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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

[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.