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Assigning defined daily doses animal: a European multi-country experience for antimicrobial products authorized for usage in pigs

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Objectives: To establish a consensus defined daily dose animal (DDDA) for each active substance (AS) and administration route for porcine veterinary antimicrobial products authorized in four European countries, thus allowing cross-country quantification and comparison of antimicrobial usage data.

Methods: All veterinary antimicrobial products authorized for porcine use in Belgium, France, Germany and Sweden were listed for each administration route. First, separate DDDAs for each product were defined based on the recommended dosing for the main indication. Second, a consensus DDDA was established by taking the mean of the DDDAs for each product within a certain category of AS plus administration route.

Results: One-hundred-and-fifty-nine, 240, 281 and 50 antimicrobial products were licensed in Belgium, France, Germany and Sweden, respectively, in February 2013. Large variations were observed for dosage and treatment duration recommendations between products and between countries for the same ASs. Only 6.8% of feed/water and 29.4% of parenteral AS groups had the same recommended dosage in the four countries.

Conclusions: This study presents a consensus DDDA list for use in the quantification and comparison of antimicrobial consumption. Four major recommendations have been formulated: (i) urgent need for harmonization of authorization and recommended summary of product characteristics (SPC) dosages; (ii) expand the developed preliminary DDDA list to include all authorized veterinary medicinal products in all EU member states and for all (food-producing) animal species; (iii) improved accessibility of country-specific SPC data would be preferable; and (iv) statement of the 'long-acting' duration of a product in the SPC.

Keywords: antimicrobial usage quantification, cross-country comparison, defined course dose animal, defined daily dose animal, porcine antimicrobial products

Introduction

Antimicrobial usage in food-producing animals is high on the European scientific and political agendas.[1] Of major concern is the development and selection of antimicrobial resistance in bacteria, impeding the adequate treatment of bacterial infections in animals and humans. A recent paper described a strong correlation between the level of animal antimicrobial usage and the level of resistance in commensal *Escherichia coli* at the national level.[2] A meta-analysis in human medicine has also described an association between antibiotic consumption and the development of antibiotic resistance.[3] The WHO refers to antimicrobial resistance as a global concern and emphasizes the importance of reliable data collection and monitoring systems.[4] When establishing these monitoring systems, harmonization of both antimicrobial consumption quantification and resistance determination is crucial for enabling objective comparisons and risk assessments within and between countries.

Gaining insight into the amount of antimicrobials used in livestock production requires an accepted method for objective comparison across animal species within and between countries in a way that represents the antimicrobial resistance selection pressure that is exerted in the best possible way. Given the huge differences in molecular weight among antimicrobial compounds, the use of a weight parameter such as the milligram or kilogram is not advisable. The European Surveillance of Veterinary Antimicrobial

Consumption (ESVAC) consortium of the EMA has recently proposed the use of the defined daily dose animal (DDDA) as a quantification unit of antimicrobial consumption.[5] This measure is derived from the established method of the defined daily dose (DDD)[6] used in human medicine since 1991. In human medicine the DDD is defined by the WHO as 'the assumed average maintenance dose per day for a drug used for its main indication in adults'.[6]

In veterinary medicine, the ESVAC consortium has defined the DDDA as 'the assumed average maintenance dose per day per kg body weight for the main indication in a specified species'.[7] The defined course dose animal (DCDA) is defined as 'the assumed average maintenance dose per day per kg body weight for the main indication in a specified species (DDDA) multiplied by the assumed duration of treatment'.[7]

In its 2012 reflection paper,[5] ESVAC requests the development of a standardized DDDA list among EU member states. To the best of our knowledge this list has not been developed yet. Quantification and cross-country analysis of antimicrobial usage in pig production in several EU countries is one of the aims of the MINAPIG consortium (www.minapig.eu). Assigning DDDAs for antimicrobials used in pig production was therefore a necessary first step. Use of the DCDA is another method for describing antimicrobial usage, which incorporates treatment duration. Establishment of the DCDA was therefore considered a useful addition to the established DDDA. ESVAC also mentions the use of the DCDA in its reflection paper.[5]

The aim of this article is to describe the procedures used to assign standardized DDDAs for four EU countries and to highlight the differences found within and between countries in dosage recommendations for the same active compounds and administration route combinations. The consensus DDDA is not to be seen as a gold standard or as a tool to assess prudent antimicrobial usage, but rather as a reference point for quantification of antimicrobial usage in a standardized manner across different countries.

Materials and methods

Data collection

Antimicrobial products authorized for use in pig production in February 2013 were listed for Belgium, Germany, France and Sweden. These data were obtained from the national regulatory institutions involved in the authorization and registration of veterinary medicinal products. In Belgium this is Het Belgische Centrum voor Farmacotherapeutische Informatie (BCFI vet),[8] for France it is the Index des Médicaments vétérinaires autorisés en France (IRCP)[9] and for Sweden it is either Fakta för förskrivare (FASS)[10] or Läkemedelsverket.[11] For Germany the university service Veterinärmedizinischer Informationsdienst für Arzneimittelanwendung, Toxikologie und Arzneimittelrecht (Vetidata)[12] was used. For each authorized product, detailed information on the active substances (ASs) in the product, the concentration, the administration route, long-acting (LA) activity (i.e. the duration of activity of an AS after administration of a dose) and whether the AS is categorized as critically important by the WHO[13] or World Organisation for Animal Health (OIE)[14] were recorded. A total of six administration routes were differentiated: feed/water, oral non-feed/water (i.e. drench, tablet), parenteral, topical, topical eye ointment and intrauterine.

In this paper antimicrobials are defined as products with an antimicrobial mechanism of action falling within WHO ATCvet first level codes[15] QD, QG, QJ and QS.[10] Zinc oxide was considered separately, since this is considered to be an alternative to antimicrobials in pig production in some EU countries. During the data collection zinc oxide was only authorized in Sweden. In Germany zinc oxide was only available in combination with colistin and in Belgium zinc oxide was only allowed as a single in-feed additive from September 2013 onwards.

Method of DDDA determination for individual products

A DDDA was assigned for each individual antimicrobial product authorized, based on the dosage for the main indication provided in the country-specific summary of product characteristics (SPC). In guidelines, prudent antimicrobial use is described as using the products in accordance with the SPC.[16–18] The recommended dosage is therefore the dosage recommended by the licence holder and might not be the proposed dosage based on the scientific literature. The DDDA was listed in mg/kg body weight (mg/kg) and per day. Doses of products with an AS expressed in IU in their SPC were recalculated to mg/kg using the conversion rates published in the second ESVAC report.[19]

When a clear main indication was stated in the SPC, this dosage was used to assign the product DDDA. The specified main indications used are listed in Table 1. In a few cases the main indication in the SPC varied between countries. In these cases the main indication was agreed upon by consensus, mainly after consulting pharmaceutical laboratories. When a dosage range was given in the SPC, the mean of the minimal and maximal dosages was selected. If no indication was listed and a range was provided, the mean value was also used.

If the SPC stated a double or even triple daily treatment with the same dosage in severe cases, it was, by consensus, agreed upon that the DDDA would consist of the mean of the normal daily dose and the double dose.

Treatment duration was also listed for each product. By the same procedure as for the DDDA assignment, the main indication was used to set the treatment duration. If the SPC provided a range or there was a discrepancy in main indication, the mean of the minimal and maximal recommended treatment durations was taken.

DDDAs for combination products were determined as the sum of the DDDAs for the separate ASs. Zinc oxide was also included if it was combined with an antimicrobial AS. Using the same procedure as that used for products with a single AS, the mean was calculated if there was a range, and when a clear main indication was stated this value was used.

LA products received an LA factor (i.e. value that represents the duration of activity of an LA product) depending on the estimated duration of antimicrobial activity to determine the number of DDDAs resulting from one treatment. These LA factors were assigned based on available research information in the European Public Assessment Reports (EPAR)

Table 1. Main indications from SPCs for ASs with several dosage recommendations for different indications; the recommended dosage for the main indication was chosen for further analysis

AS	Administration route	Main indication
Lincomycin	feed/water	enzootic pneumonia
Lincomycin + spectinomycin	feed/water	dysentery
Tiamulin	feed/water	dysentery
Tiamulin	parenteral	dysentery
Tylosin	feed/water	porcine proliferative enteropathy
Tylvalosin	feed/water	dysentery
Valnemulin	feed/water	dysentery

of the EMA or the treatment interval described in the SPC. When a clear, single duration of action for an LA product was not provided from this information, but an indication of the duration range was provided, the authors assigned the LA factor in consensus based on scientific literature data.

For topical spray or eye products it was assumed that ~3 mL of product would be used per treatment. This was based on the assumption that 1 mL will be sprayed per second and the fact that 3 s of spraying is the average duration mentioned in the SPCs for topical spray products.[20–31] For two out of three intrauterine products no information on the weight of a tablet could be traced. Therefore, these DDDAs were assigned assuming administration of one tablet as treatment for an average sow of 220 kg body weight, similar to the weights advised by ESVAC.[5]

The critical importance of a product was also listed, following the guidelines of the WHO[13] and OIE[14] for human and veterinary usage, respectively.

Assigning DDDAs across countries

The chapter 'Assignment of DDDAs and DCDA values' of the ESVAC reflection paper on collecting data on consumption of antimicrobial agents for each animal species[5] was used as a guideline to assign DDDAs over the four countries.

An individual product was first categorized based on its AS(s) and subsequently on its administration route. Products were also categorized based on whether or not they were LA products. No differentiation in DDDA was made for different age categories. Recommended dosages are normally not differentiated for different age categories. In the rare cases in which the SPC mentioned different dosages for piglets and adult animals we chose to use the recommended dosage for adult animals. This is in accordance with the procedure used in human medicine, where the DDD is assigned based on use of a medicinal product by an average adult person.[6]

The mean, median and mode were calculated for all products within each AS plus administration route category. The mean was considered to be the consensus DDDA. The same procedure was used to establish the LA factors and treatment duration. Important differences in recommended dosage and treatment duration for the individual products compared with the consensus DDDAs and DCDAs were identified.

Data analysis

Data were managed using Microsoft Excel 2010 and further analysed using IBM SPSS Statistics version 22. For each product, the difference between its DDDA and the assigned mean consensus DDDA was calculated. Differences of >10% from the consensus DDDA in AS plus administration route categories with at least two products in two different countries were analysed with a univariate general linear model to check for the effects of number of years since first authorization and country. Comparison between countries regarding the deviation from the consensus DDDA and treatment duration for each administration route was done by using a non-parametric independent samples Kruskal–Wallis test with pairwise comparison.

Results

DDDAs

There were 159, 240, 281 and 50 antimicrobial products licensed in Belgium, France, Germany and Sweden, respectively, adding up to a total of 730 products (Table 2). The oldest product was first authorized in 1955, the newest in 2013. A total of 116 unique categories based on AS, administration route and LA factor were identified, for which a DDDA and DCDA were assigned. There were 82 groups of different antimicrobial ASs or combinations of ASs combined with a similar administration route. Of these 82 AS plus administration route categories, 44 (360 products) were authorized for use in feed or water, 51 for parenteral administration (326 products), 3 (7 products) for intrauterine use, 11 (21 products) for oral non-feed/water use, 6 (15 products) for topical use and 1 (1 product) for use as eye ointment. Fifty-seven of the ASs were authorized for one administration route, 18 for two, 5 for three and 2 for four administration routes.

The ASs with the most authorized products were colistin ($n=53$ products), amoxicillin ($n=49$) and enrofloxacin ($n=44$). The number of authorized products does not necessarily equal the usage of these products.

The list of consensus DDDAs and consensus DCDAs is provided in Table S1 (available as Supplementary data at *JAC* Online).

For 11 of the 17 ASs with authorization for parenteral administration as well as feed/water administration, the mean dosages for parentally administered products were lower in comparison with products administered by feed or water having the same AS (Table 3).

Table 2 shows that 597 of 730 products (81.8%) are refereed by the OIE as critically important for veterinary usage, and 442 products (60.5%) by the WHO as critically important for human usage.

Deviation from consensus DDDA

The percentage of products deviating >10% from the mean consensus DDDA are listed per category based on AS and

Table 2. Number of antimicrobial products licensed for pigs for each country and administration route, including the number of products listed as critically important by WHO[13] or OIE[14] for human or veterinary medicine, respectively

Administration route	Belgium	France	Germany	Sweden	Total	Critically important veterinary[14]	Critically important human[13]
Feed/water	72	138	133	17	360	272	189
Parenteral	81	93	129	23	326	287	223
Oral non-feed/water	3	3	9	6	21	15	8
Topical	3	6	4	2	16	16	15
Intrauterine	0	0	6	1	7	7	7
Eye ointment	0	0	0	1	1	0	0
Total	159	240	281	50	730	597	442

Table 3. Differences in feed/water dosage prescription compared with parenteral dosage prescription

AS	Mean DDDA feed/water (*n*)	Mean DDDA parenteral	Difference	Percentage difference[a]
Amoxicillin	20.4 (34)	11.7 (13)	8.7	+42.7
Ampicillin	32.0 (7)	17.0 (3)	15.0	+46.9
Colistin	5.0 (41)	2.6 (8)	2.4	+47.7
Enrofloxacin	1.7 (1)	2.8 (38)	−1.1	−62.5
Lincomycin	6.7 (7)	10.5 (11)	−3.7	−55.1
Lincomycin + spectinomycin	6.2 (13)	15.0 (6)	−8.8	−140.7
Oxytetracycline	35.7 (19)	8.4 (8)	27.2	+76.3
Paromomycin	32.5 (1)	19.3 (1)	13.3	+40.8
Spiramycin	21.9 (2)	20.5 (3)	1.4	+6.3
Sulfadimethoxine	48.4 (2)	30.0 (1)	18.4	+38.0
Sulfadimidine	77.1 (12)	86.3 (3)	−9.2	−11.9
Tiamulin	7.8 (29)	9.3 (7)	−1.5	−18.7
Trimethoprim + sulfadiazine	29.8 (22)	18.1 (4)	11.7	+39.4
Trimethoprim + sulfadimethoxine	26.1 (7)	22.6 (1)	3.5	+13.5
Trimethoprim + sulfamethoxazole	25.0 (2)	30.0 (2)	−5.0	−20.0
Trimethoprim + sulfamethoxypyridazine	28.2 (1)	16.0 (1)	12.2	+43.3
Tylosin	14.9 (33)	10.4 (9)	4.5	+30.2

[a]A positive percentage difference means that the feed/water administration category of this AS had a higher mean recommended dosage; a negative difference means that the parenteral recommended dosage was higher.

administration route in Table S1. The number of products within a category showing deviation varied from only one (4.9%) to all of the products (100%). Thirty-one out of 82 unique combinations showed deviations >10% from the consensus DDDA. The top 20 deviating products are listed in Table 4. This list includes mainly products containing tylosin, amoxicillin and doxycycline. Fifteen of these top 20 deviating products were authorized in Germany.

Feed/water

Of the 44 AS categories authorized for feed/water administration, 3 (6.8%) did not deviate from the mean consensus DDDA because they had the same SPC dosage recommendation in the countries. These three harmonized feed/water categories were florfenicol (Belgium, France, Germany), trimethoprim/sulfamethoxazole (Belgium, Germany) and valnemulin (Belgium, Germany, Sweden). For florfenicol there were two authorized commercial products marketed by two different pharmaceutical companies. For trimethoprim/sulfamethoxazole there was one product authorized in two countries, first authorized in 2012. Valnemulin was represented by one product in three countries and was first authorized in 1999.

One of the feed/water AS categories with large variations between products in recommended dosage was tylosin, with a 10-fold difference between the minimum and maximum recommended dosage. The product with the minimum dosage and the product with the maximum dosage were both authorized in Belgium. Tylosin feed/water products were authorized between 1975 and 2012. The authorization date did not explain the deviation from the consensus DDDA ($n=33$, $P=0.32$), and neither did country ($P=0.36$). One Belgian tylosin product has a main indication of dysentery and a recommended dose of 45 mg/kg, while the SPC of the other Belgian product mentions dysentery and porcine proliferative enteropathy (PHE), with the same recommended dose of 4.5 mg/kg for both indications. This shows that for the same indication (here dysentery) the recommended dose varies between 4.5 and 45 mg/kg.

The combination of lincomycin with spectinomycin was also well represented and was a clear example of large variation in DDDA (minimum dosage 3.3 mg/kg, maximum dosage 10.0 mg/kg). The authorization dates varied between 1975 and 1998 and could not explain the deviation ($n=13$, $P=0.81$), and the country was not decisive either ($P=0.33$).

For some of the other feed/water products with a deviation of >10% from the consensus DDDA, country explained the difference: amoxicillin ($P=0.02$, Germany > France), chlortetracycline ($P<0.01$, Germany > Belgium and Sweden), colistin ($P<0.01$, Sweden > Belgium, Germany and France), neomycin ($P<0.01$, France > Germany), sulfadimidine ($P=0.02$, Germany > France), tiamulin ($P<0.01$, Germany > Belgium, Sweden and France) and trimethoprim/sulfadimethoxine ($P<0.01$, France > Germany). The year of first authorization was only statistically explanatory for feed/water sulfadimidine ($P=0.04$).

Table S1 shows the complete list of AS plus administration route categories including differences >10% from the consensus DDDA.

Parenteral

Of the 51 licensed AS plus administration route categories for parenteral administration, 29 did not deviate from the mean consensus DDDA. For 14, this was because there was only one product registered for this specific category whereas 15 categories contained several products authorized in one or more countries. Looking only at those categories containing multiple products, we found 29.4% of parenteral products that had harmonized registration over Belgium, France, Germany and Sweden.

Parenteral AS plus administration route categories with large recommended dosage variations, such as amoxicillin ($n=13$,

Table 4. Top 20 products deviating from the consensus DDDA

No.	AS	Administration route	Country	Product name	Deviation from consensus DDDA (%)[a]
1	tylosin	feed/water	Belgium	Tylosine 75% Kela	+202.4
2	oxytetracycline	feed/water	Germany	Ursocyclin-Pulver 20%	+180.4
3	lincomycin	feed/water	Germany	Lincomycinhydrochlorid Pulver 50%	+122.6
4	tylosin	feed/water	Germany	Klato lan, 1000 mg/g	+101.6
5	tylosin	feed/water	Germany	Tylogran WSP 1000 mg/g	+101.6
6	tylosin	feed/water	Germany	Tylosintartrat 100%	+101.6
7	tylosin	feed/water	Germany	Tylo-Suscit 100% Kompaktat	+101.6
8	tylosin	feed/water	Germany	Tylo-Suscit 25	+101.6
9	amoxicillin	feed/water	Germany	Aciphen Kompaktat 1000 mg/g	+96.0
10	amoxicillin	feed/water	Germany	Amoxicillin-Trihydrat 100, 100%	+96.0
11	amoxicillin	feed/water	Germany	Amoxin 100 mg/g	+96.0
12	amoxicillin	feed/water	Belgium	Moxapulvis 50%	+96.0
13	amoxicillin	feed/water	Germany	Triamox 100 W 114,8 mg/g	+96.0
14	tylosin	parenteral	Sweden	Tylan vet.	+92.5
15	tiamulin	feed/water	France	Tiamuval Tiamuline 6,5 Entérite Porc	−79.5
16	doxycycline	feed/water	Germany	Doxy 50% (500 mg/g)	+73.3
17	doxycycline	feed/water	Germany	Pulmodox 500 mg/g	+73.3
18	doxycycline	feed/water	France	Pulmodox 500 mg/g	+73.3
19	amoxicillin	parenteral	Germany	Amoxicillin 15% WDT, 150 mg/mL	+71.1
20	amoxicillin	parenteral	Germany	Belamox 200 mg/mL	+71.1

[a]A plus sign before the percentage deviation from the consensus DDDA means that this product had a higher recommended dosage compared with the mean consensus DDDA; a minus sign means that the recommended dosage was lower.

minimum 7 mg/kg, maximum 20 mg/kg) and ampicillin ($n=3$, minimum 10 mg/kg, maximum 21 mg/kg), were authorized between 1981 and 2005 and between 1983 and 1993, respectively. For amoxicillin neither the number of years since first authorization ($P=0.29$) nor country ($P=0.75$) explained the deviation from the consensus DDDA. On the other hand, the LA products of amoxicillin also had a long authorization period and no deviation occurred. Also for ampicillin, neither the first year of authorization ($P=0.39$) nor the country ($P=0.61$) was able to explain the deviation.

For parenteral sulfadimidine, country significantly influenced dosage ($P=0.03$, France > Germany).

Year of first authorization ($P=0.04$) as well as the country ($P=0.01$) were explanatory for differences in colistin ($P=0.04$). Parenteral colistin products were authorized in Belgium from 1978, while the first year of authorization for the French products ranged from 1987 to 1998 and for Germany from 2001 onwards. The mean recommended dosage was higher in Germany compared with Belgium and France.

LA ceftiofur is an AS that was first authorized in 2005 and has been granted a central marketing authorization by the European Commission,[32] and thus there was no variation between countries. The other products with central marketing authorization were of the ASs tylvalosin, tulathromycin, valnemulin and tildipirosin. In the four countries the same product was authorized for these specific ASs.

A general trend for the deviation from the consensus DDDA of feed/water ($P=0.55$) or parenteral ($P=0.78$) products versus their first year of authorization could not be found.

Intrauterine, oral non-feed/water, topical

For the 22 AS plus administration route categories authorized for intrauterine, oral non-feed/water or topical administration or as eye ointment there was no harmonization of the products. Country or year of first authorization did not explain the >10% deviation present.

Influence of countries on difference in dosage

There were marked differences between countries regarding recommended dosages [e.g. spectinomycin, oral non-feed/water, recommended dose 40 mg/kg in Belgium ($n=1$) and 150 mg/kg in Germany ($n=1$)]. Even within the same country, the differences for some ASs were huge (e.g. sulfaguanidine/sulfadimidine in France, $n=2$, minimum 38.4 mg/kg, maximum 160 mg/kg; tylosin in Belgium, $n=7$, minimum 4.5 mg/kg, maximum 45 mg/kg). Some of these AS plus administration route categories were unique to some countries (e.g. sulfaguanidine/sulfadimidine for France).

Comparison between countries showed that the mean recommended dose for feed/water administration compared with the consensus DDDA was significantly lower in Germany than in France ($P=0.03$). For topical products, Sweden had high recommended doses (mean deviation +36%) compared with the relatively low recommended doses for Germany (mean deviation −19%), although the difference was not significant. The same applied, to a lesser extent, to parenterally administered products (mean deviation: Germany −3%, Sweden +12%, difference not

Table 5. Percentage of consensus DDDA or mean treatment duration by country

Comparison/administration route	Proportion of consensus dosage/duration (%)[a]	SD	*n*	Significant difference from	*P* value[b]
DDDA/feed or water					
Belgium	95.4	37.7	72		
France	95.2	32.0	138	Germany	0.04
Germany	108.7	41.3	133		
Sweden	89.9	27.7	17		
DDDA/parenteral					
Belgium	100.4	13.4	81		
France	97.0	8.7	93	Sweden	<0.01
Germany	99.5	17.1	129	Sweden	0.02
Sweden	111.9	23.5	23		
Treatment duration/oral non-feed or -water					
Belgium	77.8	4.8	3	Germany	<0.01
France	86.7	23.1	3		
Germany	107.2	10.9	9		
Sweden	95.8	6.5	6		

[a]The consensus DDDA and the mean treatment duration are set to 100%.
[b]Kruskal–Wallis test with pairwise comparison.

significant). For feed/water products a non-significant mean deviation of +9% for Germany and −10% for Sweden was seen. A significantly higher recommended dose was observed for parentally administered products in Sweden compared with France ($P=0.02$) and Germany ($P=0.03$). Table 5 shows the deviations from the consensus DDDA and the recommended mean duration over countries.

Duration of treatment

Analysing deviations from the mean for treatment durations showed the largest variation for feed/water-administered products (mean 7.5 days, minimum 3 days, maximum 42 days).

Products in the oral non-feed/water administration category in Germany had a significantly longer treatment duration than in Belgium ($P<0.01$). For parenteral products, the variation in treatment duration (from 1 to 7 days) was not significantly different between countries.

Discussion

Data collection, establishment of DDDAs

Although highly recommended and requested by ESVAC in their latest reports, to date no other attempt has been described to establish DDDAs across countries, as far as the authors are aware. Even in human medicine only limited publications are available on discrepancies in the DDDs used in human medicine.[33,34] The current paper documents the results of the exercise for four EU countries. It may serve as a starting point for an EU-wide DDDA list. However, the authors would like to state clearly that the provided list of DDDAs is based on generalizations and simplifications and therefore does not necessarily reflect the true use in a herd or a country but rather provides a tool to allow comparison between herds or countries. As regards dosing, we argue that it is difficult to discuss the concepts of under- and overdosing objectively given the observed huge variety in recommended dosages. The DDDA was not specifically developed to describe under- or overdosing in the different countries but rather to quantify the amount of exposure of animals to antimicrobials.

Lists of antimicrobial products authorized within countries are subject to regular changes as products are updated for their recommended dosages, no longer marketed or new products are authorized. Products authorized in February 2013 were taken into account in this paper. Newer products or recent changes might not be accounted for. However, since the number of products was substantial in most AS categories, the mean consensus DDDA is not expected to be much influenced by possible recent changes.

The mean for all authorized products with the same AS and administration route was considered to be the most transparent method of establishing consensus DDDAs. No important difference in the number of products deviating >10% from the median or mode was seen compared with using the mean. Using the mean implies that there is an impact of the number of products within an AS category authorized per country. Countries with a large number of authorized products have a higher impact on the consensus DDDA. Mean, median and mode are listed in Table S1.

The main indications were selected based on available scientific information in the EPAR reports of the EMA and SPC and were set by consensus between the authors. However, for some of the products authorized in France the chosen main indication was not clearly stated in the SPC. This might partially explain the larger deviation from the mean DDDA for French products. No obvious explanation could be found for the fact that 75% of the top 20 deviating products were authorized in Germany. However, one reason might be that Germany has more authorized products, providing more scope for larger deviations.

Unique combinations licensed for administration via water or feed were analysed together, since there are many products that have licenses for both administration routes or are administered by both routes under field circumstances. However, there are also products for which the dosage differences between the feed and water SPCs are huge. Splitting feed and water administration routes would have enabled a more specific analysis of the recommended dosage and treatment duration.

LA factors were in some cases established by consensus, e.g. for LA tulathromycin and ceftiofur. Because consensus was reached using the scientific literature, this was considered the most appropriate approach. However, the EPAR reports on which the consensus was based might not provide the most accurate information, since, e.g. duration of activity might differ among individual animals, disease indications, pharmacodynamics or environmental conditions, but this uncertainty could not be taken into account. For LA products it would be advisable that the SPCs provide more detailed information on the expected duration of effect after administration of a dose.

Assumptions and simplifications

It was agreed to establish the mean consensus DDDA based on the recommended dosage for usage of the product in an adult animal for the main indication. This is in concordance with the definition of the DDD, used in human medicine.[15] Since there were products for which the recommended dosage differed among several indications, the choice of using the main indication could have influenced our results. However, for reasons of simplification and to avoid creation of an exhaustive list it was decided to use the recommended dosage for an adult animal and not to consider the other indications or the dosage recommendations for young animals.

The extent to which authorized products are actually marketed and used, and used in concordance with the recommendations of the SPC, could not be checked in a scientific way and is highly influenced by the individual therapy prescription provided by the veterinarian. Callens *et al*.[35] reported recently that correctness of dosing for antimicrobial products based on the recommendations of the SPC is being circumvented in Belgium. The only certainty is the authorization license of the product. This was therefore the basis of this research.

In this study the number of authorized products was much higher in Germany compared with Sweden. A consequence of using the methodology described here is that a country with a larger number of products will theoretically have a greater influence on the mean consensus DDDA. This is inevitable in the methodology used here, by which we tried to find a consensus DDDA that would fit best the available data.

Some of the necessary assumptions could have been circumvented if more detailed information on these matters had been provided in the SPCs. For example, knowledge of the amount of product that is applied by using a topical spray can for 1 s would help in the estimation of the total amount of AS used per treatment. It is recommended that this information is provided in future registration dossiers.

Differences in molecular formulation between products might have influenced variation in the recommended dosage in the SPC. To avoid the creation of an almost infinite list with enormous complexity it was decided to compromise on this matter by presuming the recommended dosage at AS level was the best feasible information.

Number of products and variation

For some products, large deviations with respect to the mean consensus DDDA were observed among ASs and administration routes and between or within countries. This might influence the outcomes of future antimicrobial usage calculations in the individual countries compared with national data using national DDDAs. However, using one harmonized DDDA list is the only feasible way to make a correct cross-country comparison.

That only 6.8% of feed/water and 29.4% of parenteral administration routes were harmonized between EU member states indicates the urgent need for EU-wide harmonization. It also strongly questions the concept of under- or overdosing for many products since using a half dose (severe underdosing) of a specific product from a specific company in one country may constitute overdosing with the same active compound according to the registration of another company. Comparison of antimicrobial consumption data should be conducted transparently and under the same restrictions in all countries. A uniform DDDA could be one of the requirements for this. As long as the country-specific DDDAs differ largely from the consensus DDDA, however, we should take this into account in analysing comparisons of antimicrobial usage data over countries.

The hypothesis was that country and number of years since first authorization might influence a product's recommended dosage: country might have an effect due to differences in legislation and testing requirements, and number of years since first authorization date might have an effect due to new insights or techniques.

The number of years since first authorization explains only some of the variation in recommended dosages between groups of ASs and administration routes. The country where the product is authorized/marketed also explains some of the deviations from the consensus DDDA. Yet most of the deviations of >10% could not be explained by year of first authorization or country. Differences in recommended dosage might be influenced by differences in authorization procedures from year to year and differences among countries or pharmaceutical companies, although all have to comply with the rules set by the EU commission, and hence the EMA.[32] The authors could not find a direct, plausible reason for the large differences in recommended dosages for more recently authorized products. Differences in bioavailability of the products might be among the reasons for differences in the recommended doses. However, in our attempt to develop a harmonized DDDA list this is the type of complexity that could not be taken into account to prevent the creation of an unworkably long list. Country-specific authorization procedures and different solvents, experimental circumstances or inoculation methods might explain this variation; however, retrospective validation is not possible.

The lack of distinction between feed- and water-administered products might explain the differences in treatment duration for these products as well as some of the deviation from the consensus DDDA. In general, products administered through feed have a longer recommended treatment duration compared with

the same ASs administered via water. In future DDDA-establishing exercises, consideration should be given to recording the feed administration route separately from the water route.

Critically important ASs

It was noticed that the majority of products available in porcine medicine are in the list of critically important antimicrobials for either or both WHO and OIE. Their usage in veterinary practice should be greatly reduced in the near future, according to current discussions among risk managers and policy makers.[36]

Application of the DDDA list

The DDDA list described in this article may serve as a starting point for discussion about the establishment of DDDAs in EU countries. The DDDAs can be used to make a comparable antimicrobial usage calculation between countries. The description of the approach and the path towards the establishment of the DDDA list should help future researchers in their attempt to broaden the list by adding more products from other EU countries or animal species.

Conclusions

Comparison of authorized antimicrobials for porcine veterinary usage in four EU member states showed large variation in the number and types of products as well as differences in recommended dosages. Although the process was challenging, a mean consensus DDDA was established for the first time for ASs licensed in several EU countries. It enables future comparison of antimicrobial usage data. Country and number of years since first authorization are explanatory for only a small number of ASs plus administration route categories that deviate largely from the mean consensus DDDA or the recommended treatment duration. Harmonization of authorization and SPC would strongly improve the comparability of antimicrobial usage data within and between countries.

We therefore make the following recommendations:

(i) **Harmonization**. The findings described in this paper could be perceived as indicating a lack of knowledge on optimal treatment dosage and duration. The porcine sector, as well as other sectors, would benefit from increased European or even international harmonization for veterinary medicinal product authorization, for both new and existing authorizations.

(ii) **Involvement of all member states**. Establishment of DDDAs should be performed for all EU member states, based on information from the national authorities.

(iii) **Accessibility of data**. Access (via the World Wide Web) to country-specific databases of authorized products is limited due to difficulties in traceability of data sources and language barriers. An EU-wide centralized database would ease this process.

(iv) **LA factor**. The duration of action of an LA product should be established by the manufacturer of the product using a procedure similar to that used for the recommended dosage and given in the SPC.

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Transparency declarations

None to declare.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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