Variations in the sales and sales patterns of veterinary antimicrobial agents in 25 European countries

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Objectives: To describe sales and sales patterns of veterinary antimicrobial agents in 25 European Union (EU)/European Economic Area (EEA) countries for 2011.

Methods: Data on the sales of veterinary antimicrobial agents from 25 EU member states and EEA countries for 2011 were collected at package level (name, formulation, strength, pack size, number of packages sold) according to a standardized protocol and template and presented in a harmonized manner. These data were calculated to express amounts sold, in metric tonnes, of active ingredient of each package. A population correction unit (PCU) was applied as a proxy for the animal biomass potentially treated with antimicrobial agents. The indicator used to express sales was milligrams of active substance per PCU.

Results: Substantial variations in the sales patterns and in the magnitude of sales of veterinary antimicrobial agents, expressed as mg/PCU, between the countries were observed. The proportion of sales, in mg/PCU, of products applicable for treatment of groups or herds of animals (premixes, oral powders and oral solution) varied considerably between the countries.

Conclusions: Some countries reported much lower sales of veterinary antimicrobial agents than others, when expressed as mg/PCU. Sales patterns varied between countries, particularly with respect to pharmaceutical forms. Further studies are needed to understand the factors that explain the observed differences.

Keywords: selection pressure, antimicrobial resistance, food safety, risk assessment, animal population, critically important antimicrobials

Introduction

Use of antimicrobial agents may promote the selection and dissemination of bacteria resistant to antimicrobials, and of resistance genes, as well as the emergence of new resistant bacteria through genetic mutations and gene movements. Antimicrobial resistance in bacteria causing disease in animals may limit therapeutic options and thereby have a direct impact on animal health and welfare. Furthermore, resistant bacteria and resistance genes may be disseminated from animals to humans through direct contact and via the food chain and the environment.1,2 Use of antimicrobials for animals could thereby indirectly contribute to the increasing public health burden caused by antimicrobial resistance.3

In the European Union (EU)/European Economic Area (EEA) region, most antimicrobial classes that are marketed for use in animals are the same as or closely related to those classes used in human medicine. Important exceptions are the carbapenems, streptogramins, glycolcyclines, lipopeptides, oxazolidinones and glycopeptides, which are only authorized in human medicine. The use of antimicrobial agents in animals may select for resistant bacteria and resistance determinants of importance also in human medicine. Thus, antimicrobial stewardship in veterinary medicine and animal production is important for both animal and public health.

Data on the consumption, e.g. sales data and prescription data, of antimicrobial agents as well as data on resistance are essential components to inform policies and strategies for the containment of antimicrobial resistance. Such data are needed to measure the effect of e.g. campaigns promoting responsible use, adherence to guidelines and regulatory changes or to establish whether reduction targets are met. Furthermore, data on...
consumption of antimicrobial agents is also needed for risk assessment and to identify areas where more knowledge is needed. Data must be comparable over time and preferably also between countries in order to identify and understand differences in practices and for sharing of experience.

The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project was launched by the European Medicines Agency (EMA) in September 2009 following a request from the European Commission to collect data on sales of antimicrobial agents in animals as well as by major animal species. As a first step in the project, a system to collect harmonized and standardized sales data from the EU member states and EEA countries was developed.

The main aims of this paper are to describe the organization and establishment of the ESVAC project and to present key results from data collected for 2011 with special emphasis on the antimicrobial classes with the greatest sales and on those critically important antimicrobials (CIAUs) with highest priority for human medicine as defined by the WHO.3

Methods

As a first step, the ESVAC project team established a network of national representatives (ESVAC NRs) nominated by the national competent authorities and thereafter the request from the Commission was presented in meetings with the ESVAC NRs and with other stakeholders, such as the pharmaceutical industry and veterinary associations. In parallel, a Technical Consultancy Group (TCG) consisting of experts from 10 European countries that had already published national data on consumption of veterinary antimicrobial agents was established. A representative from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) at the European Centre of Disease Control (ECDC), which is responsible for collation of data on the use of human antimicrobial agents, also participated in the TCG as an observer.

The TCG assisted in the development and the testing of the ESVAC protocol and data collection form. The draft ESVAC protocol and a standardized form for data submission were sent for consultation to all ESVAC NRs as well as other stakeholders and a pilot to test the template was performed, assisted by the TCG, before it was rolled out for use in the member states.

The Anatomical Therapeutic Chemical classification system for veterinary medicinal products (ATCvet) developed by the WHO Collaborating Centre for Drug Statistics Methodology4 is applied in ESVAC to allow uniform identification and identical coverage of the veterinary antimicrobial agents to be included in the data submitted.5

The variables to be reported for each product at package level were basically product name, pharmaceutical form (standardized terms), ATCvet code, pack size, pack size unit (standardized), number of packages sold, active ingredient(s) (ATCvet names), strength(s) and strength unit (standardized) for each active ingredient(s).5,6 These data were calculated to express amounts sold, in metric tonnes, of the active ingredients of each package.

The data collected were all sales, in amount of active ingredients, of products in specified ATCvet classes7 for use in terrestrial animals and farmed fish. Data were not currently collected by animal species. A call for data on sales for 2011 at package level according to the agreed ESVAC protocol8 and template9 was sent to the ESVAC NRs in spring 2012. Twenty-five countries provided the requested data.

The data were checked for errors in standards of data and revised the data if applicable.

The numerator used was the amount, in weight of active ingredient, by antimicrobial class or subclass and a population correction unit (PCU) was used as the denominator to correct for differences in animal demographics.5,7-9 Essentially, the PCU for each animal category was calculated by multiplying numbers of live animals (dairy cows, sheep, sows and horses) and slaughtered animals (cattle, pigs, lambs, poultry and turkeys) by a standardized theoretical weight at the time most likely for treatment. For farmed fish, data were given only as live weight slaughtered, as information on weight at treatment could not be found; for farmed fish, the PCU was taken as biomass live weight slaughtered in each country. The PCU for each country was corrected for export and import of live animals (see below).

Eurostat, the statistical office of the EU, holds data on numbers and biomass of live and slaughtered food-producing animals. Therefore, Eurostat was selected as the data source for this animal category.10 In cases where data were not available in Eurostat (e.g. for rabbits and EEA countries), national statistics were applied. For horses (a food-producing species according to EU legislation), national statistics were used. As data on numbers of dogs and cats were not available in all participating countries, these species were not included in the PCU. The Eurostat data on number of animals exported or imported for fattening or slaughter to another member state were obtained from the TRAde Control and Expert System (TRADES) database, where health certificates mandatory for transport between member states are recorded.11 The PCU for animals exported for fattening or slaughter in another member state was added to the total PCU of livestock and slaughter animals in the country of origin, because young animals are typically treated more frequently than other age classes.

In cases where the deviation between the Eurostat data and/or TRACES data and national statistics was >5% some countries used national statistics.

Antimicrobial veterinary medicinal products (VMPs) approved for use in companion animals only, i.e. tablets, were excluded from the material prior to the normalization of the sales by the PCU (1 PCU = 1 kg).

Collected data on sales of VMPs were calculated at the active substance level. The annual sales of veterinary antimicrobial agents by class/subclass and pharmaceutical form by country were expressed by the indicator mg/PCU per year; the following formula was applied to calculate the mg/PCU value: metric tonnes sold of active ingredient $\times 10^3$/PCU. Information on pharmaceutical form was used to stratify data by intended mode of administration.

Results

The data type for 22 countries were sales data (sales to farmers, veterinarians, feed mills, retailers and/or pharmacies) from wholesalers or marketing authorization holders (MAHs); for Denmark and Sweden the data were based on prescription data while Slovakia provided purchase data (purchased by wholesalers). Some countries obtained data on purchase of premedications from feed mills.

One of the major MAHs in Spain failed to report sales data in 2010, which clearly resulted in substantial underreporting for this year, indicating that the sales actually decreased from 2010 to 20119 (Table 1); therefore a decrease in sales, expressed
as mg/PCU, was observed in the 20 countries that provided data for both years. Except for Norway (due to an increase in the production of farmed fish), the PCU was relatively stable for these countries; the reduced sales (mg/PCU) were mainly accounted for by a reduction in tonnes of antimicrobial agents sold.

The sales volumes and sales patterns of the various classes and sub-classes of veterinary antimicrobial agents intended for food-producing species, including horses, expressed as the indicator mg/PCU, in the 25 EU/EEA countries are shown in Figure 1.

In all countries, tetracyclines, penicillins and sulphonamides accounted for more than half (range 53%–88%) of the total amount of antimicrobial agents sold by country, expressed as mg/PCU (Figure 2). Aggregating the data from the 25 countries, the sales of tetracyclines, penicillins and sulphonamides accounted for 37%, 23% and 11%, respectively of the total sales of veterinary antimicrobial agents in 2011.

The proportion of the total sales (mg/PCU) represented by those CIAs with the highest priority for human medicine—third- and fourth-generation cephalosporins, fluoroquinolones and macrolides—varied substantially between the 25 countries, ranging from 0.05% to 0.78%, 0.01% to 13.8% and 0% to 14%, respectively (Figure 3). The corresponding figures for aggregated sales for all the 25 countries were 0.2%, 1.6% and 8%, respectively.

The distribution of the sales of third- and fourth-generation cephalosporins, macrolides and fluoroquinolones by pharmaceutical form is shown in Figure 4.

The amount of total sales accounted for by premixes, oral powders and oral solutions varied considerably between the countries (Figure 5).

Overall, in the 25 countries (with the notable exception of five countries) the major proportion of veterinary antimicrobials was

| Table 1. Salesa, in (metric) tonnes of active ingredient, of veterinary antimicrobial agents marketed mainly for food-producing animals b, including horses, PCU and sales in mg/PCU, by country, for 2010 and 2011 |
|----------------|-----------------|----------------|----------------|----------------|
| Sales (metric tonnes) for food-producing animals | Percentage change in sales | PCU (1000 metric tonnes) | Percentage change in PCU | mg/PCU | Percentage change in mg/PCU |
| Austria | 63 | 53 | -15% | 994 | 977 | -1.8% | 63 | 54 | -13% |
| Belgium | 299 | 297 | -1% | 1660 | 1695 | 2.1% | 180 | 175 | 3% |
| Bulgaria | 42 | 399 | -0.6% | 115 | 114 | -1.1% | 66 | 66 | -0.4% |
| Cyprus | 52 | 127 | -0.4% | 517 | 520 | 0.6% | 25 | 24 | -4% |
| Czech Republic | 71 | 61 | -14% | 755 | 732 | -3.1% | 94 | 83 | -12% |
| Denmark | 119 | 106 | -11% | 2503 | 2479 | -1.0% | 47 | 43 | -10% |
| Estonia | 7.6 | 7.5 | -2% | 115 | 114 | -1.1% | 66 | 66 | -0.4% |
| Finland | 13 | 12 | -3% | 517 | 520 | 0.6% | 25 | 24 | -4% |
| France | 997 | 896 | -10% | 7538 | 7643 | 1.4% | 132 | 117 | -11% |
| Germany | 1819 | 1860 | 2.5% | 768 | 767 | -0.2% | 268 | 192 | -28% |
| Hungary | 206 | 147 | -28% | 768 | 767 | -0.2% | 268 | 192 | -28% |
| Iceland | 0.9 | 0.7 | -12% | 113 | 114 | 0.8% | 7.2 | 6.3 | -13% |
| Ireland | 96 | 87 | -9% | 1779 | 1770 | -0.5% | 54 | 49 | -9% |
| Italy | 1928 | 1663 | -14% | 4514 | 4497 | -0.4% | 427 | 370 | -13% |
| Latvia | 6.6 | 6.0 | -9% | 165 | 171 | 3.7% | 40 | 35 | -12% |
| Lithuania | 16 | 14 | -15% | 342 | 337 | -1.5% | 48 | 42 | -14% |
| Netherlands | 461 | 363 | -21% | 3155 | 3186 | 1.0% | 146 | 114 | -22% |
| Norway | 6.3 | 6.2 | -3% | 1537 | 1680 | 9.3% | 4.1 | 3.7 | -11% |
| Poland | 471 | 472 | -0.2% | 3929 | 3689 | 6.0% | 120 | 120 | 0% |
| Portugal | 181 | 164 | -10% | 1020 | 1016 | -0.3% | 178 | 161 | -9% |
| Slovakia | 11 | 12 | -9% | 247 | 247 | 0.4% | 44 | 44 | 0% |
| Slovenia | 8.4 | 7.8 | 0.02% | 181 | 182 | 1.0% | 46 | 43 | -6.0% |
| Spainc | 1746 | 1779 | 2% | 7248 | 7135 | -1.6% | 241 | 249 | 3.5% |
| Sweden | 13 | 11 | -11% | 832 | 835 | 0.3% | 15.2 | 13.6 | -11% |
| UK | 456 | 344 | -25% | 6714 | 6724 | 0.2% | 68 | 51 | -25% |

aFor Denmark and Sweden data are prescription data; for Slovenia data are purchase data; some premix data are purchase data.
bTablets excluded as they are almost solely used in companion animals; injectable antimicrobial VMPs can also be used in companion animals. A few other products may solely be used in companion animals, but as the proportional use is minor, these are included in the sales for food-producing animals.
cOne of the major MAHs failed to report sales data for 2010, resulting in an underestimate.
sold as pharmaceutical forms suitable for herd or group treatment; 48% of the sales were accounted for by oral powders, 36% by premixes and 8% by oral solutions. In total, 7% were sold as injectable preparations and 1% as intramammary preparations, bolus, intrauterine preparations and oral pastes.

Discussion

As all antimicrobial growth promoters were phased out in the EU by 1 January 2006, the datasets provided to ESVAC represent sales exclusively of antimicrobial agents sold as VMPs.

A clear difference in the sales, expressed as the indicator milligrams of active ingredient per PCU, was observed between the countries selling the most (408 mg/PCU) and the least (3.7 mg/PCU). Furthermore, the sales patterns of the various veterinary antimicrobial classes, expressed as mg/PCU, varied substantially between the countries. This is likely to be partly due to differences in the composition of the animal population (e.g. more pigs than cattle and a high proportion of veal calves within the cattle population) in the various countries, the availability of veterinary antimicrobial products on the market, prices and the general situation with regard to infectious diseases. These factors...
can, however, only partly explain the observed differences; other factors need to be considered, such as prescription habits, the possible influence of the degree of internal and external biosecurity on farms and the implementation of responsible-use campaigns.

A total of 16 of the 20 countries that reported sales to ESVAC in both 2010 and 2011 reported a decrease in sales of >5% expressed as mg/PCU. Overall, in these 20 countries a decrease of 11% was observed.\(^8\)\(^9\) Suggested explanations provided by the countries for the decline in sales from 2010 to 2011 are, among others, implementation of responsible-use campaigns, restrictions of use, increased awareness of the threat of antimicrobial resistance, and/or the setting of political targets.\(^9\) However, for some of these countries data for at least one

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**Figure 3.** Sales of macrolides, fluoroquinolones and third- and fourth-generation cephalosporins as a percentage of the total sales of veterinary antimicrobial agents for food-producing species, including horses, in mg/PCU, by country, in 2011.

**Figure 4.** Total sales, in mg/PCU, of third- and fourth-generation cephalosporins, fluoroquinolones and macrolides for food-producing animals, including horses, by pharmaceutical form in 25 EU/EEA countries in 2011.
additional year would be needed in order to ascertain whether the decline in sales genuinely constitutes a trend or merely reflects annual data fluctuations. Further analysis of the various actions taken by countries prior to data collection for ESV AC and their relation to trends in the sales and sales patterns could provide important information on the effect of interventions in different contexts.

The WHO has classified fluoroquinolones, third- and fourth-generation cephalosporins, macrolides and glycopeptides as those CIAs in human medicine with the highest priority for the development of risk management strategies with respect to antimicrobial resistance.3 No products containing glycopeptides are authorized for use in food-producing species in the EU/EEA countries. Regarding macrolides and fluoroquinolones, one or more substances are marketed for all major food-producing species (pigs, poultry and cattle) in the EU/EEA. As regards third- and fourth-generation cephalosporins, products are authorized for use in cattle and pigs but not for use in poultry. It should be noted that a restriction has been added to the marketing authorization for third- and fourth-generation cephalosporins that indicates: ‘Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans.’12

Notable variations were observed between the different countries in the proportion of total sales accounted for by the CIAs with highest priority for human medicine—comprising third- and fourth-generation cephalosporins, fluoroquinolones and macrolides. Since the major proportion of the sales of these classes/subclasses was accounted for by macrolides, the observed variation between the countries is likely to reflect in part differences between the countries in the relative proportions of the various animal species and in particular differences in pig production, in which there is substantial use of macrolides.

Another important finding was that the total sales, both in tonnes and in mg/PCU, of veterinary antimicrobial agents in the 25 EU/EEA countries were mainly accounted for by pharmaceutical forms suitable for mass or group treatment; however, this varied noticeably between the countries. This is largely explained by the differences between the countries in terms of animal demographics and size of herds.

Regarding the methods used in the present study, it should be noted that all the participating antimicrobial agents have a ‘Prescription only’ status9 and according to Directive 2001/82/EC of the European Parliament13 all veterinary medicinal products, including veterinary antimicrobial agents, have to be sold through distributors authorized by the competent authority in each country. This allowed the 25 countries to identify all distributors of antimicrobial VMPs in their country and consequently 100% data source coverage could be obtained. However, data providers may fail to deliver the data as described above for Spain for 2010 or data providers may deliver incomplete data. For those countries (20) that delivered data to the ESV AC for both 2010 and 2011, the raw data were checked manually in order to identify outliers, as described in the Methods section. It is therefore reasonable to assume that the data presented in the present paper give a good picture of the total sales of antimicrobial agents in the 25 countries.

Dermatological preparations (ATCvet group QD) and preparations for sensory organs (ATCvet group QS) were not included in the datasets. Since e.g. in France these pharmaceutical forms represent only 0.35% of the total tonnes sold (G. Moulin, unpublished data), in the Czech Republic they represent 0.2% (Lucie Pokludová, Institute for State Control of Veterinary Biologicals and Medicines, personal communication) and in Norway 0.002%,14 the contributions of these groups of antimicrobial agents, in tonnes of active ingredients, to the total amounts is thought to be minimal, and therefore the effect of the deviation is negligible. Injectable antimicrobial agents are used in both food-producing and companion animals; however, the proportion

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Figure 5. Oral solutions, oral powders and premixes as percentages of total sales, in mg/PCU, of veterinary antimicrobial agents for food-producing animals, including horses, by country, for 2011.
of use in companion animals is minor as injection of antimicrobial agents is limited to perioperative use (one injection), very ill animals and sometimes as an initial dose, and outpatient companion animals are typically treated with tablets. In France, ~1.2% of the injectable antimicrobial VMPs were used for dogs and cats (G. Moulin, unpublished data). Therefore, the assumption that all injectable antimicrobial are used in food-producing species has minimal impact on the accuracy of the data for injectable preparations.

The use of antimicrobial agents in the various animal species and production systems varies considerably; e.g. the intensity of use is much higher in calf production, especially veal calf production, than in other beef production systems and in dairy cattle. Furthermore, the potency of the various antimicrobial agents within a class can be very different; e.g. the dosage of doxycycline is about one quarter of the dosage of oxytetracycline. The dosing may also vary between formulations. Additionally, the dosing according to species may vary substantially; e.g. for fish the dosage of tetracycline for a whole course of treatment can be 800 mg/kg, which is 6-fold higher than that for terrestrial animals. The data presented in the current paper cover antimicrobials aggregated by class or subclass and the denominator is all food-producing animals together; therefore it was not possible to take into account differences in potency when reporting the data. Since the sales patterns, animal demographics and dominant types of production vary substantially between countries, comparison of the sales data between the countries should be done with great care. It should also be emphasized that the PCU only represents a technical unit of measurement and not an actual value for the animal population that could potentially be treated by antimicrobial agents. The use of PCU as denominator does, however, allow the figures to be compared between years.

Sales data will only exceptionally (e.g. intramammary preparations for dairy cattle) provide information on sales by species (or age of the treated animals) as most products are approved for two or more species. In order to implement targeted management measures for the containment of antimicrobial resistance it is important to obtain data by species, age class and production type. The next step of the ESVAC project is therefore to collect such data, with data on pigs being given priority. Also, technical units of measurement that take into account differences in potency when reporting the data. Since the sales patterns, animal demographics and dominant types of production vs.

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