# Antibiotic resistance—the interplay between antibiotic use in animals and human beings

Antibiotic-resistant bacteria were first identified in the 1940s, but while new antibiotics were being discovered at a steady rate, the consequences of this phenomenon were slow to be appreciated. Today, the excessive use of antibiotics compounded by the paucity of new agents on the market has meant the problem of antibiotic resistance is fast escalating into a global health crisis.

There is no doubt that misuse of these drugs in human beings has contributed to the increasing rates of resistance, but recently the use of antibiotics in food animals and its consequent effect on resistance levels in people has also come under scrutiny. Antimicrobials are used therapeutically and prophylactically in animals. More controversially, antimicrobials are also used as growth promoters to improve the ability of the animal to convert feed into body mass.

Some argue that the impact of use of antibiotics in animals—whether therapeutic or as growth promoters—pales by comparison with human use, and that efforts should be concentrated on the misuse of antibiotics in people. Others warn of the dangers of unregulated and unnecessary use of antibiotics, especially growth promoters in animal husbandry. There is a growing concern over the transmission of resistant bacteria via the food chain. Many questions will be difficult to resolve, such as how do you distinguish the fraction of resistance in human beings that originated from animals? If we wait to see evidence that a significant amount of antibiotic resistance really does come through the food chain, will it be too late for action?

In this forum, we present different perspectives from both human and animal medicine, to better understand the complexity of the problem of antibiotic resistance and examine the challenges that lie ahead.



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There should be little doubt that antibiotic resistance can be spread between animals and human beings. However, this view is not the same as saying that antibiotic use in animals causes the spread of antibiotic resistance to people. It is well recognised that pathogens and other bacteria are transmitted from animals to human beings via the food chain. If these bacteria possess antibiotic-resistance genes then it might be said that antibiotic resistance has been spread from animals to people. The main problem with our ability to link antibiotic use in animals with the spread of resistance to people is the limited understanding of the nature of antibiotic resistance.

Antibiotic-resistance genes often code for proteins that have been present in bacteria for an extremely long time. These proteins serve functions other than simply rendering a bacterium resistant to antibiotics. For example, some antibiotic-resistance genes code for proteins that protect the bacterial ribosome, while others code for proteins that serve as efflux pumps, both of which maintain the integrity of the bacterial cell. If these proteins have a broader evolutionary function, we might expect to see the genes in bacterial populations that have never been under the selection pressure of antibiotics, and potentially have never been exposed to human influence.

Some studies are reporting identical antibiotic-resistance genes in animal populations that are spread over wide geographical areas, including areas that have no human contact. Such data emphasise a key epidemiological concept that is often ignored in antibiotic-resistance studies. We have a very poor understanding of the background levels and distributions of specific antibiotic-resistance genes, and consequently, when we see resistance in bacteria derived from animals or animal products we are quick to conclude that this resistance is caused by the use of the antibiotic in animals. The problem of antibiotic resistance is an ecosystem problem whereby the resistance genes and resistant bacteria constantly flow among many different environments. Some studies have shown that antibiotic resistance in animal populations is likely to be from human sources, such as human sewage treatment plants. In this example, it might be possible to document transmission of antibiotic resistance from animals to people, but the animals would not have been the source of resistance. Consequently, it is very difficult to assign the amount of antibiotic resistance that passes through the food chain that is due to the use of antibiotics in these animals.

The key point is that we need to begin thinking of strategies to minimise the risk of spreading antibiotic resistance among all populations. Unfortunately, the notion that the banning of antibiotics in animals represents a viable risk-management strategy is too simplistic and potentially myopic. First, there is little evidence of a clinical benefit to people after the removal of antibiotics in animals. Second, and probably more important, this type of strategy does not consider the repercussions for animal health following the removal of the antibiotic. This important consequence could lead to the need for increased antibiotics to treat increased morbidity. Furthermore, unhealthy animals would lead to a less wholesome food product, thereby increasing the potential for foodborne illness. The types of risk-management procedures we need relate to specific interventions that should be used following specific antibiotic uses. For example, a risk-management strategy related to the use of a specific

antibiotic in poultry might investigate how the litter from the poultry house should be handled after the flock is processed and how long the poultry house should remain empty before another flock is placed in the house.

There is no reason to wait for the scientific proof concerning the impact of animal antibiotic use on human health. We need to begin designing rational risk-management policies related to antibiotic use and antibiotic resistance, especially when we consider that antibiotic resistance is an ecosystem problem. However, risk-management solutions that are based more on a perceived benefit (such as the notion that complete animal antibiotic bans will improve human health) rather than on actual science may have more serious human health implications than initially anticipated. Sufficient data exist to begin developing and implementing these types of strategies. In the end, though, it must be emphasised that the primary means of preventing the transmission of antibiotic resistance through the food chain is the same as for foodborne pathogens: use proper food handling and food preparation practices, and the risk of transmission will be dramatically diminished.



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Antibiotic use and antibiotic resistance are clearly connected. Antibiotic resistance at present is primarily associated with human use, but it would be a surprise if use in animals did not lead to antibiotic resistance, and in turn raise the possibility of that resistance translating into occasional human disease. Prophylactic use of antibiotics in animals, where mass flock exposure to antibiotics is used to prevent an epidemic, is also known as metaphylaxis. The use of antibiotics as growth promoters has, many years after the original UK Swann report,[1] attracted much debate and legislation. The gut flora of animals can clearly be a source of infection in man, especially from enteric pathogens such as salmonella, campylobacter, shigella, and perhaps enterococci. So is this resistance in the animal flora likely to produce human disease? The answer is likely to be yes, but at present I do not believe the effect to be substantial, possibly because our information base is weak. The microbiology and epidemiology is not sufficiently robust for us to reliably establish food as a source of human infections caused by resistant pathogens from antibiotic exposure in animals.

There is a need for more intense microbiological surveillance, which should include molecular genetic studies that clearly link strains of animal origin with human disease. A lot more research needs to be done, although I believe the answers will be forthcoming over the next few years. In Europe, measures to reduce resistance by banning growth promoters have been agreed upon. However, there is concern that banning antibiotics as growth promoters might lead to an increase in therapeutic use, as seems to be happening in Scandinavia. This situation needs close monitoring, because the experience in human beings is that excessive prescribing of therapeutic antibiotics leads to increased resistance.

Among the strategies to control antibiotic resistance, one key issue is to ensure appropriate prescribing through education. There is evidence in the UK that prescribing antibiotics for upper-respiratory-tract infections has been substantially reduced over the past 5 years. That has been brought about by educational campaigns, raising professional awareness, and changing public perception of the need for antibiotics. A similar strategy could work in veterinary prescription, but it will be extremely challenging to implement globally, and will need to be adapted to individual countries. Education should be aimed at many levels to capture not just professionals, but also educational institutions and the public in general.



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The WHO has recognised that antibiotic use in animals certainly affects antibiotic resistance in human beings and has published documents that acknowledge this problem.[2,3] But a common feature of almost all countries is a communication gap between the veterinary field and the public-health field that needs to be bridged. The WHO strategy for reducing resistance is applicable globally, but requires tailoring to the needs of each country. We are now addressing the implementation phase, and this is always where things get a little more complicated.

The European Union (EU) recently banned the antibiotic growth promoters avoparcin (a glycopeptide), virginiamycin (streptogramin), and tylosin and spiramycin (both macrolides). Pfizer, who produce virginiamycin, tried to sue the EU because of the ban but lost the lawsuit, when the court ruled that "the ban on the product is not a disproportionate measure given the need to protect public health". The Danish government has banned the use of the same growth promoters. Additionally, food animal producers in Denmark have voluntarily stopped using the remaining antimicrobial growth promoters in response to consumer concern. In November 2002 a symposium was held in Denmark (Beyond Antibiotic Growth Promoters in Food Animals, November 6–9, Foulum, Denmark), to assess the effects of termination of growth promoters in Denmark, and to decide whether this approach could be applicable to other countries. The results showed that the phasing out of animal growth promoters occurred without major consequences to animal health. Before implementation in Denmark there were concerns over increased disease, production costs, and salmonella shedding in both pigs and poultry. Most of these fears proved unfounded. The only adverse effects were seen in the disease status of weaning pigs. It was suggested that terminating use of these growth promoters could be applied in both industrialised and developing countries with minimum effect on food production, provided that adequate attention is

given to implementing alternative disease-prevention strategies in food animal production.

In my view, it is the total use of antibiotics that matters because the bacteria do not distinguish between whether the drug was used therapeutically, prophylactically, or for growth promotion. In Denmark, the use of antibiotics has been halved. It has come down from 210 000 kg of active antimicrobials in Danish food animals in 1994 to 94 000 kg in 2001. Some drugs, such as glycopeptides and streptogramins, were not used for therapeutic purposes, so they have completely disappeared from the classes of drugs for use in food animals. This, of course, has had an effect on rates of resistance in animals. We have used enterococci—the organisms that caused concern originally—as our indicator bacteria. Before we banned the use of avoparcin, 80% of Danish broilers had vancomycin-resistant enterococci (VRE). In 2001, after the ban, VRE levels were down to 3%. For swine there is a slower reduction. We are coming down from 20% to 3%, but that change has to do with the nature of the production system. You do not get rid of all the swine and replace them with new animals like you do for broilers (an all-in, all-out production). As a result, cleaning out the environment and getting rid of residual infections is a much slower process. Judging by termination of glycopeptide use for growth promotion, we can say now that it has taken more than 5 years to substantially reduce resistance rates in animals.

Looking at numbers of healthy people in Germany and the Netherlands who carry VRE, there has been a clear effect from the termination of growth promoters, and several studies have shown that gastrointestinal tract carriage of VRE is a risk factor for human infection. But the chain of events is complex, and proving that an infection in a hospital stemmed from agriculture would be almost impossible. We have seen the same types of VRE in patients and animals when we compare them by genetic fingerprinting, but this is, of course, only circumstantial evidence. What is important in my opinion is that the numbers of people carrying VRE to hospitals has been reduced, so the pressure on hospitals to deal with these sorts of infections has been lessened.

At the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC, San Diego, USA; Sept 27–31), Michael Osterholm (University of Minnesota, MN, USA) presented new data showing an increase in fluoroquinolone-resistant *Campylobacter jejuni* in people and animals. Also Antoine Andremont (Groupe Hospital Bichat-Claude Bernard, Paris, France) showed that *Escherichia coli* isolates from urinary tract infections had identical features to *E coli* in food animals, which suggests that we need to look not just at gastrointestinal tract infections, but at other infections too. The data I presented at ICAAC showed the effect of banning growth promoters in Europe. It was thought that food prices might soar and that farmers would experience reduced growth rates in their animals, but in actual fact, we have seen very little change in food production. Importantly, mortality rates are almost unaffected. Feed conversion is mildly reduced; it takes on average 16 g more feed per 1 kg of broiler, but this extra feed still costs less than farmers were spending on antibiotic growth promoters. It seems that the major losses are to the pharmaceutical industry, although some of the growth promoters had a mild prophylactic effect, so drug companies may see a slight increase in their therapeutic antibiotic sales. With modern farming practices, however, it seems that growth promoters are simply not necessary in the way they might have been 40–50 years ago.



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With the exception of the zoonotic infections such as non-typhoid salmonellosis, the great majority of infectious diseases in human beings are separate from animal infections in both causal pathogen and in epidemiology. Consequently, most resistance in people is generated through antibiotic use in people. For instance, meticillin-resistant *Staphylococcus aureus* (MRSA) is the most troublesome form of resistant infection encountered in human medicine,[4] yet has no connection with animals (where it is virtually unknown).

Zoonotic infections can, by definition, originate in animals, and if antibiotic resistance has been acquired in the animal donor it could be passed on to the human recipient. In fact, antibiotic treatment is only rarely indicated for non-typhoid salmonella infections, and there are few documented cases where treatment has been compromised by resistance originating from an animal source. Similarly, infections due to *Campylobacter* spp may not respond to an antibiotic in the presence of resistance from an animal source, but again documentation of resulting treatment failures is hard to find.

An intermediate group are the commensals, such as *Enterococcus faecium,* seen in healthy human beings and animals, but the link between the two remains tenuous. *E faecium* has been a particular focus of attention since VRE became a major nosocomial infection. Avoparcin, a related compound to vancomycin, has been used in many countries as a feed additive in animals, raising questions about a possible link. However, the highest incidence of VRE is in the USA, where avoparcin was never registered for use in animals, but where there is a particularly high rate of use of vancomycin in human patients, suggesting that human use is the most important factor linked with human resistance. Recently quinupristin/dalfopristin, a streptogramin combination, has been introduced for treatment of human beings after 25 years of use of a related compound, virginiamycin, in animals. Resistance to virginiamycin has been widespread in animal isolates of *E faecium*, but rare in human isolates, suggesting little spread between the two hosts, either by colonisation, or by transfer of resistance genes. Nevertheless, in 1998 virginiamycin was removed from animal use as a feed additive by the EU. The removal was based on the "precautionary principle" despite a lack of direct evidence of harm to human patients.

The EU has also signalled its intention to remove other so-called growth-promoting antibiotics by 2006. In the

USA, on the other hand, data are still being sought and risk assessments being done to determine, for instance, whether virginiamycin should be removed from animal use. The reason for these two different approaches may be accounted for by the US Food and Drug Administration's legal constraints, and the bovine spongiform encephalitis experience in the EU. The result is that in food safety matters the EU is under much pressure to act whether or not firm data are available to support the proposed action.

Since the removal of growth-promoting antibiotics there has been a decrease in the incidence of resistance in bacteria isolated from animals,[5] although no data have shown a concomitant decrease in resistance in human clinical infections. The removal was followed by an increase in the quantities of therapeutic antibiotics used in animals—eg, in Denmark, therapeutic antibiotic consumption increased by 49·7% between 1999 and 2001.[5] This rise is probably the result of increased clinical disease after cessation of feed additive antibiotic use, although the Danish authorities have stated that the economic consequences are small. Nevertheless, any benefit in antibiotic resistance moderation in animals from the removal of growth-promoting antibiotics may be in part offset by resulting disease problems and consequent use of therapeutic antibiotics.

Most human resistance is the result of human use and, conversely, most animal resistance is the consequence of animal use. However, in the case of the zoonotic infections, resistance in animals can result in an effect on human pathogen sensitivity. Zoonotic infections are a minor indication for human antibiotic use and the overall effect of animal antibiotic use on antibiotic resistance in human clinical infections seems minimal.

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An independent panel of experts reviewed the effects of antibiotics in human beings and animals and delivered their opinion at ICAAC last year (Chicago, IL, USA; Dec 16–19 2001). They concluded that the actual risk of antibiotic use is extremely small. "In 50 years of antibiotic use in animals and man, the development of resistance in animals has not made a major impact on human and animal health, and such a development seems unlikely to happen overnight now", said Ian Phillips, the chair of the debate.

Much of the debate surrounding the issue of antibiotic resistance has centred on the use of antibiotics in animals to promote growth. The case against antibiotic growth promoters has relied heavily on antibiotic-resistant enterococci, a group of bacteria that cause no disease in animals but can cause human disease. Unlike human medicine, where individual patients can be treated, animal producers must consider medication on a population basis for reasons of animal welfare, logistics, and efficiency since it is impractical to individually treat each animal in a group that consists of hundreds to tens of thousands.

The primary concern has been that the use of antimicrobials in food animals will select for resistance to those agents in intestinal bacteria, and via foodborne transmission an infection in human beings will develop that is untreatable. A newer variation on this theme has been that foodborne, commensal bacteria might transfer their resistance genes to existing susceptible normal human flora, and thereby set the stage for a non-treatable infection at a later time in the individual's life. The bacteria at issue are limited to salmonella, campylobacter, enterococci, and to an extent, *E coli* since they do infect both animals and man. A survey of the opinion of medical microbiologists[4] suggested that the overall contribution of animal sources to human resistance was less than 5%.

Since foodborne bacterial transmission is an essential component of the issue, it represents a critical control point for ensuring food safety from all pathogens, not just those with antibiotic-resistance genes. Some of the events that are needed to "go wrong" for an antibiotic-resistant foodborne disease to result in an adverse outcome for a typical patient include: (1) antibiotic resistant bacteria present in a particular group of animals; (2) selection of a pre-existing strain with resistance gene(s) or a resistance mutation in the presence of an antibiotic; (3) faecal contamination of the carcass occurs during processing leaving bacteria on the meat; (4) cooking at an inadequate temperature and duration fails to kill the bacteria or the food is recontaminated after cooking by improper handling; (5) human consumption of food results in resistant bacterial colonisation or infection; (6) infection severity requires physician care, or hospitalisation, and with an antibiotic prescribed of the same class as was used on the farm; and (7) outcome is that the treatment period is prolonged or the patient may possibly die.

It should be obvious that not all foodborne bacteria are antibiotic resistant. Thus, the central issue is not whether antibiotic use in food animals can select for resistance in particular types of bacteria, which can then cause foodborne disease in people that is more difficult to treat. The real issue is what is the frequency at which this occurs and to what extent should resources be used to intervene? In other words, should 50% of the available resources be directed to the use of antibiotics in food animals if the "resistance contribution" is 5%? It is clear that certain actions, such as the withdrawal of five antimicrobial growth promoters, has not achieved the desired effect of decreasing the prevalence of human antibiotic-resistant bacteria associated with foodborne transmission. In fact, a decrease in animal health and welfare has been reported in poultry with necrotic enteritis, and pigs with scours requiring the use of therapeutic antibiotics.

In conclusion, the use of antibiotics in food animals is essential to maintain a consistent supply of healthy animals entering the food chain. Although some antibiotic-resistant foodborne bacteria inevitably make their way through the food chain and reach consumers, the magnitude and clinical effect of that event remains unclear. In the larger

context of human antibiotic resistance, antibiotic-resistant foodborne bacteria are a minor component compared with hospital and community-acquired infections and antibiotic use. Nevertheless, the food animal production sector is doing its part to minimise antibiotic resistance while continuing to deliver a safe, high quality food supply.



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People and agricultural animals share bacterial flora, including antimicrobial-resistant flora. This fact has been amply demonstrated in studies of the intestinal commensal bacterial flora of farm workers,[6] and by disease outbreaks caused by food-associated strains of such pathogens as *Salmonella* spp, *E coli*, and *C jejuni*. Many of the genes that establish antimicrobial resistance reside on plasmids, transposons, integrons, and other mobile genetic elements; this mobility expands the opportunities for sharing of resistance determinants between agricultural and human bacteria. Recent studies show that bacterial populations within a single "species" may be differentiated, so that particular strains are best suited to colonise human beings in hospitals, and others better suited to other hosts. However, the barrier that such specialisation might offer to transfer of bacteria between animals and human beings is compromised by the possibility of transferring resistance determinants from animal-adapted strains to human-adapted strains.

There is considerable evidence that the use of antimicrobials for growth promotion, prophylaxis, and treatment of food animals increases the prevalence of resistance in these bacteria. Systematic studies of patterns of use and resistance in Denmark have shown that agricultural use of antimicrobials leads to the appearance of new resistance determinants among agricultural bacteria (these same determinants are often later seen in human isolates), and to increases in the frequency of these determinants once they have appeared. Similarly, reductions in the use of growth-promoting antimicrobials in Denmark have been followed by reductions in the prevalence of resistance to these agents in bacterial species sampled from food animals.

These considerations lead to the conclusion that use of antimicrobial agents in agriculture increases the risk of resistant infections in people. Direct documentation of this risk is easiest in the case of truly foodborne outbreaks (with little or no human-to-human transmission) of human pathogens such as campylobacter and some serovars of salmonella, in which both molecular and traditional epidemiological methods can link a particular food exposure to resistant infection. More difficult to quantify and trace precisely is the contribution of animal use to the emergence of resistance in bacteria such as *Enterococcus* spp and many strains of *E coli*, which human beings can acquire from food and carry without symptoms for long periods, possibly transmitting these bacteria to other people. Such bacteria may subsequently cause nosocomial or community-acquired infections, when they leave the human gut and infect the bloodstream, urinary tract, or other sites. Because of the delay between food exposure and infection, it will rarely be possible to find a "smoking gun" linking human infections with these bacteria to resistant bacteria acquired from animals treated with selecting antibiotics. Nonetheless, biological and mechanistic considerations make it likely that such scenarios occur. A recent theoretical model suggested that in the case of human-to-human transmitted organisms of this kind, use of antimicrobials in agriculture may hasten the appearance of resistance in human beings (by creating the selective conditions for resistance determinants to assemble and increase in frequency), although once resistance has entered the human population it will be primarily human-to-human transmission and human antimicrobial use that will determine the final prevalence of the resistant strains.[5]

The cautious tone of this comment reflects the fact that it will rarely be possible to convince a committed (and economically interested) sceptic that a particular infection, even if traceable to food from an animal that received an antibiotic that selected for resistance, would have been susceptible to that antibiotic had the animal not received the treatment. Nonetheless, convincing evidence exists for each of the key steps in this sequence of events, that is agricultural use leading to increased resistance in animal-associated bacteria, transfer of resistant bacteria from animals to human beings, and infection of human beings by these bacteria.

Some have argued that regulation of animal use of antimicrobials should await scientific certainty about the magnitude of the risk to people. While improved scientific study of these issues will be valuable, policy decisions should be made on the basis of the best available evidence, even if the evidence is uncertain. Studies of human antimicrobial use have shown that preventing the emergence of resistance is often much easier than reducing the prevalence of resistance once it has appeared, for reasons including associated-linkage selection of resistance determinants by other drugs, and the lack of a strong fitness cost to resistant strains. Extrapolation of these experiences to the agricultural context suggests that limiting use while resistance remains rare may be effective, yet it may be difficult to "shut down" resistance if restrictions on antimicrobial use are delayed until a large harm from resistant strains is demonstrable. On this basis, there are good reasons to limit agricultural use of antimicrobials, as well as to explore technical solutions (such as irradiation) and animal husbandry, slaughter, and food storage practices that will limit foodborne transmission of resistant (and other) pathogens.

## References

1 Swann MM. Report of the Joint Committee on the use of antibiotics in animal husbandry and veterinary medicine. London: HM Stationery Office, 1969.
2 WHO. WHO global strategy for containment of antimicrobial resistance. Geneva: WHO, 2001. WHO/CDS/CSR/DRS/2001.2.
3 WHO. WHO global principles for containment of antimicrobial resistance in animals intended for food. Geneva: WHO, 2000. WHO/CDS/CSR/APH/2001.4.
4 Bywater R, Casewell M. An assessment of the impact of antibiotic resistance in different bacterial species and of the contribution of animal sources to resistance in human infections. *J Med Microbiol* 2000; **46:** 643–45.
5 DANMAP 2000 and DANMAP 2001. Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals foods and human beings in Denmark. Copenhagen: Danish Veterinary Laboratory.
6 Smith DL, Harris AD, Johnson JA, Silbergeld EK, Glenn Morris Jr J. Animal antibiotic use has an early but important impact on the emergence of antibiotic resistance in human commensal bacteria. *Proc Natl Acad Sci* USA 2002; **99:** 6434–39.