

Antibiotic Resistance – The Global Perspective

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■ Introduction

Antibiotics have been used in pig production for over 60 years. They are very useful in managing bacterial infections of pigs, but the emergence of antibiotic resistance and calls for action to contain resistance are changing the availability of these drugs and our views of how they should be used. The purpose of this article is to provide some insights into antibiotic resistance and its impact on the pig industry.

■ Uses of Antibiotics in Pig Production

Antibiotics are used widely in pig production for the treatment of clinical bacterial infections (therapy), for the prevention of bacterial infection during times of stress, mixing or other high-risk periods (prophylaxis) and to enhance feed efficiency (growth promotion). There is good evidence that the primary benefit of growth promoters is actually prophylaxis of diarrhea in weaned pigs, thus the latter two categories are for practical purposes the same. Viral infections are not susceptible to antibiotics, nevertheless pigs with viral infections are sometimes treated prophylactically with antibiotics to prevent secondary bacterial infections. This is controversial because it increases resistance selection pressure without directly affecting the viral infection.

Antibiotics are most commonly administered in feed or less frequently in water to pigs at the group level (pen, barn) and this has important implications to resistance selection and control. Most producers also administer some antibiotic to individual pigs.

■ **Biology of Antibiotic Resistance**

Antibiotics are substances that are produced by other bacteria or fungi and at low concentrations kill or injure some bacteria. Examples include penicillin and tetracycline. Synthetic or semi-synthetic substances that behave in this manner are called antimicrobials (e.g. sulfonamides, fluoroquinolones), however in practice, the terms antibiotic and antimicrobial are often used synonymously.

Soon after penicillin was discovered in 1926, resistance was observed to emerge in clinically important bacteria. Similarly, resistance has emerged to every important class of antibiotics at some point after its introduction, although resistance does not appear to emerge in all species of bacteria, and the rate to which it occurs in bacterial populations is highly variable. Some bacteria are intrinsically resistant to antibiotics; for example, Gram-negative bacteria are typically intrinsically resistant to penicillin. More important, however, is resistance that is acquired through genetic mutation of bacteria. Sometimes only one mutation is required to confer full resistance, but more frequently multiple gene modifications are needed, and this can take years to develop, resulting in development of very complex genetic constructs. Resistance genes enable the bacteria to inactivate the antibiotic, pump it out of the cell, or prevent it from attaching to binding sites. These resistance genes can then be passed on to progeny cells (vertical transmission), or more importantly, the genes in the form of transmissible genetic elements can be shared with other bacteria, including those that are members of other species or genera. This horizontal spread of resistance determinants can occur by a variety of mechanisms including plasmids or by bacterial viruses (phages). These transmissible elements may encode for resistance to one antibiotic, but this usually confers resistance to other drugs in the same class (cross-resistance) because antibiotics of the same class usually have a similar mechanism of action. In many cases, however, plasmids and other transmissible elements contain genes encoding for resistance to multiple antibiotics or different classes. When this occurs, use of one antibiotic may select for resistance to a member of another, completely unrelated antibiotic (co-selection).

Some resistance existed naturally in the pre-antibiotic era; presumably a defense mechanism of some bacteria to the naturally occurring compounds from other species of bacteria in the environment. The evolution of resistance in bacterial populations, and its selection and spread within and between various species of bacteria are favoured by exposure to antibiotics. The factors that appear to be particularly important include the extent of use (e.g. number of individuals treated, number of herds treated, number of countries where drug is used), duration of treatment (resistance is normally favoured by long duration) and dose (low, sub-lethal dose favours resistance). Non-antibiotic factors also play important roles (e.g. failures of biosecurity, poor

infection control, movement of individuals, import/export of animals, travel of humans, environmental contamination).

■ Health Impacts of Resistance in Pigs and Humans

There are several mechanisms by which antibiotic resistance can increase the burden of illness in both animals and humans. The first and most obvious is that resistant bacterial infections may not respond to antibiotic therapy, although in practice, some do continue to respond despite the existence of resistance in laboratory tests. Resistance to some of the older antibiotics (e.g. tetracyclines) is now very common in enteric bacteria such as *Escherichia coli*, and these drugs are generally less effective for common infections of pigs than when first introduced several decades ago. Moreover, when treatment with one antibiotic fails, physicians or veterinarians may have to turn to other more expensive or toxic antibiotics, with another adverse effect of resistance. There is also evidence that resistant infections may be more severe or long-lasting than susceptible infections. This may have to do with the co-selection of virulence genes with antibiotic resistance genes. For example, there is a higher fatality rate with resistant than susceptible *Salmonella* infections of humans. Resistance can also increase the total number of infections. This can occur when the normal protective bacterial flora (e.g. of the gut) are reduced by antibiotic treatment. This may make individuals more susceptible to infection if they are exposed to the resistant infection during antibiotic therapy.

There is some evidence, although fragmentary, that some antibiotic use in food animals can be beneficial to public health. It is suggested that by assisting in the production of healthy animals, the prevalence of some foodborne infections is reduced. More research is needed to explore this possibility.

While examples of all of these impacts exist, it has been extremely difficult to determine the magnitude of their impact on public health, either in terms of the absolute number of people affected, or the risk faced by individuals. To assist in decision-making by regulatory officials, scientific risk assessments have been performed on some of the more important antibiotics, including fluoroquinolones and macrolides. Some risk assessments have shown large impacts of antibiotic use in animals on human health (e.g. fluoroquinolone use in chickens and resistant *Campylobacter* infections), while others have shown small impacts (e.g. macrolide use in pigs and resistant enterococcal infections).

■ International Trends in Managing Resistance

Several factors converged in the mid-1990s to create a sense of crisis in human medicine concerning antibiotic resistance. One important factor was a dramatic reduction in the number of truly new classes of antibiotics that were brought to the market by the pharmaceutical industry. Another was the emergence of so-called “super bugs”, infections that were resistant to all or at least nearly all available antibiotics. Examples include vancomycin-resistant enterococci (VRE) infections, methicillin and vancomycin-resistant *Staphylococcus aureus* ((MRSA) and multiple-antimicrobial resistant *Mycobacterium tuberculosis*. Dramatic increases in the incidence of resistance were observed in several important human pathogens, including resistance to important relatively new antibiotics, such as the fluoroquinolones.

Several expert panels were convened to address the crisis. In general they all concluded that antibiotic resistance is a serious problem, that its causes were multiple and complex, and among these, antibiotic use and abuse were important determinants. Several recommendations were made to slow the development of resistance to prolong the usefulness of existing antibiotics. Most of these were directed at antibiotic use and abuse in human medicine, however attention was also directed at antibiotic use in animals, particularly livestock, and particularly the use of antibiotics for growth promotion.

Ironically, a sense of crisis concerning resistance never really emerged in veterinary medicine. While resistance is an issue in some production-limiting diseases of animals (e.g. pathogenic *E. coli* infections in pigs and poultry), there are relatively few reports of resistance problems in some other infections. Nevertheless, emergence of resistance in some important enteropathogens of humans that have animal reservoirs, such *Salmonella* and *Campylobacter*, directed attention and calls for action at antibiotic use in animals; mainly food animals, but also companion animals.

The World Health Organization (WHO) and World Organization for Animal Health (OIE) have recently convened numerous expert consultations on antibiotic resistance issues. Not surprisingly, WHO consultations have tended to focus on public health and OIE on animal health. While some consensus emerged on the importance of antibiotic resistance in zoonotic enteropathogens and the need for increased surveillance and prudent antibiotic use, there was considerable disagreement concerning the other actions that should be taken to contain resistance, particularly increased controls on use. Beginning in 2004, it was recognized that the interests of food production, animal health and human health should be integrated, and the Food and Agriculture Organization (FAO) joined OIE and WHO in a series of joint consultations. These have also stressed the need for prudent use practices wherever antibiotics are used, good regulatory programs for

resistance control, and improved surveillance to identify emerging resistance for intervention.

As a result of these activities and recommendations, some countries have taken action and others have not. The most well-known of these actions include tighter controls on antibiotic use in some countries, up to and including an outright ban on antibiotic growth promoters in Europe. The United States has implemented a regulatory program that requires human health risk assessment of resistance prior to new antibiotic approval, and extra-label use of certain antibiotics (e.g. fluoroquinolones) is restricted. Canada has so far implemented only a few actions to curtail resistance, despite many recommendations from a national stakeholder committee in 2002.

■ Growth Promoters

Antibiotic growth promoters have received the most attention from critics of antibiotic use in animals. Often cited are the relatively large total quantities of antibiotic used for this purpose and its administration in low doses for long periods of time to large numbers of animals; factors that favour the selection of resistant bacteria. Another point of debate is whether it is justifiable to use valuable medicines to simply enhance feed efficiency, rather than to treat clinical bacterial infections. Finally, most growth promoters are related to antibiotics used for treatment of infections of humans and there is evidence that their use selects for resistance in these pathogens. For example, avoparcin was a growth promoter used in Europe and other parts of the world (not Canada or the U.S.) that was a member of the glycopeptides class of antibiotics and related to vancomycin, an antibiotic important for the treatment of multiple-drug resistant infections in humans. Its use in pigs and poultry was shown to select for VRE, although there is considerable disagreement to what extent avoparcin use was responsible for the very serious VRE problems in human medicine; poor hospital infection control and overuse of antibiotics in human medicine were certainly also important factors.

Concerns about VRE and other pathogens culminated in the now famous (or infamous, depending on your point of view) ban of antibiotic growth promoters in Denmark, and later in the whole of Europe. Much has been published on the effects of this ban and whether it was justified and successful. The WHO issued a thorough report based on the detailed surveillance and animal production data that were available in Denmark. Overall, the data showed that the ban resulted in some increased problems with diarrhea in weaned pigs, which resulted in increased therapeutic treatments with other classes of antibiotics. No detectable effects were identified in finishers and the reduction in feed efficiency in broilers was roughly equivalent to the cost of the antibiotic. No other effects on food safety or national economy were detected.

■ Critically Important Antibiotics

All antibiotics are considered important, either because they are currently needed for treatment of bacterial infections in animals and/or humans, or they have the potential for future such uses. Nevertheless, some antibiotics are more important than others because they are the last or one of the last drugs available to treat serious infection in humans or animals. Consequently, many countries and international organizations have categorized antibiotics with respect to their importance to human or animal health. Examples of the highest category of importance include fluoroquinolones and 3rd and 4th-generation cephalosporins, examples of the lower categories include tetracyclines and sulfonamides.

The appropriate use of these classification schemes is still the subject of debate. Many argue that non-human uses should be increasingly restricted as importance to humans increases. A practical problem with this approach is that importance to human health often correlates with importance to animal health. More work is needed to reconcile this issue. In Canada, resistance to most critically important antimicrobials is lower among *E. coli* and *Salmonella* of pigs. For example, **Table 1** shows the prevalence of antibiotic resistance in *E. coli* and *Salmonella* from pigs and *E. coli* from pig farm residents in Canada. Unfortunately, comparable data from the general human population in Canada are not available.

■ Prudent Antibiotic Use

Prudent use is the use of antibiotics in ways that maximize therapeutic efficacy and minimize resistance. Among options available to curtail resistance in animals, prudent use is favoured by many because it is voluntary and in theory leaves veterinarians and producers the option of using an antibiotic if they believe it justified. Many veterinary professional bodies have embraced the principles of prudent use and have published best practices. As with many voluntary practices, however, uptake is highly variable, and its effectiveness in curtailing resistance is essentially undocumented. Much probably depends on the level of awareness of the issue of resistance in the minds of those who make treatment decisions, and the importance that they apply to the long-term protection of human health over the short-term health of their livestock and economic viability of their operation.

Table 1. Frequency of antibiotic resistance in *E. coli* and *Salmonella* from pigs and *E. coli* from pig farm residents in Canada.

Category of Importance to Human Health	Antibiotics	Percent Resistant (number of isolates)		
		<i>E. coli</i> from Finisher Pigs (1322) ¹	<i>Salmonella</i> from Finisher Pigs (922) ²	<i>E. coli</i> from Pig Farm Families (555) ³
I	Amoxicillin/ Clavulanic acid	0.7	0	ND ⁴
	Ceftiofur	0	0	0
	Ceftriaxone	0	0	0
	Ciprofloxacin	0	0	0
II	Ampicillin	30.6	6.1	15.9
	Amikacin	0	0	ND
	Cefoxitin	0.7	0	ND
	Cephalothin	ND	0	2.2
	Gentamicin	1.1	0.5	1.3
	Kanamycin	10	14.4	4.1
	Streptomycin	49.6	26.5	9.6
	Trimethoprim/ Sulphamethoxazole	6.4	0.2	ND
III	Chloramphenicol	17.6	4.5	2.5
	Sulphonamide	49.9	21.9	17.3
	Tetracycline	78.9	43.4	23.6

¹ Varga et. al. (2008a)² Varga et. al. (2008b)³ Akwar, H. (2003)⁴ ND – not determined

■ Take Home Messages

Antibiotic resistance is a serious public health issue, but the magnitude of its importance to animal health is poorly understood. Most of the resistance problems in humans arise from poor antibiotic use practices in human

medicine, nevertheless, there is good evidence that antibiotic use in animals increases the prevalence of resistance in some important bacterial pathogens of humans, including *Salmonella* and *Campylobacter*. There is increasing pressure to ensure that antibiotic use in all fields, both human and animal, is prudent. Regulatory authorities are also under pressure to increase controls on approval and use of antibiotics in animals, but there is agreement that any such controls must first be justified on scientific grounds. Particular attention has focused on antibiotic growth promoters and antibiotics critically important for use in humans. There is good evidence that reductions in use of growth promoters in finisher pigs would have few adverse outcomes, but reductions in weaned pigs should be accompanied by alternate methods to deal with diarrhea. Critically important antibiotics should be reserved for therapeutic use of serious bacterial infections in pigs, and group treatments of these drugs should be discouraged.

■ References

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