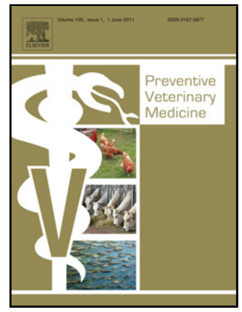
Accepted Manuscript



Title: The use of antimicrobials in global pig production: a systematic review of methods for quantification

Authors: Angkana Lekagul, Viroj Tangcharoensathien, Shunmay Yeung

PII: S0167-5877(18)30210-1
DOI: https://doi.org/10.1016/j.prevetmed.2018.09.016
Reference: PREVET 4542

To appear in: *PREVET*

Received date: 17-3-2018
Revised date: 27-8-2018
Accepted date: 16-9-2018

Please cite this article as: Lekagul A, Tangcharoensathien V, Yeung S, The use of antimicrobials in global pig production: a systematic review of methods for quantification, *Preventive Veterinary Medicine* (2018), https://doi.org/10.1016/j.prevetmed.2018.09.016

Review articles: Preventive Veterinary Medicine

The use of antimicrobials in global pig production: a systematic review of methods for quantification

Angkana Lekagul,[a, b], Viroj Tangcharoensathien[b], Shunmay Yeung[a]

[a] London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT, UK.

[b] International Health Policy Programme, Ministry of Public Health, Nonthaburi 11000, Thailand.

Background

Antimicrobial Resistance (AMR) is an increasingly serious threat to global public health. Overuse of antimicrobials can accelerate the emergence of antimicrobial resistance (World Health Organization, 2015b). In livestock industries, large amounts of antimicrobials are used for both therapeutic and non-therapeutic purposes including growth promotion (Aarestrup, 2005). In response to global concerns about AMR, in 2008, the World Organization for Animal Health (OIE) launched guidelines on the prudent use of antimicrobials in veterinary medicines, which describes the respective responsibilities of relevant stakeholders such as veterinarians, regulators, pharmaceutical industries, animal producers and consumers (World Organisation for Animal Health (OIE), 2008).

Measuring antimicrobial use is critical to understanding the magnitude and profile of antimicrobial resistance in countries. Measurement is the first step to detecting whether there is excessive and inappropriate use and monitoring whether policies aimed at optimising use are successful. Recognising this, international organizations such as FAO, OIE and WHO, have recommended that countries develop systems for monitoring antimicrobial consumption (World Health Organization, 2015a, OIE, 2016, FAO, 2016). The World Health Organization (WHO) guidelines defines antimicrobial "consumption" data captured from aggregate sales data such as form importer, local manufacturer or wholesales, whilst data on antimicrobial "use" are collected from patient-level data such as medical records and prescriptions (World Health Organization, 2017). Whilst there has been significant progress in the monitoring of antimicrobial use and consumption in the human health sector, action in the animal health sector has lagged behind (Schar et al., 2018). Some European countries established national programs for the surveillance of antimicrobial consumption in animals for more than 20 years ago, specifically DANMAP in Denmark in 1995 (Statens Serum Institut, 2012), MARAN in Netherlands in 1998 (Anonymous, 2012) and SWEDRES-SVARM (SWEDRES and SVARM, 2014). The European Medicines Agency established the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project in 2009(Agency, 2017) . ESVAC compiles, verifies and reports on antimicrobial consumption of veterinary antimicrobial agents in 29 European countries. Data are collected through a network of national focal points. Furthermore, ESVAC has been striving to set up a standardised methodology to allow for cross country comparisons. The monitoring of antimicrobial consumption serves various objectives. It monitors time trends of antimicrobial use, compares use by different antimicrobial classes, identifies high users and promotes more prudent use, and studies the association between level of usage and bacterial resistance (Collineau et al., 2017).

Currently, there is a wide variation in the availability and type of data, methods and use measurement across countries. The lack of uniformity hampers cross-country comparisons(Collineau et al., 2017). In order to guide the strengthening of existing monitoring systems and the development of new ones to facilitate cross-country comparisons, it is essential to understand the different existing methods, their strengths, limitations and operational feasibility.

This systematic review will describe and compare methods and measurement to quantify antimicrobial use in pigs, in order to contribute to the process of future guideline development of monitoring the antimicrobial use.

Abbreviations

ADD	Animal Daily Dose
ADDD	Animal Defined Daily Dose
AMR	Antimicrobial Resistance
CASP	Critical Appraisal Skills Programme
DADD	Defined Animal Daily Dosage
DDD	Defined Daily Dose
DDDA	Daily Doses Animal
DDDvet	Defined Daily Dose
DCDvet	Defined Course Dose
DPD	Daily Product Dose
EMA	European Medicines Agency
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
FAO	Food and Agriculture Organization
nDDay	Daily Dose per animal year
OIE	Organization for Animal Health
PCU	Population Correction Unit
PDD	Prescribed Daily Dose
PrDD	Product-related Daily Doses
TI	Treatment incidence

UDD	Used Daily Dose
WHO	World Health Organisation

Method

Scope of study and research question

The operational definitions of the terms used in this review are as follows.

Term	**Definition**
Antimicrobials	According to OIE definition, an antimicrobial is considered as a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (it kills or inhibits the growth of micro-organisms) at concentrations attainable *in vivo*. Anti-helminthic and substances classed as disinfectants or antiseptics are excluded from this definition (World Organisation for Animal Health (OIE), 2015).
Pig	The term refers to all stages of swine production including breeding and gestation, farrowing (from birth to weaning), nursery and feeding and finishing.
Use and consumption	As explained above WHO defines “use” data as estimates derived from patient-level data. It may focus on how and why antimicrobials are being used by health care providers and patients. “Consumption” data are usually reported when information on antimicrobial use in patients is not available. It can be collected from several sources such as import data, wholesale data or aggregated health insurance data. Consumption data provides a proxy estimate of the use of antimicrobials (World Health Organization, 2017).

	However, in this study, for simplicity the term "use" is applied to refer to both use at farm level and consumption at aggregate national or sub-national level.
Biomass	The weight or total quantity of living organisms of one animal species or of all the species in the community. Using biomass for antimicrobial consumption aims to compare the weight of animals between different species and between human and animals.

This review covers use of antimicrobials in pigs, with the following research question: "What methods and measurements are used to quantify the use of antimicrobials?"

Search strategy

- SPIDER tool

A "SPIDER" tool was applied in order to specifically identify relevant quantitative and mixed-method studies. It covers the Sample, Phenomenon of interest, Design, Evaluation and Research type) (Cooke et al., 2012).

S:	1) Surveys based on end-point antimicrobial usage: veterinary prescription, usage by pig farmer 2) Antimicrobial sales data (from pharmaceutical operators, such as importer, manufacturer, wholesaler)
P and I:	Antimicrobial use in pigs
D:	Observational studies, intervention studies
E:	Methods used for the measurement of antimicrobial use
R:	Quantitative study

- Eligibility assessment of studies and inclusion criteria

The following inclusion criteria were considered:

(i) the paper was published in, or translated into, the English language,

(ii) the study involved pigs of any age and type of production,

(iii) the study provided quantitative data on antimicrobial use with a focus or clear explanation of the methodology in pigs or other food producing animals including pigs,

(iv) The study had moderate to high ranking of a quality assessment.

- Search protocol

Literature on the use of antimicrobials in pigs was systematically reviewed between May to August 2017. Relevant scientific papers published in English peer-reviewed journal were identified using the keywords combinations in the title, abstract and content. All search terms were combined, see table 1.

<Table 1>

- Structured Database Search

Online electronic databases were searched in English language literature with restriction of the date of publication being after 2000: MEDLINE (http://ovidsp.tx.ovid.com; 1946 until present), ScienceDirect (http://www.sciencedirect.com; 1996 until present), Scopus (http://www.scopus.com; 1823 until present) and Web of Science (http://apps.webofknowledge.com; 1970 until present). The initial scope of the search focused on low- and middle-income countries. Due to the limited number of publications, it was expanded to cover studies in high-income countries.

- Grey literature

In addition to the structured database searches, articles were sourced through searches from the reference lists of key articles identified as in line with the research questions and inclusion criteria. This combination ensured that a wide range of articles from different sources was retrieved.

- Screening relevant records

After the searches, the duplicate studies and inconsistencies between titles, abstracts and keywords were removed. Then, full texts were reviewed; those which were reviews, clinical research, pharmacokinetic, biopharmaceutical studies and laboratory studies were excluded.

Studies were excluded for the following reasons:

- No report on pattern or volume of antimicrobial use in pigs
- Inappropriate study design: such as review, clinical research, pharmacokinetic and biopharmaceutical studies
- Focus on laboratory study, on human health or antimicrobial activity, relationship with AMR, specific disease related to drug recommendation
- Measurements of antimicrobial levels in farm waste, faeces and environment, residue in animal products
- Low level of quality from assessment (<50%)

Quality assessment

The methodological quality of the studies was assessed using an instrument adapted from the Critical Appraisal Skills Programme (CASP) (Critical Appraisal Skills Programme (CASP), 2014). The four criteria of quality assessment were a) aim, b) method, c) result and d) application. The answer to the four criteria are either 'yes', or 'no' or 'cannot tell'. Each criterion has certain a number of sub-criteria, there were in total eleven sub-criteria for quality assessment; see Table A2 (annex). If the assessment by the two independent reviewers (AS and VT) was 'no' or 'cannot tell', the score for that question was zero; the score for yes was one. When there were conflicting views, the reviewers discussed and sought consensus. In this review, the studies were ranked by quality criteria. The quality ranking was classified into three groups: High meant >75% of all eleven sub-criteria were met, moderate meats 50-75% were met, weak meant <50% were met.

Data extraction and synthesis

The full text of all relevant articles was reviewed and summarised using a standardised data extraction table in Excel which supported the sifting, sorting and annotation of primary source materials and data. Data extraction was categorized by three sets of variables: a) context variables: author, year of publication, year of study, title, journal, geographical area, objective and b) methodology variables: type of study, data source, sampling technique, sample size, methods for antimicrobial use measurement. See table A1 in annex for variables assessed in the study.

Results

Search processes

The search from the four database and hand search identified 2,362 articles. After screening and removal of duplications, 90 manuscripts remained for further screening. Of these 90 manuscripts, 37 manuscripts were selected on the basis of the inclusion criteria. Of these 37 manuscripts, seven articles described antimicrobials without essential information on the pattern or volume of antimicrobials use; these were excluded. Two articles were not included, because they were review articles. Another three articles were excluded as they only focused on the association between specific groups of antimicrobial and AMR. No studies were excluded due to low rank of quality assessment (<50%). In summary, a total of 12 studies were excluded from the set of 37 studies, leaving 25 manuscripts that met the inclusion criteria and were included in this systematic review.

< Figure 1>

Description of the studies

Of the 25 studies, 22 studies were published between 2010 and 2016, with the remaining three being published between 2000 and 2010. One study analysed global level use data and the others reported data from 12 countries. Twenty studies were from eight European countries of which six were conducted in Denmark; two were multi-country studies; one study in Belgium, France, Germany and Sweden, and the other included Denmark and Netherlands. Two studies were conducted in African countries (South Africa and Kenya). Another two studies reported data from China and Japan. See table 2 for characteristic of these studies.

<Table 2>

The quality assessment is reported in table A2 of the Annex. In general, the hypotheses and the objectives of the study were clearly described. Fifteen (60%) studies were ranked as high quality (meeting more than 75% of all eleven sub-criteria). Ten remaining studies were of moderate quality. None had low quality assessment.

Methods for measuring antimicrobial use

A large variation in terms of the methodological approaches and units of measurement of antimicrobial use was found.

1. Types of studies and data sources

As shown in table 2, eight studies were primarily methodological, for example comparing antimicrobial use by using different methods or variables (Carmo et al., 2017, Dupont et al., 2016, Taverne et al., 2015, Trauffler et al., 2014a, Bondt et al., 2013, Timmerman et al., 2006) or developing new methodologies (Ferner et al., 2014, van Rennings et al., 2015). Twelve studies aimed to estimate antimicrobial use (Jensen et al., 2004, Mitema et al., 2001b, Sjolund et al., 2016, Krishnasamy et al., 2015, Sjolund et al., 2015, Van Boeckel et al., 2015, Hauck et al., 2014, Hosoi et al., 2014, Bos et al., 2013, Callens et al., 2012, Eagar et al., 2012, Merle et al., 2012). One study examined both improving the national surveillance and measuring the antimicrobial use (Filippitzi et al., 2014). The remainder of studies assessed the association between the use of antimicrobials and farm management practice (Fertner et al., 2015, Vieira et al., 2011, Arnold et al., 2004).

Eleven studies (44%) presented data at national level (Carmo et al., 2017, Dupont et al., 2016, Krishnasamy et al., 2015, Van Boeckel et al., 2015, Filippitzi et al., 2014, Hauck et al., 2014, Hosoi et al., 2014, Bondt et al., 2013, Jensen et al., 2012, Eagar et al., 2012, Mitema et al., 2001b). Fourteen studies (56%) presented data at sample farm level (Sjolund et al., 2016, Fertner et al., 2015, van Rennings et al., 2015, Sjolund et al., 2015, Taverne et al., 2015, Ferner et al., 2014, Trauffler et al., 2014a, Trauffler et al., 2014b, Bos et al., 2013, Callens et al., 2012, Merle et al., 2012, Vieira et al., 2011, Timmerman et al., 2006, Arnold et al., 2004) with four of these studies complete farm data at a national level (Sjolund et al., 2016, Taverne et al., 2015, Bos et al., 2013, Vieira et al., 2011).

Data on antimicrobial use were collected from various sources. Of 25 studies, seven collected data through farm surveys (Sjolund et al., 2016, Sjolund et al., 2015, Ferner et al., 2014, Trauffler et al., 2014a, Trauffler et al., 2014b, Callens et al., 2012, Timmerman et al., 2006), six compiled national data from the surveillance of antimicrobial consumption(Carmo et al., 2017, Dupont et al., 2016, Taverne et al., 2015, Van Boeckel et al., 2015, Filippitzi et al., 2014, Bondt et al., 2013, Vieira et al., 2011), four collected data through veterinary prescriptions (Fertner et al., 2015, Bos et al., 2013, Jensen et al., 2012, Arnold et al., 2004), and four from a review of sales of pharmaceutical products (Carmo et al., 2017, Hauck et al., 2014, Hosoi et al., 2014, Eagar et al., 2012, Mitema et al., 2001b). Three studies drew information from more than one data source (van Rennings et al., 2015, Filippitzi et al., 2014, Merle et al., 2012) and one study used data on food animal antimicrobial utilization from the US, estimating the quantity of antimicrobials used in China (Krishnasamy et al., 2015).

Twenty-two studies (88%) reported antimicrobial use by major classes, while three studies (12%) reported in aggregation all classes of antimicrobial (Ferner et al., 2014, Fertner et al., 2015, Van Boeckel et al., 2015). Twenty studies (80%) reported the use of antimicrobials specific to pigs or other animal species but five studies (20%) only reported total use in all animal species (Van Boeckel et al., 2015, Ferner et al., 2014, Hauck et al., 2014, Eagar et al., 2012, Mitema et al., 2001a).

2. Numerators: the amount of antimicrobial use

Measuring numerators varied greatly, for example, by milligrams or kilograms of active ingredient and other more sophisticated adjustments such as defined daily dose, daily product dose, animal daily dose, used daily dose, prescribed daily dose, (see detail in Figure 2).

3. Denominators: the number or mass of animals

For denominator data, eight studies used national level animal population which was retrieved from government agencies such as National Statistics, Central registry for livestock (Carmo et al., 2017, Dupont et al., 2016, Taverne et al., 2015, Filippitzi et al., 2014, Hosoi et al., 2014, Bondt et al., 2013, Jensen et al., 2012, Vieira et al., 2011). Two studies applied data from the Food and Agriculture Organization (FAOSTAT) (Krishnasamy et al., 2015, Van Boeckel et al., 2015). For the twelve studies at farm level, the number of animals reported by a certain production type and the time period during the study period (Sjolund et al., 2016, Fertner et al., 2015, van Rennings et al., 2015, Sjolund et al., 2015, Ferner et al., 2014, Trauffler et al., 2014a, Trauffler et al., 2014b, Bos et al., 2013, Callens et al., 2012, Merle et al., 2012, Timmerman et al., 2006, Arnold et al., 2004).

Several studies applied different standard weights for animal (Carmo et al., 2017). For example, the weights of an animal at treatment in Denmark (32) were: weaner 15 kilograms, slaughtered pig 50 kilograms and sows 200 kilograms. In Austria (26) weights were: piglets 1.5-10 kilograms, weaners 10-30 kilograms, fattened pigs <60 kilograms, and sow and boar > 60 kilograms. In Sweden (18) weights were: sucking piglets 7 kilograms, weaners 7 kilograms, fatteners 35 kilograms and adult pigs 220 kilograms (Sjolund et al., 2015).

4. Unit of measurement: indicators used

Of the total 25 studies, there were ten different units of measurement. Nine studies calculated the total volume of antimicrobials used in the country per year (Carmo et al., 2017, Krishnasamy et al., 2015, van Rennings et al., 2015, Ferner et al., 2014, Filippitzi et al., 2014, Hauck et al., 2014, Eagar et al., 2012, Merle et al., 2012, Mitema et al., 2001b). Five of these studies (Hauck et al., 2014, Merle et al., 2012, Mitema et al., 2001b, Carmo et al., 2017, Filippitzi et al., 2014) calculated the volume of antimicrobial substances by multiplying the number of packages (package size) with the potency (strength of active substance) for each antimicrobial. One study (Eagar et al., 2012) calculated the volume of antimicrobials in kilograms of active pharmaceutical ingredient from the reports provided by pharmaceutical companies, while two other studies (van Rennings et al., 2015), (Ferner et al., 2014) used treatment data at the farms. Only one study attempted to estimate non-therapeutic antimicrobial use in livestock. This was done by multiplying the number of animals in different phases of production by the estimated feed consumed per day and the duration in days in each phase that the swine received antimicrobials through feed and doses of antimicrobials in the feed (Krishnasamy et al., 2015).

4.1 Antimicrobials use measured by milligrams of active substance per animal weight

Six studies used some measure of the biomass of animals in order to indicate the intensity of antimicrobial use (Carmo et al., 2017, Van Boeckel et al., 2015, Filippitzi et al., 2014, Hosoi et al., 2014, Trauffler et al., 2014a, Trauffler et al., 2014b). Biomass is the total weight of live animals. Two studies (Trauffler et al., 2014a, Trauffler et al., 2014b) calculated biomass at farms by multiplying the number of animals and the average weight. One study estimated biomass by using the carcass weight, which is the whole-body weight of a slaughtered animal after blood is drained, evisceration and skinning (Hosoi et al., 2014).

Biomass can be calculated by using a population correction units (PCU). The PCU provides a better measurement of animal weight exposed to antimicrobial treatment: one PCU is equivalent to one kilogram of biomass of live animal or slaughtered animals where the animal had been exposed to antimicrobials throughout their lifecycle. For example, gross weight at slaughter was 150 kilograms, but the PCU was 65 kilograms and 25 kilograms for slaughtered and fattening pigs (Agency, 2013). Two studies (Carmo et al., 2017, Filippitzi et al., 2014) calculated the total national PCU, with reference to the guidelines produced by ESVAC, by multiplying the numbers of livestock animals and slaughtered animals by the theoretical weight at the time they were exposed to antimicrobial treatment. Another study estimated the PCU by multiplying the numbers of live animals in a production period and a ratio of carcass weight to live weight of animals (Van Boeckel et al., 2015).

4.2 Antimicrobials use measured by daily dose per weight at treatment

The daily dosage is a measure of the amount of a specific active pharmaceutical ingredient (e.g. in milligrams) required to treat one kilogram of animal in one day with that antimicrobial preparation, and is based on the average dosage of a medicine per kilogram per day for a specific type of animal.

Defined Daily Dose (DDD) is a technical unit of measurement of antimicrobial consumption in humans, calculated by standard DDD-value. In animals, measuring antimicrobial by defined daily dosage is calculated by using a specified dose of medicine (Animal Daily Dose value (ADD-value)), so called Animal Daily Dose (ADD) (Dupont et al., 2016, Fertner et al., 2015, Taverne et al., 2015, Ferner et al., 2014, Trauffler et al., 2014a, Trauffler et al., 2014b, Bondt et al., 2013, Jensen et al., 2012) or by using the mean authorised dosage (Taverne et al., 2015, Bos et al., 2013, Merle et al., 2012) so called Daily Doses Animal (DDDA).

The ADD-value is specifically defined as the average maintenance dose per day for a drug used for its main indication for each animal species. The ADD-value was used in Denmark and Austria. They were based on the dose recommendations of each medicinal product registered in a country for each antimicrobial agent, administration route and animal species and when appropriate, also age group (Dupont et al., 2016, Fertner et al., 2015, Taverne et al., 2015, Ferner et al., 2014, Trauffler et al., 2014a, Trauffler et al., 2014b, Bondt et al., 2013, Jensen et al., 2012).

For the DDDA, antimicrobial use is equal to the amount of active substances divided by the total weight of the number of livestock in the farm and mean authorised dosage. Other studies applied the same formula but called the unit of measurement differently as Animal Defined Daily Dose (ADDD) (Bos et al., 2013) and Daily Dose per animal year (nDDay) (Merle et al., 2012). One study used Defined Animal Daily Dosage (DADD), which is a measure established at the level of the active ingredient, route of administration and pharmaceutical form and not at the level of a specific antimicrobial class (Taverne et al., 2015).

Product-related Daily Doses (PrDD) or Daily Product Dose (DPD) calculated the daily dose to an assumed factor of 0.8, correcting for the fact that the maximum doses are not used in every treatment (Ferner et al., 2014); this means only 80% of the maximal dosage of the active substances were administered per day per kilogram biomass (Trauffler et al., 2014a, Trauffler et al., 2014b).

4.3 Antimicrobial use measured by daily dose per treatment period

The Used Daily Dose (UDD) is the actual administered daily dose per kilogram biomass of a drug based on administered data reported by the farmer at farm level by a specific study. The formula for the UDD calculation is the weight of active substance divided by the number of treated animals,

multiplied by the average weight of animals and treatment duration. Three studies applied UDD (Carmo et al., 2017, Trauffler et al., 2014a, Trauffler et al., 2014b, Timmerman et al., 2006).
One study quantified antimicrobial use as a Prescribed Daily Dose (PDD). This was calculated for each active pharmaceutical ingredient and for each prescription according to the amount of active pharmaceutical ingredient per prescription (mg) divided by the average weight of the animals multiplied by the number of animals and treatment period (Arnold et al., 2004).

4.4 Antimicrobials use measured by daily dose per period at risk of treatment

To compare each administered antimicrobial in specific individual species, the treatment incidence was used in five studies (Sjolund et al., 2016, Sjolund et al., 2015, Filippitzi et al., 2014, Callens et al., 2012, Timmerman et al., 2006). It was defined as the number of pigs per 1,000 pigs that are treated daily with one ADD or UDD, which is equivalent to how many pigs per 1,000 pigs receive a dose of antimicrobials each day. In order to calculate the treatment incidence, the total UDD or ADD is divided by the treatment period, standard weight and population, then multiplied by 1,000. One study applied 'treatment incidence' rate for slaughtered pigs by dividing the number of ADD by 100 slaughtered pigs at risk (Vieira et al., 2011).

One study calculated 'treatment frequency' by using the sum of all UDD divided by population size. It identified how many days, on average, an animal in a herd is treated with one active pharmaceutical ingredient (van Rennings et al., 2015).

<Figure 2>

5. Volume of antimicrobial use

As described above, this review uncovered a large variation in how antimicrobial use was measured, and the actual magnitudes of use. The annual antimicrobial use in pigs ranged from 20,000 kilograms to72,300 kilograms at different farm and country levels. One study estimated 34 million kilograms of antimicrobials was found in medicated feed in pigs in China due to the massive number of livestock (Krishnasamy et al., 2015). However, more than one million kilograms were quantified in the studies in food animals in Germany (Hauck et al., 2014) and South Africa (Eagar et al., 2012) and about 63 million kilograms globally (Van Boeckel et al., 2015). On the other hand, lower use was documented in Kenya where only 15,000 kilograms of antimicrobials were used in one year in all animal species (Mitema et al., 2001b). A wide range of volume per biomass was reported, ranged from 33.9 mg per biomass in Austria (Trauffler et al., 2014a) with about 400 mg per biomass in Japan (Hosoi et al., 2014).

The ADD varied from lower than one (Fertner et al., 2015) to 16 ADD (Taverne et al., 2015) in different phases of pig production and countries. Treatment incidence per 1,000 pigs at risk per day ranged from lower than 10 (Carmo et al., 2017, Sjolund et al., 2016, Sjolund et al., 2015) to more than 200 treatment incidences (Sjolund et al., 2016, Callens et al., 2012).

However, careful interpretation across countries is needed as these measurements are not standardized. Also, the magnitudes of use are determined by the type of pig farms, animal demographic and the socio-economic context of a country. See details in table 3.

<Table 3>

Discussion

Data sources

Two main sources of data emerge from this review: national sales data and primary data collected through pig farm surveys. In many European countries, the national monitoring of antimicrobial consumption relies on national sales data of pharmaceutical products, the disadvantage of sales data is the lack of information on which species they are being used for, the indication, dose and duration of treatment. Farm or pharmaceutical company surveys apply prospective longitudinal or cross-sectional studies which provide additional detailed use by species and production types (European Medicines Agency, 2013). One study applies bottom up approach for national consumption data estimate, it collects data from some herds and extrapolates to the national level (Filippitzi et al., 2014). However, this approach could be inaccurate as the sampled farms are not designed as national representative samples.

Data sources for animal populations can be retrieved from total national data collection by government agencies such as slaughter house and production information, or it can be obtained from other sources such as the Association of Pig Farmers. Data from international organizations such as the FAOSTAT database hosted by the Food and Agriculture Organization is another source of the size of animal populations (Krishnasamy et al., 2015, Van Boeckel et al., 2015). Even though, FAOSTAT information is limited such as estimates for non-responses and incomplete report, and the lack of granularity on number of animal of species; it can be applied when data at the country is not available. Using different weights of animals at treatment across studies resulted in substantial differences in use and hinders comparability (Carmo et al., 2017, Dupont et al., 2016).

Methods and units of measurement

This systematic review describes methods for measuring antimicrobial use. All the studies in the review were conducted after 2000. Most of the literatures on the pattern of use of antimicrobials are derived from high-income countries in the European region; while very few studies were conducted in Asia and Africa, which applied the traditional measurement by weight of active substance per animal weight.

This review indicates that there is no global harmonised system for measuring antimicrobial use in animals. The proliferation of indicators using different measurements of both numerators and denominators hampers cross-country comparisons.

Several studies reported the quantity of use in kilograms of active ingredient without denominator data. Though simple, its main limitation is that it does not give any indication of intensity of use. To address this deficiency, measurements of use per weight have been widely used. However, using kilogram of active ingredients does not take into account the differences in drug strengths, doses administered and pharmacokinetics. The use of higher strengths, dosage and more treatment days led to higher antimicrobial use than those which were applied at lower strengths and dosage (van Rennings et al., 2015).

There is also a large variation in strengths and dosages of antimicrobials use in human health. In order to standardise the measurement, the DDD was developed and is now used globally to measure antimicrobial consumption in humans with standardised reporting by DDD per 1000 inhabitant-days. This facilitates international comparison on antimicrobial use (Natsch et al., 1998). However, a similar universal standardised unit of DDD measurement has not yet been developed for veterinary antimicrobial agents; hence different countries have established their own national ADD-value, based upon medicine specifications registered by their National Regulatory Authorities. The different ADD-values for veterinary medicines hampers cross country comparisons, as using different sets of ADD-values affected the estimate of use (Dupont et al., 2016, Taverne et al., 2015). Moreover, there are not only different units of measurement, but countries also name their measurement differently, such as ADD in Denmark (Jensen et al., 2004) and ADDD in Netherlands (NETHMAP and MARAN, 2013).

There has been an attempt to establish a consensus on DDDA for each active substance and administration route for veterinary antimicrobial products authorized in four European countries (Postma et al., 2015); this effort has yet to scale up to all European countries. Another approach to calculate the daily dose is by using an actual dose administered to animal. Instead of using ADD-value, a DPD is proposed to by adjusting the recommended maximum daily dose by a factor of 0.8 of maximal dose for specific medicinal products; assuming that the maximum doses are not used in every treatment (Ferner et al., 2014, Trauffler et al., 2014a, Trauffler et al., 2014b).

To differentiate antimicrobial use between herds, antimicrobial per treatment periods were calculated based on real use data at farm level. In 2006, a measurement called UDD was introduced firstly in a study in pig farms (Timmerman et al., 2006). The UDD was calculated based on the definite number of treated animals in a treatment period and the dosages of antimicrobials to animals in farms; the UDD avoids differences between ADD-values and supports comparison of use across countries and across studies. Moreover, the ratio between UDD/ADD reflects the appropriateness of dosing where the higher the ratio, the more excessive the use. Another measurement of antimicrobial use that takes into account the treatment period was PDD; it reports antimicrobial use by antimicrobial prescription. PDD also shows the veterinarian's prescribing pattern. However, antimicrobial prescription is not always equal to the actual antimicrobial administration (Chauvin et al., 2001).

There are several methods that relate to the association between the actual volume of specific antimicrobials used in a specific time period such as 'treatment frequency' (van Rennings et al., 2015) and 'treatment incidence rate' (Vieira et al., 2011). Furthermore, the 'treatment incidence' has been introduced for a comparison of data between farms, considering the period at risk of treatment (Sjolund et al., 2016, Sjolund et al., 2015, Filippitzi et al., 2014, Callens et al., 2012, Timmerman et al., 2006). The treatment incidence rate can compare the antimicrobial use per animal species and details of antimicrobial use in terms of dosage and route of administration which can be compared between herd and production types. It can be calculated based on both ADD-values or UDD. However, comparison of 'treatment incidence' to other studies should be done with caution when ADD-value is used (Sjolund et al., 2015).

The wide variation in methods and indicators across the studies, and the relative lack of swine-specific data prevent this review from making valid comparisons of antimicrobial use in swine production or documenting trends.

European experiences and international recommendations

In European countries, the European Medicines Agency (EMA) established the ESVAC project in 2009. The antimicrobial consumption reported by ESVAC members is comparable across countries by using a standardized measurement of mg of active ingredient per population correction unit (mg/PCU). The total volume of antimicrobials used in 30 European countries was 8,361.3 tonnes of active ingredients or 135.5 mg/PCU on an average of consumption in food producing animals in 2015 (European Medicines Agency, 2015).

The ESVAC project has contributed significantly to the standardised methods for antimicrobial consumption in 30 countries in Europe and has also spill over effects to developing countries, in particular Thailand (Tangcharoensathien et al., 2017). In addition to the current reporting of mg per PCU, the ESVAC project has established standardised units of measurement in three major animal species (pigs, cattle and broilers) called Defined Daily Dose (DDDvet) and Defined Course Dose (DCDvet). It aims to harmonize and standardize reporting data on veterinary antimicrobial consumption across European countries. The values are based on an assumed average DDDvet or DCDvet of active substance, which take into account differences in dosing, pharmaceutical forms and routes of administration used by these three species (European Medicines Agency, 2015).

To rectify the weakness of national sales data, in 2013, the EMA recommended that countries conduct farm surveys of veterinary prescriptions or antimicrobial administration records in the logbooks kept by farmers, specific for different species (see ESVAC guidelines of data collection at farm level) (European Medicines Agency, 2013). Though this additional data collection from farms demands substantial resources, infrastructure development and enforcement of veterinary prescriptions at farm level, the benefit is high as it provides accurate information on antimicrobial use by classes and animal species and indications, and evidence can be used to facilitate the development of specific interventions and improve the specific training and education in veterinarians and farmers.

To date, the OIE has also relied on antimicrobial sales data as indicators of actual use, and also recommends that OIE member countries to collect and report data on quantity of antimicrobial consumption in kilogram of antimicrobial agents for different types of indication (therapeutic use or growth promotion), different animal species group and different routes of administration. In the second OIE annual report in 2017 on the use of antimicrobial agents intended for use in animals, OIE recommended to use animal biomass as a denominator so that the quantitative data on antimicrobial agent can be compared among countries. Animal biomass is calculated as the total weight of the live domestic animals, used as a proxy to represent those likely to have exposed to the quantities of antimicrobial agents reported (World Organisation for Animal Health (OIE), 2017).

From the review, data of the volume of antibiotic use in low- and middle-income countries are limited while these countries have a large livestock production. Only three studies are included in this review, which includes Kenya (lower-middle-income economies), and China and South Africa (upper-middle-income economies). Data from South Africa and Kenya was reported in kilogram of antimicrobials used in all livestock. Total antibiotics were calculated by the review of sales of pharmaceutical product. Whereas, the study in China reported antimicrobials in medicated feed by estimation. The quantity of antimicrobials was calculated by using antimicrobial utilization data from the US livestock production. This review indicates an urgent need to build up national capacity to develop system which monitors antimicrobial consumption in LMIC. The monitoring systems of antimicrobial consumption can be developed in a phased manner (Schar et al., 2018).

Policy utilities

Data on antimicrobial usage is needed for a number of reasons such as monitoring time trends of use and assessing the effectiveness of interventions. Ideally it should be disaggregated by different antimicrobial classes in particular the critically important for human health. It can also be used to investigate the association between the magnitude of use and bacterial resistance (Collineau et al., 2017, Schar et al., 2018).

Conclusion

We systematically reviewed the peer-reviewed literatures on the methods and measurements for antimicrobial use in pigs globally. Ten different units of measurement were identified from 25 studies of high- and medium-quality studies; which vary greatly in term of objectives, data sources and units of measurement both numerators and denominators. The non-homogeneity of the unit of measurement limits the cross-study comparative analysis. Additionally, different levels of data such as from farm surveys and national sales data used by these studies also produce different magnitude of use across studies.

Recommendations

Given the importance of measuring antimicrobial use in monitoring progress of policies in optimizing use, at a minimum, all developing countries should develop macro-level monitoring using national sales data and report consumption by milligram of active ingredients per biomass, while at the same time, when there are improved capacities, gradually develop sentinel sites which capture prescription of antimicrobial use by species with the application of DDDvet and DCDvet. The EMA initiative on standardised units of measurement in three main animal species using DDDvet and DCDvet, should be scaled up in Europe and can be applied by developing countries in responses to the GAP-AMR which calls for monitoring and optimizing antimicrobial use.

Conflict of interest

The authors declare that they have no financial and personal relationships with other people or organisations that could inappropriately have influenced the present study and manuscript.

Funding

This study was supported by internal funding.

Acknowledgments

The authors wish to thank Professor Dame Anne Mills, LSHTM and Professor Jonathan Rushton, University of Liverpool for providing their helpful advice. We would like to acknowledge Dr Birgitte Borck Høg, National Food Institute, Technical University of Denmark and Dr Laura Mie Jensen, The Danish Veterinary and Food Administration, Dr Gérard Moulin and Dr Delphine Méheust, French Agency for Veterinary Medicinal Products, ANSES for providing helpful suggestions and discussions. We also thank Alison Dunn and Amanda Gabster for their support on proof reading.

APPENDIXES

Table A1 Variables assessed in the study

Variables	Results
1. Context variables	Author, year of publication, year of study, title, journal, geographical area, objective
2. Methodology variables	2.1 Research (Observational study: cohort studies/case–control studies/ cross-sectional surveys/routine-data-based studies); national report
	2.2 Data source: primary data (survey, interview) from pig producer, veterinarian; secondary data from company (sales data), veterinarian (prescription data), government, level of data (national or specific small-scale farm level)
	2.3 Sampling technique, if it is a primary data collection: simple random sampling, stratified sampling, cluster sampling, systematic sampling, Probability Proportional to Size (PPS), quota sampling, convenience sampling, purposive sampling, self-selection sampling, snowball sampling
	2.4 Sample size: number of respondent, response rate (%)
	2.5 Methods for antimicrobial use measurement and indicators
Comments (including strengths, weaknesses)	

Table A2 Quality assessment of included studies

Author, year	Clearly focused issue	Method					Result			Application		Rank*
		Appropr-iateness	Recruitment	Bias reduction	Data collection	Number of participants	Presentation	Sufficiently rigorous	Clear statement finding	To local population	Research value	
2016												
Carmo et al. (Carmo et al., 2017)	Y	Y	CT	CT	Y	Y	Y	Y	Y	Y	Y	H
Dupont et al. (Dupont et al., 2016)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
Sjolund et al. (Sjolund et al., 2016)	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	H
2015												
Krishnasamy et al. (Krishnasamy et al., 2015)	Y	N	N	CT	CT	CT	Y	N	Y	Y	Y	M
Rennings et al. (van Rennings et al., 2015)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
Sjolund et al. (Sjolund et al., 2015)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
Taverne et al. (Taverne et al., 2015)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
Van Boeckel et al. (Van Boeckel et al., 2015)	Y	Y	N	Y	CT	CT	Y	CT	Y	Y	Y	M
2014												
Ferner et al. (Ferner et al., 2014)	Y	Y	N	N	Y	N	N	N	Y	Y	Y	M
Fertner et al (Fertner et al., 2015)	Y	CT	N	N	Y	N	Y	Y	Y	Y	Y	M
Filippitzi et al. (Filippitzi et al., 2014)	Y	Y	CT	N	CT	CT	Y	Y	Y	Y	Y	M

Hauck et al. (Hauck et al., 2014)	Y	Y	Y	CT	CT	Y	Y	Y	Y	Y	Y	H
Hosoi (Hosoi et al., 2014)	Y	Y	CT	N	N	N	Y	Y	Y	Y	Y	M
Trauffler et al. (a) (Trauffler et al., 2014a)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
Trauffler et al. (b) (Trauffler et al., 2014b)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
2013												
Bondt et al. (Bondt et al., 2013)	Y	Y	Y	CT	CT	Y	Y	Y	Y	Y	Y	H
Bos et al (Bos et al., 2013)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
2012												
Callen et al. (Callens et al., 2012)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H
Eagar et al. (Eagar et al., 2012)	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	M
Merle et al. (Merle et al., 2012)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	H
Jensen et al. (Jensen et al., 2012)	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	H
2011												
Vieira et al. (Vieira et al., 2011)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
2006												
Timmerman et al. (Timmerman et al., 2006)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	H
2004												
Arnold et al. (Arnold et al., 2004)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	H

2001 Mitema et al. (Mitema et al., 2001a)	Y	Y	CT	N	Y	CT	Y	N	Y	Y	Y	M

*score >75 = high (H), 50-74 = medium (M) and <50 = low (L)

CT: Cannot tell

Table A3 Summary of unit of measurement from included studies

Definition and unit of measurement	Numerator	Denominator	Variable						Reference
			Amount of antimicrobials	**Dose**	**Animal weight**	**Number of animals**	**Treatme-nt period**	**Additional variable**	
By population									
A. Volume of antimicrobial use (kilogram)	1.Number of animals 2. Estimated (medicated) feed) consumed per day 3.Duration that swine received antimicrobial 4. Dose of antimicrobial	NA	Y (medicated feed)	Dose in the feed	N	Y	Y	N	Krishnasamy, 2015
B. Volume of antimicrobial use per biomass (mg/PCU; 1 PCU = 1 kilogram of biomass of livestock and slaughtered animals)	Active pharmaceutical ingredient (sold, prescription)	1. Number of slaughtered animals 2. Number of livestock 3. Number of imported/exported animals 4. AW	Y	N	N	Y	N	Average weight at treatment	Carmo, 2017
(mg/PCU)	Active substance	Numbers of live animals x (1+ production period) x ratio of carcass weight to live weight of animals	Y	N	N	Y	N	Production period, ratio of carcass/ live weight	Van Boeckel, 2015
(mg/biomass)	Active substance (sold)	Carcass weight	Y	N	Carcass	N	N	N	Hasoi, 2015
Daily dose and weight at treatment									
C. Product-related Daily Doses (PrDDkg) or **Daily Product Dose (DPD)**	Active substance (prescription)/ 80% of maximal dose	Standard weight x population	Y	80% of maximal dose	Std. weight	Y	N	N	Trauffler, 2014a; Trauffler, 2014b; Ferner, 2014
D. Animal Daily Dose (ADD) (mg/kg bodymass/day)	Active substance (administered/ prescription)/ ADD-value (average maintenance dose per day per kg	Standard weight x number of animal	Y	Maintenance dose	Std. weight	Y	N	N	Dupont, 2016; Taverne, 2015; Fetner, 2015; Ferner, 2014; Trauffler, 2014a; Trauffler, 2014b; Bondt, 2013; Jensen,

	animal of a drug use for main indication in the target species)								2011
Definition and unit of measurement	Numerator	Denominator	Variable						Reference
			Amount of antimicrobials	Dose	Animal weight	Population	Treatment period	Additional variable	
• ADD-LU (livestock unit; LU) (mg/500 kg LU biomass/day)	ADD x 500	NA	N	N	N	N	N	ADD	Ferner, 2014
• Number of animal daily doses per livestock unit (nADDsLU)	ADD-LU	Number of treated LUs (total number of LU produced in one year by all farm, in which at least treatment was recorded)	N	N	N	N	N	N	Ferner, 2014
E. Defined Daily Doses per animal year (DDDA) or **Animal Defined Daily Dose (ADDD)** or **Daily Dose per animal year (nDDay)**	Active substance (prescription)	Recommended dose x total animal mass that can be treated for one day with the supplied antimicrobials x mean total weight (kilogram) of animals on the farm	Y	Recommended dose	Mean weight	Y	N	N	Taverne, 2015; Bos, 2013; Merle, 2012
Daily dose and treatment period									
F. Used Daily Doses per kg biomass (UDDkg) (mg/ kilogram biomass/ day)	Active substance (administered)	Number of treated animals x Standard weight (kilogram) x Treatment duration (days)	Y	N	Std. weight	Y	Y	N	Timmerman, 2006; Trauffler, 2014a; Trauffler, 2014b
G. Prescribed Daily Dose (PDD) (mg/kg* day)	Active substance (prescription)	Average weight of the animals x number of animals (n) x treatment period (days))	Y	N	Avg. weight	Y	Y	N	Arnold 2004
H. Treatment frequency	UDD	Population size	N	N	N	Y	N	UDD	Rennings, 2015
I. Treatment incidence rate	ADD	Sum of delivered animals in the period * 112 (112= days of fattening period) OR 100 slaughter pig-days at risk	N	N	N	Y	N	N	Vieira, 2012
Daily dose and period at risk of being treated									

J. Treatment incidence-DDA (TI-DDA), UDDA (TI-UDDA)	DDA/ UDD(mg/kg) x 1,000 population	Y	N	Avg. weight	Y	Y	UDD, ADD	Sjolund, 2016; Sjolund, 2015; Filippitzi, 2014; Callens 2014; Timmerman 2006

Annex 1

I. Search Strategy

Structured Database Search (Search terms and results)

- MEDLINE: *N= 401 articles*
  - (antibiotic or antimicrobial).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (251,939)
  - ("use" or "utilisation" or "consume*" or "practice" or "administration" or "oral" or "feed" or "injection" or "amount" or "quantit*" or "qualit*").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (5,584,129)
  - ("livestock" or "swine" or "pig" or "farrow" or "weaner" or "sow").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (285,470)
  - ("measurement" or "indicator" or "surveillance" or "survey" or "report" or "method").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3,766,673)

- Sciencedirect: *N= 636 articles*

  "Antibiotic" AND ("swine" OR “pig”) AND ("use" OR “survey” OR “surveillance” OR “consumption”)

Filter: Topics, "pig”, “animal”; Content type, "Journal”

- Scopus: *N= 630 articles*

  (TITLE-ABS-KEY (antibiotic OR antimicrobial OR antibacterial) AND TITLE-ABS-KEY (livestock OR swine OR pig OR farrow OR weaner OR finisher OR sow) AND TITLE-ABS-KEY (use OR utilisation OR consume* OR consumption OR practice OR administration OR provision) AND TITLE-ABS-KEY (measure* OR indicator OR surveillance OR survey OR monitor))

- Web of Science: *N= 691 articles*

  TOPIC:(antibiotic OR antimicrobial OR antibacterial) AND TOPIC: (livestock OR swine OR pig OR farrow OR weaner OR finisher OR sow) ANDTOPIC: (use OR utilisation OR consume* OR consumption OR practice OR administration OR provision) AND TOPIC: (measure* OR indicator OR surveillance OR survey OR monitor)

  Filter: DOCUMENT TYPES: (ARTICLE) AND WEB OF SCIENCE CATEGORIES: (VETERINARY SCIENCES OR MICROBIOLOGY OR AGRICULTURE DAIRY ANIMAL SCIENCE)

References

AARESTRUP, F. M. 2005. Veterinary drug usage and antimicrobial resistance in bacteria of animal origin. *Basic & Clinical Pharmacology & Toxicology,* 96**,** 271-81.

AGENCY, E. M. 2013. European Surveillance
of Veterinary Antimicrobial Consumption. Web Based Sales Data and Animal Population Data Collection Protocol (version 2).

AGENCY, E. M. 2017. Sales of veterinary antimicrobial agents in 30 European countries in 2015. Trends from 2010 to 2015. *In:* EMA/184855/2017 (ed.).

ANONYMOUS 2012. Monitoring of Antimicrobial Resistance
and Antibiotic Usage in Animals in the Netherlands.

ARNOLD, S., GASSNER, B., GIGER, T. & ZWAHLEN, R. 2004. Banning antimicrobial growth promoters in feedstuffs does not result in increased therapeutic use of antibiotics in medicated feed in pig farming. *Pharmacoepidemiol Drug Saf,* 13**,** 323-31.

BONDT, N., JENSEN, V. F., PUISTER-JANSEN, L. F. & VAN GEIJLSWIJK, I. M. 2013. Comparing antimicrobial exposure based on sales data. *Prev Vet Med,* 108**,** 10-20.

BOS, M. E., TAVERNE, F. J., VAN GEIJLSWIJK, I. M., MOUTON, J. W., MEVIUS, D. J., HEEDERIK, D. J. & NETHERLANDS VETERINARY MEDICINES AUTHORITY, S. 2013. Consumption of antimicrobials in pigs, veal calves, and broilers in the Netherlands: quantitative results of nationwide collection of data in 2011. *PLoS One,* 8**,** e77525.

CALLENS, B., PERSOONS, D., MAES, D., LAANEN, M., POSTMA, M., BOYEN, F., HAESEBROUCK, F., BUTAYE, P., CATRY, B. & DEWULF, J. 2012. Prophylactic and metaphylactic antimicrobial use in Belgian fattening pig herds. *Prev Vet Med,* 106**,** 53-62.

CARMO, L. P., SCHUPBACH-REGULA, G., MUNTENER, C., CHEVANCE, A., MOULIN, G. & MAGOURAS, I. 2017. Approaches for quantifying antimicrobial consumption per animal species based on national sales data: a Swiss example, 2006 to 2013. *Euro Surveill,* 22.

CHAUVIN, C., MADEC, F., GUILLEMOT, D. & SANDERS, P. 2001. The crucial question of standardisation when measuring drug consumption. *Vet Res,* 32**,** 533-43.

COLLINEAU, L., BELLOC, C., STARK, K. D., HEMONIC, A., POSTMA, M., DEWULF, J. & CHAUVIN, C. 2017. Guidance on the Selection of Appropriate Indicators for Quantification of Antimicrobial Usage in Humans and Animals. *Zoonoses Public Health,* 64**,** 165-184.

COOKE, A., SMITH, D. & BOOTH, A. 2012. Beyond PICO: the SPIDER tool for qualitative evidence synthesis. *Qual Health Res,* 22**,** 1435-43.

CRITICAL APPRAISAL SKILLS PROGRAMME (CASP). 2014. *CASP Checklists* [Online]. Available: http://www.casp-uk.net/#!checklists/cb36. [Accessed].

DUPONT, N., FERTNER, M., KRISTENSEN, C. S., TOFT, N. & STEGE, H. 2016. Reporting the national antimicrobial consumption in Danish pigs: influence of assigned daily dosage values and population measurement. *Acta Vet Scand,* 58**,** 27.

EAGAR, H., SWAN, G. & VAN VUUREN, M. 2012. A survey of antimicrobial usage in animals in South Africa with specific reference to food animals. *J S Afr Vet Assoc,* 83**,** 16.

EUROPEAN MEDICINES AGENCY 2013. European Surveillance

of Veterinary Antimicrobial Consumption: Revised ESVAC reflection paper on collecting data on consumption of antimicrobial agents per animal species, on technical units of measurement and indicators for reporting consumption of antimicrobial agents in animals.
.

EUROPEAN MEDICINES AGENCY 2014. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2012.

EUROPEAN MEDICINES AGENCY 2015. Principles on assignment of defined daily dose for animals (DDDvet) and defined course dose for animals (DCDvet)

FAO 2016. The FAO Action Plan on Antimicrobial Resistance 2016-2020. Rome.

FERNER, C., OBRITZHAUSER, W., FUCHS, K. & SCHMEROLD, I. 2014. Development and evaluation of a system to assess antimicrobial drug use in farm animals: results of an Austrian study. *Vet Rec,* 175**,** 429.

FERTNER, M., BOKLUND, A., DUPONT, N., ENOE, C., STEGE, H. & TOFT, N. 2015. Weaner production with low antimicrobial usage: a descriptive study. *Acta Vet Scand,* 57**,** 38.

FILIPPITZI, M. E., CALLENS, B., PARDON, B., PERSOONS, D. & DEWULF, J. 2014. Antimicrobial use in pigs, broilers and veal calves in Belgium. *Vlaams Diergeneeskundig Tijdschrift,* 83**,** 215-224.

HAUCK, R., ROMER, A., REIMER, I., BENDER, A., HAAS, C., HEBERER, T. & WALLMANN, J. 2014. Analysis of the distribution of veterinary antimicrobial products to veterinarians in Germany in 2011 and 2012. *Berliner Und Munchener Tierarztliche Wochenschrift,* 127**,** 359-365.

HOSOI, Y., ASAI, T., KOIKE, R., TSUYUKI, M. & SUGIURA, K. 2014. Sales of veterinary antimicrobial agents for therapeutic use in food-producing animal species in Japan between 2005 and 2010. *Revue Scientifique Et Technique-Office International Des Epizooties,* 33**,** 1007-1015.

JENSEN, V. F., EMBORG, H. D. & AARESTRUP, F. M. 2012. Indications and patterns of therapeutic use of antimicrobial agents in the Danish pig production from 2002 to 2008. *J Vet Pharmacol Ther,* 35**,** 33-46.

JENSEN, V. F., JACOBSEN, E. & BAGER, F. 2004. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. *Prev Vet Med,* 64**,** 201-15.

KRISHNASAMY, V., OTTE, J. & SILBERGELD, E. 2015. Antimicrobial use in Chinese swine and broiler poultry production. *Antimicrob Resist Infect Control,* 4**,** 17.

MERLE, R., HAJEK, P., KASBOHRER, A., HEGGER-GRAVENHORST, C., MOLLENHAUER, Y., ROBANUS, M., UNGEMACH, F. R. & KREIENBROCK, L. 2012. Monitoring of antibiotic consumption in livestock: a German feasibility study. *Prev Vet Med,* 104**,** 34-43.

MITEMA, E., KIKUVI, G., WEGENER, H. C. & STOHR, K. 2001a. An assessment of antimicrobial consumption in food producing animals in Kenya. *Journal of Veterinary Pharmacology and Therapeutics,* 24**,** 385-390.

MITEMA, E. S., KIKUVI, G. M., WEGENER, H. C. & STOHR, K. 2001b. An assessment of antimicrobial consumption in food producing animals in Kenya. *J Vet Pharmacol Ther,* 24**,** 385-90.

NATSCH, S., HEKSTER, Y. A., DE JONG, R., HEERDINK, E. R., HERINGS, R. M. & VAN DER MEER, J. W. 1998. Application of the ATC/DDD methodology to monitor antibiotic drug use. *Eur J Clin Microbiol Infect Dis,* 17**,** 20-4.

NETHMAP AND MARAN 2013. Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands. monitoring of antimicrobial resistance and antibiotic usage in animals in the Netherlands in 2012. .

OIE 2016. The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials.
POSTMA, M., SJOLUND, M., COLLINEAU, L., LOSKEN, S., STARK, K. D., DEWULF, J. & CONSORTIUM, M. 2015. Assigning defined daily doses animal: a European multi-country experience for antimicrobial products authorized for usage in pigs. *J Antimicrob Chemother,* 70**,** 294-302.
SCHAR, D., SOMMANUSTWEECHAI, A., LAXMINARAYA, R. & TANGCHAROENSATHIEN, V. 2018. Surveillance of antimicrobial consumption in animal production sectors of low- and middle income countries: Optimizing use and addressing antimicrobial resistance. . *PLoS Med. ,* 15.
SJOLUND, M., BACKHANS, A., GREKO, C., EMANUELSON, U. & LINDBERG, A. 2015. Antimicrobial usage in 60 Swedish farrow-to-finish pig herds. *Prev Vet Med,* 121**,** 257-64.
SJOLUND, M., POSTMA, M., COLLINEAU, L., LOSKEN, S., BACKHANS, A., BELLOC, C., EMANUELSON, U., BEILAGE, E. G., STARK, K., DEWULF, J. & CONSORTIUM, M. 2016. Quantitative and qualitative antimicrobial usage patterns in farrow-to-finish pig herds in Belgium, France, Germany and Sweden. *Prev Vet Med,* 130**,** 41-50.
STATENS SERUM INSTITUT, N. V. I., NATIONAL FOOD INSTITUTE, 2012. Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark.
SWEDRES AND SVARM 2014. Swedish antibiotic utilisation and resistance in human medicine swedish veterinary antimicrobial resistance monitoring 2014.
TANGCHAROENSATHIEN, V., SOMMANUSTWEECHAI, A., CHANTHONG, B., SUMPRADIT, N., SAKULBUMRUNGSIL, R., JAROENPOJ, S., SERMSINSIRI, V. & THAI, S. A. C. W. G. 2017. Surveillance of antimicrobial consumption: methodological review for systems development in Thailand. *J Glob Health,* 7**,** 010307.
TAVERNE, F. J., JACOBS, J. H., HEEDERIK, D., MOUTON, J. W., WAGENAAR, J. A., VAN GEIJLSWIJK, I. M. & NETHERLANDS VETERINARY MEDICINES, A. 2015. Influence of applying different units of measurement on reporting antimicrobial consumption data for pig farms. *BMC Vet Res,* 11**,** 250.
TIMMERMAN, T., DEWULF, J., CATRY, B., FEYEN, B., OPSOMER, G., DE KRUIF, A. & MAES, D. 2006. Quantification and evaluation of antimicrobial drug use in group treatments for fattening pigs in Belgium. *Prev Vet Med,* 74**,** 251-63.
TRAUFFLER, M., GRIESBACHER, A., FUCHS, K. & KOFER, J. 2014a. Antimicrobial drug use in Austrian pig farms: plausibility check of electronic on-farm records and estimation of consumption. *Veterinary Record,* 175**,** 402-U36.
TRAUFFLER, M., OBRITZHAUSER, W., RAITH, J., FUCHS, K. & KOFER, J. 2014b. The use of the "Highest Priority Critically Important Antimicrobials" in 75 Austrian pig farms - Evaluation of on-farm drug application data. *Berliner Und Munchener Tierarztliche Wochenschrift,* 127**,** 375-383.
VAN BOECKEL, T. P., BROWER, C., GILBERT, M., GRENFELL, B. T., LEVIN, S. A., ROBINSON, T. P., TEILLANT, A. & LAXMINARAYAN, R. 2015. Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences of the United States of America,* 112**,** 5649-5654.
VAN RENNINGS, L., VON MUNCHHAUSEN, C., OTTILIE, H., HARTMANN, M., MERLE, R., HONSCHA, W., KASBOHRER, A. & KREIENBROCK, L. 2015. Cross-sectional study on antibiotic usage in pigs in Germany. *PLoS One,* 10**,** e0119114.

VIEIRA, A. R., PIRES, S. M., HOUE, H. & EMBORG, H. D. 2011. Trends in slaughter pig production and antimicrobial consumption in Danish slaughter pig herds, 2002-2008. *Epidemiol Infect,* 139**,** 1601-9.

WORLD HEALTH ORGANIZATION 2015a. Global Action Plan on antimicrobial resistance. Geneva, Switzerland.

WORLD HEALTH ORGANIZATION 2015b. Worldwide country situation analysis: response to antimicrobial resistance.

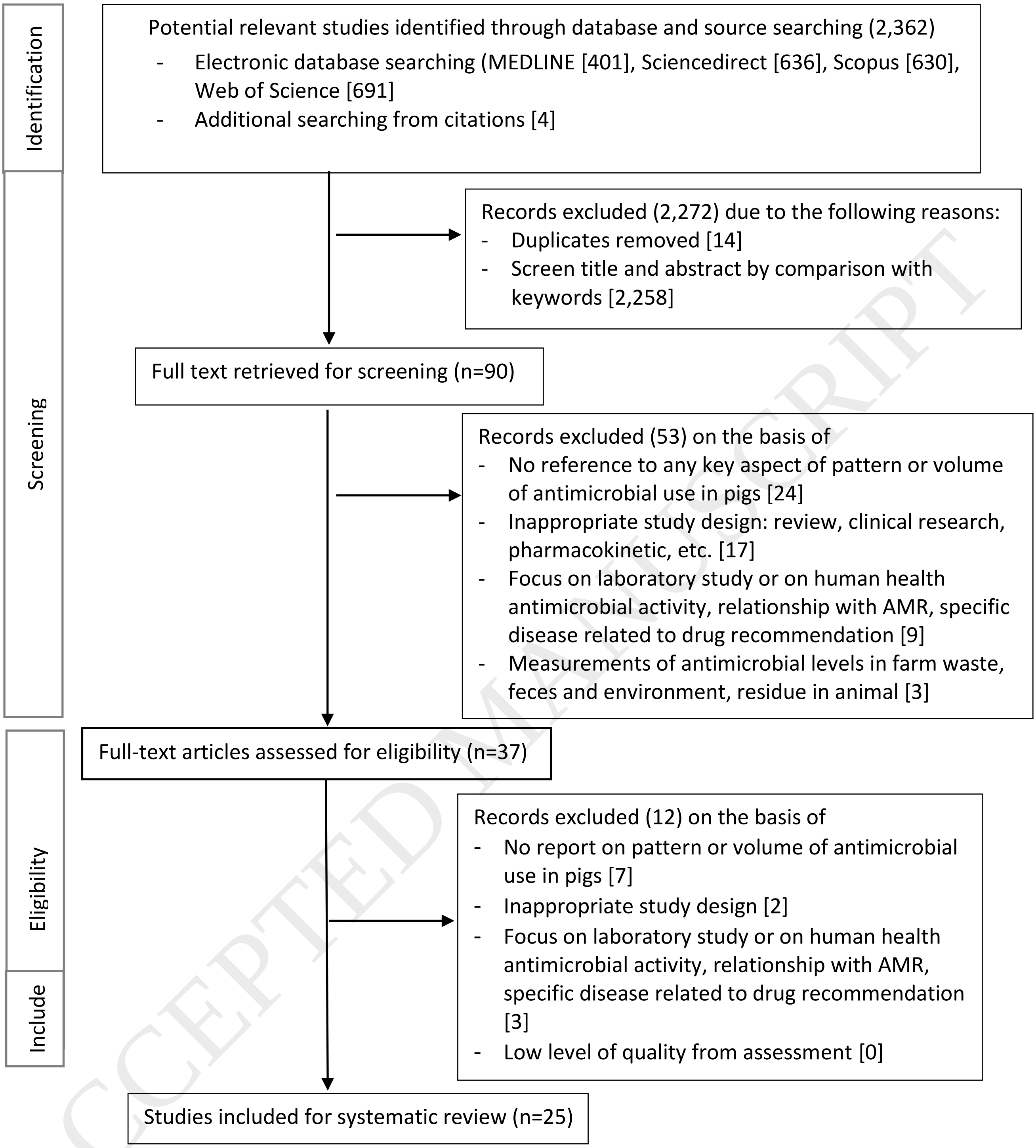
WORLD HEALTH ORGANIZATION 2017. WHO methodology for a global programme on surveillance of antimicrobial consumption.

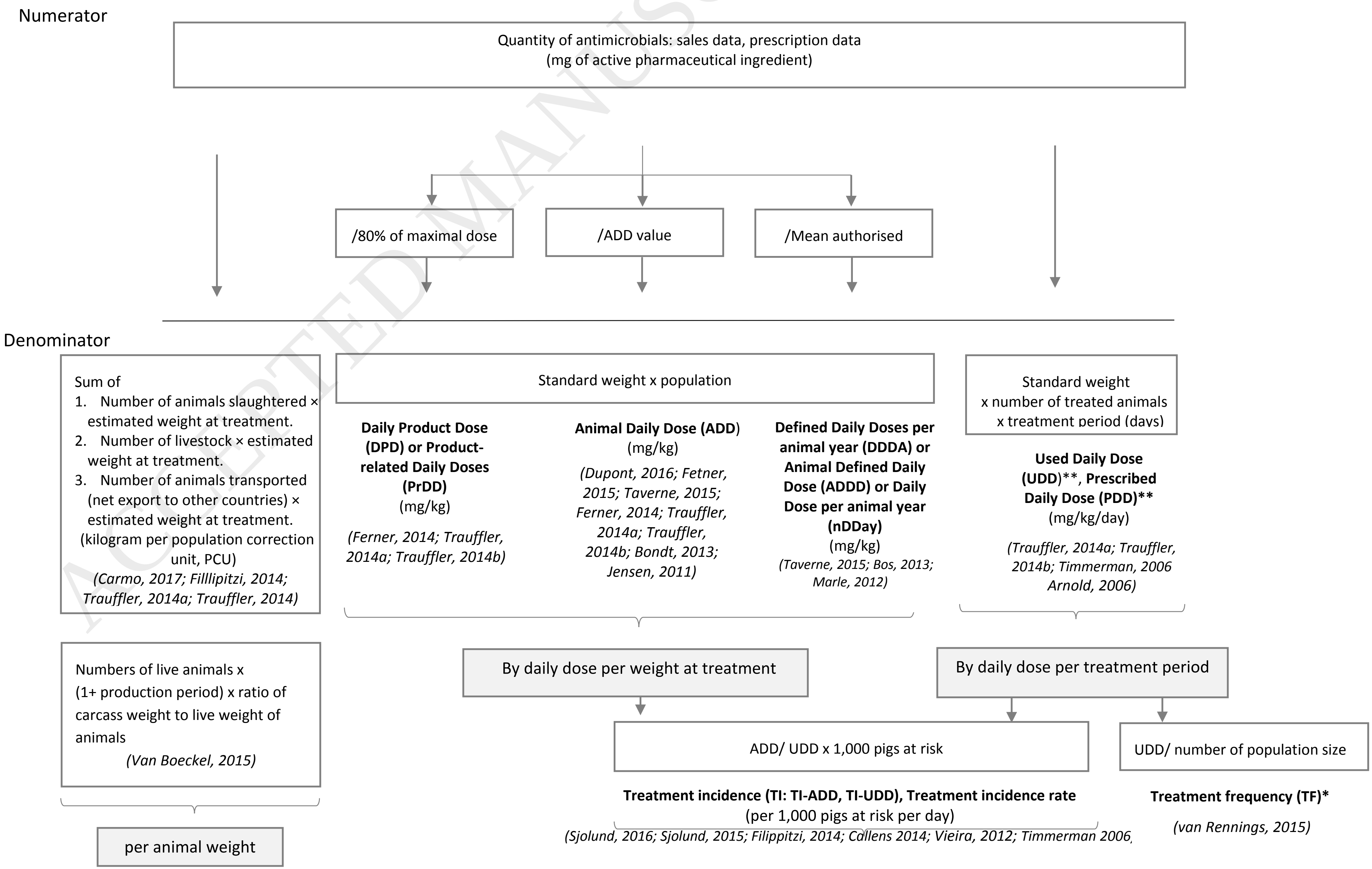
WORLD ORGANISATION FOR ANIMAL HEALTH (OIE). 2008. OIE Terrestrial Animal Health Code, Chapter 6.9. Responsible and prudent use of antimicrobial agents in veterinary medicine. Available: http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_antibio_use.htm.

WORLD ORGANISATION FOR ANIMAL HEALTH (OIE) 2015. OIE Terrestrial Animal Health Code: Glossary2015.

WORLD ORGANISATION FOR ANIMAL HEALTH (OIE) 2017. OIE Annual report on the use of antimicrobial agents intended for use in animals. Paris, France.

Figure 1 Flow diagram of the review process




Numerator
Quantity of antimicrobials: sales data, prescription data
(mg of active pharmaceutical ingredient)
/80% of maximal dose
/ADD value
/Mean authorised
Denominator
Sum of
1. Number of animals slaughtered × estimated weight at treatment.
2. Number of livestock × estimated weight at treatment.
3. Number of animals transported (net export to other countries) × estimated weight at treatment.
(kilogram per population correction unit, PCU)
(Carmo, 2017; Filllipitzi, 2014; Trauffler, 2014a; Trauffler, 2014)
Standard weight x population
Daily Product Dose (DPD) or Product-related Daily Doses (PrDD)
(mg/kg)
(Ferner, 2014; Trauffler, 2014a; Trauffler, 2014b)
Animal Daily Dose (ADD)
(mg/kg)
(Dupont, 2016; Fetner, 2015; Taverne, 2015; Ferner, 2014; Trauffler, 2014a; Trauffler, 2014b; Bondt, 2013; Jensen, 2011)
Defined Daily Doses per animal year (DDDA) or Animal Defined Daily Dose (ADDD) or Daily Dose per animal year (nDDay)
(mg/kg)
(Taverne, 2015; Bos, 2013; Marle, 2012)
Standard weight
x number of treated animals
x treatment period (days)
Used Daily Dose (UDD)**, Prescribed Daily Dose (PDD)**
(mg/kg/day)
(Trauffler, 2014a; Trauffler, 2014b; Timmerman, 2006 Arnold, 2006)
Numbers of live animals x (1+ production period) x ratio of carcass weight to live weight of animals
(Van Boeckel, 2015)
By daily dose per weight at treatment
By daily dose per treatment period
ADD/ UDD x 1,000 pigs at risk
UDD/ number of population size
per animal weight
Treatment incidence (TI: TI-ADD, TI-UDD), Treatment incidence rate
(per 1,000 pigs at risk per day)
(Sjolund, 2016; Sjolund, 2015; Filippitzi, 2014; Callens 2014; Vieira, 2012; Timmerman 2006
Treatment frequency (TF)*
(van Rennings, 2015)

By daily dose per period at risk of treatment

Figure 2 describe the ten different measurements, categorised in four groups

*Additional measurement: calculated from ADD, UDD; **Actual consumption data which calculated antimicrobial per a number of treated animal

Table 1 Search terminology to be used in literature review.

	Search term
I	antimicrobial (Free text) OR antimicrobial (MeSH term) OR antibacterial (Free text) OR antibacterial (MeSH term) OR antibiotic (Free text) OR antibiotic (MeSH term)
II	livestock (Free text) OR swine (Free text) OR pig* (Free text) OR farrow (Free text) OR weaner (Free text) OR finisher (Free text) OR sow (Free text)
III	use (Free text) OR utilisation (Free text) OR consum* (Free text) OR practice (Free text) OR administration (Free text)
IV	measure* (Free text) OR indicator (Free text) OR surveillance (Free text) OR survey (Free text) OR monitor (Free text)

Table 2 Characteristics of included studies

Characteristics	N=25
Quality assessment (mean)	
Published year	
2000-2010	3 (12%)
2010-2016	22 (88%)
Geographic area	
Europe	20* (80%)
Africa	2 (8%)
Asia	2 (8%)
Global	1 (4%)
Quality assessment	
High (>75%)	15 (60%)
Moderate (50-74%)	10 (40%)
Unit of analysis	
National level	11 (44%)
Farm level	14 (56%)
Data collection on antimicrobial use	
Farm based survey	7 (28%)
National data	6 (24%)
Prescription data	4 (16%)
Pharmaceutical product sold review	4 (16%)
Mixed method (>1 data source)	3 (12%)
Data from another country**	1 (4%)
Report by type of antimicrobials	
Sum of all antimicrobials	3 (12%)
Disaggregated by classes	22 (88%)
Report by animal species	
Sum of antimicrobials in all animal species	5 (20%)
Specific in pig/ disaggregated by animal species	20 (80%)
Unit of measurement used	(N=40)
- Volume	9 (23%)
- Volume per biomass	6 (15%)
- Daily Product Dose (DPD)	3 (8%)
- Animal Daily Dose (ADD)	8 (20%)
- Defined Daily Doses per Animal year (DDDA)	3 (8%)
- Used Daily Dose (UDD)	3 (8%)
- Prescribed Daily Dose (PDD)	1 (3%)
- Treatment incidence rate	1 (3%)
- Treatment frequency	1 (3%)
- Treatment incidence	5 (13%)

*including two multi-country studies

** the study estimated the quantity of antimicrobials used in animal feeds in China by using antimicrobial utilization data from the US livestock production.

Table 3 Summary antimicrobial usage data from studies included in this review

Unit of measurement	Antimicrobial usage data

Volume of active substances and volume per animal weight	- 67,423-72,300 kg of active substances; 110-160, 86.3-124.4, 54.9-178.6, 34-143.8 mg/biomass (different methods for calculation) (Switzerland) (12) - 34 million kg of antimicrobials in medicated feed (China) (Krishnasamy et al., 2015) - 20,373.6 kg of antimicrobials (in study farms) (Germany) (van Rennings et al., 2015) - 63,151, 000 kg (Global level) (Van Boeckel et al., 2015)* - >5,400 kg of active substances (Austria) (Ferner et al., 2014)* - 222,500 kg of active substances; 137 mg/biomass (Belgium) (Filippitzi et al., 2014)* - 1,706 tons of active substances (2011) and 1,619 tons (2012) (Germany) (Hauck et al., 2014)* - 392 to 423 mg/ biomass (Japan) (Hosoi et al., 2014) - 33.89 mg/ biomass/year (Austria) (Trauffler et al., 2014a, Trauffler et al., 2014b) - 1,538,443 kg of antimicrobials (South Africa)* - 31,622 kg of antimicrobials (Germany) (Merle et al., 2012) - 14,594 kg of antimicrobials per year (Kenya) (Mitema et al., 2001)*
Volume by daily dose per weight at treatment (ADD, DDDA, DPD)	- 9.4, 10.4, 11.6 ADD (Denmark) (13) - 0.6-7.37 ADD (Denmark) (Fertner et al., 2015) - 11.78-19.20 DDDA; 11.57-16.0 and 10.43-15.32 ADD in sow/piglet farms and finisher farms (Netherlands and Denmark) (Taverne et al., 2015) - DPD-LU 631,939; ADD-LU 576,242(Austria) (Ferner et al., 2014)* - 2.51 DPD; 1.95 ADD (Austria) (Trauffler et al., 2014a, Trauffler et al., 2014b) - 19 ADD in Netherlands and 14 ADD in Denmark (27) - 16.9 DDA and 9.6 DDDA in production and slaughtered pig farms (Netherlands) (Bos et al., 2013) - 60.86 DDDA for piglets, 28.60 DDDA for fattening pigs, 2.89 DDDA for sows Germany) (Merle et al., 2012) - 1.40-2.14 ADD for sows, 5.02-5.90 ADD for weaners, 1.12-1.37 ADD for finishers (Denmark) (Jensen et al., 2012)
Volume by daily dose per treatment period (UDD, PDD, Treatment incidence rate, Treatment frequency)	- Treatment frequency: 0.86 days for sows, 14.74 days for piglets, 6.62 days for weaners and 3.67 for fattening pigs (Germany) (van Rennings et al., 2015) - 4.88 UDD (Austria) (Trauffler et al., 2014a, Trauffler et al., 2014b) - Treatment incidence rate: Tetracycline 0.28- 0.70, Macrolide 0.40-0.44 (Denmark) (Vieira et al., 2011) - 3.3-6.1 PDD (Switzerland) (Arnold et al., 2004)
Volume by daily dose per period at risk of treatment	- TI-ADD (per 1,000 pigs at risk per day): Belgium: 176 (suckling), 406 (weaned), 33 (fattening), 143 (growing), 16 (breeding) France: 59 (suckling), 374 (weaned), 7 (fattening), 108 (growing), 22 (breeding) Germany: 245 (suckling), 633 (weaned), 53 (fattening), 243 (growing), 42 (breeding) Sweden: 76 (suckling), 21 (weaned), 6 (fattening), 23 (growing), 11 (breeding) (Sjolund et al., 2016) - TI-ADD (per 1,000 pigs at risk per day): 54.7 (suckling), 6.2 (weaned), 2.8 (fattening), 14.3(growing), 8.4 (breeding) (Sweden) (Sjolund et al., 2015) - TI-ADD (per 1,000 pigs at risk per day): 235.8, TI-UDD 200.7 (2012) (Used Callen data) (Belgium) (Filippitzi et al., 2014) - TI-ADD (per 1,000 pigs at risk per day): 235.8, TI-UDD 200.7 (Belgium) (Callens et al., 2012) - TI-ADD (per 1,000 pigs at risk per day): 178.1, TI-UDD 170.3 (Belgium) (Timmerman et al., 2006)

* Data combined other species

ADD: Animal Daily Dose, DDDA: Daily Doses Animal, DPD-LU: Daily Product Dose, LU: livestock unit, PDD: Prescribed Daily Dose, TI-ADD: Treatment incidence for Animal Daily Dose, TI-UDD: Treatment incidence for Used Daily Dose

ARNOLD, S., GASSNER, B., GIGER, T. & ZWAHLEN, R. 2004. Banning antimicrobial growth promoters in feedstuffs does not result in increased therapeutic use of antibiotics in medicated feed in pig farming. *Pharmacoepidemiol Drug Saf,* 13**,** 323-31.

BOS, M. E., TAVERNE, F. J., VAN GEIJLSWIJK, I. M., MOUTON, J. W., MEVIUS, D. J., HEEDERIK, D. J. & NETHERLANDS VETERINARY MEDICINES AUTHORITY, S. 2013. Consumption of antimicrobials in pigs, veal calves, and broilers in the Netherlands: quantitative results of nationwide collection of data in 2011. *PLoS One,* 8**,** e77525.

CALLENS, B., PERSOONS, D., MAES, D., LAANEN, M., POSTMA, M., BOYEN, F., HAESEBROUCK, F., BUTAYE, P., CATRY, B. & DEWULF, J. 2012. Prophylactic and metaphylactic antimicrobial use in Belgian fattening pig herds. *Prev Vet Med,* 106**,** 53-62.

FERNER, C., OBRITZHAUSER, W., FUCHS, K. & SCHMEROLD, I. 2014. Development and evaluation of a system to assess antimicrobial drug use in farm animals: results of an Austrian study. *Vet Rec,* 175**,** 429.

FERTNER, M., BOKLUND, A., DUPONT, N., ENOE, C., STEGE, H. & TOFT, N. 2015. Weaner production with low antimicrobial usage: a descriptive study. *Acta Vet Scand,* 57**,** 38.

FILIPPITZI, M. E., CALLENS, B., PARDON, B., PERSOONS, D. & DEWULF, J. 2014. Antimicrobial use in pigs, broilers and veal calves in Belgium. *Vlaams Diergeneeskundig Tijdschrift,* 83**,** 215-224.

HAUCK, R., ROMER, A., REIMER, I., BENDER, A., HAAS, C., HEBERER, T. & WALLMANN, J. 2014. Analysis of the distribution of veterinary antimicrobial products to veterinarians in Germany in 2011 and 2012. *Berliner Und Munchener Tierarztliche Wochenschrift,* 127**,** 359-365.

HOSOI, Y., ASAI, T., KOIKE, R., TSUYUKI, M. & SUGIURA, K. 2014. Sales of veterinary antimicrobial agents for therapeutic use in food-producing animal species in Japan between 2005 and 2010. *Revue Scientifique Et Technique-Office International Des Epizooties,* 33**,** 1007-1015.

JENSEN, V. F., EMBORG, H. D. & AARESTRUP, F. M. 2012. Indications and patterns of therapeutic use of antimicrobial agents in the Danish pig production from 2002 to 2008. *J Vet Pharmacol Ther,* 35**,** 33-46.

KRISHNASAMY, V., OTTE, J. & SILBERGELD, E. 2015. Antimicrobial use in Chinese swine and broiler poultry production. *Antimicrob Resist Infect Control,* 4**,** 17.

MERLE, R., HAJEK, P., KASBOHRER, A., HEGGER-GRAVENHORST, C., MOLLENHAUER, Y., ROBANUS, M., UNGEMACH, F. R. & KREIENBROCK, L. 2012. Monitoring of antibiotic consumption in livestock: a German feasibility study. *Prev Vet Med,* 104**,** 34-43.

MITEMA, E. S., KIKUVI, G. M., WEGENER, H. C. & STOHR, K. 2001. An assessment of antimicrobial consumption in food producing animals in Kenya. *J Vet Pharmacol Ther,* 24**,** 385-90.

SJOLUND, M., BACKHANS, A., GREKO, C., EMANUELSON, U. & LINDBERG, A. 2015. Antimicrobial usage in 60 Swedish farrow-to-finish pig herds. *Prev Vet Med,* 121**,** 257-64.

SJOLUND, M., POSTMA, M., COLLINEAU, L., LOSKEN, S., BACKHANS, A., BELLOC, C., EMANUELSON, U., BEILAGE, E. G., STARK, K., DEWULF, J. & CONSORTIUM, M. 2016. Quantitative and qualitative antimicrobial usage patterns in farrow-to-finish pig herds in Belgium, France, Germany and Sweden. *Prev Vet Med,* 130**,** 41-50.

TAVERNE, F. J., JACOBS, J. H., HEEDERIK, D., MOUTON, J. W., WAGENAAR, J. A., VAN GEIJLSWIJK, I. M. & NETHERLANDS VETERINARY MEDICINES, A. 2015. Influence of applying different units of measurement on reporting antimicrobial consumption data for pig farms. *BMC Vet Res,* 11**,** 250.

TIMMERMAN, T., DEWULF, J., CATRY, B., FEYEN, B., OPSOMER, G., DE KRUIF, A. & MAES, D. 2006. Quantification and evaluation of antimicrobial drug use in group treatments for fattening pigs in Belgium. *Prev Vet Med,* 74**,** 251-63.

TRAUFFLER, M., GRIESBACHER, A., FUCHS, K. & KOFER, J. 2014a. Antimicrobial drug use in Austrian pig farms: plausibility check of electronic on-farm records and estimation of consumption. *Veterinary Record,* 175**,** 402-U36.

TRAUFFLER, M., OBRITZHAUSER, W., RAITH, J., FUCHS, K. & KOFER, J. 2014b. The use of the "Highest Priority Critically Important Antimicrobials" in 75 Austrian pig farms - Evaluation of on-farm drug application data. *Berliner Und Munchener Tierarztliche Wochenschrift,* 127**,** 375-383.

VAN BOECKEL, T. P., BROWER, C., GILBERT, M., GRENFELL, B. T., LEVIN, S. A., ROBINSON, T. P., TEILLANT, A. & LAXMINARAYAN, R. 2015. Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences of the United States of America,* 112**,** 5649-5654.

VAN RENNINGS, L., VON MUNCHHAUSEN, C., OTTILIE, H., HARTMANN, M., MERLE, R., HONSCHA, W., KASBOHRER, A. & KREIENBROCK, L. 2015. Cross-sectional study on antibiotic usage in pigs in Germany. *PLoS One,* 10**,** e0119114.

VIEIRA, A. R., PIRES, S. M., HOUE, H. & EMBORG, H. D. 2011. Trends in slaughter pig production and antimicrobial consumption in Danish slaughter pig herds, 2002-2008. *Epidemiol Infect,* 139**,** 1601-9.