

Surveillance and monitoring of antimicrobial resistance and antibiotic consumption in humans and animals

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Summary

Surveillance and monitoring studies of antimicrobial resistance in bacteria of human and animal origin and antimicrobial consumption in humans and animals have been conducted in various countries throughout the world. In the veterinary field, in particular, programmes have been installed which target bacteria of zoonotic, foodborne and/or veterinary relevance. Each year, the European Surveillance of Veterinary Antimicrobial Consumption project summarises and evaluates antimicrobial consumption in ambulatory and hospital care in many European countries. In contrast, antimicrobial consumption data in veterinary medicine are available from only a few countries and the type of information that is collected or reported varies. To address this challenge, the European Surveillance of Veterinary Antimicrobial Consumption project was launched by the European Medicines Agency in September 2009 and has just published its first report. This comparison of the different studies for surveillance and monitoring of antimicrobial resistance and antimicrobial consumption in humans and animals shows the need to improve harmonisation.

Keywords

Ambulatory care – Clinical breakpoint – Harmonisation – Resistance development – Sales figures – Susceptibility testing.

Introduction

Surveillance and monitoring studies on antimicrobial resistance in bacteria that cause infections in humans and animals, and also in indicator bacteria, are essential when studying changes in the antimicrobial susceptibility patterns of these organisms over time and to identify emerging resistance properties. In this regard, surveillance is defined as the continuous, intensive, targeted and non-random collection of data on the incidence, prevalence and spread of antimicrobial-resistant bacteria and antimicrobial resistance genes. Monitoring is defined as the continuous routine measurement and analysis of antimicrobial susceptibility testing information to detect trends (9). Surveillance and monitoring studies are currently

conducted in many countries in both human and veterinary medicine. Since the use of antimicrobial agents is considered a driving force in the development and spread of antimicrobial resistance, studies have also been conducted to determine consumption figures of antimicrobial agents in human and veterinary medicine in various countries.

This review summarises the key features of some of these surveillance and monitoring studies on antimicrobial resistance and antimicrobial consumption, without intending to be exhaustive. Moreover, some basic information is given on the methodologies and interpretive criteria used in these studies. All these data emphasise the need for better harmonisation of such surveillance and monitoring studies (31, 37, 38, 39).

Surveillance and monitoring of antimicrobial resistance

Methodologies of antimicrobial susceptibility testing in surveillance and monitoring programmes

There is no uniform harmonised methodology of antimicrobial susceptibility testing (AST) among the various surveillance and monitoring programmes in human and veterinary medicine. In general, agar disc diffusion and broth microdilution are the most commonly used methods. However, there is a tendency to give preference to broth microdilution over agar disc diffusion since this is the more robust test method and provides quantitative results. Nevertheless, both are approved AST methods and detailed descriptions of the test conditions have been published by numerous national and international organisations, such as the Clinical and Laboratory Standards Institute (CLSI) (8, 10), the British Society for Antimicrobial Chemotherapy (2), the Deutsches Institut für Normung e.V. (14), the Comité de l'Antibiogramme de la Société Française de Microbiologie (11) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (16), among others. However, when comparing the AST procedures recommended for different organisms in detail, slight variations occur in the proposed media and supplements, incubation times and conditions, inoculum sizes, etc. Moreover, different clinical breakpoints and/or different epidemiological cut-off values are listed in the various AST documents. For a comparison of data derived from different surveillance or monitoring programmes, it is important to know which AST procedure was followed and which interpretive criteria were used to classify the organisms as susceptible, intermediate and resistant or as wild-type and non-wild-type.

There is also no harmonised set of antimicrobial agents for resistance testing in bacteria in surveillance or monitoring programmes in human or veterinary medicine. Gram-positive and/or Gram-negative bacteria may be tested for resistance to various sets of antimicrobial agents, while differences may also occur when bacteria from specific disease conditions are tested, e.g. respiratory tract infections *versus* urinary tract infections *versus* mastitis. Even when testing the same bacteria for susceptibility to the same antimicrobial agent, there may be striking differences in terms of the test ranges used:

- for the same bacteria in different programmes
- for different bacteria in the same programme.

For example, the test ranges for tetracyclines and *Escherichia coli* from broilers have varied in different countries:

- 0.12 to 16 mg/L in Sweden in 2010 (4)
- 1 to 64 mg/L in the Netherlands in 2009 (7)
- 0.12 to 256 mg/L in Germany in 2011 (H. Kaspar, personal communication).

In 2009 the test ranges for tetracyclines in the Danish monitoring system were (13):

- 0.25 to 16 mg/L for *Campylobacter*
- 2 to 32 mg/L for *Salmonella* and *E. coli*
- 1 to 32 mg/L for enterococci.

Definition of resistance in surveillance and monitoring programmes

Schwarz *et al.* (29, 30) suggested categorising bacterial isolates as 'susceptible to', 'intermediate' or 'resistant to' tested antimicrobials, making the important point that such classification requires approved interpretive criteria. Currently, two different types of interpretive criteria are available: clinical breakpoints and epidemiological cut-off values (6). The emphasis of a particular study dictates which criteria must be applied. If data are intended to guide a therapeutic approach (i.e. the aim of the study is to determine which antimicrobial agents are most likely to lead to therapeutic success), clinical breakpoints must be applied. Epidemiological cut-off values should be used to describe minimum inhibitory concentration (MIC) distributions of bacteria without clinical context. Clinical breakpoints and epidemiological cut-off values may be very similar or even identical for some bacteria/drug combinations; however, authors need to understand that epidemiological cut-off values are determined by a different approach from that used for clinical breakpoints and do not necessarily take into account the results of clinical efficacy studies or dosing and route of administration of the antimicrobial agents, nor the drug's pharmacokinetic and pharmacodynamic parameters in the respective animal species. The term 'breakpoint' should be used exclusively for clinical breakpoints and 'susceptible', 'intermediate' and 'resistant' categories should also be reserved for classifications made for the therapeutic application of antimicrobial agents.

When reporting data using epidemiological cut-off values, the term 'resistant' is inappropriate; instead, bacteria should be reported as 'wild type' if the MIC or zone diameter falls within the wild-type range, or 'non-wild type' if the MIC is higher or the zone diameter smaller than the wild-type range. Indeed, Magiorakos *et al.* (24), in an international expert proposal for interim standard

definitions of acquired resistance, clearly states that a bacterial isolate should only be considered non-susceptible to an antimicrobial agent when it tests resistant, intermediate or non-susceptible using clinical breakpoints as interpretive criteria, not epidemiological cut-offs.

Surveillance and monitoring programmes in human medicine

At any given time, there are numerous antimicrobial resistance (AMR) surveillance and monitoring studies of bacteria. Although the vast majority of these studies evaluate the antimicrobial susceptibility of human pathogens, their goals mirror, in many ways, those of AMR surveillance studies of veterinary pathogens. A large number of AMR surveillance studies, varying in scope and magnitude, have been conducted. Some have focused on a single species of microorganism, a specified time period, a specific geographic region, a single type of infection, or a limited number of antimicrobial agents, while others have been very broad in their coverage of one or more of these aspects (9). Nevertheless, publications reporting the results of these disparate studies frequently present the data in very similar ways, using a rather limited collection of table or graph formats.

Table I gives an overview of four AMR surveillance and monitoring programmes for bacteria of human origin. One of the key differences between human and veterinary AMR surveillance programmes is that human programmes predominantly monitor target pathogens while veterinary programmes, in general, monitor for antimicrobial resistance in foodborne and commensal bacteria. Data interpretation is easier in human AMR surveillance studies than in veterinary AMR surveillance studies. This is primarily because clinical breakpoints specific for the human use of antibiotics against bacteria of human origin have been established by both the CLSI and EUCAST. In the absence of clinical breakpoints, mainly for a number of older antibiotics, there are at present no alternative interpretive criteria, such as epidemiological cut-off values.

Surveillance and monitoring programmes in veterinary medicine

Table II highlights some of the key veterinary AMR surveillance and monitoring programmes. These include:

- the National Antimicrobial Resistance Monitoring System (NARMS) in the United States (www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm059103.htm)
- the Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands (MARAN)

(www.cvi.wur.nl/UK/publications/otherpublications/maran/)

- the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP)
- German Resistance Monitoring in Veterinary Medicine (GERM-Vet) (26)
- the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) (27)
- the Italian Veterinary Antimicrobial Resistance Monitoring programme (ITAVARM) (3)
- the Report on Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway in Animals and Humans (NORM/NORM-Vet) (25)
- the Veterinary Monitoring of Antimicrobial Resistance in Spain (VAV) (27)
- the Swedish Veterinary Antimicrobial Resistance Monitoring programme (SVARM) (www.sva.se/en/Fokusomraden1/Antibiotic-Resistance/SVARM-reports/)
- the Japanese Veterinary Antimicrobial Resistance Monitoring programme (JVARM) (www.maff.go.jp/nval/tyosa_kenkyu/taiseiki/monitor/e_index.html)
- the Centre Européen d'Etudes pour la Santé Animale (European Animal Health Centre) (CEESA).

For interpreting data in veterinary AMR surveillance and monitoring studies, the CLSI document M31-A3 (8) includes the largest collection of approved clinical breakpoints for bacteria of animal origin currently available, a considerable number of which represent veterinary-specific breakpoints. Many of the latter have been approved for specific disease conditions, often caused by particular bacterial species in defined animal host species. As an example, approved clinical breakpoints for enrofloxacin in cattle apply exclusively to bovine respiratory diseases due to *Pasteurella multocida*, *Mannheimia haemolytica* and *Histophilus somni*. The use of these breakpoints for other bovine bacteria and disease conditions, e.g. *Staphylococcus aureus* from bovine mastitis, is not acceptable (29, 30). Thus, the scope of application of these veterinary-specific breakpoints is clearly defined and cannot be altered. Besides CLSI-approved clinical breakpoints, EUCAST epidemiological cut-off values are often used (Table II). Only the SVARM programme follows the recommendations of the Swedish Reference Group for Antibiotics.

It is clear that the breadth of veterinary AMR surveillance and monitoring programmes is far greater than that of human AMR surveillance and monitoring programmes, since they have to include every host animal species. As with human AMR surveillance and monitoring programmes, the majority of the veterinary programmes

are government funded. Apart from the CEESA programmes, all the veterinary AMR surveillance and monitoring programmes are national programmes. Under the umbrella of CEESA, the veterinary pharmaceutical industry conducts four AMR resistance surveillance and monitoring programmes:

– VetPath: examines the antimicrobial susceptibility of major disease-causing bacterial pathogens in food animals

– European Antimicrobial Susceptibility Surveillance in Animals (EASSA): examines the antimicrobial susceptibility of foodborne and commensal bacteria in food animals

– ComPath: examines the antimicrobial susceptibility of major disease-causing bacterial pathogens in companion animals

Table I

Comparison of four surveillance and monitoring programmes for bacteria of human origin

Parameter	Surveillance and monitoring programme			
	EARS-Net	NARMS	WHONET-Argentina	CIPARS
Reference for data	EARS-Net Annual Report 2008	NARMS – Enteric Bacteria Annual Report 2008	Pan American Health Organization Annual Report 2008	CIPARS 2006 – Final Report
Study sponsorship	European Commission	United States Government	Ministry of Health	Canadian Government
Longitudinal? (years up to 2009)	Yes (10)	Yes (14)	Yes (23)	Yes (8)
Regions involved in study	Europe	United States	Argentina	Canada
Number of countries (centres) involved	32 (888 laboratories; 1,578 hospitals)	1 (50 state health departments)	1 (72)	1 (10 provincial public health laboratories)
Isolates re-identified in reference laboratory	No	Yes	No	Yes
Number of antimicrobials tested	2 to 5 required, depending on bacterial species	15 for <i>Enterobacteriaceae</i> , 9 for <i>Campylobacter</i>	6 to 12, depending on the organism	15 for <i>Enterobacteriaceae</i> , 9 for <i>Campylobacter</i>
Quantitative MIC or zone diameter determination	Often, though not required (MIC or zone diameter)	Yes (MIC)	Yes (MIC or zone diameter)	Yes (MIC)
Standardised testing methods, e.g. CLSI, SRGA, SFM	Yes – method depends on the country and laboratory	Yes (CLSI)	Yes (CLSI)	Yes (CLSI)
Collection and integration of clinical and demographic data	Demographic – yes Clinical diagnosis – no	Yes	Demographic – yes Clinical diagnosis – no	Yes
Central laboratory testing (number of laboratories performing tests)	No	Yes (1)	No (except for confirmations)	No
Molecular epidemiology	Yes, for <i>Staphylococcus aureus</i> in some countries	Yes (PFGE for some <i>Salmonella isolates</i>)	No (except for research protocols)	Yes (PFGE for some <i>Salmonella isolates</i>)
Detection of resistance mechanisms?	No	No (only in peer-reviewed publications)	No (except for research protocols)	No (only in peer-reviewed publications)
Internet access to data?	Yes	Yes	No	Yes
Ability to download data to handheld computer?	No	No	No	No
Is user able to perform custom analyses?	Yes	No	No	No
Guidelines available for interpretation of surveillance data?	No	Yes	No	Yes
Range of infection types covered	Bacteraemia and meningitis	Foodborne diarrhoeal disease, typhoid, shigellosis	All acute routine bacterial infections	Foodborne diarrhoeal disease, typhoid
Respiratory tract pathogens included?	Yes (<i>Streptococcus pneumoniae</i> , <i>S. aureus</i>)	No	Yes (<i>S. pneumoniae</i> , <i>S. aureus</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i>)	No

CLSI: Clinical and Laboratory Standards Institute
 CIPARS: Canadian Integrated Program for Antimicrobial Resistance Surveillance (www.phac-aspc.gc.ca/cipars-picra/index-eng.php)
 EARS-Net: European Antimicrobial Resistance Surveillance Network (<http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx>)
 MIC: minimum inhibitory concentration
 NARMS: National Antimicrobial Resistance Monitoring System (www.cdc.gov/narms/Net/Pages/index.aspx)

PFGE: pulsed-field gel electrophoresis
 ResistVet: Joint United States Food and Drug Administration Center for Veterinary Medicine/Mexican surveillance system for antimicrobial resistance (www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm090050.htm)
 SFM: Société Française de Microbiologie
 SRGA: Swedish Reference Group for Antibiotics
 WHONET: Greek System for the Surveillance of Antimicrobial Resistance (www.mednet.gr/whonet/)

– MycoPath: examines the antimicrobial susceptibility of major disease-causing mycoplasma species from food animals.

Of the four CEESA programmes, ComPath and MycoPath are the newest and as yet the isolates have not undergone AST. In contrast, the VetPath and EASSA programmes have

been active for a decade. For each of the CEESA programmes, isolates are collected in up to nine countries across the European Union (EU), using uniform collection methodology. It should be noted that the VetPath isolates are collected as ‘first intention’ isolates, i.e. from animals that show clinical signs of illness but have not yet been administered any antimicrobial treatment.

Table II
Comparison of several veterinary antimicrobial resistance surveillance and monitoring programmes

Parameter	Surveillance and monitoring programme					
	NARMS (United States)	MARAN (The Netherlands)	DANMAP (Denmark)	GERM-Vet (Germany)	CIPARS (Canada)	ITAVARM (Italy)
Study details						
Study sponsorship	Government	Government	Government	Government	Government	Government
Longitudinal? (years up to 2010)	Yes (15)	Yes (9)	Yes (16)	Yes (10)	Yes (9)	Yes (8)
Regions involved in study	United States	The Netherlands	Denmark	Germany	Canada	Italy
Standardised testing methods (e.g. CLSI, SRGA, SFM)	Yes (CLSI)	Yes (ISO 20776-1, or CLSI)	Yes (CLSI)	Yes (CLSI)	Yes (CLSI)	Yes (CLSI)
Clinical breakpoints used	CLSI; in absence of CLSI breakpoints, breakpoints based on MIC distribution	EUCAST ECV for foodborne and commensal bacteria; CLSI breakpoints for animal pathogens	EUCAST ECV or EUCAST breakpoints; in absence of EUCAST breakpoints, CLSI breakpoints	CLSI; in absence of CLSI breakpoints, presentation of the data as MIC distribution without categorisation	CLSI; in absence of CLSI breakpoints, breakpoints based on MIC distribution and harmonisation with NARMS	CLSI
Collection and integration of demographic data?	Yes	Yes (limited)	Yes (limited)	Yes (very detailed background information)	Yes (limited)	No
Molecular epidemiology?	Yes (PFGE for some <i>Salmonella</i> isolates)	No	No	Yes (molecular typing for selected isolates in peer-reviewed publications)	No	No
Detection of resistance mechanisms?	No (only in peer- reviewed publications)	No (only in peer- reviewed publications)	No (only in peer- reviewed publications)	No (only in peer- reviewed publications)	No (only in peer- reviewed publications)	No
Internet access to data?	Yes	Yes	Yes	No	Yes	Yes
Is user able to perform custom analyses?	No	Yes	Yes	No	No	No
Guidelines available for interpretation of surveillance data?	Yes	Yes	Yes	Yes	Yes	No
Source of samples						
Healthy animals	Yes	Yes	Yes	No	Yes	Yes
Diseased animals	No	Yes	Yes	Yes	Yes	Yes
Food	Yes	No	Yes	No	No	Yes
Healthy humans	No	No	Yes	No	No	No
Diseased humans	Yes	Yes	Yes	No	Yes	Yes
Bacteria						
<i>Salmonella</i>	Yes	Yes	Yes	Yes	Yes	Yes
<i>Campylobacter</i>	Yes	Yes	Yes	No	Yes	No
<i>Escherichia coli</i>	Yes	Yes	Yes	Yes	Yes	Yes
Enterococci	Yes	Yes	Yes	Yes	Yes	Yes
Animal pathogens	Yes (limited pathogens covered)	Yes (limited pathogens covered)	Yes (limited pathogens covered)	Yes (most major and some minor animal pathogens covered)	Yes (limited pathogens covered)	Yes (limited)

Table II (Continued)

Parameter	Surveillance and monitoring programme					
	NORM-VET (Norway)	VAV (Spain)	SVARM (Sweden)	JVARM (Japan)	CEESA EARS-Net (Pan European)	CEESA VetPath (Pan European)
Study details						
Study sponsorship	Government	Government	Government	Government	Industry	Industry
Longitudinal? (years up to 2010)	Yes (11)	Yes (15)	Yes (11)	Yes (12)	Yes (12)	Yes (12)
Regions involved in study	Norway	Spain	Sweden	Japan	Belgium, Denmark, France, Germany, Hungary, Italy, the Netherlands, Poland, Spain, the UK	Denmark, Belgium, the Netherlands, the UK, Ireland, Germany, France, Italy, Spain, Poland, Hungary, the Czech Republic
Standardised testing methods (e.g. CLSI, SRGA, SFM)?	Yes (MIC-based automated system)	Yes (CLSI)	Yes (SRGA methodology)	Yes (JSC until 2000; CLSI after 2000)	Yes (CLSI)	Yes (CLSI)
Interpretive criteria used?	Yes (EUCAST ECV; where not available, ECV based on MIC distribution)	Yes (EUCAST/CLSI)	Yes (SRGA methodology criteria)	Yes (CLSI; in the absence of CLSI, microbiologically determined)	Yes (CLSI; EUCAST breakpoints in absence of CLSI breakpoints)	Yes (CLSI; EUCAST breakpoints in absence of CLSI breakpoints)
Collection and integration of demographic data?	No	No	Yes	No	Yes	Yes
Molecular epidemiology?	No	No	No	No	No	No
Detection of resistance mechanisms?	No	No	No	No	No	No
Internet access to data?	Yes	Yes	Yes	Yes	Yes, only CEESA EARS-Net members	Yes, only CEESA VetPath members
Is user able to perform custom analyses?	Yes	Yes	Yes	No	Yes, only CEESA EARS-Net members	Yes, only CEESA VetPath members
Guidelines available for interpretation of surveillance data?	Yes	Yes	Yes	Yes	Yes	Yes
Source of samples						
Healthy animals	Yes	Yes	Yes	Yes	Yes	No
Diseased animals	Yes	Yes	Yes	Yes	Yes	Yes
Food	Yes	No	No	No	No	No
Healthy humans	No	No	No	No	No	No
Diseased humans	Yes	No	No	No	No	No
Bacteria						
<i>Salmonella</i>	Yes	Yes	Yes	Yes	Yes	No
<i>Campylobacter</i>	Yes	Yes	Yes	Yes	Yes	No
<i>E. coli</i>	Yes	Yes	Yes	Yes	Yes	No
Enterococci	Yes	Yes	Yes	Yes	Yes	No
Animal pathogens	Yes (limited)	Yes (limited)	Yes (limited)	Yes (limited)	No	Yes, all major disease-causing bacteria in cattle, swine and poultry

CEESA EARS-Net: European Animal Health Study Centre, European Antimicrobial Resistance Surveillance Network
 CEESA VetPath: Veterinary Pathogen Study Group
 CIPARS: Canadian Integrated Program for Antimicrobial Resistance Surveillance
 CLSI: Clinical and Laboratory Standards Institute
 DANMAP: Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
 EUCAST: European Committee on Antimicrobial Susceptibility Testing
 EUCAST ECV: European Committee on Antimicrobial Susceptibility Testing, Epidemiological Cut-off Values
 GERM-Vet: German Resistance Monitoring in Veterinary Medicine
 ITAVARM: Italian Veterinary Antimicrobial Resistance Monitoring
 JSC: Japanese Society of Chemotherapy

JVARM: Japanese Veterinary Antimicrobial Resistance Monitoring
 MARAN: Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands
 MIC: minimum inhibitory concentration
 NARMS: National Antimicrobial Resistance Monitoring System
 NORM-Vet: Norwegian Veterinary Antimicrobial Resistance Monitoring
 PFGE: pulsed-field gel electrophoresis
 SFM: Société Française de Microbiologie
 SRGA: Swedish Reference Group for Antibiotics
 SVARM: Swedish Veterinary Antimicrobial Resistance Monitoring
 VAV: Spanish Veterinary Antimicrobial Resistance Surveillance Network

Need for harmonisation

Franklin *et al.* (20) published a guide on the harmonisation of national AMR monitoring programmes in animals and animal-derived foods on behalf of the World Organisation for Animal Health (OIE). In addition, the OIE *Terrestrial Animal Health Code* (the *Terrestrial Code*) also contains a chapter on harmonisation of national AMR surveillance and monitoring programmes (38) (this guideline is currently under revision). The objective of both documents was to encourage the generation of comparable data from national monitoring systems in order to compare situations at the national and international level. Other stakeholders have also drawn attention to the need for harmonisation and standardisation. For instance, the European Food Safety Authority (EFSA) has issued several reports describing the need to harmonise national surveillance in Europe, most notably in the most recently published zoonoses report (17) and the Joint Opinion on Antimicrobial Resistance (22) from the European Centre for Disease Prevention and Control (ECDC), EFSA, the European Medicines Agency (EMA) and the Scientific Committee on Emerging and Newly Identified Health Risks.

The driving need for harmonisation is that surveillance schemes do not all define resistance in the same way (31). This means that it is not possible simply to compare resistance rates from different surveillance schemes as they are not always measuring the same parameter. Indeed, even within national surveillance schemes, methods of analysis have changed over time so that the percentage resistance values may not be comparable. There are two fundamental reasons for this:

- the trend for ‘resistance’ to be defined by the epidemiological cut-off value rather than by the long-established clinical breakpoint
- there is no agreed standardisation on how to define the epidemiological or wild-type cut-off value, although Turnidge *et al.* (33) and Kronvall (23) have proposed ways forward.

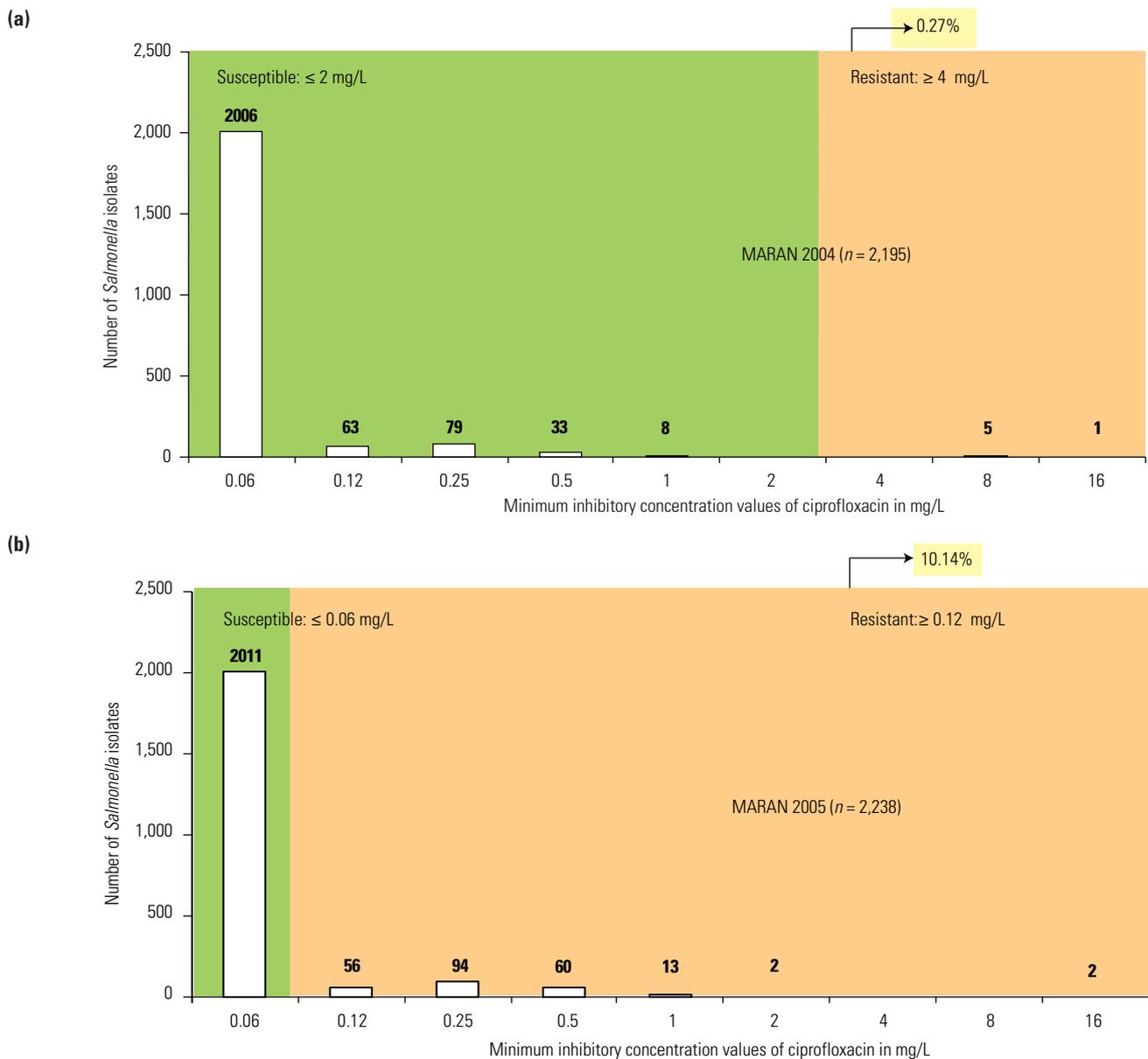
While the use of epidemiological cut-off values might be important to detect decreased susceptibility, it is inappropriate to use this value to determine the percentage of clinical resistance (32). Additionally, while it is intuitive that decreased antimicrobial susceptibility may in time lead to clinical resistance, surveillance data do not, in all cases, support this hypothesis.

European surveillance programmes, such as DANMAP, MARAN and SVARM, use epidemiological cut-off values to determine resistance, but they do not use the same values in all cases. In Spain, VAV uses a combination of epidemiological cut-off values and clinical breakpoints.

The Swedish programme, SVARM-2007 (5), states that, while it uses epidemiological cut-off values to determine ‘resistance’, it should be understood that this does not always imply clinical resistance. Similarly, Aarestrup *et al.* (1) report that an isolate might, through mutations or gene transfer, develop reduced susceptibility to a given antimicrobial but still have a sufficiently low MIC to allow successful therapy. It is for this reason that the NARMS programme in the USA, through using clinical breakpoints, truly represents an appropriate measure of clinical resistance.

A change from clinical breakpoints to epidemiological cut-off values when determining the resistance percentage does matter, depending, of course, on the class of antimicrobial and the bacteria of interest. One example that illustrates the point involves *Salmonella* and fluoroquinolones. In MARAN-2004 (34), ciprofloxacin resistance in all *Salmonella* ($n = 2,195$) was reported to be 0.3%, applying a clinical breakpoint of ≥ 4 mg/L. In MARAN-2005 (35), ciprofloxacin resistance in all *Salmonella* ($n = 2,238$) was reported to be 10.1%, as the epidemiological cut-off value of ≥ 0.12 mg/L was used, yet there was no change in the population susceptibility distribution (Figs 1a & 1b). The reader may be misled into believing that clinical resistance has increased by 37.6-fold from one year to another. Here, the differentiation between decreased susceptibility and clinical resistance is important. Similarly, the level of avian *E. coli* resistance to ciprofloxacin amounted to 0.3% before 2005 (34), but a similar level of resistance (2.6%) was defined as 50.8% afterwards (35), simply because of a change of definitions, resulting in the inclusion of decreased susceptible isolates. As an alternative to the indication of percentage of decreased susceptibility and percentage of clinical resistance, using ‘percentage of non-wild-type’ (i.e. in this example, 50.8%) may avoid misunderstandings, and can be supplemented with the ‘percentage of clinical resistance’ (i.e. 2.6%).

The changes introduced by the respective surveillance schemes occur largely as a result of the evolution of thinking on antimicrobial susceptibility distributions for wild-type bacterial populations, i.e. those strains not carrying acquired antimicrobial resistance determinants. These changes raise the question of how epidemiological cut-off values are determined. Epidemiological cut-off values have been published by EUCAST (16). In Sweden, SVARM clearly states that EUCAST values are used for interpreting susceptibility testing of zoonotic (*Salmonella* and *Campylobacter*) and indicator bacteria (*E. coli* and enterococci). Where no EUCAST cut-off value is available, a value is defined on the basis of the actual MIC distributions obtained in the SVARM programme. The SVARM-2007 programme (5) also states that this approach was used for ciprofloxacin and avian *E. coli*, despite EUCAST values being available, because the recommended EUCAST epidemiological cut-



MARAN: Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands

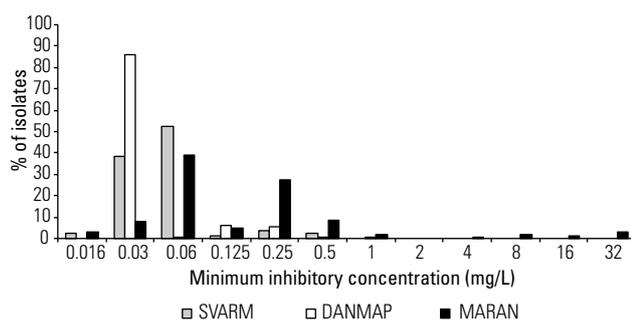
Fig. 1

Distribution of ciprofloxacin minimum inhibitory concentration values among *Salmonella* isolates collected in the Netherlands' MARAN studies of 2004 and 2005 and percentages of resistance resulting from the use of clinical breakpoints in 2004 (a) and epidemiological cut-off values in 2005 (b)

off value (0.06 mg/L) cuts through the wild-type distributions of MICs in SVARM-2007 (5), in a manner not in agreement with the concept of wild-type distributions. This causes an erroneously high frequency of resistance, i.e. 60% resistance with interpretive criteria of 0.06 mg/L as against 7% with 0.12 mg/L. Indeed, this is not only apparent from the SVARM data but is also true for MARAN-2007 (36), which, like SVARM, uses an epidemiological cut-off value of 0.12 mg/L for ciprofloxacin and *E. coli*, resulting in a decreased susceptibility of 82% for ciprofloxacin. Thus, DANMAP calculates ciprofloxacin resistance in *E. coli* as 0.06 mg/L

(12); MARAN (36) and SVARM (5) use 0.12 mg/L and VAV uses 4 mg/L (27) as the basis for resistance calculation. This has resulted in the resistance values of *Salmonella* to ciprofloxacin that are presented in the EFSA report (17) for the Netherlands being different from those presented within the Netherlands' own national surveillance monitoring programme, MARAN (36).

From these examples, it is clear that harmonising how wild-type distributions are determined is crucial. It is apparent that the EUCAST-determined wild-type distributions (largely from non-animal isolates) are not



DANMAP: Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
 MARAN: Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands
 SVARM: Swedish Veterinary Antimicrobial Resistance Monitoring

Fig. 2

Susceptibility distributions for ciprofloxacin and avian *Escherichia coli* derived from veterinary antimicrobial resistance surveillance programmes in Sweden, Denmark and the Netherlands in 2007

always consistent with those from animal surveillance. Figure 2 presents susceptibility distributions for ciprofloxacin and *E. coli* derived from SVARM (5), DANMAP (12) and MARAN (36) in 2007. The data suggest that the wild-type population of MARAN or SVARM does include that part of the population with MIC values of 0.06 mg/L, emphasising the need to reach consensus on how wild-type population distributions are determined.

Antibiotic consumption

Antibiotic consumption in human medicine

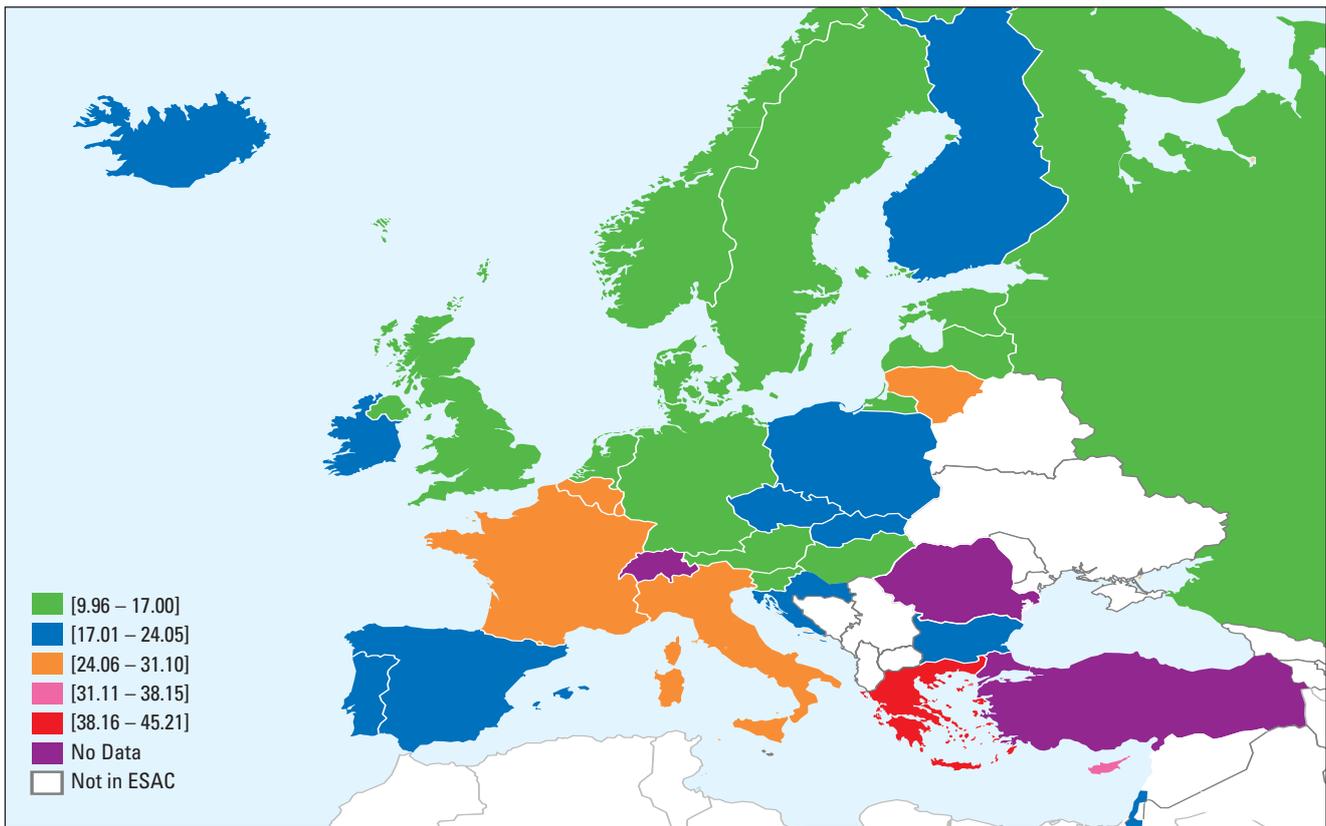
The basic unit for consumption of antimicrobial agents in human medicine is the defined daily dose (DDD). According to the definition of the World Health Organization (WHO), DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It should be noted that the number of DDIs for each antimicrobial agent is a technical unit of measurement and not necessarily a measure of good practice (19).

There are numerous studies in various countries which aim to determine the consumption of antimicrobial agents in human medicine, differentiated by their use in hospital care and in ambulatory care (i.e. outpatient care or in the care of a medical practitioner). In Germany, for example, data on antimicrobial consumption in ambulatory care were mainly derived from the databases of the health insurance companies while data on hospital consumption were obtained from two major surveillance projects: the Medical Antibiotic Use Surveillance and Evaluation (MABUSE) network and Surveillance of Antibiotic Consumption and Resistance in Intensive Care (SARI

(26). In other European countries, data on antimicrobial consumption in ambulatory care were also derived either from health insurance companies (e.g. Austria, Belgium, the Czech Republic, Spain and Luxembourg), medicines agencies (e.g. Finland, France, Italy, Denmark and Estonia), marketing research companies (e.g. Bulgaria, Hungary, Ireland, Croatia and Russia), community pharmacists (e.g. the Netherlands and Sweden), the Ministry of Health (e.g. Malta and Portugal), national institutes (e.g. Norway and Slovenia) or the National Health Fund (e.g. Poland). Data on antimicrobial consumption in hospital care were also obtained either from these sources or from national hospital networks (e.g. Ireland, Norway and Slovenia). A detailed description of consumption data, by country and year, is available from the home page of the ESAC project (<http://app.esac.ua.ac.be/public/>). This was launched in November 2001 as a monitoring programme funded by the EU Directorate-General for Health and Consumers, which aimed to collect standardised, harmonised and comparable data on antibiotic consumption. It is currently funded by the ECDC. The ESAC project collects comprehensive antimicrobial consumption data from the ambulatory and hospital-care sectors in 35 countries in Europe. When comparing the different countries by consumption data in ambulatory care, the most recent DDIs for the year 2008 varied between 9.96 (Russia) and 45.21 (Greece). Latvia (10.96), the Netherlands (11.24), Estonia (11.88), Germany (14.54), Sweden (14.60) and Austria (14.65) were at the lower end of the scale, whereas Belgium (27.66), France (27.99), Italy (28.45) and Cyprus (32.78) were at the higher end (Fig. 3). It should be noted that approximately 85% to 90% of all prescriptions in ESAC-participating countries are given in ambulatory care.

In all countries included in the ESAC project, penicillins were the most frequently used antimicrobial agents in both ambulatory and hospital care (with amoxicillin as the most prescribed drug in this class). In ambulatory care, the second most frequently used antimicrobial classes were either macrolides-lincosamides-streptogramins (e.g. Greece, Italy, France, Slovakia, Ireland and Austria) or tetracyclines (e.g. Germany, Belgium, the United Kingdom [UK], Finland and Iceland). In hospital care, the second most frequently used antimicrobial agents were either cephalosporins and other beta-lactams (e.g. Finland, Latvia, Russia, Lithuania and Bulgaria), (fluoro-) quinolones (e.g. Italy and France) or macrolides-lincosamides-streptogramins (e.g. Ireland).

From these overall consumption figures, a detailed analysis of these prescriptions has identified differences not only according to the specialisation of the prescribing doctor and the age group of the patient, but also due to region and season. Studies in Germany summarised in the GERMAP report 2008 (26) reported that the DDIs per 1,000 inhabitants and day varied between 14.5 and 17.0 in



Source: www.esac.ua.ac.be/main.aspx?c=*ESAC2&n=50220

Fig. 3
Distribution of defined daily doses among various countries included in the European Surveillance of Antimicrobial Consumption programme

western Germany but between 9.4 and 11.5 in the eastern part. General practitioners prescribed approximately 56% of the antimicrobial agents used in ambulatory care, followed by internists (14%) and paediatricians (9%). The highest prescription rate was seen among children of less than five years of age. Moreover, due to the more frequent occurrence of respiratory tract infections in winter, antimicrobial agents which are particularly active against respiratory tract pathogens (β -lactams, macrolides and fluoroquinolones) were prescribed more often during the winter months. In contrast, antimicrobial agents that are mainly used to control urinary tract infections (trimethoprim-sulfamethoxazole, nitrofurantoin) did not show seasonal variations. Similar observations on regional differences and seasonal fluctuations have been made in the ESAC study (15).

Antibiotic consumption in veterinary medicine

The OIE *Terrestrial Code* has a chapter (currently under revision) which includes recommendations for monitoring the quantities of antimicrobials used in animal husbandry by OIE Member Countries, in order to evaluate usage

patterns by antimicrobial class (39). This guideline is used by France, which gathers information on the volumes of the active ingredients sold by drug companies and attempts to apportion these volumes to the various target species. This method has the same shortcomings as those used by other countries, where the reasons behind trends, such as disease outbreaks and other prevailing conditions, are not addressed.

Grave *et al.* (21) compared sales of veterinary antibacterial agents from ten European countries, and argued that data generated from surveying the use of veterinary antibacterial agents are essential to identify and quantify risk factors for the development and occurrence of resistance in animals, as well as for their impact on human health. Whilst a number of the national AMR surveillance programmes also report on usage, it is important to understand the limitations of such data. The conclusion from Grave *et al.* (21) was that there appears to be a wide variation between countries in the use of veterinary antimicrobial agents that cannot be explained by differences in the demographics of animal species. Grave *et al.* suggest that further analyses of antimicrobial use, broken down by animal species, age group, dosing, animal

husbandry and transport of animals for slaughter in other countries, would be required to identify the factors underlying these differences. One immediate observation is that, in the Netherlands, as of May 2010, 30% of pigs were exported for slaughter, according to the Product Boards for Livestock, Meat and Eggs (www.pve.nl), thus making comparisons based on live weight at slaughter difficult. There are also significant issues with dosing, as some countries predominantly use antibiotics, depending on the product, at a licensed dose rate of 30 mg/kg, whereas, in others, the dominant antimicrobials have a licensed dose rate of 10 mg/kg. In this respect, comparisons based on the tonnage used, without correcting for the potency of the various antimicrobials, can be very misleading. There are also issues with different animal species. For example, the use of antimicrobials in grass-reared beef is completely different from the use of antibiotics in intensively reared pigs. With these factors in mind, it is clear that authors should take these issues into account before publishing their data, enabling readers to make more valid comparisons between countries.

However, even when usage data are compiled, we need to understand that these data do not always explain how the antimicrobials have been used, in what formulation, for what species or why they were chosen; the availability of this information varies throughout the EU. An additional problem with national estimates, where they exist, is the current lack of understanding of the biological relevance of these aggregated data to the antimicrobial resistance data derived from animal, human, food and environmental samples. So, while it is agreed that antimicrobial usage data are important, and indeed essential, to monitor and interpret resistance trends in both animals and people, these data should never be used as definitive proof of a causal association between the two.

Ideally, for antimicrobial usage data to have relevance to resistance-development patterns, these data should be recorded on the farm, along with the indication for treatment, the route of administration, the dose and duration and other relevant data, such as prevailing disease patterns and incidence. Only when such data are provided can information on the use of antimicrobials be used to assess cause and effect with any great accuracy. However, the collection of such data is understood to be a challenge because of the resources it would require.

There is clearly a real need to collect data on antimicrobial use throughout Europe in a consistent manner, to help in interpreting information on resistance monitoring and resistance development. These data could then be used as some of the inputs for science-based risk assessment before considering risk management options. In Europe, data are collected in several EU Member States (the Netherlands, Denmark, Sweden, the UK and France) but there are discrepancies in the type of information that is being

collected and reported. It is argued that any system should follow certain basic principles, including the following:

- data should be collected in a reliable, efficient, consistent and verifiable manner, providing confidentiality for pioneer and generic products
- cumulative data should be presented in a format that makes them scientifically useful to researchers, risk assessors and other stakeholders, yet balances the level of detail with the resources necessary to obtain it
- data should be collected together with contextual data on animal production, food production, disease prevalence and other external factors that may influence antimicrobial use.

In addition, risk managers should consult with stakeholders in interpreting the data.

The situation in Europe is improving, as a result of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project, launched by EMA in September 2009. This initiative followed a request from the European Commission to develop a harmonised system to collect and report data from Member States on the use of antimicrobial agents in animals. To gain experience in analysing and reporting such data at the Community level, the EMA has published a report in which it took existing information on the sales of veterinary antimicrobial agents from those countries with established surveillance programmes, categorised it and reported it in a harmonised manner (18). Eight countries provided aggregated data on sales of veterinary antimicrobial agents, by tonne of active ingredient, for the period between 2005 and 2009: i.e. the Czech Republic, Denmark, Finland, France, the Netherlands, Norway, Sweden and the UK, while Switzerland provided sales data for the years from 2006 to 2009. Only two countries, the Czech Republic and Finland, deviated from the inclusion criteria by including dermatological preparations and preparations for sensory organs. Sales for use in farmed fish were not included in the data from Norway and Sweden. To normalise the sales data over time within each country, by animal population, the annual sales figure of each country was divided by the estimated weight, at treatment, of the livestock and slaughter animals in the same year. This estimate of use takes into account that animals transported for slaughter or fattening in another Member State are likely to have been treated in the country of origin. The authors showed the importance of taking animal demographics into account when assessing trends in the sales of veterinary antimicrobial agents.

One major finding of the report was the substantial difference in prescribing patterns of veterinary

antimicrobial agents among countries. In general, the authors suggested that these variations may be due to differences in:

- the availability of veterinary antibacterial products on the market from country to country
- prices
- risk-management measures
- the prescribing behaviour of veterinarians
- animal production systems (e.g. veal calves as opposed to beef cattle on pasture)
- the general infectious disease situation in each country.

The report also acknowledged that antimicrobial class repartition and prescribing patterns vary among species, and so variations in animal demographics between countries may partially explain the observed correlations. However, other factors also need to be considered. The authors recognised that, since the data presented in the report were aggregated per antimicrobial class, they did not allow for more in-depth analysis, yet to identify the factors underlying the observed differences, more detailed data are needed. For example, as some agents are administered in much higher dosages than others (e.g. tetracyclines *versus* cephalosporins), we need to continue to refine our tools for analysing data on the sales of antimicrobial agents. The ESVAC project is a welcome move forward.

Clearly, any collection system needs to be robust, simple and practical, based on sales of active ingredient by formulation for the various classes of antimicrobials and

apportioning animal species to the sales. For example, the concept of the ‘average daily dose’ has the advantages of:

- more accurately predicting the exposure of animals of different weights to antibiotics
- being more easily used for comparison over time between countries
- addressing the differences in potency between antimicrobials of the same class.

Such indicators – and indeed there may be others that will be proposed as a result of the ESVAC initiative – should be developed as appropriate.

Many authorities have recognised that information presented as aggregate data collected nationally has shortfalls. This may be perfectly acceptable in small countries like the Netherlands and Denmark, where prevailing conditions may not vary that widely across their territories. However, in larger countries, such as France and Germany, conditions may vary greatly from region to region, as may disease incidence. Reporting aggregate data therefore makes it difficult to interpret the information if there have been disease outbreaks in certain species, such as pigs or poultry, in certain parts of the country, but these are unknown to the compilers of the report.

In conclusion, the authors would like to emphasise the need to collect data on antimicrobial use throughout Europe in a consistent manner, to assist in interpreting information on resistance monitoring and resistance development. Such data could then be used as partial inputs for science-based risk assessments before considering risk management options.



Surveillance et contrôle de la résistance aux antimicrobiens et de la consommation d’antibiotiques en médecine humaine et vétérinaire

P. Silley, S. Simjee & S. Schwarz

Résumé

Plusieurs pays du monde conduisent des études visant à surveiller et à contrôler la résistance aux antimicrobiens des bactéries d’origine humaine et animale, ainsi que la consommation d’antibiotiques en médecine humaine et vétérinaire. En particulier, dans le domaine vétérinaire des programmes ont été mis en place ciblant les principales bactéries, que celles-ci soient à potentiel zoonotique,

d'origine alimentaire ou importantes pour la santé animale. Chaque année, le système de surveillance européenne des consommations d'antibiotiques résume et évalue cette consommation dans plusieurs pays européens, aussi bien en médecine de ville qu'à l'hôpital. En revanche, très peu de pays recensent les informations disponibles sur la consommation d'antibiotiques en médecine vétérinaire, et le type d'informations obtenues ou notifiées varie beaucoup d'un pays à l'autre. Afin de résoudre cette difficulté, l'Agence européenne des médicaments a lancé en septembre 2009 le système européen de surveillance de la résistance aux antimicrobiens (EARSS), qui vient de publier son premier rapport. La comparaison des différentes études de surveillance et de contrôle de la résistance antimicrobienne et des consommations d'antibiotiques en médecine humaine et vétérinaire a fait apparaître la nécessité d'une harmonisation accrue en la matière.

Mots-clés

Chiffre d'affaires – Développement de la résistance – Harmonisation – Soins à l'hôpital – Soins ambulatoires – Test de sensibilité – Valeur de rupture clinique.



Vigilancia y seguimiento de la resistencia a los antimicrobianos y el consumo de antibióticos en personas y animales

P. Silley, S. Simjee & S. Schwarz

Resumen

En varios países del mundo se han llevado a cabo estudios de vigilancia y seguimiento de las resistencias a agentes antimicrobianos en las bacterias de origen humano o animal y del consumo de esos agentes por parte de personas y animales. En el terreno de la veterinaria, en particular, se han instituido programas para estudiar específicamente bacterias de importancia zoonótica, transmitidas por los alimentos y/o de interés veterinario. Cada año, como parte del proyecto de vigilancia europea del consumo de antimicrobianos [*European Surveillance of Antimicrobial Consumption*], se resume y evalúa el consumo de antimicrobianos por los pacientes de la asistencia ambulatoria u hospitalaria de muchos países europeos. En cambio, solo unos pocos países disponen de datos sobre el consumo de antimicrobianos en la medicina veterinaria, y el tipo de información obtenida es dispar. Para responder a este problema, en septiembre de 2009 la Agencia Europea del Medicamento puso en marcha el proyecto de vigilancia europea del consumo de antimicrobianos de uso veterinario [*European Surveillance of Veterinary Antimicrobial Consumption*] y acaba de publicar su primer informe. La comparación entre los estudios de vigilancia y seguimiento de la resistencia a los antimicrobianos y el consumo de estos agentes en el ser humano y en los animales pone de manifiesto la necesidad de avanzar hacia un mayor grado de armonización.

Palabras clave

Aparición de resistencias – Armonización – Asistencia ambulatoria – Asistencia hospitalaria – Cifras de ventas – Prueba de sensibilidad – Valor crítico clínico.



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