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Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals

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Impacts

- Various indicators are available to quantify antimicrobial usage from sales, deliveries or reimbursement data in human and veterinary medicine; results can differ substantially depending on the method used
- To select the most appropriate indicators of antimicrobial usage, the study objective must first be determined; if the overall aim is to compare antimicrobial usage between populations, standardised parameters should be used, whereas the quantification of exposure to antimicrobials should rely on actual parameters
- Major gaps such as the absence of a gold standard for evaluating indicators and the lack of a scientific basis to assess antimicrobial selection pressure hamper the identification of the most suitable indicator for a given study objective

Summary

An increasing variety of indicators of antimicrobial usage has become available in human and veterinary medicine, with no consensus on the most appropriate indicators to be used. The objective of this review is therefore to provide guidance on the selection of indicators, intended for those aiming to quantify antimicrobial usage based on sales, deliveries or reimbursement data.

Depending on the study objective, different requirements apply to antimicrobial usage quantification in terms of resolution, comprehensiveness, stability over time, ability to assess exposure and comparability. If the aim is to monitor antimicrobial usage trends, it is crucial to use a robust quantification system that allows stability over time in terms of required data and provided output; to compare usage between different species or countries, comparability must be ensured between the different populations. If data are used for benchmarking, the system comprehensiveness is particularly crucial, while data collected to study the association between

usage and resistance should express the exposure level and duration as a measurement of the exerted selection pressure.

Antimicrobial usage is generally described as the number of technical units consumed normalised by the population at risk of being treated in a defined period. The technical units vary from number of packages to number of individuals treated daily by adding different levels of complexity such as daily dose or weight at treatment. These technical units are then related to a description of the population at risk, based either on biomass or number of individuals. Conventions and assumptions are needed for all of these calculation steps. However, there is a clear lack of standardisation, resulting in poor transparency and comparability. By combining study requirements with available approaches to quantify antimicrobial usage, we provide suggestions on the most appropriate indicators and data sources to be used for a given study objective.

Keywords: antibiotics, technical units, quantification, antimicrobial consumption

Introduction

Antimicrobial products (antimicrobials) have been used widely and successfully for the treatment and prevention of infectious diseases in humans and animals. However, the optimism of the early period of antimicrobial discovery has been tempered by the emergence of bacterial strains resistant to these therapeutics (Levy and Marshall, 2004) that have a serious clinical impact on human (Collignon, 2012) and animal health (Vaarten, 2012). An increasing number of studies have shown that antimicrobial usage in humans (Charbonneau et al., 2006; Costelloe et al., 2010; Sun et al., 2012) and animals (Burow et al., 2013; Hammerum et al., 2014; Simoneit et al., 2015) is the main driver for the development of antimicrobial resistance.

As a consequence, international organisations have encouraged the collection of antimicrobial usage data in order to manage and minimise the further development of antimicrobial resistance (World Health Organization, 2013; World Organisation for Animal Health, 2015a). In this article, antimicrobial usage refers to the exposure of a given individual or group over a certain period of time to a certain amount of antimicrobial active substance. The collection of antimicrobial usage data includes both monitoring, i.e. the routine collection of information on antimicrobial usage (Thrusfield, 2013), and punctual data collection from the whole population or from a representative sample of the national population. The data collected can be quantitative only (i.e. amounts of antimicrobials) or include a qualitative description of usage (describing, for example, treatment indication, antimicrobial class, active substance and route of administration). Quantification is based on 'indicators' of antimicrobial usage, defined as the number of 'technical' units of measurement (i.e. the amount of antimicrobials) consumed and normalised by the population at risk of being treated in a defined period (European Medicines Agency, 2013).

An increasing variety of indicators of antimicrobial usage has become available in human and animal medicine but none has been put forward as the most appropriate to measure antimicrobial usage. The main difficulties encountered when trying to identify suitable indicators are related to i) the number of different antimicrobial usage indicators available in both human (Coenen et al.,

2014; Fortin et al., 2014) and veterinary medicine (Chauvin et al., 2001), ii) the apparent discrepancies or contradictions between the results obtained from different indicators applied to the same antimicrobial usage data (Chauvin et al., 2001; Polk et al., 2007; Dalton et al., 2007; Chauvin et al., 2008; Bruyndonckx et al., 2014), and iii) the diversity of interests, perceived utility and needs among the stakeholders involved in the collection of antimicrobial usage data (DeVincent and Viola, 2006; Benedict et al., 2012). Indeed, a range of study objectives can be pursued with the collection of antimicrobial usage data. As has been shown for the monitoring of antimicrobial resistance (Lewis, 2002; Hunter and Reeves, 2002) and for disease surveillance in general (Thrusfield, 2013), the study objective should be clearly stated at an early stage of study design in order for a monitoring or surveillance system to be successful. However, most studies do not provide a clear rationale for the selection of a certain indicator and data source to measure antimicrobial usage.

Consequently, the objective of this review article is to provide guidance to select the most suitable indicators of antimicrobial usage and data sources in accordance with a specific study objective. Indicators from both veterinary and human medicine are included for two reasons: i) some of the difficulties associated with the quantification of antimicrobial usage are common to both disciplines; each discipline can therefore benefit from the experience gained in the other, and ii) in a One Health context, barriers between the disciplines should be lowered as it becomes critical to develop a common approach to measure antimicrobial usage in humans and animals (ECDC, EFSA and EMA, 2015). The review is structured as follows: first, the principal objectives of measuring antimicrobial usage in humans and animals are described, and, for each objective, the main requirements regarding the way in which antimicrobial usage data should be measured are identified. Next, available indicators of antimicrobial usage in human and veterinary medicine are presented and compared, focusing on those calculated from antimicrobial sales, deliveries and reimbursement data. Finally, suggestions are provided to select the most suitable indicators of antimicrobial usage and data sources in accordance with the study objective. A glossary of abbreviations used in this article is available in Appendix S1 of the article supporting information.

Why measure antimicrobial usage?

The collection of antimicrobial usage data serves four main objectives. First, antimicrobial usage is measured for the monitoring of antimicrobial usage trends over time (*Objective 1*). A number of countries report annual antimicrobial usage data that are compared to the usage observed in previous years. Reports on antimicrobial usage are communicated either separately for human medicine (Petrov et al., 2005; Mölstad et al., 2008; Meyer et al., 2013; Health Protection Scotland, 2014; Australia Infection Control Service, 2014) and veterinary medicine (Ministry of Agriculture, Forestry and Fisheries of Japan, 2013; Federal Agency for Medicines and Health Products, 2013; Veterinary Medicines Directorate, 2013; Food and Drug Administration, 2014; Anses, 2014) or in a joint report (NORM and NORM-VET, 2012; Public Health Agency of Canada, 2013). European countries also report their antimicrobial usage trends over time in a joint report and using a standardised approach between countries. This work is conducted by the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) for antimicrobial usage in humans (Vander Stichele et al., 2004; Adriaenssens et al., 2011) and by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project for veterinary antimicrobial usage (European Medicines Agency, 2014).

Antimicrobial usage monitoring over time makes it possible more specifically to quantify the impact of control strategies or intervention programmes. Examples include the assessment of the effect of the European Union (EU) ban on antimicrobials as animal growth promotors initiated by Sweden in 1986 (Wierup, 2001; Casewell et al., 2003; Aarestrup et al., 2010) or the assessment of the impact of antimicrobial awareness campaigns (Huttner et al., 2010). While most of the evaluations of intervention programmes aim at quantifying the reduction in the amount of antimicrobials used, some also assess qualitatively the evolution of antimicrobial treatment practices, for example assessing medical doctors' compliance with guidelines on good antimicrobial prescription practices (Ashiru-Oredope et al., 2012). Because the need for antimicrobial treatments is closely related to the disease situation, the monitoring of antimicrobial

usage over time can also provide useful information on the temporal evolution of the health situation, for example following the introduction of new vaccines or the emergence of new diseases, e.g. the chronic wasting disease in pigs that emerged in Europe in the 1990s (Jensen et al., 2012).

Antimicrobial usage data also commonly serve to compare antimicrobial usage between different populations, for example different animal species populations (Veterinary Medicines Directorate, 2013; DANMAP, 2013; NETHMAP and MARAN, 2013), human and animal populations (ECDC, EFSA and EMA, 2015) or different countries (Goossens et al. 2007; Elseviers et al., 2007; Grave et al., 2010) (*Objective 2*). In addition, 'benchmarking' systems were implemented at hospital, outpatient clinic or farm level, with the objective of identifying high antimicrobial users and thus promoting the reduction or more prudent usage of antimicrobials relying on a sort of 'shame effect' on heavy users (Jacquet et al., 2011) (*Objective 3*). Such programmes were for example implemented in the USA and Germany to compare antimicrobial usage between the intensive care units of different hospitals (Fridkin et al., 1999; Meyer et al., 2013). Benchmarking between farms has also been routinely implemented nationwide in Denmark (Danish Veterinary and Food Administration, 2011) and in the Netherlands (Bos et al., 2013).

The monitoring of antimicrobial usage also provides useful data to study the association between antimicrobial usage and resistance (*Objective 4*), i.e. to describe how the exposure of humans and animals to antimicrobial treatments relates to the selection of resistant bacteria or genes and to their spread between different epidemiological units (including farms, hospitals or the environment). Several ecological studies conducted at national and European level showed a significant association between national and European aggregated amounts of antimicrobial sales and antimicrobial resistance prevalence (ECDC, EFSA and EMA, 2015), in both human (Goossens et al., 2005; van de Sande-Bruinsma et al., 2008) and veterinary medicine (Chantziaras et al., 2014; Garcia-Migura et al., 2014). Other studies also quantified the association between antimicrobial usage and resistance at farm level (Akwar et al., 2008; Persoons et al., 2011; Agga et al., 2014) or hospital level (Charbonneau et al., 2006). Some

studies demonstrated that the development and spread of antimicrobial resistance was related to certain antimicrobial treatment practices, including the choice of a particular administration route (Varga et al., 2009; Burow et al., 2013; Simoneit et al., 2015), use of a specific antimicrobial class, e.g. fluoroquinolone (Taylor et al., 2009), treatment duration (D'Agata et al., 2007) and number of treatment courses (Costelloe et al., 2010).

For each study objective, what are the requirements regarding the measurement of antimicrobial usage?

The study objective entails certain requirements regarding the measurement of antimicrobial usage; these are grouped into five categories: level of resolution, comprehensiveness, stability of the measure over time, ability to assess exposure to antimicrobials, and comparability of the measure between different populations (Table 1).

[Insert Table 1]

Spatial and temporal resolution

The level of resolution includes both a spatial and temporal component. The level of spatial resolution relates to where antimicrobial usage is observed; this can be at supra-national level (Wirtz et al., 2010; Adriaenssens et al., 2011; European Medicines Agency, 2014 ; Versporten et al., 2014), national level (Achermann et al., 2011; Bondt et al., 2011; Suda et al., 2014), farm level (Chauvin et al., 2008; Callens et al., 2012; Pardon et al., 2012; Persoons et al., 2012) or hospital and outpatient clinic level (Arnold et al., 2006; Dumartin et al., 2010). While low spatial resolution is sufficient to compare antimicrobial usage between different species or countries, high resolution is required to compare antimicrobial usage between farms, hospitals or outpatient clinics (i.e. the resolution level should be equal to or higher than the level of the units that are compared). For studies exploring the association between antimicrobial usage and resistance, low resolution level data has been used to quantify the association between antimicrobial usage and level of

occurrence of resistant bacteria and strains, which includes both the selection and spread of antimicrobial resistance (van de Sande-Bruinsma et al., 2008; Chantziaras et al., 2014; Garcia-Migura et al., 2014; ECDC, EFSA and EMA, 2015). On the other hand, studies conducted at high resolution level, in particular those relying on time series analysis (Monnet et al., 2004; Aldeyab et al., 2008), can be used to focus on the quantification of the selection of antimicrobial resistance following antimicrobial usage. However, in this type of epidemiological studies, other factors besides antimicrobial usage (e.g. the clonal spread of resistant strains) will always contribute to the observed occurrence of antimicrobial resistance. Spatial resolution of studies monitoring antimicrobial usage trends over time depends on the level of interest and can be low (e.g. using national-aggregated data to monitor national trends) (Wirtz et al., 2010; Grave et al., 2012) to high (e.g. using farm-level data to monitor individual usage) (Aarestrup et al., 2010).

Temporal resolution refers to the frequency with which antimicrobial usage data is collected. Many studies rely on annual antimicrobial usage data, whatever their objectives. However, a limited number of studies collected monthly data to monitor usage trends in outpatient clinics; this made it possible to describe the seasonal variability of usage (Achermann et al., 2011; Suda et al., 2014), or the association between antimicrobial usage and resistance using time series analysis (Monnet et al., 2004). Monthly collection of antimicrobial usage is also routinely implemented in Denmark for human and veterinary antimicrobial products (DANMAP, 2013) and has been used to highlight specific events, such as the effect on antimicrobial usage of the introduction of generic versions of drugs (Chauvin, 2009; Jensen et al., 2010). In animal production, it might sometimes be advisable to adapt the temporal resolution to the length of a typical production cycle, e.g. six weeks in broiler production (Persoons et al., 2012) or eight months in veal calf production (Pardon et al., 2012).

One could also consider the specificity of the study's target population as a third resolution level component. Thus in veterinary medicine, the resolution of antimicrobial usage studies increases from multispecies-aggregated data (European Medicines Agency, 2014), to species-specific data (e.g. pig production) (Obritzhauser et al., 2011), to production type data (e.g. farrow-to-finish pig

farms) (Moreno, 2014) and up to age-specific data (e.g. weaner pigs) (DANMAP, 2013). A similar consideration applies to human antimicrobial usage, where national-aggregated data are commonly subdivided into age group or hospital and outpatient usage data (ECDC, 2012), with hospital data possibly further detailed at the hospital unit level (e.g. the intensive care unit or the neonatal and pediatric unit) (Meyer et al., 2003; Grohskopf et al., 2005).

Comprehensiveness of the data collected

The comprehensiveness of antimicrobial usage measurement refers to the capacity to collect usage data from all units in the target population, e.g. from all herds or all hospitals in the country if the study is conducted at farm level or hospital level, respectively. This requirement only applies to benchmarking studies where every single hospital, outpatient clinic or farm is able to compare its own antimicrobial usage with its peers' usage (Meyer et al., 2003; Danish Veterinary and Food Administration, 2011; Bos et al., 2013). For other purposes, a sufficiently large random sample from the population should provide representative data for the whole population. However, in this approach, the sampling is of crucial importance to ensure true representativeness. This type of study often suffers from the need to rely on the willingness of farmers or hospitals to participate and on the availability of the information needed, which may result in some kind of selection bias.

It should be noted that a balance exists between resolution and comprehensiveness. Indeed, although comprehensiveness is quite easily achieved at poor resolution level (e.g. collecting national sales data from a limited number of market authorisation holders), it becomes more resource-demanding to be comprehensive at high spatial (e.g. collecting data from every farm, hospital or outpatient clinic) and temporal (e.g. collecting monthly data) resolution levels. The Danish Vetstat database collecting monthly antimicrobial usage data from all Danish pig farms represents a good example where both high resolution and comprehensiveness were achieved (Jensen et al., 2004). However, the operational costs of such system are substantial; they were estimated to be approximately 200 000 euros on a yearly routine basis for the Vetstat database (Danish Ministry of Food, Agriculture and Fisheries, personal communication, 2015).

Stability over time

Stability means that the measurement of antimicrobial usage is comparable over time; it is mostly relevant for studies aiming to monitor antimicrobial usage trends over time. Stability is challenged by several issues. First, treatment practices, e.g. average weight at treatment and treatment duration tend to change over the years (see for example Chauvin et al. (2008) who described changes in macrolides usage practices in turkey broilers). In addition, the relative importance of antimicrobial active substances and their corresponding administration routes is evolving; this might be because one usage of an active substance has been replaced by another. In France, for example, animal exposure to antimicrobials decreased by 21.7% via the oral route and increased by 8.6% via the parenteral route between 2007 and 2012, mostly due to the reduction in medicated feed usage in livestock (Anses, 2014). Antimicrobial usage was also described as varying seasonally (Ferech et al., 2006; Elseviers et al., 2007), partly following influenza activity (Coenen et al., 2014). In addition, certain characteristics of antimicrobial products themselves are evolving over time. For example, the amount of active substance per package was shown to increase over the years (as the number of units per package and the amount of active substance per unit increased) (Coenen et al., 2014), whereas antimicrobial prices tended to fall following the introduction of generic antimicrobial products (Hoffman et al., 2007). The impact of population demographic changes (including their size and structure, e.g. age group or species distribution) should also be minimised to achieve stability of antimicrobial usage measurement (Kritsotakis and Gikas, 2006).

Assessment of exposure

The extent to which the quantification of antimicrobial usage is able to assess exposure to antimicrobials, which in turn will determine the antimicrobial resistance selection pressure exerted, should also be considered as an important requirement, especially for studies exploring the association between antimicrobial usage and resistance. At this stage it is still not fully determined which of the exposure characteristics (e.g. antimicrobial spectrum of the compound

used, frequency of exposure, duration of exposure, level of dose, route of administration) is most influential in terms of the selection pressure exerted. Therefore, there is a clear need for a better understanding of these questions which will subsequently also make it possible to select the most appropriate exposure measurements to incorporate into the quantification systems. The ESVAC project proposed that the description of selection pressure should ideally include both the level of exposure (antimicrobial agent, daily dose administered and numbers of treated individuals) and the exposure duration (European Medicines Agency, 2013).

Comparability between populations

Comparability of antimicrobial usage measurement represents a major challenge and is a critical requirement for studies aiming to compare usage between different populations such as different species, countries, farms, hospitals or outpatient clinics. Indeed, comparability is threatened at the same time by i) the diversity of available antimicrobial treatments (authorised products, dosages, amount of active substance per package, recommended doses) (Postma et al., 2015), ii) the variability of antimicrobial treatment practices between populations (daily dose, weight at treatment, treatment length, mode of administration, prices), iii) the differences in the population at risk of being treated (population size and structure, average weight at treatment), and iv) the choice of the period at risk of being treated (influence of the season or the species' average lifespan).

As observed for resolution and comprehensiveness, the combination of measuring detailed exposure and aiming at good comparability is often difficult: in general, the better the information on exposure, the worse the comparability of antimicrobial usage between two populations. As an example, using Danish and Dutch lists of daily doses for pigs gives a correct estimate of exposure in each country, but impairs the comparability of their antimicrobial usage (Taverne et al., 2015). Yet, both requirements can be achieved by working within similar target populations (e.g. species, production types, age groups). This was highlighted by Bondt et al. (2013) who recommended collecting veterinary antimicrobial usage data at least at species level to be able to compare the

antimicrobial exposure between different countries using antimicrobial sales data (Bondt et al., 2013).

How is antimicrobial usage measured?

As mentioned above, antimicrobial usage is quantified using indicators defined as the number of 'technical' units of measurement consumed and normalised by the population at risk of being treated in a defined period (European Medicines Agency, 2013). The term 'technical' means that the units of measurement are not used as traditional units of measurement (e.g. kilograms) to measure a physical quantity (e.g. weight) directly, but rather as theoretical reference values to express consumption of antimicrobial agents (European Medicines Agency, 2013).

Direct and indirect access to the technical unit of measurement of antimicrobial usage

The technical units of measurement described in the literature vary substantially; they include the treatment costs, the number of antimicrobial items (i.e. the number of times an antimicrobial appears on prescription) (Scottish Antimicrobial Prescribing Group, 2014) or number of packages used or used daily, the active substance weight, the number of live kilogram-days or individual-days treated (i.e. the product of a given treatment length and a live weight or a number of individuals respectively), the number of individuals or live weight receiving a full treatment course, and the number of individuals treated daily (see Figure 1). Technical units located at the top of Figure 1 are directly accessible; this means that no estimation or approximation is needed to collect them (i.e. exact data are accessible); others require some standardisation and calculation. In addition, some technical units describe the used amount very precisely (e.g. weight of active substance) whereas others are only a remote estimate of the true usage (e.g. medication cost). At national level, information on the numbers of packages sold can be directly collected from manufacturers, wholesalers, pharmacies, prescribing doctors and hospitals or reimbursements (Coenen et al., 2014 ; Bruyndonckx et al., 2014). The corresponding weight of antimicrobial active

substance can then easily be deducted by multiplying the number of packages by the package volume and dose (Ministry of Agriculture, Forestry and Fisheries of Japan, 2013; Food and Drug Administration, 2014; European Medicines Agency, 2014). Data directly obtained from manufacturers and wholesalers are exhaustive and relatively easily accessible as they rely on computed data from a limited number of stakeholders. However, it is almost impossible to identify by whom, when and how the antimicrobial products were used. In veterinary medicine in particular, a time delay was observed between sales recorded by manufacturers and their actual usage by farmers (Anses, 2015). In addition, data collected from manufacturers and wholesalers only provide exact amounts of antimicrobials sold for all animal species together. However, many veterinary antimicrobial products are licensed for several species and one needs to reallocate the amounts sold to the different species to allow for a normalisation by the relevant population at risk. This can be achieved via several approaches, for example asking the market authorisation holders to provide an estimate of the amount of active substance sold for each species (Anses, 2014), extrapolating from cross-sectional studies at species level (Filippitzi et al., 2014), or simply reattributing the amounts proportionally to the animal species demographics (Bondt et al., 2013). However, in all of these approaches, only an approximation of the distribution will be obtained. The same issue occurs in human medicine when differentiating outpatient from hospital antimicrobial usage data obtained from wholesalers (Vander Stichele et al., 2004).

At high resolution level, antimicrobial treatment costs can be directly recorded from the hospital pharmaceutical expenditures (Arnold et al., 2006; Weese, 2006) or from the farm invoices kept by the farmer and sometimes entered into technical databases (Corrégé et al., 2014). Numbers of packages can also be directly collected at hospital level using pharmacy stock data (Ansari et al., 2003; Schwartz et al., 2007) and at farm level, using for example drug-bottle-collection containers (Dunlop et al., 1998) or farm deliveries (Hémonic et al., 2013). However, collecting *a posteriori* farm delivery data might be tedious in the absence of automated data collection systems. As only individual treatments are prescribed in human medicine, numbers of treated individuals might also directly be collected from the number of insured individuals in countries

where insurance systems are in place (Coenen et al., 2014).

In short, a limited number of technical units are directly accessible at national level, namely the number of packages and corresponding weight of active substance. Other technical units, such as the treatment costs and the number of treated individuals, can be available at high resolution level, but because the number of individual hospitals, outpatient clinics or farms is so high it becomes very resource-demanding to collect these data, especially when comprehensive data are required. As a consequence, either automated data collection systems (e.g. OsMed in Italy (Agenzia Italiana Farmaco, 2016), Vetstat in Denmark (Stege et al., 2003), Ab-register in Belgium (www.registreab.be)) are set up to collect usage data in an automated way at high resolution or indirect calculations are used to obtain an estimation of the number of technical units based on a number of assumptions (see Figure 1).

[Insert Figure 1]

Figure 1 gives an overview of different technical units of measurement that can be determined from the number of antimicrobial packages or items (and corresponding weight of active substance) in relation to different ways of describing the population at risk of being treated. First, the number of live kilogram-days treated is estimated by dividing the weight of active substance by the daily dose which corresponds to the amount of active substance used per kilogram of individual and per day. The number of individual-days treated is further obtained by dividing the number of live kilogram-days treated by the weight at treatment. Antimicrobial usage can also be expressed as a number of individuals (respectively live weight) receiving a full treatment course, dividing the number of individual-days treated (respectively number of live kilogram-days treated) by the treatment length. A complete treatment course is a course of a given length and dose and the product of the antimicrobial daily dose and the treatment length is commonly called the ‘course dose’ (Resi et al., 2001; European Medicines Agency, 2013). The number of individuals treated daily is obtained by dividing the number of individual-days by the period at risk of being treated. This period is generally set at one year, but alternative possibilities exist, e.g. using the length of the animal production period (Timmerman et al., 2006).

Measurement unit of the population at risk of being treated

The population at risk of being treated can be considered from two perspectives: i) as a denominator by which antimicrobial amounts are normalised in order to estimate precisely which proportion of the population is exposed to antimicrobials, and ii) as a variable to correct for fluctuations and differences in population demographics and thus to ensure that the measure is repeatable over time and comparable between populations (e.g. countries). The population at risk of being treated is currently expressed using two types of unit: the biomass (or live weight) at risk of being treated and the number of individuals at risk of being treated. The biomass at risk of being treated is usually approximated by the product of the number of individuals at risk of being treated and a standard body weight, the latter being either a standard weight at treatment (ECDC, EFSA and EMA, 2015) or a standard weight of live and slaughtered animals (Anses, 2014). The main advantage of using biomass is that it allows different animal species to be combined within the same population; this is the approach used by the ESVAC project to compute the Population Correction Unit (PCU) (European Medicines Agency, 2014). In Denmark, where antimicrobial usage is collected per species and age group, the biomass of a species is calculated by taking into account the average live body-weight and the average life-span of the species (DANMAP, 2013). An important limitation of the biomass concept is the question whether biomass expressed as kg of live weight is a good representation of the actual biomass of concern (microflora) over all species. Therefore it can be concluded that biomass, especially when consisting of a combination of different species, is only a very rough estimate of the population at risk of being treated.

The number of individuals at risk of being treated varies with the study resolution level. In veterinary medicine, this number usually includes both reproductive (also called present or live) and growing (or slaughtered) animals (Anses, 2013; NETHMAP and MARAN, 2013) and can be corrected for export and import of live animals (European Medicines Agency, 2014). Some studies conducted at farm level only focused on growing animals (Timmerman et al., 2006; Pardon et al., 2012). The definition of animal groups (age categories in particular), which can be based on

population or herd level data, also influences the number of individuals at risk of being treated. In human medicine, the sources used to inform the number of individuals at risk of being treated are related to the specificity of the target population in which antimicrobial usage is measured. Thus, the number of inhabitants, insured individuals and physician contacts were mostly used to measure outpatient antimicrobial usage (Coenen et al., 2014), whereas the number of occupied beds (World Health Organization, 2015a), number of finished consultant episodes (Curtis et al., 2004) or number of admitted patients (Kuster et al., 2008; DANMAP 2013) were proposed to measure antimicrobial usage at hospital level. However, because the number of occupied beds is more difficult to collect, some studies also use the number of inhabitants to estimate the population at risk of being treated in hospital (Vander Stichele et al., 2004).

Data sources

Figure 1 showed that indirect access to the technical units of measurement of antimicrobial usage requires three parameters to be estimated: the daily dose, the treatment length and the weight of the animal/patient at treatment. Here we present the sources that can be used to inform these parameters.

Data sources to inform daily doses

Daily doses can be presented using standardised international measurement units; in that case, they are conventionally termed “defined” daily doses (i.e. if national or other values are used, the term “defined” is omitted). For human antimicrobial usage, the Defined Daily Dose (DDD) was introduced and defined by WHO as the assumed average maintenance dose per day for a drug used for its main indication in a 70 kg adult (World Health Organization, 2015a). The principle is that a single DDD is attributed by Anatomical Therapeutic Chemical (ATC) code (the latter dividing the antimicrobial active substances into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties) (World Health Organization, 2015a) based on a compromise of the available information including the dose recommended in the summary of product characteristics (SPC) from various countries. The DDD

428 is expressed in milligram per day (the weight at treatment being set at 70 kg), thus the division of
429 the active substance weight by the DDD directly provides a number of individual-days treated
430 (see Figure 1). A similar definition was developed for veterinary products (Jensen et al., 2004)
431 and called Defined Daily Dose for Animals (DDDvet) (European Medicines Agency, 2015) or
432 DADD (DANMAP, 2013) or ADD_{kg} (Anses, 2014) or daily dosages (dd) (NETHMAP and MARAN,
433 2013); it is expressed in milligram per kilogram and per day. To our knowledge, no international
434 list of DDDvet has been developed so far, but several countries have created their own lists
435 (Anses, 2014; DANMAP, 2013; NETHMAP, 2013). Some discrepancies exist between their
436 respective methodologies; for example, certain countries compute daily doses for animals per
437 licensed product and per animal species (Anses, 2014; NETHMAP 2013), whereas others have
438 developed daily doses for animals listed by active substance, administration route, animal species
439 and age group (DANMAP, 2013). Moreover, where a range of doses is recommended in the SPC,
440 some countries work with median values (Jensen et al., 2004), and others with averages (Postma
441 et al., 2015), maximum values (Anses, 2014) or doses of the main indication (DANMAP, 2013;
442 World Health Organization, 2015a). Another difficulty relates to the definition of daily doses for
443 combined products, with the possibility of counting the combination either as one defined daily
444 dose, regardless of the number of active substances included in the combination (World Health
445 Organization, 2015a), or as the sum of several defined daily doses corresponding to the number
446 of combined active substances (usually two or three). When the sum of defined daily doses is
447 considered, the individual defined daily doses are either the same as those assigned to the single
448 active substance for the same species or a different one (accounting for synergies between
449 combined active substances) (European Medicines Agency, 2015). The ESVAC project is
450 currently developing a common, standardised list of DDDvet across all EU Member States, with
451 priority being given to broiler, cattle and pig antimicrobial products (European Medicines Agency,
452 2015). A first attempt to develop such a list for pig products was conducted among four European
453 countries (Postma et al., 2015) and clearly showed that huge discrepancies in recommended
454 doses may exist within and between countries for drugs containing the same active substance.
455 This was confirmed by a recent study that highlighted major differences between daily doses for

pigs in the Netherlands and in Denmark (Taverne et al., 2015), leading to significant variations in estimates of antimicrobial consumption in pigs in the Netherlands in 2012. Depending on farm types and antimicrobial classes, the usage based on Danish daily doses for animals varied from 55.6% to 171.0% of the usage estimated with Dutch daily doses. Similarly in human medicine, WHO has clearly stated that the DDD is a compromise based on available information about doses used in various countries (World Health Organization, 2015a). This shows that using DDD or DDDvet values implies a generalisation which may sometimes be unwanted. This can partially be avoided through approximating daily doses using the prescribed daily dose or the used daily dose (i.e. the dose actually administered). Different studies in human and veterinary medicine showed that both the prescribed daily doses (Chauvin et al., 2002; Jensen et al., 2004; de With, 2009; European Medicines Agency, 2015) and the used daily doses (UDDvet) (Polk et al., 2007; Callens et al., 2012; Pardon et al., 2012; Persoons et al., 2012; Merle et al., 2014) deviate from the defined daily doses. Where the used daily dose or the prescribed daily dose is lower than the defined daily dose, a calculation based on the defined daily dose will underestimate the number of live kilogram-days treated, the number of individual-days treated, the live weight and the number of individuals receiving a full treatment course as well as the number of individuals treated daily (see Figure 1), and will thus underestimate the antimicrobial usage (Polk et al., 2007; Dalton et al., 2007).

Data sources to inform treatment length

In the same way, treatment length can be estimated from i) the recommended length as defined in the SPC; this source is used to compute the Defined Course Dose for Animals (DCDvet) which is the product of the recommended treatment length and the DDDvet (European Medicines Agency, 2013); the course dose animal is also called ACD_{kg} in France (Anses, 2013), ii) the prescribed treatment length if available, and iii) the administered treatment length as described by the medical doctor, the veterinarian, the farmer or the patient himself/herself (Timmerman et al., 2006; Laanen et al., 2013). Again, recommended treatment lengths were shown to vary substantially between countries, for example for oral antimicrobial products used in pig veterinary

483 medicine (average variation of 7.5 days) (Postma et al., 2015). Administered treatment length
484 may also deviate from prescribed or recommended treatment length (Kardas, 2002; Swinkels et
485 al., 2015). If the actual treatment length is shorter than the recommended one, a calculation based
486 on the recommended treatment length will underestimate antimicrobial usage when expressed
487 as a number of individuals or a live weight receiving a full treatment course.

488 Data sources to inform weights at treatment

489 Body weights at treatment are hardly available from field studies although some studies
490 extrapolated them from age at treatment (Chauvin et al., 2005; Timmerman et al., 2006); thus
491 standard weights are usually used. For human antimicrobial usage, body weight is fixed at 70 kg
492 with the exception of a few products used exclusively in children (World Health Organization,
493 2015a). On the contrary, the average animal body weight at treatment varies substantially
494 between species, production types and age groups. If the actual weight at treatment is lower than
495 the standard body weight (e.g. if antimicrobials are administered to children of 30 kg), a calculation
496 based on the standard weight at treatment will underestimate antimicrobial usage when
497 expressed as a number of individuals-days treated, a number of individuals receiving a full
498 treatment course or a number of individuals treated daily.

499 The ESVAC project adopted a list of standardised theoretical body weights at the time most likely
500 for treatment for each species in order to compute the PCU (European Medicines Agency, 2014).
501 However, field studies conducted at national level showed that these weights differ significantly
502 between countries, due to different production (e.g. slaughter weights) and treatment practices
503 as well as different definitions of the animal age groups or categories. Thus, different standard
504 weights at treatment are presented in national reports for antimicrobial usage in livestock. For
505 example, veal calves are estimated to be treated on average at 172 kg in the Netherlands
506 (NETHMAP and MARAN, 2013), 86 kg in Denmark (Jensen et al., 2004), 70 kg in France (Anses,
507 2013) and 140 kg in the ESVAC project (European Medicines Agency, 2014). Standard weights

508 at treatment can also be defined per production type if antimicrobial usage is monitored at this
509 resolution level (DANMAP, 2013).

510 **Indicators of human and veterinary antimicrobial usage**

511 Figure 1 shows the units of measurement for the amount of antimicrobial usage (in the numerator)
512 and the population at risk of being treated (in the denominator) that lead to the calculation of
513 indicators of antimicrobial usage, as well as the relationships between the indicators. For
514 simplicity, this study includes only the indicators presented in English or French scientific articles
515 or national reports and for which the quantification of antimicrobial usage is based on antimicrobial
516 sales, deliveries and reimbursement data. However, these indicators were developed to be used
517 within a particular context and two indicators built on the same technical units of measurement
518 are not necessarily based on the exact same data sources. For example, the indicators called
519 PID and PIID are both calculated from the number of packages used daily normalised by a
520 number of individuals at risk of being treated (Coenen et al., 2014), but for the PID the
521 denominator is the number of inhabitants whereas for the PIID the denominator is the number of
522 insured individuals. Readers are invited to consult the Appendix Table S2 that provides details of
523 the indicator calculations, highlighting the numerators and the denominators that were used as
524 well as the data sources to inform them.

525

526 Comparison of antimicrobial usage indicators

527 A limited number of studies have compared several indicators applied to the same antimicrobial
528 usage data in order to achieve the same objective. In human medicine, these included some
529 studies analysing the influence of the selection of different indicator numerators (Kern et al., 2005;
530 Muller et al., 2006; Polk et al., 2007; Dalton et al., 2007) and denominators (Curtis et al., 2004;
531 Filius et al., 2005; Kuster et al., 2008) on the comparison and monitoring of antimicrobial usage
532 in hospital settings. For example, Muller et al. (2006) showed that the number of individual-days

533 treated estimated by the DDD approach at a university hospital overestimated the prescribed
534 number of treatment days by 40%. Other studies quantified the discrepancies in the estimation of
535 outpatient antimicrobial usage time trends when working with different numerators and
536 denominators (Coenen et al., 2014; Bruyndonckx et al., 2014). An example is provided by Coenen
537 et al. (2014) who explored outpatient antimicrobial usage in Belgium between 2002 and 2009 and
538 concluded that antimicrobial usage increased when expressed in DDD per 1000 inhabitants per
539 day and decreased when expressed in packages, treatments and insured individuals per 1000
540 inhabitants per day. In veterinary medicine, some authors applied several indicators based on
541 different numerators to the same data in order to compare antimicrobial usage between countries
542 (Taverne et al., 2015) or farms (Jensen et al., 2004), to monitor usage over time (Chauvin et al.,
543 2008) or to describe discrepancies between used and recommended doses (Persoons et al.,
544 2012). Bondt et al. (2013) investigated the impact of denominator selection when comparing
545 antimicrobial usage based on sales data between countries (Bondt et al., 2013). They showed
546 that antimicrobial usage based on total sales data and expressed in mg of active substance per
547 PCU strongly overestimated the true difference in usage in the Netherlands compared to
548 Denmark, even though the two countries have similar animal demographics.

549 To further illustrate the differences in outcomes when using different indicators, each indicator
550 presented in Figure 1 was applied to a notional antimicrobial usage dataset in fattening pigs and
551 human medicine. The results are presented in Appendix S3 of the Supporting Information; they
552 illustrate i) the variability observed in a given indicator calculated from different input data and
553 parameters and ii) the variability observed in a given antimicrobial usage estimate (i.e. with exact
554 same input data and parameters) calculated with different indicators. Explaining the difference in
555 outcome between indicators is easier when indicators are directly related (i.e. when numerators
556 are connected by a direct arrow in Figure 1). In the Appendix S3 example, the observed
557 correlations between indicators varied from 0.34 to 0.97 and were especially weak for indicators
558 based on a number of packages used daily or treatment costs.

559

Suggestions on technical units, indicators and data sources to be selected in accordance with the study objective

Based on the above described requirements related to the specific study objectives and the available antimicrobial usage measurement approaches, suggestions on preferred technical units and data sources are provided (Table 2).

[Insert Table 2]

Suggestions to monitor usage trends over time (*Objective 1*)

For studies aiming to monitor antimicrobial usage trends over time, data can be collected from national to local level depending on the relevant spatial resolution level. As comprehensiveness is not critical, data from a representative sample of the population is sufficient. The key requirement is stability over time, so attention should be paid to updating antimicrobial usage parameters: defined daily doses (using the DDD list regularly updated by WHO (World Health Organization, 2015b)), weight at treatment and treatment duration, as well as the size and structure of the population at risk of being treated, as these are dynamic and influential (Kritsotakis and Gikas, 2006; Chauvin et al., 2008). Technical units based on number of daily doses (i.e. number of live kilogram-days treated, live weight or number of individuals receiving a full treatment course, number of individual-days treated or number of individuals daily treated) or packages and items should be preferred, as they correct for possible changes in the relative importance of active substances and corresponding administration routes. Coenen et al. (2014) also recommended using number of packages (instead of DDD based indicators) in countries dispensing complete packages; indeed, number of packages was shown to be a better proxy of antimicrobial prescribing in case the number of units per package (i.e. the pack size) or the dose per unit was increasing over time (Coenen et al. 2014). Treatment costs are better avoided as antimicrobial prices were shown to vary with time; however, treatment costs might be considered for economic or logistical studies over short time periods, where antimicrobial prices and treatment practices are assumed to be constant. The period at risk of being treated is preferably set at one year to

586 correct for seasonal fluctuation in antimicrobial usage patterns (Ferech et al., 2006; Elseviers et
587 al., 2007); July–June years should be preferred in human medicine to capture winter peaks of
588 influenza activity within the same 12-month period (Coenen et al., 2014).

589 **Suggestions to compare usage between species or countries (*Objective 2*)**

590 To compare antimicrobial usage between species or countries, national level data can be used
591 and does not need to be comprehensive. Technical units based on the number of daily doses
592 should be preferred, although the weight of active substance might be acceptable for studies
593 conducted in specific target populations (e.g. same animal species and production type or same
594 hospital department), and focusing on the same active substance and administration route.
595 Parameters should be standardised to be able to compare antimicrobial usage based on the
596 number of live kilogram-days treated, live weight or number of individuals receiving a full treatment
597 course, number of individual-days treated or number of individuals treated daily. As differences
598 in parameters do exist between countries, species, hospitals, outpatient clinics or farms,
599 standardised values need to be defined by consensus (see Postma et al. (2015) for an example).
600 Treatment costs or number of packages and items do not correct for daily dose, weight at
601 treatment and treatment length; thus they should be avoided to compare antimicrobial usage
602 between two populations for any purposes other than economical or logistical ones. Fixed time
603 period or length of the animal production period can be used to define the period at risk of being
604 treated.

605 **Suggestions for benchmarking between hospitals, outpatient clinics or farms (*Objective*
606 ***3*)**

607 Similar recommendations can be made for the measurement of antimicrobial usage for
608 benchmarking between hospitals, outpatient clinics and farms, although, in that case, census data
609 is required to achieve comprehensiveness. Moreover, antimicrobial usage data should be
610 collected at farm, hospital or outpatient clinic level as high resolution is critical. Number of live
611 kilogram-days treated, live weight or number of individuals receiving a full treatment course,

number of individual-days treated or number of individuals daily treated should be preferred to quantify the amount of antimicrobials consumed, although treatment costs, weight of active substance or number of items or packages are acceptable for studies conducted in specific target populations (and when using the weight of active substance, focusing on the same active substance and administration route).

Suggestions to study the association between antimicrobial usage and antimicrobial resistance (*Objective 4*)

To study the association between antimicrobial usage and antimicrobial resistance, data can be collected either at national level, which includes both the selection and spread of antimicrobial resistance (i.e. ecological studies), or at farm, hospital or outpatient clinic level, where the focus is more on the selection of antimicrobial resistance following antimicrobial usage. The number of live kilogram-days treated, the number of individual-days treated and the number of individuals treated daily should be preferred as they take into account the level of exposure and the exposure duration in accordance with the ESVAC project recommendations (European Medicines Agency, 2013). On the contrary, the live weight or the number of individuals receiving a full treatment course does not vary with treatment length; these units rather describe whether or not individuals were exposed, without considering for how long. In addition, the study of the association between antimicrobial usage and resistance should ideally be based on the used daily dose, the actual weight at treatment and the actual treatment length in order to obtain an accurate description of the exposure to antimicrobials. Qualitative data (e.g. administration route, antimicrobial class and spectrum of activity) should also be collected to refine the description of the selection pressure, although at this stage, it is still unclear what exposure characteristics mostly influence the selection pressure exerted. The population at risk of being treated should be selected in accordance with the population under antimicrobial resistance monitoring. In addition, data should be collected at high temporal resolution (e.g. monthly or quarterly data) as the time delay between antimicrobial usage and resistance was shown to be short (i.e. several months) (Monnet et al., 2001).

Conclusion

Several objectives can be pursued by antimicrobial usage studies, implying a number of requirements regarding the way in which antimicrobial usage should be measured. In parallel, a variety of indicators and approaches to measure antimicrobial usage are currently available and result in substantial variation in outcomes and sometimes even apparent discrepancies. By combining study requirements with available approaches to measure antimicrobial usage, we were able to provide some suggestions on the most appropriate indicators and data sources to be used for a given study objective.

At this stage, however, it was not possible to identify a single indicator as being the most suitable for a given objective. This would require a number of data gaps to be addressed, in particular: i) the defining of gold standards for the evaluation of indicators of antimicrobial usage, including for example their sensitivity and specificity, ii) the absence of a scientific basis to identify which parameters better describe antimicrobial selection pressure, and iii) the lack of studies comparing the application of several indicators to the same antimicrobial usage data.

Additionally, in a context of limited resources, it might be difficult to develop multiple monitoring systems that would perfectly suit every individual study objective. To tackle this issue, one might consider i) developing intermediate systems that would imperfectly address a combination of several objectives, ii) promoting the development of parallel monitoring systems (e.g. public-private partnerships) or iii) developing advanced monitoring systems that could properly address several objectives, i.e. using automated data collection at high resolution to compute more accurate indicators; however, these come at a cost.

To conclude, we have shown that some difficulties in measuring antimicrobial usage are common to human and veterinary medicine, and each discipline could certainly benefit from the experience gained in the other to improve its methodology and possibly to develop a common approach that

664 would support the joint analysis of antimicrobial usage data in humans and animals (ECDC, EFSA
665 and EMA, 2015).

666

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Glossary of abbreviations.

Appendix S2. Indicators of human and animal antimicrobial usage calculated from sales, deliveries and reimbursement data.

Appendix S3. Comparison of indicators applied to the same notional antimicrobial usage data in humans and fattening pigs.

Table 1. Requirements for the measurement of antimicrobial usage in accordance with the study objective.

Study objective	Expected outcome	Requirements for the measurement of antimicrobial usage				
		Spatial and temporal resolution	Comprehensiveness	Stability over time	Assessment of exposure level and duration	Comparability between populations
1. Monitoring usage trends over time	Antimicrobial usage in a given population over period A in comparison with period B	Low to high	Low	High	Low	Low
2. Comparison of usage between different species or countries	Antimicrobial usage by individual or given biomass of species or country A in comparison with species or country B over a given period of time	Low	Low	Low	Low	High
3. Benchmarking between hospitals, outpatient clinics or farms	Antimicrobial usage by individual or given biomass in hospital/medical or veterinary practice/farm A in comparison with hospital/medical or veterinary practice/farm B over a given period of time	High	High	Low	Medium	High
4. Study the association between antimicrobial usage and antimicrobial resistance	Antimicrobial usage in a population that leads to the selection and spread of AMR over a given period of time	Low (if selection and spread of resistance are considered together) High (if focus on resistance selection)	Low	Low	High	Low

The requirement levels (i.e. low, medium, high) should be read in columns and aim to rank the relative importance of each requirement across the different study objectives.

Table 2. Recommendations for the measurement of antimicrobial usage in accordance with the study objective

	Study objective			
	1. Monitoring of usage trends over time	2. Comparison of usage between species or countries	3. Benchmarking between hospitals, outpatient clinics or farms	4. Study the association between antimicrobial usage and antimicrobial resistance
Data sources to be used				
Amount of antimicrobials (numerator)	Data collected from national to local level (farm, hospital or outpatient clinic), depending on the resolution level of interest Data can be collected from a population sample	National level data as high resolution is not critical Data can be collected from a population sample as comprehensiveness is not critical	Data at farm, hospital or outpatient clinic as high resolution is critical Census data collection as comprehensiveness is critical	National level data if both selection and spread of antimicrobial resistance are considered Data at farm, hospital or outpatient clinic level if focus on the selection of antimicrobial resistance Data can be collected from a population sample as comprehensiveness is not critical
Parameters	Used or updated standardised daily doses, weights at treatments and treatment duration (based on field studies)	Standardised daily doses, weights at treatments and treatment length	Standardised daily doses, weights at treatments and treatment length	Used daily doses, weights at treatments and treatment length should be used to describe the selection pressure
Population at risk of being treated (denominator)	Correct for changes over time in the size and structure of the population at risk of being treated	Preferably similar and specific target populations (animal species, production types, medical sector) to improve comparability	Preferably similar and specific target populations (animal species, production types, medical sector) to improve comparability	Preferably similar and specific target populations (animal species, production types, medical sector) to relate antimicrobial usage to antimicrobial resistance observed in the corresponding population
Technical unit of antimicrobial usage measurement (numerator)				
Recommended unit	Number of live kilogram-days treated, live weight or number of individuals receiving a full treatment course, number of individual-days treated, number of individuals treated daily, number of packages or items	Number of live kilogram-days treated, live weight or number of individuals receiving a full treatment course, number of individual-days treated, number of individuals treated daily	Number of live kilogram-days treated, live weight or number of individuals receiving a full treatment course, number of individual-days treated, number of individuals treated daily	Number of live kilogram-days treated, the number of individual-days treated and the number of individuals treated daily
Acceptable unit	-*	Weight of active substance (if focus on a specific target populations, active substance and administration route)	Treatment costs, weight of active substance, number of items or packages (if focus on a specific target population)	Live weight or number of individuals receiving a full treatment course

Units to be avoided	Treatment costs, weight of active substance (except if short period study where treatment prices and treatment practices are assumed to be constant)	Treatment costs (might be acceptable for comparison between species within the same country), number of items or packages	-*	Treatment costs, number of items or packages, weight of active substance
Population at risk of being treated (denominator)				
Recommended unit in human medicine	Number of individuals at risk of being treated	Number of individuals at risk of being treated	Number of individuals at risk of being treated	Number of individuals at risk of being treated
Recommended unit in veterinary medicine	Biomass at risk of being treated (if one or multiple species are included), number of individuals at risk of being treated (if only one species is included)	Biomass at risk of being treated (if one or multiple species are included), number of individuals at risk of being treated (if only one species is included)	Biomass at risk of being treated (if one or multiple species are included), number of individuals at risk of being treated (if only one species is included)	Biomass at risk of being treated (if one or multiple species are included), number of individuals at risk of being treated (if only one species is included)
Period at risk of being treated	Annual data to correct for seasonal fluctuations From July to June to capture winter peaks of influenza within the same 12-month period	Fixed time period (e.g. 1 year) or based on length of the animal production period	Fixed time period (e.g. 1 year)	Monthly or quarterly data
Appropriate indicator of antimicrobial usage (corresponding to the above recommended units)				
Recommended indicator in human medicine	In hospital: DDD/FCE, DDD/100 bed-day, DDD/100 admitted patients In outpatient clinics: PID, PIID or PCD (in countries dispensing complete packages), DDD/1000 inhabitants per year, TID, TIID, TCD, DID, DIID, DCD	In hospital: DDD/FCE, DDD/100 bed-day, DDD/100 admitted patients In outpatient clinics: DDD/1000 inhabitants per year, TID, TIID, TCD	In hospital: DDD/FCE, DDD/100 bed-day, DDD/100 admitted patients In outpatient clinics: DDD/1000 inhabitants per year, TID, TIID, TCD, DID, DIID, DCD	In hospital: DDD/FCE, DDD/100 bed-day, DDD/100 admitted patients In outpatient clinics: DDD/1000 inhabitants/year, DID, DIID, DCD
Recommended indicator in veterinary medicine	DDDvet/1000 animals/year, DCDvet/1000 animals/year, nDDay, ALEA, TI_{UDDvet}, DAPD	DDDvet/1000 animals/year, DCDvet/1000 animals/year, nDDay, ALEA, TI_{DDDvet}, DAPD	DDDvet/1000 animals/year, DCDvet/1000 animals/year, nDDay, ALEA, TI_{DDDvet}, DAPD	DDDvet/1000 animals/year, nDDay, TI_{UDDvet}, DAPD
Acceptable indicator in human medicine	-*	-*	PID, PIID, PCD	TID, TIID, TCD
Acceptable indicator in veterinary medicine	-*	Amount of active substance/1000 animals/year, amount of active substance per PCU	Treatment cost/kg carcass, amount of active substance/1000 animals/year, amount of active substance per PCU	DCDvet/1000 animals/year, ALEA

*No unit or indicator was considered in this cell.

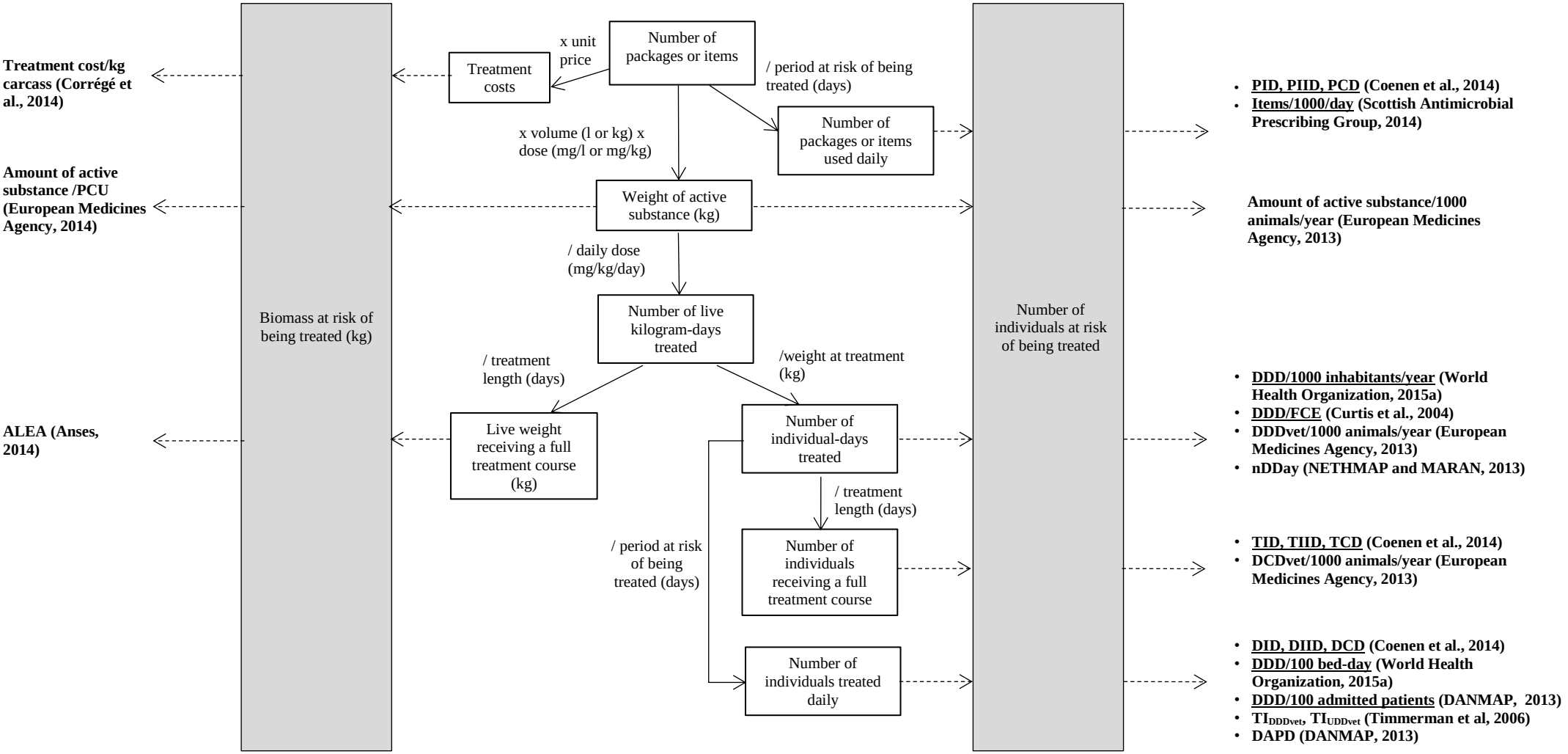

Fig. 1. Technical units of measurement indirectly accessed from number of packages or items and corresponding indicators of antimicrobial usage in humans and animals

The white boxes describe the technical units of measurement of antimicrobial usage with the solid arrows representing the calculation steps between them. The grey boxes describe the unit of measurement of the population at risk of being treated. Dashed arrows represent the normalisation of the technical unit of measurement by the population at risk of being treated that leads to the different indicators of antimicrobial usage (in bold). Underlined (respectively non-underlined) indicators are those used in human (respectively veterinary) medicine. DDD= Defined Daily Dose; DDDvet= Defined Daily Dose for Animals; DCDvet= Defined Course Dose for Animals. Please refer to the Appendix Table S2 for a detailed description of the indicators' calculation formulas. References accompanying the displayed indicators only provide illustrations of possible applications of the indicators and are not intended to be exhaustive.