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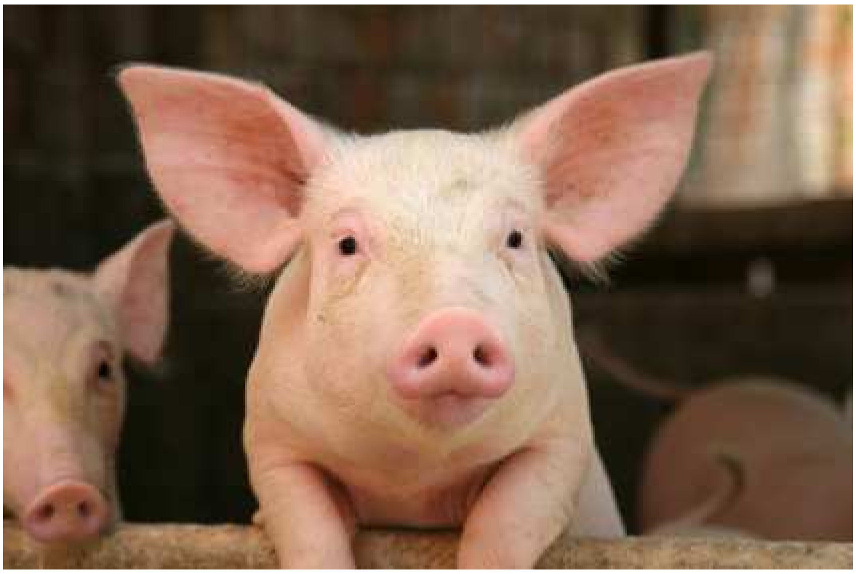
Reporting antimicrobial consumption in Danish pigs

Effect of calculation methods



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ABSTRACT

Introduction

In the Danish surveillance of antimicrobial (AM) consumption for pigs, usage is reported as either kg active compound or percentage pigs treated per day (measured in “Animal Daily Doses” (ADD)). In 2010 the Danish government instigated a system, which penalizes herds with an AM consumption exceeding defined limits (currently 2 x the overall average usage). Herd consumption is based on percentage pigs treated per day. Presently number of pen places, presumably resembling live pigs at any given time, is used as measurement for number of animals. If several generations of animals pass the stable facilities each year, this may not be a very appropriate measure. Not including the herds’ productivity may cause misclassification when pointing out herds with a high AM usage. How number of pigs is measured may also be of importance when evaluating consumption over time and comparing countries. Hence, the aims of this study were 1) to describe the consequences of using three different ways to measure number of pigs when reporting national AM consumption – both calculated as gram AM/pig, ADD/pig and mg AM/kg pork produced, and 2) to investigate association between produced growers per pen place, weight of grower when leaving grower facility and reported herd AM consumption - calculated as percentage growers treated per day, using pen places as measurement for number of pigs.

Materials and methods

Data was collected from Vetstat, Statistics Denmark and Statistics – PIGMEAT. AM consumption/pig/year was calculated using kg active compound and number of ADD divided by 1) pen places, 2) pigs slaughtered in Denmark (DK) and 3) pigs slaughtered in DK + number of exported growers (>15 kg) and finishers. Furthermore mg AM/kg pork produced was calculated based on kg pork from 1) pigs slaughtered in DK, 2) pigs slaughtered in DK + actual weight at live export (>15 kg) and lastly 3) pigs slaughtered in DK + adjusted weight at live export (81.8 kg) incl. 10% mortality. Student’s t-test was used to test for difference between means. An analysis of covariance was conducted to test for association between produced growers per pen place, weight of grower when leaving grower facility and reported herd AM consumption.

Results

The AM consumption for Danish pigs, measured in kg active compound, increased from 90,332 kg in 2005 to 100,418 kg in 2010 (i.e. 11%, $p<0,05$). Using the three different measurements for number of pigs, the increase from 2005 to 2010 constituted 12.1%, 17.7% and 0.3% and measured in ADD/pig 14.9%, 24.1% and 3.1%. The increase was significant when using number of pen places and number of pigs slaughtered in DK, but not when including live export.

Calculated as mg AM/kg pork produced an increase was seen from 2005 to 2009 of 31.4%, 18.6% and 9.0%. A significant association was found both between produced growers per pen place and reported herd AM consumption and between weight of grower when leaving grower facility and reported herd AM consumption ($P<0.05$).

Discussion and Conclusions

These results show that number of pigs should always be included when reporting AM usage. Also, there is an obvious risk of misclassification, if productivity is not taken into account. Pigs exported at >30 kg for slaughter outside DK should be included since they constitute a large percentage of the total pig production (28% in 2011) and have received most of their AM treatment before export. Measured in ADDs, usage for growers (7-30 kg) constitutes 77% of the total consumption for pigs. The export of growers is especially important since it has increased 160% from 2005 to 2010 (2.7 mio. to 7.9 mio live pigs). Furthermore it is recommended that number of growers produced per pen place and weight when leaving grower facility, might be taken into consideration if possible, when identifying herds with a high AM consumption.

Resume

Introduktion

I den danske svineindustri rapporteres antibiotikaforbruget oftest i kg aktivt stof eller procentdel dyr behandlet pr dag (målt som ”dyre doser”). I 2010 indførtes en dansk bekendtgørelse med henblik på at reducere antibiotika (AB) forbruget i danske svinebesætninger. AB forbruget beregnes her som procentdel dyr behandlet per dag. Besætninger der overstiger de fastsatte grænseværdier tildeles bøder og restriktioner. Antal stipladser, svarende til antal dyr i besætningen på ethvert givent tidspunkt, anvendes pt. som mål for antal dyr i besætningerne. Det er dog ikke sikkert antal stipladser er et passende mål for dyreantal, da adskillige generationer af dyr kan passere gennem en besætning årligt. Tages der ikke højde for produktivitet, kan dette muligvis medføre fejl i udpegningen af besætninger med højt AB forbrug. Hvordan antal dyr opgøres kan muligvis også have betydning når AB forbrug undersøges over tid og på tværs af lande. Målet med denne undersøgelse var derfor 1) at beskrive effekten af at anvende tre forskellige mål for dyreantal når AB forbruget beregnes som henholdsvis gram AB/gris, dyre doser/gris og mg AB/kg produceret svinekød, og 2) undersøge sammenhængen mellem antal producerede fravænningsgrise pr stiplads, vægt ved udgang fra klimastalden og procentdel dyr behandlet pr dag - hvor antal stipladser anvendes som mål for antal dyr.

Materialer og metoder

Data indsamledes fra Vetstat, Danmarks Statistik og Danske Slagteriers årlige udgivelser. For hvert år blev kg aktivt stof og antal dyre doser divideret med henholdsvis 1) stipladser, 2) grise slagtet i Danmark (DK) og 3) grise slagtet i DK + levende eksport (>15 kg). Ydermere blev kg aktivt stof divideret med kg svinekød produceret baseret på 1) grise slagtet i DK, 2) grise slagtet i DK + vægt ved eksport (levende) og 3) grise slagtet i DK + slagtevægt for grise eksporteret ved >15 kg (81,8 kg) justeret med 10% dødelighed. Student’s t-test blev anvendt for at teste forskelle mellem gennemsnit, En covarians analyse blev anvendt til at undersøge sammenhæng mellem antal producerede fravænningsgrise pr stiplads, vægt ved udgang fra klimastald og procentdel dyr behandlet pr dag baseret på antal stipladser.

Resultater

Uden at justere for dyreantal steg AB forbruget til danske grise 11% fra 2005-2010 (90.332 kg; 100.418 kg; P<0,05).Ved anvendelse af de tre forskellige mål for dyreantal steg forbruget fra 2005 til 2010 med henholdsvis 12,1%, 17,7% og 0,3% målt som gram AB/gris. Målt som dyre doser/gris steg forbruget 14,9%, 24,1% og 3,1%. Stigningen var signifikant, når antal stipladser og antal slagtede grise i DK blev anvendt son dyreantal. Stigningen var ikke signifikant når den levende eksport blev inkluderet. Opgjort som mg AB/kg svinekød produceret sås en stigning fra 2005 til 2009 på henholdsvis 31,4%, 18,6% og 9%. Der blev fundet en signifikant sammenhæng mellem antal producerede fravænningsgrise pr stiplads, vægt ved udgang fra klimastald og procentdel behandlede dyr baseret på antal stipladser (P<0.05).

Diskussion og konklusion

Dette studie illustrerer at antal grise altid bør inkluderes når AB forbruget rapporteres. Derudover er der en potentiel risiko for fejlslutninger, hvis produktivitet ikke tages i betragtning. Grise der vejer mere end 30 kg ved eksport bør inkluderes da de modtager størstedelen af deres AB i DK før eksport - målt i ADD anvendes 77% af det samlede AB forbrug til fravænningsgrise). Derudover udgør eksporterede fravænningsgrise en stor andel af den samlede danske produktion af grise (28% i 2011). Eksporten af levende fravænningsgrise steg desuden med 160% fra 2005 til 2010 (2,7 mio. til 7,9 mio.). Det anbefales at der så vidt muligt tages højde for antal producerede fravænningsgrise pr stiplads og vægt ved udgang af klimastald, når der udpeges besætninger med højt AB forbrug baseret på procentdel dyr behandlet per dag hvor antal stipladser er anvendt som mål for antal grise.

Monitoring and reporting methods of antimicrobial use- a literature study

1 Introduction

The association between resistant bacteria strains and use of antimicrobials (AM), especially growth promoters for production animals is well established (Lathers, 2001; Martel et al., 2001; Aarestrup et al., 2001; Agersø and Aarestrup, 2013). Data on AM usage can be helpful when researching patterns between AM consumption and emergence of AM resistant bacteria. Furthermore data on AM usage can be useful when developing treatment guidelines and legislations to curb AM consumption. Many sources have since 2000 advocated for the need to monitor veterinary antimicrobial consumption (Nicholls et al., 2001; WHO, 2001; Chauvin et al., 2002b).

Several studies on veterinary AM consumption have been published during the last decade (Casal et al., 2007; Varga et al., 2008; Jordan et al., 2009; Eagar et al., 2011; Anonymous, 2012b; Merle et al., 2012; Ozawa et al., 2012; Stolker et al., 2013). However Denmark was the first country to instigate a national monitoring programme for all veterinary drug usage at herd level (Stege et al., 2003). Since then the Netherlands and Sweden have followed suit (Anonymous, 2012b), and Germany, Austria, Finland, Norway and Belgium are currently working on implementing of similar monitoring programmes (Anonymous, 2012b, d, c; Obritzhauser, 2013b).

With detailed data on AM consumption at hand a wish arises to compare consumption both between herds and between countries. This poses several difficulties. Detail level of data varies greatly among countries, depending on each country's legislative infrastructure on registration, distribution and control of AM use (Nicholls et al., 2001). Furthermore, when comparing the AM usage across herds and countries, the consumption must be reported in the same way and using the same calculation method and measurement units. Several units have been proposed, all with different properties, advantages and disadvantages, including weight units, financial and commercial units (Chauvin et al., 2001; Anonymous, 2011e). The most widely used unit is "total kg active compound". This weight measurement is easily applicable, comparable between countries and recommended by the World Health Organization (WHO, 2003). But due to the wide range in dosage regimens between animal species and products, "total kg active compound" does not readily reflect actual therapeutic pressure (Chauvin et al., 2001).

WHO has defined a standardized unit for reporting drug consumption in humans, which takes dosage regimens into account. The unit is called "Defined daily doses" (DDD) (WHO, 2013a)). Everything needed for calculating the WHO defined DDD are available online for free (Monnet, 2013). A similar standardized measurement unit and calculation tool has not yet been developed for reporting veterinary drug consumption. Despite this, many studies on veterinary drug consumption reports the AM usage in measurement units derived from the WHO defined DDD (Jensen et al., 2004; MARAN, 2011; Callens et al., 2012; Merle et al., 2012). But - even where reporting methods are seemingly alike and all derived from the WHO defined DDD, comparing findings between studies on AM consumption are not without pitfalls. As Kuster et al. states "*reports on antibiotic use often lack complete definitions of the units of measurement, hampering comparison of data*" (Kuster et al., 2008). Different reporting- and calculation methods might affect findings, such as which herds are pointed out as heavy users (Chauvin et al., 2008) or how consumption changes over time (Dalton et al., 2007).

The Danish veterinary AM consumption is primarily reported as "total kg active compound" or "Animal daily doses" (ADD), defined as "*the daily maintenance dose per live animal for the main indication*" derived from the WHO defined DDD (Jensen et al., 2004). Several studies can be found where AM usage is also reported in ADD (Timmerman et al., 2006; Chauvin et al., 2008; Vieira et al., 2011). But, when scrutinized, it often becomes evident that between studies there are differences in the applied calculation routines and criteria used for selection of study population. This underlines the need for meticulous assessment of data collection- and calculation procedures when comparing findings from different studies.

This literature study's aims are to

- describe the monitoring and reporting methods used when reporting human and veterinary AM consumption, including an example of calculation routines used for the parameter "Animal daily doses"

- describe the structure and content of the Danish database "Vetstat" used for monitoring the Danish veterinary drug consumption.

2 Materials and methods

The literature study was conducted to identify monitoring and reporting methods applied when reporting human and veterinary AM consumption.

Electronic search engines for internet, journal and library databases were searched for articles published in English from 2000 to present (2013) using specific keywords, depending on subject investigated. Several of the included articles appeared in more than one search engine. An article was only assessed for relevance and content the first time it appeared.

Title of each article was first assessed. If the title seemed relevant, abstract was read. If abstract and following this, the article in its entirety still seemed relevant, the article was formatted into an annotated bibliography using Endnote X5 for Microsoft and into a searchable database. References in articles from the literature search were also assessed in order to identify all articles relevant to the study.

Google Scholar were used to obtain articles referenced in papers from the initial literature search, and articles which could not be assessed through the electronic search engines supplied by the University of Copenhagen.

2.1 Initial literature search

2.1.1 Monitoring and reporting methods of human AM consumption

The search engines CAB abstracts and PubMed were used.
Keywords used were: antimicrobial or antibiotic; consumption or report or usage.

CAB abstracts:
159 articles were initially assessed. Abstract were read for 43% (68/159). 23% of the articles were read in their entirety (36/159).

PubMed
250 articles were initially assessed. Abstract were read for 12% (31/250). 9% of the articles were read in their entirety (23/250).

2.1.2 Monitoring and reporting methods of veterinary AM consumption

The search engines CAB abstracts and Web of Science were used.

Keywords used were: pig or veterinary or animal, antimicrobial or antibiotic, use or usage or consumption.

CAB abstracts:
427 articles were initially assessed. Abstract were read for 16% (68/427). 6% of the articles were read in their entirety (24/427).

Web of Science:
163 articles were initially assessed. Abstract were read for 57% (35/163). 36% of the articles were read in their entirety (22/163).

2.1.3 Structure and content of the Danish database “Vetstat” used for monitoring veterinary drug consumption in Denmark

For information on monitoring and reporting methods in Denmark the literature search was supplemented with a search on the Danish Ministry of Food, Agriculture and Fisheries webpage (fvst.dk) and interviews of people closely associated with Vetstat.

For the literature search the search engines CAB abstracts, PubMed and the Danish Veterinary Association’s search engine for the members’ magazine “Dansk Veterinær Tidsskrift” were used in chronological order.

Keywords used in search in CAB abstracts and PubMed were: Vetstat; Denmark or Danish, antimicrobial or antibiotic

CAB abstracts:
18 articles were initially assessed. Abstract were read for 100% (18/18). 55% of the articles were read in their entirety (10/18).

PubMed
All articles were repeats from search in CAB abstracts.

Keywords used in search in the Danish Veterinary Association’s search engine for the members’ magazine “Dansk Veterinær Tidsskrift” were: antimicrobial or antibiotic.

The Danish Veterinary Association’s search engine for the members’ magazine “Dansk Veterinær Tidsskrift”:
57 articles were initially assessed. Abstracts were read for 100% (57/57), 29% of the articles were read in their entirety (17/59).

2.2 Assessment of literature

Primary sources in English were only included, if published in peer-reviewed journals. For research studies the following was assessed to determine credibility and differences between studies: If study population was representative for target population, sample size justification, inclusion- and exclusion criteria, percentage of non-participants, data collection procedures and how clear outcomes and calculation routines were defined.

When encountering secondary sources, it was always attempted to locate the primary source. Where this was not possible, e.g. in book chapters, author and publisher was investigated. If the author had published one or more peer-reviewed articles in English in journals with an impact factor >2 and the publisher was found to be a large publisher of scientific research the literature in question was included.

3 Results

3.1 Monitoring and reporting methods of human AM consumption

3.1.1 Data collection

Data collection on human AM consumption can be done in multiple ways depending on data availability (Clarence et al., 2008; Akalin et al., 2012; Pathak et al., 2012). In Scandinavian countries data on all human AM consumption are collected in large national IT-based databases (Ljungkvist et al., 1997; Müller-Pebody et al., 2004; Ferech et al., 2006; Muller et al., 2006; Blix et al., 2007). In countries where AM consumption are less strictly monitored at national level, data on AM usage can be recorded in IT-based databases by separate institutions - such as hospitals (Mandy et al., 2004; Muraki et al., 2013), pharmacies (Monnet et al., 2004; Chandy et al., 2013)), health care insurance companies and/or drug manufacturers (Vander Stichele et al., 2004; Anonymous, 2010c) Summarized data from these sources might be applied to give an impression of national AM consumption patterns (Vander Stichele et al., 2004).

Where IT-based data are difficult to obtain, e.g. due to lack of IT-based data on treatments, large non-registered over-the-counter sale and/or scarcely controlled import and export of drugs, data on AM consumption can be collected in various other ways. Examples are questionnaire-based studies interviewing end-consumers (Clarence et al., 2008; Pathak et al., 2012) and point prevalence studies collecting data from selected clinics, hospital departments or pharmacies (Dong et al., 2008; van den Boogaard et al., 2010; Akalin et al., 2012; Chandy et al., 2013).

3.1.2 Measurement units

The World Health Organization's (WHO) measurement unit "Defined Daily Dose" (DDD) is presently the most widely used unit when reporting AM consumption[1].
WHO defines DDD as "*the assumed average maintenance dose per day for a drug used for its main indication in adults*" (WHO, 2013a). DDD takes potency of drugs into account, and is independent of sale prices and product package sizes.
DDD was first implemented in a systematic way by the Nordic Council on Medicines. This was done in conjunction with an introduction of the Anatomical Therapeutical Classification system (ATC-system) (Wertheimer, 1986). The ATC-system identifies all drugs in a five-digit hierarchical

[1] In 50 random studies on human AM consumption published 2000-2013 82% used DDD as the primary measurement unit.

system. Products with the same active substance in the same pharmaceutical formulation are given the same ATC-code (Dahlin et al., 2001). According to the basic principles of WHO only one average maintenance dose is assigned per administration route within an ATC-code. DDDs are assigned by a WHO International Working Group (Anonymous, 2012b). When the recommended dose refers to body weight, an adult is considered to be a person of 70 kg. It should be emphasized that even special pharmaceutical forms mainly intended for children are assigned the DDD used for adults[2]. DDDs are not established for topical products, sera, vaccines, antineoplastic agents, allergen extracts, contrast media and general and local anesthetics (WHO, 2013a). The DDD/ATC system can be employed to ease benchmarking when reporting drug consumption (Natsch et al., 1998; Hutchinson et al., 2004; Meyer et al., 2004). WHO appointed DDDs are publicly available on the WHO Collaborating Centre homepage (WHO, 2013b) and an online calculator which employs the WHO's DDD/ATC system is available online for free (Monnet, 2013).

Among alternative measurement units to DDD are

- used daily doses - equivalent to actual days of treatment (Kern et al., 2005; Polk et al., 2007). Especially applicable if detailed IT-based data on day to day drug consumption are available – e.g. as in large Westernized hospitals

- prescribed daily doses –described as "days of treatment prescribed by the hospital/practitioner" by Muller et al. (Muller et al., 2006). Applicable if data on prescribed daily doses are available

- antibiotic courses – e.g. defined as "*any period during which the same agent (regardless of dose and route) was administered to the same patient on consecutive days*" (Berrington, 2010).

DDD is a measurement unit designed for pharmaco-epidemiological studies. Therefore it does not necessarily reflect recommended, used or prescribed daily dose for specific patients or individual patient groups (Monnet, 2007; WHO, 2013a). Thus it is proposed that the DDD/ATC system must be used with caution, when assessing actual used daily doses (Polk et al., 2007). This statement has been underlined by studies addressing limitations of the WHO's DDD/ATC system (Zagorski et al., 2002; Mandy et al., 2004; Shetka et al., 2005; Muller et al., 2006; Polk et al., 2007). One of the major noted shortcomings is discrepancy between actual used daily doses or prescribed daily doses and DDD, e.g. due to age of patient (e.g. pediatric patients), reduced dosage due to renal failure or simply that used daily doses or prescribed daily doses in the population investigated differs significantly from DDD-values given by the WHO. This is illustrated by Dalton et al. in a study assessing trends in AM consumption over a 6.5 year period in adult care centers. They found a 18.9% reduction in DDD per 100 bed-days, but only a reduction of 10.3% when measured as prescribed daily doses per 100 bed-days (Dalton et al., 2007).

When comparing AM consumption between studies, it is furthermore of great importance to ensure that identical calculation routines have been employed. In the United States the DDD methodology was adopted during the 1990s, but papers published did not utilize the WHO assigned DDDs, but rather adopted differing values on dosage regimens according to the sources at hand (Pallares et al.,

[2]Exceptions are made for some products used only by children e.g. growth hormones and fluoride tablets.

1993; Carling et al., 1999; Fridkin et al., 1999). This led to different "DDDs", thus hampering comparison of AM consumption between studies.

3.1.3 Choice of population measurement

It is generally agreed upon, that data on AM consumption are of more value, when related to a relevant population (Lee and Bergman, 1994; MacKenzie and Gould, 2005; Ferech et al., 2006; Anonymous, 2012c). Different measurements for population can be applied. "Number of bed-days" is often used when investigating AM consumption in hospitals (Kuster et al., 2008; Vaccheri et al., 2008; Muraki et al., 2013). "Number of admissions", "number of finished consultant episodes[3]", "number of patient days" and "number of prescriptions" have also been applied (White et al., 2000; Filius et al., 2005; Berrington, 2010) . Where AM consumption for patients not residing in hospitals or other institutions are investigated "number of inhabitants" is frequently used (Monnet et al., 2004; Ferech et al., 2006; van den Boogaard et al., 2010; Sohn et al., 2013).

3.2 Monitoring and reporting methods of veterinary AM consumption

3.2.1 Data collection

WHO acknowledged in a report from 2001 that data collection programmes on veterinary AM consumption would depend on the national situation in each specific country. Therefore WHO posed the following suggestions:

"*Collecting data from one or more of the following sources:*
- *Importers and exporters as well as production data from manufacturers.*
- *Data on intended and actual usage from manufacturers, distributers including feed mills, pharmacies and veterinary prescription records.*
- *Veterinarians, farmers and animal producers.*

(WHO, 2001)

Data collection methods on veterinary AM consumption are as diverse as for the human counterpart, although far less countries have yet established nation-wide surveillance programmes. Below are listed some examples of data collection methods used in veterinary AM consumption studies.

- National databases containing detailed consumption data at herd level from both pharmacies, drug manufacturers and wholesalers (Vieira et al., 2011; Stolker et al., 2013).

- Data from either importers, drug manufacturers or wholesalers not already collected in a database (Mitema et al., 2001).

- Data collected from slaughterhouses from paper forms completed by farmers on all treatments during a set period (Chauvin, 2005).

- Data collected directly from the herd, e.g. assessment of log journals for all treatments in the herd during a certain period (Timmerman et al., 2006; Callens et al., 2012) or questionnaires

[3] "Finished consultant episodes" (FCE) is not the same as "number of admissions" as a single admission might account for more than one FCE, if the patient is transferred form one department to another. Thus FCE is essentially a measurement for number of departmental admissions.

on treatment practices filled out by the farmer (Rajić et al., 2006; Casal et al., 2007; Rosengren et al., 2008; Varga et al., 2008; Eltayb et al., 2012; Ozawa et al., 2012).

- Data collected through the veterinarians – e.g. questionnaires on treatment practices for certain diseases (Jordan et al., 2009; Pleydell et al., 2012), last prescription made (Chauvin et al., 2002a) or collection of patient journals (Escher et al., 2011; Murphy et al., 2012).

3.2.2 Measurement units

Contrary to human medicine, there is no standardized international measurement unit available for pharmaco-epidemiological studies on veterinary drug consumption. WHO recommended in 2001 that veterinary AM consumption should be reported as total kg active compound consumed. Furthermore a call was made for a veterinary system similar to the DDD/ATC system to ease comparison between studies (WHO, 2001).

Up to this day veterinary AM consumption has been reported using several different measurements. Among these are

- money spent on AM (Chauvin et al., 2008)
- kg active compound AM (Jensen et al., 2004; Grave et al., 2010; Anonymous, 2011c)
- number of prescriptions made (Holso et al., 2005)
- percentage of herds using specific AMs (e.g. tetracycline or ceftiofur) over an extended time (Jordan et al., 2009) or according to the last made prescription (Chauvin et al., 2002a)
- used daily doses, both as "used daily doses per pig" and "used daily doses per kg pig". Callens et al defines used daily doses per kg pig as "*actually administered per day per kg pig of a drug*" (Callens et al., 2012). Used daily doses is applicable where detailed treatment data is available from the farmer (day of treatment, product given, weight of animal treated)
- used course doses – actual used doses per treatment course (Menéndez González et al., 2010)
- prescribed daily dose, calculated by Pardon et al. as amount of product on prescription divided by dosage recommendation on prescription multiplied by animal weight at beginning of treatment (Pardon et al., 2012).
- animal daily doses (ADD), also called DDD by Pol and Ruegg (Pol and Ruegg, 2007). ADD is defined by Jensen et al. as "the defined average maintenance dose for the main indication in a specified species" (Jensen et al., 2004)

Several studies report their findings using more than one of the above mentioned units, highlighting the effect of using different measurement units when reporting AM consumption (Timmerman et al., 2006; Chauvin et al., 2008; Menéndez González et al., 2010; Callens et al., 2012; Pardon et al., 2012). In a study on AM consumption in 50 Belgian pig herds, Timmerman et al. found that 17.8 % of the pigs were treated per day when consumption was calculated in ADD, whereas 17.0% of the pigs were treated per day when consumption was calculated in used daily doses (Timmerman et al., 2006). These findings are consistent with a study conducted by Pardon et al. where the percentage of animals treated per day were also found to be higher when calculated as ADD than when calculated as used daily doses (41.4% of Belgian veal calves treated per day as opposed to 37,9% of veal calves treated per day) (Pardon et al., 2012).

In a study from 2008 Chauvin et al. compared agreement between reported AM consumption when using different reporting methods for pointing out herds with a high AM consumption. They found that chosen measurement unit affected whether or not a herd was pointed out as a herd with high AM consumption. Agreement values (kappa) between reporting methods[4] ranged from 0.31-0.83 with a mean of 0.54 (Chauvin et al., 2008).

Although measurement units across studies may seem similar when reporting AM usage– e.g. the consumption is reported in ADD – it is vital to assess, if calculation methods differ in any way before comparing consumption across studies. Total kg active compound AM and ADD are currently the measurement units used, when reporting AM consumption from the Danish and Dutch national databases (DANMAP, 2011; MARAN, 2011). ADD enables reports on AM consumption to adjust for differences in dosage regimens depending on animal species and size (Lee and Bergman, 1994). ADD is the closest veterinary equivalent to the WHO standardized human measurement unit “defined daily dose” (DDD) (Wertheimer, 1986). But contrary to the WHO defined DDD, ADD is still calculated differently across borders. To calculate number of ADD, dosage per animal must be known for each product. It is most often based on standardized dosage values. Depending on preference and nationality of authors, these standardized dosage values are taken from different publications (Jensen et al., 2004; Timmerman et al., 2006; Callens et al., 2012). Therefore dosage values and calculated ADD varies accordingly. Examples are shown in table 1 of calculation routines and study population selections from studies reporting AM consumption in measurement units derived from the WHO defined DDD (p. 44-45).

To account for the large variation between weights in production animals, the parameter “standard weight” was introduced when reporting veterinary AM consumption from the Danish and Dutch national databases (Stege et al., 2003; MARAN, 2009). “Standard weight” is the estimated average weight at treatment assigned to specified age groups within production animal species (Jensen et al., 2004). “Standard weight” have also been applied in studies, where exact weight of animal at treatment is not known (Menéndez González et al., 2010; Obritzhauser, 2013b). Examples are shown in table 2 of differing “standard weights” and age groups between studies.

[4] Six reporting methods investigated- kg active compound AM, treatments, days of administration, kg live weight treated, animal daily dose to treat 1 kg live animal and euros.

	Age group	Standard weight
Denmark (Stege et al, 2003)		
	Breeding animals, gilts, suckling pigs	200 kg
	Finishers (30-110 kg)	50 kg
	Growers (7-30 kg)	15 kg
Netherlands (MARAN, 2007)		
	Breeding boars	350 kg
	Sows	220 kg
	Maiden gilts	107.5 kg
	Fattening pigs	70.2 kg
	Piglets	12.5 kg
Austria (Obritzhauser, 2013a)		
	Boars	150 kg
	Sows	150 kg
	Young sows mated	150 kg
	Young sows not mated	75 kg
	Fatteners	75 kg
	Weaners 20 - 32 kg	35 kg
	Piglets 8 - 20 kg	35 kg
Germany (Merle et al., 2012)		
	Sows	220 kg
	Fattening pigs	70.2 kg
	Weaners	25 kg
	Piglets	12.5 kg

Table 2.*Examples of age groups and standard weights for pigs.*

ADD does not necessarily reflect the prescribed-, used- or recommended daily dose and drug consumption. Data presented as ADD only gives an estimate of consumption and not an exact picture of actual use (Chauvin et al., 2001).

3.2.3 Choice of animal numbers

When evaluating AM consumption data, it is often meaningful to relate data to a relevant population (Lee and Bergman, 1994; MacKenzie and Gould, 2005; Ferech et al., 2006; Anonymous, 2012c)).

Animal number equaling animal population at risk can be assessed in several ways. Examples are

- number of pen places, resembling live animals in herd at any given time (Anonymous, 2011a; MARAN, 2011)

- number of animals produced (e.g animals slaughtered with or without export of live animals) (DANMAP, 2011)

- kg animal present per year (e.g. calculated average weight at treatment * number of animals (Anonymous, 2011f)).

We conducted a study to investigate effect of measurement of animal number, when reporting national AM consumption per pig, using pen places, number of nationally slaughtered pigs and number of nationally slaughtered pigs + pigs exported live respectively. We found that AM consumption per pig from 2005 to 2010 changed significantly when using pen places and number of nationally slaughtered pigs as measurement for animal number, but no significant change was found when live export was taken into account (Dupont, 2012).

To assess frequency of treatments the parameter "percentage animals treated per day" can be applied (Alban et al., 2012; Callens et al., 2012). To calculate "percentage animals treated per day", number of animal days, resembling animals at risk during the period investigated must be known. The Danish authorities presently use number of "pen places", presumably resembling live animals at any given time, as measurement for animal number[5] (Alban et al., 2012)

Therefore animal days are calculated by the Danish authorities as:

$$Animal\ days = Number\ of\ pen\ places * days\ in\ period$$

(Anonymous, 2011b)

Percentage animals treated per day can then be calculated as:

$$Percentage\ animals\ treated\ per\ day = \frac{ADDused}{Animal\ days} \times 100$$

Other examples are given in table 1 (page 44-45)

2.3 Structure and content of the Danish database " Vetstat" used for monitoring veterinary drug consumption

As a result of the growing concern towards AM resistant bacteria entering the human food chain an EU conference ("The Microbial Threat") was held in Denmark in 1998. One of the recommendations issued was to monitor the veterinary use of AM more closely. In order to comply with these recommendations, Denmark instigated an on-going surveillance program in 2000 of the medical consumption for (production) animals, collecting all data in the national database Vetstat (Stege et al., 2003). Vetstat is an abbreviation of "the Danish Veterinary Medicines Statistics Programme" (Vieira et al., 2011).

Vetstat is a relational database on an Oracle platform owned and managed by the Ministry of Food, Agriculture and Fisheries. Since 2002 it has been mandatory to record all drugs prescribed to production animals (Hybshmann et al, 2011).

[5] Data on number of pen places are derived from a national database (Anonymous, 2011b. Bekendtgørelse om særlige foranstaltninger til nedbringelse af antibiotikaforbruget i svinebesætninger - in Danish (Legal order on special means to lower the antimicrobial consumption in pig herds). The Danish Ministry of Justice. https://www.retsinformation.dk/Forms/R0710.aspx?id=139431. 16-06-2013).

The purposes of Vetstat are to:
"*(1) monitor veterinary usage of drugs in animal production; (2) help practitioners in their work as farm advisors; (3) provide transparency as a basis for ensuring compliance with rules and legislation and (4) provide data for pharmaco-epidemiological research." (Stege et al., 2003).*

During the nineties many legislative regulations were passed by the Danish government to curb AM sale, including regulations on veterinary profits from sale of AM (Aarestrup et al., 2010; Anonymous, 2012a). The Danish government introduced a ban on avoparcin in 1995 and virginiamycin in 1998 for use in production animals (Aarestrup et al., 2001; Grave et al., 2006). Furthermore the food animal industry in Denmark voluntarily stopped all use of AM's as growth promoters by the end of 1999 (Aarestrup et al., 2001). All AM and the largest majority of all other veterinary therapeutic drugs are prescription-only in Denmark (Anonymous, 2010a). Virtually, all sale of veterinary medicine are made through pharmacies, veterinary practitioners or feed mills. Data on medicine consumption are therefore submitted to Vetstat by these three entities (figure 1).Pharmacies and feed mills purchase drugs directly from the drug manufacturers. Veterinary practitioners purchase drugs for use in practice from pharmacies. All pharmacies, veterinary practitioners, veterinary practices and feed mills have a unique ID (Stege et al., 2003).

Content of entries to Vetstat are shown in figure 2. Presently there is no automatic linking of animal species, age group and diagnostic group. This makes it possible to make an entry containing logically diverging values e.g.: animal species "cattle", age group "finishers" and diagnostic group "furunculosis". In 2011 1.4% entries reported by pharmacies on drugs for use in cattle herds either stated an invalid age group, diagnostic group or both (Dupont, 2013c).

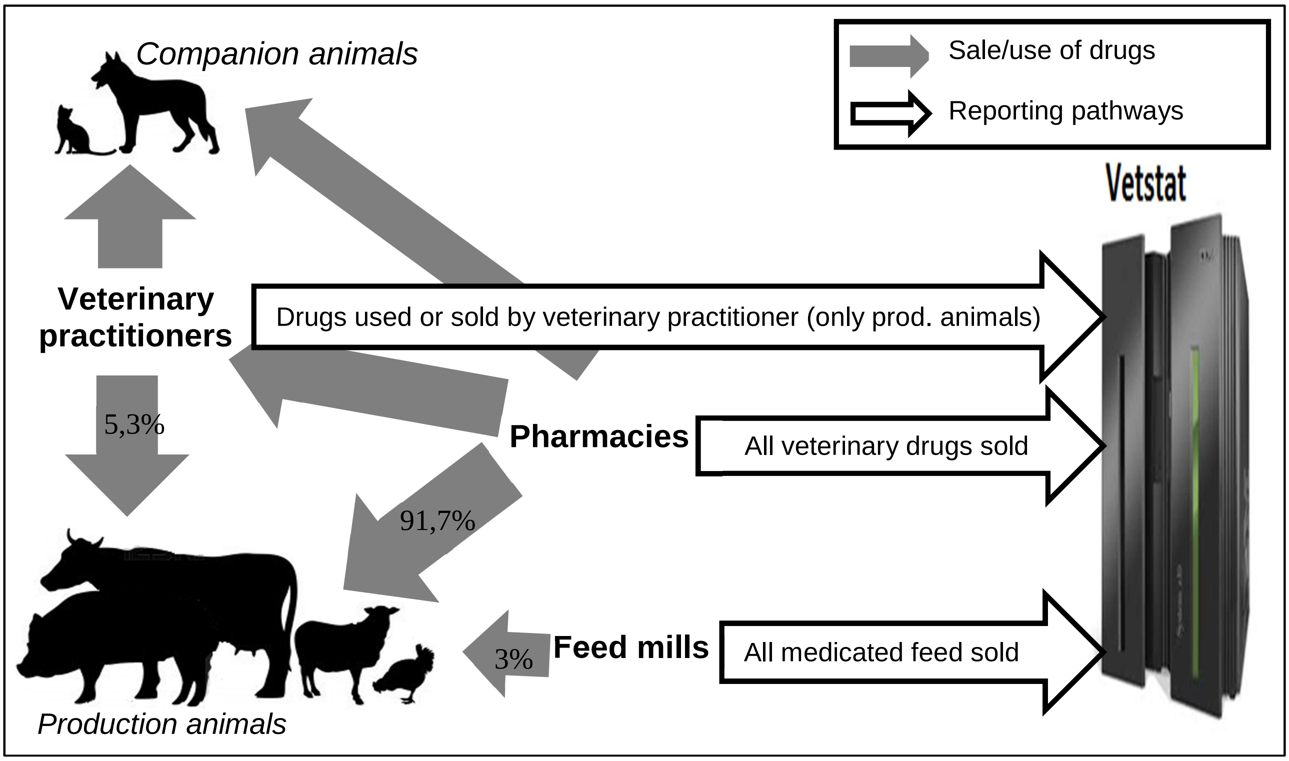

***Figure 1**. Reporting pathways- Vetstat and percentage of total kg AM active compound reported for production animals in 2011.*

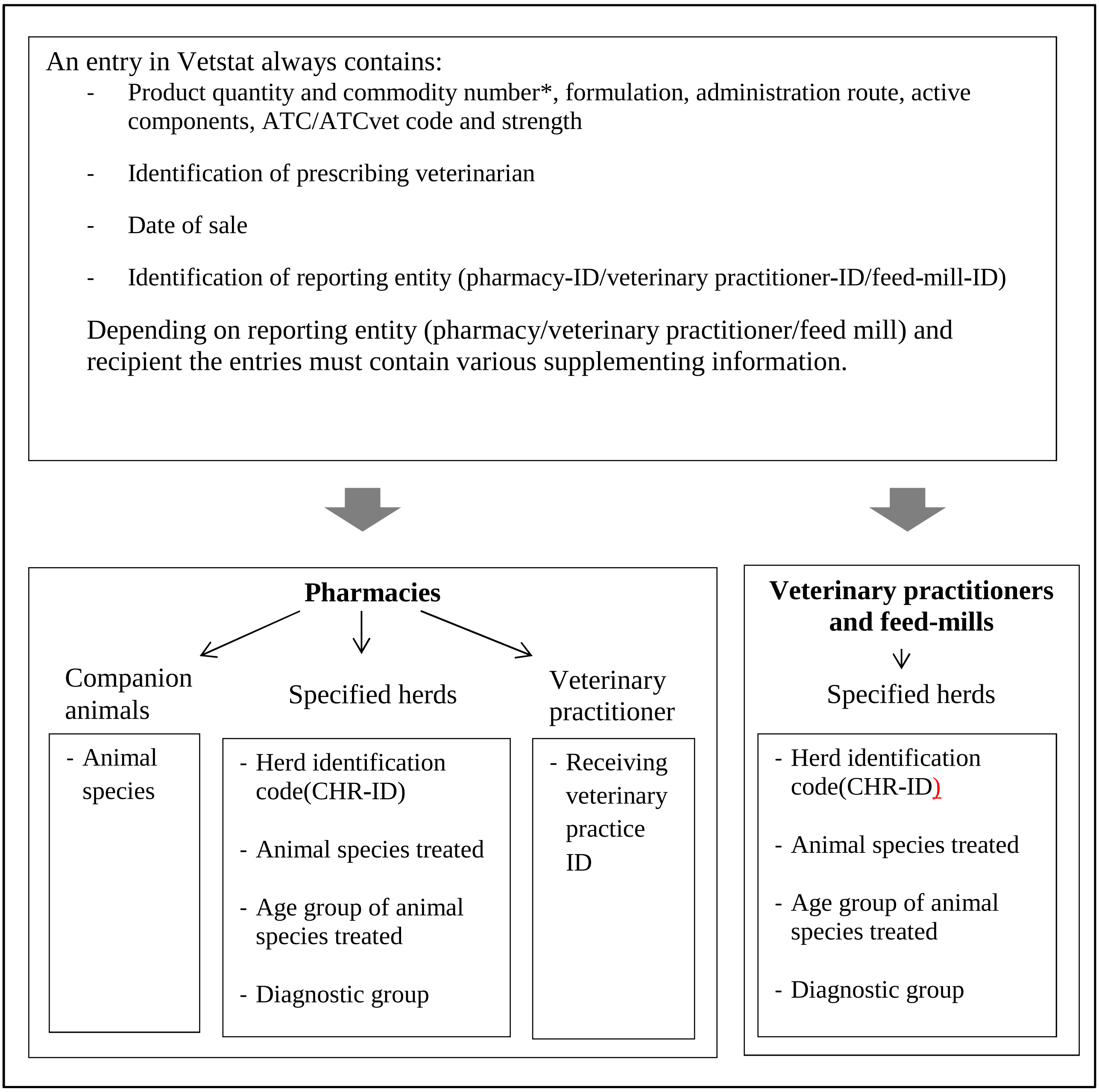

Figure 2. *Content of entries according to reporting entity and recipient of drug (Stege et al., 2003). *The Nordic commodity number identifies name of medicinal product, strength, form and size of packaging(Jensen et al., 2004).*

Vetstat's definitions of animal species, age group and diagnostic group are shown in table 3 (Stege et al., 2003; Anonymous, 2013a).

__Table 3.__ Vetstat definitions of animal species, age group (including according standard weight) and diagnostic group.

Animal species	Age group (standard weight(kg))	Diagnostic group
Pigs	Breeding animals, gilts, suckling pigs (200) Growers (15) Finishers (50)	Reproduction, urogenital system Udder Gastro-intestinal system Respiratory system Joints, limbs, hooves, CNS, skin Metabolism, digestion, circulation
Cattle	Bulls, cows (600) Calves<12 months (100) Heifers, steers (300)	
Sheep, goats	>12 months (50) <12 months (20)	
Mink	Not recorded (1)	Other (mink only)
Aquaculture	Not recorded (1)	Red mouth disease Furuncolosis Brood syndrome Other
Poultry	Broilers (0,2) Layers (1) Rearing flocks (1)	Abdominal organs coccidiosis enteritis hepatitis salpingitis other Respiratory system/organs
Other production animals*	Not recorded (1)	
Horses	Not recorded (500)	Not recorded
Pets	Not recorded (not given)	

*llamas, rabbits, deer, ostriches

Submission of data to Vetstat

All Danish pharmacies have electronic and standardized billing systems. These are linked to Vetstat, which ensures automatic transfer of data on all veterinary drug purchases (Jensen et al., 2004).

Electronic journal systems are used by most Danish veterinary practices[6]. These software-systems automatically transfer data on all treatments regarding production animals to Vetstat in connection with billing (Jensen et al., 2004). The software-systems are developed and distributed by private companies and there are no official guidelines or legislation on the setup. A few veterinarians choose to report data directly into Vetstat, either manually on the Vetstat webpage or by discs sent to the Ministry of Food, Agriculture and Fisheries (Jacobsen, 2013). According to Danish legislation veterinarians must report drugs used for production animals at least once per month (Anonymous, 2013a).

[6]TANG-dyrlægeløsning(TANG data- http://www.tang.nu/index.php/vetnet/vetnetmanagement) and Vetvision (Novasoft- http://vetvision.eu/).

Only few substances are approved for pre-mixed medicated feed for production animals. The purchases are reported directly to Vetstat by the feed-mills (Jacobsen, 2013).

Herd identification code- system

Since 1993, all Danish herds have been legally required to register in the Central Husbandry Register (CHR). CHR is owned and managed by the Ministry of Food, Agriculture and Fisheries (Jensen et al., 2004). All herds are given a unique identity code (CHR-ID) relating to the geographical coordinates of the herd in question (Madec et al., 2001). In addition to information on geographical location the register also contains data on production type and number of animals present in the herd (animal species, age group) and contact information on the farmer (Mousing et al., 1997; Hybschmann et al., 2011). It is mandatory to report all changes in number of animals to CHR no later than 7 days after the event for cattle and once per year for pigs[7] (Anonymous, 2011a).

List of veterinary products

All Danish drugs, both human and veterinary, must be approved either by the Danish Health and Medicines Authority or the European Medicines Agency. Newly approved veterinary drugs are registered into Vetstat every second week manually by a ministry employee (Jacobsen, 2013). Information must include

- commodity number
- active component(s)
- strength
- package size
- formulation
- administration route
- ATC/ATCvet code
- average daily maintenance dose per kg live animal for the main indication according to relevant animal species (DMD_{kg}).

(Jensen et al., 2004)

Dosage values in Vetstat are derived from detailed product descriptions published by the Danish Health and Medicines Authority. The product description contain information on drug content, which animal species the drug has been approved for and recommended dosage[8](Anonymous, 2013b).Where recommended dosage in the product description is given as a range, dosage value in Vetstat is calculated as mean dosage value - e.g. if 0.1-0.05 mL product per kg live weight animal recommended in the product description, the Vetstat dosage value will be 0.075 mL per kg live animal (Jacobsen, 2013).

User-access to Vetstat- data

Data on overall national AM consumption, measured as kg active compound, for all animal species and for pigs specified are presented online on the webpage of the Ministry of Food, Agriculture and Fisheries (Anonymous, 2013f).

[7]For herds with more than 300 sows, 3000 finishers or 6000 growers, information on animal numbers must be updated biannually.

[8]Available in Danish at the Danish Health and Medicines Authority's webpage: http://www.produktresume.dk/docushare/dsweb/View/Collection-72

Detailed data on all entries into Vetstat are accessible to veterinarians and farmers on Vetstat's webpage (www.vetstat.dk). Farmers can monitor all entries regarding their own herds. Veterinarians can monitor all entries submitted by themselves, and all entries for herds with whom they have a Health Advisory Agreement (HAA). HAA's are mandatory for Danish herds of a certain size (>300 sows, boars or gilts, >6000 growers or >3000 finishers. They cover rules on frequency of veterinary visits, treatment schemes and management (Anonymous, 2013c).

Automated graphic reports can be made on AM consumption for each individual herd reported as percentage animals treated per day.

Since spring 2012 it has been possible for any member of the public to obtain access to detailed data excerpts from Vetstat (Anonymous, 2011d).

4 Discussion

4.1 Data collection

Several studies have been conducted to assess both human and veterinary national AM consumption. Completeness of data may be easier to obtain, for countries where data on all AM treatments or sale are already collected in IT-based databases, such as national databases, hospitals or pharmacies (Stege et al., 2003; Holso et al., 2005; Escher et al., 2011). Where such databases do not exist, data collection often relies on the willingness of veterinarians and/or farmers to participate (Varga et al., 2008; Callens et al., 2012; Murphy et al., 2012). This may affect findings - e.g. if farmers only participate if they are willing to fill out extensive forms (Pardon et al., 2012) or have a specific interest in the subject or decline to participate if they consider the subject to be sensitive (Edwards et al., 2002). Possible non-response bias must therefore be taken into account, especially in studies where response rates are relatively low (38% (Callens et al., 2012); 22% (Dewey et al., 1999); 37% (Chauvin et al., 2002a) .

Several studies describing AM usage for countries or other similar large geographic areas utilize convenience sampling for study population selection. Examples of convenience sampling are

- study population selected through another study's participants (Dewey et al., 1999; Sawant et al., 2005; Rajić et al., 2006; Pol and Ruegg, 2007)

- study population based upon willingness to participate (e.g. enlisted through an advertisement published in a magazine (Menéndez González et al., 2010) or veterinarians suggested herds willing to participate (Merle et al., 2012)).

This might possibly affect findings as the study population may not be representative of the target population. Furthermore where data are collected from end-consumers, data might be biased due to forgetfulness of end-consumer (Vrijheid et al., 2006) or as stated by Chauvin et al, 2002- "*as various sources of information do not always provide consistent results in human medicine when respondents are direct consumers, it is likely that similar difficulties will be encountered in tracing drug usage in veterinary medicine*" (Chauvin et al., 2002b).

Even where national databases are available, validity of data should be assessed, as it has been shown that data might be incomplete or contain erroneous entries (DANMAP, 2011; Dupont, 2012;

Wolff, 2012; Espetvedt et al., 2013). Steps can be taken to ensure data validity on consumption data, such as automatic transfer of data on all veterinary drug purchases (Jensen et al., 2004) or comparing data entries with actual consumption in the investigated population (Jick et al., 2003). Furthermore, when comparing AM consumption between countries, it is important to be aware that AM consumption data from national databases can be reported in different ways.

When studies investigate national consumption patterns it might be prudent to consider study population selection and participation rates of contacted herds. This is exemplified by the studies performed by Dewey et al. (1999) and Eagar et al. (2011). In 1999 Dewey et al. (1999) published a study titled "*Use of antimicrobials in swine feed in the United States*." However it was not clear in the article, how the authors ensured that the study population was representative of the target population- which based on the title must be pig herds in the United States. Sample size needed was not given in the paper. Herds participating in the study were herds chosen on basis of a study on preweaning mortality and morbidity (Tubbs et al., 1993; Dewey et al., 1999). Participation rates of contacted herds were 22,6% (712/3184) and data was included from 17 out of 50 states, (Dewey et al., 1999). Furthermore it is not addressed in the article's discussion how representative the authors perceive their study population to be of the target population.

Another example of a study making inferences on national consumption based on a sample of herds is the study on the national AM consumption in South Africa by Eagar et al. (Eagar et al., 2011). Eagar et al. assess consumption through sales data from eight out of the twenty five drug companies in the country. No information is given on the market share of the eight participating companies. Before making conclusions based on results in this study on the national South African AM pattern, it must be taken into consideration that it is not known whether the participating eight drug companies only deliver to a specific region of South Africa, a specific production type or a specific animal species. However - contrary to Dewey et al (1999), Eagar et al. refrains from making any final conclusions on the quantity of AM consumed in South Africa. They instead make a call for legislation concerning increased surveillance of AM consumption, as they conclude that more data is needed before any decisive conclusions can be made on the total amount of AM used in South Africa.

Effect of calculation routines on AM consumption reports based on data from the Danish national database "Vetstat"

When using data from large national databases, some reporting entities might deliver better quality data than other (Espetvedt et al., 2013). Furthermore it is presently only a few databases with include information on animal species (Anonymous, 2012c). Below is an example from the Danish Vetstat database to illustrate effect of using different approaches when reporting AM consumption based on consumption data obtained from a national database.

Data on Danish veterinary drug consumption are registered into Vetstat by three reporting entities – pharmacies feed mills and veterinary practitioners (Stege et al., 2003; Jensen et al., 2004). By Danish law all use and sale of AM consumption used for productions animals must be registered into Vetstat, no later than one month after the event (Anonymous, 2013a). The completeness of data from pharmacies and feed mills are estimated to be very high, whereas data on up to 20% of AM used by veterinary practitioners have been estimated to be missing (DANMAP, 2011). Lack of reports on AM usage from veterinary practitioners may not affect reported AM consumption for Danish pigs, as only a very small percentage of AM's used for pigs comes from veterinary practitioners (less than 0,1% in 2011) (Vieira et al., 2011). Contrary to this, from 2007-2011, 36-

76% of AM's registered for use in cattle were reported through veterinary practitioners (Dupont, 2013c). Data on the Danish AM consumption for cattle are published yearly by DANMAP - the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP, 2012). To adjust for potential missing registrations by veterinary practitioners, DANMAP calculates AM consumption for cattle (kg active compound) as:

$$
\begin{aligned}
&\mathit{DANMAP\ cattle\ AM} \\
&\quad = \mathit{AM\ sold\ directly\ for\ use\ in\ cattle\ herds\ from\ pharmacies} \\
&\quad + \mathit{AM\ sold\ for\ use\ in\ cattle\ practice\ from\ pharmacies}
\end{aligned}
$$

By applying this method, AM consumption is estimated relying solely on data registered by pharmacies. Registrations by pharmacies on AM sold for use in veterinary practice do not include information on animal species (figure 2). Therefore this method is not without flaws as

- AM used in mixed practice for cattle are not included.
- AM used for non-cattle are included if used by veterinarians employed in cattle practice.

An alternative to the DANMAP method is solely to include Vetstat-data where animal species have been explicitly specified as "cattle". This method does not adjust for missing registrations by veterinary practitioners.

When comparing AM consumption, given as total kg active compound AM, according to these two methods, there is a discrepancy of 4-15% (table 3) (DANMAP, 2008, 2009, 2010, 2011, 2012).

	Vetstat	DANMAP	Discrepancy (kg active compound AM)	Discrepancy in %
2007	12741	15000	2259	15,1
2008	12923	14500	1576	10,9
2009	13232	15000	1768	11,8
2010	14027	14636	608	4,2
2011	13671	14678	1006	6,9

Table 3*.Antimicrobial consumption (kg active compound) for cattle 2007-2011 according to Vetstat and DANMAP respectively.*

This comparison highlights the importance of meticulous description of calculation routines when publishing numbers on AM consumption. DANMAP reports can be accessed at www.danmap.org.

4.2 Measurement units

Table 1 (p. 44-45) gives an impression of the multitude of different calculation methods used when reporting veterinary drug usage. Even where calculation routines seem alike, other values differ, such as dosage values or measurement for number of animals. To facilitate comparisons between studies on AM consumption, transparency of calculation methods are needed (Kuster et al., 2008). Furthermore names of variables should be easily understandable to the reader. Timmerman et al. (2006) calculates the outcome variable "Animal daily dose pig" (defined as treatment incidence based on ADDpig) based on the variable "ADDpig" (defined as the national average maintenance dose per day per kg pig). This might confuse readers, as the variable names "Animal daily dose pig" and "ADDpig" resembles each other (Timmerman et al., 2006).

"Total kg active compound AM" is presently the measurement unit recommended by WHO for reporting AM consumption (WHO, 2003). To take differences in potency of drugs and dosage regimens between animal species into account, other variables have been introduced. Among these are "ADD" (animal daily doses), "prescribed daily doses" and "used daily doses" ((Jensen et al., 2004; Timmerman et al., 2006; Chauvin et al., 2008; Menéndez González et al., 2010). ADD can be used where prescribed daily dose or used daily dose are not available – e.g. when using data collected in national databases (Jensen et al., 2004; MARAN, 2011). Dosage values are then often estimated on basis of various literature recommendations (Jensen et al., 2004; Timmerman et al., 2006). Differences in dosage values per kg live animal must therefore be taken into account, when comparing studies. Even within studies performed in the same country, sources for dosage values may differ as shown by Timmerman et al. (2006) and Callens et al. (2012). Even though both used the Belgian Compendium of Veterinary Medicines as a source for dosage values, Callens et al. (2012) also used drug instruction leaflets and Timmerman et al. (2004) used publications from the Belgian Centre for Pharmacotherapeutic information (Timmerman et al., 2006). None of the two studies include information on which source on dosage value was used for which product, further hampering direct comparison between the studies.

Within national monitoring systems, disagreements between very similar products (same active substance, same administration route) on dosage per kg live animal may also arise. Vetstat dosage values are given according to product descriptions published by the Danish Health and Medicines Authority (Anonymous, 2013b). In 2010 the Danish government instigated fines and regulations to herds where more than 5% of breeding animals, gilts and suckling pigs, 25% of growers or 7% of finishers are treated daily (calculated as ADD per 100 animals per day) (Anonymous, 2013d). This has increased the interest to obtain as low an ADD count in Vetstat as possible. This might possibly lead drug manufacturers to aim at releasing products with a broader dosage interval per kg live animal allowing farmers the possibility of treating animals with a lower dose than specified by the drug manufacturer, leading to a false low ADD count (Jensen, 2013). This would lead to skewed comparisons of ADD both between herds and between years. As a consequence the Danish Ministry of Food, Agriculture and Fisheries has recently developed their own set of dosage values for calculating ADD for national reports. This is done to be able to report AM consumption independently of drug manufacturers' differing recommendations. In the Ministry's dosage values, all products with the same active substances in the same pharmaceutical formulation have the same dosage value per kg live animal. (Jensen, 2013).

The gold standard dosage value used to calculate ADD, should take differences in dosage regimens between animal species into account and be adjusted for prolongated drugs (Menéndez González et al., 2010). Prolongated drugs work in an extended number of days after administration and therefore a does not need to be administered on a daily basis (Anonymous, 2009).

As shown in table 1 different weight groups within animal species have been applied between studies. Decision on which grouping is applied affects calculated ADD.

Calculation example:

100 mL EthacilinVet. containing 300 mg benzylpencillinprocain/mL for use in finishers – using Vetstat values for standard weight (15kg(Stege et al., 2003))

$$number\ of\ ADD = \frac{(100mL\ product * 300mg/mL)}{15mg/kg\ * 50kg} = 40\ ADD$$

If the standard weight for finishers from the Dutch database is used instead (70.2 kg (MARAN, 2011)) the calculated ADD changes (assuming that dosage per kg animal is the same in the Netherlands as used in Vetstat):

$$number\ of\ ADD = \frac{(100mL\ product * 300mg/mL)}{15mg/kg\ * 70.2kg} = 28{,}5\ ADD$$

Even though, in both cases, same amount of product have been prescribed for finishers, a direct comparison between the Danish and the Dutch ADD might lead to erroneous conclusions, as the standard weights used are different. To avoid differences in reporting methods due to different standard weights, it might be most prudent to use the variable ADDkg- defined as "the average maintenance dose per kg live animal for the main indication in a specified species", thus calculating kg of animal treated instead of number of animals treated.

In 2004 Jensen et al. conducted a study to compare dosage values given in Vetstat with prescribed dosage values according to a group of Danish veterinarians, as recommendations given by the Danish Health and Medicines Authority might not be representative of the actual treatment regiments used in practice (Jensen et al., 2004). When comparing the swine practitioners' prescribed dosage values with Vetstat's dosage values 81% of the investigated antimicrobial groups deviated <10% from the Vetstat dosage values (21/26), 8% deviated with 10-25% (2/26) and 11% deviated with >30%. In one case (chlortetracycline for oral use) deviated with more than 100%. This might be because dosage recommendations for this group varied with 100% depending on disease treated (Jensen et al., 2004). It is not stated how large a percentage of the Danish swine practitioners participated in the study. These findings are similar to those by Chauvin et al. (2002a), who found that three out of four antimicrobial groups investigated were within the range of the recommended daily dose as given by Ungemach et al. in a previously published study on European recommendations (Ungemach, 2000; Chauvin et al., 2002a). Estimations of differences between prescribed daily dose and recommended daily dosage may have improved in both studies if more veterinarians had been participating (response rate in the study by Chauvin et al. was 37% (Chauvin et al., 2002a)). These findings support the statement that calculated ADD is not necessary a direct reflection of actual prescription or usage patterns in a population.

Prescribed daily doses may diverge from the used daily doses, if treatment practices in the herds are not in compliance with the veterinarian's prescriptions (Nicholls et al., 2001). Pardon et al. investigated differences between ADD, prescribed daily doses and used daily doses for group treatments. They found that number of used daily doses were lower than number of ADD (41.4% of animals treated per day given in ADD; 37.9% of animals treated per day when given in used daily doses) (Pardon et al., 2012).

The measurement unit "used daily doses" is calculated as AM used per animal per day by the farmer (Callens et al., 2012), The measurement unit "used daily doses" is recommended by Nicholls et al., as the data collection happens close to the end-user of the drugs (Nicholls et al., 2001). Despite this, "used daily doses" poses some difficulties. It relies to a very large degree on the willingness of the farmer to participate in the study, if the study is retrospective, also on the recollection of the farmer, if there are no written records of prior treatments in the herds (Vrijheid et al., 2006; Vieira et al., 2011; Eltayb et al., 2012). Furthermore there might be a risk of misunderstandings, when collecting data on AM usage by interviews depending on the language proficiency of the interviewer, where interviews are performed in several languages (Eltayb et al., 2012; Kehinde and Ogunnowo, 2013).

4.3 Choice of animal numbers

When reporting AM consumption, it is often desirable to relate the findings to a relevant population, to estimate percentage of animals treated per day (MacKenzie and Gould, 2005). Number of animals, equaling population at risk, can be measured in several ways e.g. number of pen places or number of produced animals (Dupont et al., 2012) . Choice of measurement unit for animal number may affect findings, such as differences in AM consumption between years (Dupont, 2012) and which herds are pointed out as having a high AM consumption (Chauvin et al., 2008). This is especially true for countries with a large import or export, where consumption may be given as AM usage per animal produced or per kg pork produced. Not including the export would lead to skewed results if the animals have received the majority of their AM in the country of origin (Jensen et al., 2004; DANMAP, 2011; Anonymous, 2012c; Dupont, 2012).

When wishing to assess percentage of animals treated per day, animals at risk, equaling animal days, must be calculated. The Danish authorities presently use number of pen places, resembling live animals at any given time, to calculate animal days:

$$Animal\ days = Number\ of\ pen\ places * days\ in\ period$$

(Anonymous, 2011b)

This might lead to skewed results, if percentage treated animals, based on number of pen places, are compared between herds with a large turnover of animals, such as herds with grower facilities and herds with a lesser turnover of animals such as dairy herds (Merle et al., 2012).
A measurement must be chosen appropriate to the given study design. In a report on AM consumption in 19 European countries, the European Medicines Agency reported AM consumption as mg/kg animal present per year (Anonymous, 2011f, 2012c). This reporting method was chosen as data from some of the participating countries only included total amounts of kg active compound AM's sold for veterinary use, and no information on which animal species were treated. Applying mg/kg animal present, discrepancies between dosage values selected by the European Medicines Agency and local dosage values are avoided, thereby avoiding eventual discrepancies between actual used daily doses and calculated daily doses, such as those occurring when applying the WHO defined DDD in populations where treatment practices diverge from those given by WHO (Dalton et al., 2007). The disadvantage however is still not being able to correct for dosage values between species and potency of drugs.

Furthermore, as the European Medicines Agency calculates AM consumption based on kg animal present per year, calculation routines were investigated. It was seen, that kg animal present (also called population correction unit) was calculated as estimated weight at treatment for livestock and slaughtered animals. It was not possible to discern from the report, how average weight at treatment was calculated. They also state in the study that "*the population correction unit is purely a technical unit of measurement, used only to estimate temporal trends in individual countries and across countries*." (Anonymous, 2011f). However, as the population correction unit is not easily read and understood, some might make hastened conclusions based on the findings (Grave et al., 2010).

In the study by Vieira et al. AM usage in finishers were investigated. To estimate percentage of treated animals in herds, animals at risk per day, equaling animal days in study period, was calculated (table 2). Number of animal days was calculated as number of delivered animals multiplied with average number of days in fattening facility (112 days) (Vieira et al., 2011). Percentage treated animals could then be calculated as:

$$Percentage\ animals\ treated\ per\ day = \frac{number\ of\ ADD\ in\ period}{delivered\ animals\ in\ period * 112}$$

(Vieira et al., 2011)

When calculating animal days in this way, one needs to be aware, that the finishers delivered at the beginning of the study period might not have received the majority of their AM's in the study period, and vice versa for the finishers treated at the end of the study might not be included in animals delivered. This may not be a problem, if number of animals sent to delivery and AM consumption patterns are stable throughout the study period.

Many studies from around the globe have been published describing the human AM consumption and pitfalls arising when attempting to collect data and evaluate consumption patterns. However this is not yet the case for veterinary medicine. Only very few articles on AM consumption in Australia, Africa, Asia, South America and USA were located. However there has been an increase in articles describing the European AM consumption - especially with regards to the Danish AM consumption, courtesy of the Danish national database Vetstat. However no articles have yet been published validating the data collected in Vetstat. 12 different articles were found addressing different measurement units for reporting veterinary AM consumption (e.g. kg active compound, used daily doses, used course dose). However, no articles were found concerning effect of using different measurements for number of animals on reported AM consumption when calculating treatment incidence (percentage animals treated per day), neither was any articles found on relationship between number of animals produced and reported AM consumption if animal years was used as measurement for number of animals.

5 Conclusion

Several methods exist for monitoring and reporting AM consumption. As Chauvin et al (2002b) relates, pharmaco-epidemiology in the veterinary field are far behind its' human counterpart. In human medicine most studies on drug consumption report their findings using the WHO standardized unit DDD. This facilitates comparisons, as they all use WHO assigned dosage values, however there might be discrepancies between local dosage regimens and WHO assigned dosages (Muller et al., 2006). Therefore DDD is rather a technical unit than an actual expression of usage patterns (WHO, 2013a).

National databases, such as Vetstat, are presently the gold-standard for collecting data on national veterinary AM consumption, as they offer great opportunities to assess AM consumption both at national level and at herd level. As yet there is no veterinary equivalent to the WHO defined unit "Defined Daily Doses" used for reporting human drug consumption. Presently AM consumption in animals is most often reported as "total kg active compound AM" or in DDD-derived units, such as "Animal Daily Doses." ADD is as its' human counterpart DDD a technical unit and variations between AM usage calculated as ADD and actual usage (e.g. used daily doses or prescribed daily doses) exists (Regula et al., 2009). Care must therefore be taken when reporting AM consumption, as choice of reporting method may likely affect the outcome. Both chosen measurement unit, dosage values and choice of how to measure number of animals may affect the outcome. Furthermore, even though reporting methods used may seem similar, it is vital to assess if and how data collection and calculation methods differ before attempting to compare consumption across studies.

Reporting antimicrobial consumption in Danish pigs at national and herd level - effect of calculation methods

1 Introduction

During the last decade interest towards monitoring veterinary antimicrobial (AM) consumption has increased – both at national level and herd level (Stege et al., 2003; Anonymous, 2012d; SVARM, 2012; Obritzhauser, 2013b; Stolker et al., 2013). This as a consequence of several events, including recommendations by WHO to monitor AM consumption in production animals (WHO, 2001) and an increased awareness of correlation between AM consumption in animals and the emergence of AM resistance (Aarestrup et al., 2001; Agersø and Aarestrup, 2013).

Since 2000, data on all veterinary drug use in Denmark have been collected in the national database Vetstat according to Danish legislation (Anonymous, 2010a). Data includes detailed information such as receiving herd, animal species and age group as stated in the prescription (Stege et al., 2003). Recently other countries have also begun to monitor veterinary AM consumption more closely (Anonymous, 2012c, d). This opens up opportunities to compare AM consumption - both between herds and between countries.

When reporting AM consumption, the most widely used unit is "total kg active compound" (Regula et al., 2009; Grave et al., 2010; Eagar et al., 2011; SVARM, 2012). This weight measurement is easily applicable, comparable between countries and recommended by the World Health Organization (WHO, 2003). However, due to the wide range in dosage regimens between animal species and products, "total kg active compound" does not readily reflect actual therapeutic pressure (Chauvin et al., 2001). To take potency of drugs and differences in dosage regimens between animal species and age into account, AM consumption can be reported as e.g. "Animal Daily Doses" (ADD) defined as "the defined average maintenance dose for the main indication in a specified species" (Jensen et al., 2004). But comparing AM consumption between studies is not without pitfalls. As Kuster et al. (2008) states:" *Reports on antibiotic use often lack complete definitions of the units of measurement, hampering comparison of data.*" Differences in registration and/or calculation methods may affect reported findings (Chauvin et al., 2008; Menéndez González et al., 2010; Pardon et al., 2012).

It is generally agreed upon, that data on AM consumption are of more value when related to a relevant population (Lee and Bergman, 1994; MacKenzie and Gould, 2005; Ferech et al., 2006; Anonymous, 2012c). When choosing measurement for animal number (i.e. animal population), it might be prudent to consider possible effects on calculated findings. Choice of animal number, e.g. number of pigs produced with or without including exported live pigs, may be of particular importance when reporting the Danish AM consumption, – both when evaluating trends over time and when comparing the Danish usage with other countries. This because 1) Danish export of live growers (usually exported as ~30 kg) increased 160% from 2005 to 2011 (2.7 mio. - 7.6 mio. live exported growers) and 2) the majority of AM in Denmark are prescribed for growers (>77% of the total AM consumption for pigs calculated in ADD (Dupont, 2012)). Hence, most exported pigs have received the majority of their AM usage in Denmark prior to export.

The access to detailed data at herd level has enabled the Danish authorities to instigate the "Yellow Card"-scheme. The scheme was instigated during 2010 and points out herds where the AM consumption exceeds 2 x the national average usage, measured as percentage pigs treated per day.

Herds exceeding defined limits are subjected to fines and regulations. AM consumption is assessed on a monthly basis calculating the average AM consumption for each age group during the last nine months reported as "percentage pigs treated per day". Presently the defined limits for percentage animals treated per day are 5 % for breeding animals, gilts and suckling pigs, 25% for growers and 7% for finishers (Anonymous, 2013d). Percentage pigs treated per day is calculated by the Danish authorities as:

$$= \frac{number\ of\ ADD\ prescribed\ for\ herd\ in\ given\ period}{animal\ number\ in\ herd * days\ in\ given\ period}$$

(Jensen et al., 2004)

The Danish authorities use number of pen places, presumably resembling live pigs in herd at any time, as measurement for animal number (Anonymous, 2011b). Information on number of pen places is collected from the national Central Husbandry Register (CHR). Since 1993 all Danish herds have been legally required to register in the CHR (Anonymous, 2011a). All herds are given a unique identity code (CHR-ID) relating to the geographical coordinates of the herd in question (Madec et al., 2001). In addition CHR contains data on production type and number of animals present in the herd (animal species, age group) (Mousing et al., 1997; Hybschmann et al., 2011). By law all changes in number of animals must be reported to CHR no later than 7 days after the event for cattle and once per year for pigs[9](Anonymous, 2011a).

If animal turnover is equal for all herds, it might not pose a problem to use number of pen places as measurement for animal number. But some herds might produce more pigs or fewer pigs than the national average. Not including the herds' productivity might cause misclassification, when pointing out herds with a high percentage of treated animals (Chauvin et al., 2001; Chauvin et al., 2008). This might especially be true for herds with grower facilities (7-30 kg), where growers are introduced directly after weaning and then sold early (e.g. at 15 kg). The grower facility is the stable section with the highest animal turnover per pen place (Hansen, 1993; Udesen, 2002; Vinther, 2012). Furthermore, due to nutritional, environmental and psychological stressors recently weaned pigs are more vulnerable to diseases, and therefore potentially more in need of AM treatment than older pigs (Carroll et al., 1998; Blackwell, 2005).

During an extensive literature search no study was found which investigated effect of chosen measurement for animal number when reporting percentage animals treated (Dupont, 2013a). Therefore a pilot study was conducted.

The primary aim of this study was to

- describe AM usage for all Danish pigs, focusing on the consequences of using three different measurements for number of pigs: 1) Pen places, 2) pigs slaughtered in Denmark, and 3) pigs produced in Denmark (slaughtered in Denmark + number of live exported growers and finishers), when calculating the national AM consumption per pig per year measured as gram AM per pig and ADD per pig. Also AM usage per kg pork produced was investigated.

[9]For herds with more than 300 sows, 3000 finishers or 6000 growers, information on animal numbers must be updated biannually.

Secondary aims were investigated in a pilot study conducted in a convenience sample from Danish pig herds, participating in another study. These aims were to

- investigate association between produced growers and herd AM consumption calculated as percentage growers treated per day using pen places as measurement for animal number (Variables used: Number of pen places according to farmer; number of produced growers in 2011; AM consumption per herd for 2011 measured in ADD)

- investigate if weight when leaving grower facility was associated with herd AM consumption calculated as percentage growers treated per day using pen places as measurement for animal number.
  (Variables used: Number of pen places according to farmer; AM consumption per herd for 2011 measured in ADD; weight of growers when leaving grower facility)

Specific hypotheses investigated in relation to the pilot study (using pen places as measurement for animal number):

1) Herds which produced 6 or more growers (7-30 kg) per pen place had a higher AM consumption, calculated as percentage growers treated per day, than herds which produced less than 6 growers per pen place.
   (Variables used: Number of pen places according to farmer; number of produced growers in 2011; AM consumption per herd for 2011 measured in ADD)

2) Herds which sold growers at less than 30 kg had a higher AM consumption, calculated as percentage growers treated per day, than herds which sold growers at 30 kg or more.
   (Variables used: Number of pen places according to farmer; AM consumption per herd for 2011 measured in ADD; weight of growers when leaving grower facility)

2 Materials and methods

2.1 AM consumption at national level – effect of calculation method

2.1.1 Selection of study population and collection of data

To investigate the Danish national AM consumption for pigs, data on all AM prescribed from January 2005 to December 2011 for use in pigs herds were collected from Vetstat and analysed retrospectively. No sample size calculation was performed to calculate number of needed herds, as data for all Danish herds was accessible through Vetstat. Data included information on age group treated according to prescription[10], quantity of drugs and dosage of drug according to the Danish Health and Medicines Authority per kg live pig. Data on AM usage reported by pharmacies, veterinary practitioners and feed mills were included. Entries were excluded, if an invalid age group was given (not breeding animals, gilts and suckling pigs, growers or finishers), corresponding to 0.87% of the AM consumption measured in kg active compound per year (1.8% in 2005 to 0.02%

[10] Breeding animals, gilts, suckling pigs (Vetstat standard weight: 200 kg); growers 7-30 kg (Vetstat standard weight 15 kg); finishers 30-140 kg (Vetstat standard weight 50 kg) (Stege et al., 2003).

in 2011). Growers were defined as pigs weighing 7-30 kg, with an average weight of 15 kg at treatment as defined by Vetstat (standard weight of growers in Vetstat) and a weight of 30 kg at export (Aarestrup, 2012).

2.1.2 Quantification of antimicrobial usage

AM usage was calculated as "total kg active compound" and "number of ADD".

In Vetstat ADD is defined as "*the defined average maintenance dose for the main indication in a specified species*" (Jensen et al., 2004). "Number of ADD per year" was calculated using Vetstat procedures (Vetstat values for standard weights according to age group treated and Vetstat dosage values as given by product descriptions published by the Danish Health and Medicines Authority) (Jensen et al., 2004; Anonymous, 2013b).

$$Number\ of ADD\ per\ year\ = \frac{Total\ amount\ of\ active\ compound\ prescribed\ per\ year\ (mg)}{dosage\ pr\ kg\ live\ animal * standard\ weight\ of\ animal}$$

2.1.2 Production data

Data on the number of pen places for all Danish herds were collected from Statistics Denmark.

Data was collected retrospectively from Statistics – PIGMEAT on number of pigs slaughtered in Denmark, mean slaughter weight and number of live growers and finishers exported from Denmark produced. Statistics-PIGMEAT data include all pigs delivered to Danish slaughterhouses and all pigs exported live from Denmark. Exported live sows were excluded, as they constituted less than 5% of the total live export (2005: 4.4%; 2011: 1.4%). Exported live small growers (<15 kg) were also excluded (2005: 8.6% of the total live export; 2011: 4.8%), as most are exported at 7 kg before receiving much AM treatment (Aarestrup et al., 2008).

2.1.3 Calculations describing AM consumption at national level

AM consumption was calculated for each year as

- total kg active compound divided by number of pen places
- total kg active compound divided by number of pigs slaughtered in Denmark
- total kg active compound divided by number of pigs produced (slaughtered in Denmark + number of live exported growers and finishers)
- total number of ADD divided by number of pen places
- total number of ADD divided by number of pigs slaughtered in Denmark
- total number of ADD divided by number of pigs produced (slaughtered in Denmark + number of live exported growers and finishers).

To estimate AM usage per kg pork produced, carcass weight at slaughter was set to 81.8 kg for all finishers and sows slaughtered in Denmark[11] (Vinther, 2012). Furthermore the following estimations were made to account for live export of growers and finishers:

Kg pork slaughtered in Denmark + gross live exported weight:
Live exported growers and finishers were estimated to 30 kg and 81.8 kg produced pork per pig respectively.

Because exported growers have received the majority of their AM usage in Denmark, an adjusted estimation of kg pork produced was also made.

Kg pork slaughtered in Denmark + adjusted live exported weight incl. 10% mortality:
Live exported growers and finishers were estimated to 81.8 kg pork produced per pig. 10% mortality for exported growers was included to account for mortality between time of export and slaughter. In 2012 average mortality for Danish finishers was 3.6% (Vinther, 2012).

Mg active compound AM/kg pork produced was then estimated as

- total mg active compound divided by kg produced pork slaughtered in Denmark

- total mg active compound divided by kg produced pork slaughtered in Denmark + gross live exported weight

- total mg active compound divided by kg produced pork slaughtered in Denmark + adjusted live exported weight incl. 10% mortality.

2.1.4 Data management and statistics

Data management and calculation of AM usage were performed in SAS Enterprise Guide 4.3 for Windows. Descriptive variables were depicted in simple plots (Microsoft Excel 2010 for Windows) and examined by univariate analyses using R 2.15.1 for Windows.

Student's t-test was used to test the difference between total AM between years and between mean AM consumption per pig in year 2005 and 2011.
All levels of significance were set to $p < 0.05$.

2.2 AM consumption at herd level – effect of calculation method

2.2.1 Study design, selection of herds and data collection

A pilot study was conducted to investigate 1) a possible association between growers produced per pen place and reported herd AM consumption and 2) a possible association between weight when leaving grower facility and reported herd AM consumption. The project was designed as a cross-sectional observational study based on a convenience sample. Participating herds all had grower (7-30 kg) facilities and had participated in another study (Dupont, 2013b; Stege, 2013), where all participating herds were randomly selected (list of random numbers) among a cohort of Danish

[11] Sows constituted 2% of all pigs slaughtered in Denmark (2009-2012). No data was available on number of slaughtered sows 2005-2008.

herds with a significant reduction in AM consumption following the introduction of the Yellow-Card scheme (Anonymous, 2011b).

Sample size

To examine the primary hypothesis, we assumed that herds producing 6 or more growers per pen place had an average of 20% animals treated per day while herds producing less than 6 growers per pen place had an average of 10% animals treated per day. Using confidence level = 95% and power = 80%, the necessary sample size was calculated to 157 herds in each group (one-sided test).

Inclusion criteria

Only herds with grower facilities and a Health Advisory Agreement (HAA's) were included. HAA's are mandatory for Danish herds of a certain size (>300 sows, boars or gilts, >6000 growers or >3000 finishers. They cover rules on frequency of veterinary visits, treatment schemes and management (Anonymous, 2013c). Blue SPF herds[12] (Thomsen et al., 1992; Anonymous, 2013e) and conventional herds were included, as they constitute the two herd types, which produce the majority of Danish growers (Sørensen, 2011). Included herds had to have more than 200 pen places for breeding animals and piglets, 500 pen places for growers (7-30 kg) or 500 pen places for finishers (30-110 kg) registered in CHR at the 31st of December 2011, as we wished the study population to be representative for most Danish herds (in 2011, 75.9% herds had 500 or more pen places registered in CHR).

Exclusion criteria

Red SPF herds (breeding herds) and free-range herds were excluded. Herds were also excluded, if during the study period there had been a change of owner, change in grower facilities (new buildings/tear down of buildings), changes in production type (e.g. from integrated sow herds to growers only), if the herd had conducted a major disease eradication program, suffered severe disease outbreaks or changed veterinarian.

Data collection

For the initial study population 650 herds were selected, as we expected an exclusion of 50% and a non-response rate of 35% from included herds.

Telephone interviews were conducted with the herds' veterinarians and the farmers regarding inclusion criteria, exclusion criteria and consent of participation. Information on production of growers in 2011 was collected through questionnaires, including number of produced growers in 2011, weight when entering and leaving grower facility and number of pen places according to farmer. Where possible, management reports for 2011 were also collected. Some Danish herds utilize IT-based management systems (link http://agrosoft.eu/; http://www.bedriftslosning.dk/). Information on herd productivity is entered into the management system regularly by the farmer.

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[12] Denmark has 3 main types of herds - free range, conventional and Specific Pathogen Free (SPF) - herds. SPF-herds are enrolled in a strict health control program and must be tested for seven pathogens- Mycoplasma Hyopneumoniae, Actinobacillis pleuropneumoniae, toxigenic Pasteurella multocida, Brachyspira hyodysenteriae, Porcine Respiratory and Reproductive Syndrome, Sarcoptes scabei var. suis and Haematopinus suis (Anonymous, 2013e). SPF-herds are divided into two types according to health status and restrictions. 1) Red SPF-herds are free of all seven pathogens and are often breeding facilities. 2) Blue SPF-herds must purchase pigs from red or blue SPF herds and status must be known for all seven pathogens.

The system then enables the farmer to monitor trends in the production over time and benchmark his herd's performance e.g. compared to his other herds or the national average (Stetkær, 2004).

18.8% was included and wished to participate (122/650), 63.5% was excluded (413/650) and 17.7% did not wish to participate (115/650).

Data on all AM prescribed for study herd from the 1st of January 2011-31st of December 2011 was collected from a Vetstat extraction done the 25th of July 2012. An extract was made on the 31st of December 2011 from CHR for number of pen places for each study herd. Information on variables from questionnaires was typed twice manually into an Excel 2010 Microsoft spreadsheet by the author or student employees. All discrepancies were investigated and corrected.

Table 1 contains all variables applied in the pilot study - both collected (national databases, questionnaires and management reports) and calculated variables.

Table 1. *Variables collected from included herds.*

Variable	Source
Herd type (blue SPF/conventional)	Questionnaire
Grower pen places according to farmer 31st of December 2011	Questionnaire
Grower pen places according to CHR 31st of December 2011	CHR
Produced growers in 2011 (7-30 kg)	Questionnaire
Produced growers per pen place	Calculated: Produced growers/pen places according to farmer
Antimicrobial consumption in 2011 (number of ADD)	Vetstat
Percentage growers treated per day	Calculated: ADD/pen places according to farmer per day
Average weight of pig when entering grower facility	Questionnaire or management report
Average weight of pig when leaving grower facility	Questionnaire or management report
Location after leaving grower facility (same herd/other herd owned by same person/sold to pool/exported/other)	Questionnaire or management report

No significant differences were found between blue SPF herds and conventional herds for the variables investigated, and they were therefore pooled together in the following analyses.

2.2.2 Percentage pigs treated per day

Number of animal treatments and animals in herd must be known to calculate percentage of animals treated per day. Number of animal treatments, calculated as ADD, was collected from Vetstat and number of grower pen places in each herd was given by the respective farmer.

Number of ADD was calculated according to the Vetstat procedures:

$$\frac{active\ compound\ prescribed\ in\ mg}{recommended\ dosage\ per\ day * standard\ animal\ weight\ (15\ kg)}$$

Percentage growers treated

$$Percentage\ growers\ treated\ per\ day\ = \frac{ADD\ prescribed\ for\ growers\ in\ herd\ during\ given\ period}{number\ of\ grower\ pen\ places * days\ in\ period} * 100$$

Dosage values were collected from Vetstat. Vetstat dosage values are derived from detailed product descriptions published by the Danish Health and Medicines Authority (Anonymous, 2013b). If recommended dosage is stated as a range, dosage value in Vetstat is calculated as the mean value – e.g. if 0.1-0,05 mL product per kg live weight animal is recommended in the product description, Vetstat dosage value will be 0,075 mL per kg live animal (Jacobsen, 2013). Standard animal weight is assigned in Vetstat according to given age group - breeding animals, gilts, suckling pigs (200 kg); growers (15 kg); finishers (50 kg) (Stege et al., 2003).

Variables used: Number of pen places according to farmer; AM consumption per herd for 2011 measured as ADD.

2.2.3 Association between produced growers per pen place and percentage growers treated per day

Number of produced growers per herd in 2011 was collected from questionnaires or management reports and divided by number of grower pen places as stated by the farmer in the questionnaire.

To test for the association between produced growers per pen place and percentage growers treated per day study herds were divided into two groups based on the median value of average number of growers produced per pen place (6 growers per pen place) (figure 1). High producer herds were herds producing 6 or more growers per pen place and less producing herds were herds producing less than 6 growers per pen place.

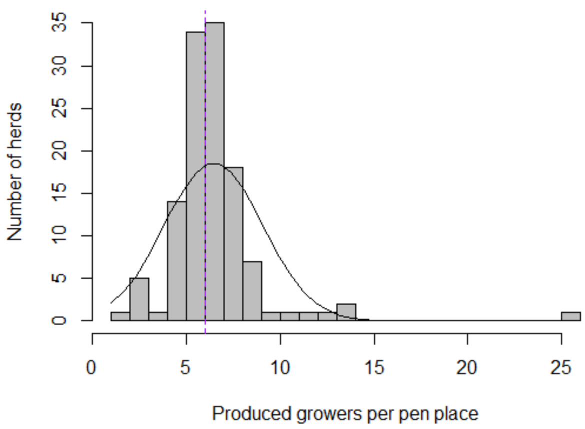

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***Figure 1**. Average number of produced growers per pen place in study herds in 2011. Black line: Normal curve. Purple line: Median 6.2.*

Variables used: Number of pen places according to farmer; number of produced growers in 2011.

2.2.4 Associaton between weight when leaving grower facility and percentage growers treated per day

We wished to investigate if weight when leaving grower facility affected reported AM consumption (calculated as percentage growers treated per day using pen places as measurement for animal number) since recently weaned growers might be more prone to diseases needing AM treatment, than older and larger growers (Aarestrup et al., 2008). Weights of growers when leaving the grower facilities were obtained from questionnaires or management reports. If weight when leaving grower facility was not stated in either the questionnaire or the management report, but all produced growers were kept as finishers until slaughter in the same herd, weight when leaving grower facility was set to 30 kg (mean weight of Danish pigs at sale from grower facility was 30.6 kg in 2012 (Vinther, 2012)).

There seemed to be a relation between produced growers per pen place and weight when leaving grower facility when data were plotted in a scatterplot (R=0.30) (figure 2).

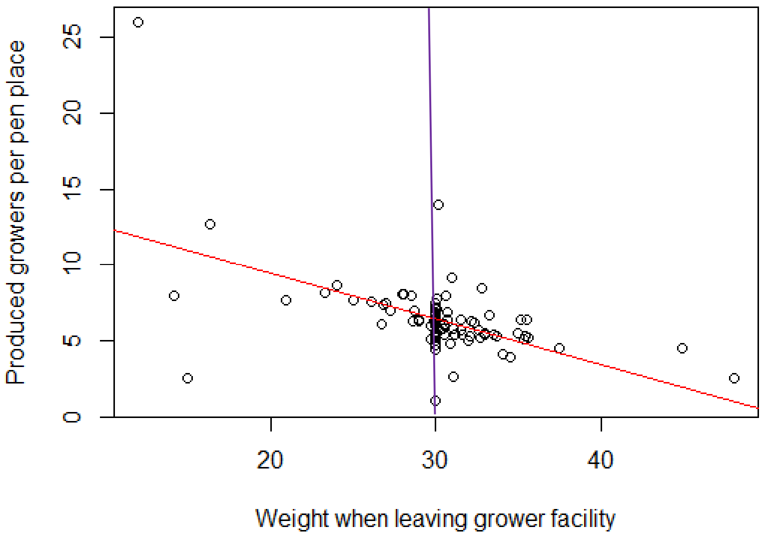

Figure 2. *Association between average weight when leaving grower facility and number of produced growers per pen place examined in 94 Danish herds during 2011. Purple line: Median 30.*

To test for the association between weight when leaving grower facility and percentage growers treated per day, herds were divided into two groups according to weight when leaving grower facility. As the median value for the average weight when leaving grower facilities was 30 kg (figure 2), this was chosen as separator-value.

- Group 1 – included herds where growers weighed less than 30 kg when leaving grower facility.
- Group 2 – included herds where growers weighed 30 kg or more when leaving grower facility.

Variables used: Number of pen places according to farmer; number of growers produced in 2011, AM consumption per herd in 2011 measured in ADD; weight of growers when leaving grower facility.

2.2.5 Data management and statistics

Data management and calculation of percentage growers treated per day were performed in SAS Enterprise Guide 4.3 for Windows. Descriptive variables were depicted in simple plots and examined by univariate analyses (Excel Microsoft Office for windows and R i386 2.15.1 for Windows).

Prior to analyses, tests for normality were conducted using Shapiro-Wilk test for normality.

Student's t-test was performed to test for differences in means of percentage growers treated per day between herds producing less than 6 growers per pen place per year and herd producing 6 or more growers per pen place per year.

A linear regression analysis was performed to investigate the relationship between percentage growers treated per day and produced growers per pen place.

Furthermore an analysis of covariance was conducted to test for association between produced growers per pen places, weight when leaving grower facility and percentage growers treated per day.

All levels of significance were set to $p < 0.05$. All tests and models were conducted using R i386 2.15.1 for Windows.

3 Results

3.1 AM consumption at national level – effect of calculation method

Data used to investigate national Danish AM consumption for pigs constituted an average of 300,000 prescriptions per year collected from Vetstat.

According to Statistics-PIGMEAT there were 4642 pig herds in Denmark in 2011 (Anonymous, 2012e). From 2005 to 2011 the total Danish pig production, including pigs slaughtered in Denmark + growers and finishers exported live from Denmark, increased with 14.2% (2005: 25.3 mio. pigs produced; 2011: 28.9 mio. pigs produced).

During the same period, number of pigs slaughtered in Denmark decreased 5.4% from 22.1 mio pigs in 2005 to 20.9 million pigs in 2011, corresponding to 85.8% and 71.0% of the total Danish pig production per year. However, the export of live growers and finishers increased with 150%, from constituting 12.6% of the total pig production in 2005 (3.2 mio.) to 27.7% in 2011 (8.0 mio.).

Of all live growers and finishers exported, growers constituted 85.2% 2005 (2.7 mio) and 95.2% in 2011 (7.6 mio), equivalent to an increase of 181.5% in the export of live growers.

3.2.1 Trends in Danish pigs' antimicrobial consumption 2005-2011.

Figure 3 shows four different methods of reporting the AM consumption, when given in weight of active compound AM: 1) Total kg active compound, 2) gram active compound per pen place, 3) gram active compound per pig slaughtered in Denmark and 4) gram active compound per pig produced (pigs slaughtered in Denmark + growers and finishers exported live from Denmark). Reporting method 2, 3 and 4 all attempt to adjust for the number of pigs, when reporting the AM consumption.

Calculated as kg active compound per year without adjusting for number of pigs, the total AM consumption per year increased with 11.1% from 2005 to 2009 (2005: 90,332 kg ; 2009: 103,730 kg), with the largest increase being from 2008 to 2009 (11.5%; 2008: 93,059 kg). From 2009 to 2011 the AM consumption decreased with 21.5% (2011: 81,408 kg), leading to an overall decrease from 2005 to 2011 of 9.9% in the AM consumption given as total kg active compound per year ($p<0,001$).

Several measurements for number of pigs can be applied, when calculating the AM consumption adjusted for number of pigs. This study investigated consequences on calculated AM consumption per pig per year when using three different measurements for number of pigs. Depending on which measurement was applied, AM consumption/pig/year was found to be very different. In 2009, where the largest difference was observed between calculated gram AM/pig, the AM consumption was calculated as 8.3gram AM/ pen places, 5.4 gram AM/ pig slaughtered in Denmark and 3.8 gram AM/pigs produced in Denmark (slaughtered in Denmark + growers and finishers exported live from Denmark) as measurement for number of pigs.

From 2008 to 2009 AM consumption/pig/year increased with 10,7% (7.5 gram to 8.3 gram) , 21.9% (4.4 gram to 5.4 gram) and 11.1% (4.4 gram to 3.8 gram) respectively, when using pen places, pigs slaughtered in Denmark and pigs slaughtered in Denmark + growers and finishers exported live from Denmark as measurement for number of pigs.

When comparing 2005 and 2009 the increase in gram AM/pig/year becomes significantly smaller when including all produced pigs (including live exported growers and finishers) than when using number of pen places as measurement for number of pigs (7.5% increase for all produced pigs compared to 18.3% increase for pen places).

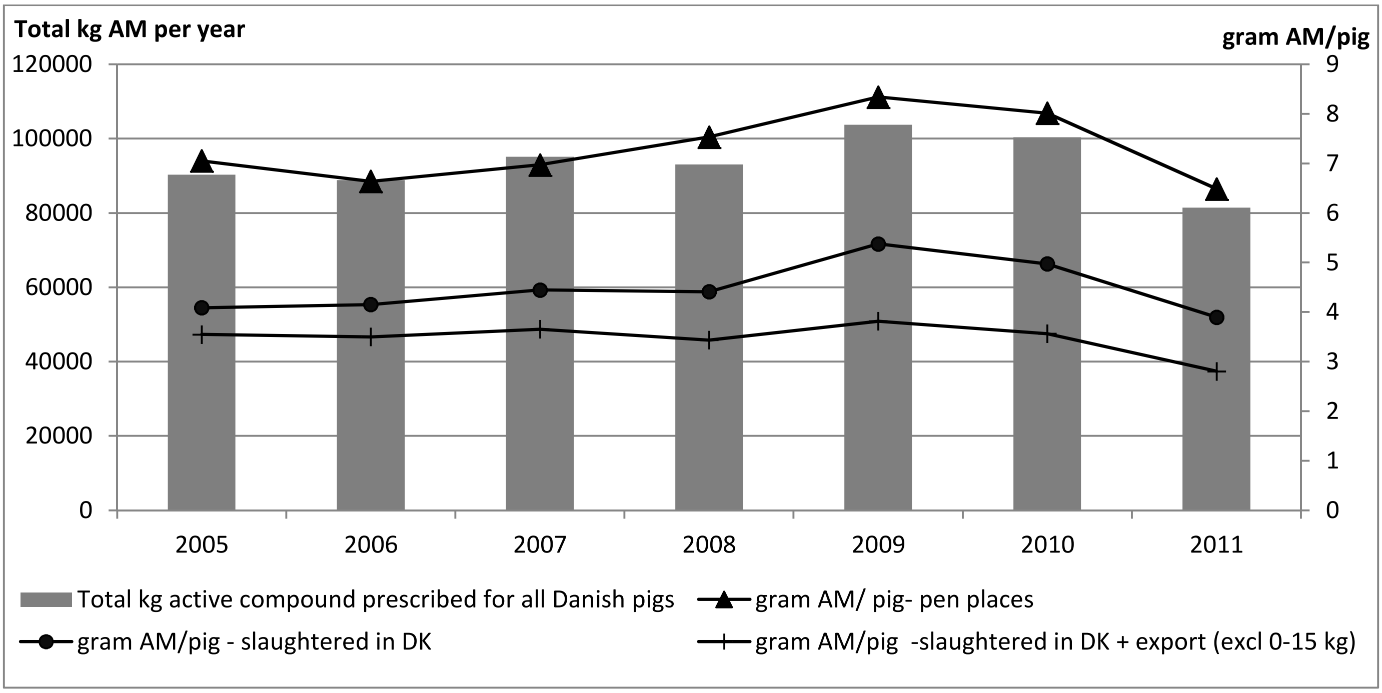

Figure 3*.Danish consumption of antimicrobials (AM) for pigs 2005-2011. Measured in total kg active compound AM and as g AM/pig/year, using 3 different measurements for animal number.*

Figure 4 shows the total AM consumption measured as ADD per year reported in four ways: 1) Total ADD, 2) ADD/pen place, 3) ADD/pig slaughtered in Denmark and 4) ADD/pig produced in Denmark (pigs slaughtered in Denmark + growers and finishers exported live from Denmark). Total number of ADD increased with 17.3% from 2005 to 2009 (2005: 248.3 mio. ADD; 2009: 291.2 mio. ADD). The largest increase in total number of ADD was also from 2008 to 2009 (7.1%). The AM consumption given as ADD decreased with 25.6% from 2009 to 2011 (2011: 224.8 mio. ADD), leading to an overall decrease from 2005 to 2011 of 1.0% (p<0,001).

The largest difference between calculated ADD/pig for the three measurements for number of pigs, was also found in 2009. Here the consumption per pig was 23.4 ADD/ pen places, 15.1 ADD/pig slaughtered in Denmark and 10.7 ADD/pig produced in Denmark (pigs slaughtered in Denmark + growers and finishers exported live from Denmark).

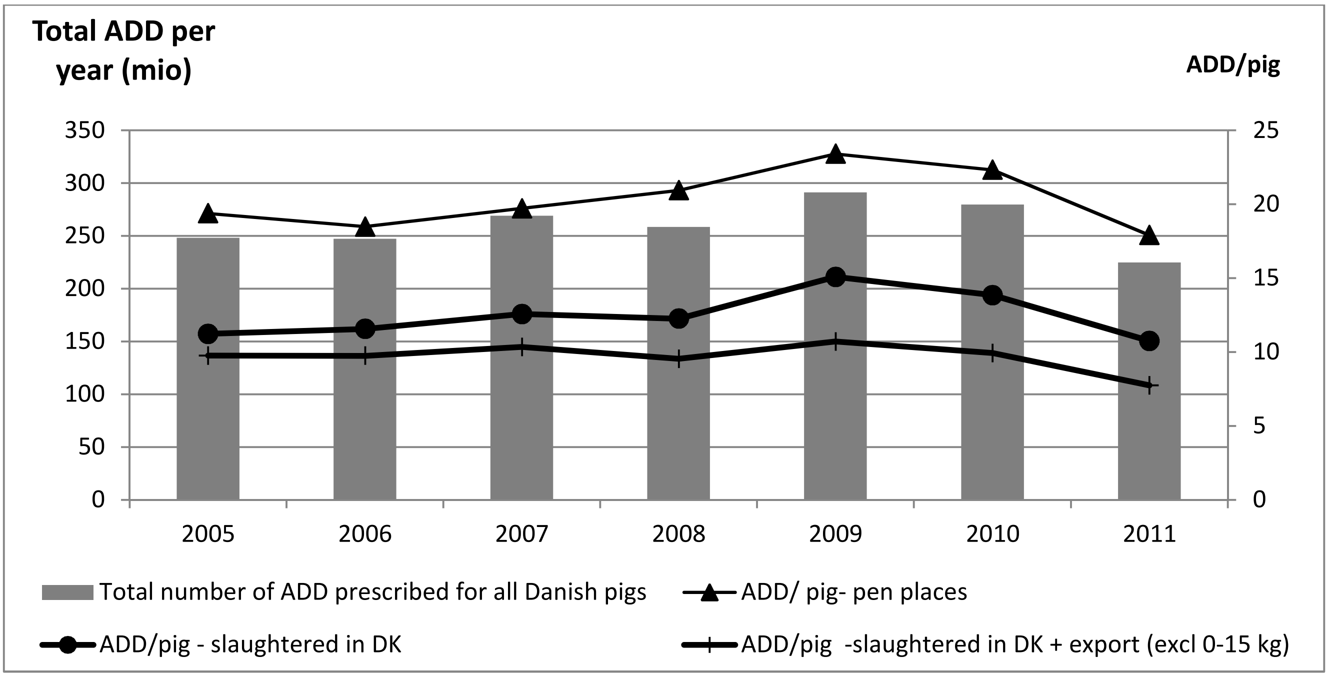

Figure 4*. Danish consumption of antimicrobials for pigs 2005-2011. Measured in Animal Daily Doses (ADD's) and as ADD/pig/year, using 3 different measurements for animal number.*

Table 2 shows a comparison of the AM consumption/pig/year between 2005 and 2010.
The consumption is shown as gram active compound AM/pig/year and number of ADD/ pig/year, using pen places, pigs slaughtered in Denmark and pigs produced in Denmark (pigs slaughtered in Denmark + growers and finishers exported live from Denmark) as measurements for animal number.

Using the three different measurements for number of pigs, the increase from 2005 to 2010, measured as gram AM/pig, constituted 12.1%, 17.7% and 0.3% respectively. When measuring the AM consumption as ADD/pig the increase was 14.9%, 24.1% and 3.1%.

A significant increase from 2005 to 2010 was observed, regardless of whether the AM consumption was measured as gram AM/pig or ADD/pig, when using number of pen places and number of slaughtered pigs in Denmark as measurement for number of pigs,. However, no significant increase was found, when using pigs produced as measurement for number of pigs (pigs slaughtered in Denmark + growers and finishers exported live from Denmark)

Table 2.*Danish consumption of antimicrobial/pig/year measured as gram AM and number of ADD in 2005 & 2010 using 3 different measurements for animal number.*

	Year		
	2005	2010	P-value
g AM/pen places	7,05	8.02	P<0,001
g AM/pigs slaughtered in DK	4.09	4.97	P<0.001
g/AM/pigs slaughtered in DK + live export	3.55	3.56	P=0.58
ADD/pen places	19.4	22.3	P<0.001
ADD/pigs slaughtered in DK	11.2	13.9	P=0.001
ADD/pigs slaughtered in DK + live export	9.6	9.9	P=0.77

Looking at the year 2009, 65 mg AM was used per kg pork produced from pigs slaughtered in Denmark (carcass weight: 81.8 kg). In comparison the usage was 55 mg AM/kg pork produced, when including pigs slaughtered in Denmark + gross weight of exported pigs, and 48 mg AM/kg pork produced, when estimating kg pork based on pigs slaughtered in Denmark + adjusted live weight of exported pigs incl. 10% mortality. I.e. compared to only including kg pork from pigs slaughtered in Denmark, AM use/kg pork was 16.2% and 27.4% lower in 2009 when also including gross live weight of exported pigs and adjusted live weight of exported pigs including 10% mortality.

When plotting the consumption as gram AM/kg pork produced, on the same graph as live exported growers, it becomes evident that there is a correlation between live exported growers and reported AM consumption calculated both as gram AM/pen place and gram AM/pig slaughtered in Denmark - i.e. not adjusted for the live export. Comparing 2005 to 2009 there was a significant increase for all three measurement methods in mg AM/kg pork produced. However, including adjusted live weight for kg live exported pigs incl. a 10% mortality, decreased the percentual difference between years from 31.4% for mg AM/kg pork slaughtered in Denmark and 18.6% for mg AM/kg pork slaughtered in Denmark + gross live weight exported to 9.0% for mg AM/ kg pork slaughtered in Denmark + adjusted live weight exported incl. 10% mortality (figure 5). There was a significant decrease from 2005 to 2011 in estimated AM consumption/kg pork using all three measurements for kg pork produced.

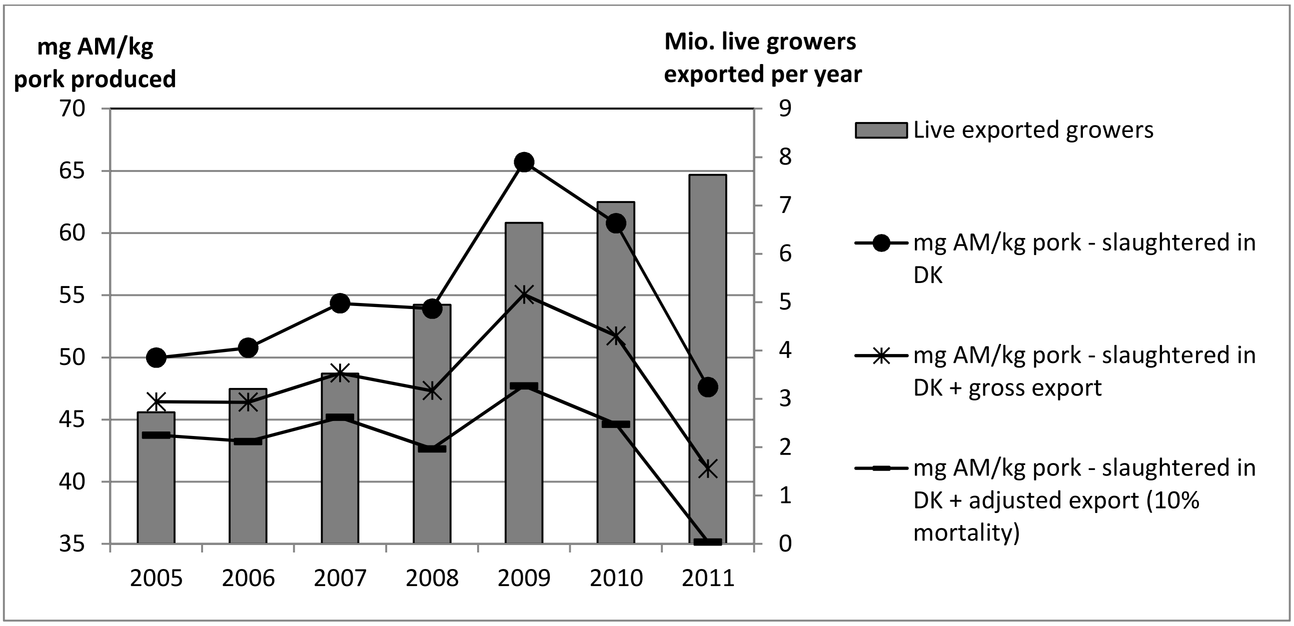

Figure 5. *Antimicrobial (AM) consumption estimated as mg AM/kg pork produced/year using three different measurements for kg produced pork and the Danish export of live growers - 2005-2011.*

3.2 AM consumption at herd level – effect of calculation method

In this study it was found that herds which produced 6 growers or more per pen place had a significantly higher AM consumption measured as percentage growers treated per day compared to herds which produced less than 6 growers per pen place. Furthermore a significant association was found between weight when leaving grower facility and percentage growers treated per day when using pen places as measurement for number of pigs.

3.2.1 Number of grower pen places and growers produced according to farmer

For the 122 participating herds average number of grower pen places was 2289 pen places according to the farmers (std. dev: 1526; minimum 300; maximum 10000).

In 2011 participating study herds produced between 800 and 63433 growers (mean: 14668; std. dev: 10961) with an average of 6.5 growers produced per pen places (std. dev: 2.6; minimum: 1; maximum: 26).

3.2.2 Association between produced growers per pen place and percentage growers treated per day

In the 122 participating herds an average of 10.2% growers were treated per day, when calculated using Vetstat defined Animal Daily Doses. This was 0.4% higher than the national average of 9.8% growers treated per day in 2011 (Vetstat.dk) (std.dev: 6.0; minimum: 0.28; maximum: 33.74). The participating herds produced an average of 6.45 growers per pen place in 2011 (std.dev: 2.6; minimum: 1; maximum: 26). The herd which produced 26 growers per pen places in 2011 only had growers from 7-12 kg.

In order to examine the association between producing many growers per pen place (hence, having a relatively larger number of young and susceptible animals per year, prone to increased AM treatment compared with less productive herds) the 122 participating herds were divided into two groups based on produced growers. 67 herds were grouped together as highly productive herds (≥6 growers per pen place) and 55 herds as less productive herds (<6 growers per pen place). In highly productive herds, 11% of growers treated per day while only 7.5% of growers were treated per day in less productive herds (p<0.001)

3.2.3 Association between weight when leaving grower facility and percentage growers treated per day

To investigate association between weight when leaving grower facility (i.e. herds producing young animals compared to herds producing older animals) and percentage growers treated per day, herds were divided into two groups - 23 herds which produced growers smaller than 30 kg and 71 herds which produced growers at 30 kg or more. Herds producing smaller growers (<30 kg) treated 13.1% of growers per day, whereas herds producing larger growers treated 9.5% per day when calculated as percentage growers treated per day with pen places as measurement for number of pigs (P<0.001). Average weight when entering the grower facilities was 7.6 kg (std. dev: 2.3 kg). Average weight when leaving the grower facilities was 30.1 kg (std. dev: 4.8 kg) (figure 6). Weight when entering grower facility was given for 77 herds. Weight when leaving grower facility was given for 94 herds.

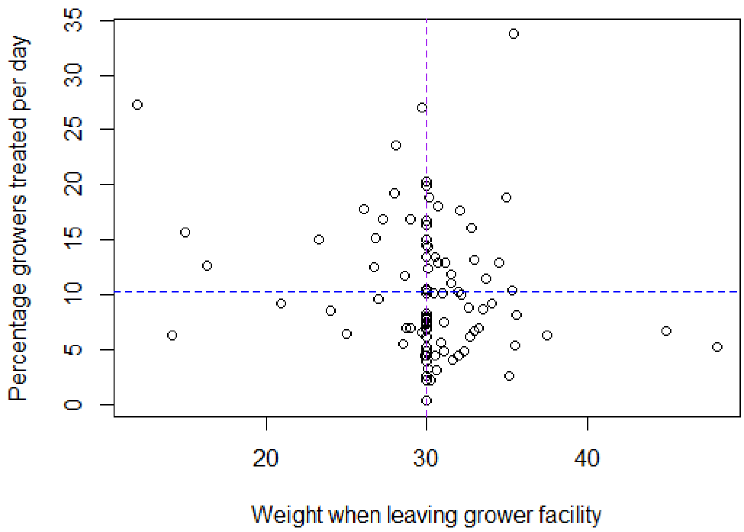

Figure 6. *Association between weight when leaving grower facility and percentage growers treated per day in 94 herds. Purple line: separator at 30 kg. Blue line: average percentage growers treated per day among study herds.*

An analysis of co-variance (ANCOVA) was conducted to test for association between produced growers per pen place, weight when leaving grower facility and percentage growers treated per day. The findings from the earlier tests were supported, as both number of produced growers per pen place and weight when leaving grower facility had a significant association with percentage growers treated per day (P=0.01). However no significant interaction between produced growers per pen place and weight when leaving grower facility was found (P=0.99) .

Figure 7 shows the association between produced growers per pen place and percentage growers treated per day in the participating herds. The herds are furthermore divided into two groups depending on weight when leaving grower facility (herds producing smaller growers <30 kg and herds producing larger growers at ≥30 kg). It is illustrated in the figure that herds which produce smaller growers (<30 kg) both have a higher number of produced growers and a higher percentage growers treated per day compared to herds which produce larger growers at 30 kg or more.

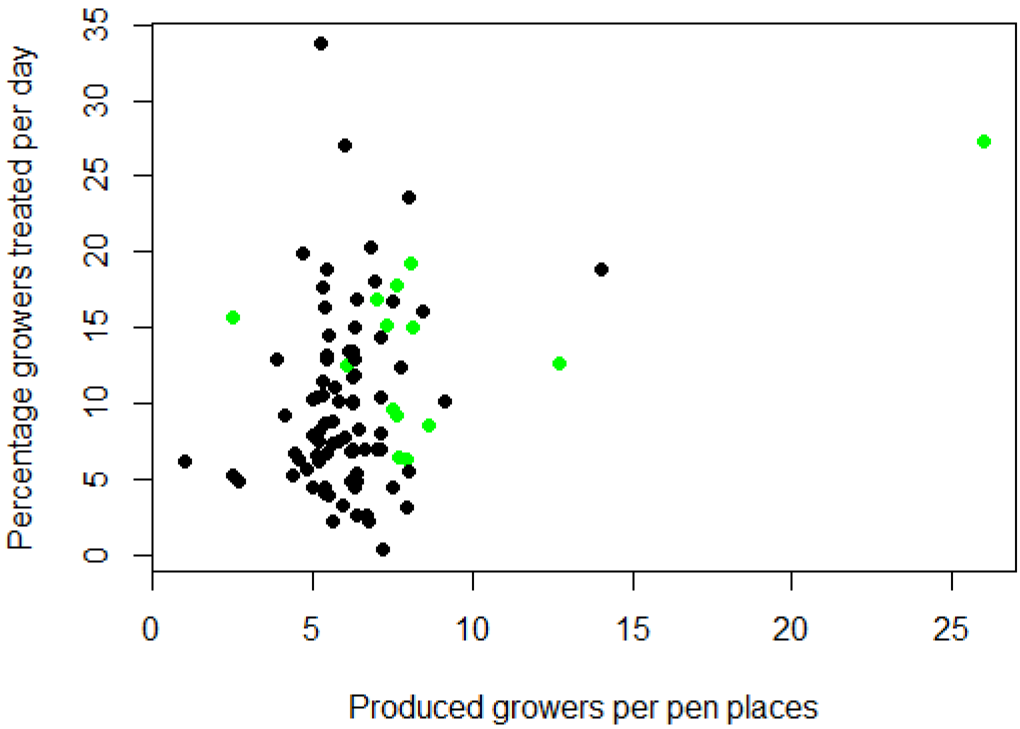

Figure 7. *Association between produced growers per pen place and percentage growers treated per day in 94 herds. Study herds (n=94) grouped according to weight of growers when leaving grower facility. Green dots: <30 kg when leaving grower facility. Black dots: ≥30 kg when leaving grower facility.*

All variables used in analyses were found to be normally distributed.

4 Discussion

4.1 AM consumption at national level – effect of calculation method

The findings in this study suggest that chosen measurement for animal number has a significant effect on reported AM consumption and not including productivity may lead to misclassification. This is in compliance with results found in studies on effect of chosen measurement unit for reporting AM consumption- e.g. kg active compound ADD, money spent on AM (Chauvin et al., 2008; Menéndez González et al., 2010; Pardon et al., 2012).

Only reporting AM consumption per pig based on either pen places or number of pigs slaughtered in Denmark led to the conclusion that there had been a significant increase from 2005 to 2010. However, from 2005 to 2010 number of pigs slaughtered in Denmark decreased from 2005 to 2011 with 8.6% while the export of live pigs increased with 160%. Thus, when including live export growers and finishers no significant increase from 2005 to 2010 was found in AM consumption/pig. This finding is in opposition with statements made in the Danish media and by Kolmos (2010) (Anonymous, 2010b; Kolmos, 2010; Kristensen, 2013b). This illustrates that different conclusions can be made, depending on used calculation methods. It also underlines the need of meticulous description of used calculation methods (Chauvin et al., 2002b; Kuster et al., 2008) and relating reports on drug consumption to as appropriate a population as possible (MacKenzie and Gould, 2005; Moulin et al., 2008).

Under Danish circumstances it might be prudent to adjust for live exported growers and finishers, as - besides from having increased with 160% over a 5 year period - the live export also constituted 27.7% of Danish pigs produced in 2011. Furthermore exported growers and finishers have received the majority of the AM before export at 30 kg. Eventually, mortality can be set high, to attempt adjustments for any treatments as finishers. In this study a 10% mortality was included in adjusted live weight exported. This is rather conservatively set, as the mortality of Danish finishers (30 kg-140 kg) in 2012 was reported to be 3.6% (Vinther, 2012). It might also be of particular importance to include live exported growers and finishers when comparing the Danish pig production's AM consumption to that of other countries. This might especially be true when comparing to countries which have almost no export of live pigs or when comparing to countries with a large import of pigs at 30 kg or more (Anonymous, 2012c). Furthermore completeness and validity of data should be assessed when comparing AM consumption between countries (Anonymous, 2011f; Grave et al., 2012; Wolff, 2012; Espetvedt et al., 2013).

A correlation was found between exported live growers and reported AM consumption calculated both as gram AM/pen place and gram AM/pig slaughtered in Denmark - i.e. not adjusted for the live export. Thus from 2005 to 2009, the increases in live exported growers, mg AM/kg pork slaughtered in Denmark and mg AM/kg pork slaughtered in Denmark + gross live weight exported are almost alike. When taking the adjusted live exported weight incl. 10% mortality into account, the increase in mg AM/kg pork produced from 2005 to 2009 constituted only 9% whereas the increase in AM consumption constituted 31.4% when estimating consumption as mg AM/kg pork slaughtered in Denmark.

Since 2009 the consumption has decreased below the consumption in 2005 regardless of calculation method. Despite this the export of live animal still increases. The decrease in consumption may be due to factors such as the instigation of the "Yellow Card"-scheme and the increased media coverage of the AM consumption in the Danish pig industry 2008-2011 (Rishøj, 2010; Anonymous, 2011b; Hansen, 2013; Kristensen, 2013a).

In this study the AM consumption was reported in both kg active compound and as ADD. This was done to ensure any trends in consumption were not due to e.g. shifts from a high consumption of drugs with a low potency to a high consumption of drugs with a high potency (DANMAP, 2011). Differences in calculated percentual increases and decreases between years were observed between gram AM/pig and ADD/pig, but no changes in significance level was found. An example of differences between kg active compound and ADD is the observed 9.9% decrease from 2005 to 2011 measured in total kg active compound, compared to the 1.0% decrease in total number of ADD during the same period. This is in agreement with studies conducted by Merle et al. ((2012) and Menéndez González et al. (2010) who also found differences between reported AM consumption when using kg active compound and measurement units such as ADD.

4.2 AM consumption at herd level – effect of calculation method

It was found that both herds with a high production (≥6 growers per pen place) and herds where growers left the facility at less than 30 kg had a significantly higher AM consumption measured as percentage growers treated per day using pen places as measurement for number of pigs than their counterparts. No interaction between high production and weight when leaving grower facility was identified. This might be due to the fact that we only had 122 participating herds (calculated sample size=157).

Using pen places as measurement for number of pigs when calculating percentage pigs treated per day, might cause herds with a high production of growers per pen place to be pointed out wrongly as herds which treat a high percentage of their animals. This is especially true where the herd has a large turnover of recently weaned animals, as it has been shown that these are more susceptible to diseases than older animals (Carroll et al., 1998; Aarestrup et al., 2008). Table 3 illustrates an example of two herds where actual percentage of treated growers are the same, but when calculating consumption given as percentage growers treated per day based on pen places, it looks as if though the high producing herd (herd 1) treats a larger percentage of their pigs than herd 2. This example serves to illustrate the difficulties when attempting to report treatment incidence in a population.

***Table 3**. Example of consequences of using number of pen places* when *calculating percentage pigs treated per day.*

	Pen places - growers	Produced growers per year	Number of grower treatments in a year	Actual percentage growers treated per day	Percentage growers treated per day based on number of pen places
Herd 1	100	600	10950	5%	30%
Herd 2	100	300	5475	5%	15%

When collecting data through questionnaires, occurring bias must be taken into account (Vieira et al., 2011). This includes skewed results if the study population was not representative of the target population and non-response bias (Edwards et al., 2002; Houe, 2004). Because the study was based on herds chosen from a convenience sample of herds participating in another study, more herds, which had been randomly selected among all Danish herds with growers, are needed to make any inferences at national level. However the relatively high respondent rate of 82.3% decreases the risk of non-respondent bias.

A decision was made to use questionnaires for collecting information on the study herds' productions, including number of pen places according to the farmer, as some farmers might not have completely accurate number of pen places registered in CHR. This was done even though information collected through questionnaires are vulnerable to recall errors and non-response bias (Edwards et al., 2002; Vrijheid et al., 2006). Furthermore, it must be taken into consideration that data derived from management reports are the farmers own assessment, and that precision of data and frequency of data collection might be very different between herds.

When comparing number of grower pen places in the study herds according to the farmer with number of pen places according to CHR for the corresponding period, a mean difference of 20% was found (std. dev: 53.7) corresponding to an average difference of 344 pen places between farmer's statement and CHR (std. dev: 583; minimum: 0; maximum: 4200) (figure 8). All tests in the pilot study were conducted using pen places according to the farmer. We also conducted all tests in the pilot study using number of pen places according to the CHR to investigate if the outcomes were identical. No test results were significantly different between the two methods.

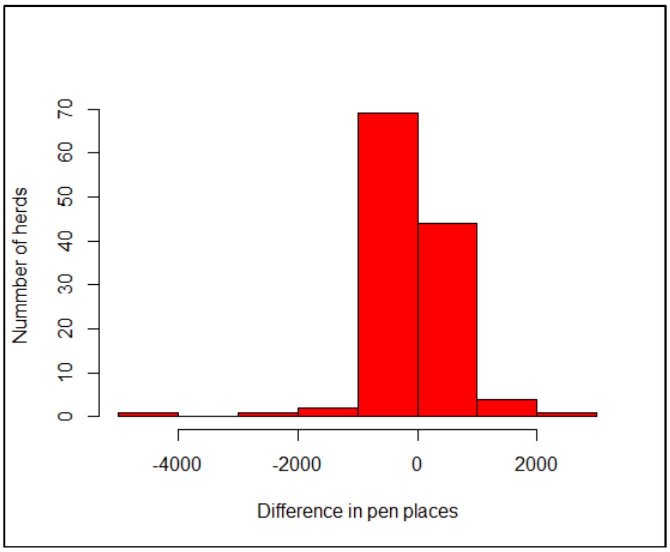

Figure 8. *Difference between number of grower pen places according to farmer and number of pen places according to CHR for participating herds.*

Conclusions

These results show that number of pigs always should be included when reporting the Danish AM usage. Also, there is an obvious risk of misclassification if productivity is not taken into account, especially in countries such as Denmark where the export of live growers and finishers constituted 27.7% of the total national pig production in 2011. Whether changes in AM consumption over years were significant or not, were found to be affected by chosen measurement for number of pigs. Furthermore the increase in estimated mg AM/kg pork produced was found to be amplified, when exported live pigs were not included. The author suggests that adjusted live exported weight including 10% mortality should be used when estimating kg pork produced for countries where pigs are exported at 30 kg or more and receive the majority of their AM below 30 kg.

In the pilot study it was found that both herds with a high production (≥6 growers per pen place) and herds where growers left the facility at less than 30 kg had a significantly higher AM consumption measured as percentage growers treated per day using pen places as measurement for number of pigs than their counterparts. This might suggest that “number of pen places” is not the most ideal measurement for number of animals when reporting actual treatment incidence, if herds in the study population have large differences in productivity.

This study underlines the importance of considering chosen reporting method (Chauvin et al., 2008; Berrington, 2010) and ensuring the same calculation methods have been used, when attempting to compare AM consumption between studies. Furthermore, when evaluating AM consumption it must be remembered that ADD is a technical unit designed for pharmaco-epidemiological purposes. It does not necessarily reflect actual used doses (Jensen et al., 2004). This problematizes the fact that Danish authorities use the term “percentage animals treated per day” when referring to ADD per 100 animals per day based on number of pen places. It might be difficult for the average consumer to understand that a treatment incidence of 5 ADD per 100 animals per day is not necessarily the same as the statement “5% of all pigs are treated every day”.

Presently plans are under way to expand the study population from the pilot study.

Author, Year	Country	Study design	Study population	Number of herds in study	Sampling	Sources on consumption data	Measurement units used
Danmap, 2011	Denmark	Retrospective longitudinal observational study	All Danish herds	All Danish herds	All Danish herds	National databases	Total kg active compound, ADD
MARAN, 2009	The Netherlands	Retrospective longitudinal observational study	All Dutch herds	All Dutch herds	All Dutch herds	National databases	Total kg active compound, ADD
Viera et al., 2011	Denmark	Retrospective longitudinal observational study	Danish finisher herds	All Danish finisher herds	All Danish herds	National databases	ADD
Merle et al., 2012	Germany	Retrospective longitudinal observational study	German live stock herds	65 live stock herds	Lacking information- 99 practices contacted	Veterinarian, farmer	Kg active compound, daily doses
Menendez Gonzalez et al., 2010	Switzerland	Prospective longitudinal observational study	Swiss dairy herds	97 herds	Convenience sampling for herds	Farmer	Kg active compound, used daily doses,used course doses
Callens et al., 2012	Belgium	Retrospective longitudinal observational study	Belgian pig herds	50 pig herds	Randomly selected herds from Belgian production animal registration database	Farmer	ADD, used daily doses
Timmerman et al., 2006	Belgium	Retrospective longitudinal observational study	Belgian pig herds	50 pig herds	Randomly selected herds from Belgian production animal registration database	Farmer	ADD, used daily doses

Table 1. Examples of calculation routines and criteria used for selection of study population from studies applying calculation methods derived from the WHO defined DDD. ADD=Animal daily doses

Author, Year	Calcula-ted unit	Calculated as	Dosagevalues from	Consumption reported as	Calculated as
Danmap, 2011	ADD	$\frac{active\ compound\ prescribed\ in\ mg}{recommended\ dosage\ per\ day * standard\ animal\ weight}$	Danish Health and Medicines Authority	ADD/pig produced/ year	$\frac{ADDs\ prescribed\ per\ year}{Animals\ produced\ per\ year\ (slaughter + live\ export}$
MARAN, 2009	ADD	$\frac{active\ compound\ prescribed\ in\ mg}{recommended\ dosage\ per\ day * standard\ animal\ weight}$	Not given	ADD/animal year	$\frac{ADDs\ prescribed\ per\ year}{Animals\ present\ (resembling\ pen\ places)}$
Viera et al., 2011	*ADD*	$\frac{active\ compound\ prescribed\ in\ mg}{recommended\ dosage\ per\ day * standard\ animal\ weight}$	Danish Health and Medicines Authority	Treatment incidence rate	$\frac{\sum ADDs\ prescribed\ in\ period}{\sum(delivered\ finishers\ in\ period * fattening\ period} * 100$
Merle et al., 2012	Daily doses	$\frac{active\ compound\ used\ in\ mg}{recommended\ dosage\ per\ day * standard\ animal\ weight}$	Summary of product characteristics	Daily doses/animal year	$\frac{number\ of\ daily\ doses}{population\ size\ (respective\ sum\ of\ herd'sanimals)}$
Menendez Gonzalez et al., 2010	Used daily doses	$\frac{active\ compound\ used\ in\ mg}{used\ dosage\ per\ day * standard\ animal\ weight}$	Farmers	Treatment incidence of used course doses	$\frac{number\ of\ used\ course\ doses}{animal\ years\ at\ risk\ (1)} * 100$
	Used course doses	$\frac{active\ compound\ used\ in\ mg}{used\ dosage\ per\ course * standard\ animal\ weight}$	Farmers		
Callens et al., 2012	ADD	$\frac{activecompoundusedinmg}{recommendeddosageperdayperkgpig}$	Belgian Compendium for Veterinary Medicines and drugs' instruction leaflets	Treatment incidence of ADD/used daily doses	$\frac{activecompoundusedinmg}{UDDorADD\left(\frac{mg}{kg}\right) * daysatrisk(2) * kgpig} * 100$
	Used daily doses (UDD)	$\frac{active\ compound\ used\ in\ mg}{used\ dosage\ per\ day\ per\ kg\ pig}$	Farmers		
Timmer-man et al., 2006	ADD	$\frac{activecompoundusedinmg}{recommendeddosageperdayperkgpig}$	Belgian Compendium for Veterinary Medicines and publications from BCPI (3)	Treatment incidence of ADD/used daily doses	$\frac{activecompoundusedinmg}{UDDorADD\left(\frac{mg}{kg}\right) * observation\ period * kgpig(4)} * 100$
	Used daily doses	$\frac{active\ compound\ used\ in\ mg}{used\ dosage\ per\ day\ per\ kg\ pig}$	Farmers		

Table 1.Continued.(1)No calculation method given (2)Total lifetime of finishers (3)Belgian Centre for Pharmacotherapeutic Informaton(4) number of animals in observed group/median body weight at treatment.

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