

Antibacterial Resistance and Antibiotic Use in Animals

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Originally published as a National Pork Board Factsheet.

Background

There is currently increased scientific and public interest regarding the administration of therapeutic and subtherapeutic antimicrobials to animals, due primarily to the emergence and dissemination of multiple antimicrobial resistant zoonotic bacterial pathogens^{9,14}. The recent isolation and detection of multi-drug resistant *enterococci*, *Campylobacter* and *Salmonella typhimurium* DT104 from animal sources or their immediate environment has recharged this debate^{1,8,9,13,14}. Regardless it is clear that the use of antimicrobials (therapeutic and sub-therapeutic) in both animals and humans select for resistant bacterial populations. The question then becomes “are the populations of resistant bacteria observed in animals and humans independent or do they share a common pool with antimicrobial resistant bacteria in animals posing a threat to human health?”^{1,8}.

How does antimicrobial resistance arise?

The increased prevalence of bacterial antimicrobial resistance is an outcome of evolution and is a natural phenomenon. One must remember that any population of organisms, including bacteria, naturally includes variants with unusual traits, in this case the ability to fend off the action of an antimicrobial. However, the use of antimicrobials in humans and animals over the past 50 years has inadvertently accelerated the development of resistance by increasing the selection pressure exerted on these microorganisms. Once antimicrobial pressure has been introduced into an environment, resistance can quickly be selected and disseminated^{4,10}. With time, antimicrobial resistance can move from one microbial species to the next and can quickly become established as a normal component of the animal gut flora^{4,6,7,10}.

Resistance genes and mechanisms existed long before the introduction of antimicrobials into clinical medicine. Antibiotic resistant bacteria have been isolated from deep within glaciers in Canada’s high Arctic regions, estimated at over 2000 years old² and from examination of historic bacterial cultures before the antimicrobial era began¹¹. The microorganisms that produce antibiotics must also possess resistance mechanisms which protect them from the action of their own antibiotic and are a potential source of antibiotic resistance genes^{4,12}. Lastly, investigators have even shown⁴ that a number of human and animal antibiotics were in fact contaminated with chromosomal DNA of the antibiotic-producing organism, including identifiable antibiotic resistance genes¹². They further proposed that the presence of DNA encoding drug resistance in antibiotic preparations has been a factor in the rapid development of bacterial multiple antibiotic resistance.

Antibacterial resistance mechanisms

The majority of antimicrobial resistant phenotypes are obtained by the acquisition of external genes that may provide resistance to an entire class of antimicrobials^{3,4,6,9,10}. Bacterial antimicrobial resistance generally develops through one of five mechanisms: (a) permeability changes in the bacterial cell membrane which limit the amount of antimicrobial entering into the bacterium; (b) active efflux of the antimicrobial out of the bacterium; (c) alteration of the target site of antimicrobial action; (d) enzymatic inactivation or destruction of the antimicrobial and (e) creation of altered enzymatic pathways around those targeted by the antimicrobial^{4,10}. The majority of antimicrobials used in veterinary medicine can be inactivated or blocked by one or more of these mechanisms. In fact, bacteria have the capability to employ multiple mechanisms at the same time, possibly rendering combination treatments ineffective.

In recent years, a number of these antimicrobial resistance genes have become associated with large, transferable, extrachromosomal DNA elements, called plasmids, on which may be other DNA mobile elements, termed transposons and integrons^{3,4,10}. These mobile DNA elements have been shown to possess genetic determinants for several different antimicrobial resistance mechanisms and may be responsible for the rapid dissemination of resistance genes among different bacterial genera and species^{4,6,7,10}. In fact, some of these determinants have been found to contain genes encoding resistance to commonly used disinfectants and heavy metals in addition to antimicrobial resistance genes¹⁰.

Approaches to confront the antibiotic resistance situation

The emergence of antimicrobial resistance among human and veterinary bacterial pathogens is a serious crisis and several strategies have been proposed to try to circumvent and control this dilemma. Prevention should be the ultimate goal and vaccines and competitive exclusion products have been suggested as a strategy that can be used to decrease the therapeutic use of antimicrobials^{1,5,8,14}. Pharmaceutical companies continue to make great advances in developing new antimicrobial agents, however these discoveries cannot be expected to solve the problem in the near future. It is thus necessary to introduce guidelines on the prudent use of antimicrobials to avoid further increases in bacterial resistance, such as those put forward by the American Veterinary Medical Association and the American Association of Swine Practitioners.

Improved surveillance of emerging antimicrobial resistant bacterial phenotypes is also critical to the development of new treatment guidelines and intervention strategies, as well as helping shape national policy regarding the antimicrobial use in animal husbandry. The most prominent surveillance program in the United States related to agriculture is the National Antimicrobial Resistance Monitoring System (NARMS) established in January 1996 by FDA, USDA, and CDC to monitor trends in antimicrobial susceptibilities of zoonotic bacterial pathogens (*Salmonella*, *Campylobacter*). Bacterial isolates included in NARMS are obtained from human and animal clinical specimens, healthy farm animals, and from food-producing animal carcasses at slaughter. Additionally, veterinary diagnostic laboratories should play a key role in the timely detection of resistant bacterial pathogens with regards to submission of clinical specimens for the historical "culture and sensitivity" testing.

There is also an urgent call for research that focuses on improving our understanding of how bacterial antimicrobial resistance develops, disseminates, and persists in the animal production environment. Studies that investigate optimal uses of antimicrobials (dose, interval, duration, narrow vs. broad spectrum) in animals in hopes of minimizing bacterial resistance development are needed as well. Also, there are new technologies on the horizon such as bacterial genome mapping which is likely to produce entirely new classes of antimicrobials, however, this is many years down the road. This will most likely result in a "window of vulnerability" where bacterial pathogens of animal and human origin will become increasingly resistant to current available antimicrobials. Therefore, research should also be directed at improving hygienic and other preventive efforts in an attempt to contain and/or reduce bacterial antimicrobial resistance.

Concluding statements

In summary, the increased prevalence of antimicrobial resistance among bacterial pathogens has severe implications for the future treatment and prevention of infectious diseases in both animals and humans. Although much scientific information is available on this subject, many aspects of the development of antimicrobial resistance still remain uncertain. What is known is that the development and dissemination of bacterial antimicrobial resistance is the result of numerous complex interactions among antimicrobials, microorganisms, and the surrounding environments. Although research has linked the use of antibiotics in agriculture to the emergence of antibiotic resistant foodborne pathogens, debate still continues whether

this role merits further regulation or restriction. Clearly pork producers and veterinarians must be able to treat animals if they become ill, however, the misuse or inappropriate use of antimicrobials in swine could negatively effect consumer confidence in pork products.

Points to Remember

1. The driving force behind the emergence and spread of bacterial antimicrobial resistance is the selection pressure exerted by antimicrobial use in human and veterinary medicine.
2. Antimicrobials used in food animals are also used for human therapy.
3. Antimicrobials are important for animal welfare but need to be used judiciously.
4. Therapeutic antimicrobials should be used for as long as needed, over as short a dosage period as advised, and at the appropriate dosage regimen.
5. Records should be kept regarding the administration of all antimicrobials.
6. Veterinary supervision and coordination is essential for the appropriate use of antimicrobials.
7. When possible, veterinary diagnostic laboratories offering bacterial diagnosis with antimicrobial susceptibility testing should be employed before therapy is initiated.
8. Surveillance is an essential tool for the containment of antimicrobial resistance.
9. Antibiotic resistance mechanisms most likely evolved from genes present in antibiotic producing microbes.
10. Antibiotic resistance occurs primarily by means of one of five main mechanisms, additionally, multiple mechanisms may be present in a bacterium.
11. There is no single solution for minimizing antimicrobial resistance; rather, a coordinated multidisciplinary approach will be required to address this issue.

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Information developed for the Pork Information Gateway, a project of the U.S. Pork Center of Excellence supported fully by USDA/Agricultural Research Service, USDA/Cooperative State Research, Education, and Extension Service, Pork Checkoff, NPPC, state pork associations from Iowa, Kentucky, Missouri, Mississippi, Tennessee, Pennsylvania, and Utah, and the Extension Services from several cooperating Land-Grant Institutions including Iowa State University, North Carolina State University, University of Minnesota, University of Illinois, University of Missouri, University of Nebraska, Purdue University, The Ohio State University, South Dakota State University, Kansas State University, Michigan State University, University of Wisconsin, Texas A & M University, Virginia Tech University, University of Tennessee, North Dakota State University, University of Georgia, University of Arkansas, and Colorado State University.