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Antimicrobial resistance monitoring and surveillance in the meat chain: A report from five countries in the European Union and European Economic Area

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Abstract

Background

The emergence of antimicrobial resistance (AMR) in zoonotic foodborne pathogens (*Salmonella*, *Campylobacter*) and indicator microorganisms (*E. coli*, enterococci) is a major public health risk. Zoonotic bacteria, resistant to antimicrobials, are of special concern because they might compromise the effective treatment of infections in humans.

Scope and approach

In this review, the AMR monitoring and surveillance programmes in five selected countries within European Union (EU) and European Economic Area (EEA) are described. The sampling schemes, susceptibility testing for AMR identification, clinical breakpoints (clinical resistance) and epidemiological cut-off values (microbiological resistance) were considered to reflect on the most important variations between and within food-producing animal species, between countries, and to identify the most effective approach to tackle and manage the antimicrobial resistance in the food chain.

Key findings and conclusions

The science-based monitoring of AMR should encompass the whole food chain, supported with public health surveillance and should be conducted in accordance with `Zoonoses Directive` (99/2003/EC). Such approach encompasses the integrated AMR monitoring in

food animals, food and humans in the whole food (meat) chain continuum, e.g. pre-harvest (on-farm), harvest (in abattoir) and post-harvest (at retail). The information on AMR in critically important antimicrobials (CIA) for human medicine should be of particular importance.

Keywords: antimicrobial resistance, foodborne pathogens, monitoring, surveillance, public health.

1. Introduction

In the last decade the antimicrobial resistance (AMR) associated with zoonotic foodborne pathogens of bacterial origin is recognized as a major public health concern. Zoonotic foodborne bacteria are infectious agents which may be transferred from animals to humans via food ingestion (WHO, 2015). Zoonotic agents are believed to be responsible for up to 75% of infectious diseases in humans (Heymann, 2004; Behravesh et al., 2012). Therefore, food-producing animals (cattle, sheep, pigs and poultry) are of particular importance for emergence and transfer of AMR through the food consumption taking into consideration the intensive, on-farm production practice frequently associated with misuse/overuse of antimicrobials (Bischt et al., 2009).

It is well known that from 1940's, introduction of antibiotics to treat infectious diseases in humans and animals revolutionized medicine. When it comes to food animals, antibiotics are used not only to treat them against infectious diseases but also to prevent disease development (metaphylaxis) and to promote their growth. However, the overuse and misuse of antibiotics in food animals can lead to selective pressure on microorganisms and may result in development and spread of antibiotic resistance (Cogliani et al., 2011). The first integrated analysis on antimicrobial consumption in veterinary and human medicine at the level of European Union (EU) and European Economic Area (EEA) was conducted in 2015 (ECDC/EFSA/EMA, 2015); the report aimed to provide better insight to the occurrence of antimicrobial resistance in bacteria originated from humans and food animals. The excessive veterinary use of antimicrobials applicable mainly for food-producing animal species, including horses, in 26 European Union and European Economic Area countries was estimated to be in total 7,982 tonnes per year, with the highest level of antimicrobial consumption in pigs, cattle and poultry; additionally, the overall quantity of antibiotic

consumption in humans was in total 3,399.8 tonnes per year. Evidently, a significant amount of antimicrobial agents per year are consumed in both, food animals and humans in EU and EEA countries. Such practice may have important consequences for public health, as it may promote development of antibiotic-resistant bacteria and transfer of resistance genes to humans (WHO, 2011a). Nowadays, this causes serious treatment failures or necessitate the use of second-line antimicrobials for therapy, more severe and longer-lasting disease, increased hospitalization rates, including increased mortality, sequelae, and ultimately, higher costs to society (WHO, 2011a). Having in mind the complexity of the international food trade characterized with a longer food supply chain, as well as possibility for transfer of foodborne pathogens from one country/continent to another within a short period of time, antibiotic resistance became a growing international health issue; it deserves immediate attention by health, veterinary, food and environmental authorities on the global scale.

Antimicrobial resistance associated with major zoonotic foodborne pathogens (*Salmonella*, *Campylobacter*) occurring in food animals can spread to people via food/water consumption and direct animal-human contact. In addition, commensal bacteria (e.g. *E. coli*, enterococci), can also form a reservoir of resistance genes in environment, farm and food animals (Barton, 2000). This may facilitate transfer between bacterial species, including the transfer to pathogens capable of causing disease in both humans and animals which may be difficult to cure (EFSA, 2008).

In the European Union (EU) and European Economic Area (EEA), AMR became a very serious public health challenge. The magnitude of the problem is highlighted by the fact that more than 25 000 people die each year from infections caused by antibiotic resistant bacteria (ECDC/EMEA, 2009). The resistance rate to antibiotics is high among both, Gram-positive and Gram-negative bacteria that cause serious infections in humans and reaches 25% or more in several EU Member States (ECDC/EMEA, 2009). The ineffective antibiotic treatments result in extra healthcare costs and productivity losses of at least EUR 1.5 billion each year. In addition, there is a gap between the burden of infections due to multidrug-resistant bacteria and the development of new, effective antibiotics to tackle the problem. There are numerous studies to highlight the problem related to AMR and to identify the sources and causes for development of this phenomenon, but it is still uncertain how much it can be contributed to the food chain, in particular meat chain.

The aim of this paper was to review the AMR monitoring and surveillance schemes in five selected EU and EEA countries with focus on the contribution of the meat chain to emergence, development and spread of antimicrobial resistance to humans. An overview of the sampling schemes, susceptibility testing for AMR profile identification, clinical breakpoints (clinical resistance) and epidemiological cut-off values (microbiological resistance) were considered, including the most important differences between and within food-producing animal species, between countries, and identification of the most effective risk mitigation strategies to tackle the antimicrobial resistance in the meat chain.

98 Table 1. Summary of selected studies linking AMR to the meat chain

Authors	Type of article	Research focus	Module in the meat chain				
			1	2	3	4	5
Andersen et al. (2006)	Journal Article	Antimicrobial resistance among *Campylobacter* jejuni from raw poultry meat in retail in Denmark				X	
DANMAP (2014)	Scientific Report	Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark	X	X	X	X	X
ECDC (2014)	Summary Report	The European Union Summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2014	X	X	X		X
EFSA (2014)	Scientific Report	Technical specifications on randomised sampling for harmonised monitoring of antimicrobial resistance in zoonotic and commensal bacteria	X	X	X	X	
Gallay et al. (2007)	Journal Article	*Campylobacter* antimicrobial resistance among humans, broiler chickens and pigs. France		X			X
Leegard et al. (2000)	Journal Article	Emerging antimitotic resistance in *Salmonella*					X

		typhimurium in Norway					
Lindmark et al. (2004)	Journal Article	Genetic characterisation and antimicrobial resistance of *Campylobacter jejuni* isolated from meats, water and humans in Sweden				X	X
MARAN (2013)	Scientific Report	Monitoring of antimicrobial resistance and antibiotic usage in animals in the Netherlands in 2012	X	X	X	X	
NORM-VET (2013)	Scientific Report	Usage of antimicrobial agents and occurrence of antimicrobial resistance in Norway	X	X	X		X
RESAPATH (2012)	Scientific Report	French Surveillance network for antimicrobial resistance in pathogenic bacteria from animal origin	X				
SVARM (2014)	Scientific Report	Consumption of antibiotics and occurrence of antibiotic resistance in Sweden	X	X	X		X

99 Modules: 1 = Farm; 2 = Abattoir; 3 = Meat Processing; 4 = Retail; 5 – Consumers

A literature review was performed by analysing published scientific papers and the major sources of information originated from the scholarly databases such as Web of Science, EBSCO and ScienceDirect. The official web-sites of selected national monitoring and surveillance schemes were also analysed, including the European Antimicrobial Resistance Surveillance Network (EARS-Net) and Antimicrobial Consumption Interactive database (ESAC-Net). This review identified relevant articles (research and review papers, technical reports by international organizations) and databases, published in domains of zoonotic foodborne pathogens and related antimicrobial resistance, including the public health impact. The selection criteria chosen to identify the relevant articles within the scope of this review and the objectives of this paper were as follow: 1) focus on the specific AMR monitoring and surveillance programmes with well-established databases regarding meat chain-associated antimicrobial resistance; 2) focus on the potential for improvement of harmonization of national monitoring and surveillance systems and future research. However, some geographical restrictions were taken, by including selected countries with intensive experience and well-established AMR monitoring and surveillance programmes. Therefore, monitoring and surveillance programmes on antimicrobial usage and antimicrobial resistance of the major zoonotic foodborne pathogens with public health importance (*Salmonella*, *Campylobacter*) and indicator bacteria (*E. coli*, *Enterococcus* spp.) were reviewed in four EU Member States (MSs) (Denmark, Sweden, France and Netherlands) and one EEA country (Norway) (Table 2).

120 Table 2. Monitoring and surveillance programmes of four selected EU member states and 1 EEA country

Programme	Type of surveillance			Country	Source
	animals	food	humans		
Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP)	x	x	x	Denmark (EU)	www.danmap.org
French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin (RESAPATH)	x		x	France (EU)	www.resapth.org https://www.anses.fr/en/thematique/veterinary-medicine-anmv
Monitoring of Antimicrobial Resistance and Antibiotic Usage in the Netherlands (MARAN)	x	x	x	The Netherlands (EU)	http://www.wageningenur.nl/en/Expertise-Services/Research-Institutes/Central-Veterinary-Institute.htm
Swedish Veterinary Antimicrobial Resistance Monitoring (SVARM)	x		x	Sweden (EU)	http://www.sva.se/en/antibiotika/svarm-reports
Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM/NORM-VET)	x	x	x	Norway (EEA)	www.vetinst.no/eng/Research/Publications/Norm-Norm-Vet-Report

2. AMR status in the EU and EEA

Antimicrobial resistance is a serious public health threat in Europe. For invasive bacterial infections, prompt treatment with effective antimicrobial agents is especially important and this is usually the single most effective intervention to reduce the risk of fatal outcome. Ongoing increase of antimicrobial resistance in invasive bacterial isolates according to the report by European Antimicrobial Resistance Surveillance Network / EARS-Net (EARS, 2014) to a number of key antimicrobial groups (3rd and 4th generation of cephalosporins, fluoro- and other-quinolones, glycopeptides, macrolides and ketolides), as well as penicillin's and aminoglycosides to a certain degree (WHO, 2011b), is of great concern and should be considered as the highest priority. The antimicrobial resistance situation in Europe shows large variations depending on the bacterium, antimicrobial group and geographical region (ECDC, 2014). These variations between the EU Member States (MSs) and EEA countries (Norway, Iceland and Switzerland) might be also due to the lack of uniformity in sampling schemes, laboratory methods used for identification of AMR profile, approach regarding clinical breakpoints (clinical resistance) and epidemiological cut-off values (microbiological resistance), as well as defined priorities regarding public health impact. To overcome this issue, the `Zoonoses Directive` (EU, 2003a) was issued, to support the harmonization of national monitoring and surveillance schemes for foodborne diseases, including AMR. The importance of protecting human health against diseases and infections transmissible directly or indirectly between animals and humans (zoonoses) was stressed, including foodborne zoonoses. It implies that EU MSs shall ensure that integrated data on the occurrence of zoonoses and zoonotic agents and related antimicrobial resistance in animals, food and humans are collected, analysed and published without delay (Figure 1). However, up to the time of writing this article, substantial differences exists between the MSs regarding specific aspects in implementation of national monitoring and surveillance systems for zoonotic foodborne pathogens and AMR, which create certain difficulties in interpreting and extrapolating data between MSs.

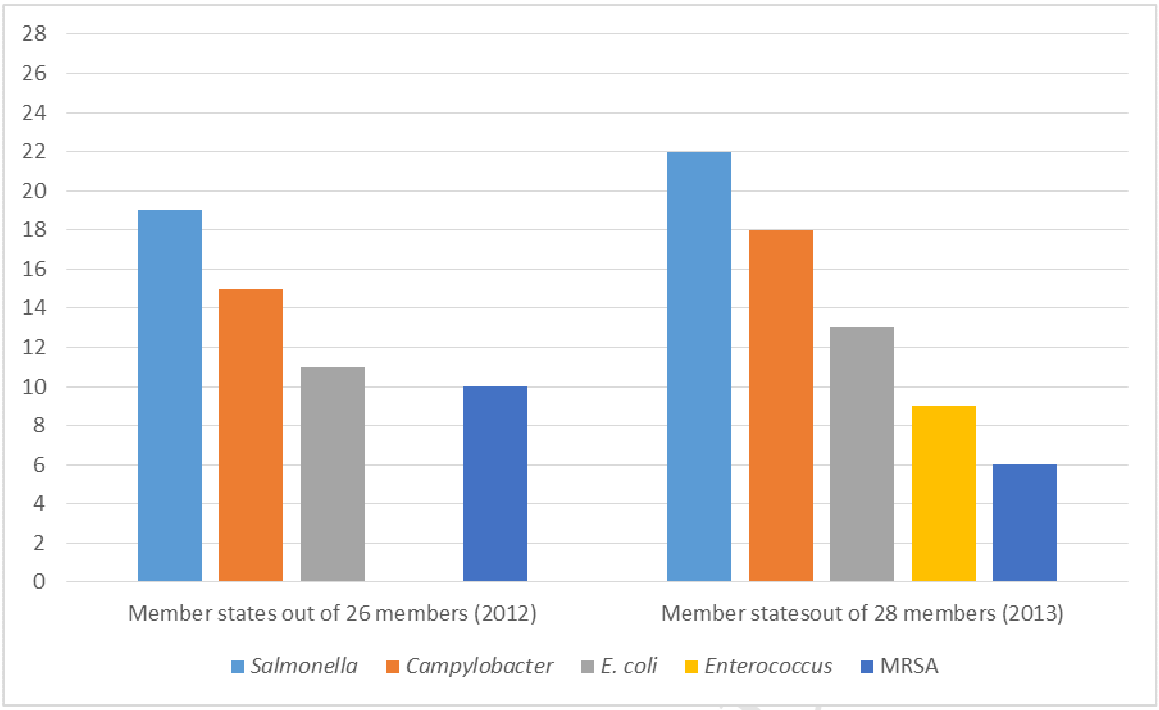


Figure 1. Number of Member States' submissions of antimicrobial resistance in zoonotic (*Campylobacter*, *Salmonella*, MRSA) and indicator bacteria (*E. coli*, *Enterococcus*) in animals, food and humans (Adapted from EFSA/ECDC, 2015)

2.1. AMR in Humans

The first concerns about antimicrobial resistance in humans were raised in Denmark, in 1994 and 1995, due to usage of the growth promoting antimicrobial (avoparcin). This led to the occurrence of vancomycin resistant *Enterococcus faecium* in humans (Bates et al., 1994; Aarestrup, 1995). During this period of time, there was also a growing awareness and a general public concern about overuse of antibiotics in Danish pig and poultry production and the effects on antimicrobial resistance.

In France, a comprehensive study was conducted to define the antimicrobial profiles and patterns related to *Campylobacter*-associated infections in humans and to compare this with *Campylobacter* isolated from broiler chicken and pigs (Gallay et al., 2007). The database originated from 1986-1990 was compared with trends from 1999-2004; it was reported that resistance to nalidixic acid increased dramatically (3 fold), while the patterns of resistance to quinolones and fluoroquinolones for *C. jejuni* were similar between 1999 and 2004, in human

and broiler isolates. Skurnik et al. (2006) carried out a study to determine the level of antimicrobial resistance in *E. coli* of animal faecal origin in several animal populations with different exposure to human contact (wild animals, farm animals and pets). It was proven that occurrence of antimicrobial resistance in *E. coli* isolated from animal faecal material happened due to anthropogenic influence. Obviously, the emergence, development and spread of antimicrobial resistance is a dynamic process flowing into both directions - zoonotic impact (animal/food-human) and anthropogenic (humans-animals). French Agency for Food, Environmental and Occupational Health & Safety released a report on the usage of colistin (ANSES, 2015), an antibiotic used in veterinary medicine (in livestock), which is also of the highest importance in human medicine. Due to its toxicity, colistin is only prescribed for the treatment of severe human infections involving bacteria resistant to all other therapeutic options (including bacteria resistant to last-generation cephalosporins and carbapenems). Initially, it was considered that colistin, because of the absence of any mechanism for transferring resistance to this antibiotic between bacteria, shouldn`t be included in the list of critically important antibiotics used in veterinary medicine. However, in 2015, the first transferable mechanism for resistance to colistin (the *mcr-1* gene) was described in China in pigs and chickens, in meat sold at retail, and also among bacterial strains isolated in humans. European Medicines Agency recommended additional monitoring of off-label use of colistin and restrictions on indications to therapy or metaphylaxis and removing all indications for prophylactic to minimise any potential risk associated with a broader use (EMA, 2016); consequently ANSES revised its risk assessment and included the colistin in the list of veterinary antibiotics of critical importance.

In Netherlands, the epidemiological link of antimicrobial resistance between animals and humans was investigated in an integrated study carried out by van den Boggard and Stobberingh (2000); it was concluded that use of antibiotics in food animals may provoke the emergence and dissemination of resistant bacteria. It is observed that the level of resistance of pathogenic foodborne bacteria (*Salmonella*, *Campylobacter*) and commensal bacteria (*E. coli*, *Enterococcus*) increases after the introduction of antibiotic. It is known that commensal bacteria are a reservoir of resistance genes for pathogenic (foodborne) bacteria. Their level of resistance may serve as a good indicator for selection pressure from antibiotic usage and for prediction of resistance in pathogens. Monitoring of resistance in indicator bacteria (*Escherichia coli* and *enterococci*) in different ecological compartments, e.g. in environment (manure, water, feed), animals, food of animal origin (meat), patients and healthy humans,

199 should provide valuable data on resistance prevalence and facilitate the understanding of the
200 resistance transfer from animals to humans and vice versa.

201 In a study carried out in Sweden from 2000-2004, genetic characterization of *Campylobacter*
202 isolates associated with antimicrobial resistance was conducted to provide better
203 understanding of epidemiological link between AMR in humans, meats and water. This study
204 confirmed the link between meat consumption and antimicrobial resistance in humans and
205 also enabled focusing on identification and eradication of the major reservoirs with common
206 clones of the public health importance (Lindmark et al., 2004).

207 In Norway, the study carried out from 1975-1998, revealed the emergence of multi-resistant
208 *Salmonella Typhimurium* DT104 isolates collected from humans; the first multi-resistant
209 isolate appeared in 1994, while in 1998 already 23% of domestically acquired isolates were
210 multi-resistant (Leegard et al., 2000).

211 Significant increase in the rate of gram-negative microorganisms isolated from humans
212 (blood and cerebrospinal liquor), as well as foodstuffs had been observed in EU, from 2011-
213 2014 (ECDC, 2014). Additionally, a possible relationship between antimicrobial usage in
214 food animals and the occurrence of AMR in humans was conducted (ECDC, 2015).

215 It is estimated that 11,381.8 tonnes of active substance with antimicrobial effect was used in
216 humans and food animals in 26 EU/EEA countries in 2012 (ECDC/EFSA/EMEA, 2015)
217 (Figure 2).

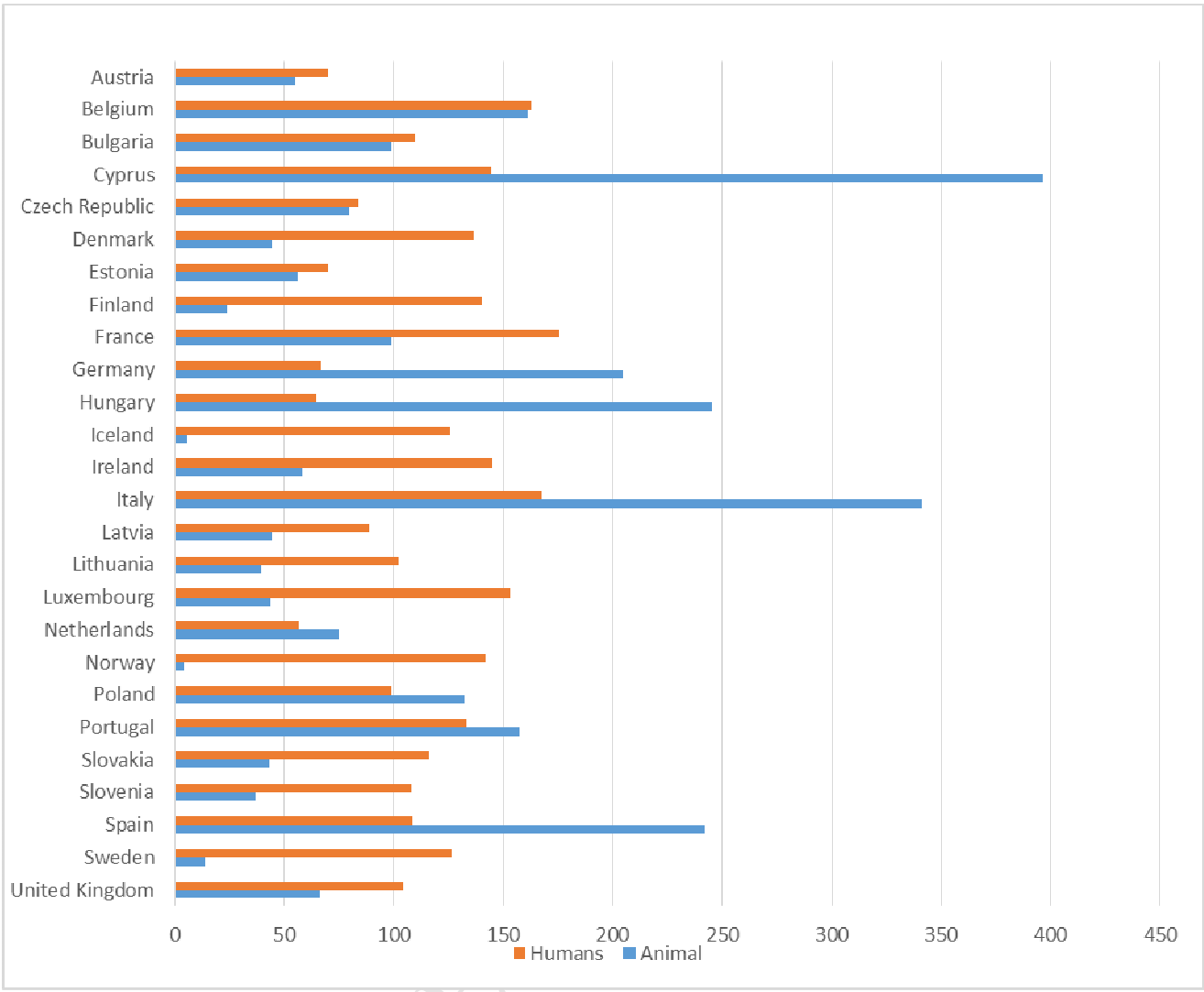


Figure 2. Comparison of biomass-corrected consumption of antimicrobials (mg/kg) in humans and food-producing animals by 26 EU/EEA countries in 2012 (Adapted from ECDC/EFSA/EMEA, 2015)

A resistance to third-generation cephalosporin's in *Klebsiella pneumoniae* and *Escherichia coli* increased significantly at EU/EEA level as well as in many of the individual MSs. 3rd generation cephalosporin resistance was often associated with fluoroquinolone and aminoglycoside resistance. Resistance trends in gram-positive bacteria showed a more diverse pattern across Europe. The percentage of EU/EEA population from which the methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated, continued to decrease over the last four years, from 18.6 % to 17.4 % in 2011 and 2014, respectively. The significantly increasing four-year trend for vancomycin resistance in *Enterococcus faecium* (commensal microorganism) was observed from 2013. EU data regarding AMR for *Salmonella* in humans indicated increased resistance associated with ampicillin, cefotaxime, chloramphenicol,

232 ciprofloxacin, gentamicin, kanamycin, nalidixic acid, streptomycin, sulphonamides,
233 tetracycline's and trimethoprim. The AMR reported for *Campylobacter* was mainly
234 connected with amoxicillin, ampicillin, ciprofloxacin, erythromycin, gentamicin, nalidixic
235 acid and tetracycline (EFSA, 2011). These findings are closely related to the prevailing use of
236 certain class of antibiotics in selected EU and EEA countries (Table 3).

237 Table 3. Most commonly used antimicrobials in selected EU/EEA countries

Country	Programme	Cattle	Pigs	Poultry	Combined cattle, pigs and poultry	Food producing animal consumption in tonnes active (ECDC/EFSA/EMEA, 2015)
Denmark	DANMAP	1. Penicillin's b-Lactase sensitive 2. Tetracycline's 3. Sulphonamides and Trimethoprim	1. Tetracycline's 2. Penicillin's b-Lactase sensitive 3. Macrolides	1. Tetracycline's 2. Macrolides 3. Penicillin's (others)	N/A**	107 tonnes
France	RESAPATH	N/A*	N/A*	N/A*	1. Tetracycline's, 2. Sulphonamides, 3. Penicillin's,	761.5 tonnes
The Netherlands	MARAN	1. Penicillin's 2. Combinations 3. Tetracycline's	1. Tetracycline's 2. Penicillin's 3. Trimethoprim/ Sulphonamides	1. Macrolides / lincosamides 2. Quinolones 3. Polymixins	N/A**	245.7 tonnes
Sweden	SVARM	N/A*	N/A*	N/A*	1. Benzyl penicillin 2. Sulphonamides 3. Tetracycline's	10.6 tonnes
Norway	NORM-VET				**1.** Penicillin's **2.** Sulphonamides **3.** Aminoglycosides	7.1 tonnes

238 * Breakdown of antimicrobials for individual species unavailable
239 **Breakdown of antimicrobials for combined species unavailable

2.2. AMR in Food (Meat) Animals

Development and increase of AMR in humans has a connection with antibiotic use in another ecological compartment – food animals. Therefore, the Member States (MSs) of the EU followed a monitoring system since 2003 (EU, 2003a; Directive 2003/99/EC that sets rules for monitoring on AMR and provides Member States, a. to ensure that monitoring provides comparable data on the occurrence of AMR in zoonotic agents and b. to assess the trends and sources of AMR in their territory). In 2013, based on the proposals issued by EFSA, the European Commission put forward and discussed with the MSs a new legislation on the harmonised monitoring of antimicrobial resistance in zoonotic (*Salmonella*, *Campylobacter)* and commensal bacteria (*Escherichia coli* and *Enterococcus* spp.) in food-producing animals and food; a list of combinations of bacterial species, food producing animal populations and food products was defined, panel of antimicrobials and tests to be used are recommended and priorities for the monitoring of antimicrobial resistance from a public health perspective were set up (EU, 2013; Commission Decision 2013/652/EC on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria). Such approach should provide better consistency between EU MSs, regarding sampling, method of susceptibility testing and reporting, as well as improve the comparability of the data generated among MSs.

A comprehensive study of AMR in bacteria isolated from food animals to antimicrobial growth promoters and therapeutic agents was carried out in Denmark, in 90's (Aarestrup et al., 1998). The acquired resistance to all used growth promoting antimicrobials was confirmed, with most frequent occurrence of resistance observed to avilamycin, avoparcin, bacitracin, flavomycin, spiramycin, tylosin and virginiamycin. The occurrence of resistance varied according to animal origin and bacterial species. The highest levels of resistance were observed among indicator bacteria (enterococci), while less resistance was observed among pathogenic zoonotic bacteria (*Salmonella, Campylobacter*). Similarly like in other EU MSs, the thermo-tolerant *Campylobacter* was the most commonly reported pathogen associated with gastrointestinal bacterial infections in humans. Broilers are identified as the primary source of infection, though other sources may also exist, e.g. water from untreated water sources and other infected animals. The particular resistance found in *C. jejuni* isolates was to ciprofloxacin and nalidixic acid. Among the *Salmonella* isolates (*S. Typhimurium* and *S. Derby*) from healthy Danish pigs, relatively high levels of resistance (34% - 49%) were observed to ampicillin, sulphonamide, and tetracycline (DANMAP, 2014). In indicator

bacteria (enterococci), a high level of resistance in *Enterococcus faecalis* isolated from broilers was observed to tetracycline (49%), followed by erythromycin (27%) and chloramphenicol (2%). Parallel to that, a very high occurrence of resistance to tetracycline (83%) and moderate to high occurrence of resistance to erythromycin (49%) and chloramphenicol (24%) was found in *E. faecalis* isolates from pigs. The occurrence of resistance to tetracycline has increased over the last five years, which may lead to the increase of potential risk of spreading the antimicrobial resistance, via horizontal gene exchange, to other pathogenic bacteria (DANMAP, 2014).

In France (RESAPATH, 2012) it is estimated that the resistance level in *S. Typhimurium* isolated from cattle is very high, especially to amoxicillin (89%), tetracycline (92%) and sulphonamides (72%). The resistance level in *E. coli* isolated from pigs was extremely high to amoxicillin (97%), gentamycin (94%), tetracycline (98%), enrofloxacin (94%) and trimethoprim-sulphonamides (97%). In hens and broilers, the extreme level of resistance in *E. coli* was confirmed to amoxicillin (98%), ceftiofur (97%), gentamycin (96%), tetracycline (98%), flumequine (97%), enrofloxacin (97%) and trimethoprim-sulphonamides (97%).

In Netherlands, the antimicrobial resistance detected in *S. Typhimurium* was predominantly associated with pigs, but was also found (although less predominant) in cattle and poultry. Resistance of *S. Enteritidis* was mainly present in poultry and more specifically in laying hens and contaminated eggs, while resistance in *S. Dublin* was observed mainly in cattle (MARAN, 2013).The highest resistance levels of *C. jejuni* isolated from poultry were observed for tetracycline and the quinolones (ciprofloxacin and nalidixic acid) raising a public health concern, and much lower in isolates from laying hens. However, resistance to macrolides, e.g. erythromycin, the first choice antibiotic in human infections (critically important antibiotic), was still low. This is in line with finding that macrolide resistance was not detected in *C. coli* from pig meat. Surveillance in indicator bacteria (*E. coli*) showed resistance to ampicillin, tetracycline's, sulphonamides and trimethoprim and it was commonly detected in broilers, turkey, pigs and veal calves. Although resistance to fluoroquinolones decreased, it was still commonly present in indicator *E. coli* from poultry sources. The promising results were reported regarding resistance to 3rd generation cephalosporins (critically important antibiotics) which was low in most animal species. Susceptibility testing of enterococci is considered of lesser priority than *E. coli* and from 2013 and onwards poultry, pigs and cattle are sampled every three years instead of annually (MARAN, 2013).

In Sweden, the majority of submissions for testing on antimicrobial resistance originated from clinical samples associated with diseased animals. Therefore, data may be biased taking into consideration the samples from treated animals or from herds where antibiotic treatment is common, versus clinically healthy animals where antimicrobial treatments were rare. Isolates are classified as susceptible or resistant by Epidemiological Cut Off Values (ECOFFs) issued by European Committee of Antimicrobial Susceptibility Testing (EUCAST). In *E. coli*, clinical samples from pigs, taken on-farm (faeces) or post-mortem (faecal material from intestines), the resistance to streptomycin (50%), trimethoprim-sulphamethoxazole (46%), ampicillin (40%) and tetracycline (25%) was the most common trait. Multi-resistance occurred in 42% (50/118) of the isolates in 2014, which is higher than in previous years (38% in 2013, 24% in 2012, 25% in 2011, 15% in 2010, 19% in 2009 and 14% in 2008). The reason for this increase remained uncertain. In *E. coli* samples obtained from cattle (calves no more than a few weeks old, when the resistance in enteric bacteria is usually high) during the period 2012-2014, resistance was higher than in previous years for streptomycin (42%), tetracycline (31%) and ampicillin (24%). Multi-resistance occurred in 76% (22/29) of the isolates from 2014, compared to 70% in 2013, 50% in 2012 and 40% in 2007-2011. In broilers, laying hens and turkeys, the occurrence of ESBL-producing *E. coli* from faeces and environment is monitored and the epidemiology of this resistance is studied. The majority of isolates (75%) were susceptible to all antibiotics tested (SVARM, 2014).

In Norway, the situation regarding antimicrobial resistance to *Salmonella* spp. in food animals is very good since those animal populations are almost free from *Salmonella* spp.

To maintain this favourable situation, Norway runs an extensive surveillance programme that covers both live animals (cattle, pigs and poultry) and meat samples (NORM-VET, 2013). However, in 2013, the resistance to fluoroquinolones was found in *S. Virchow* from pig, while the multi-resistant *S. Typhimurium* was isolated from one pig herd (resistance to tetracycline, ampicillin, sulfamethoxazole and streptomycin). The isolates of *Campylobacter jejuni* in broilers were obtained from caecal samples and all broiler flocks slaughtered before 50 days of age were tested for the presence of *Campylobacter* spp. In 2013, one *C. jejuni* isolate per positive flock (total of 96 flocks) was submitted for susceptibility testing. The highest rate of resistance was detected for fluoroquinolones (ciprofloxacin [5.2%], nalidixic acid [5.2%]), tetracycline (3.1%) and streptomycin (2.1%). These findings confirmed that the prevalence of antimicrobial resistance among *C. jejuni* isolates from Norwegian broilers is low. This is also in line with common practice in Norwegian poultry flocks where therapeutic use of antimicrobial agents in broilers is relatively low and the products applicable for such

use contain either amoxicillin or phenoxymethylpenicillin; nalidixic acid is not used in poultry at all. *Escherichia coli* and *Enterococcus* spp. are monitored as indicator bacteria. *E. coli* isolates were obtained from samples from a total of 204 layer flocks and 131 turkey flocks; the highest resistance was found to tetracycline (12.8% and 7%, respectively), ampicillin (9.2% and 12.8%, respectively), sulfamethoxazole (11.3% and 9.2%, respectively), trimethoprim (5.9% and 3.7%, respectively) and streptomycin (4.3% and 4.6%, respectively). It is known that acquired resistance to cephalosporins among gram negative bacteria (e.g. *E. coli*) has called on special attention in recent years. Production of extended-spectrum beta-lactamases (ESBLs) or transferable AmpC are major mechanisms behind such resistance (Babic et al., 2006). ESBL producing *E. coli* were not detected in any of the 204 samples taken from layer flocks, indicating prevalence below 1.8%. However, the results from the broiler production revealed very high resistance to 3rd generation cephalosporin's (43%). In *E. faecalis*, the resistance was determined from samples taken from layers and turkey; the highest level of resistance was found in tetracycline (31.5% and 41.5%, respectively), erythromycin (10.1% and 18.2%, respectively), bacitracin (3.3% and 18.2%, respectively) and narasin (1.1% and 12.1%, respectively).

2.2.1. Meat/Meat products.

The occurrence of antimicrobial resistance associated with bacteria found on/in meat/meat products was investigated in many studies carried out in European countries.

In Denmark, Andersen et al. (2006) conducted a study to determine the antimicrobial resistance of *Campylobacter jejuni* in raw poultry meat at retail level. The highest level of resistance was reported to tetracycline, nalidixic acid and ciprofloxacin, while low resistance was observed to macrolides (antibiotics important for human health). Wielinga et al. (2014) conducted a study to evaluate the evidence-based policy to control antimicrobial resistance in the food chain. They investigated the conflict of interest between the major stakeholders from agriculture, veterinary, health and commercial level and concluded that success of the national surveillance and monitoring programmes can be only achieved if all stakeholders, from farm-to-fork, are involved.

In France, Granier et al. (2011) conducted a review to assess AMR in *Listeria monocytogenes*, in food and environmental isolates, from 1996 to 2006. More than two hundred strains were collected and selected on the basis of a unique pulsed-field gel

electrophoresis (PFGE) profile. Half of the strains were isolated from food samples and a quarter from food processing plants. Out of the total number of isolates, 20% belonged to meat (pork, 10%; poultry, 5%; and beef, 5%) while other originated from dairy and sea products. Resistance to erythromycin, tetracycline-minocycline, and trimethoprim was reported. Further, a comprehensive one-year study was carried out to establish prevalence and characterization of *Campylobacter jejuni* in retail chicken meat in French outlets (Guyard-Nicodeme et al., 2015). *Campylobacter* was detected in 76% of collected samples and resistance to tetracycline was the most common (53.6%), followed by ciprofloxacin (32.9%) and nalidixic acid (32%). All tested isolates were sensitive to erythromycin, chloramphenicol and gentamycin.

In Netherlands, Bruin et al. (2010) reported on prevalence and quantity of highly resistant *Enterobacteriaceae* (HRE), including ESBLs, in retail meat. The tested retail meat samples were chicken (52%), beef (29%), pork (9%), and other sources (9%). The ESBL producing *E. coli* was recovered from 18% of tested samples and all ESBL positive samples were chicken (34% positive). Resistance levels were very high to ampicillin (98%) and amoxicillin/clavulonic acid (80%), and low to cotrimoxazole (7%), gentamicin (5%), while resistance wasn`t observed to piperacillin/tazobactam, meropenem and ciprofloxacin. Since majority of tested chicken meat samples were ESBL positive it is concluded that chicken meat is a potential source of pandemic ESBL producing *E. coli* in the community and hospitals. Overdevest et al (2011) also confirmed the high prevalence of ESBL producing *E. coli* in retail chicken meat (79.8%). Genetic analysis showed that the predominant ESBL genes in chicken meat and human rectal swab specimens were identical. These findings implied that the role of ESBLs in chickens and its possible transmission to humans should be further investigated and clarified. Since it is well-known that restrictive use of antibiotics may result in lower resistance rates, Van der Broucke-Grauls (2014) speculated how powerful restrictive use should be to minimize the rise of antimicrobial resistance? The author gives an opinion that the resistance to antimicrobials in the future will slowly continue to rise, in spite of restricted use of antimicrobials since recently. It was concluded that the emergence of antimicrobial resistance is clearly of multi factorial nature and it is still uncertain what are the main contributors leading to this phenomenon. In Netherlands, a movement toward lower antibiotic use in animal husbandry already started. The use of 3rd generation cephalosporins was completely stopped in broilers and pigs, in March 2010. The promising results were reduction in resistance in *E. coli* from chicken, pigs, and calves. The future will bring the

answer whether this change is sufficient to slow down the rising resistance in humans (Van der Broucke-Grauls, 2014).

In Sweden, Ge et al. (2003) conducted a study to determine antimicrobial resistance in retail chicken meat. They reported that around 94% of tested meat samples were contaminated with *Campylobacter* strains that were resistant to at least one of seven antimicrobials in the panel. The resistance to tetracycline was the highest (82%), followed with doxycycline (77%), erythromycin (54%), nalidixic acid (41%) and ciprofloxacin (35%). Egervarn et al. (2014) studied the prevalence of *E. coli*, with transferable ESBL and AmpC beta-lactamases, and *Salmonella* on meat imported into Sweden (imported pork, beef and broiler meat). The authors highlighted that increased occurrence of *Enterobacteriaceae* (including *E. coli*) with transferable ESBL/AmpC beta-lactamases in humans may be linked with food (meat) producing animals. The prevalence of ESBL/AmpC-producing *E. coli* was 2-13% in pork meat, 0-8% in beef and 15-95% in broiler meat. Interestingly, the highest prevalence of ESBL/AmpC-producing *E. coli* was reported in South American broiler meat (95%), followed by broiler meat from Europe, (excluding Denmark) (61%) and from Denmark (15%). The results of the study implicated that meat imported into Sweden may present a significant source of human exposure to ESBL/AmpC-producing *E. coli.* This is particularly important since the ingestion of this organism by consumers may lead to transfer of resistance genes ($bla_{CTX\text{-}M\text{-}2}$ and $bla_{CTX\text{-}M\text{-}8}$), via conjugation, to another bacterium, including those with human pathogenic potential. Yavari (2012) carried out a comprehensive review in Sweden, selected European countries and USA on antibiotic resistance in *Salmonella enterica*, emphasizing the role of food animal control. A success of national monitoring and surveillance programme for control of AMR in Sweden is a consequence of efficient policy towards controlling the antibiotic resistance by effective management and regular prevention programs, and controlling different ecological/production compartments such as feed, food animals and humans. Such policy also resulted in effective collaboration of different organization in Sweden and led to decrease in the consumption of antibiotic in animals. Subsequently, low consumption of antibiotics in animals and humans led to the low prevalence of *Salmonella*. The success of any disease control program lies in the effectiveness and intensity of inter-sectoral cooperation. The communication between veterinary organizations and health care providers is essential to exchange the knowledge and relevant information. The international collaboration is also needed to achieve more effective control over spread of salmonellosis and to target antibiotic resistance (Yavari, 2012).

In Norway, Mo et al. (2016a) reported that *E. coli* resistant to extended-spectrum cephalosporins was found in broiler production and consequently in broiler meat, in spite of the restrictive policy indicated that the usage of antimicrobials is rare. The isolates from intestinal microbiota of broilers and from chicken meat in retail were compared to establish the epidemiological link via clones and resistance plasmids. Interestingly, it was revealed that clonal expansion via horizontal transfer, supported with stability of plasmid containing $bla_{CMY-2,}$ is maintained and disseminated within the broiler farms in Norway despite the absence of selective pressure due to low use of antimicrobials. In subsequent study Mo et al. (2016b) investigated the risk factors for occurrence of cephalosporin-resistant *E. coli* in Norwegian broiler flocks. The authors concluded that implementation of a high level of biosecurity is of crucial importance for decrease in the occurrence of cephalosporin-resistant *E. coli* in broiler flocks. The most important biosecurity risk factors were to minimize the number of people entering the broiler house during production cycles, as well as rigorous cleaning and disinfection routines between production cycles. These measures could result with decrease of resistance only if there is no selection pressure from antimicrobial use in the broiler production.

2.3. Sampling plans

Monitoring of antimicrobial resistance in EU MSs should be based on isolates obtained from clinical samples regularly submitted to a diagnostic laboratory or on actively collected isolates from healthy or diseased animals and meat products in all production stages: 1) pre-harvest (farm), 2) harvest (abattoir) and 3) post-harvest (retail) (EFSA, 2008, 2014b). The selection of isolates from clinical infections usually depends on the submission of samples taken on farm from local veterinarian, while sampling at slaughterhouse and retail will usually depend on regular visits by competent authority according to the national plan for AMR monitoring and surveillance.

2.3.1. Pre-harvest (on farm)

The objective of AMR monitoring is to collect and test for antimicrobial susceptibility of at least 170 representative *Salmonella* spp. isolates obtained respectively from the populations of laying hen flocks, broiler flocks and fattening turkey flocks in the MS, on a yearly basis (*Salmonella* National Control Programme/NCP); the sampling should be carried out either by the Competent Authority (CA) or under its supervision, by the Food Business Operator

(FBO). In addition, FBO should take the responsibility to submit for susceptibility testing the *Salmonella* strains which are randomly selected and originate from different (positive) flocks and, optimally, from different farms.

Two sampling approaches are suggested: 1) a stratified sampling strategy, e.g. proportional allocation within a sampling frame of *Salmonella* spp. strains deriving from the isolate collections available from the official laboratories and/or other laboratories designated by the CA, and 2) a simple random sampling (SRS), e.g. within the sampling frame of flocks involved in the NCP and which have tested positive for *Salmonella*. It is suggested to design the sampling plan as a quarterly SRS of the flocks tested positive for *Salmonella*.

2.3.2. Harvest (at abattoir)

The objective is to collate and test for antimicrobial susceptibility of at least 170 representative isolates of *Salmonella* spp. obtained respectively from carcasses of broilers, fattening turkeys, fattening pigs and bovines under 1 year of age. A collection of representative caecal samples (the number to be determined in each MS according to the estimation of the annual production) should be conducted to obtain isolates as follows: *E. coli* from broilers, fattening turkeys, fattening pigs and bovines under 1 year of age; *Campylobacter jejuni* from broilers and fattening turkeys; and isolates of Extended Spectrum Beta-Lactamase (ESBL)-/AmpC-/carbapenemase-producing *E. coli* from broilers, fattening turkeys, fattening pigs and bovines under 1 year of age. Under voluntary basis, the isolates of *E. faecium* and *E. faecalis* (indicator organisms) may be also taken from broilers, fattening turkeys, fattening pigs and bovines under 1 year of age, as well as isolates of *Campylobacter coli* from broilers and fattening pigs.

2.3.3 Post-harvest (retail meat)

The objective is to collect 300 representative random samples of fresh meat of broilers, pig meat and bovine meat, respectively and to test them for the presence of ESBL-/AmpC-/carbapenemase-producing isolates of *E. coli*. In case a MS has a lower level of meat production on a yearly basis, e.g. production of less than 100 000 tonnes of poultry meat per year, less than 100 000 tonnes of pig meat per year and less than 50 000 tonnes bovine meat per year, 150 samples of fresh pig, bovine and broiler meat should be tested at retail, instead of 300 samples. A `*retail*` means an outlet selling directly to the final consumer for domestic consumption, e.g. outlets/supermarkets, specialist shops and markets, but excluding catering activities, restaurants and wholesalers.

The sampling design is based on a proportionate stratified sampling scheme at the MS level. The samples are allocated proportionally to the size of the human population in the regions

accounting for at least 80 % of the national population. At the second level, the sampling should be conducted at retail outlets. At the third level, samples within the different meat categories should be selected. The 300/150 samples (of each meat category) should be allocated in proportion to the size of the human population.

In Denmark, sampling for *Salmonella* spp. includes isolates from healthy pigs (caecum samples) and pork (carcass swabs) collected at abattoirs as part of national surveillance and control programmes, as well as from human cases. The structured surveillance programme of antibiotic resistance to *Salmonella* in Danish pigs and pork started from 2011. *Salmonella* isolates from broiler, layer hens and cattle farms, as well as isolates from other types of meat (Danish and imported) are not presented. Interestingly, the monitoring and surveillance plan include only resistance among *S. Typhimurium* since the numbers of poultry flocks and meat samples infected or contaminated with *S. enteritidis* decreased over the last ten years (DANMAP, 2014). For *Campylobacter*, randomly collected samples are taken from broilers and cattle at slaughter and from fresh broiler meat ready for retail. Isolates from human cases originate from three out of five geographical regions in Denmark. The results for resistance profile of *Campylobacter jejuni* in Denmark indicated that 85-95% of the human campylobacteriosis cases are caused by *C. jejuni*. For Enterococci, a random collection of *Enterococcus* isolates from healthy pigs and broilers at slaughter (*E. faecalis* only*)* and from domestic fresh broiler meat, pork and beef sold at wholesale and retail outlets (both *E. faecalis* and *E. faecium*) was conducted. Enterococci (*E. faecalis)* from imported broiler meat, beef and pork were also included. Only one isolate per farm or meat sample is included in the final report. There are no specific sampling plans for testing of Extended Spectrum Beta-Lactamase (ESBL)-/AmpC-/carbapenemase-producing *E. coli* from broilers, fattening turkeys, fattening pigs and bovines.

In France, the collection of samples for AMR survey in bacteria isolated from the food chain is carried out by the French Agency for Food Safety (AFSSA, Paris). To assess a risk for emergence and dissemination of antimicrobial resistance between ecological compartments, and consumers, the sampling is conducted in animals, food and environment. The collection of samples is carried out in such a way that data may be compared between these compartments, at national and international level. Two types of epidemiological surveillance networks have been set up. The first type is based on gathering *Salmonella* zoonotic strains in AFSSA where they are systematically tested for their antimicrobial susceptibility (Martel et

al., 2000). *Salmonella* strains isolated from environment, food producing animal and food are collected under the `*Salmonella* Network` programme, which is targeted national epidemiological surveillance system set up to monitor non-human *Salmonella* throughout the food chain. The network was officially created in 1997 and today includes nearly 150 public and private veterinary laboratories in 94 departments across France. The second type of surveillance is managed by AFSSA and serves as a multi-centric system to collect antibiotic susceptibility data on pathogenic strains isolated in local public veterinary diagnostic laboratories. Each network has been designed for one particular type of investigation. Data on AMR are summarized in French surveillance network for antimicrobial resistance in pathogenic bacteria of animal origin which started from 1982 (firstly in bovines) and nowadays in called `RESAPATH`. From 2000, the surveillance system was expanded to pigs and poultry and, in 2007, to other animal species such as small ruminants, companion animals or horses (RESAPATH, 2012). However, there is no specific information on sampling plans employed in this national programme, except that sampling will encompass harvesting of faeces or caeca from diseased animals, on farm and/or abattoir. Commensal bacteria (*E. coli*, *Enterococcus faecium*) and zoonotic strains (*Campylobacter* spp. and some *Salmonella* isolates) are isolated according to type: bovine, porcine, or avian.

In Netherlands, sampling is implemented according to national plan for monitoring of AMR and antibiotic usage in animals (MARAN, 2013). Sampling strategy has a goal to obtain annual collections of *E. coli* and *Salmonella enterica*, representative of the Dutch food-producing animal bacterial populations, including isolates obtained from retail. The samples are regularly taken from poultry populations on farm (the faecal samples) and/or abattoir (caecal samples), as well as poultry meat at retail (Leverstein-van Hall et al., 2011). Additional data on sampling plan were not available in Dutch national plan. Further, the Dutch approach to AMR encompasses all ecological compartments where human health is threatened by antibiotic resistant bacteria, e.g. healthcare sector, food producing animals, food and environment. This is an integrated approach based on the `One Health` concept. The main focus lies in healthcare and food-producing animals because the emergence and spread of antibiotic resistant bacteria starts from food-producing animals and subsequent transfer to

humans; the healthcare settings may be also environments where the transfer of resistance genes due to excessive use of antibiotics may be facilitated.

In Sweden, the sampling is carried out to cover all respective sectors - animal, food and humans. The collected samples are tested in designated public health laboratories coordinated by the Public Health Agency of Sweden and veterinary/food laboratories coordinated by the National Veterinary Institute. The results are jointly interpreted and reported in an integrated manner by both institutions (SVARM, 2014). Clinical isolates are taken from food-producing animals (on farm), e.g. pigs, cattle and sheep, and from humans (isolates from blood culture). Information on the indication for sampling was not available for many samples and the majority of submissions were likely from animals with disease. Therefore, data may be biased towards samples from treated animals or from herds where antibiotic treatment is common.

In Norway, the sampling of indicator organisms (*Escherichia coli* and *Enterococcus* spp.), which form the normal enteric microbiota, is carried out to determine the prevalence of acquired antimicrobial resistance. This can be used as an indicator of the selective pressure from use of antimicrobial agents in various populations. These bacteria may form a reservoir of transferable resistance genes from which antimicrobial resistance can be spread to other bacteria, including those responsible for infections in animals or humans. Faecal samples are taken via boot swabs from layer flocks and from turkey, including ESBL-producing *E. coli* from turkey fillets at retail. The sampling of isolates of zoonotic food borne pathogens, e.g. *Salmonella* spp., *Campylobacter* spp., *Yersinia enterocolitica* and non-zoonotic pathogen - *Shigella* spp. is also conducted. Human clinical isolates are collected from blood, urine and cerebrospinal fluid. The sampling plan is carried out according to provisions given in Regulation 652/2013/EC on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria. *Salmonella* spp. isolates are taken from each population of laying hens, broilers and fattening turkeys sampled in the framework of the national control programmes (EU, 2003b); carcasses of broilers, fattening turkeys, fattening pigs, and bovines under one year of age, are also collected. *Campylobacter jejuni* isolates are collected from caecal samples gathered at slaughter from broilers and from fattening turkeys.

2.4. Antimicrobial susceptibility testing

Susceptibility testing aims to quantify drug potency against specific pathogenic bacteria and to establish what measures can be taken to safely formulate the drug so it is a viable option for therapeutic treatments. It is also used to establish if changes in pathogenic behaviour against already tested drugs is occurring due to microbial resistance. When EUCAST defines a microorganism as "s*usceptible"* this generally means that the microorganism is susceptible to the therapy and that success when this specific antimicrobial agent is used is high. The opposite is defined when the microorganism is resistant to selected antimicrobial agent. When determining the ability of antimicrobials to be successful against a specific pathogen, the following information should be taken into consideration, e.g. the site of infection, ability of antimicrobial to reach infection site, as well as formulations available and dosage regimes (EFSA/ECDC, 2016).

Disk diffusion is one of the oldest approaches to antimicrobial susceptibility testing (AST) and remains one of the most widely used AST methods in routine clinical microbiology laboratories; it is very suitable for application and almost all antimicrobial agents can be tested since it requires no special equipment (Matuschek et al., 2014). Disk diffusion proved to be a reproducible and accurate method for AST if performed according to recommendations (Woods, 1995). European Committee on Antimicrobial Resistance Testing (EUCAST), with assistance from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) suggested a disc diffusion test with diameter breakpoints correlated with the EUCAST minimum inhibitory concentration (MIC) breakpoints (Matuschek et al., 2014), defined by inhibition zone diameters (IZD) expressed in mm. The MIC is used to describe the effect a new drug has on a specific organism. It identifies the minimum concentration required by an antimicrobial to inhibit the growth of an organism visually, after an overnight incubation period. It is the most widely used method for antimicrobial susceptibility testing (AST) in clinical laboratories throughout the EU/EEA (EUCAST, 2015). The disk diffusion method is widely used in France (L'Observatoire National de l'Epidémiologie de la Résistance Bactérienne aux antibiotiques/ONERBA) and Sweden (Swedish Veterinary Antimicrobial Resistance Monitoring/SVARM).

Although disk diffusion is the most widely used method for measurement of antimicrobial activity against *Salmonella* in routine clinical laboratories, since it is inexpensive and relatively easy to perform, the dilution method (where the MIC is determined in mg/L) is a more accurate measurement than disk diffusion; it is considered as the gold standard for AST.

Therefore, for monitoring purposes the micro-broth dilution is recommended as the preferred testing method. However, there is a good to excellent correlation between the values obtained in mm and in mg/L. Validated methods of gradient strip diffusion or disk diffusion according to EUCAST protocols are also accepted. The dilution method is routinely used by Danish, Dutch and Norwegian national monitoring systems for antimicrobial resistance – DANMAP, MARAN and NORM-VET, respectively.

2.4.1. Clinical breakpoints

Clinical breakpoints are developed for laboratory testing on antimicrobials to determine therapeutic value against new and already developed antimicrobials. Organisms may be graded as susceptible (s) - when a micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success; intermediate (I) - when a level of antimicrobial agent activity is associated with uncertain therapeutic effect; and resistant (R) - when a level of antimicrobial activity is associated with a high likelihood of therapeutic failure (EUCAST, 2012). Regardless of the method used to determine susceptibility, the purpose is to assimilate drug potency required to inhibit or kill a pathogen within the body, by using pharmacokinetics and pharmacodynamics.

2.4.2. Epidemiological cut-off values (ECOFFs)

Standardised epidemiological cut off values (ECOFFs) are described by the EU Reference Laboratory for Antimicrobial Resistance (EURL-AR, 2013) as "*essential for the comparison of antimicrobial susceptibility monitoring results*". For the purpose of monitoring, EURL-AR recommend the use of EUCAST ECOFFs which allows categorisation of bacteria as follows: (i) wild type (for a species with the absence of acquired and mutational resistance mechanisms to the drug in question) or (ii) non-wild type (for a species with the presence of an acquired or mutational resistance mechanism to the drug in question).

When bacteria are identified as having resistance, the MIC and IZD displays two major sub-populations: i) one is a fully susceptible set of isolates, and ii) the other is a fully resistant population. The change to being resistant may be due to changes in the cell walls, which make it permeable and there may be the possibility of isolates to fall between resistant and susceptible. MIC testing of the isolates, after culturing, can verify the reduction in susceptibility of the pathogen to antimicrobial agents. ECOFFs are derived by testing a suitable number of isolates from a wild-type population, to ensure that an identified organism

658 can be treated in order to determine the likelihood of success or failure of a specific
659 antimicrobial for clinical purposes. Accordingly, the epidemiological cut off values
660 recommended by the EURL-AR for interpretation of AST results are defined for *Salmonella*
661 spp., *Campylobacter coli*, *Campylobacter jejuni*, *Escherichia coli*, *Staphylococcus aureus*,
662 *Enterococcus faecium* and *E. faecalis* (EURL-AR, 2013).

663

664 **3. Harmonization of national AMR monitoring and surveillance programmes**

665 Surveillance of antimicrobial resistance at targeted intervals or ongoing monitoring of the
666 prevalence of resistance in bacteria from environment, food animals, food and humans is of
667 utmost importance for food safety in the context of public health (OIE, 2016). Monitoring of
668 bacteria from food products of animal origin intended for human consumption should be
669 collected in different stages along the food (meat) chain, i.e. pre-harvest (on farm), harvest (at
670 abattoir) and post-harvest (processing, packaging, storage, distribution and retail).

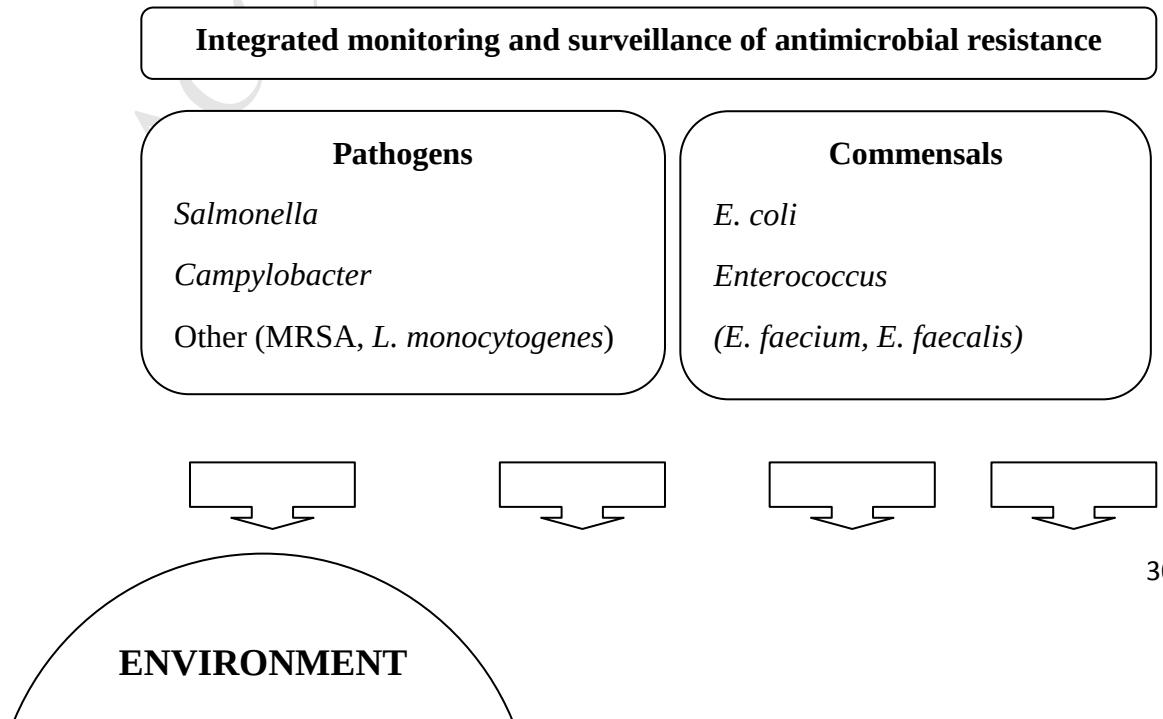
671 National antimicrobial resistance monitoring and surveillance programmes should be science-
672 based and may include the following components: a) statistically based surveys (veterinary
673 practitioners, farmers), b) sampling and testing of food animals on farm, at live animal
674 markets and, at slaughter, c) an organized sentinel programme, e.g. targeted sampling of food
675 animals, herds, flocks and vectors (birds, rodents), d) analysis of veterinary practice and
676 diagnostic laboratory records, e) sampling and testing of products of animal origin intended
677 for human consumption (OIE, 2016).

678 Sampling strategy should be based on the characteristics of the national livestock production
679 systems, on the basis of available information and to assess which sources are likely to
680 contribute most to a potential risk to animal and human health. For example, sampling at pre-
681 harvest level (on farm) may encompass feed and composite faecal sample, at harvest level (at
682 abattoir) the faecal content from the gut (ampulla recti for pigs/bovine and caecal samples for
683 broilers), as well as swabs from carcasses to assess the overall hygiene at slaughter and the
684 level of microbiological contamination of carcass/meat. Post-harvest level (processing,
685 packaging, distribution and retail) should include sampling of food to assess the overall
686 microbiological contamination from slaughter to consumer.

The monitoring of bacterial microorganisms should be focused on animal bacterial pathogens relevant to national priority to detect the emerging resistance that may pose a threat to animal and human health and to guide veterinarians in their prescribing decisions (minimizing the use of critically important antibiotics for human health). Major zoonotic foodborne pathogens (*Salmonella*, *Campylobacter*) should be monitored in food animals and feed, food of animal origin and humans. For *Salmonella*, serovars of public health importance should be included (*S. Typhimurium* and *S. Enteritidis*); other serovars should be also included based on the epidemiological situation in country. For *Campylobacter*, the most important serovars for public health should be monitored (*C. jejuni and C. coli*) and they should be monitored primarily from poultry and derived food products. Both, *Salmonella* and *Campylobacter* isolates should be identified to the species level and serotyped according to internationally standardised procedures, preferably at the nationally designated laboratories.

Other, emerging, zoonotic pathogens may be also included in the national resistance monitoring and surveillance plan, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Listeria monocytogenes*.

The monitoring of commensal bacteria, such as *E. coli* and enterococci (*Enterococcus faecium* and *Enterococcus faecalis*) should be carried out in environment (farm surroundings; manure, soil, water), because they represent the natural reservoir for transfer of antimicrobial resistance genes to pathogenic bacteria, feed and food animals (the samples of gut content should be taken preferably at abattoir), food of animal origin, as well as humans; this is important in order to establish a possible epidemiological link between food animals and humans and to provide a better overview to the use and misuse of specific antimicrobial agents (Figure 3).



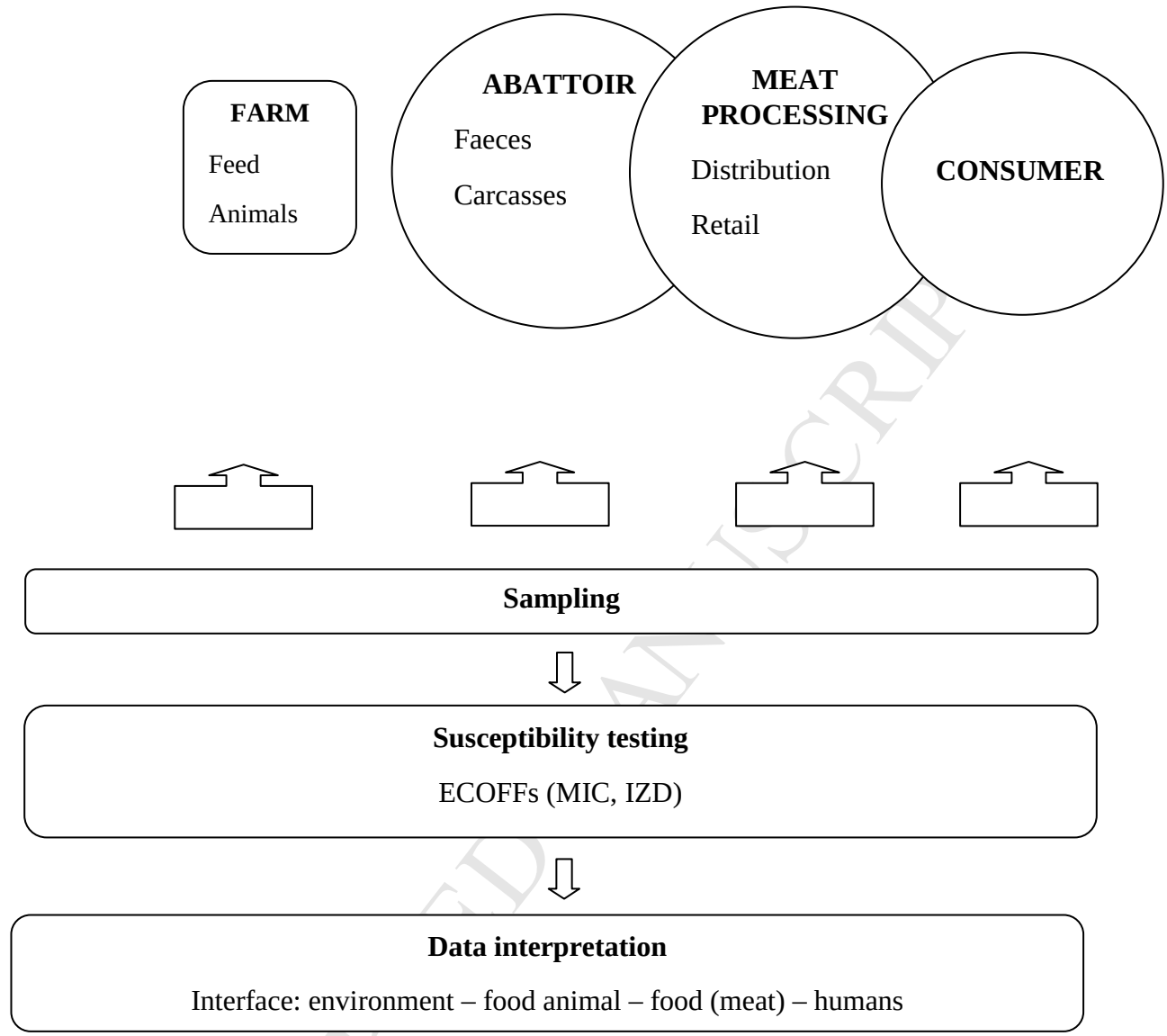


Figure 3. A framework of integrated monitoring and surveillance of antimicrobial resistance in the meat chain

A bacterial isolate should be always preserved until the reporting is completed. Preferably, selected isolates should be permanently preserved and stored. The maintenance of database of isolates originated from the previous years may also enable the epidemiological retrospective studies.

Overall, a consistency in sampling (target number of isolates per animal population and per module in the food chain, e.g. farm, abattoir, retail), method of susceptibility testing, the panel of antimicrobials and tests to be included, as well as reporting system, is of essential importance to improve the comparability of data generated between EU MSs and EEA

countries. This should be achieved by the vigorous implementation of recommendations issued by EFSA on randomised sampling for harmonised monitoring of antimicrobial resistance in zoonotic and commensal bacteria (EFSA, 2014b). Currently, a substantial differences exists between five selected EU and EEA countries regarding design and implementation of the national AMR monitoring and surveillance system (Table 4).

Table 4. Comparative overview of the national AMR monitoring and surveillance systems in five selected EU and EEA countries

Sampling and testing / Country	†Zoonotic pathogens		♯Commensals		Susceptibility testing	
	*Food animal, matrix, module	Humans	Food animals	Humans	Disk diffusion	Dilution method
Denmark	*Salm* (P, c, A; P, cs, A) *Camp* (B, A; C, A; fb, R)	*Salm Typhimurium* (f) *Camp Jejuni* (f)	Ec (P, c, A; C, c, A; B, c, A; fb/fp/fc, R) En (P, c, A; B, c, A; fb/fp/fc, R)	na		x
France	*Salm* (P, f/c, F/A; C, f/c, F/A; B, f/c, F/A) *Camp* (P, f/c, F/A; C, f/c, F/A; B, f/c, F/A)	na	Ec (P, f/c, F/A; C, f/c, F/A; B, f/c, F/A) En (P, f/c, F/A; C, f/c, F/A; B, f/c, F/A)	na	x	
Netherlands	*Salm* (B, f, F; B, c, A; fb, R) *Camp* (B, f, F; B, c, A;	*Salm Typhimurium, Enteritidis* (f)	Ec (P, f, F; C, f, F; B, f, F; fb/fp/fc, R)	na		x

	fb, R)	*Camp* *Jejuni* (f) STEC (f)	En (P, c, A; fp, R)			
Sweden	*Salm* (P, f, F; C, f, F; S, f, F) *Camp* (P, f, F; C, f, F; S, f, F)	*Salm* (bl), *Camp* (bl)	Ec (P, f/c, F/A, C, f, A; B, c, A) En (P, f/c, F/A, C, f, A; B, c, A)	na	x	
Norway	*Salm* (P, f/c, F/A; C, f/c, F/A; B, f/c, F/A) *Camp* (B, c, A)	*Salm Typhimurium, Enteritidis* (bl, u, cf), *Camp Jejuni* (bl, u, cf), *Yer enterocoilitca* (bl, u, cf), ‡*Shi* (bl, u, cf)	Ec (B, f, F; fb, R) En (B, f, F; fb, R)	na		x

747 *Food animal: P (pigs), C (cattle), S (sheep), B (broilers)

748 Matrix (sample): c (caecum), f (faeces), cs (carcass swabs), fb (fresh broiler meat), fp (fresh pork meat), fc
749 (fresh cattle meat), bl (blood), u (urine), cf (cerebrospinal fluid)

750 Module in the meat chain: F (farm), A (abattoir), R (retail)

751 †Zoonotic bacteria: *Salm* (*Salmonella*), *Camp* (*Campylobacter*), *Yer* (*Yersinia*), STEC (Shiga toxin producing *E.*
752 *coli*)

753 ‡Non-zoonotic bacteria: *Shi* (*Shigella*)

754 ♯Commensals: Ec (*Escherichia coli*), En (*Enterococcus faecium, Enterococcus faecalis*)

755 na: not applicable (the lack of data)

756

4. Conclusion

Over the last decade, the AMR associated with zoonotic foodborne pathogens is recognized as a major public health concern in Europe. Zoonotic foodborne bacteria are infectious agents which may be transferred from animals to humans via food consumption. Modern food-animal production uses large amounts of antibiotics not only for therapeutic purposes but also to prevent disease and promote animal growth. As a result, large numbers of healthy animals are routinely or often exposed to antibiotics. Such intensive, on-farm production practice, can trigger a development of bacterial resistance towards antimicrobials. Food-producing animals (cattle, sheep, pigs and poultry) are of particular importance for emergence and transfer of AMR which may be transferred to humans. The use of antibiotics in one sector or environmental compartment or country may influence the spread of resistance in others. The special importance should be given to commensal microbiota (*E. coli*, enterococci). These bacteria can also acquire antimicrobial resistance as a response to selective pressures and may form a reservoir of resistance genes in environment, farm and food animals, with the potential for transferring resistance to pathogenic bacteria which, in turn, may cause infection in humans difficult to cure. Infections with foodborne pathogens (*Salmonella*, *Campylobacter*), resistant to antimicrobials, may result in serious treatment failures or necessitate the use of second-line antimicrobials for therapy.

The review of available scientific and professional literature regarding contribution of the meat chain to development and transfer of AMR from meat animals to humans, revealed that in five selected countries – four EU MSs (Denmark, France, Netherlands and Sweden) and one EEA country (Norway), healthy or diseased food-producing animals (cattle, pigs and poultry) and derived meats are regularly sampled - on farm, at abattoir and retail. The differences between these five countries regarding sampling schemes and susceptibility testing were evident (Table 4). A substantial difference was observed regarding food animal category, sample matrix (faeces, caecum, fresh meat) and module in the meat chain (farm, abattoir, retail) where sampling was conducted. In all five countries, detection and susceptibility testing for *Salmonella* and *Campylobacter*, as well as *E. coli* and enterococci was included in the national plan, although the selection of food animal category, matrix and module in the meat chain differed. The susceptibility testing for major zoonotic foodborne pathogens in humans (samples from blood, urine, cerebrospinal fluid) was carried out regularly for *Salmonella typhimurium* and *Campylobacter jejuni* - in Denmark, Netherlands,

Sweden and Norway; data from France were scarce and mostly related to individual studies regarding AMR profile of *L. monocytogenes*, *Campylobacter* and *Salmonella*. In Norway, other pathogens were also regularly included in the national AMR monitoring plan (*Yersinia enterocolitica* and *Shigella*, in humans). Data on susceptibility testing for commensals in humans were not available in neither of the five selected countries. The disk diffusion method is widely used in France and Sweden, while the dilution method is routinely used in Denmark, Netherlands and Norway.

Integrated monitoring and surveillance of antimicrobial resistance in commensal and zoonotic foodborne bacteria from humans, animals and food is an essential source of information when formulating measures to improve food safety and protect consumers from exposure to resistant bacteria from foods. To harmonise the sampling and susceptibility testing and provide better consistency between EU MSs, the EFSA guidelines for the monitoring of antimicrobial resistance (e.g. target number of isolates per animal population - on farm, at abattoir and at retail; method of susceptibility testing; a panel of antimicrobials to be included and test ranges) should be applied. Such approach is also needed to improve the comparability of data generated among EU MSs.

The effective risk mitigation strategies to tackle the antimicrobial resistance in the food (meat) chain context should be based on promotion of inter-sectoral cooperation at national and international level. Veterinary, agricultural and pharmaceutical authorities at the national level should give consideration to establishing a regulatory framework for authorizing and controlling veterinary medicines, including critically important antibiotics for veterinary medicine and human health. Integrating monitoring and surveillance in the environment-food animal-food (meat)-humans continuum is of utmost importance to tackle successfully the issue of antimicrobial resistance. The essential point is to reduce the need for antibiotics in food animal production systems by improving animal health through biosecurity measures, e.g. disease prevention (introduction of effective vaccines) and good hygiene and management practices – on farm and at abattoir. Future research needs should be based on knowledge gaps such as: securing comparable national data on the occurrence of antibiotic resistance in relevant bacteria from environment, food animals, food products and humans, including the use of various types of antibiotics in different categories of food animals; actively using surveillance data in epidemiological research and risk assessment, including the evaluation of interventions; improve the understanding of mechanisms of resistance

development and transfer; and development of new antibiotics and alternative approaches to antibiotic therapy.

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Antimicrobial resistance monitoring and surveillance in the meat chain: A report from five countries in the European Union and European Economic Area

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Highlights

- The emergence of antimicrobial resistance (AMR) in zoonotic foodborne pathogens.
- Resistant zoonotic bacteria compromise the effective treatment in humans.
- AMR monitoring and surveillance programmes reviewed in 5 EU/EEA countries.
- Sampling, susceptibility testing, clinical and epidemiological cut-off values.
- Integrated AMR monitoring in food animals, food and humans in the whole meat chain.