

Defining the scope of the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet): a bottom-up and One Health approach

Rodolphe Mader^{1*} on behalf of EU-JAMRAI†, Clémence Bourély², Jean-Philippe Amat³, Els M. Broens⁴, Luca Busani⁵, Bénédicte Callens⁶, Paloma Crespo-Robledo⁷, Peter Damborg⁸, Maria-Eleni Filippitzi^{9,10}, William Fitzgerald¹¹, Thomas Grönthal¹², Marisa Haenni¹³, Annet Heuvelink¹³, Jobke van Hout¹³, Heike Kaspar¹⁴, Cristina Muñoz Madero⁷, Madelaine Norström¹⁵, Karl Pedersen¹⁶, Lucie Pokludova¹⁷, Fabiana Dal Pozzo⁶, Rosemarie Slowey¹⁸, Anne Margrete Urdahl¹⁵, Alkiviadis Vatopoulos¹⁹, Christos Zafeiridis²⁰ and Jean-Yves Madec¹

¹University of Lyon, French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Laboratory of Lyon, Antibiotic Resistance and Bacterial Virulence Unit, 31 Avenue Tony Garnier, 69007 Lyon, France; ²Direction générale de l'alimentation, Bureau de la santé animale, 75015 Paris, France; ³University of Lyon, French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Laboratory of Lyon, Epidemiology and Support to Surveillance Unit, 31 avenue Tony Garnier, 69007 Lyon, France; ⁴Utrecht University, Faculty of Veterinary Medicine, Department of Biomolecular Health Sciences, Yalelaan 1, 3584 CL Utrecht, The Netherlands; ⁵Istituto Superiore di Sanità, Center for Gender-Specific Medicine, Viale Regina Elena 299, 00161 Rome, Italy; ⁶Antimicrobial Consumption and Resistance in Animals—AMCRA, Galileelaan 5/02, 1210 Brussels, Belgium; ⁷Agencia Española del Medicamento y Productos Sanitarios (AEMPS), Coordinación del Plan Nacional Antibióticos (PRAN), calle Campezo 1, EDF. 8. 28022 Madrid, España; ⁸University of Copenhagen, Department of Veterinary and Animal Sciences, Stigbøjlen 4, 1870 Frederiksberg C, Denmark; ⁹Sciensano, Veterinary Epidemiology Unit, Belgian Research Centre for Health, Rue Juliette Wytsmanstraat 14, 1050 Brussels, Belgium; ¹⁰Laboratory of Economics of Animal Production, Faculty of Veterinary Medicine, Aristotle University of Thessaloniki, 54124, Greece; ¹¹Limerick Regional Veterinary Laboratory, Department of Agriculture, Food and the Marine, Knockalishen, Limerick V94 WK44, Ireland; ¹²University of Helsinki, Department of Equine and Small Animal Medicine, Viikintie 49, 00790 Helsinki, Finland; ¹³Royal GD, Arnsbergstraat 7, 7418 EZ Deventer, The Netherlands; ¹⁴Federal Office of Consumer Protection and Food Safety, Mauerstrasse 39-42, 10117 Berlin, Germany; ¹⁵Norwegian Veterinary Institute (NVI), Pb 64, N-1431 Ås, Norway; ¹⁶National Veterinary Institute, Department of Animal Health and Antimicrobial Strategies, Ulls väg 2B, SE-751 89 Uppsala, Sweden; ¹⁷Institute for State Control of Veterinary Biologicals and Medicines (ISCVBM), Hudcova 56 A, Brno, The Czech Republic; ¹⁸Department of Agriculture, Food and the Marine Laboratories, Backweston, Celbridge, Co. Kildare W23 VW2C, Ireland; ¹⁹University of West Attica, Department of Public Health Policy, School of Public Health, Athens, Greece; ²⁰Ministry of Rural Development and Food, 2 Acharnon St., Athens, Greece

*Corresponding author. E-mail: mader.rodolphe@gmail.com

†Partners are listed in the Acknowledgements section.

Received 10 May 2021; accepted 11 November 2021

Background: Building the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet) was proposed to strengthen the European One Health antimicrobial resistance (AMR) surveillance approach.

Objectives: To define the combinations of animal species/production types/age categories/bacterial species/specimens/antimicrobials to be monitored in EARS-Vet.

Methods: The EARS-Vet scope was defined by consensus between 26 European experts. Decisions were guided by a survey of the combinations that are relevant and feasible to monitor in diseased animals in 13 European countries (bottom-up approach). Experts also considered the One Health approach and the need for EARS-Vet to complement existing European AMR monitoring systems coordinated by the ECDC and the European Food Safety Authority (EFSA).

Results: EARS-Vet plans to monitor AMR in six animal species [cattle, swine, chickens (broilers and laying hens), turkeys, cats and dogs], for 11 bacterial species (*Escherichia coli*, *Klebsiella pneumoniae*, *Mannheimia haemolytica*, *Pasteurella multocida*, *Actinobacillus pleuropneumoniae*, *Staphylococcus aureus*, *Staphylococcus pseudintermedius*, *Staphylococcus hyicus*, *Streptococcus uberis*, *Streptococcus dysgalactiae* and *Streptococcus*

suis). Relevant antimicrobials for their treatment were selected (e.g. tetracyclines) and complemented with antimicrobials of more specific public health interest (e.g. carbapenems). Molecular data detecting the presence of ESBLs, AmpC cephalosporinases and methicillin resistance shall be collected too.

Conclusions: A preliminary EARS-Vet scope was defined, with the potential to fill important AMR monitoring gaps in the animal sector in Europe. It should be reviewed and expanded as the epidemiology of AMR changes, more countries participate and national monitoring capacities improve.

Introduction

Antimicrobial resistance (AMR) cannot be tackled effectively without well-performing monitoring systems, covering the animal and human sectors.^{1,2} Currently, the ECDC coordinates the European Antimicrobial Resistance Surveillance Network (EARS-Net), which monitors AMR in invasive bacterial isolates from humans with bloodstream infections or meningitis,³ and the European Food and Waterborne Diseases and Zoonoses Network (FWD-Net), which monitors AMR in human *Salmonella* and *Campylobacter* infections.⁴ In the food sector, the European Food Safety Authority (EFSA) coordinates active monitoring of AMR in indicator commensal bacteria (*Escherichia coli* primarily, but countries may also report for *Enterococcus faecalis* and *Enterococcus faecium*) and zoonotic bacteria (*Salmonella* spp., *Campylobacter coli* and *Campylobacter jejuni*), according to Directive 2003/99/CE and Commission Implementing Decision (EU) 2020/1729.⁵ Caecal samples from healthy food-producing animals (cattle under 1 year, chickens, turkeys and swine) are taken at slaughterhouse, as well as samples of meat thereof at retail. As no European system currently monitors AMR in clinical isolates from diseased animals, data on AMR hotspots in specific animal infections are still lacking at a European level, although necessary to tailor strategies to rationalize antimicrobial usage in the animal sector.⁶ However, national monitoring systems for AMR in clinical isolates from diseased animals are in place in at least 12 European countries.⁷ In addition, veterinary AMR monitoring programmes exist outside of Europe.⁸

In this context, the EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI), co-funded by the Third Health Programme of the EU, proposed to establish the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet), to strengthen a One Health AMR surveillance approach in Europe.⁶ During EU-JAMRAI, it was agreed that EARS-Vet should work as a European network of national monitoring systems in diseased animals (similarly to EARS-Net) and aim to complement and integrate with the AMR monitoring systems of the ECDC and EFSA. Its objectives shall be to report on the AMR situation, follow AMR trends and detect emerging AMR in bacterial pathogens of animals in Europe. This information would contribute to: advising policy makers on interventions to mitigate AMR in the animal sector; monitoring the impact of European efforts to tackle AMR in the animal sector; evaluating or revising marketing authorizations of veterinary antimicrobials; supporting antimicrobial stewardship initiatives, especially the development of veterinary antimicrobial treatment guidelines; generating missing epidemiological cut-off values (ECOFFs) and then clinical breakpoints for the interpretation of antimicrobial susceptibility testing (AST) results in veterinary medicine; assessing the risk of

transmission of resistant bacteria or resistance genes between animals and humans via non-food-related routes, e.g. by direct contact between humans and companion or food-producing animals; and estimating the burden of AMR in animal health, e.g. attributable animal deaths caused by infections with antimicrobial-resistant bacteria.

Following a review and analysis of national AMR monitoring systems in clinical animal isolates,⁷ EARS-Vet plans to follow EUCAST standards, collect quantitative data (MICs or inhibition zone diameters) and interpret AST results using ECOFFs. However, until harmonization on the AST method is reached among participating countries, AST data produced by different standards shall be accepted by EARS-Vet, similarly to what EARS-Net did for two decades before accepting only those produced according to EUCAST standards.⁶

A major step in the design of EARS-Vet was the definition of its monitoring scope, i.e. the combinations of animal species/production types/age categories/bacterial species/specimens (i.e. sample types)/antimicrobials to be monitored in EARS-Vet. The present study aims to describe these combinations and the bottom-up and One Health approach that was followed to determine them.

Methods

Bottom-up approach: collection and analysis of 13 national veterinary AMR monitoring scopes

To define an EARS-Vet scope composed of combinations that are both relevant and feasible to monitor in Europe, the national veterinary AMR monitoring scopes of 13 countries were collected and analysed. Such data collection was done by completing an Excel template recording the combinations of animal species/production types/age categories/bacterial species/specimens/antimicrobials monitored by 10 countries with a national monitoring system (the Czech Republic, Denmark, Estonia, Finland, France, Germany, Ireland, the Netherlands, Norway and Sweden) or considered as future monitoring targets in three countries that were in the process of establishing a monitoring system (Spain) or planning to build their system (Belgium and Greece) at the time of study (2019–20). The national scopes of Belgium, Greece and Spain were defined via the consultation of relevant national experts, who were advised to follow the recommendations of the World Organisation for Animal Health in this regard.⁹ These national veterinary AMR monitoring scopes, which may already reflect a One Health perspective, were analysed to identify the most frequently included animal species, production types, age categories, bacterial species, specimens and antimicrobials.

One Health approach: exploring the feasibility for countries to monitor AMR in the bacterial species monitored by EARS-Net

Due to possible One Health implications and to explore integration opportunities between EARS-Net and EARS-Vet, the 13 countries sharing their

national veterinary AMR monitoring scope were also asked about the feasibility to monitor AMR in clinical animal isolates for seven of the eight bacterial species monitored by EARS-Net (*E. coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *E. faecalis* and *E. faecium*), among the animal species already included in their national monitoring scope. *Streptococcus pneumoniae*, also monitored in EARS-Net, was not included in this survey as it is primarily a human pathogen. For each combination of animal species/bacterial species, countries had the choice between three answers: (i) the monitoring is feasible and the combination is already included in the national scope ('feasible and included'); (ii) the monitoring is feasible, but the combination is not included in the national scope ('feasible, but not included'); or (iii) the monitoring is 'currently not feasible'. Justifications were required in the case of answering (ii) or (iii).

Expert consensus on the EARS-Vet scope

Guided by the information generated through the bottom-up and One Health approach, a group of 26 experts (veterinary and human microbiologists, veterinary epidemiologists and Ministry representatives) from 14 European countries (the 13 countries that shared their national scope and Italy) defined the EARS-Vet scope by consensus through six teleconferences in 2020. The decision process followed this stepwise approach: (i) determination of the animal species; (ii) determination of the bacterial species within each selected animal species; (iii) determination of accepted clinical specimens for each combination of animal species/bacterial species; (iv) determination of stratification per production type and/or age category for each combination of animal species/bacterial species/specimen; and (v) determination of the antimicrobials for each combination of animal species/bacterial species/specimen/production type/age category.

Results

National veterinary AMR monitoring scopes were collected from 13 countries, with 10 of these having a monitoring system in place and 3 others in the process of establishing or planning to build their systems. These scopes are available in Table S1 (available as [Supplementary data](#) at JAC Online).

Determination of the animal species

Figure 1 shows the animal species included in the 13 national scopes. All countries incorporated cattle and swine, with a majority also including chickens and turkeys among food-producing animals. Nine countries included companion animals (cats and dogs) and four included horses. The expert panel decided to monitor in EARS-Vet the six animal species most frequently included in national scopes: cattle, swine, chickens, cats, dogs and turkeys.

Determination of the bacterial species within each selected animal species

Bacterial species determination was performed in two steps, first by considering national scopes and then by exploring the feasibility to include more EARS-Net bacteria in the EARS-Vet scope.

Figure 2 shows the bacterial species included in the 13 national scopes for each of the six chosen animal species. The expert group decided to include in the EARS-Vet scope the most frequently reported bacterial species within each animal species. No threshold defined the selection of bacterial species, but, in practice, none was selected if included by fewer than three countries. *Salmonella* was not included as it was not considered a major animal pathogen in Europe. Moreover, AMR monitoring in this bacterium has already been covered and prioritized from a public health perspective by EFSA. Although *S. aureus* is not considered among the most frequent causes of clinical infection in cats, dogs and chickens, the expert group decided to include it for these animal species (in addition to cattle where it is a frequent cause of mastitis) to address a possible risk for public health through direct contact.

The feasibility of monitoring AMR in clinical animal isolates for seven bacterial species monitored by EARS-Net (*E. coli*, *P. aeruginosa*, *K. pneumoniae*, *A. baumannii*, *S. aureus*, *E. faecalis* and *E. faecium*) is described in detail in Tables S2 and S3. The combinations that most countries found feasible to monitor and already had in their national scope were *E. coli* in cattle and swine, and *S. aureus* in cattle, whereas no country included *A. baumannii*.

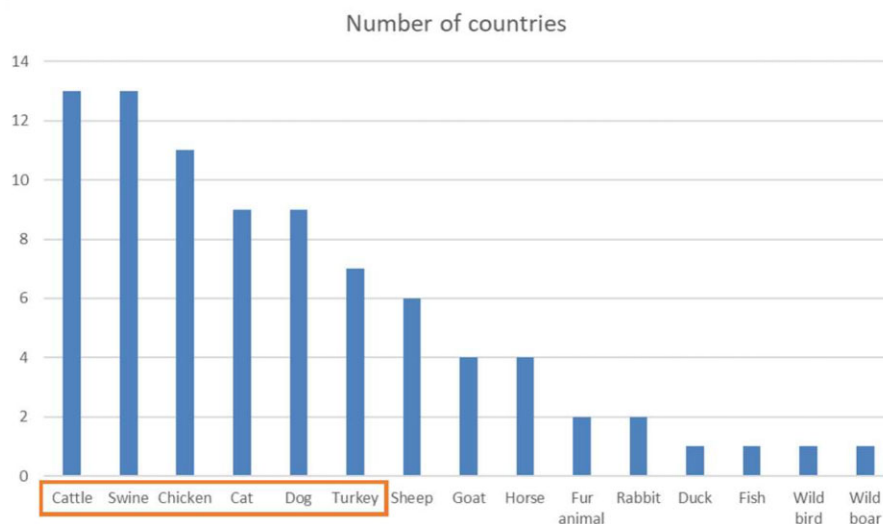


Figure 1. Distribution of the animal species present in the national veterinary AMR monitoring scopes of 13 European countries (the orange box indicates the animal species selected for the EARS-Vet scope). This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

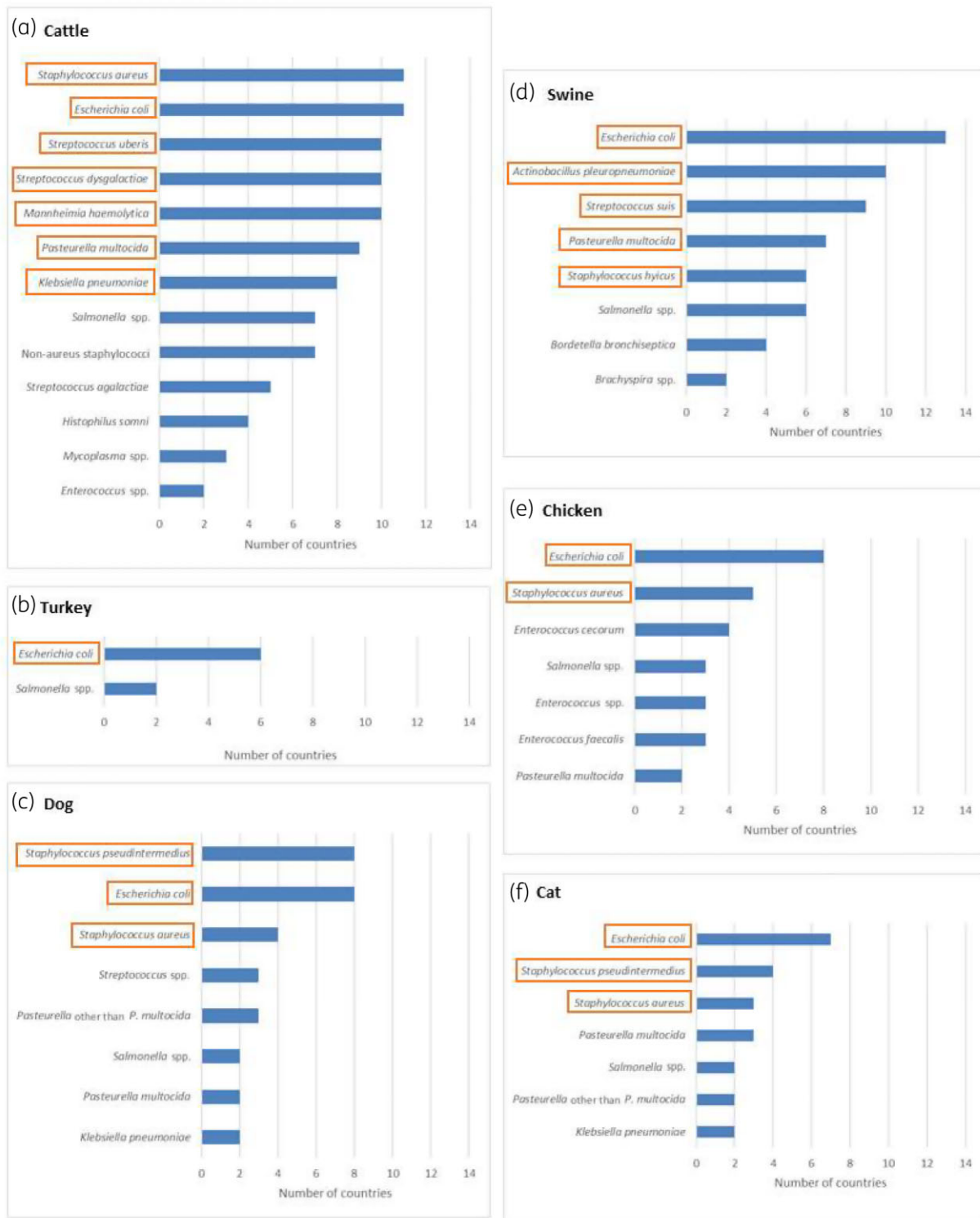


Figure 2. Distributions of the bacterial species present in the national veterinary AMR monitoring scopes of 13 European countries per cattle, swine, turkey, chickens, cats and dogs (orange boxes indicate the bacterial species selected for the EARS-Vet scope). Only bacterial species selected by at least two countries are displayed. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

Combinations of bacterial species/animal species that were categorized 'feasible, but not included' were assessed in order to evaluate whether countries could expand their monitoring systems as part of the EARS-Vet programme. For only 16 (out of 42) animal species/bacterial species combinations the answer 'feasible, but not included' was given. However, the number of countries never exceeded three, except for the combination dog/*E. faecalis*. The most frequent reason for such an answer was that the bacterium was not a monitoring priority. The most common reason for reporting 'currently not feasible' for an EARS-Net bacterium was that it was too rarely obtained from animal clinical specimens (countries used thresholds ranging from 10 to 100 isolates minimum per year). Finally, the expert group concluded that the EARS-Vet scope should not include more bacterial species than those initially selected, based on national scopes.

Determination of accepted specimens for each animal species/bacterial species combination

Table 1 summarizes expert decisions on the specimens to be accepted within EARS-Vet. The monitoring of AMR could be stratified per specimen only for *E. coli* in cattle, between milk samples (in the case of mastitis), inner organs or blood (in the case of septicaemia) and faeces or intestinal content (in the case of diarrhoea). In swine, it was decided to monitor *E. coli* in faeces or intestinal

content only, as national systems rarely monitor it in blood or inner organs. When it comes to *E. coli* from swine faecal or intestinal samples, 8 of the 10 countries with a monitoring system in place monitor AMR only for virulent isolates or stratify their monitoring between virulent and non-virulent isolates, identified by PCR, serotyping, haemolytic profile or a combination of them. Thus, the expert group advised EARS-Vet to collect data on the haemolytic profile, serotypes and virulence factors of swine *E. coli* to stratify AMR monitoring based on typing information.

Determination of stratification per production type and age category for each animal species/bacterial species/specimen combination

Some participating countries stratify their national monitoring per production type and age category. For instance, in the Czech Republic, AMR monitoring in swine pathogens is stratified between pre-weaning piglets, post-weaning piglets, fattening pigs and sows. However, this is not systematic across national monitoring systems. Experts pointed out that this information was often missing in their national databases, except for chickens, where broilers and laying hens are most often distinguished. Therefore, EARS-Vet could stratify its monitoring per production type for chickens only and not per age category (Table 1).

Table 1. Proposed animal species, production types, specimens and bacterial species to be monitored in EARS-Vet

Animal species	Production type	Specimens	Bacterial species
Cattle	any	faeces or intestinal content blood and inner organs milk	<i>E. coli</i> ^a <i>E. coli</i> <i>E. coli</i> <i>K. pneumoniae</i> <i>S. aureus</i> <i>S. uberis</i> <i>S. dysgalactiae</i> <i>M. haemolytica</i> <i>P. multocida</i>
		lungs and other samples from the lower or upper respiratory tract	<i>E. coli</i> ^a <i>Staphylococcus hyicus</i> <i>S. suis</i> <i>P. multocida</i> <i>A. pleuropneumoniae</i>
Swine	any	faeces or intestinal content inner organs (including lungs, spleen, joints etc.)	<i>E. coli</i> ^a <i>Staphylococcus hyicus</i> <i>S. suis</i> <i>P. multocida</i> <i>A. pleuropneumoniae</i>
		lungs and inner organs	<i>E. coli</i> <i>E. coli</i> <i>S. aureus</i> <i>S. aureus</i>
Chicken	broilers	inner organs (including spleen, bone marrow, joints etc.)	<i>E. coli</i>
	laying hen	inner organs (including spleen, bone marrow, joints etc.)	<i>E. coli</i>
Turkey	broilers	inner organs (including spleen, bone marrow, joints etc.)	<i>S. aureus</i>
	laying hen	inner organs (including spleen, bone marrow, joints etc.)	<i>S. aureus</i>
Dog	-	inner organs (including spleen, bone marrow, joints etc.)	<i>E. coli</i>
	-	urine skin and ear	<i>E. coli</i> <i>S. pseudintermedius</i> <i>S. aureus</i>
Cat	-	urine	<i>E. coli</i>
		skin and ear	<i>S. pseudintermedius</i> <i>S. aureus</i>

^aInformation on the virulence profile shall be collected in EARS-Vet.

Determination of antimicrobials for each animal species/bacterial species/specimen/production type combination

Different countries often monitor different antimicrobial agents for a given combination of animal species/bacterial species/specimen/production type. Therefore, the expert group decided that EARS-Vet should monitor AMR for different categories of antimicrobials: antimicrobial classes (e.g. tetracyclines), when resistance to one agent (e.g. oxytetracycline) usually implies resistance to all other agents of the class; individual antimicrobial agents (e.g. neomycin), when resistance to these agents does not usually imply resistance to the other members of their antimicrobial classes, due to disparate resistance mechanisms (e.g. aminoglycosides); and antimicrobials used to detect specific resistance phenotypes, e.g. methicillin resistance in staphylococci.

When it comes to an antimicrobial class or antimicrobials used to detect a specific resistance phenotype, EARS-Vet shall accept and collate AMR data that correspond to different antimicrobial agents, as in EARS-Net.³

Figure 3 shows the antimicrobial categories included for each of the bacterial species selected for swine. Similar figures are available for cattle (Figure S1), chickens and turkeys (Figure S2) and cats and dogs (Figure S3). In general, the antimicrobial categories most frequently included in national scopes were selected for the EARS-Vet scope, with a few notable exceptions: cephalosporins and penicillins+ β -lactamase inhibitors were not selected for *Pasteurella multocida*, *Mannheimia haemolytica* and *Actinobacillus pleuropneumoniae*, as resistance to β -lactams is not common in Europe and penicillins alone are already included;¹⁰ third-generation cephalosporins were not selected for staphylococci, as *in vitro* susceptibility testing of these agents is less reliable than other antimicrobials testing resistance to cephalosporins indirectly (i.e. those used for monitoring methicillin resistance);¹¹ amphenicols were not selected when they were not commonly used to treat the conditions in question (e.g. to treat mastitis in cattle) according to the experts, although frequently included in national scopes for several combinations of animal species/bacterial species; sulphonamides and trimethoprim were not included as separate classes in swine/*E. coli*, as they are mostly used as fixed combinations in clinical practice;¹² tildipirosin was not included for respiratory pathogens, as two other macrolides were already included in the EARS-Vet scope (tulathromycin and tilmicosin); and fusidic acid was not included for *S. aureus* and *Staphylococcus pseudintermedius* in cats and dogs, as this drug and its derivatives are only used for topical treatment in veterinary medicine¹³ (in that regard, little evidence exists between AST results and clinical efficacy when it comes to topical agents¹¹).

For bacterial species included in both EARS-Vet and EARS-Net (no common bacterial species between EARS-Vet and the AMR monitoring component of FWD-Net),⁴ all AST results for antimicrobial classes that are important from a public health perspective and monitored by EARS-Net shall also be collected,³ even though they were not frequently included in national scopes. Thus, for *E. coli* and *K. pneumoniae*, EARS-Vet shall collect AST results for piperacillin/tazobactam, carbapenems and tigecycline and, for *S. aureus*, vancomycin, rifampicin, linezolid and daptomycin.

The complete EARS-Vet scope at an antimicrobial agent level is presented in Table 2 for swine. Similar tables are available for cattle

(Table S4), chickens and turkeys (Table S5) and cats and dogs (Table S6). The lists of antimicrobial agents were determined to maximize country participation and minimize the diversity of accepted antimicrobial agents by EARS-Vet. For example, in the case of isolated *E. coli* from cats, countries reported in their national scopes: enrofloxacin, ciprofloxacin, marbofloxacin, danofloxacin among fluoroquinolones. However, all countries reporting marbofloxacin and/or danofloxacin also reported enrofloxacin, whereas some countries reported only enrofloxacin or only ciprofloxacin. Thus, the list for *E. coli* from cats comprises only enrofloxacin and ciprofloxacin.

Finally, by selecting the most frequently included antimicrobial compound for each combination, three sets of antimicrobials could be proposed and used by veterinary laboratories to cover all the combinations of veterinary relevance of the EARS-Vet scope: set A for *E. coli* and *K. pneumoniae*, ampicillin, amoxicillin+clavulanic acid, cefotaxime or ceftiofur (cefotaxime being preferred for the detection of ESBL-producing Enterobacterales), cefquinome, cefalexin, ceftiofur, nalidixic acid or flumequine, enrofloxacin, tetracycline, colistin, gentamicin, neomycin, streptomycin and sulfamethoxazole/trimethoprim; set B for *P. multocida*, *M. haemolytica* and *A. pleuropneumoniae*, penicillin or ampicillin, enrofloxacin, tulathromycin, tilmicosin, tiamulin, gentamicin, florfenicol, tetracycline and sulfamethoxazole/trimethoprim; set C for *S. aureus*, *S. pseudintermedius*, *Streptococcus suis*, *Streptococcus dysgalactiae* and *Streptococcus uberis*, penicillin, oxacillin (to detect methicillin-resistant *S. pseudintermedius*), ceftiofur (to detect MRSA), ceftiofur or cefotaxime, enrofloxacin, lincomycin, erythromycin, tetracycline, gentamicin, streptomycin, florfenicol and sulfamethoxazole/trimethoprim.

Countries may of course supplement these sets with antimicrobials of more local clinical relevance, as well as with antimicrobials included in the EARS-Vet scope with a public health perspective only (e.g. carbapenems for *E. coli*). However, field veterinary laboratories should not provide AST results for these latter antimicrobials to their customers, so as not to promote their use.

In addition to phenotypical AMR data, as a starting point for molecular AMR monitoring, the expert group also recommended EARS-Vet to collect molecular results confirming the presence of a methicillin resistance profile or differentiating isolates with ESBLs and AmpC cephalosporinases, when this information is available and by specifying the method used. However, not all countries could systematically provide this information. At the time of study, among the 10 countries with a monitoring system in place, 8 and 4 systematically tested the presence of *mec* genes in the case of suspected MRSA or methicillin-resistant *S. pseudintermedius*, respectively (9 countries monitor *S. pseudintermedius*); 5 and 3 systematically confirmed the presence of an ESBL or AmpC profile when suspected phenotypically. Other countries also carried out these analyses, but not systematically.

Discussion

In this work, consensus among experts was reached on the combinations of animal species/bacterial species/specimens/production types/antimicrobials to be monitored in EARS-Vet. Although with a primary focus on animals, strong efforts were made to define a scope that is relevant from a One Health perspective.

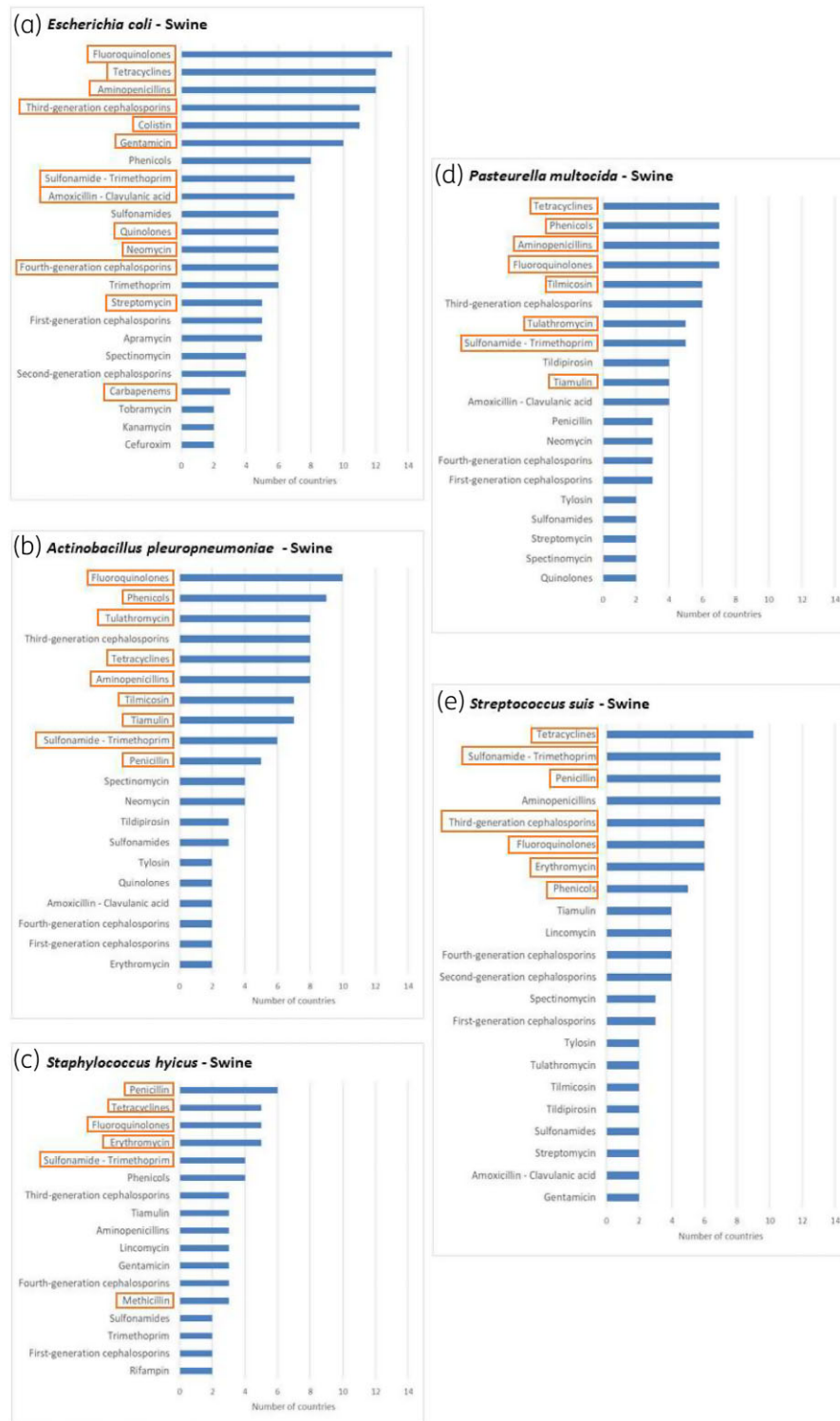


Figure 3. Distribution of antimicrobial categories present in the national veterinary AMR monitoring scopes of 13 European countries for *E. coli*, *S. suis*, *S. hyicus*, *A. pleuropneumoniae* and *P. multocida* isolated from swine (orange boxes indicate the antimicrobial categories selected for the EARS-Vet scope). Only antimicrobial categories selected by at least two countries are displayed. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

Table 2. Proposed EARS-Vet scope in terms of bacterial species and antimicrobials for swine

Bacterium	Antimicrobial category	Antimicrobial agents
<i>E. coli</i>	aminopenicillins	amoxicillin, ampicillin
	amoxicillin+clavulanic acid	amoxicillin+clavulanic acid
	third-generation cephalosporins	cefotaxime, ceftiofur
	fourth-generation cephalosporins	cefquinome, cefepime
	quinolones	flumequine, nalidixic acid
	fluoroquinolones	enrofloxacin, ciprofloxacin
	tetracyclines	tetracycline
	colistin	colistin
	gentamicin	gentamicin
	neomycin	neomycin
	streptomycin	streptomycin
	sulphonamide/trimethoprim	sulphonamide/trimethoprim
	piperacillin/tazobactam	piperacillin/tazobactam
	carbapenems	imipenem, meropenem, ertapenem
	tigecycline	tigecycline
<i>S. hyicus</i>	penicillin	penicillin
	methicillin	oxacillin, ceftiofur
	fluoroquinolones	enrofloxacin, ciprofloxacin
	erythromycin	erythromycin
	tetracyclines	tetracycline
	sulphonamide/trimethoprim	sulphonamide/trimethoprim
<i>S. suis</i>	penicillin	penicillin
	third-generation cephalosporins	ceftiofur
	fluoroquinolones	enrofloxacin, ciprofloxacin
	erythromycin	erythromycin
	amphenicols	florfenicol, chloramphenicol
	tetracyclines	tetracycline
	sulphonamide/trimethoprim	sulphonamide/trimethoprim
	penicillin (only for <i>A. pleuropneumoniae</i>)	penicillin
<i>P. multocida</i> and <i>A. pleuropneumoniae</i>	aminopenicillins	amoxicillin, ampicillin
	fluoroquinolones	enrofloxacin, marbofloxacin, ciprofloxacin
	tulathromycin	tulathromycin
	tilmicosin	tilmicosin
	amphenicols	florfenicol, chloramphenicol
	tetracyclines	tetracycline, oxytetracycline, doxycycline
	sulphonamide/trimethoprim	sulphonamide/trimethoprim
	tiamulin	tiamulin

This work was based on 13 national veterinary AMR monitoring scopes. Such a bottom-up approach proved particularly helpful to guide expert discussions, by providing information about what is relevant and feasible to monitor in a large part of Europe. Most of the 10 countries with a national monitoring system in place are Northern and Central European countries, but the inclusion in this work of two Southern European countries, Spain and Greece, improved European representativeness. Collecting the national scope of countries building or planning to build their system also enabled us to anticipate a future expansion of the network. However, they might not have the experience to assess accurately their capacity to monitor some combinations of animal species/production types/age categories/bacterial species/specimens/antimicrobials. For countries with a system in place, a strength of our approach has been direct interaction with national coordinators, rather than solely relying

on AMR monitoring reports as a source of information. It helped locate and share non-published data in some countries and revealed that surrogate antimicrobials are sometimes used. For example, AMR data for enrofloxacin can be published in a report, but ciprofloxacin (which is not authorized for animal use) is actually tested as a surrogate antimicrobial. It enabled us to better understand what epidemiological data are collected by monitoring systems, e.g. when AMR data are reported for poultry and not per poultry species. Finally, some countries need to collect AST results over several years to reach a sufficient sample size to calculate meaningful resistance proportions. Thus, some monitoring results are only present in some yearly reports. With our interactive approach with coordinators, we could overcome these challenges and consider more recent combinations being monitored, for example when test panels have changed since their last monitoring report.

The expert group decided to include six animal species in the EARS-Vet scope, covering both food-producing and companion animals. The three countries that were either building or planning to build their system (Spain, Belgium and Greece) did not include companion animals in their scope, as focusing on food-producing animals was the priority at their stage.

Major bacterial pathogens, considered as important drivers for veterinary antimicrobial usage in Europe, were selected for each animal species. Some of them are also directly relevant for public health, such as *S. aureus*, which is still an important AMR monitoring gap in the animal sector that EARS-Vet could contribute to filling.

Different specimens were selected in the EARS-Vet scope, depending on the animal species/bacterial species combination. Invasive samples, if they are not contaminated, ensure that isolated bacteria are the cause of infection. However, it can be challenging or impossible to identify the cause of infection for samples taken from sites with a commensal flora or when there is a high risk of contamination. This is the case, for example, where *E. coli* is isolated from faecal samples. Although laboratories usually investigate the serotypes or virulence factors of *E. coli* from piglets, it is not commonly performed for *E. coli* isolates from calves. This might introduce a source of bias in the EARS-Vet monitoring to be considered when interpreting results. By comparison with the human sector, EARS-Net includes only invasive samples (from blood and CSF), but this is not the case for the Global Antimicrobial Resistance Surveillance System, coordinated by the WHO, which also includes for instance stool samples for the monitoring of *Salmonella* spp. and *Shigella* spp.¹⁴

Information on production type and age is essential for AMR monitoring, as they can dramatically influence AMR levels within the same animal species. Although it did not seem possible for EARS-Vet to widely collect such information (except for production types in chickens), this difficulty could be overcome as production type and age category can often be inferred from the bacterial species and/or specimen. For example, pathogens isolated from cattle milk almost exclusively originate from adult dairy cows and *E. coli* from swine faecal samples typically originate from piglets with neonatal or post-weaning diarrhoea. In practice, countries should still be able and encouraged to report data on production type and age to EARS-Vet for any kind of isolate.

Antimicrobials of both animal and human relevance were selected in the EARS-Vet scope. They cover all categories of the Antimicrobial Advice *ad hoc* Expert Group of EMA, which were defined based on their potential consequences to public health (due to increased AMR) when used in animals, but also considering the need to use them in veterinary medicine.¹² Three sets of antimicrobials covering all the combinations of veterinary relevance in the EARS-Vet scope were also defined and could be useful to countries or diagnostic laboratories aiming to customize their antimicrobial testing panels. In the future, EARS-Vet should recommend optimal dilution ranges for the three antimicrobial sets. However, EUCAST ECOFFs have not yet been established for all EARS-Vet combinations. Teale and Borriello¹⁵ have recently proposed dilution ranges for several bacterial species (*A. pleuropneumoniae*, *E. coli*, *M. haemolytica*, *P. multocida*, *S. aureus* and *Streptococcus* spp.) and many antimicrobials of the EARS-Vet scope, that were designed where possible to include both clinical breakpoints and ECOFFs (where available from

EUCAST). In addition to phenotypical information, some molecular results shall also be collected to confirm methicillin resistance or differentiate ESBL from AmpC isolates, as a starting point towards molecular monitoring. However, most national monitoring systems are based on the passive data collection of AST results from routine veterinary diagnostic laboratories, which do not test antimicrobials reserved for humans and rarely confirm phenotypes at a molecular level. Thus, wide country participation in this area would require specific external funding. In the meantime, EARS-Vet could still act as a platform for the collection and sharing of such data, even if extensive molecular monitoring is not yet feasible.

With this scope, EARS-Vet has the potential to fill important AMR monitoring gaps in Europe, by covering companion animals, animal bacterial pathogens and antimicrobials of relevance to veterinary medicine, which are not covered in EARS-Net and the EFSA monitoring. However, integration between these three European monitoring systems shall be possible. Both EARS-Vet and the EFSA monitoring include cattle, swine, chickens and turkeys in their scopes. In terms of bacterial species, *E. coli* is included in both systems, which is sensible as previous studies have shown different proportions and evolutions of AMR between commensal and pathogenic *E. coli* in food-producing animals.^{16,17} In the EFSA monitoring, antimicrobials are selected from a public health perspective and are monitored as individual compounds. Still, many of the antimicrobials monitored by EFSA in commensal *E. coli* have also been included in the EARS-Vet scope for *E. coli* (ampicillin, cefotaxime, chloramphenicol, nalidixic acid, ciprofloxacin, colistin, gentamicin, tetracycline, tigecycline, meropenem, imipenem and ertapenem). In terms of molecular analyses, EARS-Vet, just as EFSA, plans to collect data on ESBL and AmpC detection for *E. coli*.

Integration between EARS-Net and EARS-Vet shall be possible for *E. coli*, *S. aureus* and *K. pneumoniae*. All antimicrobial categories monitored by EARS-Net for those three bacterial species are included in EARS-Vet, although aforementioned limitations regarding the collection of AMR data for antimicrobials that are not authorized represents a challenge for broad country participation. In addition, antimicrobial groupings may vary between EARS-Net and EARS-Vet, as tested antimicrobial compounds often differ in veterinary and human medicine. For instance, EARS-Net collates resistance data for ciprofloxacin, levofloxacin and ofloxacin to monitor fluoroquinolone resistance in *E. coli*,³ whereas EARS-Vet plans to accept AST results for enrofloxacin, marbofloxacin and ciprofloxacin for *E. coli* from cattle mastitis. In contrast to EARS-Net, it was also decided for EARS-Vet not to monitor aminoglycosides and macrolides as antimicrobial classes, but as individual compounds, since they may have different resistance profiles (e.g. neomycin versus gentamicin or erythromycin versus tulathromycin).³ In terms of molecular monitoring, commonalities between EARS-Net and EARS-Vet consist of the collection of data on ESBL detection for *E. coli* and *K. pneumoniae*, as well as *mec* gene detection for *S. aureus*.

Integrated data analyses between EARS-Net, EARS-Vet and the EFSA monitoring should be possible for *E. coli*, which could act as a monitoring indicator across animal species and the three European monitoring systems. In terms of antimicrobials, integrated data analyses could be carried out for aminopenicillins, aminoglycosides, third-generation cephalosporins, fluoroquinolones and carbapenems. Information on ESBL detection shall be collected in the three systems, although systematically only in the

EFSA monitoring. Although molecular analyses, and especially whole genome sequencing, are expected to be conducted more and more frequently, integrated molecular monitoring of AMR is expected to remain limited in the mid-term. Comparisons of AMR levels should be done with caution in light of possible biases, which remain to be explored in EARS-Vet. Comparisons of AMR trends should be preferred to direct comparisons of AMR prevalence as sampling biases are likely to be rather constant over time. In particular, EARS-Vet could complement the pool of data being analysed in the Joint Inter-Agency Antimicrobial Consumption and Resistance Analyses,¹⁸ to better understand the complex epidemiology of AMR across sectors and contribute to devising more efficient interventions against AMR.

Finally, it is noteworthy to point out that the EARS-Vet scope should be reviewed and expanded, as the epidemiology of AMR changes, more countries participate and the feasibility to monitor specific combinations changes.

Acknowledgements

We are very grateful to all professionals involved in the definition of national veterinary AMR monitoring scopes and consulted experts from the Federation of Veterinarians in Europe, ECDC, EMA, EFSA and EUCAST, as well as to Lucie Collineau (French Agency for Food, Environmental and Occupational Health and Safety) for providing sound feedback on this work.

EU-JAMRAI partners

Evelyne JOUVIN-MARCHE, Marie-Cécile PLOY, Sadika BERNARD, Yohann LACOTTE, Céline PULCINI, Marielle BOUQUEAU, Anton HLAVA, Vera BUHMANN, Eline VANDAELE, Lieven DE RAEDT, Blazanka HUNJAK, Bojana RAČKOVIĆ, Barbora MACKOVÁ, Helena ŽEMLIČKOVÁ, Ute WOLFF SÖNKSEN, Sissel SKOVGAARD, Jüri RUUT, Ljudmila LINNIK, Arina ZANUZDANA, Nadiya OZCELİK, Flora KONTOPIDOU, Mariana TSANA, Alkiviadis VATOPOULOS, Achilleas GIKAS, Aimilia MAGKANARAKI, Alessandra COZZA, Domenico MARTINELLI, Rosa PRATO, Annalisa PANTOSTI, Francesca PRESTINACI, Luca BUSANI, Roberta CRETI, Uga DUMPIS, Asta DAMBRAUSKIENE, Astra VITKAUSKIENE, Silvija KIVERYTE, Agniete MAZZELLA, Rolanda VALINTELIENE, Robertas PETRAITIS, Jasper CLAESSEN, Rosa PERÁN, Elma SMEETS, Pita SPRUIJT, Svein HØEGH HENRICHSEN, Christine ÅRDAL, Mari MOLVIK, Oliver KACELNIK, Anne Margrete URDAHL, Dorota ŻABICKA, Sérgio GOMES, Razvan CIORTEA, Maja ŠUBELJ, Nina JEMEC, António LÓPEZ NAVAS, Cristina MUÑOZ MADERO, Laura ALONSO IRUJO, María SANTACREU GARCÍA, Gloria OLIVA, Marta MASSANÉS, Elena FERRAGUT, Eusebi CASTAÑO, Casimiro JIMÉNEZ GUILLÉN, Marisol FRAGOSO, Germán PEÑALVA, José Miguel CISNEROS, Milena ESTEVEZ, Sophie MONTEAU, María José GONZÁLEZ DE SUSO, Pilar GALLEGU BERCIANO, Daniele ALIOTO, Lotta EDMAN, Axana HAGGAR, Elisabet LINDAL, Jakob OTTOSON, Anna NORDENFELT, Björn BENGTTSSON, Patriq FAGERSTEDT, Birgitta LYTSY, Jean Yves MADEC, Lucie COLLINEAU, Rodolphe MADER, Anne BERGER-CARBONNE, Karl PEDERSEN, Monika LARSSON, Annicka REUSS, Anne SWALUE, Cristina PORTUGAL, Hans Fredrik WILHELMSEN, Jesús OTEO-IGLESIAS, Janicke FISCHER, Helga Katharina HAUG, Maria da GRACA FREITAS and María del Pilar LÓPEZ ACUÑA.

Funding

This work was supported by the Health Programme of the EU (2014–2020) under grant agreement no. 761296.

Transparency declarations

None to declare.

Disclaimer

The views expressed in this publication are those of the authors and do not necessarily reflect the opinion of consulted experts and organizations.

Supplementary data

Tables S1 to S6 and Figures S1 to S3 are available as [Supplementary data](#) at JAC Online.

References

- 1 WHO. Global Action Plan on Antimicrobial Resistance. <https://www.who.int/publications/i/item/9789241509763>.
- 2 European Commission. A European One Health Action Plan Against Antimicrobial Resistance (AMR). https://ec.europa.eu/health/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf.
- 3 ECDC. Antimicrobial Resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report for 2019. <https://www.ecdc.europa.eu/sites/default/files/documents/surveillance-antimicrobial-resistance-Europe-2019.pdf>.
- 4 ECDC. EU Protocol for Harmonised Monitoring of Antimicrobial Resistance in Human *Salmonella* and *Campylobacter* Isolates. <https://www.ecdc.europa.eu/sites/default/files/documents/antimicrobial-resistance-Salmonella-Campylobacter-harmonised-monitoring.pdf>.
- 5 European Food Safety Authority, ECDC. The European Union Summary Report on Antimicrobial Resistance in Zoonotic and Indicator Bacteria from Humans, Animals and Food in 2017/2018. <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2020.6007>.
- 6 Mader R, Damborg P, Amat J-P *et al*. Building the European Antimicrobial Resistance Surveillance network in veterinary medicine (EARS-Vet). *Euro Surveill* 2021; **26**: pii=2001359.
- 7 Mader R, Muñoz Madero C, Aasmäe B *et al*. Review and analysis of national monitoring systems for antimicrobial resistance in animal bacterial pathogens in Europe: a basis for the development of the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet). <https://zenodo.org/record/5205371>.
- 8 FDA. NARMS 2017 Animal Pathogen AMR Data. <https://www.fda.gov/animal-veterinary/national-antimicrobial-resistance-monitoring-system/2017-animal-pathogen-amr-data>.
- 9 World Organisation for Animal Health. Harmonisation of national antimicrobial resistance surveillance and monitoring programmes. In: *Terrestrial Animal Health Code*. 2018.
- 10 Michael GB, Bossé JT, Schwarz S. Antimicrobial resistance in *Pasteurellaceae* of veterinary origin. *Microbiol Spectr* 2018; **6**. doi:10.1128/microbiolspec.ARBA-0022-2017.
- 11 EUCAST. *Breakpoint Tables for Interpretation of MICs and Zone Diameters, Version 11.0*. 2021.
- 12 De Briyne N, Atkinson J, Borriello SP *et al*. Antibiotics used most commonly to treat animals in Europe. *Vet Rec* 2014; **175**: 325.
- 13 EMA. Categorisation of antibiotics in the European Union. https://www.ema.europa.eu/en/documents/report/categorisation-antibiotics-european-union-answer-request-european-commission-updating-scientific_en.pdf.

- 14** WHO. Global Antimicrobial Resistance Surveillance System: Manual for Early Implementation. <https://www.who.int/publications/item/9789241549400>.
- 15** Teale C, Borriello P. A proposed scheme for the monitoring of antibiotic resistance in veterinary pathogens of food animals in the UK. *Vet Rec* 2021; **189**: e201.
- 16** Hendriksen RS, Mevius DJ, Schroeter A et al. Occurrence of antimicrobial resistance among bacterial pathogens and indicator bacteria in pigs in different European countries from year 2002 – 2004: the ARBAO-II study. *Acta Vet Scand* 2008; **50**: 19.
- 17** Bourély C, Chauvin C, Jouy É et al. Comparative epidemiology of *E. coli* resistance to third-generation cephalosporins in diseased food-producing animals. *Vet Microbiol* 2018; **223**: 72–8.
- 18** ECDC, European Food Safety Authority, EMA. Third Joint Inter-Agency Report on Integrated Analysis of Antimicrobial Agent Consumption and Occurrence of Antimicrobial Resistance in Bacteria From Humans and Food-Producing Animals in the EU/EEA, JIACRA III. <https://www.ecdc.europa.eu/sites/default/files/documents/JIACRA-III-Antimicrobial-Consumption-and-Resistance-in-Bacteria-from-Humans-and-Animals.pdf>.