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Abstract
In order to be able to compare antimicrobial usage data between countries with a uniform quantification method a Defined Daily Dose Animal (DDDA) per active substance was defined. Information of 731 antimicrobial products licensed for use in porcine medicine in four EU countries was used to establish mean DDDAs for 83 unique active substances (AS) including combinations of different AS. Common DDDAs were defined in spite of large variations in the authorized dosages for the same active substances and administration routes. These DDDAs will be used to quantify and compare antimicrobial usage in pig production in four EU countries.

Introduction
High antimicrobial usage in food producing animals is of major concern. To compare usage data between countries, a uniform quantification method is needed. This requires the definition of a Defined Daily Dose Animal (DDDA) for each active substance (AS) to be able to compare the number of animals treated based on the amount of antimicrobials used. Such DDDAs have not been defined in most countries. Therefore, we attempted to assign DDDAs for antimicrobials used in pig production in four EU countries.

Material and Methods
Based on the Summary of Product Characteristics (SPC), DDDAs (Dewulf.J. et al., 2012) were calculated for antimicrobial products licensed in Sweden (n=51), Germany (n=281), France (n=240) and Belgium (n=159). Products were categorized based on their AS(s), long acting characteristics and administration route. Dosages for the main indication were used to calculate the mean, modus and median doses for each AS including combinations of AS. When a dose range was indicated for an AS without stating a main indication, the minimum and maximum doses were used to calculate the mean dose for the particular AS. Dosages for combination products were calculated after adding all included ASs for each product. The mean dose obtained for each AS including combination products for the four countries was then determined to be the consensus DDDA. Long acting (LA) products received a LA factor depending on the duration of the activity to determine the number of DDDAs resulting from one treatment. Whether the product was categorized as critically important by the World Health Organization (WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR), 2011) or World Organisation for Animal Health (75th International Committee, 2007) was registered as additional information.

Results
A total of 83 unique (including combinations of) AS were categorized. The most common administration routes were feed/water (n=360) and parenteral (n=327). Colistin (n=53) and amoxicillin (n=49) were the most commonly licensed antimicrobials. However, enrofloxacin (n=44) and ceftiofur (n=33), WHO and OIE critically important antimicrobials, were also well represented.

Large differences between SPC dosages were observed for the same AS and the same administration route. Differences were more prominent for older products in comparison to more recently authorized products. Large differences were seen in feed/water tetracycline (n=6, min=20 mg/kg, max=85 mg/kg), chlortetracycline (n=15, min=15 mg/kg, max=85 mg/kg) and oxytetracycline (n=19, min=20 mg/kg, max=100 mg/kg). There were also remarkable differences between countries.
(i.e. spectinomycin oral drench, Belgium (n=1), authorized dose = 40 mg/kg, Germany (n=1), authorized dose = 150 mg/kg). Even within the same country the differences for some AS were huge (i.e. sulphaguanidin + sulphadimidin France, n=2, min=38.40 mg/kg, max=160 mg/kg and tylosin Belgium, n=7, min=4.5 mg/kg, max= 45 mg/kg). More recently registered products like enrofloxacin show minor deviations in authorized doses between countries (n= 38, min=2.5 mg/kg, max=3.8 mg/kg). European Union harmonized products like cefitiofur have, as harmonization suggests, the same authorized dose in all four countries. Parenteral dosages were generally lower compared to those for oral preparations.

Discussion
This report is the first attempt to define general DDDAs as far as the authors are aware. The listing and comparison of available products and their SPCs revealed remarkably huge variations in authorized doses of the same compound between countries and even between commercial products within countries making the selection of one defined daily dose difficult. Therefore criteria as described above were determined to allow an objective selection of the DDDAs. Since a large number of products from several countries were included, we consider the determined DDDAs as representative; however including more products from other countries will likely further influence the mean DDDAs. Also the numbers and kinds of marketed products changes over time which may further influence the mean DDDAs. To enhance comparability between countries it would be hugely beneficial if one, preferably global, list of DDDAs would be determined. Our effort may be a first step towards such a harmonization.

Conclusion
Comparison of antimicrobials licensed for pigs in four EU countries showed large variations in number and types of products registered as well as differences in dosages. Despite the large variations, a methodology was developed to define common DDDAs for used AS. These DDDAs will be used to quantify and compare antimicrobial usage in pig production in four EU countries.

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References
75th International Committee, 2007. OIE List of Antimicrobials of Veterinary Importance.
