The Effects of Restricting Antimicrobial Use in Food-Producing Animals on Antimicrobial Resistance in Humans: a Review

Tim Florschütz

Examiner: Dr. Lapo Mughini Gras
Daily Supervisor: Dr. Jenny Deng

Layman Summary

Antimicrobials are a group of drugs that are widely used to treat bacterial infections. Bacteria respond to antimicrobials by a range of processes, together called antimicrobial resistance (AMR). Examples of AMR are enzymes that are able to break down antimicrobial drugs or pumps that keep the drug out of the bacterial cell. As a result, the effect of antimicrobial drugs is reduced, leading to a longer sickbed or even increased risk of mortality for infected people. AMR has a sizeable impact on human health, with a disease burden in the European Union similar to the combined burden of influenza, tuberculosis and HIV. Whether bacteria are resistant to a certain antimicrobial drug is dependent on whether or not the bacteria possess a so-called resistance gene; a gene that encodes for the enzymes or other proteins that are required to resist the action of an antimicrobial drug. These genes are naturally present in some of the individual bacteria and can sometimes be passed between bacteria that come into contact with each other, a process called horizontal transfer. Usage of antimicrobials can promote the occurrence of resistance; when antimicrobials are used, the bacteria that do not possess resistance genes die in greater numbers than those that do possess resistance. Subsequently, the resistant bacteria are able to multiply and take the place of the susceptible bacteria, leading to a bacterial population with a larger proportion of resistant bacteria than before. This link between AMR and antimicrobial use (AMU) is well-known and the reason why prudent use of antimicrobials is necessary.

AMR is not only affected by AMU in humans, but also by AMU in food-producing animals. In animals, antimicrobials are used to treat and prevent bacterial infections. Low doses of antimicrobials were also widely used in the past to promote growth of food-animals, but this use is declining and is banned in many countries. Nevertheless, the total AMU in food-producing animals outweighs that in humans. In animals, AMU promotes AMR in the same way as it does in humans. These resistant bacteria can end up on meat or eggs and be transferred to humans through consumption of these products. This means that reducing AMU in animals could potentially reduce AMR in both humans and animals. However, reducing AMU in animals could lead to an increase in bacterial infections in animals, which has a negative impact on both animal well-being and food production. As such, it is important for policy-makers to know what the effects of a restriction in AMU would be on human AMR, so they are able to weigh the advantages and disadvantages. However, the size and shape of the relationship between AMU in food-producing animals and AMR in humans is still uncertain. As such, this review provides an overview of the available evidence of the effects of restricting or banning AMU in food-producing animals. All included studies showed that restricting animal AMU leads to a decrease in human AMR, but the size of the effect differed greatly between studies. This is partly explained by the differences between studies in the investigated bacteria and antimicrobials. However, for most studies the change in animal AMU following a ban is not well-known. As such, it is not clear whether a limited change in AMR is due to a limited change in AMU or otherwise. As such, further research that also quantifies the change in AMU is needed to more reliably assess the effect of animal AMU restrictions.

Abstract

Resistance to antimicrobials is an important and growing concern for human health worldwide, as it reduces the efficacy of antimicrobial treatments, leading to longer illness and increased mortality. Antimicrobial use in food-producing animals can increase the prevalence of antimicrobial resistant bacteria in animals. Subsequently, this resistance can be transmitted to humans through the foodborne pathway. Reducing antimicrobial use in food-producing animals could therefore limit resistance in humans. In light of possible negative effects of reducing antimicrobial use, it is important that the effects of a restriction in antimicrobial usage can be predicted, so a cost-benefit analysis can be made to inform policy makers. This review provides an overview of the available research on the effects of restricting antimicrobial use in food-producing animals on antimicrobial resistance in humans. A literature search resulted in 14 papers being included, that constructed either a model or analysing a change in policy. All included papers showed a decrease in resistance in humans following a restriction in antimicrobial use, with the exception of one paper where no significant difference was observed for one of the antimicrobials investigated. The effect sizes varied to a large extent between studies, which can be partly ascribed to the different bacteria and antimicrobials investigated. However, a lack of information on the change in antimicrobial use is a major shortcoming of almost all studies. More research is needed to reliably estimate the impact of restricting antimicrobial use in food animals on resistance in humans. This future research should also focus on quantifying the change in antimicrobial usage following a restriction.

Keywords: antimicrobial use, antimicrobial resistance, food-producing animals, policy change, model

Introduction

Antimicrobial resistance (AMR) is an important cause of death worldwide, with 1.27 million deaths in 2019 directly attributable to AMR (Murray et al., 2022). In the European Union, 170 disability adjusted life-years (DALYs) per 100,000 were attributable to AMR, which is similar to the combined burden in DALYs of three important infectious diseases; influenza, tuberculosis and HIV (Cassini et al., 2018, 2019). Prevalence of AMR is increased by antimicrobial use (AMU), due to selective pressure. In addition to AMU in humans, usage of similar antimicrobials in food animals can increase human exposure to AMR through resistant bacteria in food. AMU in food-producing animals outweighs that in humans and is projected to increase worldwide (Emes et al., 2022; Tiseo et al., 2020). This suggests that reducing AMU in food-producing animals could bring considerable benefits to human health. Furthermore, reducing animal AMU could limit the rise of AMR in animals, in turn preventing loss of treatment efficacy in animals. However, as antimicrobials are used in animals to cure or prevent infections and to promote growth, usage reductions could themselves have a negative impact on production and animal well-being. Therefore, it is imperative for informed policy-making that the effects of reducing AMU in food producing animals on human AMR are quantified to allow for cost-benefit analysis.

Quantifying the relationship between animal AMU and human AMR is difficult, firstly because their interaction forms a complex one health system. AMR in humans is driven by AMU in humans, with resistant bacteria also being transmitted between humans. Furthermore, veterinary AMU can lead to a rise in AMR in food-producing animals. These resistant bacteria could then be transmitted to humans via food. Additionally, sewage from human origin and pollution originating from the pharmaceutical industry might spread resistance to the environment, which could spread to surface water and ground water. Lastly, even the use of metals sprays and fertilisers in agriculture can co-select for resistance (Holmes et al., 2016).

A further difficulty is the large number of so-called bug-drug-animal-combinations, which generally limits the available evidence for a specific combination of bacterium (bug), antimicrobial (drug) and animal species. Differences between bacteria can mean considerable differences in the dynamics of

resistance spread, mainly determined by whether the bacterium is normally commensal or exclusively pathogenic. Examples of bacteria that are typically commensal and non-pathogenic are *Echinococcus spp.* and *E. coli*, whereas *Salmonella* is considered exclusively pathogenic. However, there are pathogenic subtypes of *E. coli* that can cause human disease. Furthermore, non-pathogenic commensal bacteria carrying resistance can transmit resistance genes to other bacteria, including pathogenic ones (Summers, 2006). It should be noted that the actual transfer rate of resistance genes between commensal and pathogenic *E. coli* strains is difficult to measure accurately (Zhang et al., 2022).

Specifically for foodborne illnesses, the foods that are the most important source of infection differ between bacteria. For *Campylobacter spp.*, about half of the foodborne infections in the Americas and Europe are attributed to poultry consumption. Beef and dairy consumption are the only other foods contributing more than 10% of the attributable infections. On the other hand, the most important sources of foodborne *Salmonella* infections in Europe and the Americas are eggs, poultry and pork consumption. Only 4% of cases in Europe and 8.8% of cases in the Americas are attributed to beef consumption. For *E. coli*, only information specifically on the Shiga-toxin producing variant was available; in this variant, beef consumption is the main source of infection in Africa, the Americas, Europe and the Eastern Mediterranean, with infections attributed to poultry or pork consumption being relatively rare (Hoffmann et al., 2017). Reducing AMU in food-producing animals would have little effect on AMR in humans for bacteria for which the animal in question constitutes a relatively unimportant route (e.g. *Salmonella* in cattle).

Differences between drugs and, most importantly, their usage levels, also play a considerable role in the dynamics of AMU-AMR interplay. Due to these differences, studies cannot be directly compared with studies that investigate a different type of antimicrobial. Something that is important to consider when comparing antimicrobial groups, is that for their effects on resistance in humans to be important, the antimicrobials or other drugs from their antimicrobial group that are used in food-producing animals need to be important for human medicine. Worldwide, β-lactam antibiotics are the most widely used class of antimicrobials in humans (WHO, 2022). The β-lactam antibiotics carbapenems, 3rd, 4th and 5th generation cephalosporins, monobactams and penicillins have been listed as antimicrobials of critical importance for human health. Most of these antimicrobials are also used in veterinary practice worldwide (WHO, 2017). Due to this widespread use and importance, there is considerable risk of emerging antimicrobial resistance and a sizeable burden to human health. In 2019, resistance to third generation cephalosporins had the third largest worldwide attributable death count of all antimicrobial classes, with 141,000 deaths. Of these, 59,900 were attributable to *E. coli* (Murray et al., 2022). In the EU, third-generation cephalosporin-resistant *E. coli* had the largest health burden attributable to resistance (Cassini et al., 2019).

Another important group are the quinolone antimicrobials, of which most contain a fluor atom and are therefore referred to as fluoroquinolones, which are considered critically important for human medicine (WHO, 2017). In 2019, the number of global attributable deaths due to resistance (excluding multiresistance) was highest for fluoroquinolones (Murray et al., 2022), emphasising the need for reducing resistance to this antimicrobial group. Lastly, streptogramin antimicrobials are classified by the WHO as highly important for human medicine (WHO, 2017). Compared to β-lactam and quinolone antimicrobials, the death count attributable to bacterial AMR are relatively limited, at 23,100, of which 14,300 were caused by resistant *E. faecium* (Murray et al., 2022).

When the aforementioned differences are not taken into account, the observed relationship loses strength. A recent and comprehensive meta-analysis of the effect of restricting AMU in food-producing animals on AMR in humans and animals found a strong positive relationship between these two factors (Tang et al., 2017). A subsequent stratified analysis showed that the effect was largest when

restricting growth promoters and nonsignificant when restricting only a single antibiotic or antibiotic class (Tang et al., 2019). However, all bug-drug-combinations were pooled together, meaning that cost-effectiveness relationships cannot be analysed for interventions on specific antimicrobials (Emes et al., 2022).

Due to the aforementioned difficulties, the size and shape of the relationship between AMU in food-producing animals and AMR in humans is still uncertain. Furthermore, the effects that a reduction in animal AMU can have on animal welfare is often not considered. This means that policymakers do not know what effects on public health can be expected following a restriction or ban on AMU in animals. As such, policies have to be based on the precautionary principle alone, probably hindering implementation of these policies, which could have considerable future benefits to human health. This review aims to provide more insight into the expected benefits of restricting AMU in food-producing animals by giving an overview of the available evidence.

In this paper, the results of a literature search are presented that was performed to gather as many studies as possible on the relationship between antimicrobial usage in animals and antimicrobial resistance in humans. Together, these studies give, in part due to their differing methods, a comprehensive overview of the effects of AMU restrictions in food producing animals on AMR in humans.

Methods

The search query, which is given in the appendix, was entered into PubMed on the 21st of July 2023 and into Scopus on the 31st of July 2023. Articles were screened on title, then on abstract. For inclusion in the review, articles were required to assess a change in antimicrobial usage in food-producing animals and the resulting effect on antimicrobial resistance in humans. An AMU change includes a change in animal AMU policy (e.g. a ban or introduction of an antimicrobial or use restriction) or a scenario analysis on changing AMU. The effect of resistance in humans can be expressed as resistance prevalence in humans or human exposure to resistant antimicrobials in food. Only papers written in English were considered for inclusion. There was no restriction in study year or geographical location. Studies that were referenced by the included studies or by reviews that were identified during the literature search were also assessed for eligibility. The papers were mentioned and discussed grouped by antimicrobial class.

Results and discussion

Literature search

The search query gave 391 results in PubMed and 321 in Scopus. Six original research papers were included from PubMed and one additional paper from Scopus. Eight reviews were obtained from PubMed and Scopus. The reference lists of papers and reviews supplied an additional seven papers. Duplicates retrieved from the two databases were removed. An overview of the total 14 papers grouped by antimicrobial class can be seen in table 1, with table 2 providing the main outcome measures of these papers.

The included studies are either analyses of the effects of previous restriction or bans of AMU in food-producing animals on AMR in humans, that are hereafter referred to as policy change analyses (PCA). In addition, models that quantify exposure and/or risk of infection are also included, which will be referred to as exposure-based models (EBM).

β-lactams

As shown in table 1, five included studies investigated the relationship between veterinary use of β-lactam antibiotics and human resistance to this class of antimicrobials. Two of these studies analysed a change in policy regarding antimicrobials (Casey et al., 2023; Dutil et al., 2010), the other three used an exposure-based modelling approach (Collineau et al., 2020; de Freitas Costa et al., 2022; Zhang et al., 2022). Two studies focused specifically on ceftiofur, the others on all β-lactams or even medically important antimicrobials in general. Three of the studies investigated AMR in *E. coli*, the other two in *S. enterica* serovar Heidelberg (Table 1).

Starting with the policy change analyses, Dutil et al. investigated a period from 2005 through 2007 when broiler chicken

Table 1 Bug-drug-animal combinations of included studies

Name	Year	Type	Bacterium	Country	Human AMR	Animal AMU	Animal
				β-lactams			
Dutil	2010	PCA	S. enterica H.	Canada	Extended spectr. cephalosporins	Ceftiofur	Chickens
Collineau	2020	EBM	S. enterica H.	Canada	Ceftiofur	Ceftiofur	Broilers
de Freitas Costa	2022	EBM	E. coli	NL	Extended spectr. β-lactams	β-lactams*	Broilers
Zhang	2022	EBM	E. coli	US	β-lactams	β-lactams*	Cattle
Casey	2023	PCA	E. coli	US	Extended spectr. cephalosporins	MIA	Food A.
				(Fluoro)quinolones			
Anderson	2001	PCA	C. jejuni	NL/US/ Canada	Fluoroquinolones	Fluoroquinolones	Cattle
Skjøt-Rasmussen	2009	PCA	C. jejuni	DK	Nalidixic acid, ciprofloxacin	Fluoroquinolones	Broilers
Innes	2020	EBM	Campylobacter	US	Fluoroquinolones	Enrofloxacin	Broilers
				Glycopeptides			
Klare	1999	PCA	Enterococci	D	Vancomycin	Avoparcin	Food A.
Bogaard	2000	PCA	Enterococci	NL	Vancomycin	Avoparcin	Food A.
				Polymyxins			
Wang	2020	PCA	E. coli	China	Colistin	Colistin	Food A.
				Streptogramin			
Smith	2003	EBM	E. faecium	*	QD	Virginiamycin	Food A.
Kelly	2004	EBM	E. faecium	US	QD	Virginiamycin	Food A.
Cox	2004	EBM	E. faecium	US	QD	Virginiamycin	Food A.
				Tetracyclines			
Casey	2023	PCA	E. coli	US	Tetracyclines	MIA	Food A.

PCA, policy change analysis; EBM, exposure-based model; AMR, antimicrobial resistance; AMU, antimicrobial usage; NL, the Netherlands; US, the United States; DK, Denmark; D, Germany; MIA, medically important antimicrobials; QD, Quinupristin-Dalfopristin; Food A., Food animals.
*, not clearly specified

hatcheries in the Canadian province of Québec voluntarily interrupted the off-label in-ovo use of ceftiofur. This temporary suspension was prompted among other things by a rise in the incidence of ceftiofur-resistant *S. enterica* serovar Heidelberg isolated from chicken meat. The paper investigated the ceftiofur resistance rates in S. Heidelberg infections in humans in Canada around the temporary suspension and reinstitution of ceftiofur. In the period when in ovo use of ceftiofur was withdrawn, ceftiofur resistance dropped significantly from 36% to 8% in human S. Heidelberg isolates. Following the partial reinstitution of ceftiofur use in ovo, resistance in human S. Heidelberg samples rose non-significantly from 8% to 12% (Dutil et al., 2010).

More recently, Casey et al. investigated the effect of Senate Bill 27 (SB27), that was implemented in California on the 1st of January 2018 and that restricted the use of medically important antibiotics in food-producing animals to prescription-only. The antibiotic classes in question included among several others the β-lactams cephalosporins and penicillins. The paper investigated the effect of SB27 on antimicrobial resistance in *E. coli* from urinary tract infection (UTI) samples, considering resistance to aminoglycosides, extended-spectrum cephalosporins, fluoroquinolones and tetracyclines. Aminoglycosides and fluoroquinolones were included as a negative control as these had already been banned for poultry use in the U.S. The study used an augmented synthetic control analysis to assess the effect, in short this entails constructing a synthetic version of California where SB27 had not been passed, using a weighted combination of other U.S. states. This synthetic California was then used to predict post-policy counterfactual resistance trends. This approach showed that following SB27, the prevalence of extended-spectrum cephalosporin resistance in California dropped by 7.1% compared with synthetic California. Resistance to aminoglycosides, fluoroquinolones and

tetracyclines did not change compared to synthetic California (Casey et al., 2023).

These two papers show that suspending or restricting the use of β-lactam antibiotics on farms can have a marked effect on the prevalence of antimicrobial resistance in humans in a relatively short timeframe. A major shortcoming of these studies, which the authors themselves also addressed, was that antimicrobial usage is poorly quantified. For Canada, drug use monitoring in poultry farms is virtually non-existent, although the authors commented that abattoir surveillance indicated usage in more than 78% of the farms before the voluntary ban (Dutil et al., 2010). The U.S. Federal Drug Authority (FDA) only reports nationwide aggregated estimates of drug sales, making it impossible to evaluate usage trends specifically for California. However, prior to SB27 (in 2011-2017) cephalosporins only made up <1% of nationwide food animal antimicrobial sales by weight (Casey et al., 2023). As such, it is difficult to extrapolate these findings to other countries because the current usage level of antimicrobials may have a marked effect on the effect of reducing usage. However, seeing significant reductions in human AMR due to limiting AMU in two different countries and in different bacteria strengthens the association between these two.

Of the three included papers on β-lactams that constructed a model, the paper by Collineau et al. was the only one focused on *S. enterica* serovar Heidelberg. They used a farm-to-fork quantitative microbial risk assessment (QMRA) model that assesses the risk of infection in humans with ceftiofur resistant S. Heidelberg associated with ceftiofur resistance in S. Heidelberg in broiler chicken meat in Canada. They also evaluated the effect of several possible control measures, including three scenarios on ceftiofur use at hatcheries. Scenario 1 represents the baseline scenario where 31% of the flocks received ceftiofur and in scenarios 2 and 3 two different ways of assessing the effect of completely withdrawing ceftiofur use in hatcheries were explored. In scenario 2 a reduction factor was applied based on observations on the effect of a previous ceftiofur ban on retail samples in Canada. In scenario 3, resistance rates in *E. coli* as a complementary approach was used. Finally, scenario 4 represents a worst-case scenario where all flocks received ceftiofur. In the baseline scenario, 21,732 (standard error 1900) human infections with resistant S. Heidelberg were expected for the entirety of Canada. This was an overestimation compared to surveillance data, but it was still in the same order of magnitude. Scenarios 2 and 3, the withdrawal of ceftiofur in two different ways led to a decrease of 91% and 25% of resistant S. Heidelberg infections. Meanwhile, increasing ceftiofur use to 100% led to an increase in resistant infections of 92% (Collineau et al., 2020). These reductions in resistance are somewhat similar to those found by Dutil et al. on the same antibiotic and bacterium. As such, it is clear that reducing ceftiofur use in chickens can have a profound effect on the number of human infections with ceftiofur resistant S. Heidelberg.

Two further papers investigated the influence of animal AMU on β-lactam-resistant *E. coli* in humans using an exposure-based model. De Freitas Costa et al. built a multidirectional dynamic model to assess the transmission of extended spectrum beta-lactamase producing *E. coli* (ESBL-EC) between broiler flocks, farmers and the general population. As part of a scenario analysis, they investigated the influence of six interventions on the ESBL-EC prevalence in the general population. Reducing the proportion of farms with a high level of antimicrobial usage from 0.01 to 0.0075 had a fairly limited effect as it reduced ESBL-EC prevalence in the general population by 1.5%. This contrasts with interventions such as reducing in-flock spread (51% reduction in prevalence) or reducing cross-contamination in the kitchen or meat consumption (18% reduction), that had a markedly higher effect (de Freitas Costa et al., 2022). This can be explained by the fact that the modelled reduction in AMU is probably also quite low; the intervention entails only 0.25% of the farms switching to a lower usage pattern. These farms do constitute 25% of the high-use farms, but as a definition of high AMU usage is not reported, it is impossible to quantify the change in total AMU. Furthermore, the most important source of foodborne *E. coli* infections in Europe is beef, representing between 40 and

Table 2 Intervention effects of included studies

Name	Year	Type	Intervention in animals	Effect measure	Effect
β-lactams					
Dutil	2010	PCA	Voluntary ceftiofur ban	AMR in Salmonella isolated from humans	Decrease from 36% to 8%
Collineau	2020	EBM	Ceftiofur use from 31% to 0% of flocks	Human infections with resistant Salmonella H.	91% or 25% decrease
de Freitas Costa	2022	EBM	Lower number of farms with high AMU	ESBL-EC prevalence in humans	1.5% decrease
Zhang	2022	EBM	AMU from 100% to 0%	Resistant bacteria load in beef	72%, 85% or 91% decrease
Casey	2023	PCA	Ban on medically important antimicrobials	AMR prevalence in urine from UTI patients	7.1% decrease
(Fluoro)quinolones					
Anderson	2001	PCA	10 years after introduction of AMU	AMR prevalence in human isolates	Increase from 1.3% to 29%
Skjøt-Rasmussen	2009	PCA	Fluoroquinolone use restricted in animals	AMR prevalence in isolates from chicken faeces, meat and humans	No change in faeces, lower in Danish than imported meat
Innes	2020	EBM	Percentage point rise in animal AMR	Human AMR to fluoroquinolones	0.23 percentage point increase
			Kg of enrofloxacin	Externality costs	$1,500
Glycopeptides					
Klare	1999	PCA	Ban on Avoparcin use as growth promoter	Vancomycin-resistant *Enterococci* in humans	Decrease from 6% to 3%
Bogaard	2000	PCA	Ban on Avoparcin use as growth promoter	Vancomycin-resistant *Enterococci* in humans	Decrease from 12% to 6%
Polymyxins					
Wang	2020	PCA	Ban on colistin use as a growth promoter	mcr-1 positive *E. coli* in human faecal samples	Decrease from 14.3% to 6.3%
Streptogramins					
Smith	2003	EBM	No virginiamycin use in animals	Hospital prevalence (number of patients)	12 to 2 (R_0<<1) ±200 to ±190 (R_0>>1)
Kelly	2004	EBM	Ban on virginiamycin use as growth promoter	Prevalence of SREF in hospitalised people	>2% to <1% (R_0<<1) >8% to ±5% (R_0≈1) ±34% to ±33% (R_0>>1)
Cox	2004	EBM	Doubling of exposure to animal AMR	Risk of an ICU outbreak of resistant *Enterococci*	Doubled, in certain human AMU bandwidth
Tetracyclines					
Casey	2023	PCA	Ban on medically important antimicrobials	AMR prevalence in urine from UTI patients	No difference

PCA, policy change analysis; EBM, exposure-based model; AMR, antimicrobial resistance; AMU, antimicrobial usage; ESBL-EC, extended-spectrum beta-lactamase-producing *E. coli*; UTI, urinary tract infection; ICU, intensive care unit.

50% of infections depending on region. Source attribution to poultry in this WHO study was 0% (Hoffmann et al., 2017), severely limiting the effect of AMU limitations in broilers.

Zhang et al. also investigated β-lactam-resistant E. coli (BR-EC) and performed a farm-to-fork quantitative microbial exposure assessment among U.S. beef consumers. Their model quantifies changes in microbial prevalence and concentration during all steps in the beef supply chain in order to quantify exposure to BR-EC in one serving for intact beef cuts, non-intact beef cuts and ground beef. They estimated that 90.1% of the cattle in the U.S. are raised on conventional feedlots, where antibiotics are allowed. As part of a scenario analysis they varied the proportion of cattle on conventional feedlots in steps of 10% from 0% to 100% to assess the influence of animal AMU on BR-EC exposure. A change from 90.1% to 0% conventionally-raised cattle was associated with a decrease in colony forming units per serving of 69% for intact beef cuts, 84% for non-intact beef cuts and 90% for ground beef (Zhang et al., 2022). Although this study quantifies exposure and not prevalence in the

population, it does show that reducing AMU in animals can have a profound impact on AMR exposure via the food route. It is also reasonable to assume that a reduction in exposure will also reduce AMR prevalence, especially as the previously mentioned studies also show this association, albeit most of them in chicken.

Using different methods, all five studies mentioned have shown a positive association between animal AMU and human AMR, indicating that reducing or even banning AMU would reduce AMR in the general population. However, quantifying this relationship remains difficult, in the first place because it is often unknown what the antimicrobial usage level before a policy change or scenario was. However, a few general associations can be seen. If AMU levels were already low for a certain drug, as was the case for cephalosporins prior to SB27 (Casey et al., 2023), the effect on resistance will also be relatively limited. A similar limited effect was seen when modelling a small number of farms decreasing their AMU (de Freitas Costa et al., 2022). On the other hand, when AMU is more widespread, as was estimated for Québec around the voluntary ceftiofur ban (Dutil et al., 2010), the effect of stopping will be dramatically larger. The same is true for modelled changes in AMU (Collineau et al., 2020; Zhang et al., 2022). A larger reduction in AMU leading to a larger reduction in AMR may seem like an open door, but observing the outline of a dose-response relationship is an important suggestion for causality. Another cause of these differences could be the different dynamics between bacteria. However, the limited number of studies here prevent clear conclusions from being made regarding these differences.

The effect that a reduction in animal AMU appears to have on β-lactam resistance in humans offers an opening for health gains in humans. As quantifying the AMU-AMR relationship is difficult, it is particularly challenging to predict the size of these health gains. An interesting approach to this problem is to calculate conservative (or upper-bound) estimates of the maximum attributable number of cases using a so-called outcome-attribution assessment. Sometimes also called a "backward-chaining" approach, these studies differ from exposure-based methods in that they start at for example the number of infections or the number of deaths attributed to a certain infection and then try to calculate the fraction of that number that can be attributed to antimicrobial use. This approach does not offer the opportunity of scenario analysis and gives relatively rough estimates, but it can circumvent certain knowledge-gaps and gives a good estimate of the maximum health impact. A good overview of such studies, and exposure-based models, can be found in a paper by McEwen (McEwen, 2012).

As can be seen in table 3, two such studies have been carried out that try to quantify the yearly mortality attributable to β-lactam usage in the United States. The first one is a report by the Institute of Medicine (IOM) that quantified the human health risks from subtherapeutic penicillin or tetracycline use in animals. They estimated a yearly attributable excess mortality of 6 for the entire United States (Institute of Medicine, 1989). A more recent paper investigated mortality from penicillin/aminopenicillin resistant E. faecium attributable to penicillin use in food animals and estimated a yearly excess mortality for the United States of 0.4 (Cox et al., 2009). The difference between these studies can be partly attributed to the fact that the IOM paper investigated the cumulative effect of two antimicrobials, but it also shows the difficulty in getting consistent results in such a study. Overall, the impact of animal AMU on human mortality seems very small in these studies; Cox et al. used resistance data from 2004, when the total death count in the U.S. was almost 2.4 million (Miniño et al., 2006), compared to which 0.4 deaths seem almost irrelevant. However, an important point that these studies forgo is that antimicrobial usage leads to an increasing health burden in the future. As long as alternative and last-resort antimicrobial treatments are still available the number of deaths from AMR will not be disconcertingly high. However, continued irresponsible antimicrobial usage will lead to increasing levels of resistance in first-line antimicrobials and therefore to increasing usage of last-resort antimicrobials. When this in turn leads to increasing resistance to last-resort

antimicrobials, the human health burden and mortality will increase to significant levels. Furthermore, both these estimates are for the United States, while disease burden due to AMR is highest in developing countries (Murray et al., 2022). Coupled with the lack of new antimicrobials under development, ensuring responsible antimicrobial use and curtailing antimicrobial resistance is very important for human health.

Quinolones

Three studies were included that investigated quinolone antimicrobials. All these studies focused on resistant Campylobacter infections, two of which due to eating poultry meat (Anderson et al., 2001; Innes et al., 2020; Skjøt-Rasmussen et al., 2009). Eating poultry is the primary source of Campylobacteriosis, accounting for 40% of infections in Europe and more than 50% in America, Africa and the Eastern Mediterranean (Hoffmann et al., 2017).

The first study, by Anderson et al., is a risk assessment on the human health impact of resistant *C. jejuni* from fluoroquinolone use in beef cattle. Their risk assessment starts at retail beef and quantifies exposure through beef consumption, but does not include AMU at the farm. The second part of the model, however, pools information on resistance levels in beef samples from different countries grouped by the number of years since the introduction of fluoroquinolones in food animals. As such, it gives an idea of the effects of introducing an antimicrobial in veterinary practice on human exposure to resistance. The incidence of resistance increased from 1.3% prior to introduction to between 1 and 8% after one year of fluoroquinolone use and up to 11% after 7 years and 29% after 10 years of use. A worst-case scenario is also included based on prevalence from Spain and Thailand, where fluoroquinolones are used widespread or prophylactically, leading to high resistance levels of 50-84% (Anderson et al., 2001). Resistance figures from different countries can be hard to compare, but all countries show an upward temporal trend post approval, indicating a clear link between animal AMU and human exposure to resistant bacteria.

Translation of resistant *C. jejuni* exposure to a number of infections is difficult as no exhaustive dose-response research was available at the time. However, under the assumption that resistance to fluoroquinolones does not increase *C. jejuni* virulence and its likelihood to infect, the number of infections does not change when AMR increases, only the fraction of infected people with a resistant strain does. In the United States an estimated 950 cases seek treatment per year, meaning that after 10 years of fluoroquinolone use the number of people with a resistant strain would increase from 10 to 80 per year to 280 per year (Anderson et al., 2001). These people would have to be treated with a different antibiotic, in turn stimulating AMR to that drug and further limiting treatment options and increasing disease burden and ultimately mortality. However, this does not take into account the relatively limited fraction of Campylobacter cases that are attributable to beef, being an estimated 15.1% in America and 16% in Europe (Hoffmann et al., 2017). An increase of AMR in cattle would therefore translate to an increase in AMR in only part of the cases.

A second paper, by Skjøt-Rasmussen et al., that looked at quinolone antibiotics and *C. jejuni* investigated the trends in AMR around a restriction in fluoroquinolone use in animals. This policy change, in 2003, withdrew fluoroquinolones for animal use, except when a susceptibility test showed that the bacteria that caused the infection were resistant to all other antimicrobial agents available to that animal species. Resistance to two fluoroquinolone antimicrobials was assessed; nalidixic acid and ciprofloxacin. During 1997 to 2007, resistance to ciprofloxacin and nalidixic acid in faecal samples from Danish broiler chickens remained at the same level. However, after the ban (in 2004, 2005 and 2007), resistance to ciprofloxacin and nalidixic acid was significantly higher in *C. jejuni* from imported chicken meat compared to Danish broiler chicken meat. In humans, resistance was significantly higher in both domestically acquired and travel associated cases compared to Danish broiler chicken meat and comparable to isolates from imported broiler chicken meat. A possible explanation for this is that

consumption of imported broiler chicken meat was increasing during that time (Skjøt-Rasmussen et al., 2009). This study shows that a policy change may not always have the clear effect that was expected beforehand; around the fluoroquinolone use restriction in animals the resistance levels in broiler chickens did not change. However, it is unclear how widespread the use of these antimicrobials was before the ban and what effect the ban had on usage. The fact that resistance is higher in imported meat suggests that fluoroquinolone use may have been lower in Danmark compared to other countries, even before the ban. In order to robustly quantify the effect of an intervention, the antimicrobial use before and after the intervention needs to be established well.

The final included study on quinolone antimicrobials constructed an external costs model; these are side effects of, in this case, antimicrobial usage that affect society and are not reflected in the price of antimicrobials. The model was developed to be used for all antimicrobials, but was parametrised as a case study of fluoroquinolone resistance in Campylobacter spp. due to enrofloxacin (a fluoroquinolone antimicrobial) in the US, before this drug was banned for animal use in 2013. The model focuses on the foodborne pathway and is in essence a compartmental model that considers both a human and a food animal pool, where resistance is transferred from animals to humans via food. Resistance in animals increases due to AMU and decreases due to fitness loss associated with resistance genes. Parametrisation on 1999 United States data led to an estimated total excess human cost from Campylobacter infections of $33 million, of which $18 million was attributable to chickens. An additional percentage point of fluoroquinolone resistance in chickens would have led to an additional 0.23 percentage points of resistance in humans and $435,000 extra societal costs. Lastly, an additional kilogramme of enrofloxacin administered to chickens imposed about $1,500 as externality costs on human society, translating to 7 cents per chicken from fluoroquinolone-resistant *Campylobacter* alone. The model assumed a steady state in resistance to increase transparency, but this may lead to underestimation of externality costs if resistance rates would have continued to climb due to continued AMU (Innes et al., 2020).

As for the studies on β-lactams, the included studies on fluoroquinolones suffer from a lack of data regarding antimicrobial usage. The limited effect of restricting fluoroquinolone use seen by Skjøt-Rasmussen is difficult to interpret as it is unclear to what extent antimicrobial usage changed following the restriction. Andersen et al. show a clear increase in human AMR prevalence following introduction of fluoroquinolones in animals and resistance is shown to be higher in countries where fluoroquinolone use is more widespread. However, as AMU quantification is lacking here as well, it is unclear whether the discrepancy between these studies stems from a difference in AMU quantities or from another underlying mechanism. The external costs model by Innes et al. is an exception, as enrofloxacin sales in US poultry production were estimated by the Federal Drug Authority. Furthermore, AMR was actively monitored in Campylobacter from poultry products and human infections during the introduction of enrofloxacin in broiler chickens in the United Sates and campylobacteriosis is attributable largely to poultry products, this study was able to give critical insights into the AMU-AMR relation (Innes et al., 2020). The study clearly shows that increased resistance in chickens will lead to increased resistance in humans and that there is a quantifiable link between animal AMU and human AMR. Furthermore, the fact that the study also provides external costs allows for cost-benefit analyses of reducing enrofloxacin use in poultry. Adapting the provided model to other bug-drug-animal combinations would allow for similar analyses under different circumstances.

Streptogramins

Three studies were included that investigated streptogramin antimicrobials. All three studies are based on the same model and assess the relationship between animal use of virginiamycin and quinupristin-dalfopristin (QD) resistant *E. faecium* in humans. QD is a streptogramin that was used mainly to treat vancomycin-resistant *E. faecium*. The efficacy of QD was potentially threatened by

virginiamycin use in animals, which was used as a growth promoter in food animals in the United States (Cox & Popken, 2004; Kelly et al., 2004; Smith et al., 2003).

Smith et al. created a model to describe the qualitative dynamics of the interaction between virginiamycin use in food animals and quinupristin-dalfopristin resistant *Enterococci* in humans. The goal of this study was not to obtain risk estimates, but to assess critical parameters in emergence of streptogramin resistance. As such, the model is not parametrised for a specific situation. They concluded that emergence of streptogramin resistant *E. faecium* (SREF) or multi-resistant *E. faecium* (MREF) will probably rely on an interaction between streptogramin use in medicine and the long history of virginiamycin use in food animals. Resistance spread depends on the epidemic potential; quasi-epidemic transmission, with an R_0 of around 1, would allow a strain to persist for a long period of time, thereby increasing disease burden. As such, the effects of a virginiamycin ban would be highest when R_0 is around 1, lower when R_0 is considerably lower than 1 and lowest when R_0 is considerably higher than 1 (Smith et al., 2003).

Similar results were found by Kelly et al., who built upon the model initially presented by Smith et al. They used elements of the initial model to create a compartmental model representing the dynamics of AMR in both animals and the human hospital population. The model is used to describe the expected public health effects of banning virginiamycin use as a growth promoter in animals. This study also shows that the effects of a ban on animal AMU are highly dependent on the epidemic potential of the resistant bacterium; when the R_0 in hospitals is low, community prevalence is the main driver of resistance prevalence and a ban would have a large impact. On the other hand, for a high R_0 most cases are acquired inside the hospital itself and human AMU is the main driver of resistance; a ban on animal AMU would consequently have little effect (Kelly et al., 2004). These two studies identify the R_0 in hospitals as an additional parameter that would influence the effects of restricting animal AMU on human AMR. This further underlines that the effectiveness of a ban is dependent on the dynamics in the hospital. As such, restricting animal AMU is not guaranteed to reduce human AMR considerably.

In 2004, Cox et al. further extended the model by Smith et al. to represent the stochastic dynamics of resistance spread when resistance prevalence is still low. They applied the resulting model to real data to quantify the risks for human patients treated with QD from virginiamycin use in animals. This model is in essence a compartmental model where individuals transition between unexposed, exposed, colonised and amplified (i.e. colonised and highly contagious) states. Parameter estimates were obtained using Monte Carlo Bayesian uncertainty analysis, conditioned on the observed levels of virginiamycin use and resistance in humans. The R_0 is estimated at 0.02, meaning that resistance will not become endemic. However, virginiamycin use in animals might still increase the risk of outbreaks of resistant bacteria in IC units, as opposed to endemic infections. The probability of an outbreak occurring on an ICU withing 8 years was largely determined by the prescription rate of QD in hospitals. Depending on the prescription rate doubling animal AMU could double the risk of a human AMR *Enterococci* outbreak. However, this is heavily dependent on the prescription rate; when this rate is under $1*10^{-4}$ or over $3*10^{-3}$ the outbreak risk approaches 0 or 1 respectively, independent of the exposure to animal AMR (Cox & Popken, 2004). This study again shows the complexity of the animal AMU-human AMR system; the effect of restricting animal AMU cannot be seen separately from human AMU, as this also exerts selective pressure on resistant bacteria. As such, isolated interventions (e.g. solely reducing animal AMU) may have a limited effect on AMR prevalence, depending on the transmission rates between animals and humans (Emes et al., 2022; van Bunnik & Woolhouse, 2017). Furthermore, when AMR has become highly prevalent or endemic in the population, reducing AMU on farms may have almost no effect (Emes et al., 2022). On the other hand, these studies also again confirm that reducing animal AMU can, under the right

circumstances, have a considerable effect on the prevalence of AMR in humans.

Glycopeptides, Polymyxins & Tetracyclines

Relatively few studies were included on glycopeptide, polymyxin and tetracycline antimicrobials; two, one and one respectively, all policy change analyses. Both Klare et al. and van den Bogaard et al. investigated the effects of banning avoparcin use in food animals on carriage of vancomycin-resistant *Enterococci* on non-hospitalised humans. Both studies found a significant decrease in resistance; in Saxony-Anhalt resistance decreased from 12% in 1994 to 3% in 1997, in the Netherlands a decrease from 12% in 1997 to 6% in 1999 was seen (Klare et al., 1999; van den Bogaard et al., 2000). Interestingly, in the United States, where avoparcin was never allowed as a feed additive, vancomycin resistance was not found in non-hospitalised people (Coque et al., 1996). Furthermore, a study in the Netherlands showed that 10% of meat eaters carried vancomycin resistant *Enterococci*, but none of the vegetarians (Schouten et al., 1997). This showed a clear link between AMU in animals and AMR in humans and the importance of the food route in this case.

More recently, Wang et al. investigated the effects of a ban in 2017 on colistin use as a growth promoter in China on the prevalence of mcr-1 positive *E. coli* in animals and humans. Between 2016 and 2019 the prevalence of mcr-1 positive *E. coli* decreased from 14.3% to 6.3%. Meanwhile, the overall prevalence of colistin resistant *E. coli* infections in humans also decreased significantly, from 1.7% to 1.3%. A strong point about this study is that the authors were also able to quantify the decrease in antimicrobial usage; sales of colistin sulfate premix decreased from $71.5 million in 2015 to $8.0 million in 2018. At the same time, production decreased from 27,170 tonnes to 2,497 tonnes (Wang et al., 2020). This shows that a large decrease in AMU of almost tenfold can have a significant effect on AMR prevalence. However, AMR prevalence does not decrease at the same rate as AMU, indicating the difficulty of completely eradicating AMR and suggesting that other sources may also play a role in causing human resistance.

As mentioned in the section on β-lactam antimicrobials, Casey et al. investigated the effects of banning routine preventive use of antibiotics in food animals on resistance to several antimicrobials in *E. coli* from human urine samples. For tetracyclines, no difference was seen between prevalence in California and the synthetic control California. Around the time of the ban, there was a nationwide trend of decreasing tetracycline use in animals, potentially masking a trend specifically for California. Furthermore, due to trade between states, people in California can be exposed to meat from other states and vice versa, decreasing the effect of state-specific measures (Casey et al., 2023). These results show that it can be difficult to disentangle the effects of an intervention from general trends and that local measures do not always have the desired effect.

Conclusion

The included studies all showed that restricting or banning usage of certain antimicrobials was associated with a decrease in antimicrobial resistance in humans. This was observed by both policy change analyses and exposure based models and across all investigated antimicrobial groups. The only exception was Casey et al., who did not find a significant difference for tetracycline resistance (although they did find a significant difference for extended spectrum cephalosporins). Although all other studies found a positive association between AMU in food animals and AMR in humans, the size of the effect differed greatly; from a 1.5% decrease in ESBL-EC prevalence (de Freitas Costa et al., 2022) to a 91% decrease in human infections with resistant Salmonella Heidelberg (Collineau et al., 2020). A major difficulty in comparing these differences in outcome is the lack in AMU quantification that all studies (except for Innes et al.) suffer from. When prior AMU or the effect of an intervention on AMU is not quantified, it is impossible to say whether a lack of effect stems from absence of a relationship between AMU and AMR or from a lack of effect of the intervention on AMU.

Further difficulties arise from the considerable variation in bug-drug-animal-

combinations. Due to the differences in dynamics between bacteria species and antimicrobial groups results cannot be pooled together. As such, often only very limited information is available on a specific combination. Lastly, comparing study results is further hampered by the variation in outcome measures; exposure to resistant antimicrobials cannot be readily translated to resistance prevalence or the number of infections. As such, although the results of this review show an effect of AMU restrictions on human AMR across different circumstances, quantifying or predicting the magnitude of that effect remains a challenge. Therefore, further research on this topic is essential to inform policymakers. For these future studies, it is important to quantify changes in AMU in animals in addition to AMR, as that is imperative for quantifying their relationship. In that light, AMU monitoring systems can play an important role. Furthermore, it is advisable that researchers either agree upon one outcome measure or present several different ones in order to improve the comparability between studies. In light of the important disease burden caused by AMR and the potential effects of AMU reductions, informed policymaking on animal AMU could potentially prevent many deaths worldwide.

Literature

Anderson, S. A., Yeaton Woo, R. W., & Crawford, L. M. (2001). Risk assessment of the impact on human health of resistant Campylobacter jejuni from fluoroquinolone use in beef cattle. *Food Control*, *12*(1), 13–25. https://doi.org/10.1016/S0956-7135(00)00014-1

Casey, J. A., Tartof, S. Y., Davis, M. F., Nachman, K. E., Price, L., Liu, C., Yu, K., Gupta, V., Innes, G. K., Tseng, H. F., Do, V., Pressman, A. R., & Rudolph, K. E. (2023). Impact of a Statewide Livestock Antibiotic Use Policy on Resistance in Human Urine Escherichia coli Isolates: A Synthetic Control Analysis. *Environmental Health Perspectives*, *131*(2), 1–8. https://doi.org/10.1289/EHP11221

Cassini, A., Colzani, E., Pini, A., Mangen, M. J. J., Plass, D., McDonald, S. A., Maringhini, G., van Lier, A., Haagsma, J. A., Havelaar, A. H., Kramarz, P., & Kretzschmar, M. E. (2018). Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): Results from the burden of communicable diseases in Europe study, European Union and European economic countries, 2009 to 2013. *Eurosurveillance*, *23*(16), 1–20. https://doi.org/10.2807/1560-7917.ES.2018.23.16.17-00454

Cassini, A., Högberg, L. D., Plachouras, D., Quattrocchi, A., Hoxha, A., Simonsen, G. S., Colomb-Cotinat, M., Kretzschmar, M. E., Devleesschauwer, B., Cecchini, M., Ouakrim, D. A., Oliveira, T. C., Struelens, M. J., Suetens, C., Monnet, D. L., Strauss, R., Mertens, K., Struyf, T., Catry, B., … Hopkins, S. (2019). Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases*, *19*(1), 56–66. https://doi.org/10.1016/S1473-3099(18)30605-4

Collineau, L., Chapman, B., Bao, X., Sivapathasundaram, B., Carson, C. A., Fazil, A., Reid-Smith, R. J., & Smith, B. A. (2020). A farm-to-fork quantitative risk assessment model for Salmonella Heidelberg resistant to third-generation cephalosporins in broiler chickens in Canada. *International Journal of Food Microbiology*, *330*(February), 108559. https://doi.org/10.1016/j.ijfoodmicro.2020.108559

Coque, T. M., Tomayko, J. F., Ricke, S. C., Okhyusen, P. C., & Murray, B. E. (1996). Vancomycin-resistant enterococci from nosocomial, community, and animal sources in the United States. *Antimicrobial Agents and Chemotherapy*, *40*(11), 2605–2609. https://doi.org/10.1128/aac.40.11.2605

Cox, L. A., & Popken, D. A. (2004). Bayesian Monte Carlo uncertainty analysis of human health risks from animal antimicrobial use in a dynamic model of emerging resistance. *Risk Analysis*, *24*(5), 1153–1164.

https://doi.org/10.1111/j.0272-4332.2004.00516.x

Cox, L. A., Popken, D. A., & Mathers, J. J. (2009). Human health risk assessment of penicillin/aminopenicillin resistance in enterococci due to penicillin use in food animals. *Risk Analysis*, *29*(6), 796–805. https://doi.org/10.1111/j.1539-6924.2009.01202.x

de Freitas Costa, E., Hagenaars, T. J., Dame-Korevaar, A., Brouwer, M. S. M., & de Vos, C. J. (2022). Multidirectional dynamic model for the spread of extended-spectrum-β-lactamase-producing Escherichia coli in the Netherlands. *Microbial Risk Analysis*, *22*(July), 100230. https://doi.org/10.1016/j.mran.2022.100230

Dutil, L., Irwin, R., Finley, R., Ng, L. K., Avery, B., Boerlin, P., Bourgault, A. M., Cole, L., Daignault, D., Desruisseau, A., Demczuk, W., Hoang, L., Horsman, G. B., Ismail, J., Jamieson, F., Maki, A., Pacagnella, A., & Pillai, D. R. (2010). Ceftiofur resistance in Salmonella enterica serovar Heidelberg from chicken meat and humans, Canada. *Emerging Infectious Diseases*, *16*(1), 48–54. https://doi.org/10.3201/eid1601.090729

Emes, D., Naylor, N., Waage, J., & Knight, G. (2022). Quantifying the Relationship between Antibiotic Use in Food-Producing Animals and Antibiotic Resistance in Humans. *Antibiotics*, *11*(1), 1–14. https://doi.org/10.3390/antibiotics11010066

Hoffmann, S., Devleesschauwer, B., Aspinall, W., Cooke, R., Corrigan, T., Havelaar, A., Angulo, F., Gibb, H., Kirk, M., Lake, R., Speybroeck, N., Torgerson, P., & Hald, T. (2017). Attribution of global foodborne disease to specific foods: Findings from a World Health Organization structured expert elicitation. *PLoS ONE*, *12*(9), 1–26. https://doi.org/10.1371/journal.pone.0183641

Holmes, A. H., Moore, L. S. P., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., Guerin, P. J., & Piddock, L. J. V. (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet*, *387*(10014), 176–187. https://doi.org/10.1016/S0140-6736(15)00473-0

Innes, G. K., Randad, P. R., Korinek, A., Davis, M. F., Price, L. B., So, A. D., & Heaney, C. D. (2020). External Societal Costs of Antimicrobial Resistance in Humans Attributable to Antimicrobial Use in Livestock. *Annual Review of Public Health*, *41*(1), 141–157. https://doi.org/https://doi.org/10.1146/annurev-publhealth-040218-043954

Institute of Medicine. (1989). Human Health Risks With the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed. In *Human Health Risks With the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed*. The National Academies Press. https://doi.org/10.17226/19030

Kelly, L., Smith, D. L., Snary, E. L., Johnson, J. A., Harris, A. D., Wooldridge, M., & Morris, J. G. (2004). Animal growth promoters: To ban or not to ban? A risk assessment approach. *International Journal of Antimicrobial Agents*, *24*(3), 205–212. https://doi.org/10.1016/j.ijantimicag.2004.04.007

Klare, I., Badstübner, D., Konstabel, C., Böhme, G., Claus, H., & Witte, W. (1999). Decreased incidence of VanA-type vancomycin-resistant enterococci isolated from poultry meat and from fecal samples of humans in the community after discontinuation of avoparcin usage in animal husbandry. *Microbial Drug Resistance*, *5*(1), 45–52. https://doi.org/10.1089/mdr.1999.5.45

McEwen, S. A. (2012). Quantitative human health risk assessments of antimicrobial use in animals and selection of resistance: A review of publicly available reports. *OIE Revue Scientifique et Technique*, *31*(1), 261–276. https://doi.org/10.20506/rst.31.1.2116

Miniño, A., Heron, M., Smith, B., & Kochanek, K. (2006). *Deaths: Final data for 2004*. https://www.cdc.gov/nchs/data/hestat/finaldeaths04/finaldeaths04.htm

Murray, C. J., Ikuta, K. S., Sharara, F., Swetschinski, L., Robles Aguilar, G., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., Johnson, S. C., Browne, A. J., Chipeta, M. G., Fell, F., Hackett, S.,

Haines-Woodhouse, G., Kashef Hamadani, B. H., Kumaran, E. A. P., McManigal, B., … Naghavi, M. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*, *399*(10325), 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0

Schouten, M. A., Voss, A., & Hoogkamp-Korstanje, J. A. A. (1997). VRE and meat. *The Lancet*, *349*(9060), 1258. https://doi.org/10.1016/S0140-6736(05)62460-9

Skjøt-Rasmussen, L., Ethelberg, S., Emborg, H. D., Agersø, Y., Larsen, L. S., Nordentoft, S., Olsen, S. S., Ejlertsen, T., Holt, H., Nielsen, E. M., & Hammerum, A. M. (2009). Trends in occurrence of antimicrobial resistance in Campylobacter jejuni isolates from broiler chickens, broiler chicken meat, and human domestically acquired cases and travel associated cases in Denmark. *International Journal of Food Microbiology*, *131*(2–3), 277–279. https://doi.org/10.1016/j.ijfoodmicro.2009.03.006

Smith, D. L., Johnson, J. A., Harris, A. D., Furuno, J. P., Perencevich, E. N., & Morris, J. G. (2003). Assessing risks for a pre-emergent pathogen: Virginiamycin use and the emergence of streptogramin resistance in Enterococcus faecium. *Lancet Infectious Diseases*, *3*(4), 241–249. https://doi.org/10.1016/S1473-3099(03)00581-4

Summers, A. O. (2006). Genetic linkage and horizontal gene transfer, the roots of the antibiotic Multi-Resistance Problem. *Animal Biotechnology*, *17*(2), 125–135. https://doi.org/10.1080/10495390600957217

Tang, K. L., Caffrey, N. P., Nóbrega, D. B., Cork, S. C., Ronksley, P. E., Barkema, H. W., Polachek, A. J., Ganshorn, H., Sharma, N., Kellner, J. D., Checkley, S. L., & Ghali, W. A. (2019). Comparison of different approaches to antibiotic restriction in food-producing animals: Stratified results from a systematic review and meta-analysis. *BMJ Global Health*, *4*(4), 1–13. https://doi.org/10.1136/bmjgh-2019-001710

Tang, K. L., Caffrey, N. P., Nóbrega, D. B., Cork, S. C., Ronksley, P. E., Barkema, H. W., Polachek, A. J., Ganshorn, H., Sharma, N., Kellner, J. D., & Ghali, W. A. (2017). Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *The Lancet Planetary Health*, *1*(8), e316–e327. https://doi.org/10.1016/S2542-5196(17)30141-9

Tiseo, K., Huber, L., Gilbert, M., Robinson, T. P., & Van Boeckel, T. P. (2020). Global trends in antimicrobial use in food animals from 2017 to 2030. *Antibiotics*, *9*(12), 1–14. https://doi.org/10.3390/antibiotics9120918

van Bunnik, B. A. D., & Woolhouse, M. E. J. (2017). Modelling the impact of curtailing antibiotic usage in food animals on antibiotic resistance in humans. *Royal Society Open Science*, *4*(4). https://doi.org/10.1098/rsos.161067

van den Bogaard, A. E., Bruinsma, N., & Stobberingh, E. E. (2000). The effect of banning avoparcin on VRE carriage in The Netherlands [2]. *Journal of Antimicrobial Chemotherapy*, *46*(1), 146–148. https://doi.org/10.1093/jac/46.1.146

Wang, Y., Xu, C., Zhang, R., Chen, Y., Shen, Y., Hu, F., Liu, D., Lu, J., Guo, Y., Xia, X., Jiang, J., Wang, X., Fu, Y., Yang, L., Wang, J., Li, J., Cai, C., Yin, D., Che, J., … Shen, J. (2020). Changes in colistin resistance and mcr-1 abundance in Escherichia coli of animal and human origins following the ban of colistin-positive additives in China: an epidemiological comparative study. *The Lancet Infectious Diseases*, *20*(10), 1161–1171. https://doi.org/10.1016/S1473-3099(20)30149-3

WHO. (2017). Critically Important Antimicrobials for Human Medicine: 5th revision. In *World Health Organization*.

WHO. (2022). Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2022. In *World Health Organization*.

Zhang, Y., Schmidt, J. W., Arthur, T. M., Wheeler, T. L., Zhang, Q., & Wang, B.

(2022). A Farm-to-Fork Quantitative Microbial Exposure Assessment of β-Lactam-Resistant Escherichia coli among U.S. Beef Consumers. *Microorganisms*, *10*(3). https://doi.org/10.3390/microorganisms10030661

Appendix

Search query, used in PubMed (21-7-2023, 391 results) and Scopus (31-7-2023, 321 results):

((((((("antimicrobial resistance") OR ("antibiotic resistance")) OR (AMR)) AND (((human) OR (general public)) OR (hospital))) AND (((((((((("food-producing animals") OR (livestock)) OR ("food animals")) OR (cattle)) OR (poultry)) OR (broiler)) OR (sheep)) OR (goat)) OR (pigs))) AND ((("antimicrobial use") OR ("antibiotic use")) OR (AMU))) AND ((((((quantification) OR (model)) OR ("risk assessment")) OR (association)) OR (relationship)) OR (pathway))