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Comparing antimicrobial exposure based on sales data

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ABSTRACT

This paper explores the possibilities of making meaningful comparisons of the veterinary use of antimicrobial agents among countries, based on national total sales data. Veterinary antimicrobial sales data on country level and animal census data in both Denmark and the Netherlands were combined with information about estimated average dosages, to make model calculations of the average number of treatment days per average animal per year, at first based on the assumption that the treatment incidence is the same in all species and production types. Secondly, the exposure in respectively animals for meat production and dairy and other cattle (excluding veal and young beef) was estimated, assuming zero use in the dairy and other cattle, and thirdly by assuming respectively 100% oral and 100% parenteral administration. Subsequently, the outcomes of these model calculations were compared with treatment incidences calculated from detailed use data per animal species from the national surveillance programmes in these two countries, to assess their accuracy and relevancy.

In Denmark and in the Netherlands, although the computed antimicrobial exposure would seem to be a reasonable estimation of the exposure for all animals as a whole, it differs significantly from the measured exposure for most species. The differences in exposure among animal species were much higher than the overall difference between the two countries. For example, the overall model estimate of 9 treatment days per year for Denmark is a severe overestimation of the true use in poultry (i.e. 3 days), and the overall model estimate of 13 treatment days per year for the Netherlands is a severe underestimation of the true use in veal calves (i.e. 66 days).

The conclusion is that simple country comparisons, based on total sales figures, entail the risk of serious misinterpretations, especially if expressed in mg per kg. The use of more precise model calculations for making such comparisons, taking into account differences in dosages and in farm animal demographics, only slightly reduces this risk. Overall model estimates are strongly influenced by animal demographics and a very inaccurate indication of the true differences in exposure, per animal species. To get an appropriate certainty about the true differences in antimicrobial exposure between countries it is an absolute necessity to have reliable information about the use per animal species.

1. Introduction

Antimicrobial exposure is considered an important risk factor for emerging antimicrobial resistance which poses risk to human health (Gould and MacKenzie, 2002).

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Because of the effects of antimicrobial use in food animals on antimicrobial exposure and consequently the risk of development of antimicrobial resistance, it is important to gain quantitative insight into the use of veterinary antimicrobial agents (Mevius et al., 1999). Some European countries already have developed or are developing sophisticated surveillance systems. The European Medicines Agency (EMA) is currently carrying out a project called European Surveillance of Veterinary Antimicrobial Use (ESVAC), for a standardized collection of data on *sales* of veterinary antimicrobial agents in Europe (EMA, 2011). The ESVAC project was launched in September 2009; the terms of reference included a request to develop a harmonized approach for the collection and reporting of data on the use of antimicrobial agents in animals from the EU Member States.

An initial goal of the ESVAC project is to gain insight into the use per country and the trends both on country level and EU level and one of the intended uses of the collected data is to aid interpretation of patterns and trends regarding antimicrobial resistance. The data on country level will undoubtedly also be used for making international comparisons among countries, including comparisons with overall antimicrobial and antimicrobial resistance in specified species. Although dedicated drug monitoring systems, on species level or even on farm level, are needed to assess the true use levels of antimicrobial agents, it is expected that for most countries in the coming years knowledge about antimicrobial use will be primarily based on national total sales data.

There is not yet a scientifically sound, generally accepted and easily applicable method for performing country comparisons of veterinary antimicrobial use. Recent papers express the use in milligram (mg) of active substance sold per kg meat produced and/or kg live animal present (Ungemach et al., 2006; Grave et al., 2010; EMA, 2011), which is fairly easy attainable but seems to be a very rough indicator. The calculated differences in “mg per kg” (whether live biomass, slaughtered weight, or a mixture of these as in the “population correction factor” (PCU)[1]) will probably be interpreted as differences in the level of antimicrobial exposure. However, the use differs significantly among different species (Bondt et al., 2011; DANMAP, 2011), and the effect of different animal demographics among countries on the total national use may be high: some countries have relatively large pig or poultry populations, while other countries have in the main extensively held animals like dairy cows, beef cattle (suckling) and sheep; it has not yet been determined whether average country levels of antimicrobial use might be an accurate indicator for the true use levels in the different subsectors of the animal population.

Furthermore, the differences in “mg per kg” among countries may also reflect application of different pharmacotherapeutic groups with significant differences in potency, hence differences in dosage.

For international comparison, an alternative method is therefore needed in the coming years, because in most countries basically only total sales figures will be available. This article explores the possibilities of making meaningful comparisons of the veterinary use of antimicrobial agents among countries, based on total sales data, by assessing the accuracy of three different model calculations for the comparison of antimicrobial exposure in Denmark (DK) and the Netherlands (NL). As both countries have reasonably accurate use data on animal species and production type level, the outcomes of the model calculations based on total sales data will be compared with the measured use data per species. Our research questions were as follows:

- Are national total sales data suitable for making meaningful country comparisons of veterinary use of antimicrobials?
- What is the accuracy of the outcomes of the model calculations, based on total sales data, i.e. can these models substitute national drug monitoring systems on species level?
- What will be the more adequate model to quantify the use of antimicrobials for country comparisons?

2. Materials and methods

Quantifying antimicrobial exposure requires information about the amount and potency of active substances used in a certain time period, and animal population data. The level of exposure (**E**) could for example be expressed as the amount of active substance used (X, expressed in mg) per animal body weight (Y, expressed in kg live body weight) per year, i.e. $E = X/Y$. However, this expression is inadequate due to at least two complications. The first complication concerns the quantity X: one mg of active substance in one country is not equivalent to one mg of active substance in another, due to differences in patterns of use (choice and dosing of used antimicrobial agents) and hence differences in average potency and in average dosage. The second complication concerns the quality of Y: one kg of animal in one country differs from 1 kg of animal in another, due to substantial differences in animal demographics.

In view of these complications, the Animal Defined Daily Dose (abbreviated ADD, used to designate the DDD for animals) was introduced, which is the defined average maintenance dose of a specified medicine per kg of a specified animal per day, applied for its main indication (Jensen et al., 2004; Chauvin et al., 2008). The ADD depends on species and may also differ among countries. The ideal method for gaining insight into the true exposure to antimicrobial agents is to calculate the number of ADDs (NADD) used per animal per year as applied in human pharmacoepidemiology with the number of Defined Daily Dosages (DDD) per 1000 inhabitant-days (WHO, 2012). NADD represents the treatment days. Because animal body weight and dosage is highly variable per species, NADD calculated per animal species is a more appropriate measure in veterinary pharmacology.

Calculating NADD requires detailed information about the amount of individual active substances or even individual medicines used per animal species. Such detailed

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[1] EMA (2011) introduced the PCU, which is purely a technical unit of measurement. A PCU is a kg of different categories of livestock and slaughtered animals.

Table 1
Total sales of veterinary antimicrobial agents in the Netherlands and Denmark in 2010, in tonnes of active substance and in percentage of total sales (including use in minor species).

Pharmacotherapeutic group	Netherlands		Denmark	
Intestinal antiinfectives[a]	10[f]	2%	1	1%
Tetracyclines	217	50%	36	28%
Oxytetracycline	140	32%	6	4%
Doxycycline	75	17%	20	16%
other tetracyclines	2	0%	10	8%
Amphenicols[e]	2[f]	1%	1	1%
Penicillins	66[g]	15%	38	30%
Narrow spectrum penicillins[b]	7[f]	2%	37	29%
Other penicillins[e]	59	14%	1	1%
1st and 2nd generation cephalosporins[c]	0.3	0%	0.4	0%
3rd and 4th generation cephalosporins	0.7	0%	0.1	0%
Trimethoprim/sulfonamides	78	18%	15	12%
Macrolides	37[f]	8%	14	11%
Fluoroquinolones	2	0%	0	0%
Other quinolones	5	1%	1	1%
Others (e.g. pleuromutilins)[d]	1[f]	0%	11	8%
Combinations[e]	14[f]	3%	11	9%
Total	433	100%	127	100%

Sources: FIDIN (2012), Bondt et al. (2011), DANMAP, 2011.

[a] Intestinal anti-infectives comprise aminoglycosides (almost 100% orally administered) and orally administered colistin.

[b] Narrow spectrum penicillins comprise beta-lactamase sensitive and resistant penicillins (ATC Vet code QJ01CE and QJ01CF).

[c] In Denmark first and second generation cephalosporins are only used in pets (majority) and intramammary, in the Netherlands mostly for food producing animals (intramammary).

[d] Others comprise pleuromutilins and polymyxins, excluding orally administered colistin.

[e] All antibacterials usually used in combination, like lincosamides/spectinomycin, streptomycin in combination (combined with betalactamase sensitive penicillin, which is usually used alone, and therefore is noted in a separate row).

[f] Quantity of sales estimated based on farms in MARAN sample survey (Bondt et al., 2011).

[g] Part of the sales of penicillins is included in 'Combinations'.

information is available in the Danish Vetstat database (DANMAP, 2011) and in the Dutch sample survey (Bondt et al., 2011), but not in most other countries. Table 1 shows the total sales figures for Denmark (DANMAP, 2011) and the Netherlands (Bondt et al., 2011). National sales figures only comprise the total sales per group of antimicrobial agents, without being further specified per species.

To estimate the exposure to veterinary antimicrobial agents using sales data, the total amount of antimicrobial agents sold in a certain country in a certain year (***S***) must be related to the size of the farm animal population (*P*). In this study, only the major animal species cattle, pigs and poultry were included. Minor species like sheep, fur animals and farmed fish were not included, nor were horses and other companion animals. The expression of ***S*** must take into account the differences in dosages (i.e. ADDs) and the expression of *P* must take into account the demographic features of the animal population.

Suppose there are ***I*** types of antimicrobial agents sold in a country with ***J*** categories of animals (species and production type). To explore the possible methods, following notations are used:

i: denotes an antimicrobial agent sold in a certain country, $i = 1, 2, \ldots, I$;
j: denotes a category of animals present in the country, $j = 1, 2, \ldots, J$;
$\mathbf{D_{ij}}$: denotes the ADD of antimicrobial agent *i* for animal category *j*, measured in mg per kg per 24 h;
$\mathbf{S_i}$: denotes the amount of antimicrobial agent *i* sold in a certain year and country in tonnes;
$\mathbf{S_j}$: denotes the total amount of antimicrobial agents sold in a certain year and country in animal category *j*;
$\mathbf{S_{ij}}$: denotes the amount of antimicrobial agent *i* sold/used for animals in the category *j* in tonnes;
$\mathbf{T_j}$: denotes the total live weight of farm animals in category *j* being treated with antimicrobials in a certain year, according to their standard dosages;
$\mathbf{T_{ij}}$: denotes the total live weight of farm animals in category *j* being treated with antimicrobial agent *i* according to the standard dosage;
$\mathbf{W_j}$: denotes the average live treatment weight of the animals in kg in category *j*;
$\mathbf{N_j}$: denotes the numbers of farm animals in category *j* averagely present in a certain year;
$\mathbf{NADD_{ij}}$: denotes the number of daily doses from antimicrobial agent *i* an average farm animal in category *j* received for in a certain year, according to the standard dosage;
$\mathbf{NADD_j}$: denotes the number of daily doses from all antimicrobial agents, which an average farm animal in category *j* received, in a certain year, according to their standard dosages;
NADD: denotes the number of daily doses from all antimicrobial agents an average animal of all categories received, in a certain year, according to their standard dosages.

All variables denote the values for a certain time frame, in this case one year. Theoretically, when information about $\mathbf{S_{ij}}$ is available, $\mathbf{T_{ij}}$ can be calculated as S_{ij}/D_{ij} and NADD_{ij} can be calculated as the total biomass in animal category *j* being treated with antimicrobial *i* divided by the total treatable live weight (population at risk), i.e.

$$\text{NADD}_{ij} = \frac{T_{ij}}{W_j N_j} = \frac{S_{ij}}{D_{ij} W_j N_j}, \tag{1a}$$

where the total treatable live weight of animals in category *j* is calculated as $W_j N_j$. This is the ideal information about exposure to antimicrobial agents in different animal categories, based on use/sales data per species. The exposure in animal category *j* to all antimicrobial agents, NADD_j, can then be calculated as:

$$\text{NADD}_{ij} = \frac{\sum_{i=1}^{I} T_{ij}}{W_j N_j} \tag{1b}$$

And the exposure for all animal species as a whole can be calculated as the weight-weighted average of the exposure for the different animal categories:

$$\text{NADD} = \frac{\sum_{J=1}^{J} \text{NADD}_j W_j N_j}{\sum_{J=1}^{J} W_j N_j} \tag{1c}$$

In practice, however, the information about the use/sales per species ($\mathbf{S_{ij}}$) is not available in most countries. Alternative methods should therefore be used to assess NADD_j and NADD with additional parameters. The proposed method calculates the following parameters:

- the average dosage for antimicrobial agent *i* (denoted as $\bar{D}_i$) for the whole animal population, which is calculated as the weight-weighted average of the ADDs for different animal categories, i.e.:

  $$\bar{D}_i = \frac{\sum_{J=1}^{J} D_{ij} W_j N_j}{\sum_{J=1}^{J} W_j N_j}. \tag{2a}$$

  The average dosage $\bar{D}_i$ depends therefore on the ADDs for the individual species and the proportion of biomass for each species in the total population. The dosage $\bar{D}_i$ represents the average amount of antimicrobial agent *i* (in milligrams) required to treat one kilogram of the mean national animal during one day, and can best be described as an overall 'potency indicator'.
- the average treatment weight of the animal category *j* (denoted as $\bar{W}_j$) in the population 'at risk' of being treated with antimicrobial agents in a certain year. The average treatment weights per head (kg) are estimated as follows (Jensen et al., 2004): cows/bulls 600, heifers 300, young cattle for veal and beef production 86 (Bondt et al., 2011), female calves < 12 months 86,[2] breeding pigs 200, piglets (below 20 kg) 10, fattening pigs 50, turkeys 6, broilers 1.0, other poultry 1.0.[3] The total treatable weight (denoted as $\bar{W}$) is then calculated by summing up the weights in all the categories, i.e.

  $$\bar{W} = \sum_{J=1}^{J} \bar{W}_j N_j. \tag{2b}$$

  In general, we use census data to determine the number of animals in different categories. For the number of poultry no census data from the Eurostat database (Eurostat, 2012) were available, therefore farm census data of FAO (FAO, 2012) were used. Laying hens were excluded, as these animals will not or very scarcely be treated with antimicrobial agents during egg production.
- the total biomass being treated with antimicrobial agent *i* (denoted as T_i), which is estimated as: $\bar{T}_i = S_i/\bar{D}_i$. The total amount of biomass being treated (*T*) with all antimicrobial agents is then estimated as:

  $$\bar{T} = \sum_{i=1}^{I} \bar{T}_i. \tag{2c}$$

  With these parameters, the estimator for the true level of exposure to all production animals as a whole (denoted as $\widehat{\text{NADD}}$) is defined as:

$$\widehat{\text{NADD}} = \frac{T}{\bar{W}}. \tag{2d}$$

When the true exposure NADD and NADD_j is known from collected use data on species level, a simple accuracy measure ε can be defined for the estimator $\widehat{\text{NADD}}$. The accuracy measures ε represent the error percentage of the estimated exposure to the true exposure. The more accurate an estimator is, the closer the percentage will be to zero.

$$\varepsilon = \left(\frac{\widehat{\text{NADD}}}{\text{NADD}} - 1 \right) \times 100\%. \tag{3a}$$

We consider an estimator reasonably accurate when the absolute value of the error percentage is smaller than 30%.

To apply the method described above, assumptions need to be made concerning the categories of animals receiving their shares of the total sales of antimicrobial agents (i.e. S_j). At first, a general assumption in the estimation of an average dosage (overall 'potency indicator') is that all animal categories get an equal exposure to antimicrobial agents, which is definitely not true. On the contrary, it is common knowledge that certain categories of the farm animals only get limited amounts of antimicrobial agents, for example grown cattle.

Using the calculation method and assumptions described above, the following outcomes for Exposure (**E**) are possible, all expressed in an estimated number of daily doses or treatment days per biomass year ($\widehat{\text{NADD}}$):

A. Total sales (tonnes) divided by the total live treatment weight of the livestock and an overall average dosage (E_A).
B. Total sales (tonnes) divided by the live treatment weight of only animals for meat production and the average dosage for those animals (E_B).

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[2] Treatment weight of female calves is assumed to be equal to that of calves for veal and beef production.

[3] For *Gallus gallus*, all animals were calculated with an average weight of 1.0 kg, which is slightly below the actual live adult weight of parent and grandparent flocks of broilers and laying hens. The number of laying hens were used only to calculate the amount of "other poultry"; for The Netherlands this number comes from Dutch national census data (CBS) and for Denmark it was estimated on the basis of egg production figures.

C. Two estimates, i.e. one for each subpopulation, firstly meat animals (pigs, calves for veal and young beef production, poultry except laying hens), secondly dairy and other cattle.
   a. The total estimated sales (tonnes) orally administered, divided by the live treatment weight of animals for meat production and the average dosage for that category of animals ($E_{\text{C oral}}$).
   b. The total estimated sales parenterally administered, divided by the live treatment weight of the dairy and other cattle, and the average dosage for that category of animals ($E_{\text{C parental}}$).

To assess the accuracy and relevancy of the outcomes of the three model calculations, the true levels of exposure (i.e. NADD_j) for the Netherlands and for Denmark were determined using collected data on species level from Vetstat and the Dutch sample survey. For each species and type of antimicrobial agent the used quantity was divided by the treatable weight, and the estimated average dosage. Exactly the same approach was followed as in the three model calculations, however, this time based on collected use data per species, instead of total sales data.[4] The use in minor species was excluded, which is 11% of the total sales in Denmark (mainly fur animals, fish, and companion animals) and an estimated 5% in the Netherlands (van Geijlswijk et al., 2011; FIDIN, 2012). The 2010 data for Denmark are extracted from the VetStat database in February 2012 and therefore might deviate slightly from the data as published in the DANMAP 2010 report. In the Netherlands, a yearly sample survey is carried out on approximately 400 farms, in which the antimicrobial use is determined on a detailed level. The actual use in the Netherlands might differ from the quantities, as measured in the sample survey. Denmark has the Vetstat system, which covers 100% of the farms.

In the Netherlands and Denmark every authorized medicine is assigned a dedicated ADD. The ADD is determined by the administration route and often also the species, e.g. with in many cases much higher doses used for poultry. The applied ADDs in this research are a compromise based on a review of the available information in the Dutch sample survey and the Danish Vetstat system, thus including doses applied in Denmark and the Netherlands.[5]

3. Results

Table 2 shows the estimated average dosages (i.e. $\bar{D}_i$) per antimicrobial group calculated as described before (parameter (2a)). The dosages in Table 2 represent the average number of milligrams of a certain group of active substances required to treat one kilogram of animal in one day. The table shows the large differences in dosage among species and also illustrates the fact that most antimicrobial agents are administered orally.

Table 2
Estimated average dosage per group of antibacterial agents for NL and DK, expressed in mg per kg live weight per day (ADDkg).

	Admin. route[a]	Cattle	Poultry	Pigs
Intestinal anti-infectives	o	10	10	10
Oxytetracycline	o	35	65	30
Oxytetracycline	p	7		7
Doxytetracycline	o	10	15	10
Other tetracyclines	o	3		25
Amphenicols	o		20	10
Amphenicols	p	15		10
Narrow spectrum penicillins	o		17	
Narrow spectrum penicillins	p	13		13
Other penicillins	o	35	25	15
Other penicillins	p	10		10
Cephalosporins 1/2 gen	o	1		
Cephalosporins 3/4 gen	p	1		2
Trimethoprim/sulfonamides	o	35	60	27
Trimethoprim/sulfonamides	p	16		16
Macrolides	o	25	60	13
Macrolides	p	2		2
Fluoroquinolones	o	3	10	
Fluoroquinolones	p	4		3
Other quinolones	o	18	11	20
Others (e.g. pleuromutilins)	o, p	10		10
Combinations	o	10	140	9
Combinations	p	15		15
Combinations	im	1		

[a] Administration routes: oral (o), parenteral (p), intra-mammary (im).

Table 3 shows the size of the major livestock species (cattle, pigs, poultry) in both countries, and the estimated average weights during treatment.

Table 4 shows the use for the Netherlands, expressed in tonnes, based on the total sales data combined with the shares per species, antimicrobial group and administration route from the sample survey. Table 5 shows the use for Denmark, extracted from the Vetstat database. It was roughly estimated that in the Netherlands and Denmark respectively half and two-thirds of the sales of combinations comprise intramammaries.

Fig. 1 shows the outcomes of the three different model calculations based on total sales data, expressed in number of daily doses or treatment days per biomass year (NADD). For these calculations the data from Tables 1 (total sales, including the use in minor species), 2 and 3 were used.

Fig. 2 shows the best possible estimates of the true exposure to antimicrobial agents in 2010, based on the collected use data per species from DANMAP-2010 and MARAN, as presented in Tables 4 and 5 (Bondt et al., 2011; DANMAP, 2011).

Fig. 2 reveals the large differences in antimicrobial exposure among species.

Table 6 indicates the accuracy of the outcomes of the three different model calculations (Fig. 1), based on the percentual error of the true exposure (Fig. 2).

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[4] For sows/piglets the use of sows, piglets and weaners is included, and the weight at treatment of piglets with a live weight of less than 20 kg plus breeding pigs (see Table 3). The use level of fattening pigs is calculated using the weight of fattening pigs of at least 20 kg as denominator (see Table 3). For veal and young beef in Denmark the nominator comprises the use of all calves, whereas the weight of only the male animals for veal and young beef production was used as denominator. Therefore in Fig. 2 the NADD for veal and young beef in Denmark will be a maximum value.

[5] As the WHO Collaborating Centre for Drug Statistics Methodology states on their website (www.whocc.no), the defined daily dose, in this paper 'ADD', "is sometimes a dose that is rarely if ever prescribed, because it is an average of two or more commonly used dose sizes".

Table 3
Animal demographics in the Netherlands and Denmark in 2010 and estimated treatment weights; percentage of total weight in brackets.

		Number of animals (in 1000s)[a]		Estimated average treatment weight[b]	Total treatment weight of animals (in 1000 tonnes)	
		The Netherlands	Denmark		The Netherlands	Denmark
Total of cattle population	Cat.	3960	1630		1381 (68%)	599 (48%)
Bovine animals aged between 1 and 2 years: Female	B	560	284	300	168	85
Bovine animals aged between 1 and 2 years: Male	A	56	34	300	17	10
Bovines animals of 2 years and over: Female	B	1747	748	600	1048	449
Bovines animals of 2 years and over: Male	B	20	12	600	12	7
Calves for slaughter	A	921	6	86	79	1
Other calves: Female	B	580	266	86	50	23
Other calves: Male	A	77	281	86	7	24
Weight veal and young beef production	A				103 (5%)	35 (3%)
Weight dairy and other cattle	B				1278 (63%)	564 (45%)
Total of the pig population		12,206	12,293		590 (29%)	643 (51%)
Piglets with a live weight of less than 20 kg	A	4649	4146	10	46	41
Pigs with a live weight between 20 and 50 kg	A	2031	3469			
Fattening pigs between 50 and 80 kg	A	2111	2699			
Fattening pigs between 80 and 110 kg	A	1919	675			
Fattening pigs of at least 110 kg	A	388	7			
Fattening pigs of at least 20 kg		6449	6850	50	322	343
Breeding pigs with a live weight of 50 kg and higher[c]	A	1107	1297	200	221	259
Poultry (×1000 animals)					61 (3%)	10 (1%)
Turkeys	A	1167	201	6.0	7	1
Other poultry, excluding layers	A	54,367	8323	1.0	54	8
Total of the whole livestock population					2032 (100%)	1252 (100%)
Total of category A: animals for meat production	A				754 (37%)	688 (55%)
Total of category B: dairy and other cattle	B				1278 (63%)	564 (45%)

[a] Eurostat (2012).

[b] Jensen et al. (2004), Bondt et al. (2011).

[c] Breeding pigs comprises mainly sows, but also includes growing gilts above 50 kg. Therefore the estimated average weight is below the average adult weight of sows.

4. Discussion

4.1. Estimated differences

The true average NADD[6] for all animals will be approximately 13 for the Netherlands and 9 for Denmark, based on the use data per species. This outcome indicates that the average use for all animals of major species in the Netherlands is approximately 40% higher than the overall average use in Denmark. This result is similar to model calculation E_A. The overall average NADD is mainly determined by the differences in the largest animal categories, i.e. pigs and cattle. In most countries a large use in poultry will play a minor role in the overall average, because of the limited size of this subsector, not in numbers but in biomass. In terms of risk assessment, a high use in poultry may be very relevant, but an overall average use level will not reveal such information.

The use data per species reveal that the antimicrobial use in pigs (total) in the Netherlands was 35% higher than in Denmark. The differences in use in sows/piglets and fattening pigs might be due to the fact that in Denmark the use in pigs between 25 and 30 kg is ascribed to sows/piglets, and in the Netherlands to fattening pigs, which complicates a distinct comparison. Besides, the use level for sows/piglets is an average of the use in respectively sows and piglets, and will probably be an overestimation of the true use in sows and a serious underestimation of the true use level in piglets (Bondt et al., 2011). The use in dairy and other cattle appears to be relatively low, in both countries. The most remarkable difference between NL and DK is the large production of veal and young beef in the Netherlands, with a high antimicrobial use. Another striking difference is the very low use level in poultry in Denmark, compared to the Netherlands.

The calculated error percentages show that an overall national average of NADD is unsuitable to indicate the true levels of exposure, in the different animal species.

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[6] The average exposure for all animals was calculated as the weighted average of the antimicrobial exposure calculated per animal species. The total treatable weight of the corresponding animal species, as shown in Table 3, was used as the weighting factor.

Table 4

Antibiotic use per species in the Netherlands in 2010, per group of antimicrobials, administration route and species in tonnes, based on use data in Dutch sample survey.

	Adm. route	Total	Cattle	Veal calves and young beef	Poultry	Pigs	Fattening pigs	Sows, piglets
Intestinal anti-infectives	o	9.50	0.44	5.79	1.99	1.28	0.19	1.09
Oxytetracycline	o	130.59	1.51	78.11	1.13	49.83	15.43	34.41
Oxytetracycline	p	2.13	1.45	0.00	0.00	0.68	0.40	0.28
Doxytetracycline	o	71.53	0.56	14.16	8.70	48.10	33.11	14.99
Other tetracyclines	o	1.50	0.99	0.50	0.00	0.00	0.00	0.00
Amphenicols	o	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Amphenicols	p	2.19	0.52	1.43	0.00	0.23	0.20	0.04
Narrow spectrum penicillins	o	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Narrow spectrum penicillins	p	6.97	3.62	0.07	0.97	2.31	0.52	1.80
Other penicillins	o	48.94	0.25	27.90	10.61	10.19	1.81	8.38
Other penicillins	p	7.05	2.90	0.34	0.00	3.81	1.11	2.71
Cephalosporins 1/2 gen	o	0.25	0.25	0.00	0.00	0.00	0.00	0.00
Cephalosporins 3/4 gen	p	0.70	0.64	0.03	0.00	0.03	0.00	0.03
Trimethoprim/sulfonamides	o	66.20	0.93	23.15	9.91	32.21	11.99	20.22
Trimethoprim/sulfonamides	p	8.01	6.48	0.04	0.00	1.49	0.20	1.29
Macrolides	o	33.79	0.00	10.12	3.09	20.58	17.48	3.10
Macrolides	p	1.07	0.64	0.19	0.00	0.24	0.10	0.15
Fluoroquinolones	o	0.79	0.55	0.15	0.03	0.05	0.01	0.04
Fluoroquinolones	p	0.79	0.55	0.15	0.03	0.05	0.01	0.04
Other quinolones	o	4.47	0.19	0.63	3.61	0.04	0.01	0.03
Others (e.g. pleuromutilins)	o, p	1.24	0.00	0.00	0.00	1.24	0.55	0.68
Combinations	o	3.04	0.09	0.00	2.67	0.28	0.09	0.19
Combinations	p	10.64	7.36	1.23	0.00	2.04	0.40	1.65
Total		411.37	29.93	163.99	42.74	174.70	83.60	91.11

Table 5

Antibiotic use per species in Denmark in 2010, per group of antimicrobials, administration route and species in tonnes, based on use data in Vetstat database.

	Adm. route	Total	Cattle	Veal calves and young beef	Poultry[a]	Pigs	Fattening pigs[b]	Sows, piglets[b]
Intestinal anti-infectives	o	1.19	0.02	0.18	0.00	0.99	0.02	0.98
Oxytetracycline	o	0.06	0.00	0.01	0.00	0.04	0.01	0.03
Oxytetracycline	p	5.25	1.26	0.48	0.00	3.50	1.31	2.20
Doxytetracycline	o	18.86	0.00	0.00	0.23	18.63	6.79	11.83
Other tetracyclines	o	10.16	0.03	0.01	0.00	10.12	3.60	6.52
Amphenicols	o	0.05	0.00	0.00	0.01	0.04	0.00	0.04
Amphenicols	p	0.50	0.03	0.36	0.00	0.11	0.01	0.10
Narrow spectrum penicillins	o	0.04	0.00	0.00	0.04	0.00	0.00	0.00
Narrow spectrum penicillins	p	23.70	7.25	0.27	0.00	16.17	6.75	9.42
Other penicillins	o	5.13	0.00	0.04	0.26	4.83	1.31	3.52
Other penicillins	p	5.15	0.83	0.16	0.00	4.16	0.17	3.99
Cephalosporins 1/2 gen	o	0.07	0.07	0.00	0.00	0.00	0.00	0.00
Cephalosporins 3/4 gen	p	0.10	0.05	0.00	0.00	0.05	0.00	0.05
Trimethoprim/sulfonamides	o	3.34	0.54	0.35	0.02	2.42	0.10	2.33
Trimethoprim/sulfonamides	p	7.34	0.73	0.13	0.00	6.48	0.04	6.44
Macrolides	o	15.48	0.00	0.03	0.20	15.25	4.88	10.37
Macrolides	p	2.52	0.15	0.04	0.00	2.32	1.10	1.22
Fluoroquinolones	o	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Fluoroquinolones	p	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other quinolones	o	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Others (e.g. pleuromutilins)	o, p	10.46	0.00	0.00	0.01	10.45	5.23	5.22
Combinations	o	0.19	0.00	0.01	0.00	0.18	0.00	0.18
Combinations	p	5.45	0.59	0.27	0.00	4.58	0.24	4.34
Total		115.01	11.55	2.36	0.77	100.34	31.56	68.78

[a] Excluding consumption of 0.124 tonnes active substance in game birds.

[b] Consumption in weaners below 30 kg is included in consumption sows/piglets, not in fattening pigs.

Some indications on species level seem to be accurate, but that is only coincidental. The estimated overall average ($\widehat{\text{NADD}}$) is quite accurate, but can only be interpreted correctly if also the NADDs on species level are available. If for example we exclude the use and the biomass of the calves for veal and young beef production, the overall average for the Netherlands strongly decreases from 13 to 10 ADDs, whereas the average for Denmark remains at the level of 9 ADDs. In this example the overall average for NL is nearly equal to the average for DK, due to the fact that the weight of ‘dairy and other cattle’ in NL is more than twice as high as the weight of these animals in DK, as shown in

Table 6
Accuracy of model estimations; expressed as error percentage of true NADD value per species (ε).

	Estimation A. All animals		Estimation B. Meat animals		Estimation C. Meat animals		Estimation C. Dairy and other cattle	
	NL	DK	NL	DK	NL	DK	NL	DK
Pigs (total)	**−30%**	−34%	68%	−34%	40%	−45%	n.r.	n.r.
Sows/piglets	−31%	−53%	67%	−53%	39%	−61%	n.r.	n.r.
Fattening pigs	**−30%**	**2%**	69%	**2%**	40%	**−15%**	n.r.	n.r.
Poultry	−55%	175%	**8%**	175%	**−10%**	129%	n.r.	n.r.
Veal calves young beef	−80%	52%	−51%	52%	−59%	**27%**	n.r.	n.r.
Dairy and other cattle	202%	258%	n.r.	n.r.	n.r.	n.r.	44%	321%
Average All animals[a]	**7%**	**8%**	156%	**8%**	113%	**−10%**	−49%	**26%**
Average Meat animals[b]	−49%	−32%	**22%**	−32%	**2%**	−43%	n.r.	n.r.

Findings expressed in bold face are considered ‘accurate’, i.e. error percentage below 30%. n.r. means not relevant.

[a] Overall average, based on true NADD values per species, for all species.

[b] Overall average, based on true NADD values per species, for the meat producing species (pigs, poultry, veal calves).

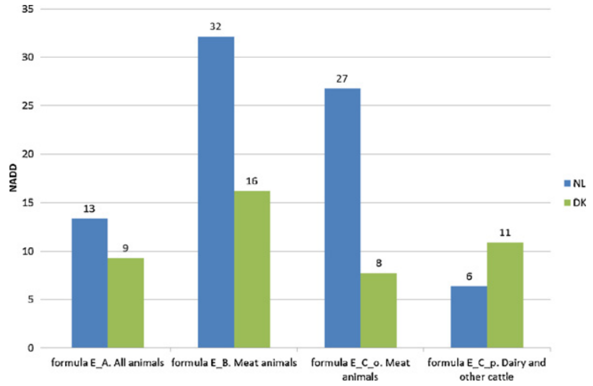

Fig. 1. Model estimations of antibiotic use in 2010, expressed in NADD, based on total sales data and using different formulas. In formula E_A the ADDs were calculated by dividing the total sales by the total live treatment weight of the livestock and an overall average dosage. In formula E_B the total sales were divided by the live treatment weight of only animals for meat production and the average dosage for those animals. In formula $E_{C\text{o}}$ the orally administered sales were divided by the live treatment weight of animals for meat production and the average dosage for that category of animals. In formula $E_{C\text{p}}$ the parenterally administered sales were divided by the live treatment weight of the dairy and other cattle, and the average dosage for that category of animals. Meat animals comprises Category A in Table 3; Dairy and other cattle (except calves for veal and young beef production) is Category B.

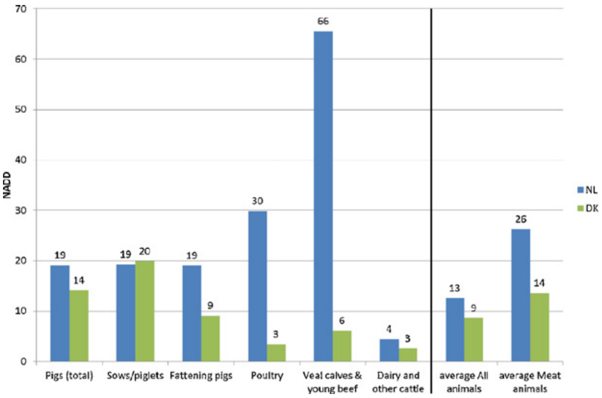

Fig. 2. Antibiotic use in 2010, expressed in NADD, based on collected data per species. Two averages, for respectively all species and only meat producing species, are included in this figure, for comparison with the outcomes of the model estimates in Fig. 1. The average All animals is the weight-weighted average of the true NADD values per species, for all species. The average Meat animals is the weight-weighted average of the true NADD values per species, for the meat producing species (pigs, poultry, veal calves).

Table 3. Thus, the relatively low use and high biomass of dairy and other cattle has much more impact on the overall average for the Netherlands, than the higher use levels in pigs and poultry. In contrast, in Denmark cattle and pigs contribute more equally to the total animal biomass.

In model calculation E_C, the key assumption was that the animals for meat production only get orally administered antimicrobials. From the comparison of the outcomes of calculation E_C, as shown in Fig. 1, and the outcomes in Fig. 2, it can be concluded that calculation E_C leads to a substantial underestimation of the use in pigs, the major category of animals for meat production in Denmark (only 8 ADDs in model calculation $E_{C\text{oral}}$, 14 ADDs based on use data per species), and an overestimation of the use in dairy and other cattle. Apparently, in Denmark the animals for meat production receive more antimicrobials by parenteral administration than in the Netherlands. A dosage for oral use, expressed in mg per kg per day, is usually higher than the dosage for parenteral use. This difference in administration routes applied in Denmark versus the Netherlands also contributes to the overall difference between the countries, when measuring in mg per kg.

4.2. *Method to calculate the level of exposure*

From a theoretical point of view, the best way to quantify exposure to antimicrobial agents in a population is to closely monitor the applied treatment of individual animals, or at least of individual farms, and relate this to the total population at risk. This method requires a very detailed (preferably automated) registration of drug application, or prescription, respectively, on every farm. Some countries already installed such centralized systems for drug monitoring, like Denmark (on prescription level), other countries are in the process of installing it (Norway, the Netherlands and Belgium for instance). Additional advantages of registration on all individual farms are the possibility of benchmarking and interventions by a supervisory body. A cheaper and less ambitious, but also useful option is the monitoring of total sales on national level, combined with a representative sample survey for the collection of use data per animal species, as it was done in the Netherlands since 2004.

The main challenges for the estimation of antimicrobial exposure are defining an accurate way of quantifying the amount of antimicrobial agents used, and defining the size of the population 'at risk' of being treated. From an epidemiological perspective, it would be ideal to compare the amounts used with the 'population at risk', being the live biomass at a given point. This is comparable with the methods used in human medicine: use per 1000 inhabitants-days, assuming that the average size per human is constant. The use in dosages per kg live biomass at risk represents the selection pressure, which is exerted on the live animals during their lifespan. Simple comparisons using total sales data automatically ignore the impact of differences in age (size) and composition of the animal population at risk, and the impact of differences in the average dosage ('potency') of the used antimicrobials. The NADD is a useful proxy for the number of daily doses or treatment days per animal per year. However, the actual exposure might still differ from the calculated levels, because actual treatment weights and applied dosages might be different from the assumptions.

The outcome of model calculation E_A reveals the impact of the difference in average dosage of the used antimicrobials: comparing the sales in mg per kg treatable weight, respectively 213 mg per kg in NL and 101 mg per kg in DK, indicates an extremely high use level in the Netherlands, more than twice the level of Denmark. However, after adjustment for average potency, the remaining overall difference in exposure is approximately 40%: respectively 13 treatment days in NL, 9 in DK (model calculation E_A, average for All animals). The average potency of the used antimicrobials is substantially higher in Denmark, since macrolides and pleuromutilins, which are administered in low doses, are both almost equally used as tetracyclines, whereas in the Netherlands a much higher proportion of the use is tetracyclines. In model calculation E_B (average for Meat animals), the use level in the animals for meat production is overestimated, because of the assumption of zero use in dairy and other cattle.

Still, the method of dividing an amount of active compound consumed in a population by a defined daily dosage (ADDkg) could induce a false estimation of the number of days of treatment realized, because often the real prescribed daily dosage differs from the defined dosage (Chauvin et al., 2002). For that reason, WHO states that drug consumption data presented in DDDs only gives a rough estimate of consumption and not an exact picture of actual consumption (WHO, 2012). For instance, it is impossible to distinct application of high doses during a short period of time from application of low doses during a longer period of time, though the selection pressure derived from those strategies will obviously differ. Pardon et al. (2012) compared authorized doses (ADDs) with applied doses (UDDs) and came to the conclusion that veal calf producers in Belgium tended to closely follow the veterinarian's prescriptions, but also some overdosing and underdosing was found. In the Netherlands, the poultry farms register every day when medication is administered, resulting in a number of treatment days per herd per production round. Combining a method like that with the calculation of ADDs would give the most detailed information.

However, calculation of ADDs enables researchers to assess trends in drug use and to perform comparisons between population groups. The defined daily dosage should be considered as a measure of quantity rather than treatment days, but still is a much better measure of exposure than measures in mg active substance.

4.3. Explanations for differences in use

In the comparison of the two countries, the estimates per animal species showed limited differences in use in pigs and in dairy and other cattle, and very large differences in poultry and veal and young beef cattle (Fig. 2). An analysis of the possible reasons for these substantial differences was no part of our study. The animal production in Denmark might differ from the Netherlands in many ways, e.g. infection pressure (number of animals per km^2), climate, robustness of animals, scale and quality of housing systems (van der Fels-Klerx et al., 2011) and/or feed quality. Furthermore, there might be relevant differences in legislation, regarding both antimicrobials and feed additives, in farming and veterinary practices (Hughes et al., 2012; Chauvin et al., 2002) and also in awareness, skills and knowledge among farmers and veterinarians. The large difference in use in the veal and beef production might relate to the fact that male calves Denmark are mainly used for "young beef" production, whereas the Netherlands mainly produces veal calves. Also, the Netherlands receive calves from many other countries for fattening, thus exposing the young calves to more stressful conditions, including long transports and mixing of calves from many origins. Finally, for an adequate evaluation of the (differences in) use levels information from several sources is needed, for example about disease outbreaks.

4.4. Assumptions applied to estimate antimicrobial use in different categories of animals

The main assumption in model calculation E_A was that the exposure level to antimicrobial agents is evenly distributed to all animals. This results in a very straightforward estimation of the overall average exposure. However, the validity of this estimated exposure is low, because substantial differences in use levels among species are to be expected.

The assumption in model calculation E_B that the use in dairy and other cattle is negligible, may lead to a substantial overestimation of the number of ADDs for the animals for meat production, especially in countries with a relatively large dairy cattle population.

For model calculation E_C, the differentiation between oral and parenteral administration is crucial. It is expected that future sales data in the European ESVAC project will be requested on package level, and therefore the administration route will be known. The accuracy of estimates from this approach depends on the therapeutic practices in the individual country. The remaining challenge will be an accurate assignment of the sales to the different species.

Obviously, the discussed approaches strongly influence the outcomes of the model estimates for the exposure to antimicrobial agents. It should be stressed that the assessed calculations are only three of many possible ways to estimate an exposure level. Furthermore, the differences among species appear to be much more important than the overall difference between the two countries. This means that it is impossible to gain insight into true exposure levels without reliable information about the use per animal species.

4.5. Census data versus production data

In our calculations the sales of antimicrobial agents during a certain year were related to the size of the live animal population in that same year. The application of census data is the clearest and most direct way to determine the size of the population at risk. However, it includes an estimation of the average treatment weight in growing animals (also within age group for census data). Alternatively, the average live weight, estimated from growth curves could be applied. Although often just based on sample surveys, census data represent the size of the population averagely present during a year. It is meaningless to determine the size of the population at risk by adding up the live weight of dairy cows and sows and the weight of slaughtered animals, since slaughterweight severely overestimates the denominator (in biomass-year) for growing animals, particularly when these are slaughtered before one year of age, and more so the younger the animal is at slaughter; additionally, fattening and slaughter might take place in different countries. However, such a theoretical unit for the size of the animal population could still be suitable to show trends in the sales within a country, but certainly not for estimating true exposure or comparing the use among countries.

5. Conclusions

This paper explores the possibilities of making meaningful comparisons of the veterinary use of antimicrobial agents among countries, based on national total sales data and animal census data. It is argued that for adequate country comparisons both the average dosage of the used antimicrobial agents ('potency indicator') and the differences in farm animal demographics have to be taken into account.

Although our analysis seems to confirm the finding of Grave et al. (2010)[7] that the level of antimicrobial use in Denmark is lower than in the Netherlands, it is obvious that a straightforward model calculation based on total sales data and expressed in mg per kg biomass (or PCU), indicating a 110% higher use in the Netherlands compared to Denmark, strongly overestimates the true difference in use. This is in spite of the fact that the farm animal demographics in these two countries seem to be quite similar. The overestimation will be even more severe when comparisons are made between countries with substantial differences in animal demographics, e.g. countries with mostly dairy cattle compared to countries with mostly animals for meat production. Taking the large difference in 'potency indicator' (average dosage) into account, the overall average use in the Netherlands turns out to be approximately 40% higher than the use in Denmark, according to model estimate E_A. An analysis on species level reveals that the differences in use among animal species and production types were much higher than the computed overall average difference between the two countries.

This paper clearly shows that total national sales data are not suitable for country comparisons of selection pressure on species level. All of the assessed model estimates are strongly influenced by animal demographics and veterinary practices, and therefore unsuitable to indicate the true levels of exposure in the different animal species. Every simple country comparison based only on total sales figures entails the risk of serious misinterpretations, especially if expressed in mg per kg. This also applies to the comparison of countries that are generally considered to be similar in animal demographics, like Denmark and the Netherlands. For meaningful and accurate country comparisons of exposure levels, it is vital to have reliable information about the use per animal species.

Reliable insight into the true levels of exposure is an important step towards assessing the risks of emergence and spread of antimicrobial resistance. However, a solid risk assessment requires additional information, for instance about the compliance to authorized dosing regimens and other parameters indicating the level of prudence, concerning the prescription and application of antimicrobial agents in food producing animals ('antibiotic stewardship').

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[7] The outcome of these calculations cannot directly be compared to the results of the study of Grave et al. (2010), because Grave et al. did not adjust for differences in potency of antimicrobial agents and did not express the size of the livestock in the live weight of the animals averagely present during the year, but in an adding up of the produced weight of slaughtered animals and the live weight of dairy cows. Besides, Grave et al. (2010) reported about the year 2007, whereas this paper is about 2010.

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