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# Impact of antimicrobial use in animals on antimicrobial resistance in humans

Antimicrobial resistance is selected for in human and veterinary medicine alike, and resistance may be transferred from animals to humans and vice versa.





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## Introduction

Antimicrobial (antibiotic, antifungal, antiviral, and antiparasitic) resistance (AMR) is defined as the development in microorganisms such as bacteria, fungi, viruses, and some parasites of traits that prevent antimicrobials from working against these microorganisms. Antimicrobial resistance occurs naturally. However, (mis)use and overuse of antimicrobials in humans as well as in animals has been shown to accelerate the selection and emergence of resistant microorganisms. Antimicrobial resistance may be selected for in human and veterinary medicine alike, and resistance may also be transferred from animals to humans and vice versa. AMR is currently considered one of the biggest threats to global health and food security.

## Use of antimicrobials in animals

The vast majority of antimicrobials administered to animals are used in the livestock sector where they are given for three major reasons: treatment of infection, prevention of infection (prophylaxis), and for growth promotion to increase weight gain in animals reared for food. In some parts of the world, use in the livestock sector has risen in the last century due to increasing intensification of livestock production. This is primarily due to a historical trend toward highly intensive animal production systems using more antimicrobials rather than less intensive systems. However, in many parts of the world the use of antimicrobials in animals has substantially decreased in recent times. In Europe, for example, the use of therapeutic and prophylactic antimicrobials in animals fell by more than 32% between 2011 and 2017 (European Medicines Agency 2019). This has been possible due to the implementation of higher biosecurity measures alongside improved husbandry and management practices, which together have led to a reduction in antimicrobial use in many countries (Laanen et al. 2013; Postma et al. 2016).

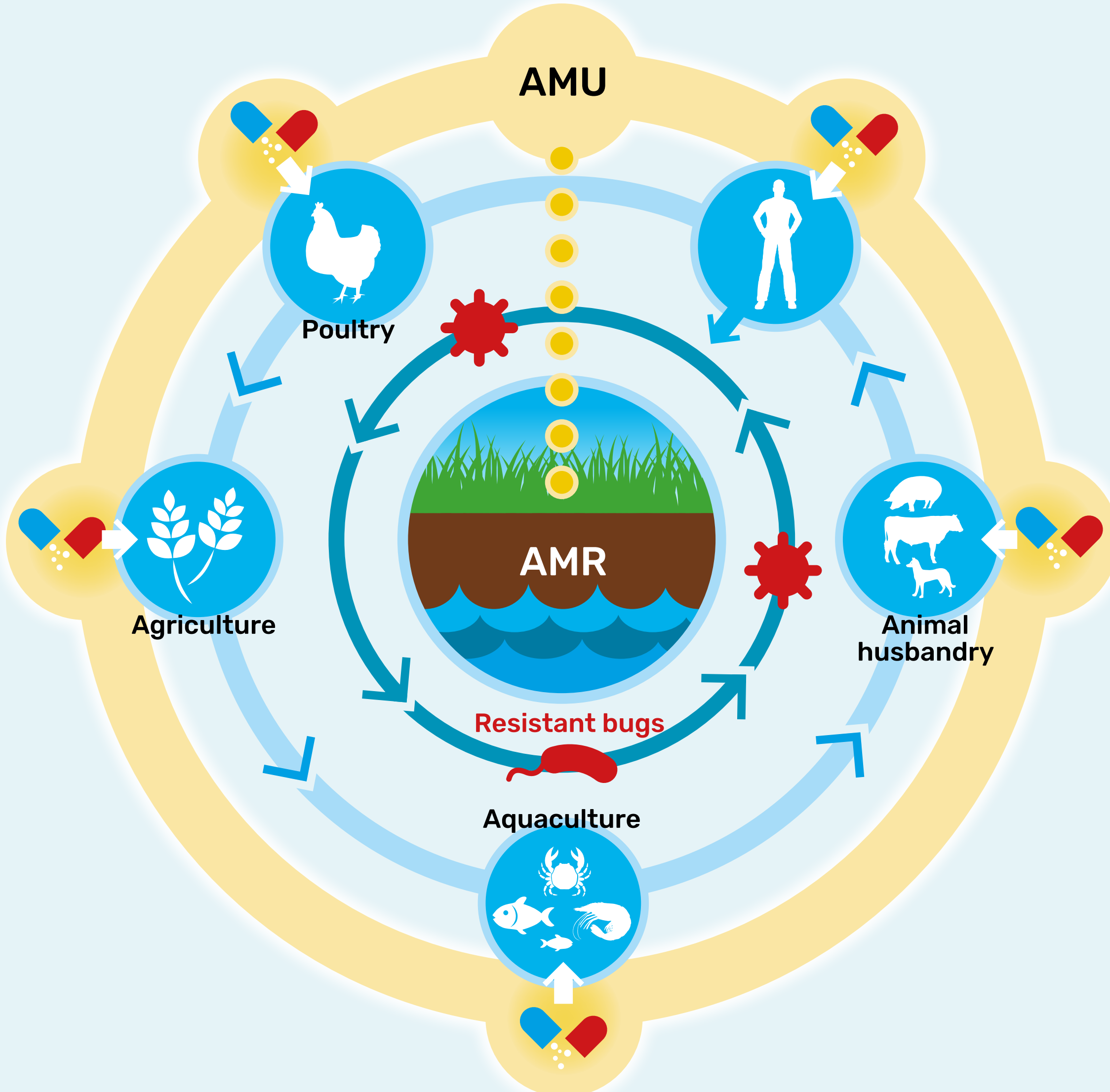
The use of antimicrobials for prophylaxis and growth promotion in livestock is a controversial practice as it involves administration of antimicrobials to healthy animals. Since any administration of antimicrobials increases the chance of resistant microbes developing, it is vital that their use is prioritised to those situations where they are most needed. In Europe, the use of antimicrobials for growth promotion was banned in 2006 and a large number of Asian countries have also already banned, or are in the process of banning, the use of antimicrobial growth promoters.

**It has long been established that farmers and farm workers have higher levels of AMR than people who do not live in the proximity of livestock.**

Antimicrobials are also used in companion animals; however, overall quantities administered to pets are significantly lower than those used in the livestock sector. Generally, antimicrobial use for pets mirrors use in humans, with administration most common for treatment of infections as well as pre- and post-surgery. Strategies similar to those proposed for reduction of antimicrobial use in humans should also be effective in this sector, with higher rates of vaccination, better rapid diagnostics, and improved awareness for veterinarians and pet owners all predicted to help reduce unnecessary use.

## Transmission of AMR from animals to humans

Antimicrobial resistance arises as a result of natural selection. Bacteria and other microorganisms begin counteracting the




TRANSMISSION OF ANTIMICROBIAL RESISTANCE BY SPREADING RESISTANT MICROORGANISMS

effects of antimicrobials and develop resistance under selective pressure: among the population of microorganisms, some strains acquire resistance genes via mutations in the genetic material. These mutations are further carried or transferred to other bacteria through horizontal gene transfer and also passed on to the offspring by vertical transfer. The transfer of resistance between animals and humans has been studied extensively.

There are actually three different transmission routes, by which an exchange of resistance may come about:

**_ 1. Direct Transmission**

Resistant traits (bacteria or genes) may be transferred from animals to humans and vice versa through direct contact. This comes as no surprise, since every contact between living beings results in an exchange of bacteria and other microorganisms. Whether milking cows or handling pigs, whenever a human touches an animal or has close contact with animals, bacteria and microbial resistance genes alike will be exchanged. It has long been established that farmers and farm workers have higher levels of AMR than people who do not live in the proximity of livestock. Likewise, hospitals can act as a hotspot for AMR, exposing both humans and animals that live nearby. Companion animals should not be overlooked in the whole debate concerning transmission of resistance either. Direct contact between pet owners and their pets is very natural, but it also provides an excellent opportunity for transmitting resistance. It therefore comes as no surprise that an increasing amount of scientific literature describes the resistance transmission from companion animals to humans and vice versa. For methicillin resistant *Staphylococcus aureus* (MRSA), this direct contact between animals and humans may be the major route of transmission.

**Vegetables are not exactly safe either; bacteria harbouring resistance genes have been found on and in vegetables.**

**_ 2. Transmission via food**

AMR can also make its way to humans through the consumption of food that contains resistant microorganisms or genes. The most obvious route of foodborne transmission seems to be the consumption of meat, milk, or eggs. Yet, if these animal products are for instance cooked or pasteurised, and if hygienic measures are well respected in the kitchen, there will be little or no transfer of (resistant) microorganisms. The consumption of raw animal products, however, involves a higher risk of transfer. Vegetables are not exactly safe either; bacteria harbouring resistance genes have been found on and in vegetables. This may be caused, for instance, by using manure as a fertiliser or by irrigating with contaminated water. Eating raw vegetables is thus not totally risk-free. The food-borne route is perhaps the most important for enteric bacterial pathogens, such as *Salmonella enterica, Campylobacter jejuni,* and *Yersinia enterocolitica.*

**_ 3. Transmission via the environment**

A final route of transmission is through the environment. Bacteria living in the soil, for instance, may become antibiotic resistant through the transfer of resistance genes from human or animal bacteria or through residues of antibiotics (e.g. in manure) that end up on the land. Whenever contact with a contaminated environment occurs, resistance may be transferred.

## AMR in humans due to animal/veterinary use of antimicrobials

There is evidence of adverse human health consequences due to resistant microorganisms resulting from usage of antimicrobials in animals. Three important bacterial genera - Enterococcus, Escherichia, and Campylobacter - and, to a lesser extent, Salmonella and Clostridium, are normal gut flora of food animals though they can also be serious human pathogens. The majority of studies have investigated the transmission of antibiotic-resistant bacteria from animals to farm workers, frequently before and after the introduction of antibiotics at their workplace. Direct spread of resistant bacteria from animals to people was first reported by Levy et al. who found strains of tetracycline-resistant *E. coli* in the gut flora of chicken caretakers similar to the strains found in the chickens receiving tetracycline-laced feed (Levy et al. 2019). Advances in genetic methods of analysis offer stronger evidence for the animal origin of bacteria that inhabit or infect humans. The rise of antibiotic-resistant bacteria in farm animals and consumer products like meat and fish has been documented. One study found ciprofloxacin-resistant *Campylobacter spp*. present in 10% to 14% of consumer chicken products tested (Gupta et al. 2019). There was also a correlation found between contamination of retail chicken with ceftiofur-resistant bacteria *Salmonella enterica* and incidence of human infections related to this type of isolate across Canada (Dutil et al. 2010). In three countries (the United States, Spain, and the Netherlands) a close temporal relationship has been recognized between the introduction of fluoroquinolone (sarafloxacin and enrofloxacin) therapy in poultry and the development of fluoroquinolone-resistant Campylobacter in human infections (Smith et al. 1999). Molecular and epidemiological tracking support the hypothesis that the resistance genes present in Salmonella outbreaks in humans and animals in Europe and the United States likely originated in aquaculture farms in East Asia (Cabello 2006).

## Impact of AMR in humans due to animal use of antimicrobials

Development of AMR in pathogenic microorganisms is a major public health problem that demands the most urgent attention in global health security. According to the WHO, diseases caused by foodborne pathogens are becoming more difficult or even impossible to treat because of their increasing resistance to antibiotics (WHO 2018). The food animal pathogens which commonly cause livestock-associated infections of the gastrointestinal tract as well as other parts of the body, such as *Staphylococcus aureus (S. aureus), Campylobacter spp., Salmonella spp. and Escherichia coli,* can cause more serious diseases if the strain is multi-drug-resistant. In the United States alone, there are an estimated 1.5 million cases of infection with *Campylobacter spp.* and 1.35 million cases of infection with *Salmonella spp.* each year, costing USD 270 million and USD 400 mil-

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lion respectively in direct medical costs. The European Centre for Disease Prevention and Control (ECDC) and the European Food Safety Authority (EFSA) have suggested that Campylobacteriosis and Salmonellosis continuously contribute resistance to common antimicrobial drugs. In addition, 28.3% of human *Salmonella spp.,* particularly *Salmonella Typhimurium*, were multi-drug resistant (resistance to three or more antimicrobials) (EFSA and ECDC 2017). People infected with drug resistant pathogens untreatable by first-line antibiotics need more expensive drugs and longer duration of treatment in hospitals, which increases the financial burden to their families and society as a whole.

## Countermeasures to control animal use of antimicrobials

To reduce antimicrobial use (AMU) globally, a collaborative approach across all the One Health sectors (human health, animal health, and the environment) is required. At a national level, data on sales of veterinary antimicrobials can be useful for guiding policy decisions aimed at reducing overall consumption or, more specifically, sales of particular antimicrobial classes such as the critically important antimicrobials (CIAs) for human medicine. Several international and national guidelines have been proposed for prudent use of antimicrobials in veterinary medicine. The World Organization for Animal Health (OIE) provides guidelines for the responsible use of antimicrobial agents in veterinary medicine with the aim of reducing overall AMR burden. In its guidelines, OIE also defines the respective responsibilities of the competent authority and stakeholders (OIE 2019).

In the United States, the Center for Veterinary Medicine (CVM) of the Food and Drug Administration (FDA) approves and monitors all drugs intended for veterinary use, in both pets and food-producing animals. New drugs purposed for use in animals are authorized under three marketing statuses: veterinary feed directive (VFD), veterinary prescription (Rx), and over-the-counter (OTC). VFD and Rx drugs are restricted to use only under a veterinarian's prescription. The FDA considers that "improved feed efficiency" or "increased weight gain" are not applicable conditions for use of any medically important antimicrobial in animals; however, they can be used for treatment, control, or prevention (FDA 2013). CVM's guidance document (GFI#152) classifies all medically important antimicrobials as critically important or highly important as per their relevance to human medicine (FDA 2003). FDA's VFD rule ensures a veterinarian's recommendation in order to use medically important antimicrobials in feed or water (FDA 2015).

At the national level, European Union (EU) countries have implemented the European Commission "Guidelines for the prudent use of antimicrobials in veterinary medicine" (2015/C 299/04) as part of their National Action Plans. The EU has banned the use of antimicrobials as growth promoters as of the European Parliament's regulation (EC) No 1831/2003 (European Parliament 2003). Stricter rules are being devised which will require EU trading partners to abstain from utilizing antibiotics as growth promoters in order to continue trading with the EU (EU Parliament 2018). Furthermore, according to new rules, metaphylactic (group treatment of animals when one is found to be infected) antimicrobial use will not be banned but permitted only if no alternative option is available (EU Parliament 2018a). EU guidelines on judicious use of antimicrobials also put emphases on treatment of individual animals after appropriate diagnosis and on raising farming standards to control infection in the first instance. Antimicrobials listed as critically important by the WHO, which are not authorized to be used in food animals, can only be used off-label (EU Commission 2015).

South Africa has drafted technical guidelines for the prudent use of antimicrobials in veterinary medicine that emphasize that antimicrobials should be used under the control of a veterinarian, who should encourage judicious use (Schellack et al. 2017). Currently, there is no legislation limiting the use of antimicrobials as growth promoters in South Africa. The South African *Antimicrobial Resistance National Strategy Framework* suggests the use of narrow-spectrum antimicrobials that are not used in human medicine to be used as growth promoters. The strategy framework also recommends devising legislature and policy reforms to limit the use of critical important antimicrobials as growth promoters by 2020 (DAFF 2018). In Kenya, the Ministry of Agriculture, Livestock, Fisheries and Irrigation devised *Guidelines for the Prudent use of Antimicrobials in Animals* in 2018 based on 2015 EU guidelines emphasizing individual animal treatment, improving farming practices, and veterinarian oversight (MALF Kennya 2018).

In India, antimicrobials are extensively used for prophylaxis, treatment, and growth promotion. Although the Department of Animal Husbandry, Dairying and Fisheries (DAHDF) requested States to advise veterinarians on careful use of antibiotics and ban the mixing of antibiotics in feed, there is no uniform policy or guidelines for judicious use of antimicrobials (Moa 2014). Similarly, in Pakistan, antimicrobials are broadly used for prophylaxis, treatment, and growth promotion in veterinary practice without the constraint of any governing law (CDDEP 2018).

In low- and middle-income countries, Thailand is leading in terms of observing strict regulations limiting antimicrobial use in animals, including implementing a ban on the use of antimicrobials as growth promoters in 2015. Likewise, Indonesia and Vietnam also banned the use of antimicrobials as growth promoters early in 2018 but they have comparatively fewer restrictions on antimicrobial use in animals and antimicrobials are frequently used for both prophylactic and treatment purposes in these countries (Coyne et al. 2019).

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