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Antibiotic use in animals—prejudices, perceptions and realities

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Regulatory authorities have suspended the use of some antibiotics as growth promoters in animal feed. The subject remains a hotly debated topic around the world. Controversy surrounds whether such use in animals presents a real risk of increasing resistance in human pathogens, and hence a human health problem. Views tend to be polarized. Proponents of the bans point to falling rates of resistance in animal and human isolates as a direct result; detractors question whether evidence exists for a link between growth promoter use and resistance in human pathogens and cite a decline in animal health among the undesirable effects. The article by Phillips *et al.* in this issue puts one view, this article aims to consider the merits of the arguments put forward by both sides and looks to a way forward.

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Nothing in the area of antimicrobial use has generated more vigorous debate recently than the use of antimicrobials in animals, especially food-producing animals. National and regional regulators have been buffeted by the winds of prejudices and perceptions, and the selective use of scientific data by many participants to promote their side of the debate. Essentially two positions have emerged. The first states that resistance to antimicrobials of human importance has been generated in animals, is spread to humans with the potential to cause major harm, and therefore we must take action to minimize it. The second position states that resistance to antimicrobials of human importance has been generated in animals, but that the evidence that is has spread to humans and caused major harm is minimal or non-existent, and therefore no action is required, and further that the action taken to date is unwarranted. Such is the position taken by the article by Phillips *et al.*[1] in this issue of the journal.

Which position is right? Both agree that resistance to antibiotics of human importance has been generated in some food animals, and for the obvious reason that analogues of human drugs have been used. Indeed most classes of antibiotics used in animals have human analogues, and are capable of selecting for resistance to human antibiotics. The important exceptions are the ionophores (e.g. monensin, narasin, salinomycin, lasalocid), the quinoxalines (e.g. olaquindox), bambermycins (flavophospholipol) and avilamycin. Evidence of harm to humans has been more difficult to find. Much debate revolves around the rates of transmission of resistant strains to humans. The debate continues as there are virtually no studies that accurately quantify these rates. Recent attempts to quantify rates in the context of risk assessment have not taken into account any variation in susceptibility to colonization among individuals or communities.[2] For zoonotic pathogens such as salmonellae and campylobacters, transmission and disease can occur whether or not the organism is resistant. As neither of these gastrointestinal pathogens requires routine antibiotic treatment, only a small proportion of infected individuals will be affected by resistance, although it will affect those with the most serious illness. For the commensal organisms *Escherichia coli* and *Enterococcus faecium*, the direct evidence for harm is less clear. It is likely that these species are more important as reservoirs of resistance genes that can be transmitted to human gut flora. The evidence for this remains largely circumstantial, although there are recent animal model studies that support this conclusion.[3,4] The real difference between the two opinions lies in whether action should be taken, or should have been taken, to ameliorate the resistance generated in food animals.

In response to continued pressure from the 'major harm' position, the European Union adopted the 'precautionary principle' and suspended the use of the 'growth promoter' in-feed antibiotics: avoparcin, virginiamycin, spiramycin, tylosin and bacitracin because of their ability to select for resistance to antimicrobials of human importance. It has not, however, applied this principle to the use of fluoroquinolones in food animals, presumably because they are not used as in-feed 'growth promoters'. Adopting the 'precautionary principle' reduces the opportunities to find out if there is a real human risk. The United States has taken a different approach. The Center for Veterinary Medicine at the Food and Drug Administration has preferred instead to apply the 'principle of proof', gathering evidence that a problem has emerged before taking action. The Center has recently withdrawn a fluoroquinolone from use in poultry based on this principle. Adopting the principle of proof requires that resistance emerges, by which time the 'genie is out of the bottle'.

No matter what opinion might be held, amplifying resistance to human antibiotics in food animals is inherently problematic. Even if transmission to humans is infrequent, amplifying the resistance reservoir will make transmission via food or less direct mechanisms more likely. The trend to large consolidated food production and

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distribution systems exacerbates the problem. Transmitted resistance may initially be rare in humans, but a second amplification through the use of antibiotics in the community and/or because of hospital spread can easily change that. It would not even matter if the original resistant strain or gene originated in humans and was spread to animals. This second amplification step is frequently ignored when the risk of human disease is estimated. There are many more food animals than humans, thus the potential size of the resistance reservoir is very large. Almost all intensively raised food animals, such as chickens, pigs and feedlot cattle, are exposed to antibiotics during their growth, often for quite legitimate reasons. The facilities used for intensive farming act in much the same way as intensive care units in hospitals: cross-infection is common, vulnerability to infection is high, and antibiotic use is often prolonged. It is therefore not hard to see why colonization with some types of resistant bacteria has been high in intensively raised species. Using antibiotics with no human implications in this setting such as ionophores or avilamycin would eliminate the risk (assuming resistance to these agents is not linked). For other agents that have human analogues used in-feed or for therapeutic purposes, risk assessments should be undertaken to determine the likely impact on human health.

It is hard to know what reviews such as those by Phillips *et al*. are trying to achieve. Perhaps that they are attempting to reverse the bans imposed by the European Union on the in-feed antibiotics noted above. A recent article by most of the same authors attempted to demonstrate a negligible impact of these bans on human health but a significant impact on animal health.[5] What this article failed to point out was that many of the problems were of low prevalence in human infections in Europe to start with because of the lack of major second amplification, unlike what has occurred in the USA. Hence, the benefit to Europe could be that it has reduced the risk, particularly of *vanA E. faecium*, because it has reduced human exposure and carriage rates. In contrast, increasing resistance to fluoroquinolones in campylobacter and salmonella is being seen in Europe, possibly because these are still permitted for use in food animals, not for growth promotion but for disease treatment and prevention.

There is a third choice of principle: the 'prudent use principle'. Although more difficult to define, this principle is based on an understanding of the ecology of resistance (where are the reservoirs and how big are they?), transmission of both resistant bacteria and resistance genes (how do bacteria and their resistance genes spread?), the relationship between antibiotic use and resistance amplification (how does antibiotic use increase the size of the reservoirs?), and a knowledge of effective interventions (what control mechanisms result in the greatest reduction in the reservoirs?). The prudent use principle is NOT the writing and dissemination of prudent use guidelines. Rather it is the principle that allows those guidelines to be written, as well as providing rational guidance for risk assessments. Some of the information required to apply the prudent use principle is lacking; further studies are urgently needed to assist in risk assessments that are now being widely applied to resistance.

It is time to move on from the debate. All participants would benefit by considering antibiotic use in animals in the broader context of antibiotic use overall, i.e. in humans, food animals, companion and other animals, agriculture and horticulture. We have learnt a lot from the widespread and intensive use of antibiotics in humans: unnecessary use is prevalent, broad-spectrum agents are 'addictive', reservoirs of resistance can be amplified by antibiotic use or transmission of resistant strains, or by a combination of both, and facilities where many vulnerable individuals are clustered (hospitals, long-term care facilities, day-care centres) rapidly amplify resistance and multiresistance. Resistance in any setting including animal husbandry is undesirable because it will reduce efficacy. We can and must apply what we have learnt from humans to all settings of antimicrobial use. Animals need antibiotics for all the same reasons as humans and strategies must be put in place to preserve their efficacy. The veterinary profession and the farmers must join the medical profession in improving antibiotic use and control spread of resistant bacteria and genes. This is the position advocated by the World Health Organization in its global strategy.[6] The medical community itself needs to be seen to be delivering on controlling resistance, but neither can the veterinary and farming communities ignore their responsibilities. If the debate is turned into a partnership, everyone will be a winner.

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