TITLE: Antimicrobial resistance and antimicrobial use animal monitoring policies in Europe: Where are we?

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Abstract

Antimicrobial resistance has been recognized by the World Health Organization (WHO) as one of the top three threats to human health. Any use of antibiotics in animals will ultimately also affect humans, and vice-versa. The importance of the appropriate monitoring of its usage and resistance has been repeatedly emphasized, as well as the need for global policies in this respect. Under the auspices of the EU research project EFFORT, the mapping of antimicrobial usage and resistance monitoring programs in ten European countries was performed, with a critical comparison with international and European guidelines/policies. Regarding the monitoring of resistance, we did not find important differences between countries. However, the current resistance monitoring systems are focused on food animal species (and fecal samples), ignoring, for example, companion animals. The scenario is different considering the monitoring of antibiotics use. In the recent years, there has been a significant effort to harmonize methodologies. Despite this, the reporting of antimicrobials use is still voluntary. A need for stronger policies was identified.

Keywords: Antimicrobial Resistance (AMR); monitoring; policies; animals; Antimicrobial use (AMU)

Text

Introduction

Antimicrobial resistance (AMR) is recognized as one of the major global public health threats, with different reports emphasizing its economic impact (1,2), and the return to a “pre-antibiotics” era (3). It is a perfect example of a “one health” issue, as any use of antibiotics in animals will ultimately affect humans (and vice-versa)(4–6), with an associated environmental component (7–9), that recognizes no national boundaries (10). The development of resistance to antimicrobial drugs is a natural phenomenon, but the overuse and inappropriate use of these drugs, is associated with increased resistance. Therefore, the appropriate monitoring of the use of and development of resistance to these drugs are essential, if one is to achieve control of this problem.

The World Health Organization (WHO) has recently recognized that there are significant gaps in (monitoring/surveillance) methods and no global consensus on standards for data collection and reporting of AMR across medical, veterinary and agricultural sectors (WHO, 2014). It is generally accepted that the comparison of results between countries is only possible when the results were obtained using the same (or similar/equivalent) procedures.

Under the activities of the “Ecology from Farm to Fork Of microbial drug Resistance and Transmission” (EFFORT) EU-FP7 project, we conducted the mapping of the current monitoring activities related to antimicrobial use and resistance, in the ten European countries participating on the project: Belgium, Bulgaria, Denmark, France, Germany, Italy, Netherlands, Poland, Spain and Switzerland. Here we present the results of this mapping activity, as well as a critical comparison between the mapping results and the current related international guidelines/policies, from a gap analysis perspective.

Materials and methods

Initially, we took a very practical approach, having in mind the question: If a (European) country wants to set up monitoring systems to control the use and development of resistance to antimicrobials in animals, to which guidelines and policies should the competent authorities be looking at? As a follow-up, we then did a critical comparison with individual countries policies, from a gaps identification perspective. In a second step, we mapped what countries are currently doing to monitor antibiotic use and resistance and finally did a gap analysis.

International policy framework

The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) provided a guidance document with key information for the design of programs of integrated surveillance of antimicrobial (use) and resistance. Despite not being legally binding to countries, it does provide a generic overview of what countries need and show how to achieve the mentioned goals.

European policy framework on monitoring of *resistance* in animals

On a more specific EU level, *Directive 2003/99/EC* set out the goals on the monitoring of zoonoses and zoonotic agents and related antimicrobial resistance. By definition, as a "Directive", it left up to the countries to decide how to achieve these goals; This was followed in 2007, by the publication of *Decision 2007/407/EC* (by definition, a "Decision" is a binding legislative act on those to whom it is addressed, being directly applicable) specifically focusing on the harmonized monitoring of AMR in *Salmonella* in poultry and pigs. The most relevant and current related policy is probably *Decision 2013/652/EU*. It has a broader scope, addressing the monitoring and reporting of AMR in zoonotic and commensal bacteria (including *Salmonella* spp., *Campylobacter jejuni* (*C. jejuni*) and *Campylobacter coli (C. coli),* indicator commensal *Escherichia coli (E. coli),* commensal *Enterococcus faecalis* and *Enterococcus faecium* (*E. faecalis* and *E. faecium*) and *Salmonella* spp. and *E. coli* producing Extended-Spectrum β-Lactamases (ESBL), AmpC β-Lactamases (AmpC) and Carbapenemases). Technical specifications on randomized sampling for harmonized monitoring of AMR in these bacteria have been provided by EFSA (12).

Global and European policy framework on monitoring of *use* in animals

At the global level, OIE (Office International des Epizooties) provides guidelines on how to perform the monitoring of the quantities and use patterns of antimicrobial agents in aquatic animals, in its chapter 6.3 of the Aquatic Animal Health Code; the equivalent for food-producing animals in provided in chapter 6.8 of the Terrestrial Animal Health Code.

Coordinated by the European Medicines Agency (EMA), the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project was launched in September 2009, following a request to develop an approach for the harmonized collection and reporting of data on the use of antimicrobial agents in animals in the Member States (SANCO/E2/KDS/rzD(2008)520915). ESVAC provides data collection, reporting and analysis protocols, that can be followed by countries (13).

Mapping exercise

Initially, we mapped monitoring activities related to antimicrobial *use* and *resistance* including animals and food in countries participating in EFFORT in place in 2014. For this, we used a surveillance mapping methodology developed as part of another FP7 project (RISKSUR www.fp7-risksur.eu). After an initial online training, data collectors received a MS Word template to be completed with information regarding use of antimicrobials in their country, including: method to collect use data, animal populations known (size), indicator of use used, availability (or not) of Defined Daily Dose Animals

(DDDAs - also known as DDDvet in ESAVC project), the assumed average maintenance dose per day per kg body weight for the main indication in a specified species), classes of antimicrobials for which data was collected, specifications about the inclusion (or not) of premixes data, question about the potential existence of specific policies to discourage or alert about the overconsumption of antimicrobials and if veterinarians were allowed to sell antimicrobials or not. A similar procedure was used to collect the information about the monitoring of resistance, but via an MS Access database template. This database was completed with information about each monitoring activity/component like: the geographical focus of it, legal framework, target species and sectors, sampling points and samples collected, microorganisms tested, means of data acquisition, resistance criteria and whether the monitoring activity was funded and performed by the public or private sector.

Results

Resistance

No major differences were found in the way the monitoring of resistance is being performed in the analysed European countries (Table 1). Testing resistance in microorganisms like *Campylobacter jejuni*, *Campylobacter coli*, *E. coli* and *Salmonella* spp. is being done in all the countries. In addition, few countries (ex. France) have national programmes for veterinary pathogens. The focus of the monitoring programs is in the major food producing species (poultry, cattle and pigs). Slaughterhouses are the most common sample collection points, and the vast majority of the collected samples consist of faecal material. The monitoring activities are mostly active, and under the control of the public sector.

Table 1: Summary of the activities to monitor antimicrobial resistance, in animals, as of 2014, in the EFFORT participating countries.

	Microorganisms tested	Animals species tested	Collection of samples	Samples collected	Means of data acquisition	Antimicrobial susceptibility test	Resistance criteria	Public vs Private
Belgium	*Campylobacter coli ; Campylobacter jejuni ; Salmonella ; E. col ; Enterococci*	Poultry (broilers, laying hens and turkey) ; Pigs (finishers) ; Cattle (beef, dairy, veals)	Abattoir	Caecal; Faecal; Carcasses, meat and meat products (for poultry)	Active and passive	Dilution method and Diffusion method	Clinical break-point and Epidemiological cut-off value	All public
Bulgaria	*Campylobacter coli; Campylobacter jejuni; Carbapenemase; E. coli; ESBL producers; Salmonella, Staphylococcus spp.*	Poultry (broilers, laying hens); Pigs (finishers) ; Cattle (beef, dairy, veals); Sheep	Abattoir	Feces	Active	Diffusion method	Clinical break-point	Public
Denmark	*Campylobacter coli; Campylobacter jejuni;E. coli; Enterococci; Salmonella spp.; Staphylococcus spp.*	Poultry (broilers); Pigs (sows/boars, finishers); Cattle (beef); other	Abattoirs; Farms; Retailers; breeding herds	Caecal; Blood; Cloacal; Rectum; Meat (pork, beef and broiler)	Active	Dilution method	Epidemiological cut-off value	Public
France	*Campylobacter coli ; Campylobacter jejuni ; E. coli; Enterococci; Pasteurella spp.; Salmonella spp.; Staphylococcus spp.; Streptococcus spp.*	Birds (non-poultry); Cats; Cattle (beef, dairy, veals), Dogs, Donkeys, Ducks, Fish, Goats, Horses, Pigs (suckling piglets, weaners, sows/boars, finishers); Poultry (broilers, laying hens); Rabbits; Sheep; Turkey	Abattoir, Veterinary clinics and farms	Caecal; Environmental; Different samples sent to the laboratory for diagnosis	Active and Enhanced passive	Dilution method and Diffusion method	Epidemiological cut-off value; Veterinary breakpoint established by CA-SFM vet	Public and Private
Germany	*Campylobacter coli ; Campylobacter jejuni ; E. coli; Salmonella spp.; Methicillin-resistant Staphylococcus spp. (MRSA);* *In addition several animal pathogens (passive system)*	Poultry (broilers, laying hens and turkey) ; Pigs (sows/boars, finishers) ; Cattle (beef, dairy, veals)	Abattoirs; Farms; Retailers;	Caecal; Environmental; Meat (pork, beef, broiler and turkey meat); isolates from clinical samples sent for testing	Active and Passive	Dilution method	Epidemiological cut-off value;	Public
Italy	*Campylobacter coli; Campylobacter jejuni; Carbapenemase; E. coli; ESBL producers; Salmonella spp.; AmpC producers*	Poultry (broilers, laying hens and turkeys); Cattle (beef); Pigs (finishers)	Farms; Abattoirs; Various points of the food chain	Faeces; Environmental; Dairy products; Meat; Swabs from carcasses	Active and Passive	Dilution method	Epidemiological cut-off value	Public
Netherlands	*Campylobacter jejuni; Salmonella spp.; Enterococci; AmpC producers; Carbapenemase producers; E. coli; ESBL producers; MRSA; Pasteurella spp; Staphylococcus spp.; Streptococcus spp.; Listeria spp.; Mannheimia haemolytica; Histophilus somni; Klebsiella; Enterobacter; Actinobacillus pleuropneumoniae; Bordetella bronchiseptica; Haemophilus parasuis*	Poultry (broilers, laying hens, turkeys); Cattle (dairy, veals); Pigs (suckling piglets, weaners, sows/boars, finishers); Horses; Sheep; Goat	Farms; Abattoirs; Veterinary clinics.	Faeces; Clinical samples	Active and Passive	Dilution method and Diffusion method; Other	Epidemiological cut-off value; Clinical break-point; Other	Public and Private
Poland	*E. coli; Salmonella spp.; Staphylococcus spp.; Streptococcus spp.; MRSA; Pasteurella; mastitis agents*	Poultry (broilers, laying hens and turkeys) ; Cattle (beef and dairy) ; Pigs (suckling piglets, weaners, sows/boars, finishers)	Farms; Abattoirs	Rectal swabs; Cloacal swabs; Environment (boot swabs, dust, faeces); Diagnostic specimens (milk, faeces, organs, lesions)	Active, Enhanced passive and Passive	Dilution method and Diffusion method	Epidemiological cut-off value; Clinical break points	Public
Spain	*Campylobacter spp.; Enterococcus spp.; E. coli; Salmonella*	Cattle ; Gallus gallus (fowls) ; Broilers ; Laying hens ; Pigs (fattening) ;	All food chain; slaughterhouses.	Faeces; Lymph nodes	Active	Dilution method	EUCAST CLSI	Public
Switzerland	*Campylobacter coli; Campylobacter jejuni; Enterococci; Carbapenemase; E. coli; ESBL producers; Salmonella spp.; AmpC producers; MRSA*	Poultry (broilers); Cattle (veals); Pigs (finishers)	Abattoirs	Rectal swabs; Cloacal swabs; Nasal swabs; Diverse (evaluation of resistance in Salmonella)	Active and Passive	Dilution method	Epidemiological cut-off value	Public

Use

Table 2 summarizes the monitoring activities regarding the use of antimicrobials in the ten countries.

Sales data (from pharmacies, feed companies, wholesalers and/or pharmaceutical companies) is the main source to derive/extrapolate use/consumption when such data is not available at national level. Besides this, automated data collection is in place in Denmark and The Netherlands, in combination with veterinary prescriptions data. In France, information is also collected via a retrospective longitudinal study.

The antimicrobial use data is not divided by species in Belgium, Bulgaria and Italy. In the other countries included in this study, it is not always possible to disaggregate the consumption in the individual species (eg. dogs and cats are reported together in Denmark and France) and there is no common way of grouping the different animal species (eg. "cattle" is reported in a single category (dairy+beef) in Denmark, France and Poland while in the Netherlands usage data for rosé and white veal calves are reported separately from other cattle (dairy+beef)).

In none of the countries are the size of all the animal population species (live and slaughtered, when applicable), known.

"Total weight of Active Substance" is the indicator of usage reported in seven countries: Belgium, Bulgaria, Denmark, France, Germany, and The Netherlands. In Belgium and France, "Weight of Active Substance per biomass at risk to be treated" (units: mg AS/PCU) is also used, and this is the only indicator used in Italy, Poland, Spain and Switzerland. Additionally, France uses the Animal Level of Exposure to Antimicrobials (ALEA, the DCDA divided by the biomass) and the Netherlands the "Number of days treated per individual" (Total amount of Kg, irrespective of active ingredient, by Kg of active substance/year, by pharmaco-therapeutic group (DDDA nat and DDDAfarm/year)).

A list of DDDA`s is not available in Bulgaria, Germany, Italy, Poland, Spain and Switzerland. Belgium has established it (for pigs and poultry) by product, active substance, administration route and age group; Denmark by product, administration route and age group, France by product and The Netherlands by active substance and ATCvet category.

All the countries have data collected and available for all the antimicrobial classes (according with the ATCvet index list). Premixes data are included in the usage data in all the countries, except in Germany and The Netherlands.

Denmark, Germany and The Netherlands have in place specific policies to discourage, or alert to the “overconsumption” of antimicrobials, in opposition to the other seven countries.

Veterinarians are allowed to sell antimicrobials in Belgium, France, Germany, Poland, The Netherlands and Switzerland.

Table 2: Summary of the activities to monitor antimicrobial use, in animals, as of 2014, in the EFFORT participating countries.

	Data collection	Consumption separated by species	An. pop. unknown (l=live; s=slaughtered)	Indicator of usage	DDDAs available?	AM classes collected	Premixes included	"Yellow card"?	Vets sell?
Belgium	Sales (feed companies and wholesalers)	No	Cats (l); Dogs (l); Ducks (s); Fish (l&s); Goats (s); Horses (s); Pigs: suckling piglets (l&s), weaners (s), sows/boars (s); Poultry: laying hens (s); Rabbits (s); Sheep (s); Turkey (s)	Total weight of AS; Weight of AS per biomass at risk to be treated	Yes (by product, AS, administration route, age group, for pigs and poultry)	all	Yes	No	Yes
Bulgaria	Sales (wholesalers and pharmaceutical companies)	No	Cats (l); Dogs (l); Birds (non-poultry) (l&s); Ducks (l&s); Fish (l&s); Rabbits (l&s); Turkey (l&s)	Total weight of AS	No	all	Yes	No	No
Denmark	Automated data collection; Sales (pharmacies and feed companies); veterinary prescriptions	Yes: dogs+cats (pharmacy data); cattle (dairy+beef); fish; goats; pigs (weaners, sows/boars, finishers); poultry (broilers, laying hens), sheep, turkey; horses (pharmacy data)	Birds (non-poultry) (l&s); Cats (l); Dogs (l); Donkeys (l); Fish (l); Horses (l&s); Pigs: suckling piglets (s), weaners (s), sows/boars (s); Poultry: laying hens (s); Rabbits (l&s); Sheep (l&s); Turkey (l&s)	Total weight of AS	Yes (by product, administration route, age group)	all	Yes	Yes	No
France	Retrospective longitudinal study; Sales (pharmaceutical companies)	Yes:Dogs+cats; Cattle; fish; horses; Pigs; poultry (including turkeys and ducks); rabbits; sheep+goats	Birds (non-poultry) (l); Cattle: beef (s), dairy (s), veals (l); Ducks (l); Fish (l); Horses (s); Pigs: suckling piglets (l&s), weaners (l); finishers (l); Poultry: broilers(l), laying hens (l); Rabbits (l); Turkey (l)	Total weight of AS; Weight of AS per biomass at risk to be treated ; ALEA	Yes (by product)	all, except QJ01R	Yes	No	Yes
Germany	Sales (pharmaceutical companies)	Yes:Pigs (weaners, finishers); poultry (broilers); turkey	Birds (non-poultry) (l&s); Donkeys (l); Fish (l&s); Goats (l&s); Pigs: suckling piglets (l&s); Rabbits (l&s); Sheep (l&s)	Total weight of AS	No	all	No	No	Yes
Italy	Sales (pharmaceutical companies)	No	Cats (l)	Weight of AS per biomass at risk to be treated	No	all	Yes	No	No
Netherlands	Automated data collection; Sales (pharmaceutical companies); Veterinary prescriptions	Yes: cattle; pigs; poultry (broilers); turkey	Birds (non-poultry) (l&s); Ducks (l&s); Fish (l&s); Rabbits (s)	Total weight of AS; Number of days treated per individual (DDDAnat and DDDAfarm)	Yes (by AS, ATC vet category)	all	No	Yes	Yes
Poland	Sales (wholesalers)	Yes: cattle; goats; pigs; poultry; sheep	Cats (l); Dogs (l); Birds (non-poultry) (l&s); Ducks (l&s); Fish (l&s); Rabbits (l&s); Turkey (l&s)	Weight of AS per biomass at risk to be treated	No	all, except QJ01R	Yes	No	Yes
Spain	Sales (pharmaceutical companies)	Yes: birds (non-poultry); cats; dogs; fish; goats; horses; fish, salmon, trout; cattle; poultry; pigs	Cats (l); Dogs (l); Birds (non-poultry) (l&s); Ducks (l&s); Fish (l&s); Rabbits (l&s); Turkey (l&s)	Weight of AS per biomass at risk to be treated	No	all, except QJ01R and QJo1X	Yes	No	No
Switzerland	Sales (pharmaceutical companies)	No.	Birds (non-poultry) (l&s); Cats (l); Cattle: beef (l), veals (l); Dogs (l); Donkeys (l); Ducks (l&s); Fish (l&s); Goats (l); Pigs: suckling piglets (l&s), weaners (l&s), sows/boars (s), finishers (l); Poultry: broilers (l), laying hens (l); Rabbits (l); Turkey (l&s)	Weight of AS per biomass at risk to be treated	No	all	Yes	No	Yes

Discussion

The EC Decision 652/2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria, is binding on all the EU countries (14). Considering this, it was not surprising that few differences were found on the way countries are monitoring the level of resistance. However, there are several aspects that this policy does not cover, that should be addressed in upcoming policies. The current monitoring activities are mostly focused on food producing animals. But, for example, fish (aquaculture) are not considered (being aware that this is not a developed sector in all the EU countries). Considering some recent reports (15), particular attention should be given to this section, in the near future. The mandatory monitoring is mostly performed via faecal material. While most of the prudent use guidelines in veterinary medicine recommend a good diagnosis, antibiogramme use and epidemiological knowledge of animal disease, no strong regulations have been established to support the best practice in veterinary laboratories. This way, resistance developing microorganisms that live in different body organs (lungs, mammary gland, uterus, etc.) might be missed. The direct sampling and analysis of food samples is also not mandatory. Including these analyses in the routine European mandatory activities would be labour and financially demanding, and cross-contamination issues would have to be carefully taken into account. In any case, it would certainly help to clarify, and above all to quantify, the different transmission AMR pathways between humans and animals, areas that despite progress in the past few years, still have significant knowledge gaps. Metals exposure (like silver and zinc oxide) has been recognized as a factor contributing to AMR selection (16,17), but the current policies do not mandate the monitoring of resistance to these agents. Antimicrobial resistant bacteria have been repeatedly identified in “environmental” samples

(7–9), but despite this, the monitoring of resistance via "environmental" samples is currently not mandatory. Having this information would be quite useful to better understand the spread of resistance between humans, animals and the environment.

The vast majority of the current monitoring activities are "active" (*vs* passive collection of information) and manage and funded by the public authorities of each country. Considering that antimicrobials are a public good, these approaches make sense, and facilitate both the harmonization and transparency of methods. On the other hand, it is the private industry/owners that mostly make the use of antimicrobials, thereby benefiting from them. It is also true that they are the ones directly affected with all the adverse consequences (both in humans and animals) of the existence of resistance. Therefore, an increased involvement of the private industry would be desirable.

The scenario is significantly different regarding the monitoring of the use of antimicrobials. This can perhaps be mostly explained by the fact that there is currently not any binding European policy that mandates countries to report their use of antimicrobials in the animal sector, with specific guidelines. The legal framework for veterinary medicinal products currently under revision can be an opportunity to change this policy reality, and it does seem that at least report sales quantities will become mandatory, with mandatory monitoring to be implemented in two to three years.

The ESVAC project has been certainly contributing for the collection of harmonized data. However, most of the data collected still refers to sales data, and not use data. This scenario is planned to change in a relatively near future(18). Collecting the actual use data at the farm level, is certainly a demanding task for different agents involved in this sector, but it is, at the same time, the most accurate way. An antibiotic sold, is not an antibiotic used, and only the recording of the actual use will avoid the need for approximations, corrections and use of other indicators of use.

Knowing the animal population at risk, i.e., the denominator regarding the use of the antimicrobials, is critical. In the analyzed countries, the major food producing animal populations are known (poultry, cattle and pigs), but this is not always true for other "minor" species. The use/sales of antimicrobials is reported in such a way that does not always allow the differentiation between the different species, types and stages of production, and this is critical when it comes to identifying the species and stages of the food chain where prevention and control measures should focus on. Currently, the same antibiotic commercial product can be commercialized/is indicated for different animal species, creating an additional hurdle when it comes to the quantification of its use in a specific species.

The usefulness of having a "yellow card" policy has been recognized in Denmark (19). Under this policy, a farmer receives a yellow card if he/she uses antimicrobials in a quantity two times higher than the national average. However, such policies only exist in Denmark and The Netherlands. The same way, the implementation of policies that restrict the sales of antimicrobials by veterinarians have had positive impact (20), but at the moment such policies only exist in half of the analyzed countries.

Conclusion

The current European policies regarding the monitoring of resistance in animals, provide specific guidelines when it comes to food producing animals. However, most of the analyses to be performed are based on faecal samples, and, for example, companion animals, food and the environment are not even considered. Important gaps that we here suggest to be addressed in upcoming policies.

At the moment, there is not an European policy that mandates countries to report their use of antimicrobials in animals, and most of the data available is based on sales, and not use data.

Considering the unanimously recognized significant dimension of the AMR problem, these scenarios should be urgently changed. The EU ban on the usage of growth promoters in 2006 provided a strong global message, and the EU is recognized as an AMR best practices region (Plantady, 2016, personal communication). Developing and implementing the policies suggested in this paper, should inform policy development in other regions where similar activities may still be lacking.

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