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EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

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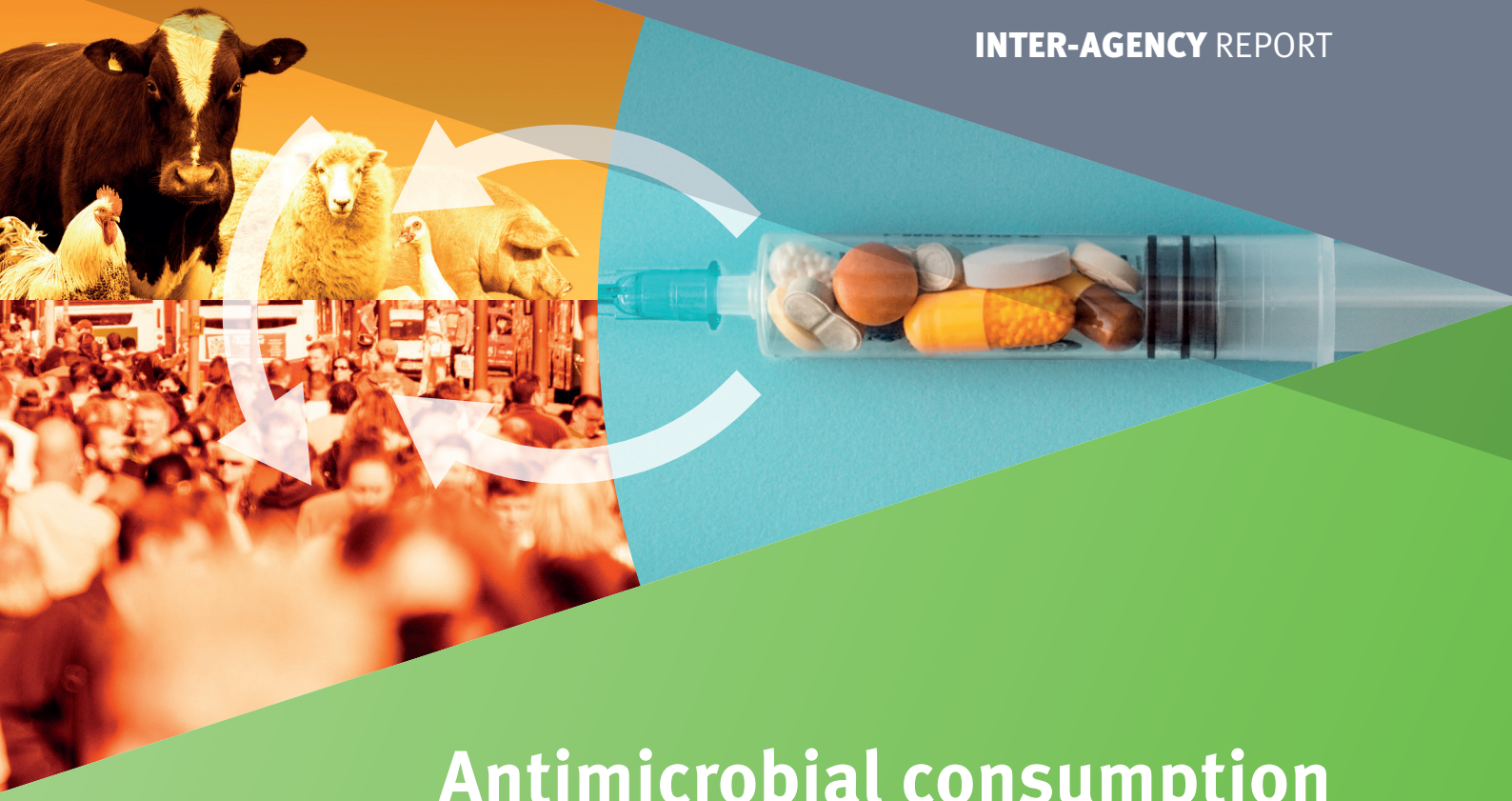
European Food Safety Authority

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

INTER-AGENCY REPORT



Antimicrobial consumption and resistance in bacteria from humans and animals

Third joint inter-agency report on integrated analysis of antimicrobial agent consumption and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA

JIACRA III
2016–2018

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This joint report is based on data provided by the above-mentioned networks and major contributions from the following experts: Ole Heuer, Liselotte Diaz Högberg, Joana Gomes Dias, Christina Greko (chair), Elias Iosifidis, Chantal Quinten, Jonas Samuelsson, Vera Vlahović-Palčevski, Klaus Weist, Therese Westrell, and Dominique Monnet (ECDC); Pierre-Alexandre Belœil, Ernesto Liebana, Karoline Nørstrud, Bernd-Alois Tenhagen and Marc Aerts (EFSA), and Claire Chauvin, Kari Grave, Gérard Moulin, Arno Muller, Barbara Freischem, Kristine Ignate, Helen Jukes, Zoltan Kunsagi, Filipa Mendes Oliveira and Ana B. Vidal (EMA). Special thanks go to Christina Greko for chairing the working group.

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Procedures for adoption of the report

Representatives of the different surveillance/monitoring networks of the countries, who are in charge of providing the data were consulted during the preparation of the joint report. ECDC, EFSA and EMA have each established their own procedure for endorsement or adoption of the joint report according to their internal rules.

ECDC adopted the report on 11 June 2021, after consultation with the European Antimicrobial Resistance Surveillance Network (EARS-Net), the European Surveillance Antimicrobial Consumption Network (ESAC-Net), the Food and Waterborne Diseases and Zoonoses Network (FWD-Net), and the ECDC Advisory Forum. EFSA approved the report on 17 May 2021, after consultation with its Scientific Network for Zoonosis Monitoring Data. EMA adopted the report on 11 May 2021. Before endorsement, the report was circulated for consultation to the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) network.

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Abbreviations

AMC	antimicrobial consumption
AMEG	Antimicrobial Advice ad hoc Expert Group (EMA)
AmpC	a group of enzymes that degrade beta-lactam antimicrobials
AMR	antimicrobial resistance
AST	antimicrobial susceptibility testing
ATC	anatomical therapeutic chemical classification system
ATCvet	anatomical therapeutic chemical animals
BIOHAZ	Panel on Biological Hazards (EFSA)
BSI	bloodstream infections
CHMP	Committee for Medicinal Products for Human Use (EMA)
CI	confidence interval
CLSI	Clinical and Laboratory Standards Institute
CPE	carbapenemase-producing Enterobacterales
CRE	carbapenem-resistant Enterobacterales
CVMP	Committee for Medicinal Products for Veterinary Use (EMA)
DDD	defined daily dose
DDDvet	defined daily dose for animals (by animal species/type of animal)
EARS-Net	European Antimicrobial Resistance Surveillance Network (ECDC)
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
ESAC-Net	European Surveillance of Antimicrobial Consumption Network (ECDC)
ESBL	extended-spectrum beta-lactamase
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption (EMA)
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAO	Food and Agriculture Organization
FWD-Net	Food- and Waterborne Diseases and Zoonoses Network (ECDC)
JIACRA	Joint Interagency Antimicrobial Consumption and Resistance Analysis
MAH	marketing authorisation holder
MDR	multidrug-resistant
MIC	minimum inhibitory concentration
MRSA	meticillin-resistant *Staphylococcus aureus*
NPHRL	national public health reference laboratory
OR	odds ratio
PCU	population correction unit
PL CI	profile likelihood confidence interval
PLS-PM	Partial Least Squares Path Modelling
SIMR	summary indicator of microbiological resistance
SPC	Summary of Product Characteristics
spp.	species (plural)
TESSy	The European Surveillance System (ECDC)
VMP	veterinary medicinal product
WHO	World Health Organization
WHO CC	World Health Organization Collaborating Centre for Drug Statistics Methodology

List of countries[1]

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

1 According to ISO 3166 — Codes for the representation of names of countries and their subdivisions

Executive summary

This report was produced as a collaboration between the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA). It is the third joint inter-agency report on integrated analysis of antimicrobial agent consumption and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals (JIACRA), prepared by the three agencies at the request of the European Commission (EC).

Antimicrobial resistance (AMR) constitutes a significant public health problem in Europe as well as in other parts of the world, representing a serious social and economic burden and a threat to animal health and production. The main driver behind AMR is antimicrobial consumption (AMC), in both humans and food-producing animals. Recognising that human and animal health are interconnected, this report is based on a 'One-Health' approach.

Aim and scope of the report

This report provides an integrated analysis of possible relationships between AMC in humans and food-producing animals and the occurrence of AMR in bacteria from humans and food-producing animals.

Methods

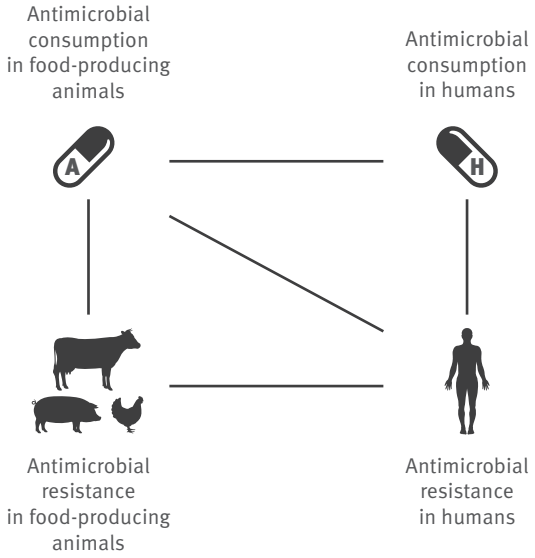
The results and conclusions of this report are mainly based on data from 2016, 2017 and 2018. For the comparison between AMC in food-producing animals and humans, data from the intermediate year 2017 were used, and for trend analyses data for 2014 and 2015 were also included. Some analyses involving AMR in bacterial isolates from animals also included the years 2014 and 2015, as different animal species are monitored in even and odd years, respectively.

The data originate from five different surveillance/monitoring networks coordinated by the agencies and cover the European Union (EU) Member States, two European Economic Area (EEA) countries (Iceland and Norway) and Switzerland (for data on food-producing animals). The data were collected as part of ongoing clinical and epidemiological surveillance/monitoring and not specifically for the purposes of this report. Differences between the data collection systems of the networks are acknowledged (e.g. bacterial isolates from humans are sampled from clinically-ill individuals in a healthcare setting, while isolates from food-producing animals are sampled from healthy animals, either at the farm or at slaughter). The integrated analyses of data from humans and food-producing animals presented here focused on particular combinations of antimicrobials and bacterial species considered of importance for public health. These analyses did not consider the potential effects of co-selection of resistance genes. To facilitate the comparison between AMC in humans and in food-producing animals, data for AMC in humans, expressed as defined daily doses (DDDs) per 1 000 inhabitants per day, were converted into mg of active antimicrobial substance used per kg of estimated biomass. To allow analyses of the relationships between AMC and AMR in pigs and poultry, respectively, a proxy for AMC in each species was obtained in the form of a technical estimation from sales data.

Through a series of univariate analyses, the potential relationships between consumption of selected antimicrobial classes and AMR in selected bacteria in humans and food-producing animals were examined. The potential relationships between AMR in bacteria from humans and AMR in bacteria from food-producing animals, and between AMC in humans and AMC in food-producing animals were also examined (Figure I-II).

Finally, five primary key indicators, originating from the harmonised indicators for AMC and AMR developed by ECDC, EFSA and EMA, were jointly presented at national level. For humans, the primary indicators included the total consumption of antimicrobials for systemic use expressed as DDD per 1000 inhabitants and per day, the proportion of meticillin-resistant *Staphylococcus aureus* (MRSA) and the proportion of third-generation

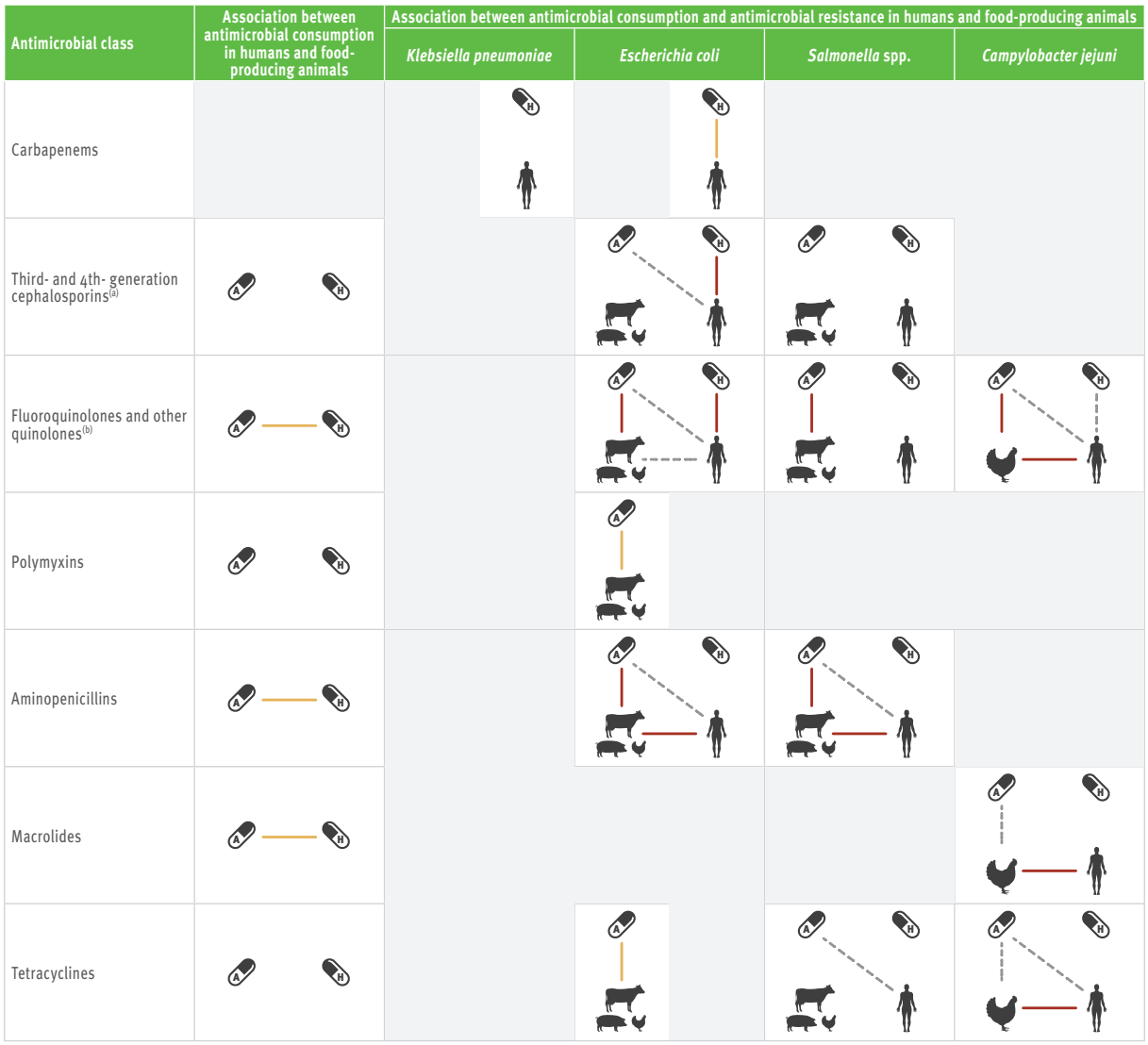
Figure I: Schematic overview of the potential associations between antimicrobial consumption and antimicrobial resistance in humans and food-producing animals investigated in this report



The relationship between AMC in humans and AMR in bacteria from food-producing animals was not addressed in this report.

For analyses covering one sector (food-producing animals or humans), only univariate analyses were performed.

Figure II: Schematic overview of the potential associations between antimicrobial consumption and antimicrobial resistance in humans and food-producing animals investigated in this report

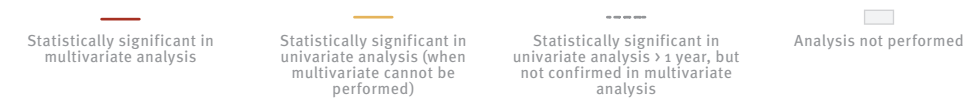


a) For antimicrobial resistance, only data on third-generation cephalosporins are included.

b) For antimicrobial resistance, only data on fluoroquinolones are included.

Each box contains the elements (represented as per the symbols below) for which associations were investigated:

The lines indicate significant associations:



cephalosporin resistant *Escherichia coli*. For food-producing animals, the primary indicators presented included the overall sales, expressed as mg/population correction unit (PCU) and the proportion of indicator *E. coli* from broilers, fattening turkeys, fattening pigs and calves, weighted by PCU, that were completely susceptible to a predefined panel of antimicrobials. Results were based on the years 2014–2018.

Total EU/EEA population-weighted mean antimicrobial consumption in humans and food-producing animals

In 2017, the EU/EEA population-weighted mean AMC in 29 EU/ EEA countries, expressed in mg of active substance per kg estimated biomass, was 130.0 mg per kg in humans (range 52.8–212.6) and 108.3 mg per kg in food-producing animals (range 3.1–423.1). However, the results for food-producing animals and humans varied by country and by antimicrobial class.

AMC in 2017 was lower in food-producing animals than in humans in 20 of 29 EU/EEA countries. In one country AMC was similar, and in the eight remaining countries AMC was higher in food-producing animals than in humans. This was different compared to the time periods covered in previous JIACRA reports, where the overall AMC in food-producing animals was higher than in humans. This shift was explained by a statistically significant decrease in the population-weighted mean AMC in food-producing animals (based on data from 27 EU/EEA countries) between 2014 and 2018 (Figure III).

Carbapenems

Carbapenems are not authorised for use in food-producing animals in the EU and therefore only carbapenem consumption in humans was analysed in this report.

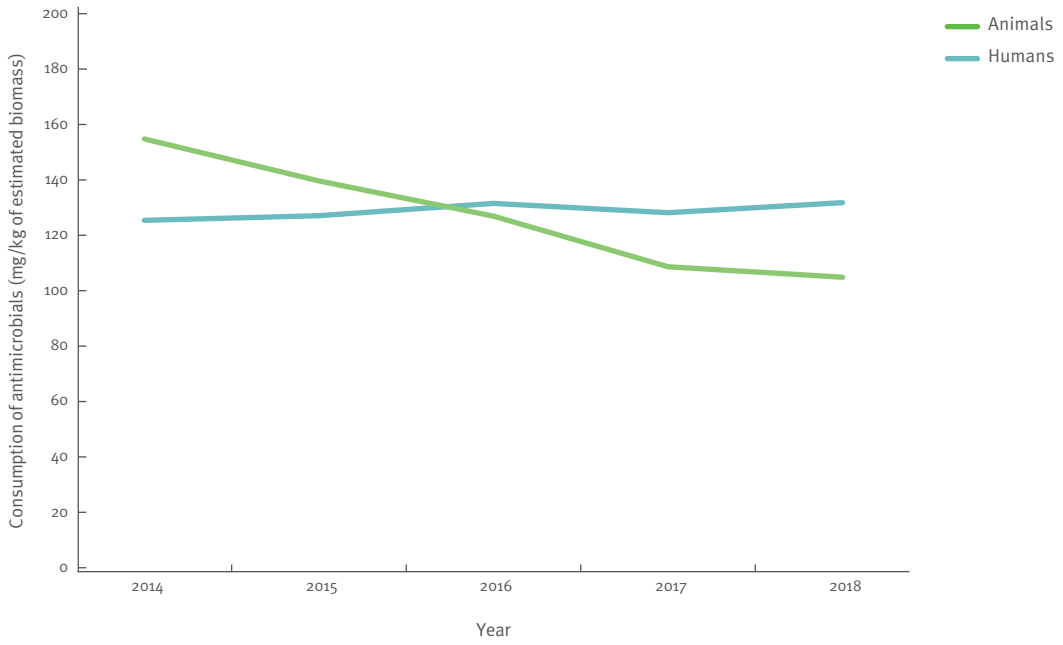
A statistically significant positive association was found between consumption of carbapenems in humans and resistance to carbapenems in invasive *Escherichia coli* isolates from humans for all years (2016–2018) (Figure II).

Third- and fourth-generation cephalosporins

The EU/EEA population-weighted consumption of third- and fourth-generation cephalosporins in 2017 was markedly higher in humans than in food-producing animals.

Statistically significant positive associations between resistance to third-generation cephalosporins in invasive *E. coli* isolates from humans and the consumption of third- and fourth-generation cephalosporins, both in humans and in food-producing animals (in relation to indicator *E. coli* from healthy animals at slaughter), were found for all years (2016–2018). However, the only

Figure III: Population-weighted mean of the total consumption of antimicrobials in humans[a] and food-producing animals[b] in 27 EU/EEA countries[c] for which data were available for both humans and food-producing animals, for 2014–2018



(a) For humans: ATC J01 Antibacterials for systemic use.
(b) For food-producing animals: ATCvet QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51, QP51AG
(c) AT, BE, BG, CY, DE, DK, EE, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK.

significant relationship retained in the multivariate analysis model of resistance in *E. coli* isolates from humans was the consumption of third- and fourth-generation cephalosporins in humans (R^2=0.69, 95% confidence interval: 0.41–0.92) (Figure II).

A separate analysis of data from food-producing animals based on the time periods 2015–2016, 2016–2017 and 2017–2018 showed a statistically significant association between the prevalence of extended-spectrum beta-lactamase (ESBL)-producing and AmpC beta-lactamase-producing *E. coli* and consumption of third- and fourth-generation cephalosporins.

Fluoroquinolones

The EU/EEA population-weighted consumption of fluoroquinolones and other quinolones in 2017 was higher in humans than in food-producing animals in most countries, but the relative difference in consumption between humans and food-producing animals was less than that observed for third- and fourth-generation cephalosporins. A statistically significant positive association between consumption of fluoroquinolones and other quinolones in humans and consumption of these antimicrobials in food-producing animals was observed for all years (2016–2018) - i.e. countries with high consumption among humans tended to also have a high consumption in food-producing animals and vice versa (Figure II).

A statistically significant positive association was found between consumption of fluoroquinolones and other quinolones in humans and resistance to fluoroquinolones in invasive *E. coli* from humans for all years (2016–2018). The same was observed for consumption of fluoroquinolones and other quinolones in food-producing animals and resistance to fluoroquinolones in indicator *E. coli* from food-producing animals for all years (2014–2018). Both associations were also observed in the multivariate analyses (R^2=0.64, 95% confidence interval: 0.47–0.83 and R^2=0.63, 95% confidence interval 0.47–0.82, respectively). A statistically significant positive association was also found between fluoroquinolone resistance in invasive *E. coli* isolates from humans and both consumption of fluoroquinolones and other quinolones in food-producing animals and fluoroquinolone resistance in indicator *E. coli* isolates from the different food-producing animal species (broilers, turkeys, pigs and calves) for all years (2016–2018). However, these associations were not confirmed in the multivariate analyses (Figure II).

For *Salmonella* spp., a statistically significant positive association was only found between consumption of fluoroquinolones and other quinolones in poultry and resistance to fluoroquinolones in *Salmonella* spp. from poultry. In the multivariate analysis, a direct effect from the consumption of fluoroquinolones and other quinolones in food-producing animals on the occurrence of resistance in *Salmonella* spp. from food-producing animals was also found (R^2=0.46, 95% confidence interval 0.24–0.97) (Figure II).

The consumption of fluoroquinolones and other quinolones in both food-producing animals and humans was significantly associated with fluoroquinolone resistance in *Campylobacter jejuni* from humans. Fluoroquinolone resistance in *C. jejuni* from turkeys and broilers was significantly associated with fluoroquinolone resistance in *C. jejuni* from humans. For poultry, consumption of fluoroquinolones and other quinolones was associated with fluoroquinolone resistance in *C. jejuni*. The multivariate analysis showed a direct effect of both consumption of fluoroquinolones and other quinolones in poultry (R^2=0.40, 95% confidence interval 0.18–0.67) and resistance in *C. jejuni* from poultry on the occurrence of fluoroquinolone resistance in *C. jejuni* from humans (R^2=0.79, 95% confidence interval 0.43–0.94) (Figure II).

Polymyxins

Polymyxins (colistin) were almost exclusively used in food-producing animals and the EU/EEA population-weighted mean consumption of polymyxins in food-producing animals by far outweighed consumption in humans in 2017. This was despite the fact that sales of polymyxins in animals declined by nearly 70% between 2011 and 2018. In 2017, large variations were observed between countries and a few countries reported no consumption of polymyxins in food-producing animals.

The consumption of polymyxins in food-producing animals overall, as well as specifically in poultry and pigs, was significantly associated with resistance to polymyxins in *E. coli* from food-producing animals for all years (single or combined years within 2014–2018 depending on analysis) (Figure II).

Multivariate analysis was not performed as data on polymyxin resistance in bacterial isolates from humans were not available.

Aminopenicillins

In 2017, the EU/EEA population-weighted consumption of aminopenicillins was lower in food-producing animals than in humans, except in two countries where consumption was similar in both sectors. A statistically significant positive association was observed between consumption of aminopenicillins in humans and in food-producing animals for all years (2016–2018) (Figure II).

In food-producing animals, statistically significant positive associations between consumption of aminopenicillins and ampicillin resistance were found for all years (2016 and 2018) in indicator *E. coli* and for 2016 in *Salmonella* spp. from poultry. Similarly, a statistically significant positive association between ampicillin resistance in indicator *E. coli* from food-producing animals (turkeys, broilers, pigs and calves) and ampicillin resistance in invasive *E. coli* from humans was observed for all years (2016–2018), and between *Salmonella* spp. from turkeys and from humans in 2018. Statistically significant positive associations were also observed in the univariate analyses between consumption of

amino-penicillins in food-producing animals and resistance to aminopenicillins in invasive *E. coli* and in *Salmonella* spp. (particularly *S.* Typhimurium), respectively, from humans. In both the multivariate analysis for *E. coli* and for *Salmonella* spp., aminopenicillin resistance in bacterial isolates from humans was significantly associated with resistance in bacterial isolates from food-producing animals (R^2=0.50, 95% confidence interval 0.23–0.77 and R^2=0.36, 95% confidence interval 0.02–0.81, respectively), which, in turn, was significantly associated with consumption of aminopenicillins in food-producing animals (R^2=0.59, 95% confidence interval 45–78, and R^2=0.41, 95% confidence interval 0.24–0.88, respectively) (Figure II).

Macrolides

The EU/EEA population-weighted consumption of macrolides was similar in food-producing animals and humans in 2017. A statistically significant positive association between consumption of macrolides in humans and in food-producing animals was observed for 2016 and 2017) (Figure II).

In food-producing animals, statistically significant positive associations were observed between the consumption of macrolides in poultry and resistance to macrolides in *C. jejuni* from poultry for both years studied (2016 and 2018). Resistance to macrolides in *C. jejuni* from turkeys in 2016 was associated with resistance to macrolides in *C. jejuni* from humans for only one of the two years studied (2016). In the multivariate analysis, macrolide resistance in *C. jejuni* from humans was related to macrolide resistance in *C. jejuni* from poultry, but the latter only explained about one quarter of the variance of macrolide resistance in *C. jejuni* from humans (R^2=0.23, 95% confidence interval 0.01–0.68) (Figure II).

Tetracyclines

In 2017, the EU/EEA population-weighted consumption of tetracyclines was markedly higher in food-producing animals than in humans, with large variations in consumption among food-producing animals between countries.

In humans, a statistically significant positive association was observed between the consumption of tetracyclines and the occurrence of tetracycline resistance in *S.* Enteritidis in 2017.

In food-producing animals, statistically significant positive associations were observed between consumption of tetracyclines and tetracycline resistance in indicator *E. coli*, as well as tetracycline resistance in *C. jejuni* and *Salmonella* spp. from poultry (for *Salmonella* spp. only for 2018).

A statistically significant positive association was found between tetracycline resistance in *C. jejuni* from turkeys (2016 and 2018) and from broilers (2016) and tetracycline resistance in *C. jejuni* from humans.

Statistically significant associations were observed between tetracycline consumption in food-producing animals and tetracycline resistance in *Salmonella* spp. and *C. jejuni* from humans for all years (2016–2018) and for *S.* Typhimurium for 2016 and 2018.

In the multivariate analysis for *C. jejuni*, tetracycline resistance in *C. jejuni* from humans was related to tetracycline resistance in *C. jejuni* from poultry (R^2=0.62, 95% confidence interval 0.38–0.87) (Figure II).

Primary key indicators

Substantial variations of all five primary key indicators were observed among EU/EEA countries, and between years within each country. In a few countries, the key indicators were all either at a consistently high or consistently low level during the study period (2014–2018).

In most countries, the key AMC indicators decreased, both for food-producing animals and in humans.

For key AMR indicators, the proportion of *E. coli* from food-producing animals with complete antimicrobial susceptibility increased in the majority of EU/EEA countries, whereas the proportion of *E. coli* from humans with resistance to third-generation cephalosporins increased in 12 countries and decreased in 11 countries. The proportion of *Staphylococcus aureus* resistant to meticillin (i.e. MRSA) decreased in most EU/EEA countries.

For all four time-intervals studied (2014–2015, 2015–2016, 2016–2017, 2017–2018), there was a statistically significant negative association between the primary key indicators in food producing animals, consumption of antimicrobials and the occurrence of completely susceptible indicator *E. coli*. Thus, there was a clear and consistently lower probability of detecting completely susceptible indicator *E. coli* when consumption of antimicrobials was higher.

Conclusion

When assessed per kg biomass, the overall antimicrobial consumption was lower in food-producing animals than in humans during the timeframe covered in this report (2016–2018). This is the first time this has happened since JIACRA was initiated (time series starting in 2011). This change is the result of a significant decrease in AMC among food-producing animals, suggesting that the measures taken at country-level to reduce the use of antimicrobials in food-producing animals are effective.

The multivariate analysis proved to be a useful approach for assessing the statistical significance and relative strength of associations between the occurrence of AMR in bacteria from humans, AMR in bacteria from food-producing animals and AMC in both food-producing animals and humans. The analyses showed that the relative strength of these associations differed markedly depending on antimicrobial class, microorganism and sector. In contrast to the second JIACRA report, this third report includes multivariate analyses for additional

antimicrobial classes and, in many cases, also includes data from a larger number of countries. This makes direct comparison of results from the second and third JIACRA report difficult, but, when applicable, the results were consistent overall.

In both food-producing animals and humans, associations were observed between the consumption of an antimicrobial class and bacterial resistance to the antimicrobials in this class in the same population. One example is consumption of carbapenems, third- and fourth-generation cephalosporins and quinolones in humans, which were all associated with resistance in *E. coli* from humans. In food-producing animals, similar associations were found for several microorganisms and antimicrobial classes. This highlights the need for increased focus on antimicrobial stewardship to reduce the selective pressure on bacteria to reduce the burden of AMR in the EU/EEA.

Resistance in bacteria from humans was associated with resistance in bacteria from food-producing animals which, in turn, was related to antimicrobial consumption in animals. The most consistent positive association between AMR in bacteria from food-producing animals and AMR in bacteria from humans was found for *Campylobacter* spp. This is consistent with, and probably a consequence of the fact that *Campylobacter* spp. are found in food-producing animals and cause food-borne infections in humans. The lack of consistency in the results for *Salmonella* spp., another food-borne bacterium, is most likely due to differences in the resistance patterns of *Salmonella* serovars and clonal spread of certain strains across Europe.

The findings of ecological analyses that make use of aggregated data at national level, as included in this report, should be considered as hypotheses for subsequent targeted research to confirm the observed associations and provide better explanations where these are lacking. The availability of more detailed and comprehensive data would allow for more refined analyses and provide more robust results. Although the various surveillance and monitoring systems for AMC and AMR serve different primary purposes, the agencies continue to work on further harmonisation and integration of surveillance across sectors, to better understand the relationship between consumption and resistance. Nevertheless, by taking a 'One-Health' approach, the JIACRA report collates surveillance data on AMC and AMR in both humans and food-producing animals in a unique manner, putting them into perspective and bringing to light the progress that has been made. JIACRA outputs also provide relevant information for use in the classification of antimicrobials depending on the impact on public and animal health.

Overall, the findings suggest that further interventions to reduce AMC will have a beneficial impact on the occurrence of AMR, which underlines the need to promote prudent use of antimicrobial agents and infection control and prevention in both humans and food-producing animals. The high levels of AMC and AMR still being reported in bacterial isolates from both food-producing animals and humans from several countries show that these interventions should be reinforced.

1. Introduction

Following requests from the European Commission (EC) based on the Action Plan against the rising threats from Antimicrobial Resistance [1], three agencies – the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) – have previously collaborated on the analysis of possible relationships between the antimicrobial consumption (AMC) in human and veterinary medicine and the occurrence of antimicrobial resistance (AMR) in bacteria from humans and food-producing animals in the European Union/European Economic Area (EU/EEA). For some analyses limited to food-producing animals data from Switzerland were also included. As a result, two Joint Inter-agency Antimicrobial Consumption and Resistance Analysis (JIACRA) reports have been published to date, covering the period 2011 to 2015 [2,3].

The compilation of this third JIACRA report arises from another request, based on the ongoing commitment in the new 'European One-Health Action Plan against Antimicrobial Resistance (AMR)', adopted by the EC in June 2017 [1]. In line with Regulation (EU) 2019/5[1], the joint inter-agency report (i.e. JIACRA report) should be updated by the three agencies at least every third year. This third report includes an analysis of AMC and AMR surveillance data, mainly from 2016 to 2018.

2. Aim and scope of the report

As for the two previous JIACRA reports, the aim of this third report is to provide an integrated analysis of the relationships between AMC in human and veterinary medicine and the occurrence of AMR in bacteria from humans and food-producing animals. The data included in the analysis originate from five different surveillance networks coordinated by the three agencies. For this report, ECDC provided data on AMC in humans and data on AMR in bacterial isolates from cases of human infection. EFSA provided data on AMR in bacteria from food-producing animals, and EMA provided data on AMC in food-producing animals. All data were originally reported to the agencies by the countries participating in the respective surveillance system. The surveillance systems coordinated by ECDC cover EU/EEA countries, the system coordinated by EFSA and EMA includes EU/EEA countries and Switzerland. United Kingdom participated as member of the EU during the years covered by this report.

3. Brief update regarding the surveillance systems providing data for the report

According to Regulation (EC) No 851/2004[2], ECDC has a mandate to gather and analyse data and information on emerging public health threats and developments for the purposes of protecting public health in the EU. Surveillance is conducted in accordance with Decision No 1082/2013/EU[3] on serious cross-border threats to health. Data on AMR in bacterial isolates from humans included in this report 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). Data on AMC in humans were obtained from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net).

Based on Article 33 in Regulation (EC) No 178/2002[4], EFSA is responsible for analysing data on zoonoses, AMR and food-borne outbreaks collected from the countries in accordance with Directive 2003/99/EC[5], and for reporting annually on the results. For AMR, a specific EU Summary Report is produced in collaboration with ECDC on an annual basis. The EU Summary Report on AMR includes data related to AMR in bacterial isolates from both food-producing animals and foodstuffs, collected under Directive 2003/99/EC, and bacterial isolates from human cases, derived from FWD-Net, coordinated by ECDC.

The main responsibility of the EMA 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 to develop a harmonised approach to the collection and reporting of data on the consumption of antimicrobial agents in animals. The ESVAC reports present data on the consumption of veterinary antimicrobial agents from EU and EEA countries, provided at package level in accordance with a standardised protocol and template [4].

3.1 Surveillance of antimicrobial consumption in humans

ESAC-Net is a network of national surveillance systems coordinated by ECDC providing independent data on AMC in all EU Member States, as well as two EEA countries (Iceland and Norway) [5]. It collects and analyses AMC data from the community (primary care) and the hospital sector. The data collected are used to provide timely information and feedback to EU/EEA countries on indicators of AMC that form a basis for prudent use of antimicrobials.

Antimicrobials are grouped according to the anatomical therapeutic chemical (ATC) classification. The following are antimicrobials: anti-bacterials for systemic use (ATC group J01); antimycotics for systemic use (ATC group J02); antifungals for systemic use (ATC group D01BA); drugs for treatment of tuberculosis (ATC group J04A); antivirals for systemic use (ATC group J05); nitroimidazole derivatives used orally and rectally as antiprotozoals (ATC group P01AB) and intestinal anti-infectives (ATC group A07AA). Only antimicrobials from ATC group J01, anti-bacterials for systemic use or its respective subgroups are included in the analyses for AMC in humans in the present report.

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

- Reporting of national AMC data at the medicinal product level as number of packages sold or reimbursed. For this option, a valid national registry of antimicrobials available in the country is required (national registry data). This is the preferred reporting option.
- Reporting of national AMC data at ATC substance level as an aggregated number of defined daily doses (DDD) per 1 000 inhabitants per day (when national registry data are not reported).

Data are uploaded into the European Surveillance System (TESSy) database and used for reporting after a validation process and final approval by the national Operational Contact Points and/or National Focal Points for AMC. ECDC provides an annual analysis of the trends in AMC in humans, overall and by ATC group and subgroup, as well as comparisons between countries. Public access to information on AMC in humans in EU/EEA countries is provided through an ESAC-Net interactive database and an annual ECDC summary report on AMC in humans.

Most countries report data on sales, one-third of the countries report reimbursement data and a few report both sales and reimbursement data. The major limitation of reimbursement data is that they do not include

2 Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European Centre for disease prevention and control https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32004R0851

3 Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health and repealing Decision No 2119/98/EC https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32013D1082

4 Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002, laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1418924147681&uri=CELEX:32002R0178

5 Directive 2003/99/EC of the European Parliament and of the Council of 17 November 2003 on the monitoring of zoonoses and zoonotic agents, amending Council Decision 90/424/EEC and repealing Council Directive 92/117/EEC https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32003L0099

antimicrobials dispensed without a prescription and non-reimbursed prescribed antimicrobials (for example, the antimicrobials prescribed through private healthcare systems). On the other hand, sales data may represent an overestimated AMC data. In addition, countries might upload different types of data or report from different data sources, from one year to another, which could also introduce bias in the consumption rates reported. The number of countries that change data provider and/or types of data is small.

ESAC-Net reports consumption separately for the community and the hospital sector. A few countries do not report consumption data from the hospital sector, for these countries the figures reported represent an underestimation of the total national consumption. However, the overall consumption of antimicrobials in the community has been shown to be a representative sample of around 90% of the total consumption (when expressed as DDD per 1 000 inhabitants and per day and reported for the ATC group J01). Most of the countries reporting AMC data to ESAC-Net have a full coverage of the total population. For countries reporting data with less than 95% population coverage for consumption the national consumption figures expressed in tonnes of active antibiotic substances are extrapolated to 100% to refer to the total national consumption.

Twenty-nine countries reported AMC data for the period 2016–2018 for the community, and a few countries could not report data for the hospital sector as there was no surveillance system in place to collect data from this sector.

ESAC-Net aims to comply with ECDC's long-term surveillance strategy for 2021–2027, which targets improved routine surveillance outputs. It includes reusable, state-of-the art and annually updated online content of the ESAC-Net database, including data interpretation relevant to public health, which may gradually replace current annual surveillance reports.

3.2 Surveillance of antimicrobial consumption in food-producing animals

The ESVAC project, coordinated by EMA, collects harmonised data on overall sales of antimicrobial veterinary medicinal products (VMPs) from the EU Member States, Iceland and Norway. The sales data are collected from various national sources: wholesalers, marketing authorisation holders, feed mills and pharmacies.

For 2016 and 2017, the sales data cover 27 EU Member States, Iceland, Norway and Switzerland, while for 2018 the data cover 28 EU Member States, Iceland, Norway and Switzerland.

Antimicrobial classes included in the surveillance are covered by the following ATCvet codes: QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51 and QP51AG.

For each country, data are uploaded into the ESVAC database by the ESVAC national contact point or by the appointed national data manager and are subsequently subjected to a standardised validation process and final approval by the ESVAC main national contact point. The reporting countries can upload or re-upload data to the ESVAC database at any time – e.g. for correction purposes.

To normalise the sales data for the food-producing 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 food-producing animal population. The PCU model takes into account export and import of animals for fattening and slaughter. The PCU is purely a technical unit of measurement, used only to estimate sales corrected by the food-producing animal population in the 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 Annex 2 to EMA's report 'Trends in the sales of veterinary antimicrobial agents in nine European countries: 2005–2009' [6].

The food-producing animal population data used for the calculation of the PCU are uploaded on the Agency's website from Eurostat, and for export and import of animals, data are taken from TRACES (TRAde Control and Expert System run by DG SANTE of the EC). These reference data are subsequently validated and approved by the main ESVAC national contact points (NC). When such data are not available in Eurostat or TRACES, corresponding data are uploaded by the main ESVAC NCs.

The main indicator applied in this report to express the overall sales by class/subclass of veterinary antimicrobials is mg active ingredient normalised by the population correction unit (mg/PCU), which is the amount of antimicrobials sold in tonnes × 109, divided by the PCU in kg.

Because VMPs are typically marketed for more than one species, the sales data as such do not provide information on sales by food-producing animal species. Therefore, technical derived estimates have been calculated for pigs and poultry for the purposes of this report (see Section 4.3).

Further details on the evolution of the ESVAC activity are provided on the ESVAC website [7].

3.3 Surveillance of antimicrobial resistance in bacterial isolates from humans

Surveillance of antimicrobial resistance in bacteria from humans through FWD-Net

FWD-Net currently covers surveillance of 18 diseases that are acquired by humans through the consumption of food or water, or contact with animals. AMR data are collected as part of the case-based datasets for salmonellosis and campylobacteriosis and, since

the 2013 data collection, as part of the molecular surveillance of *Salmonella* species and *Campylobacter* species isolates. The case-based dataset contains data to inform and monitor clinical treatment and therefore the results are interpreted using clinical breakpoints for assessing treatment options by default. The isolate-based data are submitted by the National Public Health Reference Laboratories that conduct reference testing of isolates and can report the actual results of the antimicrobial susceptibility testing (AST) as minimum inhibitory concentration (MIC) or inhibition zone diameter. The number of EU/EEA countries reporting AMR data in 2016–2018 was 24–26 for *Salmonella* spp. and 19–21 for *Campylobacter* spp.

Surveillance of antimicrobial resistance in bacteria from humans through EARS-Net

EARS-Net monitors AMR in clinical isolates of bacteria isolated from blood and cerebrospinal fluids of humans, and covers eight bacteria of public health importance: *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Enterococcus faecium*. Data originate from routine AST performed at approximately 900 local medical microbiology laboratories serving more than 1300 hospitals in the EU/EEA. Further details on the methodology can be found in the EARS-Net reporting protocol [8], and a more detailed description of the data and its interpretation in the EARS-Net 2018 annual report [9].

EARS-Net data on AMR in *E. coli*, *K. pneumoniae* and *S. aureus* from 30 EU/EEA countries were included in this third JIACRA report. *S. aureus* data were only presented as a key AMR indicator.

3.4 Monitoring antimicrobial resistance in bacterial isolates from food-producing animals and food

Directive 2003/99/EC on the monitoring of zoonoses and zoonotic agents set out generic requirements for the monitoring and reporting of AMR in isolates of zoonotic *Salmonella* spp. and *Campylobacter* spp., as well as in selected other bacterial species – in so far as they present a threat to public health – from food-producing animals and food in the EU/EEA countries. Within the framework of AMR monitoring in food-producing animals and food, the occurrence of AMR is typically defined as the proportion of bacterial isolates tested for a given antimicrobial and found to present any degree of acquired reduced phenotypic susceptibility – i.e. to display 'microbiological resistance'. Epidemiological cut-off values (ECOFFs) are used as interpretative criteria of microbiological resistance.

In line with the general requirements of Directive 2003/99/EC, EFSA provided specific guidance on the monitoring and reporting of AMR in *Salmonella* spp. and *Campylobacter* spp. [10] and in indicator *E. coli* and enterococci [11]. The monitoring of AMR in food-producing animals covered zoonotic agents – in the first instance *Salmonella* spp. and *Campylobacter* spp. – on a mandatory basis, and indicator organisms in the commensal flora, such as *E. coli* on a voluntary basis. The monitoring of AMR in zoonotic organisms focused on the animal populations to which the consumer is most likely to be exposed through food derived thereof, such as domestic fowl (mainly broilers), pigs and cattle. The antimicrobials recommended for inclusion in the harmonised monitoring by EFSA consisted of a concise set of substances, selected according to their relevance for human therapeutic use (e.g. critically important antimicrobials (CIAs) with highest priority for human medicine) and/or of epidemiological relevance.

The AMR monitoring in food-producing animals and food was further harmonised by Commission Implementing Decision 2013/652/EU[6] implementing Directive 2003/99/EC. This Commission Implementing Decision sets out monitoring priorities from a public health perspective and described those combinations of bacterial species, antimicrobial substances, food-producing animal populations and food products which should be monitored as a minimum requirement from 2014 onwards. The Commission Implementing Decision also defines the frequency of the monitoring and the extent to which the sampling is required.

Since the implementation of the Commission Implementing Decision, the monitoring of AMR in zoonotic *Salmonella* spp. and *Campylobacter jejuni*, as well as in indicator *E. coli*, domestically produced from the major food-producing animal populations, has become mandatory (Table 1). Data are collected from all EU Member States, two EEA countries (Norway and Iceland) and Switzerland. Indicator *E. coli* and *Campylobacter* spp. isolates derive from active monitoring programmes, based on representative random sampling of carcasses of healthy animals, sampled at the slaughterhouse to collect caecal samples. For *Salmonella* spp. from broilers, laying hens and fattening turkeys, isolates are included which originate from *Salmonella* national control programmes, as well as isolates from carcasses of broilers and fattening turkeys, sampled as part of the hygiene criteria process. For *Salmonella* spp. isolates are included originating from the carcasses of fattening pigs and bovine animals under one year of age, sampled as part of the verification of the hygiene criteria process. The target number of organisms of each bacterial species which should be examined is 170 from each type of domestic animal (this is reduced to 85 organisms from poultry and pigs, if production is less than 100 000 tonnes per annum). From 2014 onwards, poultry/poultry meat was monitored in 2014, 2016 and 2018, and pigs and bovines under one year, pork and beef were monitored in 2015, 2017 and 2019. Within each Member State, the various types of livestock and meat from those

6 Commission Implementing Decision of 12 November 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32013D0652

livestock should be monitored when production exceeds 10 000 tonnes slaughtered per year.

Commission Implementing Decision 2013/652/EU stipulates that culture using selective media for cephalosporin-resistant *E. coli* should be performed. Caecal samples from broilers, fattening turkeys, fattening pigs and bovines under one year of age, as well as from broiler and turkey meat, pork and beef collected at retail sites, should be examined for cefotaxime-resistant *E. coli* using selective media incorporating the third-generation cephalosporin cefotaxime.

All presumptive extended-spectrum beta-lactamase (ESBL)-, AmpC beta-lactamase- or carbapenemase-producing *E. coli* isolates identified through selective plating, as well as all those randomly selected isolates of *Salmonella* spp. and *E. coli*, recovered from non-selective media that are resistant to cefotaxime or ceftazidime or meropenem, are further tested with a second panel of antimicrobial substances. This second panel of antimicrobials includes cefotaxime and ceftazidime, with and without clavulanic acid (to investigate whether synergy is observed with clavulanic acid), as well as the antimicrobials cefoxitin, cefepime, temocillin, ertapenem, imipenem and meropenem. The second panel of antimicrobials is designed to enable phenotypic characterisation of ESBL, AmpC and carbapenem resistance.

3.5 Primary key indicators

A list of harmonised key AMC and AMR indicators was published jointly by ECDC, EFSA and EMA to support EU/EEA countries with their progress in reducing AMC and AMR in both humans and food-producing animals [12]. The list includes a total of 15 indicators, divided into primary and secondary indicators. The indicators are based on data already collected through the monitoring systems, as described above. In this report, only the primary key indicators used in the different sectors in a 'One-Health' approach are included (Table 2).

A full description, rationale for selection and limitations for each of these primary key indicators can be found in the initial report. Any comparison of the changes in the different sectors needs to be carried out with caution, given the differences in the data collected and the loss of detail resulting from the combination of data into indicators. Indicators should not be directly compared between countries, but should be used for comparisons within the country [12].

Table 1: Bacterial species included in mandatory AMR monitoring in food-producing animals from 2014 onwards, as set out in Commission Implementing Decision 2013/652/EU

Food-producing animal populations	Year of sampling	*Salmonella* spp.	*Campylobacter jejuni*	*Campylobacter coli*	*Escherichia coli*
Broilers	Even years (e.g. 2014, 2016, 2018)	M, NCP, PHC	M, CSS	V	M, CSS
Laying hens		M, NCP	-	-	-
Fattening turkeys		M, NCP, PHC	M, CSS	V	M, CSS
Bovines aged < 1 year	Odd years (e.g. 2015, 2017)	M, PHC	-	-	M, CSS
Fattening pigs		M, PHC	-	-	M, CSS

CSS: caecal samples from healthy food-producing animals at slaughter; M: mandatory monitoring; NCP: salmonella national control plans; PHC: process hygiene criteria; V: voluntary monitoring.

Table 2: Overview of the five primary key indicators

Sector	Antimicrobial Consumption (AMC)	Antimicrobial resistance (AMR)
Humans	Total consumption of antibacterials for systemic use (defined daily doses per 1 000 inhabitant and per year)	Proportion of meticillin-resistant *Staphylococcus aureus* (MRSA) Proportion of 3rd-generation cephalosporin-resistant *Escherichia coli* (3GCR *E. coli*)
Food-producing animals	Overall sales of veterinary antimicrobials (milligram/population correction unit)	Proportion of indicator *E. coli* from broilers, fattening turkeys, fattening pigs and calves, weighted by PCU, completely susceptible to the predefined panel of antimicrobials

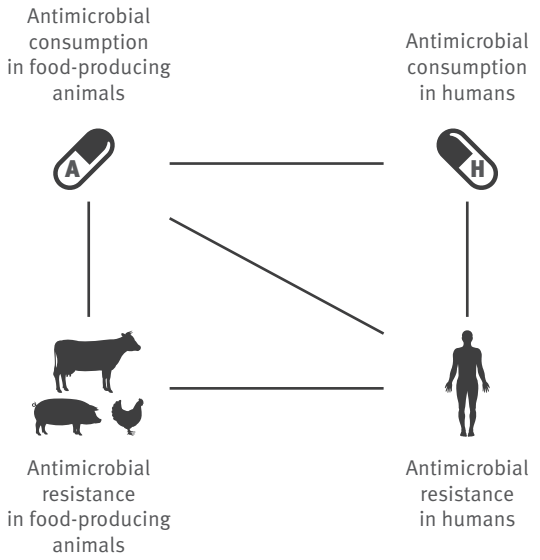
4. Methods

Four data sets were available from the monitoring systems currently in place (see Chapter 3). These four sets of data and the potential relationships between them, which are addressed in this report, are illustrated in Figure 1.

The analysis included the relationships between AMC and AMR within the food-producing animal and human populations, as well as the relationship between equivalent datasets, AMR in humans versus AMR in food-producing animals, and AMC in humans versus AMC in food-producing animals (Figure 1). Potential relationships were investigated through a series of univariate analyses addressing selected antimicrobial class and bacterial organism combinations of interest. The relationship between AMC in humans and AMR in food-producing animals was not addressed in this report.

In a second step, multivariate analyses were performed for the selected antimicrobial class and bacterial organism combinations of interest to assess relationships between AMR in bacteria from humans and AMC in both human and food-producing animal populations, as well as AMR in bacteria in food-producing animals. This was done accounting for the characteristics of the data analysed, in particular the relatively small number of observations in a number of countries involved in the ecological analysis, and multicollinearity among dependent variables.

Figure 1: Schematic overview of the potential associations between antimicrobial consumption and antimicrobial resistance in humans and food-producing animals investigated in this report



The relationship between AMC in humans and AMR in bacteria from food-producing animals was not addressed in this report.

For analyses covering one sector (food-producing animals or humans), only univariate analyses were performed.

4.1 Rationale for the selection of antimicrobial/bacterium combinations for analysis

An overview of the rationale for the selection of antimicrobial/bacterium combinations included in the analysis is available in Table 3. In the current report, only data on AMR obtained in domestically produced animals have been used. This is because available data on AMR in bacteria recovered from meat (broiler meat, pork and beef), as well as related information on the origin of the meat – domestically produced or imported – were considered insufficient. Basically, there were too few reporting countries for a meaningful investigation of associations between the consumption of antimicrobials in food-producing animals and the occurrence of AMR in certain bacteria present on meat. Only antimicrobial classes and organisms which are considered to be particularly important were selected for analysis.

The EU Antimicrobial Advice ad hoc Expert Group (AMEG) list [13] and the WHO list of critically important antimicrobials [14] were taken into account when selecting the combinations of antimicrobials and bacterial organisms for detailed analysis. In particular, fluoroquinolones, polymyxins and third- or fourth-generation cephalosporins have been considered as three of the classes of antimicrobial agents most urgently requiring management of the risks from AMR. Macrolides were also included, as they are ranked as highest-priority critically-important antimicrobials by WHO. The third- and fourth-generation cephalosporins and fluoroquinolones have been introduced into veterinary medicine much more recently than compounds such as the aminopenicillins and tetracyclines. In most of the reporting countries, resistance to the latter classes is relatively common. This differs in many (but not all) cases from the situation for fluoroquinolones and third- and fourth-generation cephalosporins.

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. *Salmonella* spp. and *Campylobacter* spp. are well-recognised causes of foodborne zoonoses and, although infections in humans may arise from imported food or be related to travel, it is considered important to include these bacteria. *Salmonella* spp., in particular, can show extensive resistance, thus compromising treatment options in both humans and animals when treatment is considered necessary.

Infections with pathogenic vero-toxin producing *E. coli* is a food-borne zoonosis. With the exception of such infections, clonal transmission of *E. coli* between animals and humans is probably of low frequency. However, resistance genes, for example carried on plasmids in commensal intestinal bacteria in animals, can be disseminated between different animal hosts and humans [15].

4.2 Overall consumption of antimicrobials in humans and food-producing animals

Human consumption data from 29 EU/EEA countries (ATC group J01, antibacterials for systemic use) from 2016 and 2017 were retrieved from the TESSy database, hosted by ECDC, in July 2019 and for 2018 in December 2019. Where available, data on consumption in the hospital sector and in the community were aggregated to provide total consumption. For those countries reporting on community consumption only (four countries for 2016 and three countries for 2017 and 2018), this figure was used as a surrogate for the total consumption. To facilitate the comparison between AMC in humans and in food-producing animals, these data were subsequently converted into mass of active substance per antimicrobial class and country (expressed in tonnes). Detailed information on the conversion methodology used can be found in Annex A.2.

National consumption data on the quantity of antimicrobials used for food-producing animals belonging to the ATCvet groups QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51 and QP51AG are based on sales from wholesalers, retailers, marketing authorisation holder (MAH), feed mills and prescription data (two countries). In the current report, data has been analysed using the latest 2021 ATCvet index from the WHO Collaborating Centre version that is available at https://www.whocc.no/atcvet/atcvet_index/ and contains all valid ATCvet codes. The data on the overall consumption for food-producing animals 2016 and 2017 used in the analysis represents the datasets uploaded to the ESVAC database by 22 January 2020. For 2018, the data represent the datasets uploaded in the database by 26 June 2020. In the analysis of overall consumption data, injectables, oral powders, oral solutions, intramammaries and intrauterine devices are included which cover antimicrobials sold for use in all food-producing animal species, including horses.

Table 3: Combinations of antimicrobial classes and bacteria selected for analysis and rationale for the selection

Antimicrobial class	WHO categorisation	AMEG categorisation	*Campylobacter* spp.	*Salmonella*	*Escherichia coli*	*Klebsiella pneumoniae*
Carbapenems	CIA	Category A			Carbapenems are antimicrobials of major clinical significance in humans. Resistance to carbapenems is emerging in several bacterial species capable of causing serious, invasive infections. This class of antimicrobials is not authorised for use in animals in EU.	
Third- and fourth-generation cephalosporins	Highest priority CIA	Category B		These antimicrobial subclasses constitute one of the first-line therapies for invasive gram-negative bacterial infections in humans in many EU/EEA countries.		
Fluoroquinolones and other quinolones	Highest priority CIA	Category B	Fluoroquinolones and macrolides are used to treat infections with *Campylobacter* spp. in humans when treatment is considered necessary by the clinician.	This antimicrobial class constitutes one of the first-line therapies for invasive gram-negative bacterial infections in humans in many EU/EEA countries.		
Polymyxins	Highest priority CIA	Category B		Colistin, a polymyxin, may be the only choice for treatment of serious invasive infections caused by multidrug-resistant gram-negative bacteria. Use of colistin in EU/EEA hospitals, mainly in intensive care, is increasing. A high consumption of colistin has been reported in food-producing animals in some countries [16]; though current data indicate major decreases in several countries [4]. Data on resistance to colistin in isolates from humans were not available for this report.		
Aminopenicillins	CIA	Category C (with inhibitors) and D (without inhibitors)		An antimicrobial class that has been widely used in food-producing animals and humans for many years. Resistance to aminopenicillins and to other antimicrobials is common in bacteria from humans and food-producing animals. This may play a role in co-selection through the genetic linkage of resistance genes.		
Macrolides	Highest priority CIA	Category C	See fluoroquinolones above			
Tetracyclines	HIA	Category D	An antimicrobial class widely used in food-producing animals for many years. Resistance to tetracyclines and to other antimicrobials, which is common, may play a role in co-selection through the genetic linkage of resistance genes.			

AMEG: Antimicrobial Advice ad hoc Expert Group; CIA: critically important antimicrobial; HIA: highly important antimicrobial; WHO: World Health Organization.
Shaded cells mean that the corresponding combinations were not analysed in this report.

Data on the mean weights for adults and respective different age groups [17] were used together with Eurostat data on the population in the EU-27 in 2012, taken by one-year age classes to calculate a human EU-population-and-age-class-weighted mean body weight of 62.5 kg (see Annex A.2). Country-specific EU estimates for the weight of children and young adolescents up to 18 years were not available at EU level from Eurostat. Therefore suggested estimates from the European Food Safety Authority [119] of the selected default values were used in the absence of actual measured data. The mean EU body weight was used to calculate the estimated biomass of the population under ESAC-Net surveillance.

All EU/EEA population-weighted means of AMC in humans, expressed as DDD per 1 000 inhabitants or mg/kg biomass, are calculated by multiplying consumption data for each country with the corresponding Eurostat population, and dividing the product by the total population of all participating EU/EEA countries.

Data on the biomass of food-producing animals expressed in PCU for the period 2016 and 2017 were obtained from the ESVAC-database, hosted by EMA, on 22 January 2020. For 2018, the data represent the datasets uploaded in the database by 26 June 2020. In the following, the term 'milligrams per kilogram of estimated biomass' will be used as a synonym of 'milligrams per human EU population- and age class-weighted biomass' and 'milligrams per PCU'.

4.3 Technically-derived estimates of the sales of veterinary antimicrobials for pigs and poultry

In the absence of AMC data specifically relating to pigs and poultry from most of the EU/EEA countries, the sales of the antimicrobial classes/sub-classes included in the analysis at the food-producing animal species level were estimated using a structured approach. Sales data from the ESVAC database for 2016–2018 were used to establish sales estimates of antimicrobial veterinary medicinal products (VMP) used in pigs and poultry that contained aminopenicillins – i.e. ampicillin and amoxicillin without and with beta-lactamase inhibitors and metampicillin – belonging to the ATCvet groups QA07AA98, QA07AA99, QJ01CA01, QJ01CA04, QJ01CR01, QJ01CR02, QJ01CR50, QJ01RA01, QJ01RA95 and QJ01RV01; third- and fourth-generation cephalosporins, fluoroquinolones, other quinolones, polymyxins, macrolides and tetracyclines belonging to ATCvet groups QA07AA and QJ01. The selected antimicrobials cover antimicrobial VMPs for oral administration and injectables. The data used for the technical estimation of consumption for pigs and poultry for 2016 and 2017 represent the data available in the ESVAC database on 22 January 2020. For 2018, the data represent the datasets uploaded in the database by 26 June 2020.

For each of the antimicrobial VMP presentations included in the analysis, information on authorised target food-producing species was obtained from the Summary of Product Characteristics (SPC) of each country. The total annual sales (weight of active ingredient) of each VMP presentation were then distributed between the authorised target food-producing species according to its biomass – i.e. the population correction unit (PCU) ratio in the corresponding country. The biomass ratio for pigs and poultry is defined as the fraction of the biomass (PCU) of these species for the total food-producing animal biomass (PCU) in the respective country. For some VMPs the SPC data indicated poultry as a target species and consequently, estimates could not be derived for turkey and chickens. In order to have harmonised data across countries, sales were estimated for poultry, and thus AMR data for turkey and broilers were aggregated for the analyses of the second JIACRA report [3]. The AMR data used for the analyses in the current report cover bovine animals under one year. However, since cattle in general is typically given as the target species in the product information, sales for bovines under one year could not be estimated with the approach used.

The sales (weight of active substance) attributed to pigs and poultry were subsequently used to calculate the indicator expressing the exposure to antimicrobials – i.e. number of defined daily doses animals (DDDvet) per kilogram of food-producing animal biomass per species (DDDvet/kg biomass) per year and country. The DDDvet system, established by EMA, provides standardised units of measurement for the reporting of data on consumption by species, taking into account differences in dosing between species, antimicrobials and administration routes/formulations. Where possible, the principles for assignment of DDDvet [18] are harmonised with the principles for assignment of DDDs in human medicine. Similar to the DDD established for human medicinal products, DDDvet is a technical unit of measurement solely intended for drug consumption studies and outputs should not necessarily be assumed to reflect the daily doses recommended or prescribed.

It should be emphasised that the estimates obtained on sales for pigs and poultry using this methodology are purely technically-derived estimates. The calculated numbers of DDDvet used per kilogram of food-producing animal biomass per year and country should therefore not be considered as the exact exposure of pigs and poultry to antimicrobials in the ESVAC participating countries (see Annex A2).

4.4 Data on antimicrobial resistance in bacterial isolates from food-producing animals

For the purpose of comparing AMC and AMR data, a summary indicator of microbiological resistance (SIMR) at national level was calculated as the weighted mean of the proportion of AMR in broilers, turkeys, pigs and calves (bovine under one year). This took into consideration AMR data assessed in 2014 and 2015; 2015 and 2016; 2016 and 2017, and 2017 and 2018. The PCU values of the four (or two when considering *Campylobacter*

spp. data) food-producing animal categories in the countries were used as weighting factors. An additional SIMR in bacteria from poultry was also constructed by addressing data on both broilers and turkeys for 2016 and 2018. For the countries which did not have data on AMR in turkeys available due to the small size of the turkey production sector, the SIMR in poultry equalled the occurrence of AMR assessed in broilers. SIMR were compared to corresponding AMC data in food-producing animals.

In the food-producing animal sector, the reporting of AMR data at the individual isolate level allowed phenotypic resistance profiles to be characterised according to the harmonised panel of antimicrobial substances tested. A completely susceptible indicator *E. coli* isolate is one defined as being non-resistant to all of the antimicrobial substances included in the harmonised set of substances tested. The key indicator of complete susceptibility has been used to investigate the associations between the occurrence of complete susceptibility and total AMC in food-producing animals (see Section 3.5).

4.5 Data on antimicrobial resistance in bacterial isolates from humans

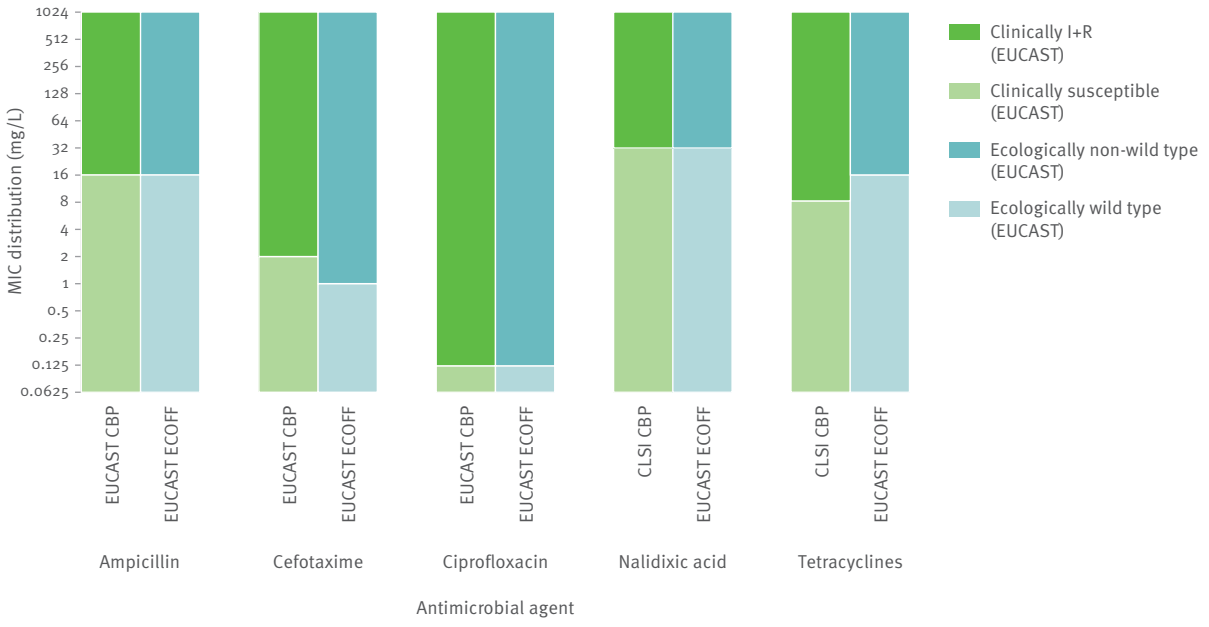
Salmonella spp. and *Campylobacter* spp.

The method of testing for antimicrobial susceptibility and the selection of the isolates to be tested varies among countries. The methods and interpretive criteria used for AST of *Salmonella* spp. and *Campylobacter* spp. isolates from humans can be found in the corresponding ESFA-ECDC reports [19–21]. Quantitative data were interpreted by ECDC based on the European Committee on Antimicrobial Susceptibility Testing (EUCAST) ECOFF values, where available. Where ECOFFs did not exist, EUCAST or Clinical and Laboratory Standards Institute (CLSI) clinical breakpoints were applied. EUCAST changed the definitions of susceptibility testing categories S, I and R as of 2019 [22], but as data for this report was collected before this change, the old definitions of S – susceptible, I – intermediate and R – resistant are used. For the qualitative SIR data, I and R results were combined into one category. Alignment of the susceptible category with the 'wild type' category based on ECOFFs, and of the I+R category with the ECOFF-based 'non-wild type' category provides better comparability and more straightforward interpretation of the resistance data for most antimicrobial agents included. When analysed in this way, there is generally close concordance (± 1 dilution) across categories for the antimicrobials included for *Salmonella* spp. and *Campylobacter* spp. (Figure 2 and Figure 3).

Invasive *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus*

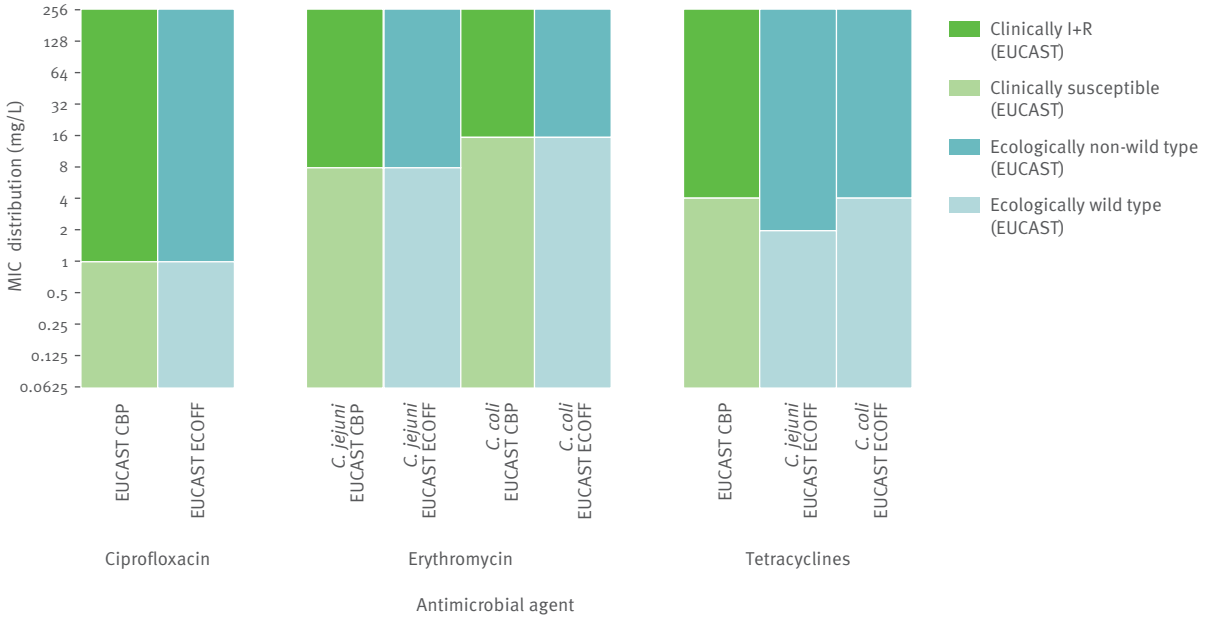
Data from 2016, 2017 and 2018 were retrieved from the TESSy database, hosted by ECDC, and through ECDC's decentralised data storage for antimicrobial resistance and healthcare-associated infections (ARHAI) in November 2019. Data on *S. aureus* were only used for Chapter 13 on primary key indicators. The antimicrobial agents included in the panel for initial determination of susceptibility in invasive *E. coli*, *K. pneumoniae* and *S. aureus* isolates varied among countries. To allow

Figure 2: Comparison of clinical breakpoints for resistance (intermediate and resistant categories combined) and epidemiological cut-off values used to interpret minimum inhibitory concentration (MIC) data reported for *Salmonella* from humans and food-producing animals, 2017 breakpoint data



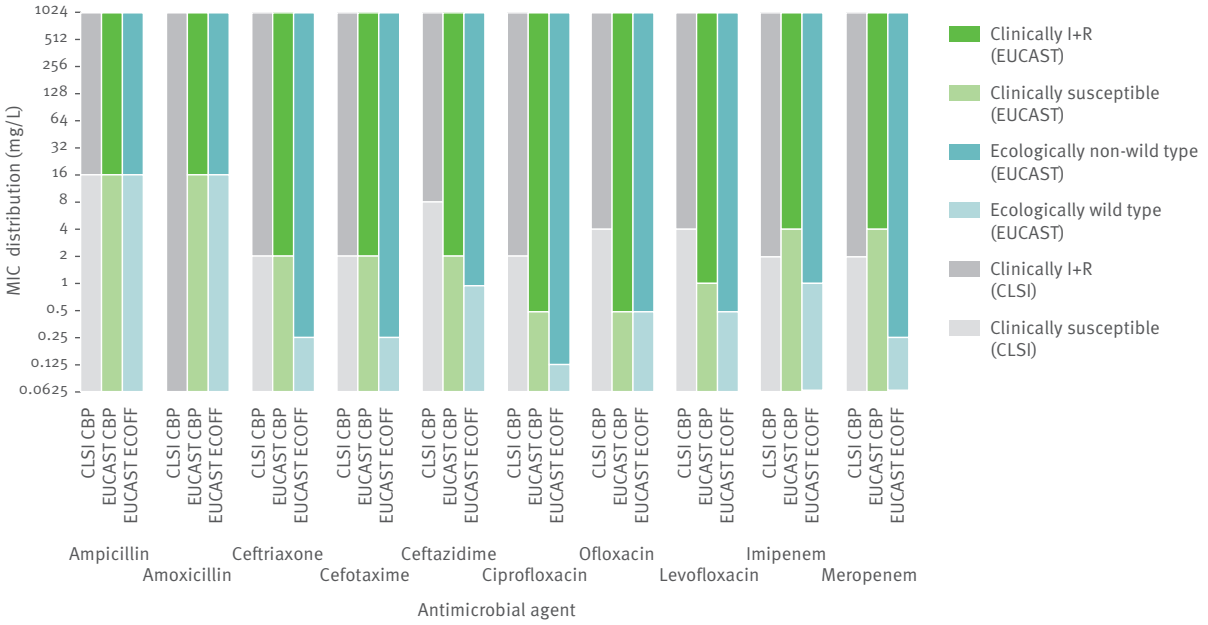
EUCAST: The European Committee on Antimicrobial Susceptibility Testing, CBP: Clinical breakpoint, ECOFF: Epidemiological cut-off values

Figure 3: Comparison of clinical breakpoints for resistance (intermediate and resistant categories combined) and epidemiological cut-off values used to interpret minimum inhibitory concentration (MIC) data reported for *Campylobacter* spp. from humans and food-producing animals, 2017 breakpoint data



EUCAST: The European Committee on Antimicrobial Susceptibility Testing, CBP: Clinical breakpoint, ECOFF: Epidemiological cut-off values

Figure 4: Comparison of clinical breakpoints for resistance (intermediate and resistant categories combined) and epidemiological cut-off values used to interpret minimum inhibitory concentration (MIC) data reported for *Escherichia coli* from humans and food-producing animals, 2017 breakpoint data



EUCAST: The European Committee on Antimicrobial Susceptibility Testing, CBP: Clinical breakpoint, ECOFF: Epidemiological cut-off values

for comparison, results are presented at antimicrobial group level, merging test results from several antimicrobial agents and giving priority to the most resistant result. The panel of microorganism-antimicrobial agent combinations are shown in Table 4.

Susceptibility results were interpreted according to the clinical guidelines used by the local laboratory. During the period 2016 to 2018, the vast majority of the countries used EUCAST clinical breakpoints, while a few laboratories still used Clinical and Laboratory Standards Institute (CLSI) clinical breakpoints. In 2017, approximately 89% of the participating laboratories used EUCAST, or EUCAST-related clinical breakpoints, which is an improvement on previous years and increases the comparability of the data. For more information, the reader should refer to the EARS-Net reports for 2016 to 2018 [9, 23, 24].

In order to allow for comparison between clinical isolates of invasive *E. coli* from humans and commensal *E. coli* from food-producing animals, the term 'resistance' in human data refers to isolates tested as both I- intermediate or R –resistant. This approach did not provide as good alignment with the categories based on ECOFFs as it did for *Salmonella* spp. and *Campylobacter* spp. As a result, there was a difference of one to four dilution steps, depending on antimicrobial, between the non-susceptible clinical levels and the non-wild type (microbiologically resistant) based on ECOFFs (Figure 4). For consistency, clinically intermediate resistant and clinically resistant results for *K. pneumoniae* were also merged into a non-susceptible category, even though no comparisons were made with data from food-producing animals.

4.6. Data sources and methodology for primary key indicators

The primary key indicators for AMC in humans and food-producing animals for the period 2014 to 2018 were included in this report. The methodology for defining each indicator and the calculations of the EU/EEA means are further described in the referenced source reports from ECDC, EFSA and EMA [12].

For humans, the total consumption of antimicrobials for systemic use, expressed as DDD per 1 000 inhabitants and per day at national level and as an EU/EEA population-weighted mean, were extracted from the ESAC-Net report [25]. For food-producing animals, the overall sales expressed as mg/PCU at national level and as an aggregated overall sales for 25 EU/EEA countries were extracted from the ESVAC report [4].

The primary key indicators for AMR in humans include the proportion of meticillin-resistant *S. aureus* (MRSA) and third-generation cephalosporin-resistant *E. coli*. National and EU/EEA population-weighted mean percentages for the period 2014 to 2018 were extracted from the EARS-Net report [26].

For the primary key indicator of AMR in food-producing animals – which is the proportion of *E. coli* from broilers, fattening turkeys, fattening pigs and calves, weighted by PCU, completely susceptible to a predefined panel of antimicrobials – data were extracted from EFSA/ECDC reports [27]. Two consecutive years were considered together since the AMR monitoring in the food-producing animal populations is performed on a biannual basis (2014–2015, 2015–2016, 2016–2017, 2017–2018).

The statistical assessment of trends for the EU/EEA means followed used in the source reports from ECDC, EFSA and EMA.

4.7 Statistical methods

Spearman's rank correlation test

To assess whether there was an association between AMC (expressed in mg per kg of estimated biomass) in food-producing animals and in humans at the EU level, a Spearman's rank correlation test was used. Spearman's rank correlation coefficient is a non-parametric measure used to assess the degree of statistical association between two variables and the test does not depend on any assumptions about the distribution of the data. The Spearman's rank correlation coefficient is identified by rho (ρ) and varies from -1 (perfect negative rank correlation) to 1 (perfect positive rank correlation).

Logistic regression

Logistic regression models were used to assess statistically significant associations between (1) consumption of antimicrobial agents in humans and occurrence of resistance in bacteria from humans, (2) consumption of antimicrobial agents in food-producing animals and occurrence of resistance in bacteria from humans, (3) occurrence of resistance in bacteria from food-producing animals and occurrence of resistance in bacteria from humans, and (4) consumption of antimicrobial agents in food-producing animals and occurrence of resistance in bacteria from food-producing animals.

Table 4: Antimicrobial agents and confirmation tests included in the antimicrobial groups, EARS-Net 2016–2018

Antimicrobial agent/antimicrobial class	Test and antimicrobial agents included in panels for testing
Carbapenems	Meropenem, imipenem
Third-generation cephalosporins	Cefotaxime, ceftazidime, ceftriaxone
Aminopenicillins	Ampicillin, amoxicillin
Fluoroquinolones	Ciprofloxacin, ofloxacin, levofloxacin
Meticillin	Cefoxitin, oxacillin or molecular MRSA confirmation tests

Three different candidate logistic regression models were considered:

Model 1: a logistic model where the relationship between the predictor (x) and the logit of the probability of interest is linear

$$\log\left\{\frac{P(y=1)}{P(y=0)}\right\} = \beta_0 + \beta_1 \mathrm{x}$$

The other two models allow additional curvature in this relationship.

Model 2: a logistic model where the predictor is log-transformed

$$\log\left\{\frac{P(y=1)}{P(y=0)}\right\} = \beta_0 + \beta_1 \log_2(\mathrm{x} + 0.001)$$

Model 3: a logistic model where the predictor is quadratic-transformed

$$\log\left\{\frac{P(y=1)}{P(y=0)}\right\} = \beta_0 + \beta_1 \mathrm{x}^2$$

Other, and more complex models could of course be considered. However, the above three candidate models, each modelling a different type of relationship, are expected to fit all datasets analysed in this report sufficiently well. Moreover, for all three models, the strength of the association between the predictor (x) and the logit of the probability of interest is represented by a single parameter, the slope parameter β_1, or correspondingly, by the odds ratio OR = exp(β_1). If a 95% confidence interval (CI) for the OR contains the value 1, there is no statistical evidence from the available data that the predictor is associated with the outcome (the null hypothesis of no association cannot be rejected at the level of significance 0.05). A CI with a lower bound exceeding the value 1 implies a significant positive statistical association (an increase in the predictor's value is associated with an increase in the odds of the outcome). A CI with an upper bound below the value 1 implies a significant negative statistical association (an increase in the predictor's value is associated with a decrease in the odds of the outcome).

The three models differ, however, in their interpretation of the OR = exp(β_1):

- Model 1: the effect of the predictor (x) is 'homogeneous': the value of the OR = exp(β_1) corresponds to a 1-unit increase in the predictor (x). For example, an OR = 1.09 represents an increase of 9% in the odds of the outcome by a 1-unit increase of x (e.g. from x = 1 to 2 or x = 10 to 11).
- Model 2 and 3: the effect of the predictor (x) is 'heterogeneous': the value of the OR no longer corresponds to a 1-unit increase in the predictor (x):
  - Model 2: the effect of x levels off for increasing x, so that the OR = exp(β_1) corresponds to an increase larger than a 1-unit increase for larger x-values; it corresponds (approximately) to a doubling of the predictor x. For example, an OR = 1.09 represents an increase of 9% in the odds of the outcome by an approximate increase of x = 1 to 2 or x = 10 to 20, etc.
  - Model 3: the effect of x rises with increasing x, so that the OR = exp(β_1) corresponds to an increase smaller than a 1-unit increase for larger x-values; more precisely, it corresponds to an increase in the predictor x to sqrt(x2+1). For example, OR = 1.09 represents an increase of 9% in the odds of the outcome by an increase of x = 1 to sqrt(2) ≈ 1.414, or x = 10 to sqrt(101)≈10.050.

All three logistic models were fitted to the data for a particular antimicrobial agent/bacteria combination and the model with the lowest Akaike's Information Criterion (AIC) [28] was chosen as the final model. If data from several years or periods (combination of years) were available for that particular antimicrobial agent/bacteria combination, the model selection was based on the collapsed data and afterwards the final model was fitted to all years/periods separately. The parameters and the standard errors of the final logistic model are estimated using the method of Williams [29], accounting for so-called overdispersion (a phenomenon related to violations of the basic assumption underlying the logistic regression model, being the binomial distribution for the number of positive events out of the number of tests).

Logistic regression models were fitted only when five or more countries reported information on both the outcome of interest and predictor, and where the total number of isolates tested within each country was equal to 10 or more.

Outputs

The results of the final selected models are summarised in tables. The tables show the countries that were included in the analysis next to the model chosen, and the point and interval estimates.

Next to the tables, graphs visualise the data together with the fitted curve of the final model, selected for each antimicrobial agent/pathogen. Such graphs are only included if the association is statistically significant (at a level of significance of 0.05), or in a matrix-plot over several years/periods, if it was for at least one year/period. Corresponding graphs for borderline significant results (e.g. p-value between 0.055 and 0.10) are available in Annex A1.2. The size of the bubbles displayed in the graphs reflects the number of tests involved, with a bigger size indicating a larger number of tests. The use of such bubbles rather than points of the same size visualises, at a single glance, the differences in the values for the predictor and the outcome of interest. It also shows the differences in the underlying number of tests between countries, and consequently the differences in their contribution to the final fitted curve (larger bubbles having more impact on the fit than small bubbles).

Data outliers (outlying countries on the graphs) were identified by visually inspecting the graphs and omitting the outliers in a subsequent sensitivity analysis, when considered appropriate. If found to be relevant, the results of the sensitivity analyses were commented on in the text.

Partial Least Squares Path Modelling

To further assess potential relationships between the resistance to antimicrobials in bacteria from humans and AMC in humans (in the community and at the hospital), AMC in food-producing animals (pigs and poultry) and resistance in bacteria from food-producing animals (pigs and poultry), multivariate analyses were performed using Partial Least Squares Path Modelling (PLS-PM). PLS-PM was selected as a convenient tool to investigate multiple relationships between blocks of variables (represented through latent variables as a mean of summarising measured variables into fewer factors) without requiring assumptions on data distributions [30].

Multivariate analyses were based on data reported for 2017 and 2018. Data on AMR in isolates from pigs and poultry were recorded in 2017 and 2018, respectively. Data on AMR in isolates from humans were calculated by pooling the corresponding data collected in 2017 and 2018, and AMC in humans was calculated as the mean of 2017 and 2018 data. For countries that did not report AMC data on hospital consumption, this consumption was estimated by using other countries' partition between hospital and community consumption. All data were standardised (i.e., mean = 0 and variance = 1) prior to inclusion in the model. Analyses based on data reported for 2016 are presented in Annex 1.4 (Figure A1.4. 1 to Figure A1.4.7).

The typical outcomes of PLS-PM are presented in Table 5 and illustrated in Figure 5.

Full initial model

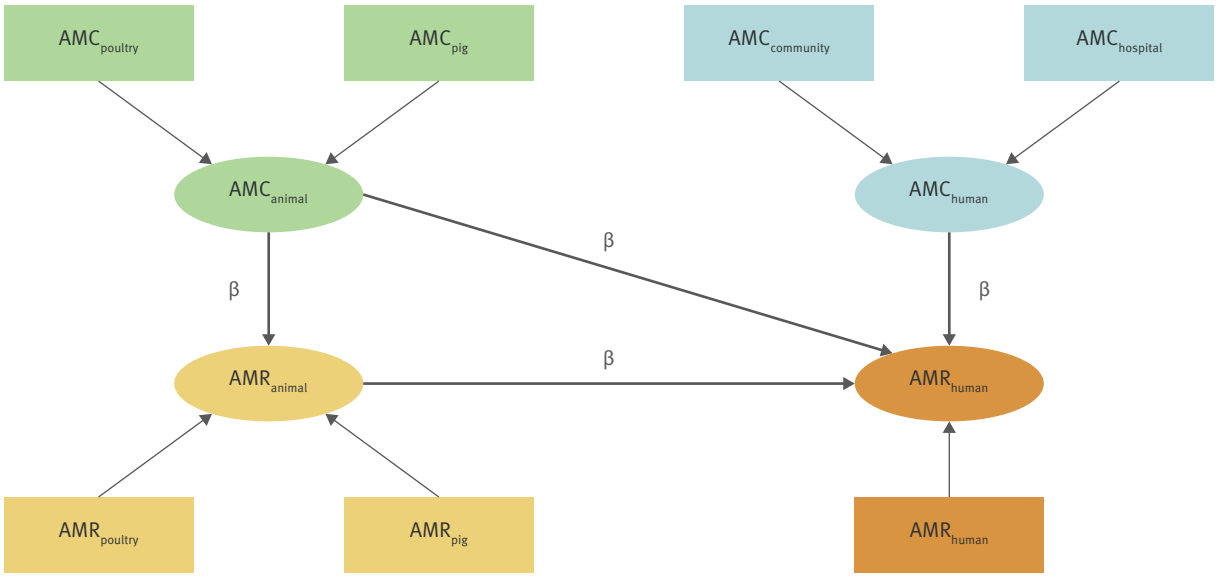
The full initial model computed is presented with related outcomes (Figure 5), according to the usual representation of PLS-PM. Indicators, also called 'manifest variables', are presented in green rectangles; they correspond to measured data on AMR and AMC. The variables displayed in blue ovals are 'latent variables', which were obtained from 'manifest variables'. Models were formative since latent constructs were formed by their indicators, as shown by arrows going from rectangles to ovals in Figure 5.

Models were fitted using R PLS PM package [31]. The non-significant relationships ($p>0.05$) were discarded from the model in a step-by-step backward process.

Table 5: Outcomes of PLS-PM models used in the multivariate analyses

Outcomes	Characteristics
R^2	Indicates the amount of variance in the dependent variable explained by the independent latent variables. Its value is usually considered high when it is greater than 0.50 or 0.60, depending on the authors.
Path coefficients (β)	Usually placed next to the corresponding arrow, they are coefficients of the paths between latent variables, which vary between -1 and +1, and are standardised. The closer to |1| the coefficient, the stronger the path.
Effects Direct effects Indirect effects	Corresponds to the effect of one latent variable on another one. It corresponds to the path coefficient when the effect is direct, but is termed an indirect effect when a latent variable mediates this effect indirectly, such as the indirect effect of AMC by food-producing animals on resistance in human isolates, mediated by resistance in food-producing animals.

Figure 5: Diagram showing the initial model considered to assess the potential relationships between resistance in bacteria from humans (AMR_{human}) and antimicrobial consumption in humans (AMC_{human}), antimicrobial consumption in food-producing animals (AMC_{animal}) (whether as direct or indirect influential factor), and resistance in bacteria in food-producing animals (AMR_{animal})



5. Antimicrobial consumption in humans and food-producing animals

5.1 Total tonnes of active substance and estimated biomass

In this section, data for 2017 were chosen for the analysis. The summary data for 2016 and 2018 can be found in Annex A1.1.

In 2017, 4 122 and 6 558 tonnes of active antimicrobial substances were sold for consumption in humans and for food-producing animals, respectively, in the 29 EU/EEA countries delivering consumption data for both humans and food-producing animals (Table 6). In 2016 and 2018, there were 28 and 29 countries, respectively, delivering data for both sectors (Annex A1.1).

The estimated biomass covered by the surveillance in 2017, expressed in 1 000 tonnes, was 31 649 for humans and 60 532 for food-producing animals, respectively. The proportion of the total biomass (sum of the biomass of food-producing animals and humans) accounted for by the food-producing animal population varied considerably between countries (from 34% to 88%). This variation, as well as the different human population numbers in the EU/EEA countries, underlines the need to account for differences in population size between human and food-producing animal sectors within a country and, between countries when comparing consumption in humans and food-producing animals.

5.2 Population biomass-corrected consumption

Overall consumption

The comparison of the EU/EEA population-weighted mean consumptions of antimicrobials in humans and food-producing animals (expressed in mg per kg of estimated biomass) is shown in Figure 6 and Table 6. When comparing the overall consumption of antimicrobials between the human and food-producing animal sectors in 2017, the EU/EEA population-weighted mean consumption (expressed in milligrams per kilogram of estimated biomass) was 130.0 mg/kg in humans (range 52.8–212.6 mg/kg; median 122.8 mg/kg) and 108.3 mg/kg (range 3.1–423.1 mg/kg; median 61.9 mg/kg) in food-producing animals, respectively.

The EU/EEA population-weighted mean proportion of the total AMC in the hospital sector was 10%. Three countries did not report hospital sector AMC data for 2017. When interpolating these data, the EU/EEA median and the population-adjusted mean (expressed as mg per kg biomass) increased by less than 3%.

In 20 of 29 countries, the population biomass-corrected consumption was lower or much lower in food-producing animals than in humans, in one country the consumption was similar (< 2% difference) in both groups and in the eight remaining countries, the consumption was higher or much higher in food-producing animals than in humans. There was no association between the consumption in human and food-producing animals within country (Spearman's rank correlation coefficient, rho = 0.32).

Consumption by class

Consumption of selected antimicrobial classes, aggregated for the 29 EU/EEA countries for which data were available both for humans and food-producing animals, is shown in Figure 7.

Penicillins, first- and second-generation cephalosporins and macrolides were the highest selling classes in human medicine, when expressed in milligrams per kilogram of estimated biomass. For food-producing animals, tetracyclines and penicillins were the highest selling classes in 2017, accounting for 30% and 27% of the sales, respectively, of the total sales expressed in milligrams per kilogram of estimated biomass. It should be noted that no veterinary medicinal products containing monobactams and carbapenems have been assigned a maximum residue level value and consequently they are prohibited for use in food-producing animals in the EU/EEA countries. Therefore, there is no consumption of such antimicrobials in food-producing animals. Likewise, pleuromutilins are not authorised for systemic use in humans and thus no such consumption was reported in humans.

The overall population-corrected consumption of penicillins, cephalosporins (all generations) and fluoroquinolones and other quinolones in humans, expressed in mg per kg of estimated biomass, was higher than the consumption of these classes in food-producing animals. For the other antimicrobial classes addressed, the opposite was the case.

Figures with data from all 29 EU/EEA countries included can be found in Sections 6.1–12.1. The range, median and mean of the consumption of the selected classes in humans and food-producing animals, expressed in mg per kg of estimated body weight, are summarised in Table 7.

Temporal trends

The EU/EEA population-weighted average consumption of antimicrobials in humans, expressed in mg/kg estimated biomass, remained stable in the period from 2014 to 2018 for the 27 countries included in the analysis (p = 0.12, linear regression) (Figure 8).

Table 6: Amount of antimicrobial active substance[a], estimated biomass and antimicrobial consumption in humans and food-producing animals[a], 29 EU/EEA countries for which data were available both for humans and food-producing animals, 2017

Country	Hospital consumption data included	Amount of active antimicrobial substance (tonnes)			Estimated biomass (1,000 tonnes)			Antimicrobial consumption (mg/kg estimated biomass)	
		Humans[b]	Food-producing animals[c]	Total	Humans	Food-producing animals	Total	Humans	Food-producing animals
Austria	No	41	45	85	548	954	1502	74.4	46.8
Belgium	Yes	104	221	325	709	1683	2393	146.3	131.3
Bulgaria	Yes	52	50	101	444	375	819	116.7	132.3
Croatia	Yes	33	21	54	260	296	555	122.8	71.5
Cyprus	Yes	8	45	54	53	107	161	153.1	423.1
Denmark	Yes	49	94	143	359	2398	2757	135.3	39.4
Estonia	Yes	6	6	12	82	111	193	73.2	56.7
Finland	Yes	41	10	51	344	507	851	118.8	19.3
France	Yes	762	483	1244	4175	7039	11214	181.6	68.6
Germany[d]	No	339	767	1106	5158	8609	13766	63.8	89.0
Greece	Yes	143	117	260	673	1243	1916	212.6	93.9
Hungary	Yes	51	147	199	612	771	1383	84.0	191.0
Iceland	No	2	1	3	21	125	146	111.4	4.6
Ireland	Yes	44	98	143	299	2114	2413	148.8	46.6
Italy	Yes	560	1058	1618	3787	3864	7651	147.9	273.8
Latvia	Yes	11	6	17	122	176	298	88.6	33.3
Lithuania	Yes	19	12	31	178	333	511	107.3	34.8
Luxembourg[d]	Yes	6	2	8	37	55	92	158.4	35.0
Malta	Yes	4	2	6	29	15	43	140.6	121.0
Netherlands[c]	Yes	58	188	246	1068	3341	4408	52.8	56.3
Norway	Yes	45	6	50	329	1861	2190	136.0	3.1
Poland	Yes	294	750	1044	2373	4539	6912	123.9	165.2
Portugal	Yes	78	135	213	644	1002	1646	133.3	134.8
Romania	Yes	207	263	470	1228	2916	4144	168.8	90.1
Slovakia	Yes	38	14	52	340	225	564	111.6	61.9
Slovenia	Yes	13	7	19	129	184	313	97.8	36.5
Spain	Yes	556	1770	2326	2908	7684	10592	191.1	230.3
Sweden	Yes	70	9	79	625	804	1429	112.1	11.8
United Kingdom	Yes	488	234	722	4115	7202	11317	118.6	32.5
29 EU/EEA countries		**4122**	**6558**	**10680**	**31649**	**60532**	**92181**	**130.0[e]**	**108.3[e]**

(a): Calculated from the exact figures (not from the rounded figures).

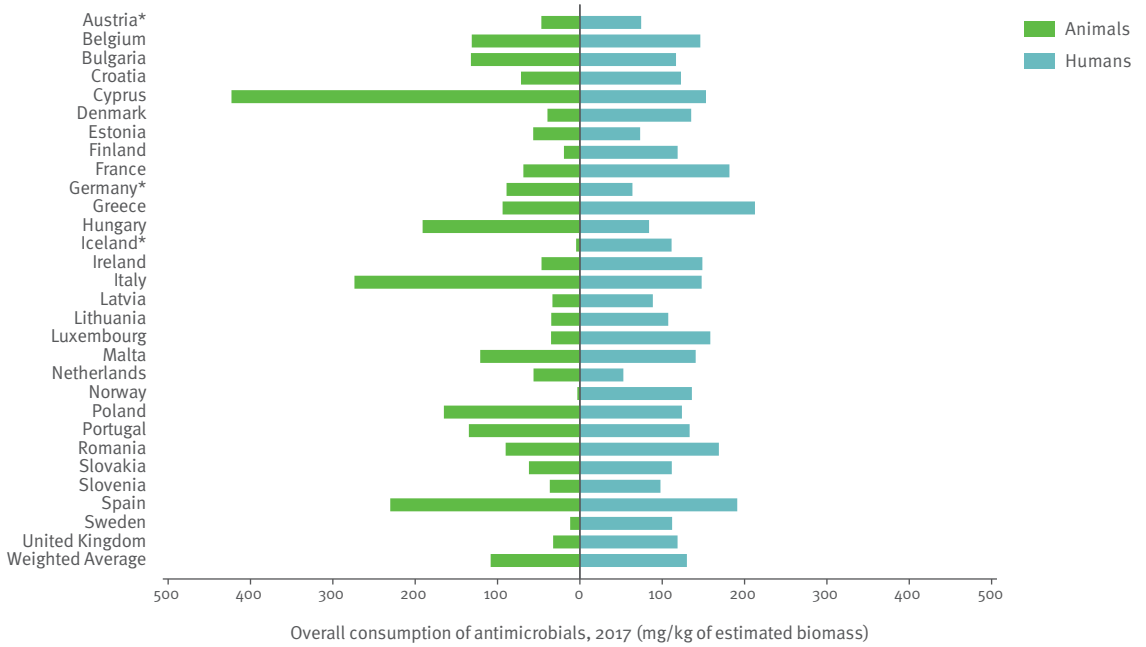
(b): ATC J01 Antibacterials for systemic use.

(c): ATCvet QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51, QP51AG.

(d): For countries reporting less than 95% data coverage for consumption in humans (Germany 85%, the Netherlands 92% and Luxembourg 90.5%) the consumption in tonnes of active substance is extrapolated to 100%.

(e): Population weighted mean.

Figure 6: Comparison of biomass-corrected consumption of antimicrobials (milligrams per kilogram estimated biomass) in humans (a) and food-producing animals (b) by country, in 29 EU/EEA countries for which data were available both for humans and food-producing animals, 2017



Asterisk (*) denotes that only community consumption was provided for human medicine. The population-weighted mean proportion (%) of hospital sector AMC out of the 2017 total national AMC for EU/EEA countries that provided data for both sectors is 15%.

Notes: 1) The estimates presented are crude and must be interpreted with caution. For limitations hampering comparison of antimicrobial consumption in humans and food-producing animals, see Section 15.1. The weighted mean figure represents the population-weighted mean of data from those countries included.

(a): ATC J01 Antibacterials for systemic use.

(b): ATCvet QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51, QP51AG.

Table 7: Range, median and population-weighted mean consumption of antimicrobials overall and for the classes selected for analysis in humans and food-producing animals, and correlation analysis of antimicrobial consumption in humans and food-producing animals, 29 EU/EEA countries* for which data were available both for humans and food-producing animals, 2017

Antimicrobial class	Antimicrobial consumption (mg/kg estimated biomass)						Correlation coefficient[b] (p-value)
	Humans			Food-producing animals			
	Range	Median	Mean[a]	Range	Median	Mean	
Third- and fourth-generation cephalosporins	0.1–11.4	2.8	4.0	<0.01–0.8	0.2	0.2	0.32 (0.087)
Fluoroquinolones and other quinolones	2.2–24.0	6.4	7.7	<0.01–15.3	1.1	2.8	0.72 (<0.001)
Polymyxins	0–0.2	0.03	0.06	0–14.9	1.7	3.7	0.36 (0.056)
Aminopenicillins[c]	7.3–128.8	50.0	66.3	0.1–78.3	11.2	26.1	0.54 (0.003)
Macrolides	1.2–18.0	6.4	7.9	0–22.0	5.7	8.0	0.46 (0.013)
Tetracyclines	0.2–11.7	1.4	3.1	0.05–173.5	22.3	33.0	-0.32 (0.095)
Total consumption[d,e]	**52.8–212.6**	**122.8**	**130.0**	**3.1–423.1**	**61.9**	**108.3**	**0.33 (0.082)**

* AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK.

(a): Population weighted mean.

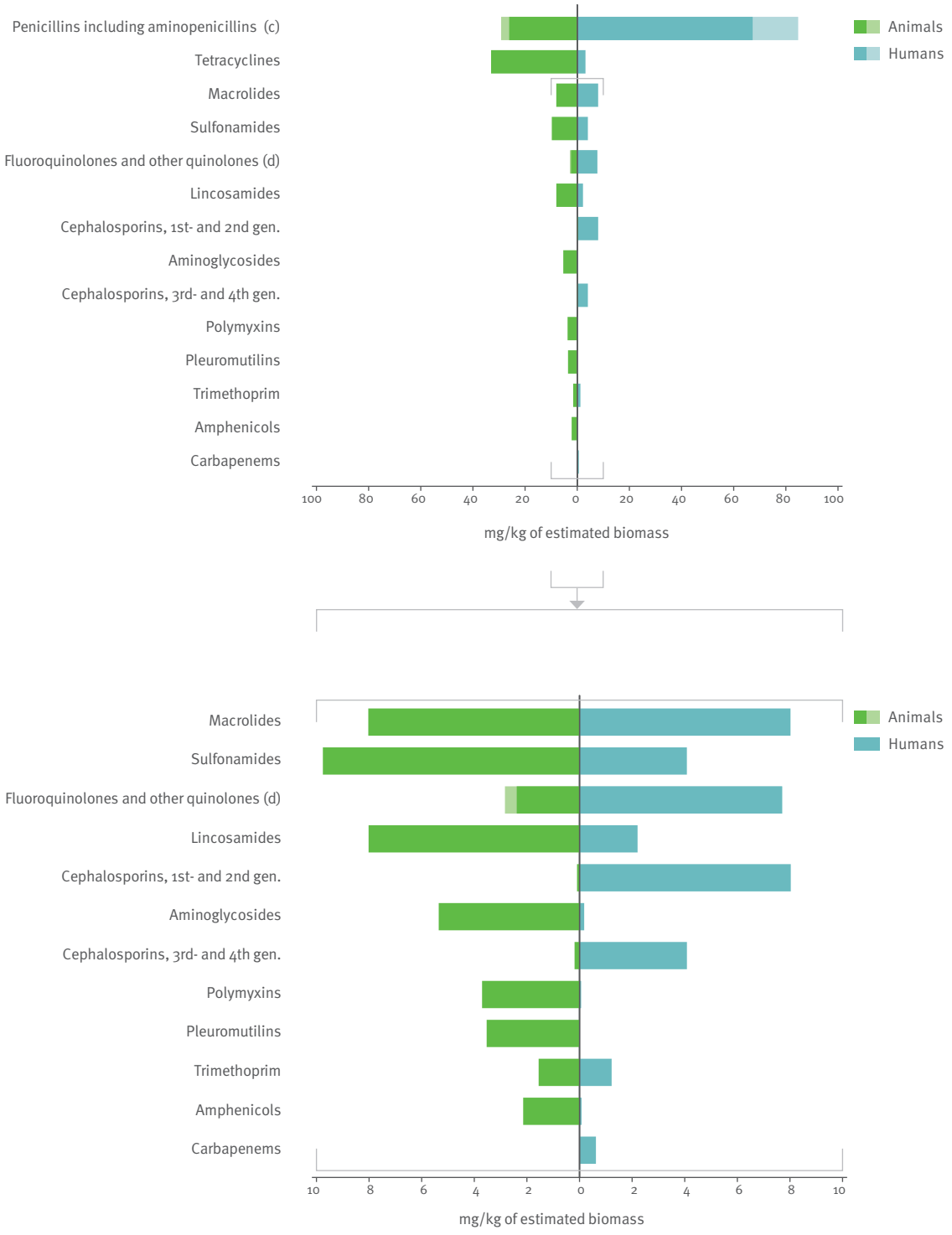
(b): Spearman's rank correlation coefficient (rho) for consumption in humans and consumption in food-producing animals.

(c): Includes ampicillin and amoxicillin without and with beta-lactamase inhibitors and metampicillin belonging to the ATCvet QA07AA98, QA07AA99, QJ01CA, QJ51CA, QJ01CR01, QJ01CR02, QJ01CR50, QJ51CR01, QJ51CR02, QJ51CR50, QJ51RA01, QJ51RV01, QG51AA03, QG51AG04, QG51AG05 and QG51AG07.

(d): For humans: ATC J01 Antibacterials for systemic use.

(e): For food-producing animals: ATCvet QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51, QP51AG.

Figure 7: Comparison of consumption of antimicrobial classes in humans (a) and food-producing animals (b), in 29 EU/EEA countries for which data were available, both for humans and food-producing animals, 2017



(a): ATC J01 apart from monobactams (ATC group J01DF), other cephalosporins and carbapenems (J01DI), streptogramins (J01 FG), glycopeptides, imidiazoles, nitrofurans, steroid antimicrobials and other antimicrobials (J01XX).

(b): ATCvet QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51, QP51AG.

(c): Aminopenicillins are shown in dark colour and all other penicillins in light colour.

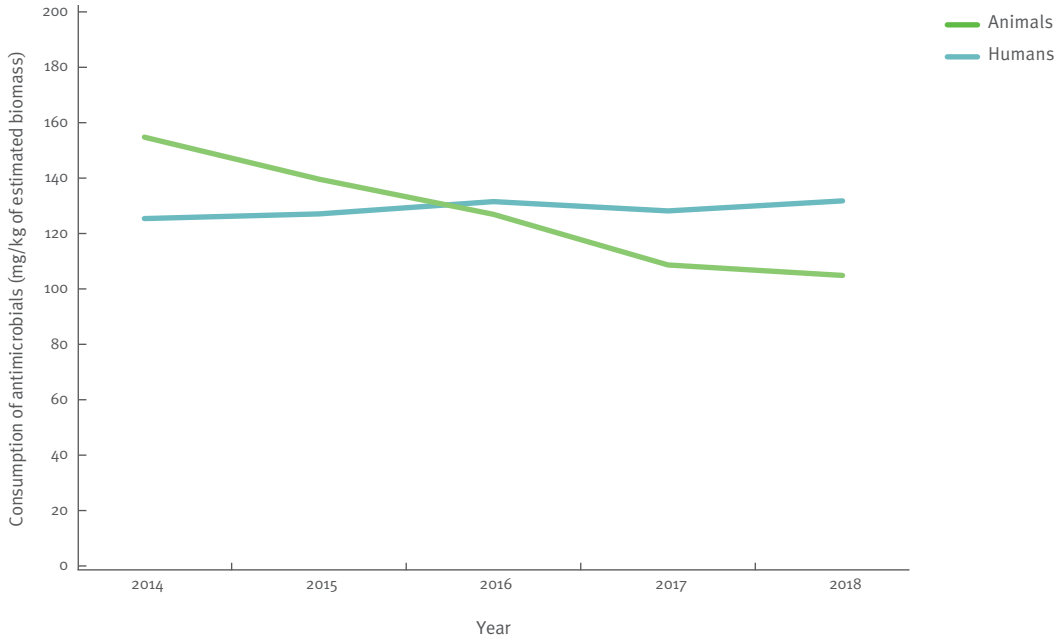
(d): Fluoroquinolones and other quinolones are shown in dark and light colour, respectively.

Notes: 1) The x-axis scale differs between graphs A and B.2). The estimates presented are crude and must be interpreted with caution. For limitations hampering comparison of antimicrobial consumption by humans and food-producing animals, see Chapter 15.1.

For the EU/EEA population-weighted mean consumption of antimicrobials in food-producing animals, expressed in mg/kg estimated biomass, there was a significant change for the 27 countries included in the analysis (p = 0.002, linear regression). A decline of 32% was observed between 2014 and 2018 (Figure 8). This was primarily due to a reduction in the consumption of the two highest selling classes – i.e. tetracyclines (-39%) and penicillins (-19%). The reduction of the consumption of tetracyclines was observed primarily for those substances with the highest dosing (-51%), while for the tetracyclines with lowest dosing (doxycycline), a 12% reduction was observed. This shows that there has not been a substantial shift from high-dose to low-dose tetracyclines [4]. During the period 2014 to 2018 the reduction in sales of penicillins for food-producing animals was almost solely accounted for by aminopenicillins without enzyme inhibitors; thus there was no change to the lower dosing penicillins.

For injectables the EU/EEA population-weighted mean consumption of antimicrobials in food-producing animals was stable (+1%) between 2014 and 2018. A decline of 34% in the overall population-weighted mean consumption of veterinary medicinal products for group treatment was observed for this period. This reduction mainly related to premixes (-56%), while for oral powder plus oral solution, the decline was 18%.

Figure 8: Population-weighted mean of the total consumption of antimicrobials in humans (a) and food-producing animals (b) in 27 EU/EEA countries (c) for which data were available, both for humans and food-producing animals, for 2014 to 2018



(a) For humans: ATC J01 Antibacterials for systemic use.
(b) For food-producing animals: ATCvet QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51, QP51AG
(c) AT, BE, BG, CY, DE, DK, EE, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK.

6. Carbapenems

Carbapenems are a last-line group of antibiotics and are mainly used in hospitals for treatment of patients with confirmed or suspected infections involving multidrug-resistant gram-negative bacteria. In the recent WHO AWaRe classification, carbapenems belong to the 'Watch' group of antimicrobials, with the exception of meropenem-vaborbactam, which is in the 'Reserve' group [32]. Carbapenems are considered by WHO as Critically Important Antimicrobials (CIA) in human medicine [14].

According to the AMEG categorisation, carbapenems belong to Category A with the indication 'Avoid' use in veterinary medicine in the EU [13]. Substances in this category are not authorised in veterinary medicine and, in the absence of evaluation for maximum residue limits, cannot be used for food-producing animals. These antibiotics may only be used exceptionally in individual companion animals, in compliance with the prescribing 'cascade'.

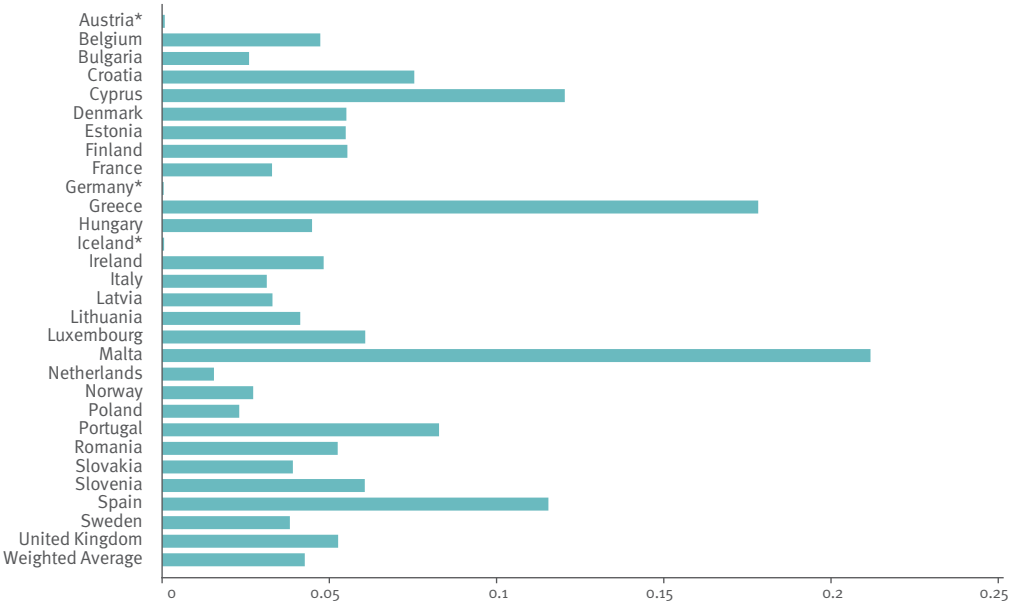
6.1 Consumption in humans and food-producing animals by country

As mentioned above, carbapenems are not approved for use in animals, and data provided below are only for human AMC.

In 2017, the consumption of carbapenems in hospitals constituted 55–100% of the total consumption of carbapenems and in most of the countries (15/24), this percentage was greater than 99%.

In 2017, the mean consumption of carbapenems in humans equalled 0.04 DDD per 1 000 inhabitants per day. The corresponding range was <0.01–0.21 (median 0.05) DDDs per 1 000 inhabitants per day. The consumption of carbapenems in humans by country in 2017 is shown in Figure 9.

Figure 9: Consumption of carbapenems in humans expressed as DDD per 1 000 inhabitants and per day, by country, EU/EEA, 2017



An asterisk (*) denotes that only community consumption was provided for human medicine. The population-weighted mean proportion (%) of the hospital sector from the 2017 total national consumption of carbapenems for EU/EEA countries providing data for both sectors is 94.4%. The weighted mean figure represents the population-weighted mean of data from included countries.

6.2 Consumption in humans and resistance in bacterial isolates from humans

Klebsiella pneumoniae

A borderline statistically significant positive association was reported between the consumption of carbapenems and carbapenem resistance in invasive *K. pneumoniae* isolates for 2016 and 2018, while no significant association was reported for 2017 (Table 8).

Escherichia coli

A statistically significant positive association was reported between consumption of carbapenems and resistance to carbapenems of invasive *E. coli* isolates for all years 2016–2018 (Table 9, Figure 10).

6.3 Resistance in bacterial isolates from humans and from food-producing animals

The use of carbapenems is not authorised in food-producing animals in the EU. Resistance to carbapenems in food-producing animals is extremely rare; occasional findings have been recorded in pigs and chickens since 2011.

Since 2014, resistance to meropenem has been tested in both indicator *E. coli* and *Salmonella* spp. within the framework of the mandatory monitoring of AMR in food-producing animals. It has been occasionally detected in pigs through the specific monitoring of ESBL/AmpC-producing *E. coli*. In both 2015 and 2017, one single isolate of a VIM-1 producing *E. coli* was detected per year in pigs at slaughter in Germany. Repeated detection of a VIM-1 producing *E. coli* associated with a certain plasmid indicates that this plasmid may occur at a very low prevalence on pig farms [33].

In addition, in 2017 and 2018, 20 countries (18 Member States and two non-Member States) performed extensive specific monitoring of carbapenemase-producing *E. coli* on a voluntary basis. In total, 5 208 samples from fattening pigs; 2 827 samples from calves under one year of age; 6 168 samples from broilers; 2 419 samples from fattening turkeys, 4 846 samples from pig meat, 4 615 samples from bovine meat and 4 615 samples from broiler meat were tested. This gives a grand total of 30 698 samples, all of which tested negative for carbapenemase-producing *E. coli*. In 2015 and 2016, a total of 6 751 (2015) and 11 935 (2016) samples, respectively, were investigated, of which two samples from broilers and one from broiler meat, collected in Romania in 2016 tested positive for blaOXA-162 (blaoxa-48-like) carriers.

K. pneumoniae is not considered a zoonotic bacterium and not routinely tested for AMR in the food-producing animal sector in most countries.

A meaningful correlation analysis between resistance in isolates from food-producing animals and from humans was therefore not possible.

6.4 Multivariate analysis

The occurrence of carbapenem-resistance in Enterobacterales from food-producing animals is extremely rare and the use of this antimicrobial in food-producing animals is prohibited. Therefore, a multivariate analysis for the emergence of carbapenems resistance in *E. coli* or *K. pneumoniae* in relation to the use of carbapenems and resistance to these antimicrobials in food-producing animals, as well as carbapenem use in humans, could not be performed.

Table 8: Consumption of carbapenems in humans expressed as DDD per 1 000 inhabitants and per day, and the probability of resistance to carbapenems in invasive *Klebsiella pneumoniae* from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure A1.2.1)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	2.30	0.084	0.89–5.93
2017	AT, BE, BG CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.09	0.752	0.64–1.85
2018	AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (N=28)	2	3.56	0.091	0.81–15.51

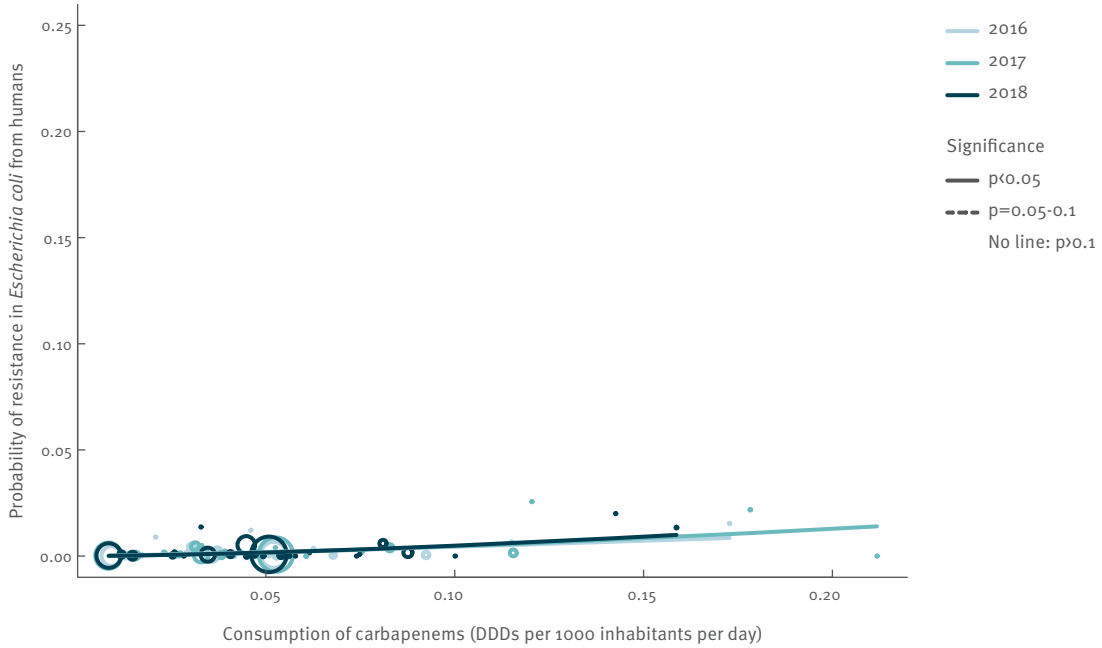
CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 9: Consumption of carbapenems in humans, expressed as DDD per 1 000 inhabitants per day, and the probability of resistance to carbapenems in invasive *Escherichia coli* from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 10)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, BG, CY, DE, DK, EE, EL, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=27)	2	2.34	0.037	1.05–5.21
2017	AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=28)	2	2.85	<0.001	1.72–4.74
2018	AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (N=28)	2	2.95	0.018	1.21–7.22

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 10: Consumption of carbapenems in humans and the probability of resistance to carbapenems in invasive *Escherichia coli* from humans, EU/EEA, 2016–2018 (see also Table 9)



The figure displays results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

7. Third- and fourth-generation cephalosporins

Third- and fourth- generation cephalosporins are essential for treatment of severe and invasive infections, such as acute bacterial meningitis, gonococcal infections in all age groups and disease due to *Salmonella* spp. in children. They are among the few alternatives for treatment of severe (life-threatening) sepsis and respiratory tract infections in various animal species, where resistance to antibiotics in AMEG Categories C ('Caution') and D ('Prudence') has been confirmed.

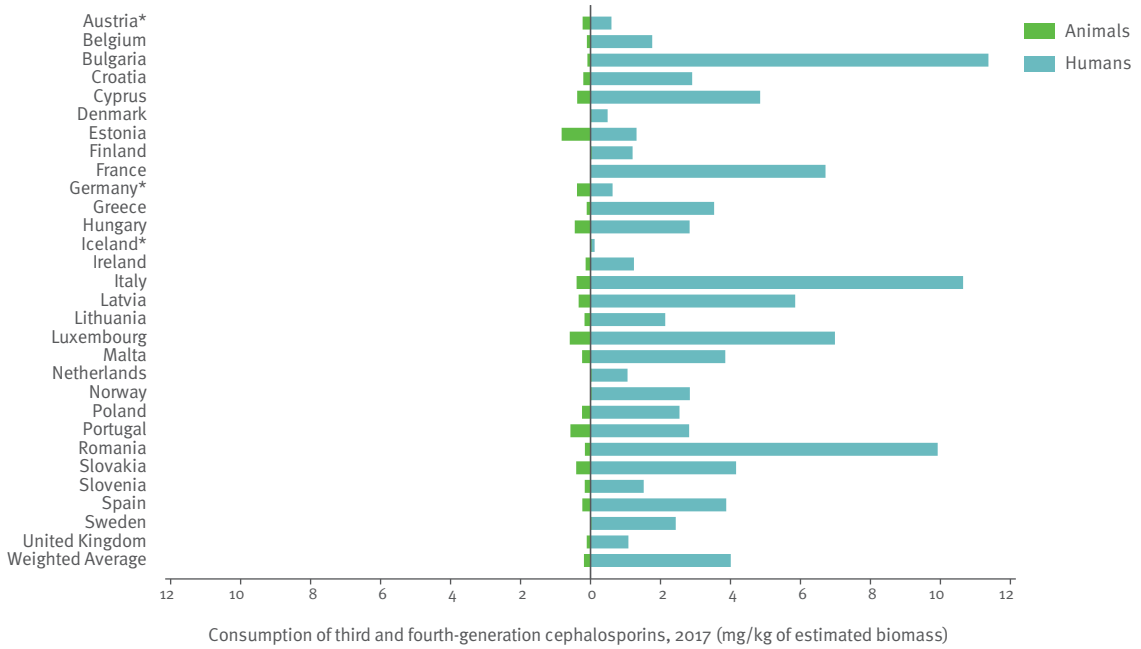
In the recent WHO AWaRe classification the third- and fourth-generation belong to the 'Watch' group of antimicrobials, with the exception of ceftazidime-avibactam, which is in 'Reserve' [32]. Third- and fourth-generation cephalosporins are considered by WHO as Highest Priority Critically Important Antimicrobials (HPCIA) in human medicine [14]. This class has also been categorised as Veterinary Critically Important Antimicrobial Agents (VCIA) in the OIE list of antimicrobials of veterinary importance [34]. According to the AMEG categorisation, third- and fourth-generation cephalosporins belong to Category B, with the indication 'Restrict' use in veterinary medicine in the EU [13]. This means that the risk to public health resulting from veterinary use needs to be mitigated by specific restrictions. The third- and fourth-generation cephalosporins should only be used for the treatment of clinical conditions in animals when there are no antibiotics in the lower Categories C ('Caution') or D ('Prudence') that could be clinically effective.

Fifth generation cephalosporins are not licensed for use in animals. They are in WHO's 'Reserve' list and are also considered as HPCIA by WHO. AMEG categorises them as A ('Avoid'). However, they are not considered in this chapter.

7.1 Consumption in humans and food-producing animals by country

In 2017, the EU/EEA population-weighted mean consumption of third- and fourth-generation cephalosporins in humans and food-producing animals was 4.0 and 0.2 mg/kg of estimated biomass, respectively (Figure 11). The corresponding ranges were < 0.1–11.4 (median 2.8) in humans and < 0.01–0.8 (median 0.2) mg/kg in food-producing animals, respectively. In Figure 11 the biomass-corrected consumption in humans and food-producing animals is shown by country. For all countries included in the

Figure 11: Biomass-corrected consumption of third- and fourth-generation cephalosporins in humans and food-producing animals in 29 EU/EEA countries for which data were available, both for humans and food-producing animals, 2017



An asterisk (*) denotes that only community consumption was provided for human medicine. The population-weighted mean proportion (%) of the hospital sector from the 2017 total national consumption of third- and fourth-generation cephalosporins for EU/EEA countries providing data for both sectors was 68.0%.

Notes: 1) The estimates presented are crude and must be interpreted with caution. For limitations hampering the comparison of consumption of antimicrobials in humans and food-producing animals, please see Chapter 15.11.2). The weighted mean figure represents the population-weighted mean of data from those countries included.

analysis, the consumption of third- and fourth-generation cephalosporins in food-producing animals was lower than that reported in human medicine in 2017.

There was no association between the consumption of third- and fourth-generation cephalosporins in humans and in food-producing animals (Spearman's rank correlation coefficient, rho = 0.32) at the national level in 2017.

7.2 Consumption in humans and resistance in bacterial isolates from humans

Escherichia coli

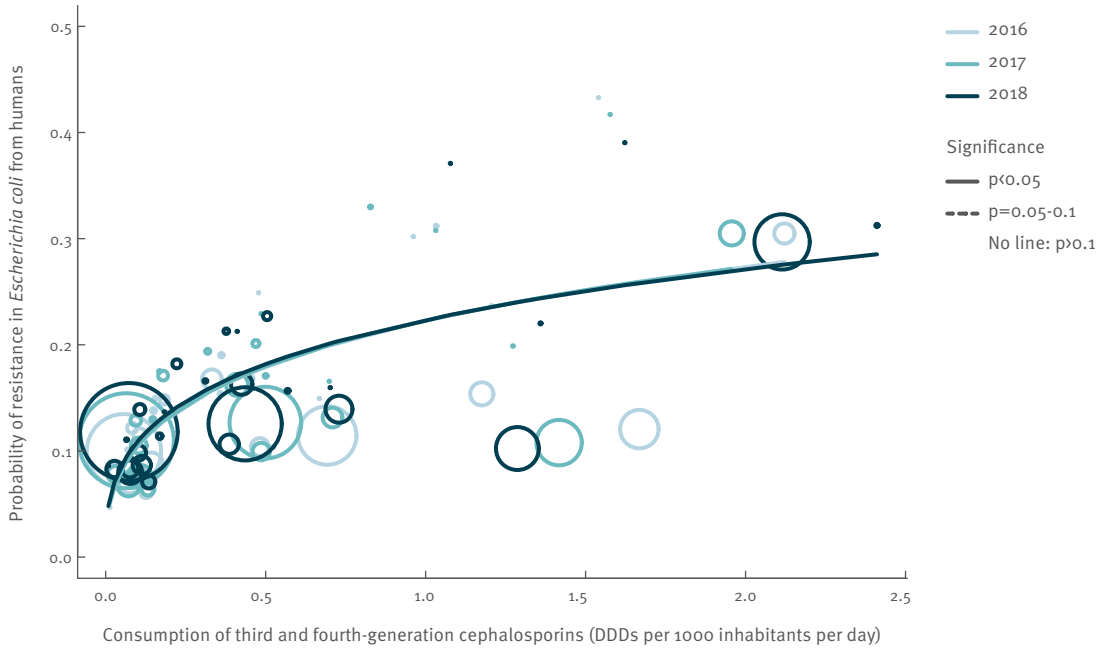
A statistically significant positive association between the total consumption (community and hospital) of third- and fourth-generation cephalosporins and resistance to third-generation cephalosporins in invasive *E. coli* isolates from humans was found for 2016, 2017 and 2018, with odds ratios being constant over the years (Table 10, Figure 12).

Table 10: Consumption of third- and fourth-generation cephalosporins in humans, expressed as DDD per 1 000 inhabitants and per day, and the probability of resistance to third-generation cephalosporins in *Escherichia coli* from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 12)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.31	<0.001	1.20–1.44
2017	AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.31	<0.001	1.19–1.45
2018	AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (N=29)	2	1.29	<0.001	1.19–1.41

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 12: Consumption of third- and fourth-generation cephalosporins in humans and probability of resistance to third-generation cephalosporins in *Escherichia coli*, EU/EEA, 2016–2018 (see also Table 10)



The figure displays results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Salmonella

A statistically significant association was found between the consumption of third- and fourth-generation cephalosporins in humans and the occurrence of resistance to third-generation cephalosporins of *Salmonella* spp., only for 2018, not for 2016 and 2017 (Table 11, Figure 13).

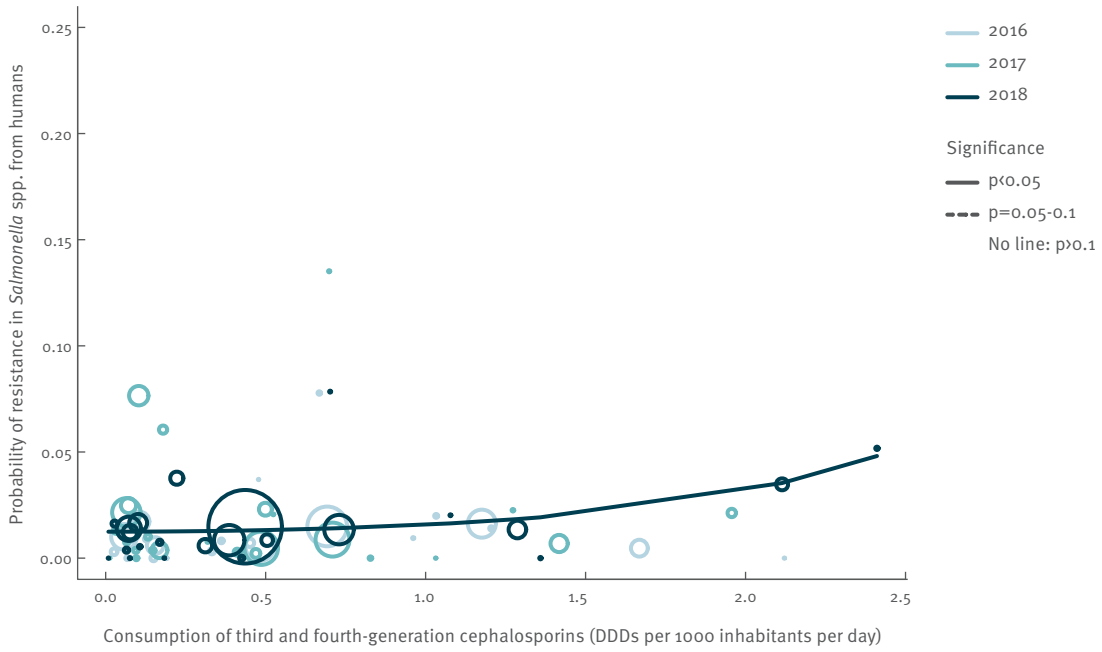
In a sub-analysis, a statistically significant association between the consumption of third- and fourth-generation cephalosporins in humans and resistance to third-generation cephalosporins was only observed for *S.* Enteritidis in 2018. No such association was observed for *S.* Enteritidis in the other years, or for *S.* Typhimurium including the monophasic variant (Table 12, Figure 14, Table 13).

Table 11: Consumption of third- and fourth-generation cephalosporins in humans, expressed as DDD per 1 000 inhabitants per day, and probability of resistance to third-generation cephalosporins in selected *Salmonella* from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 13)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PT, RO, SI, SK, UK (n=24)	3	0.91	0.763	0.51–1.65
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=25)	3	0.98	0.954	0.47–2.05
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, PL, PT, RO, SI, SK, UK (n=23)	3	1.27	0.027	1.03–1.56

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 13: Consumption of third- and fourth-generation cephalosporins in humans and probability of resistance to third-generation cephalosporins in *Salmonella*, EU/EEA, 2016–2018 (see also Table 11)



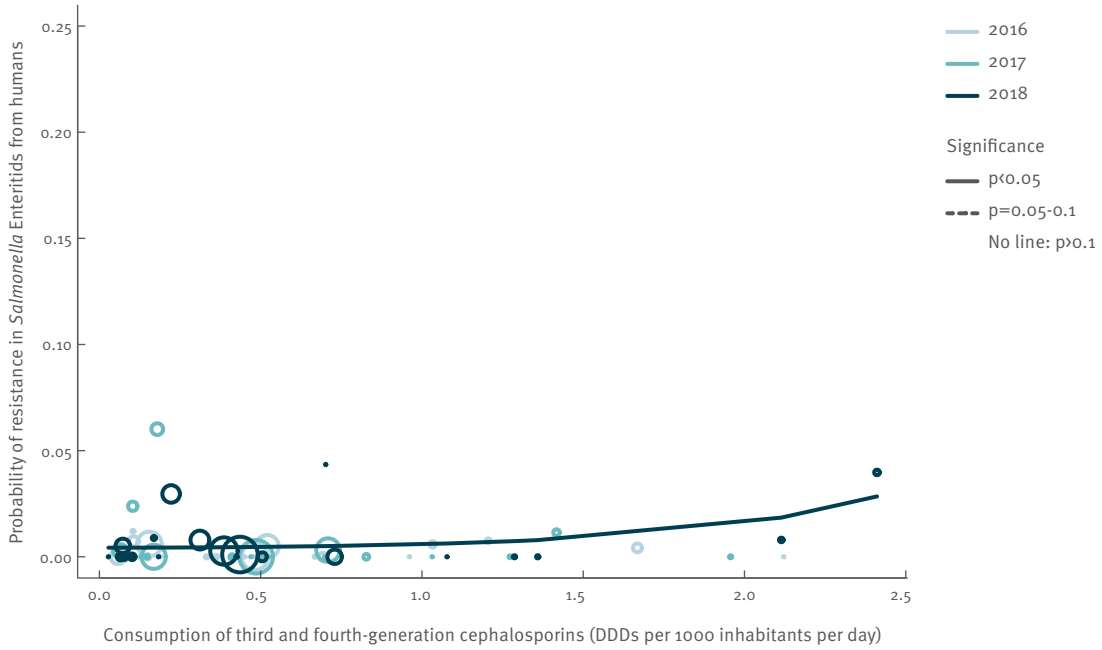
The figure displays results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Table 12: Consumption of third- and fourth-generation cephalosporins in humans, expressed as DDD per 1 000 inhabitants per day, and the probability of resistance to third-generation cephalosporins in *Salmonella* Enteritidis from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 14)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PT, RO, SI, SK, UK (n=23)	3	1.19	0.596	0.63–2.26
2017	AT, BE, CY, DE, EE, ES, FI, FR, HU, IE, IT, LT, LU, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=22)	3	0.60	0.620	0.08–4.50
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, MT, NL, PL, PT, RO, SI, SK, UK (n=22)	3	1.39	0.034	1.03–1.89

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 14: Consumption of third- and fourth-generation cephalosporins in humans and the probability of resistance to third-generation cephalosporins in *Salmonella* Enteritidis, EU/EEA, 2016–2018 (see also Table 12)



The figure displays results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Table 13: Consumption of third- and fourth-generation cephalosporins in humans, expressed as DDD per 1 000 inhabitants per day, and the probability of resistance to third-generation cephalosporins in *Salmonella* Typhimurium, including monophasic variant from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, MT, NL, NO, PT, RO, SI, SK, UK (n=23)	2	1.28	0.213	0.87–1.88
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=25)	2	0.83	0.193	0.63–1.10
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, MT, NL, PL, PT, RO, SI, UK (n=21)	2	1.04	0.723	0.85–1.26

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

7.3 Consumption in food-producing animals and resistance in bacterial isolates from food-producing animals

As third- and fourth-generation cephalosporins are not licensed for use in poultry, it should be noted that data on consumption of these drugs only includes consumption in other animal species.

Escherichia coli from food-producing animals

In order to investigate possible relationships between the consumption of third- and fourth-generation cephalosporins and cephalosporin resistance, the SIMR to cefotaxime in *E. coli* from food-producing animals was compared with the consumption of third- and fourth-generation cephalosporin in food-producing animals (expressed in mg per kg of estimated biomass) for the two-year intervals 2014–2015, 2015–2016, 2016–2017 and 2017–2018 (mean consumption over the respective years) at the national level (Table 14). The category 'food-producing animals' includes broilers, turkeys, pigs and calves, sampled at slaughter, for each time interval.

Although some disparity in consumption of third- and fourth-generation cephalosporins was recorded among the countries considered, cefotaxime resistance was always reported at low to very low levels, or was undetected. Although positive associations between cefotaxime resistance in indicator *E. coli* and the consumption of third- and fourth-generation cephalosporins in food-producing animals were observed for each time interval, none of the associations was statistically significant. For the period 2014–2015, the association was assessed as borderline statistically significant and illustrated in Figure A1.2.2. In addition, one influential data outlier (one outlying country in the graphs) was detected. Following a sensitivity analysis, this outlier was removed and after that there was a statistically significant positive association between consumption and resistance for the periods 2014–2015, 2015–2016 and 2016–2017, while the association for 2017–2018 was borderline statistically significant (Table A1.5.1, Figure A1.5.1).

Indicator *Escherichia coli* and *Salmonella* from pigs

The estimated consumption of third- and fourth-generation cephalosporins in pigs was compared with the occurrence of resistance to cefotaxime in indicator *E. coli* and *Salmonella* spp. from slaughter pigs for 2017 for 31 and five reporting countries, respectively. The corresponding analysis was not performed in poultry, since there is no veterinary medicinal product based on third- or fourth-generation cephalosporins authorised in poultry in the EU. Therefore, there is no consumption of these substances in poultry. No sub-analysis for specific *Salmonella* serovars in pigs was conducted, as there were not enough data available.

Although variations in consumption of third- and fourth-generation cephalosporins in pigs were observed among the countries considered, cefotaxime resistance in indicator *E. coli* and *Salmonella* spp. from slaughter pigs was typically reported at very low levels. None of the associations assessed for 2017 were statistically significant (Table 15).

Table 14: Consumption of third- and fourth-generation cephalosporins in food-producing animals, expressed in mg per kg of estimated biomass, and probability of resistance to third-generation cephalosporins in indicator *Escherichia coli* from food-producing animals (logistic regression, see also Figure A1.2.2)

Year	Countries	Model	Odds ratio	p-value	95% CI
2014–2015	AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=26)	2	1.31	0.067	0.98–1.74
2015–2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=28)	2	1.12	0.454	0.83–1.53
2016–2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.23	0.218	0.88–1.72
2017–2018	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK (n=27)	2	1.22	0.134	0.94–1.59

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 15: Estimated consumption of third- and fourth-generation cephalosporins in pigs, expressed as DDDvet/kg of estimated biomass/year, and probability of resistance to cefotaxime in indicator *Escherichia coli* from pigs and *Salmonella* from pigs* (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
Indicator *E. coli*					
2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=31)	2	1.13	0.314	0.89–1.42
Salmonella					
2017	BE, CZ, DE, DK, ES, FR, HR, HU, IE, IT, MT, PL, PT, SK (n=14)	2	1.90	0.211	0.69–5.24

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.
* *Salmonella* spp. isolates derive from pig carcasses.

Prevalence of ESBL- and/or AmpC-producing *Escherichia coli* from food-producing animals and consumption of third- and fourth-generation cephalosporins

The prevalence of ESBL and/or AmpC-producing *E. coli* has been retained as one of the key indicators of AMR in food-producing animals in the EU [12]. It is defined as the proportion of samples from broilers, fattening turkeys, fattening pigs and bovine animals aged under one year, weighted by PCU, that are identified as positive for presumptive ESBL and/or AmpC-producing *E. coli* when performing specific monitoring for ESBL-/AmpC-/carbapenemase-producing *E. coli* in food-producing animals. The specific monitoring, which has been in place since 2015, comprises culture of caecal samples on medium containing cefotaxime for selective isolation of ESBL-/AmpC-/carbapenemase-producing *E. coli* (Commission Implementing Decision 2013/652/EU).

The prevalence of ESBL and/or AmpC producers in food-producing animals was compared with the national consumption of third- and fourth-generation cephalosporins in food-producing animals (expressed in mg per kg of estimated biomass) for the time periods 2015–2016, 2016–2017 and 2017–2018 at national level. As the statutory specific monitoring of ESBL and/or AmpC producers foresees testing of the food-producing animal populations on a biannual basis, two consecutive years were considered together in all analyses. Both data on the prevalence of ESBL and/or AmpC producers and the national consumption of third- and fourth-generation cephalosporins were available together for 28, 29 and 31 countries, respectively.

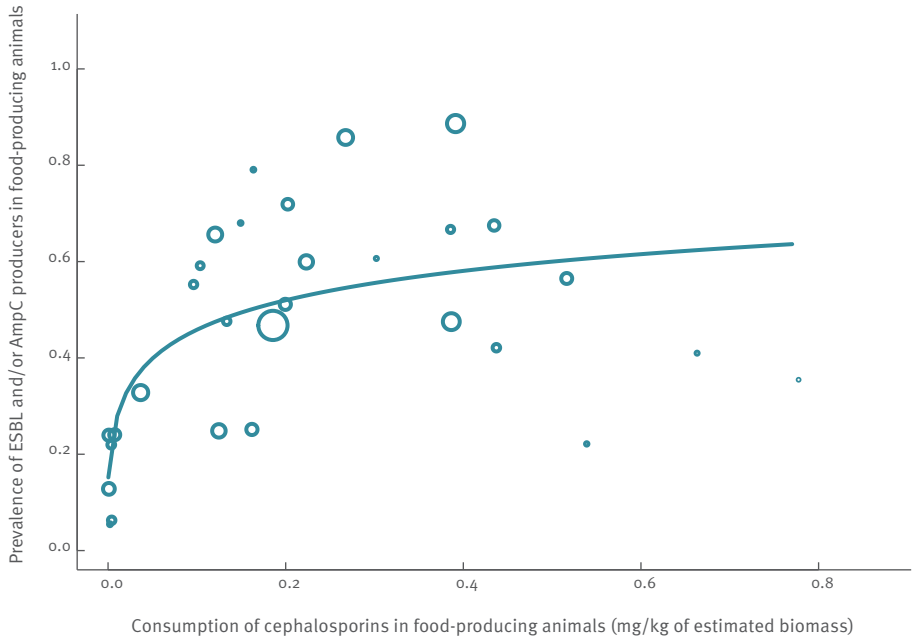
Marked variations in the prevalence of ESBL- and/or AmpC-producers and the consumption of third- and fourth-generation cephalosporins were observed among the countries included in the analyses (Table 16, Figure 15). The prevalence of ESBL- and/or

Table 16: Association between consumption of third- and fourth-generation cephalosporins in food-producing animals (expressed in mg per kg estimated biomass) and prevalence of ESBL-and/or AmpC-producing *Escherichia coli* in food-producing animals (logistic regression, see also Figure 15)

Year	Countries	Model	Odds ratio	p-value	95% CI
2015-2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=28)	2	1.25	<0.001	1.12–1.40
2016-2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.28	<0.001	1.14–1.44
2017-2018	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=31)	2	1.29	<0.001	1.14–1.46

CI: confidence interval. Odds ratio varies from 0 to infinity. When odds ratio equals 1 or CI includes 1, the association is not considered statistically significant. Food-producing animals include broilers, turkeys, pigs and veal calves.

Figure 15: Consumption of third- and fourth-generation cephalosporins in food-producing animals and the prevalence of ESBL- and/or AmpC-producing *Escherichia coli* in food-producing animals for 2016–2017 (see also Table 18)



The figure displays results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles reflects the amount of available resistance data per country.

AmpC-producers ranged between 90% in some countries to very low levels. Consumption of third- and fourth-generation cephalosporins varied from zero to less than 1 mg per kg of estimated biomass. For all time intervals, significant positive associations of the same magnitude were observed between the probability of detecting an ESBL- and/or AmpC-producing *E. coli* and the consumption of third- and fourth-generation cephalosporins (Table 16).

7.4 Resistance in bacterial isolates from humans and food-producing animals

Escherichia coli from humans and food-producing animals

Data on the resistance of invasive *E. coli* from humans to third-generation cephalosporins (2016 to 2018) were compared with the resistance to third-generation cephalosporins of indicator *E. coli* from broilers and turkeys (2016 and 2018) as well as from pigs and calves (2017).

No statistically significant associations were found for any tested combination and year, though a borderline statistically significant positive association was reported for broilers for 2016 and 2018 (Table 17).

Resistance to third-generation cephalosporins in isolates of *Salmonella* from humans and from food-producing animals

Data on the occurrence of resistance to third-generation cephalosporins of *Salmonella* spp. from humans (2016–2018) were compared with the occurrence of resistance to third-generation cephalosporins of *Salmonella* spp. from broilers and turkeys (2016, 2018) as well as from pig carcasses (2017) (Table 18). A subanalysis for specific *Salmonella* serovars was not possible due to insufficient data.

Resistance to third-generation cephalosporins in *Salmonella* spp. from humans only had a statistically significant positive association with the level of resistance to third-generation cephalosporins of *Salmonella* spp. from turkeys in 2018 (Table 18, Figure 16). That association was linked to a very high resistance rate in isolates from turkeys in one country (Figure 16). For all other years and combinations, no evidence of a statistically significant association was found.

Table 17: Association between resistance to third-generation cephalosporins in *Escherichia coli* from food-producing animals, and from humans, 2016–2018 (logistic regression, see also Figure A1.2.3)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Broilers	2016	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.10	0.078	0.99–1.21
	2018	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.09	0.057	1.00–1.19
Turkeys	2016	AT, DE, ES, FR, HU, IT, NO, PL, PT, RO, SE, UK (n=12)	2	1.08	0.272	0.94–1.25
	2018	AT, DE, ES, FR, HU, IT, NO, PL, PT, RO, SE, UK (n=12)	2	1.05	0.461	0.92–1.21
Pigs	2017	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=30)	2	0.94	0.236	0.85–1.04
Calves	2017	AT, BE, DE, DK, ES, FR, HR, IT, NL, NO, PT (n=11)	2	1.14	0.127	0.96–1.36

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 18: Association between resistance to third-generation cephalosporins in *Salmonella* from food-producing animals and from humans, 2016–2018 (logistic regression, see also Figure 16)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Broilers	2016	AT, BE, CY, DE, DK, EL, IS, FR, HU, IE, IT, MT, PT, RO, SI, SK, UK (n=17)	2	1.17	0.146	0.95–1.46
Broilers	2018	AT, BE, CY, DE, DK, ES, FR, HU, IE, IT, MT, PL, PT, RO, SI, SK, UK (n=17)	2	1.13	0.111	0.97–1.32
Turkeys	2016	AT, DE, ES, FR, HU, UK (n=6)	2	1.12	0.145	0.96–1.32
Turkeys	2018	AT, CY, ES, FR, HU, IE, IT, PL, UK (n=9)	2	1.16	0.001	1.07–1.26
Pigs*	2017	BE, DE, DK, ES, FR, HU, IE, IT, MT, PL, PT, SK (n=12)	2	0.79	0.396	0.46–1.36

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.
* *Salmonella* spp. isolates derive from pig carcasses

7.5 Consumption in food-producing animals and resistance in bacterial isolates from humans

To investigate a possible relationship between the consumption of third- and fourth- generation cephalosporins in food-producing animals with resistance to third-generation cephalosporins in bacteria causing infections in humans, the occurrence of AMR in *E. coli* and *Salmonella* spp. from humans was compared with consumption of third- and fourth- generation cephalosporins in food-producing animals (expressed in milligrams per kg of estimated biomass) for 2016, 2017 and 2018.

Escherichia coli

A statistically significant positive association was found between consumption of third- and fourth-generation cephalosporins in food-producing animals and resistance to third-generation cephalosporins in invasive *E. coli* isolates from humans for all years (Table 19, Figure 17).

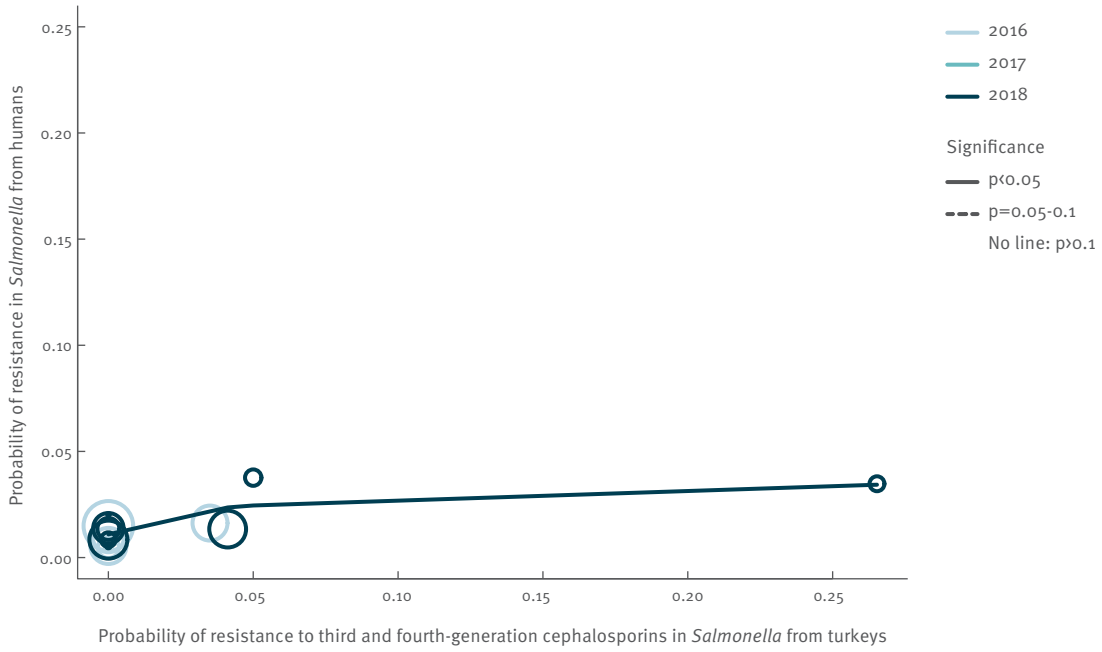
Salmonella

No statistically significant association was found between consumption of third- and fourth-generation cephalosporins in food-producing animals and resistance to third-generation cephalosporins in *Salmonella* isolates from humans for 2016–2018 (Table 20, Table 19).

No statistically significant associations were found between consumption of third- and fourth-generation cephalosporins in food-producing animals and resistance to third-generation cephalosporins in *S.* Enteritidis isolates from humans for 2016–2018 (Table 21).

No statistically significant associations were found between consumption of third- and fourth-generation cephalosporins in food-producing animals and resistance to third-generation cephalosporins in *S.* Typhimurium isolates from humans for 2016–2018 (Table 22).

Figure 16: Probability of resistance to third-generation cephalosporins in *Salmonella* from turkeys and humans, EU/EEA, 2016 and 2018 (logistic regression, see also Table 18)



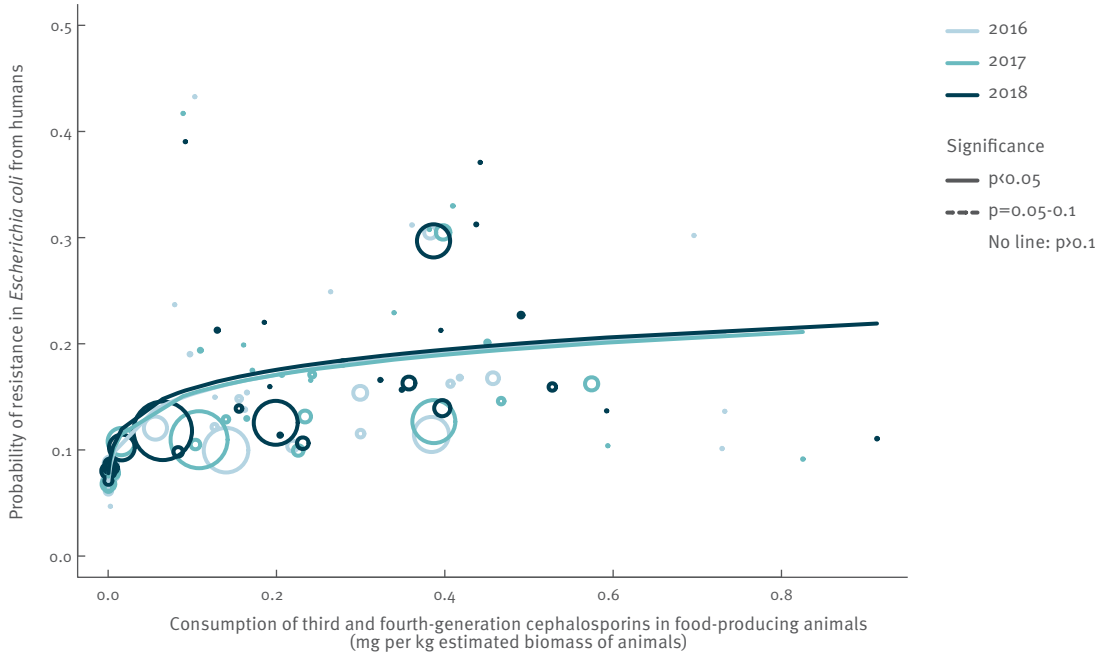
The figure displays results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Table 19: Association between consumption of third- and fourth-generation cephalosporins in food-producing animals, expressed in mg/PCU, and probability of resistance to third-generation cephalosporins in *Escherichia coli* from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 17)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.15	0.005	1.04–1.26
2017	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.14	0.003	1.04–1.24
2018	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.14	0.001	1.05–1.23

CI: confidence interval. Odds ratio varies from 0 to infinity. When odds ratio equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 17: Consumption of third- and fourth-generation cephalosporins in food-producing animals, expressed in mg/PCU, and probability of resistance to third-generation cephalosporins in *Escherichia coli* from humans, EU/EEA, 2016–2018 (see also Table 19)



The figure displays results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles reflects the amount of available resistance data per country.

Table 20: Association between consumption of third- and fourth-generation cephalosporins in food-producing animals, expressed in mg/PCU, and probability of resistance to third-generation cephalosporins in *Salmonella* from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PT, RO, SI, SK, UK (n=23)	3	0.28	0.335	0.02–3.70
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=25)	3	0.17	0.511	0.00–35.45
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, PL, PT, RO, SI, SK, UK (n=23)	3	0.40	0.586	0.01–10.55

CI: confidence interval. Odds ratio varies from 0 to infinity. When odds ratio equals 1 or CI includes 1, the association is not considered statistically significant.

Table 21: Association between consumption of third- and fourth-generation cephalosporins in food-producing animals, expressed in mg/PCU, and probability of resistance to third-generation cephalosporins in *Salmonella* Enteritidis from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PT, RO, SI, SK, UK (n=22)	2	1.02	0.878	0.77–1.36
2017	AT, BE, CY, DE, EE, ES, FI, FR, HU, IE, IT, LT, LU, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=22)	2	1.07	0.765	0.68–1.70
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, MT, NL, PL, PT, RO, SI, SK, UK (n=22)	2	1.36	0.288	0.77–2.41

CI: confidence interval. Odds ratio varies from 0 to infinity. When odds ratio equals 1 or CI includes 1, the association is not considered statistically significant.

Table 22: Association between consumption of third- and fourth-generation cephalosporins in food-producing animals, expressed in mg/PCU, and probability of resistance to third-generation cephalosporins in *Salmonella* Typhimurium from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PT, RO, SI, SK, UK (n=22)	2	1.18	0.385	0.82–1.70
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=25)	2	1.02	0.824	0.85–1.23
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, MT, NL, PL, PT, RO, SI, UK (n=21)	2	1.09	0.287	0.93–1.26

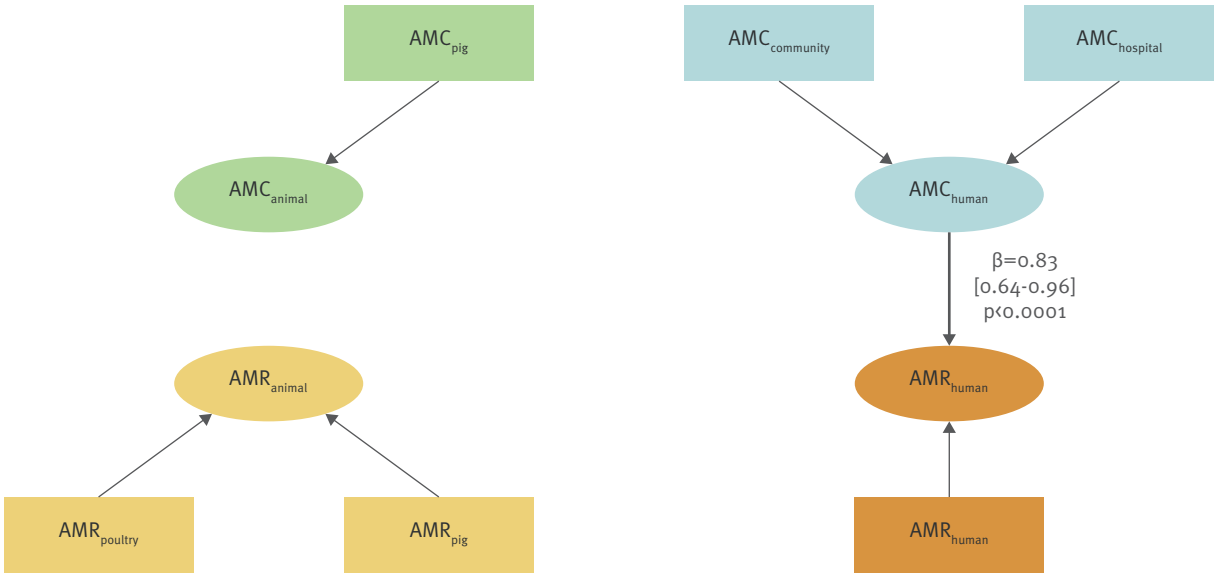
CI: confidence interval. Odds ratio varies from 0 to infinity. When odds ratio equals 1 or CI includes 1, the association is not considered statistically significant.

7.6. Multivariate analysis

The only significant relationship retained in the final model of resistance to third-generation cephalosporins in invasive *E. coli* from humans related to the strong ($p<0.001$) direct effect of the consumption of third- and fourth-generation cephalosporins in humans (Figure 18). According to the R^2, 69% of the variance of resistance is explained by the corresponding latent variable third- and fourth-generation cephalosporin consumption in humans (R^2 95% confidence interval: 0.41–0.92).

For *Salmonella* spp., the data was limited to 12 countries and no multivariate model could be fitted.

Figure 18: Diagram of PLS-PM model of resistance to third-generation cephalosporins in human invasive *Escherichia coli* (2017–2018), considering resistance to third-generation cephalosporins in indicator *E. coli* from food-producing animals (pigs in 2017 and poultry in 2018), consumption of third- and fourth-generation cephalosporins in humans (2017–2018 mean, expressed as DDD per 1 000 inhabitants and per day) and in food-producing animals (in pigs for 2017, expressed as DDDvet/kg of estimated biomass)



Total of 28 countries: AT*, BE, BG, CY, DE*, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS*, IT, LT, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (Goodness-of-fit=0.706).

* For these countries, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

8. Fluoroquinolones and other quinolones

Quinolones consumed in 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 *Streptococcus pneumoniae*, *Salmonella* spp. and *Campylobacter* spp. Quinolones are among few alternatives for treatment of diarrhoeas in piglets (*E. coli*) or severe (life threatening) sepsis in various animal species (Enterobacterales).

In the recent WHO AWaRe classification, fluoroquinolones belong to the 'Watch' group of antimicrobials [32]. Quinolones are considered by WHO as Highest Priority Critically Important Antimicrobials (HPCIA) in human medicine [14].

Fluoroquinolones have been categorised as Veterinary Critically Important Antimicrobial Agents (VCIA) in the OIE list of antimicrobials of veterinary importance. Other quinolones are categorised as Veterinary Highly Important Antimicrobial Agents (VHIA) [34].

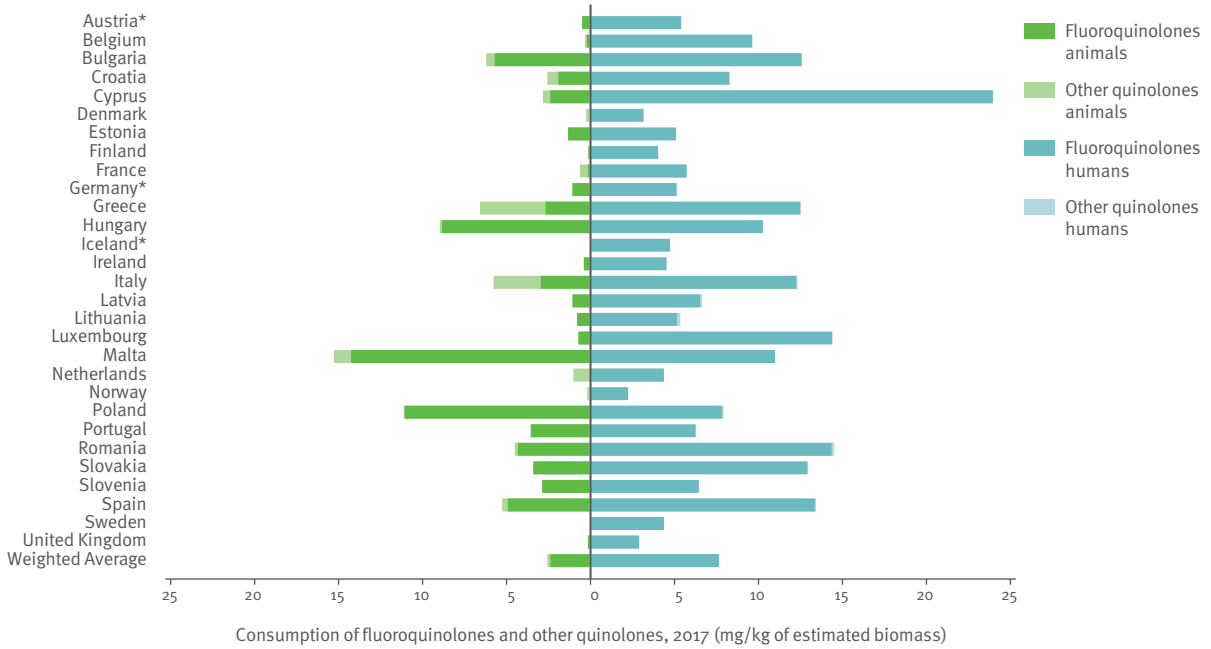
According to the AMEG categorisation, fluoroquinolones belong to Category B with the indication of 'Restrict' use in veterinary medicine in the EU [13]. This means that the risk to public health resulting from veterinary use needs to be mitigated by specific restrictions. Fluoroquinolones should only be used for the treatment of clinical conditions in animals when there are no antibiotics in Categories C ('Caution') or D ('Prudence') that could be clinically effective.

8.1 Consumption in humans and food-producing animals by country

In 2017, the population-weighted mean consumption of fluoroquinolones in humans and food-producing animals was 7.6 and 2.4 mg per kg of estimated biomass, respectively. The corresponding ranges were 2.2–24.0 (median 6.4) and 0–14.3 (median 1.1) mg per kg, respectively. Mean, range and median were similar for fluoroquinolones and other quinolones (Table 7). Population-corrected consumption of fluoroquinolones and other quinolones in humans and food-producing animals by country is shown in Figure 19. Consumption of quinolones other than fluoroquinolones was mainly observed in food-producing animals, particularly in some countries, while in humans, the consumption was negligible.

The population corrected consumption of fluoroquinolones was lower in food-producing animals than in humans in most countries in 2017. In two countries,

Figure 19: Population-corrected consumption of fluoroquinolones and other quinolones in humans and food-producing animals in 25 EU/EEA countries for which data were available both for humans and food-producing animals, 2017



An asterisk (*) denotes that only community consumption was provided for human medicine. The population-weighted mean proportion (%) of the hospital sector from the 2017 total national consumption of quinolones and fluoroquinolones for EU/EEA countries providing data for both sectors was 12.4%.

Notes: 1) The estimates presented are crude and must be interpreted with caution. For limitations hampering the comparison of antimicrobial consumption in humans and food-producing animals, please see Section 14. 2) The weighted mean figure represents the population-weighted mean of data from those countries included.

the consumption was higher in food-producing animals than in humans. There was a marked variation between countries in the quantity of fluoroquinolones consumed in humans and/or food-producing animals. There was a significant association between the national level consumption of fluoroquinolones in humans and in food-producing animals (Spearman's rank correlation coefficients: rho 0.72, p-value ‹0.001) (Table 7). There was also a significant association between the national level consumption of fluoroquinolones and that of fluoroquinolones and other quinolones in both humans and food-producing animals (Spearman's rank correlation coefficients: rho = 1, p-value ‹0.001 and rho = 0.95, p-value ‹0.001, respectively).

8.2 Consumption in humans and resistance in bacterial isolates from humans

Escherichia coli

To investigate the possible associations between the consumption of fluoroquinolones and other quinolones and the occurrence of resistance to fluoroquinolones in invasive *E. coli* isolates from humans, the total consumption of fluoroquinolones and other quinolones in humans, expressed as DDD per 1 000 inhabitants and per day, was analysed against the occurrence of fluoroquinolone resistance in invasive *E. coli* isolates from humans, for 2016, 2017 and 2018.

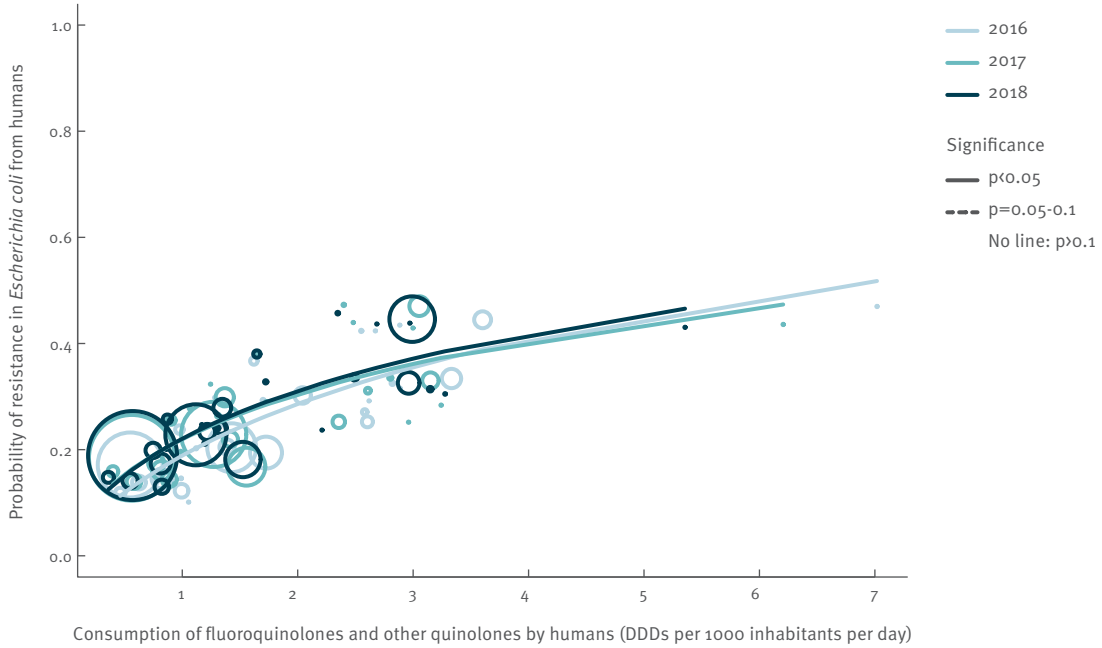
For all three years, a statistically significantly positive association was observed between consumption of fluoroquinolones and other quinolones in humans and resistance in invasive *E. coli* isolates from humans to fluoroquinolones (Table 23, Figure 20).

Table 23: Consumption of fluoroquinolones and other quinolones in humans, expressed as DDD per 1 000 inhabitants per day, and the probability of resistance of fluoroquinolones in *Escherichia coli* from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 20)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.38	‹0.001	1.24–1.53
2017	AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.33	‹0.001	1.19–1.50
2018	AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.41	‹0.001	1.27–1.57

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When odds ratio equals 1 or 95% CI includes 1, the association is not considered statistically significant.

Figure 20: Consumption of fluoroquinolones and other quinolones in humans and probability of resistance to fluoroquinolones in *Escherichia coli* from humans, EU/EEA, 2016–2018 (see also Table 23)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles reflects the amount of available resistance data per country.

Salmonella

No evidence of a statistically significant association was found between the consumption of fluoroquinolones and other quinolones in humans and the probability of fluoroquinolone resistance in *Salmonella* spp. isolates from humans, although the association was borderline significant in 2017 (Table 24). When removing outliers in terms of resistance, the association became significant for 2017 but remained non-significant for the other two years.

In a sub-analysis, no evidence of a statistically significant association was found between the consumption of fluoroquinolones and other quinolones in humans and fluoroquinolone resistance of *S.* Enteritidis isolates and *S.* Typhimurium isolates (including monophasic variant) from humans (Table 25 and Table 26).

Campylobacter jejuni

A statistically significant positive association was reported between the consumption of fluoroquinolones and other quinolones in humans and resistance to fluoroquinolones in *C. jejuni* isolates from humans for all three years 2016 to 2018 (Table 27, Figure 21).

Table 24: Consumption of fluoroquinolones and other quinolones in humans, expressed as DDD per 1 000 inhabitants and per day, and probability of resistance to fluoroquinolones in *Salmonella* isolated from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure A1.2. 4)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PT, RO, SI, SK, UK (n=24)	3	0.96	0.305	0.89–1.04
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=26)	3	1.03	0.060	1.00–1.06
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK (n=24)	3	1.01	0.669	0.98–1.04

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When odds ratio equals 1 or 95% CI includes 1, the association is not considered statistically significant.

Table 25: Consumption of fluoroquinolones and other quinolones in humans, expressed as DDD per 1 000 inhabitants and per day, and probability of resistance to fluoroquinolones in *Salmonella* Enteritidis from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, DE, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PT, RO, SI, SK, UK (n=22)	3	0.95	0.378	0.84–1.07
2017	AT, BE, CY, DE, EE, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=23)	3	1.02	0.405	0.98–1.06
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK (n=23)	3	1.01	0.806	0.96–1.06

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When odds ratio equals 1 or 95% CI includes 1, the association is not considered statistically significant.

Table 26: Consumption of fluoroquinolones and other quinolones in humans, expressed as DDD per 1 000 inhabitants per day and probability of resistance to fluoroquinolones in *Salmonella* Typhimurium, including the monophasic variant from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, MT, NL, NO, PT, RO, SI, SK, UK (n=22)	1	0.63	0.161	0.33–1.20
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=25)	1	0.92	0.542	0.70–1.21
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, PL, PT, RO, SI, SK, UK (n=23)	1	0.77	0.180	0.52–1.13

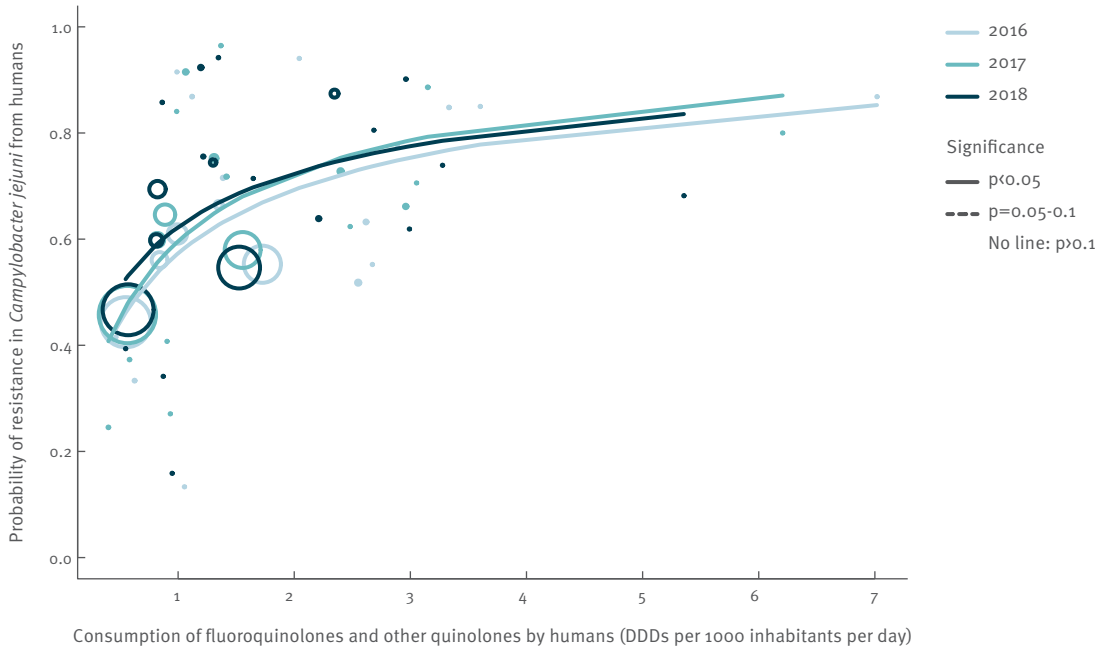
CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When odds ratio equals 1 or 95% CI includes 1, the association is not considered statistically significant.

Table 27: Consumption of fluoroquinolones and other quinolones in humans, expressed as DDD per 1 000 inhabitants per day and the probability of resistance to fluoroquinolones in *Campylobacter jejuni* isolates from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 21)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, CY, DK, EE, ES, FI, FR, IS, IT, LT, LU, MT, NL, NO, PT, RO, SI, SK, UK (n=19)	2	1.68	0.011	1.13–2.51
2017	AT, CY, DK, EE, ES, FI, FR, IE, IS, IT, LT, LU, MT, NL, NO, PT, SI, SK, UK (n=19)	2	1.78	0.004	1.21–2.63
2018	AT, CY, DK, EE, ES, FI, FR, IE, IS, IT, LT, LU, MT, NL, PL, PT, RO, SI, SK, UK (n=20)	2	1.59	0.047	1.01–2.52

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When odds ratio equals 1 or 95% CI includes 1, the association is not considered statistically significant.

Figure 21: Consumption of fluoroquinolones and other quinolones in humans and the probability of resistance to fluoroquinolones in *Campylobacter jejuni* from humans, EU/EEA, 2016–2018 (see also Table 27)



Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of resistance data available per country.

8.3 Consumption in food-producing animals and resistance in isolates of bacteria from food-producing animals

Escherichia coli from food-producing animals

To investigate possible relationships between the consumption of fluoroquinolones and other quinolones in food-producing animals and fluoroquinolone resistance in bacteria from food-producing animals, the SIMR to ciprofloxacin in *E. coli*, was compared with the consumption of fluoroquinolones and other quinolones in food-producing animals (expressed in mg per kg of estimated biomass) for the two-year intervals 2014–2015, 2015–2016, 2016–2017 and 2017–2018 (mean consumption over the respective years) at national level. The category 'food-producing animals' includes broilers, turkeys, pigs and calves for all time intervals.

Marked variations in ciprofloxacin resistance in indicator *E. coli*, were observed between countries involved in the analysis. Consumption of fluoroquinolones and other quinolones ranged between a few units and more than 10 mg per kg of estimated biomass (Figure 22).

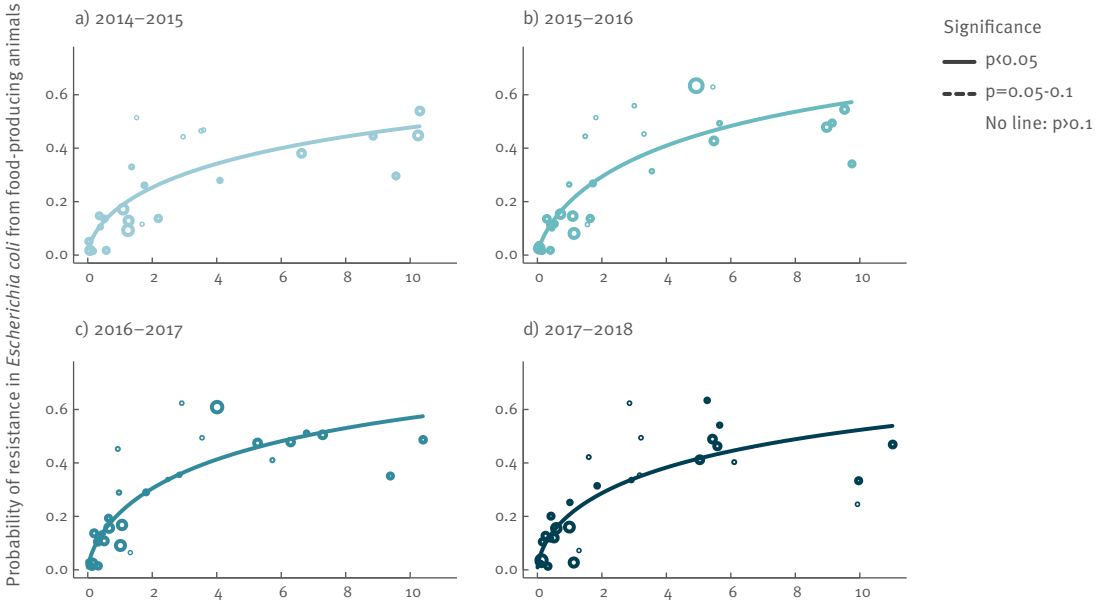
Statistically significant positive associations between ciprofloxacin resistance in indicator *E. coli*, and fluoroquinolones and other quinolones consumption in food-producing animals were observed in all the time intervals (Table 28, Figure 22). The assessment of the relationships between consumption and resistance is based on a full range of values.

Table 28: Association between consumption of fluoroquinolones and other quinolones in food-producing animals, expressed in mg/kg of estimated biomass/year, and probability of resistance to fluoroquinolones in *Escherichia coli* from food-producing animals (logistic regression, see also Figure 22)

Year	Countries	Model	Odds ratio	p-value	95% CI
2014–2015	AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=26)	2	1.53	<0.001	1.32–1.79
2015–2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=28)	2	1.67	<0.001	1.45–1.92
2016–2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.61	<0.001	1.41–1.82
2017–2018	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, MT, PL, PT, RO, SE, SI, SK, UK (n= 30)	2	1.54	<0.001	1.36–1.75

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or 95% CI includes 1, the association is not considered statistically significant. The category 'food-producing animals' includes broilers, turkeys, pigs and calves.

Figure 22: Consumption of fluoroquinolones and other quinolones in food-producing animals and probability of resistance to ciprofloxacin in indicator *Escherichia coli* from food-producing animals in (a) 2014–2015, (b) 2015–2016, (c) 2016–2017 and (d) 2017–2018 (see also Table 28)



The figure displays curves of logistic regression models. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country. The category 'food-producing animals' includes broilers, turkeys, pigs and calves. The category 'quinolones' includes both fluoroquinolones and other quinolones.

Escherichia coli, *Salmonella* and *Campylobacter jejuni* from pigs and poultry

The estimated consumption of fluoroquinolones and other quinolones in pigs (expressed as DDDvet/kg of estimated biomass) was compared with the occurrence of resistance to ciprofloxacin in indicator *E. coli* and *Salmonella* from slaughter pigs in 2017 for 31 and six reporting countries, respectively (Table 29). The association for indicator *E. coli* was statistically significant, whereas the association for *Salmonella* was borderline significant.

The estimated consumption of fluoroquinolones and other quinolones in poultry, expressed as DDDvet/kg of estimated biomass, was compared with the poultry SIMR to ciprofloxacin in *E. coli*, *Salmonella* and *C. jejuni* from poultry (broilers and turkeys) in 2016 (Table 29). Both data on ciprofloxacin resistance and consumption of fluoroquinolones and other quinolones in poultry were available together in 19 countries for *Salmonella*, 29 countries for indicator *E. coli*, and 27 countries for *C. jejuni* in 2016 and in 27 countries for *Salmonella*, 18 countries for indicator *E. coli*, and 25 countries for *C. jejuni* in 2018. The associations assessed between the consumption of fluoroquinolones and other quinolones and resistance to ciprofloxacin in indicator *E. coli*, *Salmonella* spp. and *C. jejuni* in 2016 were all positive and statistically significant (Table 29, Figure 23, Figure 24).

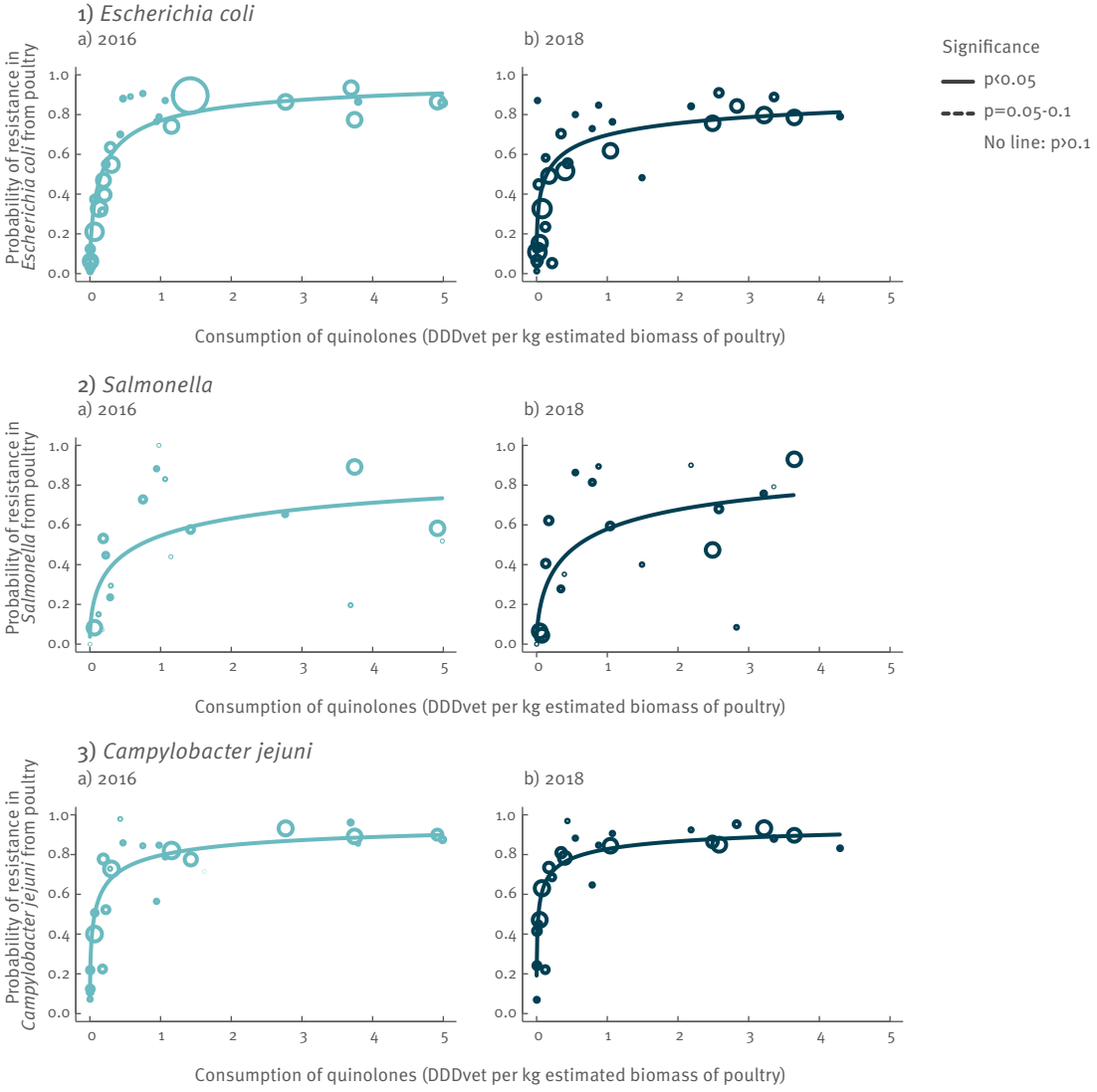
Table 29: Association between consumption of fluoroquinolones and other quinolones in pigs and poultry, expressed as DDDvet/kg of estimated biomass/year, and probability of resistance to fluoroquinolones in bacteria from slaughter pigs and poultry (logistic regression, see also Figure 23 and Figure 24)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Pigs						
Escherichia coli	2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=31)	2	1.48	<0.001	1.24–1.77
*Salmonella**	2017	BE, CZ, DE, DK, ES, FR, HR, HU, IE, IT, MT, PL, PT, SK (n=14)	2	1.27	0.067	0.98–1.63
Poultry						
Escherichia coli	2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.59	<0.001	1.45–1.74
Escherichia coli	2018	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.35	<0.001	1.22–1.49
Salmonella	2016	AT, BE, CY, CZ, DE, DK, EL, ES, FR, HR, HU, IE, IT, PL, PT, RO, SI, SK, UK (n=19)	2	1.43	0.004	1.12–1.84
Salmonella	2018	AT, BE, CY, CZ, DE, DK, EL, ES, FR, HR, HU, IE, IT, MT, PL, PT, RO, SI, SK, UK (n=20)	2	1.52	0.002	1.16–1.98
Campylobacter jejuni	2016	AT, BE, BG, CH, CY, CZ, DE, DK, EL, ES, FI, HR, HU, IE, IS, IT, LT, LU, LV, NO, PL, PT, RO, SE, SI, SK, UK (n=27)	2	1.42	<0.001	1.31–1.55
Campylobacter jejuni	2018	AT, BG, CH, CY, CZ, DE, DK, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=27)	2	1.35	<0.001	1.26–1.45

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

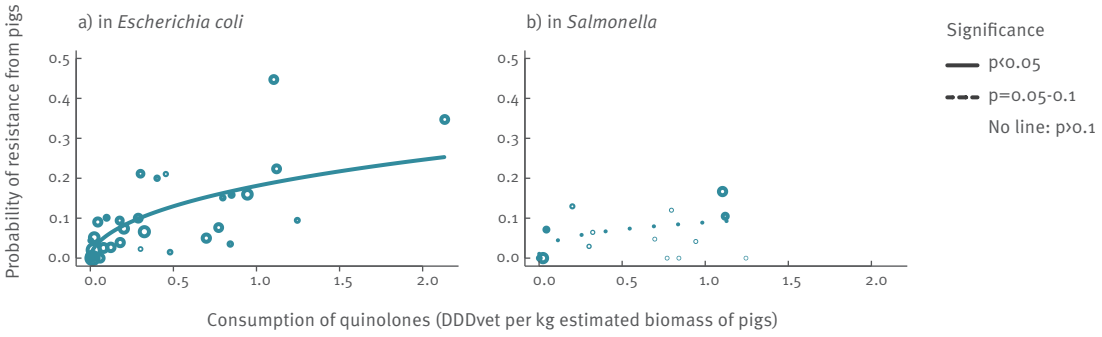
* *Salmonella* spp. isolates derive from pig carcasses

Figure 23: Consumption of fluoroquinolones and other quinolones in poultry, expressed as DDDvet/kg of estimated biomass/year, and probability of resistance to ciprofloxacin in (1) indicator *Escherichia coli*, (2) *Salmonella* and (3) *Campylobacter jejuni* from poultry in 2016 (a) and 2018 (b) (see also Table 29)



The figure displays curves of logistic regression models. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Figure 24: Consumption of fluoroquinolones and other quinolones in pigs, expressed as DDDvet/kg of estimated biomass/year, and probability of resistance to ciprofloxacin in (a) indicator *E. coli* and (b) *Salmonella* from slaughter pigs in 2017 (see also Table 29)



The figure displays results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

8.4 Resistance in bacteria from humans and in bacterial isolates from food-producing animals

Escherichia coli from humans and from food-producing animals

Data on the occurrence of resistance to fluoroquinolones in invasive *E. coli* isolated from humans (2016 to 2018) were compared with the occurrence of resistance to fluoroquinolones in indicator *E. coli* isolated from broilers and turkeys (2016 and 2018), pigs and calves (2017) (Table 30).

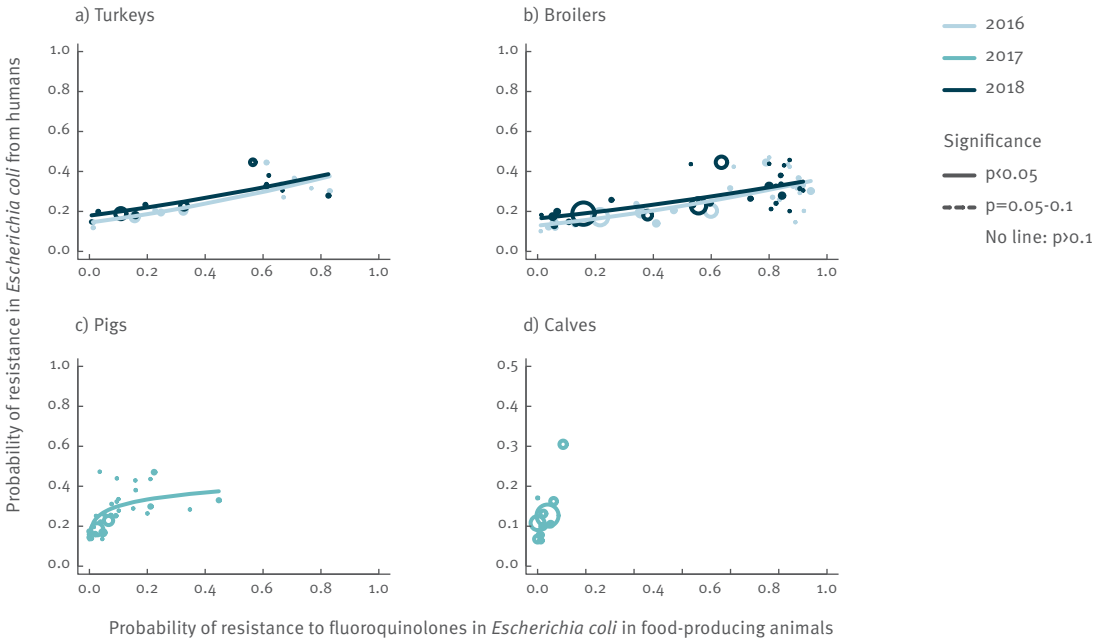
A statistically significant positive association was found between resistance of fluoroquinolones in indicator *E. coli* from broilers, turkeys, pigs and calves and fluoroquinolone resistance of invasive *E. coli* from humans for all years tested (Table 30, Figure 25).

Table 30: Association between resistance to fluoroquinolones in *Escherichia coli* from humans and food-producing animals, 2016–2018 (logistic regression, see also Figure 25)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Broilers	2016	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	1	3.96	<0.001	2.41–6.54
Broilers	2018	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	1	2.98	<0.001	1.87–4.78
Turkeys	2016	AT, DE, ES, FR, HU, IT, NO, PL, PT, RO, SE, UK (n=12)	1	4.64	<0.001	2.57–8.39
Turkeys	2018	AT, DE, ES, FR, HU, IT, NO, PL, PT, RO, SE, UK (n=12)	1	3.61	<0.001	1.91–6.83
Calves	2017	AT, BE, DE, DK, ES, FR, HR, IT, NL, NO, PT (n=11)	2	1.16	0.003	1.05–1.27
Pigs	2017	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.17	<0.001	1.09–1.25

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 25: Probability of resistance to fluoroquinolones in *Escherichia coli* from humans and food-producing animals, EU/EEA, 2016–2018 (see also Table 30)



The figure displays results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Salmonella from humans and food-producing animals

Data on the occurrence of fluoroquinolone resistance in *Salmonella* from humans (2016 to 2018) were compared with the occurrence of fluoroquinolone resistance in *Salmonella* from broilers and turkeys (2016, 2018) and from pigs (2017). No evidence of a statistically significant association was found for any of the tested combinations (Table 31).

With regard to data on the occurrence of fluoroquinolone resistance in *S.* Typhimurium, including its monophasic variant, from humans and from food-producing animals, only the data for pigs were sufficient for analysis and only for 2017. No evidence of a statistically significant association was found for the tested combination (Table 32). For *S.* Enteritidis there were not enough data to perform the analysis for any of the years.

Table 31: Association between resistance to fluoroquinolones in *Salmonella* from food-producing animals and from humans, 2016–2018 (logistic regression)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Broilers	2016	AT, BE, DE, DK, EL, IS, FR, HU, IE, IT, MT, PT, RO, SI, SK, UK (n=16)	2	1.04	0.515	0.92–1.18
Broilers	2018	AT, BE, CY, DE, DK, ES, FR, HU, IE, IT, MT, PL, PT, RO, SI, SK, UK (n=17)	2	1.02	0.567	0.95–1.09
Turkeys	2016	AT, DE, ES, FR, HU, UK (n=6)	2	1.00	0.977	0.84–1.20
Turkeys	2018	AT, CY, ES, FR, HU, IE, IT, PL, UK (n=9)	2	0.96	0.548	0.84–1.10
Pig*	2017	AT, DE, DK, ES, FR, HU, IE, IT, MT, PL, PT, SK, (n=12)	2	1.04	0.503	0.93–1.17

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.
* *Salmonella* spp. isolates derive from pig carcasses.

Table 32: Association between resistance to fluoroquinolones in *Salmonella* Typhimurium, including monophasic variant, from food-producing animals (pigs) and humans, 2017 (logistic regression)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Pigs	2017	BE, DE, DK, ES, FR, IE, IT (n=7)	2	1.06	0.240	0.96–1.18

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Campylobacter jejuni from humans and food-producing animals

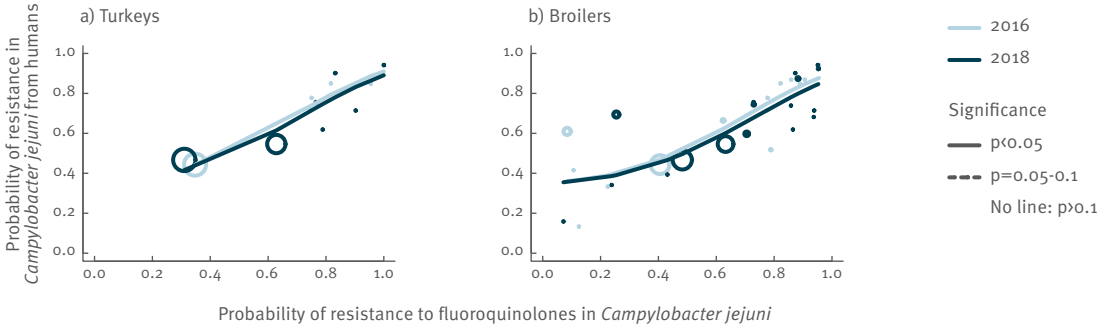
A statistically significant positive association was found between fluoroquinolone resistance in *Campylobacter jejuni* from turkeys and fluoroquinolone resistance of *C. jejuni* from humans for 2016 and 2018 (Table 33, Figure 26). A statistically significant positive association was also found between fluoroquinolone resistance in *C. jejuni* from broilers and fluoroquinolone resistance of *C. jejuni* from humans for 2016 and 2018.

Table 33: Association between resistance to fluoroquinolones in *Campylobacter jejuni* from food-producing animals and from humans, 2016–2018 (logistic regression, see also Figure 26)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Broilers	2016	AT, CY, DK, ES, FI, IS, IT, LT, NO, PT, RO, SI, SK, UK (n=14)	3	16.46	<0.001	5.65–47.84
Broilers	2018	AT, CY, DK, ES, FI, FR, IE, IS, IT, LT, NL, PL, PT, RO, SI, SK, UK (n=17)	3	12.83	<0.001	4.46–36.97
Turkeys	2016	AT, ES, IT, PT, RO, UK (n=6)	3	18.00	<0.001	9.63–33.65
Turkeys	2018	AT, ES, FR, IT, PL, PT, UK (n=7)	3	14.85	0.001	3.080–71.60

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 26: Probability of resistance to fluoroquinolones in *Campylobacter jejuni* from food-producing animals and humans, 2016 and 2018 (see also Table 33)



The figure displays results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

8.5 Consumption in food-producing animals and resistance in bacterial isolates from humans

To investigate possible relationships between the consumption of fluoroquinolones or other quinolones in food-producing animals and fluoroquinolone resistance in bacteria causing infections in humans, the occurrence of resistance in invasive *E. coli* and *Salmonella* from humans was compared with the total consumption of fluoroquinolones and quinolones (milligrams per kilogram of estimated biomass) in food-producing animals for 2016, 2017 and 2018 at the national level.

Escherichia coli

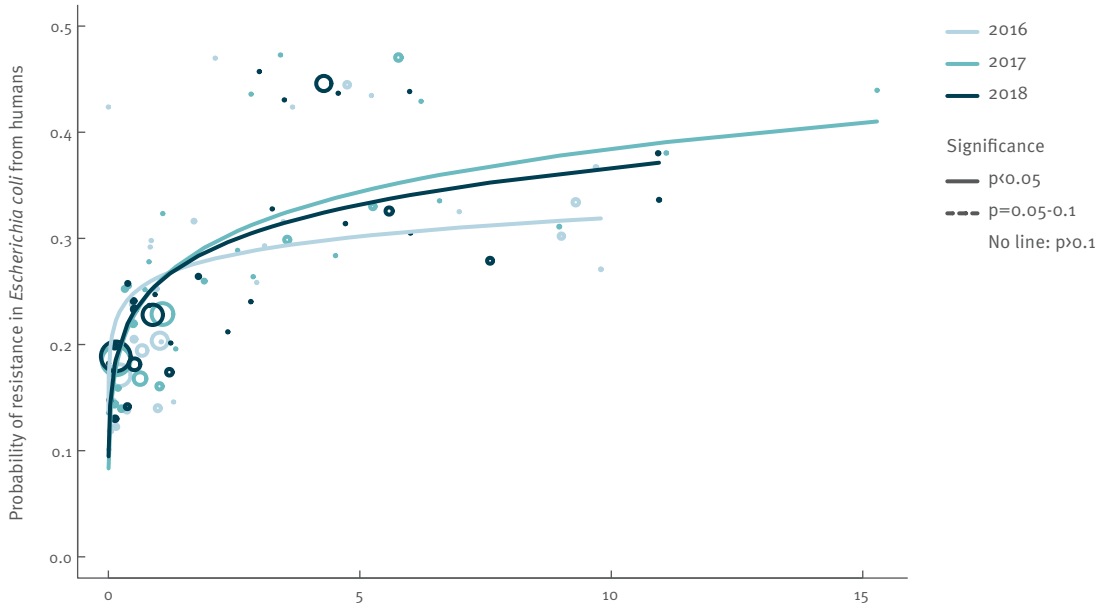
A statistically significant positive association was reported between the total quinolone consumption in food-producing animals and fluoroquinolone resistance in invasive *E. coli* isolates from humans for all the years (Table 34, Figure 27).

Table 34: Association between consumption of fluoroquinolones and other quinolones in food-producing animals, expressed in mg/kg biomass, and probability of resistance to fluoroquinolones in *Escherichia coli* from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 27)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.09	0.028	1.01–1.17
2017	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.19	<0.001	1.13–1.26
2018	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.17	<0.001	1.10–1.23

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 27: Consumption of fluoroquinolones and other quinolones in food-producing animals and probability of resistance to fluoroquinolones in *Escherichia coli* from humans, EU/EEA, 2016–2017 (see also Table 34)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Salmonella

No statistically significant associations were reported between the total quinolone consumption in food-producing animals and fluoroquinolone resistance in *Salmonella* from humans for any of the years (Table 35).

No statistically significant associations were reported between the total quinolone consumption in food-producing animals and fluoroquinolone resistance in *S.* Enteritidis isolates from humans for any of the years (Table 36). However, when outliers in terms of resistance were removed, the association became significant for 2016.

No statistically significant associations were reported between the total quinolone consumption in food-producing animals and fluoroquinolone resistance in *S.* Typhimurium isolates, including its monophasic variant, from humans for any of the years (Table 37).

Table 35: Association between consumption of fluoroquinolones and other quinolones in food-producing animals, expressed in mg/kg biomass, and probability of resistance to fluoroquinolones in *Salmonella* isolated from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PT, RO, SI, SK, UK (n=24)	2	0.99	0.821	0.90-1.09
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=26)	2	1.07	0.250	0.96-1.19
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK (n=24)	2	0.99	0.703	0.91-1.07

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 36: Association between consumption of fluoroquinolones and other quinolones in food-producing animals, expressed in mg/kg biomass, and probability of resistance to fluoroquinolones in *Salmonella* Enteritidis from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PT, RO, SI, SK, UK (n=22)	3	1.00	0.619	0.99–1.02
2017	AT, BE, CY, DE, EE, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=23)	3	1.00	0.290	1.00–1.01
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK (n=23)	3	1.00	0.893	0.99–1.01

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 37: Association between consumption of fluoroquinolones and other quinolones in food-producing animals, expressed in mg/kg biomass, and probability of resistance to fluoroquinolones in *Salmonella* Typhimurium, including the monophasic variant from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, MT, NL, NO, PT, RO, SI, SK, UK (n=22)	1	0.98	0.861	0.80–1.20
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=25)	1	0.95	0.281	0.86–1.05
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, PL, PT, RO, SI, SK, UK (n=23)	1	0.96	0.546	0.85–1.09

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Campylobacter jejuni

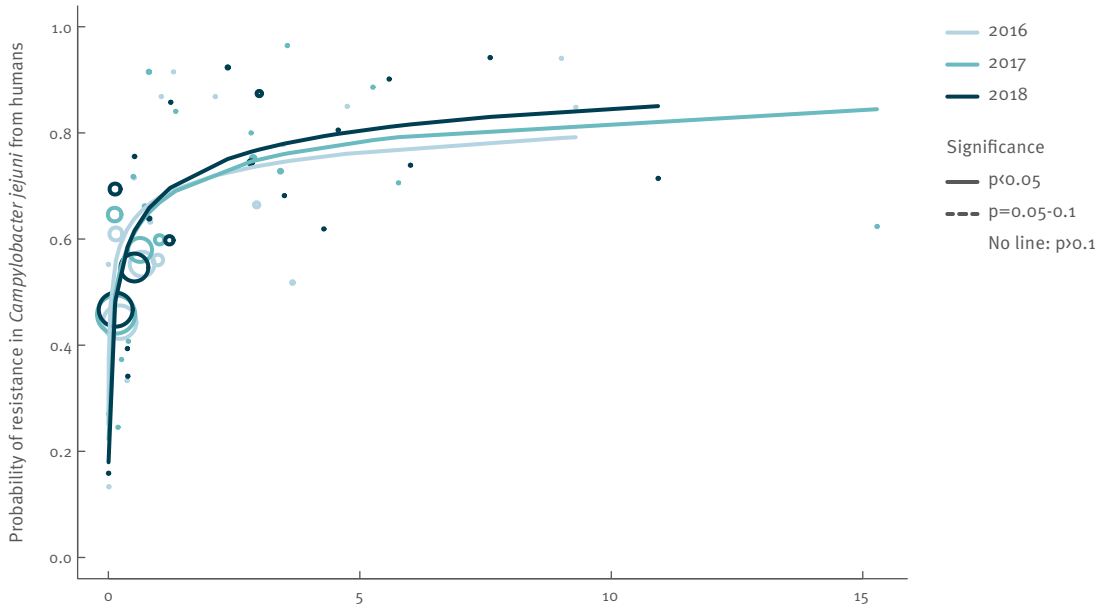
A statistically significant positive association was reported between the total consumption of fluoroquinolones and other quinolones in food-producing animals and fluoroquinolone resistance in *Campylobacter jejuni* isolates from humans for all the years (Table 38 and Figure 28).

Table 38: Association between consumption of fluoroquinolones and other quinolones in food-producing animals, expressed in mg/kg biomass, and probability of resistance to fluoroquinolones in *Campylobacter jejuni* from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 28)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, CY, DK, EE, ES, FI, FR, IS, IT, LT, LU, MT, NL, NO, PT, RO, SI, SK, UK (n=19)	2	1.20	0.002	1.07–1.35
2017	AT, CY, DK, EE, ES, FI, FR, IE, IS, IT, LT, LU, MT, NL, NO, PT, SI, SK, UK (n=19)	2	1.29	0.281	0.86–1.05
2018	AT, CY, DK, EE, ES, FI, FR, IE, IS, IT, LT, LU, MT, NL, PL, PT, RO, SI, SK, UK (n=20)	2	1.33	‹0.001	1.18–1.51

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 28: Consumption of fluoroquinolones and other quinolones in food-producing animals and probability of resistance to fluoroquinolones in *Campylobacter jejuni* from humans, EU/EEA, 2016–2017 (see also Table 38)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

8.6 Multivariate analysis

Escherichia coli

As reported in the univariate analysis, in both humans and food-producing animals, the consumption of fluoroquinolones and other quinolones was very significantly related to resistance in invasive *E. coli* from humans and resistance in commensal *E. coli*, respectively (Figure 29).

According to the R^2, 64% (95% confidence interval 47–83) of the variance of resistance in food-producing animals is explained by the corresponding latent variable: fluoroquinolones and other quinolones consumption in food-producing animals, while 63% (95% confidence interval 47–82) of the variance of resistance in humans is explained by the latent variable: fluoroquinolones and other quinolones consumption in humans.

Salmonella

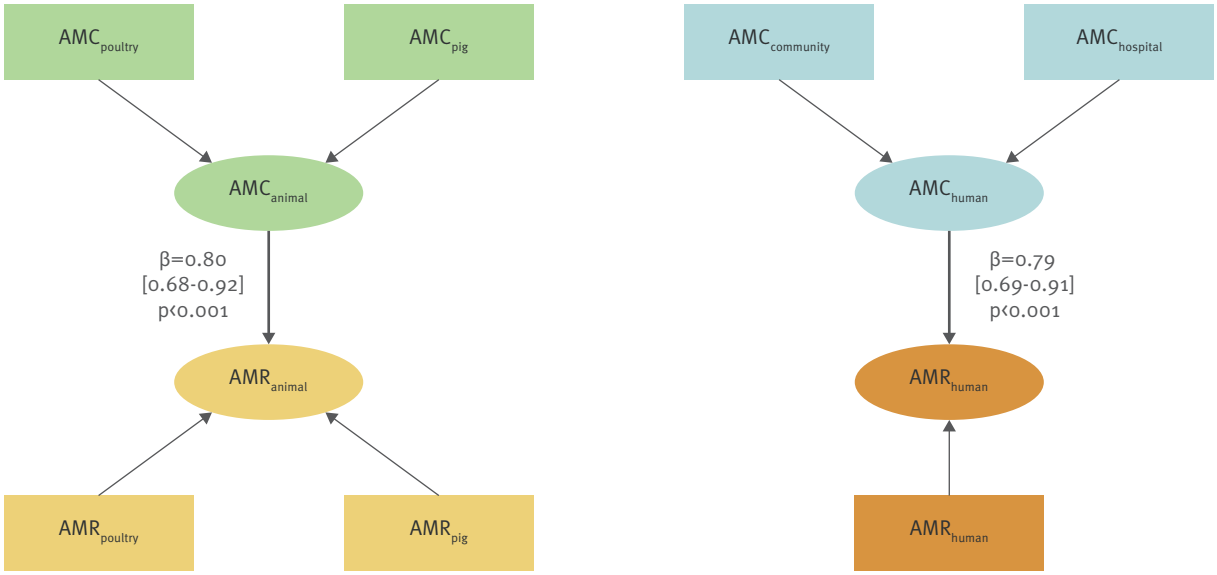
Multivariate analysis involved only 12 countries for which all necessary data were available.

The only significant relationship retained in the final PLS-PM model (Figure 30) related to the effect of fluoroquinolones and other quinolone consumption in food-producing animals (poultry and pigs) on resistance in food-producing animals. According to R^2, 46% (95% confidence interval: 24–97) of the variance of the resistance in food-producing animals is explained by the corresponding latent variable consumption of fluoroquinolones and other quinolones in food-producing animals.

Campylobacter jejuni

Given the limited data available on resistance in *Campylobacter jejuni* from pigs, the model only included data on consumption and resistance in *C. jejuni* from poultry, so 19 countries were involved in the model (Figure 31). According to R^2, 79% (95% confidence interval 43–94) of the variance of resistance in humans is explained by resistance in food-producing animals where, conversely variance is poorly explained by consumption of fluoroquinolones and quinolones (R^2 = 0.40 [0.18–0.67]). Consumption of fluoroquinolones and other quinolones in humans was a non-significant latent variable in the model.

Figure 29: Diagram of the PLS-PM of resistance to fluoroquinolones in human invasive *Escherichia coli* (2017 and 2018), considering resistance to fluoroquinolones in indicator *E. coli* from food-producing animals (pigs 2017 and poultry 2018) and consumption of fluoroquinolones and other quinolones in humans (2017–2018 mean, expressed as DDD per 1 000 inhabitants and per day), and in food-producing animals (pigs in 2017 and poultry in 2018 - expressed as DDDvet/kg of estimated biomass)

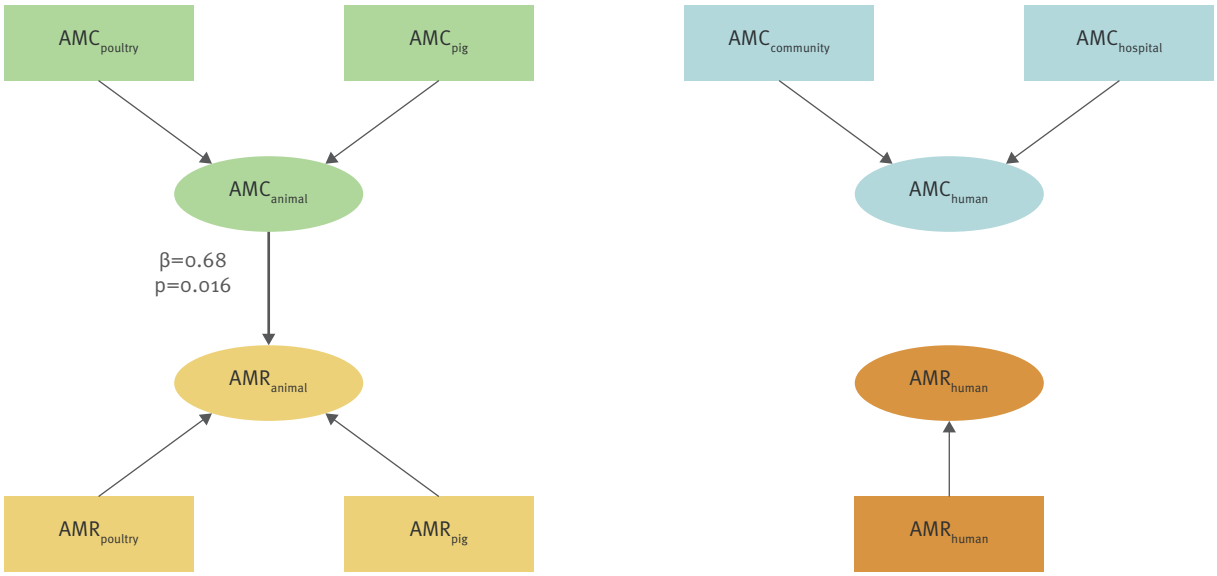


28 countries: AT*, BE, BG, CY, DE*, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS*, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK.

* For these countries, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

(Goodness-of-fit=0.700).

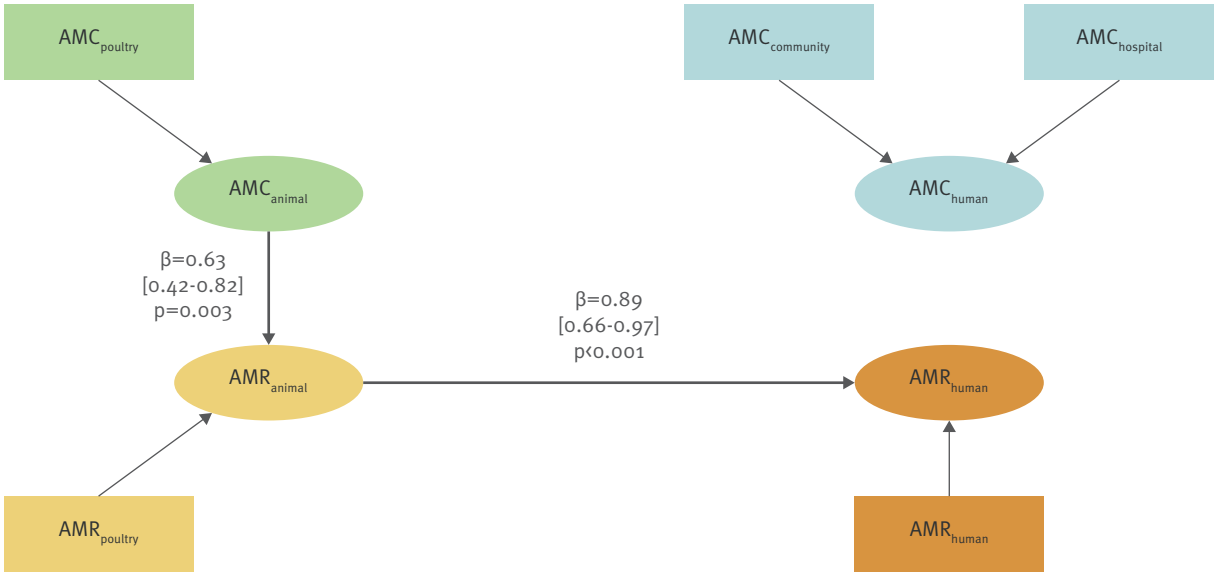
Figure 30: Diagram of the PLS-PM model of resistance to fluoroquinolones in *Salmonella* from humans (in 2017 and 2018), considering resistance to fluoroquinolones in *Salmonella* from food-producing animals (in poultry in 2018 and in pig in 2017) and consumption of fluoroquinolones and other quinolones in humans (2017-2018 mean, expressed as DDD per 1 000 inhabitants and per day) in food-producing animals (in poultry for 2018 and in pigs for 2017, expressed as DDDvet/kg of estimated biomass)



12 countries involved: BE, DE*, DK, ES, FR, HU, IE, IT, MT, PL, PT, SK (Goodness-of-fit=0.532).

* For this country, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

Figure 31: Diagram of the PLS-PM model of resistance to fluoroquinolones in *Campylobacter jejuni* in humans (in 2017 and 2018), considering resistance to fluoroquinolones in *C. jejuni* from food-producing animals (poultry in 2018) and consumption of fluoroquinolones and other quinolones in humans (expressed as DDD per 1 000 inhabitants per day for 2017 and 2018) in food-producing animals (poultry in 2018, expressed as DDDvet/kg of estimated biomass)



19 countries: AT*, CY, DK, EE, ES, FI, FR, IE, IS, IT, LT, NL, NO, PL, PT, RO, SI, SK, UK.

* For this country, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

9. Polymyxins

Polymyxins – mainly colistin in parenteral form – have been used in hospitals as last-resort antibiotics to treat infections caused by multidrug-resistant gram-negative bacteria that are resistant to carbapenems. In veterinary medicine there are few alternatives for treatment of colibacillosis (e.g. weaning diarrhoea in pigs) caused by bacteria resistant to AMEG Category C ('Caution') and D ('Prudence') antibiotics.

In the recent WHO AWaRe classification, polymyxins belong to the 'Reserve' group of antimicrobials [32].

Polymyxins are considered by WHO as Highest Priority Critically Important Antimicrobials (HPCIA) in human medicine [14].

This class has also been categorised as Veterinary Highly Important Antimicrobial Agents (VHIA) in the OIE list of antimicrobials of veterinary importance [34].

According to the AMEG categorisation, polymyxins belong to Category B with the indication 'Restrict' use in veterinary medicine in the EU [13]. This means that the risk to public health resulting from veterinary use needs to be mitigated by specific restrictions. Polymyxins should only be used for the treatment of clinical conditions in animals when there are no antibiotics in Categories C ('Caution') or D ('Prudence') that could be clinically effective.

9.1 Consumption in humans and food-producing animals by country

In 2017, the population-weighted mean consumption of polymyxins in humans and food-producing animals was 0.06 and 3.2 mg per kg of estimated biomass, respectively. The corresponding ranges were 0–0.2 (median 0.03) and 0–14.9 (median 1.5) mg per kg, respectively. The population-corrected consumption of polymyxins in humans and food-producing animals by country is shown in Figure 32A. Due to the large differences between consumption in humans and food-producing animals, consumption in humans is also illustrated separately in Figure 32B using a different scale.

Overall in 2017, the consumption of polymyxins in food-producing animals by far outweighed that reported in humans, although there was no consumption in food-producing animals in Finland, Iceland and Norway and lower consumption in food-producing animals than in humans in two countries. In addition, there was wide variation between countries in the quantities of polymyxins consumed in food-producing animals. There was no significant association within country between consumption of polymyxins in humans and consumption in food-producing animals (Spearman's rank correlation, rho = 0.36).

9.2 Resistance in bacterial isolates from humans

The distribution of polymyxin resistance in isolates originating from humans is difficult to assess through EARS-Net as susceptibility testing is generally not part of the initial routine antimicrobial susceptibility test panel, but is performed at reference-laboratory level following the referral of multidrug-resistant isolates. In addition, polymyxin susceptibility determination is methodologically challenging, making results from agar dilution, disk diffusion and gradient diffusion unreliable. A joint EUCAST and CLSI subcommittee has issued recommendations confirming that broth microdilution is so far the only valid method for determination of colistin susceptibility [35]. A survey among EARS-Net participating laboratories in 2017 showed that a majority of the local laboratories that responded did not test for colistin locally, or used methods that were not recommended by EUCAST (unpublished data, ECDC/UK NEQAS). This leads to the conclusion that EARS-Net data are currently not suitable for surveillance of polymyxin susceptibility.

9.3 Consumption in food-producing animals and resistance in bacterial isolates from food-producing animals

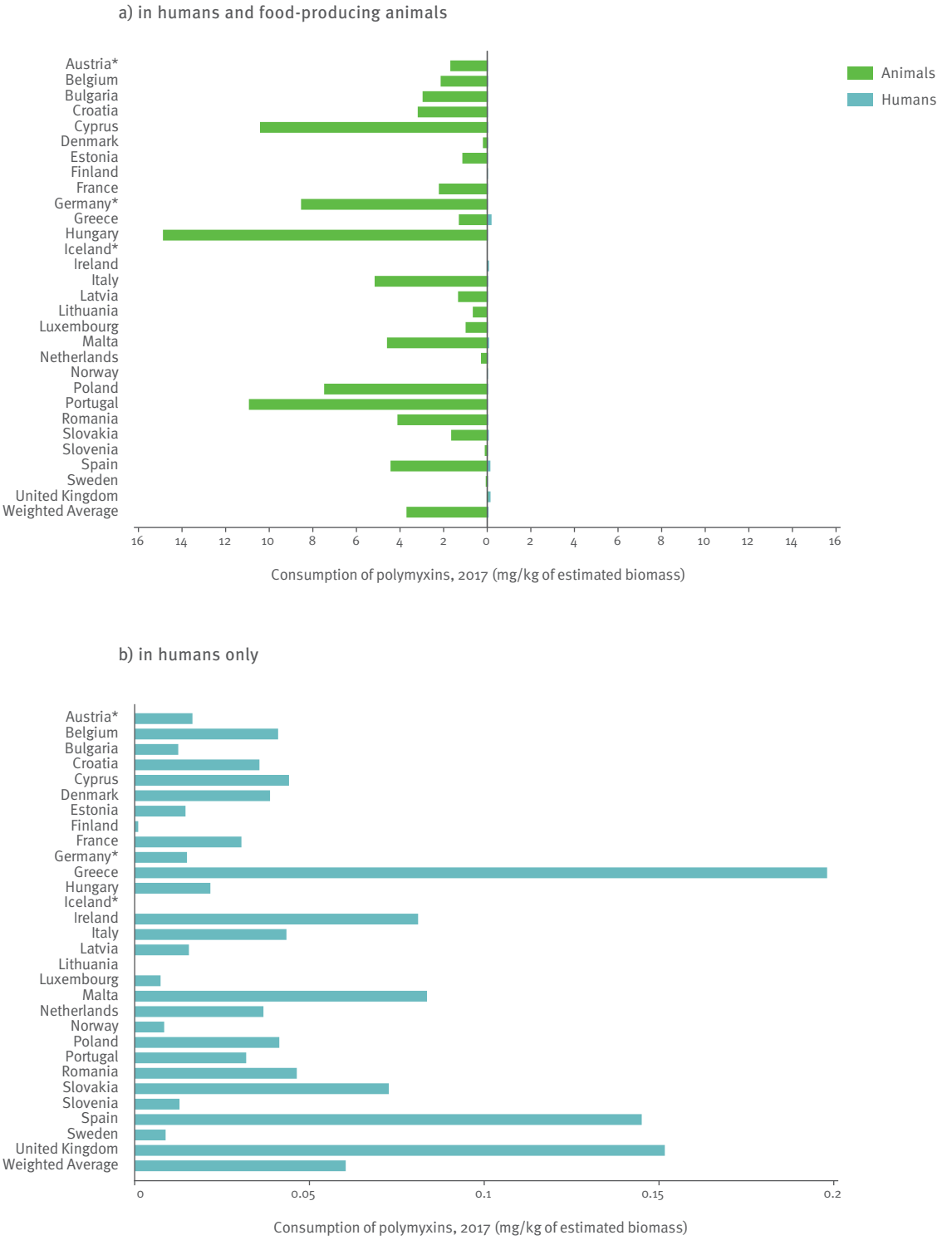
Susceptibility testing to colistin in bacteria from food-producing animals commenced on a mandatory basis in the EU, with relevance to EEA countries, in 2014. In this report, susceptibility to colistin was only addressed for indicator *E. coli*, as ECOFFs for colistin in *Salmonella* serovars are still awaiting determination by EUCAST.

Escherichia coli from food-producing animals

In order to investigate possible relationships between the consumption of polymyxins and colistin resistance, the SIMR to colistin in *E. coli* from food-producing animals was compared with the consumption of polymyxins in food-producing animals (expressed in mg per kg of estimated biomass) for the two-year intervals 2014–2015, 2015–2016, 2016–2017 and 2017–2018 (mean consumption over the respective years) at the national level (Table 39, Figure 33). The category 'food-producing animals' includes broilers, turkeys, pigs and calves at slaughter for all time intervals.

Colistin resistance observed in indicator *E. coli* from food-producing animals was low in the countries included in the analysis. Consumption of polymyxins ranged from zero in three countries up to nearly 40 mg per kg of estimated biomass. Statistically significant positive associations between colistin resistance in indicator *E. coli* and polymyxin consumption in food-producing animals were observed in all the time periods.

Figure 32: Population-corrected consumption of polymyxins in humans and food-producing animals by country in 29 EU/EEA countries (a) and in humans only (b) in 2017



An asterisk (*) denotes that only community consumption data was provided for human medicine. The population-weighted mean proportion (%) of the hospital sector from the 2017 total national consumption of polymyxins for EU/EEA countries providing data for both sectors is 50.1%.

Notes: 1) The estimates presented are crude and must be interpreted with caution. For limitations hampering comparison of antimicrobial consumption by humans and food-producing animals, please see Section 14.

2) The weighted mean figure represents the population-weighted mean of data from those countries included.

3) There was no consumption of polymyxins in food-producing animals in Finland, Iceland and Norway.

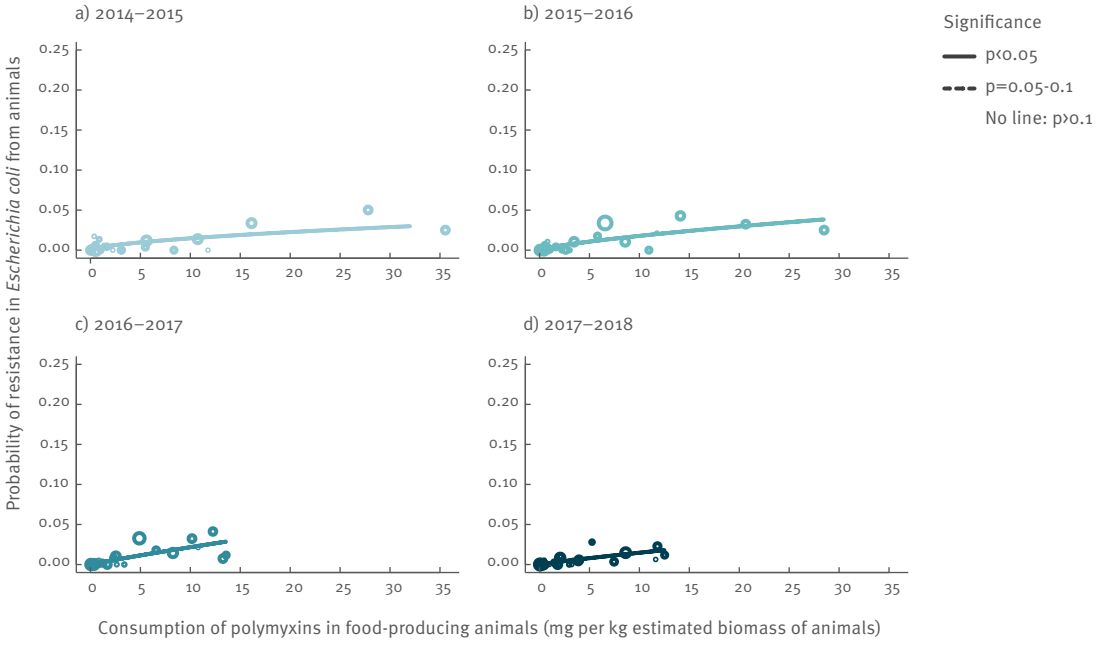
4) There was no consumption of polymyxins in humans in Iceland and Lithuania.

Table 39: Association between consumption of polymyxins in food-producing animals, expressed in mg/kg of estimated biomass, and probability of resistance to polymyxins in indicator *Escherichia coli* from food-producing animals (logistic regression, see also Figure 33)

Year	Countries	Model	Odds ratio	p-value	95% CI
2014–2015	AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=26)	2	1.53	<0.001	1.21–1.94
2015–2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=28)	2	1.68	<0.001	1.39–2.05
2016–2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.91	<0.001	1.50–2.44
2017–2018	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, MT, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.87	<0.001	1.43–2.43

CI: confidence interval. Odds ratio varies from 0 to infinity. When odds ratio equals 1 or CI includes 1, the association is not considered statistically significant. The category 'food-producing animals' includes broilers, turkeys, pigs and calves.

Figure 33: Consumption of polymyxins in food-producing animals and probability of resistance to colistin in indicator *Escherichia coli* from food-producing animals, for the periods (a) 2014–2015, (b) 2015–2016, (c) 2016–2017 and (d) 2017–2018 (see also Table 39)



The figure displays curves of logistic regression models. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country. The category 'food-producing animals' includes broilers, turkeys, pigs and calves. For all the graphs, the scale of the Y-axis was adjusted to the range of probabilities of resistance observed (i.e. to a maximum of 0.25).

Indicator *Escherichia coli* from pigs and poultry

The estimated consumption of polymyxins in pigs and poultry were compared with the occurrence of resistance to colistin in indicator *E. coli* from slaughter pigs in 2017 for 31 countries and from poultry (broilers and turkeys) for 29 countries for 2016 and for 30 countries for 2018.

Where detected, colistin resistance in indicator *E. coli* from pigs was typically reported at very low levels. In poultry, the levels of resistance observed were generally slightly higher than those in pigs, although still low (Figure 34).

The associations between consumption of polymyxins and resistance to colistin in indicator *E. coli* in pigs in 2017 and between consumption of polymyxins and resistance to colistin in indicator *E. coli* in poultry in 2016 were significantly positive (Table 40, Figure 34).

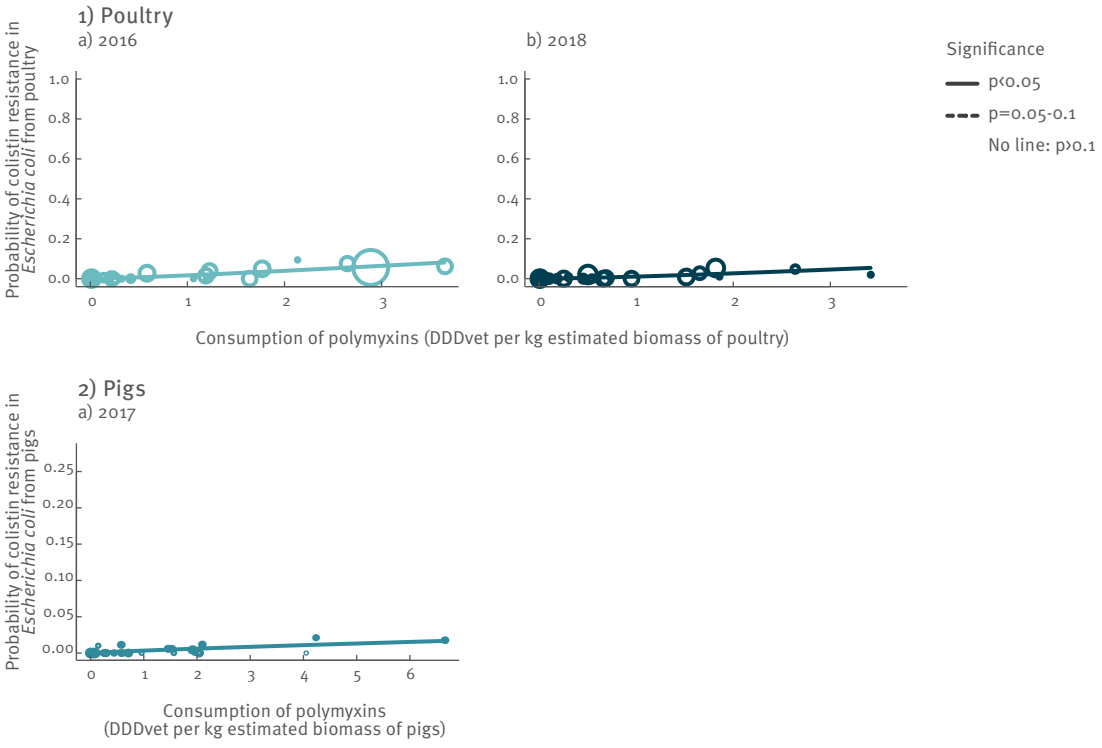
Table 40: Association between consumption of polymyxins in pigs and poultry, expressed as DDDvet/kg of estimated biomass/year, and probability of resistance to polymyxins in indicator *Escherichia coli* isolates from slaughter pigs and poultry (broilers and turkeys) and in *Salmonella* isolates from pigs (logistic regression, see also Figure 34)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Indicator *E. coli*						
Poultry	2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	2.42	‹0.001	1.81–3.25
Pigs	2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=31)	2	1.80	‹0.05	1.25–2.6
Poultry	2018	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, MT, NO, PL, PT, RO, SE, SI, SK, UK (n=30)	2	2.58	‹0.001	1.73–3.87
Salmonella spp.						
Pigs*	2017	BE, CZ, DE, DK, ES, FR, HR, HU, IE, IT, MT, PL, PT, SK (n=14)	2	1.55	0.478	0.46–5.2

CI: confidence interval. Odds ratio varies from 0 to infinity. When odds ratio equals 1 or CI includes 1, the association is not considered statistically significant. The category 'poultry' includes broilers and turkeys.

* *Salmonella* spp. isolates derive from pig carcasses.

Figure 34: Consumption of polymyxins in pigs or poultry and probability of resistance to colistin in indicator *Escherichia coli* isolates from (1) poultry in 1.a) 2016 and 1.b) 2018, and 2.a) from slaughter pigs in 2017 (logistic regression, see Table 40)



The figure displays curves of logistic regression models. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country. The category 'poultry' includes broilers and turkeys.

10. Aminopenicillins

Aminopenicillins are commonly used first-line antibiotics in human medicine, but alternatives are available for most of the indications. Exceptions are infections with *Listeria* and with enterococci. In veterinary medicine aminopenicillins are approved for use in food-producing and companion animals for a wide range of indications, including gastrointestinal and urinary tract infections, respiratory infections and mastitis.

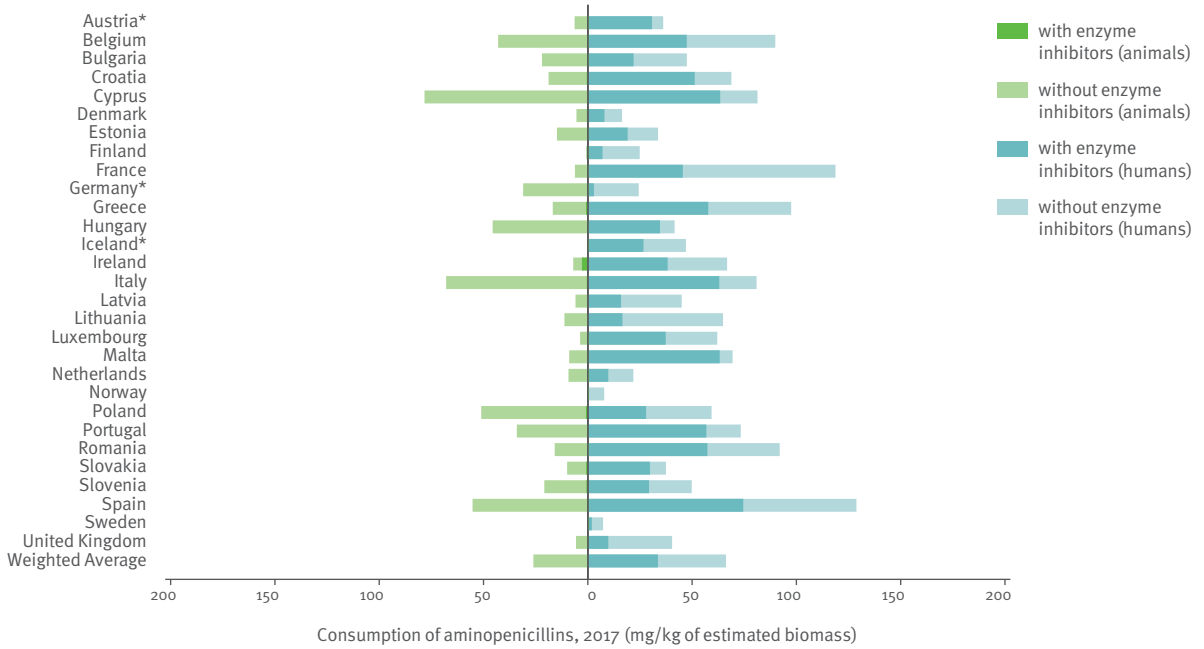
In the recent WHO AWaRe classification, aminopenicillins belong to the 'Access' group of antimicrobials [32]. Aminopenicillins are considered by WHO as Critically Important Antimicrobials (CIA) in human medicine [14]. This class has also been categorised as Veterinary Critically Important Antimicrobial Agents (VCIA) in the OIE list of antimicrobials of veterinary importance [34].

According to the AMEG categorisation, aminopenicillins in combination with beta-lactamase inhibitors belong to Category C ('Caution') and the aminopenicillins without beta-lactamase inhibitors to the Category D ('Prudence') [13]. Compared to aminopenicillins alone, amoxicillin-clavulanic acid has a wider spectrum and thereby a higher selection pressure for multidrug resistant organisms. Aminopenicillins combined with an enzyme inhibitor are therefore in Category C ('Caution') rather than in Category D ('Prudence').

10.1 Consumption in humans and food-producing animals by country

In 2017, the EU/EEA population-weighted mean consumption of aminopenicillins in combination with beta-lactamase inhibitors in humans and food-producing animals was 33.6 and 0.3 mg per kg of estimated biomass, respectively, in the 29 EU/EEA countries included in the analysis. The corresponding ranges were 0.1–74.5 (median 29.8) and 0.003–2.8 (median 0.2) mg per kg, respectively. In 2017, the population-weighted mean consumption of aminopenicillins without beta-lactamase inhibitors in humans and food-producing animals was 32.6 and 25.8 mg per kg of estimated biomass, respectively. The corresponding ranges were 5.4–73.2 (median 20.4) and 0.1–78 (median 10.9) mg per kg, respectively. Population-corrected consumption of aminopenicillins in humans and food-producing animals by country is shown in Figure 35.

Figure 35: Biomass-corrected consumption of aminopenicillins in humans and food-producing animals in 29 EU/EEA countries for which data were available both for humans and food-producing animals, 2017



An asterisk (*) denotes that only community consumption was provided for human medicine. The population-weighted mean proportion (%) of the hospital sector from the 2017 consumption of aminopenicillins for EU/EEA countries providing data for both sectors was 14.6% and 4.8%, with and without enzyme inhibitors respectively.

Notes: 1) The estimates presented are crude and must be interpreted with caution. For limitations hampering comparison of antimicrobial consumption in humans and food-producing animals, please see Chapter 15.11. The weighted mean figure represents the population-weighted mean of data from those countries included.

The population corrected consumption of aminopenicillins was lower in food-producing animals than in humans in 2017, except in two countries with similar consumption (‹4% difference).

There was a significant association within country between consumption of aminopenicillins in humans and food-producing animals (Spearman's rank correlation, rho = 0.54).

10.2 Consumption in humans and occurrence of resistance in bacterial isolates from humans

Escherichia coli

A borderline statistically significant positive association between the consumption of aminopenicillins in humans and the occurrence of resistance to aminopenicillins in invasive *E. coli* isolates from humans was reported for 2016 and 2017. No statistically significant association was found for 2018 (Table 41).

Salmonella

No statistically significant associations between the consumption of aminopenicillins in humans and the occurrence of resistance to aminopenicillins in *Salmonella* spp. isolates from humans was reported for 2016–2018 (Table 42).

A borderline statistically significant association between the consumption of aminopenicillins in humans and the occurrence of resistance to aminopenicillins in *S.* Enteritidis isolates from humans was observed for 2017. No statistically significant associations were found for 2016 and 2018 (Table 43).

A statistically significant positive association between the consumption of aminopenicillins in humans and the occurrence of resistance to aminopenicillins in *S.* Typhimurium, including monophasic variant from humans was reported for 2017 (Table 44, Figure 36). No statistically significant associations were found for 2016 and 2018 (Table 44).

Table 41: Association between consumption of aminopenicillins in humans, expressed as DDD per 1 000 inhabitants per day, and probability of resistance to aminopenicillins in *Escherichia coli* from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure A1.2. 5)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=28)	2	1.14	0.062	0.99–1.30
2017	AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=28)	2	1.15	0.066	0.99–1.32
2018	AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=28)	2	1.10	0.110	0.98–1.24

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 42: Association between consumption of aminopenicillins in humans, expressed as DDD per 1 000 inhabitants per day, and probability of resistance to aminopenicillins in *Salmonella* from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PT, RO, SI, SK, UK (n=25)	2	0.97	0.805	0.75–1.25
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=26)	2	1.11	0.494	0.83–1.49
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK (n=24)	2	1.11	0.426	0.86–1.43

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 43: Association between consumption of aminopenicillins in humans, expressed as DDD per 1 000 inhabitants per day, and probability of resistance to aminopenicillins in *Salmonella* Enteritidis from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PT, RO, SI, SK, UK (n=23)	2	0.80	0.488	0.43–1.50
2017	AT, BE, CY, DE, EE, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=23)	2	1.42	0.052	1.00–2.02
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK (n=23)	2	1.24	0.239	0.86–1.79

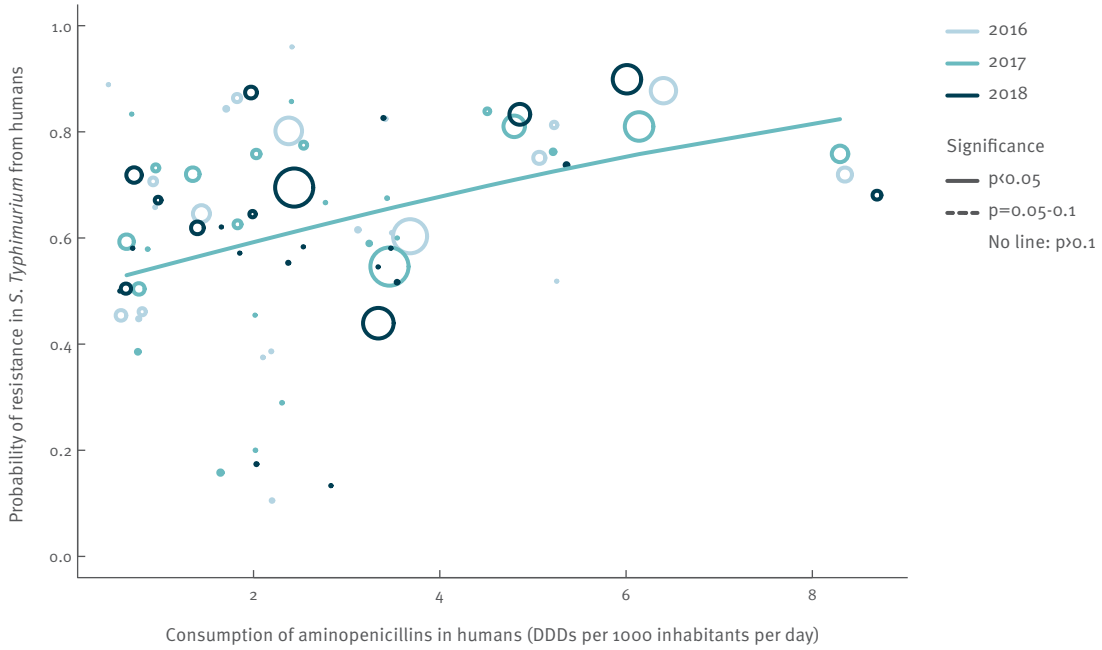
CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 44: Association between consumption of aminopenicillins in humans, expressed as DDD per 1 000 inhabitants per day, and probability of resistance to aminopenicillins in *Salmonella* Typhimurium including monophasic variant from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 36)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, MT, NL, NO, PT, RO, SI, SK, UK (n=23)	2	1.12	0.248	0.93–1.35
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=25)	2	1.20	0.037	1.01–1.43
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK (n=24)	2	1.13	0.156	0.96–1.33

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 36: Consumption of aminopenicillins in humans, expressed as DDD per 1 000 inhabitants per day, and probability of resistance to aminopenicillins in *Salmonella* Typhimurium, including monophasic variant, from humans, EU/EEA (see also Table 44)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

10.3 Consumption in food-producing animals and resistance in bacterial isolates from food-producing animals

Escherichia coli from food-producing animals

To investigate possible relationships between the consumption of aminopenicillins and ampicillin resistance, the SIMR to ampicillin in *E. coli* from food-producing animals was compared with the consumption of aminopenicillins in food-producing animals (expressed in mg per kg of estimated biomass) for the two-year intervals 2014–2015, 2015–2016, 2016–2017 and 2017–2018 (mean consumption over the respective years) at the national level (Table 45, Figure 37). The category 'food-producing animals' includes broilers, turkeys, pigs and calves for all time intervals.

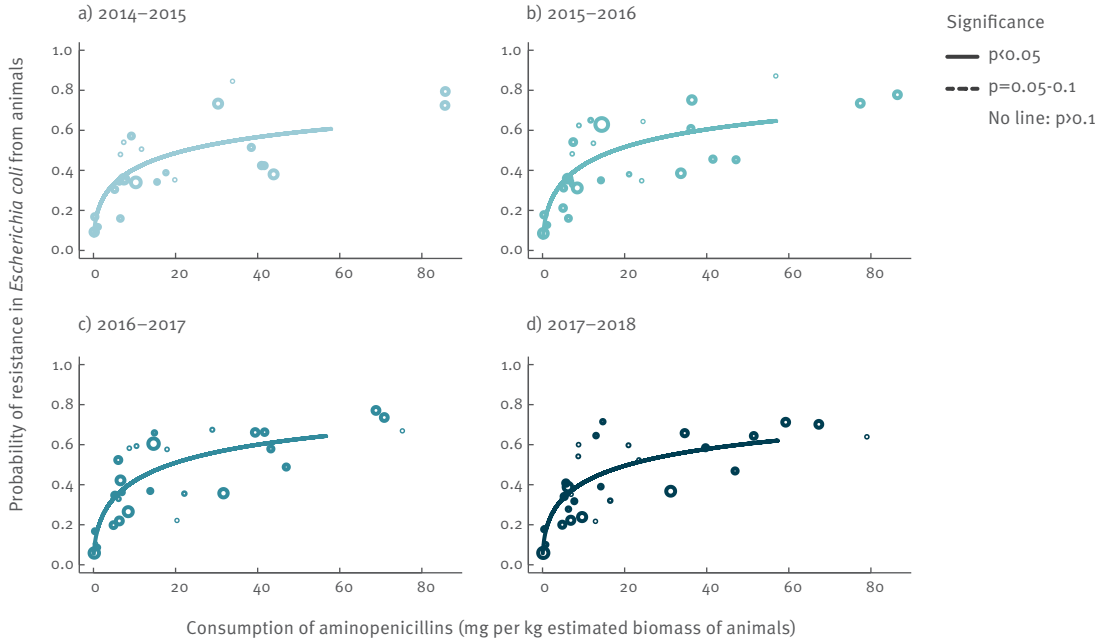
Marked variations in ampicillin resistance in indicator *E. coli* were observed between countries involved in the analysis. Consumption of aminopenicillins ranged from a few units to more than 80 mg per kg of estimated biomass. The assessment of the relationships between consumption and resistance is based on a full range of values. Statistically significant positive associations between ampicillin resistance in indicator *E. coli* and aminopenicillin consumption in food-producing animals were observed for all the time intervals.

Table 45: Association between consumption of aminopenicillins in food-producing animals, expressed in mg/kg of estimated biomass/year, and probability of resistance to aminopenicillin in indicator *Escherichia coli* from food-producing animals (logistic regression, see also Figure 37)

Year	Countries	Model	Odds ratio	p-value	95% CI
Indicator *E. coli*					
2014-2015	AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=26)	2	1.38	<0.001	1.21–1.57
2015-2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=28)	2	1.43	<0.001	1.25–1.63
2016-2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.44	<0.001	1.29–1.62
2017-2018	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, MT, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.40	<0.001	1.26–1.56

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or 95% CI includes 1, the association is not considered statistically significant. The category 'food-producing animals' includes broilers, turkeys, pigs and calves.

Figure 37: Consumption of aminopenicillins in food-producing animals and probability of resistance to ampicillin in indicator *Escherichia coli* from food-producing animals in (a) 2014–2015, (b) 2015–2016, (c) 2016–2017 and (d) 2017–2018 (see also Table 45)



The figure displays curves of logistic regression models. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country. Category 'food-producing animals' includes broilers, turkeys, pigs and calves.

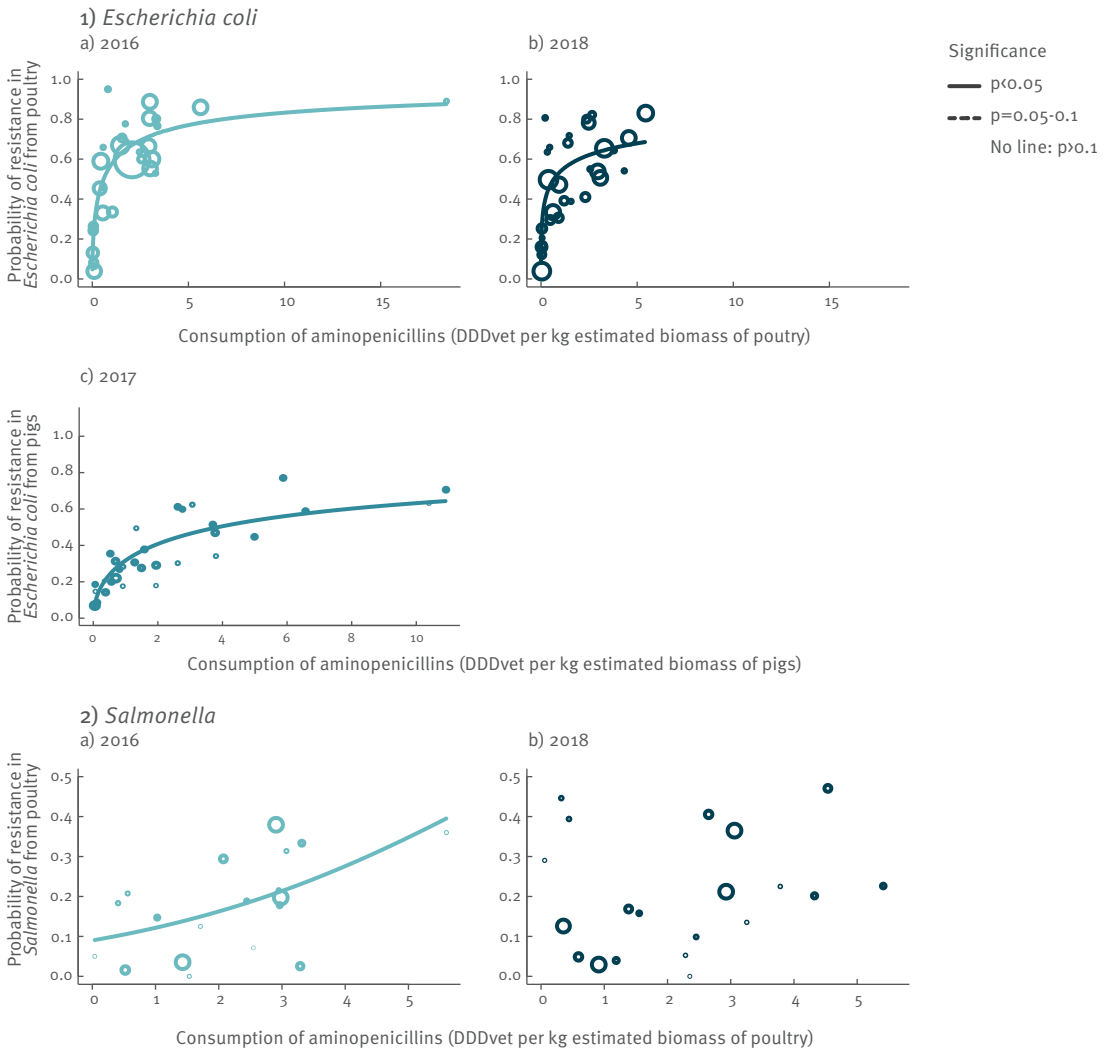
Escherichia coli and *Salmonella* from poultry and pigs

The estimated consumption of aminopenicillins in pigs and in poultry were compared with the occurrence of resistance to ampicillin in indicator *E. coli* and *Salmonella* spp. from poultry (broilers and turkeys) in 2016 for 29 and 19 countries, and in 2018 for 30 and 18 countries, respectively, and in indicator *E. coli* from slaughter pigs in 2017 for 31 countries.

Where detected, aminopenicillin resistance in indicator *E. coli* from pigs and calves was typically reported at high levels. In poultry, the levels of resistance observed were generally higher than those reported in pigs or calves (Figure 38).

The association assessed between consumption of aminopenicillins and resistance to ampicillin in indicator *E. coli* in pigs in 2017 was significantly positive (Table 46). The associations detected between consumption of aminopenicillins and resistance to ampicillin in indicator *E. coli* in poultry in 2016 and 2018 were both significantly positive (Table 46, Figure 38).

Figure 38: Consumption of aminopenicillins in pigs and poultry and probability of resistance to ampicillin in (1) indicator *Escherichia coli* isolates from poultry and pigs and (2) *Salmonella* from poultry in 2016 and 2018 (see also Table 46)



The figure displays curves of logistic regression models. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Table 46: Association between consumption of aminopenicillins in poultry and pigs, expressed as DDDvet/kg of estimated biomass/year, and probability of resistance to ampicillin in indicator *Escherichia coli* from slaughter pigs and poultry (broiler and turkeys) and *Salmonella* isolates from poultry and pigs (logistic regression, see also Figure 38)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Indicator *E. coli*						
Poultry	2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.48	<0.001	1.31-1.67
Poultry	2018	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.29	<0.001	1.17-1.43
Pigs	2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=31)	2	1.48	<0.001	1.34-1.65
Salmonella spp.						
Poultry	2016	AT, BE, CY, CZ, DE, DK, EL, ES, FR, HR, HU, IE, IT, PL, PT, RO, SI, SK, UK (n=19)	2	1.40	0.019	1.08-1.82
Pigs*	2017	BE, CZ, DE, DK, ES, FR, HR, HU, IE, IT, MT, PL, PT, SK (n=14)	2	1.07	0.669	0.77-1.51
Poultry	2018	AT, BE, CY, CZ, DE, DK, EL, ES, FR, HR, HU, IE, IT, MT, PL, PT, RO, SI, SK, UK (n=20)	1	1.11	0.433	0.85-1.44

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant. The category 'poultry' includes broilers and turkeys.

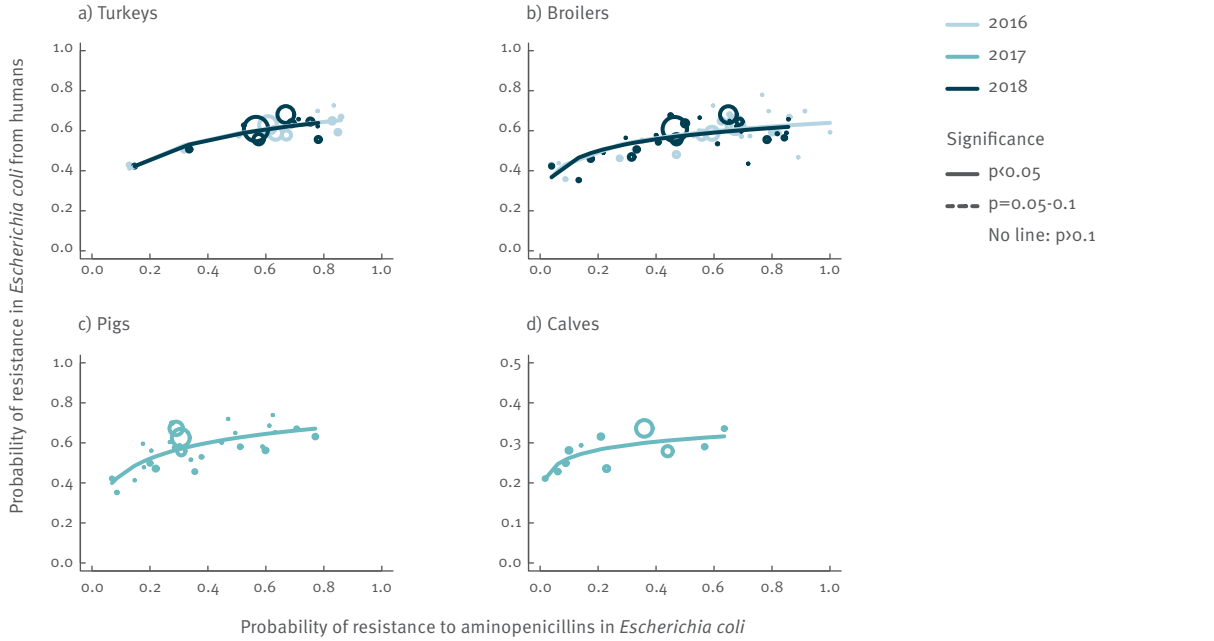
* *Salmonella* spp. isolates derive from pig carcasses.

Table 47: Association between resistance to aminopenicillins in *Escherichia coli* from food-producing animals and from humans, 2016–2018 (logistic regression, see also Figure 39)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Broilers	2016	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=28)	2	1.27	<0.001	1.16–1.40
Broilers	2018	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=28)	2	1.26	<0.001	1.14–1.40
Turkeys	2016	AT, DE, ES, FR, HU, IT, NO, PL, PT, RO, UK (n=11)	2	1.44	<0.001	1.26–1.64
Turkeys	2018	AT, DE, ES, FR, HU, IT, NO, PL, PT, RO, UK (n=11)	2	1.44	<0.001	1.24–1.68
Pigs	2017	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=29)	2	1.38	<0.001	1.23–1.56
Calves	2017	AT, BE, DE, DK, ES, FR, HR, IT, NL, NO, PT (n=11)	2	1.18	0.001	1.07–1.30

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 39: Probability of resistance to aminopenicillins in *Escherichia coli* from food-producing animals - a) turkeys, b) broilers, c) pigs and d) calves - and from humans, EU/EEA, 2016–2018 (see also Table 47)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

10.4 Resistance in bacterial isolates from humans and from food-producing animals

Escherichia coli

Data on occurrence of aminopenicillin resistance in *E. coli* isolates from food-producing animals were associated with aminopenicillin resistance of invasive *E. coli* isolates from humans.

For all years a statistically significant positive association was found between resistance of indicator *E. coli* to aminopenicillins in food-producing animals (turkeys and broilers for 2016 and 2018 and pigs and calves for 2017) and the occurrence of resistance to aminopenicillins in invasive *E. coli* isolates from humans (Table 47, Figure 39).

Salmonella

Data on occurrence of aminopenicillin resistance in *Salmonella* spp. from food-producing animals were associated with aminopenicillin resistance of *Salmonella* spp. from humans.

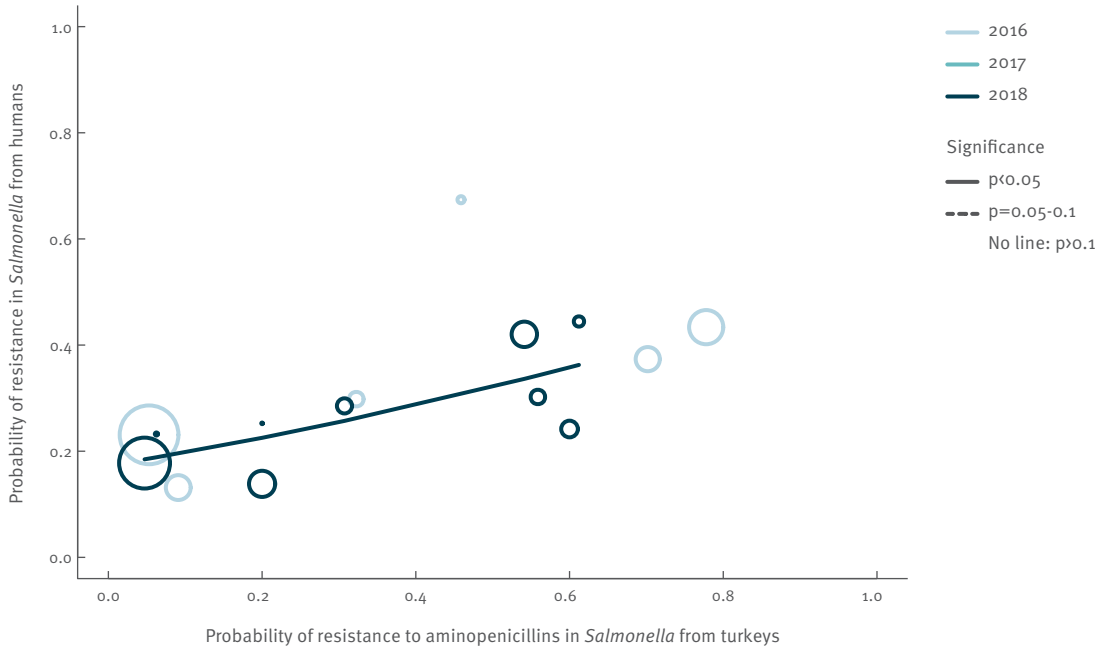
A statistically significant positive association was found for 2018 between resistance of *Salmonella* spp. to aminopenicillins in turkeys and the occurrence of resistance to aminopenicillins in *Salmonella* spp. from humans (Table 48, Figure 40). A borderline statistically significant positive association was found between resistance of *Salmonella* spp. to aminopenicillins in broilers and the occurrence of resistance to aminopenicillins in *Salmonella* spp. from humans in 2018 and 2016 (Table 48).

Table 48: Association between resistance to aminopenicillins in *Salmonella* from food-producing animals and from humans, 2016–2018 (logistic regression, see also Figure 40 and Figure A1.2. 7)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Turkeys	2016	AT, DE, ES, FR, HU, UK (n=6)	1	5.24	0.147	0.56–49.22
Turkeys	2018	AT, CY, ES, FR, HU, IE, IT, PL, UK (n=9)	1	5.10	0.006	1.61–16.17
Broilers	2016	AT, BE, CY, DE, DK, EL, ES, FR, HU, IE, IT, MT, PT, RO, SI, SK, UK (n=17)	2	1.20	0.076	0.98–1.47
Broilers	2018	AT, BE, CY, DE, DK ES, FR, HU, IE, IT, MT, PL, PT, RO, SI, SK, UK (n=17)	2	1.24	0.057	0.99–1.56
Pigs	2017	AT, DE, DK, , ES, FR, HU, IE, IT, , MT, PL, PT, SK (n=12)	2	0.96	0.889	0.57–1.64

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 40: Probability of resistance to aminopenicillins in *Salmonella* from food-producing animals (turkeys) and from humans, EU/EEA, 2016–2018 (see also Table 48)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

With regard to data on the occurrence of aminopenicillin resistance in *S.* Typhimurium, including monophasic variant, from humans and from food-producing animals, only the data from pigs were sufficient for analysis and only for 2017. No evidence of a statistically significant association was found for the tested combination (Table 49).

10.5 Consumption in food-producing animals and resistance in bacterial isolates from humans

Escherichia coli

A statistically significant positive association was reported between consumption of aminopenicillins in food-producing animals and aminopenicillin resistance of invasive *E. coli* isolates in humans for 2016–2018 (Table 50, Figure 41).

Table 49: Association between resistance to aminopenicillins in *Salmonella* Typhimurium, including monophasic variant, from food-producing animals (pigs) and humans, 2017 (logistic regression)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Pigs	2017	BE, DE, DK, ES, FR, IE, IT (n=7)	2	1.18	0.897	0.10–13.83

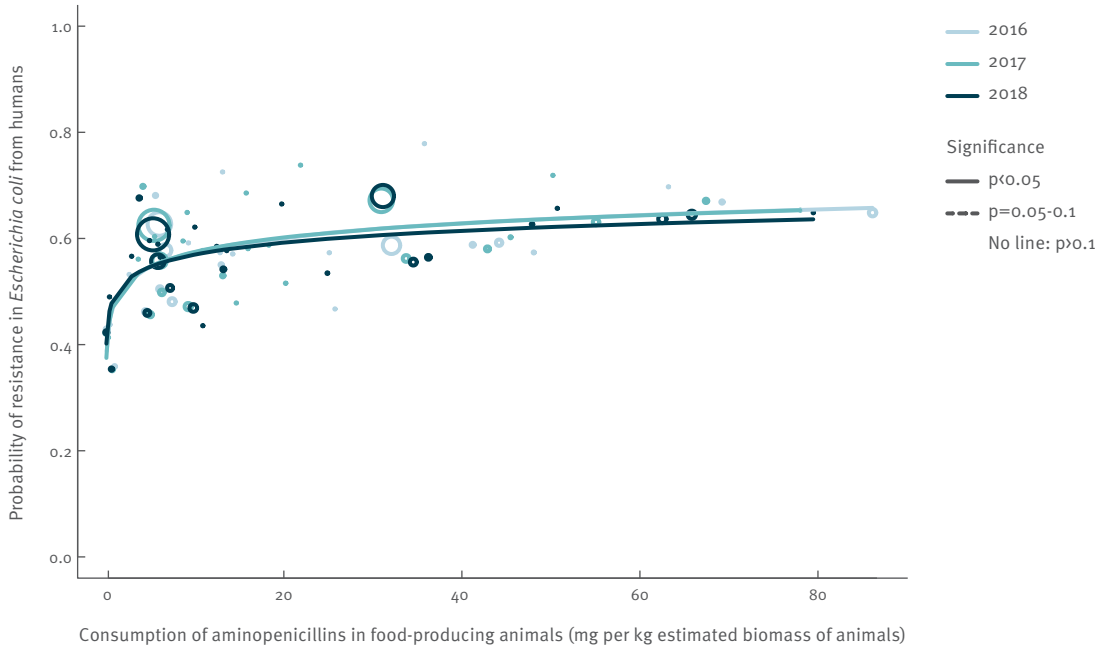
CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 50: Association between consumption of aminopenicillins in food-producing animals, expressed in mg/PCU, and probability of resistance to aminopenicillins in *Escherichia coli* from humans, EU/EEA, 2016–2018 (logistic regression, see Figure 41)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, RO, SI, SK, UK (n=28)	2	1.12	<0.001	1.06–1.18
2017	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=29)	2	1.12	<0.001	1.07–1.18
2018	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=29)	2	1.10	<0.001	1.05–1.15

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 41: Consumption of aminopenicillins in food-producing animals, expressed in mg/PCU, and probability of resistance to aminopenicillins in *Escherichia coli* from humans, EU/EEA, 2016–2018



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Salmonella

A statistically significant association was observed between consumption of aminopenicillins in food-producing animals and aminopenicillin resistance of *Salmonella* from humans for 2016 and 2018, but not for 2017 (Table 51, Figure 42).

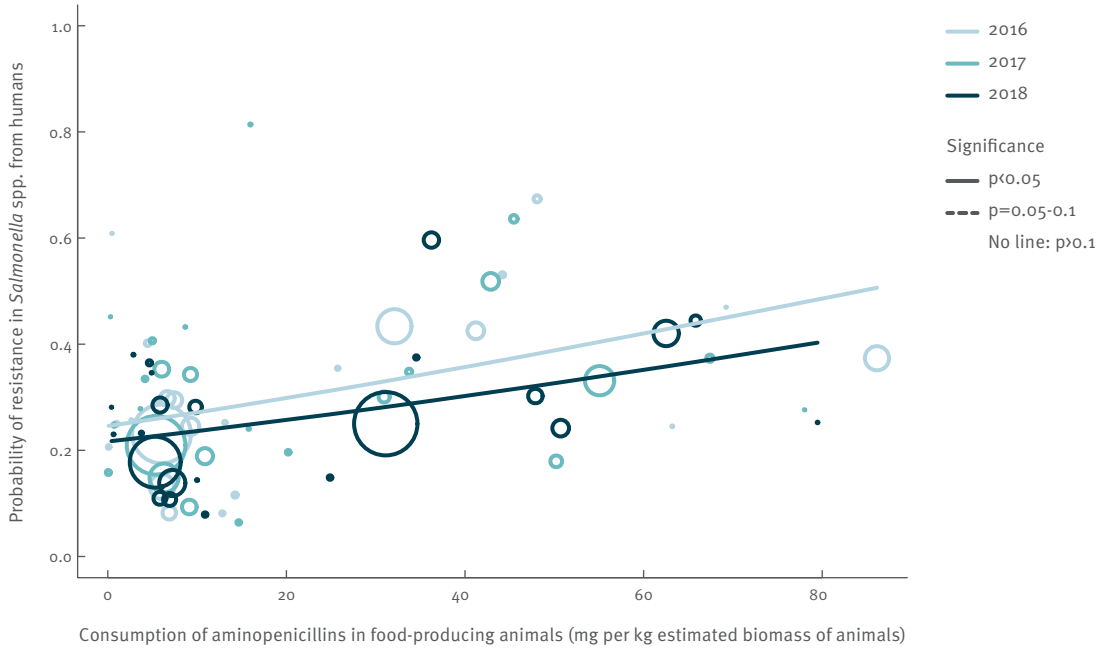
No statistically significant association was observed between consumption of aminopenicillins in food-producing animals and aminopenicillin resistance of *S.* Enteritidis from humans for 2016–2018, although the association was borderline significant for 2018 (Table 52).

Table 51: Association between consumption of aminopenicillins in food-producing animals, expressed in mg/PCU, and probability of resistance to aminopenicillins in *Salmonella* from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 42)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PT, RO, SI, SK, UK (n=24)	1	1.01	0.016	1.00–1.02
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=26)	1	1.01	0.350	0.99–1.02
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK (n=24)	1	1.01	0.030	1.00–1.02

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 42: Consumption of aminopenicillins in food-producing animals, expressed in mg/PCU, and probability of resistance to aminopenicillins in *Salmonella* from humans, EU/EEA, 2016–2018



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Table 52: Association between consumption of aminopenicillins in food-producing animals, expressed in mg/PCU, and probability of resistance to aminopenicillins in *Salmonella* Enteritidis from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure A1.2. 8)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NL, NO, PT, RO, SI, SK, UK (n=22)	2	1.16	0.474	0.78–1.72
2017	AT, BE, CY, DE, EE, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=23)	2	1.12	0.248	0.92–1.36
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK (n=23)	2	1.22	0.083	0.97–1.54

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

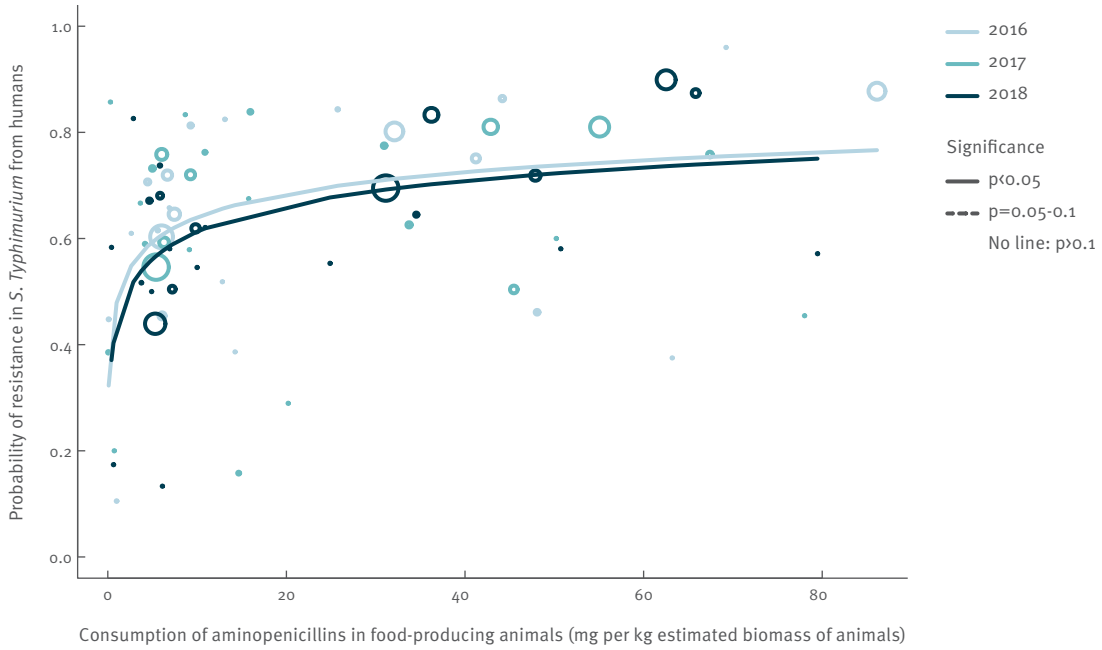
A statistically significant association was observed between consumption of aminopenicillins in food-producing animals and aminopenicillin resistance of *S.* Typhimurium, including monophasic variant from humans for 2016 and 2018 but not for 2017 (Table 53, Figure 43).

Table 53: Association between consumption of aminopenicillins in food-producing animals, expressed in mg/PCU, and probability of resistance to aminopenicillins in *Salmonella* Typhimurium, including monophasic variant from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 43)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PT, RO, SI, SK, UK (n=22)	2	1.22	0.018	1.03–1.44
2017	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, MT, NL, NO, PL, PT, RO, SI, SK, UK (n=25)	2	1.08	0.260	0.94–1.24
2018	AT, BE, CY, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK (n=24)	2	1.24	0.004	1.07–1.44

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 43: Consumption of aminopenicillins in food-producing animals, expressed in mg/PCU, and probability of resistance to aminopenicillins in *Salmonella* Typhimurium from humans, EU/EEA, 2016–2018



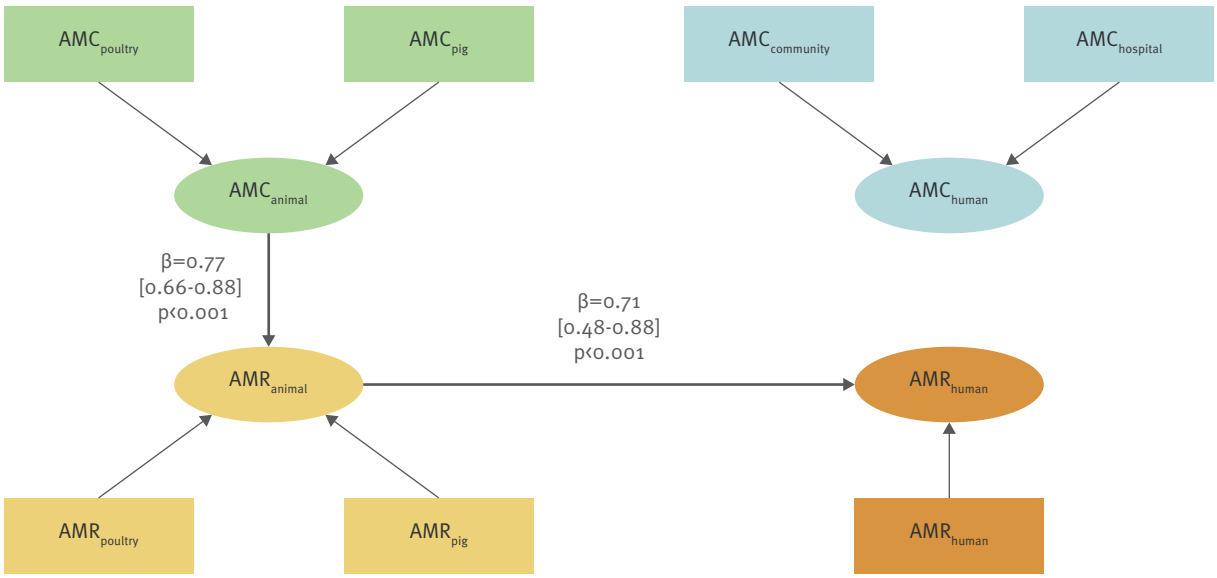
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

10.6 Multivariate analysis

Escherichia coli

As indicated in the univariate analyses, there was a significant strong association of aminopenicillin consumption in animals and resistance to aminopenicillin in *E. coli* from food-producing animals. The association of aminopenicillin consumption in humans and resistance to aminopenicillins in humans was borderline significant in the univariate analysis, and not significant in the multivariate model. The positive association between resistance to ampicillin in food-producing animals and aminopenicillin-resistance in isolates from humans was confirmed by the multivariate analysis. According to the R^2, 59% (95% confidence interval 45–78) of the variance of resistance in food-producing animals is explained by the aminopenicillin consumption in food-producing animals and 50% (95% confidence interval 23–77) of the variance of resistance in humans is explained by resistance in food-producing animals (Figure 44).

Figure 44: Diagram of the PLS-PM of resistance to aminopenicillins in human invasive *Escherichia coli* (2017 and 2018), considering resistance to aminopenicillins in indicator *E. coli* from food-producing animals (pigs 2017 and poultry 2018) and consumption of aminopenicillins in humans (2017–2018 mean, expressed as DDD per 1 000 inhabitants per day) and in food-producing animals (pigs in 2017 and poultry in 2018 - expressed as DDDvet/kg of estimated biomass)



27 countries: AT*, BE, BG, CY, DE*, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS*, IT, LT, LV, MT, NL, NO, PL, PT, RO, SI, SK, UK.

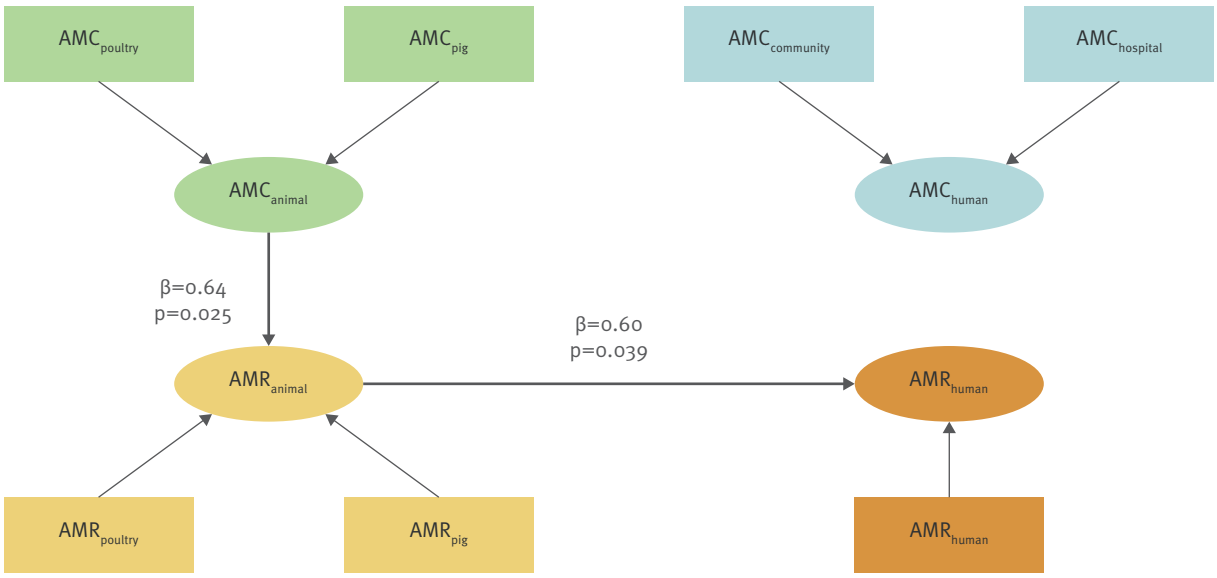
* For these countries, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

(Goodness-of-fit=0.665)

Salmonella

In the multivariate model, based on only 12 countries, the association of aminopenicillin consumption in food-producing animals and *Salmonella* spp. resistance to aminopenicillin was confirmed. Only 41% (95% confidence interval 24–88) of the resistance rate variance was explained by the amino-penicillin consumption latent variable. No significant associations were detected between aminopenicillin consumption in humans and aminopenicillin resistance in *Salmonella* spp. from humans. The relationship between resistance to ampicillin in food-producing animals and resistance to aminopenicillins in humans was significant. According to R^2, only 36% of resistance rate variance was explained (with a wide 95% bootstrap confidence interval: 2–81) (Figure 45).

Figure 45: Diagram of the PLS-PM of resistance to aminopenicillins in human *Salmonella* (2017 and 2018), considering resistance to aminopenicillins in *Salmonella* from food-producing animals (pig 2017 and poultry 2018) and consumption of aminopenicillins in humans (2017–2018 mean, expressed as DDD per 1 000 inhabitants and per day), and in food-producing animals (pigs in 2017 and poultry in 2018 - expressed as DDDvet/kg of estimated biomass)



12 countries: BE, DE*, DK, ES, FR, HU, IE, IT, MT, PL, PT, SK.

* For this country, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

(Goodness-of-fit=0.354).

11. Macrolides

Macrolides are important in human medicine for treatment of *Legionella* spp., *Campylobacter* spp., invasive multidrug-resistant *Salmonella* spp. and *Shigella* spp. infections in humans. They are also among the few alternative antibiotics for treatment of haemorrhagic digestive tract disease in pigs (*Lawsonia intracellularis*) and are important for treatment of mycoplasma infections in pigs and poultry.

In the recent WHO AWaRe classification, macrolides belong to the 'Watch' group of antimicrobials [32]. Macrolides are considered by WHO as Highest Priority Critically Important Antimicrobials (HPCIA) in human medicine [14]. This class has also been categorised as Veterinary Critically Important Antimicrobial Agents (VCIA) in the OIE list of antimicrobials of veterinary importance [34].

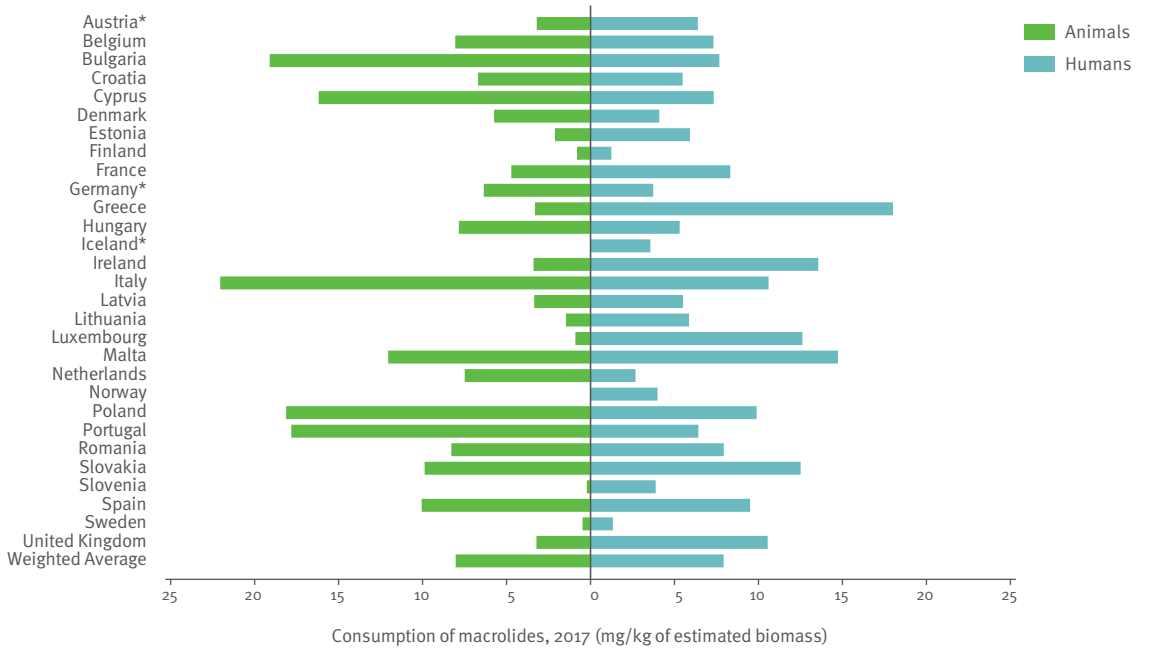
According to the AMEG categorisation, macrolides belong to Category C ('Caution'), with the indication that they should be used with caution in veterinary medicine in the EU [13]. For those substances proposed for inclusion in this category, general alternatives exist in human medicine in the EU but there are few alternatives in veterinary medicine for certain indications. These antibiotics should only be used in animals when there is no available substance in Category D ('Prudence') that would be clinically effective.

11.1 Consumption in humans and food-producing animals by country

The population-weighted mean consumption of macrolides in humans and food-producing animals was 7.9 and 8.0 mg per kg estimated biomass, respectively. The corresponding ranges were 1.2–18 (median 6.4) mg per kg for humans and 0–22 (median 5.7) mg per kg for food-producing animals, respectively. Population-corrected consumption of macrolides in humans and food-producing animals by country is shown in Figure 46.

In 16 countries, the consumption was lower in food-producing animals than in humans. There was no consumption of macrolides in food-producing animals in Iceland. The amount of macrolides consumed in food-producing animals and in humans varied among countries. There was a significant association between the levels of consumption of macrolides in humans and in food-producing animals (Spearman's rank correlation coefficient, rho = 0.46) at the national level.

Figure 46: Population-corrected consumption of macrolides for humans and food-producing animals in 29 EU/EEA countries for which data were available both for humans and food-producing animals, 2017



An asterisk (*) denotes that only community consumption was provided for human medicine. The population-weighted mean proportion (%) of the hospital sector from the 2017 total national consumption of macrolides for EU/EEA countries providing data for both sectors is 4.4%.

Notes: 1) The estimates presented are crude and must be interpreted with caution. For limitations hampering the comparison of antimicrobial consumption in humans and food-producing animals, please see Section 14. 2) The weighted mean figure represents the population-weighted mean of data from those countries included.

11.2 Consumption in humans and occurrence of resistance in bacterial isolates from humans

Campylobacter jejuni

No statistically significant association was found between the consumption of macrolides in humans and the occurrence of macrolide resistance of *C. jejuni* in humans, although the association was borderline significant in 2018 (Table 54).

11.3 Consumption in food-producing animals and resistance in bacterial isolates from food-producing animals

Campylobacter jejuni from poultry

The estimated consumption of macrolides in poultry (expressed as DDDvet/kg of estimated biomass) was compared with the occurrence of resistance to erythromycin in *C. jejuni* from from broilers and turkeys (SIMR) in 2016 and 2018 (Table 55, Figure 47). Resistance in *C. jejuni* from turkeys is only accounted for in those countries with a substantial turkey production sector. Resistance to erythromycin in *C. jejuni* from poultry was very low or absent in many countries for both years, while a few countries had up to 18% resistant isolates.

Table 54: Association between consumption of macrolides in humans expressed as DDD per 1 000 inhabitants per day, and probability of resistance to macrolides in *Campylobacter jejuni* from humans, EU/EEA, 2016–2018 (logistic regression see also Figure A1.2. 9)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, CY, DK, EE, ES, FI, FR, IS, IT, LT, LU, MT, NL, NO, PT, RO, SI, SK, UK (n=19)	3	1.00	0.957	0.92–1.08
2017	AT, CY, DK, EE, ES, FI, FR, IE, IS, IT, LT, LU, MT, NL, NO, PL, PT, SI, SK, UK (n=20)	3	1.03	0.228	0.98–1.09
2018	AT, CY, DK, EE, ES, FI, FR, IE, IS, IT, LT, LU, MT, NL, PL, PT, RO, SI, SK, UK (n=20)	3	1.04	0.097	0.99–1.09

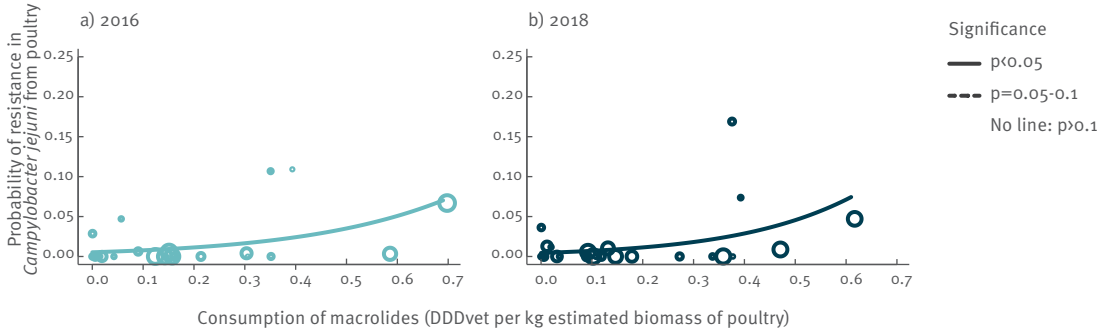
CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 55: Consumption of macrolides in poultry, expressed as DDDvet/kg of estimated biomass/year, and probability of resistance to macrolides in *Campylobacter jejuni* from poultry (logistic regression, see also Figure 47)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, BG, CH, CY, CZ, DE, DK, EL, ES, FI, HR, HU, IE, IS, IT, LT, LU, LV, NO, PL, PT, RO, SE, SI, SK, UK (n=27)	1	47.1	0.009	2.59–856
2018	AT, BG, CH, CY, CZ, DE, DK, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=27)	1	115	0.014	2.65–4987

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.
The category 'poultry' includes data from broilers and turkeys for AT, DE, ES, HU, IT, PL, PT, RO and UK, and broiler data for the other countries included in the analysis.

Figure 47: Consumption of macrolides in poultry and probability of resistance to macrolides in *Campylobacter jejuni* from poultry (broilers and turkeys) in 2016 and 2018 (see also Table 55)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

11.4 Resistance in bacterial isolates from humans and from food-producing animals

Campylobacter jejuni

In 2017–18, overall resistance to erythromycin was reported at 2.0% (2017) and 1.8% (2018) in *C. jejuni* isolates from humans, 1.3% in isolates from broilers, 1.1% in isolates from fattening turkeys and 1.2% of isolates from calves.

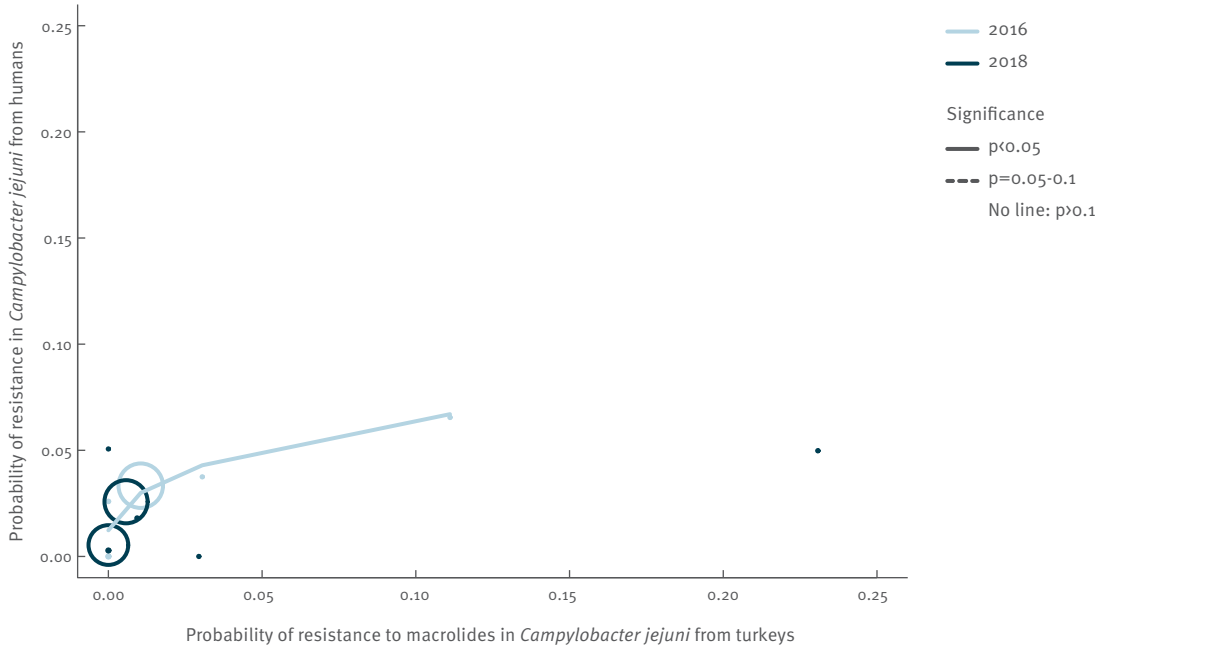
A statistically significant positive association was found between macrolide resistance in *C. jejuni* from turkeys and macrolide resistance of *C. jejuni* from humans for 2016, but not for 2018 (Table 56, Figure 48). No evidence of statistically significant association was found between macrolide resistance in *C. jejuni* from broilers and macrolide resistance of *C. jejuni* from humans for 2016 and 2018, although the association was borderline significant in 2018 (Table 56).

Table 56: Association between resistance to macrolides in *Campylobacter jejuni* from food-producing animals and humans, 2016–2018 (logistic regression, see also Figure 48 and Figure A1.2. 10)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Broilers	2016	AT, CY, DK. ES, FI, IS, IT, LT, NO, PT, RO, SI, SK, UK (n=14)	2	1.03	0.810	0.80–1.33
Broilers	2018	AT, CY, DK, ES, FI, FR, IE, IS, IT, LT, NL, PL, PT, RO, SI, SK, UK (n=17)	2	1.15	0.090	0.98–1.34
Turkeys	2016	AT, ES, IT, PT, RO, UK (n=6)	2	1.29	0.008	1.07–1.56
Turkeys	2018	AT, ES, FR, IT, PL, PT, UK (n=7)	2	1.15	0.305	0.88–1.48

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 48: Probability of resistance to macrolides in *Campylobacter jejuni* from turkeys and humans, 2016 and 2018, (see also Table 56)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

11.5 Consumption in food-producing animals and resistance in bacterial isolates from humans

No statistically significant associations were reported between consumption of macrolides in food-producing animals and macrolide resistance of *Campylobacter jejuni* from humans for 2016–2018, although the association was borderline significant in 2018 (Table 57).

11.6 Multivariate analysis

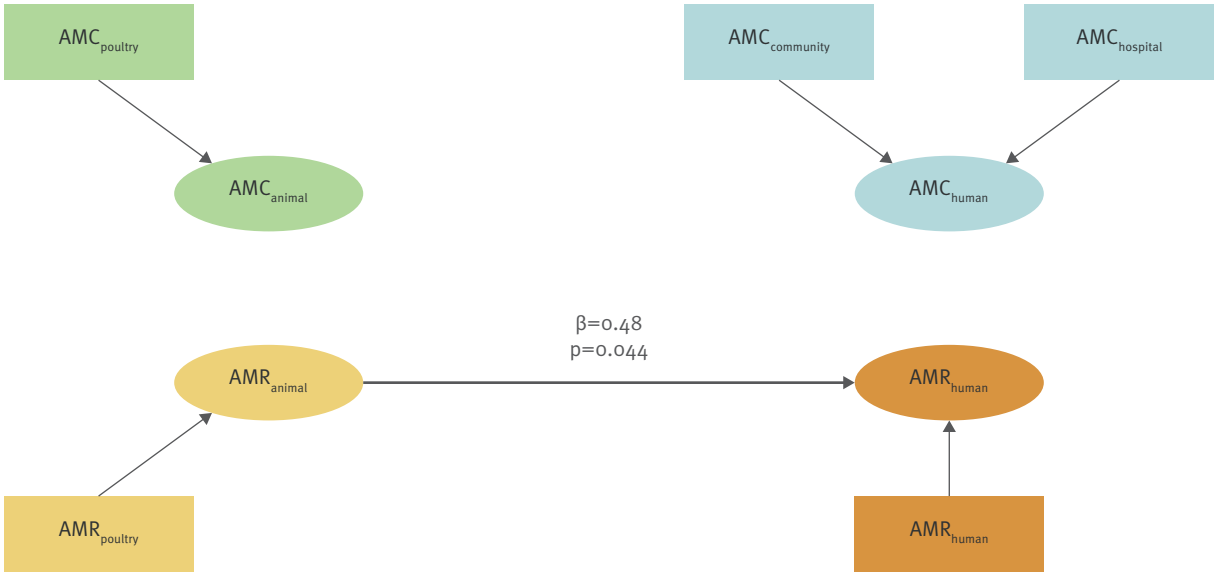
Resistance to macrolides in *C. jejuni* from poultry was significantly related to the resistance rate in humans, but less than a quarter of the variance was explained ($R^2 = 0.23$, 95% confidence interval 0.01–0.68) (Figure 49).

Table 57: Association between consumption of macrolides in food-producing animals (expressed in mg per kg of estimated biomass/year) and probability of resistance to macrolides in *Campylobacter jejuni* causing infections in humans (logistic regression, see also Figure A1.2. 11).

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, CY, DK, EE, ES, FI, FR, IS, IT, LT, LU, NL, NO, PT, RO, SI, SK, UK (n=18)	3	1.00	0.442	1.00–1.00
2017	AT, CY, DK, EE, ES, FI, FR, IE, IS, IT, LT, LU, MT, NL, NO, PL, PT, SI, SK, UK (n=20)	3	1.00	0.311	1.00–1.01
2018	AT, CY, DK, EE, ES, FI, FR, IE, IS, IT, LT, LU, NL, PL, PT, RO, SI, SK, UK (n=19)	3	1.00	0.063	1.00–1.00

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 49: Diagram of the PLS-PM of resistance to macrolides in *Campylobacter jejuni* from humans (2017 and 2018), considering resistance to macrolides in *C. jejuni* from food-producing animals (poultry 2018), consumption of macrolides in humans (2017–2018 mean, expressed as DDD per 1 000 inhabitants and per day) and consumption of macrolides in poultry (in 2018, expressed as DDDvet/kg of estimated biomass)



18 countries: AT*, CY, DK, ES, FI, FR, IE, IS, IT, LT, NL, NO, PL, PT, RO, SI, SK, UK.

* For this country, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

12. Tetracyclines

Tetracyclines have a broad spectrum of activity, including both aerobic and anaerobic gram-positive and gram-negative bacteria. They are therefore used to treat a wide range of bacterial infections, especially in general practice. Tetracyclines are primary agents for infections in humans caused by *Brucella* spp., *Rickettsia* spp., *Coxiella burnetti*, *Borrelia* spp., *Treponema pallidum*, *Chlamydia* spp., *Mycoplasma pneumoniae*, *Plasmodium* spp., *Entamoeba histolytica* and *Mycoplasma marinum*.

Tetracyclines are approved for use in food-producing and companion animals for a wide range of indications including respiratory infections, mastitis and joint-ill. Formulations exist for use in group and individual animals, for systemic and local treatments.

In the recent WHO AWaRe classification, the tetracyclines were assigned to different categories. While some are in the 'Access' category (e.g. doxycycline, tetracycline) others are on the 'Watch' list (e.g. chlortetracycline, oxytetracycline). However, some tetracyclines are also categorised as 'Reserve' (e.g. eravacycline, minocycline, omadacycline) [32]. The latter are not authorised for use in animals.

Tetracyclines are considered by WHO as Highly Important Antimicrobials (HIA) in human medicine [14].

This class has also been categorised as Veterinary Critically Important Antimicrobial Agents (VCIA) in the OIE list of antimicrobials of veterinary importance [34].

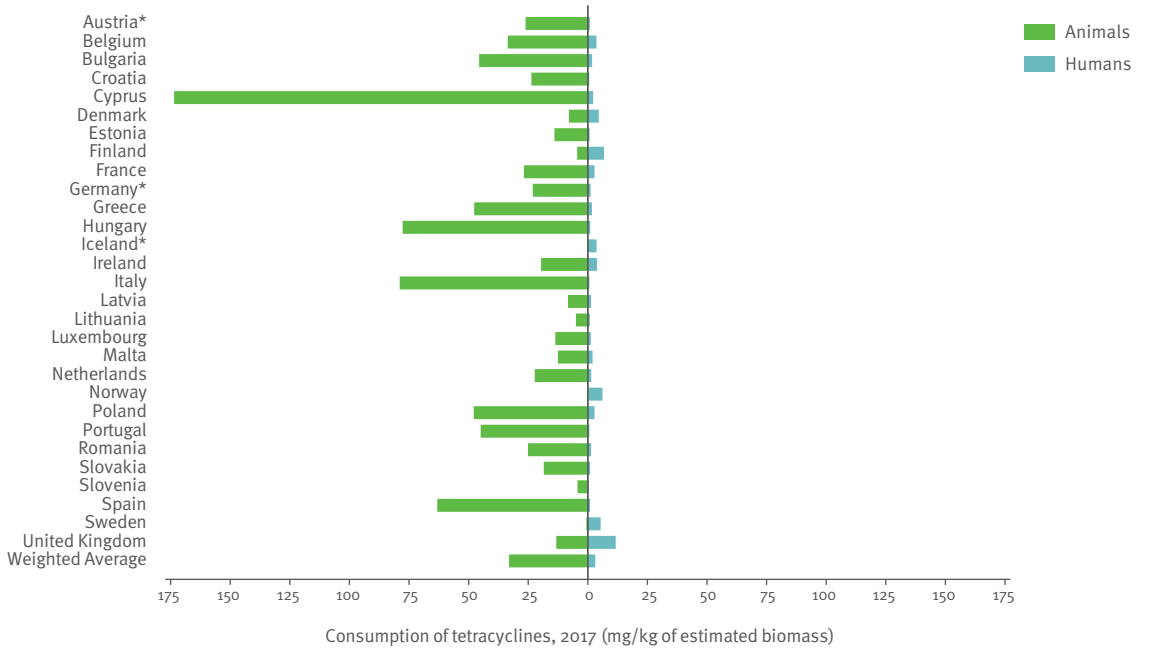
According to the AMEG categorisation, tetracyclines belong to Category D ('Prudence') with the indication that they should be used prudently in veterinary medicine in the EU [13]. Responsible use principles should be adhered to in everyday practice to keep the risk from use of these classes as low as possible.

12.1 Consumption in humans and food-producing animals by country

The population-weighted mean consumption of tetracyclines in humans and food-producing animals was 3.1 and 33.0 mg per kg of estimated biomass, respectively. The corresponding ranges were 0.2–11.7 (median 1.4) and 0.1–173.5 (median 22.3) mg per kg, respectively. Population-corrected consumption of tetracyclines in humans and food-producing animals by country is shown in Figure 50.

In 25 countries, the amounts of tetracyclines consumed in food-producing animals were far greater than in humans in 2017. In four countries, the consumption in

Figure 50: Population-corrected consumption of tetracyclines for humans and food-producing animals in 29 EU/EEA countries for which data were available both for humans and food-producing animals, 2017



An asterisk (*) denotes that only community consumption data was provided for human medicine. The population-weighted mean proportion (%) of the hospital sector from the 2017 total national consumption of tetracyclines for EU/EEA countries providing data for both sectors is 1.6%.

Notes: 1) The estimates presented are crude and must be interpreted with caution. For limitations hampering comparison of antimicrobial consumption in humans and food-producing animals, please see Section 14. 2) The weighted mean figure represents the population-weighted mean of data from those countries included.

food-producing animals was lower than in humans. The variation between countries in the quantities of tetracyclines consumed in food-producing animals was very wide. There was no significant association within country between consumption of tetracyclines in humans and food-producing animals (Spearman's rank correlation, rho = -0.32).

12.2 Consumption in humans and resistance in bacterial isolates from humans

Tetracyclines are generally not used for treatment of *E. coli* infections in humans, and resistance to tetracyclines in invasive *E. coli* isolates from humans is not under surveillance.

Salmonella

No evidence of a statistically significant association was found between total (community and hospital) consumption of tetracyclines and the occurrence of tetracycline resistance of *Salmonella* spp. isolates from humans for 2016–2018 (Table 58).

A statistically significant positive association was found between the consumption of tetracyclines and the occurrence of tetracycline resistance in *S.* Enteritidis for 2017, while no such association was found for *S.* Enteritidis in the other years or for *S.* Typhimurium (including monophasic variant) during the period 2016–2018 (Table 59, Figure 51, Table 60). When outliers in terms of resistance were removed, the association also became significant for *S.* Enteritidis for 2016, but no other associations changed in terms of significance.

Campylobacter jejuni

No evidence of a statistically significant association was found between the consumption of tetracyclines in humans and the occurrence of tetracycline resistance in *C. jejuni* isolates from humans for 2016–2018 (Table 61).

Table 58: Association between consumption of tetracyclines in humans, expressed as DDD per 1 000 inhabitants per day, and probability of resistance to tetracyclines in *Salmonella* from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PT, RO, SI, SK, UK (n=22)	2	0.93	0.695	0.66–1.32
2017	AT, BE, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PL, PT, RO, SI, SK, UK (n=22)	2	1.11	0.527	0.80–1.56
2018	AT, BE, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, NL, PL, PT, RO, SI, SK, UK (n=20)	2	1.08	0.618	0.80–1.45

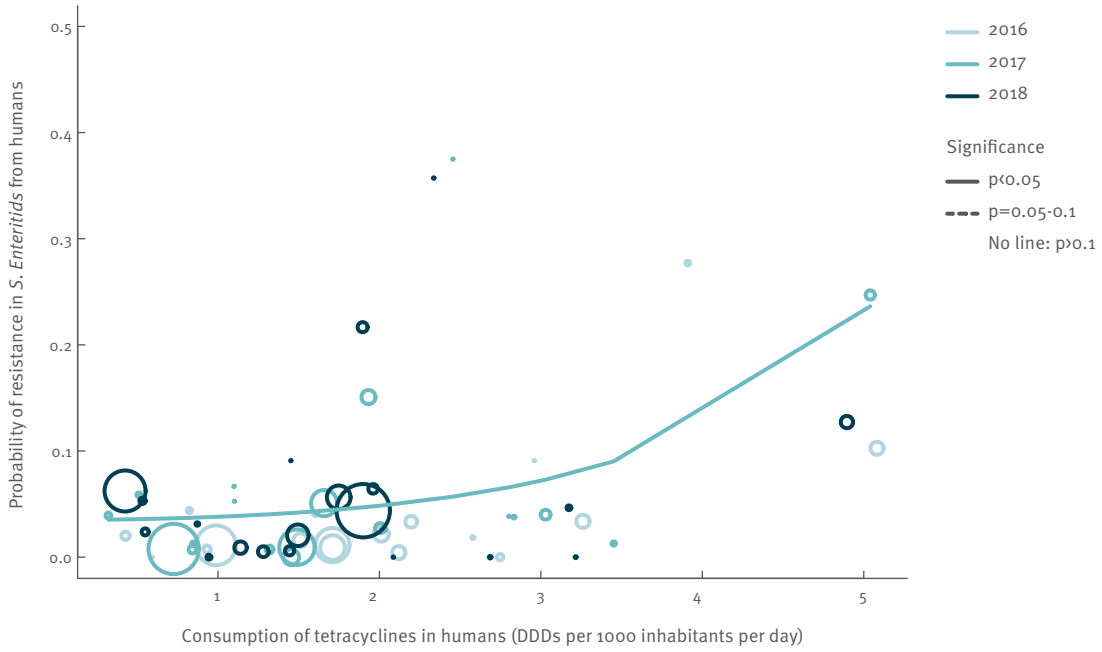
CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 59: Association between consumption of tetracyclines in humans, expressed as DDD per 1 000 inhabitants per day, and probability of resistance to tetracyclines in *Salmonella* Enteritidis from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 51)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, DE, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PT, RO, SI, SK, UK (n=20)	3	1.03	0.703	0.88–1.21
2017	AT, BE, DE, EE, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PL, PT, RO, SI, SK, UK (n=20)	3	1.09	0.021	1.01–1.17
2018	AT, BE, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, NL, PL, PT, RO, SI, SK, UK (n=20)	3	1.05	0.351	0.95–1.15

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 51: Consumption of tetracyclines in humans and probability of resistance to tetracyclines in *Salmonella* Enteritidis from humans, EU/EEA, 2016–2018 (see also Table 59).



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Table 60: Association between consumption of tetracyclines in humans, expressed as DDD per 1 000 inhabitants per day, and probability of resistance to tetracyclines in *Salmonella* Typhimurium including monophasic variant from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PT, RO, SI, SK, UK (n=21)	3	0.99	0.646	0.92–1.05
2017	AT, BE, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PT, RO, SI, SK, UK (n=21)	3	0.97	0.316	0.92–1.03
2018	AT, BE, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, NL, PT, RO, SI, SK, UK (n=19)	3	0.97	0.272	0.92–1.02

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 61: Association between consumption of tetracyclines in humans, expressed as DDD per 1 000 inhabitants per day, and probability of resistance to tetracyclines in *Campylobacter jejuni* isolates from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, CY, DK, EE, ES, FI, FR, IT, LT, LU, NL, NO, PT, RO, SI, SK, UK (n=17)	3	0.99	0.685	0.93–1.05
2017	AT, CY, DK, EE, ES, FI, FR, IE, IT, LT, LU, MT, NL, NO, PT, SI, SK, UK (n=18)	3	0.98	0.409	0.92–1.04
2018	AT, CY, DK, EE, ES, FI, FR, IE, IT, LT, LU, NL, PL, PT, RO, SI, SK, UK (n=18)	3	0.98	0.400	0.94–1.03

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

12.3 Consumption in food-producing animals and resistance in bacterial isolates from food-producing animals

Escherichia coli isolates from food-producing animals

To investigate possible relationships between the consumption of tetracyclines and tetracycline resistance, the SIMR to tetracyclines in indicator *E. coli*, was compared with the consumption of tetracyclines in food-producing animals (expressed in mg per kg of estimated biomass) for the two-year intervals 2014–2015, 2015–2016, 2016–2017 and 2017–2018 (mean consumption over the respective years) at national level (Table 62). The category 'food-producing animals' includes broilers, turkeys, pigs and calves.

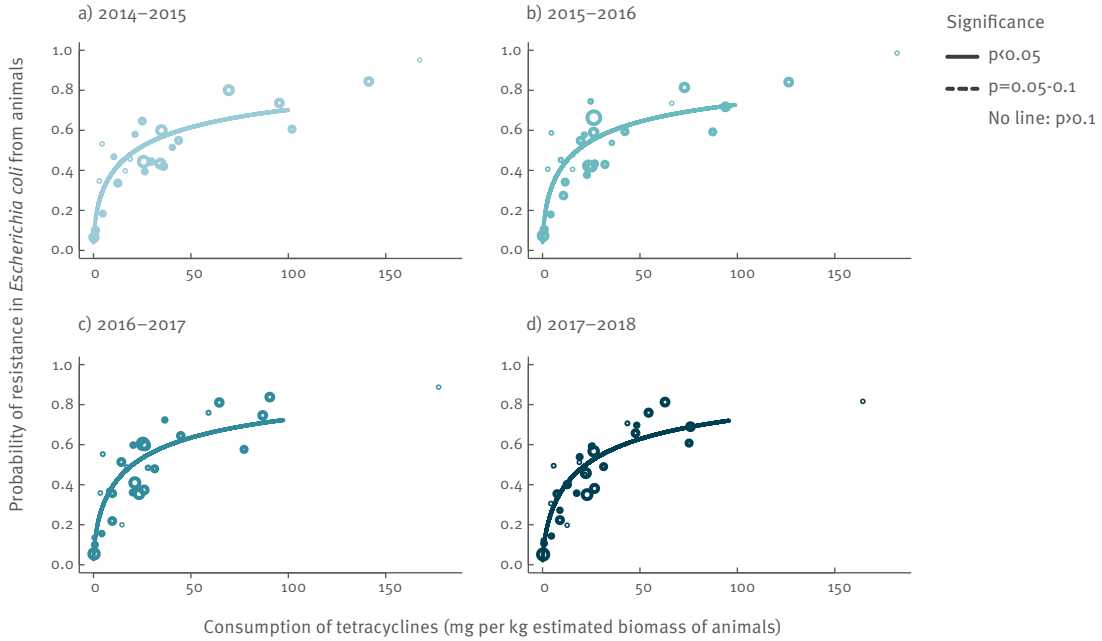
Marked variations in tetracycline resistance in indicator *E. coli*, *Salmonella* spp., *C. jejuni* and *C. coli* were observed between the countries included in the analysis. The consumption of tetracyclines ranged between a few mg per kg estimated biomass to 150 mg per kg of estimated biomass. Statistically significant positive associations between tetracycline resistance in indicator *E. coli* and tetracycline consumption in food-producing animals were observed in all the two-year intervals considered.

Table 62: Association between consumption of tetracyclines by food-producing animals (expressed in mg per kg of estimated biomass/year) and probability of resistance to tetracyclines in indicator *Escherichia coli* from food-producing animals (logistic regression, see also Figure 52)

Year	Countries	Model	Odds ratio	p-value	95% CI
2014-2015	AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=26)	2	1.48	<0.001	1.31–1.67
2015-2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=28)	2	1.49	<0.001	1.31–1.69
2016-2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.52	<0.001	1.35–1.72
2017-2018	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, MT, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.57	<0.001	1.41–1.75

CI: confidence interval. Odds ratio varies from 0 to infinity. When odds ratio equals 1 or CI includes 1, the association is not considered statistically significant. The category 'food-producing animals' includes broilers, turkeys, pigs and calves.

Figure 52: Consumption of tetracyclines in food-producing animals, expressed in mg per kg of estimated biomass/year, and probability of resistance to tetracyclines in indicator *Escherichia coli* for (a) 2014–2015, (b) 2015–2016, (c) 2016–2017 and (d) 2017–2018 (see also Table 59)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country. Category 'food-producing animals' includes broilers, turkeys, pigs and calves for all three time considered intervals.

Escherichia coli, *Salmonella* and *Campylobacter jejuni* in pigs and poultry

The estimated consumption of tetracyclines in poultry and pigs (expressed as DDDvet/kg of estimated biomass) was compared with the occurrence of resistance to tetracyclines in indicator *E. coli* from slaughter pigs in 2017 (31 countries) and from poultry in 2016 (29 countries) and 2018 (27 countries). It was also compared to the resistance of *C. jejuni* from poultry in 2016 (27 countries) and 2018 (25 countries), and *Salmonella* spp. from pigs in 2017 (six countries), and poultry in 2016 (19 countries) and 2018 (18 countries) (Table 63, Figure 53, Figure 54).

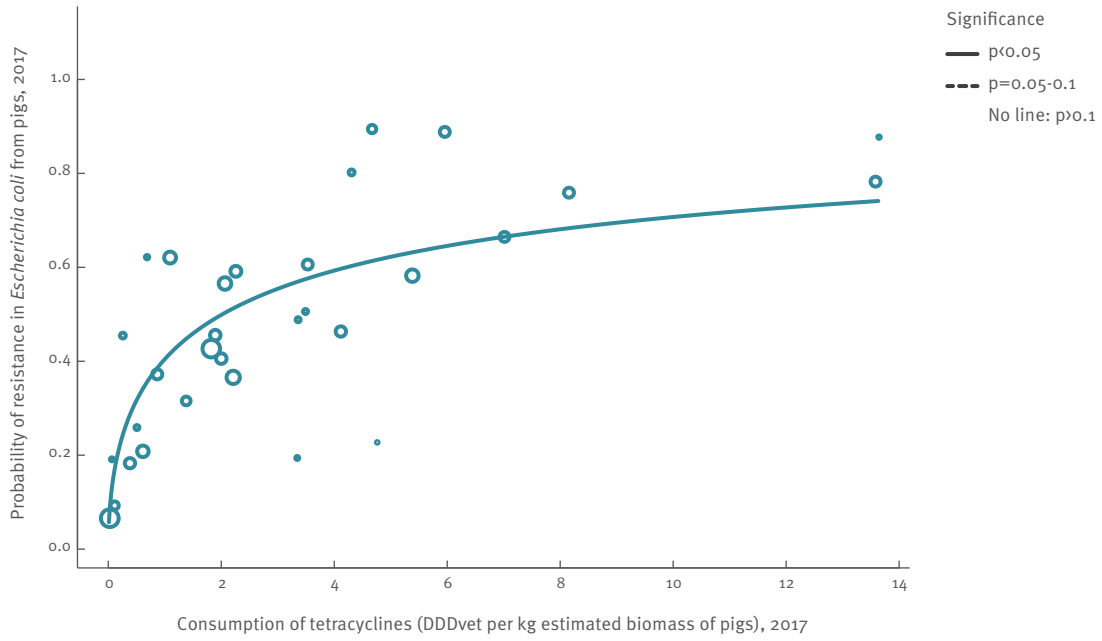
There was a significant positive association of the estimated consumption of tetracyclines in poultry and resistance to *E. coli* and *C. jejuni* from poultry in 2016 and 2018 (Figure 54). A significant positive association was also found for consumption of tetracyclines in pigs and resistance of *E. coli* from pigs in 2017 (Figure 53). No significant association was found between tetracycline

Table 63: Association between consumption of tetracyclines in pigs and poultry, expressed as DDDvet/kg of estimated biomass/year, and probability of resistance to tetracyclines in bacteria from slaughter pigs and poultry (logistic regression, see also Figure 53)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Indicator *Escherichia coli*						
Poultry	2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	1.34	‹0.001	1.19–1.50
Poultry	2018	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, MT, PL, PT, RO, SE, SI, SK, UK (n=30)	2	1.30	‹0.001	1.18–1.45
Pigs	2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=31)	2	1.47	‹0.001	1.27–1.69
Salmonella						
Poultry	2016	AT, BE, CY, CZ, DE, DK, EL, ES, FR, HR, HU, IE, IT, PL, PT, RO, SI, SK, UK (n=19)	3	1.06	0.185	0.97–1.17
Poultry	2018	AT, BE, CY, CZ, DE, DK, EL, ES, FR, HR, HU, IE, IT, MT, PL, PT, RO, SI, SK, UK (n=20)	3	1.06	0.039	1.00*–1.10
Pigs**	2017	BE, CZ, DE, DK, ES, FR, HR, HU, IE, IT, MT, PL, PT, SK (n=14)	3	1.00	0.768	0.99–1.01
Campylobacter jejuni						
Poultry	2016	AT, BE, BG, CH, CY, CZ, DE, DK, EL, ES, FI, HR, HU, IE, IS, IT, LT, LU, LV, NO, PL, PT, RO, SE, SI, SK, UK (n=27)	2	1.24	‹0.001	1.11–1.38
Poultry	2018	AT, BG, CH, CY, CZ, DE, DK, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=27)	2	1.31	‹0.001	1.16–1.48

CI: confidence interval. Odds ratio varies from 0 to infinity. When odds ratio equals 1 or CI includes 1, the association is not considered statistically significant.
* exact value 1.003
** *Salmonella* spp. isolates derive from pig carcasses.

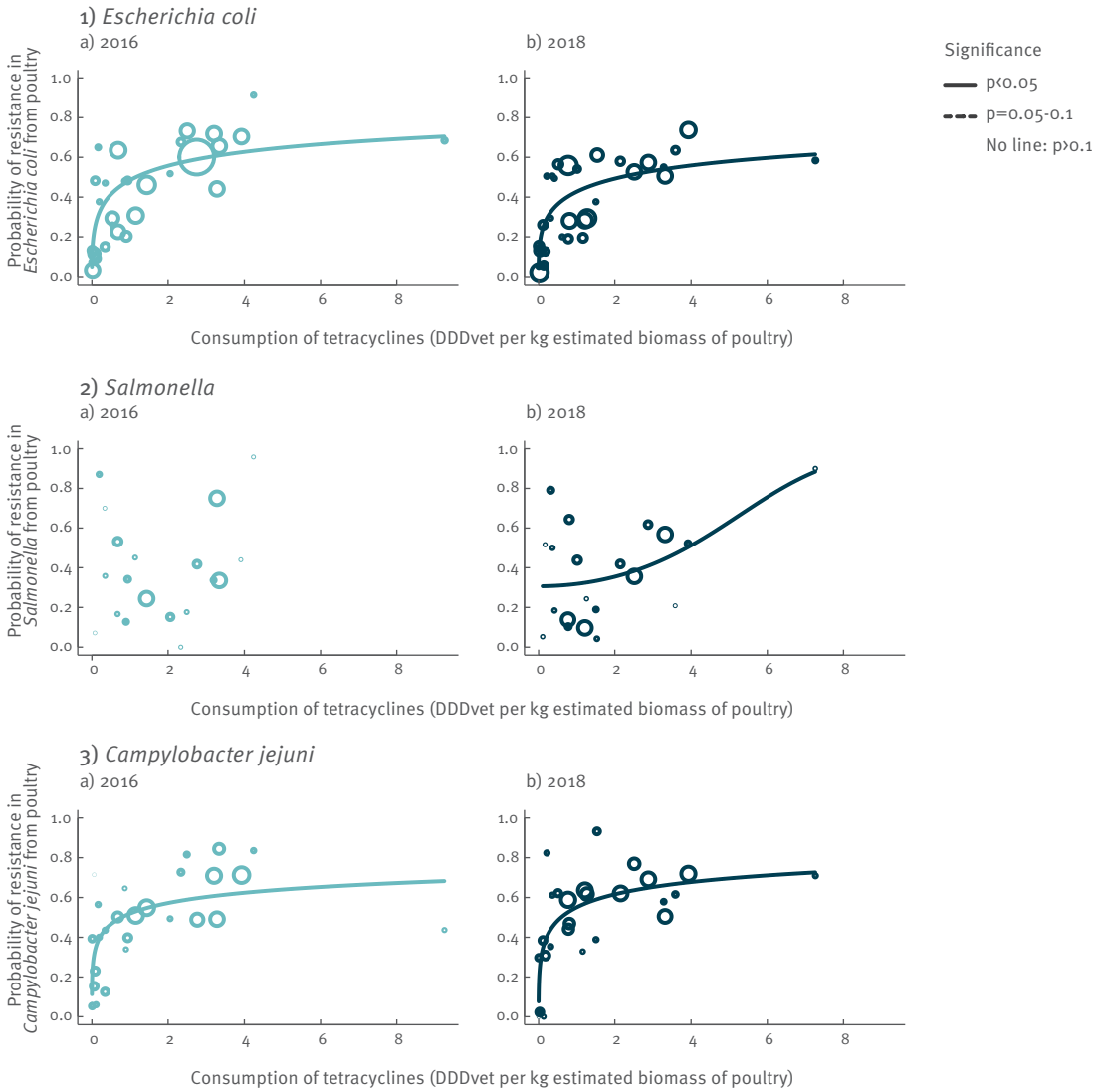
Figure 53: Consumption of tetracyclines in pigs expressed as DDDvet/kg of estimated biomass/year and probability of resistance to tetracyclines in indicator *Escherichia coli* from slaughter pigs for 2017 (see also Table 63)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

consumption in pigs and poultry and antimicrobial resistance in *Salmonella* spp. in pigs for 2017 and poultry for 2016. Although in 2018 the positive association of use in poultry with resistance to tetracycline in poultry was significant (Table 53), it is noteworthy that the significance of the effect of consumption disappears when the outlier is excluded in both directions (characterised by an outlying consumption and an outlying proportion of resistance). Given the 2018 data, without the outlier data, the cloud is very scattered and has no clear pattern at all, as with the 2016 cloud.

Figure 54: Consumption of tetracyclines in poultry, expressed as DDDvet/kg of estimated biomass/year, and probability of resistance to tetracyclines in (1) indicator *Escherichia coli*, (2) *Salmonella* and (3) *Campylobacter jejuni* from poultry in 2016 and 2018 (see also Table 63)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

12.4 Resistance in bacterial isolates from humans and from food-producing animals

Resistance to tetracyclines of *Salmonella* spp. and *Campylobacter* spp. has been detected both in humans and food-producing animals, but it varies markedly among EU/EEA Member States. Resistance of invasive *E. coli* from humans is not routinely monitored and therefore not included in the analysis.

Salmonella

Data on the occurrence of tetracycline resistance of *Salmonella* spp. from humans (2016–2018) were compared with the occurrence of tetracycline resistance of *Salmonella* spp. from broilers and turkeys (2016, 2018) as well as from pigs (2017). No evidence of a statistically significant association was found for all tested combinations (Table 64). When outliers for resistance in bacteria from humans were removed, the association became significant for turkeys in 2016 but the number of countries included was low (N = 5).

With regard to the data on the occurrence of tetracycline resistance in *S.* Typhimurium, including monophasic variant, from humans and food-producing animals, only the data from pigs were sufficient for analysis and only for 2017. No evidence of a statistically significant association was found for the combination tested (Table 65).

Data on tetracycline resistance in *S.* Enteritidis from pigs and poultry were too scarce for a meaningful analysis.

Campylobacter jejuni from humans and food-producing animals

A statistically significant positive association was found between tetracycline resistance in *C. jejuni* from turkeys and broilers and tetracycline resistance of *C. jejuni* from humans for 2016 and 2018 (Table 66, Figure 55).

Table 64: Association between resistance to tetracyclines in *Salmonella* from food-producing animals and from humans, 2016–2018 (logistic regression)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Broilers	2016	AT, BE, CY, DE, DK, EL, ES, FR, HU, IE, IT, PT, RO, SI, SK, UK (n=16)	3	1.29	0.713	0.33–5.01
Broilers	2018	AT, BE, DE, DK, ES, FR, HU, IE, IT, PL, PT, RO, SI, SK, UK (n=15)	3	0.50	0.349	0.12–2.12
Turkeys	2016	AT, DE, ES, FR, HU, UK (n=6)	2	2.29	0.160	0.72–7.30
Turkeys	2018	AT, ES, FR, HU, IE, IT, PL, UK (n=8)	2	1.38	0.126	0.91–2.07
Pigs	2017	BE, DE, DK, ES, FR, HU, IE, IT, PL, PT, SK (n=11)	2	1.14	0.639	0.65–2.00

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 65: Association between resistance to tetracycline in *Salmonella* Typhimurium, including monophasic variant, from pigs and from humans, 2017 (logistic regression)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Pigs	2017	BE, DE, DK, ES, FR, IE, IT (n=7)	2	1.95	0.407	0.40–9.36

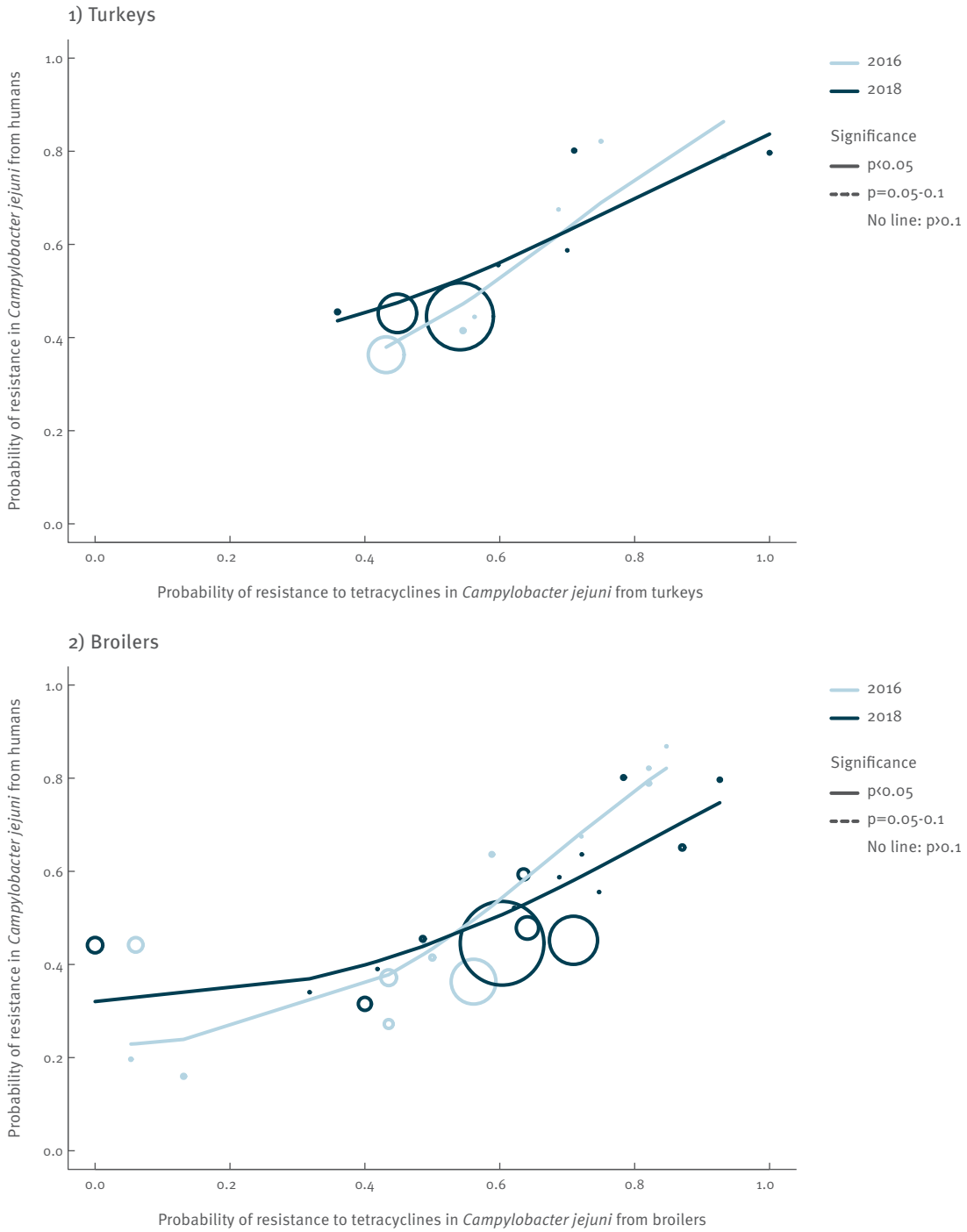
CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 66: Association between resistance to tetracyclines in *Campylobacter jejuni* from food-producing animals and humans (logistic regression, see also (Figure 55)

Food-producing animal	Year	Countries	Model	Odds ratio	p-value	95% CI
Turkeys	2016	AT, ES, IT, PT, RO, UK (n=6)	3	30.82	<0.001	5.28–180.03
Turkeys	2018	AT, ES, FR, IT, PL, PT, UK (n=7)	3	8.79	0.001	2.56–30.19
Broilers	2016	AT, CY, DK. ES, FI, IT, LT, NO, PT, RO, SI, SK, UK (n=13)	3	46.12	<0.001	14.04–151.44
Broilers	2018	AT, CY, DK, ES, FI, FR, IE, IS, IT, LT, NL, PL, RO, SI, SK, UK (n=16)	3	8.50	<0.001	3.84–18.84

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 55: Probability of tetracycline resistance in *Campylobacter jejuni* from food-producing animals and humans, 2016 and 2018 (see also Table 66)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

12.5 Consumption in food-producing animals and resistance in bacterial isolates from humans

Salmonella

Statistically significant associations were observed between the total tetracycline consumption in food-producing animals and tetracycline resistance in *Salmonella* from humans for all three years 2016–2018 (Table 67, Figure 56). When outliers in terms of resistance were removed, the association for 2016 became borderline significant, but the results remained the same for the other two years.

No statistically significant associations were reported between the total tetracycline consumption in food-producing animals and tetracycline resistance in *Salmonella* Enteritidis from humans for any of the years 2016–2018 (Table 68).

Statistically significant associations were observed between the total tetracycline consumption in food-producing animals and tetracycline resistance in *S.* Typhimurium from humans for 2016 and 2018 (Table 69).

Campylobacter jejuni

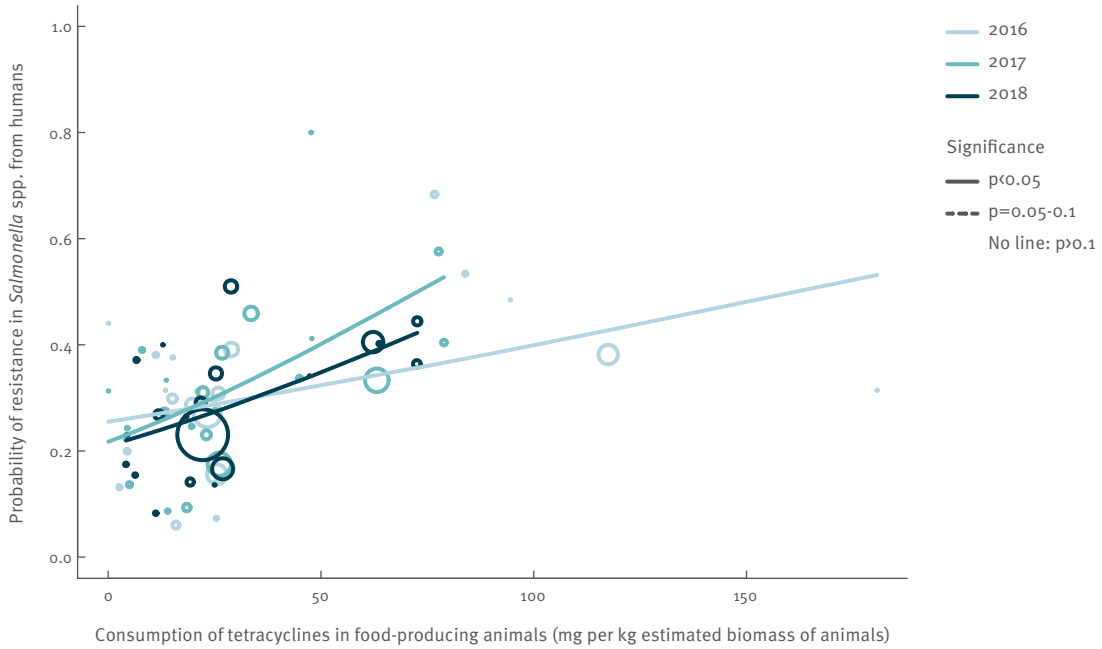
A statistically significant association was found between the total tetracycline consumption in food-producing animals and tetracycline resistance in *Campylobacter jejuni* from humans for all the years 2016–2018 (Table 70, Figure 58).

Table 67: Association between consumption of tetracyclines in food-producing animals, expressed in mg/kg biomass, and probability of resistance to tetracyclines in *Salmonella* isolated from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 56)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, CY, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PT, RO, SI, SK, UK (n=22)	1	1.01	0.039	1.00–1.01
2017	AT, BE, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PL, PT, RO, SI, SK, UK (n=22)	1	1.02	0.002	1.01–1.03
2018	AT, BE, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, NL, PL, PT, RO, SI, SK, UK (n=20)	1	1.01	0.005	1.00–1.02

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 56: Consumption of tetracyclines in food-producing animals, expressed in mg/kg biomass, and probability of resistance to tetracyclines in *Salmonella* isolated from humans, EU/EEA, 2016–2018 (see also Table 67)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Table 68: Association between consumption of tetracyclines in food-producing animals, expressed in mg/kg biomass, and probability of resistance to tetracyclines in *Salmonella* Enteritidis isolated from humans, EU/EEA, 2016–2018 (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, DE, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PT, RO, SK, SI, UK (n=20)	3	1.00	0.548	1.00–1.00
2017	AT, BE, DE, EE, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PL, PT, RO, SK, SI, UK (n=20)	3	1.00	0.722	1.00–1.00
2018	AT, BE, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, NL, PL, PT, RO, SK, SI, UK (n=20)	3	1.00	0.883	1.00–1.00

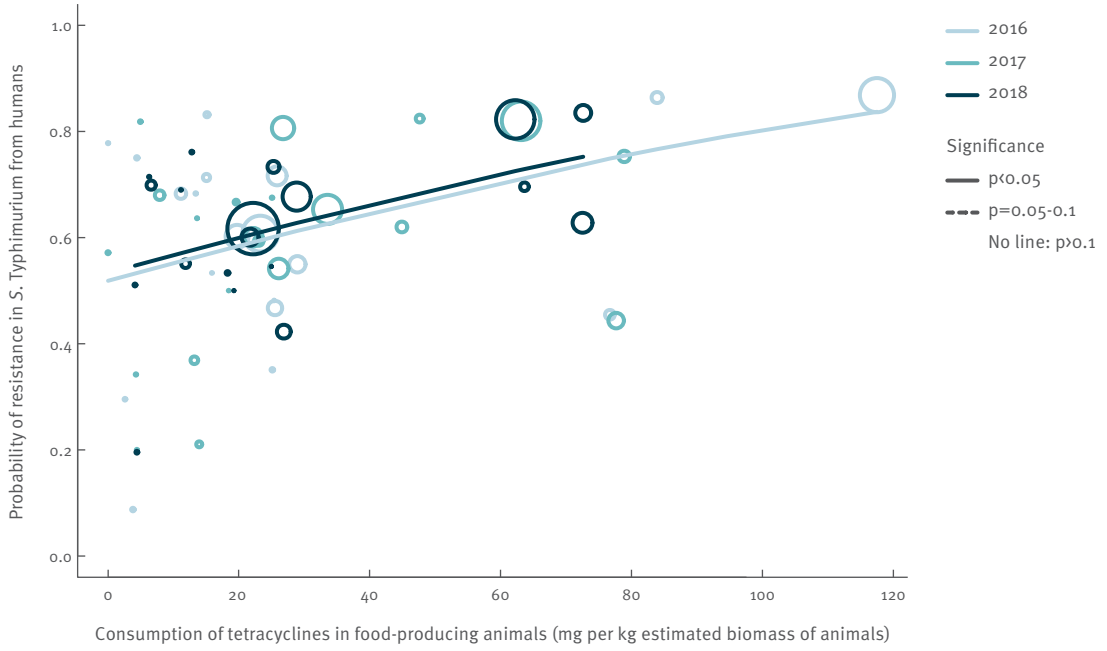
CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Table 69: Association between consumption of tetracyclines in food-producing animals, expressed in mg/kg biomass, and probability of resistance to tetracyclines in *Salmonella* Typhimurium, including its monophasic variant isolated from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 57)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, BE, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PT, RO, SI, SK, UK (n=21)	1	1.01	0.043	1.00–1.03
2017	AT, BE, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, NL, NO, PT, RO, SI, SK, UK (n=21)	1	1.01	0.107	1.00–1.03
2018	AT, BE, DE, DK, EE, ES, FI, FR, HU, IE, IT, LT, LU, NL, PT, RO, SI, SK, UK (n=19)	1	1.01	0.028	1.00–1.03

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 57: Consumption of tetracyclines in food-producing animals, expressed in mg/kg biomass, and probability of resistance to tetracyclines in *Salmonella* Typhimurium isolated from humans, EU/EEA, 2016–2018 (see also Table 69)



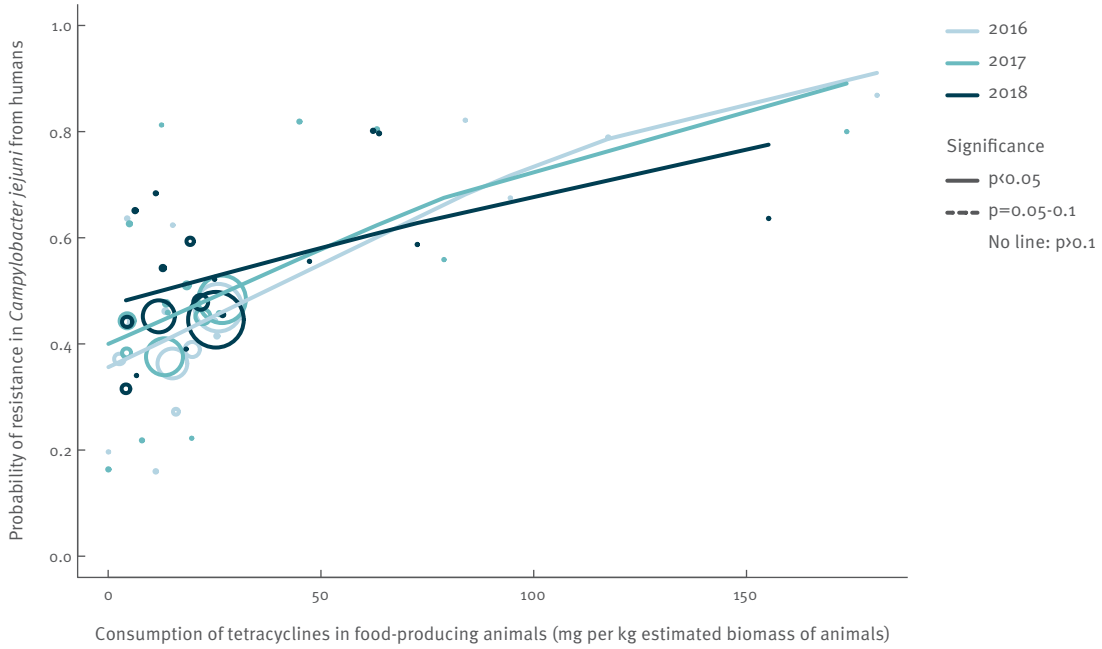
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Table 70: Association between consumption of tetracyclines in food-producing animals, expressed in mg/kg biomass, and probability of resistance to tetracyclines in *Campylobacter jejuni* isolated from humans, EU/EEA, 2016–2018 (logistic regression, see also Figure 58)

Year	Countries	Model	Odds ratio	p-value	95% CI
2016	AT, CY, DK, EE, FI, FR, IT, LT, LU, NL, NO, PT, RO, SK, SI, ES, UK (n=17)	1	1.02	<0.001	1.01–1.02
2017	AT, CY, DK, EE, FI, FR, IE, IT, LT, LU, MT, NL, NO, PT, SK, SI, ES, UK (n=18)	1	1.01	0.013	1.00–1.03
2018	AT, CY, DK, EE, ES, FI, FR, IE, IT, LT, LU, NL, PL, PT, RO, SK, SI, UK (n=18)	1	1.01	0.028	1.00–1.02

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure 58: Consumption of tetracyclines in food-producing animals, expressed in mg/kg biomass, and probability of resistance to tetracyclines in *Campylobacter jejuni* isolated from humans, EU/EEA, 2016–2018 (see also Table 70)



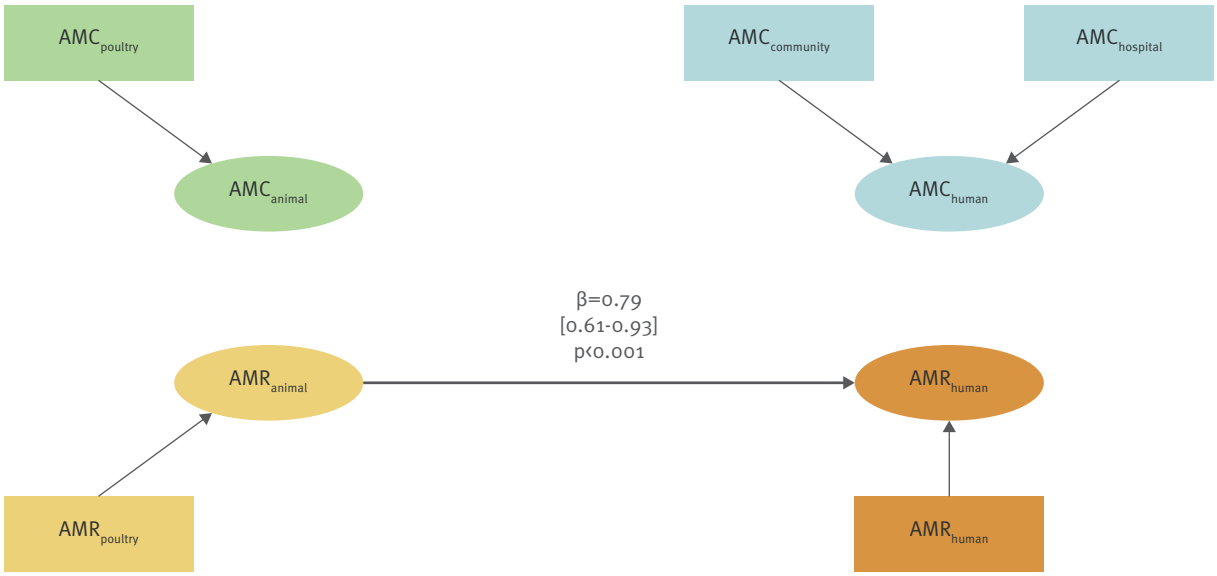
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

12.6 Multivariate analysis

For *Salmonella* spp. multivariate analysis only involved 11 countries for which all data were available. No significant relationship could be assessed.

For *Campylobacter jejuni*, from data available in 17 countries, the direct effect of resistance in poultry on resistance in human isolates was estimated to be 0.789. Sixty-two percent of the variance of *C. jejuni* resistance rate in humans could be explained by the model (95% confidence interval 38–87) (Figure 59). No significant association was observed between tetracycline use in poultry and resistance of *C. jejuni* in poultry, or between tetracycline consumption in humans and resistance of *C. jejuni* in humans.

Figure 59: Diagram of the PLS-PM of resistance to tetracyclines in *Campylobacter jejuni* from humans (2017 and 2018), considering resistance to tetracyclines in *C. jejuni* from food-producing animals (poultry 2018), consumption of tetracyclines in humans (2017-2018 mean, expressed as DDD per 1 000 inhabitants per day) and consumption of tetracyclines in poultry (in 2018, expressed as DDDvet/kg of estimated biomass)



17 countries: AT*, CY, DK, ES, FI, FR, IE, IT, LT, NL, NO, PL, PT, RO, SI, SK, UK

* For this country, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

13. Primary key indicators of antimicrobial consumption and resistance

13.1 Trends in key indicators

Primary key indicators of AMC and AMR have been suggested by ECDC, EFSA and EMA [12]. Table 71 displays the level of the five proposed primary key indicators and their changes over time (2014–2018). The purpose of this joint description is mainly to provide an in-country comparison of the values over the years, in order to identify policy needs and challenges. More detailed information on the data used for the indicators, along with statistical trend analyses for individual countries, can be found in the enhanced surveillance reports published by the respective agencies [4, 5, 9, 27].

The EU/EEA population-weighted mean of the total AMC in humans in 30 EU/EEA countries showed a statistically significant decreasing trend, when expressed as DDD from 21.1 per 1 000 inhabitants per day in 2014 (country range: 10.26–31.04) to 20.1 in 2018 (country range: 9.78–34.05).

The EU/EEA population biomass-corrected AMC in food-producing animals decreased from 155.9 mg/PCU (country range 3.1 mg/PCU – 418.8 mg/PCU) in 2014 to 105.6 mg/PCU (country range 2.9 mg/PCU – 466.3 mg/PCU) in 2018. For the 27 countries included in the comparison in Chapter 5, the overall change was significant. However, despite the decreasing trend observed at European level, an increase in antimicrobial consumption was still observed in some European countries for both food-producing animals and humans.

The EU/EEA population-weighted mean percentage for MRSA decreased significantly from 19.6% (country range 1.0%–56.0%) in 2014 to 16.4% (country range <0.1%–43.0%) in 2018. At national level, similar decreases in the percentage of MRSA were noted for most countries. The EU/EEA population-weighted mean percentage for *E. coli* resistant to third-generation cephalosporins increased significantly, from 14.2% (country range 13.3%–40.4%) in 2014 to 15.1% (country range 6.8%–38.7.%) in 2018. At national level, more than half of the countries reported an increase in the percentage of *E. coli* resistant to third-generation cephalosporins (Table 71).

Marked variations in the levels of complete susceptibility in *E. coli* from food-producing animals were observed among the countries included in the analyses (Figure 60, a–d). Complete susceptibility in *E. coli* from food-producing animals ranged between 94.7% in one country to very low levels >5% in a number of others. In most (19) countries the proportion of completely susceptible *E. coli* tended to increase (>1 percentage unit), while only three countries saw a decrease of more than 1 percentage unit (Table 71).

13.2. Antimicrobial consumption and proportion of complete susceptibility in *Escherichia coli* from food-producing animals

Complete susceptibility (CS), in the context of this report and the analysis which was performed, refers to susceptibility to each of the substances in the standard panel of antimicrobials tested. The analysis was possible for indicator *E. coli* from food-producing animals, but not for *E. coli* from humans, where no standard susceptibility panel is agreed.

In order to investigate the possible relationship between overall AMC and complete susceptibility in commensal bacteria in food-producing animals, the occurrence of complete susceptibility to the common set of antimicrobials tested for commensal indicator *E. coli* isolates from food-producing animals was compared with the total AMC in food-producing animals (expressed in mg per kg of estimated biomass) for 2014–2015, 2015–2016, 2016–2017 and 2017–2018 at national level. As the mandatory monitoring of AMR foresees testing of the animal populations on a biannual basis, two consecutive years were considered together in all analyses. The category 'food-producing animals' included broilers, turkeys, pigs and calves at slaughter for all periods. Both data on complete susceptibility and overall AMC were available together for 26, 28, 29 and 28 countries, respectively.

There were marked variations in the levels of complete susceptibility and the overall AMC among the countries (Figure 60, a–d). Complete susceptibility ranged between 80% in some countries and very low levels, or zero. Total AMC varied from a few mg per kg of estimated biomass to 300 or 400 mg per kg of estimated biomass in the four time intervals, respectively.

For all intervals, significant negative associations of the same magnitude were observed between the probability of complete susceptibility and the overall consumption of antimicrobials in food-producing animals (Table 72).

Table 71: Primary key indicators of antimicrobial consumption and resistance, EU/EEA countries, 2014 to 2018*

		Indicator	2014	2015	2016	2017	2018
Austria	AMC	AMC Humans**	12.1	12.1	11.4	11.9	10.4
		AMC Animals***	56.3	50.7	46.1	46.8	50.1
	AMR	% 3GCR EC Humans	9.7	9.9	10.4	9.9	10.6
		% MRSA Humans	7.8	7.5	7.1	5.9	6.4
		% Complete S EC Animals*		43.5	45.6	47.7	47.1
Belgium	AMC	AMC Humans**	24.0	24.4	24.2	22.8	22.3
		AMC Animals***	158.3	150.1	140.1	131.3	113.1
	AMR	% 3GCR EC Humans	10.7	10.6	11.5	10.5	9.8
		% MRSA Humans	13.5	12.3	12.2	8.5	9.1
		% Complete S EC Animals*		35.6	34.0	25.5	24.6
Bulgaria	AMC	AMC Humans**	20.0	20.1	19.2	20.5	21.0
		AMC Animals***	82.9	121.9	155.3	132.3	119.6
	AMR	% 3GCR EC Humans	40.4	40.0	43.3	41.7	39.0
		% MRSA Humans	20.8	13.1	14.3	13.7	17.6
		% Complete S EC Animals*		0.0	2.3	9.0	10.4
Croatia	AMC	AMC Humans**	19.4	19.7	18.7	18.6	18.8
		AMC Animals***	108.6	95.6	87.9	71.5	66.8
	AMR	% 3GCR EC Humans	11.3	13.4	15.4	17.1	15.7
		% MRSA Humans	21.3	24.5	25.3	28.5	26.4
		% Complete S EC Animals*		29.4	28.6	31.3	32.8
Cyprus*	AMC	AMC Humans**	22.2	26.6	28.4	28.9	NA
		AMC Animals***	391.5	434.2	453.4	423.1	466.3
	AMR	% 3GCR EC Humans	28.8	28.5	30.2	30.8	37.1
		% MRSA Humans	36.0	43.4	38.8	31.2	40.2
		% Complete S EC Animals*		2.8	0.7	4.9	5.7
Czech R	AMC	AMC Humans**	17.1	17.4	NA	NA	NA
		AMC Animals***	79.5	68.1	61.2	63.6	57.0
	AMR	% 3GCR EC Humans	15.7	16.0	16.2	14.6	15.9
		% MRSA Humans	13.0	13.7	13.9	13.2	13.6
		% Complete S EC Animals*		35.8	36.7	35.4	50.4
Denmark	AMC	AMC Humans**	17.1	17.5	17.0	16.2	15.6
		AMC Animals***	44.2	42.2	40.8	39.4	38.2
	AMR	% 3GCR EC Humans	7.8	8.5	8.1	7.8	8.3
		% MRSA Humans	2.5	1.6	2.0	2.5	1.7
		% Complete S EC Animals*		48.3	47.4	50.1	50.3
Estonia	AMC	AMC Humans**	11.9	12.1	12.0	11.6	11.8
		AMC Animals***	77.1	65.2	64.0	56.7	53.3
	AMR	% 3GCR EC Humans	9.8	12.2	10.1	9.1	11.1
		% MRSA Humans	3.1	4.0	3.5	2.1	3.3
		% Complete S EC Animals*		42.3	43.0	59.3	61.8
Finland	AMC	AMC Humans**	19.1	18.1	17.4	15.7	15.5
		AMC Animals***	22.3	20.4	18.6	19.3	18.7
	AMR	% 3GCR EC Humans	6.3	6.6	7.6	7.7	8.3
		% MRSA Humans	2.6	1.9	2.2	2.0	2.0
		% Complete S EC Animals*		73.7	74.1	78.8	78.4
France	AMC	AMC Humans**	24.9	25.6	25.6	24.7	25.3
		AMC Animals***	107.0	70.2	71.9	68.6	64.2
	AMR	% 3GCR EC Humans	10.9	11.9	12.1	10.8	10.2
		% MRSA Humans	17.4	15.7	13.8	12.9	12.1
		% Complete S EC Animals*		26.5	27.9	26.9	28.8
Germany	AMC	AMC Humans**	13.4	13.1	12.8	12.3	11.9
		AMC Animals***	149.3	97.9	89.2	89.0	88.4
	AMR	% 3GCR EC Humans	11.0	10.6	11.5	12.7	12.6
		% MRSA Humans	12.9	11.3	10.2	9.1	7.6
		% Complete S EC Animals*		34.9	34.4	43.3	42.4
Greece	AMC	AMC Humans**	31.0	33.2	33.1	34.2	34.0
		AMC Animals***	NA	57.2	63.5	93.9	90.9
	AMR	% 3GCR EC Humans	21.3	21.1	19.0	19.4	21.3
		% MRSA Humans	37.1	39.4	38.8	38.4	36.4
		% Complete S EC Animals*		NA	10.1	5.0	4.4
Hungary	AMC	AMC Humans**	15.2	15.8	14.4	14.6	14.8
		AMC Animals***	193.1	211.4	187.1	191.0	180.6
	AMR	% 3GCR EC Humans	16.5	16.8	16.8	20.1	22.7
		% MRSA Humans	23.1	24.7	25.2	23.6	23.1
		% Complete S EC Animals*		22.5	21.6	20.2	19.8
Iceland	AMC	AMC Humans**	17.1	17.6	18.2	18.8	20.4
		AMC Animals***	4.9	4.9	4.7	4.6	4.9
	AMR	% 3GCR EC Humans	3.9	1.7	4.7	7.5	8.6
		% MRSA Humans	3.3	0.0	1.3	1.4	0.0
		% Complete S EC Animals*		NA	NA	76.5	71.9
Ireland	AMC	AMC Humans**	21.0	23.0	22.0	20.9	22.7
		AMC Animals***	47.6	51.0	52.1	46.6	46.0
	AMR	% 3GCR EC Humans	11.7	12.4	12.2	12.9	13.9
		% MRSA Humans	19.4	18.1	14.3	16.3	12.4
		% Complete S EC Animals*		27.7	27.4	25.7	30.3

		Indicator	2014	2015	2016	2017	2018
Italy	AMC	AMC Humans**	24.5	24.5	24.0	20.9	21.4
		AMC Animals***	332.4	322.0	294.8	273.8	244.0
	AMR	% 3GCR EC Humans	29.7	30.8	30.5	30.5	29.7
		% MRSA Humans	33.6	34.1	33.6	33.9	34.0
		% Complete S EC Animals*		12.8	11.3	8.7	12.9
Latvia	AMC	AMC Humans**	12.6	13.1	12.9	13.9	13.3
		AMC Animals***	36.7	37.6	29.9	33.3	36.1
	AMR	% 3GCR EC Humans	10.9	18.9	24.9	22.9	21.3
		% MRSA Humans	8.2	5.6	4.2	5.7	5.7
		% Complete S EC Animals*		34.3	38.8	41.8	41.5
Lithuania	AMC	AMC Humans**	15.1	15.8	15.6	15.7	17.5
		AMC Animals***	35.5	35.1	37.7	34.8	33.1
	AMR	% 3GCR EC Humans	8.9	16.4	15.0	17.5	16.6
		% MRSA Humans	7.8	8.5	11.3	8.8	8.4
		% Complete S EC Animals*		21.3	20.1	27.1	28.1
Luxembourg	AMC	AMC Humans**	23.2	23.5	22.9	22.6	22.2
		AMC Animals***	40.9	34.6	35.5	35.0	33.6
	AMR	% 3GCR EC Humans	13.3	13.0	13.6	10.4	13.7
		% MRSA Humans	12.0	8.9	10.2	9.5	7.7
		% Complete S EC Animals*		NA	NA	NA	48.9
Malta	AMC	AMC Humans**	22.4	21.2	20.9	22.6	20.9
		AMC Animals***	NA	NA	NA	121.0	150.9
	AMR	% 3GCR EC Humans	11.6	12.2	14.9	16.6	16.0
		% MRSA Humans	43.6	49.4	37.1	42.1	36.4
		% Complete S EC Animals*		NA	NA	NA	NA
Netherlands	AMC	AMC Humans**	10.3	10.4	10.1	9.8	9.7
		AMC Animals***	68.4	64.4	52.7	56.3	57.5
	AMR	% 3GCR EC Humans	6.1	6.3	7.0	6.8	8.0
		% MRSA Humans	1.0	1.3	1.2	1.5	1.2
		% Complete S EC Animals*		38.1	40.1	39.2	41.1
Norway	AMC	AMC Humans**	16.9	16.8	16.2	15.7	15.3
		AMC Animals***	3.1	2.9	2.9	3.1	2.9
	AMR	% 3GCR EC Humans	6.2	6.5	6.1	6.4	7.1
		% MRSA Humans	1.0	1.2	1.2	1.0	0.9
		% Complete S EC Animals*		82.4	80.0	82.9	84.6
Poland	AMC	AMC Humans**	21.2	24.1	22.0	25.4	24.4
		AMC Animals***	140.8	138.9	129.4	165.2	167.4
	AMR	% 3GCR EC Humans	11.2	12.5	14.8	17.1	18.2
		% MRSA Humans	20.6	15.8	16.4	15.2	15.9
		% Complete S EC Animals*		26.4	23.5	15.4	16.4
Portugal	AMC	AMC Humans**	18.0	18.8	19.0	17.8	18.6
		AMC Animals***	201.6	170.2	208.0	134.8	186.6
	AMR	% 3GCR EC Humans	17.3	16.8	16.8	16.2	16.3
		% MRSA Humans	47.4	46.8	43.6	39.2	38.1
		% Complete S EC Animals*		6.4	5.9	6.6	7.8
Romania*	AMC	AMC Humans**	26.6	28.0	24.4	24.5	25.0
		AMC Animals***	109.0	100.5	85.1	90.1	82.7
	AMR	% 3GCR EC Humans	30.1	27.4	23.7	19.9	22.0
		% MRSA Humans	56.0	57.2	50.5	44.4	43.0
		% Complete S EC Animals*		7.4	8.7	12.9	20.1
Slovakia	AMC	AMC Humans**	21.2	24.2	23.6	20.0	22.0
		AMC Animals***	65.9	51.0	50.4	61.9	49.3
	AMR	% 3GCR EC Humans	32.3	31.5	31.2	33.0	31.2
		% MRSA Humans	28.0	28.1	27.1	29.2	26.6
		% Complete S EC Animals*		23.4	25.9	20.0	20.0
Slovenia	AMC	AMC Humans**	13.1	13.3	12.1	12.2	13.2
		AMC Animals***	33.4	26.4	30.3	36.5	43.2
	AMR	% 3GCR EC Humans	13.2	14.0	13.8	13.0	11.4
		% MRSA Humans	13.1	9.2	11.0	9.0	11.7
		% Complete S EC Animals*		24.7	20.0	18.8	20.6
Spain	AMC	AMC Humans**	17.1	17.5	27.5	26.8	26.0
		AMC Animals***	418.8	402.0	362.5	230.3	219.2
	AMR	% 3GCR EC Humans	12.6	12.0	15.4	13.1	13.9
		% MRSA Humans	22.1	25.3	25.8	25.1	24.2
		% Complete S EC Animals*		4.0	3.4	6.2	7.1
Sweden	AMC	AMC Humans**	14.0	13.5	13.2	12.8	12.4
		AMC Animals***	11.5	11.8	12.1	11.8	12.5
	AMR	% 3GCR EC Humans	6.1	6.5	8.7	7.7	8.7
		% MRSA Humans	1.0	0.8	2.3	1.2	1.9
		% Complete S EC Animals*		69.8	68.9	71.3	70.8
UK	AMC	AMC Humans**	20.8	20.1	19.7	19.3	18.8
		AMC Animals***	62.5	56.8	39.3	32.5	29.5
	AMR	% 3GCR EC Humans	10.7	11.8	10.0	11.0	11.8
		% MRSA Humans	11.3	10.8	6.7	6.9	7.3
		% Complete S EC Animals*		17.9	19.7	23.2	33.7

Footnote: AMC antimicrobial consumption; in 2014 Spain reported reimbursement data but then changed to sales data in 2016, resulting in a substantial technical increase in AMC compared with previous years, as the reimbursement data included consumption without a prescription and other non-reimbursed courses.

* Percentage of complete susceptible *Escherichia coli*. Each value of the 'complete susceptibility indicator' for *E. coli* in food-producing animals represents a combination of two years (i.e. 2015 represents data combined from 2014 and 2015, etc.

** Defined Daily Doses per 1 000 inhabitants per day.

*** Milligram per Population Correction Unit, AMR: antimicrobial resistance.

% 3GCR EC: Percentage *Escherichia coli* resistant to third-generation cephalosporins, % MRSA: Percentage *Staphylococcus aureus* resistant to meticillin.

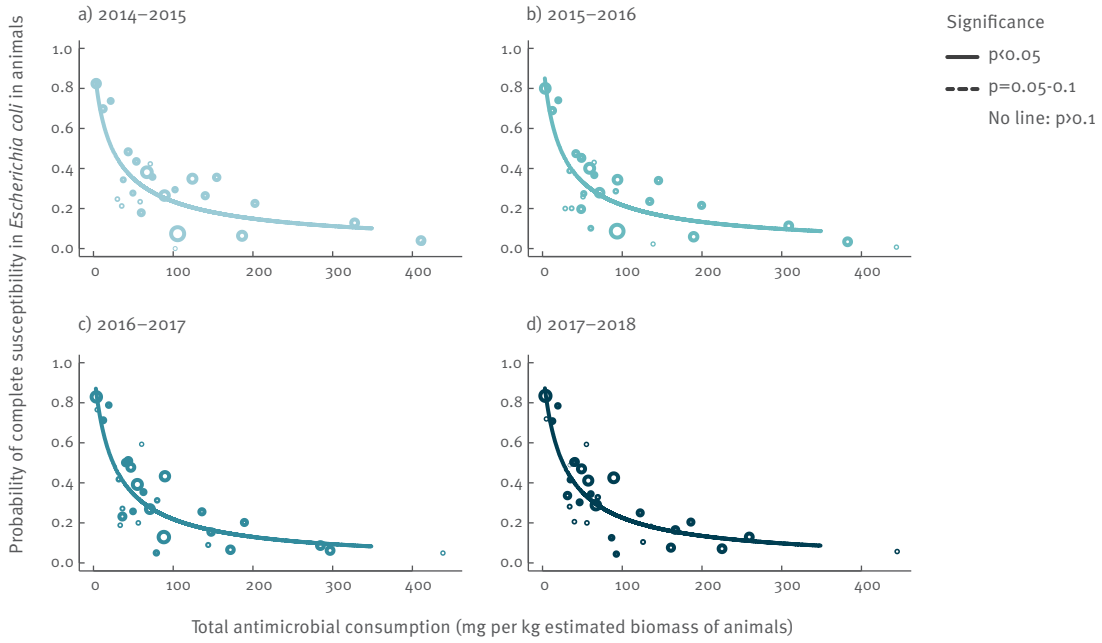
Colours of cells are assigned by allocating a baseline darkest green to the lowest value for AMC humans, AMC food-producing animals, % 3GCR EC and % MRSA and a baseline darkest red to the highest value for AMC humans, AMC food-producing animals, % 3GCR EC and % MRSA. For % complete S EC from food-producing animals, darkest green is assigned to the highest value and darkest red to the lowest. Other values are assigned a weighted blend of colour, depending on their position on the scale.

Table 72: Association between total national AMC in food-producing animals (expressed in mg per kg of estimated biomass) and complete susceptibility to the harmonised set of substances tested in indicator *Escherichia coli* from food-producing animals (logistic regression, see also Figure 60, a-d)

Year	Countries	Model	Odds ratio	p-value	95% CI
2014–2015	AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=26)	2	0.57	<0.001	0.47–0.69
2015–2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=28)	2	0.55	<0.001	0.46–0.67
2016–2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=29)	2	0.53	<0.001	0.45–0.64
2017–2018	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=31)	2	0.54	<0.001	0.46–0.63

CI: confidence interval. Odds ratio varies from 0 to infinity. When odds ratio equals 1 or CI includes 1, the association is not considered statistically significant. Food-producing animals include broilers, turkeys, pigs and veal calves for all periods considered.

Figure 60: Total national consumption of antimicrobials in food-producing animals and probability of complete susceptibility to the harmonised set of substances tested in indicator *Escherichia coli* isolates from food-producing animals for (a) 2014–2015, (b) 2015–2016, (c) 2016–2017 and (d) 2017–2018 (see also Table 72)



The figure displays the results of logistic regression analyses. Dots represent the countries included in the analysis. The size of the dots indicates the amount of available resistance data per country. The category 'food-producing animals' includes broilers, turkeys, pigs and veal calves for all three time intervals.

14. Key findings and discussion

14.1 Antimicrobial consumption in humans and food-producing animals

Key findings

- In 2017, the overall total antimicrobial consumption in 29 EU/EEA countries expressed in tonnes of active substance was one third higher in food-producing animals than in humans, while the estimated biomass of food-producing animals was twice as high as the estimated biomass for humans.
- The EU/EEA population-weighted mean as well as median consumption in these 29 EU/EEA countries, expressed in milligrams per kilogram of estimated biomass, was considerably higher in humans than in food-producing animals in 2017.
- For most of these 29 countries the population biomass-corrected consumption was lower, or much lower, in food-producing animals than in humans.
- The EU/EEA population-weighted mean consumption of third- and fourth-generation cephalosporins and quinolones (fluoroquinolones and other quinolones), the use of which AMEG recommends restriction in animals, was considerably lower in animals than in humans in the 29 EU/EEA countries in 2017.
- Expressed in milligrams per kilogram of estimated biomass, the overall mean antimicrobial consumption in food-producing animals in 27 EU/EEA countries decreased between 2014 and 2018, while the EU/EEA population-weighted mean consumption in humans in these 27 countries remained relatively stable during this period. From 2016, onwards, a shift was observed and consumption was at a similar level in both sectors. For the subsequent years (2017 to 2018) the overall mean antimicrobial consumption was higher for humans than in food-producing animals.

Discussion

The observed reduction in the overall mean antimicrobial consumption in food-producing animals for the 27 EU/EEA countries between 2014 and 2018 is strongly influenced by a substantial reduction in consumption among those countries that initially had a higher consumption [4].

The reduction in the overall mean AMC in food-producing animals across the 27 EU/EEA countries between 2014 and 2018 can be explained for the most part by the reduced use of tetracyclines and penicillins. The reduction in the consumption of tetracyclines has not been caused by a shift from high-dose to low-dose tetracyclines. As for penicillins, the reduction in consumption can be almost exclusively explained by a reduction in the use of aminopenicillins without enzyme inhibitors during this period. The dosing for premixes is typically much higher than for the other group treatment pharmaceutical forms – i.e. oral powder and oral solution. For premixes, the overall mean antimicrobial consumption in food-producing animals across the 27 EU/EEA countries declined substantially during the period 2014–2018, while a modest decline was observed for oral powder and oral solution (grouped together). There has therefore not been a shift from use of premixes to lower dosing pharmaceutical group treatment forms.

Generally, in many of the 27 EU/EEA countries there have been a variety of measures implemented which are assumed to have led to the decline in the consumption of antimicrobials for food-producing animals. These include increased focus on prevention of bacterial diseases; implementation of national action plans to reduce the occurrence of resistance; campaigns to promote prudent use of antimicrobials; restrictions on use of certain antimicrobials in food-producing animals; prescription control measures, awareness-raising regarding the threat of antimicrobial resistance and antibiotic stewardship and/or the setting of targets for reduction of sales [4].

The population-weighted mean of the total consumption of antimicrobials in humans, expressed in milligram per kilogram of estimated biomass, in the 27 EU/EEA countries for 2014–2018 remained stable, with aminopenicillins accounting for more than half of total consumption. Although the population-weighted mean consumption in the 27 EU/EEA countries did not show significant change, an increasing number of countries saw decreasing trends in antimicrobial consumption. As reported to the ESAC-Net, stable or decreasing trends in the EU/EEA-population-weighted mean of AMC in humans were observed for tetracyclines, macrolides, third-generation cephalosporins, carbapenems and quinolones, while an increasing trend was observed only for glycopeptides. The trends observed may reflect antimicrobial stewardship activities in EU/EEA countries, including awareness campaigns connected to the European Antibiotic Awareness Day since its introduction in 2008 [36, 37].

14.2 Carbapenems

Key findings

- Significant associations were found between the use of carbapenems and resistance to carbapenems in invasive *E. coli* in the human sector.
- In food-producing animals, carbapenem resistance is extremely rare.

Discussion

In humans, carbapenems are almost exclusively used in hospitals and for treatment of infections caused by multidrug-resistant gram-negative bacteria. Recent data from ECDC have indicated that the EU/EEA population-weighted mean consumption of carbapenems did not show a statistically significant change between 2009 and 2018 [36]. The same report found that six countries had a significant increase in carbapenem use and only two had a significant decrease. Although carbapenem consumption is still at a relatively low level compared to the overall consumption of antimicrobials for systemic use in the hospital sector, the increasing rates in some countries, combined with the emergence and spread of carbapenem-resistant bacteria (including *Acinetobacter* spp., Enterobacterales and *Pseudomonas aeruginosa*) is a matter of concern. Global shortages of piperacillin-tazobactam in 2016 and 2017 could have had an impact on the use of other antimicrobials, such as carbapenems. However, when assessed using the EU/EEA population-weighted mean for carbapenem consumption, there was no evidence for this, at least at EU/EEA level [36].

Carbapenem resistance in *E. coli* from humans remains low, with an overall EU/EEA population-weighted mean percentage of 0.1% between 2016 and 2018. However, compared to previous JIACRA reports, this is the first time (2016–2018) that we have seen a statistically significant positive association between the level of carbapenem consumption and carbapenem resistance in *E. coli* in EU/EEA countries. *E. coli* is a common cause of infection both in the community and the healthcare sector. Carbapenem resistance in *E. coli* is mediated mainly by a range of carbapenemase genes which are often located on plasmids and can be exchanged between other Enterobacterales and other gram-negative bacteria. Therefore, the potential spread of carbapenem resistance to other bacteria or in the community through *E. coli* is a concern.

The EU/EEA population-level proportion of carbapenem resistant *K. pneumoniae* reported to EARS-Net increased rapidly between 2006 and 2012, although since then the situation seems to have stabilised slightly [37]. Nevertheless, carbapenem resistance in *K. pneumoniae* remains a major public health challenge, with EU/EEA percentages seven-fold higher in 2018 (7.5%) than in 2006 (0.96%), and large variability between the EU/EEA countries (0% to 63.9% in 2018) [38]. Contrary to the previous JIACRA report, where a statistically significant association between human carbapenem consumption and carbapenem resistance in *K. pneumoniae* could be established for all years between 2013 and 2015, results in this study were less conclusive and showed borderline or non-significant associations for 2016 to 2018.

This study did not include other risk factors for the spread of carbapenem-resistant *K. pneumoniae*, as assessing the role of infection prevention and control routines and clonal spread was outside the scope of this study. *K. pneumoniae* can be resistant to carbapenems as a result of various mechanisms, but most frequently through the production of carbapenemase enzymes. Although *K. pneumoniae* carbapenemase (KPC) still plays an important role among the carbapenemases produced by *K. pneumoniae*, recent outbreaks of carbapenemase (NDM-1 and OXA-48)-producing *K. pneumoniae* have highlighted the concomitant increase in virulence, transmissibility and antimicrobial resistance among certain *K. pneumoniae* strains. These strains pose a considerably higher risk to human health than was previously the case with the broader *K. pneumoniae* population. Options for action to address this threat include timely and appropriate diagnosis, high standards of infection prevention and control and antimicrobial stewardship [39].

Carbapenems are not authorised for use in animals in the EU. Therefore, in the AMEG categorisation, carbapenems belong to Category A, with the indication 'Avoid' use in veterinary medicine in the EU. Only a limited number of carbapenemase-producing Enterobacterales (CPE) has been found in food-producing animals. Since 2012, when carbapenemase-producing *E. coli* and *Salmonella* spp. were first isolated from pig herds and broiler flocks in Germany, these bacteria have only been sporadically detected, predominantly in pigs and pig meat. Under Commission Implementing Decision 2013/652/EU EU-wide monitoring was undertaken on a voluntary basis but this became mandatory as of 1 January 2021, in accordance with Commission Implementing Decision 2020/1729/EU[7]. Any rise in carbapenem resistance is therefore likely to be promptly detected. Until 2019, under this monitoring framework, twelve isolates were identified (some suspected isolates from 2019 still need confirmation) and repeated detection on farms was the exception [40]. While the first detected isolates produced VIM-1 carbapenemases, more recent findings have also included other carbapenemases, leading to the assumption that these might originate from human sources [41, 42]. Sporadic detection of CPE has also been reported in companion animals [43].

14.3 Third- and fourth-generation cephalosporins

Key findings

- The overall consumption of third- and fourth-generation cephalosporins in food-producing animals was much lower than that observed in humans. No statistically significant association was observed between consumption in humans and in food-producing animals at national level.
- Total AMC of third- and fourth-generation cephalosporins in humans (community and hospital) was significantly and positively associated with resistance to third-generation cephalosporins in invasive *E. coli* from humans. In *Salmonella*, a positive

7 Commission Implementing Decision (EU) 2020/1729 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria and repealing Implementing Decision 2013/652/EU https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2020.387.01.0008.01.ENG

association was only observed for *Salmonella* spp. and *S.* Enteritidis in 2018.

- No association was observed between consumption of third- and fourth-generation cephalosporins in food-producing animals and resistance to third-generation cephalosporins in *E. coli* from food-producing animals. However, when taking into consideration the mandatory monitoring programmes for selective isolation of ESBL/AmpC-producing *E. coli* in food-producing animals, a significant positive association was found between consumption of cephalosporins in food-producing animals and the key indicator of the proportion of samples positive for ESBL-/AmpC-producing *E. coli* (prevalence of ESBL-/AmpC-producing *E. coli*) in food-producing animals.
- No statistically significant association was observed between resistance to third-generation cephalosporins in *E. coli* from food-producing animals and humans. However, a significant positive association was found between resistance of *Salmonella* spp. from turkeys and resistance of *Salmonella* spp. from humans in 2018.
- The consumption of third- and fourth-generation cephalosporins in food-producing animals was significantly and positively associated with resistance to third-generation cephalosporins in invasive *E. coli* from humans. No such association was observed with resistance to third-generation cephalosporins in *Salmonella* spp. from humans.
- The multivariate analysis showed that the only significant relationship retained in the final model of resistance to third-generation cephalosporins in invasive *E. coli* from humans was the strong direct impact of the consumption of these classes of antimicrobials in humans.

Discussion

Increased use of third- and fourth-generation cephalosporins in humans has already been observed in previous JIACRA reports. In human medicine, about half of the third- and fourth-generation cephalosporins are used in hospitals. In the three countries where consumption data were only available for the community, the consumption of third- and fourth-generation cephalosporins may therefore be considerably underestimated. Consumption of third- and fourth-generation cephalosporins in food-producing animals is generally low. No products containing these drugs are licensed for poultry and no products are available as feed or water medication. This limits the potential group treatments in animals. Moreover, it has been recommended that their use be limited in animals and in some countries use has decreased substantially in recent years [4, 44, 45].

Resistance to third-generation cephalosporins in invasive *E. coli* from humans was found to be mostly related to the human consumption of third- and fourth-generation cephalosporins. This is in line with the expected higher impact of direct exposure within the population to the antimicrobial, compared to exposure to resistant bacteria from other exposed populations. This reinforces the need to use third- and fourth-generation cephalosporins judiciously, not only in veterinary but also in human medicine. The same association was observed for *Salmonella* spp. and *S.* Enteritidis in 2018, in contrast to the other years. A similar association was found for *S.* Enteritidis and *S.* Infantis in JIACRA II. As most infections with *Salmonella* are considered foodborne and *Salmonella* is not a permanent coloniser of the human gut, this association was unexpected.

In animals, association was not established between consumption and resistance to third-generation cephalosporins either in indicator *E. coli* or in *Salmonella* spp. Association was not observed when all four major food-producing animal species were considered, or when only pigs were considered in 2017, as third- and fourth-generation cephalosporins are not licensed for use in poultry. For cattle, specific data on AMC were not available. Nevertheless, when all four food-producing animal species were considered, a sensitivity analysis and a subsequent removal of one influential outlier showed that certain associations between consumption of third- and fourth-generation cephalosporins and resistance in indicator *E. coli* were affected, as they became significantly positive. In addition, an association was found between the consumption of third- and fourth-generation cephalosporins and the key indicator of prevalence of ESBL-/AmpC-producing *E. coli* in food-producing animals. This indicates that the selective isolation approach may be more sensitive for detecting the impact of cephalosporin consumption on cephalosporin resistance, explaining the observed association.

ESBL/AmpC-encoding genes also provide resistance specifically to aminopenicillins, suggesting that use of aminopenicillins may also select for bacteria harbouring such genes. Moreover, the genes encoding ESBL/ApmC-production tend to be located on mobile genetic elements that also may harbour genes encoding AMR to other antimicrobials [46]. Further analyses of the association between consumption of aminopenicillins, and of non-beta-lactam antimicrobials, would be of interest to better understand factors influencing the prevalence of ESBL/AmpC-encoding genes. However, this was considered beyond the scope of the present report.

Use in animals occurs not only in meat-producing animals (excluding poultry) but in the case of cattle also in dairy cows, where cephalosporins can be used in the treatment of mastitis [47] or for other conditions, such as metritis or respiratory disease [48]. Enteric bacteria from young calves (0–2 months of age) that may be exposed to cephalosporins via waste milk (i.e. milk that may not be sold for human consumption after cows have been treated with antimicrobials) [49] have been shown to have very high resistance rates to third-generation cephalosporins [50]. However, these animals do not enter the food chain at that age and their enteric flora changes as they increase in age. Milk that may also harbour *E. coli* resistant to third-generation cephalosporins

is commonly heat-treated before being marketed for consumption [51]. Detailed investigation of AMC and AMR data by animal species, age and production type would therefore be optimal. However, there are also complicating factors in some countries. For example, a certain amount of third- and fourth-generation cephalosporins may also be used in the treatment of companion animals [52, 53], especially cats [54], further adding to the differences between the treated animal population and the population where AMR is monitored. The use of these drugs in animal populations that are not included in the AMR data may have contributed to the observed lack of association between AMC and AMR on the animal side. Use of third- and fourth-generation cephalosporins should ideally continue to be low in the animal sector in order to avoid an increase in AMR similar to that recorded in the human sector.

The inconsistency in lack of association between resistance to third-generation cephalosporins in animals and humans and the significant association of AMC in animals and AMR in humans cannot be explained by the data as there was no association of use in animals with use in humans. However, in the multivariate model, this latter association was not confirmed. There are also differences for consumers in the degree of exposure to resistant bacteria derived from the different ages, classes and production types of animals. Moreover, exposure to resistant bacteria via the food chain is also dependent on standard food hygiene procedures, such as slaughterhouse practices or pasteurisation of milk and dairy products.

14.4 Fluoroquinolones and other quinolones

Key findings

- Consumption of fluoroquinolones and other quinolones was higher in humans than in animals overall, and in all individual countries except two. There was a significant association between the consumption of fluoroquinolones and other quinolones in humans and in animals at national level.
- Consumption of fluoroquinolones and other quinolones in humans was significantly associated with resistance to fluoroquinolones in invasive *E. coli* and *C. jejuni* from humans.
- There was a significant positive association between consumption of fluoroquinolones and other quinolones in animals and resistance in *E. coli* from food-producing animals (SIMR). In poultry, a significant association between consumption and resistance was observed in all three bacteria considered (*E. coli*, *Salmonella*, *C. jejuni*) in pigs, a significant association was only detected in *E. coli* (and a borderline association for *Salmonella*).
- A significant positive association between fluoroquinolone resistance in isolates from animals and from humans was observed for *E. coli* (all animals) and *C. jejuni* (only data from poultry).
- There was a significant positive association between consumption of fluoroquinolones and other quinolones in animals and resistance in invasive *E. coli* and in *C. jejuni* from humans.
- In the multivariate analysis on *E. coli*, the association between consumption of fluoroquinolones and other quinolones in animals and resistance in commensal *E. coli* from animals was highly significant. Similarly, the association between the consumption of fluoroquinolones and other quinolones in humans and resistance in invasive *E. coli* from humans was highly significant.
- For *Salmonella*, the only significant relationship in the model was that between the consumption of fluoroquinolones and other quinolones in animals and resistance in animals.
- For *Campylobacter*, a significant association was observed between resistance in animals and resistance in humans in the multivariate analysis. The resistance in animals was significantly correlated with consumption in animals, but R^2 was low (0.40).

Discussion

Fluoroquinolones are highest-priority critically important antimicrobials [14] and their use should be restricted in animals [13]. In line with this, consumption of fluoroquinolones was higher in humans than in animals in all countries except two. Other quinolones were not commonly used and when used, this was mainly in animals. The significant association observed between the consumption of fluoroquinolones and other quinolones in humans and in animals means that a country having a high consumption in one sector would tend to have a high consumption in the other, and vice versa. This has to be considered when analysing the results of the association of consumption with resistance as it may mask existing associations or evoke statistical associations that have no biological correlate. The reason for this association is not clear. It seems likely that countries either make efforts to restrict the use of fluoroquinolones in both sectors or they do not. However, more research into national policies is needed to understand this association.

Consumption of fluoroquinolones and other quinolones in humans was significantly associated with resistance to fluoroquinolones in invasive *E. coli*, as could be expected and has been found in previous studies [2, 55–57] and the previous JIACRA report. Most of the consumption of fluoroquinolones occurs in the community. The association between the consumption of fluoroquinolones and other quinolones and the resistance of invasive *E. coli* might be explained by the high proportion of community-associated infections reported for this microorganism [58]. In contrast, no such association was observed for non-typhoidal *Salmonella*, either in the univariate, or in the multivariate model. As most salmonella infections are food-borne, the bacteria are commonly not exposed to antimicrobials that are consumed by humans other than during the infection.

Moreover, most salmonella infections in humans will not be treated with antimicrobials. The same applies to *C. jejuni*. Most *Campylobacter* infections in humans are attributed to animal sources, especially broiler meat [59, 60], and guidelines do not advocate routine treatment of such infections with antimicrobials. In line with the food-borne origin of the infections, a significant association between fluoroquinolone-resistance in animals and humans was found (as in previous JIACRA reports). However, for *C. jejuni* a significant association was also found between consumption of fluoroquinolones and other quinolones in humans and resistance to fluoroquinolones in *C. jejuni* from humans. This has not been observed in previous JIACRA reports and it was not confirmed in the multivariate model. It is not clear from the data whether this association could be an artefact, caused by the association of consumption in humans and in animals. Alternative explanations include an adapted human *C. jejuni* flora that conflicts with the colonisation of the human intestines with *Campylobacter* (which is only temporary). Further studies are needed to confirm the observed association.

There was a significant positive association between consumption of fluoroquinolones and other quinolones in animals and resistance in *E. coli* from all animals taken together (SIMR) and for poultry and pigs when considered separately. Strong associations between consumption of fluoroquinolones and other quinolones and resistance in *E. coli* have been described previously in national [55, 56] and international ecological studies [2, 57] and are in line with the findings of this study. It should be noted that the level of resistance differed substantially between poultry on the one hand and pigs and calves on the other, with much higher fluoroquinolone resistance observed in poultry [27]. This is in line with expectations based on the antimicrobial consumption of fluoroquinolones, which is substantially higher in poultry than in pigs and calves (e.g. in Germany [61] and France [62, 63]) and has been demonstrated previously [3]. The association was confirmed in the multivariate analysis.

In poultry, this association was also seen with resistance of *Salmonella* and *C. jejuni*, again in line with previous results. In pigs, the positive association for *Salmonella* was not significant (1.88 [0.94–3.76]). Only six countries were included in the analysis and the number of isolates and the diversity of *Salmonella* serovars needs to be considered. An association with resistance of *C. jejuni* in pigs could not be studied as *C. jejuni* is rarely isolated from pigs.

A significant positive association between fluoroquinolone resistance in isolates from animals and invasive *E. coli* from humans was also observed for *E. coli* (all animals). As invasive *E. coli* are mostly not of food-borne origin, this association is difficult to explain. One explanation refers again to the association found between consumption in humans and consumption in animals. Both are also associated with resistance of *E. coli* in the respective populations, making it difficult to separate the different effects based on the data that were available for the analysis. The alternative explanation is that the role of *E. coli* from animals for human invasive infections has so far been severely underestimated. However, this does not seem likely as numerous studies have shown that isolates in bloodstream infections and in animals differ [15, 64].

In line with the previously described associations, there was also a significant positive association between consumption of fluoroquinolones and other quinolones in animals and resistance in *E. coli* and in *C. jejuni* from humans. No such association was found for *Salmonella* from humans. This is plausible for *C. jejuni* because of the food-borne nature of the infections and it is confirmed by the strong association of resistance in animals and resistance in humans. The reasons for the associations with respect to *E. coli* are less clear. Again, an artefact caused by the associations of consumption in animals and humans cannot be excluded (see above). However, the effect, mediated through the resistance in *E. coli* from animals, was also observed in the multivariate model. The failure to demonstrate the association for *Salmonella* may be associated with the limited number of isolates, combined with the heterogeneity of serovars.

14.5 Polymyxins

Key findings

- Across the EU, the consumption of polymyxins (colistin) in 2017 was much higher in food-producing animals than in humans (3.2 mg/kg biomass versus 0.06 mg/kg biomass, respectively). The analysis showed no association within country between the consumption of polymyxins in humans and consumption in animals.
- Statistically significant positive associations have been found between colistin resistance in indicator *E. coli* and polymyxin consumption in animals for all time periods examined from 2014 to 2018. Significant associations still existed after the performance of regression analyses for pigs and poultry separately.
- Associations between polymyxin consumption and resistance in animals and resistance in humans were not studied, as the availability of polymyxin susceptibility data from humans was limited in the data sources used for this report.

Discussion

The consumption of colistin in human medicine was very low compared to the overall consumption of other antimicrobial classes (<1%). However, the EU/EEA population-weighted mean consumption in the hospital sector increased substantially between 2009 to 2018, from 0.004 to 0.007 DDD per 1 000 inhabitants per day, with a statistically significant increase in nine countries [36]. Colistin has re-emerged as a last resort option to treat MDR gram-negative healthcare-associated infections. Usage is highest in southern European countries where infections due to carbapenem-resistant Enterobacterales (CRE) have become a serious

healthcare problem and are associated with prolonged hospitalisation and increased risk of mortality [65, 66]. Colistin resistance among CRE isolates can develop and disseminate rapidly with the increased use of colistin in hospitals [67, 68] and outbreaks of colistin-resistant CRE (CCRE) have been reported in healthcare institutions in the EU [69, 70]. Options for the treatment of CCRE are extremely limited.

In the animal sector, colistin has been used for several decades, mostly as a group treatment for enteric diseases such as colibacillosis in pigs and poultry. Sales for use in food-producing animals in 2017 varied markedly between reporting countries. This variation cannot be directly linked to predominance of specific animal species or husbandry systems in different countries [16]. Colistin is categorised as a highest-priority critically-important antimicrobial by WHO, recognising its use as last resort for serious human infections (WHO 2019), which is why its use in animals has come under examination. Following the discovery of a new horizontally-transferable mechanism of resistance (MCR-1) in 2015, EMA proposed targets for the reduction of colistin use to 5 mg/PCU for high and moderate consumer countries, and 1 mg/PCU for others, to be achieved by 2020 [16]. ESVAC [4] reported that between 2011 and 2018, the sales of polymyxins had declined by 69.8% in the 25 countries that provided data over the period, with most of the reduction occurring from 2014 onwards. Polymyxins accounted for 3.3% of the total antimicrobial sales for food-producing animals in the 31 countries providing data to ESVAC in 2018.

Mutational colistin resistance has long been recognised in animal isolates; in many cases the mechanisms are unstable, potentially explaining why historically levels of resistance remained low (EMA 2016). Following identification of the plasmid-mediated *mcr-1* gene in 2015, other *mcr* genes (*mcr-2* to *mcr-10*) have been reported in Enterobacterales [71–79] and retrospective analysis of strain collections showed that mcr genes had already been around in *E. coli* from animals for several years [80]. *Mcr* genes have been found in similar plasmids in the same bacterial species isolated from food-producing animals, food, humans and the environment, indicating the possibility for transmission between the compartments [81, 82]. However, due to lack of data on the medical side the potential association of resistance in isolates from animals and isolates from humans cannot yet be estimated.

The levels of resistance in indicator *E. coli* isolates from pigs and calves have remained very low. Levels of resistance in *E. coli* from broilers and turkeys have also remained low overall, but have shown minor variation, with higher levels of resistance reported in individual countries [27].

Despite the low levels of resistance in isolates from food-producing animals, in our analysis a significant positive association was found between the consumption of colistin in animals and resistance to colistin in *E. coli* from food-producing animals. This association existed irrespective of whether the SIMR or the specific data on pigs and poultry were considered. This observation suggests there is a potential to further reduce the resistance levels through measures to reduce consumption of colistin. However, the persistence of resistance may also be dependent on the influence of factors such as co-selection by other antimicrobials and the fitness cost of resistance mechanisms [83]. The co-occurrence of ESBL genes (including *blaCTX-M-15*, more typically associated with human *E coli* strains) with *mcr-1* on plasmids in E. coli isolates from animal sources has been demonstrated, and in in vitro studies mcr genes can be co-selected by third-generation cephalosporins [84, 85]. Encouraging findings were reported recently following the withdrawal of colistin as an antimicrobial growth promoter by China in 2017. Epidemiological studies showed that the substantial reduction in sales of colistin in animals was rapidly followed by a significant reduction in the prevalence of mcr-1 in both the animal and human sectors [86].

Mandatory monitoring in the EU under Commission Implementing Decision 2013/652/EU is based on phenotypic susceptibility and does not discriminate between different colistin resistance mechanisms. Molecular testing is required to confirm the underlying mechanisms of resistance and to gain a better understanding of the epidemiology of E. coli carrying the *mcr* gene in animals [80], including potential transmission to humans. However, several studies have shown that overall, mcr genes contribute substantially to the level of phenotypic resistance to colistin in *E. coli* from animals [80].

Data on resistance to polymyxins in human isolates are not included in this report. Due to the absence of routine testing for susceptibility to colistin in many countries and inconsistent use of the EUCAST-recommended methods, EARS-Net data are still not considered suitable for polymyxin susceptibility surveillance. Efforts are needed to overcome this deficit and to enable a better understanding of the potential association of polymyxin-resistance in isolates from humans and animals. In response to the need for enhanced surveillance of carbapenem- and/or colistin-resistant human pathogenic Enterobacterales (CCRE), a project has been established as part of EURGen-Net. In the future, this project will determine colistin resistance mechanisms through genomic methodologies [87].

14.6 Aminopenicillins

Key findings

- Consumption of aminopenicillins without beta-lactam inhibitors was higher in humans than in food-producing animals. Aminopenicillins with beta-lactam inhibitors were mainly used in the human sector. There was a significant association between the consumption of aminopenicillins in humans and in animals at the national level.
- In humans, a statistically significant positive association between consumption of aminopenicillins and

resistance to aminopenicillins was only found for one year (2017) for *S.* Typhimurium.

- In food-producing animals, statistically significant positive associations between consumption of aminopenicillins and resistance to aminopenicillins in *E. coli* (SIMR) were found over the study periods. In pigs and in poultry, significant positive associations were found between estimated consumption per species and resistance to aminopenicillins in indicator *E. coli* for all the years and for *Salmonella* spp. for 2016.
- Comparing resistance to aminopenicillins in *E. coli* from humans and in indicator *E. coli* from food-producing animals, statistically significant positive associations were observed. A statistically significant positive association was found between aminopenicillin resistance of *Salmonella* spp. from humans and turkeys in 2018.
- Statistically significant positive associations were found between consumption of aminopenicillins in food-producing animals and resistance to aminopenicillins in invasive *E. coli* from humans for all three years, and for *Salmonella* spp. and *S.* Typhimurium, including monophasic variant, for 2016 and 2018.
- In the multivariate analysis of *E. coli*, aminopenicillin resistance in bacteria from humans was significantly related to resistance in bacteria from food-producing animals, which, in turn, was significantly linked to the consumption of aminopenicillins in such animals.
- The multivariate analysis of *Salmonella* spp. reached the same conclusion as for *E. coli*, although the model did not provide such a good fit for explaining the variance in resistance observed in *Salmonella* from humans.

Discussion

This is the first time that data on human use of aminopenicillins (J01CA01, J01CA04) and inhibitor combinations (J01CR02) have been presented in comparison with their consumption in animals. Consumption of aminopenicillins in humans was higher than in animals when compared as mg/kg estimated biomass. Aminopenicillins with and without beta-lactamase inhibitors were the most commonly-used penicillins at EU/EEA level, as well as in most countries [25]. In most of the antimicrobial stewardship programmes, aminopenicillins are preferred (i.e. for respiratory tract infections) to other antimicrobial agents with broader antimicrobial spectrum, such as cephalosporins or fluoroquinolones, contributing to the high use in human medicine.

The explanation for the significant association observed between the consumption of aminopenicillins in humans and in animals could be similar to that for fluoroquinolones and other quinolones. A country with a high aminopenicillin consumption in one sector would tend to have a high aminopenicillin consumption in the other sector, and vice versa. More research into national policies is needed to understand this association.

A high level of resistance to aminopenicillins in *E. coli* isolates from humans has been documented for all EU/EEA countries and this has been the case for years [38]. In particular, more than half of the *E. coli* isolates reported for 2018 (EARS-Net) were resistant to at least one of the antimicrobial groups under regular surveillance and aminopenicillin resistance was present in over 90% of the single or multiple resistant phenotypes [9]. In the univariate analysis, a borderline association was found between the occurrence of aminopenicillin resistance in invasive *E. coli* from humans in 2016 and 2017 and consumption of aminopenicillins in humans across the different countries. However, in the multivariate analysis, aminopenicillin resistance in *E. coli* from humans was not correlated to aminopenicillin consumption in human healthcare. This could be explained by several factors, including the high level of aminopenicillin resistance in all EU/EEA countries with limited variation between countries, although there were substantial differences in aminopenicillin consumption. Another explanation could be successful antimicrobial stewardship interventions in different countries. Moreover, the co-selection of resistance could also explain these findings as aminopenicillin resistance in *E. coli* is frequently associated with resistance to other antimicrobial classes. For example, resistance to beta-lactams is mainly mediated by beta-lactamases and the use of other beta-lactams, such as cephalosporins, may have added to the selection pressure.

The level of aminopenicillin resistance in *Salmonella* from humans was not associated with aminopenicillin use in humans. For *S.* Enteritidis and for *S.* Typhimurium, including the monophasic variant, the association between aminopenicillin use in humans and aminopenicillin resistance of these bacteria from humans was respectively borderline significant or significant for only one year. These findings are in line with the use of other antimicrobial classes in humans and resistance of *Salmonella* and, as already discussed, may be explained by the fact that infections caused by *Salmonella* are considered food-borne and *Salmonella* is not a permanent coloniser of the human gut.

Resistance to aminopenicillins is also very frequently found in indicator *E. coli* and some *Salmonella* serovars from food-producing animals. In this report, we found significant associations between aminopenicillin use and aminopenicillin resistance, mainly in indicator *E. coli* from animals, and sometimes also in *Salmonella*. This is in line with the findings of a previous study conducted on a small dataset of seven EU countries. In this study, the level of aminopenicillin use strongly correlated with the level of aminopenicillin resistance in commensal *E. coli* isolates in pigs, poultry and cattle at national level [88] and with a reduction in aminopenicillin resistance in countries where antimicrobial use in animals has decreased in recent years [89].

Amoxicillin combined with clavulanic acid is far less used than aminopenicillins without enzyme inhibitor in food-producing animals, and there are limited data on

how this could contribute to resistance selection in animals [90]. However, this may not be the case in humans. In a retrospective observational study across 18 hospital departments, consumption of amoxicillin with clavulanic acid significantly correlated with resistance of *E. coli* isolates to amoxicillin with clavulanic acid [91]. In contrast, consumption of amoxicillin alone was not associated with amoxicillin resistance in *E. coli* isolates [91].

In both univariate and multivariate analyses, aminopenicillin resistance in *E. coli* and *Salmonella* isolates from humans was associated with aminopenicillin resistance in indicator *E. coli* and *Salmonella* from animals, as well as consumption of aminopenicillins in animals. This is in line with current evidence, that humans and animals may share identical beta-lactamase-producing Enterobacterales, suggesting interspecies transfer [92–95]. However, a recent study using 'One-Health' genomic surveillance of *E. coli* isolates from humans and livestock in the east of England found only limited evidence that severe human infections caused by *E. coli* had originated in livestock from the same region [64]. These contradictory findings warrant further research into the sources of aminopenicillin-resistant *E. coli* and *Salmonella* spp. in humans.

14.7 Macrolides

Key findings

- The total population-weighted mean consumption of macrolides (expressed in mg per kg of estimated biomass) was similar in food-producing animals and humans in the 29 EU/EEA countries delivering consumption data for both sectors for 2017. The median population-weighted mean consumption in the 29 countries was slightly higher in humans than in food-producing animals. The analysis showed significant association within countries between the consumption of macrolides in humans and consumption in food-producing animals.
- Although a statistically significant association was not found between the consumption of macrolides in humans and the occurrence of macrolide resistance of *C. jejuni* in humans for 2016–2017, the association was borderline significant in 2018.
- Statistically significant positive associations were observed between the consumption of macrolides in food-producing animals and resistance to macrolides in *C. jejuni* from food-producing animals. However, in food-producing animals, resistance to macrolides in *C. jejuni* was only found in a few countries and the association was largely driven by one country with high use, a high level of resistance and many data points.
- Resistance to macrolides in *C. jejuni* from turkeys in 2016 was associated with resistance in *C. jejuni* in humans; however, data were only available from six countries and no association was found for 2018.
- In the multivariate analyses, macrolide resistance in *C. jejuni* in humans could be related to the resistance in food-producing animals, but only a quarter of its variance was explained by this latent variable.

Discussion

The absence of a significant association between the consumption of macrolides in humans for most of the years and resistance to macrolides in *C. jejuni* from humans was expected. This is because *Campylobacter* only colonise the human intestines on a transient basis and are therefore infrequently co-exposed through antimicrobial consumption in humans. Moreover, most *Campylobacter* infections are food-borne and source attribution studies have shown that broilers play a major role as a source of human infections [59].

Gastroenteritis caused by *Campylobacter* spp. is mostly self-limiting and antimicrobial therapy is normally not required. However, macrolides are one of the few antibiotics available that are efficient for the treatment of serious *Campylobacter* infections in humans.

14.8 Tetracyclines

Key findings

- In most countries, the amount of tetracyclines consumed by food-producing animals is markedly higher than that consumed by humans. Large variations in the consumption of food-producing animals were noted among countries. No significant association was observed between the consumption of tetracyclines by humans and food-producing animals.
- In food-producing animals, and in pigs and poultry specifically, significant positive associations were observed between the estimated consumption of tetracyclines in animals and resistance to tetracyclines in *E. coli* from animals during the period studied. The same was observed for the estimated consumption of tetracyclines in poultry and resistance to tetracycline in *C. jejuni* from poultry. For *Salmonella*, a significant positive association of consumption in animals was only found for resistance in poultry in 2018.
- There was a significant positive association between tetracycline resistance in *C. jejuni* from broilers and turkeys and in *C. jejuni* from humans for 2016 and 2018.
- Significant associations were observed between consumption of tetracyclines in food-producing animals and resistance to tetracycline in *C. jejuni* in humans.
- In the multivariate analysis for *C. jejuni*, a significant association between resistance to tetracycline in poultry and resistance to tetracycline in humans was found.

Discussion

Tetracyclines are not routinely used for treatment of Enterobacterales infections in humans. Therefore, there are no surveillance data on tetracycline resistance in invasive *E. coli* from humans. For the monitoring of resistance in *Salmonella* isolates from humans, tetracyclines

are included as an epidemiological marker to separate strains, and to assess any possible linkage to a potential animal origin of the resistance. For *Campylobacter* spp., tetracyclines are a treatment option in humans.

No significant associations were found between consumption of tetracyclines in humans and resistance to tetracyclines in *Salmonella* spp. or *C. jejuni* from humans. Neither *Salmonella* spp. nor *C. jejuni* are permanent colonisers in humans. Consequently, they are only exposed to antimicrobial treatments during infections. In contrast, in food-producing animals, *C. jejuni* and *E. coli* are permanent colonisers of the gut and therefore exposed to any antimicrobial treatment these animals receive. Here, tetracyclines are the most sold and used antimicrobials [4]. Therefore, a statistically significant positive association between consumption of tetracyclines and resistance to tetracyclines in *E. coli* and *C. jejuni* could be expected and was observed.

S. Enteritidis and *S.* Typhimurium in poultry are controlled in accordance with Regulation (EC) No. 2160/2003 and therefore rare in broilers and turkeys. In pigs, there is no European control programme in place and *Salmonella* are prevalent on farms in many countries. Nevertheless, in contrast to the previous JIACRA report, we did not find a significant association between resistance in *Salmonella* among pigs and consumption of tetracyclines. Whether this is due to differences in the proportions of various serovars in the countries is not clear, and beyond the scope of this report. An insufficient number of available isolates is a frequent reason for an association not being established for *Salmonella* spp. [96]. However, such an association was observed in poultry, but only for 2018.

The association between resistance of *C. jejuni* from broilers and turkeys and resistance in humans may be explained by the dominant role of these poultry species and their meat as sources of human *Campylobacter* infections [59].

The multivariate analysis indicated that there is a significant association between the resistance to tetracyclines observed in *C. jejuni* from poultry and humans. The resistance data from animals included in this analysis were from poultry. Consumption of poultry meat and the handling of poultry and poultry meat are important transmission routes for *Campylobacter* spp. infections in humans. The consumption of tetracyclines is generally higher in pigs than in poultry [61, 62]. To assess the impact of the consumption of tetracyclines in pigs on resistance in *Campylobacter*, more resistance data on *Campylobacter coli* would be needed as this is the by far the dominant *Campylobacter* spp. in pigs.

14.9 Primary key indicators of antimicrobial consumption and resistance

Key findings

- There was substantial variation in all five primary key indicators among countries and between years within the countries.
- In some countries, the primary key indicators were all high, in others all low, but in most countries, the level of the indicator was variable when compared to the other countries.
- Primary key indicators for AMC decreased in most countries in both food-producing animals and humans.
- Primary key indicators of AMR in humans showed divergent trends. While the proportion of MRSA decreased in most countries, the proportion *E. coli* resistant to third-generation cephalosporins increased in 12 countries, and decreased in 11.
- The primary key indicator of AMR in food-producing animals is inverse to that for humans as it measures the proportion of *E. coli* isolates susceptible to all tested substances instead of the proportion resistance. This proportion increased in a majority of countries and decreased in only three.
- A statistically significant negative association between higher AMC in food-producing animals and the occurrence of completely susceptible indicator *E. coli* in food-producing animals was observed for all four time-intervals studied. There was a clear and consistent reduction in the probability of indicator *E. coli* in food-producing animals being completely susceptible when more antimicrobials were consumed.

Discussion

In 2017, to facilitate assessments of the progress in reducing AMC and AMR, EFSA, EMA and ECDC suggested key indicators for both [12]. Variability among the indicators between countries suggests potential room for improvement, and variability over time indicates changes in AMC and AMR that may help when evaluating management measures to reduce them. While it is not the purpose of the indicators to compare countries, they may help identify key areas for action by putting the national indicator into perspective.

The observed reduction in the primary AMC indicators for humans and food-producing animals underlines the efforts taken by the EU/EEA countries to reduce antimicrobial consumption and prevent the spread of resistant bacteria. The heterogeneous trends in AMC in relation to the human primary AMR indicators show that the development of AMR is not necessarily parallel if different bacterial species and resistance mechanisms are involved. However, for further analysis of these divergent trends, more detailed data are needed that are not covered by the indicators.

Changes over time in primary key indicators on AMC and AMR for both humans and food-producing animals may help EU/EEA countries to customise interventions using a 'One-Health' approach. This feedback via primary key indicators may help each EU/EEA country to focus on exploring potential barriers in the event of an increase in AMR and AMC in humans or food-producing animals, or to explore facilitators, in the event of a decrease in AMC and AMR.

The proportion of indicator *E. coli* isolates from the most important production animals (i.e. broilers, fattening turkeys, fattening pigs and calves) that are completely susceptible to the entire harmonised panel of antimicrobials has been retained as the primary key indicator in food-producing animals. The harmonised AMR monitoring in the EU yields data based on use of the same panel of antimicrobials – defined in the legislation – and applying harmonised criteria (ECOFF) to interpret microbiological resistance. Adherence to legislation by the Member States guarantees this uniformity. The assumption underlying the choice of this specific indicator is that only *E. coli* which is rarely, if ever, exposed to antimicrobials, will be completely susceptible. The occurrence of complete susceptibility can therefore be used to assess the development of AMR in relation to the total use of antimicrobials (total AMC) in food-producing animals.

In the context of this report and in the analysis performed, complete susceptibility refers to susceptibility to each of the substances in the standard panel of antimicrobials tested. Therefore analysis was possible for indicator *E. coli* from food-producing animals, where a standard panel of antimicrobials was tested, but not for *E. coli* from humans.

The wide range in values observed, both for the total AMC in food-producing animals and in the occurrence of complete susceptibility in indicator *E. coli* observed in food-producing animals, tended to separate different countries rather than split them into amorphous clusters and provided a range of data highly suitable for analysis by logistic regression.

The total AMC in food-producing animals and the proportion of completely susceptible *E. coli* isolates in food-producing animals both varied substantially between countries. A statistically significant negative association was consistently detected between total AMC and the occurrence of complete susceptibility to all of the antimicrobials in the harmonised panel tested. The odds ratio estimates obtained by the models were remarkably consistent for all two-year periods considered, indicating that a two-fold increase in total AMC (expressed in mg per kg of estimated biomass and per year) resulted in a decrease by about 50% in the occurrence of complete susceptibility in *E. coli*. The consistency of the outputs, and the availability of data from a large number of countries, suggest that the association between complete susceptibility and total AMC is a key area for investigation in analyses of the type performed in the JIACRA report.

The ability of individual antimicrobials to influence the occurrence of complete susceptibility in indicator *E. coli* probably differs. This ability might be partly dependent on factors such as the availability and molecular arrangement of resistance genes in the gut microbiota or environment which can be acquired (through gene transfer) by indicator *E. coli*. Total AMC in food-producing animals is particularly influenced by those antimicrobials which are most frequently used in animals. In this respect, tetracyclines, sulfonamides and penicillins (including aminopenicillins) may be particularly important in both influencing the acquisition of resistance genes by indicator *E. coli* and in their proportionately large contribution to the total AMC.

Indicator *E. coli* is selected as the reporting organism instead of zoonotic organisms, since it is expected to better represent the overall AMR situation, including resistance due to plasmid-mediated AMR genes. Plasmid-mediated AMR genes are considered to be a more significant part of the total resistance that could be transferred from the agricultural sector to human healthcare than most antimicrobial-resistant zoonotic pathogens. A general and abundant species representing the overall AMR situation, such as indicator *E. coli*, is therefore more relevant than less abundant zoonotic species.

The availability of more detailed data on AMC in animals at the species or production level in the coming years may allow for possible further study and more detailed analyses.

14.11 Limitations

Inherent characteristics of analysed data

The data analysed in this report were obtained from a number of EU initiatives and networks. These data were collected for purposes other than the main objective of this study, which was to investigate potential relationships between AMC and AMR. The level of granularity[8] of the data available for analysis is a limitation that may impact the results obtained. With more refined data on the target population and use in different animal species and production, more refined analyses could have been be made. Nevertheless, in spite of the limitations, the analyses performed provide an overview and are considered useful for describing the overall impact of AMC in humans and animals and its effect on AMR in bacteria from humans and animals.

Uncertainty and imprecision of measurements

Antimicrobial consumption data

Although based on the best data currently available for the EU/EEA, AMC expressed in mg per kg of estimated biomass and per year for humans and food-producing animals is a crude indicator that must be interpreted

8 The term granularity reflects here whether the AMC and AMR data relate to an individual farm or hospital, or a region or a country and how representative the measurements of AMC and AMR are in relation to the corresponding population.

with caution because it does not account for differences in dosing between antimicrobial substances and pharmaceutical formulations.

Data on AMC in food-producing animals are currently only available as total sales (i.e. for all food-producing animal species). Total antimicrobial sales data do not allow the assessment of antimicrobial use by animal species as many of the antimicrobial veterinary medicinal products (VMP) are authorised with indications for use in more than one animal species – e.g. pigs, poultry, sheep and goats (see example in Table A2.3.1.). Therefore it is not possible to determine from sales data how much the antimicrobial VMP is used for treatment of each animal per species for which a VMP is authorised. In order to enable analysis of the occurrence of AMR in bacteria from pigs and poultry together with consumption data, sales data were used to obtain technical estimates of antimicrobial consumption in these species (see Annex 2). This estimation methodology is based on the animal species the VMP is authorised for (i.e. the proportion of sales of a VMP for a certain species is calculated by weighting the total sales by the estimated biomass of the various animal species for which the antimicrobial VMP is authorised). However if, for example, product A is authorised for cattle, pigs, horses and poultry but in real life this product is almost solely used for pigs, the estimates for sales of product A are underestimated for pigs and overestimated for poultry. Therefore, the limitations of the technically-derived estimates of AMC for pigs and poultry must be borne in mind when interpreting the results of analyses including such data.

The denominator kilogram of biomass used for AMC in humans may be an overestimate, as data on the weights of humans are uncertain and the ages at risk through treatment (children and the elderly being more frequently treated than other age groups) were not taken into account [97]. For AMC in animals, the denominator is a sum of the mass of different animal species and does not account for differences in the relative composition of the total national animal populations, as AMC may differ markedly between the various animal populations (i.e. production sectors) and by age category (age at risk) of a given animal species. Nevertheless, there is a good correlation between AMC in humans expressed as DDD per 1 000 inhabitants and per day and in mg per kg of estimated biomass and per year, both at the overall level and for each antimicrobial class [2].

It is estimated that in all EU/EEA countries, overall AMC in the community represents, on average, 90% of the total (community and hospital sector data) AMC in humans. In a few countries only reporting community AMC in humans, total AMC (expressed as mg per kg biomass) in humans was slightly underestimated. However, when interpolating the missing hospital sector data for these countries to the average proportion of 10% of the total national consumption, the EU/EEA median and the population-adjusted average (expressed as mg per kg biomass) increased only marginally, by less than 3%. Thus, the missing data did not have a significant influence on the overall AMC at the EU/EEA level.

The average proportion of the hospital sector consumption out of the total national consumption differs when considering specific antimicrobial classes or subclasses. For example, in human medicine carbapenems are almost exclusively used in the hospital sector, whereas the vast majority of fluoroquinolones are consumed in the community. There are significant differences in AMC between animals and humans for each antimicrobial class at EU/EEA level. Adding interpolated missing hospital sector data for antimicrobial classes to the human consumption would not significantly change the existing differences between AMC in animals and humans (expressed in mg/kg biomass). For example, this would be the case for comparison of polymyxin consumption, where the vast majority of polymyxins are consumed by food-producing animals or for consumption of third- and fourth-generation cephalosporins, where the vast majority are consumed by humans (Figure 7).

Data coverage of community AMC in humans was not 100% in all those countries included. The countries with less than 95% data coverage of community AMC were Germany (85%), the Netherlands (92%) and Luxembourg (90.5%). In these countries the consumption in tonnes of active substance is extrapolated to 100%.

Other limitations that may hamper the comparison of AMC in humans and in food-producing animals were discussed in the first JIACRA report [2].

Antimicrobial resistance data

In food-producing animals, the representative nature of the sampling performed and the adoption of identical AST methodologies facilitated the standardised investigation of associations between AMC and AMR in different reporting countries. At the same time, the Commission Implementing Decision 2013/652/EU only targets the main food-producing animal populations and some bacteria/animal population combinations are tested and reported on a voluntary basis. In many instances, this means that data are only available for certain countries and therefore meaningful associations cannot be established with the approach chosen for this report. Moreover, for *Salmonella* spp. in particular, limited prevalence in the animal population leads to a lack of isolates available for resistance testing. This limits the number of countries where sufficient data are available (i.e. the number of data pairs available for the correlation analysis).

Some populations, such as companion animals, sheep, and dairy cows, are not covered by the statutory monitoring of AMR in animals. Companion animals may exchange bacteria with family members and others as they are in close contact with people [98]. Moreover, regulations on use, which preclude use of any antibiotics that do not have a maximum residue limit in food-producing animals, permit occasional use of antibiotics 'off label' in companion animals using the cascade

approach. Food-producing animals not covered by the resistance monitoring are still included in the AMC (sales) data, which may have an impact on the associations studied between AMC and AMR in animals. In some instances, this effect should not be underestimated – e.g. with respect to use of third- and fourth-generation cephalosporins which is frequent in dairy cows in many countries.

Furthermore, genetic linkage of AMR genes and the issue of deriving combined resistance to some or all antimicrobials within an antimicrobial class are factors that increase the complexity of this type of analysis. Consequently, the analysis did not attempt to evaluate AMC and AMR in food-producing animals and humans for all available combinations of antimicrobials and bacterial organisms, but focussed on certain combinations of interest for which sufficient data were available.

Available data on AMR in bacteria from meat were disregarded in the context of this report. Testing of meat is only mandatory for some bacteria. The data were therefore considered insufficient to perform meaningful analyses. Unlike bacterial isolates sampled from the intestinal flora of healthy animals at slaughter, the bacteria present on meat may additionally be influenced by production processes which influence bacterial survival and therefore, the bacterial load on food items. Furthermore, the sources of bacteria on meat include not only the animals from which the meat was derived, but also the people involved in meat production, as well as the environment in which meat was prepared or stored. Cross-contamination between meats originating from different national sources might also occur. Meat samples may represent domestic production and/or meat originating from other Member States or imports from third countries. Therefore it is essential to distinguish between these sources for a meaningful analysis of AMR in bacteria from meat in relation to AMC in animals, because there may be differences in exposure to antimicrobials in the countries.

The comparisons between AMR in relevant bacteria from food-producing animals and humans may be hampered by the difference in sampling for the two sectors. AMR data from humans were based on the testing of clinical isolates. These isolates are primarily tested to guide treatment and the selection of isolates is heavily influenced by the test strategy. Minimum inhibitory concentrations are evaluated based on clinical breakpoints. For this report, this was applicable to invasive *E. coli* isolates from humans. For *Salmonella* spp. and *Campylobacter* spp., AST results are interpreted using ECOFFs, or aligned closely with the ECOFF for data already interpreted. In food-producing animals a unified sampling scheme is applied, based on EU legislation and the interpretation of resistance using ECOFFs. Samples and isolates do not originate from clinical cases but from randomly chosen, presumably healthy animals and populations.

AMR data for *Salmonella* spp. and *Campylobacter* spp. were, in general, directly comparable between both sectors as evaluation criteria were similar (Figure 2 and Figure 3). In contrast, findings on *E. coli* were less so, with a difference of one to four dilution steps, depending on the antimicrobial, between the ECOFFs and clinical breakpoints used in the sectors (Figure 4). Furthermore, *E. coli* from humans and food-producing animals originated from different types of bacterial populations under surveillance. AMR in invasive *E. coli* isolates from human blood-stream infections was compared to AMR in primarily non-pathogenic indicator commensal *E. coli* isolates from healthy food-producing animals. Differences in AMR exhibited by clinical and non-clinical isolates from animals have been identified in *E. coli* from poultry and cattle. However, these differences are not systematic – i.e. for certain animal/antimicrobial substance/bacterial combinations resistance was higher in non-clinical isolates while in others taken from the same populations the opposite applied [51, 99]. Without characterisation of the bacteria from the two populations, involving both 'traditional' methods (e.g. serotyping) and molecular characterisation of resistance genes – for example, any apparent associations between the two populations in relation to AMR are difficult to assess.

About two-thirds of the data from human *Salmonella* spp. and *Campylobacter* spp. isolates were from the national public health reference laboratories (NPHRLs). These data may not always constitute a representative selection of the *Salmonella* and *Campylobacter* infections in the countries as only a few countries submit all isolates for testing at the central reference laboratory level. Due to the role of the NPHRLs, there is a risk of over-representation of isolates that are difficult to type or of strains from outbreaks (although this has less impact for *Campylobacter* spp. where outbreaks are rare or more difficult to detect than for *Salmonella* spp.). A couple of countries also focus the testing on *Salmonella* serovars with resistance patterns of particular concern (e.g. high-level fluoroquinolone resistance or MDR, for surveillance or research purposes). For this reason, and also to account for differences in resistance patterns by *Salmonella* serovar, separate analyses for the two main *Salmonella* serovars, *S.* Enteritidis and *S.* Typhimurium including its monophasic variant, were performed where possible. However the number of corresponding isolates from animals was frequently limited, due to the successful control programmes for *Salmonella*, especially in poultry.

When comparing the results of this report to those of JIACRA I and II, changes in the data collection need to be considered. For the animal data, changes were mainly made between 2013 and 2014, when Commission Implementing Decision 2013/652/EU became effective. Since 2014, no major change has occurred in the animal database.

Finally, in order to include as many data points as possible, particularly for *Salmonella* spp. and the respective serovars, a minimum of ten isolates tested for the bacteria and drug combination per country and year was set. Such a low cut-off is sensitive to random variation,

which may have resulted in large variations in the proportion of non-susceptible isolates.

Ecological data and ecological analysis

This report provides an integrated multivariate ecological study of available data on AMC and AMR in bacteria from humans and food-producing animals, provided by the EU-wide surveillance/monitoring programmes. The report investigated, in an exploratory manner, the impact of the consumption of antimicrobials in both human and animal sectors on the occurrence of AMR in selected pathogenic and non-pathogenic bacteria in these sectors in 2016, 2017 and 2018. At the same time, it used the data generated to investigate AMR in humans in relation to AMC in the food-producing animals. Both AMC and the occurrence of AMR were considered at the population level, whether animal or human, in each country and then compared across countries.

The potential direct relationships between AMC in humans and AMR in animals were not addressed in this report. Investigation of this relationship would ideally require data relating to a bacterial organism occurring in humans where the bacterium is exposed to AMC, with the additional condition that this bacterium is relatively frequently acquired by animals from humans. Since data relevant to such situations are not currently available, this analysis was not performed.

Although ecological studies are particularly useful for generating hypotheses, they cannot establish causation, no matter how strong the associations discerned, since traditional criteria for causality are not met. The findings of ecological analyses, such as those presented in this report, are not causal assessments. Therefore, it cannot be excluded that, while detecting a statistically significant association, concomitant phenomena were observed without any causal relationship. It is important to take this into account when interpreting the results of the analyses presented in this report.

The statistical units of the ecological analyses were countries, limiting the size of the data sets to a maximum of 30 units. Outliers – i.e. country data that were characterised by extraordinarily high or low AMC or AMR – were observed throughout the analyses. These might have a significant impact on the results, as logistic regression may be sensitive to such outliers. Sensitivity analyses were performed when deemed appropriate. The distribution of countries in graphs of consumption versus resistance do not provide details of the epidemiology or underlying reasons for observed differences, but they provide a starting point which might be useful as a tool in stimulating relevant investigations.

Inherent characteristics of the statistical methods used

Partial Least Squares Path Modelling (PLS-PM)

The datasets analysed in the univariate and the multivariate analysis were not exactly the same. The multivariate analysis included data on AMR in bacteria from animals for 2017 and 2018, and corresponding pooled or averaged data on AMR in bacteria from humans. In contrast to the results of the univariate analyses, those for the multivariate models cannot be expressed as odds ratios, since PLS-PM is based on a linear assessment of the relationship between the latent variables.

PLS-PM was elected to perform multivariate analyses, as it allows presenting and accounting for the biological knowledge of the complex relationships between AMC and AMR data, as represented in Figure 1. For AMR in bacteria from humans, AMC in animals could be considered as either a direct or an indirect independent variable –in the latter case, through impact on AMR in bacteria from food-producing animals, possibly subsequently transmitted to humans. PLS-PM is also particularly suitable when there is multicollinearity between independent variables and few observations in relation to the number of independent variables. Although PLS-PM does not impose sample size assumption, a minimum of twenty observations are frequently mentioned in the literature as required. Within the framework of this report, given the strength of the relationships, the small number of independent variables and the low complexity of the relationship network, some models were still computed by including between 10 and 20 observations. In such cases, no bootstrap was performed to estimate confidence intervals. The limited number of observations should be kept in mind when interpreting the results of multivariate analysis.

The multivariate analysis should be considered as both structural representation and assessment of the relationships that could be explored between all data available, still summarising data components (data measured in different animal species or in different settings) through latent variables. The multivariate models determined both the significance and the magnitude of the relationships between AMR in bacteria from humans and i) AMC in humans (as a combination of consumption in the community and in hospitals) and ii) AMR in bacteria from animals (as a combination of AMR data on pigs and poultry), while considering the impact of AMC in animals (as a combination of AMC data in pigs and poultry). Not all the potential relationships were addressed independently in a two-by-two assessment at the food-producing animal/species level as in the univariate analysis, but they were addressed simultaneously.

The PLS-PM models assessed the relationships between AMR in bacteria from humans and corresponding AMC and AMR in bacteria from pigs and poultry only (and AMR in bacteria from poultry only for *C. jejuni* models). As AMC and AMR in other animal species, as well as AMR in other reservoirs, could also play a role, the results of PLS-PM models were an attempt to estimate the relative influence of the parameters addressed in the analysis. They should therefore not be interpreted as a comprehensive overview of the determinants of AMR in bacteria from humans.

Other factors influencing interpretation of results

Antimicrobial consumption

The use of antimicrobials for humans and animals differs considerably (see Annex A1.1). In humans in the community, oral medication of individuals is by far the most common. In contrast, the most common method for medicating food-producing animals is orally, giving medication to groups of animals. Such groups can be small, such as a pen of piglets, or large – all the animals in a stable. Children, elderly people and young animals are more likely to need antimicrobial treatment than adult individuals. Furthermore, the lifespan of animals reared for slaughter is mostly short.

Occurrence of the target bacterium

The analyses performed in this report used available data from the EU/EEA countries and other reporting countries. The associations detected for *E. coli*, as well as for *C. jejuni* and related antimicrobials in poultry, were usually much stronger than for *Salmonella* spp., where statistically significant associations were much less frequently detected. The prevalence of *Salmonella* spp. and specific serovars varies greatly between countries and populations. In most countries, *Salmonella* spp. is not ubiquitous, whereas *E. coli* is ubiquitous and *C. jejuni* is very common in the species of poultry studied. Thus, there may be countries with high or low AMC in a sector, but a lack of general exposure to the target bacteria because of its limited occurrence. The first JIACRA report commented in detail on these aspects and in particular, the role of clonal spread of resistant bacteria, which is often significant in *Salmonella* spp. The investigation of associations between AMC and AMR for bacteria such as *Salmonella* spp., which are not ubiquitous, probably needs to be studied in more detail.

Clonal spread

Successful global dissemination of specific clones/lineages with antimicrobial resistant genes has been described in *E. coli* responsible for intestinal and extraintestinal infections, both in humans and animals [100]. *Escherichia coli* multilocus sequence type (MLST) ST131 is the most prevalent pandemic extraenteric pathogenic clone found in the human sector (causing community and healthcare-acquired infections), companion animals, poultry and occasionally in other food-producing animals [100, 101]. One of the characteristics of this lineage is acquisition of antimicrobial resistance, mainly to the extended spectrum cephalosporins, typically by production of CTX-M beta lactamases, and frequently to the fluoroquinolones [100, 102]. Recently, carbapenem and colistin resistance has been found in *E. coli* ST131 [103, 104]. Other prevalent *E. coli* clonal complexes include STc12, STc14, ST410 with varying percentages of antimicrobial resistance [100].

In *Salmonella*, clonal spread is common and antimicrobial use in animal husbandry and possibly also in humans seems to facilitate the dissemination of particularly resistant clones. Some examples of clonal lineages with AMR patterns of concern are monophasic *S.* Typhimurium DT193 with resistance patter ASSuT [105], highly-ciprofloxacin resistant and multidrug-resistant *S.* Kentucky ST198 [106] and ESBL-producing *S.* Infantis [107]. While the former is primarily associated with pigs, the latter two are poultry-related, all three being among the top serovars in human salmonella infections in the EU/EEA.

For *Campylobacter*, clonal spread was previously not considered an issue, but this may rather reflect the absence of typing methods able to differentiate between *Campylobacter* bacteria. With the introduction of genome sequencing, a large genetic diversity has been revealed in *Campylobacter*, although some sequence types or clonal complexes have also been found to be more common in certain areas in both humans and animals (primarily poultry) or in the environment [108–110]. However, the cross-border spread of such types still needs to be explored.

Clonal spread of resistant bacteria could interfere in the analysis of the association between antimicrobial use and resistance in ecological studies, such as these conducted in this third JIACRA report. This is particularly the case for analyses involving *Salmonella*. However, this is complex and, in the case of successful pandemic *E. coli* clones including the ST131, global spread can be attributed to many factors, including their resistance to antimicrobials to which most of humans and animals are exposed [100, 102].

15. Conclusions

This is the first time that the EU/EEA population-weighted average AMC in humans overall exceeds AMC in food-producing animals when measured in mg/kg biomass. AMC in food-producing animals has decreased in many countries, resulting in a lower total figure. This indicates that measures taken to reduce AMC in food-producing animals at country-level have had a positive effect. An overall decrease in EU/EEA population-weighted AMC was also observed in humans for the same time period, when measured in DDD per 1 000 inhabitants per day and including all 30 EU/EEA countries.

Many of the associations observed between AMC and AMR within or between sectors fit well with the current knowledge of the epidemiology of AMR and infections relating to the bacterial species studied. Nevertheless, the limitations described should be considered when interpreting the findings. In ecological analyses, such as those presented in this report, the findings should be considered as hypotheses for subsequent testing, through focused research or refinement of data that could provide better explanations in some cases. For *E. coli*, a positive association between AMC and AMR was observed in almost all antimicrobial classes with data reported for both sectors. Positive associations between AMC and AMR were frequently also found in *C. jejuni*, especially in the animal sector but not in *Salmonella*. This is partly explained by the typically larger datasets available for *E. coli* and *C. jejuni* compared to *Salmonella*. Moreover, factors other than AMC influence the occurrence of resistance. For certain serovars of *Salmonella*, spread of resistant multi-drug resistant clones is important in the epidemiology and this impacts the assessment of relations between AMC and AMR. A better understanding of the relative importance of the spread of resistant clones and/or the influence of AMC could be gained if data on genotypic resistance and molecular strain typing were available for analysis. This would also generally complement the analyses of associations between AMR in food-producing animals and in humans. For the typically food-borne bacterial genera, *Salmonella* and *Campylobacter*, travel and trade in food may also influence the outcome of analyses.

The most consistent positive association between AMR in bacteria from food-producing animals and AMR in bacteria from humans was found for *Campylobacter* spp. This is probably a consequence of the fact that *Campylobacter* spp. are found in food-producing animals and cause food-borne infections in humans. The lack of consistency in the results for *Salmonella* spp., another food-borne bacterium, is most likely due to differences in resistance patterns of *Salmonella* serovars and clonal spread of certain strains across Europe.

There was a difference between the antimicrobial classes studied in terms of significant associations observed between AMC and AMR. For example, there were many significant observations for fluoroquinolones and less for third- and fourth-generation cephalosporins. This could reflect differences in how the respective classes are used, or differences in the epidemiology of the resistance determinants involved, or both.

As in previous JIACRA reports, complete susceptibility to a standardised panel of antimicrobial classes showed a statistically significant negative association with total AMC in food-producing animals. Both parameters (complete susceptibility and total AMC) showed a wide variation among countries. This suggests that measures to encourage prudent use should cover all antimicrobial classes consumed to take into account the potential impact of co-selection of AMR. In this report there is no similar analysis for the data from humans as suitable data was not available. In future reports an analysis using a harmonised list of substances for animals and humans might facilitate interesting insights into the effect of total antimicrobial usage in humans and food-producing animals on AMR in humans.

The multivariate analysis proved to be a useful approach for assessing the statistical significance and relative strength of associations between the occurrence of AMR in bacteria from humans and AMR in bacteria from food-producing animals, and AMC in both food-producing animals and humans. In contrast to the second JIACRA report, this third report includes multivariate analyses for additional antimicrobial classes and, in many cases, also includes data from a larger number of countries. This makes direct comparison with the results of the second and third JIACRA reports difficult, but when applicable the results were consistent overall.

Multivariate analysis was sometimes not feasible or relevant due to absence of data or absence of AMC (e.g. AMR data on colistin or tetracycline for *E. coli* in humans, no AMC of carbapenems in animals). The analyses show that the relative strength of the associations between consumption and resistance within the human sector and between consumption in food-producing animals and resistance in bacteria from humans, may differ markedly. The interpretation of analyses is sometimes complicated by an observed correlation between AMC in food-producing animals and humans (fluoroquinolones and aminopenicillins), as this makes it difficult to differentiate between an effect of AMC in food-producing animals on AMR in humans and the direct effect of AMC in humans on AMR in humans.

Other factors that could be considered in multivariate analysis are resistance to other antimicrobials (co-resistance) and the potential effects of co-selection of resistance through the use of other antimicrobials. Further factors, if available, could be information on

travel by humans, transfer of patients between hospitals, import and trade of food, food of non-animal origin, trade of live animals both between and within countries and exposure of animals or humans to bacteria with AMR via the environment.

For a first time, the five primary key indicators suggested by ECDC, EFSA and EMA were presented for each country in a 'One-Health' approach. These indicators are key parameters for monitoring trends in overall AMC and AMR in both humans and food-producing animals.

The availability of more detailed and comprehensive AMC-data would allow more refined analyses in relation to AMR data and make the corresponding outputs more robust. AMC data should preferably be collected so that analysis for relevant sub-groups is possible. For example, AMC in the hospital sector versus the community for all EU/EEA countries, or AMC in animal categories that are likely to have characteristic treatment patterns, such as sows and sucklers, slaughter pigs, calves, dairy production, beef production, laying hens, broilers and turkeys. Future availability of AMC by animal species and relevant categories, expressed with dose-corrected metrics will help to address this. The development of the mandatory monitoring of AMR in animals will also provide even more robust data-sets for analysis.

Other improvements to existing systems were highlighted in previous JIACRA reports and several of these recommendations remain valid. The systems from which data are derived are designed for other primary purposes, and lack of data in one sector obviously limits possibilities for analysis from a 'One-Health' perspective. Although the various surveillance and monitoring systems for AMC and AMR serve different primary purposes, the agencies continue to work on further harmonisation and integration of surveillance across sectors to better understand the relationship between consumption and resistance. Monitoring of AMR could also include animal pathogens, commensal flora from both healthy humans and humans with infection, and information on the origin of the animals, particularly where importation from other sources may influence the occurrence of AMR.

Overall, the findings suggest that further interventions to reduce and improve AMC will have a beneficial impact on the occurrence of AMR. This underlines the need to promote prudent use of antimicrobial agents and infection control and prevention in both humans and in food-producing animals. The remaining high levels of AMC and AMR reported in both food-producing animals and humans from several countries show that interventions to tackle the situation should be reinforced.

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Annex 1 – Additional analyses

A1.1. Antimicrobial consumption

Table A1.1.1: Amount of antimicrobial active substance[a], estimated biomass and antimicrobial consumption in humans and food-producing animals[a], 28 EU/EEA countries for which data were available both for humans and food-producing animals, 2016

Country	Hospital consumption data included	Amount of active antimicrobial substance (tonnes)			Estimated biomass (1,000 tonnes)			Antimicrobial consumption (mg/kg estimated biomass)	
		Humans[b]	Food-producing animals[c]	Total	Humans	Food-producing animals	Total	Humans	Food-producing animals
Austria	No	38	44	82	544	957	1501	69.2	46.1
Belgium	Yes	109	240	349	707	1715	2422	153.6	140.1
Bulgaria	Yes	49	61	110	447	393	840	109.1	155.3
Croatia	Yes	33	27	60	262	302	564	123.8	87.9
Cyprus	No	8	46	54	53	102	155	147.1	453.4
Denmark	Yes	50	99	149	357	2420	2776	140.9	40.8
Estonia	Yes	6	7	13	82	113	195	75.5	64.0
Finland	Yes	45	10	54	343	521	864	130.0	18.6
France	Yes	757	514	1271	4165	7143	11308	181.3	71.9
Germany[d]	No	339	779	1118	5136	8734	13870	64.5	89.2
Greece	Yes	142	80	222	674	1258	1932	210.9	63.5
Hungary	Yes	51	156	207	614	832	1446	83.1	187.1
Iceland	No	2	1	3	21	120	141	108.3	4.7
Ireland	Yes	48	102	150	295	1963	2258	160.9	52.1
Italy	Yes	621	1213	1834	3792	4116	7907	163.7	294.8
Latvia	Yes	10	5	16	123	180	303	84.1	29.9
Lithuania	Yes	19	13	32	181	338	519	104.7	37.7
Luxembourg[d]	Yes	5	2	7	36	55	91	139.1	35.5
Netherlands[c]	Yes	59	182	241	1061	3446	4507	54.2	52.7
Norway	Yes	45	6	51	326	1896	2222	139.4	2.9
Poland	Yes	289	570	860	2373	4407	6780	122.0	129.4
Portugal	Yes	80	211	291	646	1014	1660	135.9	208.0
Romania	No	264	265	529	1235	3116	4351	213.7	85.1
Slovakia	Yes	51	12	63	339	242	581	149.2	50.4
Slovenia	Yes	13	5	18	129	178	307	97.0	30.3
Spain	No	499	2725	3224	2903	7518	10420	171.6	362.5
Sweden	Yes	72	10	82	616	805	1421	116.8	12.1
United Kingdom	Yes	505	281	786	4086	7142	11229	123.5	39.3
28 EU/EEA countries		**4208**	**7706**	**11873**	**31546**	**61026**	**92571**	**133.2[e]**	**125.6[e]**

(a): Calculated from the exact figures (not from the rounded figures).
(b): ATC J01 Antibacterials for systemic use.
(c): ATCvet QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51, QP51AG.
(d): For countries reporting less than 95% data coverage for consumption in humans (Germany 85%, the Netherlands 92% and Luxembourg 90.5%), the consumption in tonnes of active substance was extrapolated to 100%.
(e): Population-weighted mean.

Table A1.1.2: Range, median and population-weighted mean consumption of antimicrobials overall and for the classes selected for analysis in humans and food-producing animals, and correlation analysis of antimicrobial consumption in humans and food-producing animals, 28 EU/EEA countries* for which data were available both for humans and food-producing animals, 2016

Antimicrobial class	Antimicrobial consumption (mg/kg estimated biomass)						Correlation coefficient[b] (p-value)
	Humans			Food-producing animals			
	Range	Median	Mean[a]	Range	Median	Mean	
Carbapenems	0.01–2.87	0.64	0.46	-	-	-	N/A
Third- and fourth-generation cephalosporins	0.1–11.8	2.4	3.9	<0.01–0.7	0.2	0.2	0.19 (0.328)
Fluoroquinolones and other quinolones	2.6–26.5	6.7	8.1	<0.01–9.8	1.0	3.2	0.74 (<0.001)
Polymyxins	0–0.19	0.02	0.04	0–22.0	1.1	6.5	0.25 (0.207)
Aminopenicillins[c]	7.2–126.8	48.3	68.7	0.1–86.3	11.3	29.0	0.48 (0.011)
Macrolides	1.4–14.7	6.7	8.4	0–29.2	4.1	8.9	0.42 (0.024)
Tetracyclines	0.3–12.2	1.6	3.2	0.06–180.7	22.2	40.9	-0.36 (0.058)
Total consumption[d,e]	**56.8–242.0**	**130.0**	**132.2**	**2.9–453.4**	**58.1**	**126.3**	**0.26 (0.187)**

* AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK.

(a): Population-weighted mean.

(b): Spearman's rank correlation coefficient (rho) for consumption in humans and consumption in food-producing animals.

(c): Includes ampicillin and amoxicillin without and with beta-lactamase inhibitors and metampicillin belonging to the ATC vet groups/codes QA07AA98, QA07AA99, QJ01CA, QJ51CA, QJ01CR01, QJ01CR02, QJ01CR50, QJ51CR01, QJ51CR02, QJ51CR50, QJ51RA01, QJ51RV01, QG51AA03, QG51AG04, QG51AG05 and QG51AG07.

(d): For humans: ATC J01.

(e): For animals: ATCvet QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51, QP51AG.

N/A: not applicable.

Table A1.1.3: Amount of antimicrobial active substance[a], estimated biomass and antimicrobial consumption in humans and food-producing animals[a], 29 EU/EEA countries for which data were available both for humans and food-producing animals, 2018

Country	Hospital consumption data included	Amount of active antimicrobial substance (tonnes)			Estimated biomass (1,000 tonnes)			Antimicrobial consumption (mg/kg estimated biomass)	
		Humans[b]	Food-producing animals[c]	Total	Humans	Food-producing animals	Total	Humans	Food-producing animals
Austria	No	37	48	85	551	957	1509	67.1	50.1
Belgium	Yes	103	195	298	712	1724	2437	145.8	113.1
Bulgaria	Yes	53	48	100	441	400	841	118.6	119.6
Croatia	Yes	33	20	53	257	293	550	123.7	66.8
Cyprus	No	8	53	61	54	115	169	151.0	466.3
Denmark	Yes	48	94	142	361	2447	2808	134.1	38.2
Estonia	Yes	6	6	12	82	114	196	76.3	53.3
Finland	Yes	42	9	51	345	497	841	121.1	18.7
France	Yes	772	456	1228	4183	7107	11290	179.3	64.2
Germany[d]	No	350	753	1103	5175	8518	13692	65.3	88.4
Greece	Yes	136	113	249	671	1244	1915	202.5	90.9
Hungary	Yes	52	150	202	611	832	1443	85.3	180.6
Iceland	No	3	1	3	22	116	138	129.7	4.9
Ireland	Yes	48	99	146	302	2142	2444	158.9	46.0
Italy	Yes	567	932	1499	3780	3819	7600	149.9	244.0
Latvia	Yes	10	6	16	121	167	288	83.8	36.1
Lithuania	Yes	24	11	34	176	324	499	134.4	33.1
Luxembourg[d]	Yes	7	2	9	38	55	92	177.1	33.6
Malta	Yes	4	2	6	30	14	44	124.3	150.9
Netherlands[c]	Yes	60	184	244	1074	3201	4275	54.3	57.5
Norway	Yes	44	6	50	331	1928	2258	134.1	2.9
Poland	Yes	335	782	1117	2374	4673	7046	141.2	167.4
Portugal	Yes	81	192	273	643	1028	1671	138.3	186.6
Romania	No	280	231	511	1221	2788	4009	227.9	82.7
Slovakia	Yes	40	12	52	340	247	586	118.1	49.3
Slovenia	Yes	14	8	22	129	180	309	107.1	43.2
Spain	Yes	551	1724	2275	2916	7865	10782	187.0	219.2
Sweden	Yes	71	10	81	633	783	1415	112.1	12.5
United Kingdom	Yes	485	213	698	4142	7216	11358	116.8	29.5
29 EU/EEA countries		**4263**	**6358**	**10622**	**31713**	**60792**	**92505**	**133.3[e]**	**104.6[e]**

(a): Calculated from the exact figures (not from the rounded figures).
(b): ATC J01 Antibacterials for systemic use.
(c): ATCvet QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51, QP51AG.
(d): For countries reporting less than 95% data coverage for consumption in humans (Germany 85%, the Netherlands 92% and Luxembourg 90.5%) the consumption in tonnes of active substance is extrapolated to 100%.
(e): Population-weighted mean.

Table A1.1.4: Range, median and population-weighted mean consumption of antimicrobials overall and for the classes selected for analysis in humans and food-producing animals, and correlation analysis of antimicrobial consumption in humans and food-producing animals, 29 EU/EEA countries* for which data were available both for humans and food-producing animals, 2018

Antimicrobial class	Antimicrobial consumption (mg/kg estimated biomass)						Correlation coefficient[b] (p-value)
	Humans			Food-producing animals			
	Range	Median	Mean[a]	Range	Median	Mean	
Carbapenems	0.01-2.67	0.75	0.62	-	-	-	N/A
Third- and fourth-generation cephalosporins	0.08–11.5	2.9	4.1	‹0.01–0.9	0.2	0.2	0.38 (0.045)
Fluoroquinolones and other quinolones	2.0–21.5	6.1	7.3	‹0.01–10.9	1.2	2.9	0.79 (‹0.001)
Polymyxins	0–0.95	0.04	0.2	0–12.8	1.8	3.4	0.13 (0.513)
Aminopenicillins[c]	7.4–124.7	50.1	67.4	0.06–79.7	9.8	26.6	0.48 (0.008)
Macrolides	1.1–16.1	6.8	7.6	0–27.9	4.9	8.0	0.32 (0.095)
Tetracyclines	0.3–10.9	1.7	3.0	0.07–155.2	21.7	31.7	-0.32 (0.088)
Total consumption[d,e]	**56.8–227.9**	**129.7**	**133.3**	**2.9–466.3**	**57.5**	**104.6**	**0.28 (0.136)**

* AT, BE, BG, CY, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK.

(a): Population-weighted mean.

(b): Spearman's rank correlation coefficient for consumption in humans and consumption in animals.

(c): Includes ampicillin and amoxicillin without and with beta-lactamase inhibitors and metampicillin belonging to the ATCvet groups/codes QA07AA98, QA07AA99, QJ01CA, QJ51CA, QJ01CR01, QJ01CR02, QJ01CR50, QJ51CR01, QJ51CR02, QJ51CR50, QJ51RA01, QJ51RV01, QG51AA03, QG51AG04, QG51AG05 and QG51AG07.

(d): For humans: ATC J01.

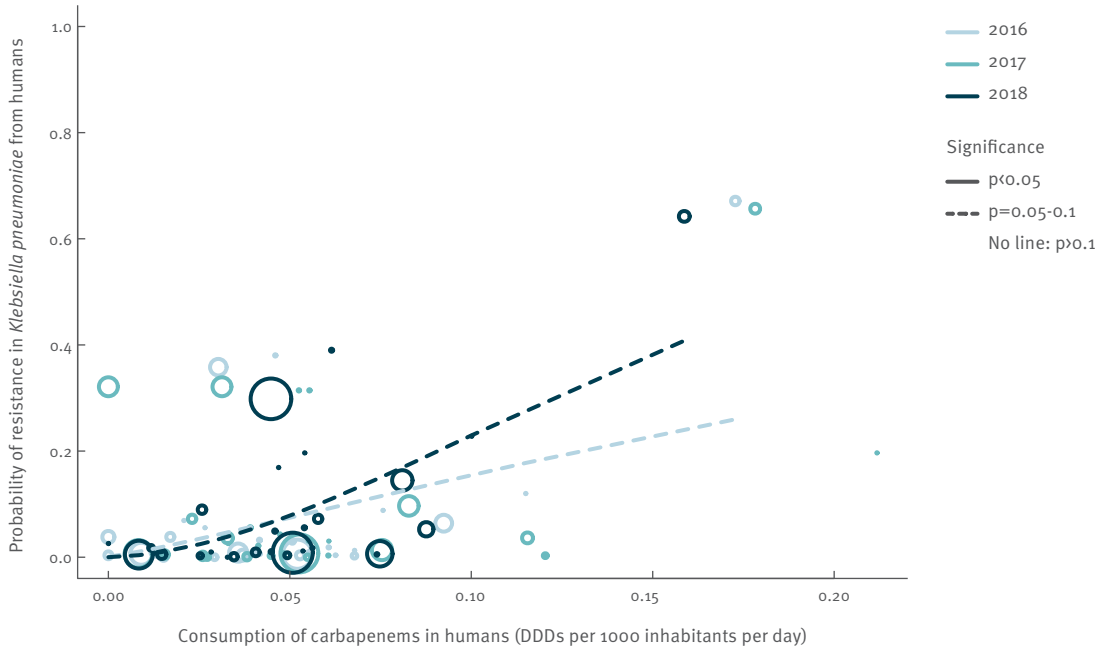
(e): For animals: QA07AA, QA07AB, QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AG, QJ01, QJ51, QP51AG.

N/A: not applicable.

A1.2 Univariate analysis - graphs for correlations with borderline statistically significant results

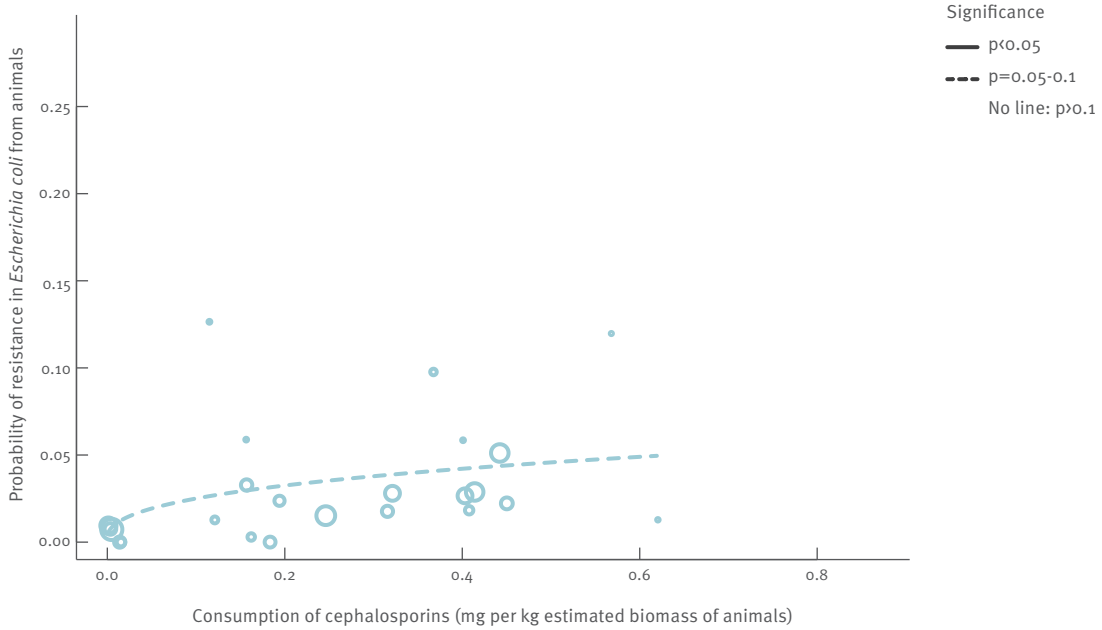
This section provides graphs for correlations with borderline significant results (e.g. p-value between 0.055 and 0.10).

Figure A1.2.1: Consumption of carbapenems in humans (DDD per 1 000 inhabitants per day) and probability of resistance to carbapenems in invasive *Klebsiella pneumoniae* from humans, EU/EEA, 2016-2018 (see also Table 8)



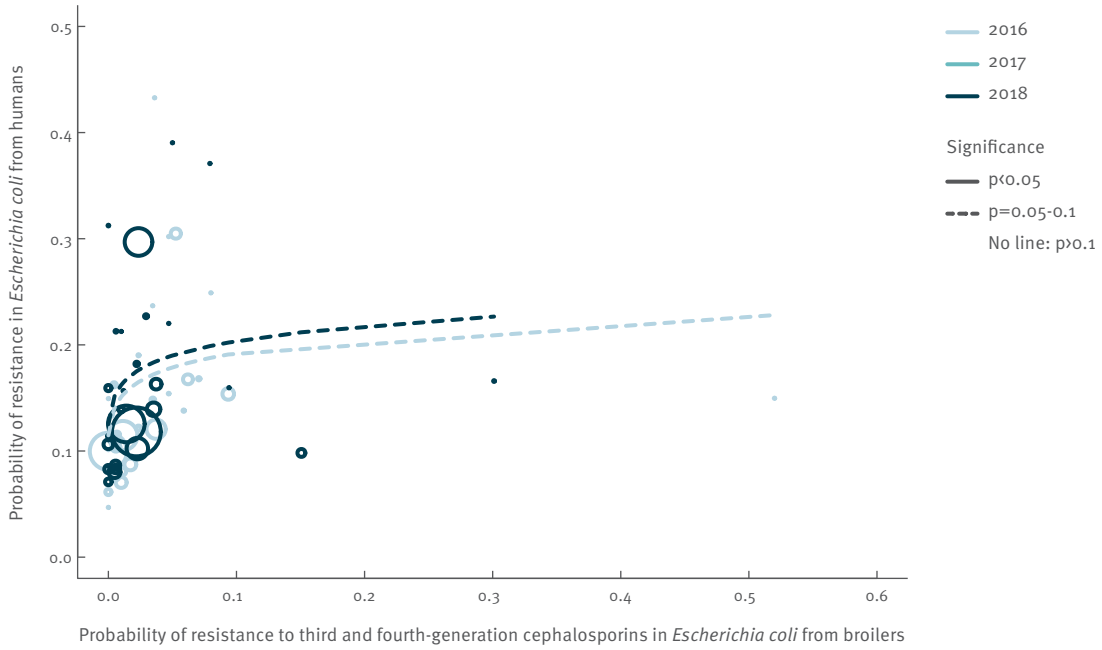
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Figure A1.2.2: Consumption of third- and fourth-generation cephalosporins in food-producing animals (mg per kg estimated biomass) and probability of resistance to third-generation cephalosporins in indicator *Escherichia coli* from food-producing animals, EU/EEA, 2014–2015 (see also Table 14)



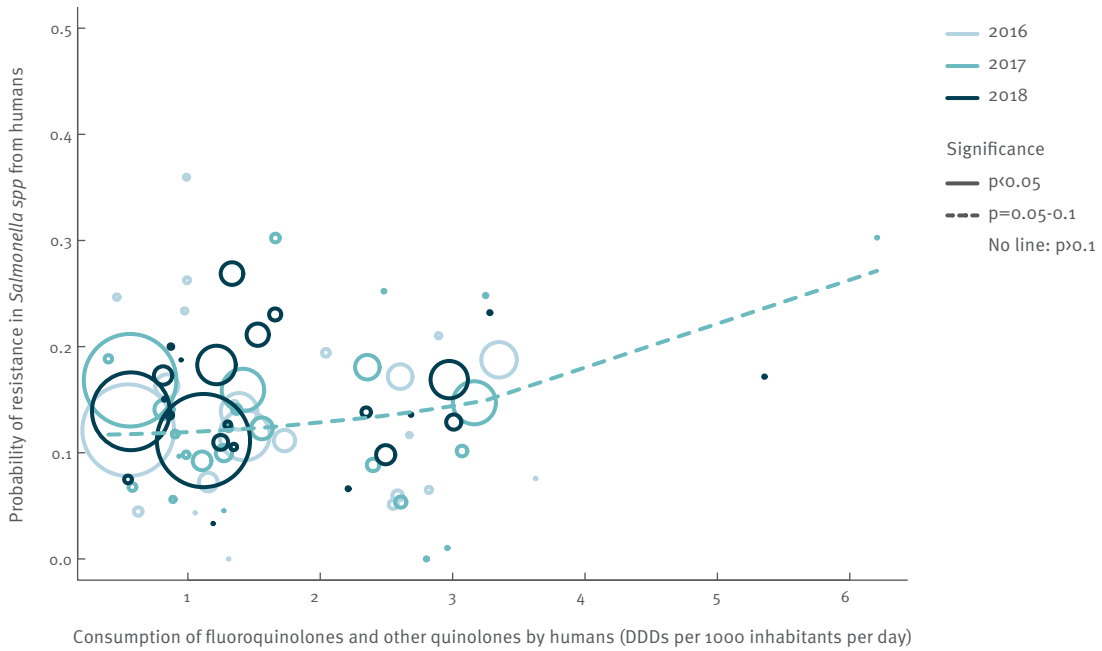
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Figure A1.2.3: Probability of resistance to third-generation cephalosporins in *Escherichia coli* from broilers and from humans, EU/EEA, 2016 and 2018 (see also Table 17)



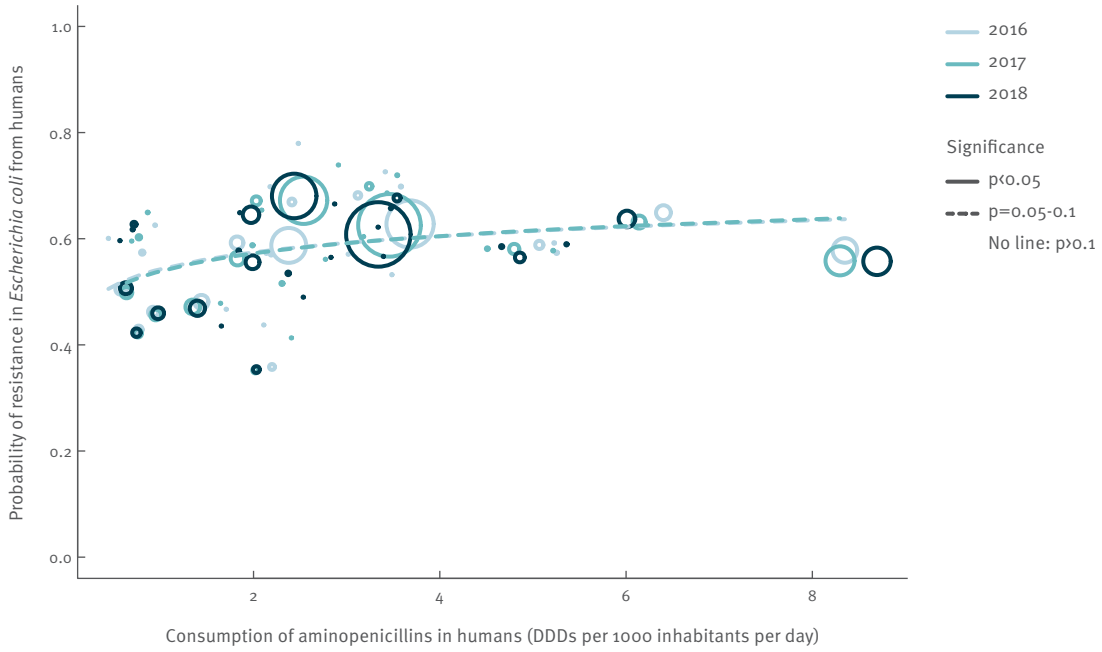
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Figure A1.2.4: Consumption of fluoroquinolones and other quinolones in humans (DDD per 1 000 inhabitants and per day) and probability of resistance to fluoroquinolones in *Salmonella* spp. from humans, EU/EEA, 2016–2018 (see also Table 24)



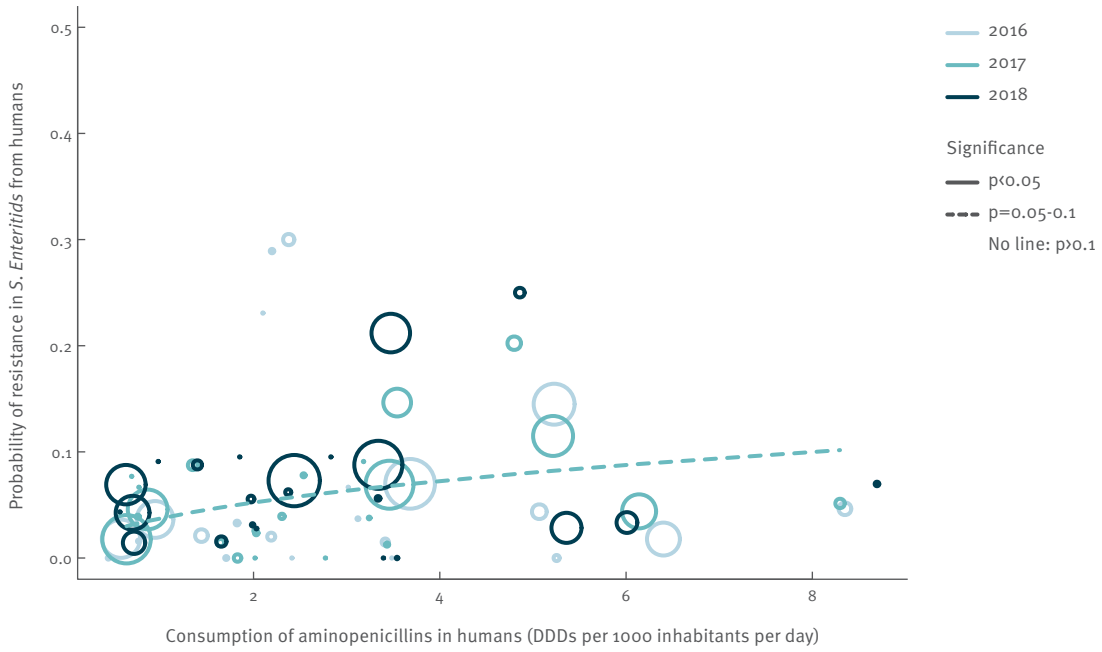
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Figure A1.2.5: Consumption of aminopenicillins in humans (DDD per 1 000 inhabitants and per day) and probability of resistance to aminopenicillins in *Escherichia coli* from humans, EU/EEA, 2016–2018 (see also Table 41)



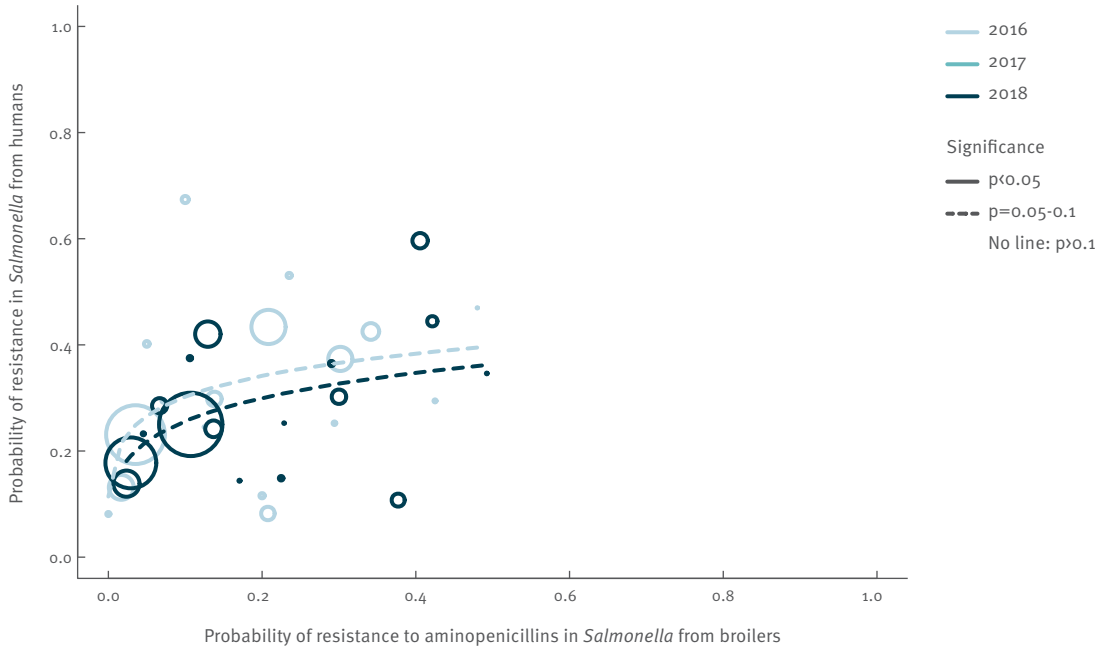
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Figure A1.2.6: Consumption of aminopenicillins in humans (DDD per 1 000 inhabitants per day) and probability of resistance to aminopenicillins in *Salmonella* Enteritidis from humans, EU/EEA, 2016–2018 (see also Table 43)



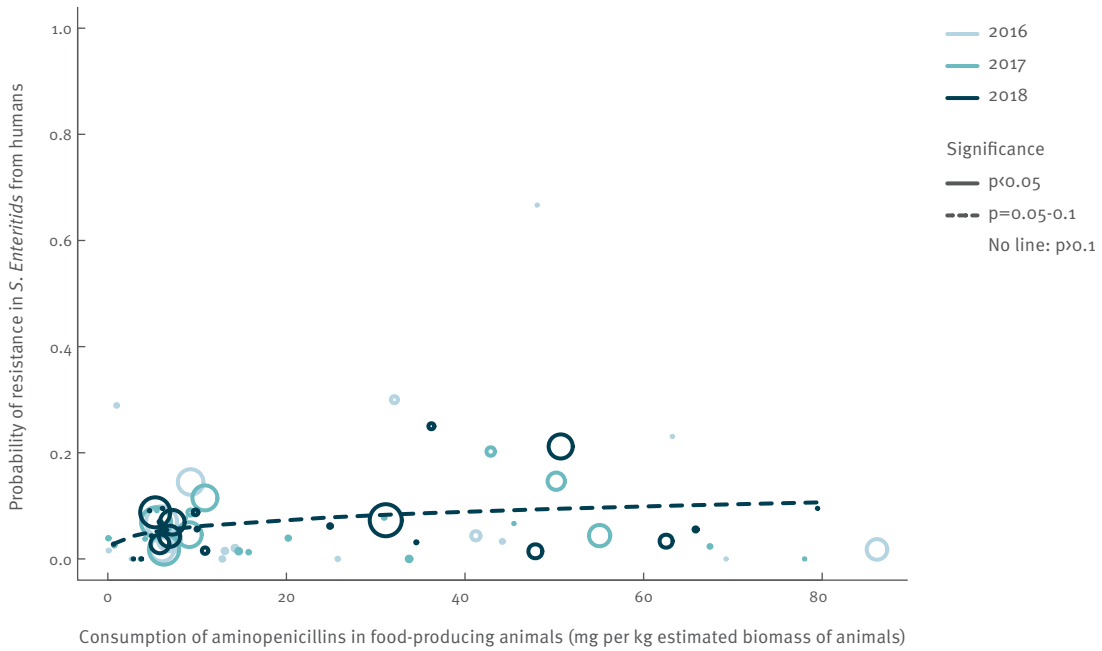
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Figure A1.2.7: Probability of resistance to aminopenicillins in *Salmonella* from food-producing animals (broilers) and from humans, EU/EEA, 2016 and 2018 (see also Table 48)



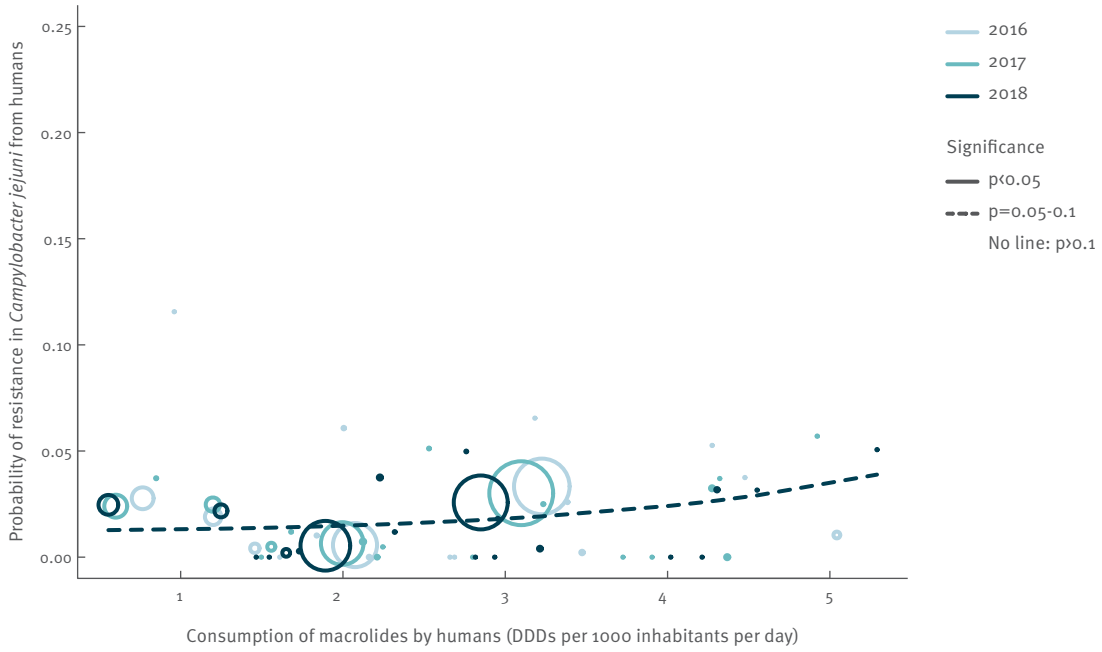
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Figure A1.2.8: Consumption of aminopenicillins in food-producing animals (mg per kg estimated biomass) and probability of resistance to aminopenicillins in *Salmonella* Enteritidis from humans, EU/EEA, 2016–2018 (see also Table 52)



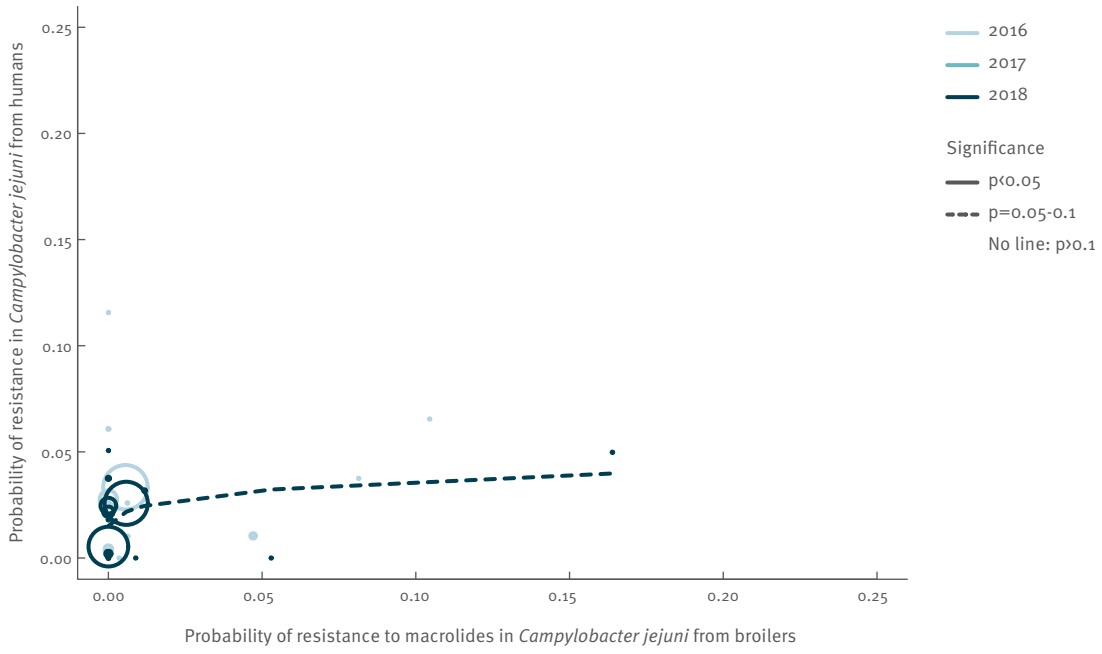
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Figure A1.2.9: Consumption of macrolides in humans (DDD per 1 000 inhabitants and per day) and probability of resistance to macrolides in *Campylobacter jejuni* from humans, EU/EEA, 2016–2018 (see also Table 54)



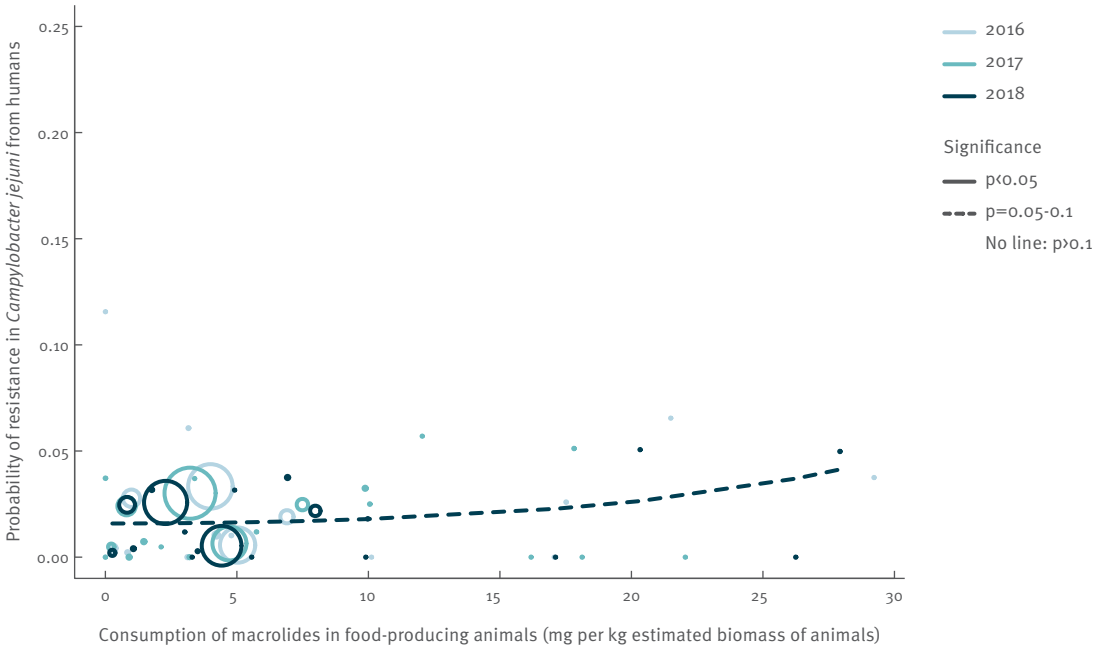
The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Figure A1.2.10: Probability of macrolide resistance in *Campylobacter jejuni* from broilers and from humans, EU/EEA, 2016 and 2018 (see also Table 56)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

Figure A1.2.11: Consumption of macrolides in food-producing animals (mg per kg estimated biomass) and probability of resistance to macrolides in *Campylobacter jejuni* from humans, EU/EEA, 2016–2018 (see also Table 57)



The figure displays the results of logistic regression analyses. Bubbles represent the countries included in the analysis. The size of the bubbles indicates the amount of available resistance data per country.

A1.3 Multivariate models performed on summary indicators

Deviating from the usual multi-block nature of the data, an attempt to fit models to SIMR parameters is presented below. These models only concern *E. coli*.

Cephalosporins

As observed in PLS-PM models performed on multi-block manifest variables, a significant relationship was identified between consumption of third- and fourth-generation cephalosporins in humans and resistance in invasive *E. coli* from humans (Figure A1.3.1). The fraction of the variance of resistance in bacteria from humans that could be explained was 59% (95% bootstrap confidence interval 29–84).

It should be noted that in a model of this type path coefficients may be directly related to correlation coefficients between variables.

Figure A1.3.1: Diagram of the PLS-PM of resistance to third--generation cephalosporins in invasive *Escherichia coli* from humans (2017 and 2018) considering (a) resistance to third-generation cephalosporins in indicator *E. coli* from food-producing animals (pigs and calves < 1 year in 2017 and poultry in 2018), (b) consumption of third- and fourth-generation cephalosporins in humans (mean for 2017–2018, mg per kg estimated biomass), and (c) consumption of third- and fourth-generation cephalosporins in food-producing animals (mean for 2017–2018, mg per kg estimated biomass), 26 EU/EEA countries*

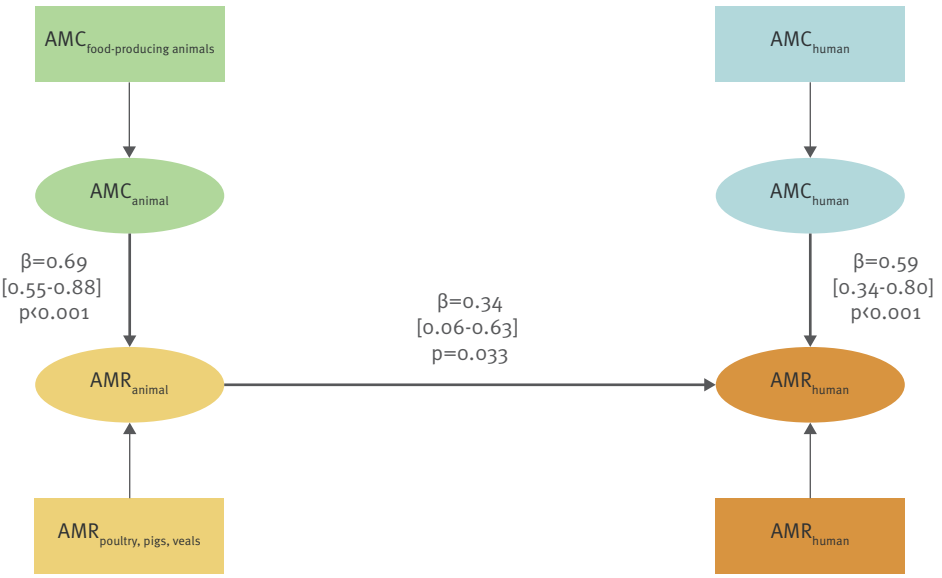
* AT†, BE, BG, CY, DE†, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS†, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK.

† For these countries, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

Fluoroquinolones

As seen in PLS-PM models performed on multi-block manifest variables, significant relationships were observed between consumption and resistance both in animals and humans, and between resistance in bacterial isolates from animals and from humans (Figure A1.3.2). The indirect effect of consumption of fluoroquinolones and other quinolones in animals on resistance to fluoroquinolones in invasive *E. coli* from humans was estimated at 0.232, whereas the direct effect of consumption in humans was assessed at 0.588. The model explained about 72% (95% confidence interval 54–89) of the variance of resistance in bacterial isolates from humans and only 48% (95% confidence interval 31–78) of the variance of resistance in bacterial isolates from animals.

Figure A1.3.2: Diagram of the PLS-PM of resistance to fluoroquinolones in invasive *Escherichia coli* from humans (2017 and 2018) considering (a) resistance to fluoroquinolones in indicator *E. coli* from food-producing animals (pigs and veal in 2017, and poultry in 2018), (b) consumption of fluoroquinolones and other quinolones in humans (mean for 2017–2018, mg per kg estimated biomass), and (c) consumption of fluoroquinolones and other quinolones in food-producing animals (mean for 2017–2018 mean, mg per kg estimated biomass), 26 EU/EEA countries*



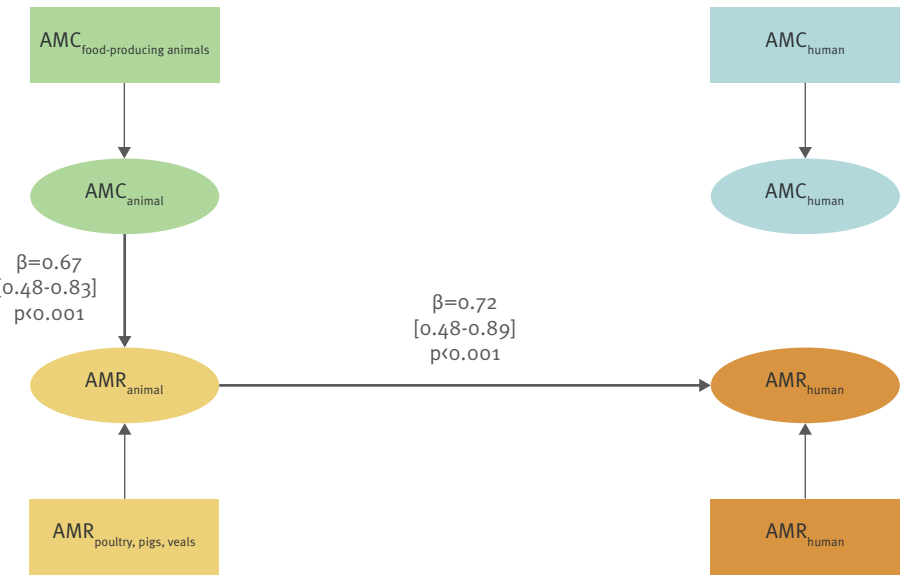
* AT†, BE, BG, CY, DE†, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS†, IT, LT, LV, NL, NO, PL, PT, RO, SE, SI, SK.

† For these countries, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

Aminopenicillins

The model fitted to the SIMR parameters was very similar to the model for multi-block manifest variables (Figure A1.3.3). The model explained about 52% (95% confidence interval 23–80) of the variance of resistance in bacterial isolates from humans and 44% (95% confidence interval 23–69) of the variance of resistance in bacterial isolates from food-producing animals.

Figure A1.3.3: Diagram of the PLS-PM of resistance to aminopenicillins in invasive *Escherichia coli* from humans (2017 and 2018) considering (a) resistance to aminopenicillins in indicator *E. coli* from food-producing animals (pigs and veal in 2017, and poultry in 2018), (b) consumption of aminopenicillins in humans (mean for 2017–2018, mg per kg estimated biomass), and (c) consumption of aminopenicillins in food-producing animals (mean for 2017–2018,– mg per kg estimated biomass), 25 EU/EEA countries*



* AT†, BE, BG, CY, DE†, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS†, IT, LT, LV, NL, NO, PL, PT, RO, SI, SK.

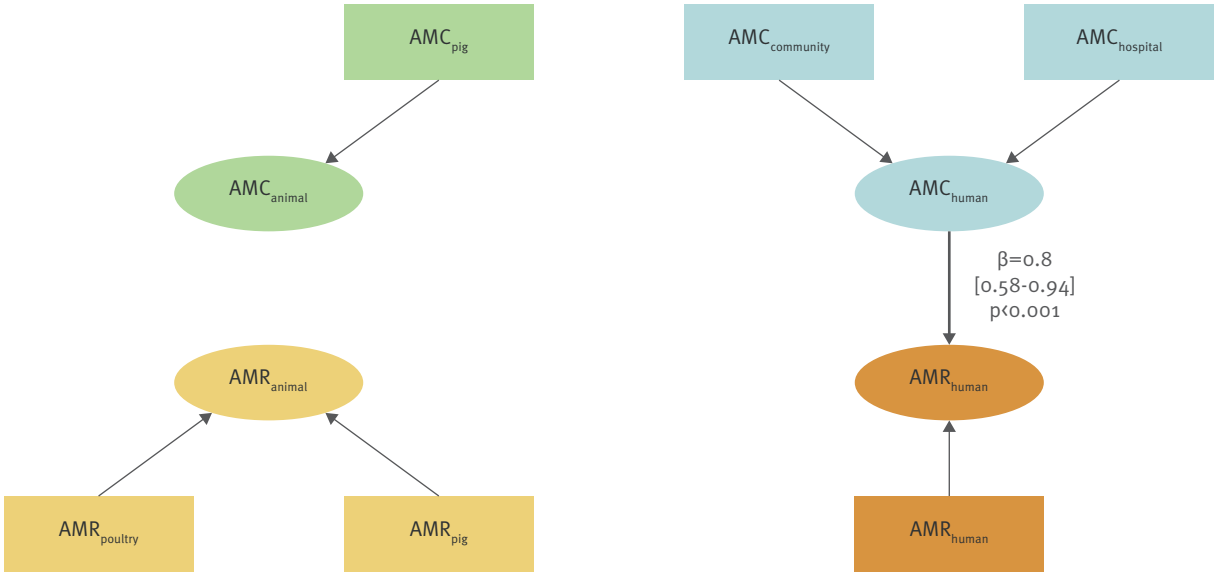
† For these countries, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

A1.4 Multivariate models performed on 2016–2017 data

This section presents results from the multivariate models performed on data from 2016 and 2017. Results based on data from 2017 and 2018 are presented in the main report text.

Cephalosporins

Figure A1.4.1: Diagram of PLS-PM model of resistance to third-generation cephalosporins in invasive *Escherichia coli* from humans (2016–2017) considering (a) resistance to third-generation cephalosporins in indicator *E. coli* from food-producing animals (pigs in 2017 and poultry in 2016), (b) consumption of third- and fourth-generation cephalosporins in humans (mean for 2016–2017, DDD per 1 000 inhabitants per day) and (c) consumption of third- and fourth-generation cephalosporins in food-producing animals (in pigs in 2017, DDDvet per kg estimated biomass), 28 EU/EEA countries*



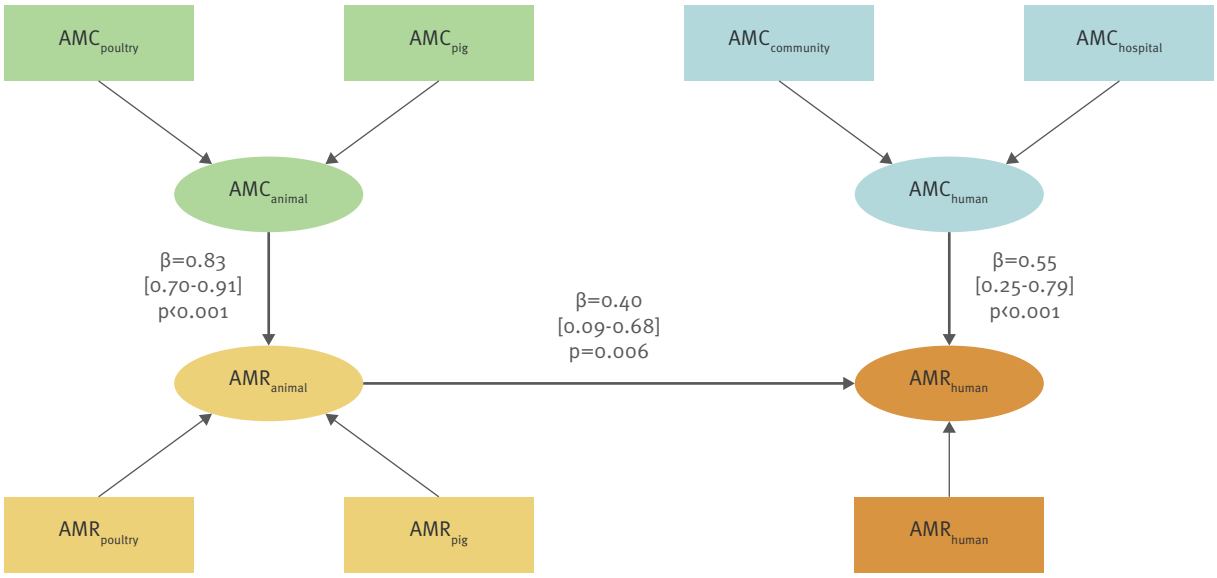
* AT†, BE, BG, CY, DE†, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS†, IT, LT, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK

† For these countries, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

Goodness of fit = 0.669; R^2 = 0.74 [95% CI: 0.60–0.89].

Fluoroquinolones and other quinolones

Figure A1.4.2: Diagram of the PLS-PM of resistance to fluoroquinolones in invasive *Escherichia coli* from humans (2016 and 2017) considering (a) resistance to fluoroquinolones in indicator *E. coli* from food-producing animals (pigs in 2017 and poultry in 2016), (b) consumption of fluoroquinolones and other quinolones in humans (mean for 2016–2017, DDD per 1 000 inhabitants per day), and (c) consumption of fluoroquinolones and other quinolones in food-producing animals (pigs in 2017 and poultry in 2016, DDDvet per kg estimated biomass), 27 EU/EEA countries*

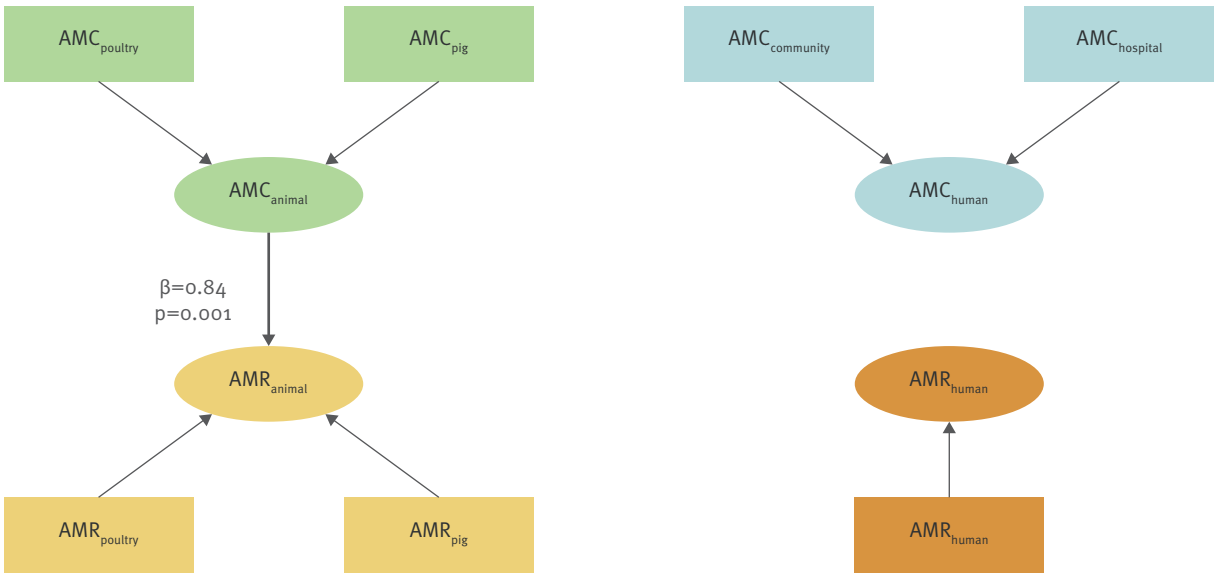


* AT†, BE, BG, CY, DE†, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS†, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK.

† For these countries, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

Goodness-of-fit = 0.737; R^2 AMRanimal = 0.69 [95% CI: 0.49–0.83]; R^2 AMRhuman = 0.74 [0.60–0.89].

Figure A1.4.3: Diagram of the PLS-PM model of resistance to fluoroquinolones in *Salmonella* spp. from humans (2016 and 2017) considering (a) resistance to fluoroquinolones in *Salmonella* spp. from food-producing animals (poultry in 2016 and pigs in 2017), (b) consumption of fluoroquinolones and other quinolones in humans (mean for 2016–2017, DDD per 1 000 inhabitants per day), and (c) consumption of fluoroquinolones and other quinolones in food-producing animals (poultry in 2016 and pigs in 2017, DDDvet per kg estimated biomass), 12 EU/EEA countries*

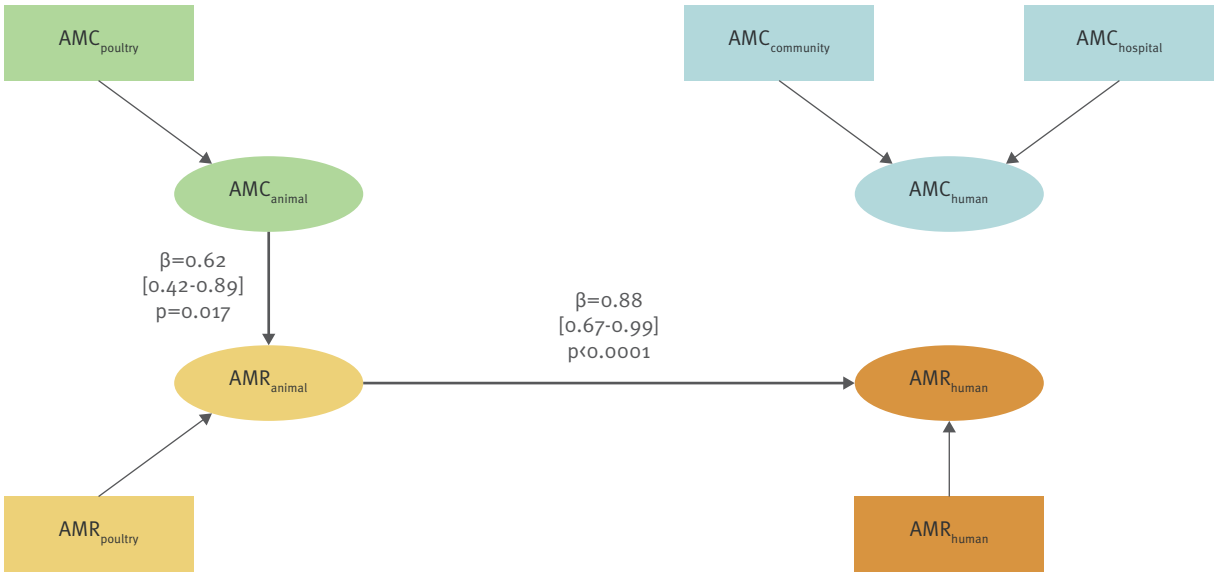


* BE, DE†, DK, ES, FR, HU, IE, IT, MT, PL, PT, SK,

† For this country, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

Goodness-of-fit = 0.647; R^2 AMRanimal = 0.6; data insufficient for estimating 95% CI)

Figure A1.4.4: Diagram of the PLS-PM model of resistance to fluoroquinolones in *Campylobacter jejuni* in humans (2016 and 2017) considering (a) resistance to fluoroquinolones in *C. jejuni* from food-producing animals (poultry in 2016), (b) consumption of fluoroquinolones and other quinolones in humans (mean for 2016–2017, DDD per 1 000 inhabitants per day), and (c) consumption of fluoroquinolones and other quinolones in food-producing animals (poultry in 2016, DDDvet per kg estimated biomass), 14 EU/EEA countries*



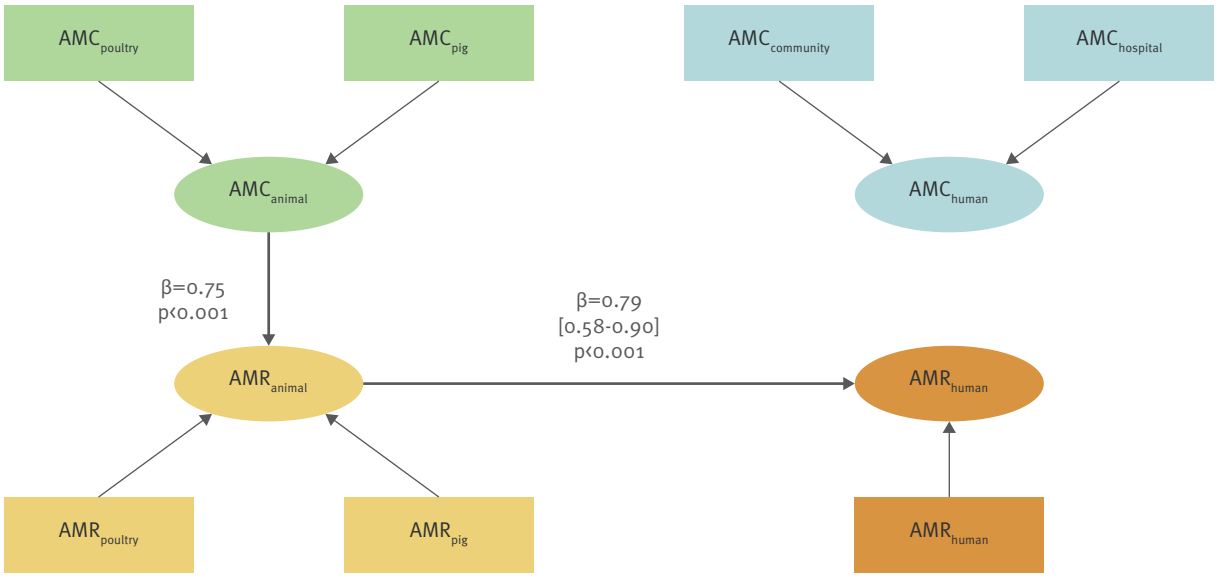
* AT†, CY, DK, ES, FI, IS, IT, LT, NO, PT, RO, SI, SK, UK.

† For this country, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

No goodness of fit estimate; R^2 AMRanimal = 0.39 [95% CI: 0.17–0.80]; R^2 AMRhuman = 0.78 [0.45–0.98].

Aminopenicillins

Figure A1.4.5: Diagram of the PLS-PM of resistance to aminopenicillins in invasive *Escherichia coli* from humans (2016 and 2017) considering (a) resistance to aminopenicillins in indicator *Escherichia coli* from food-producing animals (pigs in 2017 and poultry in 2016), (b) consumption of aminopenicillins in humans (mean for 2016–2017, DDD per 1 000 inhabitants per day), and (c) consumption of aminopenicillins in food-producing animals (pigs in 2017 and poultry in 2016, DDDvet per kg estimated biomass), 26 EU/EEA countries*

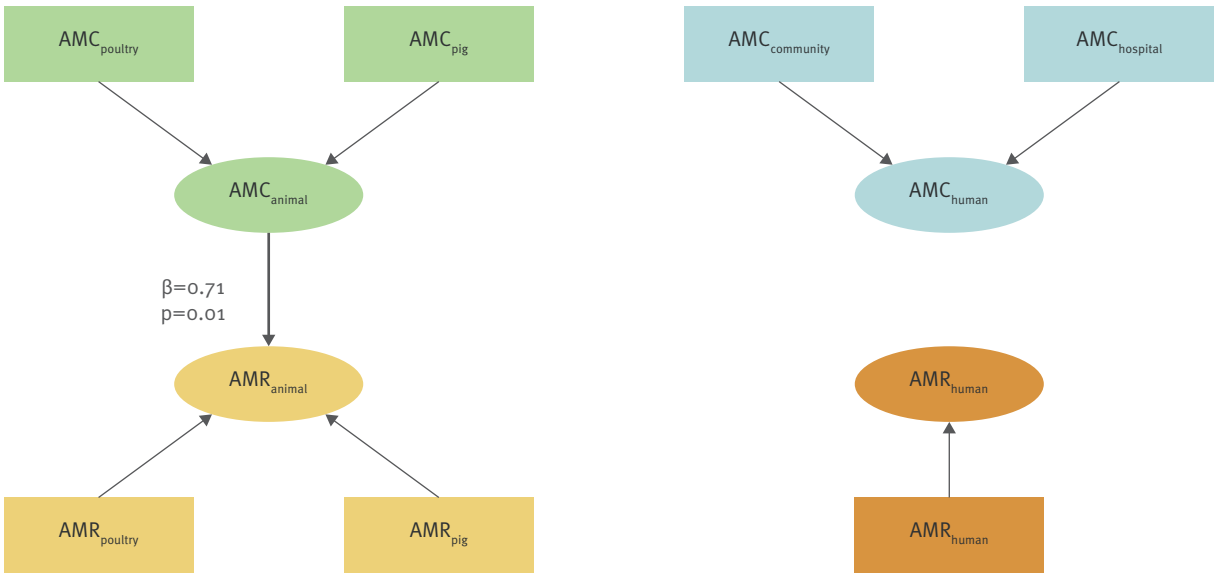


* AT†, BE, BG, CY, DE†, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS†, IT, LT, LV, NL, NO, PL, PT, RO, SI, SK, UK.

† For these countries, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

Goodness-of-fit = 0.625; R^2 AMRanimal = 0.57 [95% CI: 0.49–0.78]; R^2 AMRhuman = 0.62 [0.34–0.82].

Figure A1.4.6: Diagram of the PLS-PM model of resistance to aminopenicillins in *Salmonella* spp. from humans (2016 and 2017) considering (a) resistance to aminopenicillins in *Salmonella* spp. from food-producing animals (poultry in 2016 and pigs in 2017), (b) consumption of aminopenicillins in humans (mean for 2016–2017, DDD per 1 000 inhabitants per day), and (c) consumption of aminopenicillins in food-producing animals (poultry in 2016 and pigs in 2017, DDDvet per kg estimated biomass), 11 EU/EEA countries*



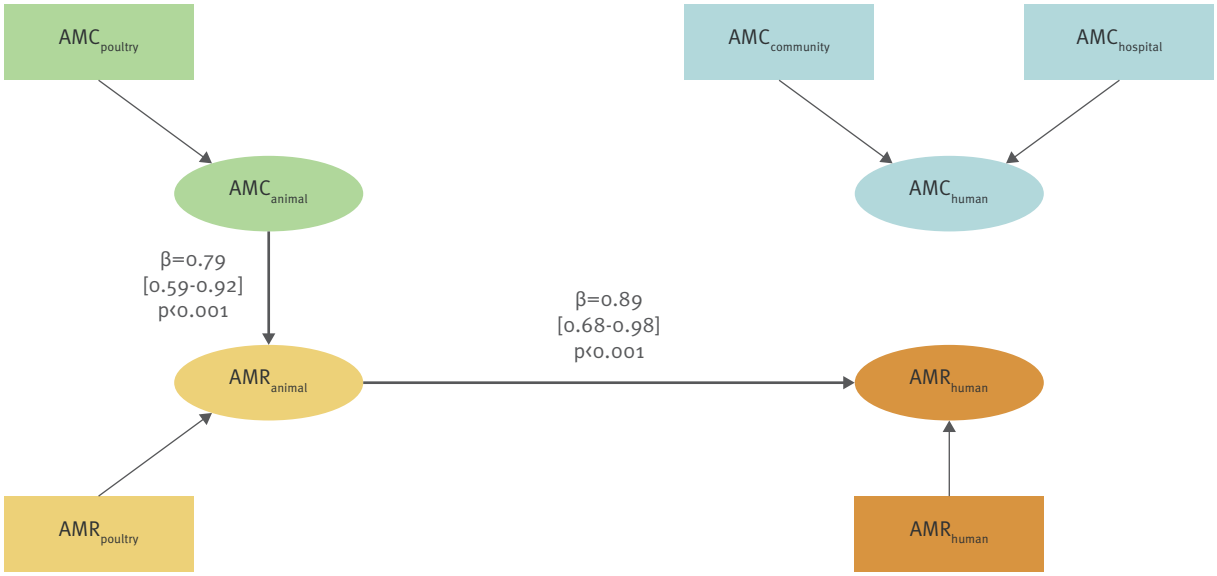
* BE, DE†, DK, ES, FR, HU, IE, IT, PL, PT, SK.

† For this country, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

Goodness of fit = 597; R^2 AMRanimal = 0.51 [95% CI: 0.28–0.97].

Tetracyclines

Figure A1.4.7: Diagram of the PLS-PM of resistance to tetracyclines in *Campylobacter jejuni* from humans (2016 and 2017) considering (a) resistance to tetracyclines in *C. jejuni* from food-producing animals (poultry in 2016), (b) consumption of tetracyclines in humans (mean for 2016–2017, DDD per 1 000 inhabitants per day), and (c) consumption of tetracyclines in food-producing animals (poultry in 2016, DDDvet per kg estimated biomass), 14 EU/EEA countries *



* AT†, CY, DK, ES, FI, IE, IT, LT, NO, PT, RO, SI, SK, UK.

† For this country, data on human consumption in the hospital sector were not available, and hospital consumption was estimated from the proportion reported by the other countries for the same year.

Goodness-of-fit = 0.63; R^2 AMRanimal = 0.35 [95% CI: 0.35-0.84]; R^2 AMRhuman = 0.78 [0.46–0.96].

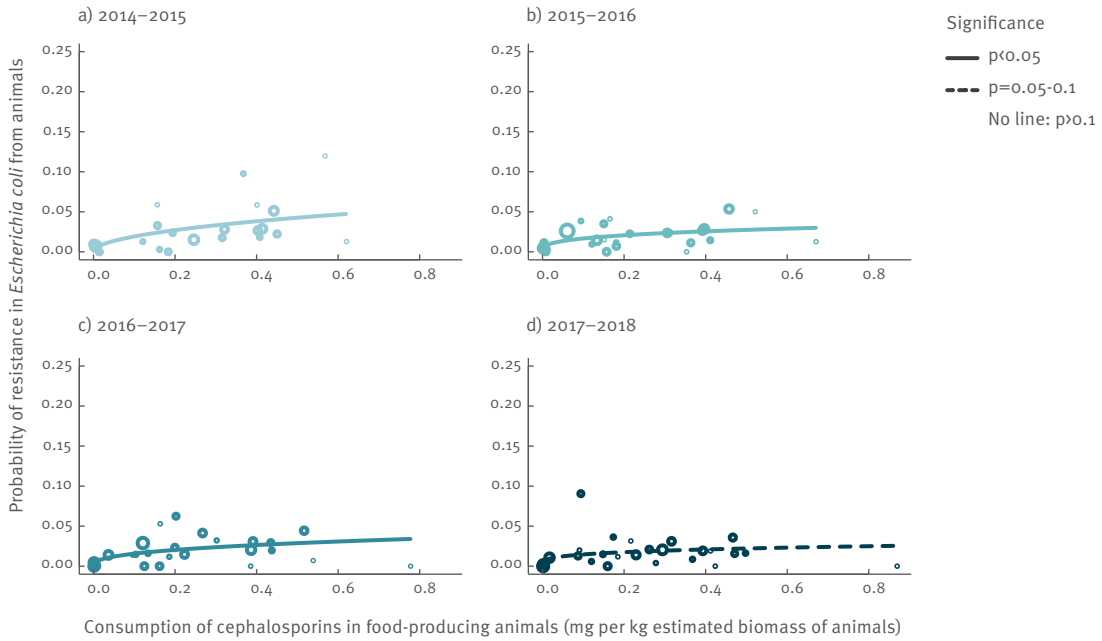
A1.5 Sensitivity analyses

Table A1.5.1: Sensitivity analysis: consumption of third- and fourth-generation cephalosporins in food-producing animals, expressed in mg per kg of estimated biomass, and probability of resistance to third-generation cephalosporins in indicator *Escherichia coli* from food-producing animals, once one data outlier has been removed from the analysis (logistic regression)

Year	Countries	Model	Odds ratio	p-value	95% CI
2014–2015	AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IE, IT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=25)	2	1.43	0.016	1.07–1.90
2015–2016	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=27)	2	1.25	0.005	1.07–1.45
2016–2017	AT, BE, BG, CH, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK (n=28)	2	1.31	0.004	1.09–1.57
2017–2018	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LV, NL, NO, PL, PT, RO, SE, SI, SK (n=26)	2	1.198	0.097	0.97–1.48

CI: confidence interval. The odds ratio (OR) varies from 0 to infinity. When OR equals 1 or CI includes 1, the association is not considered statistically significant.

Figure A1.5.1: Sensitivity analysis: association between consumption of third-fourth-generation cephalosporins in food-producing animals (mg per kg estimated biomass) and probability of resistance to third-generation cephalosporins in indicator *Escherichia coli* from food-producing animals, EU/EEA, once one data outlier is removed from the analysis (see also Table A1.5.1)



Annex 2 – Methods

A2.1 Comparison of how antimicrobials are used in food-producing animals and humans

Table A2.1.1 summarises some of the differences in how antimicrobials are used in humans and food-producing animals.

Table A2.1.1: Use of antimicrobials in humans and food-producing animals

	Humans	Food-producing animals and products thereof	Comments
Patient characteristics			
Species	One	Many	–
Individual weight	Variable	Very variable	Animal weights can vary from e.g. 50 g (one-day-old chicks) up to 1 ,000 kg
Lifespan	Long	Short in most cases	Food-producing 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 oninto efficient administration for group treatment

Adapted from 'Antibiotiques en médecine vétérinaire: caractéristiques et évolution de l'exposition des animaux d'après les données du système national de surveillance' [111].

A2.2 Method to calculate human consumption indicators for antimicrobial classes

Reporting of human AMC data to ESAC-Net

The reporting of AMC is done at the substance level (ATC codes, 5th ATC group level) including information on the route of administration (e.g. oral, parenteral, inhalation), galenic form (solution, powder) and salt, where applicable, and expressed in defined daily doses (DDD) as defined by the WHO Collaborating Centre for Drug Statistics Methodology (WHO CC).

The current report contains ESAC-Net AMC data for the ATC group J01, antibacterials for systemic use, reported for 2016–2018 using the 2019 ATC/DDD index from the WHO CC. The latest ATC/DDD index is available at http://www.whocc.no/atc_ddd_index and contains all valid ATC codes and corresponding DDDs.

For countries reporting the 'standard version', based on the numbers of items (e.g. tables), their strength and strength unit, the numbers of DDDs for a specific antimicrobial (substance level, 5th ATC group level) are derived from TESSy calculation.

Countries reporting the 'light version' are already reporting aggregated numbers of DDDs per ATC code and the route of administration.

ESAC-Net consumption indicator expressed as DDD per 1 000 inhabitants and per day

ESAC-Net 2016–2018 AMC data, expressed as DDD per 1 000 inhabitants per day, were used throughout the report for the logistic correlation analyses and for the multivariate analysis.

The denominator data needed to calculate DDD per 1 000 inhabitants per day represent the total population under surveillance. By default, TESSy uses Eurostat population data, except where countries are using their own national population data.

The latest available AMC results, expressed as DDD per 1 000 inhabitants per day at the 4th ATC group level, are publicly available in the ESAC-Net interactive database on the ESAC-Net webpages [5].

ESAC-Net conversion of number of DDDs to weight of active substances

Based on the TESSy dataset with AMC data reported by the countries for the community and the hospital sector, the numbers of DDDs consumed at the substance level (5th ATC group level) were converted to weight according to the ATC/DDD index 2019.

Each line of the dataset contains information on the ATC codes (5th ATC group level), the routes of administration including the inhalation form in the case of inhalation as route of administration, the type of salt if applicable, the unit of measurement (e.g. grams, milligrams, international units) and the numbers of units defining one DDD.

The dataset allows calculation of the weight of the antimicrobial at the substance level, based on the number of DDD. The weight sums of the ATC codes are grouped into the respective antimicrobial classes according to the ATC classification. The weight is expressed in tonnes or in milligram per kilogram human biomass, using the population under surveillance and the standard human body weight (e.g. Table 6 and Tables A1.1.1 to A1.1.4 of Annex A1). For the weight calculations, only DDD allocations for ATC codes listed in the ATC/DDD index of the WHO CC were taken into consideration.

Since the DDD allocation for colistin (ATC code J01XB01) is defined in million units (MU) and not in weight units, a conversion factor was applied to calculate the weight of consumption expressed as DDD. In humans, colistin is almost exclusively used as colistin methane sulphonate with a concentration of 12 700 IU/mg [112, 113]. Therefore a conversion factor of one million units (MU) = 78.74 mg was applied.

For 'combined products' containing two or more active substances (antibacterials), for which DDDs are expressed in unit doses, the weight was calculated in grams based on the number of grams of each substance per DDD.

For countries reporting less than 95% population data coverage for consumption in humans (Germany 85%, the Netherlands 92% and Luxembourg 90.5%) the consumption in tonnes of active substance is extrapolated to 100% population.

Calculation of standard human body weight

The authors reached the consensus that, with data currently available, mg per kg of body weight is an acceptable unit of measurement for comparing AMC 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 was used, taking into account the distribution of the population (children, adult, the elderly men and women). Data on international human body weights are scarce. For instance, in relation to AMC, the definition of the DDD mentions that it is based 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 Eurostat 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' [114], 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 were proposed, depending on age (Table A2.2.1).

Eurostat publishes data on the EU population by age and gender for all EU/EEA countries and for the whole EU. These data are available in the EUROSTAT table entitled 'demo_pjan'.

Methodology

Table A2.2.1: Standard body weights for children as proposed 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

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

- For children below one year of age, average body weight was calculated as Eurostat only provides population data by year.
- For children aged 1–18 years (including toddlers, other children and adolescents), a mean body weight was calculated as defined in Table A.2.2.1.
- A standard body weight for humans was calculated using the calculated mean child body weight and the standard body weight for adults proposed by EFSA (see above).

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

Mean body weight for children below one year of age

The mean 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.

Mean body weight for children

The mean body weight for children was obtained by calculating a weighted mean of the calculated mean body weight for children below one year of age, and the proposed body weights for the categories of children aged over one year 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 aged 0 to 18 years, the weighted mean of the EFSA proposed body weight by class of children from 1–18 years of age and of the aforementioned calculated body weight for children under 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 mean child body weight (34.6 kg) to the population aged under 20 years and the proposed 70 kg for the population aged 20 years or older 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.

A2.3 Technically-derived estimates of the sales of veterinary antimicrobials for pigs and poultry

Sales datasets

Antimicrobial VMPs included

Sales data on each antimicrobial VMP presentation included in the analysis were aminopenicillins - i.e. ampicillin and amoxicillin without and with beta-lactamase inhibitors - belonging to the ATCvet groups QA07AA98, QA07AA99, QJ01CA01, QJ01CA04, QJ01CR01, QJ01CR02, QJ01CR50, QJ01RA01, QJ01RA95 and QJ01RV01, third- and fourth-generation cephalosporins, fluoroquinolones, other quinolones, polymyxins, macrolides and tetracyclines belonging to ATCvet groups QA07AA and QJ01. The data were derived from the ESVAC database by country and year. The selected antimicrobials cover injectables, premixes, oral solutions and oral powders.

Identification of authorised target species

For each of the antimicrobial VMP presentations included in the datasets, information regarding the authorised target species was identified mainly by using the national Summary of Product Characteristics (SPC). In cases where an SPC could not be located or if the information was unclear, the relevant country was asked to provide this information. For some VMPs, the SPC data indicated 'poultry' as the target species (as opposed to specifying chickens or turkeys) and to have harmonised data across countries, sales were estimated for poultry. The AMR data cover bovines under one year of age, but since 'cattle' in general is typically given as the target species in the SPC, sales for bovines under one year of age could not be estimated using this approach.

Sales data of VMPs solely indicated for use in animals other than pigs and poultry (e.g. those containing pradofloxacin and cefovecin) were excluded from further analyses.

Estimation of antimicrobial sales for pigs and poultry

Weighting of the sales

For each country and year the sales of each of the antimicrobial VMP presentations included were distributed to species by weighting according to the biomass (population correction unit=PCU) ratio of pigs and/or poultry and other species. The biomass ratio was defined as the fraction of the biomass (PCU) of pigs and poultry, respectively, of the total biomass (PCU) of animals potentially at risk of receiving antimicrobial treatment.

The animal species (and categories) included in the calculation of the PCU used to report the ESVAC sales data are cattle, pigs, poultry, sheep, goat, fish, rabbits and horses. The data sources used, animal categories included and the methodology for the calculation of the PCU are described in Annex 2 of the Agency's report 'Trends in the sales of veterinary antimicrobial agents in nine European countries: 2005–2009' [6].

An example of the calculation of the biomass ratio is given in Equation A1.

Calculation example of the animal biomass ratio of each antimicrobial VMP presentation authorised for pigs:

Equation A1: Pig biomass ratio = Biomass (PCU) pigs (kg)/Σ Biomass (PCU) all species (kg)

Example:

Annual sales of antimicrobial VMP X authorised for pigs and poultry in country Y = 100 mg of active ingredient Z

Biomass all target species = Biomass pigs (1×108 kg) + biomass poultry (0.5×108 kg) = 1.5×108 kg

Weighted sales by target species:

Pigs = (1×108/1.5×108) × 100 = 66.7 mg

Poultry = (0.5×108/1.5×108) × 100 = 33.3 mg

Estimating antimicrobial exposure in pigs and poultry

The estimated sales (weight of active substance) for each antimicrobial substance and form for each of the three species were used to calculate the numbers of defined daily dose animals (DDDvet) sold. The DDDvet values, established by EMA [115], provide standardised fixed units of measurement for the reporting of data on consumption, taking into account differences in daily dosing between the various species, antimicrobial substances and forms (in this case oral and injectable forms) between the various species (here pigs and poultry) and are assigned by kilogrammes of animals [18].

The indicator used to express exposure of pigs and poultry, respectively, to the selected antimicrobials is the number of DDDvet per kilogramme of animal biomass (species) per year (Equation A.2)

Indicator expressing exposure to an antimicrobial substance

Equation A2: Numbers DDDvet*/Biomass species (kg)

*For antibacterial VMPs for systemic treatment (injectables, oral powders and oral solution) DDDvet is assigned per kg of animal.

Calculation examples of exposure of pigs to antimicrobial X for administration orally and by injection, respectively:

Formulae and examples for calculation of exposure are shown in Equations A3 and A4.

Equation A3: (Sum of sales of oral antimicrobial X pigs (mg)/DDDvet oral pigs (mg/kg))/Biomass (PCU) pigs (kg)

Equation A4: (Sum of sales of injectable antimicrobial X pigs (mg)/DDDvet injectable pigs (mg/kg))/Biomass (PCU) pigs (kg)

Example:

Annual sales of antimicrobial injectable X for pigs in country Y = 2×109 mg

DDDvet of antimicrobial injectable X = 10 mg/kg

Biomass of pigs in country Y = 1×108 kg

(2×109/10)/ 1×108 = 2 DDDvet per kg animal

The outputs of the calculations were subsequently aggregated by antimicrobial class or sub-class and species and by year and country.

It should be noted that the applied methodology only provides a crude estimate of antimicrobial consumption for pigs and poultry and numbers of DDDvet per kilogram of animal biomass per year cannot be assumed to represent actual animal exposure to antimicrobials in these animal species in the countries considered. This indicator is a proxy for exposure to antimicrobials used for the analysis of the association between AMC and the occurrence of resistance.

Examples of the calculations used to distribute antimicrobial sales by target animal species and estimating antimicrobial exposure in pigs and poultry

Example 1: Weighting of sales

Table A2.3.1 and Table A2.3.2 provide examples on weighting of sales for an injectable and an oral VMP.

Example 2: Calculation of #DDDvet per kilogram animal biomass per year

An example of calculation of outputs for pigs and poultry is given in Table A2.3.3. The weight of active ingredient used in the calculations corresponds to the sum of the sales by animal species of all VMPs (orals and/or injectables) containing the antimicrobial substance A.

Validation of the technically derived estimates of veterinary antimicrobial consumption in pigs and poultry

The data used to obtain the technically derived estimates were acquired from the ESVAC database by country and year. A standardised methodology was applied for the calculation and the analysis was performed by EMA. The technically derived estimates of the antimicrobial consumption per species used for the analysis in the current report are based on an allocation of the proportion of total sales of each VMP that are used in each of the animal species for which a VMP is indicated. For example, if

Table A2.3.1: Weighting of sales of an injectable VMP

Target species	Pigs	Poultry	Sheep, goats
Biomass (1 000 t)	380	40	80
Total biomass (1 000 t)		500	
Animal biomass ratio	0.76	0.08	0.16
Sales (kg of active ingredient)		25	
Weighted sales by animal species (kg of active ingredient)	19	2	4

Table A2.3.2: Weighting of sales of an oral VMP

Target species	Pigs	Poultry	Sheep, goats
Biomass (1 000 t)	380	40	80
Total biomass (1 000 t)		500	
Animal biomass ratio	0.76	0.08	0.16
Sales (kg of active ingredient)		10	
Weighted sales by animal species (kg of active ingredient)	7.6	0.8	1.6

Table A2.3.3: Weighting of sales of an oral VMP

Target species	Pigs	Poultry	Sheep, goats
Weighted sales by animal species (kg of active ingredient)	150	20	45
DDDvet (mg/kg)	2.5	10.0	Excluded from calculations
# DDDvet active ingredient	60 000 000	2 000 000	
Biomass of each animal species (1, 000 t)	380	40	
Exposure by animal species (DDDvet per kg biomass per year)	0.16	0.05	

a VMP is approved for the two species - pigs and poultry-only, the total sales reported for that product (in tonnes of active ingredient) would be divided proportionally between the two groups based on the animal biomass data.

The technically derived estimates were validated by comparing these data against data obtained through a pilot study launched by EMA in April 2018 with the participation of six volunteering countries – Austria, Czechia, Denmark, France, Netherlands and Spain (data from the pilot project are not publicly disclosed). Like the technically derived estimates, data for the pilot project, also known as the stratification of sales data project, were obtained from the ESVAC database but for the pilot project the sales by animal species were estimated by the participating countries. The data sources used by the six countries participating in the pilot project to obtain sales by species of each VMP varied, but were typically Marketing Authorisation Holders (MAHs), and for some countries also wholesalers, veterinarians or prescription data. Therefore the methodology for obtaining the estimates in the pilot study was not completely standardised, as for the technical estimation.

For both the EMA technically derived estimates and the pilot project data, the following dosage forms were selected for the validation process: oral solutions, oral powders, premixes, tablets and injectable preparations. However, intramammary and intrauterine preparations are excluded, since these two forms are mainly used in cattle.

For the analysis of technically derived estimates included in this third JIACRA report, antimicrobial consumption in pigs and poultry was expressed by applying standardised units of measurement (i.e. defined daily dose animals (DDDvet)) [116] and by taking into account the biomass of pigs and poultry that could potentially be treated with antimicrobials. The results for the validation of estimates for pigs and poultry are shown in Table A2.3.4 and Table A2.3.5, respectively.

Table A2.3.4: Comparison of mean values for pigs, expressed in tonnes and in number of defined daily doses (DDDvet) per kg estimated biomass for pigs, of antimicrobial agents, obtained from the technically derived estimates and through a pilot study of six EU countries*, 2016

Antimicrobial class	Mean, tonnes (pigs)		Difference, tonnes	Spearman's rank correlation coefficient (rho) (p-value)	Mean #DDDvet per kg estimated biomass (pigs)		Difference, DDDvet per estimated biomass (pigs)	Spearman's rank correlation coefficient (rho) (p-value)
	Technically derived estimates	Estimates from the pilot study			Technically derived estimates	Estimates from the pilot study		
Third-andfourth4th-generation cephalosporins	0.18	0.23	-0.05	r=0.829, p=0.058	0.05	0.13	-0.07	r=1, p=0.003
Aminopenicillins	110.1	103.6	+6.5	r=0.943, p=0.017	2.3	2.2	+0.07	r=0.829, p=0.058
Fluoroquinolones	2.9	2.6	+0.2	r=0.771, p=0.103	0.4	0.3	+0.09	r=0.943, p=0.016
Macrolides	24.2	19.3	+4.9	r=0.943, p=0.017	1.3	1.1	+0.2	r=0.971, p=0.028
Polymyxins	27.5	26.5	+1.0	r=1, p=0.003	1.7	1.7	+0.04	r=1, p=0.003
Tetracyclines	114.0	130.8	+13.3	r=1, p=0.003	3.3	3.3	+0.04	r=0.943, p=0.017
Total	**45.2**	**47.2**	**-1.9**	**r=0.943, p=0.017**	**1.3**	**1.4**	**-0.1**	**r=0.886, p=0.033**

* AT, CZ, DK, ES, FR, NL

Table A2.3.5: Comparison of mean values for poultry, expressed in tonnes and in number of defined daily doses (DDDvet)/biomass for poultry, of antimicrobial agents obtained from the technically estimates (EMA) and through a pilot study of six EU countries*, 2016

Antimicrobial class	Mean, tonnes (pigs)		Difference, tonnes	Spearman's rank correlation coefficient (rho) (p-value)	Mean #DDDvet per kg estimated biomass (pigs)		Difference, DDDvet per estimated biomass (pigs)	Spearman's rank correlation coefficient (rho) (p-value)
	Technically derived estimates	Estimates from the pilot study			Technically derived estimates	Estimates from the pilot study		
Third-andfourth4th-generation cephalosporins	0	0	0	-	0	0	0	-
Aminopenicillins	8.9	15.9	-7.1	r=1, p=0.003	0.9	1.5	-0.6	r=0.829, p=0.058
Fluoroquinolones	7.0	6.4	0.6	r=1, p=0.003	0.9	0.9	0.01	r=1, p=0.003
Macrolides	4.6	8.1	-3.5	r=0.943, p=0.017	0.1	0.1	-0.02	r=0.886, p=0.033
Polymyxins	1.5	3.0	-1.5	r=0.886, p=0.033	0.4	0.8	-0.47	r=0.886, p=0.033
Tetracyclines	16.5	29.1	-12.5	r=0.829, p=0.058	1.1	1.4	-0.3	r=0.258, p=0.658
Total	**5.6**	**10.4**	**-4.8**	**r=1, p=0.003**	**0.5**	**0.8**	**-0.3**	**r=0.943, p=0.005**

* AT, CZ, DK, ES, FR, NL

The results indicate that, for all antimicrobial classes except for third- and fourth-generation cephalosporins, the technically derived estimates in mean tonnes of antimicrobial consumption in pigs for all six countries were higher than the estimates from the pilot project. When DDDvet and estimated biomass are taken into consideration, the differences observed between the mean values acquired through the two methodologies were less notable.

For poultry, the mean value of the technically derived estimates used for all six countries in tonnes was lower for all antimicrobial classes, except for fluoroquinolones, than that obtained from the pilot study. The comparison of number of DDDvet sub-divided by the estimated biomass of poultry indicated that the differences observed in mean values acquired through the two methodologies were less notable, except for aminopenicillins.

Both the technically derived estimates and data obtained through the pilot study have their advantages and limitations. Although both datasets may not diverge substantially overall for the six countries for which data have been compared, the results should be interpreted with caution until the technically derived estimates of antimicrobial consumption per species are replaced with actual antimicrobial use data, which would enable some of the limitations of these methods to be overcome.

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