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We are delighted that the International Pig Veterinary Society Congress 2004, decided to select South Africa as the host country for the 20th IPVS Congress. The Pig Veterinarians of South Africa will ensure that this congress lives up to the best traditions of previous congresses; incorporating an interesting and topical scientific programme, fascinating accompanying persons tours and an excellent social programme, allowing delegates the opportunity to network with their overseas colleagues.

This, the first IPVS congress on the African continent, will undoubtedly be of enormous benefit in generating solutions to the emerging pig veterinary challenges, especially those related to exotic and changing viral diseases, decreased use of antimicrobials and nutritional advances. The congress is important to further pig veterinary science in South Africa, to encourage younger veterinarians to join the pig industry, as a vehicle to generate funds for research and to improve the pig industry in Southern Africa.

South Africa is a magnificent and beautiful country, and offers tourists value for money. Thus, pre and post congress tours will be a major attraction for delegates to come to South Africa. Durban, in KwaZulu Natal, is a vibrant multi-cultured city with magnificent beaches, easily accessible game parks, theme villages and a moderate winter climate making it an ideal tourist destination. We urge our colleagues throughout the world to use this opportunity to get a glimpse of the continent's rich and fascinating wonders and to enjoy the hospitality of their African friends

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FOOD SAFETY IN RELATION TO ANTIBIOTIC RESISTANCE

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Introduction

Bacterial resistance to antibiotic drugs is a serious public health problem worldwide. There are also some antibiotic resistance problems in veterinary medicine, although they are not perceived to be as serious as in human medicine. The traditional response to resistance has been to turn to new drugs as they become available on the market, but the sustainability of this approach is undermined by a marked reduction in discovery of new drug classes in recent years. Therefore, there is increasing pressure to protect those drugs already available for use in animals and humans through prudent use. Prudent antibiotic use maximizes therapeutic effect while minimizing resistance (1).

The fraction of the antibiotic resistance problem in public health that is attributable to antibiotic use in livestock is a subject of considerable uncertainty and debate. A substantial number of national and international expert panels have reported on this issue. There is some consensus that among clinically important infections in humans, especially those of the respiratory, gentiurinary systems and skin, most resistance problems probably arise from use of antibiotics in humans (2,3). However, many scientists believe that animal uses of antibiotics also contribute to resistance problems in human pathogens, although the magnitude of the contribution is uncertain and much debated. The main route of exposure is thought to be foodborne, through resistance among foodborne enteric pathogens such as *Salmonella enterica*, and *Campylobacter jejuni*, and commensals such as *E. coli* and *Enterococcus* spp. There are a number of mechanisms whereby antibiotic resistance can increase the public health burden of these infections transmitted through food. Therefore, antibiotic resistance is a food safety issue.

Antibiotic resistance is a local, national and an international problem because resistant bacteria respect few boundaries and are carried easily between farms, towns and countries by people, animals and food. Solutions to the problem must also be local, national, and international, and involve a combination of government regulation, international cooperation, and input from producers, veterinarians, pharmaceutical companies and consumers. The objectives of this paper are to describe and characterize antibiotic resistance as a food safety problem, and to discuss implication to the pig industry.

Antibiotic resistance in foodborne bacteria from pork

Before antibiotics were developed over 50 years ago, resistance occurred among some species of bacteria, but it was much less common is now the case (3). Since that time, bacteria have evolved by developing mechanisms to resist the effects of antibiotics. In some cases, resistance is slow to develop, and some species are still nearly fully susceptible to drugs after many years of exposure, however, other species develop resistance after only a very short period of time (4). Eventually, some degree of resistance emerges to nearly all antibiotics. Resistance begins with spontaneous mutations of genes, either on a chromosome or a plasmid. The mutation persists in the population if it confers an advantage to survival, most often through antibiotic selection pressure. In some situations, the resistance gene may be transmitted from one bacterium to another through mobile genetic elements. Such spread can occur between bacteria of the same or different species and genera (5). Resistance to one member of a family or class of antibiotics (e.g. penicillins) usually confers some degree of resistance to other members of the same class (cross-resistance). Some genetic elements contain a series of linked genes that confer resistance to multiple antibiotics, and in these cases, use of one antibiotic can select for resistance to completely unrelated drugs (co-selection). This can be important at the population level. For example, vancomycin resistance in enterococci in pigs in Denmark persisted after the removal of avoparcin as an antibiotic growth promoter, while resistance in enterococci in poultry rapidly declined after a similar ban (6). The persistence in pigs was attributed to the use of an unrelated drug, tylosin, because the tylosin resistance gene was located on the same transposon as the vancomycin resistance gene (7).

Antibiotic use practices affect resistance selection. Important factors include among others, the class of drug, the dose and duration of exposure. Resistance selection is favoured by long-term, low-dose exposure, as frequently occurs with in-feed uses (e.g. antibiotic growth promoters), or with mass medications (e.g. herd treatment). Once acquired, resistant organisms can spread, and this may be enhanced by a variety of farm management practices, for example, vertical transmission is favoured in integrated production systems, and horizontal spread can be a problem in systems where mixing of animals from different sources occurs, and hygiene is poor (8).

Pigs are potential reservoirs of certain bacteria that cause infections in humans. The most important are *Salmonella enterica*, *Campylobacter spp* (mainly *C. coli*), *Yersinia enterocolitica* and commensals such as *E. coli* and *Enterococcus* spp. Although direct contact may occur through occupational exposure on farms or slaughterhouses, transmission

through contaminated food is believed to be most important. Foodborne transmission occurs when carcasses are contaminated at slaughter, and there is a failure to remove or kill all contaminating bacteria during pork processing and cooking, either by industry or in the home.

Not all of these foodborne bacteria are resistant to antibiotic drugs, and in fact some bacteria that are completely susceptible to antibiotics are capable of causing very serious illness in humans. Nevertheless, there is good evidence that resistant infections tend to be more severe, longer lasting and less responsive to therapy than susceptible infections (9). Resistance is best known in *Salmonella* and *Campylobacter*. Resistant strains of *Salmonella enterica* have been a problem in many countries for decades (10). Frequently, these strains are resistant to multiple antibiotics and some appear to be particularly pathogenic (e.g. *Salmonella* Typhimurium DT 104). This strain has been isolated from many countries around the world, and has chromosomal genes encoding resistance to ampicillin, chloramphenicol, streptomycin, the sulfonamides, and tetracycline (resistance type, ACSSuT). Some strains are also resistant or have decreased susceptibility to gentamicin, trimethoprim, and/or fluoroquinolones. This strain may infect pigs, humans and a wide range of other species. The role of antibiotic use in pigs in the selection of resistance in strains of this type is unknown.

Among *Campylobacter*, resistance to a variety of antibiotics may occur, but resistance to macrolides and fluoroquinolones has received the most attention because these are critically important drugs for treatment of the infection in humans (11). The majority of these infections are due to *Campylobacter jejuni*, which predominate in poultry, cattle and other reservoirs, and a minority to *Campylobacter coli*, which predominate in pigs. Resistance to fluoroquinolones among *Campylobacter* (especially *C. jejuni*) was observed to increase in several countries after the approval for use of this class of drugs in livestock. Resistance to fluoroquinolones occurs very quickly in *Campylobacter*, and is therefore of considerable concern (26).

Resistance may also spread indirectly, and there are concerns about practices that contribute to a pool of resistance genes in the food supply and the environment. One such contribution is through resistance selection in commensal bacteria, and the best studied are *E. coli* and enterococci. Enterococci are normal inhabitants of the intestines of animals and humans, but also in the environment and food, and are opportunistic pathogens known for their resistance to antibiotic drugs. There is evidence that the widespread use avoparcin, a glycopeptide antibiotic growth promoter, in pigs and poultry in Europe and other regions of the globe, contributed to a pool of enterococci resistant to vancomycin, a related glycopeptide important for the treatment of various infections in humans. Epidemiological studies in pigs showed that avoparcin use selected for VRE (13). It is probable that this pool of resistance facilitated the development of vancomycin-resistant enterococci (VRE) as a major public health problem in some countries of the world. VRE from animals may colonize humans, but perhaps only briefly. These animal strains may cause disease in humans, but they may also affect public health indirectly, by donating the vancomycin resistance gene to human strains of enterococci.

Risk assessment for antibiotic compounds in relation to human health

It is clear that use of antibiotics in animals can select for resistance in bacteria, that some of these resistant bacteria may be transmitted through contaminated foods to humans, and that these bacteria may cause illness in humans, either directly or indirectly. There is however, considerable uncertainty and debate concerning the frequency with which this occurs, and the magnitude of the impact on public health. Although we have learned a great deal about these impacts through laboratory-based and epidemiological research and antibiotic resistance surveillance programs, there are still many gaps in our understanding of the epidemiology of resistance. In large part, these gaps persist because of the complexity of the transmission pathways, both direct and indirect, through the farm-to-fork continuum, and through the environmental pathway to humans. This complexity is a significant barrier to direct study of the problem through conventional epidemiological research. Therefore, there is increasing reliance on the discipline of risk assessment to estimate the risks to human health posed by antibiotic use in humans.

Some of the risk assessments published to date are summarized in Table 1 and three examples are briefly described here. One of the assessments (14) estimated the human health impact of antibiotic use in animals, specifically subtherapeutic penicillin or tetracycline in animal feed in the U.S. Using methods that identified the annual number of cases of salmonellosis reported annually in the U.S., the fraction of human cases due to resistant *Salmonella* infections, the fatality rate among cases, and the fraction of deaths associated with infection of farm origin attributable to subtherapeutic use of antibiotics in feed, the investigators concluded that the number of people dying each year in the U.S. from resistant *Salmonella* infections, and accounting for uncertainty, was somewhere between 1 and 400. The U.S. Food and Drug Administration (FDA) published the second example in 2000. FDA undertook a quantitative assessment of the human health impact of fluoroquinolone resistant *Campylobacter* attributed to the consumption of chicken (15). The report estimated that in one year the mean number of people in the U.S. that had an adverse health effect due to fluoroquinolone-resistant *Campylobacter* infection was 9,261. The third example is a risk assessment of macrolide (tylosin) use in cattle, poultry and swine, and was published in 2003 (16). The outcome of interest was human illness caused by macrolide-resistant *Campylobacter* or macrolide-resistant *Enterococcus faecium* and treated with a macrolide

antibiotic. The model for swine estimated that the annual probability of an adverse health event in the U.S related to macrolide resistance was <1 in 53 million for *Campylobacter* and <1 in 21 billion for *E. faecium*.

The risk assessments conducted to date have been moderately useful in supporting regulatory decision-making, which is their main purpose. It is clear that fully quantitative risk assessments are very demanding of resources (financial and human expertise) and of data. Until recently, tissue residues concerns dominated the pre-market and post-market assessment of human safety of antibiotic products. Drug licensing authorities have only recently started to incorporate antibiotic resistance considerations in these assessments. Consequently, the methodologies for assessing these risks are only now being developed, and it remains to be seen whether qualitative or quantitative models will be needed for future assessments. One problem is that currently available quantitative risk assessments do not completely address the broad range of potential human health impacts, or the spectrum of antibiotics and organisms relevant to a comprehensive assessment of risk. The U.S. FDA has published a recommended qualitative approach for assessing resistance risks in new animal drug applications, while allowing pharmaceutical companies the option of investing in more detailed (and more expensive) quantitative assessments (17). Applicants must submit data to support the ranking of the drug as high, medium or low in terms of potential for release of resistance in animals, exposure of humans to resistant organisms, and in the overall characterization of risk. The intent is to use the outcome of the risk assessment to manage risk, by selection of approved species of livestock, route of administration, duration of treatment, etc.

Increasingly, regulatory and public health agencies are turning to categorization of antibiotics with respect to their importance to human health as a way to assess and manage risk. The U.S. F.D.A., the World Health Organization and Health Canada are some of the organizations that have developed such categorized lists (17). The criteria used to undertake the categorization varies, but in general include the importance of the drugs to treat serious illness in humans, the availability of suitable alternative treatments, and the usefulness of the drug in treating enteric infections in humans. The main purpose is to identify antibiotics of critical importance to human health. Public health agencies advocate the limited use of such antibiotics in animals.

Prudent use of antibiotics

Antibiotics are incredibly valuable therapeutic agents for people and animals. It is very important to use antibiotics prudently in order to preserve their long-term effectiveness in any species. Prudent use is affected by a very large number of factors, including the pharmacological and pharmacokinetic properties of veterinary drugs, indications for use, availability of alternative treatments and disease prevention methods, farm management characteristics, treatment decision-making methods of farmers and veterinarians, standards of veterinary practice, antibiotic delivery mechanisms, pharmaceutical company marketing practices, and national drug regulations and enforcement. A variety of organizations, including the World Health Organization (WHO) has developed prudent use principles (1). Examples include: requirement for proper diagnosis, laboratory test results and veterinary prescription, following of label doses, use of good husbandry practices, use of alternatives to antibiotics (e.g. vaccines) and limiting of the use of antibiotics for growth promotion and disease prophylaxis.

A logical extension of prudent use principles are antibiotic treatment guidelines. These have been developed in some countries, including Denmark and the U.S. (18). In general, these guidelines identify the 1st, 2nd and 3rd choice of antibiotics for treatment of specific diseases in livestock. The ranking of drugs for this purpose favours classes of antibiotics of less importance to human health, and balances efficacy, cost and other factors. The Danish antibiotic use policy included the above factors and stated a preference for narrow-spectrum antibiotics, a priority of older over newer antibiotics, and stated a limitation to antibiotics approved for treatment of the given food-animal species. To be effective, treatment guidelines should be evidence based, relevant to local conditions and management systems, developed in consultation with veterinary practitioners who will actually be using them, and will be regularly updated.

Antimicrobial growth promoters

Antimicrobial growth promoters (AGPs) are the most controversial form of antibiotic used in animal production. They have been banned in some regions, notably Europe, however they continue to be widely used in North America and many other parts of the world. Their use is advocated or challenged, depending on your point of view, from three main standpoints: their role in selection of antibiotic resistance, their usefulness in promoting growth and feed conversion, and their role in disease prophylaxis. In practice, however, it is difficult or impossible to completely separate the growth promotion from disease prophylaxis roles.

There is clear evidence that some AGPs exert considerable selection pressure for antimicrobial resistance. The use of chlortetracycline, sulfonamides and other in-feed antimicrobials has been shown to increase the risk of resistance in *E. coli* of finisher pigs (19). Studies conducted in Denmark showed a link between the use of avoparcin in pig feed and vancomycin resistance in enterococci (13). The termination of AGP use in Denmark, a country with superb antibiotic use and antibiotic resistance monitoring, provided an opportunity to observe the impact of a nation-wide ban on resistance in a variety of bacteria in pigs (6). Overall, the evidence showed that the ban resulted in a clear reduction in

resistance to a range of antibiotics (e.g. macrolide, stgreptogramin, glycopeptide) in enterococci of pigs after the use of the corresponding AGP was terminated in pigs.

In pigs, AGPs are still used in some countries to prevent diarrhea (e.g. olaquindox for *Lawsonia intracellularis*) (20). AGPs are often used in poultry to prevent necrotic enteritis, a bacterial infection caused by *Clostridium perfringens*, and in cattle to prevent liver abscesses. It is reported that benefits are less evident in conditions of good hygiene (20). Depending on the drug and species of animal, AGPs have been reported to enhance production by 0-11% through enhanced feed efficiency or other means. Studies in Denmark following the termination of AGP use showed that effects were minor to negligible in poultry and finisher pigs, however more substantial effects (2.6% reduction in growth rate and 0.6% increase in mortality) were seen in weaner pig production (6).

Conclusion

Antibiotics are important for the treatment of bacterial infections in pigs. Unfortunately, such use may also select for antibiotic resistance in bacteria of food safety importance, such as *Salmonella* and *Campylobacter*. Resistance to antibiotics increases the public health burden due to these infections, although the magnitude of the impact attributable to antibiotic use in pigs is unknown. Resistance may also occur in target pig pathogens, including *E. coli*, which is an animal health problem. In order to preserve the effectiveness of these important drugs for human and veterinary medicine, it is important to use them prudently. Among other things, this involves a reduction in unnecessary use (e.g. AGPs in finisher rations), preference for drugs of lesser importance to human health, and increased use of non-antimicrobial disease control practices.

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