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Antimicrobial use and resistance: The risk to humans

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Introduction

Development of resistance to antimicrobials has been well-documented for some bacteria (Levy 1997; Salyers and Amabile-Cuevas 1997). Of particular concern is resistance to antimicrobial drugs of clinical importance. Amidst worries that the ability to treat bacterial infections might soon return to the “pre-antibiotic era,” researchers are now seeking alternative therapies and prevention measures as well as developing new classes of antimicrobials for use in human and animal medicine.

To help solve the complex problem of reducing resistance, it is useful to identify activities that are major contributors to the emergence of resistance and whose alteration or elimination would slow the loss of antibiotic efficacy. Antibiotic use is the major selection pressure influencing this situation, and because large amounts of antibiotics are used in animal agriculture, this practice has been considered a major contributor to perceived increases in antimicrobial resistance and subsequent losses of valuable therapies for human health.

Most researchers and healthcare professionals agree that use of antibiotics in human medicine is a dominant contributor to the high prevalence of resistant bacterial pathogens affecting human health today. Use of antibiotics in animal agriculture also provides a pressure selecting for resistant bacteria and has been hypothesized to contribute to a global “pool” of resistance genes. Because it is well-established that some bacteria, both resistant and susceptible, can be transferred from animals to humans and subsequently cause disease under some conditions, it is natural to suppose that use of antibiotics in animals increases the levels of resistance among food-borne pathogens infecting people (Fey et al. 2000; Molbak et al. 1999).

Why has the use of antibiotics in animals been identified as a major component of the apparent escalating prevalence of resistant bacteria? If the use of antibiotics in animals has this effect, why are antibiotics still used in animal agriculture? The reason that the arguments persist over the use of antibiotics in animals is not due to the question of whether this use results in increasing resistance. The real questions that need resolution are along the lines of: How much does animal agricultural use affect resistance? How significantly does animal antibiotic use impact human health? What are the repercussions to the removal of antibiotics from animals on human and animal health? This paper will focus on these questions.

Background levels of resistance

An assumption that is often made implicitly when investigating antimicrobial resistance is that resistant bacteria detected on a farm, near a farm, in a processing plant/slaughterhouse, or on a food item have obtained this resistance because of the use of antibiotics in animals. For example, a recent study (Chee-Sanford et al. 2001) investigated the presence of tetracycline resistance genes in groundwater near swine operations. These genes were found in the groundwater and matched genes found in the swine wastewater lagoons. The authors logically concluded that these genes existed in the environment as a direct result of agriculture. Unfortunately, the results of other studies demonstrate the difficulty with making such sweeping conclusions.

Resistant bacteria, when found on agricultural premises or associated with animal-derived foods, can be resistant for reasons entirely independent of the use of antibiotics in animals. In fact, there are studies that document the introduction of “food-borne” bacterial pathogens onto agricultural premises from human sources, such as human wastewater plants (Kinde et al. 1996). The discharge of wastewater from animal agricultural facilities (Aminov et al. 2002; Chee-Sanford et al. 2001), human sewage treatment plants (Kinde et al. 1997; Kinde et al. 1996), hospitals (Guardabassi et al. 1998; Reinthaler et al. 2003), and pharmaceutical plants (Guardabassi et al. 1998) has been associated with increased levels of zoonotic pathogens as well as increasingly resistant and virulent organisms. Antibiotics are often discharged from these sites, and these antibiotics in the environment can act as a selection pressure further influencing the acquisition of resistance genes (Kummerer 2003; Kummerer and Henninger 2003). All of these pressures must be accounted for in our determination of risks and in the estimation of the amount of risk attributable to animal antibiotic use.
Antibiotic use in animal agriculture

There are many ways in which antibiotics are used in animal agriculture and many terms that attempt to describe these uses. Unfortunately, considerable confusion exists regarding these uses and terms. For example, the American Veterinary Medical Association (AVMA) defines “therapeutic” as an antibiotic use that is intended for the treatment, control, or prevention of bacterial infections (American Veterinary Medical Association 1998). This definition thus relates to the treatment of disease in individual animals, but also accounts for a population-based medicine. The term metaphylaxis, which refers to the medication of the entire herd or flock in order to treat sick animals and prevent infection in the remainder of the population, would thus be considered a therapeutic use. Prophylactic antibiotic use, which would include the use of antibiotics in the absence of disease but at a time when there is an expected increase in the incidence of disease, would also fit under this definition. On the contrary, the Union of Concerned Scientists and other groups use the term “nontherapeutic” to include all uses of antibiotics in the absence of disease, including use for growth promotion, metaphylaxis and prophylaxis (Mellon and Benbrook 2001).

Unfortunately, a population-based approach to medicine is difficult for people to comprehend. In many modern US agricultural facilities, large numbers of animals are raised together, often in close confinement. An antibiotic can be administered to the entire herd or flock in the face of the progressing disease. Some view this as a “misuse” or “abuse” of antibiotics because “healthy” animals are being treated. However, all animals in this facility can be considered to be exposed to the pathogen, and without treatment, many of these exposed animals would eventually develop disease. Those that survive the outbreak may be affected in “subclinical” ways, such as being smaller, growing slower, or being generally less healthy than they would have been without the disease. For these animals, the antibiotic can prevent these untoward health effects.

When considering the removal of an antibiotic from use, the debate typically focuses on the potential benefit of decreased resistance following the removal (WHO 2003b). However, there may also be costs associated with the removal of the antibiotic. Any animals that are affected by subclinical disease processes can have lower weights, increased fecal contamination and more errors at the time of processing, all of which can result in higher levels of foodborne pathogen contamination on the carcass. Studies that simultaneously evaluate the potential benefits and costs to human and animal health following the removal of antibiotics are needed. It is critical to remember that the meat inspection process is intended to deliver a wholesome food supply, and thus the presence of subclinical animal disease that could negatively impact human health is outside of the scope of the current meat inspection process.

Antibiotic use, antibiotic resistance and policy

Between 1995 and 2000, the European Union banned the use of the antibiotics avoparcin, bacitracin, spiramycin, tylosin, and virginiamycin for growth-promoting purposes. There was a public health perception that these uses were having an effect on the increasing incidence of antimicrobial resistance in human pathogens and therefore were increasing the risk to human health. Such an approach, often referred to as the “Precautionary Principle,” aims to reduce potential risks through actions based on incomplete data. However, this approach can occasionally be misdirected as well as counter-productive by focusing resources away from more appropriate solutions (Starr 2003).

Following the ban of these antibiotics, the main effect that has been documented in humans has been a reduction in the prevalence of resistant enterococci isolated from the feces of animals on the farms and humans in the community (Aarestrup et al. 2001; Boerlin et al. 2001; Bruinsma et al. 2003). The amount of antibiotic that has been used therapeutically in these animal production systems has increased following the ban (Casewell et al. 2003), but the importance of this increase is debated (Casewell et al. 2003; WHO 2003a). Finally, the incidence of certain diseases in animals has increased, such as necrotic enteritis in broiler chickens (WHO 2003a). Improvements in human health following the bans are debatable.

Many will cite the successes in the European Union as evidence that antibiotics used for growth-promoting purposes should be eliminated immediately. However, the applicability or generalizeability of the European “experiment” to US agriculture needs to be questioned. The WHO document that addresses the impact of the termination of antibiotic growth promoters in Denmark (WHO 2003a) is frequently cited as proof that these antibiotic uses can be eliminated in the US without serious repercussions. However, the document clearly states that “under conditions similar to those found in Denmark, the use of antimicrobials for the sole purpose of growth promotion can be discontinued” (WHO 2003a). It is not clear that the interpreted results of the antibiotic removal in Denmark can be generalized to the US. Studies are desperately needed that focus on the applicability of management strategies over varying spatial scales and across national and international boundaries.

In relation to antimicrobial resistance, there is no reason to wait on the implementation of rational risk management policies. However, risk management solutions that
are based more on a perceived benefit 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 scientifically-sound risk reduction strategies. Hopefully the scientific avenues that exist in the U.S. for implementing policy change will be used to redefine the ways in which antibiotics are used in animal agriculture in order to best serve human and animal health.

References


