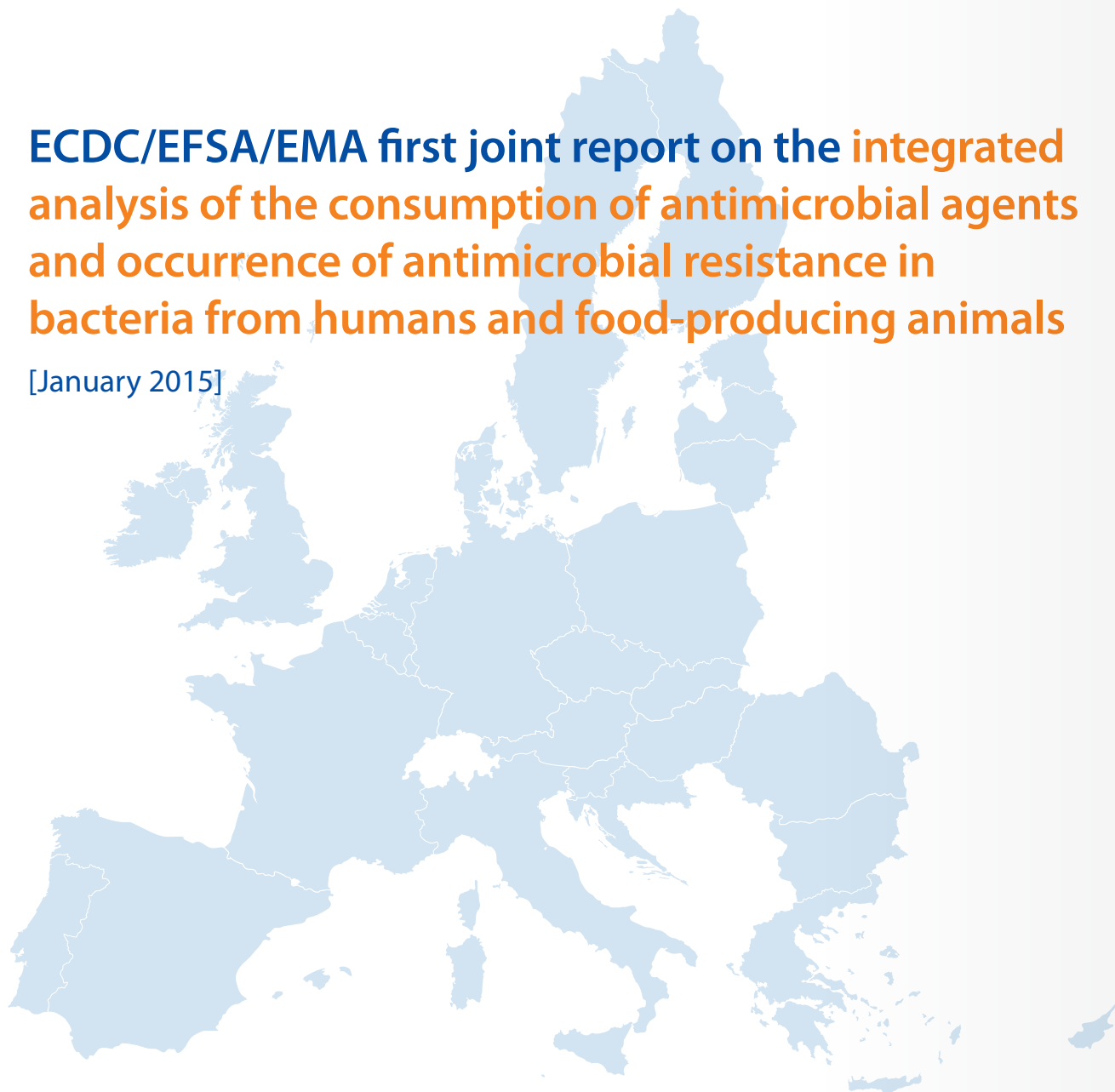


Report

European Food Safety Authority (EFSA)
European Centre for Disease Prevention and Control (ECDC)
European Medicines Agency (EMA)

ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals

[January 2015]



Joint Report - ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals

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SCIENTIFIC REPORT OF ECDC, EFSA AND EMA

ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals¹

European Centre for Disease Prevention and Control^{2,3}

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ABSTRACT

The ECDC, the EFSA and the EMA have for the first time jointly explored associations between consumption of antimicrobials in humans and food-producing animals, and antimicrobial resistance in bacteria from humans and food-producing animals, using 2011 and 2012 data currently available from their relevant five EU monitoring networks. Combined data on antimicrobial consumption and corresponding resistance in animals and humans for EU MSs and reporting countries were analysed using logistic regression models for selected combinations of bacteria and antimicrobials. A summary indicator of the proportion of resistant bacteria in the main food-producing animal species was calculated for the analysis, as consumption data in food-producing animals were not available at the species level. Comparison of antimicrobial consumption data in animals and humans in 2012, both expressed in milligrams per kilogram of estimated biomass, revealed that overall antimicrobial consumption was higher in animals than in humans, although contrasting situations were observed between countries. The consumption of several antimicrobials extensively used in animal husbandry was higher in animals than in humans, while consumption of antimicrobials critically important for human medicine (such as fluoroquinolones and 3rd- and 4th-generation cephalosporins) was higher in humans. In both humans and animals, positive associations between consumption of antimicrobials and the corresponding resistance in bacteria were observed for most of the combinations investigated. In some cases, a positive association was also found between antimicrobial consumption in animals and resistance in bacteria from humans. While highlighting findings of concern, these results should be interpreted with caution owing to current data limitations and the complexity of the antimicrobial resistance phenomenon, which is influenced by several factors besides antimicrobial consumption. Recommendations to address current data limitations for analyses of this type were identified. In any case, responsible use of antimicrobials in both humans and animals should be promoted.

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KEY WORDS

antimicrobial resistance, consumption of antimicrobials, ecological analysis

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ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals¹

Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report

Abstract

The ECDC, the EFSA and the EMA have for the first time jointly explored associations between consumption of antimicrobials in humans and food-producing animals, and antimicrobial resistance in bacteria from humans and food-producing animals, using 2011 and 2012 data currently available from their relevant five EU monitoring networks. Combined data on antimicrobial consumption and corresponding resistance in animals and humans for EU MSs and reporting countries were analysed using logistic regression models for selected combinations of bacteria and antimicrobials. A summary indicator of the proportion of resistant bacteria in the main food-producing animal species was calculated for the analysis, as consumption data in food-producing animals were not available at the species level. Comparison of antimicrobial consumption data in animals and humans in 2012, both expressed in milligrams per kilogram of estimated biomass, revealed that overall antimicrobial consumption was higher in animals than in humans, although contrasting situations were observed between countries. The consumption of several antimicrobials extensively used in animal husbandry was higher in animals than in humans, while consumption of antimicrobials critically important for human medicine (such as fluoroquinolones and 3rd- and 4th-generation cephalosporins) was higher in humans. In both humans and animals, positive associations between consumption of antimicrobials and the corresponding resistance in bacteria were observed for most of the combinations investigated. In some cases, a positive association was also found between antimicrobial consumption in animals and resistance in bacteria from humans. While highlighting findings of concern, these results should be interpreted with caution owing to current data limitations and the complexity of the AMR phenomenon, which is influenced by several factors besides antimicrobial consumption. Recommendations to address current data limitations for analyses of this type were identified. In any case, responsible use of antimicrobials in both humans and animals should be promoted.

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1. Summary and recommendations

1.1. Summary

This is the first integrated report by the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) analysing possible relationships between the consumption² of antimicrobial agents and the occurrence of antimicrobial resistance in humans and food-producing animals³.

ECDC, EFSA and EMA are agencies of the European Commission (EC). This report was prepared following a mandate from the EC. Data included in this report are from the agencies' surveillance networks, which receive information annually from the reporting countries. Further details on each network are provided in Chapter 4.

The report utilises data from 2011 and 2012, from five different surveillance networks, collecting information from the EU Member States (MSs), Iceland, Norway, Croatia and from Switzerland⁴. The datasets used have been established for purposes other than the current integrated analyses, and the analyses focused on certain combinations of antimicrobials and bacterial species (see section 5.3 for further details).

Antimicrobial consumption data from humans are normally reported as defined daily doses (DDD) per 1 000 inhabitants and per day. The corresponding data are currently reported for food-producing animals by weight of active substance per population correction unit (PCU) and per year. A fully comparable unit of measurement is not available. To make a comparison possible, data on consumption of antimicrobials for humans were converted to mass of active substance. When comparing the consumption of antimicrobials from humans and food-producing animals in 2012, the average consumption expressed in milligrams per kilogram of estimated biomass was 116.4 mg/kg in humans (range 56.7–175.8 mg/kg) and 144.0 mg/kg in animals (range 3.8–396.5 mg/kg). Consumption in food-producing animals was lower or much lower than in humans in 15 of 26 countries, in three countries it was similar, and in eight countries consumption in food-producing animals was higher or much higher than in humans.

Data on antimicrobial consumption in food-producing animals are not available by species in the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) reports. To analyse the relationship between consumption of antimicrobials and resistance in bacteria from food-producing animals, a summary indicator of resistance in the main three food-producing animals species was calculated on the basis of the weighted mean by PCU of the proportions of resistant bacteria in each of those animal species. Overall, a positive association was observed between antimicrobial consumption in food-producing animals and occurrence of resistance in bacteria from such animals for most of the combinations investigated. The strongest associations between consumption and resistance in food-producing animals were found for the antimicrobials studied in relation to indicator *Escherichia coli*. Positive associations were also noted for *Salmonella* spp. and *Campylobacter* spp.

A positive association was observed between the total consumption of 3rd- and 4th-generation cephalosporins in humans and the occurrence of resistance to 3rd-generation cephalosporins (the

² In this report the term "consumption" has been preferred to similar terms such as "use", "usage" or "sales".

³ A number of different animal species may be treated with antimicrobials; this report considers primarily antimicrobial consumption and resistance in food-producing animals.

⁴ For this report data were provided from the EU Member States, Iceland, Norway, Croatia and depending on the network, Switzerland; these are referred as "countries" or "reporting countries".

cephalosporin used for the susceptibility testing) in *E. coli* from humans. A positive association was also observed between the total consumption of fluoroquinolones in humans and the occurrence of fluoroquinolone resistance in *E. coli* from humans. No association was found between the consumption of fluoroquinolones in humans and the occurrence of fluoroquinolone resistance in *Salmonella* spp., *S. enterica* subsp. *enterica* serovar Enteritidis and serovar Typhimurium from cases of human infection.

For both cephalosporins and fluoroquinolones, positive associations were found between occurrence of resistance in indicator *E. coli* originating from food-producing animals and the occurrence of resistance in *E. coli* from humans.

No associations were observed between the consumption of 3rd- and 4th-generation cephalosporins in food-producing animals and the occurrence of resistance to this sub-class in selected bacteria from humans. No associations were observed between the consumption of fluoroquinolones in food-producing animals and the occurrence of resistance in *Salmonella* spp. and *Campylobacter* spp. from cases of human infection.

Positive associations were noted for consumption of macrolides in food-producing animals and the occurrence of resistance in *Campylobacter* spp. from cases of human infection, and for consumption of tetracyclines and the occurrence of resistance in *Salmonella* spp. and *Campylobacter* spp.

In the reported analyses, associations between the consumption of selected combinations of antimicrobials and the occurrence of resistance in bacteria were observed for most of the combinations addressed in humans and animals. The epidemiology of resistance is complex, and several factors aside from the amount of antimicrobial consumption influence the level of resistance.

Differences between the systems for collection and reporting of data on antimicrobial consumption and resistance in bacteria from humans and food-producing animals, at the time of data collection (2011–2012), unavoidably hamper direct comparisons. Owing to the characteristics of these data, the interpretation criteria and differences in units of measurement, the results which indicate associations of potential concern should be interpreted with caution.

1.2. Recommendations

To improve the integrated analyses, more detailed and comprehensive data are required. Future developments of ESVAC with collection of data by species and reporting of these data by DDD for animals will make that possible. Additional information, such as antimicrobial consumption by animal species and collection of resistance data from all countries, from relevant animal species and food, at a detailed level, including production type, is required. Resistance patterns among indicator commensal *E. coli* derived from humans from the community would most likely be a good indicator of the relative exposure to resistant bacteria through food consumption and the direct effect of antimicrobial consumption in humans. Other factors that would have to be considered are resistance to other antimicrobials (co-resistance), travel by humans, import and trade of food, and trade of live animals both between and within countries.

The findings in ecological analyses⁵ such as those presented in this report should be considered as hypotheses for subsequent testing by focused research that in time could provide more definitive explanations for the observed associations.

⁵ Ecological analyses can be used to investigate in an exploratory manner the impact of risk-modifying factors on health/non-health outcomes based on populations defined either geographically or temporally. Both risk-modifying factors and outcomes are considered at the population level in each geographical or temporal unit and then compared and their potential association assessed using standard statistical methods. For example, consumption of antimicrobials and occurrence of resistance in a given population may be compared across a number of countries. Although ecological studies are particularly useful for generating hypotheses since they can use existing data sets, they are limited by the fact that

Improvement of existing systems should enable better integrated analyses of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the future.

In particular, this refers to the following on-going actions aiming to:

- refine existing surveillance systems by providing more detailed information on antimicrobial consumption by age and gender in humans and by species and production types in animals;
- provide enhanced data on hospital consumption in more countries;
- provide more comprehensive data on foods—types, prevalence of bacteria and resistance;
- provide isolate-based data to enable analysis of the effects of co-selection.

Any improvement of data collection should be coordinated between the different surveillance networks, with the overarching aim of integrated analysis of the data.

Monitoring of antimicrobial resistance should also include:

- animal pathogens;
- commensal flora from both healthy and diseased persons;
- information about the origin of the food and/or animals.

Finally, there is a need to promote responsible use of antimicrobials in both humans and animals.

2. Terms of reference and scope

In 2012, the European Commission (EC) requested the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) to produce a common analysis of the data from surveillance systems on the consumption of antimicrobials and on the impact of antimicrobial consumption on the occurrence of antimicrobial resistance in bacteria from humans, animals and food in the EU. The request from the EC indicated that the report should be produced with harmonised and transparent presentation of the data, and at regular intervals. EU agencies are distinct bodies from the EU institutions—separate legal entities set up to perform specific tasks under EU law.

The request was based on the Communication of 15 November 2011 from the Commission to the European Parliament and the Council—Action Plan against the rising threats from Antimicrobial Resistance (AMR) (European Commission, 2011) —which sets out key actions and undertakings of the Commission for a successful fight against AMR. Actions 9 and 10 are requests to "*Strengthen surveillance systems on AMR and antimicrobial consumption in human medicine (action no 9) and in animal medicine (action no 10)*".

This first joint report on the integrated analysis of the relationship between available data on consumption of antimicrobial agents⁶ and the occurrence of antimicrobial resistance in humans and food-producing animals is the result of the request from the European Commission and was prepared by experts from the three above-mentioned agencies.

they cannot look at cause and effect in individuals and therefore establish causation, not matter how strong the associations discerned. It is important to take this into account when interpreting the results of such studies.

⁶ OIE definition "Antimicrobial agent": "a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kill or inhibit the growth of micro-organisms) at concentrations attainable in vivo. Anthelmintics and substances classed as disinfectants or antiseptics are excluded from this definition" (<http://www.oie.int/index.php?id=169&L=0&htmfile=glossaire.htm>).

The aim of the work behind this report is to analyse data available in reports from five different surveillance systems by an integrated analysis. The scope is limited to a comparison of consumption of antimicrobials in food-producing animals and humans and to the analysis of the prevalence of resistance to certain antimicrobials in selected bacteria: *Campylobacter* spp., *Salmonella* spp. and (indicator/pathogenic) *E. coli*; and fluoroquinolones, 3rd- and 4th-generation cephalosporins and tetracyclines, and also for *Campylobacter* spp. and macrolides. In addition, an analysis of the relationship between consumption of carbapenems in human medicine and resistance to carbapenems in bacteria from humans was performed.

The early stage of maturity of some of the systems for collecting and analysing data is acknowledged. As the work of each of the networks progresses towards a more detailed and accurate gathering and analyses of data, a more refined report can be produced. Owing to the complexity of the tasks and limited resources, it is envisaged that reports of this type will be produced not yearly, but on a multiyear basis.

ECDC provided data on antimicrobial consumption in humans as well as resistance monitoring data on isolates from cases of human infection. The EFSA provided data on monitoring of antimicrobial resistance in bacteria from food and food-producing animals. The EMA provided data on antimicrobial consumption in food-producing animals. All the data collected by the networks were originally provided by the reporting countries.

This report first presents consumption and resistance data, and then explores possible relationships between the data.

Numerous studies in human medicine have shown a correlation between consumption of antimicrobials and resistance in bacteria isolated from infections in humans (Bell et al., 2014; van de Sande-Bruinsma et al., 2008). These correlations are not addressed in this report as it focusses on zoonotic bacteria.

Representatives of the different surveillance/monitoring networks of the MSs in charge of providing the data and the European Union Reference Laboratory for Antimicrobial Resistance (EURL-AR) were consulted at the finalisation of the preparation of the joint report.

ECDC, EFSA and EMA have each established their own procedure for approval of the joint report according to their internal rules.

The ECDC approved the report on 26 January 2015, after consultation with the European Antimicrobial Resistance Surveillance Network (EARS-Net), the European Surveillance Antimicrobial Consumption Network (ESAC-Net) and the Food and Waterborne Diseases and Zoonoses Network (FWD-Net).

The European Food Safety Authority approved the report on 27 January 2015. The report was circulated for consultation with the Scientific Network for Zoonosis Monitoring Data. The report was presented to the 21-22 January 2015 BIOHAZ Panel meeting for information.

The European Medicines Agency approved the report on 16 January 2015. Before approval the report was circulated for consideration to the ESVAC network. The report was circulated at the 13-15 January 2015 CVMP plenary meeting for information.

3. Acknowledgements

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- ECDC: EARS-Net, ESAC-Net and FWD-Net;

- EFSA: Scientific Network for Zoonosis Monitoring Data;
- EMA: ESVAC.

This joint report is based on data provided by the above-mentioned networks and on the major contributions of the following experts:

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- EFSA: Pierre-Alexandre Belœil, Ernesto Liebana-Criado, Rob van Oosterom, Pascal Sanders, Christopher Teale and John Threlfall.
- EMA: Kari Grave, Christina Greko, Kristine Ignate, Zoltan Kunsagi, Gérard Moulin (Chair) and Jordi Torren-Edo.

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4. Description of the existing monitoring or surveillance systems

The European Centre for Disease Prevention and Control (ECDC) has a mandate to gather and analyse data and information on emerging public health threats and developments for the purpose of protecting public health in the European Community according to Regulation 851/2004/EC (Official Journal of the European Union, 2004b). The collection of data related to antimicrobial resistance and antimicrobial consumption is included as part of the European Surveillance System (TESSy) through several networks. Data included in this report regarding the occurrence of resistance in humans were obtained from two surveillance networks—the European Antimicrobial Resistance Surveillance Network (EARS-Net) and the Food- and Waterborne Diseases and Zoonoses Network (FWD-Net)—whereas data regarding consumption of antimicrobials in humans were obtained from one surveillance network: the European Surveillance of Antimicrobial Consumption Network (ESAC-Net).

Based on Article 33 in Regulation (EC) 178/2002 (Official Journal of the European Communities, 2002), the European Food Safety Authority (EFSA) is responsible for examining data on zoonoses, antimicrobial resistance and food-borne outbreaks collected from the MSs in accordance with Directive 2003/99/EC (Official Journal of the European Union, 2003a) and for preparing the EU Summary Report from the results. Regarding antimicrobial resistance data a specific EU Summary Report on antimicrobial resistance is produced in collaboration with ECDC on a yearly basis. It includes data related to the occurrence of antimicrobial resistance both in isolates from animals and foodstuffs, collected in the framework of Directive 2003/99/EC (Official Journal of the European Union, 2003a), and in isolates from human cases, derived from the surveillance network FWD-Net coordinated by ECDC.

The European Medicines Agency (EMA) is a decentralised body of the European Union (EU), located in London. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project was launched by the agency in September 2009, following a request from the European Commission (EC) to develop a harmonised approach to

the collection and reporting of data on the consumption of antimicrobial agents in animals from the MSs. The ESVAC reports present data on the consumption of veterinary antimicrobial agents from EU/European Economic Area (EEA) countries, provided at package level according to a standardised protocol and template.

4.1. Surveillance of antimicrobial consumption in humans

4.1.1. Description of collected data

ESAC-Net is the continuation of the former ESAC project (managed by the University of Antwerp until June 2011) and is a Europe-wide network of national surveillance systems coordinated by ECDC providing independent reference data on antimicrobial consumption in EU MSs, Iceland and Norway. It collects and analyses antimicrobial consumption data from the community (primary care) and from hospitals.

Antimicrobials are grouped according to the anatomical therapeutic chemical (ATC) classification. The three major categories of antimicrobials considered in ESAC-Net are the antibacterials for systemic use (ATC group J01), antimycotics and antifungals (J02 and D01BA) and antivirals (J05). In addition, data on antimycobacterials (J04) and a few antimicrobials outside the ATC J-group are collected. Only antimicrobials that are "antibacterials for systemic use" (ATC J01) are included in the present report.

There are two options for reporting ESAC-Net data to ECDC:

- the preferred standard option, i.e. reporting of national antimicrobial consumption data at the medicinal product level, expressed as number of packages sold or reimbursed. For this option, a valid national registry of available antimicrobials is required (national registry data);
- a "light" version, i.e. when national registry data are not available, reporting of aggregated numbers of DDD (defined daily doses) from national antimicrobial consumption data at the ATC substance level.

In addition, ESAC-Net encourages participants to report data by age group, gender and type of prescriber, as well as to report quarterly data rather than yearly data.

Most countries report data on sales, one-third of the countries report reimbursement data and a few report both sales and reimbursement data.

Data are uploaded into the TESSy database and used for reporting after a validation process and final approval by national ECDC contact points nominated by the reporting countries. The reporting countries can at any time upload or re-upload data to TESSy, e.g. for correction purposes.

ECDC ensures the annual analysis of the trends in overall antimicrobial consumption and in the different ATC groups, as well as comparisons between countries. Public access to information on antimicrobial consumption in Europe is provided through an ESAC-Net interactive database and an annual ECDC EU summary report on antimicrobial consumption.

4.1.2. Strength of the system

The ESAC-Net collects data from all 30 EU/EEA countries. For most of these countries, complete national consumption was reported. The standardised ESAC-Net reporting protocol, built upon the former ESAC project, is essential to ensure comparability with other multinational surveillance networks.

The quality of antimicrobial consumption data also depends on the type of data available for a given sector. For most of the countries ESAC-Net can differentiate between antimicrobial consumption data from the community (primary care) and from hospitals.

Data provided through the standard option of the reporting protocol are very valuable. First, the level of detail of these data (complete registry of products) allows a better quality check of the provided consumption data. Second, it provides the opportunity to carry out fine-grained analyses (such as analyses on the availability of products or changes in the content of products; or studies on the number of packages consumed to estimate the number of prescriptions). Such analysis is not possible when data are reported via the "light version" by providing aggregated numbers of DDD consumed only for the ATC groups under surveillance.

4.1.3. Impediments to comparing the data

For ESAC-Net, countries provide sales or/and reimbursement data that each have limitations. The major limitation of reimbursement data is that they do not include antimicrobials dispensed without a prescription and non-reimbursed prescribed antimicrobials (for example the antimicrobials prescribed through private healthcare systems). For this reason, countries that report reimbursement data and where it is known that a substantial proportion of antimicrobials are dispensed without a prescription are indicated as such when ESAC-Net results are published.

Countries, from one year to another, might deliver different type of data or from different data sources, which could also introduce bias in the consumption rates reported. The number of countries that each year change data provider and/or types of data is small.

ESAC-Net reports consumption separately for the community and the hospital sector, but some countries that are not able to split data according to the healthcare sector reported totals from both sectors combined (total care). Because consumption in the community represents around 90 % of the total consumption (when expressed as DDD per 1 000 inhabitants and per day), ESAC-Net reports the total care consumption as community consumption for those countries not able to split the data. For these countries, the figures reported for the community are overestimated and the antimicrobials normally used in the hospitals will be reported in the community sector; thus, the pattern of consumption will be slightly different from that seen in countries providing separate data for community and hospitals.

Although all countries are able to report antimicrobial consumption for the community, one-third of them cannot report data for the hospital sector as there is no surveillance system in place to collect data from this sector.

Finally, ESAC-Net reports the hospital consumption using the whole population and not hospital activity indicators, which may not be completely comparable in terms of trends.

4.1.4. On-going actions to improve the system

To improve the reporting of hospital antimicrobial consumption, ESAC-Net is developing a hospital-based surveillance of antimicrobial consumption. This surveillance will enable countries not currently reporting data for the hospital sector to do so in the future. In addition, consumption data will be collected by type of hospital as well as by hospital activity indicator in order to relate consumption to actual hospital activity.

ESAC-Net intends to comply with ECDC's long-term surveillance strategy for 2014–2020, which targets improved routine surveillance outputs. It includes reusable online content (the publicly available ESAC-

Net interactive database), which could replace large parts of the lengthy surveillance reports. These reports will, in turn, be shorter and focus more on data interpretation relevant to public health.

4.2. Surveillance of antimicrobial consumption in food-producing animals⁷

4.2.1. Description of collected data

The ESVAC project annually collects harmonised data on sales of veterinary antimicrobial medicinal products at package level from most of the EU MSs and Iceland, Norway and Switzerland; these data are not stratified by animal species. These data are collected from various national sources (wholesalers, marketing authorisation holders (MAHs), feed mills and pharmacies) and presented by antimicrobial class or sub-class. In the analysis of data, products formulated as tablets, which are almost exclusively used for companion animals, are analysed separately. The remaining products are mainly used for food-producing animals and data on these products are used for the analyses presented in the current report.

Denmark collects prescription data and the Netherlands collects data by species at farm level. Automated data collection systems are being implemented in some other countries (e.g. Belgium, Finland, Germany and Norway). Other countries, such as France, Sweden and the United Kingdom have established a certain stratification of the sales data by animal species. Comparable consumption data by species and production type are not available.

In order to normalise the consumption data for the animal population that can be subjected to treatment with antimicrobial agents, a population correction unit (PCU) is used as a proxy for the size of the animal population at risk of being treated. The PCU is purely a technical unit of measurement, used only to estimate sales corrected by the animal population in individual countries; 1 PCU = 1 kg of different categories of livestock and slaughtered animals. The data sources used and the methodology for the calculation of PCU are comprehensively described in Appendix 2 to EMA's report "Trends in the sales of veterinary antimicrobial agents in nine European countries: 2005–2009" (EMA/ESVAC, 2011).

4.2.2. Strength of the system

The collection of data at package level and calculations to determine the mass of active substance are harmonised, resulting in standardised data from all participating countries. The ESVAC team and ESVAC network jointly discuss the analysis and potential improvements. Twenty-four EU MSs and two EEA countries delivered data at package level for 2012. This covers 95 % of the food-producing animal population in the EU/EEA countries.

4.2.3. Impediments to comparing data

The national consumption data for antimicrobial agents (nominator) cover all food-producing animal species, including horses. This means that the animal population "at risk" of being treated with antimicrobial agents (denominator) includes all food-producing species. The consumption of antimicrobial agents by the various animal species varies considerably. For example, the consumption of antimicrobial agents in extensively reared sheep and goats is generally relatively low, while consumption in intensively reared calves can be substantial. Therefore, the interpretation of these data should take into account the distribution of the PCU value between the species in the various countries.

⁷ See: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp&mid=WC0b01ac0580153a00&isenabled=true

It should also be emphasised again that the PCU only represents a technical unit of measurement and not a real value for the animal population that could potentially be treated by antimicrobial agents.

4.2.4. On-going actions to improve the system

The ESVAC project is developing a system to collect data on consumption of antimicrobial agents per animal species and to establish technical units of measurement for the reporting consumption of antimicrobial agents by species. Further information can be found on the EMA ESVAC website⁸.

4.3. Surveillance of antimicrobial resistance in humans

4.3.1. Surveillance of antimicrobial resistance in humans through FWD-Net

4.3.1.1. Description of collected data

FWD-Net was established at ECDC in 2007. It currently covers surveillance on 19 diseases that are acquired by humans through the consumption of food or water, or contact with animals: anthrax, botulism, brucellosis, campylobacteriosis, cholera, cryptosporidiosis, echinococcosis, giardiasis, hepatitis A, leptospirosis, listeriosis, salmonellosis, shigellosis, toxoplasmosis, trichinellosis, tularaemia, typhoid/paratyphoid fever, verocytotoxin-producing *E. coli* (VTEC)/Shiga toxin-producing *E. coli* (STEC) infection and yersiniosis. Antimicrobial resistance data are collected as part of the case-based datasets for salmonellosis and campylobacteriosis, and partly also for STEC/VTEC infections. The monitoring of antimicrobial resistance in human isolates in 2011–2012 was conducted by MSs in accordance with Decision No 2119/98/EC (Official Journal of the European Communities, 1998)⁹ setting up a network for the epidemiological surveillance and control of communicable diseases in the Community.

MSs are requested to annually provide antimicrobial resistance data as part of the general FWD data call and report their data to TESSy at ECDC. The antimicrobial resistance data consist of clinical antimicrobial susceptibility testing (AST) results interpreted with clinical breakpoints, with some exceptions, and originate from testing at local laboratories, hospitals or the National Public Health Reference Laboratories (NPHRLs).

The antimicrobial resistance data are primarily analysed for, and published in, the joint EFSA-ECDC EU Summary Report (EFSA/ECDC, 2014) on antimicrobial resistance in zoonotic and indicator bacteria obtained from humans, animals and food thereof.

4.3.1.2. Strength of the system

In 2012, antimicrobial resistance data were provided for 26% of all laboratory-confirmed non-typhoidal salmonellosis cases and 18 % of the laboratory-confirmed campylobacteriosis cases. Considering that over 90 000 salmonellosis cases and almost 220 000 campylobacteriosis cases were reported in 2012, this provides a good overview of the antimicrobial resistance situation at the EU level and a sizeable dataset for analysis. The number of countries reporting antimicrobial resistance data is also increasing over time, with 21 and 15 EU/EEA countries reporting data for *Salmonella* spp. and *Campylobacter* spp., respectively.

⁸ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp&mid=WCOB01ac0580153a00

⁹ As of 22 October 2013, Decision No 2119/98/EC was replaced by decision No 1082/2013/EU on serious cross-border threats to health.

4.3.1.3. Impediments to comparing data

Several problematic issues have been identified when it comes to comparability of the antimicrobial resistance data collected in FWD-Net. The methods of measuring antimicrobial susceptibility and the origin of the data submitted vary markedly between countries. In several countries, the NPHRLs measure antimicrobial susceptibility in only a fraction of the isolates and the remaining isolates are tested by hospital or local laboratories, whose methods are not reported to the NPHRLs. The guidelines used for the interpretation of the measurements can also vary between and within countries for different antimicrobials, with both international and national guidelines sometimes being used. Direct comparisons between antimicrobial resistance data from humans and animal and food isolates are also hampered because of the use of different test methods, different interpretive criteria and fundamental differences in underlying testing populations. Results of antimicrobial susceptibility testing performed on isolates from infections in humans in a clinical setting are by default interpreted using clinical breakpoints for assessing treatment options. In contrast, animal bacterial isolates from monitoring programmes originate from healthy food-producing animals and, consequently, both animal and food isolates are generally interpreted based on epidemiological cut-off values (ECOFFs). Since the clinical breakpoint and the ECOFF differ for some critically important antimicrobials, direct comparison of resistance between the human isolates and animal/food isolates for these antimicrobials is not possible in respect of these antimicrobials.

4.3.1.4. On-going actions to improve the system

In order to increase the quality and comparability of antimicrobial resistance data collected from different EU/EEA countries, ECDC has launched a protocol for harmonised monitoring of antimicrobial resistance in human *Salmonella* spp. and *Campylobacter* spp. isolates. The protocol, which was published in 2014 (ECDC, 2014), is primarily targeted at NPHRLs to guide the susceptibility testing needed for EU-level surveillance and reporting to ECDC. It also provides guidance on how to improve the comparison of results with the results obtained from antimicrobial resistance monitoring performed in isolates from food-producing animals and food products. The protocol was developed by ECDC in close co-operation with FWD-Net and facilitates the implementation of the Commission action plan on antimicrobial resistance (EC, 2011). The protocol defines the priority panels of antimicrobials to be monitored to fulfil the agreed surveillance objectives. The panels for both *Salmonella* spp. and *Campylobacter* spp. isolates are, to the largest extent possible, in agreement with the panel of antimicrobials agreed to be tested in food and animal isolates. European Committee on Antimicrobial Susceptibility Testing (EUCAST) methods and interpretive criteria are recommended and the protocol also provides methods for detection and confirmation of two specific resistance phenotypes of particular concern in *Salmonella* spp., namely extended-spectrum beta-lactamase (ESBL) producers and carbapenemase producers. The reporting countries are encouraged to submit the results of susceptibility testing as "quantitative" values (minimum inhibitory concentration (MIC) in milligrams per litre or zone diameter in millimetres) to facilitate comparison of data over time, and to allow comparison with quantitative antimicrobial resistance data from food-producing animals and food isolates that takes account of ECOFFs for the relevant bacterial species.

4.3.2. Surveillance of antimicrobial resistance in humans through EARS-Net

4.3.2.1. Description of collected data

Monitoring of antimicrobial resistance in human isolates in 2011–2012 was conducted by MSs in accordance with Decision No 2119/98/EC (Official Journal of the European Communities, 1998)¹⁰ setting up a network for the epidemiological surveillance and control of communicable diseases in the Community. For clinical isolates of bacteria from bloodstream infections (BSIs) and meningitides in humans, this is performed by the EARS-Net, which is the largest publicly funded system of surveillance of antimicrobial resistance in Europe. EARS-Net is based on a network of representatives from the countries reporting routine clinical AST data from national antimicrobial resistance surveillance initiatives. Data are annually reported to ECDC and originate from approximately 900 laboratories serving more than 1 300 hospitals in Europe. Data are reported by EU/EEA countries for the following eight pathogens/pathogenic species which are considered of public health importance: *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Enterococcus faecium*. Only invasive isolates (i.e. from blood and cerebrospinal fluid) are included in EARS-Net. The antimicrobial substance and pathogen combinations to be reported are defined in the EARS-Net reporting protocol. Data are reported as categorised AST results (susceptible, intermediate, resistant) on a single isolate basis. In addition, a number of countries provide quantitative results.

4.3.2.2. Strength of the system

EARS-Net collects data from all 30 EU/EEA countries. A major strength of the EARS-Net surveillance is the use of a clear case definition for invasive isolates. EARS-Net data are exclusively based on invasive isolates from blood or cerebrospinal fluid. This restriction prevents some of the inconsistencies that otherwise arise from national differences in clinical case definitions, different sampling frames or heterogeneous health care. All 28 EU MSs (and two other EEA countries) participate in EARS-Net. The majority of the participating countries have good national coverage, and many of the participating laboratories have reported data for several consecutive years, which enables accurate trend analyses.

4.3.2.3. Impediments to comparing data

Interpretation of the results of inter-country comparisons should be made with caution. A number of factors may introduce bias, resulting in over- as well as underestimation of resistance percentages. Some of the most important potential sources of bias are differences in the population coverage, sampling methods, laboratory routines and capacity. Moreover, case ascertainment of patients with BSIs is strongly linked to diagnostic habits and procedures, and the frequency by which blood cultures are taken. EARS-Net encourages the use of EUCAST clinical breakpoints; results based on other interpretive criteria used by the reporting countries are accepted for the analysis. Some countries report data from large national surveillance systems with a high national coverage, while other countries report data from a smaller subset of local laboratories and hospitals. In some countries, the population under surveillance is not constant and may change over the years.

¹⁰ As of 22 October 2013, Decision No 2119/98/EC was replaced by decision No 1082/2013/EU on serious cross-border threats to health.

4.3.2.4. On-going actions to improve the system

The quality of the antimicrobial susceptibility tests and procedures used by the laboratories are continuously measured through their participation in an annual external quality assessment (EQA) exercise offered to the participating laboratories. The EQA exercise is an important element of the surveillance system aiming to maintain and develop the ability of the laboratories to correctly determine susceptibility of bacterial isolates, and thereby ascertain the comparability of data reported to ECDC. Another on-going action of major importance for the quality of the surveillance system is the gradual implementation of EUCAST guidelines in the countries: at present, only 64 % of the participating laboratories adhere to EUCAST guidelines. In addition, the EARS-Net reporting protocol is updated annually to reflect identified needs and continuously improve data quality.

4.4. Monitoring antimicrobial resistance in food-producing animals and food¹¹

According to Directive 2003/99/EC (Official Journal of the European Union, 2003a) on the monitoring of zoonoses and zoonotic agents, reporting countries are obliged to monitor and report antimicrobial resistance in zoonotic *Salmonella* spp. and *Campylobacter* spp. isolates from food-producing animals and food. In addition, and until 2012, Commission Decision No 2007/407/EC (Official Journal of the European Union, 2007) provided some detailed requirements on the harmonised monitoring and reporting of antimicrobial resistance of salmonella isolates from various poultry populations and pigs, sampled under the corresponding national *Salmonella* control and surveillance programmes. EFSA provided specific non-binding guidelines for the monitoring and reporting of antimicrobial resistance in *Salmonella* spp. and *Campylobacter* spp. (EFSA, 2007) and in indicator *E. coli* and enterococci (EFSA, 2008).

4.4.1. Description of collected data

The monitoring of antimicrobial resistance in healthy food-producing animals and food covers both zoonotic agents, in the first instance *Salmonella* spp. and *Campylobacter* spp., and indicator organisms of the commensal flora, such as *E. coli*, *Enterococcus faecium* and *Enterococcus faecalis*. Monitoring of zoonotic resistance focuses on the animal populations to which the consumer is most likely exposed through food derived thereof, such as domestic fowl, pigs, turkeys and cattle. Antimicrobial substances included in the harmonised monitoring consist of a concise set of antimicrobials selected according to their relevance to human therapeutic use (e.g. critically important antimicrobials (CIAs) for human medicine) and/or of epidemiological relevance, as shown in **Table 1**. ECOFFs are used as interpretative criteria of resistance. ECOFFs separate the naive, susceptible wild-type bacterial populations from isolates that have developed reduced susceptibility to a given antimicrobial agent (Kahlmeter et al., 2003). The ECOFFs may differ from breakpoints used for clinical purposes, which are defined against a background of clinically relevant data, including therapeutic indication, clinical response data, dosing schedules, pharmacokinetics and pharmacodynamics. In the EU Summary Reports on resistance from 2004 to 2012, ECOFFs were applied to interpret MIC data in order to define resistant *Salmonella* spp., *Campylobacter* spp., indicator *E. coli* and indicator enterococcal isolates from food-producing animals and food. The occurrence of resistance is defined as the proportion of bacterial isolates tested for a given antimicrobial and found to present reduced susceptibility, i.e. to display "microbiological resistance".

¹¹ See: <http://www.efsa.europa.eu/en/efsajournal/doc/2598.pdf>

Table 1. Harmonised set of antimicrobial substances used for the monitoring of resistance in zoonotic *Salmonella* spp. and *Campylobacter* spp. and indicator *E. coli* and enterococci isolates from food-producing animals and food over the period 2007–2013 (EFSA, 2007; 2008)

<i>Salmonella</i> spp.	<i>Campylobacter coli/C. jejuni</i>	Indicator <i>E. coli</i>	<i>Enterococcus</i> spp.
Ampicillin	Erythromycin	Ampicillin	Ampicillin
Cefotaxime	Ciprofloxacin	Cefotaxime	Chloramphenicol
Chloramphenicol	Tetracycline	Chloramphenicol	Erythromycin
Ciprofloxacin	Nalidixic acid	Ciprofloxacin	Gentamicin
Gentamicin	Gentamicin	Gentamicin	Linezolid
Nalidixic acid		Nalidixic acid	Quinupristin/dalfopristin
Sulfonamides		Sulfonamides	Streptomycin
Tetracycline		Tetracycline	Tetracycline
Trimethoprim		Trimethoprim	Vancomycin

4.4.2. Strength of the system and impediments to comparing data

EFSA provides detailed specifications on minimum requirements for the harmonised monitoring of antimicrobial resistance in food-producing animals so that comparable data may be obtained across the EU MSs and other EEA countries. Guidelines have been recommended for the monitoring of antimicrobial resistance in *Salmonella* spp. and *Campylobacter* spp. (EFSA, 2007) and in indicator *E. coli* and enterococci (EFSA, 2008). Implementation of the recommendations by the reporting country, which typically deal with harmonisation of protocols on sampling strategies, the method of susceptibility testing, the antimicrobials to be tested and the criteria for categorising isolates as susceptible or resistant, has enabled the comparison of the occurrence of resistance between different countries.

The isolates subjected to susceptibility testing have typically been derived from active monitoring programmes in healthy animals and food, ensuring representativeness of resistance data, especially in the case of indicator bacteria and *Campylobacter* spp., whereas antimicrobial resistance data from susceptibility testing of *Salmonella* spp. have remained more dependent on the prevalence of the bacteria. Moreover, an EQA system, based on regular training and yearly proficiency test trials, is included in resistance monitoring programmes to detect any potential differences between the laboratories performing susceptibility tests relating to methods and interpretative criteria at both national and EU levels, coordinated by the National Reference Laboratories on antimicrobial resistance within each reporting country and the EU Reference Laboratory on antimicrobial resistance. These have contributed to enhance harmonisation of resistance monitoring in food-producing animals in the EU and comparability of resistance data reported.

The effects of consumption of antimicrobials in a given country and animal species, as well as trends in the occurrence of resistance, can be studied more easily in indicator organisms than in food-borne pathogens, such as *Salmonella* spp., because all food-producing animals generally carry these indicator bacteria. Until recently, monitoring of resistance in indicator *E. coli* and enterococci was performed on a voluntary basis and limited data were reported by a number of reporting countries to EFSA.

4.4.3. On-going actions to improve the system

The implementation of the EFSA specifications by the EU MSs and other EEA countries has led to more harmonised and comparable data on resistance; nevertheless, further enhancements are still required. In light of the experience accrued from the production of the EU Summary Reports on antimicrobial

resistance, the latest scientific opinions issued by EFSA on the issue of resistance and efforts to increase the comparability between the findings from the food and animal sector with those gathered in the humans, EFSA issued considerations and proposals for the revision of existing legislation on monitoring of antimicrobial resistance in 2012.

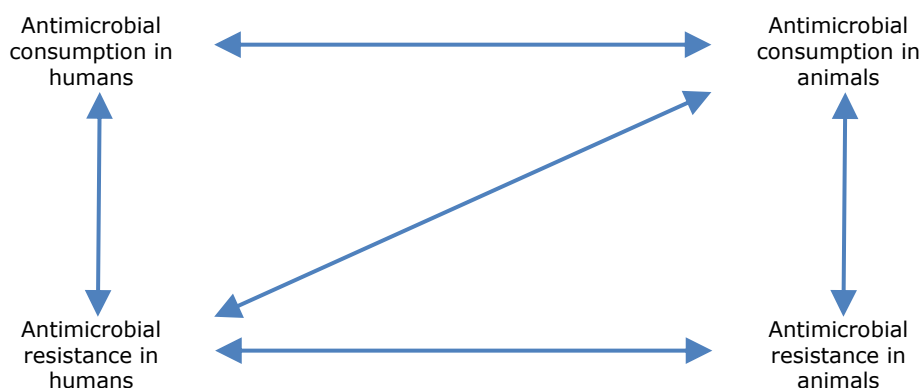
Subsequently, in 2013, the EC adopted new legislative provisions to improve harmonisation of monitoring and reporting of resistance in food-producing animals and food thereof (Commission Implementing Decision 2013/652/EU (Official Journal of the European Union, 2013)). The new legislation provides for monitoring resistance in indicator commensal *E. coli* isolates on a mandatory basis. Randomised, representative sampling should no longer be stratified at the level of the different animal species (e.g. *Gallus gallus*, cattle, pigs) but should be performed at the level of the major food-producing animal populations which are domestically produced, such as broilers, laying hens, fattening pigs, fattening turkeys and veal calves, in order to obtain more informative and comparable results. An aim of such sampling is the collection of data that could be combined with data on consumption of antimicrobials. The harmonised panel of antimicrobials used, in particular for *Salmonella* spp. and *E. coli*, is broadened with the inclusion of substances, such as colistin and ceftazidime, that are either important for human health or can provide clearer insight into the mechanisms involved in resistance to extended-spectrum cephalosporins. As regards the laboratory methodologies, microdilution is the method to be used, with concentration ranges including both the EUCAST ECOFF and the EUCAST clinical breakpoint so that comparability with human data is possible. The specific monitoring of ESBL-, AmpC- and carbapenemase-producing *Salmonella* spp. and indicator commensal *E. coli* is foreseen. The collection and reporting of data is to be performed at the isolate level, in order to enable more in-depth analyses to be conducted, in particular on the occurrence of multidrug resistance. The Commission Implementing Decision No 2013/652/EU (Official Journal of the European Union, 2013) entered into force in 2014.

5. Methodological considerations and included data

The earlier chapters of this report have summarised the availability and characteristics of data at the European level on antimicrobial consumption and resistance to selected antimicrobials in both humans and food-producing animals and food derived thereof. Derived from these monitoring systems in place in the reporting countries, four fields of data are available, corresponding to data on antimicrobial consumption and resistance in both human and animal populations. These four fields of data and the potential relationships between them which were investigated in this report are illustrated in **Figure 1**.

The analytical approach followed in this report will primarily address the relationship between consumption and resistance within the animal and human populations (as illustrated by the vertical arrows in **Figure 1**). The approach will also consider potential additional links that could be established between equivalent data from the two populations—resistance in humans, resistance in animals, consumption in humans and consumption in animals—as illustrated by the horizontal arrows in **Figure 1**. In fact, any positive association between resistance data in humans and in animals might reflect the transfer of resistant bacteria between the human and animal populations and/or some similarities in the consumption of antimicrobials among human and animal populations. Assessing the existence of these horizontal links will provide relevant information for assessing a potential relationship between antimicrobial consumption in animals and resistance in humans (as illustrated by the diagonal arrow in **Figure 1**). The relationship between antimicrobial consumption in humans and antimicrobial resistance in food-producing animals was not analysed.

Figure 1. Available fields of data related to antimicrobial consumption and resistance in humans and food-producing animals in the reporting countries and the possible relationships investigated in this report



5.1. Consumption of antimicrobials by humans and food-producing animals

5.1.1. Numerator

Data on the quantity of antimicrobials sold for systemic use in humans in 2012 (ATC group J01) are reported by ESAC-Net as numbers of DDD per 1 000 inhabitants per day (ESAC-Net 2012)¹². To facilitate a comparison between consumption of antimicrobials for humans and for animals, these data were converted back into mass of active substance per antimicrobial class and country and expressed as tonnes (**Table 5**). In certain cases, e.g. for combinations such as sulfonamides-trimethoprim, approximations had to be calculated.

When available, data on hospital and community consumption were summed. For countries reporting only community consumption, this figure was used as a surrogate for total consumption.

Figures for consumption, in tonnes, of antimicrobials for food-producing animals (including horses) were taken from the fourth ESVAC report (2012 data; (EMA/ESVAC, 2014); see **Table 6**). Antimicrobials included were from the following ATCvet groups: QA07A, QG01A, QG01B, QG51A, QJ01, QJ51, QP51A.

5.1.2. Denominator

Data on the human populations covered by surveillance of community consumption of antimicrobials were taken from ESAC-Net. Data on average weights of different age groups (EFSA, 2012a) were used together with Eurostat data on the population in EU-27 in 2012 by one-year age classes to calculate a human EU population and age class weighted average body weight of 62.5 kg (see Annex B, section 2.2). This body weight was used to calculate the biomass of the population under ESAC-Net surveillance.

Data on the biomass of food-producing animals expressed as PCU in 2012 were taken from the fourth ESVAC report (2012 data; (EMA/ESVAC, 2014); see section 4.2.1 and **Table 7**).

In the following, the term “milligrams per kilogram estimated biomass” will be used as a synonym of “milligrams per human EU population- and age class-weighted biomass” and “milligrams per PCU”.

¹² <http://www.ecdc.europa.eu/en/publications/Publications/antimicrobial-consumption-europe-esac-net-2012.pdf>

5.2. Rationale for the analysis of consumption and resistance in bacteria from food-producing animals and humans

Data available on resistance in bacteria recovered from meat and reported by MSs were considered insufficient (i.e. there were too few reporting MSs) for a meaningful investigation of associations between the consumption of antimicrobials in animals and the occurrence of resistance in certain bacteria present on meat (broiler meat, pork and beef).

Bacteria from meat sampled at the point of retail may originate from the intestine or skin of the animals slaughtered, but there are other possible sources of contamination during the subsequent preparation and storage of meat which can also contribute to the bacterial flora at retail. These different potential sources include personnel, equipment and surfaces and provide one possible explanation for the differences in resistance which can be observed when comparing bacteria from animals and bacteria from meat derived from those animals. In particular, indirect selection for bacterial sub-populations, in the immediate environment and on equipment and surfaces of the production line, following exposure to antibacterial substances other than pharmaceuticals, could result in a decrease in susceptibility to antimicrobials (Zou et al., 2014).

A further important consideration is whether the meat sampled represents domestic production or meat which may have been imported; distinguishing between these sources is essential for a meaningful analysis of meat in relation to antimicrobial consumption in animals, because differences in exposure to antimicrobials may occur in different countries. Factors such as the cross-contamination of meat in, for example, cutting plants might also need to be taken into account, because some plants may handle both domestically produced and imported meats.

Thus, a simple analysis between consumption of antimicrobials and resistance in bacteria from meat could be misleading, if adjacent relevant information cannot be assessed. An analysis of associations between antimicrobial consumption in food-producing animals and the degree of resistance occurring in bacteria from meat has therefore not been performed.

5.3. Rationale for selecting particular combinations of organism and antimicrobial for detailed analysis

The limitations relating to the degree to which consumption can be linked to particular species or production types of animals, the occurrence of genetic linkage of antimicrobial resistance genes and the issue of cross-resistance between some or all antimicrobials within an antimicrobial class are all factors which increase the complexity of this type of analysis. The analysis presented here did not attempt to evaluate consumption and resistance for all available combinations of antimicrobials and bacterial organisms, but was done only for selected antimicrobial classes which are considered to be particularly important. Tetracyclines are also included as an example of a broad-spectrum antimicrobial class widely used in animals for a long period of time. Consequently, the analysis did not attempt to evaluate consumption and resistance for all available combinations of antimicrobials and bacterial organisms.

Bacteria and antimicrobial combinations considered of highest priority have been listed or mentioned in several publications, including those of the World Health Organization (WHO) (2007) and Codex Alimentarius (2011), the EC Action Plan on AMR (European Commission, 2011) and the Joint Opinion from the ECDC, EFSA and EMA on antimicrobial resistance focused on zoonotic infections (ECDC/EFSA/EMA/SCENIHR, 2009). Resistance to fluoroquinolones and 3rd- or 4th-generation cephalosporins in *Salmonella* spp. and *E. coli* is therefore included because these two antimicrobials constitute the first-line therapy for invasive Gram-negative bacterial infections in humans in many EU

MSs. These two classes of antimicrobials have also been considered as two of the classes of antimicrobial agents most urgently requiring management of the risks from antimicrobial resistance. Similarly, macrolides, fluoroquinolones and, on occasions, tetracyclines are used to treat *Campylobacter* spp. infections in humans when treatment is considered necessary by the clinician (invasive infections with these organisms are rare). *Salmonella* spp. and *Campylobacter* spp. are recognised food-borne zoonoses and, although infections in humans may arise from imported food or relate to travel, it is considered important to investigate these combinations. *Salmonella* spp., in particular, can show extensive resistance, thus compromising treatment options in both humans and animals when treatment is considered necessary.

Resistance to carbapenems is emerging in humans in several bacterial species. Although this class of antimicrobials is not authorised for use in animals, carbapenem resistance in bacteria from animals has been reported in a few cases. Carbapenems are a good example of antimicrobials of major clinical significance the epidemiology of resistance to which seems as yet not to include a significant animal reservoir of resistant organisms (EFSA, 2013).

Tetracycline resistance has been included in the analysis of *Campylobacter* spp., *Salmonella* spp. and *E. coli* because antimicrobials from this class are widely used in animals, particularly in pigs. They also play a possible role in co-selection through the genetic linkage of resistance genes; there are also different patterns of use in humans and animals in the EU. This contrasts with 3rd- and 4th-generation cephalosporins and fluoroquinolones, which have more recently been introduced into veterinary medicine. In most of the reporting countries, resistance to tetracyclines is relatively common in many bacteria from animals, and this differs in many (but not all) cases from the situation for fluoroquinolones and 3rd- and 4th-generation cephalosporins.

On the human side, the consumption of cephalosporins, fluoroquinolones, macrolides and tetracyclines in the community, in hospitals and in total (both in the community and in hospitals) was compared with the occurrence of resistance in *E. coli* (3rd- and 4th-generation cephalosporins and fluoroquinolones), *Salmonella* spp. (cephalosporins, fluoroquinolones and tetracyclines) and *Campylobacter* spp. (fluoroquinolones, macrolides and tetracyclines) from infections in humans, and presented by drug class.

5.4. Method for analysis of the relationship between antimicrobial consumption and resistance

5.4.1. Consumption and resistance data from food-producing animals

Combinations of (sub-)classes of antimicrobials and bacteria of interest were selected and subsequently analysed for any relationship between antimicrobial consumption and resistance in animals (**Table 2**). Consumption data on the selected antimicrobial (sub-)classes for the years 2011 and 2012, expressed in milligrams per PCU, published elsewhere within the framework of the ESVAC project were used. Consumption data encompass all food-producing animal species, including horses and farmed fish.

Data on resistance to antimicrobial substances of interest in commensal indicator *E. coli* and zoonotic *C. coli*, *C. jejuni* and *Salmonella* spp. and *S. Typhimurium* reported by the MSs for the years 2011/2012, and published in the 2011/2012 EU Summary Report on antimicrobial resistance issued by EFSA/ECDC (EFSA/ECDC, 2013; EFSA/ECDC, 2014), were used for the purpose of the analysis. In this framework, resistance was defined as the proportion of isolates exhibiting reduced susceptibility out of the whole set of tested isolates from a given animal species in a country. ECOFFs (defining “microbiological” resistance) were used as interpretative criteria of reduced susceptibility. Data were

from MSs that reported resistance in *Salmonella* spp. and *E. coli* isolates from domestic fowl, pigs and cattle, in *C. coli* isolates from domestic fowl and pigs, and in *C. jejuni* isolates from cattle and domestic fowl. For certain MSs, older resistance data were occasionally used as proxy for 2011/2012 data, so that the three (or two) animal categories could be addressed together.

Table 2. Combinations of bacteria and (sub)classes of antimicrobials assessed for the relationship between antimicrobial consumption and resistance in animals

Resistance data		Consumption data
Bacteria	Antimicrobials used for testing	Antimicrobial (sub-)classes
Indicator <i>E. coli</i>	Tetracyclines Cefotaxime Ciprofloxacin Ciprofloxacin	Tetracyclines 3 rd - and 4 th -generation cephalosporins Fluoroquinolones Fluoroquinolones and other quinolones
<i>C. jejuni</i> and <i>C. coli</i>	Tetracyclines Erythromycin Ciprofloxacin Ciprofloxacin	Tetracyclines Macrolides Fluoroquinolones Fluoroquinolones and other quinolones
<i>Salmonella</i>	Tetracyclines Cefotaxime Ciprofloxacin Ciprofloxacin	Tetracyclines 3 rd -generation cephalosporins Fluoroquinolones Fluoroquinolones and other quinolones

For the purpose of comparing consumption and resistance data, a “summary indicator” of resistance at the MS level, Ind_{Res} , was calculated as the weighted mean of the proportion of resistance in cattle, domestic fowl and pigs. The PCU values of the three (or two when considering *Campylobacter* spp. data) animal categories in the MS were used as weighting factors.

$$Ind_{Res} = \frac{1}{PCU_{cattle} + PCU_{fowl} + PCU_{pigs}} \cdot (PCU_{cattle} \cdot Res_{cattle} + PCU_{fowl} \cdot Res_{fowl} + PCU_{pigs} \cdot Res_{pigs})$$

Consumption and resistance data used in the framework of this analysis are presented in Annex A of this report. To assess the relationships between the domestic consumption of a number of antimicrobial classes and the “summary indicator” of corresponding resistance in *Salmonella* spp., *C. coli*, *C. jejuni* and indicator *E. coli* isolates at the country level, logistic regression models were fitted and corresponding curves plotted for the years 2011 and 2012.

5.4.2. Consumption and resistance data from humans

The consumption of cephalosporins, fluoroquinolones, macrolides and tetracyclines in the community, in hospitals and in total was compared with the occurrence of resistance in invasive *E. coli* (3rd-generation cephalosporins, fluoroquinolones), non-typhoidal *Salmonella* spp. (cephalosporins, fluoroquinolones and tetracyclines) and *Campylobacter* spp. (fluoroquinolones, macrolides and tetracyclines) from infections in humans, and presented by drug class (see **Table 3**).

Table 3. Combinations of bacteria and (sub)classes of antimicrobials assessed for the relationship between antimicrobial consumption and resistance in bacteria from humans

Resistance data		Consumption data
Bacteria	Antimicrobials used for testing	Antimicrobial (sub-)classes
<i>E. coli</i>	Ceftriaxone Cefotaxime Ceftazidime Ciprofloxacin Ofloxacin Levofloxacin Meropenem Imipenem	3 rd -and 4 th -generation cephalosporins Fluoroquinolones Carbapenems
<i>C. jejuni</i> and <i>C. coli</i>	Tetracyclines Erythromycin Ciprofloxacin	Tetracyclines Macrolides Fluoroquinolones
<i>Salmonella</i> spp.	Tetracyclines Cefotaxime Ciprofloxacin	Tetracyclines 3 rd - and 4 th -generation cephalosporins Fluoroquinolones
<i>K. pneumoniae</i>	Meropenem Imipenem	Carbapenems

5.4.3. Statistical methodology

To assess the associations between (1) data on antimicrobial consumption in humans and resistance in isolates of *K. pneumoniae*, *E. coli*, *Salmonella* spp. and *Campylobacter* spp. from humans, (2) data on national consumption in food-producing animals and resistance in bacterial isolates from food-producing animals and (3) data on national consumption for food-producing animals and resistance in isolates from humans, logistic regression models were fitted and corresponding curves plotted at the country level for the years 2011 and 2012. Graphs reveal patterns, differences and uncertainty that are not readily apparent in tabular output. The logistic regression deals naturally with the binomial nature of the event of interest (reduced sensitivity vs. naive sensitivity in animals; clinical resistance vs. sensitivity in humans). All logistic models were performed using the LOGISTIC procedure of SAS software (SAS, 1999). The odds ratio¹³ (OR) was used to show the strength of association between the predictor (consumption data) and the response of interest (probability of microbiological/clinical resistance), and 95 % confidence intervals (CIs) for ORs were calculated.

All logistic regressions were performed estimating logit models with grouped data (each country being a group) and accounting for small sample sizes (number of countries involved in the model) and possible overdispersion, which may arise when estimating a logit model with grouped data – deviance and Pearson chi-square are large, relative to the degrees of freedom. CIs for logit regression coefficients were computed by profile likelihood (PL) which produces better approximations, especially in smaller samples. The intervals produced are not generally symmetric around the coefficient estimate. To account for possible over-dispersion, the over-dispersion correction proposed by Williams (1982) and offered by the LOGISTIC procedure of SAS software was used resulting in modified coefficients and ORs as well as modified standard errors and CIs. The outliers and influential points were also subsequently addressed. Likelihood ratio test was used to assess the relevance of the models fitted.

To assess the possible association between levels of resistance observed in bacterial isolates from humans and animals, Spearman’s rank correlation coefficient (a non-parametric measure of statistical

¹³ Odds ratio can vary from 0 to infinity. When the OR equals 1 or the confidence interval includes 1, the association is not considered statistically significant.

dependence between two variables) was used, accounting for the fact that levels of resistance were not normally distributed. The same approach was applied where comparing data on consumption of antimicrobials in animals and in humans.

During the preparation of the report, a publication from Chantziaras et al. (2014) was discussed with the main author and one of the co-authors. The publication evaluates associations between antimicrobial consumption and occurrence of resistance in commensal *E. coli* isolates from pigs, poultry and cattle, using data from publicly available national or international reports from seven European countries using a polynomial regression analysis and determination of Spearman's rank correlation coefficient. Differences between the approaches taken were that the JIACRA report applied a weighting of resistance data according to PCU and a logistic regression analysis, as they were considered most appropriate for the dataset available for the JIACRA report.

6. Consumption of antimicrobials in humans and food-producing animals

6.1. Total tonnes of active substance and estimated biomass

In 2012, 3 400 and 7 982 tonnes of active substance of antimicrobials were sold for use in humans and food-producing animals, respectively, in the 26 EU/EEA countries (**Table 4**). The estimated biomass, expressed as 1 000 tonnes, was 28 884 for humans and 55 421 for animals, respectively. The proportion of the total biomass (sum of the biomass of food-producing animals and humans) accounted for by the human population varied considerably between countries (from 13 to 59%). This variation underlines the need to correct for differences in population size when comparing consumption in humans and food-producing animals.

Table 4. Consumption of antimicrobials by humans and food-producing animals, in tonnes, the estimated biomass of the corresponding populations in 1 000 tonnes and consumption expressed as milligrams per kilogram biomass¹⁴ in 26 EU/EEA countries in 2012¹⁵

Country	Consumption in hospitals included	Consumption in tonnes active substance			Estimated biomass in 1 000 tonnes			Consumption in mg/kg biomass	
		Humans	Animals	Total	Humans ¹⁶	Animals	Total	Humans	Animals
Austria	No	37.1	53.0	90.1	528	966	1 494	70.2	54.9
Belgium	Yes	112.7	267.2	379.9	693	1 658	2 351	162.6	161.1
Bulgaria	Yes	49.8	38.4	88.2	455	388	843	109.4	98.9
Cyprus	Yes	7.8	45.0	52.8	54	113	167	144.4	396.5
Czech Republic	No	55.2	53.7	108.9	657	673	1 330	84.1	79.8
Denmark	Yes	47.5	107.0	154.5	349	2 424	2 773	136.2	44.1
Estonia	Yes	5.9	7.3	13.2	84	131	215	70.1	56.0
Finland	Yes	47.3	12.2	59.5	338	511	849	140.1	23.8
France	Yes	719.2	761.5	1 480.7	4 092	7 618	11 710	175.8	99.1
Germany	No	291.7	1 707.5	1 999.2	4 357	8 338	12 695	66.9	204.8
Hungary	No	41.3	178.5	219.8	611	727	1 338	67.5	245.5
Iceland	Yes	2.5	0.7	3.2	20	116	136	125.9	5.9
Ireland	Yes	41.5	100.0	141.5	286	1 725	2 011	144.9	58.0
Italy	Yes	621.6	1 534.3	2 155.9	3 712	4 500	8 212	167.5	341.0
Latvia	Yes	11.3	6.7	18.0	128	162	290	88.8	44.1
Lithuania	Yes	19.2	13.4	32.6	188	339	527	102.0	39.4
Luxembourg	Yes	4.8	2.2	7.0	31	50	81	153.1	43.6
Netherlands	Yes	54.5	245.7	300.2	963	3 279	4 242	56.7	74.9
Norway	Yes	44.1	7.1	51.2	312	1 851	2 163	141.6	3.8
Poland	No	238.5	516.4	754.9	2 408	3 908	6 316	99.0	132.2
Portugal	Yes	83.0	156.5	239.5	624	996	1 620	133.1	157.1
Slovakia	Yes	39.2	10.2	49.4	338	235	573	115.9	43.2
Slovenia	Yes	13.9	6.8	20.7	129	183	312	108.3	37.0
Spain	No	320.7	1 693.0	2 013.7	2 954	6 996	9 950	108.6	242.0
Sweden	Yes	74.8	10.6	85.4	593	783	1 376	126.2	13.5
United Kingdom	No	414.9	447.4	862.3	3 982	6 749	10 731	104.2	66.3
All		3 399.8	7 982.0	11 381.8	28 884	55 421	84 305	116.4¹⁷	144.0

¹⁴ Calculated from the exact figures (not rounded as shown).

¹⁵ Many limitations hamper the comparison of consumption of antimicrobials for humans and animals. The estimates presented are crude and must be interpreted with caution.

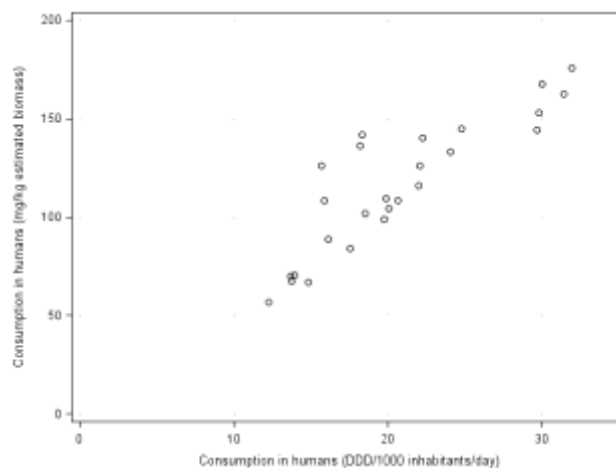
¹⁶ Population covered by data in ESAC-Net.

¹⁷ Population-weighted mean.

6.2. Reporting consumption in humans by numbers of DDD per 1 000 inhabitants and per day and by milligrams per kilogram estimated biomass

As mentioned earlier, in reports from ESAC-Net the consumption of antimicrobials in humans is reported by use of the indicator DDD per 1 000 inhabitants and per day, while in reports from ESVAC data are presented as milligrams per PCU. Therefore, to facilitate comparisons between the use of antimicrobials in the human and veterinary domains, data from ESAC-Net were converted into milligrams per kilogram estimated biomass. The two measures are not equivalent as the DDD takes differences in dosing into account, while milligrams per kilogram does not. For example, the DDD of phenoxymethylpenicillin is 2 g, while for doxycycline it is 0.1 g. DDD may also vary considerably within an antimicrobial class, for example in the macrolides (range 0.3-3 g). Thus, for example, a country where phenoxymethylpenicillin is preferred over doxycycline and some of the macrolides may well rank low in DDDs per 1 000 inhabitants and per day when compared with a country where the opposite preferences are the case, but much higher in milligrams per kilogram estimated biomass. A scatter plot of the two measures in the dataset is shown in **Figure 2** (data from ESAC-Net and **Table 4**). A significant correlation between measures was observed. The three most notable outliers seen in the graph are all Scandinavian countries, where use of phenoxymethylpenicillin and methenamine is comparatively high. It is possible that this partly explains why these countries rank comparatively low when consumption is expressed as DDD per 1 000 inhabitants and per day and relatively higher when expressed as milligrams per kilogram estimated biomass.

Figure 2. Scatter plot of consumption in humans reported as total DDD per 1 000 inhabitants and per day and total milligrams of active substance per kilogram estimated biomass for the 26 countries included (data for 2012)



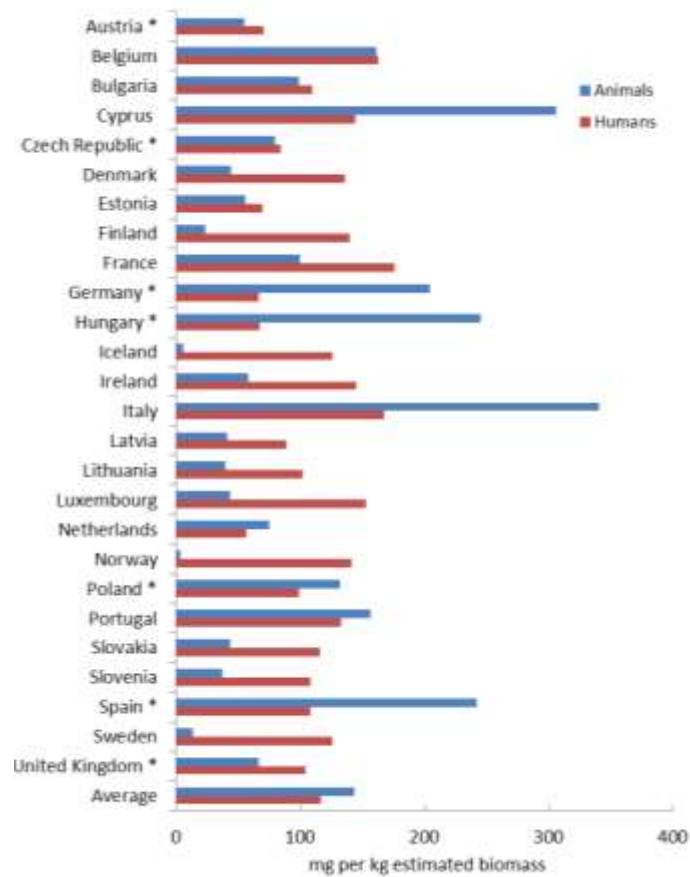
Note: Spearman's rank correlation, $\rho = 0.87$; p -value < 0.0001

6.3. Population biomass-corrected consumption of antimicrobials in humans and food-producing animals

A comparison of average consumption of antimicrobials for humans and food-producing animals, expressed as milligrams per kilogram estimated biomass, is shown in **Figure 3** and **Table 4**. When comparing the consumption of antimicrobials in the human and food-producing animal domains in 2012, the average consumption expressed in milligrams per kilogram of estimated biomass was 116.4 mg/kg in humans (range 56.7–175.8 mg/kg) and 144.0 mg/kg in animals (range 3.8–396.5 mg/kg).

In 15 of 26 countries, consumption was lower or much lower in food-producing animals than in humans, in three countries consumption was similar in the two groups, and in eight countries consumption in food-producing animals was higher or much higher than in humans. There was no correlation between consumption in human and veterinary medicine within country (Spearman's rank correlation, $\rho = -0.01$).

Figure 3. Comparison of biomass-corrected consumption of antimicrobials (milligrams per kilogram estimated biomass) in humans and food-producing animals by country in 26 EU/EEA countries in 2012^{18,19,20}



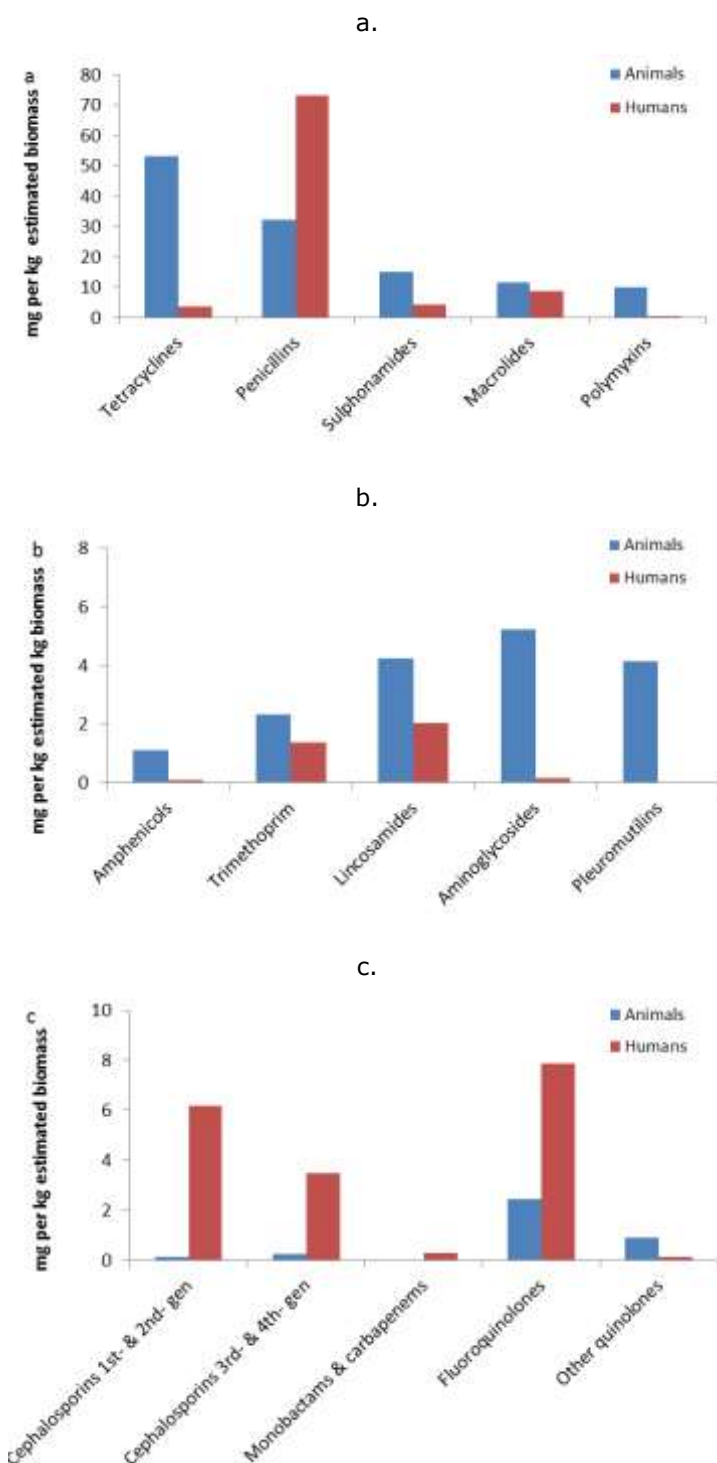
¹⁸ Many limitations hamper the comparison of consumption of antimicrobials in humans and animals. The estimates presented are crude and must be interpreted with caution.

¹⁹ Asterisk (*) indicates that only community consumption data were available for human medicines.

²⁰ The average figure represents the population-weighted mean of data from included countries.

Figure 4. a–c. Comparison of consumption of selected antimicrobial classes for humans and food-producing animals in 26 EU/EEA countries in 2012

Note that the scale on the y-axis differs between the figures^{21,22}



²¹ Many limitations hamper the comparison of consumption of antimicrobials in humans and animals. The estimates presented are crude and must be interpreted with caution.

²² Classes not included for human medicine were glycopeptides, imidazoles, nitrofurans, streptogramins, steroid antimicrobials and other antimicrobials (ATC code J01XX). Substances not included for food-producing animals were bacitracin, paromycin and spectinomycin.

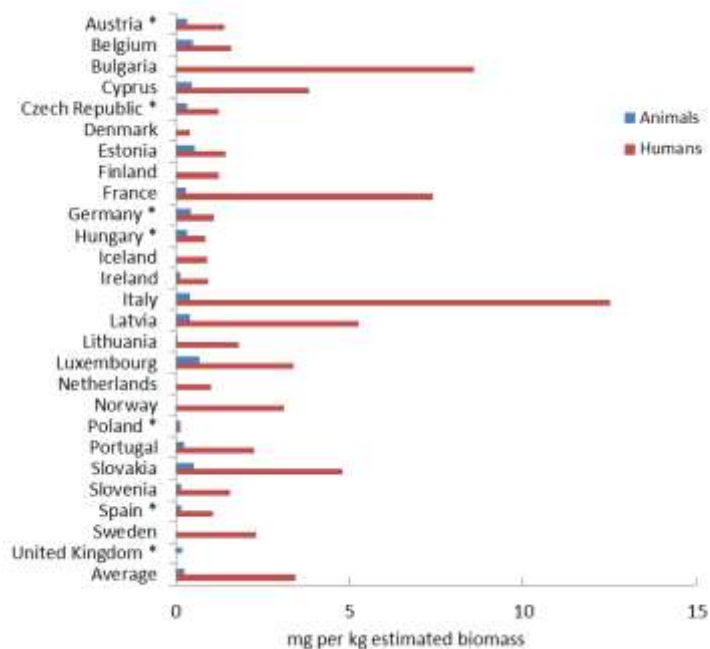
6.4. Comparison of overall consumption, expressed as milligrams per kilogram estimated biomass, by antimicrobial class

Consumption of selected antimicrobial classes, aggregated for the 26 EU/EEA countries, is shown in **Figure 4**. Penicillins, macrolides and fluoroquinolones were the highest selling classes in human medicine, when expressed as milligrams per kilogram estimated biomass. For food-producing animals, tetracyclines, penicillins and sulfonamides were the highest selling classes. Monobactams and carbapenems are not approved for use in food-producing animals in EU/EEA countries and no such consumption was reported for food-producing animals. Likewise, pleuromutilins are not authorised for systemic use in humans and no such consumption was reported for humans. Population-corrected consumption of penicillins, cephalosporins (all generations) and fluoroquinolones for humans, expressed as milligrams per kilogram estimated biomass, was higher than consumption of these classes for food-producing animals. For the other classes included in the figures, the opposite was the case.

6.5. Comparison of consumption, expressed as milligrams per kilogram estimated biomass, of 3rd- and 4th-generation cephalosporins by country

Third- and 4th-generation cephalosporins are regarded by the WHO as CIAs of highest priority. The average consumption (population-weighted mean) of 3rd- and 4th-generation cephalosporins for humans and food-producing animals was 3.50 and 0.24 mg/kg estimated biomass, respectively. The corresponding ranges were 0.02–12.52 and < 0.01–0.68 mg/kg, respectively. In **Figure 5** the biomass-corrected consumption for humans and food-producing animals is shown by country. Generally, in human medicine, 3rd- and 4th-generation cephalosporins are mostly used in hospitals. In a majority (16 of 20) of the countries from which data from both community and hospitals were reported, > 70 % of the consumption of 3rd- and 4th-generation cephalosporins expressed as milligrams per kilogram estimated biomass occurred in hospitals (range 30–98 %). Therefore, figures for countries where only data on community consumption are available are probably considerably underestimated in the case of 3rd- and 4th-generation cephalosporins. Nevertheless, consumption in food-producing animals was, with two exceptions, much lower than in human medicine. In both cases, this was observed in countries that did not report consumption for hospitals. It is likely that, if data on hospital consumption had been available in these countries, consumption for food-producing animals would have been lower than the total consumption for humans in these countries as well. There was no correlation within country between consumption of 3rd- and 4th-generation cephalosporins for humans and for food-producing animals (Spearman's rank correlation, $\rho = 0.32$).

Figure 5. Biomass-corrected consumption of 3rd- and 4th-generation cephalosporins for humans and food-producing animals by country in 26 EU/EEA countries in 2012^{23,24,25}



6.6. Comparison of consumption, expressed as milligrams per kilogram estimated biomass, of fluoroquinolones by country

Fluoroquinolones are regarded by the WHO as CIAs of highest priority. The population-weighted mean consumption of fluoroquinolones in humans and food-producing animals was 7.04 and 2.47 mg/kg estimated biomass, respectively. The corresponding ranges were 2.24–16.03 and 0.01–10.98 mg/kg, respectively. Population-corrected consumption in humans and food-producing animals by country is shown in **Figure 6**.

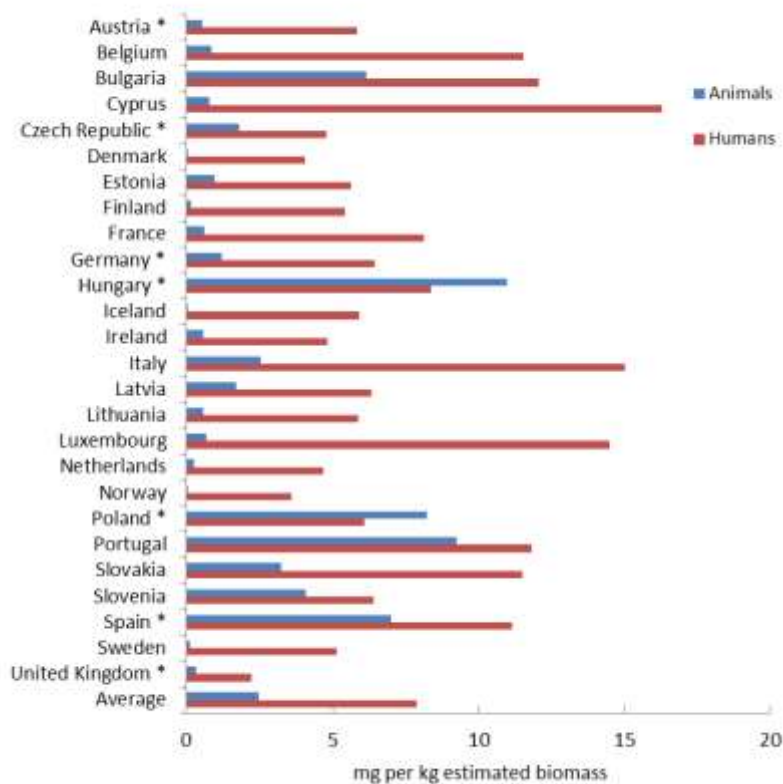
In contrast to the 3rd- and 4th-generation cephalosporins, in human medicine fluoroquinolones are mostly used in the community. In the countries with complete datasets, consumption in hospitals ranged from 3 to 23 % of the total consumption expressed as milligrams per kilogram estimated biomass. Thus, underestimation of the consumption in humans is less of a problem for this class than for 3rd- and 4th-generation cephalosporins. Overall, in most countries the consumption of fluoroquinolones was lower in food-producing animals than in humans, but the difference was less striking than for the 3rd- and 4th-generation cephalosporins. Also, the variation between countries in the quantity of fluoroquinolones used by humans or animals was very wide. There was a significant correlation within country between consumption of fluoroquinolones in humans and food-producing animals (Spearman’s rank correlation, rho = 0.63, p-value = 0.0005).

²³ Many limitations hamper the comparison of consumption of antimicrobials in humans and food-producing animals. The estimates presented are crude and must be interpreted with caution.

²⁴ Asterisk (*) denotes that only community consumption data were available for human medicine. Figures for human sales in these countries probably represent a considerable underestimate.

²⁵ The average figure represents the population weighted-mean of data from included countries.

Figure 6. Population-corrected consumption of fluoroquinolones for humans and food-producing animals by country in 26 EU/EEA countries in 2012^{26,27,28}



6.7. Discussion on comparison of consumption

6.7.1. Limitations

About 10 % of the total consumption of antimicrobials, expressed as DDD per 1 000 inhabitants, is used in hospitals, but, when expressed as tonnes of active substance, the proportion of hospital consumption of the overall consumption in those 19 countries providing data from both the community and hospital sector (**Table 4**) varied between 13 and 28 %. This may give an indication of the magnitude of the underestimates in the six countries that provided only figures on community consumption in the comparisons presented in this report.

Data coverage in the monitoring of community consumption (human medicine) is not 100 % in all included countries. Countries with less than 95 % data coverage for community consumption were Germany (85 %) and the Netherlands (92 %). In those countries, the consumption expressed as tonnes, without correction for population or biomass, will be an underestimate.

The criteria for inclusion of antimicrobials were not identical in the human and animal surveillance systems, as data for animals are not limited to antimicrobials for systemic use (QJ01). In human medicine, antimicrobials are also found in ATC groups other than J01 (e.g. A07 and J04). Thus, nominator data for human medicine are an underestimate of the total consumption.

²⁶ Many limitations hamper the comparison of consumption of antimicrobials in humans and food-producing animals. The estimates presented are crude and must be interpreted with caution.

²⁷ Asterisk (*) denotes that only community consumption data were available for human medicine.

²⁸ The average figure represents the population-weighted mean of data from included countries.

The weights used to estimate human biomass are derived from different published surveys. It is uncertain how representative the weights used are for the EU human populations in 2012. For example, Swedish data indicate that elderly people have a lower average weight than younger adults²⁹.

The denominator data for consumption of antimicrobials for animals are a sum of the biomass of different food-producing species. The consumption of antimicrobials varies considerably between the various animal species and production types. Differences between countries can partly be explained by differences in animal demographics. This must be taken into account when interpreting data. Information on the composition of the animal populations (expressed as PCU) can be found in the fourth ESVAC report (EMA/ESVAC, 2014); see also **Table 7** in the present report.

For the estimation of biomass of the populations of live food-producing animals, standard weights at an age when animals are most likely to receive treatment are used, whereas the calculated human EU population- and age class-weighted biomass is based on an EU average weight. Thus, the calculations of the two denominators are not based on the same principle. Data on consumption of antimicrobials by age class are reported to ESAC-Net by only a few countries. In many countries, the consumption of antimicrobials is probably higher in children, adolescents and the elderly than in adults in general, but this could not be taken into consideration because of the lack of data. Consequently, the biomass estimated by use of the standard weight of 62.5 kg may be an overestimate and must be interpreted with caution.

Only datasets from countries with data available on consumption of antimicrobials for both humans and food-producing animals were included, which totalled 26 EU/EEA countries.

6.7.2. Discussion on results

When comparing the consumption of antimicrobials in the human and food-producing animal domains in 2012, the average consumption expressed in milligrams per kilogram of estimated biomass was 116.4 mg/kg in humans (range 56.7-175.8 mg/kg) and 144.0 mg/kg in animals (range 3.8-396.5 mg/kg). Consumption in food-producing animals was lower or much lower than in humans in 15 of 26 countries, in three countries it was similar, and in eight countries consumption in food-producing animals was higher or much higher than in humans, but the overall consumption of antimicrobials (population weighted mean) was higher for animals than for humans. This is because four of the countries where consumption of antimicrobials for animals was higher than for humans are also countries with large food-producing animal populations, thereby having a large impact on the average.

The consumption of 3rd- and 4th-generation cephalosporins was much lower for animals than for humans. This antimicrobial class is predominantly used in hospitals, and therefore the comparison may be misleading for countries not reporting such hospital consumption. This is less problematic for the consumption of fluoroquinolones, where community consumption dominates. In most countries, the consumption of fluoroquinolones was lower for animals than for humans, but there was more variation between countries than for cephalosporins. There was a significant but weak correlation (Spearman's rank correlation, $\rho = 0.63$) between within-country consumption of fluoroquinolones for humans and food-producing animals. This is probably explained by a cluster of countries with comparatively high consumption both for humans and for animals.

As mentioned, limitations hamper the comparison of consumption of antimicrobials for humans and food-producing animals. The estimates presented here are crude and must be interpreted with caution. Still, they are based on the best existing data at this time. The main weakness is that the indicator

²⁹ <http://www.scb.se/sv/Hitta-statistik/Statistik-efter-amne/Levnadsforhallanden/Levnadsforhallanden/Undersokningarna-av-levnadsforhallanden-ULFSILC/12202/12209/>

used, i.e. milligrams per kilogram biomass, does not take into account differences in dosing between the antimicrobials and between human and animals. To improve this, an agreed and comparable unit of measurement is needed. Furthermore, for more meaningful discussions, data at an animal species level are needed. Nevertheless, the presented data illustrate that there are wide variations between countries both in the overall consumption figures and in the consumption of the 3rd- and 4th-generation cephalosporins and fluoroquinolones.

7. Antimicrobial consumption in food-producing animals and resistance in bacteria from food-producing animals

7.1. Comparison between consumption of antimicrobials for food-producing animals and resistance in food-producing animals

Significant positive associations between antimicrobial consumption and resistance in food-producing animals were generally observed for the combinations of bacteria/antimicrobial substances considered, the different relationships observed for the years 2012 and 2011 are illustrated graphically in **Figure 7-Figure 10** in this section, and in **Figure 26-Figure 29**, in Annex D.

A high degree of variability in the consumption of, and resistance to, tetracyclines (**Figure 7/Figure 26**) was observed among the countries that addressed indicator *E. coli*, *Salmonella* spp., *C. coli* and *C. jejuni* in both years studied (12, 10, 5 and 9 countries respectively). For *C. coli* isolates, the low number of country points made the association less obvious. Overall, positive associations between national consumption of tetracyclines in animals and resistance to tetracycline in bacterial isolates from the animal species considered were observed, but were of only borderline statistical significance when considering data on *Salmonella* spp. in 2011 and on *C. coli* in 2012. Considering data on *C. jejuni* in 2011 and 2012, the removal of the outlier/influential points on the far right of the graphs did not modify the significance of the positive association.

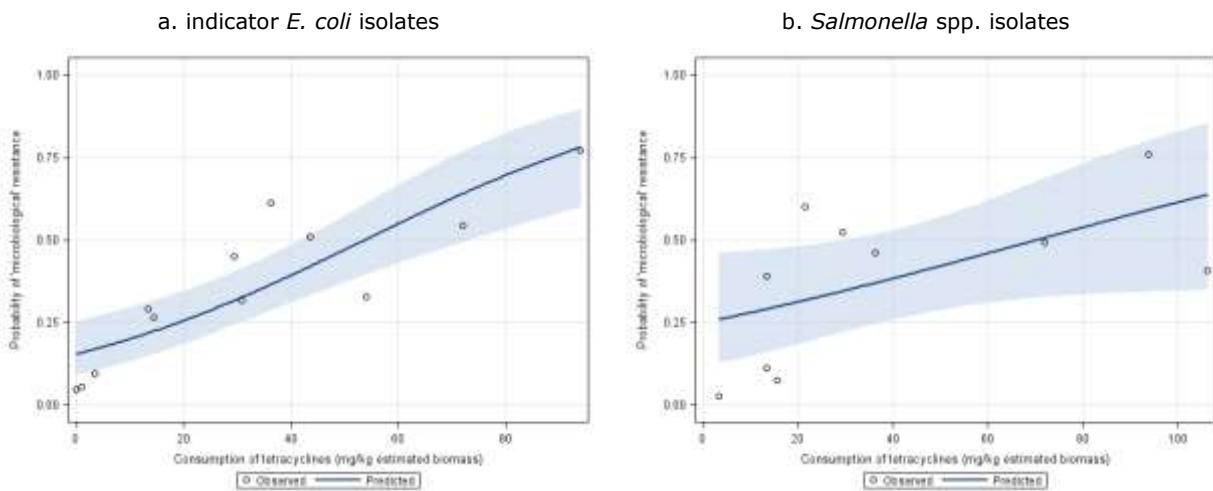
Data on resistance to cefotaxime in indicator *E. coli* and isolates of *Salmonella* spp. from cattle, domestic fowl and pigs, available in 11 and 10 countries, respectively, were compared with data on consumption of 3rd- and 4th-generation cephalosporins in both years studied (**Figure 8/Figure 27**). Although some disparity in consumption of 3rd- and 4th-generation cephalosporins was recorded among the countries considered, cefotaxime resistance in both types of bacteria was typically reported at low levels. Nevertheless, logistic regression analyses showed positive associations between the quantity of 3rd- and 4th-generation cephalosporins consumed at country level and the risk of reduced susceptibility to cefotaxime, although observed at a borderline significance regarding isolates of *Salmonella* spp. in 2012.

A similar pattern, in which the relationship is characterised by variation in the quantity of macrolides used in food-producing animals in the reporting countries involved and low levels of corresponding resistance to erythromycin, was also observed, although to a lesser degree, considering data on *C. jejuni* isolates in nine countries in 2011 and 2012. In *C. coli*, higher levels of resistance to erythromycin were reported in the five countries included in the analysis in both years (**Figure 9/Figure 28**). In both *Campylobacter* spp., significant positive associations between consumption and resistance were observed. Removal of the influential points shown on the far right of the graphs for both *C. coli* and *C. jejuni* in 2012 altered the significance of the positive association; the association was therefore significantly affected by some countries.

Regarding the relationship between national consumption of fluoroquinolones and other quinolones and the risk of reduced susceptibility to ciprofloxacin, associations were assessed in indicator *E. coli*, *Salmonella* spp., *C. coli* and *C. jejuni* isolates through data reported by 8, 11, 5 and 9 countries,

respectively (**Figure 10/Figure 29**). A third relationship pattern was typically observed for *E. coli*, *C. jejuni*, *C. coli* and *Salmonella* spp. with two distinct groups of MSs, with one group reporting low amounts of consumption and lower resistance and the other group reporting high amounts of consumption and higher resistance, the latter group playing an important role in the assessment of the relationship between use and resistance.

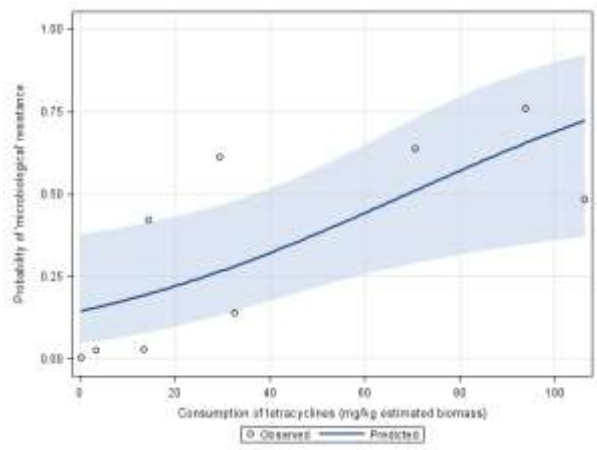
Figure 7. Logistic regression analysis curves with OR estimates and 95 % profile-likelihood confidence intervals (PL CIs) of the national consumption of tetracyclines in food-producing animals and the probability of “microbiological” resistance to tetracyclines in (a) indicator *E. coli* isolates (MIC > 8 mg/L) from cattle, domestic fowl and pigs, (b) *Salmonella* spp. isolates (MIC > 8 mg/L) from cattle, domestic fowl and pigs and (c) *C. jejuni* isolates (MIC > 2 mg/L) from cattle and domestic fowl for the year 2012¹—dots represent the countries included in the analysis.



Countries included:
 AT, BE, CH, DE, DK, ES, FI, FR, NL, NO, PL, SE
 p-value < 0.05; OR = 1.032; 95 % PL CI: [1.019, 1.047]
Note: the association remains significantly positive after ignoring the point displayed on the graph upper right corner:
 p-value < 0.05; OR = 1.033; 95 % PL CI: [1.014, 1.052]

Countries included:
 BE, DE, DK, EE, ES, FI, IT, LV, NL, SE
 p-value < 0.05; OR = 1.016; 95 % PL CI: [1.000, 1.034]

c. *C. jejuni* isolates

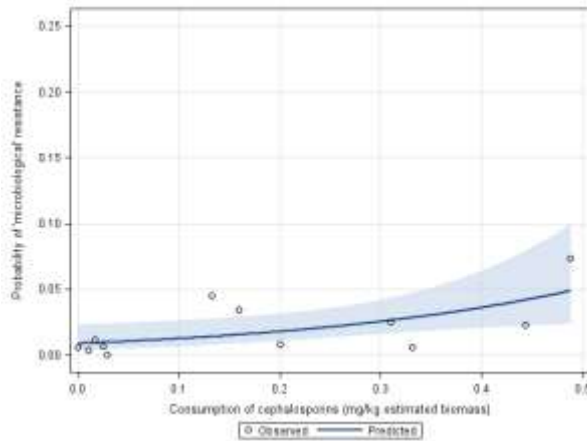


Countries included: AT, CH, DE, DK, ES, FI, IT, NL, NO
 p-value < 0.05; OR = 1.026; 95 % PL CI: [1.006, 1.050]
Note: the association remains significantly positive after ignoring the point displayed on the middle right side of the graph: p-value < 0.05; OR = 1.038; 95 % PL CI: [1.012, 1.073]

¹In the absence of 2012 resistance data, proxy data for years prior to 2012 may have been used.

Figure 8. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of 3rd-generation cephalosporins in food-producing animals and the probability of “microbiological” resistance to cefotaxime in (a) indicator *E. coli* isolates (MIC > 0.25 mg/L) from cattle, domestic fowl and pigs and (b) *Salmonella* spp. isolates (MIC > 0.5 mg/L) from cattle, domestic fowl and pigs for the year 2012¹—dots represent the countries involved in the analysis

a. indicator *E. coli* isolates

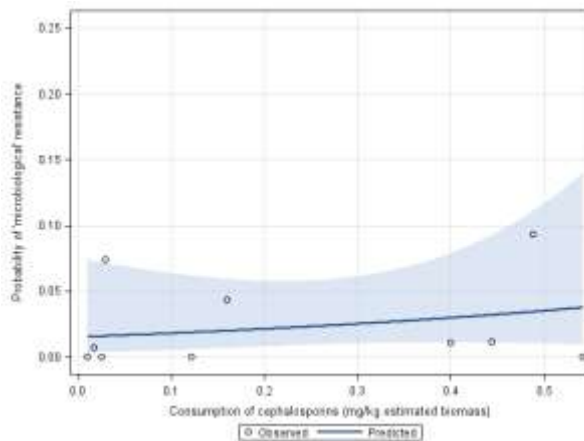


Countries included:

AT, BE, CH, DE, DK, ES, FI, NL, NO, PL, SE

p-value < 0.05; OR_{0.1-unit increment} = 1.429; 95 % PL CI: [1.079, 1.930]

b. *Salmonella* spp. isolates



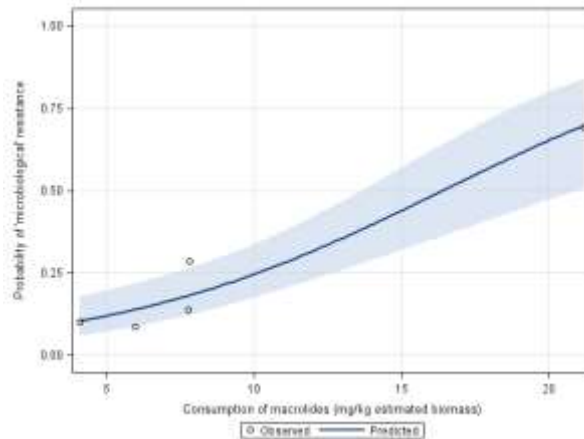
Countries included: BE, DE, DK, EE, ES, FI, IE, IT, NL, SE

p-value < 0.05; OR_{0.1-unit increment} = 1.186; 95 % PL CI: [0.752, 1.967]

¹In the absence of 2012 resistance data, proxy data for years prior to 2012 may have been used.

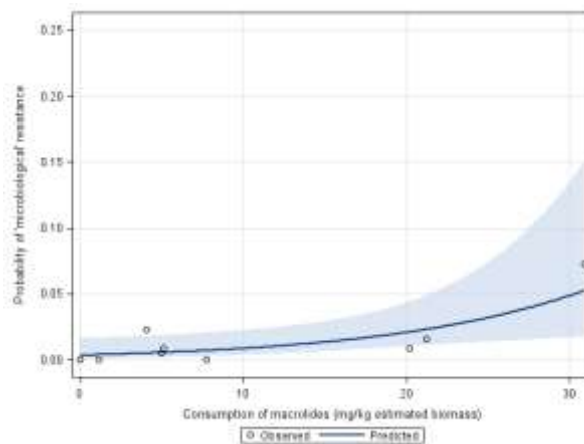
Figure 9. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of macrolides in food-producing animals and the probability of “microbiological” resistance to erythromycin in (a) *C. coli* isolates (MIC > 16 mg/L) from domestic fowl and pigs and (b) *C. jejuni* isolates (MIC > 4 mg/L) from cattle and domestic fowl for the year 2012¹—dots represent the countries involved in the analysis

a. *C. coli* isolates



Countries included: CH, ES, FR, HU, NL
 p-value < 0.05; OR = 1.192; 95 % PL CI: [1.118, 1.278]

b. *C. jejuni* isolates



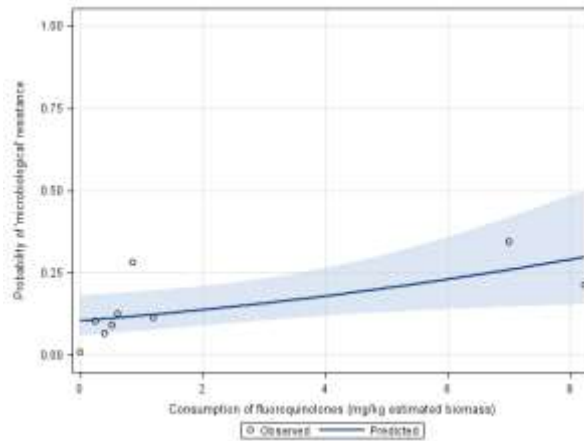
Countries included: AT, CH, DE, DK, ES, FI, IT, NL, NO
 p-value < 0.05; OR = 1.091; 95 % PL CI: [1.018, 1.176]

¹In the absence of 2012 resistance data, proxy data for years prior to 2012 may have been used.

Figure 10. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of (A) fluoroquinolones and (B) fluoroquinolones and other quinolones in food-producing animals and the probability of “microbiological” resistance to ciprofloxacin in (1) indicator *E. coli* isolates (MIC > 0.03 mg/L) from cattle, domestic fowl and pigs, (2) *Salmonella* spp. isolates (MIC > 0.06 mg/L) from cattle, domestic fowl and pigs and (3) *C. jejuni* isolates (MIC > 1 mg/L) from cattle and domestic fowl for the year 2012¹—dots represent the countries involved in the analysis

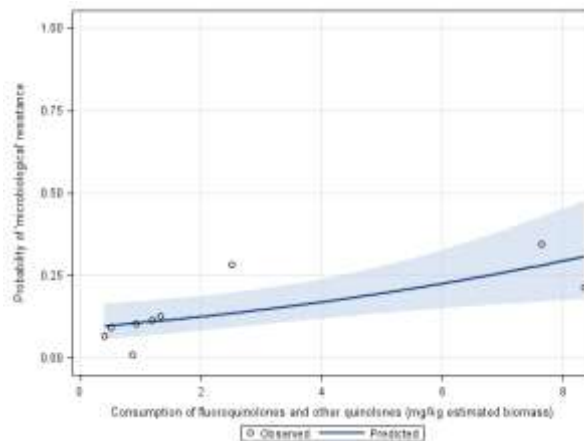
1) indicator *E. coli* isolates

a.



Countries included: AT, BE, CH, DE, DK, ES, FR, NL, PL
 p-value < 0.05; OR = 1.170; 95 % PL CI: [1.015, 1.344]

b.



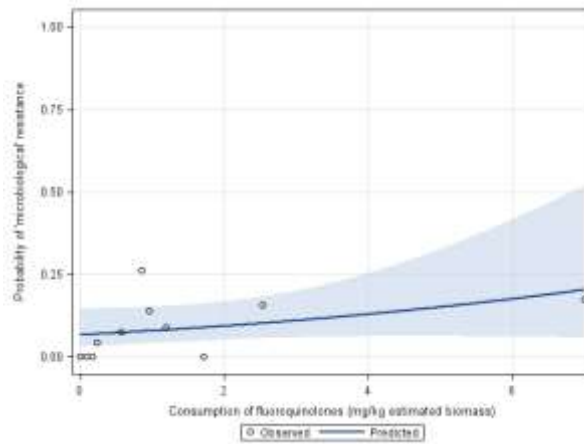
Countries included: AT, BE, CH, DE, DK, ES, FR, NL, PL
 p-value < 0.05; OR = 1.195; 95 % PL CI: [1.052, 1.356]

Note: the association remains not significantly after ignoring the two points displayed on the right side of the graph: p-value < 0.05; OR = 2.415; 95 % PL CI: [1.596, 3.652]

¹In the absence of 2012 resistance data, proxy data for years prior to 2012 may have been used.

2) *Salmonella* spp. isolates

a.



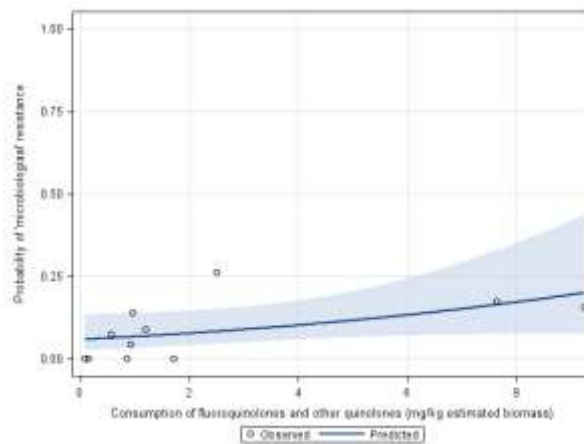
Countries included: BE, DE, DK, EE, ES, FI, IE, IT, LV, NL, SE

OR = 1.198; 95 % PL CI: [0.896, 1.536] – not significant

Note: the association remains not significantly positive after ignoring the point displayed on the right side of the graph:

OR = 1.761; 95 % PL CI: [0.717, 4.173]

b.



Countries included: BE, DE, DK, EE, ES, FI, IE, IT, LV, NL, SE

p-value < 0.05; OR = 1.162; 95 % PL CI: [0.970, 1.379]

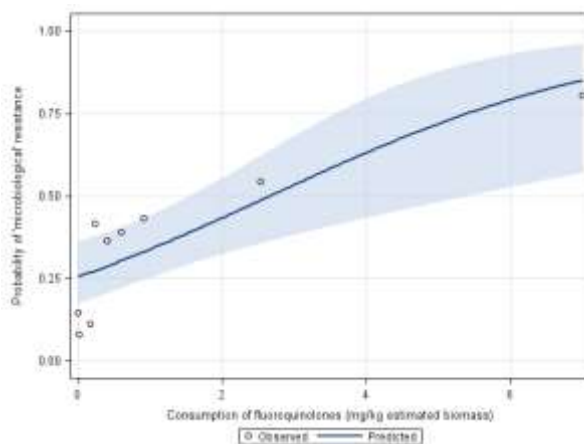
Note: the association is significantly positive after ignoring the two points displayed on the right side of the graph:

p-value < 0.05; OR = 3.132; 95 % PL CI: [1.484, 6.912]

⁴In the absence of 2012 resistance data, proxy data for years prior to 2012 may have been used.

3) *C. jejuni* isolates

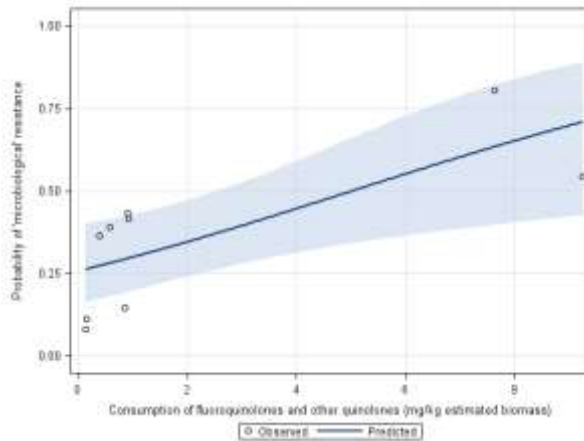
a.



Countries included: AT, CH, DE, DK, ES, FI, IT, NL, NO
p-value < 0.05; OR = 1.496; 95 % PL CI: [1.208, 1.971]

Note: the association remains significantly positive after ignoring the point displayed on the upper right corner of the graph: p-value < 0.05; OR = 1.970; 95 % PL CI: [1.124, 3.617]

b.



Countries included: AT, CH, DE, DK, ES, FI, IT, NL, NO
p-value < 0.05; OR = 1.236; 95 % PL CI: [1.056, 1.445]

¹In the absence of 2012 resistance data, proxy data for years prior to 2012 may have been used.

7.2. Discussion of the comparison between consumption of antimicrobials in food-producing animals and resistance in bacteria from food-producing animals

7.2.1. Limitations of data

This analysis aimed at investigating the potential relationships between data on antimicrobial consumption in food-producing animals and resistance to antimicrobials in food-producing animals, collected under the framework of the existing monitoring systems of consumption and resistance at the EU/EEA level. A summary indicator of resistance embracing the different animal species addressed by resistance monitoring was first constructed and then compared with data on the national consumption of antimicrobials in food-producing animal species at the country level. The number of substances sold, per animal species, could not be inferred from the national overall consumption data, usually because of variable consumption of a given substance among the various food-producing animal species addressed. Nevertheless, although consumption data referred to all food-producing animal species and “summary indicators” of resistance covered only three animal species in the case of *E. coli* and *Salmonella* spp. and two species regarding *Campylobacter* spp., the summary indicators of resistance still enabled the comparison with consumption data to be made, as these species are the most important ones in terms of population size, production and consumption of antimicrobial substances.

The calculation of the summary indicator of resistance, at the country level, incorporated resistance data from the three/two animal species according to the bacterium considered, and a number of countries were discarded from the analysis because of insufficient resistance data relating to one or two animal species. In order to maximise the number of countries involved in the analysis, proxy data on resistance, assessed in years prior to 2011/2012, were used to compute the summary indicators of resistance for the years 2011 and 2012. Nevertheless, the prerequisite of having available resistance data for the animal species meant that this approach resulted in a limited number of countries being included in the analysis. Inclusion of additional countries in the analysis, in particular those reporting intermediate amounts of consumption and levels of resistance, would have allowed better assessment of the relationships between consumption and resistance; a striking example concerns the assessment of the association between consumption of fluoroquinolones or fluoroquinolones plus other quinolones and the resistance to ciprofloxacin, which was driven by two groups of countries with very different profiles in terms of both consumption and resistance. The data available for the analysis did not include data from countries with intermediate situations, which hampers the validation of the assumed linearity between exposure and risk.

The limited number of countries involved in the analysis, and the particular situations in some of them (outliers) regarding amounts of consumption and levels of resistance, may partially explain the overdispersion phenomenon observed in these data. Overdispersion can also arise from dependence among the observations related to unobserved heterogeneity that operates at the level of groups rather than individuals. Isolates are grouped into naturally occurring clusters, in this case into countries. It seems reasonable to suppose that isolates originating from the same country (i.e. the same domestic production sectors) are not independent, as they are exposed to many common factors, such as clonal spread within sectors, biosecurity levels, management and husbandry practices and/or varying prescribing practices across countries, that may produce the same outcome (antimicrobial susceptibility status).

The weighting factor is based on the relative PCU of the animal species included in the analyses used as a relative indicator of the size of the animal reservoir of bacteria; it does not account for the prevalence of the bacterial species (*Salmonella* spp., *Campylobacter* spp.) in these animal species. While indicator *E. coli* and *Campylobacter* spp. isolates mainly derive from active monitoring

programmes, based on representative random sampling of carcasses of healthy animals sampled at the slaughterhouse, salmonella isolates derive from either National Control Plan surveillance programmes or passive programmes preferentially performed at farm level. Overall, in sectors and countries where salmonella prevalence is low, the available salmonella isolates obtained from the programmes may be very few, and, therefore, the resistance assessed in isolates of *Salmonella* spp. may be less representative of the exposure of the total population to antimicrobials than that estimated in indicator *E. coli*. This may also be influenced by the frequency distribution of the prevalent salmonella serovars, whose displayed resistance traits were shown to vary, significantly, from one to another. Indeed, the isolate sample size has an effect on accuracy and precision of the assessed occurrence of resistance.

Sampling design, in the framework of the resistance monitoring in the countries addressed, may have impacted on the analysis in another way. The sampling strategy might not be uniform between countries; in particular, sub-populations of cattle targeted by resistance monitoring can differ between countries, resulting in, for example, differing proportions of isolates being obtained from dairy cows, suckler cows and veal calves. Data from domestic fowls and pigs primarily derive from broilers and fattening pigs.

7.2.2. Interpretation of results

The analyses performed and the corresponding graphs displaying logistic regression curves, for 2011 and 2012, illustrated the consistency/reproducibility of the observation of positive associations between consumption and resistance, which were mostly statistically significant, over these two years (the analysis did not attempt to describe any trends over time). ORs were used to assess the strength of the associations. It is of note that the magnitudes of ORs were linked to the amounts of consumption expressed in milligrams per PCU recorded in the countries considered, those numbers being indirectly linked to posologies, which may vary significantly between the antimicrobial substances addressed. For example, ORs of the same magnitude (about 1) were obtained for an 0.1 mg/PCU increment considering cefotaxime, while an increment of 1 mg/PCU was observed when considering tetracycline. In the framework of this analysis, point estimates of ORs are not comparable between bacteria and antimicrobial classes for a given increment of consumption expressed in milligrams per PCU, as this measure of weight of antimicrobial active ingredient does not reflect the different potencies of different substances and therefore does not allow standardised comparison of usage between different substances.

The antimicrobials which have been included differ in a number of aspects which might have an impact on the association demonstrated between the consumption of antimicrobials in food-producing animals and the level of resistance detected. Firstly, the milligrams per PCU does not take into account that there are wide variations in the dosing age regimen, time of treatment in the animal's life and the interval between treatment and slaughter (the point at which resistance may have been assessed), and these factors may vary between antimicrobial classes and animal species. In the different animal species, longitudinal studies of the relationship between animal treatment and antimicrobial resistance carriage at slaughter often show a decrease in resistance according to the time elapsed between the last treatment and slaughter.

Development of antimicrobial resistance is a function of selection pressure and an evolution process at the bacterial level leading to selection and maintenance of successful genes, mobile genetic elements and/or clones. "Old" drugs, such as tetracyclines (chlortetracycline, oxytetracycline, tetracycline) have been used therapeutically for more than half a century in veterinary medicine (as well as an antimicrobial growth promoter during the first 25 years of use), while doxycycline was approved about 20 years ago. The history of exposure of animals to antimicrobials over a long period of time may

differ between the reporting countries, and prolonged exposure is likely to lead to the selection of different resistance genes and mobile genetic elements and their stable establishment in the different animal species. Consequently, the consumption of a given class of substances recorded in a country does not necessarily reflect the cumulative consumption of the class over time. This can be contrasted with the fluoroquinolones, which have been marketed in most countries for about 20 years, and consumption of which is generally much lower than consumption of tetracyclines in most of the reporting countries. Most fluoroquinolone resistance has been associated with selection of mutational resistance during treatment of *E. coli* and *Campylobacter* spp., although plasmid-mediated resistance is becoming more common, particularly in *Salmonella* spp. The route of administration of the different substances of this sub-class as well as the consumption of quinolones may vary significantly among animal species, as administration by oral route for group treatment is primarily used in poultry while individual injectable treatments are mainly employed in cattle and pigs. The process of selection of antimicrobial resistance through mutation differs between bacterial species, with rapid and stable selection of resistant mutants in *Campylobacter* spp. contrasting with several step mutations followed by fitness adaptation in the Enterobacteriaceae.

The degree to which co-resistance to several compounds occurs will also have an effect on the observed associations, and co-resistance may also have been influenced by previous antimicrobial consumption over a number of years. Therefore, the different patterns of association detected may reflect quite different stages in the evolution of resistance; this analysis does not take into account consumption in the years preceding consumption only those years selected for investigation. In the case of mutational resistance, no external genetic material is required for resistance to develop within the bacterial population; resistant strains occur spontaneously in the bacterial population and are then selected by antimicrobial consumption. The competition between susceptible and resistant strains will lead to maintenance or disappearance of resistant mutants according to their fitness and adaptation process through compensatory mutations. This is not the case for 3rd-generation cephalosporin resistance, which usually develops not via mutation but through the selection of strains carrying mobile genetic elements coding for cephalosporin resistance, which can be transferred by conjugation (i.e. horizontally) to susceptible recipient strains. In such circumstances, the degree to which a bacterial population is "isolated" from the general population can influence the development of resistance.

The analysis assessed the relationship between amount of consumption of certain classes of antimicrobials and the corresponding resistance to a representative substance of the same class. The co-selection phenomenon was not taken into account in this report because isolate-based data were not available from sufficient MSs. Nevertheless, an attempt to illustrate the impact of the co-selection phenomenon on the assessment of the relationship between data on consumption and resistance is shown in **Textbox 1**. Analysis of multidrug resistance is complex and may involve other factors (for example resistance to quaternary ammonium disinfectants). Particular multidrug resistance patterns may be associated with the spread of certain bacterial clones and the degree to which such clones influence the overall resistance figures is a topic for investigation. It seems likely that refinements in data collection (for example phage typing of salmonella isolates) will be required before this aspect can be fully addressed in reports similar to this.

The comparison of point distribution on the graphs of the national consumption of 3rd-generation fluoroquinolones alone or added to other quinolones and risk of ciprofloxacin resistance in *E. coli*, *C. coli* or *C. jejuni* isolates illustrates the impact of use of other quinolones in certain countries. For the bacterial species, the graphs show shifts to the right of two points, corresponding to the contribution of quinolone consumption. From a microbiological point of view, these shifts are logical because of the cross-resistance between quinolones and fluoroquinolones, which are similarly detected by the use of ECOFFs for ciprofloxacin resistance. Quinolones select for the first mutation step leading to ciprofloxacin resistance in *E. coli* and subsequent steps increase resistance levels (a single mutation

confers resistance to both quinolones and fluoroquinolones in *Campylobacter* spp.). A further factor to be considered in *Salmonella* spp. is the dissemination of plasmid-mediated resistance to quinolones mediated by *qnr* genes, which in turn may provide opportunities for co-selection of unrelated antimicrobials if transmitted on the same plasmid.

Some of the graphs display marked differences in the occurrence of resistance for a given level of consumption. This is clearly shown by the graph of ciprofloxacin resistance in *C. coli*, where three countries with approximately the same low level of consumption of ciprofloxacin show differences in the occurrence of resistance to this antimicrobial. There could be a number of explanations for this phenomenon, including differences in the consumption of fluoroquinolones in years prior to the year of analysis. Other possible explanations include movements of bacteria and animals between countries, dissemination of resistance down production pyramids and the effect of co-selection, as well as the high impact of one animal species in the calculations, which were performed to generate an average level of resistance. Conversely, some graphs show that some countries with a relatively high level of consumption have a lower level of resistance than countries with a more moderate consumption (3rd-generation cephalosporins and *Salmonella* spp.). In this example, the differences in the scale of the axes are noteworthy, because the relation between resistance and consumption at very low levels of resistance is likely to be influenced greatly by events such as the degree of containment achieved or, conversely, widespread dissemination which occurred from a single source as a result of animal movements (e.g. resistant bacteria spreading widely from a single farm or other premises). Therefore, where the level of resistance is very low, events unrelated to consumption might have a large proportional effect on the total level of resistance observed. Some features of these data may be explained by factors which relate to particular countries in which some production models rely on extensive movements across Europe between countries from breeding sites to sites used for fattening livestock. For tetracyclines and *Campylobacter* spp., the distribution of outliers and whether or not recent initiatives to markedly reduce the consumption of antimicrobials, including tetracyclines, has influenced their situation requires further investigation, including any changes observed when different years are analysed. Finally, in the graphs concerning *Salmonella* spp. and tetracyclines, co-selection and the spread of resistant clones (which often have genetic resistance "islands" linking resistance genes, among which tetracycline resistance genes are frequently represented) are likely to have markedly affected the occurrence of resistance and may assist in explaining the observed distribution.

Textbox 1.

An attempt to study the impact of co-selection on the assessment of the relationship between antimicrobial consumption and resistance, using an example of resistance data in indicator *E. coli* in 2011

Based on a method derived from that proposed by Søggaard (1989) and reviewed by Monnet et al. (2001), an empiric attempt was made to account for the co-selection phenomenon when comparing data on consumption and resistance in animals. The assumption was that an observed occurrence of resistance was the result of simultaneous actions of several antimicrobials on a given bacterial population accounting for the multidrug-resistance traits of this population.

Various fractions of the consumption of these antimicrobials should be taken into account while modelling the relationship between consumption and resistance. For this purpose, the coupling fraction, cf_{BA} , for an antimicrobial B (to explain resistance to antimicrobial A is defined as the percentage of isolates resistant to A that were also resistant to B. The fractions accounted for each animal population, broilers, pigs and cattle, by weighting them according to their PCU. The corrected antimicrobial A consumption, $corrConsumption_A$, was then calculated using the following formula, where $Consumption_A$ is the quantity of antimicrobial A sold expressed in milligrams per PCU, $Consumption_B$ is the consumption of antimicrobial B and cf_{BA} is the coupling fraction for B to explain resistance to A, etc.:

$$corrConsumption_A = Consumption_A + cf_{BA} \cdot Consumption_B + cf_{CA} \cdot Consumption_C + \dots$$

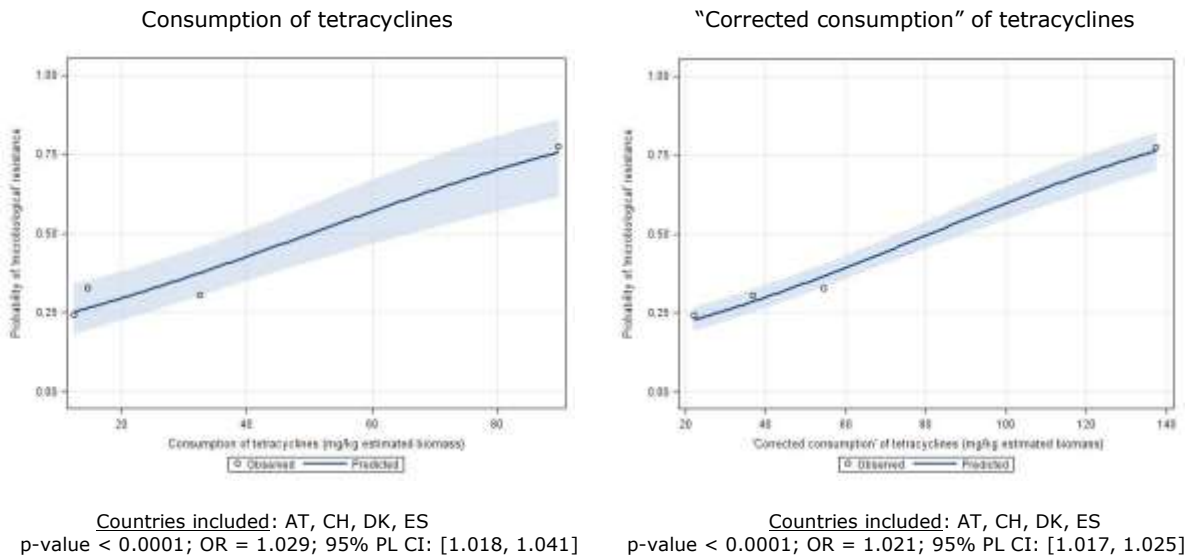
The percentage of isolates (resistant to A that were also resistant to B) were derived from the isolate-based data on indicator *E. coli* in cattle, domestic fowl and pigs reported by a limited number of four countries for the year 2011.

The attempt addresses data on resistance to tetracyclines and 3rd- and 4th-generation cephalosporins in indicator *E. coli* and the corresponding domestic consumption in four countries for the year 2011 (**Figure 11**). Overall, a higher degree of association may be observed. For 3rd- and 4th-generation cephalosporins, the use of "corrected" consumption data results in the association becoming significant. In addition, although the point estimates of the ORs remain of the same magnitude, the ranges of the CIs have been narrowed by "correction" performed on the consumption data. Although remaining low, the max-rescaled R-square increases while correcting consumption data on tetracyclines and 3rd- and 4th-generation cephalosporins or is unchanged while correcting for consumption data on fluoroquinolones.

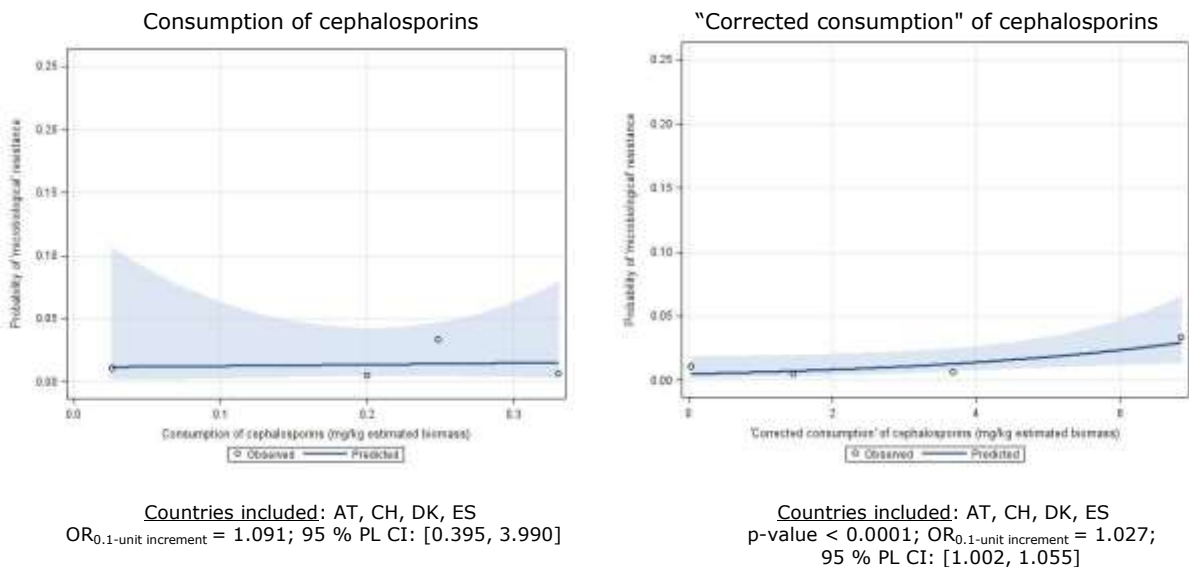
A limitation of this approach is that consumption data expressed in milligrams per PCU are used as a proxy for data on consumption of antimicrobials. In addition, the limited number of resistance data reported at isolate level greatly limited the number of countries included in this analysis.

Figure 11. Logistic regression curves with 95 % CIs of the domestic consumption and “corrected” consumption of tetracyclines and 3rd- and 4th-generation cephalosporins and the corresponding probability of “microbiological” resistance to tetracycline and cefotaxime in indicator *E. coli* from cattle, domestic fowl and pigs—dots represent the countries included in the analysis

a. Tetracyclines—indicator *E. coli* 2011



b. Cephalosporins—indicator *E. coli* 2011



8. Antimicrobial consumption in humans and resistance in bacteria from humans

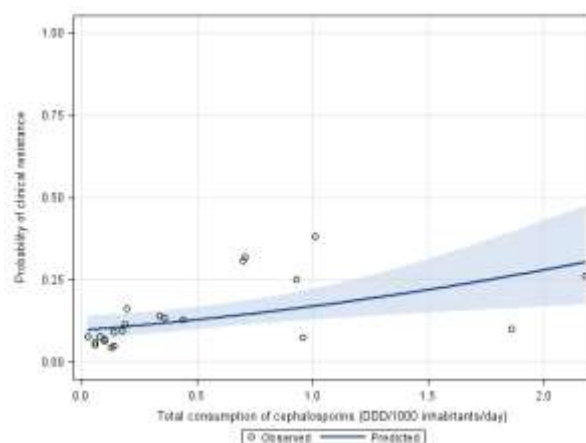
8.1. Consumption of 3rd- and 4th-generation cephalosporins for humans and occurrence of resistance in *E. coli* and *Salmonella* spp. from humans

Third- and 4th-generation cephalosporins (primarily 3rd generation) are used for the treatment of infections caused by both Gram-positive and Gram-negative bacteria, including infections caused by *E. coli* and *Salmonella* spp. Third- and 4th-generation cephalosporins are considered by WHO as CIAs which should be reserved for the treatment of severe infections in humans (3rd revision—WHO list of critically important antimicrobials (CIA) (WHO, 2012)), indicating that non-human use of these antimicrobials should be avoided when possible.

Data on occurrence of cephalosporin resistance in *E. coli* from BSIs were reported from 28 EU and two EEA countries in 2012.

In order to investigate possible correlations between the consumption of 3rd- and 4th-generation cephalosporins and the occurrence of resistance to 3rd-generation cephalosporins in *E. coli*, the consumption of such antimicrobials in the community, in hospitals and in total was plotted against the occurrence of 3rd-generation cephalosporin resistance in *E. coli* isolated from BSIs (**Figure 12**). Significant associations between resistance and consumption in the community, in hospitals and in total, were observed. For all countries included in the analysis, higher levels of consumption correlated with higher levels of percentages of 3rd-generation cephalosporin resistance. The majority of countries reported data. Therefore, the consumption of 3rd- and 4th-generation cephalosporins appears to be associated with 3rd-generation cephalosporin resistance in *E. coli* from humans. The occurrence of country outliers with a relatively high percentage of resistance despite a lower consumption suggests that factors other than the national antimicrobial consumption in humans may contribute.

Figure 12. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national total (community and in hospitals) consumption of 3rd- and 4th-generation cephalosporins in humans and the probability of clinical resistance to 3rd-generation cephalosporins in *E. coli* isolates from human BSIs for the year 2012—dots represent the countries involved in the analysis.



Countries included: BE, BG, CY, DK, EE, FI, FR, GR, HR, IE, IS, IT, LT, LU, LV, MT, NL, NO, PT, RO, SE, SI, SK
p-value < 0.005; OR = 1.909; 95 % PL CI: [1.222, 2.928]

Data on the occurrence of 3rd- and 4th-generation cephalosporin resistance in *Salmonella* spp., *S. Typhimurium* or *S. Enteritidis* from human cases were reported from 18 EU countries in 2012. Four countries reported fewer than 25 isolates and these results are not included in the analysis.

Correlations between the 3rd- and 4th-generation cephalosporin consumption in the community, in hospitals and in total (community and hospitals) were investigated for *Salmonella* spp., *S. Typhimurium* and *S. Enteritidis*. A positive correlation between consumption in hospitals and occurrence of resistance was found for resistance in *Salmonella* spp. (graph not shown). As the majority of countries did not report sufficient details on consumption data, or did not report data on resistance in *Salmonella* spp., the results should be interpreted with caution. In particular, the data on hospital consumption and occurrence of resistance were limited as only six to eight countries reported data on consumption and at the same time data on resistance in *Salmonella* spp., *S. Enteritidis* or *S. Typhimurium*. Moreover, the proportion of consumption in the community to the total consumption varied considerably between countries (10-95 %).

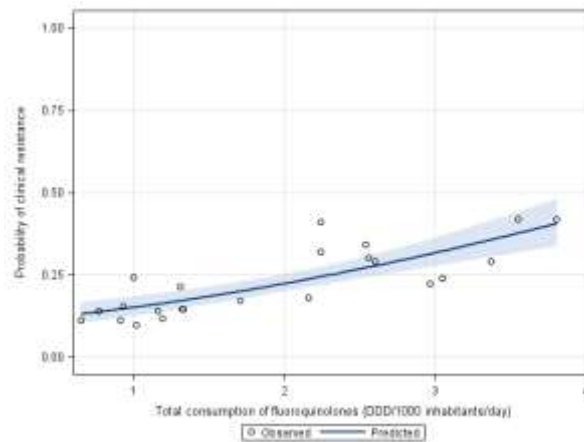
8.2. Consumption of fluoroquinolones in humans and occurrence of fluoroquinolone resistance in *E. coli*, *Salmonella* spp. and *Campylobacter* spp. from humans

Quinolones consumed by humans are almost exclusively fluoroquinolones, which are used for the treatment of infections with both Gram-positive and Gram-negative bacteria, including *E. coli* infections and serious infections caused by *Salmonella* spp. and *Campylobacter* spp. Although fluoroquinolones are considered by WHO as CIAs, they are widely used both in hospitals and in the community.

Data on the occurrence of resistance in *E. coli* originating from human BSIs were reported from all EU countries and two EEA countries in 2012. The number of *E. coli* isolates obtained per country was in most cases more than 1 000 and ranged from 134 to 9 470.

In order to investigate any possible associations between the consumption of fluoroquinolones and the occurrence of resistance to fluoroquinolones in *E. coli*, the consumption of fluoroquinolones in the community, in hospitals and in total was plotted against the occurrence of fluoroquinolone resistance in invasive *E. coli*. Strong correlations between resistance and consumption in the community and in total were observed for *E. coli* in 2012 (**Figure 13**). In both cases, higher consumption correlated with a higher proportional increase in the occurrence of fluoroquinolone resistance. Similar results were obtained when analysing data from 2010 and 2011 (data not shown). As significant associations were observed for all three years, and because almost all countries reported data, it seems reasonable to conclude that the consumption of fluoroquinolones, especially in the community, contributes to the occurrence of fluoroquinolone resistance in *E. coli* in humans. Correlations between fluoroquinolone consumption and fluoroquinolone resistance in *E. coli* have been described previously, and it is not surprising to see the correlation between fluoroquinolone consumption in the community and resistance in invasive *E. coli*. Demographic analyses done at ECDC on EARS-Net data showed that *E. coli* is the microorganism that causes the highest proportion of community-associated infections among the Gram-negative bacteria reported to EARS-Net (using a crude two-day cut-off between date of blood culture and hospitalisation) (Heuer et al., 2014)

Figure 13. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national total (community and in hospitals) consumption of fluoroquinolones for humans and the probability of clinical resistance to fluoroquinolones in *E. coli* isolates from human BSIs for the year 2012—dots represent the countries involved in the analysis



Countries included: BE, BG, CY, DK, EE, FI, FR, GR, HR, IE, IS, IT, LT, LU, LV, MT, NL, NO, PT, RO, SE, SI, SK
 p-value < 0.001; OR = 1.614; 95 % PL CI: [1.383, 1.886]

Data reported from Denmark and the Netherlands were interpreted by use of ECOFF values for *Salmonella* spp. Therefore, these data are not comparable to resistance data reported from the other countries and should be interpreted with caution. Moreover, the low level of resistance to fluoroquinolones indicated by ECOFFs is not regarded as therapeutically relevant by many clinicians for the treatment of invasive salmonella infections.

In 2012, 20 countries reported data on *Salmonella* spp., 21 reported on *S. Typhimurium* and 20 reported on *S. Enteritidis* (only countries reporting more than 25 isolates were included in the analysis). Resistance varied among countries. The occurrence of fluoroquinolone resistance ranged from 0 % to 18.2 % in *Salmonella* spp., from 0 % to 4.3 % in *S. Typhimurium* and from 0 % to 14.2 % in *S. Enteritidis*. The five countries reporting the highest occurrence of fluoroquinolone resistance in *Salmonella* spp. were Malta (18.2 %), France (12.8 %), the United Kingdom (9.1 %), the Netherlands (6.3 %) and Estonia (3.3 %). The lowest occurrence of resistance (0 %) in *Salmonella* spp. was reported from Greece and Latvia. In the case of *S. Typhimurium*, the five countries reporting the highest occurrence of fluoroquinolone resistance were the United Kingdom (4.3 %), the Netherlands (4.0 %), Denmark (2.6 %), Romania (1.9 %) and Ireland (1.7 %). The rest of the countries (12) reported 0 % occurrence of resistance in *S. Typhimurium*. The five countries reporting the highest occurrences of fluoroquinolone resistance in *S. Enteritidis* were the United Kingdom (14.2 %), the Netherlands (9.6 %), Malta (7.4 %), Estonia (3.6 %) and Slovakia (1.6 %), and the lowest occurrence (0 %) was observed in 11 countries. The occurrence of fluoroquinolone resistance in *S. Typhimurium* from the Netherlands and Denmark was interpreted by use of ECOFF values and may explain the relatively higher occurrence in these countries than in the majority of countries.

When comparing data on consumption of fluoroquinolones with the occurrence of fluoroquinolone resistance in *Salmonella* spp., *S. Enteritidis* and *S. Typhimurium*, no correlation of consumption with resistance was observed, either when plotting resistance against the total consumption or when split into consumption of fluoroquinolones in the community and consumption in hospitals. As non-typhoidal *Salmonella* spp. are not a normal part of the human intestinal microbiota and are rarely transmitted between humans, it is assumed that resistance in non-typhoid *Salmonella* spp. may, for the most part, be transmitted to humans via consumption of contaminated food. Furthermore, the data used for the

analysis did not include data from patients reporting a history of recent travel to other countries. For this reason, no conclusions regarding the impact of travel can be drawn from this report.

In 2012, 14 countries reported data on the occurrence of fluoroquinolone resistance in *Campylobacter coli* and 15 reported data on the occurrence of resistance in *C. jejuni* (only countries reporting more than 25 isolates were included in the analysis). The occurrence of fluoroquinolone resistance varied between countries and was in general higher than in *E. coli* and *Salmonella*. For *C. coli*, occurrence of resistance varied from 42.0 % to 86.4 %. The highest occurrences were observed in Spain (86.4 %), Lithuania (84.0 %) and Slovenia (74.5 %) and the lowest occurrence of fluoroquinolone resistance (42.0 %) was observed in the United Kingdom. In *C. jejuni*, occurrence of resistance varied from 30.7 % to 91.9 %. The highest occurrences were observed in Lithuania (91.9 %), Spain (84.1 %) and Hungary (79.4 %) and the lowest occurrence of fluoroquinolone resistance (30.7 %) was observed in Slovakia.

When comparing data on consumption with occurrence of fluoroquinolone resistance, a positive correlation was seen for *C. coli* for fluoroquinolone consumption in the community but no other correlations with resistance were observed for *Campylobacter* spp. The data should be interpreted with caution as the majority of countries reported limited data. *Campylobacter* spp. are not a part of the normal human intestinal flora and are in general not transmitted between humans. Undercooked chicken and contaminated ready-to-eat food are the most common sources of campylobacteriosis in the EU. It is therefore assumed that occurrence of resistance in *Campylobacter* spp. from humans is influenced by resistance in *Campylobacter* spp. from food-producing animals. Other explanations could be that spread of certain clones has an influence, the occurrence of resistance has reached such a high level that it does not follow the consumption pattern or that *Campylobacter* spp. causing infection are from imported meat. As cases with a known history of travel were not included in the FWD-Net data used for the analysis, travel outside the reporting country will have little influence on the result.

8.3. Consumption of macrolides in humans and occurrence of erythromycin resistance in *Campylobacter coli* and *Campylobacter jejuni* from humans

Macrolides are used for the treatment of infections caused by *Campylobacter* spp. (gastroenteritis) and Gram-positive bacteria, including respiratory infections suspected to be caused by *Mycoplasma pneumoniae*. Macrolides are considered by WHO (2011) as CIAs with the highest priority for human medicine. Macrolides are used both in hospitals and in the community.

Data on occurrence of erythromycin resistance in *C. coli* and *C. jejuni* from human cases were reported from 14 and 16 countries in 2012, respectively (only countries reporting more than 25 isolates were included in the analysis).

In order to consider any correlation between the macrolide consumption and the occurrence of resistance to erythromycin in *Campylobacter* spp., the consumption of macrolides in the community, in hospitals and in total was plotted against the occurrence of erythromycin resistance in *C. jejuni* and *C. coli*. For *C. coli*, the number of countries reporting data on both resistance and consumption varied from six to nine. Positive correlations between resistance in *C. coli* and consumption in hospitals and in total were observed. Owing to the small number of countries included in the analysis, the results should be interpreted with caution. For *C. jejuni*, no correlations between resistance and consumption were observed. *Campylobacter* spp. are zoonotic bacteria originating from food-producing animals and antimicrobial consumption in the animals is expected to affect the resistance level. Furthermore, selection of erythromycin resistance in *Campylobacter* spp. may be due to consumption of macrolide antimicrobials in the human sector.

8.4. Tetracycline consumption in humans and occurrence of tetracycline resistance in *Salmonella* spp. and *Campylobacter* spp. from humans

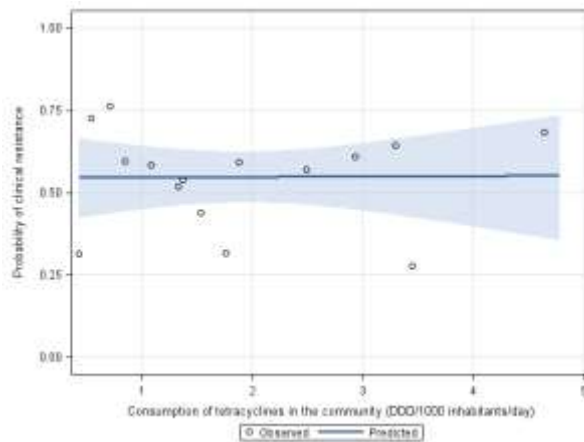
Tetracyclines are broad-spectrum antimicrobial agents used for treatment of infections caused by both Gram-negative and Gram-positive bacteria, including long-term treatment for acne caused by *Propionibacterium acnes*.

Data on the occurrence of tetracycline resistance in *Salmonella* spp., *S. Typhimurium* and *S. Enteritidis* from human cases were reported by 16 or 17 countries in 2012 (only countries reporting more than 25 isolates were included in the analysis).

In 2012, the number of isolates obtained varied between countries, from 72 to 6 168 for *Salmonella* spp., from 27 to 1 654 for *S. Typhimurium* and from 25 to 1 624 for *S. Enteritidis*.

In order to investigate a possible association between the consumption of tetracyclines and the occurrence of tetracycline resistance in *Salmonella* spp., the consumption of tetracyclines in the community, in hospitals and in total was plotted against the occurrence of tetracycline resistance in *Salmonella* spp. and *S. Typhimurium*. In all cases no correlations were observed. For *S. Enteritidis* sufficient data on tetracycline resistance and consumption in the community, in hospitals and in total were reported from 15, 10 and 11 countries, respectively. In general, it can be concluded that the occurrence of resistance to tetracyclines in humans can be high despite a low consumption, and the highest occurrence of tetracycline resistance is observed in *S. Typhimurium*, followed by *Salmonella* spp. and *S. Enteritidis* (see examples **Figure 14**). It is therefore likely that the high occurrence of resistance in *Salmonella* spp. is due to consumption of tetracyclines elsewhere, e.g. in food-producing animals, or to co-selection of multidrug-resistant (MDR) strains, although the spread of certain clones may be important, as may be imported meat and processed meat products, which may be contaminated with tetracycline-resistant salmonella organisms. Other sources of infection, for example infections caused by reptiles, should also be taken into consideration. For example an extensive reptile-associated outbreak of tetracycline-resistant *S. Typhimurium* in at least one EU country in the period under analysis was shown to have originated in a country outside the EU/EEA area and to have its reservoir in infant mice imported into the EU from the USA and fed to reptiles (corn snakes kept as pets) (Harker et al., 2011).

Figure 14. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of tetracyclines in the community in humans and the probability of clinical resistance to tetracycline in *S. Typhimurium* from human infections for the year 2012—dots represent the countries involved in the analysis



Countries included: AT, DK, ES, FR, HU, IE, IT, LT, LU, NL, NO, RO, SI, SK, UK
 p-value = 0.96; OR = 1.006; 95% PL CI: [0.775, 1.308] – not significant

Data on the occurrence of tetracycline resistance in *C. coli* and *C. jejuni* from cases of human infections were reported from 10 countries in 2012 (only countries reporting more than 25 isolates were included in the analysis).

In 2012, the number of isolates obtained varied between countries from 42 to 102 for *C. coli* and from 56 to 1 241 for *C. jejuni*. Occurrence of resistance to tetracyclines varied in *C. coli* from 30.9 % to 79.5 % and in *C. jejuni* from 11.6 % to 72.0 %.

In order to consider correlation between the consumption of tetracyclines and the occurrence of resistance to tetracyclines in *Campylobacter* spp., the consumption of tetracyclines in the community, in hospitals and in total was plotted against the occurrence of tetracycline resistance in *C. coli* and *C. jejuni*. No correlation between resistance to tetracyclines and consumption of tetracyclines in the community, in hospitals or in total was observed. As the majority of countries reported limited consumption data or did not report data on tetracycline resistance in *Campylobacter* spp., it is appropriate to comment on *C. jejuni* only for the nine countries that reported data on resistance and consumption in the community. In these cases no correlation was observed.

Textbox 2.

Carbapenem consumption and carbapenem-resistant *Klebsiella pneumoniae* and *E. coli* from humans and a view on carbapenemase-producing Enterobacteriaceae from food-producing animals in Europe

Carbapenems are used for treatment of infections caused by MDR Gram-negative bacteria, including the treatment of blood and urinary tract infections caused by MDR *E. coli*. Carbapenems are almost exclusively used in hospitals. The proportion of total hospital antimicrobial consumption accounted for by carbapenems varies between countries, from 0.61 to 9.84 % in 2012, with very small amounts also used in the community (0 to 0.27 % of the total community consumption 0 % to 0.59 % in 2012). Susceptibility testing has been performed in *K. pneumoniae* and *E. coli* by use of either meropenem or imipenem, and results interpreted by use of clinical breakpoints. The use of different antimicrobial agents or interpretive criteria may influence the result.

*Consumption of carbapenems and occurrence of carbapenem-resistant *K. pneumoniae**

In 2012, all 27 EU and two EEA countries and Croatia reported data on consumption of carbapenems (seven countries reported only data on community consumption: Austria, the Czech Republic, Germany, Hungary, Poland, Spain and the United Kingdom). All 27 EU countries and Norway and Iceland reported data on occurrence of carbapenem-resistant *K. pneumoniae*. Overall, 16 282 *K. pneumoniae* isolates from BSIs were reported, of which 1 235 were resistant to carbapenem. For countries reporting data on consumption both in the community and in hospitals, the consumption varied from 0.013 to 0.16 DDDs per 1 000 inhabitants and per day. The highest percentages of carbapenem-resistant *K. pneumoniae* were reported from Greece (60.5 %), Italy (28.8 %), Romania (13.7 %) and Cyprus (9.2 %). No carbapenem-resistant *K. pneumoniae* was observed in eight of the reporting countries.

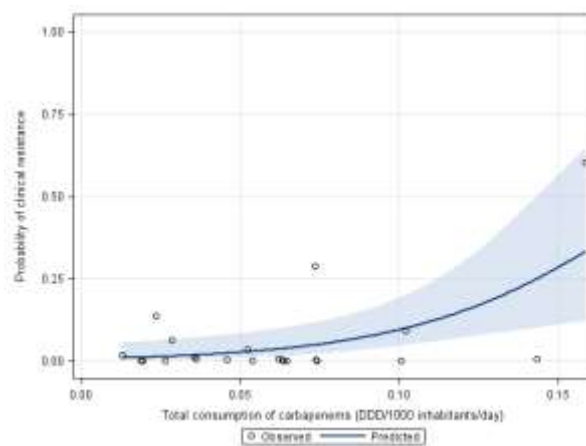
Figure 15 shows data from countries reporting consumption on carbapenems and data on carbapenem-resistant *K. pneumoniae* in 2012. Greece had the highest occurrence of carbapenem-resistant *K. pneumoniae* and was also among the countries with the highest consumption; Cyprus and Italy had moderate percentages of carbapenem-resistant *K. pneumoniae* and consumption. Portugal had a high consumption compared with the other countries, but the occurrence of carbapenem-resistant *K. pneumoniae* was still at a low level. Several countries with a moderate level of consumption have observed emergence of resistance. Austria, Hungary, Poland, Spain and the United Kingdom, which reported a low level of consumption, since 2011 have seen the emergence of carbapenem-resistant *K. pneumoniae*, but these countries did not report consumption in hospitals. Carbapenems are among CIAs as defined by WHO that should be reserved for treatment of severe infections in humans. Therefore, consumption is expected to be in hospitals and consumption in the above-mentioned countries reporting only community consumption data is probably underestimated. This may explain the occurrence of carbapenem-resistant *K. pneumoniae* in these countries. Another possibility is that the occurrence of carbapenem-resistant *K. pneumoniae* observed in these EU countries was associated with travel to countries outside the EU, where such strains are more common, rather than with the consumption of carbapenems in EU countries themselves. Indeed, in several EU countries, the emergence of carbapenem-resistant bacteria has been related to travel outside the country (Walsh, 2010).

Several countries did not observe any carbapenem-resistant *K. pneumoniae* and the consumption of carbapenems was low. Nevertheless a statistically significant increase in carbapenem-resistant *K. pneumoniae* with increase in the total consumption was observed for 2011 and 2012 (**Figure 15**). Even though this correlation was based on two-thirds to three-quarters of the countries, the possibility

of consumption in some countries selecting for carbapenem-resistant *K. pneumoniae* cannot be excluded.

Large differences in the reported percentage of carbapenem-resistant *K. pneumoniae* exist, possibly because other factors, such as infection control practices and management, influence the clonal spread of carbapenemase-producing *K. pneumoniae* within hospitals. Carbapenem-resistant *K. pneumoniae* has now been reported through EARS-Net in almost three-quarters of the countries, and carbapenem-resistant *E. coli* has been reported in more than half of the countries. Carbapenem-resistant *E. coli* was observed in all countries in which carbapenem-resistant *K. pneumoniae* had been detected. The occurrence of carbapenem-resistant *E. coli* was less than 1 % in both years, except in Bulgaria and Greece in 2012, where the prevalence of carbapenem-resistant *E. coli* was 2.6 % and 1.4 %, respectively. In *Salmonella* spp., carbapenemase producers were not reported.

Figure 15. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national total (community and in hospitals) consumption of carbapenems for humans and the probability of clinical resistance to carbapenems in *K. pneumoniae* from human infections for the year 2012—dots represent the countries involved in the analysis



Countries included: BE, BG, CY, DK, EE, EL, FI, FR, HR, IE, IT, LT, LU, LV, MT, NL, NO, PT, RO, SE, SI, SK
p-value = 0.002; OR_{0.1-unit increment} = 14.229; 95 % PL CI: [2.606, 93.477]

Surveillance and detection of carbapenemase-producing Enterobacteriaceae in food-producing animals

Carbapenems are not approved for use in animals and *K. pneumoniae* is not considered a zoonotic bacterium. The prevalence of carbapenemase-producing bacteria in food-producing animals is not known, but recently carbapenem-resistant *E. coli* has been detected in livestock pigs and carbapenem-resistant *Salmonella* has been detected in both livestock pigs and poultry (EFSA, 2013; Fischer et al., 2012a; Fischer et al., 2012b) although the source of such organisms is not known. Carbapenemase-producing *Acinetobacter* spp. have also been reported from cattle in France and from horses in Belgium (Poirel, 2012; Smet et al., 2012). The occurrence and possible spread of carbapenemase-producing bacteria in food-producing animals is thus considered important for the assessment of potential zoonotic risks (EFSA, 2013) and has therefore been included in the latest report of harmonised monitoring of antimicrobial resistance by EFSA, where it is recommended that phenotypic testing for carbapenemase-producing in *Salmonella* spp. and *E. coli* is performed consistently (EFSA, 2012b). Based on this recommendation, monitoring of carbapenemase-producing bacteria in food-producing animals and meat thereof is part of the European monitoring programme for foodborne antimicrobial resistance and includes, in addition to mandatory susceptibility testing to carbapenems, a selective isolation procedure on voluntary basis (2013/652/EU (Official Journal of the European Union, 2013)).

9. Antimicrobial consumption in food-producing animals and resistance in bacteria from humans

The majority of *Salmonella* spp. and *Campylobacter* spp. causing human infections in EU MSs are zoonotic in origin and most likely originate in food production animals. The most common salmonella serovars are Enteritidis and Typhimurium. *S. Enteritidis* is often found to be resistant to fluoroquinolones, while *S. Typhimurium* is often MDR. Other MDR serovars such as *S. Infantis* and *S. Virchow* have also been implicated in both sporadic cases and outbreaks, and *S. Kentucky* is increasing in importance in some MSs (Westrell et al., 2014). Other sources of contamination with antimicrobial-resistant salmonella strains (e.g. reptiles (Harker et al., 2011)) may also be a factor in some countries, and should also be taken into consideration (see section 8.4).

The common *Campylobacter* species causing infections are *C. jejuni* and *C. coli*, with *C. jejuni* by far the most predominant, while *C. coli* is normally more resistant to antimicrobials.

The relationship and interaction between those populations of *E. coli* in humans (*E. coli* causing BSIs) and in animals (commensal *E. coli*), for which susceptibility data are available and which have been analysed in this report, is not completely understood. The degree of interaction or common linkage between these populations of *E. coli* is clearly important in assessing if any observed associations between antimicrobial consumption in food-producing animals and resistance in humans are also supported by epidemiological observations, which might include the potential for spread of mobile genetic elements, such as plasmids. The resistance patterns observed in certain zoonotic or pathogenic bacteria from humans may therefore reflect use of antimicrobials in food animals, although comprehensive assessment requires consideration of additional information. Some prevalent strains of *E. coli* causing BSIs in humans are not linked to *E. coli* present in food-producing animals.

For this investigation, data on antimicrobial consumption in food-producing animals in combination with data on the occurrence of resistance in *E. coli*, *Salmonella* spp., particularly *S. Enteritidis* and *S. Typhimurium*, and *Campylobacter* spp. from humans have been analysed to investigate possible correlations between such consumption and resistance. This comparison is not straightforward as some of the bacterial species may predominantly originate from one particular type of animal (e.g. *S. Enteritidis* from poultry) whereas other serovars (e.g. *S. Typhimurium*) have a more ubiquitous host range. Moreover, only data on the total consumption in food-producing animal are available and analysis cannot be made at the level of animal species.

As zoonotic and other bacteria causing infections in humans may be transmitted to humans through various routes, it is probable that the consumption of antimicrobials in food-producing animals also affects resistance in humans. The proportion of bacteria resistant to a certain antimicrobial may also be influenced by resistance to other antimicrobials (co-resistance). Even non-antimicrobial substances, such as metals and disinfectants, may influence co-selection. Bacteria exhibiting resistance to more than one antimicrobial may select for certain clones. Moreover, travel, trade and imports of meat and other food items are factors which may influence the analyses, depending on the antimicrobial-bacterium combinations studied.

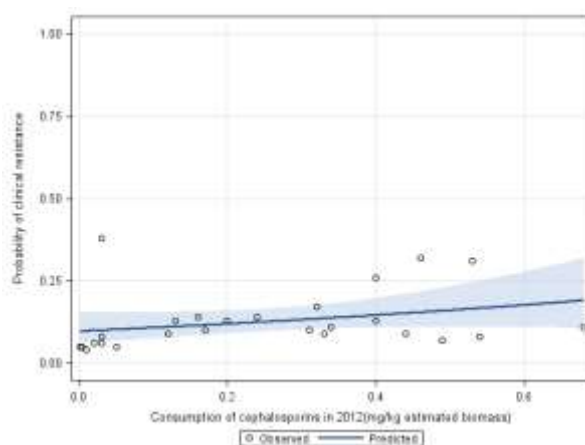
9.1. Comparison between consumption of 3rd- and 4th-generation cephalosporins in food-producing animals and resistance in bacteria from humans

In order to investigate a possible relationship between the consumption of 3rd- and 4th-generation cephalosporins in food-producing animals with data on resistance in bacteria causing infections in humans, the occurrence of resistance in *E. coli* and *Salmonella* spp. isolated from humans was

compared with consumption of 3rd- and 4th-generation cephalosporins in food-producing animals (expressed in milligrams per PCU) in 2011 and 2012 (**Figure 16**).

Figure 16 shows cephalosporin resistance in *E. coli* from human BSIs plotted against the total consumption of 3rd- and 4th-generation cephalosporins in food-producing animals in 2011 and 2012. Despite accounting for overdispersion in data and although most countries reported data, no linear association was found. As positive correlations for total consumption by humans, consumption in the community and consumption in hospitals were found (**Figure 12**), this suggests that resistance observed in *E. coli* in humans is likely to have been primarily affected by consumption in human medicine, whereas the consumption of 3rd- and 4th-generation cephalosporins used in animals seems to exhibit a smaller effect.

Figure 16. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of 3rd- and 4th-generation cephalosporins in food-producing animals and the probability of clinical resistance to 3rd- and 4th-generation cephalosporin in *E. coli* isolates from human BSIs for the year 2012—dots represent the countries involved in the analysis



Countries included: AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, SE, SI, SK, UK
OR = 1.122; 95 % PL CI: [0.962, 1.308] - not significant

In general, the occurrence of resistance to 3rd- and 4th-generation cephalosporins in isolates of *Salmonella* spp., *S. Typhimurium* and *S. Enteritidis* from humans was low (see section 8.1). A significant positive correlation between cephalosporin resistance in *Salmonella* spp. and *S. Enteritidis* from humans and consumption of 3rd- and 4th-generation cephalosporins in food-producing animals was observed in 2011 and 2012 (data not shown); the positive correlation observed in *S. Typhimurium* was not statistically significant.

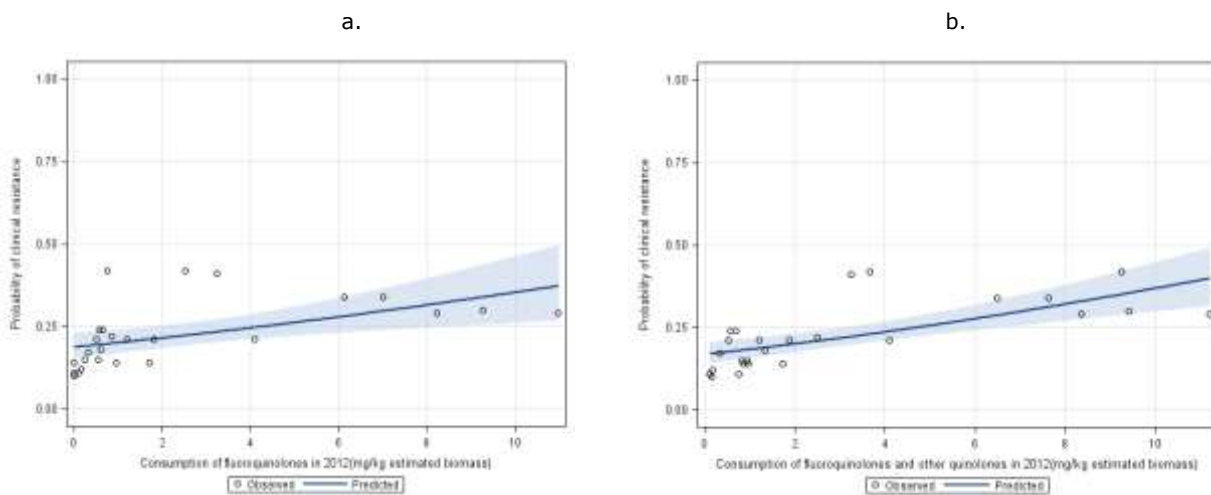
Although *S. Typhimurium* and *S. Enteritidis* are, for the most part, food-borne zoonotic bacteria in EU countries, sources other than food derived from domestically produced animals, such as traded or imported food, may be the source of isolates of *Salmonella* spp. responsible for food-borne infections in humans. It is noteworthy that data on *S. Enteritidis* and *S. Typhimurium* may be limited and thereby give rise to some of the outlier observations. Other factors also exist, such as the spread of certain clones regardless of antimicrobial consumption.

9.2. Comparison between consumption of fluoroquinolones in food-producing animals and resistance in bacteria from humans

In order to investigate possible relationships between the consumption of fluoroquinolones, or other quinolones, in food-producing animals and fluoroquinolone resistance in bacteria causing infection in humans, the occurrence of resistance in *E. coli*, *Salmonella* spp. and *Campylobacter* spp. from humans was compared with the total consumption in food-producing animals of fluoroquinolones and quinolones (milligrams per PCU) in 2011 and 2012, at the country level.

A positive association between fluoroquinolone resistance in *E. coli* from humans and the total consumption in animals (fluoroquinolones alone and fluoroquinolones plus other quinolones) was observed (**Figure 17**). This result should be interpreted with caution as only a fraction of *E. coli* from human BSIs may originate from domestically produced animals. Other sources could be the intake of meat produced outside the reporting country, travel or transmission of *E. coli* between humans. In the previous chapter a correlation between resistance in human bacteria and human consumption of antimicrobials in the community and in total was observed (see Chapter 8.2) which could explain the presence of outliers, i.e. countries with a high occurrence of resistance and a low consumption of quinolones in food-producing animals and or a high consumption of quinolones in food-producing animals and low occurrence of resistance.

Figure 17. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of fluoroquinolones (a) or fluoroquinolones plus other quinolones (b) in food-producing animals and the probability of clinical resistance to fluoroquinolones in *E. coli* isolates from human BSIs for the year 2012—dots represent the countries involved in the analysis



Countries included: AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, SE, SI, SK, UK
p-value < 0.05 OR = 1.090; 95 % PL CI: [1.030, 1.153]

Countries included: AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, SE, SI, SK, UK
p-value < 0.001; OR = 1.112; 95 % PL CI: [1.063, 1.162]

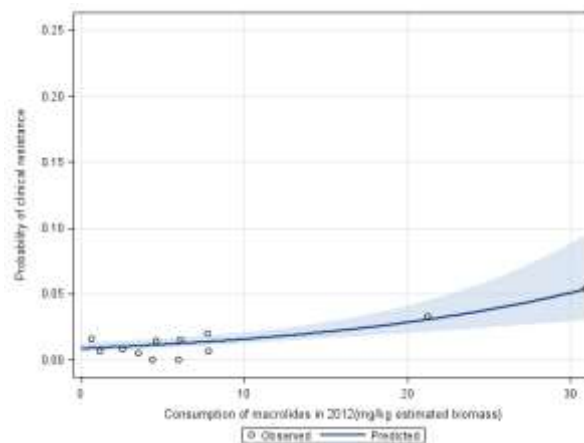
No associations were observed between the consumption of fluoroquinolones in food-producing animals and the occurrence of resistance in *Salmonella* spp. and *Campylobacter* spp. from cases of human infection (data not shown).

No associations were observed between the consumption of 3rd- and 4th-generation cephalosporins in food-producing animals and the occurrence of resistance to this sub-class in selected bacteria from humans (**Figure 34**)

9.3. Comparison between consumption of macrolides in food-producing animals and resistance in bacteria from humans

Possible relationships between occurrence of resistance in *C. jejuni* isolates from humans and total consumption of macrolides in animals in 2011 and 2012 were assessed at the country level and a significant positive association was discerned (**Figure 18**). Considering *C. coli*, data available limited the number of countries to be included in the analysis and final models either did not fit or were not interpretable.

Figure 18. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of macrolides in food-producing animals and the probability of clinical resistance to erythromycin in *C. jejuni* isolates from human infections for the year 2012—dots represent the countries involved in the analysis



Countries included: AT, EE, ES, FR, HU, IT, LT, LU, NL, SI, SK, UK
p-value < 0.05; OR = 1.062; 95 % PL CI: [1.033, 1.090]

9.4. Comparison between consumption of tetracyclines in food-producing animals and resistance in bacteria from humans

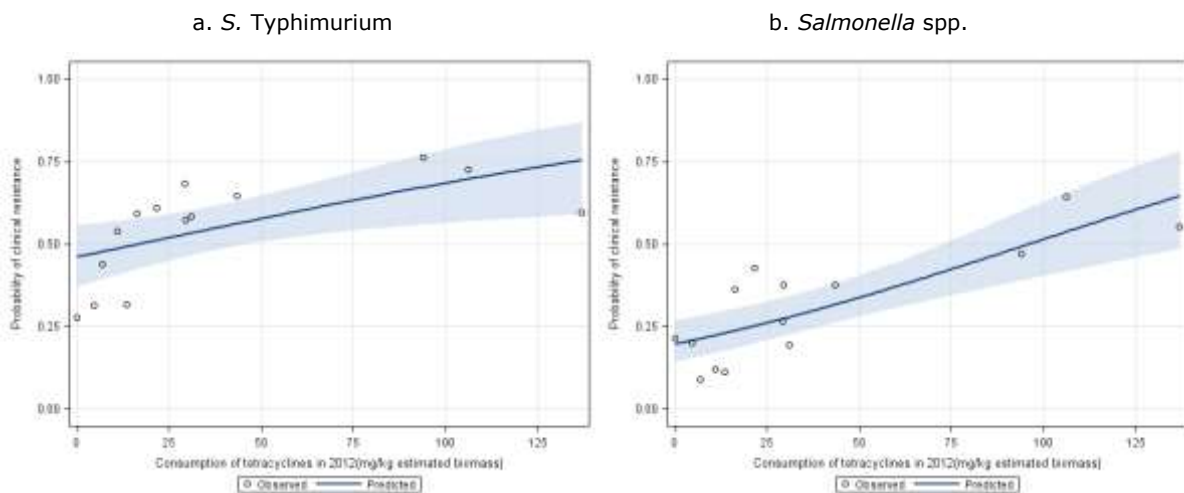
Data on resistance to tetracyclines were obtained for *Salmonella* spp., *S. Typhimurium*, *S. Enteritidis*, *C. coli* and *C. jejuni* from human infections and compared with the consumption of tetracyclines in animals in 2011 and 2012.

For *Salmonella* spp., around one-third of the countries reported data on both resistance in human cases of salmonellosis and tetracycline consumption in animals in 2011 and 2012 (**Figure 19**). Typically, the occurrence of tetracycline resistance in *S. Typhimurium* was high compared with that recorded in *S. Enteritidis*. Significant positive associations were observed in *Salmonella* spp. and *S. Typhimurium* between consumption of tetracyclines in animals and resistance in isolates from human infections in both years. In contrast, in *S. Enteritidis* from human cases, no significant correlations were observed. Considering these results, it would appear that the consumption of

tetracyclines in food-producing animals in the reporting countries, and particularly in pigs and cattle, may have selected for tetracycline resistance in isolates of *S. Typhimurium* involved in human infections, although the potential impact of other sources (e.g. reptiles) should also be taken into consideration. Animal consumption data were not available at animal species level, but *S. Typhimurium* is frequently observed in pigs and pork and tetracyclines are frequently used in pig production, and also used in calves in some countries. In contrast, tetracyclines are probably used to a lesser extent in poultry, the main reservoir of strains of *S. Enteritidis* causing infections in the reporting countries.

For *Campylobacter* spp., data available were even more limited than for *Salmonella* spp. Eight or nine countries reported sufficient data for *C. jejuni* and four or five countries for *C. coli*. Nevertheless, even though data were limited, significant positive associations between data on consumption in food-producing animals and resistance in *C. jejuni* (Figure 20) (2011 and 2012 data) and *C. coli* (only for 2011, data not shown) from human cases of infection were observed.

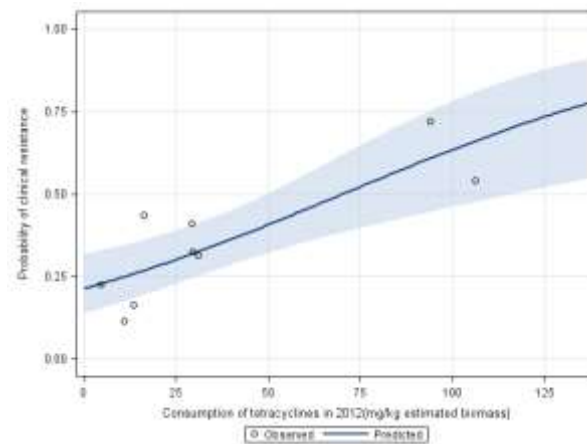
Figure 19. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of tetracyclines in food-producing animals and the probability of clinical resistance to tetracycline in (a) *S. Typhimurium* isolates from human infections and (b) *Salmonella* spp. isolates from human infections for the year 2012—dots represent the countries involved in the analysis



Countries included: AT, DK, ES, FR, HU, IE, IT, LT, LU, NL, NO, SI, SK, UK
 p-value < 0.05 OR = 1.009; 95 % PL CI: [1.002, 1.017]

Countries included: AT, EE, ES, FR, HU, IE, IT, LT, LU, NL, NO, SI, SK, UK
 p-value < 0.001; OR = 1.015; 95 % PL CI: [1.008, 1.022]

Figure 20. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of tetracyclines in food-producing animals and the probability of clinical resistance to tetracycline in *C. jejuni* isolates from human infections for the year 2012—dots represent the countries involved in the analysis



Countries included: AT, EE, ES, IT, LU, NL, SI, SK, UK

p-value < 0.001; OR = 1.019; 95 % PL CI: [1.009, 1.030]

10. Comparison between the occurrence of resistance in bacteria originating from humans and from food-producing animals

In order for a bacterium with an animal reservoir to cause infection in humans via ingestion of meat, the bacterium needs to survive the meat production chain and also to be infectious to humans. Some *Salmonella* serovars are present in animals at high levels but rarely cause infections in humans, whereas others frequently cause infections in humans. *S. Typhimurium* and *S. Enteritidis* are commonly isolated from cases of gastroenteritis and are therefore relevant when considering resistance in bacterial pathogens causing human disease that may originate from food-producing animals. In the case of *Campylobacter* spp., both *C. coli* and *C. jejuni* are zoonotic, but infections caused by *C. jejuni* are most common in humans. The animal species with the largest proportion of *C. coli* is pigs, although the occurrence of *C. coli* is normally markedly reduced post harvest. In the case of *E. coli*, some types which infect humans, particularly pathogenic VTEC types, such as *E. coli* O157:H7, have their primary reservoir in food-producing animals. Moreover, several studies recognise that a proportion of *E. coli* involved in human infections may originate from food-producing animals, including resistant isolates (Lazarus et al., 2014; Manges and Johnson, 2012). The proportion of *E. coli* infections in humans, other than VTEC, with a zoonotic origin is unknown, and further studies are needed to quantify the transfer of such organisms from food-producing animals to humans. Most analyses on drug-resistant *E. coli* from cases of infection in humans have been performed on isolates from BSIs. Such isolates probably possess a variety of virulence genes and virulence mechanisms not found in commensal *E. coli* from food-producing animals.

When comparing resistance data from different sources, it is important that data are obtained using harmonised methods. Importantly, the interpretation criteria used for antimicrobial susceptibility testing should ideally be either clinical breakpoints or ECOFFs for all data included. In the present

comparison of fluoroquinolone resistance, this was not always possible. Therefore, human data interpreted by use of clinical breakpoints were included and compared with data from animals interpreted by use of ECOFFs. Nevertheless, analysis can still be made regarding possible associations between resistance in humans and resistance in animals. Bias in these data may be caused by use of different test substances as data on animal isolates are obtained by use of ciprofloxacin and human data are obtained by use of other fluoroquinolone compounds.

For the comparison of resistance in humans and animals, data available were limited. For this study, it was decided to include data from humans if 25 or more isolates were reported and from animals if 10 or more isolates were included. It was also decided to perform an analysis in cases where five or more countries reported data from both food-producing animals and humans.

In general, the number of countries reporting data of the selected species from both human infection and from animals is limited and constitutes a limitation in the integrated analysis.

10.1. Comparison between occurrence of cephalosporin resistance in bacteria originating from food-producing animals and the occurrence of resistance in humans

Data on the occurrence of cephalosporin-resistant *E. coli* from BSIs were analysed and compared with the occurrence of cephalosporin resistance in *E. coli* from cattle (six countries), pigs (six countries) and poultry (nine countries). A significant positive correlation (Spearman's rank correlation coefficient) was discerned when compared with resistance in poultry (p-value = 0.0261) and resistance in the three animal species considered together (p-value = 0.0153) (summary indicator of resistance), while no significant association was observed for cattle and pigs.

For *S. Typhimurium*, only three or four countries reported data from both cases of human infection and at least one animal species; these data were therefore considered too limited and no analyses were performed. For *S. Enteritidis*, seven countries reported data on resistance in isolates from cases of human infection and resistance in isolates from poultry. As resistance to 3rd- and 4th-generation cephalosporins was not observed in *S. Enteritidis*, no analysis was performed. It is difficult to draw conclusions based on the few countries reporting data on *S. Enteritidis*.

10.2. Comparison between occurrence of fluoroquinolone resistance in bacteria originating from food-producing animals and the occurrence of fluoroquinolone resistance in humans

The number of countries reporting data on both fluoroquinolone resistance in humans and food-producing animals was very limited. For *E. coli*, a comparison of resistance in humans and resistance in cattle, pigs, poultry and the summary indicator of resistance considering an average between animal species was performed and a significant correlation (Spearman's rank correlation coefficient) was observed when compared with resistance in pigs (p-value = 0.0016), poultry (p-value = 0.0199) and the average of all animal species (p-value = 0.0065).

For *Salmonella* spp., very limited data were also reported. For *S. Typhimurium*, only three or four countries reported data = from cases of human infection and at least one of the animal species included in the analysis. For *S. Enteritidis*, eight countries reported data from human infection and poultry but, because of very low prevalence of resistance in food-producing animals in *S. Enteritidis*, available data did not permit meaningful analyses.

For *C. coli*, only three and four countries reported data from human infections and data from pigs and poultry, respectively. Therefore, no analysis could be performed. For *C. jejuni*, five countries reported data on resistance from both human infections and in poultry.

10.3. Data available from humans and food-producing animals for tetracycline and macrolide resistance

Very limited data were reported on macrolide resistance in both humans and food-producing animals (between two and five countries in each category). Therefore, no analysis could be performed. For tetracycline resistance, very limited data were reported. In *E. coli* from blood infections, resistance to tetracyclines was not tested. For *S. Typhimurium*, only two or three countries reported data on tetracycline resistance in humans and tetracycline resistance in cattle, pigs or poultry. The same was observed for *C. jejuni* and *C. coli*. Considering *S. Enteritidis* from human infections and poultry six countries reported data. Therefore, no analysis was performed.

11. Discussion

This report is the product of the first concerted effort by ECDC, EFSA and EMA to investigate possible relationships, at the EU/EEA level and in Switzerland, between the consumption of the antimicrobial agents and occurrence of antimicrobial resistance in the human and food-producing animal domain. It constitutes an attempt to provide an integrated ecological study between available data on consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals, provided by the EU-wide surveillance/monitoring programmes. The report investigated the occurrence of resistance in a selection of pathogenic and non-pathogenic bacteria in 2011 and 2012 in the human and the animal domain in relation to the consumption of antimicrobials in these domains, and also using data generated to investigate possible links between the consumption of antimicrobials in food-producing animals domain and the occurrence of resistance in humans.

The report also acknowledges the complexity of addressing potential relationships between consumption and resistance in both domains, taking into account factors influencing emergence and spread of resistance, antimicrobial consumption and consumption patterns, pathways and dissemination of resistance, measuring and monitoring resistance, measuring the consumption of antimicrobials and regulatory activities, both voluntary and legislative, in the relevant sectors. How antimicrobials are used in both sectors is also reviewed in an annex to the report (Annex B), highlighting both similarities and differences in their mode of use, particularly in relation to preventive medication in the animal domain, which is not common in the human domain.

11.1. Systems for surveillance antimicrobial consumption

In the human domain, consumption of antimicrobials is monitored through ESAC-Net. Most countries report data on consumption, one-third of the countries report reimbursement data and a few report both sales and reimbursement data. For animals, consumption data are collected through the ESVAC project, which collects annually harmonised data on consumption of veterinary medical products (VMPs) at package level from most of the EU/EEA countries; these data are not broken down by animal species. Data are collected from a variety of national sources and presented by antimicrobial class or sub-class. In order to standardise the consumption data for the animal population that can be subjected to treatment with antimicrobial agents, a PCU is used as a proxy for the size of the whole animal population at risk of being treated. There is no indicator for the normalisation of consumption data for animals that is directly comparable to the indicators used for consumption by humans.

11.2. Systems for monitoring of antimicrobial resistance

In surveillance of resistance, there are considerable differences between the human and animal domains. In the human domain, collection of data is carried out through FWD-Net, and through the EARS-Net. FWD-Net collects resistance data on 19 pathogens, predominantly those transmitted through food and water, e.g. *Campylobacter* spp., *Salmonella* spp. and VTEC/STEC. Participating countries report their data to TESSy at ECDC. The resistance data on *Campylobacter* spp. and *Salmonella* spp. from humans are published in the joint EFSA/ECDC EU Summary Report on antimicrobial resistance in zoonotic and indicator bacteria obtained from humans, food-producing animals and food. In contrast, EARS-Net is based on a network of representatives from the MSs collecting routine clinical AST data from national resistance surveillance initiatives. Data are reported for eight pathogens which are considered of public health importance (e.g. *E. coli*, *K. pneumoniae*, *S. aureus*). These data, which originate from approximately 900 laboratories serving more than 1 300 hospitals in Europe, are annually reported to ECDC. All EU MSs provide data, and there are considerable differences in the numbers of isolates reported by individual countries. For some bacteria, the interpretive criteria used to assess AST results may differ slightly between the reporting countries. The obligation for the countries to report on antimicrobial resistance in humans is laid down in Commission Decision No 2119/98/EC (Official Journal of the European Communities, 1998)³⁰. The extent of the reporting is not specified and the extensive acquisition of data by the surveillance networks is therefore largely based on voluntary reporting.

In the animal domain, countries are obliged to monitor and report antimicrobial resistance in zoonotic *Salmonella* spp. and *Campylobacter* spp. isolates from healthy individuals of the main food-producing animal species and meat thereof. In addition, there are detailed requirements on the harmonised monitoring and reporting of antimicrobial resistance of *Salmonella* spp. isolates from various poultry populations and pigs, sampled under the corresponding national control and surveillance programmes of *Salmonella* spp. on a statistically calculated basis. Nevertheless, reported data on isolates from foods were considered insufficient in this framework for meaningful analyses. Thus, food-related data are very limited and as yet conclusions cannot be drawn with confidence from the information submitted by MSs.

Antimicrobial substances included in the harmonised monitoring consist of a concise set of antimicrobials selected according to their relevance to human therapeutic use. In both sectors, the levels of resistance are, in theory, measured using ECOFFs according to EUCAST guidelines, but such measuring is more rigidly applied in the animal sector, whereas in the human sector approximately 60 % of the participating laboratories adhere to EUCAST guidelines. For most antimicrobials surveyed, the ECOFFs approximate to clinical levels but for some, particularly for *Salmonella* spp., this is not the case for the monitoring of resistance to fluoroquinolones, where the ECOFF is considerably below what is regarded as a therapeutic level. For this reason, some human laboratories report occurrence of resistance interpreted with clinically relevant criteria (either EUCAST or CLSI clinical breakpoints), whereas others report occurrence interpreted with microbiologically relevant ECOFF criteria. Reporting to EFSA of resistance in animal isolates is almost universally interpreted with ECOFFs. These discrepancies make correlation studies difficult, and results, although indicative of correlations in some instances, have to be interpreted with caution.

A further difference between the two domains is that the *E. coli* isolates from cases of human infection are, for the most part, disease-related isolates and as such may well have been exposed to antimicrobials following treatment of the patients from whom they have been isolated. In contrast, *E. coli* isolates from animals are indicator commensal organisms which, until recently, have been

³⁰ As of 22 October 2013, Decision No 2119/98/EC was replaced by decision No 1082/2013/EU on serious cross-border threats to health

collected on a voluntary basis from a limited number of MSs. Such isolates have most probably not been implicated in disease in their hosts, and therefore may not have been exposed to antimicrobials. Indicator commensal *E. coli* derived from humans from the community would most likely be a good indicator of the relative exposure to resistant bacteria through food consumption and the direct effect of antimicrobial consumption in humans.

11.3. Comparison of consumption of antimicrobials in humans and food-producing animals

In 15 of 26 countries, consumption of antimicrobials was lower or much lower in food-producing animals than in humans, in three countries consumption was similar in the two groups, and in eight countries consumption in food-producing animals was higher or much higher than in humans. The overall consumption of antimicrobials was lower for humans than for animals. This difference is explained by the influence on the average of a limited number of countries with large animal populations. Moreover, antimicrobial substances requiring relatively high dosing, such as tetracyclines, are mainly used in animals. Only a few quantitative comparisons of consumption of antimicrobials between the human and animal domains have been published previously (DANMAP, 2013; Moulin et al., 2008; Swedres-Svarm, 2013; Wierup et al., 1987). With the exception of Danmap (2013), an approach similar to the one in the present study was used. The unit of measurement, milligrams per kilogram estimated biomass, has certain limitations, and the results should be interpreted with caution. In countries such as Denmark, where data on consumption of antimicrobials for food-producing animals are available by species, the use of DDD per 1 000 individuals per day, for both the human domain and for a particular animal species, are possibly allowing for a better comparison. Future developments of ESVAC with collection of data by species and reporting these data by DDD for animals will make that possible.

The WHO has prioritised 3rd- and 4th-generation cephalosporins and fluoroquinolones, considering them to be among the critically important antimicrobials in human medicine. The consumption of 3rd- and 4th-generation cephalosporins is higher in the human domain than in the animal domain. As these antimicrobials are mainly used in hospitals (e.g. in intensive care units), it is important that their use in both sectors is limited to situations where other antimicrobials are not expected to be effective. For fluoroquinolones, there was more variation between countries in the quantity used in both domains, but in most countries reported consumption was higher in the human sector than for animals. The variation could be explained by differences in the general occurrence of resistance to other antimicrobials but could also be related to other factors, such as number of products on the market, price, availability of diagnostic services and prescribing habits. The Committee for Medicinal Products for Veterinary Use (CVMP) has recommended that, in veterinary medicine, 3rd- and 4th-generation cephalosporins and fluoroquinolones should be reserved for conditions where other antimicrobials are not expected to be effective, and some countries have introduced legislation to support that.

11.4. Consumption of antimicrobials in humans and resistance in bacteria from humans

A positive association was observed between the total consumption of 3rd- and 4th-generation cephalosporins in humans and the occurrence of cephalosporin resistance in *E. coli* from humans. An association was also observed when data were split into hospital and community consumption. Therefore, the analyses support the hypothesis of selection for 3rd- and 4th-generation cephalosporin resistance in *E. coli* from humans by consumption of this sub-class. Since country outliers with a relatively high occurrence of resistance despite a low consumption were observed, factors other than the national consumption in humans may be important.

For fluoroquinolones, strong associations between the total consumption in humans and the occurrence of fluoroquinolone resistance in *E. coli* from humans were observed. An association was also observed when analysing community consumption alone. As links were seen for both years studied, and because almost all countries reported data, it seems reasonable to conclude that the consumption of fluoroquinolones, especially in the community, promotes selection of fluoroquinolone resistance in *E. coli* in humans. Associations between fluoroquinolone consumption and fluoroquinolone resistance in *E. coli* have been described previously, and the correlation between fluoroquinolone consumption in the community and resistance in invasive *E. coli* is not unexpected.

When comparing data on consumption of fluoroquinolones with the occurrence of fluoroquinolone resistance in *Salmonella* spp., *S. Enteritidis* and *S. Typhimurium*, no correlation of consumption of this antimicrobial class with resistance was observed in isolates from humans, either when plotting resistance against the total consumption or when splitting consumption of fluoroquinolones into consumption in the community and consumption in the hospital sector. For *Campylobacter* spp., the only association observed was for the community consumption of fluoroquinolones and resistance to fluoroquinolones in *C. coli*. No other association was observed between any of the antimicrobials included in the analysis and the occurrence of the resistance in *Campylobacter* spp. in humans. Comparison of the occurrence of resistance in *Salmonella* spp. and *Campylobacter* spp. from humans and the consumption of fluoroquinolones in humans was, to a large extent, hampered by, for example, low numbers of human isolates.

11.5. Consumption of antimicrobials in food-producing animals and resistance in bacteria from food-producing animals

Overall, a positive association between consumption of the selected antimicrobial classes/sub-classes and occurrence of resistance in bacteria from food-producing animals was observed. The strongest associations between consumption and resistance were detected for the antimicrobials studied in relation to indicator *E. coli*. Positive associations were discerned, but these were generally less marked in *Salmonella* spp. and *Campylobacter* spp. than in indicator commensal *E. coli*.

These differences in the strength of association probably reflect both the degree to which each organism is representative of the entire bacterial population within the animal populations sampled and differences in the epidemiology of each organism (for example, clonal spread only partly related or unrelated to antimicrobial consumption in *Salmonella* spp., particularly *S. Typhimurium* and *S. Enteritidis*). For *Salmonella* spp. and *Campylobacter* spp., the prevalence of the bacteria has an impact on the accuracy with which levels of resistance are assessed. Where a particular part of an animal production sector is affected with *Salmonella* spp./*Campylobacter* spp., then, ideally, only consumption in that sector should be addressed in the analysis, but such surveillance data are not available.

11.6. Consumption of antimicrobials in food-producing animals and resistance in bacteria from humans

As part of the analyses for this report, the hypothesis that consumption of antimicrobials in food-producing animals may contribute to the occurrence of resistance in humans was addressed using available data on consumption of antimicrobials in food-producing animals and occurrence of resistance in humans. Comparisons in humans were also analysed as antimicrobial consumption in human medicine is presumably the most important driver of resistance in humans. Such analyses are mainly relevant for bacteria with a possible zoonotic aspect (*Salmonella* spp., *Campylobacter* spp. and *E. coli*).

The results show that the occurrence of resistance in *E. coli* causing BSIs in humans could be correlated with consumption of antimicrobials in food-producing animals and in humans. For use of

cephalosporins in humans (in hospitals and in total), a positive association between consumption and resistance was observed. A positive association between consumption in food-producing animals and resistance was also observed. Moreover, resistance in the isolates from humans correlated positively with resistance in isolates from some animal species and vice versa. For fluoroquinolones, similar positive correlations were observed except that resistance correlated with the consumption in the community and not with consumption in hospitals. These differences may be related to differences in the relative extent to which cephalosporins and fluoroquinolones are used in hospitals and in the community in different countries.

11.7. Limitations of the study

In order to compare consumption of antimicrobials in humans and food-producing animals, it was necessary to convert data for human medicine to milligrams per kilogram estimated biomass. There are many limitations with this measure, and they hamper the comparison. Notably, the overall numerator does not take the differences in dose of different antimicrobials into account. In some countries, data for human medicine do not cover hospital consumption or the whole population. Further, the denominator used for consumption of antimicrobials in human medicine may be an overestimate as data on human weights are uncertain, and as age "at risk" for treatment was not taken into account. Taken together, data on consumption of antimicrobials for human medicine, expressed as milligrams per kilogram estimated biomass, is likely to be an underestimate. A further limitation is that the denominator used for consumption of antimicrobials in animals is a sum of the mass of different animal species and does not account for differences in the relative composition of the national animal populations summed, although antimicrobial use may differ markedly between the various animal populations (i.e. production sectors) of a given animal species. When examining these data, it is important that all these limitations are kept in mind.

A further significant limitation is that consumption data for the different food-producing animal species are not available, which hampers more precise identification of correlations between consumption by animal species and resistance. Other sources of contamination with antimicrobial-resistant *Salmonella* spp. strains (e.g. companion animals or plant produce) may be a factor in some MSs, and should also be taken into consideration. Another related limitation is that consumption and resistance data are not available for all countries and also that there are differences in the reporting of resistance by different countries, although a number of countries and related available data have not been included in the analysis, as the "summary indicator" of resistance required resistance data on the three animal species addressed. By construction, this indicator is partly associated with the structure of animal production in the reporting countries, which could be different to food consumption by humans.

The lack of data on the occurrence of resistance in isolates from food of animal origin has also been highlighted. Besides transmission of antimicrobial resistance via the environment and contact with animals carrying resistant bacteria, transmission is also possible by foodstuffs, especially food of animal origin. To date, the precise attribution of the different transmission routes of the various foodborne pathogens to the total burden of disease in humans is not known because of shortage in data. The same goes for the attribution of different transmission routes and pathogens to food-borne antimicrobial resistance. Within the farm-to-fork concept, the relation between resistance in foodstuffs and humans could be unravelled by using sufficient and harmonised data on the prevalence of resistant bacteria in the different foodstuffs and the consumption patterns. Such data are scarce and reported by only a few countries. In this report, the impact of food-borne antimicrobial resistance could therefore not be specified and quantified. Instead, we provided a comparison of data on antimicrobial resistance in food-producing animals and in humans.

There are also differences in the interpretation of resistance (clinical break-points, ECOFFs) to some antimicrobials (e.g. fluoroquinolones), both within countries for isolates from humans and between animal and human isolates, with the isolates from animals interpreted with ECOFFs. This aspect is further addressed in the Annex C.

An individual bacterial isolate may be resistant to several different antimicrobials simultaneously. Many different patterns of multidrug resistance can occur in individual bacteria within a bacterial population. Use of one antimicrobial can thus select for bacteria which are resistant not only to that antimicrobial but also to other antimicrobials (co-selection). In addition, some resistance mechanisms confer resistance to a number of different antimicrobials, which may be from different classes (cross-resistance). When investigating the association between antimicrobial use and antimicrobial resistance, the phenomena of co-selection and cross-resistance are therefore additional factors which may influence observed associations. This analysis has concentrated on investigating the associations between consumption of an antimicrobial or antimicrobial class and resistance to that antimicrobial or class; future refinement of the analysis could take account of these other additional factors. EU surveillance programmes are increasingly collecting the more detailed information which would be required for such analysis, in particular isolate-based data, providing information on the relative frequency of different MDR patterns.

Another limitation relates to biases inherent in the ecological analyses, such as those conducted in the framework of this report. The report utilises data collected at national level over a limited period of time on antimicrobial consumption in humans and food-producing animals and on antimicrobial resistance in bacteria isolated from diseased people and bacteria isolated from healthy food-producing animals. As this ecological study is based on population data at the national level, the significant correlations observed must be considered in the light of the complexity of the relationship between consumption and resistance (see Annex C, section 3.1). This kind of study investigates only the possible link between global antimicrobial consumption (proxy for exposure) in humans/animal populations and the occurrence of resistance in bacteria isolated from the different populations (outcome). Since both exposure and outcome are ascertained simultaneously, the temporal sequence of exposure and outcome cannot be clearly assured. Such studies are susceptible to other internal validity limitations, such as information biases related to their retrospective and national nature and confounding factors.

National human and animal exposures were compared. In humans, isolates are obtained from clinical cases which can be associated with recent antimicrobial exposure. Isolates from healthy animals come from different animal species, with large variation in conditions of life and antimicrobial exposure. Data on occurrence of the antimicrobial resistance are obtained from phenotypic methods according to different methods of interpretation. The same phenotype of antimicrobial susceptibility can result from the expression of different resistance genes and the spread of mobile genetic elements which may harbour these genes. Results are expressed and analysed at bacterial species level (or at serovar level for *Salmonella*) but without information about their epidemiology in the different animal species (clones). The phenotypic expression of resistance to the same antimicrobial in isolates from humans and food animals is not necessarily indicative of correlation in terms of identity of the organism and the resistance mechanisms therein.

In summary, the findings of these ecological analyses should be considered as hypotheses for subsequent testing by targeted research (e.g. at farm/hospital level) that in turn can provide better explanations for the associations observed by ecological studies. In that sense, ecological studies should be complemented with more targeted studies, as they may address effects of a number of factors, such as those referred to in Annex C, section 3.1. For example, trade-related and sociological factors such as the movement of animals and people between countries and the importation of

contaminated food from countries outside the reporting countries have also not been taken into account. The results of this ecological analysis should be read in the light of other reports demonstrating a relationship between antimicrobial resistance and individual exposure to antimicrobials (pharmacology), group exposure to antimicrobials (observational, including cross-sectional, cohort and time series studies) and interventional studies (quasi-experimental, randomised controlled clinical trials).

The results and conclusions in this report are based on thorough scientific interpretation of available antimicrobial resistance and consumption data from the human and animal domains in the reporting countries. Owing to the limitations and conditions mentioned above, the results of these ecological analyses should be interpreted with caution.

12. Conclusions

This first report analyses data provided by MSs and other EEA countries during the period 2011–2012 and is the first integrated report by ECDC, EFSA and EMA analysing possible relationships between the consumption of antimicrobial agents and occurrence of antimicrobial resistance in the human and food-producing animal sectors.

The report is the product of an on-going collaboration between the three EU agencies, including harmonisation of approaches, expertise and previous joint publications on related subjects.

The analyses have been made possible by the fact that, in the reporting countries, data are available on consumption of and resistance to antimicrobials in humans and for food-producing animals. This provides a unique opportunity to perform ecological studies (integrated analysis). Furthermore, the surveillance systems have improved considerably since their implementation. In both domains, the surveillance systems are increasingly harmonised, more detailed data are being collected, and more countries are participating, which should facilitate similar analyses in the future.

Ideally, for the present type of analyses, there should be an acceptable degree of harmonisation of materials and methods, interpretation criteria (resistance) and units of measurement (antimicrobial consumption). In the present datasets, sample selection and methodologies for susceptibility testing are not fully standardised across the sectors, and neither are the interpretation criteria. This is also true for data on consumption of antimicrobials, where the units of measurement differ.

The analyses showed that, in 15 of 26 countries, average antimicrobial consumption was lower or much lower in food-producing animals than in humans, in three countries consumption was similar in the two groups, and in eight countries consumption in food-producing animals was higher or much higher than in humans. In most countries, the consumption of fluoroquinolones was higher in the human sector than in the animal sector. In all countries, consumption of 3rd- and 4th-generation cephalosporins was much higher in humans than in food-producing animals.

Overall, associations were observed between antimicrobial consumption and resistance prevalence for the selected bacterium–antimicrobial combinations which were analysed, in animals, in humans, and from animals to humans. For *Salmonella* spp., this was less clear, underlining the fact that resistance epidemiology is complex and influenced by many factors aside from use of a particular class of antimicrobials, for example co-selection and clonal spread. Such factors could not be taken into account in the analyses.

It is expected that improvement of existing systems will enable better-integrated analyses of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the future.

In particular, this refers to the following on-going actions aiming to:

- refine existing surveillance systems by providing more detailed information on antimicrobial consumption by age and gender in humans and by species and production types in animals;
- provide enhanced data on hospital consumption in more countries;
- provide more comprehensive data on foods—types, prevalence of bacteria and resistance;
- provide isolate-based data to enable analysis of the effects of co-selection.

It is important that any improvement of data collection is coordinated between the different surveillance networks, aiming at integrated analysis of the data.

With the aim of having fully integrated surveillance systems in the EU, monitoring of antimicrobial resistance should also include:

- animal pathogens;
- commensal flora from both healthy and diseased persons;
- information about the origin of the food and/or animals.

The results of ecological studies which demonstrate associations should be complemented by other epidemiological and molecular studies to investigate possible epidemiological and causal pathways underpinning the associations observed. When correlation has been identified in terms of phenotypic resistance, in-depth identification and molecular characterisation of isolates from humans and food-producing animals, including the resistance mechanisms therein, are desirable.

Finally, there is a need to promote responsible use of antimicrobials in both humans and animals.

1. Annex A

1.1. Legislation of medicinal products

The European system offers different routes for obtaining a marketing authorisation for a medicinal product. Under the centralised procedure, companies submit an application to the EMA. The EMA's Committee for Medicinal Products for Human Use (CHMP) or Committee for Medicinal Products for Veterinary Use (CVMP) carries out a scientific assessment of the application and gives a recommendation on whether or not to grant a marketing authorisation. Once granted by the European Commission, the centralised marketing authorisation is valid in all EU MSs³¹. This allows the MAH to market the medicine and make it available to patients and healthcare professionals throughout the EU on the basis of a single marketing authorisation. The use of the centralised procedure is compulsory for certain medicines, and most innovative medicines, including newly developed antimicrobials, have to go through this procedure. The majority of medicines do not fall within the scope of the centralised procedure but are authorised by national competent authorities (NCAs) in the MS. When a company wants to authorise a medicine in several MSs, it can use one of the following procedures: the decentralised procedure, whereby companies can apply for simultaneous authorisation of a medicine in more than one EU MS if it has not yet been authorised in any EU country and it does not fall within the mandatory scope of the centralised procedure; or the mutual-recognition procedure, whereby companies that have a medicine authorised in one or more EU MS can apply for this authorisation to be recognised in other EU countries. This process allows MSs to rely on each other's scientific assessments. Data requirements for obtaining a marketing authorisation in the EU are the same, irrespective of the authorisation route for a medicine.

1.1.1. Regulation of human medicinal products

To guarantee the protection of public health and to ensure the availability of high-quality, safe and efficacious medicines for European citizens, all medicines must be authorised before they can be placed on the market in the EU. The requirements and procedures for the marketing authorisation for medicinal products for human use, as well as the rules for the constant supervision of products after they have been authorised, are primarily laid down in Directive 2001/83/EC (Official Journal of the European Communities, 2001a) and in Regulation (EC) No 726/2004 (Official Journal of the European Union, 2004c). Further details on the regulatory system can be found on the EC website³² as well as on the EMA website³³.

New legislation governing the development and authorisation of medicines for use in children aged 0-17 years was introduced in the EU in December 2006. This piece of legislation—Regulation (EC) No 1901/2006 as amended (Official Journal of the European Union, 2006)—was introduced to ensure the availability of high-quality information about medicines used by children.

The European Parliament adopted a non-legislative resolution on antimicrobial resistance which emphasised the need for a more prudent use of antimicrobials and the development of new medicinal products in the light of emerging MDR organisms. In response to the European Parliament resolution, the EC issued in 2011 an EU-wide plan to combat antimicrobial resistance³⁴. The action plan contains actions to promote, in a staged approach, unprecedented collaborative research and development efforts to bring new antimicrobials to patients by public-private collaboration in a longer term

³¹ Norway, Iceland and Liechtenstein have, through the European Economic Area agreement, adopted the complete Community acquis on medicinal products, and consequently are parties to the centralised procedure. Switzerland's legislation is not addressed in this text.

³² http://ec.europa.eu/health/human-use/index_en.htm

³³ <http://www.ema.europa.eu>

³⁴ http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf

perspective and enabling fast-track procedures for the marketing authorisation of new antimicrobials. The action plan also highlights the requirements of strengthen the surveillance systems on resistance and antimicrobial consumption in human and veterinary medicine.

Antimicrobials for human use have to be used in accordance with the Summary of Product Characteristics (SPC) of the marketing authorisation. In certain cases (e.g. treatment of neonates), the vast majority of treatment of infections by antimicrobials is not in accordance with the SPC, mainly because the SPC is based on studies with adults and therefore does not include an indication for treatment of children. Such use outside the terms of the SPC would be a so-called "off-label" use of medicinal products which is not regulated by EU legislation. It is the marketing authorisation which defines the approved indications, and any departure from those terms will remain, in most MSs, the responsibility of the prescribing physician.

1.1.2. Regulation of veterinary medicinal products

The regulation of marketing authorisations for veterinary medicinal products is harmonised in the EU/EEA by Regulation (EC) No 726/2004 (Official Journal of the European Union, 2004c) and Directive 2001/82/EC (Official Journal of the European Communities, 2001b), as amended. As indicated above, there are several routes for obtaining a marketing authorisation. Although it is currently not obligatory, most new antimicrobials are authorised by the Commission, leading to the same approved conditions of use all over EU/EEA.

Pharmacologically active substances that may be used in food-producing animals have to be listed in *Table 1* of the Annex to Commission Regulation (EU) No 37/2010 (Official Journal of the European Union, 2009). The table details, among others, the food-producing animal species for which maximum residue limits (MRLs) are established. *Table 2* of that annex contains substances that are prohibited from being used in any food-producing species; some of these substances are included in **Table 8** in the present report, because they are used in companion animals for which no MRLs are required.

All medicinal products for animals are authorised following a risk assessment procedure during which the quality, safety for animals and safety for consumers (where relevant), impact on the environment and efficacy are assessed. This assessment includes the assessment of the risk of antimicrobial resistance from the use of those products on animals. The market for veterinary medicinal products is much smaller than that of medicinal products for humans. The global market for human pharmaceuticals is worth 40 times more than its veterinary equivalent³⁵. As a result, authorised medicinal products might not be available for the treatment of diseases in animals in certain countries. Legal provisions allow, by exception, the use of medicines not in accordance with the SPC, by Directive 2001/82/EC (Official Journal of the European Communities, 2001b), as amended. Article 1(16) of this Directive defines "off-label" use as follows: "*The use of a veterinary medicinal product that is not in accordance with the summary of the product characteristics (SPC), including the misuse and serious abuse of the product*". Veterinarians can apply the so-called "cascade" which is a set of structured steps that indicate the medicines that can be used off-label in a certain situation (Articles 10 and 11 of EU Directive 2004/28/EC (Official Journal of the European Union, 2004a)).

Veterinary antimicrobials are in practice "prescription only"; this status makes it compulsory that a veterinarian prescribes a veterinary antimicrobial before the use of an antimicrobial.

³⁵ IFAH-Europe (2008) Facts and Figures about the European Animal Health Industry. Available online: <http://www.ifaheurope.org/ifah-media/publications.html?year=2014>

1.2. How antimicrobials are used in humans and food-producing animals

1.2.1. General considerations

The efficacy of an antimicrobial treatment is a function of both its antibacterial activity and the immune response of the individual (human or animal) treated. During such clinical recovery, return to a normal physiological state results from a pattern of the immune response, the bacterial lesion at infection site, the major organ burden, the local inflammatory response and the recovery capacity. Clinical cure is not always associated with bacteriological cure, as clinical recovery may result in the healthy carriage of the pathogen or the expression of a chronic disease. Conversely, bacteriological cure may not systematically mean clinical recovery, in particular whenever tissue lesion, acute inflammatory response and high major organ burden leads to major tissue lesions or even to death.

1.2.2. How antimicrobials are used in humans

In the reporting countries, antimicrobials for systemic use are legally available on prescription only (see section 1.1.1. of this annex), although existing data on the actual practice in the EU/EEA countries suggest that a small number of antimicrobials are sold without prescription (Safrany and Monnet, 2012).

Antimicrobials can be given for different reasons. The two major reasons are:

- *Treatment.* The patient receiving the antimicrobial shows clinical signs of an infectious disease. If the pathogen is not identified using microbiological techniques or rapid test diagnostics, then the treatment is considered empirical. Usually antimicrobials with a broader spectrum are selected so as to cover the assumed infectious agents while accounting for their local antimicrobial susceptibilities. If the pathogen has been identified, the empirical treatment should be replaced by a antimicrobial therapy specifically targeted at the identified pathogen.
- *Prophylaxis.* The patient receiving the antimicrobial does not show any sign of infection. Prophylaxis is used to prevent the patient who is or will be at risk from developing an infectious disease. Examples are patients with a severe chronic disease, such as cystic fibrosis or immunosuppression, who in certain circumstances are given medical prophylaxis to prevent them developing an infection. Surgical prophylaxis is administered prior to the start of surgical interventions in patients with specific individual risks or undergoing types of operations associated with a high risk of postoperative surgical site infections. Another type of application of antimicrobial prophylaxis is the deployment of infectious agents during clusters or outbreaks of severe infections; individuals with proven or probable close contacts to infected patients can receive antimicrobials.

Use of antimicrobials also differs depending on the type of healthcare sector. Most of the use happens in the “primary care sector”, i.e. in the community. On average, around 10 % of the total use occurs in the hospital sector. In addition, the patterns of consumption in terms of choice of substances and dose differ between healthcare sectors.

In the community, the range of diseases treated with antimicrobials is rather limited, with the majority of the cases being non-complicated respiratory or urinary tract infections. For these reasons, antimicrobials should be used only when indicated and, when prescribing antimicrobials, narrow-spectrum drugs should be used, preferably following national guidelines. In the community, almost all the antimicrobials prescribed are for oral use (parenteral use represents less than 1 %), mostly for ease of use by the patients themselves.

In the hospital sector, infections are often much more severe and the variety of infections is greater than in the community. Moreover, microorganisms found in hospitals are also often more resistant to antimicrobials than those responsible for infections in the community. In the hospital sector, the treatment of infections is more complex because of the large range of type of infections, pathogens and patient case-mix. Therefore, compared with the community, specific antimicrobial prescribing practices, such as prescribing of broader spectrum antimicrobials, higher doses and longer treatments, are required in hospitals although antimicrobial stewardship tends to limit their harmful impact in terms of resistance. Even if the total number of antimicrobials used in hospitals is much lower than that used in the community, the density of consumption in one place causes a huge selection pressure on the microorganisms present in the hospitals, leading to the emergence and spread of MDR pathogens.

Another point to note is the blurring of the borders separating the community and hospital sectors in terms of antimicrobial consumption. For instance, the situation in nursing homes, which are considered primary care or community settings, tends to be more similar to what is found in hospital (relatively high density of prescribing, more resistant pathogens, frail people in one place). On the other hand, patients discharged early from hospital and continuing their antimicrobial course at home, or receiving outpatient care (such as outpatient parenteral antimicrobial therapy), are examples of hospital sector-related antimicrobial use which is moving into the community.

Antimicrobial consumption can be reported by different indicators. Historically, the weight of active substances or the price was used. Both indicators have many limitations, the former when comparing active substances with different doses and the latter when comparing the use of drugs over time, as values of currency may change. Used in Scandinavian countries for decades, the defined daily dose (DDD) was developed by the WHO Collaborating Centre for Drug statistics Methodology to overcome the limitations of the previous indicators. When the surveillance of antimicrobial consumption in EU/EEA countries started in 2001, the indicator chosen for reporting consumption of antimicrobials in humans was numbers of DDDs per 1 000 inhabitants and per day. As this indicator has also its own limitations, more recently a new indicator of antimicrobial use had been developed and used. In Europe, no national figures on the number of prescriptions are readily available, but the number of packages or boxes of antimicrobials sold or reimbursed is available. Under the assumption that for each prescription one package or box is delivered to the patient, this indicator has also been used as a proxy indicator for the number of prescriptions. In the USA, days of therapy has recently been introduced as a new indicator to report antimicrobial use in US hospitals.

Table 5. Consumption, in tonnes of active ingredient, of antimicrobials authorised for human medicine (presented according to the ATC classification), by country, 2012

Country	Antimicrobial consumption in humans (tonnes of active ingredient)																
	Hospital consumption included	Tetracyclines	Amphenicols	Penicillins	1 st - and 2 nd -generation cephalosporins	3 rd - and 4 th -generation cephalosporins	Monobactams and carbapenems	Sulfonamides	Trimethoprim	Macrolides	Lincosamides	Fluoroquinolones	Other quinolones	Aminoglycosides	Polymyxins	Other antimicrobials	Total
Austria	No	0.4	0.00	21.8	3.2	0.7	<0.1	0.4	0.2	4.1	2.6	3.1	0.0	<0.1	<0.1	0.5	37.1
Belgium	Yes	2.7	0.20	80.3	5.7	1.1	0.5	1.9	0.4	5.7	1.9	8.0	0.0	0.1	<0.1	4.1	112.7
Bulgaria	Yes	1.1	0.31	22.6	6.6	3.9	0.1	3.5	0.7	2.8	2.3	5.5	0.0	0.3	0.0	0.0	49.8
Cyprus	Yes	0.1	0.00	4.6	1.1	0.2	0.1	0.2	<0.1	0.4	0.0	0.9	0.0	<0.1	<0.1	0.1	7.8
Czech Republic	No	0.8	<0.1	32.5	3.5	0.8	0.2	3.8	1.0	6.5	1.2	3.2	0.0	0.6	<0.1	1.2	55.2
Denmark	Yes	2.2	0.00	35.5	1.4	0.1	0.3	2.1	0.5	2.1	0.1	1.4	0.0	<0.1	<0.1	1.7	47.5
Estonia	Yes	0.1	0.00	3.0	1.0	0.1	0.0	0.3	0.1	0.6	0.1	0.5	0.0	<0.1	<0.1	0.1	5.9
Finland	Yes	3.4	0.00	16.4	13.0	0.4	0.3	0.9	1.0	1.1	0.7	1.8	0.0	<0.1	0.0	8.2	47.3
France	Yes	13.4	<0.1	478.9	18.7	30.3	1.7	18.5	3.7	45.0	2.3	33.3	1.0	1.0	0.1	71.3	719.2
Germany	No	6.5	0.00	137.0	39.3	4.8	0.1	20.1	4.6	22.0	23.3	28.1	<0.1	0.1	0.1	5.7	291.7
Hungary	No	0.3	0.00	23.1	3.1	0.5	0.0	2.8	0.6	2.9	2.2	5.1	0.2	<0.1	<0.1	0.5	41.3
Iceland	Yes	0.1	0.00	1.8	0.1	0.0	0.0	0.1	0.0	0.1	<0.1	0.1	0.0	<0.1	0.0	0.1	2.5
Ireland	Yes	1.5	<0.1	29.7	2.2	0.3	0.2	0.8	0.8	4.0	0.2	1.4	0.0	<0.1	<0.1	0.4	41.5
Italy	Yes	3.1	1.98	383.5	15.4	46.5	3.1	13.5	2.8	52.3	1.5	55.8	2.0	1.0	0.1	39.0	621.6

Country	Antimicrobial consumption in humans (tonnes of active ingredient)																
	Hospital consumption included	Tetracyclines	Amphenicols	Penicillins	1 st - and 2 nd -generation cephalosporins	3 rd - and 4 th -generation cephalosporins	Monobactams and carbapenems	Sulfonamides	Trimethoprim	Macrolides	Lincosamides	Fluoroquinolones	Other quinolones	Aminoglycosides	Polymixins	Other antimicrobials	Total
Latvia	Yes	0.2	<0.1	5.6	0.9	0.7	0.0	1.2	0.3	0.6	0.1	0.8	<0.1	0.6	<0.1	0.2	11.3
Lithuania	Yes	0.2	0.00	12.8	2.2	0.3	0.1	0.7	0.1	1.0	0.1	1.1	<0.1	0.1	0.0	0.5	19.2
Luxembourg	Yes	0.1	<0.1	2.9	0.5	0.1	0.0	0.1	0.0	0.4	0.1	0.5	0.0	<0.1	<0.1	0.1	4.8
Netherlands	Yes	1.8	0.00	33.2	2.0	1.0	0.2	3.1	1.1	3.4	1.3	4.5	<0.1	0.1	<0.1	2.7	54.5
Norway	Yes	2.4	<0.1	22.6	1.3	1.0	0.2	0.8	0.5	2.4	0.7	1.1	0.0	<0.1	<0.1	11.3	44.1
Poland	No	5.8	0.00	129.8	20.1	0.3	0.0	28.5	6.1	21.0	12.2	14.7	0.0	0.2	<0.1	0.0	238.5
Portugal	Yes	0.5	<0.1	54.4	5.1	1.4	0.8	3.2	0.7	5.5	0.3	7.4	0.0	0.1	<0.1	3.5	83.0
Slovakia	Yes	0.3	<0.1	21.8	4.9	1.6	0.1	1.1	0.2	3.6	1.0	3.9	0.0	<0.1	<0.1	0.6	39.2
Slovenia	Yes	<0.1	0.00	10.1	0.4	0.2	0.1	1.2	0.2	0.5	0.2	0.8	<0.1	<0.1	<0.1	0.1	13.9
Spain	No	1.4	0.00	231.1	9.9	3.2	0.0	7.3	1.5	14.5	1.8	33.0	0.5	<0.1	0.0	16.5	320.7
Sweden	Yes	4.2	<0.1	50.5	1.3	1.4	0.4	1.6	0.6	0.8	1.6	3.0	0.0	<0.1	<0.1	9.4	74.8
United Kingdom	No	53.4	<0.1	265.7	15.4	0.1	0.0	3.9	12.2	49.0	0.9	8.9	<0.1	0.1	0.3	4.9	414.9
Total (26 countries)	n.a.	105.9	2.5	2 110.9	178.3	101.0	8.5	121.5	39.9	252.3	58.8	227.7	3.8	4.7	0.8	182.9	3 399.8

1.2.3. How antimicrobials are used in food-producing animals

There are three reasons for administering antimicrobials to the animals:

- *Treatment*. This refers to the treatment of an individual animal, or a group of animals, showing clinical signs of an infectious disease.
- *Metaphylaxis*. This refers to the administration of the product at the same time to a group of clinically healthy (but presumably infected) in-contact animals, to prevent them from developing clinical signs, and to prevent further spread of the disease. The presence of the disease in the group/flock must be established before the product is used. A metaphylaxis claim will always have to be combined with a treatment claim.
- *Prevention*. This refers to the administration of an antimicrobial veterinary medicinal product to an individual healthy animal to prevent infection. Such a claim will be considered only in those situations where the risk of infection is very high and the consequences are severe. Prevention claims are not expected to be common and will be carefully scrutinised to ensure that the intended use complies with responsible use principles. The need for prevention must be fully justified for each target species and indication.

In some parts of the world, antimicrobial agents are used as “growth promoters” at low doses in animal feeding-stuff without a therapeutic purpose but to improve productivity. On 1 January 2006, the authorisations of all antimicrobial agents for use as growth promoters were withdrawn in the EU by Regulation (EC) No 1831/2003 (Official Journal of the European Union, 2003b).

Antimicrobial agents may be administered via the food or water to groups of farm animals or the whole herd. This is typically done in poultry production, in which individual treatment is difficult because of the large number of animals in each flock (except for some specific cases, e.g. breeders). Group medication is also common in pigs and intensively reared calves. In adult cattle, but also in adult pigs, individual treatments, e.g. with injectables, is common practice. Companion animals are almost exclusively treated individually.

According to the EU agri-environmental indicator, in 2010 almost two-thirds of livestock in the EU was on holdings of 100 or more livestock animals, this proportion having decreased slightly between 2005 and 2010. Almost half of the EU livestock is cattle, the majority of which are to be found on holdings with 100 or more head of cattle; pigs are also mostly found on holdings with 100 or more head. Data from FAO indicate that the number of live animals in Europe (41 countries) in 2012 was as follows: cattle and buffaloes, 121 896 932; pigs, 183 940 345; poultry birds, 2 314 442 750; goats, 16 557 060; horses, 5 783 491; rabbits and hares, 119 695 000; and sheep, 128 618 357 (source: FAO Statistical Databases (FAOSTAT)³⁶).

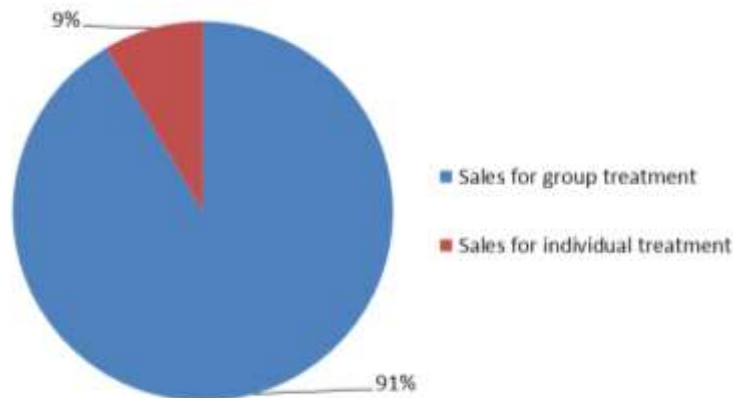
Official figures for companion animals are often not available, but it is estimated that about 25 % of European households own at least one cat or one dog (The European Pet Food Industry (FEDIAF) Facts & Figures, 2012³⁷).

Pharmaceutical forms applicable for group treatment (premix, oral powder and oral solution) are the biggest-selling veterinary antimicrobial veterinary medicinal products, accounting for 91 % of consumption (**Figure 21**); products for individual treatment includes injection, bolus, oral paste and intramammary and intrauterine preparations (EMA/ESVAC, 2014).

³⁶ <http://faostat3.fao.org/faostat-gateway/go/to/download/O/OA/E>

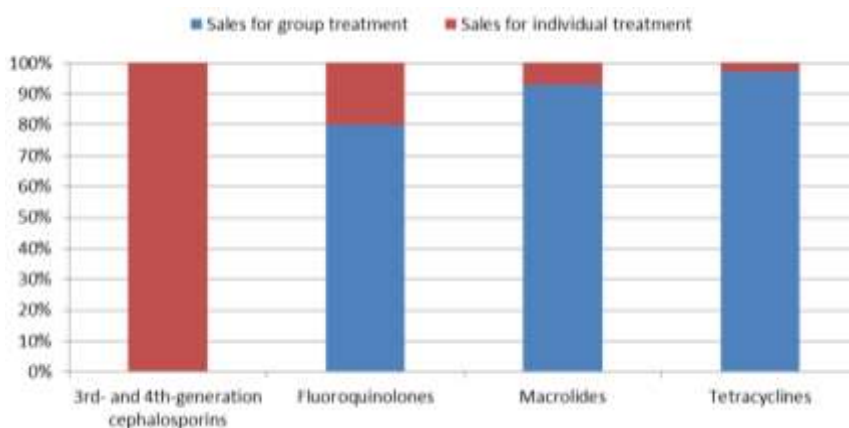
³⁷ <http://www.fediaf.org/facts-figures/>

Figure 21. Distribution of consumption, in milligrams per PCU, of veterinary antimicrobial agents for food-producing animals (including horses), stratified into forms applicable for group treatment and for treatment of individual animals. Data consist of total consumption in the 26 EU/EEA countries for 2012³⁸



In the case of most antimicrobial classes, consumption by animals is typically of pharmaceutical forms applicable for group treatment. The exceptions are 3rd- and 4th-generation cephalosporins, which are used solely for individual treatment (injectable and intramammary preparations) (**Figure 22**) (EMA/ESVAC, 2014).

Figure 22. Distribution of consumption, in milligrams per PCU, of 3rd- and 4th-generation cephalosporins, fluoroquinolones, macrolides and tetracyclines, stratified into forms applicable for group treatment and for treatment of individual animals. Based on data on consumption for food-producing animals (including horses) in 26 EU/EEA countries for 2012 (EMA/ESVAC, 2014)



³⁸ http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/10/WC500175671.pdf

1.2.4. Data on antimicrobial consumption in food-producing animals

Table 6. Consumption, in tonnes of active ingredient, of veterinary antimicrobials applicable mainly for food-producing animal species, including horses, by antimicrobial class (presented according to ATCvet hierarchical system, tablets not included), by country, 2012

Country	Antimicrobial consumption in food-producing animals (tonnes of active ingredient)															
	Tetracyclines	Amphenicols	Penicillins	1 st -and 2 nd -gen. cephalosporins	3 rd -and 4 th -gen. cephalosporins	Sulfonamides	Trimethoprim	Macrolides	Lincosamides	Fluoroquinolones	Other quinolones	Aminoglycosides	Polymyxins	Pleuromutilins	Other ¹	Total
Austria	29.9	0.3	7.9	0.1	0.3	5.7	0.8	4.4	0.3	0.5		1.3	0.7	0.4	0.4	53.0
Belgium	60.0	1.4	76.5	0.1	0.8	71.7	14.4	12.3	5.2	1.4	2.7	1.6	9.6	2.4	6.7	267.2
Bulgaria	17.3	0.5	4.3	0.02	0.01	1.0	0.1	6.5	1.2	2.4	0.1	1.6	1.5	1.0	1.0	38.4
Cyprus	14.2	0.1	7.4	0.004	0.1	8.7	1.7	2.4	5.6	0.1	0.3	0.6	0.9	2.5	0.4	45.0
Czech Republic	20.0	0.4	12.3	0.2	0.2	8.6	0.8	3.8	0.3	1.2	0.05	1.7	0.6	3.2	0.4	53.7
Denmark	32.5	0.8	27.4	0.1	0.1	11.1	2.2	12.4	2.5	0.02	2.1	3.6	0.6	9.3	2.4	107.0
Estonia	1.8	0.02	2.6	0.1	0.1	0.1	0.02	0.5	0.1	0.1		0.6	0.6	0.6	0.2	7.3
Finland	1.8	0.1	6.4	0.04	0.01	2.5	0.5	0.6	0.1	0.1		0.03		0.1		12.2
France	323.0	4.7	80.9	1.6	2.3	141.4	21.2	57.9	4.4	4.6	5.3	54.8	50.1	5.7	3.6	761.5
Germany	599.3	5.4	564.5	0.5	3.7	161.6	26.2	133.0	16.4	10.0		31.4	123.6	22.3	9.6	1 707.5
Hungary	99.5	2.0	32.6	0.2	0.2	4.9	1.1	4.3	4.5	8.0	0.2	1.9	5.7	12.8	0.6	178.5
Iceland	0.04		0.3		< 0.001	0.04	0.01			< 0.001	0.02	0.2		0.003		0.7
Ireland	37.2	2.0	21.7	0.6	0.2	19.7	1.5	6.7	0.4	1.0		8.4	0.2	0.01	0.5	100.0
Italy	478.2	16.9	358.1	1.1	1.8	174.0	22.8	139.0	59.6	11.4	30.2	22.0	135.3	51.5	32.3	1 534.3
Latvia	2.5	0.005	1.6	0.03	0.1	0.2	0.05	0.3	0.02	0.3	0.001	0.7	0.4	0.4	0.1	6.7
Lithuania	2.4	0.2	4.9	0.3	0.02	0.9	0.2	1.5	0.1	0.2	0.1	1.5	0.4	0.2	0.4	13.4
Luxembourg	0.8	0.05	0.4	0.02	0.03	0.4	0.1	0.1	0.04	0.03	0.001	0.04	0.1	0.02	0.1	2.2
Netherlands	96.6	3.0	54.7	0.2	0.1	41.0	7.8	25.5	0.9	0.8	2.3	6.0	3.2	2.2	1.5	245.7
Norway	0.2	0.2	2.8		0.001	1.5	0.3	0.003		0.02	1.4	0.6		0.1	0.004	7.1
Poland	211.1	7.1	129.4	0.9	0.5	44.6	3.2	22.8	5.3	32.2	0.5	35.6	15.6	4.3	3.3	516.4

Country	Antimicrobial consumption in food-producing animals (tonnes of active ingredient)															
	Tetracyclines	Amphenicols	Penicillins	1 st -and 2 nd -gen. cephalosporins	3 rd -and 4 th -gen. cephalosporins	Sulfonamides	Trimethoprim	Macrolides	Lincosamides	Fluoroquinolones	Other quinolones	Aminoglycosides	Polymyxins	Pleuromutilins	Other ¹	Total
Portugal	55.5	1.0	26.7	0.1	0.2	2.9	0.7	14.2	6.7	9.2	0.2	3.4	18.5	13.9	3.2	156.5
Slovakia	2.6	0.1	3.4	0.1	0.1	0.3	0.1	0.2	0.1	0.8		1.1	0.5	0.9	0.1	10.2
Slovenia	0.8	0.2	2.7	0.03	0.03	0.3	0.1	0.2	0.2	0.7	0.003	0.5	0.0	0.1	0.8	6.8
Spain	656.9	11.6	261.8	0.3	1.1	56.2	9.6	148.3	115.7	49.0	4.4	97.6	177.1	81.0	22.2	1 693.0
Sweden	0.8	< 0.001	6.5		0.01	1.6	0.3	0.5	< 0.001	0.1		0.3	0.1	0.1	0.2	10.6
United Kingdom ²	197.6		81.8	0.7	1.3	65.0	12.8	40.9	5.0	2.3		13.6		14.2	12.2	447.4
Total 26 countries	2 942.6	58.0	1 779.8	7.3	13.3	826.3	128.7	638.0	234.7	136.3	49.8	290.8	545.2	229.2	102.0	7 982.0

¹ Bacitracin, paromycin and spectinomycin (classified as 'Other antibacterials' in the ATCvet system)

² Polymyxins and amphenicols are aggregated with 'Others' for confidentiality reasons.

Table 7. Estimated PCU (in 1 000 tonnes) of the population of food-producing animal species¹ (including horses), by country, for 2012

Country	Estimated number of population correction units (PCUs) (in 1 000 tonnes)							
	Cattle	Pigs	Poultry	Sheep/goats	Fish	Rabbits	Horses	Total
Austria	435	384	81	35			30	966
Belgium	461	916	167	16	0.6	4	94	1 658
Bulgaria	134	62	45	99		0.01	48	388
Cyprus	16	51	13	32		0.2	2	113
Czech Republic	284	198	112	17	21	10	32	673
Denmark	410	1 808	105	2	34		66	2 424
Estonia	61	43	17	6	0.4		4	131
Finland	222	171	65	11	12.7		30	511
France	3 465	1 855	1 146	665	234	52	200	7 618
Germany	3 129	3 957	903	144	20		185	8 338
Hungary	144	277	180	96		0.01	31	727
Iceland	19	6	5	47	7		31	116
Ireland	1 007	267	83	304	36		28	1 725
Italy	1 746	991	715	611	195	33	210	4 500
Latvia	109	33	15	0.3			5	162
Lithuania	206	75	45	6			7	339
Luxembourg	37	11	0.03	0.03			2	50
Netherlands	991	1 475	496	99	46	3	169	3 279
Norway	221	127	66	101	1 321		14	1 851
Poland	1 542	1 345	901	18			102	3 908
Portugal	237	343	199	177	9	8	22	996
Slovakia	99	49	51	33			2	235
Slovenia	100	26	35	12	1	0.04	10	183
Spain	881	3 321	728	1 459	274	75	258	6 996
Sweden ²	304	202	81	51			145	783
United Kingdom	1 709	733	1 040	2 700	172		395	6 749
Total 26 countries	17 970	18 724	7 295	6 742	2 384	184	2 121	55 421

¹ For animal categories included, see Annex 3. ² Farmed fish not included.

Table 8. List of substances reported sold in ESVAC

Class/sub-class	Substances		
Tetracyclines			
	Chlortetracycline	Doxycycline	Oxytetracycline
	Tetracycline		
Amphenicols			
	Chloramphenicol ¹	Florfenicol	Thiamphenicol
Penicillins			
Beta-lactamase-sensitive penicillins			
	Benzathine benzylpenicillin	Benzathine phenoxymethylpenicillin	Benzylpenicillin
	Penethamate hydriodide	Phenoxymethylpenicillin	Procaine benzylpenicillin
Beta-lactamase-resistant penicillins			
	Cloxacillin	Dicloxacillin	Nafcillin
	Oxacillin		
Penicillins with extended spectrum			
	Amoxicillin	Ampicillin	Metampicillin ²
Cephalosporins³			
1st-generation cephalosporins			
	Cefacetrile	Cefadroxil ²	Cefalexin
	Cefalonium	Cefapirin	Cefazolin
3rd-generation cephalosporins			
	Cefoperazone	Cefovecin ²	Ceftiofur
4th-generation cephalosporins			
	Cefquinome		
Sulfonamides and trimethoprim			
Sulfonamides			
	Formosulfathiazole	Phthalylsulfathiazole	Sulfacetamide
	Sulfachlorpyridazine	Sulfaclozine	Sulfadiazine
	Sulfadimethoxine	Sulfadimidine	Sulfadoxine
	Sulfafurazole	Sulfaguanidine	Sulfamerazine
	Sulfamethizole	Sulfamethoxazole	Sulfamethoxypyridazine
	Sulfanilamide	Sulfapyridine	Sulfaquinolaxaline
	Sulfathiazole	Sulfamonomethoxine	
Trimethoprim and derivatives			
	Trimethoprim		
Macrolides and lincosamides			
Macrolides			

Class/sub-class	Substances		
	Erythromycin	Gamithromycin	Oleandomycin ²
	Spiramycin	Tildipirosin	Tilmicosin
	Tulathromycin	Tylosin	Tylvalosin
Lincosamides			
	Clindamycin ²	Lincomycin	Pirlimycin
Aminoglycosides			
	Amikacin ²	Apramycin	Dihydrostreptomycin
	Framycetin	Gentamicin	Kanamycin
	Neomycin	Streptomycin	
Quinolones			
Fluoroquinolones			
	Danofloxacin	Difloxacin	Enrofloxacin
	Ibafloxacin ²	Marbofloxacin	Norfloxacin ²
	Orbifloxacin ²	Pradofloxacin ²	
Other quinolones			
	Cinoxacin ²	Flumequine	Oxolinic acid
Imidazole derivatives			
	Metronidazole ¹		
Pleuromutilins			
	Tiamulin	Valnemulin	
Polymyxins			
	Colistin	Polymyxin B ²	
Nitrofuran derivatives			
	Furazolidone ¹		
Others			
	Bacitracin	Furalfadone ¹	Nitroxoline ²
	Novobiocin	Spectinomycin	Paromomycin
	Rifaximin	Natamycin	

¹ Included in Table 2 (prohibited substances) of the Annex to Commission Regulation (EU) No 37/2010.

² MRLs not established for any food-producing species.

³ MRLs not established for poultry (not allowed to be used).

2. Annex B

2.1. Comparison of how antimicrobials are used in food-producing animals and humans

Table 9 summarises some of the differences in how antimicrobials are used in humans and in food-producing animals.

Table 9. The use of antimicrobials in humans and in food-producing animals

	Humans	Food-producing animals and products thereof	Comments
Patient characteristics			
Species	One	Many	–
Number of individuals	507 416 607 (EU-28 countries, year 2014 ³⁹)	1 898 767 540 (EU-28 countries, year 2013 ⁴⁰)	Ratio humans/animals: about 1 to 4
Biomass (kg)	31 713 537 938 (number of individuals in the EU-28 countries in 2014 multiplied by 62.5 kg/person)	Meat: 45 073 838 750 Eggs: 6 689 713 000 Milk: 155 919 234 300 Honey: 191 119 000 (EU-28 countries, 2012 ⁴¹) Fish: 2 588 521 149 (EU-28 countries, 2012 ⁴²) Total: 210 462 426 199	Ratio human biomass/animal meat ⁴³ : 41 %/59 %
Individual weight	Variable	Very variable	Animals can be treated with doses of 50 g (one-day-old chicks) up to 1 000 kg
Lifespan	Long	Short in most cases	Food animals are consumed by humans as food
Conditions for treatment			
Individual treatment	Yes	Yes	Companion animals, horses, dairy cows, adult cattle, adult pigs
Group treatment	Exceptional	Yes	Group treatment on farms
Route of administration	Oral (e.g. tablets, syrup), injectables and others	Oral (in feed or drinking water), injectables and others	Medicines for animals are focussed into efficient administration for group treatment

Adapted from http://agriculture.gouv.fr/IMG/pdf/12_MOULIN_DGAL_14nov_GMF_cle8bfb48.pdf

³⁹ Eurostat: <http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&plugin=1&language=en&pcode=tps00001>

⁴⁰ FAOSTAT live animals. Heads of cattle, buffaloes, sheep, goats, pigs, horses, asses, mules, chickens, ducks, geese, guinea fowls, turkeys, rabbits, hares, pigeons and other birds. No fish or bees included. <http://faostat3.fao.org/download/Q/QA/E>

⁴¹ FAOSTAT livestock primary. Kilograms of indigenous cattle, buffalo, sheep, goat, pigs, horse, mule, ass, chicken and other poultry. Fish production not included. <http://faostat3.fao.org/download/Q/QL/E>

⁴² FAOSTAT aquaculture. Fish, crustaceans, molluscs and others.

⁴³ The ratio excludes eggs, milk, honey and fish. <http://data.fao.org/dataset?entryId=033ae7cf-b322-4dc5-8dfe-140140c56008&tab=about>

2.2. Calculation of standard human body weight

2.2.1. Introduction

The authors reached the consensus that mg/kg of body weight is an acceptable unit of measurement to compare antimicrobial consumption in the food-producing animal and human sectors. For food-producing animals, the PCU was used for the calculations. For the human sector, a standardised body weight taking into account the distribution of the population (children, adult, the elderly, men, women) was used. Data on international human body weights are scarce. For instance, in relation to antimicrobial consumption, the definition of the DDD mentions that it is based on an adult of 70 kg. In addition, although there are many publications on body mass index and obesity, they do not provide data on body weight. For this reason, the authors made the decision to estimate a standard human body weight from published EU data.

2.2.2. Existing data

In its scientific opinion entitled "Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data" (EFSA, 2012a), EFSA proposed standard body weights for adults and children. These standard body weights were defined based on a review of EFSA publications and surveys. For adults, the standard body weight was defined as 70 kg. For children, different body weights, depending on age, were proposed (**Table 10**).

Eurostat publishes data on the EU population by age and gender for all MSs and for the whole EU. These data are available in the EUROSTAT table entitled "demo_pjan".

Table 10. Proposed standard body weights for children by EFSA

Age (years)	Mean (kg)
Infants (0–3 months)	4.8
Infants (3–6 months)	6.7
Infants (6–12 months)	8.8
Toddlers (1–3 years)	11.9
Other children (3–10 years)	23.1
Adolescents (10–14 years)	43.4
Adolescents (14–18 years)	61.3

2.2.3. Methodology

To compare antimicrobial consumption between humans and food-producing animals, the following methods, based on data provided by EFSA and EUROSTAT were applied to define a standard human body weight:

1. An average body weight for children below one year of age was calculated as Eurostat provides population data only by year.
2. An average body weight for children aged 1–18 years (including toddlers, other children and adolescents as defined in **Table 10**) was calculated,
3. A standard body weight for humans was calculated using the proposed adult body weight and the calculated average child body weight.

The EUROSTAT population for the EU-27 in 2012 was used as reference data for the population.

Average body weight for children below one year of age

The average weight for children below one year of age was calculated by taking a weighted mean of the proposed body weights of the three categories and using the number of months of each age category as weight.

Average body weight for children

The average body weight for children was obtained by calculating a weighted mean of the calculated average body weight for children below one year of age and the proposed body weights for the categories of children above one year of age and using the number of children in each category extracted from Eurostat as weight for the mean.

To estimate a standard body weight for children from 0 to 18 years of age, the weighted mean of the EFSA proposed body weight by class of children from 1 to 18 years of age and of the aforementioned calculated body weight for children below one year was computed. The Eurostat population figures were used to weight the different classes of children. The standard body weight for children was estimated as 34.6 kg.

Standard human body weight

The standard human body weight was calculated by applying the weighted mean of the average child body weight (34.6 kg) to the population below 20 years of age and the proposed 70 kg for the population older or equal to 20 years of age and using the corresponding population figures extracted from Eurostat as weight for the mean.

Based on this methodology, the calculated standard human body weight was 62.5 kg.

3. Annex C

3.1. On the complexity of the relation between antimicrobial consumption and resistance

3.1.1. Factors influencing the emergence and spread of resistance

Fundamental to the spread of bacteria resistant to an antimicrobial or antimicrobials is the process of selection, whereby a single resistant bacterium in a population is provided with the opportunity to become more prevalent as a result of the killing or suppression of the previously dominant sensitive population. Such opportunities are afforded by selection following the application of an antimicrobial or antimicrobials to which the organism exhibits reduced susceptibility or clinical resistance. The single resistant organism then survives to reproduce, often in an exponential progression, until a new equilibrium is reached, thereby becoming the principal organism in the bacterial population (Baquero, 2011).

Several genetic, bacterial and environmental factors interact in the selection and dissemination of antimicrobial resistance in bacteria at different levels. For antimicrobials used for therapy, the principal genetic and bacterial factors are the resistance determinants, the genetic environment of the resistance determinants within the bacterial cell and the bacterial strain. These factors, and their interactions in the development and subsequent transmission of resistance within and between clones, strains or even species, are summarised in **Table 11**, and described in more detail below.

Table 11. Factors contributing to the selection and dissemination of antimicrobial resistance

Genetic/bacterial factors	Description	Process of resistance transmission	Further considerations
Resistance determinants	<ul style="list-style-type: none"> • Size • Mechanism of resistance (mutation or gene located on mobile genetic element) • Functions encoded • Copy number 	<ul style="list-style-type: none"> • Vertical spread • Horizontal spread 	<ul style="list-style-type: none"> • Cross-resistance
Genetic environment	<ul style="list-style-type: none"> • Chromosome • Mobile genetic elements 	<ul style="list-style-type: none"> • Reproduction • Conjugation • Transformation • Transduction 	<ul style="list-style-type: none"> • Co-resistance • Fitness in cell
Bacterial species	<ul style="list-style-type: none"> • Expressed resistance phenotype 	<ul style="list-style-type: none"> • Spread of bacterial population • Carriage by host (food animal, human being) 	<ul style="list-style-type: none"> • Antimicrobial susceptibility • Growth rate • Associated virulence characteristics • Host factors (e.g. farm, hospital)

3.1.1.1. Resistance determinants

Bacterial cells can harbour numerous genes or mutations, which may be located on the chromosome, on mobile genetic elements, or on both. Some specific bacterial species are naturally resistant because of the absence or inaccessibility of target structures for antimicrobial action. In other bacterial species, the core genome may contain genes encoding resistance to an antimicrobial. When such resistance is a

species property, it is defined as “natural” or “intrinsic” resistance. Chromosomally located genes encoding resistance defined as “intrinsic” represent about 3 % of the bacterial genome (Fajardo et al., 2008). In contrast, “acquired resistance” results from the acquisition of mutations or resistance genes located on mobile genetic elements. These processes are variable and are dependent on the bacterial species as well as numerous external factors such as those listed above.

3.1.1.2. Genetic environment

In bacterial cells, genes or mutations encoding resistance to antimicrobials may be present on the chromosome or on mobile genetic elements such as integrons, transposons, resistance islands, integrative/conjugative elements and plasmids, or on both. The spatial organisation of such resistance determinants and their regulation is fundamental for the multiplication and transmission of antimicrobial resistance genes within and between bacterial species and their expansion through clonal spread, or by horizontal transfer of mobile genetic elements. Plasmids or other mobile genetic elements may be directly transmitted between bacteria by conjugation. In addition, part of bacterial genome, released by cell lysis, can be partially acquired by competent cell by transformation and can also be transferred by transduction when bacterial cells are infected by bacteriophages.

3.1.1.3. Bacterial species, clones, cross-resistance and co-resistance

A major consideration in the acquisition of antimicrobial resistance is the inherently clonal nature of bacterial populations. This is a consequence of their asexual reproduction, acting in combination with a diversity of events, such as the repeated use of the same drugs at the same location (e.g. farms), as is the case for exposure to antimicrobials. In theory, a clone is a bacterial population derived from a unique bacterial cell. Organisms within that clone should be genetically identical and should respond in similar ways to antimicrobial selection pressure. In a bacterial species, numerous different clones may be present and their development will be dependent of their survival capacities in different environments. Such clones can harbour and disseminate different plasmids or mobile genetic elements, which are considered to be major vehicles for the dissemination of resistance within and between bacterial species. Furthermore, mutations causing resistance to certain antimicrobials might occur and be clonally spread because of further vertical transmission in the reproductive process, and be selected when environmental pressure occurs.

Numerous genes and mutations are involved in encoding antimicrobial resistance mechanisms which may affect several substances of a specific antimicrobial class. The situation in which a single antimicrobial resistance mechanism is associated with resistance to several antimicrobials in the same class and/or other classes is defined as “cross-resistance”. This can be caused by a single mechanism affecting single targets that influence the effects of different antimicrobials or because of unspecific efflux mechanisms.

Alternatively, the simultaneous presence of different antimicrobial genes giving rise to resistance to several different classes is defined as “co-resistance”. Antimicrobial treatment with one compound of any one of these antimicrobial classes may select this type of MDR clone and co-select resistance for the different antimicrobial families.

3.1.1.4. Clonal spread of resistance

Clonal spread of antimicrobial resistance strains in food animals and in the community has been demonstrated in *Salmonella* spp., extended-spectrum beta-lactamase (ESBL)-producing *E. coli*, staphylococci (e.g. methicillin-resistant *Staphylococcus aureus* (MRSA)) and vancomycin-resistant enterococci (VRE), and to a lesser extent in *Campylobacter* spp. Although antimicrobial consumption is

undoubtedly an important risk factor in the clonal spread of, for example, VRE in poultry, such spread can take place without any obvious direct antimicrobial involvement. Thus, clonal spread of both pathogens and non-pathogens in human and animal hosts, both within countries and across country boundaries, can profoundly affect conclusions about antimicrobial consumption and resistance development, as in many cases resistance which is spread by this means cannot be directly linked to antimicrobial consumption.

3.1.1.5. Other factors

Other factors influencing the emergence and spread of resistance are related to the microbiota (any exposure of a bacterial population to antimicrobials results in a selective pressure on the microbiota in favour of resistant strains), the host (e.g. animal species, disease status, age, immunity to infection), the bacterial population and the environment. Environmental factors are in general related to the modes of transmission of the drug-resistant bacterial strain and the genes. Animals can be exposed to antimicrobial-resistant bacteria present in their environment (e.g. litter, farm equipment), through contaminated feed, water, or the farm environment. Transmission also can be related to their parents (sows to piglets, cows to calves) or their origin (poultry breeding flocks via hatcheries). All of these routes are influenced by other factors such as:

- managerial practices on the farm;
- hygiene (cleaning, disinfection, use of biocides), biosecurity measures, management of slurry, farm organisation, all of which influence transmission of bacteria between animals and environment;
- soil/water contamination by a low level of antimicrobials and heavy metals, which may also be a source of selective pressure on bacteria in an animal environment.

3.1.2. Antimicrobial use and selection pressure

Studies of the relationship between antimicrobial treatment and risk of selection of resistance in both humans and animals show the inter-relation among drug concentration, duration of exposure and bacterial load. If the pathogen bacterial load is low (e.g. when a treatment is administered at the beginning of infection), treatment duration can be short provided the dose is efficient, which limits the exposure of intestinal microbiota and the risk of selection. If treatment starts late in the course of infection, a higher dose and a longer duration may be needed, which results in greater exposure of the microbiota, thereby increasing the risk of selection of resistance. Moreover, in the animal production sector, antimicrobial treatment may be administered to individuals or groups of animals according to herd management. When treatments are targeted at an individual or a limited number of sick animals, the quantities of antimicrobials consumed will be lower than when large groups of animals with different levels of infection are treated simultaneously. The same quantity of drug can be related to a sub-dosing in group treatments for a longer period or a correct treatment for a group. Thus, information about the daily dose, duration of treatment, number of animal treated, as well as consumption data, may be important in assessing the likelihood of resistance development. This complementary information is not available in the ecological analyses performed in the framework of this report.

3.1.3. Pathways of dissemination of resistance

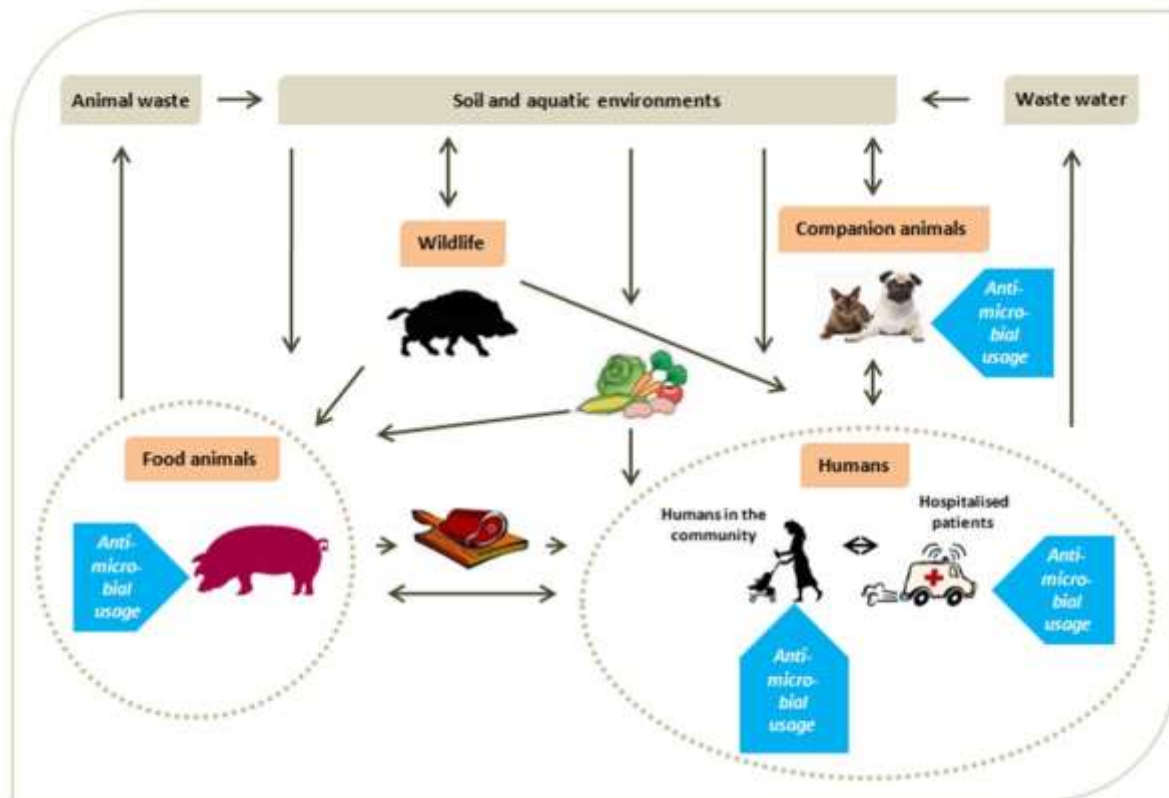
The main events contributing to the acquisition by animals or humans of antimicrobial-resistant bacteria are the intake of contaminated feed, food or water and contact with surface material or other material, such as faeces, which has become contaminated with antimicrobial-resistant bacteria.

Bacterial cells containing resistance genes or mutations can be disseminated by different pathways in different ecosystems. As components of animal slurry, they can reach the soil and water environment through deposit of manure as fertiliser on arable land, and then can be mobilised by rain and water flow to reach the watershed and rivers. As components of human sewage, they can be transferred by flow to waste water treatment plants and then, if they survive water treatment (filtration, disinfection), or if resistance genes are transferable to bacterial species adapted to a water environment, reach rivers and potable water. Moreover, access to slurry or sewage by wildlife animals, such as birds, pets, mice, rats and insects, may contribute to the local, regional and/or global dissemination of resistance (e.g. wild migrating birds). Resistant bacteria can be also transferred from soil or water to plants and can contaminate feed and food produced during cultivation and the processing of plants.

Bacterial contamination of carcasses/meat by the gastro-intestinal flora of food-producing animals may primarily occur during the slaughter process. Contamination of milk can also contribute to human exposure to resistant bacteria. Such contamination may take place as a result of failure in the pasteurisation process or when milk is consumed in the raw, untreated state, by direct contamination from the milk-producing animal or by contamination in bulk milk tanks before distribution to the consumer (EFSA, 2015). A further route by which resistant bacteria may reach the consumer is by consumption of uncooked or lightly cooked eggs which contain resistant organisms. Surface contamination of eggs with resistant bacteria is also a potential route for the transmission of such bacteria, particularly in some countries outside the EU (Threlfall et al., 2014). Resistant bacteria can also reach consumers through the consumption of food of non-animal origin which may have been contaminated with drug-resistant bacteria during cultivation/processing. The number of resistant bacteria reaching the consumer by these routes is extremely difficult to quantify, and is dependent on the country of origin of the product and the hygiene systems within such countries.

Occupational exposure of farm workers and veterinarians has been also reported, as has exposure of owners of companion animals and family members. Such exposure is particularly relevant in the case of livestock-associated MRSA. Exposure of people by contact with food or animals that are contaminated with resistant bacteria could be another route for transfer. As some bacteria can survive in biofilms or in dust, they can be present on different materials and vehicles, or in animals and plants, food or feed, and then move from one environment to another by travel and transportation (**Figure 23**).

Figure 23. Exchange of resistance mechanisms and bacteria between different reservoirs



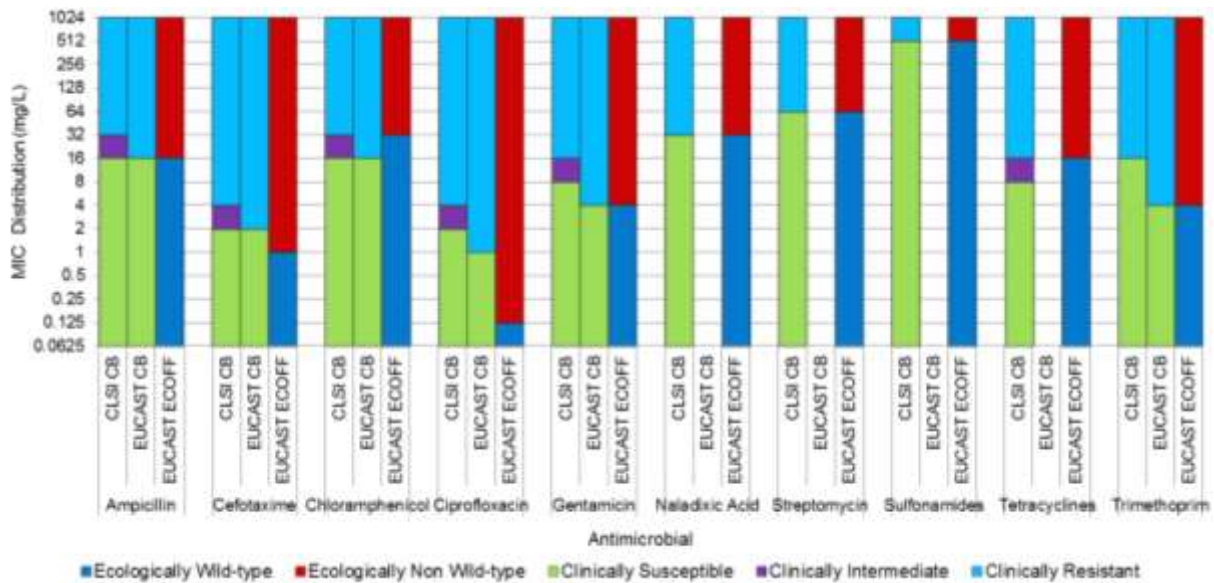
3.2. Measuring and monitoring of antimicrobial resistance in humans and food-producing animals

3.2.1.1. Measurement of resistance

In the first instance, the measurement of antimicrobial resistance is dependent on the definitions used, such as threshold values used to categorise bacteria as resistant or susceptible, or the study of a specific mechanism that confers resistance (e.g. enzymatic degradation of an antimicrobial by ESBL-producing enzymes). Indeed, in the EU, for some antimicrobials, the epidemiological cut-off (ECOFF) distinguishing wild-type susceptible strains from non-wild-type ones differs from the clinical breakpoint used for diagnosis and prognostic of treatment outcomes (see EUCAST). The conclusion of a study can differ according to the cut-off used.

A second consideration is whether the organism is resistant to a single antimicrobial or to more than one antimicrobial. Bacteria may exhibit co-resistance to different families of antimicrobials because of the presence of multiple resistance genes on genetic elements. In such cases, relationships between antimicrobial consumption will not necessarily be synonymous.

Figure 24. Comparison of clinical breakpoints and epidemiological cut-off values (ECOFFs) used to interpret MIC data reported for *Salmonella* spp. from humans, animals or food



Note: CLSI (M100-S22 2012), EUCAST clinical breakpoints (2011), EUCAST ECOFFs (as in EFSA, 2007). Empty fields mean that no breakpoint is available.

Adapted from EFSA/ECDC report (EFSA/ECDC, 2014)

A third consideration is the choice of specimens to be included. In human medicine, the four options for the choice of specimen are (1) surveillance cultures that detect colonisation (usually performed for research or infection control purposes), (2) any clinical cultures taken during routine care of the patient (which, if positive, do not necessarily indicate infection), (3) microbiologically and clinically documented infections (i.e. a positive culture plus signs and symptoms of infection) and (4) site-specific cultures (e.g. blood cultures) (Wener et al., 2010). The last three options are more commonly available, but the risk factors identified by using these samples may be more appropriate for developing infections rather than those for the harbouring of resistant bacteria. Only the first option, the use of surveillance cultures, will identify asymptomatic carriers. For veterinary medicine, data about antimicrobial resistance have, for the most part, been derived from zoonotic or indicator bacteria isolated from asymptomatic carrier animals.

Antimicrobial resistance can be measured in several ways. The most common method is to measure the proportion of resistant isolates among all isolates at the diagnostic laboratory. For example, a hospital's "antibiogram" may note that 20 % of all enterococci detected in its laboratory are resistant to vancomycin.

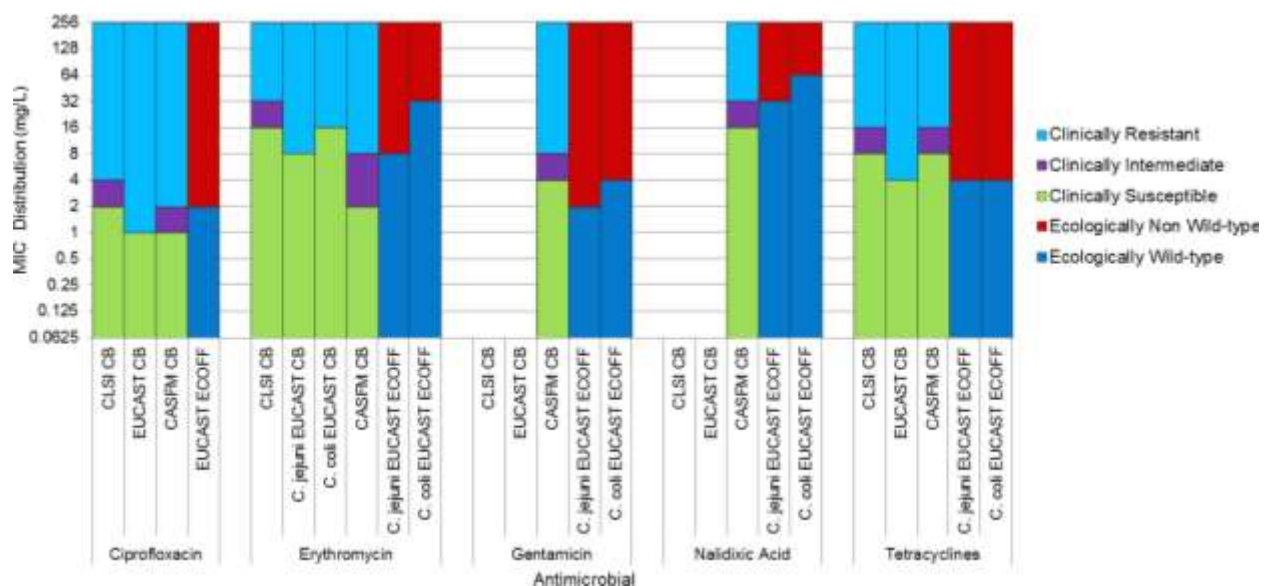
A major drawback when using this method is that an increase in the proportion of organisms that are resistant may not necessarily reflect an increase in the absolute number of clinical cases caused by resistant organisms. A decrease in the total number of isolates because of a reduction in the number of susceptible ones with a same number of resistant isolates leads, mathematically, to an increase in the drug-resistant proportion of a population.

From a public health point of view, the consequences of antimicrobial use, it is most important to know the burden of resistance. The best way to measure the burden of resistance is by using a "rate". Several "rates" have been proposed for reporting resistance in medical settings: it could be the number of resistant isolates, observed by unit of time or by hospital bed per unit time or by occupied

bed per unit time, or per hospital admission per unit time. These rates are more or less difficult to collect (Schwaber et al., 2004) and require precise definition of the population monitored. They can be obtained for a defined medical setting.

Laboratory-based surveillance can be valuable to inform treatment guidelines and to provide information on trends and alerts to emerging resistance problems. This type of surveillance does not provide the information needed to measure the impact of resistance, including the consequences of antimicrobial resistance for patients as a result of failure of treatment that results in prolonged illness and excessive mortality, or how much of the population or which patient groups are affected. For this purpose, targeted surveillance based on defined populations and epidemiological samples would be necessary to provide the information need to estimate the impact of antimicrobial resistance (WHO, 2014).

Figure 25. Comparison of clinical breakpoints and ECOFFs used to interpret MIC data reported for *Campylobacter* spp. from humans, animals or food



Note: CLSI (2010), EUCAST clinical breakpoints (2012), Comité Antibiogramme–Société Française de Microbiologie (CA-SFM) (2010), EUCAST. Empty fields mean that no breakpoint is available.

Adapted from EFSA/ECDC report (EFSA/ECDC, 2014).

3.2.1.2. Monitoring of resistance

The emergence and spread of antimicrobial resistance constitutes a significant public health problem. Owing to rising levels of resistance in a number of bacterial species (including zoonotic bacteria) causing infections in humans, the available treatment options for patients suffering from bacterial infections are becoming more and more limited.

In order to guide prevention and control efforts aimed at limiting the emergence and spread of antimicrobial resistance in humans, baseline data on the occurrence of resistance in humans and adjacent reservoirs are needed. Monitoring of antimicrobial resistance in animals and humans may provide important information on occurrence and development of resistance and may even allow early detection of resistant strains of public health importance. Data from resistance monitoring are needed to inform clinical therapy decisions, to guide policy recommendations, to provide data for risk assessments and to assess the impact of intervention strategies.

Appropriate strategies for monitoring of antimicrobial resistance should reflect pre-identified scientific or public health objectives. Ideally, resistance monitoring systems should include relevant indicators and pathogens of public health importance and monitor resistance to antimicrobials of importance for therapeutic use in humans.

For monitoring purposes, data collection can be based on results of routine microbiological diagnostics and antimicrobial susceptibility testing results. In cases where specific organisms of major public health importance are identified (e.g. MRSA, VRE), targeted surveys may provide more timely and adequate data to inform decision making at local or national level.

3.3. Clonal spread of organisms exhibiting resistance to antimicrobials in the human population and in food-producing animals

A fourth consideration is the effect of *clonal spread* of organisms exhibiting resistance to antimicrobials. By definition, a clone is a group of highly similar cells that share a *common ancestry*, meaning that they are derived from the same ancestor. On this basis, isolates of bacterial species that are indistinguishable in genotype are considered to be a clone, with the implication that they are descended from the same recent ancestor. Clones are difficult to define with precision since bacteria are not truly asexual, and recombinational replacements result in diversification of the ancestral genotype of a clone, to produce a cluster of increasingly diverse but related genotypes (Spratt, 2004).

Clonal spread of bacteria conferring resistance to antimicrobials occurs in both food production animals and humans, and in both pathogens and non-pathogens, and is not necessarily directly linked to the use of antimicrobials in a particular host or country. The implications of clonal spread in assessing the prevalence of resistance are considerable, and pose difficulties for comparative studies of resistance in human and animal populations in relation to antimicrobial consumption. For example, the clonal spread of a MDR strain of *Salmonella* spp. through a food animal population can be quite different from that of a strain of, for example, MRSA CC398 in the community or in a hospital environment.

In the first instance a MDR salmonella organism may become established in a food animal population without the involvement of antimicrobials and, although antimicrobial use can contribute to its persistence and dissemination, such use may not be responsible alone for its appearance. An example of this is provided by the appearance and subsequent epizootic spread, in the late 1980s/1990s, of a clone of *S. Typhimurium* definitive phage type (DT) 104 exhibiting chromosomally-mediated resistance to five unrelated antimicrobials (Threlfall, 2000). Retrospective studies have suggested that the MDR epidemic clone of DT 104 was simultaneously introduced into bovine animals in the United Kingdom and into North America from countries in South-East Asia, and that antimicrobial consumption in affected countries in the northern hemisphere was not a major factor in its epizootic spread. Following its dissemination via the food chain, the strain was responsible for many thousands of infections in humans in affected countries, but, as with food-producing animals, antimicrobial consumption in the human population was not a major contributory factor. More recent examples include the on-going multi-country spread of a MDR "clonal complex" of a monophasic variant of *S. Typhimurium* exhibiting chromosomally mediated resistance to four unrelated antimicrobials, which has spread extensively in pigs in several European countries, and has also caused many human infections (EFSA, 2010; Hopkins et al., 2010; Lucarelli et al., 2010). Although antimicrobial use in pigs in different EU countries may have contributed to the appearance of this clonal complex, such use does not seem to be related to its subsequent spread. Similarly, a clone of a strain of *S. Kentucky* ST 198 exhibiting high-level resistance to ciprofloxacin and associated with poultry has recently reported to be spreading epidemically, with infections reported in several EU countries and the USA (Le Hello et al., 2011). In contrast to such clusters of epidemiologically related healthy carriage in food-producing animals, clonal outbreaks of

MDR *Salmonella* in hospitals are rare in developed countries. Although such events have been reported, predominantly in high-dependency units (Anderson et al., 1977; McCartney et al., 1993) outbreaks of non-typhoidal salmonella infections are more common in developing countries in South-east Asia, the Indian sub-continent (Anderson et al., 1977) and sub-Saharan Africa (Gordon, 2011). In such outbreaks, the strains are generally MDR, but there is no evidence that antimicrobial consumption in food-producing animals plays a role in either their formation or dissemination, and antimicrobial consumption in the human population appears to have been key factor in their diffusion.

In contrast to *Salmonella*, outbreaks in the human population caused by the clonal spread of drug-resistant *Campylobacter* spp. strains are uncommon, and hospital outbreaks are rare. A number of *Campylobacter* genotypes, as defined by clonal complex and including both *C. jejuni* and *C. coli*, are associated with farm animals, including those from poultry, bovine, ovine and porcine sources. Although human campylobacteriosis is very widespread, point source clonal outbreaks, and particularly hospital outbreaks, that can be identified and controlled by public health action are rare. Where they do occur, such outbreaks are often associated with poor food preparation at particular institutions, unpasteurised milk or milk pasteurisation failures or contaminated water. Nevertheless, antimicrobial resistance is increasing among campylobacter infections and is common among isolates from other sources, specifically retail poultry meat. In a recent UK-wide survey to investigate the antimicrobial susceptibility of isolates of *Campylobacter* spp. in retail poultry meat, antimicrobial resistance was present in all lineage clusters, but statistical testing showed a non-random distribution (Wimalaratna et al., 2013). For all antimicrobials tested, resistant isolates were distributed among relatively distant lineages, indicative of widespread acquisition. There was also limited evidence of clustering of resistance phenotypes within lineages, indicative of local expansion of resistant strains, i.e. clonal spread of resistant organisms in poultry at a local level.

Clonal spread of MDR *E. coli* pathogenic to humans is an increasingly important issue, particularly in relation to the spread of ESBL-producing strains in the community and in hospitals. The potential contribution of food-producing animals or foods to public health risks caused by ESBL-producing bacteria is related to specific plasmid-mediated ESBL genes encoded by a number of organisms and to the subsequent horizontal dissemination of such genes through bacteria in human and animal populations. Although there are a large number of genes which encode ESBL enzymes, not all are equally prevalent among human and animal bacteria. The predominant ESBL families encountered are CTX-M, TEM and SHV, and the bacterial species most commonly identified with these genes is *E. coli*, with the clonal lineages B2-*E. coli* O25:H4-ST131, D-*E. coli* O25a-ST648 and D-*E. coli*-ST69 and -ST393 being increasingly detected among both humans and food animals (Liebana et al., 2013). Furthermore, a recent comparative analysis of ESBL-positive *E. coli* isolates from animals (poultry), animal food products and cases of human infection from the United Kingdom, the Netherlands and Germany demonstrated the existence of different clonal complexes lineages among ESBL-positive isolates from human sources and poultry, with only 1.2 % of isolates tested sharing the same multilocus sequence typing (MLST) lineage (Wu et al., 2013). The results suggest that minimising human-to-human transmission is essential to control the spread of ESBL-positive *E. coli* in humans and, furthermore, that antimicrobial practices in humans and animal may not be directly comparable in relation to their ability to select for and promote the spread of ESBL-positive *E. coli* in the two populations.

A further example of clonal spread of a drug-resistant organism in an animal population without the direct involvement of antimicrobials is provided by a study of an increased occurrence of VRE in Swedish broilers since 2000 (Nilsson et al., 2009). In this country the proportion of VRE-positive samples increased gradually from < 1 %, in 2000, to slightly over 40 % in 2005. Species identification, antimicrobial susceptibility determination, vancomycin resistance genotyping, MLST and characterisation of Tn1546 in the VRE isolates demonstrated that all isolates tested were *Enterococcus*

faecium and carried the *vanA* gene. A majority of the isolates had similar antibiograms, the same MLST and the Tn1546 transposon. These studies demonstrated that the increase in VRE isolates in broilers in Sweden from 2000 to 2005 was the result of the spread of one major clone and, furthermore, as avoparcin had not been used in broiler production in Sweden since 1986, this clonal spread had taken place without any obvious antimicrobial selective pressure (Nilsson et al., 2009).

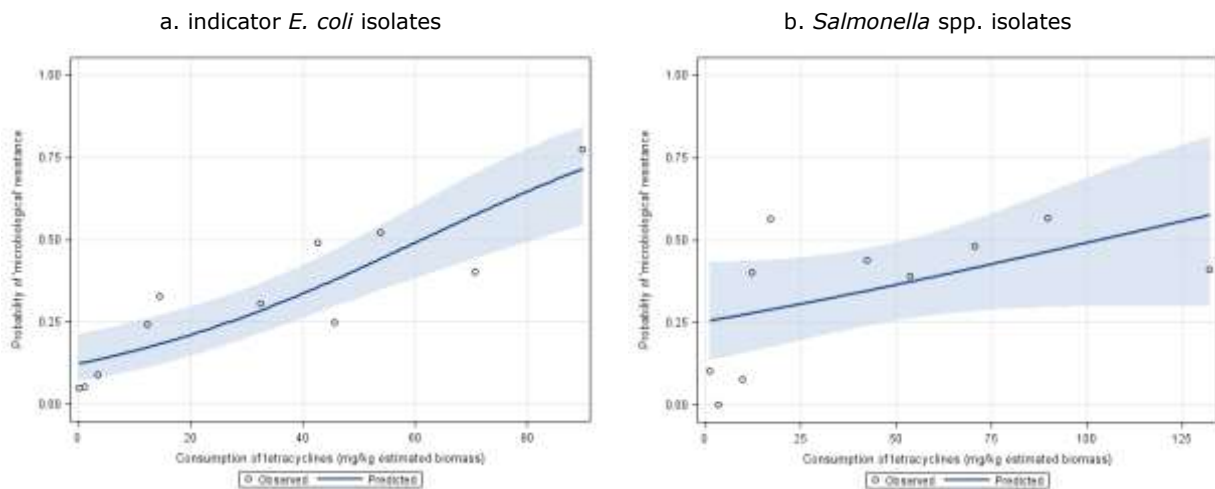
In conclusion, clonal spread of resistant strains in food-producing animals and the community has been demonstrated for *Salmonella* spp., ESBL-producing *E. coli*, MRSA and VRE, but to a much lesser extent for *Campylobacter* spp. In comparison with MRSA, clonal spread of these organisms is much less common in the hospital environment. Although antimicrobial use is undoubtedly an important risk factor in the clonal spread of, for example, ESBL-producing organisms in cattle (Snow et al., 2012) and poultry (Leverstein-van Hall et al., 2011), such spread can take place without any obvious direct antimicrobial involvement, as described above. Thus, clonal spread of both pathogens and non-pathogens can profoundly affect conclusions about antimicrobial consumption and resistance development, as in many cases resistance which is spread by this means may not be directly linked to antimicrobial consumption in either the human or animal sectors.

A fourth key parameter is the prevalence of resistance. In hospitals, if resistance is rare, the probability of misclassification is low. In such cases clinical samples may be most appropriate for studying antimicrobial resistance. Conversely, if resistance is common, use the outcome of colonisation may be preferable, as this generally precedes infection and affects more patients (D'Agata, 2005).

4. Annex D

4.1. Comparison between antimicrobial consumption and resistance from animals in 2011

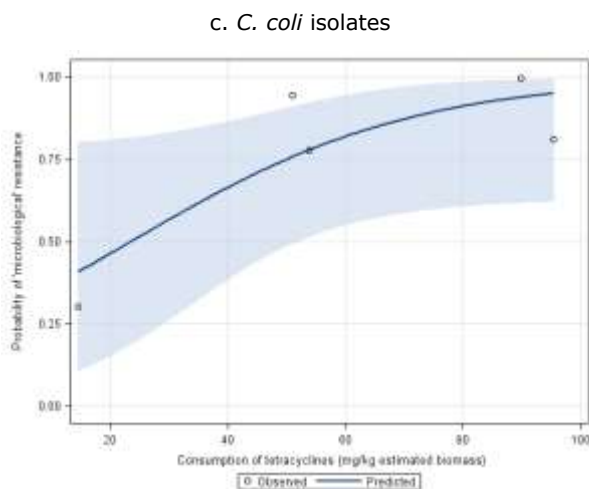
Figure 26. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of tetracyclines in food-producing animals and the probability of “microbiological” resistance to tetracyclines in (a) indicator *E. coli* isolates (MIC > 8 mg/L) from cattle, domestic fowl and pigs, (b) *Salmonella* spp. isolates (MIC > 8 mg/L) from cattle, domestic fowl and pigs, (c) *C. coli* isolates (MIC > 2 mg/L) from domestic fowl and pigs and (d) *C. jejuni* isolates (MIC > 2 mg/L) from cattle and domestic fowl for the year 2011¹—dots represent the countries involved in the analysis



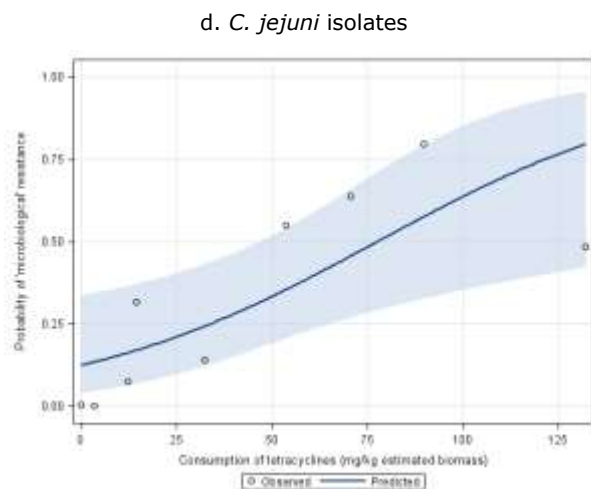
Countries included: AT, BE, CH, DE, DK, ES, FI, NL, NO, PL, SE
p-value < 0.05; OR = 1.033; 95 % PL CI: [1.020, 1.047]

Note: the association remains significantly positive after ignoring the point displayed on the graph upper right corner:
p-value < 0.05; OR = 1.029; 95 % PL CI: [1.013, 1.048]

Countries included: BE, DE, DK, EE, ES, FI, IE, IT, NL, SE
OR = 1.011; 95 % PL CI: [0.998, 1.024]



Countries included: CH, ES, FR, HU, NL
p-value < 0.05; OR = 1.042; 95 % PL CI: [1.003, 1.100]

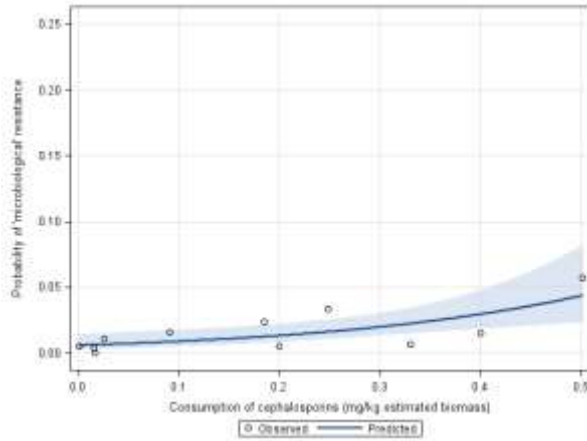


Countries included: AT, CH, DE, DK, ES, FI, IT, NL, NO
p-value < 0.05; OR = 1.025; 95 % PL CI: [1.008, 1.048]
Note: the association remains significantly positive after ignoring the point displayed on the graph middle right side:
p-value < 0.05; OR = 1.049; 95 % PL CI: [1.029, 1.074]

¹In the absence of 2011 resistance data, proxy data for years prior to 2011 may have been used.

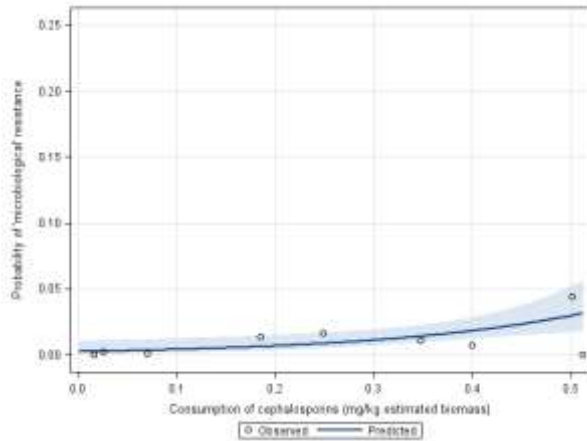
Figure 27. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of 3rd-generation cephalosporins in food-producing animals and the probability of “microbiological” resistance to cefotaxime in (a) indicator *E. coli* isolates (MIC > 0.25 mg/L) from cattle, domestic fowl and pigs and (b) *Salmonella* spp. isolates (MIC > 0.5 mg/L) from cattle, domestic fowl and pigs for the year 2011¹—dots represent the countries involved in the analysis

a. indicator *E. coli* isolates



Countries included: AT, BE, CH, DE, DK, ES, FI, NL, NO, PL, SE
 p-value < 0.05; OR_{0.1-unit increment} = 1.498; 95 % PL CI: [1.169, 1.951]

b. *Salmonella* spp. isolates

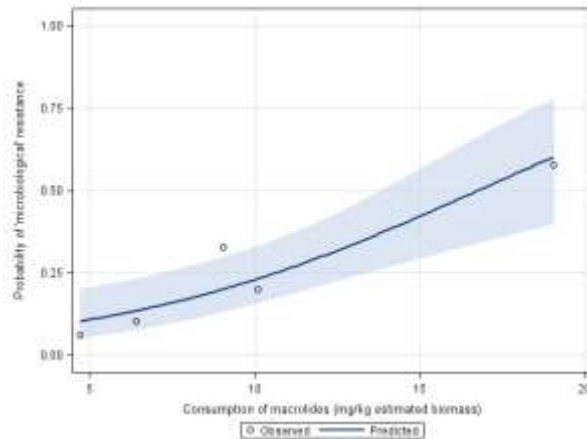


Countries included: BE, DE, DK, EE, ES, FI, IE, IT, NL, SE
 p-value < 0.05; OR_{0.1-unit increment} = 1.635; 95 % PL CI: [1.197, 2.375]

¹In the absence of 2011 resistance data, proxy data for years prior to 2011 may have been used.

Figure 28. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of macrolides in food-producing animals and the probability of “microbiological” resistance to erythromycin in (a) *C. coli* isolates (MIC > 16 mg/L) from domestic fowl and pigs and (b) *C. jejuni* isolates (MIC > 4 mg/L) from cattle and domestic fowl for the year 2011¹—dots represent the countries involved in the analysis

a. *C. coli* isolates



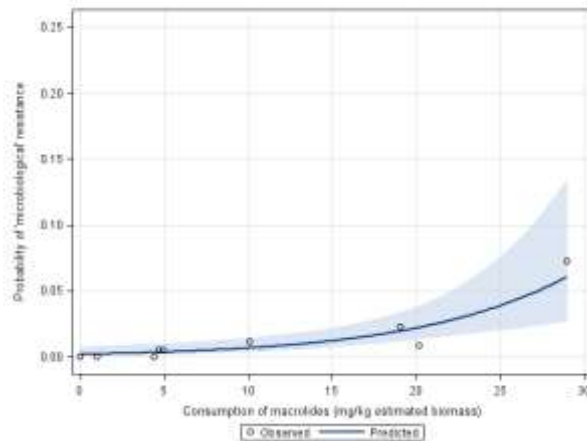
Countries included: CH, ES, FR, HU, NL

p-value < 0.05; OR = 1.197; 95 % PL CI: [1.097, 1.314]

Note: the association remains significantly positive after ignoring the point displayed on the graph upper right corner:

p-value < 0.05; OR = 1.346; 95 % PL CI: [1.004, 1.905]

b. *C. jejuni* isolates



Countries included: AT, CH, DE, DK, ES, FI, IT, NL, NO

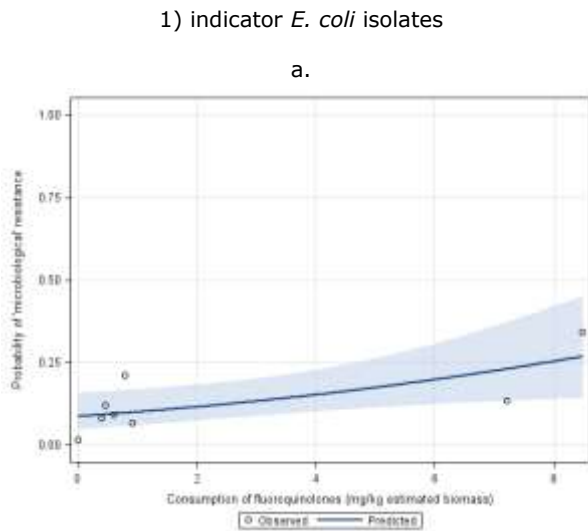
p-value < 0.05; OR = 1.125; 95 % PL CI: [1.059, 1.201]

Note: the association remains significantly positive after ignoring the point displayed on the graph right side:

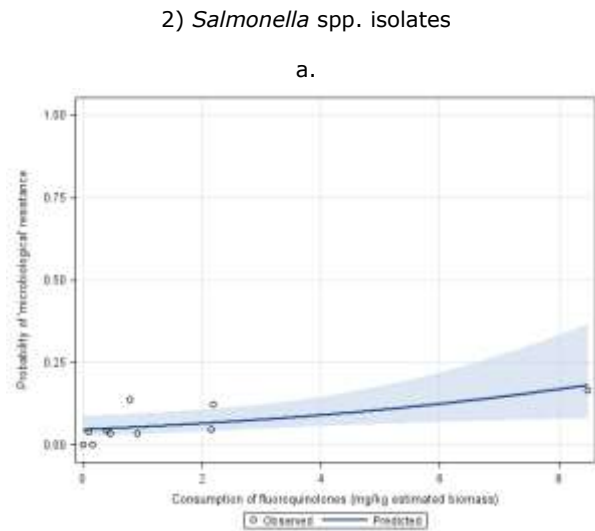
p-value < 0.05; OR = 1.099; 95 % PL CI: [1.002, 1.212]

¹In the absence of 2011 resistance data, proxy data for years prior to 2011 may have been used.

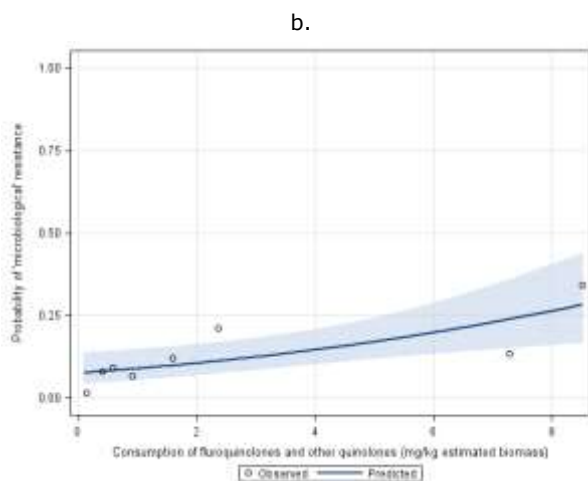
Figure 29. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of (A) fluoroquinolones and (B) fluoroquinolones plus other quinolones in food-producing animals and the probability of “microbiological” resistance to ciprofloxacin in (1) indicator *E. coli* isolates (MIC > 0.03 mg/L) from cattle, domestic fowl and pigs, (2) *Salmonella* spp. isolates (MIC > 0.06 mg/L) from cattle, domestic fowl and pigs, (3) *C. jejuni* isolates (MIC > 1 mg/L) from cattle and domestic fowl and (4) *C. coli* isolates (MIC > 1 mg/L) from domestic fowl and pigs for the year 2011¹—dots represent the countries involved in the analysis



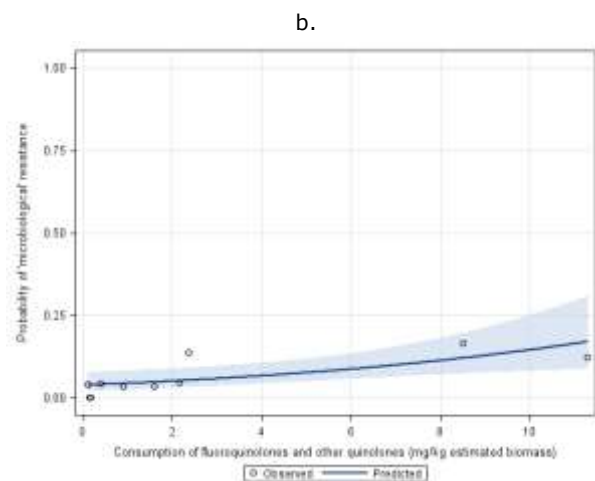
Countries included: AT, BE, CH, DE, DK, ES, NL, PL
 p-value < 0.05; OR = 1.173; 95 % PL CI: [1.026, 1.339]



Countries included: BE, DE, DK, EE, ES, FI, IE, IT, NL, SE
 p-value < 0.05; OR = 1.195; 95 % PL CI: [1.022, 1.380]
 Note: the association does not remain significantly positive after ignoring the point displayed on the right side of the graph:
 OR = 1.829; 95 % PL CI: [0.896, 3.699]



Countries included: AT, BE, CH, DE, DK, ES, NL, PL
 p-value < 0.05; OR = 1.203; 95 % PL CI: [1.064, 1.361]
 Note: the association does remain significantly positive after ignoring the two points displayed on the graph right side:
 p-value < 0.05; OR = 2.149; 95 % PL CI: [1.481, 3.145]

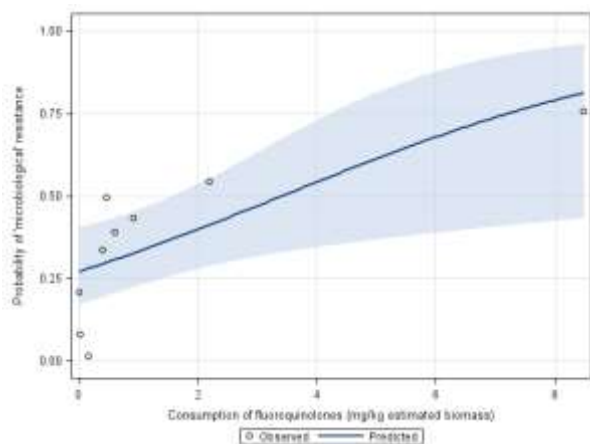


Countries included: BE, DE, DK, EE, ES, FI, IE, IT, NL, SE
 p-value < 0.05; OR = 1.154 ; 95 % PL CI: [1.041,1.279]
 Note: the association remains significantly positive after ignoring the two points displayed on the graph right side:
 p-value < 0.05; OR = 2.589; 95 % PL CI: [1.485, 4.862]

¹In the absence of 2011 resistance data, proxy data for years prior to 2011 may have been used.

3) *C. jejuni* isolates

a.

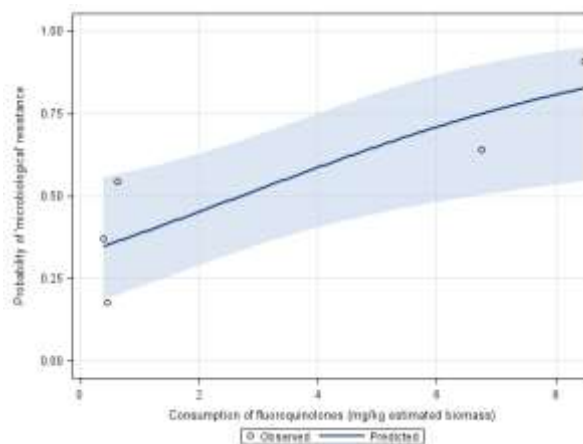


Countries included: AT, CH, DE, DK, ES, FI, IT, NL, NO
 p-value < 0.05; OR = 1.337; 95 % PL CI: [1.086, 1.768]

Note: the association remains significantly positive after ignoring the point displayed on the graph upper right corner:
 p-value < 0.05; OR = 2.39; 95 % PL CI: [1.111, 5.582]

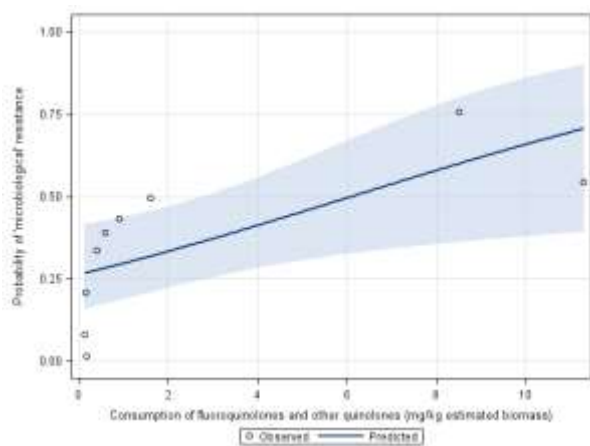
4) *C. coli* isolates

b.



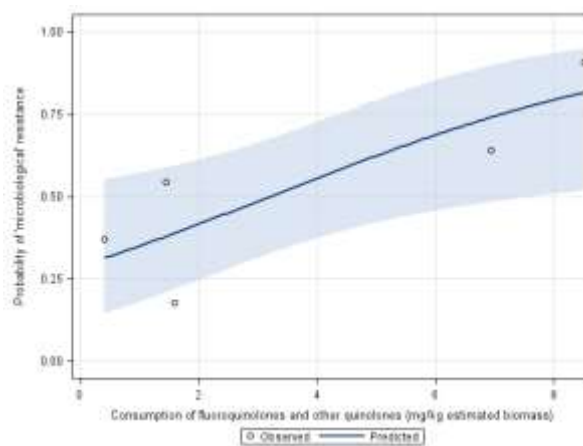
Countries included: CH, ES, FR, HU, NL
 p-value < 0.05; OR = 1.312; 95 % PL CI: [1.078, 1.656]

b.



Countries included: AT, CH, DE, DK, ES, FI, IT, NL, NO
 p-value < 0.05; OR = 1.184; 95 % PL CI: [1.034, 1.377]

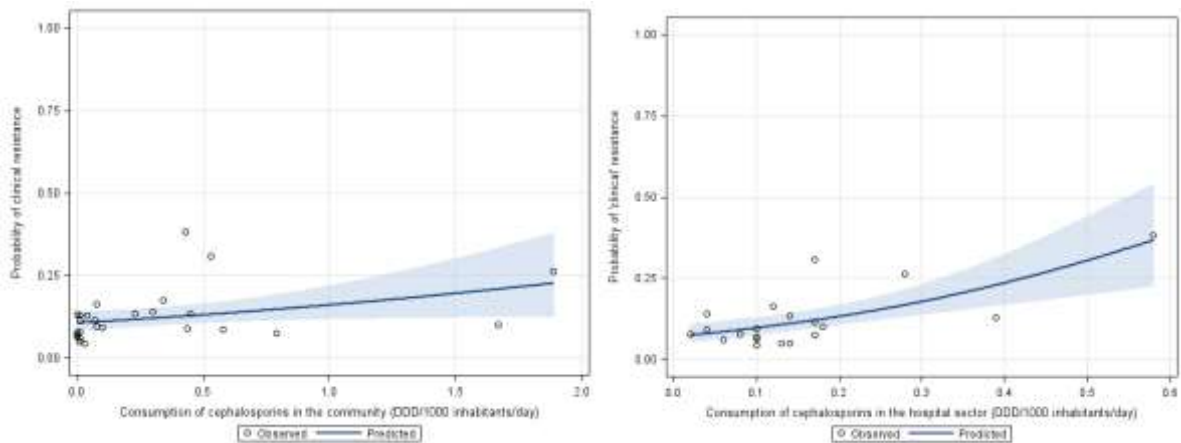
b.



Countries included: CH, ES, FR, HU, NL
 p-value < 0.05; OR = 1.326; 95 % PL CI: [1.063, 1.720]

4.2. Comparison between antimicrobial consumption in humans and resistance in bacteria from humans

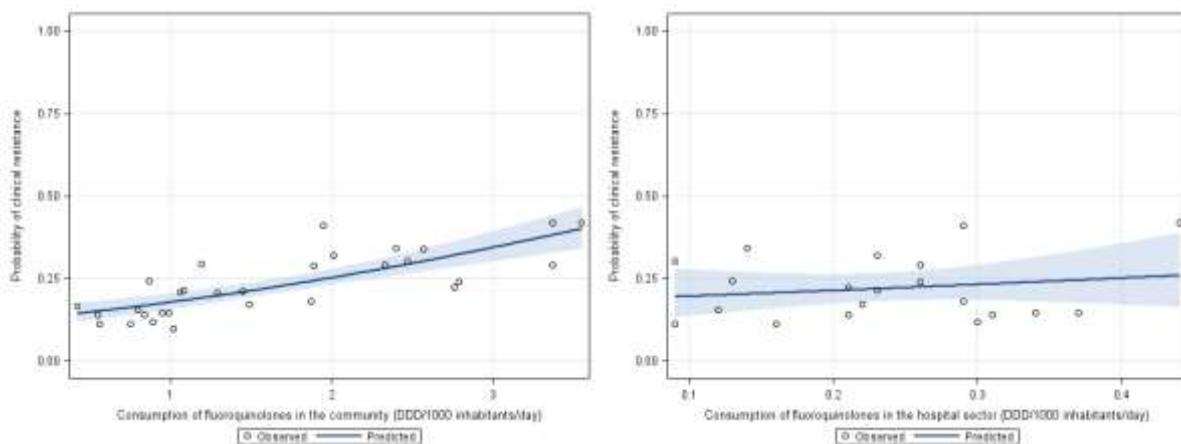
Figure 30. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national community and hospital consumption of 3rd- and 4th-generation cephalosporins in humans and the probability of clinical resistance to 3rd-generation cephalosporins in *E. coli* isolates from human BSIs for the year 2012—dots represent the countries involved in the analysis



Countries included: AT, BE, BG, CZ, DE, DK, EE, FI, FR, GR, HR, HU, IE, IT, LV, LT, LU, MT, NL, NO, PL, PT, SK, SI, ES, SE, UK
p-value = 0.049; OR = 1.618; 95 % PL CI: [1.002, 2.519]

Countries included: BE, BG, DK, EE, FI, FR, GR, HR, IE, IT, LT, LU, LV, MT, NL, NO, PT, SE, SI, SK
p-value < 0.05; OR_{0.1-unit increment} = 1.421;
95 % PL CI: [1.196, 1.681]

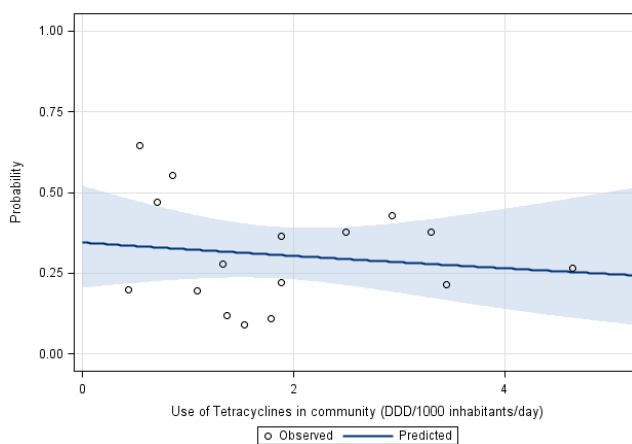
Figure 31. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national community and hospital consumption of fluoroquinolones in humans and the probability of clinical resistance to fluoroquinolones in *E. coli* isolates from human BSIs for the year 2012—dots represent the countries involved in the analysis



30 countries included: AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, GR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK
p-value < 0.0001; OR = 1.555; 95 % PL CI: [1.360, 1.778]

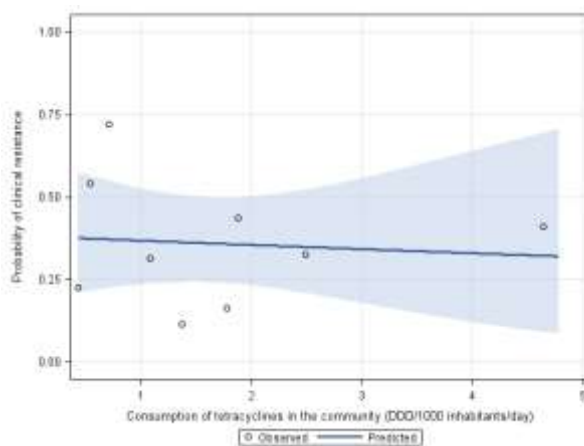
20 countries included: BE, BG, DK, EE, FI, FR, GR, HR, IE, IT, LT, LU, LV, MT, NL, NO, PT, SE, SI, SK
p-value = 0.44; OR = 2.873; 95 % PL CI: [0.196, 41.794] - not significant

Figure 32. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of tetracyclines in the community in humans and the probability of clinical resistance to tetracycline in *Salmonella* spp. from human infections for the year 2012—dots represent the countries involved in the analysis



16 countries included: AT, EE, ES, FR, GR, HU, IE, IT, LT, LU, NL, NO, RO, SI, SK, UK
 p-value = 0.58; OR = 0.910; 95 % PL CI: [0.645, 1.260] - not significant

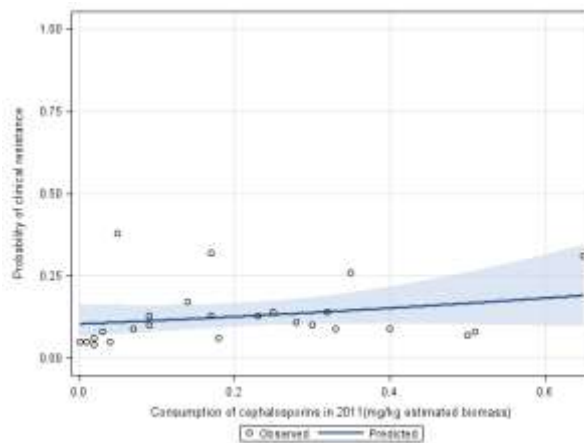
Figure 33. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of tetracyclines in the community in humans and the probability of clinical resistance to tetracycline in *C. jejuni* from human infections for the year 2012—dots represent the countries involved in the analysis



Countries included: AT, EE, ES, IT, LU, NL, SI, SK, UK
 p-value = 0.58; OR = 0.910; 95 % PL CI: [0.645, 1.260] - not significant

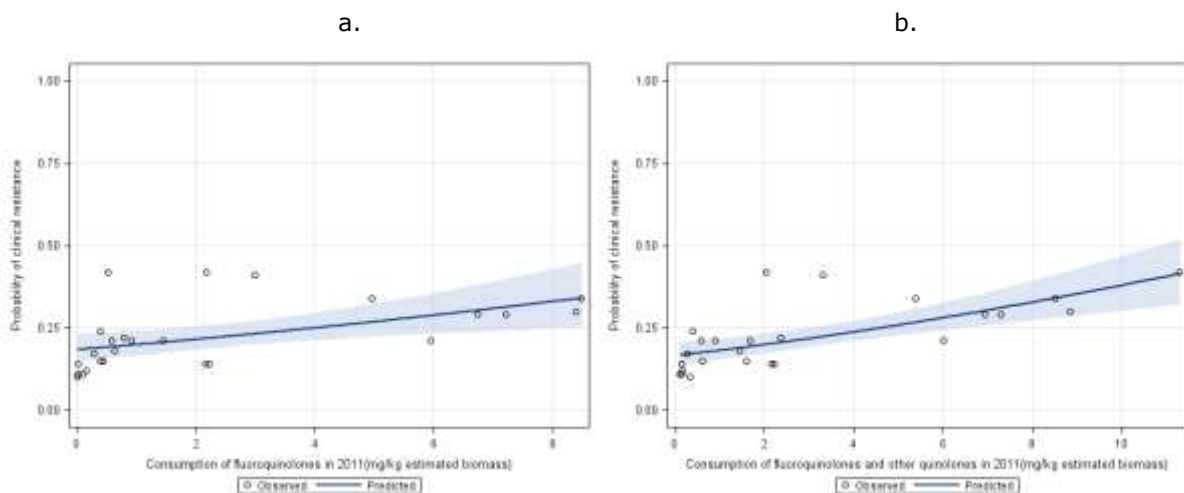
4.3. Comparison between antimicrobial consumption in food-producing animals and resistance in bacteria from humans, 2011

Figure 34. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of 3rd- and 4th-generation cephalosporins in food-producing animals and the probability of clinical resistance to 3rd- and 4th-generation cephalosporins in *E. coli* isolates from human BSIs for the year 2011—dots represent the countries involved in the analysis



25 countries included: AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, SE, SI, SK, UK
 p-value = 0.23; OR=1.116; 95 % PL CI [0.933, 1.327] - not significant

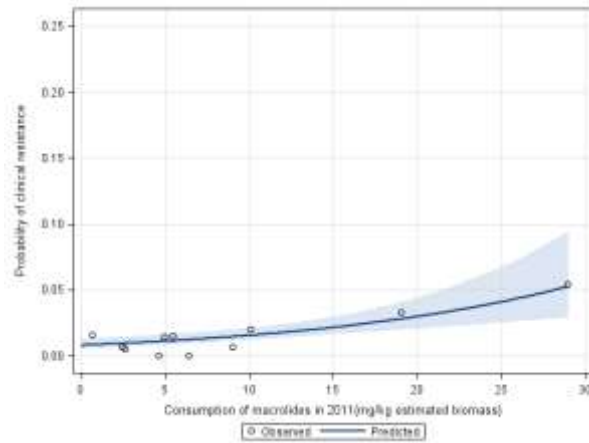
Figure 35. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of (a) fluoroquinolones and (b) fluoroquinolones plus other quinolones in food-producing animals in 2011 and the probability of clinical resistance to fluoroquinolones in *E. coli* isolates from human BSIs for the year 2012—dots represent the countries involved in the analysis



25 countries included: AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, SE, SI, SK, UK
 p-value = 0.006; OR = 1.103; 95 % PL CI: [1.029, 1.180]

25 countries included: AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, SE, SI, SK, UK
 p-value < 0.0001; OR = 1.119; 95 % PL CI [1.066, 1.175]

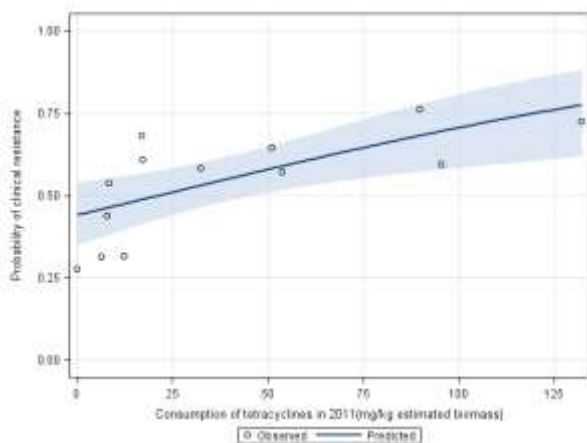
Figure 36. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of macrolides in food-producing animals in 2011 and the probability of clinical resistance to erythromycin in *C. jejuni* isolates from human infections for the year 2011—dots represent the countries involved in the analysis



Countries included: AT, EE, ES, FR, HU, IT, LT, LU, NL, SI, SK, UK
 p-value < 0.001; OR = 1.068; 95 % PL CI [1.033, 1.101]

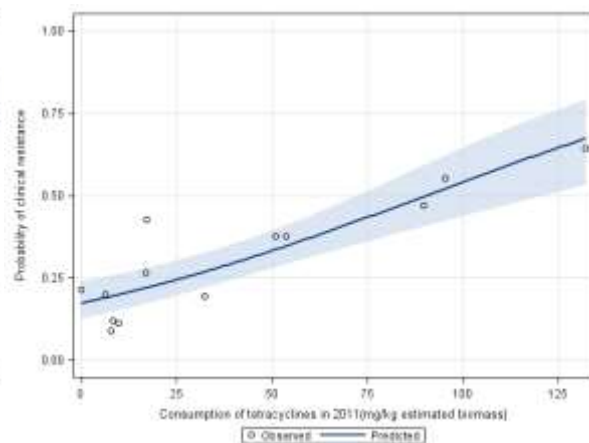
Figure 37. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of tetracyclines in food-producing animals in 2011 and the probability of clinical resistance to tetracycline in (a) *S. Typhimurium* isolates from human infections and (b) *Salmonella* spp. isolates from human infections for the year 2012—dots represent the countries involved in the analysis

a. *S. Typhimurium*



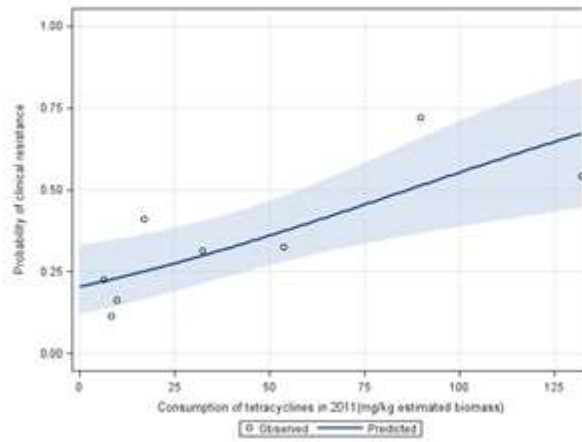
Countries included: AT, DK, ES, FR, HU, IE, IT, LT, LU, NL, NO, SI, SK, UK
 p-value = 0.003; OR = 1.011; 95 % PL CI [1.004, 1.019]

b. *Salmonella* spp.



Countries included: AT, EE, ES, FR, HU, IE, IT, LT, LU, NL, NO, SI, SK, UK
 p-value < 0.001; OR = 1.017; 95 % PL CI [1.011, 1.024]

Figure 38. Logistic regression analysis curves with OR estimates and 95 % PL CIs of the national consumption of tetracyclines in food-producing animals in 2012 and the probability of clinical resistance to tetracycline in *C. jejuni* isolates from human infections for the year 2012—dots represent the countries involved in the analysis



Countries included: AT, EE, ES, FR, HU, IT, LT, NL, SI, SK, UK
p-value = 0.001; OR = 1.016; 95 % PL CI [1.006, 1.027]

5. Annex E

5.1. Abbreviations

AMR	antimicrobial resistance
AST	antimicrobial susceptibility testing
ATC	anatomical therapeutic chemical
BSI	bloodstream infections
CA-SFM	Comité Antibiogramme–Société Française de Microbiologie
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIA	critically important antimicrobial
CLSI	Clinical and Laboratory Standards Institute
CVMP	Committee for Medicinal Products for Veterinary Use
DDD	defined daily dose
DT	definitive phage type
EARS-Net	European Antimicrobial Resistance Surveillance Network
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECOFF	epidemiological cut-off value
EEA	European Economic Area
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EP	European Parliament
EQA	External Quality Assessment
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESBL	extended-spectrum beta-lactamase
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAO	Food and Agriculture Organization
FAOSTAT	FAO Statistical Databases
FEDIAF	The European Pet Food Industry
FWD-Net	Food- and Waterborne Diseases and Zoonoses Network
JIA CRA	Joint Interagency Antimicrobial Consumption and Resistance Analysis
MAH	marketing authorisation holder
MDR	multidrug-resistant
MIC	minimum inhibitory concentration
MLST	multi-locus sequence typing
MRL	maximum residue limit
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MS	Member State
NCA	National Competent Authority
NPHRL	National Public Health Reference Laboratories
OR	odds ratio
PCU	population correction unit
PL CI	profile-likelihood confidence interval
SPC	Summary of the Product Characteristics
spp.	species (plural)
STEC	Shiga-toxin-producing <i>Escherichia coli</i> (synonymous with VTEC)
TESSy	The European Surveillance System
VMP	veterinary medicinal product
VRE	vancomycin-resistant enterococci
VTEC	verocytotoxin-producing <i>Escherichia coli</i> (synonymous with STEC)
WHO	World Health Organization

ISO Code	Country
AT	Austria
BE	Belgium
BG	Bulgaria
CR	Croatia
CY	Cyprus
CZ	Czech Republic
DK	Denmark
EE	Estonia
FI	Finland
FR	France
DE	Germany
GR	Greece
HU	Hungary
IE	Ireland
IS	Iceland
IT	Italy
LV	Latvia
LT	Lithuania
LU	Luxembourg
MT	Malta
NL	Netherlands
NO	Norway
PL	Poland
PT	Portugal
RO	Romania
SL	Slovakia
SI	Slovenia
ES	Spain
SE	Sweden
CH	Switzerland
UK	United Kingdom

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