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Transmission of antimicrobial resistance from livestock agriculture to humans and from humans to animals

Chantal Morel



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TRANSMISSION OF ANTIMICROBIAL RESISTANCE FROM LIVESTOCK AGRICULTURE TO HUMANS AND FROM HUMANS TO ANIMALS

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The emergence of a resistant pathogen reduces the effectiveness of antibiotics in preventing or treating an infection caused by a micro-organism, thus increasing morbidity and mortality and leading to higher economic costs to livestock producers. An understanding of the underlying disease dynamics is crucial in finding appropriate solutions to containing the rise in antimicrobial resistance. This report synthesises the evidence on the potential modes of transmission of antimicrobial resistance between humans and animals and vice versa. In particular, the important role of the environment in the transmission chain is discussed as well as practices to break this link. This report also illustrates some of the commonly shared antibiotic classes that are used in human medicine and animal production, and the overall trends in the usage of these antibiotics. While information on transmission of resistance is sparse, the report highlights several priority areas where future research could focus in order to bring a greater understanding of these interactions.

Key words: Antibacterial, DNA

JEL codes: Q1

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1. Introduction

Antimicrobials are drugs that kill or stop the growth of living micro-organisms and include antibiotics, antimycobacterial drugs (which are antibiotics specifically for the treatment of mycobacterial infections such as TB), antivirals, antifungals, antiparasitals. As antibiotics receive the most attention, the term antimicrobial resistance (AMR) is often used interchangeably with antibiotic resistance. While this review uses the term AMR, the data mainly relates to antibiotic use and antibiotic resistance in humans and in animals.

Antibiotics, or antibacterials, are drugs that can kill or inhibit the growth of bacteria that cause infections in people, animals and plants (ECDC, 2016a). Bacteria are resilient in that they adapt rapidly in response to changes in their environment. The emergence of a pathogens' resistance to antibiotics is an adaptation of the microorganism to its environment. In practice, resistance reduces the effectiveness of an antibiotic in preventing or treating an infection caused by the micro-organism, thereby increasingy morbidity and mortality, and consequently leading to higher economic costs to livestock producers. An understanding of the underlying disease dynamics is crucial in that it is not the animals or humans who become resistant to antibiotics, but rather the bacteria that colonise and potentially infect animals and humans.

Some bacteria have natural resistance to certain antibiotics (intrinsic or inherent resistance). However, when bacteria that are normally susceptible to antibiotic treatment become resistant because of genetic changes (acquired resistance), this becomes a serious concern for public health and animal health (ECDC 2016b). A susceptible bacterium can become resistant through the acquisition of mobile genetic elements from another bacterium that is already resistant – horizontal gene transfer[1] (most common) or through a novel genetic mutation in its DNA (chromosomal resistance), (WHO, 2011a). One resistance gene can then confer resistance to two or more antibiotics within the same antibiotic class[2] resulting in cross-resistance. In addition, as different resistant genes that confer resistance to different antibiotic classes are often located together in the bacteria's DNA they can be transferred simultaneously resulting in co-resistance. More specifically, horizontal gene transfer can lead to the simultaneous spread of resistance to several unrelated classes of antibiotics, especially if the resistance genes are co-located on the transmissible genetic element. In humans, the genes for antibiotic resistance in one species of bacteria can spread to other species of bacteria through the exchange of genetic material. As a result, consumption of one type of antibiotic can lead to resistance to not only this antibiotic, but also to others within the same class or outside the class (WHO, 2011a).

When a novel mutation in the DNA causes the bacterium to become resistant, the spread of the strain through reproduction is the primary method of spreading this resistance. Rapid reproduction of bacteria means that the organisms, with this newly acquired resistance, can quickly become dominant in a bacterial population within an individual or an animal. This is particularly true if the use of an antibiotic to which the strain is resistant has eliminated competing bacteria in the close environment. Eventually all resistant bacteria are selected for, as the antibiotic kills those remaining susceptible bacteria around them, in what can be seen as the continuous fight for "ecological space" (ECDC, 2016a). Once resistance has developed, bacteria often retain it for long periods in the absence of exposure to antibiotics. This can lead to the persistence of resistance to antibiotics that are rarely or no longer in use (WHO, 2011).

All resistant bacteria survive in the presence of the relevant antibiotic, and continue to grow and multiply causing illness or death (ECDC, 2016a). The subsequent spread of the resistant organisms in animals or humans (or both), including those that have not themselves consumed any antibiotics, allows for a wide dispersion of the resistant pathogens. The emergence and spread of resistant organisms is more common when there is high antibiotic consumption in a population (ECDC, 2016a).

Multidrug resistance is a particular concern as there are few treatment options that remain relevant for all micro-organisms, such as bacteria responsible for healthcare-associated infections, for food- and waterborne infections, tuberculosis, and sexually transmitted diseases. In practice, the challenge with

[1] Horizontal gene transfer: the transfer of genes between organisms through other ways than reproduction.

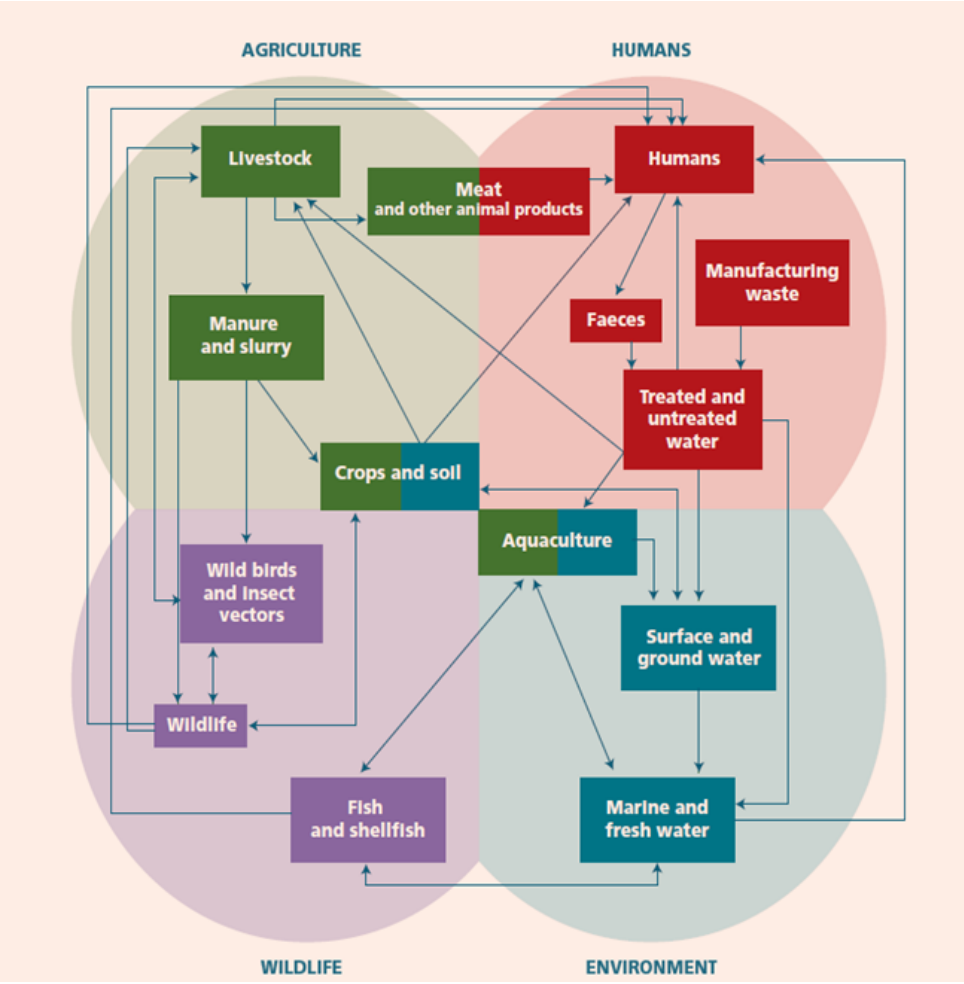
[2] There are over 15 different classes of antibiotics and they differ in their chemical structure and their action against bacteria. One antibiotic may be effective against only one or multiple types of bacteria (ECDC, 2016b).

multidrug-resistant bacteria lies in the limited number of remaining options for treatment (ECDC, 2016a). An additional concern is that genes for resistance and virulence can sometimes be transferred together, leading to the threat of greater virulence and pathogenicity. These are sometimes referred to as "superbugs" (WHO, 2011a).

2. The modes of circulation of antibiotic resistance between humans, animals, plants and the environment

The 2016 Food and Agriculture Organisation of the United Nations (FAO) study emphasizes the existence of a "substantial body of evidence" supporting the idea that the emergence of AMR in bacteria in livestock is linked to the emergence of AMR in bacterial populations that colonize and infect humans (Singer et al., 2003, ECDC/EFSA/EMA, 2015) However, the report also cites evidence that the emergence of AMR in bacteria in humans appear to originate mainly from antimicrobial usage in humans, whilst most AMR bacteria amongst livestock appear to originate from antimicrobial use in livestock. Despite these seemingly parallel developments, there is nevertheless consensus within the scientific literature that there are routes for spillover of AMR from bacterial populations in humans and those in food-producing animals, and vice versa.

Figure 1. The linkages between epidemiological settings in which antibiotics are used and bacteria can be transmitted



Source: Wellington (2013) and adapted by FAO (2016).

A better understanding of the interface between animals, the environment and humans, and vice versa, in the transmission of AMR is critical in order to find solutions to minimising these transmissions. In effect, there are three main pathways of resistance transmission between animals and humans.

- Direct contact between humans and animals
- The food chain
- The environment (usually linked to agricultural production) such as water, air and soils.

Transmission between animals and humans through direct contact and vice-versa

Resistant bacteria are common in livestock and there are examples of how farmers and their families have become colonized with the same resistant bacteria as their animals, as highlighted in Kock (2012), Price (2012), Huijsdens (2006), van den Bogaard (2001). These bacteria can then be brought into the wider population. The spread of resistant bacteria from direct contact with animals is well documented in cases such as certain MRSA strains isolated from livestock, in particular from pigs (ECDC 2016a). Veterinarians can also be carriers of resistant bacteria (Garcia-Graells, 2012). For example, farmers who handle cattle, pigs and poultry have a greater chance of being infected with methicillin-resistant *Staphylococcus aureus (MRSA-398)* than other people in the community (Garcia-Alvarez, 2012; Lewis, 2008). It should also be noted that transmission through direct contact could also happen the other way around, from humans to animals, which confounds the picture of causation and is discussed later in this paper.

Transmission from animals to humans via the food chain

The most common transmission route is via AMR bacteria (and genetic material) through food distribution and consumption, the majority of such bacteria colonise the host gastrointestinal tract (Lazarus, 2015). All animals and humans have bacteria, but the extensive use of antibiotics in livestock production has led to some becoming colonized with antibiotic resistant bacteria. At the slaughter and processing stages, these bacteria can be transferred to the food product. Food products of animal origin may sometimes be contaminated with bacteria and drug-resistant bacteria can remain on the meat. When not handled or cooked properly, the bacteria can spread to humans (CDC, 2013). Food products are assumed the primary route for transmitting resistant bacteria and resistance genes from animals to humans. Fruit and vegetables contaminated through human and/or animal waste, or contaminated water are also thought to be a potential transmission route (WHO, 2011a). These bacteria can be commensal in animals, so called “healthy carriers” in that they are not themselves symptomatic, but are pathogenic in humans. They can also be commensal in both humans and animals, but can later convey resistance to food-borne pathogens in the human gastrointestinal tract (Singer, 2003).

Once the environment is contaminated, there are different possible routes for resistant bacteria to be transmitted by animals to humans through the broader food chain. For example, vegetables can be contaminated with antibiotic-resistant bacteria from animal manure, human faeces and/or waste water, or water that is used for irrigation (CDC, 2013; ECDC, 2016). Moreover, antibiotic resistant bacteria have been found in numerous water sources such as drinking wells, rivers and effluent from wastewater treatment plants (Marathe, 2013; Graham, 2014; Kristiansson, 2011). In theory, bacteria (including resistant bacteria) can be transmitted across borders on food items such as meat, fruit, vegetables, seeds, grain (Grami, 2015).

Residues can persist in feed and animal waste and can contaminate soil and water, thereby affecting the aquatic and environmental microbiomes (Yu and Silbergeld, 2014) that can ultimately affect humans. When some classes of antibiotics are given to livestock residues of these antibiotics might be excreted in the animal faeces, potentially exerting selection pressure on the bacterial populations in the soil or water environment in which they are ultimately excreted (Woolridge, 2012; AAM, 2009). However, as stressed in the FAO (2016) report, evidence on the relative importance of the different mechanisms in transferring resistance is limited (Hong, 2011; McEwen, 2006; Novo, 2013; Woolhouse, 2015), and it is difficult to make generalizations as antibiotics may give different results under different conditions (Kumar, 2005; Kemper, 2008; AAM, 2009).

The role of the environment

The exposure of bacteria to antibiotics is generally considered as the main driver of the development and spread of antibiotic resistance. Essentially, the environment can play two important roles in this process:

- It can be a vector for the transmission of many human pathogens, including resistant bacteria. For example, bacteria in soil and water have been found to carry a pool of resistance genes that can act as a reservoir of resistance for human pathogens (Forsberg et al., 2012; Lupo et al., 2012; APUA, 2008).
- It can be the source of resistant pathogens. Almost all classes of antibiotics are of natural origin and resistance can develop naturally in the environment or in response to the exposure to antibiotics used in human medicine or veterinary medicine. The main clinical resistance mechanisms present today originate from environmental bacteria. With an increased selection pressure from antibiotic use and pollution, they can be an important source for novel resistance factors that can be transmitted into human pathogens through horizontal gene transfer (Uppsala Health Summit Expert Workshop Report, 2015).

The contamination of the environment by antibiotics and antibiotic-resistant bacteria has four main sources:

- antibiotic production facilities
- human usage
- animal usage
- plant use.

These areas pose different risks for the selection of resistant bacteria and the spread of such bacteria (Pruden, 2013). The risks for environmental contamination were discussed at the Uppsala Health Summit Expert Workshop in 2015 and the key outcomes are summarised in the following sections.

Environmental contamination from antibiotic production facilities

Pharmaceutical production facilities are defined sources for environmental emissions of antibiotics and are relatively easy targets for resource-efficient pollution control. However, production sites for active pharmaceutical ingredients (APIs) are far more numerous and located in many countries throughout the world. When emissions take place far away from where the products are eventually sold and used can create further difficulties in the monitoring and control of emissions. Moreover, the lack of specified emission standards, lack of transparency, and cutting corners in an effort to minimize prices are also considered major problems in some countries.

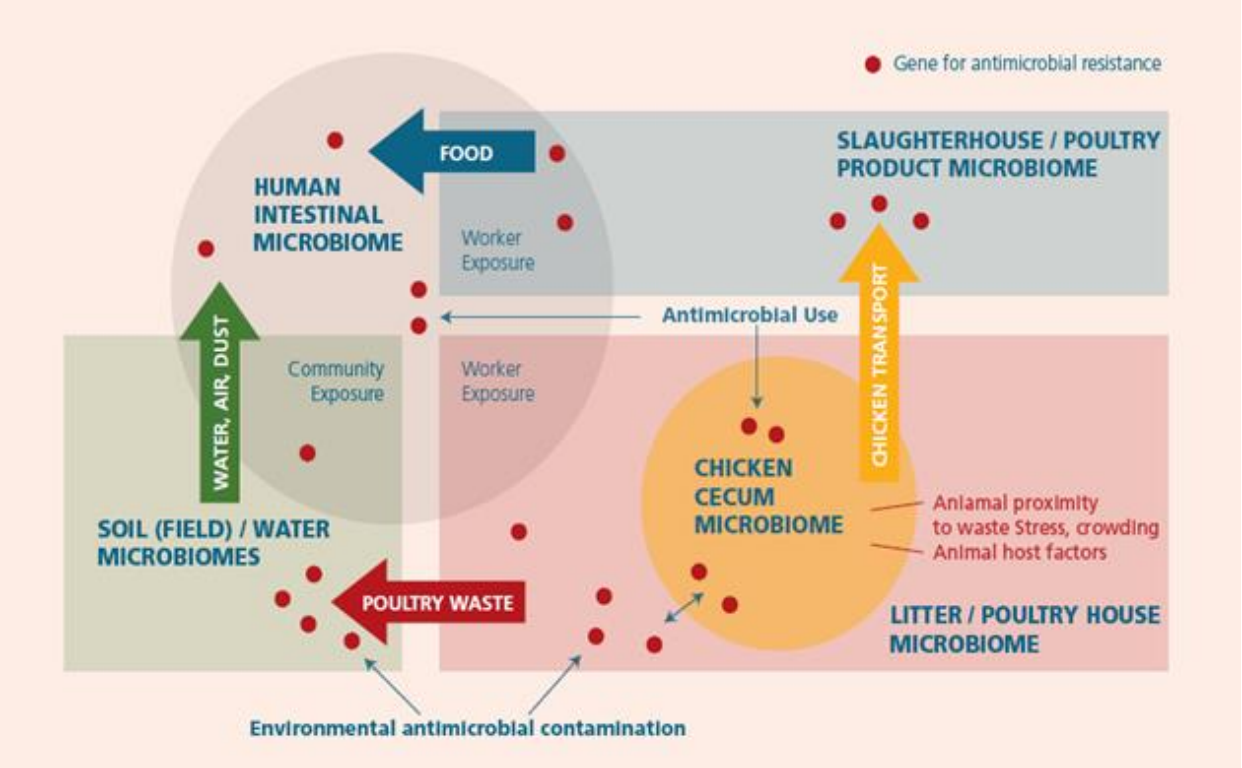
Environmental contamination from human antibiotic use

A large proportion of many drugs used in human medicine can be excreted in an active form into the environment. Crucially, traditional wastewater treatment plants are not designed for the removal of antibiotic residues, or the inactivation of antibiotic resistance genes. Many experts suspect that low levels of residual antibiotics in sewage select for antibiotic resistant strains and this may pose a risk when biological treatments are used (although overall this remains an open question) (Gullberg, 2011). Modern wastewater treatment facilities therefore represent a crucial node for control of the global spread of AMR.

Environmental contamination from animal and plant antibiotic use

The emission of antibiotics from animal and plant production into the environment is considered substantial and may cause a substantial health risk on farms and to the wider population. Once in the environment these excreted antibiotics end up together with potential pathogens from agricultural settings. Figure 2 demonstrates a conceptual framework for the spread of AMR genes in a poultry production system and the role of environmental contamination in this process.

Figure 2. A conceptual framework for the spread of AMR genes in a poultry production system



Source: Davis (2011).

3. The shared use of antibiotics between animals and humans

Antibiotics are used to treat sick animals, as well as for disease prevention (prophylaxis) and to stem contagion in animals in contact with sick ones (metaphylaxis). More specifically, antibiotics are mainly used to treat respiratory and enteric infections of intensively farmed animals, especially during the early part of life for broiler chickens, pigs and calves. They are also used to treat infections like mastitis in dairy cows, a common problem in cows with a high milk output (WHO, 2011). Moreover, the increase in intensive fish farming globally has led to the practice of using antibiotics in fish feed. They are also used for growth promotion in production systems in some countries and this has led to much controversy, and in some countries limiting or banning antibiotics in the feed.

There is substantial overlap between the drugs that are necessary for human use and those that are currently used in animal production. The use of many classes of antibiotics (macrolides, tetracyclines, quinolones, beta-lactams, aminoglycosides) are common in both human and animal health. For example, Table 1 shows the list of antimicrobial classes that are licensed for veterinary use in the European Union and their main indications. The World Organisation for Animal Health (OIE) also has, and reviews periodically, the List of Antimicrobial Agents of Veterinary Importance and collects data on antimicrobial agents intended to be used in animals. Crucially, the use across humans and animals includes highest priority critically important antimicrobials (HPCIA) that are considered essential for human health. There is substantial evidence that suggests that highest priority antibiotics are still used for growth promotion. In summary, the overarching picture of antibiotic use is characterised by extensive shared use between humans and animals. The OIE, as part of its List of Antimicrobial Agents of Veterinary Importance, recommends restrictions on the use of fluoroquinolones, third and fourth generation cephalosporins and colistin. In addition, the OIE recommends phasing out the use of antibiotics as growth promoters, giving priority to the classes in the World Health Organisation (WHO) category of Highest Priority Critically Important Antimicrobials.

Table 1. List of the main antimicrobial classes licensed for veterinary use in the European Union

Antimicrobial class	Veterinary use in the EU	Major indications	Risk to public health	Hazard of zoonotic relevance	Probability of AMR transfer
Aminoglycosides (e.g. gentamicin, neomycin)	Species: cattle, sheep, goats, horses, dogs and cats	• Septicaemias • Digestive, respiratory and urinary infections	Risk profiling required	Enterobacteriaceae *Enterococcus* spp.	High
Cephalosporins (3rd and 4th generation)	Species: cattle, pigs, horses, dogs and cats	• Septicaemias • Respiratory infections • Mastitis	High	Enterobacteriaceae	High
(Fluoro) quinolones	Species: cattle, pigs, chickens, turkeys, rabbits, dogs and cats	• Septicaemias • Infections (e.g. colibacillosis)	High	*Campylobacter* spp. Enterobacteriaceae	High
Macrolides (including ketolides)	Species: cattle, sheep, pigs, and poultry	• Mycoplasma infections (pigs and poultry) • Haemorrhagic digestive disease and proliferative enteropathies (leitis) associated with *Lawsonia intracellularis* (pigs) • Respiratory infections • (cattle and sheep) • Liver abscesses (cattle)	Low to limited	*Campylobacter* spp. *Salmonella* spp.	High
Penicillins (natural- Lactamase- sensitive)	Species: cattle, sheep, poultry, horses, dogs and cats	• Septicaemias • Respiratory infections • Mastitis	Low or limited	None specific	High
Penicillins (broad spectrum beta-lactamase-sensitive) Aminopenicillins	Species: cattle, sheep, pigs, poultry and dogs	• Pasteurellosis and colibacillosis (poultry) • *Streptococcus suis* infections (pigs) • Respiratory infections (cattle and pigs)	Further risk profiling required	Enterobacteriaceae *Enterococcus* spp.	High
Penicillins (narrow spectrum beta-lactamase resistant)	Species: cattle and sheep	• Metritis • Mastitis	Low or limited	None specific	High
Penicillins (Beta-lactamase protected broad spectrum) - Co-amoxiclav	Species: cattle, pigs, dogs and cats	• Respiratory infections • Mastitis • Metritis • Colibacillosis (cattle and pigs)	Further risk profiling required	Enterobacteriaceae *Enterococcus* spp.	High
Polymyxins (including colistin or polymyxin E)	Species: cattle, sheep, pigs and poultry	• Septicaemias • Colibacillosis • Urinary infections • Gram-negative digestive infections	Currently under evaluation	Enterobacteriaceae	Low*
Rifamycin (rifampicin)	Species: cattle	• Mastitis • Metritis	Low or limited	None specific	High
Tetracyclines	Species: cattle, sheep, goats, pigs, horses and poultry	• Respiratory diseases • Bacterial enteritis • Urinary tract infections • Metritis • Mastitis • Pyodermatitis • Keratoconjutivitis (cattle) • Chlamydiosis • Heartwater • Anaplasmosis • Actinomycosis • Actinobacilosis • Ehrlichiosis • Resistant strains of *Staphylococcus aureus*	Low or limited	*Brucella* spp.	High

*May need to be reassessed in the light of new evidence of the emergence of plasmid-mediated colistin resistance in animals and humans (Catry *et al.*, 2015, Skov *et al.*, 2016).

Source: FAO 2016 adapted from EMA 2014 survey results.

Magnitudes and overall trends of usage in animal production

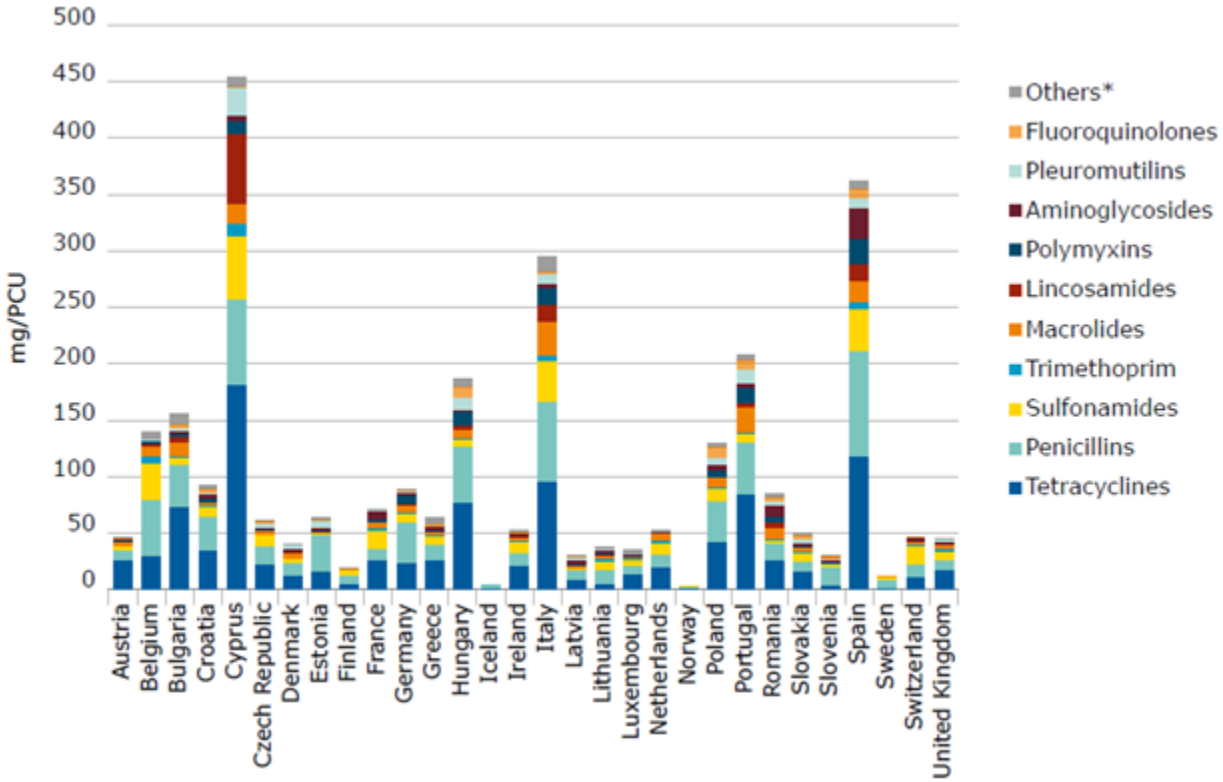
Globally, the volume of antibiotic use is estimated to be higher in animals than in humans, although the relative proportions vary substantially between countries. However, there are difficulties when it comes to defining an antibiotic. For example, Ionophores are classified as antibiotics in the United States, but not in the European Union and this can cause problems when comparing usage figures. In overall terms, veterinary prescriptions make up a relatively small but increasing proportion of total use in livestock

production. It has been estimated, based on several modelling assumptions, that the average global use could be at 45, 148 and 172 milligrams of antimicrobials per kilogram for cattle, chicken and pigs, respectively, per kilogram of animal produced annually (van Boeckel 2015). In Europe, good data are available on antibiotic usage in animals from the European Medicines Agency (EMA), which has been tasked with collecting data from EU Member States and with developing a harmonized approach to surveillance of antibiotic usage in animals. At the global level, the OIE collect data on the use of antimicrobial agents in animals on an annual basis. The first and second reports are published and publicly available, and the third report was published in 2018. Figure 3 shows the sales of veterinary antimicrobial classes used in food-producing species in Europe in 2016.

Figure 4 presents a summary of the antimicrobial agents sold by antimicrobial class as a percentage of the total sales for food-producing species for 2016. In overall terms, antimicrobial sales in the 30 European countries were largely accounted for by three classes of antibiotics; tetracyclines (32.8%), penicillins (25.0%), and sulfonamides (11.8%). These three classes of antibiotics accounted for about 70% of total sales in 2016.

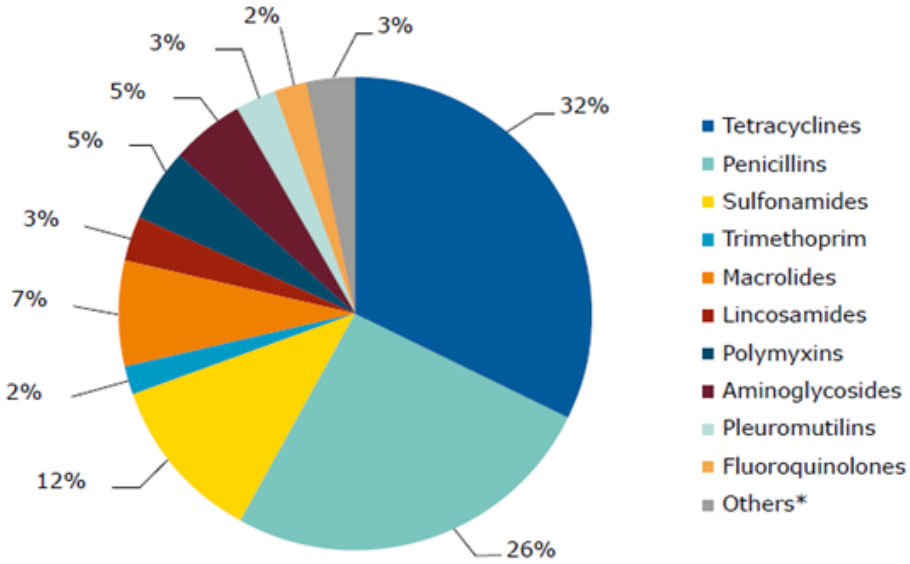
For the 30 countries in the survey, the sales of tetracyclines, penicillins and sulphonamides, (mg/POU), accounted for about 70% of total sales in 2016. At the global level, the OIE indicated a similar situation to the one in Europe with tetracyclines accounting for about 37.1%, followed by polypeptides at 15.7%, penicillins at 9.8% and macrolides at 8.9% (2017 OIE Annual Report on Antimicrobial Agents Intended for Use in Animals). It should be noted that the OIE figures were based on the survey results reported from 107 countries.

Figure 3. Sales for food producing species (mg/PCU) of the various antimicrobial classes for 30 European countries, 2016



Note: * Amphenicols, cephalosporins, other quinolones and other antibacterials (classified as such in the ATCvet system).
1. Differences between countries can be partly explained by differences in animal demographics, in the selection of antimicrobial agents, in dosage regimes, in type of data sources, and veterinarians prescribing habits
Source: Eighth ESVAC Report: Trends from 2010 to 2016.

Figure 4. Total sales of antimicrobial agents by antimicrobial class as percentage of the total sales for food-producing species (mg/PCU), aggregated for the 30 European countries 2016



Note: * Amphenicols, cephalosporins, other quinolones and other antibacterials (classified as such in the ATCvet system)
Source: Eighth ESVAC Report: Trends from 2010 to 2016.

The proportion of CIAs with the highest priority in human medicine, defined by WHO as 3rd and 4th generation cephalosporins, fluoroquinolones, and macrolides[3] (WHO, 2011b; WHO, 2011a), varied substantially between the 30 countries. In overall terms, the sales of 3rd and 4th generation cephalosporins, fluoroquinolones and polymixins accounted for 0.2%, 2.1% and 6.8%, respectively of the total sales of antimicrobials VMPs in 2016 (Figure 5).

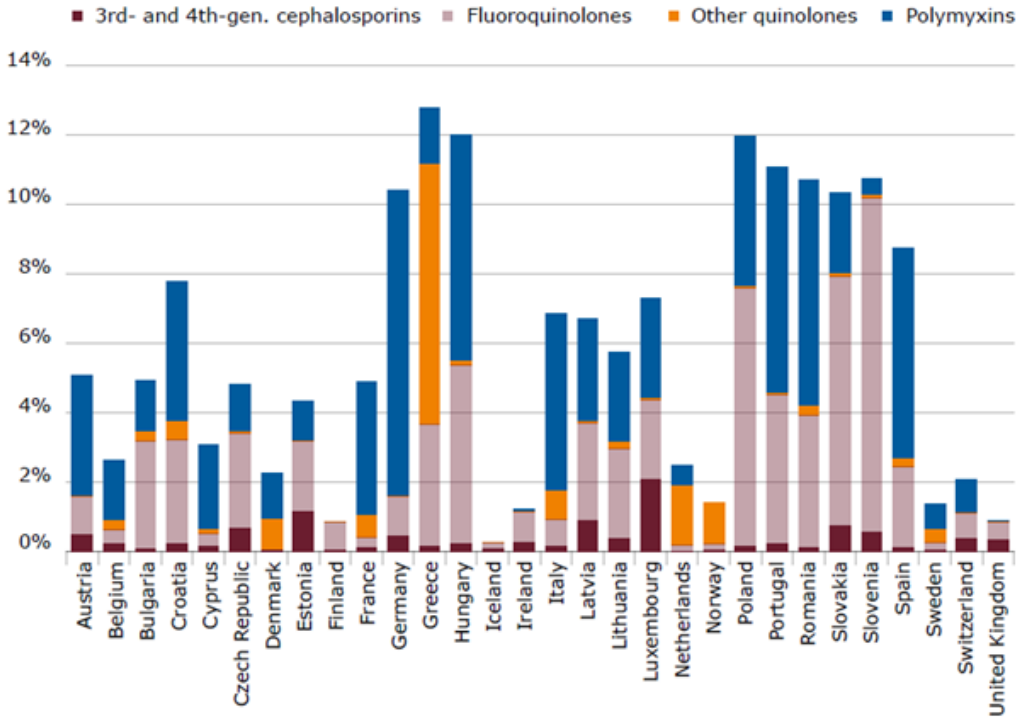
However, for the 30 countries providing data to ESVAC for the years 2010–2016, there was an overall decline in sales across countries in the survey (except Spain). Several explanations have been made for this decline, including policy responses, measurement changes such as the implementation of responsible-use campaigns, restrictions on use, changes in the collection systems, changes in animal demographics, benchmarking and the increased awareness of the threat of antimicrobial resistance, amongst others (EMA/ESVAC, 2016).

Overall, in many European countries there has been good progress in improving antibiotic usage, and generally lowering the unnecessary use of antibiotics in food producing animals. The global trends are also changing due to a combination of factors including changes to the regulatory environment and greater veterinary oversight. However, on a global level, antibiotics are still widely used by farmers in some countries without veterinary supervision due to their low price and easy over-the-counter availability (Laxminarayan, 2015). The continued global growth in demand for animal products associated with economic growth and globalization may result in an increase in demand for antibiotics in livestock production, *ceteris paribus*. However, countries, at a global level, are in the process of implementing their National Action plans based on the Global Action Plan on the "prudent use"[4] of antibiotics in livestock production.

[3] Glycopeptides are also CIA but are not covered in this paper.

[4] This concept means no prophylactic, sub-therapeutic or growth promoting use of antimicrobials. Therapeutic use – use intended to treat infections – is, however, part of prudent use (Uppsala Health Summit post conference report 2015).

Figure 5. Proportion of the total sales of 3rd and 4th generation cephalosporins, fluoroquinolones, other quinolones and polymyxins for food-producing species, in mg/PCU, for 30 European countries, 2016



*Variations between the countries should be interpreted with great care due to the large differences in dosing between these classes/sub-classes of antimicrobials.
* No sales of other quinolones in Austria, Estonia, Finland, Germany, Iceland, Ireland, Switzerland and the United Kingdom.
* No sales of polymyxins in Finland, Iceland and Norway
Source: Eighth ESVAC Report: Trends from 2010 to 2016.

4. Antibiotic usage for growth promotion in food animal production

Animal growth promotion

In many countries, producers add antibiotics to the feed, and/or water, of terrestrial food animals in sub-therapeutic concentrations to achieve faster growth and better feed efficiency. While the mechanisms underlying antibiotic growth promotion (AGP) are not completely understood; nevertheless, antibiotics have been widely used in animal production since the 1950s, leading to a rise in the overall usage of antibiotics in many countries (WHO 2011). In the United States, for example, the use of antibiotics as AGPs increased fiftyfold between 1951 and 1978 (from 110 tonnes to 5 580 tonnes), while the use of antibiotics to treat infections in people and animals increased tenfold during the same period (Black 1984, Mellon 2001). During this period many bacterial strains from both humans and animals went from being susceptible to antibiotics to being resistant (WHO 2011a), even if direct or linear causation effects between the use of antimicrobials and the development of resistance cannot always be established. In the United Kingdom, the prevalence of tetracycline-resistant *Escherichia coli* in poultry increased from 3.5% to 63.2% only four years after its introduction in 1957 (Sojka, 1961).

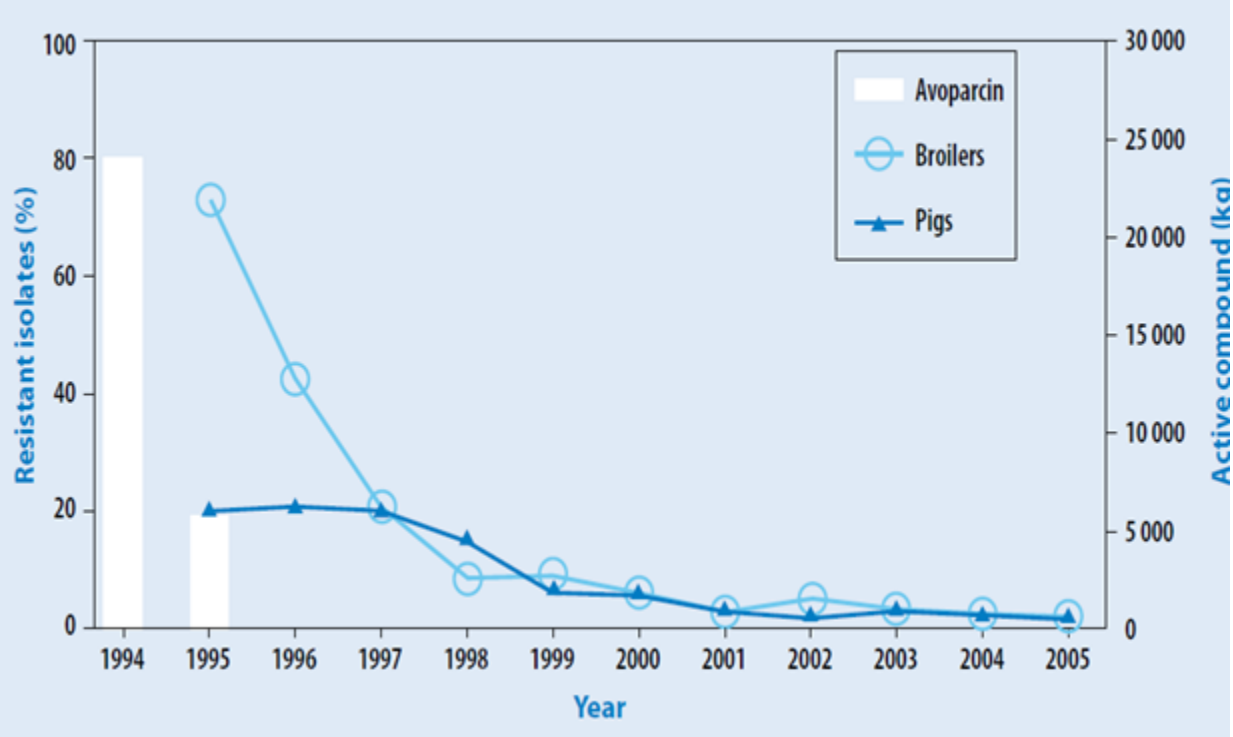
The 2011 WHO Report noted that initially almost all antibiotics were permitted for use as AGPs. However, in 1968 concerns started to surface about potential adverse effects on human health, leading to the appointment of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine, chaired by M.M. Swann. The Swann report recommended withdrawing the use of antibiotics as AGPs if they were needed for therapeutic purposes in human or animal medicine or they could confer

cross-resistance to antibiotics used in people -- laying the foundation for prudent use policies and regulations in many western European countries (WHO, 2011). Despite this evolution, the global use of AGPs continued until 1986, when their use was banned in Sweden. As more information became available resulting in a better understanding of the potential health risks due to the development and spread of cross-resistance to antibiotics used to treat people, many European countries followed the Swedish approach. Following various risk assessments the WHO has recommended (1997) that the use of AGPs be stopped or phased out (WHO 2001a), and since 2006 all AGPs have been banned in the European Union, on the advice of the Scientific Steering Committee (SSC 1999).

The effect of withdrawing AGPs in the European Union due to threat of a rise in antimicrobial resistance has been studied, especially in Denmark where they have been used in swine and broiler chicken production. The animal reservoir of *Enterococci* resistant to the AGPs used had decreased significantly (WHO 2003). The withdrawal of avoparcin as an AGP in the European Union in 1997 was found to reduce vancomycin resistant *Enterococci in* food animals and in the general population (due to the relationship conferring cross-resistance between the two) (Hammerum, 2007; van den Bogaard, 2000; Klare, 1999). Figure 6 shows the trend in glycopeptide resistance in *enterococcus faecium* from broiler chickens and pigs and the avoparcin usage in animals in Denmark from 1994–2005.

The beneficial effects on animal growth from antimicrobial growth promoters have been found to be relatively limited where production systems have been optimized (Uppsala Health Summit, 2015). The understanding of this development has evolved over time as AGPs have been phased out in some countries. For example, in Denmark antibiotic consumption per kilogram of pig produced fell by more than 50% between 1992 and 2008 (as an assumed result of the implementation of policies to discontinue the use of antibiotics as AGPs), while over the same period there was a marked rise in pig productivity, suggesting that the change in antibiotic consumption did not harm long-term output (Aarestrup, 2010).

Figure 6. Trends in glycopeptide resistance amongst *enterococcus faecium* from broiler chickens and pigs and avoparcin usage amongst animals in Denmark, 1994–2005



Source: WHO (2011a).

Overall, while Europe has moved away from the use of antibiotics as AGPs, they continue to be used in some parts of the world. The 2015 USDA report indicated that the use of antibiotics for purposes other than disease treatment[5] is associated with a 1%-3% increase in productivity. Based on this finding, the authors estimated the effects of possible restrictions on the production use of antibiotics in livestock production (already using antibiotics as AGPs before the restrictions) would only see a 1%-2% reduction in production due to higher costs. However, producers not using antibiotics in this way before the restrictions would respond to the higher prices by increasing production and farm revenues. The report also noted that limiting antibiotic use would likely affect animal industries differently, depending on the type of production system.

Several changes have taken place in relation to the dual use of antimicrobials in animals and humans. Fluoroquinolones, such as ciprofloxacin which is commonly used in animals, were withdrawn from use in poultry in 2000 in part due to findings that human infections with fluoroquinolone-resistant *Campylobacter* species had become increasingly common and were associated with consumption of poultry (WHO, 2011). Although the effect of continued circulation of fluoroquinolone resistant *Campylobacter* species from poultry flocks and from people who have acquired a fluoroquinolone-resistant enteric infection during foreign travel will continue to cause fluoroquinolone-resistant *Campylobacter* infection and other enteric infections, this restriction is expected to help reduce the burden of such resistant infection in the United States (Nelson, 2007). Recent changes in Federal Drug Agency (FDA) policy in 2017 means that no medically important antibiotics are being approved as AGPs on the market. In addition, the FDA now requires that all antibiotics that are mixed in animal feed are subject to strict veterinary oversight.

Prophylactic or preventative use

In the European Union, feed additives containing antibiotics for growth promotion have been banned from use in food-producing animals. These include avoparcin in 1997; ardacin, bacitracin zinc, virginiamycin, tylosin phosphate and spiramycin in 1998; and flavophospholipol, salinomycin sodium, avilamycin and monensin sodium in 2006 (WHO, 2011) In the United States, the policy discussions tend to combine the use of antibiotics for prophylaxis and metaphylaxis, and use of antibiotics for the purposes of growth promotion/production. Indeed, most surveys from which the United States Department of Agriculture (USDA) draws it statistics do not always distinguish between these uses (USDA, 2015). One example of this limitation, cited by USDA, is the Agricultural and Resource Management Surveys (ARMS) broiler questionnaires, in which respondents are asked whether they raise birds without antibiotics in their feed/water unless the birds were sick. Such lack of specification in this questioning makes the estimation of prophylactic use difficult to decipher. While lacking a clear picture of use, there are however calls in the United States to also restrict prophylactic use (Lawrence, 2012; Mellon, 2013; WHO, 2000).

At a global level, prophylactic or preventative use covers a wide range of uses ranging from the unnecessary routine use without veterinary oversight to targeted use, prescribed by a veterinarian at therapeutic dosage for specific situations and limited time. In May 2018, the 182 OIE Member countries adopted a new proposal that defines the preventative use of antimicrobials in livestock production. The adopted standards define that veterinary medical use of antimicrobial agents means the administration of an antimicrobial agent to an individual or a group of animals to treat, control or prevent infectious disease; to treat means to administer an antimicrobial agent to an individual or a group of animals showing clinical signs of an infectious disease; to control means to administer an antimicrobial agent to a group of animals containing sick animals and healthy animals (presumed to be infected), to minimise or resolve clinical signs and to prevent further spread of the disease, to prevent means to administer an antimicrobial agent to an individual or a group of animals risk of acquiring a specific infection or in a specific situation where infectious disease is likely to occur if the drug is not administered. The Veterinary Medicinal Products (VMP) containing antimicrobial agents should only be used on the prescription of a veterinarian, or other suitably trained person authorised to prescribe VMP containing antimicrobial agents in accordance with national legislation and under the supervision of a veterinarian".

[5] This would include both use as prophylaxis and for the purposes of growth promotion.

The role of husbandry practices in transmitting resistance from animals to humans

Livestock production conditions are widely believed to affect the growth and transmission of resistance. First, simply raising livestock means that large numbers of animals come in direct contact with humans, thereby increasing the chances of the spread of infections and diseases. In addition, contact between confined animals as well as proximity to people also increases the chances for transmission. Moreover, the Confined Animal Feeding Operations (CAFO), which characterises most factory farms, are often close to major urban areas. The intensity of antibiotic use is often greater due to challenges associated with hygiene and infection control in such settings. In addition, intensive systems also produce large quantities of waste, with an estimated 75-90% of antibiotics being excreted, mostly un-metabolized into the environment (Marshall and Levy, 2011). This type of contamination may increase the risk of transferring AMR genes to bacteria in the environment and to pathogenic or commensal bacteria in wildlife (Otte, 2007; Hong, 2011).

However, evidence on the relative importance of the different mechanisms in transferring resistance is limited (Mcewan, 2006; Honey, 2011; Novo, 2013; Woolhouse 2015; and FAO, 2016). Resistant bacteria from animals may spread through air vents intended to keep the animals cool, through manure spread on land, and through waste water into streams and rivers and often into public water supply systems. Furthermore, where large-scale intensive systems import animal feed and breeding stock on a global scale (Rushton, 2010), this may introduce novel strains of pathogenic and non-pathogenic resistant bacteria, which can go on to mix with existing microbial communities on intensive farms (FAO, 2016).

Pigs and chickens are often kept in intensive, indoor, high-density production systems where they are prone to infectious diseases (McEwan and Fedorka-Cray, 2002). While the rule in human medicine is to treat patients individually, in the case of food animals such as pigs and broiler chickens, they are usually treated with antibiotics collectively (herd/flock), with high dosage, frequency and duration of treatment. A crucial part of reducing the use of antibiotics in animal production is to reduce the prevalence of disease in livestock. This can be achieved in several ways including improving animal housing, lowering animal density (more space per animal) and lowering the stress levels among the animals.

5. The transmission of resistant genes from the commonly used antibiotics in animal agriculture

For some antibiotics there is growing concern about shared use across animals and humans stemming from the shared risks associated with antimicrobial resistance. According to the FAO, enteric bacterial isolates detected in food-producing animals and meat are commonly resistant to ampicillin, tetracycline, co-trimoxazole and streptomycin. Studies have found the range of types of resistance observed to be broader in poultry and chicken, with notable additional levels to quinolones and third-generation cephalosporins, both of which are HPCIA (FAO, 2016). The report finds increased AMR prevalence and multidrug resistance in isolates derived from commercial abattoirs, which source their chickens from medium- and large-scale commercial farms. Tetracycline resistance is described as the most common along the meat value chain, starting with small-scale farms, and correlated with farmers commonly reporting its use. Differences in AMR patterns have been observed between isolates from beef carcasses at the abattoir and those from retail beef in some supply chains, which could suggest contamination occurring at a later stage in the supply chain (FAO, 2016).

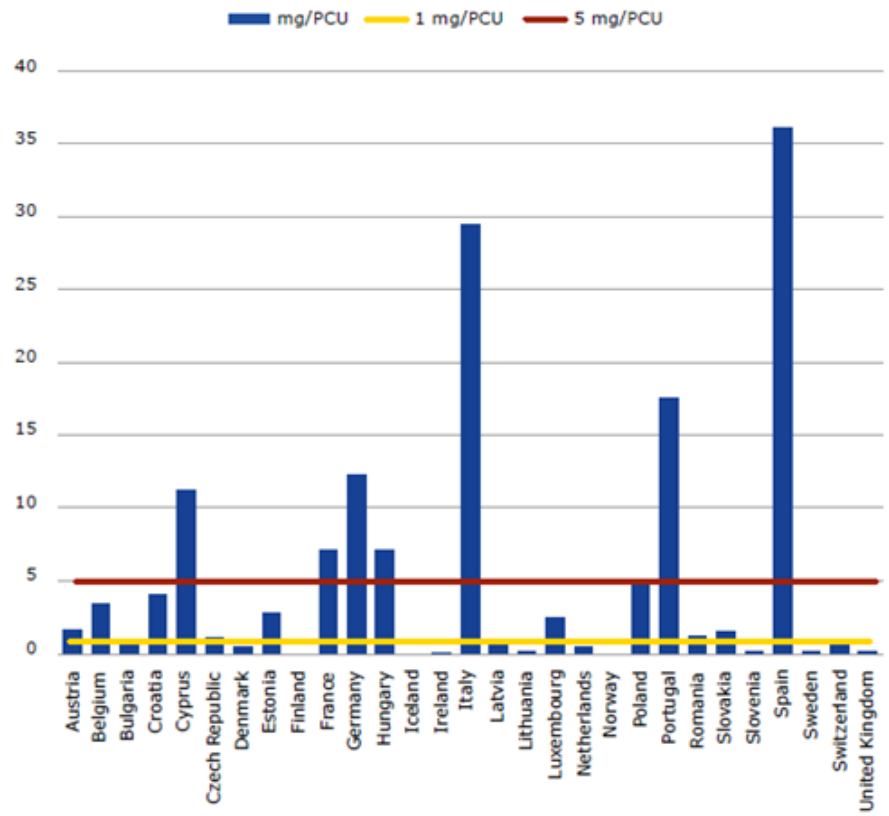
Of particular concern is the shared use of colistin, a polymyxin that has been in regular use in veterinary medicine for decades for the treatment of gram-negative gastrointestinal infections, but was not used in human health. Now, despite its systemic toxicity, it is also needed for human use due to growing levels of resistance to the available alternatives. With the increasing number of hospital outbreaks of carbapenemase-producing enterobacteriaceae and other multidrug-resistant bacteria over the last decade, colistin has been introduced (or re-introduced) as a last-resort treatment in many hospitals, especially in southern Europe. Figure 7 shows the sales of colistin for use in food-producing animals in 2014 (EMA/ESVAC). The resistance gene mcr-1 has been identified in isolates from clinical cases of veterinary colibacillosis and in invasive human pathogens (EMA, 2016). The EMA noted that the increasing frequency of the mcr-1 gene in veterinary isolates compared to human isolates combined with much higher

use of colistin in livestock compared to humans, along with genetic determinants usually seen in animal environments, is suggestive of a flow from animals to humans (EMA, 2016).

In Europe, the overall prevalence of colistin resistance remains low in food animals. The 2016 FAO report emphasized that the recent detection of resistance to colistin in food-borne pathogens in humans, livestock, meat and vegetables across different countries raises the potential role of global travel and trade in the transboundary spread of resistance genes (Skov and Monnet, 2016; Doumith, 2016; Liu, 2016; Kluytmans van den Bergh, 2016; Zurfuh 2016 as cited in FAO, 2016). EMA has stressed the need for evidence to determine the lowest possible level of effective colistin use that can be achieved, while maintaining animal welfare without increasing the use of fluoroquinolones and 3rd- and 4th-generation cephalosporins, or the overall use of antibiotics (EMA/ESVAC, 2015).

In Japan, the government revoked the designation of Colistin as a feed additive as of 1 July 2018 and has limited the use of colistin as a veterinary drug to use as a second-line drug. These measures have been taken to reduce the quantity of colistin use in animal production, and in turn to reduce the potential spread of resistant colistin from animals to humans. According to the data in Japan's national monitoring system, i.e. Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM), between 2000 and 2015, the ratio of *E.coli* having mcr-1 gene has been contained at a low level, with the highest figure of 2.3% in cases of *E.coli* isolates from healthy animals.

Figure 7. Sales of colistin for use in food-producing animals, 2014



Source: EMA/ESVAC, 2014.

Some examples of antibiotic-resistant pathogens

42. Most of the known cases of antibiotic resistance being transmitted from animals to humans (either directly from animals to humans or via the environment or food chain) involve mainly *Salmonella and Campylobacter*, and then *E. coli*, *Staphylococcus aureus,* and *Enterococcus* to a lesser degree. These

cases are described in Table 2, which shows the sources of AMR (bacteria and bacterial genes) in different animal production settings.

Table 2. Sources of AMR (bacteria and bacterial genes) in different animal production settings

Bacterial species	Antimicrobial resistance pattern	Infections commonly observed in humans	Animal sources of human infection	Other known sources of human infection
***Campylobacter* spp.**	Fluoroquinolones	Gastrointestinal (sequelae: *Guillain-Barré syndrome)*	Food-producing animals (poultry)	Raw unpasteurized milk, water
***Enterococcus* spp.**	Aminoglycosides Ampicillin Vancomycin		Food-producing animals (poultry)	
***Escherichia* coli**	Quinolones Sulphonamides Trimethoprim	Gastrointestinal, UTI, HUS		
LA-MRSA			Food-producing animals (pigs, calves, cows)	
***Salmonella* spp.** (non-typhoidal)	Cephalosporins Quinolones Tetracyclines	Gastrointestinal	Food-producing animals (pigs, cows, poultry)	

Source: Adapted by the FAO (2016) from Furuya and Lowry (2006).

Antibiotic resistant Salmonella

Antibiotic resistant *Salmonella* is associated with longer and more frequent hospitalization, longer duration of illness, higher risk of invasive infection and greater risk of death in the two years following an infection (WHO 2011). Antibiotic resistant *Salmonella* appears to be mainly associated with pigs and pig products, although these organisms have also been isolated from cattle and poultry in some EU countries (Hopkins, 2010). The foods implicated in these infections are usually beef, pork, poultry and dairy products, and sometimes eggs and fresh produce. Resistance patterns detected in *Salmonella* in animals often reflect the selective pressures resulting from antibiotic usage in animal production. Resistance in *Salmonella* from animals for the most part resembles the occurrence of resistance in corresponding foodstuffs and in humans (EFSA, 2010).

Multidrug resistance is widespread in several *Salmonella serovars*, and in particular in *S. Typhimurium* in many European countries as well as in other parts of the world (ECDCD). Globally, there have been reports of resistance to quinolones in *Salmonella* from food animals and their products. Levels vary considerably across European countries, the serovars and the different animal species (being high amongst poultry), as well as the various food products (EFSA, 2010). Increasing rates of quinolone resistance in animal *Salmonella* isolates has been partially linked to a subsequent increase in human infections via the consumption of contaminated eggs and egg products (Meakins, 2008). While resistance to third-generation cephalosporins in *Salmonella* from animals and people is low at present in Europe, but there are growing concerns about the emergence and spread of Salmonella strains that harbour transferable resistance to expanded-spectrum cephalosporins, especially those that produce extended-spectrum β-lactamases (ESBLs – enzymes) (WHO, 2011). Another major concern is related to foreign travel and the increasing emergence of *Salmonella* strains of animal origin that contain transferable AmpC-like β-lactamases that also inactivate extended-spectrum cephalosporins (WHO, 2011).

Several clones of *S. Typhimurium* resistant to a wide range of antibiotics, including some of the HPCIAs emerged in the early 1960s. These clones have spread widely in both humans and food-producing animals (WHO, 2011a). Of particular concern is the emergence and rapid spread in certain animal populations of a variety of monophasic *S. Typhimurium* in many countries since the late 1990s (Scallan, 2011). In Europe, these new strains have spread and caused numerous human infections. As not all laboratories fully serotype all isolates of putative *S. Typhimurium*, the true incidence in the human population is currently unknown (WHO, 2011). It is generally thought that these organisms are associated with pigs and pig products, although they have also been isolated from cattle and chickens in parts of Europe (Hopkins).

Antibiotic resistant Campylobacter

Campylobacter infection often causes diarrhoea, which can be associated with fever and severe abdominal pains. In most cases the symptoms are self-limiting and normally do not require antibiotic treatment. When therapy is required, macrolides are often the first-line therapy or sometimes fluoroquinolones. However, if there is resistance to first-line treatment the choice of treatment becomes limited and treatment failure as well as greater duration and severity of illness can occur (WHO, 2011). Another concern is that *Campylobacter* easily acquires resistance to antibiotics, and *Campylobacter* from poultry meat is frequently resistant, including to fluoroquinolones in many countries (European FSA). While overall mortality from campylobacteriosis is generally low, it is higher in patients with comorbidities and those infected with antibiotic-resistant strains (Endtz, 1991). Infections with macrolide-resistant *Campylobacter* are often associated with more frequent invasive illnesses as well as death (WHO, 2011).

Several studies have demonstrated a time-limited association between fluoroquinolone in animal production and the emergence and rise in quinolone resistance in human and animal isolates of *Campylobacter species* (WHO, 2011). The connection between the levels of use in food-producing animals and Campylobacter resistance to fluoroquinolones is well understood. High to very high levels of ciprofloxacin resistance; in particular, in isolates from broiler chickens, pigs and cattle suggest that they may act as reservoirs of resistant *Campylobacter* (FAO/OIE/WHO, 2003; ECDC, 2009; European FSA, 2010). In countries where fluoroquinolones use has been banned in food animal production (e.g. Australia, Denmark and Norway), the rates of resistance have been found to be low, despite fluoroquinolone remaining in use in human medicine for over 20 years (WHO, 2011).

Antibiotic resistant E. coli

48. The emergence of resistant *E. coli* in humans can directly cause disease, or transfer resistance genes to pathogenic bacteria, leading to treatment failure, increased severity of illness, prolonged duration of illness, and even death amongst vulnerable patients. Many *E. coli* strains from animal and water sources that contaminate food can harbour resistance genes capable of being transferred to human-adapted bacteria or pathogens, while passing through the gut (WHO, 2011). Of particular concern is the rapid worldwide emergence of ESBL-producing *E. coli* strains that exhibit transferable resistance to the HPCIAs. Crucially, such bacteria also often exhibit resistance to other first-line antibiotics such as fluoroquinolones (WHO, 2011a). ESBLs are of particular concern due to their ability to break down β-lactam antibiotics, rendering common front-line drugs such as penicillins and cephalosporins ineffective (WHO, 2011).

The recent rise in ESBL-producing *E. coli* strains has been seen in human infections, as well as in bacteria isolated from food-producing animals such as cows and chickens. As such, food and the environment are believed to be important sources contributing to the rise of such resistant bacteria (Melvius 2010). However, in this case the transmission pathway is not always clear. The FAO report (2016) points to a study suggesting that resistance patterns of *E. coli* isolated from children at outpatient clinics in the meat value chain study areas reflected the commonly used antimicrobials in *human* medicine, such as ampicillin, co-trimoxazole, streptomycin and amoxicillin-clavulanic acid, with lower levels of resistance to third-generation cephalosporins and ciprofloxacin. This would suggest that possible exposure pathways for humans include more than just contaminated meat (FAO, 2016).

6. Summary and possible considerations for future work

The scope and scale of the evidence on the transmission of antibiotic resistance between humans and animals (and vice versa) and the environment is limited, but increasing. While concrete evidence exists in cases of *Salmonella, Campylobacter, E coli, Staphlococcus aureus, and Enterococcus* there is little evidence of other cases. As noted in the 2016 FAO report, evidence on the relative importance of the different modes of transmission of resistant pathogens is still not well understood (Hong et al., 2011; McEwen, 2006; Novo et al., 2013; Woolhouse et al.; 2015), and it is difficult to make generalizations on such transmission as resistant bacteria can behave differently in the different environments (Kumar et al., 2005; Kemper, 2008; AAM, 2009). While the information and data on AMR is improving across species and countries, there is a need for more in-depth research in the following areas:

- *Differences amongst species.* Other bacteria (excluding those listed above) may be considered less relevant because they may only cause disease in humans (e.g. *Streptococcus pneumoniae*), and are rare in animals, or vice versa.
- *Traceability and well-designed studies*, including animals, plants, humans and the environment.
- *Surveillance challenges.* There are enormous logistical difficulties in establishing surveillance systems capable of detecting transmission from animals to humans and vice versa. Such systems would ideally be able to include whole genome sequencing to understand resistance patterns. This relates to the number of actors involved in the process; public health, veterinary and food authorities, as well as the private sector such as meat and dairy suppliers. Developing an approach for collection and reporting of data on national sales of antimicrobial agents (the task demanded by the EC of the EMA and implemented by ESVAC) is very complex (EMA, 2017). This complexity is also reflected in the global reports of the OIE annual collection of data on the use of antimicrobial agents in animals.
- *AMR*. There are sin many countries substantial differences between the systems for the collection and reporting of data on antimicrobial consumption and resistance in bacteria from humans and animals and this makes direct comparisons difficult (JIACRA, 2016). Consumption data from humans are reported as defined daily doses (DDD) per 1 000 inhabitants and per day, while in food-producing animals the corresponding data are currently reported by weight of active substance per population correction unit per year. (JIACRA, 2016). At the global level, good progress is being made to define a denominator to allow the calculation of mg of antimicrobial agents per kg of animal biomass. This will allow not only the comparison between animals, but also allow comparison with human use in the future.
- *Pharmaceutical industry-related data collection challenges*. In some cases, the provision of resistance data from the private sector may present a conflict of interests as such information could work against sales.
- *Scientific challenges related to detecting actual transmission*. Making the genetic link alone is not sufficient. Most studies that are conducted are cross-sectional by nature – they compare unrelated samples from different populations. If the same gene is found in both populations, one does not necessarily know the direction of transfer (human to animal, animal to human, or both from the environment, or else human to human and animal to animal, connected by the environment or some other link).
- *Resistance does not necessarily lead to illness.* In foodborne, disease outbreaks caused by bacteria from animals (e.g. *salmonellosis*) occur relatively rapidly after the consumption of the infected food. However, with resistant bacteria the situation is very different. Humans do not get sick from commensal *E. coli, or MRSA* just after consumption. Rather the bacteria are often only detected either in routine screenings, unrelated to the acquisition of colonization, or in the case of infection. But again, colonization could have occurred long before and one cannot determine whether the person had other chances of acquiring this strain (Tenhagen 2017).
- *Media attention often leads to funds being prioritized towards certain areas of research.* Investigations into the zoonotic aspect of *S. aureus* were mostly driven by the identification of Methicillin-resistant *Staphlococcus aureus* in food animal populations about ten years ago. Prior to

that, *S. aureus* was mainly considered a hospital-associated pathogen. The emergence of a similar type of bacteria in food animals led to some media attention and benevolent funding bodies for research on the topic (Tenhagen 2017).

- *Pathogens that could demonstrate transmission are not necessarily the ones of most interest.* EFSA enterococci are considered the gram positive indicator counterpart to *E. coli* in that they have similar functions and levels of use can be linked to levels of resistance.
- There are only a few *systems dynamic models* that look at flows of antimicrobial use, environment and antimicrobial resistance through the food animal supply chain.

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