Resistance and Antimicrobial Usage in Animals in the Netherlands (MARAN) covers two systems of data collection. First, the federation of the Dutch veterinary pharmaceutical industry (FIDIN)

reports annually the overall sales of antimicrobial agents. Second, the Wageningen Economic Research Institute of the Wageningen University and Research (formerly the Landbouw-Economisch Instituut, LEI Wageningen UR) monitors the antimicrobial use per animal species. This was first conducted on a stratified sample of farms, but then the large animal production sectors implemented centralized registration systems, monitoring the use on all farms.

Monitoring of annual sales data of all antimicrobial veterinary medicinal products at the level of packages sold in the Netherlands started in 1998. FIDIN reports the total amount of antimicrobial agents (active ingredient in kilograms) sold in the Netherlands at the level of pharmacotherapeutic groups. These data are estimated to cover about 98% of all sales in the Netherlands. Actual consumption can differ from the amounts sold, as a result of stockpiling and cross-border use. The figures give information about the total sales for all animals, not per individual animal species, and are supplemented with antimicrobial veterinary medicinal product data of non-FIDIN members. Since 2011, data have been calculated according to the SDa (Netherlands Veterinary Medicines Authority) method for all antimicrobial veterinary medicinal products, which means only the active base substance mass (excluding the mass of salts and esters) is calculated, including topical applications such as ointments, eye drops, and sprays.

Monitoring of purchased antimicrobial agents on farms in the Farm Accountancy Data Network (FADN) by LEI Wageningen UR started in 2004. In the Netherlands, veterinary antimicrobial agents are sold to the end users (farmers) almost exclusively by veterinarians. Antimicrobial veterinary medicinal product consumption data derived from veterinarians' invoices from farms in the FADN and additional veal calf farmers were used for this survey. In the beginning, the FADN contained a stratified sample of around 1,500 agricultural and horticultural farms in the Netherlands that is representative of Dutch livestock farming ([40]). On these farms, economic data and key technical figures, all animal medicine data and veterinary services are recorded. This provides information about the true exposure of farm animals to antimicrobial agents and gives insight into the underlying factors that could explain changes in antimicrobial use.

Sales data are converted to the number of defined doses per animal year. Applied antimicrobial veterinary medicinal products are converted to treated animal mass × days by national conversion factors (determined by the nationally authorized dosages and pharmacokinetics of the drug to compensate for duration of action) and

related to the animal mass present on a farm. Results are calculated for a period of a year and expressed as the number of days an average animal is treated in that year on that particular farm ($DDDA_F$), which is the TF for one year based on DDDA conversion.

The SDa was established to promote responsible use of veterinary prescription drugs in Dutch animal husbandry. Since 2011, the SDa has prepared husbandry-related consumption reports using consumption data from all farms in the largest sectors of food production animals: pigs, veal calves, broilers, cattle (starting in 2012), and turkeys (starting in 2013). As of 2016, antimicrobial use is also monitored in meat rabbits. Another variable, $DDDA_{NAT}$, is calculated, that represents the days of treatment within one year for an average animal of a certain sector of the whole country. While the calculation method for treated body mass (numerator) is the same, totaled for all farms per sector, the denominator is represented by the whole sector nationwide ([29], [41]).

Since 2012, the DDDAF is also used to benchmark farms. According to the use of antimicrobials, farms are assigned to a Target, Signaling or Action Zone. The threshold for the Action Zone was first defined as the 75. percentile of the antimicrobial use of the year 2011, splitted into type of farm and sector, and farms exceeding this threshold must take measures to reduce the use immediately. The thresholds are re-evaluated annually since then. A benchmarking method for veterinarians was introduced in March of 2014 and was based on prescription data recorded in 2012. The system aims at documenting prescription patterns of veterinary practitioners and works with the same three benchmark zones, using the Veterinary Benchmark Indicator (VBI) ([41]).

Sweden

In Sweden, statistics on total sales of antimicrobial agents for use in animals have been available since 1980. Data are compiled through the Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM) system by the National Veterinary Institute. To analyze trends by animal species, information from different sources is used to supplement the sales data.

Overall sales are expressed as kilograms of active substance and are analyzed by the animal population. For antimicrobial agents sold for group treatment in pigs, data are expressed in milligrams of active substance/kilograms of slaughtered pig. In poultry, data are analyzed by calculating milligrams of active compound/kilograms of slaughtered chicken. Raw data on sales

are obtained from the Swedish eHealth Agency and represent the sales of products containing antimicrobial agents sold by pharmacies. When products are dispensed for animals, the animal species as given on the prescription is recorded and reported to the Swedish eHealth Agency jointly with the sales, unless the product is sold for use in a veterinary practice (on requisition). For the overall statistics, the data include all products with antimicrobial agents as active substances marketed in Sweden and sold for use in terrestrial animals in certain ATCvet classes. Conclusions on antimicrobial consumption in different animal species or different ways of administration are drawn solely from the sold drugs (e.g., drugs for use in certain animal species or certain ways of administration). In dogs, data are recorded as sold packages. Växa Sweden publishes a yearly report related to the livestock organizations' work to improve animal health and welfare in dairy cows (42). For statistics on the incidence of antimicrobial treatments of dairy cows enrolled in the Swedish milk recording scheme, data are retrieved from a database of veterinarian-reported disease events and treatments (43). Here, antimicrobial use is expressed in treatments per 100 completed/interrupted lactations for systemic treatment of mastitis and in absolute numbers of dose applicators sold for drying off (intramammary use). To compare the consumption of antimicrobial agents in humans and in animals, data are expressed in milligrams per estimated kilograms of biomass, where the animal body mass is estimated by applying the method for calculation of PCU (23). This unit roughly corresponds to the total biomass of major animal populations, excluding dogs and cats.

A review of data from 1980 to 2000 is presented in the report "SVARM 2000." SVARM and Swedres-SVARM reports can be found on the website of the Swedish National Veterinary Institute SVA (http://www.sva.se/en/antibiotics/svarm-reports) (25).

United Kingdom

In the United Kingdom, antimicrobial sales data include antimicrobial agents for systemic, intramammary, and oral use by certain ATCvet code groups of antibiotics. Total annual sales of all veterinary medicines are supplied by marketing authorization holders to the Veterinary Medicines Directorate, where they are collated. From these data, the total weight in tonnes of each antimicrobial active substance is calculated. Data on antimicrobial consumption is estimated in relation to the animal population (livestock, companion animals, and horses) using the PCU as described by ESVAC (24) (www.gov.uk).

Monitoring Systems in non-European Countries

Several non-European countries, including Australia, Canada, Japan, New Zealand and the United States, collect and publish overall veterinary antimicrobial sales data (44–48). Holders of marketing authorizations for veterinary antimicrobial agents are required by law to provide annual quantities (kilograms) sold in each of these countries. In Australia, registrants are requested to estimate proportions used in different species, and Canada, New Zealand, and the United States have declared intentions to follow suit (48, 49). Annual quantities of antimicrobial agents sold are typically reported by drug class, route of administration and, where possible, animal species. Australia, Japan, and New Zealand also provide basic information on numbers of major food animal species in their reports (4- to 5-year intervals) (44, 46, 47). Canadian annual antimicrobial consumption data are adjusted by PCU as developed by ESVAC (45).

Canada and the United States also collect and publish selected species-specific data. The Canadian Integrated Program for Antimicrobial Resistance conducts active surveillance of antimicrobial use on sentinel broiler chicken and grower-finisher pig farms in Canada (45). The numbers of farms included are proportional to the production volume in each participating province. Participation is voluntary, and the farms are recruited by practicing veterinarians, who collect the information on antimicrobial use, herd demographics, and animal health via questionnaires administered to the farmers. For broiler chickens, collected antimicrobial information pertains to sampled flocks, including antimicrobial exposure at the hatchery and farm levels through injection, water, and feed administration. For pigs, antimicrobial use information is limited to the grower-finisher stage of production. Antimicrobial use data are presented qualitatively (broiler chickens, pigs) as antimicrobial exposure by route of administration and quantitatively (pigs, feed administration only) as kilograms of active ingredient per 1,000 pig-days at risk to standardize the number of pigs and duration of treatment (45).

The U.S. Department of Agriculture collects farm-level information on antimicrobial use practices through periodic surveys (50). The National Animal Health Monitoring System conducts nationally representative livestock, poultry, and aquaculture commodity studies that involve voluntary administration of questionnaires to farmers. Major commodities are surveyed at 5- to 7-year intervals, and information on farm management and policies related to antimicrobial use is collected,

including reasons for use, numbers of animals treated, antimicrobial class, and route of administration. The Agricultural Resource Management Survey is a survey of farmers that focuses on farm finances but also periodically collects some information on antimicrobial use (2004 and 2009 for pigs and 2006 and 2011 for broilers) (50).

International Monitoring Activities
The ESVAC Project
The ESVAC project has become a worldwide leader collecting data on veterinary antimicrobial consumption at the supra-national level.

Background
In 2008, the European Commission requested the EMA to develop a harmonized approach for the collection and reporting of data on the use of antimicrobial agents in animals from European Union and European Economic Area member states, based on national sales figures in at least major species groups such as poultry, pigs, veal, other ruminants, pets, and fish. This also included the identification of already existing data and surveillance systems on the national level in the member states. To ensure an integrated approach, the EMA was asked to also consult other European Union agencies such as European Food Safety Authority (EFSA) and European Centre for Disease Prevention and Control (ECDC), as well as the European Reference Laboratory on Antimicrobial Resistance. Following this request, the ESVAC project started its first activities in 2009.

Reporting
The number of countries reporting data to the ESVAC project increased from 9 in 2009 to 30 in 2015. These countries account for approximately 95% of the food-producing animal population in the region. Reporting takes place on a voluntary basis so far, but a new regulation is envisaged that will make reporting mandatory (51). Currently, the ESVAC project is in a pilot stage, during which harmonized overall sales data are collected and analyzed. The main indicator used to express sales is milligrams of active substance sold per PCU (mg/PCU).

Since 2015, data have been collected through a Web-based system in accordance with the ESVAC data collection protocol (52). Reporting includes product information, information on the animal species, packages sold, information on the active substance (using the ATCvet codes), and the calculation of tons of active substances sold during the year. Additional information is collected using a questionnaire (e.g., source of infor-

mation, sales or purchase data, version of ATCvet classification used). The groups of veterinary antimicrobial agents to be included in ESVAC are also defined.

Some data are collected not directly from the member states, but from other European Union agencies. The data source for numbers and biomass of food-producing animals slaughtered, as well as data on livestock food-producing animals is Eurostat, the Statistical Office of the European Union. In cases for which data are not available in Eurostat (e.g., for rabbits), national statistics are applied. For horses (a food-producing species according to European Union legislation), national statistics provided by the ESVAC national representatives are used.

Animals exported for fattening or slaughter in another member state are likely to have been treated with antimicrobial agents in the country of origin, and therefore it is important to correct this for the major species (cattle, pigs, poultry, and sheep). Such data are therefore obtained from the Trade Control and Expert System (TRACES) of the European Union, because these are based on health certificates, which are obligatory for all animals passing any border. The ESVAC data collection form and protocol as well as annual reports and other ESVAC documents are published on the ESVAC website (www.ema.europa.eu).

ESVAC Strategy 2016 to 2020
The EMA has developed an ESVAC strategy for 2016 to 2020. The strategy aims to enable the analysis of European-level trends in antimicrobial usage per animal species using data that is standardized between countries. To reach this goal, the harmonization of data collection and analysis methodologies is crucial. The EMA will provide guidance to member states on the collection of data per species, with a specific focus on the three major food-producing species: pigs, cattle, and broilers (poultry) (53).

The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)
AGISAR supports implementation of WHO's Global Action Plan on Antimicrobial Resistance. With respect to monitoring antimicrobial usage in animals, AGISAR maintains guidance on integrated surveillance of antimicrobial resistance and developing indicators/metrics to assess antimicrobial usage in the food chain in member countries. AGISAR also provides support to WHO capacity-building activities (e.g., training modules, protocols) on integrated surveillance of antimicrobial re-

sistance, including collection of antimicrobial usage data (54).

AGISAR's guidance document on integrated surveillance of antimicrobial resistance is intended to assist countries to develop and maintain integrated programs for surveillance of antimicrobial resistance among foodborne bacteria and relevant antimicrobial use in humans and animals (55). These programs are needed to study trends in antimicrobial use and resistance, identify the need for interventions to address antimicrobial resistance, and measure the impact of these interventions in both animal and human health. Chapter 2 of the guidance addresses surveillance of the use of antimicrobial agents in animals and humans and builds on prior work of WHO as well as the World Organization for Animal Health (OIE), ESVAC, and individual countries. Three main activities are identified: (i) measuring quantities of antimicrobial agents sold (antimicrobial consumption), (ii) collecting information on antimicrobial prescribing, and (iii) collecting information on the actual intake of antimicrobial agents by humans or animals. Various options to undertake these activities are presented, along with examples of templates or protocols, and these largely comprise the various methods used by individual countries and the European Union, which have been described previously in this chapter, and proposed by the OIE (see the following section on the OIE). Important elements include methods for collection of national antimicrobial sales data and methods for collection of data to the species level from pharmacies, veterinary clinics, or farms (e.g., continuous data collection from pharmacies, longitudinal or point prevalence studies at the farm level, species stratification studies). Guidance is also provided on standardized reporting (e.g., use of indicators such as kilograms of active ingredient or milligrams of active substance per PCU, DDDAs) and integrated analysis and reporting of antimicrobial use and of antimicrobial resistance data from human and animal sectors, including examples from established integrated programs (e.g., DANMAP, Canadian Integrated Program for Antimicrobial Resistance, The National Antimicrobial Resistance Monitoring System [NARMS], and the Joint Interagency Antimicrobial Consumption and Resistance Analysis [JIACRA] Report). For countries planning to undertake integrated surveillance, AGISAR's guidance recommends beginning with a small-scale pilot project for surveillance of antimicrobial use and antimicrobial resistance to serve as a proof-of-principle and to allow further refinement and development of an integrated program. Several important steps for such a pilot project are described:

establishing governance, building a situation analysis, planning, implementation, identification of key success factors, and evolution toward integrated analysis and reporting (55).

The OIE

The OIE is responsible for improving animal health globally. The OIE has made several important contributions to the monitoring of antimicrobial drug usage in animals, including the development of international standards for monitoring and building a global database on the use of antimicrobial agents in animals.

OIE standards for monitoring the quantities and usage patterns of antimicrobial agents used in food-producing animals and aquatic animals are published in the Terrestrial Animal Health Code and Aquatic Animal Health Code, respectively (56, 57). These standards include recommendations that address the objectives of antimicrobial usage monitoring, various sources of antimicrobial use data (e.g., pharmaceutical manufacturers, importers, veterinarians, farmers), the types of data that should be monitored (e.g., weight of active ingredient, dosage regimens, numbers of food-producing animals by species), and options for reporting antimicrobial usage data (e.g., total usage by antimicrobial class, by animal species, and by route of administration). The OIE determined through a 2017 survey that 73% of 146 countries reported quantitative data between 2013 to 2016 (58).

The OIE, WHO, and the Food and Agriculture Organization of the United Nations (FAO) have formed a tripartite collaboration to address antimicrobial resistance in the food chain. As part of this collaboration, the OIE was tasked with developing a global database on the usage of antimicrobial agents in animals (58). The OIE has also committed, in its 2016 Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials, to supporting member countries in developing and implementing antimicrobial usage monitoring systems and to building and maintaining an international database for the collection, analysis, and reporting of antimicrobial usage in animals, taking into account the animal populations in each country (59).

A template for the collection of harmonized data was sent to 180 OIE member countries in 2016, and responses were received from 143 (79%) countries, representing all five OIE regions. Results of the survey showed that 59% of responding member countries authorized antimicrobial agents as growth promoters. OIE reported that many countries face challenges in collection of quatitative data on antimicrobial use in animals (58).
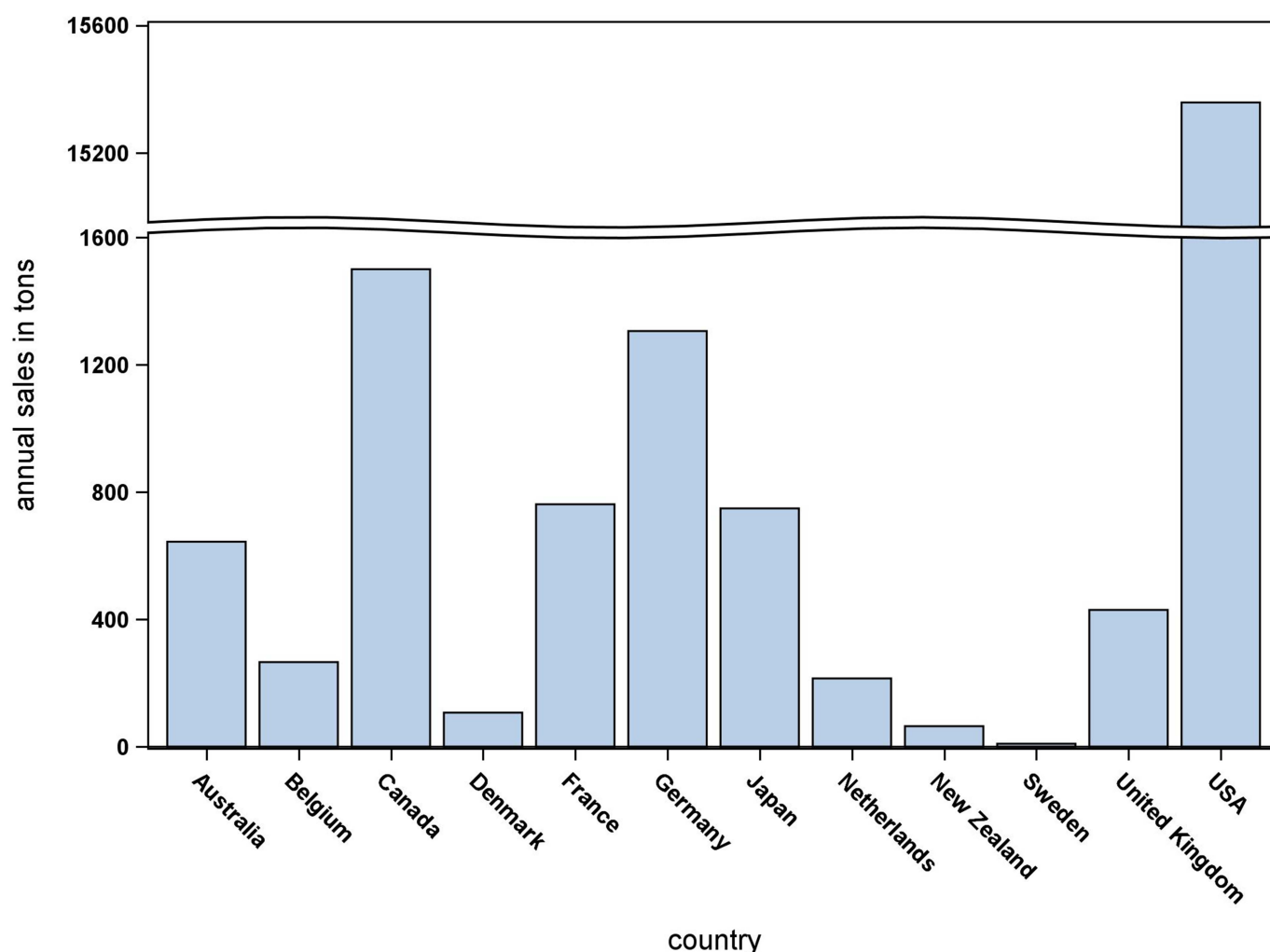
The FAO

As mentioned above, the FAO participates with WHO and the OIE in a tripartite collaboration. One of its roles is to support the development of local capacity for surveillance and monitoring of antimicrobial use in the food and agriculture sectors (60).

OVERVIEW OF ANTIMICROBIAL CONSUMPTION IN LIVESTOCK

Due to the huge variety of monitoring systems, it is challenging to provide a harmonized overview of the use of antimicrobial agents around the world. Nevertheless, data from national reports on monitoring antimicrobial consumption in animals are shown here as selected examples; total annual sales are shown in Figure 1. Total sales of antimicrobial agents in the veterinary sector are described in the text along with, where available, data per animal species (pigs, cattle, and poultry). For comparison, one should keep in mind that sales data per animal species are often generated by assuming that a drug is used for one (main) species, even if it is approved for use in other species as well. In addition, differences in reporting at the national level (see "Monitoring of Antimicrobial Drug Usage in Food-Producing Animals: Selected Examples" above) are frequent. Because of these differences, data have to be interpreted with caution and are not directly comparable between countries. For descriptions and results of each monitoring system, the corresponding national reports should also be

FIGURE 1 Annual sales of antimicrobial agents in tons (2014; Australian data from 2009/2010). Note that these figures are not adjusted for livestock population sizes and figures for Australia, Canada and the United States include sales of ionophores and/or coccidiostats (see text).

read. If not stated otherwise, the amount always corresponds to the amount of active compound. As described above, some countries have additional systems in place to monitor the use of antimicrobial agents in certain animal species, using different measures and definitions. A few results from these systems are also presented in "Other Countries" below, where we compare data from selected countries. Data on animal populations, if available, are shown here for pigs, cattle, and poultry.

In general, at least for the European countries, an overall decrease in the amount of antimicrobial agents sold in the veterinary sector has been observed during the past years. The antimicrobial classes sold most often are tetracyclines, penicillins, and sulfonamides. Sales of antimicrobial agents that are critically important for human medicine are usually low and/or show a decreasing trend, but this is not the case for all countries included here.

European Countries

The overall sales of antimicrobial agents in Belgium in 2015 were 260.27 tons according to the Belgian Veterinary Surveillance of Antibacterial Consumption national consumption report 2015 (32). Belgian livestock numbers included 6.4 million pigs and 2.5 million cattle in 2015 (61), as well as 294.71 million slaughtered animals (poultry) in 2014 (62).

In Denmark, the total consumption of antimicrobial agents in the veterinary sector in 2015, including agents used for companion animals, was 108.6 tons of active compound, showing a 5% decrease from the previous year. The main reason for this was a 5% decrease in antimicrobial usage in the pig industry, which is the main user of antimicrobial agents for animals in Denmark. The total antimicrobial consumption in pigs was 81.5 tons of active compound in 2015, a decrease of 4.5 tons (5%) compared with 2014. The overall consumption of antimicrobial agents in cattle remained at approximately 13 tons, similar to 2014. The total consumption of antimicrobial agents in poultry (all species) was 2.4 tons of active compound, an increase of 58% compared with 2014 due to disease outbreaks in broiler production. This is the highest amount recorded since the DANMAP program began (28). The animal population in Denmark in 2015 was the following: 12.7 million pigs (63), 522,000 cattle slaughtered, and 561,000 dairy cows, as well as 114.23 million broilers and 598,000 turkeys (28).

In France, a total of 514.26 tons of antimicrobial agents were sold in 2015, of which 185.45 tons were sold for pigs, 124.35 tons for cattle, and 98.98 tons for poultry. This is a 64% decline of sales for pigs compared to 1999, 10.4% for cattle, and 37% for poultry (34).

According to Eurostat, the pig population in 2015 consisted of 13.3 million animals—19.4 million cattle (61), 777 million broilers, 49,9 million layers, and 209,9 million other poultry (slaughtered animals) (34).

In Germany, the total sales of antimicrobial agents for usage in animals in 2016 were 742 tons of active compound. Between 2011 and 2016, the amount of sold antimicrobial agents decreased by 56.5%, from 1,706 to 742 tons. From 2015 to 2016, a reduction of 7.8%, or 63 tons of the total sales was recorded. A decrease can also be seen in the sales of antimicrobial agents that are critically important in human medicine (64). The animal population in Germany in 2016 consisted of 12.5 million cattle and 27.4 million pigs; there were 40.2 million layers in 2015 (65).

In the Netherlands, sales of antimicrobial veterinary medicinal products, including topical applications such as ointments, eye drops, and sprays, were 206 tons in 2015. Total sales decreased by 58.4% from 2009 to 2015, while the weight of livestock animals was stable with a small increase during the same period of time. In 2015, the animal population in the Netherlands consisted of 7.59 million pigs, 863,000 turkeys, 49.11 million broilers, 58.64 million other poultry, and 4.27 million cattle (29).

The total sales of antimicrobial agents to the veterinary sector of Sweden were 10.5 tons in 2015. The sales of antimicrobial agents for pigs were 2.13 tons of active substance, compared to 3.37 tons in 2010 (25). The Swedish animal population in 2015 included 1.48 million cattle, 1.36 million pigs, and 9.41 million layers (66).

According to the One Health Report 2015 (24), the total sales of antimicrobial agents for animal use comprised 420 tons in 2013 in the United Kingdom. The livestock population was 4.9 million pigs, 9.8 million cattle, and 163 million poultry in 2013 (67).

Other Countries

In Australia, no distinction is made in data on antimicrobial consumption for therapeutic or prophylactic use. Growth promoters and coccidiostats may be applied without intervention by a veterinarian, and they are listed separately. For the years 2009 to 2010, the total sales of antimicrobial agents for therapeutic and growth promotion purposes (including ionophores and coccidiostats) in food-producing animals were 644.0 tons of active compound in Australia, of which only 288.0 tons were labeled for therapeutic purposes (including prophylactic usage). Of those antimicrobial agents sold for therapeutic purposes, 37.6 tons were sold for cattle and sheep, 160.9 tons for poultry, and 89.4 for pigs. The numbers

of livestock in 2013 were 1.74 million pigs, 12.12 million cattle, and 108.4 million chickens according to the inventory of the Australian Bureau of Statistics ([68](#)).

In Canada, antimicrobial agents are used in productive animals for the treatment and prevention of disease and to improve feed efficiency/promote growth. In 2014, 1,500 tons of antimicrobial active ingredients (including ionophores and coccidiostats) were sold in the veterinary sector. This number is 5% higher than in 2013 but 12% lower than reported in 2006. From 2010 to 2014, there was a 1% increase. After adjusting for animal populations and weights (PCU), overall sales of antimicrobial agents for use in animals in Canada were relatively stable over the period of 2006 to 2012. ([69](#)). The livestock population in 2015 included 8.5 million cattle, 27.9 million pigs, and 630.6 million poultry ([70](#)).

In Japan, the overall amount of antimicrobial agents sold for use in animals in 2013 was approximately 780 tons of active compound. Additionally, around 200 tons of feed additives were distributed, including ionophores. The number of slaughtered animals in 2013 was 1.19 million cattle, 16.94 million pigs, 653.99 million broilers, and 86.23 million other poultry ([47](#)).

The total sales of antimicrobial agents in 2014 in New Zealand were 64.44 tons. Livestock numbers in this country in 2014 included 8.5 million cattle, 672,108 pigs slaughtered, 118 million broilers, and 3.85 million layers ([46](#)).

The total annual domestic sales of antimicrobial agents (including ionophores) to the veterinary sector in 2015 in the United States were 15,577 tons of active compound, including drug applications labeled for both food-producing and non-food-producing animals. From 2009 through 2015, domestic sales and distribution of antimicrobial agents approved for use in food-producing animals increased by 24%, and they increased by 1% from 2014 through 2015. Reporting on estimates of amounts sold per animal species started in 2016. The U.S. population of productive animals comprised 68.3 million pigs (1 December 2015), 91.99 million cattle (1 January 2016), 349.57 million layers during the year, 8.69 billion broilers, and 233.1 million turkeys (1 December 2015) ([71](#)).

As shown in "Monitoring of Antimicrobial Drug Usage in Food-Producing Animals: Selected Examples," countries calculate or estimate different variables to describe and analyze antimicrobial consumption in the veterinary sector and/or animal husbandry. Also, there are differences in the legal framework that determines the method of reporting, the responsibilities, and the kind of data collected, even if looking solely at sales data. Additionally, some countries also apply a benchmarking of farms and/or veterinarians, which might influence the choice of antimicrobial classes and number of treatments. All these facts are important to know when interpreting data.

Moreover, sales data have to be seen in relation to the animal population in the country in question. Animal populations can be estimated from different data (slaughtered animals, number of animals at a certain date, average number of animals throughout the year, etc.) and expressed by different measures (e.g., heads, kilograms live weight, kilograms slaughtered animals), and there is no harmonized approach on a global level. Detailed information on how the animal populations are estimated in each country can be found in the respective national reports.

Within the ESVAC project, a harmonized calculation of European data is possible. [Figure 2](#) shows the PCU-corrected overall sales for food-producing animals (including horses) in milligrams per PCU (mg/PCU), by country, for the year 2014 ([72](#)). It can be seen that sales data differ significantly between countries. In Scandinavia, sales are very low in comparison to all other countries. The highest sales are reported in Spain, Cyprus, and Italy. However, the data presented here are limited in their informative value, because many factors are not considered in the calculation. For example, the compositions of the animal populations in the countries play an important role, as do the husbandry systems. Thus, any comparison is poor as long as systems for data collection, reporting, and calculation of variables are not harmonized and do not take into account use data by animal species. Until harmonization is reached on an international level, every system has to be looked at separately, especially when interpreting trends over time. All important background information has to be taken into account when analyzing the results of each monitoring system.

FINAL REMARKS

The monitoring of antimicrobial drug usage in animals has now been established in several countries, but there is still a long way to go before most countries around the world have systems in place for the collection, analysis, and reporting of comprehensive antimicrobial use data. This is essential so that we have much better information on the types and quantities of antimicrobial agents that are being used in the various animal species around the world. We need this information for improving awareness, identifying opportunities for improved antimicrobial stewardship, assisting in the interpretation of
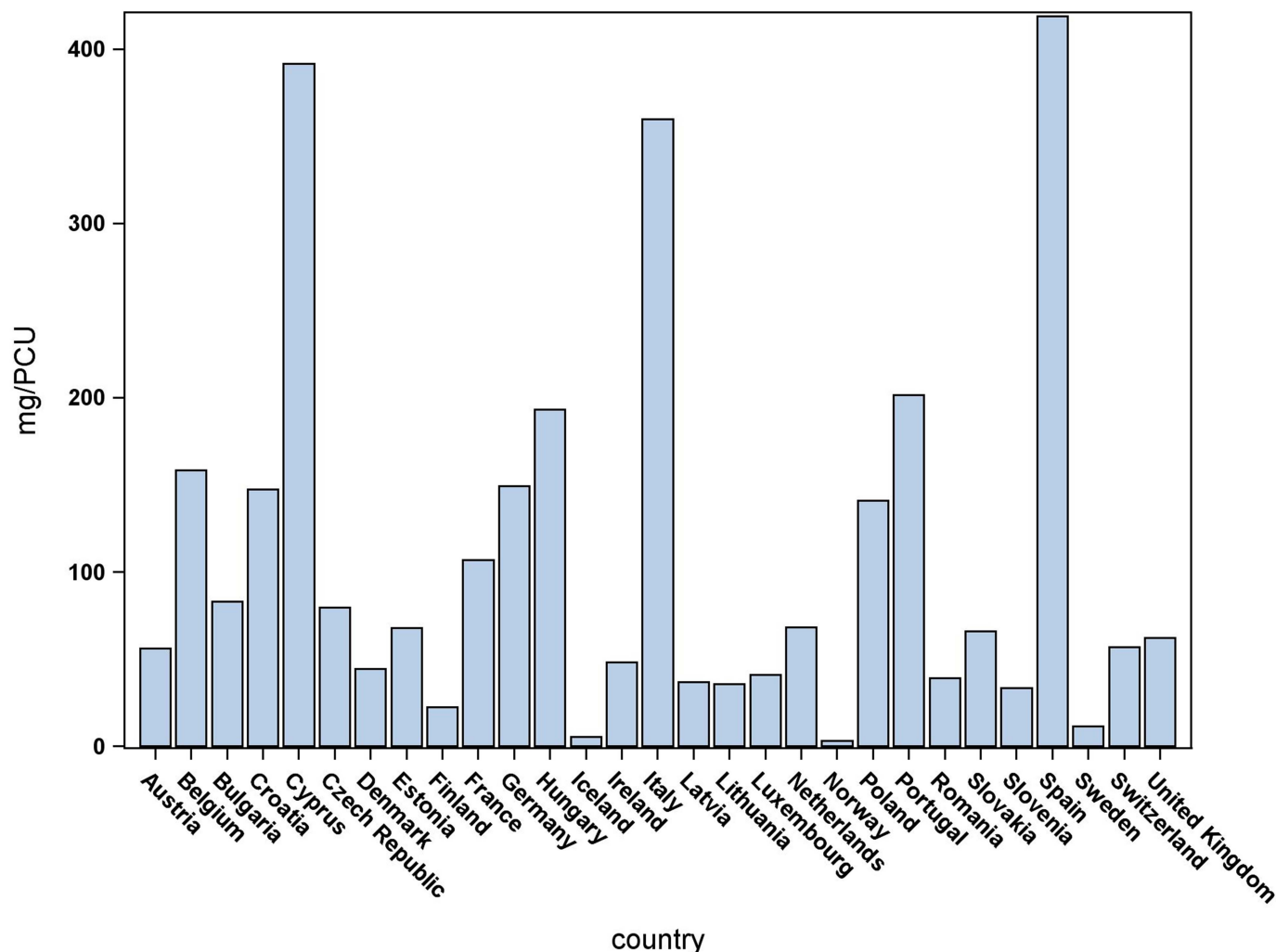
FIGURE 2 PCU-corrected sales data (mg/PCU) according to the ESVAC report 2016 (72)

antimicrobial resistance, and assessing the effectiveness of efforts to reduce unnecessary antimicrobial use. Antimicrobial resistance is a global problem, and to effectively address it we need a global program for integrated surveillance of antimicrobial use and resistance in animals and humans. Improved surveillance of this type is a cornerstone of the WHO Global Action Plan on Antimicrobial Resistance, as it is of many other international organizations and individual countries.

A very few countries have sophisticated, centralized, comprehensive antimicrobial use monitoring systems based on high-quality data from one or more of a variety of sources, including pharmaceutical companies, pharmacies, veterinarians, and farmers, covering most if not all animal species and humans. Most other countries, however, currently obtain and report little more than very basic national sales data. As described previously, when coupled with animal population data and strati-

fied to at least the species level, these sales data can provide useful information on overall trends and enable very basic interpretations of antimicrobial resistance data and simple comparisons between countries. However, to accomplish other important functions, such as benchmarking of antimicrobial use at the level of veterinary practices and farms, it is necessary to comprehensively monitor use at those levels. This is much more challenging and requires the cooperation and support of many affected parties so that the necessary high-quality and refined data are collected, shared, analyzed, and utilized in a timely manner. The most progress to date has been made in Europe, where there is longer national-level experience with antimicrobial use monitoring. In addition, directives related to antimicrobial use monitoring have been issued at the European Union level, requiring member states to collect and report use data. Furthermore, the ESVAC project has provided impor-

tant guidance and support for collection and reporting of use data. In addition, many European countries have capitalized on the prescription-only availability of antimicrobial agents and mandatory treatment record-keeping by veterinarians and farmers in the development of their monitoring systems. Unfortunately, the situation is different in many countries outside of Europe, and they may have to develop other approaches for their monitoring systems. More broadly, there is a need for research and development regarding technologies for collection, sharing, and reporting of antimicrobial use data at the user level. There is also a need for innovation and engagement of veterinary and producer organizations to improve motivation and compliance among end users with regard to data collection and sharing.

Eventually, antimicrobial use monitoring should extend from the major food animal species and humans to include fish, aquaculture, and all other animal and plant species that are treated with antimicrobial agents. This is important from a public health point of view, because companion animals, in particular, have close contact with people, including highly vulnerable populations, but it is also important for animal health, to improve the long-term effectiveness of antimicrobial agents for the treatment of infections in animals.

APPENDIXES Glossary of Terms and Definitions Describing Antimicrobial Drug Usage in Animals (modified from reference 1)

Term	Definitions, interpretation, and Examples
Part I: General terms and definitions	
Animal Unit: number	Definition: animal kept or place. Interpretation: If looking at a period of time, one should consider the overall number of animals kept during this period (e.g., over several production cycles; see below). It is also possible to calculate an average number of animals.
LSU Livestock unit Unit: (standardized) number	Definition: The number of livestock units is calculated based on their live weight by using appropriate conversion keys, taking into account the different groups of productive livestock, age, and usage categories. The reference unit used for the calculation of livestock units (1 LSU) is the grazing equivalent of one adult dairy cow producing 3,000 kg of milk annually, without additional concentrated foodstuffs. One LSU is equivalent to 500 kg live weight. The conversion keys for LSUs indicated in different literature sources are diverse. Interpretation: Livestock unit is a measure that can be calculated for every animal species and that allows comparison between different kinds of livestock. Example: LSU coefficients according to EUROSTAT [source: http://ec.europa.eu/eurostat/statistics-explained/index.php/Glossary:Livestock_unit_(LSU)]: Bovine animals Under 1 year old: 0.400 Over 1 but less than 2 years old: 0.700 Male, 2 years old and over: 1.000 Heifers, 2 years old and over: 0.800 Dairy cows: 1.000 Other cows, 2 years old and over: 0.800 Sheep and goats: 0.100 Equidae: 0.800 Pigs Piglets with a live weight of under 20 kg: 0.027 Breeding sows weighing 50 kg and over: 0.500 Other pigs: 0.300 Poultry Broilers: 0.007 Laying hens: 0.014 Ostriches: 0.350 Other poultry: 0.030 Rabbits, breeding females: 0.020

ESVAC PCU	The PCU is used by ESVAC as a proxy for the size of the animal population of a country.
	Definition: The PCU for each animal category is calculated by multiplying the number of livestock animals (dairy cows, sheep, sows, and horses) and slaughtered animals (cattle, goat, pigs, sheep, poultry, rabbits, and turkeys) by the theoretical weight at the most likely time for treatment according to Appendix 2 of the ESVAC report for 2005–2009.
	Interpretation: The PCU is used as the term for estimated weight. It is purely a technical unit of measurement, used only to estimate sales corrected by the animal population in individual countries and across countries. In the ESVAC report, 1 PCU = 1 kg of different categories of livestock and slaughtered animals.
	Example: The PCU is calculated for each species, weight class, and/or production type. Here we take an example for pigs of country X.
	PCU domestic:
	• Number of pigs slaughtered × estimated weight at treatment: 10,000 × 65 kg = 650,000 kg
	• Number of livestock sows × estimated weight at treatment: 240 kg: 3,000 × 240 kg = 720,000 kg
	PCU export:
	• Number of animals transported to another country for fattening × estimated weight at treatment: 1,000 × 25 kg = 25,000 kg
	PCU import:
	• Number of animals imported from another country for slaughter × estimated weight at treatment: 500 × 65 kg = 32,500 kg
	Total PCU pigs = total $PCU_{Domestic}$ + total PCU_{Export} − total PCU_{Import}:
	Total PCU pigs = (650,000 kg + 720,000 kg) + 25,000 kg − 32,500 kg = 1,362,500.00 kg
TAR	Definition: The sum of the lifetime (in days) of all single animals on a farm within a defined period of time.
Time at risk (on a farm)	Interpretation: The duration of stay of an animal on a farm may be shorter than the observation period. The TAR compensates for this problem by recording the duration of stay on a farm in days for every animal.
Unit: (animal) days	TAR is a term that originates from human medicine, where it is also called "person time." In Switzerland it is also called "animal years at risk," meaning the time during which an animal could be treated.
	Example: 10,000 animals are kept in a broiler farm for 35 days. Afterwards, 2,000 animals are housed out, while the other animals stay another 5 days. For a time period of 40 days this results in
	TAR (farm) = (10,000 broilers × 35 days) + (8,000 broilers × 5 days) = 390,000 (animal) days
	If, subsequently, the farm is subject to a service period of 10 days, during which no animals are kept, this time at risk is valid also for the time period of 50 days.
Withdrawal time	Definition: The minimum time that has to be followed after a drug has been administered to an animal until this animal can again be used for food production.
Unit: days	Interpretation: The adherence to a defined withdrawal time ensures that maximum residual limits of pharmacologically active substances in food are not exceeded.
Duration of effect	Definition: The period during which a therapeutically effective level of active substance is present at the target site.
Unit: days	The duration of effect depends on the drug and the affected organ system (see also one-shot products)
(Production) cycle	Definition: A group of animals (herd) that is at once housed in an empty stable or compartment, fattened, and housed out. Some of the animals may also be housed out earlier than the rest.
	Interpretation: In livestock farming, the administration of drugs is often recorded in relation to the production cycle. During evaluations, one should carefully choose the time period and number of housed animals during this period. If data on housing in and out and on the number of animals per production cycle are not available, it is possible to estimate the number of animals by using the number of animal places and overall assumptions on the number of production cycles per year.
	Example: In Germany, the following average numbers are currently valid (source: KTBL, Betriebsplanung Landwirtschaft 2012/2013):
	Pig: weaner (8.1–28 kg) = 6.89 fattening cycles/stable/year
	Pig: fattening pig (28–118 kg) = 2.83 fattening cycles/stable/year
	Poultry: broilers = 7.46 fattening cycles/stable/year
	Poultry: laying hens = 0.90 cycles/stable/year
	Poultry: turkey = 2.17 fattening cycles/stable/year

ATC code	Definition: Anatomical therapeutic chemical (ATC) classification system for drugs of the WHO. Interpretation: The classification of active substances is based on the organ system where they are effective (e.g., cardiovascular or gastrointestinal system) and the classes of active substances. Therefore, several ATC codes exist for some substances due to their application in different organ systems (e.g., six for tetracycline). The first letter of the ATC code indicates the anatomic group (1. level); the following double figure, the therapeutic subgroup (2. level); the next letter marks the pharmacological subgroup (3. level); and the last letter, the chemical subgroup (4. level). The 5. level indicates the chemical substance. Example: For tetracycline, the following six ATC codes exist: A01AB13, D06AA04, J01AA07, S01AA09, S02AA08, S03AA02. J01AA07 is the ATC code for systemically applied tetracycline.
ATCvet code	Definition: This system is based on the ATC code from human medicine and has been adapted for veterinary purposes. Interpretation: As a general rule, each ATC code starts with a Q. For veterinary purposes, additional codes are defined if necessary. Example: The following codes exist for oxytetracycline: QD06AA03 (local application), QG01AA07 (gynecological application), QJ01AA06 (systemic application), QS01AA04 (ophthalmologic application).
Combination products	Definition: Combination products contain two or more active substances (e.g., antibiotic substances), that complement each other in their effect. Interpretation: The analysis of such products should be done by active substance. Active substances with a supportive effect to the antibiotic, which have no bactericidal or bacteriostatic effect clinically themselves, are not analyzed separately. Example: Penicillin in combination with streptomycin is analyzed as a combination product of two antibiotics. Amoxicillin in combination with clavulanic acid is not regarded as a combination product, because clavulanic acid has no antibiotic effect.
Products with long-term effects One-shot products	Definition: These are drugs that maintain a constant level of active substance for considerably more than 24 h (up to several days) after one application and that are administered less than once a day. There is no definite labeling of these products. Interpretation: With these drugs, a long duration of effect is reached with a single application or a few applications. When analyzing antibiotic consumption, attention should be paid to these products, because their application should not alter results. The indicated duration of effect should be multiplied by an appropriate factor to adequately display the real duration of effect.

Part II: Terms and definitions based on quantities

Dose Unit: mg or g per animal	Definition: The amount of active substance administered to a single animal in one application. Interpretation: The dose depends on the administered active substance, animal species, body weight, and disease to be treated.
Dosage Unit: mg/kg body weight $$\text{Dosage} = \frac{\text{Dose}}{\text{Animal weight}}$$	Definition: The amount of an active substance administered in one application per kg bodyweight. Interpretation: The dosage depends on the active substance administered. The dosage of the respective active substance per animal allows calculation of the dose, and it facilitates comparison of the treatment amount independently from the body weight of an individual animal.
DDDA (defined daily dose animal) ESVAC defined daily dose for animals DDDvet Unit: mg or g per animal per day	Definition: The DDDA is the average recommended daily maintenance dose of an active substance per animal and is defined for every target animal species, age group, and productive livestock group. The definition is established using specialized information (from drugs containing the same active substance) and expert opinions regarding the main indication the active substance is administered for. The dose is defined for animals with a standardized body weight that differs depending on the literature source. Interpretation: The principles of standardization of doses comply with the calculation of the DDD in human medicine, where the dose is calculated for a man of 70 kg body weight for every ATC code. The DDDA was first established in Denmark with the abbreviation ADD ([7]). In the Netherlands, the concept of DDDA is applied under the term DDD in veterinary medicine. An international procedure was published by the EMA within the ESVAC activity. ESVAC, in 2016, prioritized establishing DDD for animals (DDDvet) values for antimicrobials used in three major food-producing animal species: pigs, cattle, and broilers (poultry). The values are based on average daily dose of active substance according to the manufacturer's instructions. They take account of differences in dosing, pharmaceutical form, and route of administration used in the different species.
DDDA$_{kg}$ (DDDA per kg) Unit: mg/kg body weight	Definition: The average recommended maintenance dosage of an active substance per kg body weight of a target animal species; it corresponds to the recommended dose.

UDD (used daily dose)
Unit: mg or g per animal and day

$$UDD = \frac{\text{Overall amount of active substance administered in the animal population}}{\text{No. of animals} \times \text{days of treatment}}$$

Definition: The daily dose of an active substance per animal which is actually administered by the farmer or the veterinarian.

Amount (of active substance)
$UDD_{population}$ (used daily dose per population)
Unit: kg

Definition: The sum of UDDs of an active substance in the observed population (e.g., in a herd).
Interpretation: The amount of an applied active substance depends on the number of treated animals and on the dose chosen by the veterinarian.
When analyzing the amount, drugs administered in very high doses (e.g., tetracycline) are overestimated in their relevance, but drugs administered in very low doses are underestimated. Because the modern active substances in particular (e.g., fluoroquinolones) are usually administered in low doses, the situation can be misinterpreted when looking at the amounts.
Example 1: Treatment of 100 sucklers at 15 kg over 5 days with tetracycline (recommended reference dose: 85 mg/kg):
   Amount = 100 sucklers × 15 kg × 85 mg/kg × 5 days = 640 g
Example 2: Treatment of 100 sucklers at 15 kg over 3 days with enrofloxacin (recommended reference dose: 2.5 mg/kg):
   Amount = 100 sucklers × 15 kg × 2.5 mg × 3 days = 11.25 g

UDD_{kg} (UDD per kg)
Unit: mg/kg body weight and day

$$UDD_{kg} = \frac{\text{Overall amount of active substance administered in the animal population}}{\text{No. of animals} \times \text{body weight} \times \text{days of treatment}}$$

$$UDD_{kg\,est} = \frac{\text{Overall amount of active substance administered in the animal population}}{\text{No. of animals} \times \text{standard weight} \times \text{days of treatment}}$$

Definition: The actually administered dosage of an active substance per day and per kg body weight of the treated animal species.
Interpretation: The UDD_{kg} animal allows comparison between populations regarding the active substance. It has to be taken into account that these comparisons can only be done for one active substance and that it is not possible to draw overall conclusions regarding antibiotic usage including more than one active substance.
If the applied dosage is estimated from overall amounts, this is done usually on the basis of a standardized average animal weight that can differ depending on the source of the literature. In this case UDD_{kg} turns to an estimate due to the unknown body weights in the actual case of treatment. Note, in addition, that standard body weights are not harmonized in the literature.

PDD (prescribed daily dose)
Unit: mg or g per animal and day

$$UDD = \frac{\text{Overall amount of active substance prescribed for the animal population}}{\text{No. of animals} \times \text{days of treatment}}$$

Definition: The daily dose of an active substance per animal as prescribed by the veterinarian.
Interpretation: The PDD originates from human medicine and helps to describe prescribing patterns. In Germany the prescription by the veterinarian and the administration of a drug (on the farm) are recorded simultaneously on the same form. The determination of UDD and PDD therefore usually leads to identical results.

Part III: Terms and definitions based on applications

Single application (= application unit)
nUDD (number of used daily doses)
Unit: number
  nUDD (sum of single applications) = treated animals × days of treatment × active substance(s)

Definition: The application of one active substance (or sometimes one drug) in one animal on one day. From this, the sum of all single applications in a population under observation over the observation period is calculated.
Interpretation: This term quantifies the real application frequency of active substances (or drugs) and days.
The number of nUDDs depends on the applied drug, the number of days of treatment, and the number of animals treated. If a drug is applied more often than once a day, this is seen as only a single application. Hence, if the drug is applied by feed or water, the whole daily ration represents one application.
The term is usually not related to the active substance and is summarized from all applications. But nUDD for specific active components or even for special drugs under study may be calculated with the same concept.
Example 1: Treatment of 100 pigs over 5 days with tetracycline (mono preparation):
   nUDD = 100 pigs × 5 days × 1 active substance = 500 single applications
Example 2: Treatment of 100 pigs over 5 days with sulfadimethoxine and trimethoprim (combination preparation):
   nUDD = 100 pigs × 5 days × 2 active substances = 1,000 single applications

Adjusted single application (by duration of effect)
nUDD$_{adjust}$ (number of adjusted used daily doses)
Unit: number
nUDD$_{adjust}$ = treated animals × factor × active substance

Definition: For drugs with a long-acting effect, the single application should be adjusted by multiplication with a preparation-specific factor. This factor should take into account the time over which an antibiotic effect is expected.
Interpretation: This term allows comparison between applications of preparations with long-term effects and other drugs. Currently, there is no official list of long-acting products. Therefore, there is also no access to up-to-date information on preparation-specific factors, and information on levels of effect (in organs) is often absent.
So, for the time being, the factor should be chosen so that it corresponds to the average duration of treatment that is expected when using a classic preparation.

TF (treatment frequency)
Unit: single application/animal
nUDD$_{population}$ (number of used daily doses per population)

$$TF = \frac{\text{Sum of single applications}}{\text{Number of animals cared for in a population}}$$

Definition: The TF indicates on how many days on average an animal in a population is treated with an active substance (or drug).
Interpretation: The TF is independent from the applied amount and exclusively considers the application of active substances (or drugs). For every treatment, the sum of single applications in a population is divided by the number of animals in that population.
Different time periods can be considered in the calculation by adding all single applications of a period defined in one farm and dividing it by the number of animals kept on the farm during this period.
The TF is a population-based value, which is comparable directly between farms and regions and years. For the application of drugs (without considering the number of active substances included), the TF is sometimes called the animal treatment index.
If applying drugs with a long-acting effect, the number of adjusted single applications may be used in the calculation.
Example 1: Treatment of 100 out of 500 pigs in a farm over 5 days with tetracycline (mono preparation):
    TF = (100 pigs × 5 days × 1 active substance)/500 pigs = 1
I.e., on average, every animal in the population was treated for one day with one active substance.
Example 2: Treatment of 100 out of 500 pigs over 5 days with penicillin and streptomycin (combination preparation):
    TF = (100 pigs × 5 days × 2 active substances)/500 pigs = 2
I.e., on average, every pig in the population was treated for two days with one active substance.

TI (treatment incidence/treatment density)
Unit: %

$$TI = \frac{\text{Total amount of drugs}}{\text{UDD} \times \text{duration of production cycle} \times \text{total weight of animals treated}}$$

$$= \frac{\text{nUDD}}{\text{Duration of production cycle} \times \text{number of animals within population}}$$

$$= \frac{\text{Sum of single applications}}{\text{Duration of production cycle} \times \text{number of animals within population}}$$

Definition: The TI is calculated by dividing the overall amount of the applied active substance by the product of the UDD, the overall weight of the treated animals, and the duration of the production cycle.
Interpretation: If the UDD is not known exactly and has to be estimated from the total amount, the TI is calculated as the overall number of UDDs over the duration of the production cycle times the number of animals in the population. For a flock or a farm in which all animals are treated (e.g., an oral treatment for all poultry) the TI again simplifies to the ratio of the number of days treated to the number of days at risk. With this, TI can be interpreted as the percentage treated time at risk.
Example: See above, calculation of treatment density):
TI = (10,000 broilers × 7 days)/390,000 (animal) days = 0.179
I.e., 17.9% of the time at risk, a treatment took place.

Overview of National Monitoring Systems for Antibiotic Consumption

Country	Name of monitoring system or report	Since	Responsible for reporting	Frequency of reporting	Voluntary or mandatory	Type of data	Major metric	Animal species
AU	Quantity of antimicrobial products sold for veterinary use in Australia	Earlier than 2005	Pharmaceutical companies	Annually	Voluntary	Sales data	Total annual sales by species in kg active substances	Food-producing animals, companion animals
BE	BelVet-SAC	2007	Wholesalers, distributors, feed mills	Annually	Mandatory	Sales data	Total sales in mg active substances per kg biomass	Predominantly livestock
BE	AB register (private)	Not yet				Use data		
BE	SANITEL MED (official)	Not yet				Use data		
CA	CIPARS	2006	Pharmaceutical companies	Annually	Voluntary	Sales data	Total annual sales by species in kg active substances	Food-producing animals, companion animals
DE	AMG (official)	2014	Farmers	Half-yearly	Mandatory	Use data	Treatment Frequency (TF)	All fattening animals (cattle, pigs, poultry)
DE	QS (private)	2012	Farmers	Quarterly	Voluntary	Use data	Therapy index (TI)	Fattening animals (pigs, poultry)
DE	DIMDI-AMV (official)	2011	Pharmaceutical companies, wholesalers	Annually	Mandatory	Sales data	Total annual sales in kg active substances	All animals
DK	DANMAP/VETSTAT	1995/2000	Pharmacies, vets, feed mills	Monthly	Mandatory	Sales data/ use data	DADD, DAPD	Food-producing animals and mink; voluntary: pets
FR		1999	Pharmaceutical labs	Annually	Voluntary	Sales data	Total annual sales by species in mg active substances per kg bodyweight; ALEA, number of ACDkg, number of ADDkg	Livestock animals, domestic carnivores, horses, rabbits, fish
JP	JVARM	1999	Pharmaceutical companies	Annually	Mandatory	Sales data	Total annual sales by species in kg active substances	Food-producing animals
NL	MARAN	See following rows						
NL	FIDIN	1998	Pharmaceutical companies	Annually	Voluntary	Sales data	Total annual sales in kg active substances	Food-producing animals
NL	FADN (LEI)	2004–2011	Veterinarians	Annually	Voluntary	Use data	Defined doses per animal year on a farm	Pigs, veal calves, broilers, cattle (sentinel farms)
NL	FADN (SDa)	2011	Veterinarians	Annually	Mandatory	Use data	$DDDA_F$, $DDDA_{NAT}$ per sector (species, production group)	Pigs, veal calves, broilers, cattle, turkeys; pets (certain drugs); mink and rabbits from 2016/2017
NZ	2011–2014 Antibiotic sales analysis	2010/2011	Pharmaceutical companies	Annually	Mandatory	Sales data	Total annual sales by species in kg active substances	Food-producing animals, companion animals
SE	SVARM	1980	Pharmacies	Annually	Mandatory	Sales data	Total sales in mg per PCU; sales in mg active substances (or other unit) per species	All terrestrial animals
UK	One Health report	Earlier than 2011	Pharmaceutical companies	Annually?	Mandatory	Sales data	Total sales in mg active substances per PCU	Livestock, horses, companion animals
USA	FDA, Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals	2009	Pharmaceutical companies	Annually	Mandatory	Sales data	Total sales in kg active substances	Food-producing animals

Abbreviations: AU, Australia; BE, Belgium; CA, Canada; DE, Germany; DK, Denmark; FR, France; JP, Japan; NL, the Netherlands; NZ, New Zealand; SE, Sweden; UK, United Kingdom; DADD, Defined Animal Daily Dose; DAPD, DADD per 1000 animals per day (treatment proportion); ALEA, animal level of exposure to antimicrobials; ACD_{kg}, Animal Course Dose = Body weight treated (in kg), $DDDA_F$, days an average animal is treated in a year on a particular farm; $DDDA_{NAT}$: Defined Daily Dose Animal per sector.

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