Does Antimicrobial Use in Animals Affect Human Health?

Mike Apley, *DVM, PhD*
Department of Veterinary Diagnostic and Production Animal Medicine
Iowa State University
Ames, Iowa 50011-1250

Yes! As veterinarians we positively impact human and animal health every day by using antimicrobials to treat or prevent disease. It is also necessary to recognize that this use may contribute to susceptibility shifts in pathogens with zoonotic potential. As a profession, and as an industry, we need to work toward carefully determining both positive and negative effects due to antimicrobial use in animal agriculture.

Our multiple responsibilities are best summarized by the veterinarians oath. "Being admitted to the profession of veterinary medicine, I solemnly swear to use my scientific knowledge and skills for the benefit of society through the protection of animal health, the relief of animal suffering, the conservation of livestock resources, the promotion of public health, and the advancement of medical knowledge..."

Frequently asked questions include the following:

1. Has it been established that antimicrobial-resistant zoonotic pathogens may be transferred from animals to humans?

There are five references which have been cited by the Centers for Disease Control and Prevention (CDC) as demonstrating the link between antimicrobial use in food animals and the transfer of resistant *Salmonella* to human patients (Table 1).[1] These are not the only published studies on this subject. Several studies are also commonly referred to as demonstrating the link between *Salmonella* infections and the consumption of raw or undercooked eggs.[2,3] Due to the nature of epidemiological studies, any one of these articles may be questioned as to the validity of the causal links established during the investigation. However, it is unreasonable to dismiss categorically the possibility and reality of these types of transfer.

We are sticking our heads in the sand if we do not recognize the zoonotic potential of *Salmonella spp*. It is a similar maneuver to deny that use of antimicrobials will affect the minimal inhibitory concentration (MIC) profile of a bacterial population if the antimicrobial is able to inhibit part of that population at the concentration administered.

Table 1. Key articles addressing the passage of Zoonotic Salmonella isolates displaying resistance to various antimicrobials.

Author-Title	Reference	Postulated link
Salmonellosis-Kentucky	Morbidity and Mortality Weekly Report, July 22 1977	*Salmonella typhimurium*-Unpasteurized milk
Lyons RW, et al. An Epidemic of Resistant Salmonella in a Nursery	JAMA 243:546-547, 1980	*Salmonella heidelberg*-Dairy calves to mother to hospital nursery
Holmberg SD, et al. Drug-Resistant *Salmonella* From Animals Fed Antimicrobials	N Engl J Med 311:617-622, 1984	*Salmonella newport* through hamburger
Tacket CO, et al. An Outbreak of Multiple-Drug Resistant *Salmonella* Enteritis From Raw Milk	JAMA 253:2058-2060, 1985	*Salmonella typhimurium*-raw milk
Spika JS, et al. Chloramphenicol-Resistant *Salmonella Newport* Traced Through Hamburger to Dairy Farms	N Engl J Med 316:565-570, 1987	Salmonella newport in meat

Personally, I recognize the use of antimicrobials in food producing animals as a component of increasing minimal inhibitory concentrations (MICs) in pathogens of potential zoonotic importance. The extent of this component has not been quantified. We must also recognize the potential for contamination of human origin during the animal production or post-slaughter phases of animal agriculture. Those that dismiss the possibility of the transfer of human pathogens and parasites to food animals should review the epidemiology of *Taenia saginata* and *Cysticercus bovis*.

Does this mean that antimicrobials should automatically be withdrawn from uses that could have an effect on the susceptibility of zoonotic pathogens? No. It does call for judicious use of antimicrobials in food producing animals and monitoring of changes in the sus-

ceptibility of potential zoonotic pathogens. This type of use and monitoring is in the best interest of all parties, as it maintains the therapeutic viability of antimicrobials in veterinary medicine. **Healthy animals are necessary for healthy food.**

2. What proportion of resistance problems in human medicine are due to veterinary and producer use of antimicrobials?

This is a logical follow up to the first question. The debate centers around *Salmonella*, *E. coli,* and *Campylobacter*. The debate may further be compartmentalized to therapeutic and "subtherapeutic" uses of antimicrobials in food animals. A working definition of "subtherapeutic use" is needed before we can adequately address the issue. Members of the human health community have also expressed concern about the therapeutic application of antimicrobials on a herd- or flock-wide basis.[4]

The issue of *Salmonella* resistance is especially germane to our discussion, as recent publications by members of the human health community claim that most of the *Salmonella typhimurium* infections in humans are of animal origin.[5,6] They support this argument with case studies such as in Table 1, and reports of the high infectious dose required for oral transmission of *Salmonella* to humans. A lack of development of resistance to ciprofloxacin by human, pre-treatment isolates of *Salmonella* is also cited as evidence that resistant *Salmonella*, which develop during therapy in humans, are not passed to other humans.[5]

The real picture is that the exact contribution of food animal antimicrobial use to decreased susceptibility in human isolates of *Campylobacter, E. coli,* and *Salmonella* is not known. The degree of change in antimicrobial susceptibility of potential zoonotic pathogens necessary to affect clinical outcomes in human medicine has also not been characterized. It is important that each organism be discussed within the context of the appropriate epidemiology and that we continue to counter sensationalist statements concerning the use of antimicrobials in animal agriculture. It is equally important that the debate over the extent of animal agriculture contribution to decreased susceptibility in human medicine not impede the progress of the veterinary profession in minimizing any component that exists.

3. What resistance problems are affecting human therapeutics?

Bacterial pathogens presenting major therapeutic challenges in human medicine due to resistance include:[7]

Streptococcus pneumoniae
Staphylococci
Salmonella
Shigella
E.coli
Enterococci
Pseudomonas
Mycobacterium tuberculosis
Neisseria gonorrhea

4. Is the human medical profession addressing problems within its own ranks?

The CDC has initiated a 4 million-dollar campaign to educate physicians and patients on prudent use of antimicrobials. *(It is interesting to note that no funding has been appropriated to assist in the veterinary process.)* Most of us have seen ads aimed at patients to encourage adherence to the physician's directions. Specialty medical practice groups have also worked together with the CDC to develop principles of judicious use. An example is a supplement to the journal *Pediatrics; Principles of Judicious Use of Antimicrobial Agents for Pediatric Upper Respiratory Tract Infections*.[8] This set of principles addresses otitis media, pharyngitis, acute sinusitis, cough illness/bronchitis, and the common cold. A large part of these principles address the need to carefully diagnose the condition and the lack of therapeutic effect from antimicrobials in many presentations. The fact that these principles are needed is evidenced by Table 2.[9]

Table 2. Leading Indications for Outpatient Antimicrobial Therapy in Humans (1992).[9]

Diagnosis	Number of Prescriptions
Otitis media	23,468,000
Upper respiratory infection	17,922,000
Bronchitis	16,324,000
Pharyngitis	13,110,000
Sinusitis	12,961,000

Yes, the human medical profession is addressing inappropriate use within its own ranks. It is my experience that most public health officials readily admit there are a lot of problems on the human side of the fence. As guardians of both human and animal health, we as veterinarians are obligated to also aggressively address the issue of judicious use.

5. Aren't there public health benefits from antimicrobial use in food animals?

Yes. Several groups are working on quantifying this effect. Benefits such as reduced pathogen load and improved product quality need to be examined and brought forth to balance the current debates. It is clear that veterinarians and producer groups must address the issues of *"...the protection of animal health, the relief of animal suffering, the conservation of livestock resources..."*.

Where to from here?

At the time of this writing, the American Veterinary Medical Association is forming a steering committee to address educational initiatives for the Judicious use of Antimicrobials in Veterinary Medicine. Other current initiatives involve the American Association of Bovine Practitioners, Academy of Veterinary Consultants, American Association of Swine Practitioners, and the American Academy of Veterinary Pharmacology and Therapeutics. Producer groups active on this issue include the National Cattlemen's Beef Association and the National Pork Producers Council. Veterinary and producer groups encompassing poultry and aquaculture are also involved.

The American Academy of Veterinary Pharmacology and Therapeutics was one of the sponsors of a meeting in College Park, Maryland in January, 1998.[10] A task force was convened following the meeting to address the issues covered. The task force report suggested pursuing prudent use of antimicrobials by focusing on maximizing the therapeutic outcome while following principles, which, at least theoretically, minimize the chance of resistance development. These principles were defined as using antimicrobials:

- for proven clinical indications,
- only when indicated,
- at the appropriate dosage regimen,
- as long as necessary,
- as short as possible.

We are usually able to derive regimens for a given indication that have a good chance of therapeutic success. The "as long as necessary" and "as short as possible" principles give an indication of the work to be done to define the relationship between length of therapy and the potential for resistance development in specific antimicrobial/pathogen relationships. While admonishing the practitioner to "minimize the chance for resistance development" is certainly a noble cause, it is somewhat hypocritical given the current state of knowledge. We do know some specific regimen principles, such as achieving a maximal serum concentration 8-10 times the MIC of a pathogen with fluoroquinolones to suppress resistance in some organisms.[11] However, there is a lot of work to do to describe the regimens best suited to resistance suppression in the antimicrobial/pathogen combinations commonly encountered in practice.

Responsible antimicrobial use is only one step towards minimizing public health risk from bacteria with reduced antimicrobial susceptibility. As veterinarians, we are in the position to reduce animal suffering, decrease the need for antimicrobial use and minimize the opportunity for foodborne illness in humans through other means as well. A balanced approach includes the following strategies.

1. Reduce the number of sick cattle by managing the environmental, genetic, nutritional, husbandry and preventive medicine programs for each livestock operation.

2. Know the bacteria you are attempting to treat and determine effective antibacterial choices by utilizing records, susceptibility testing, and label indications supported by clinical trials.

3. Actively pursue continuing education on the appropriate application of susceptibility testing results to antimicrobial regimen selection. Know the most effective way to modify the dose for each antimicrobial group (e.g., time above MIC vs. peak concentration)

4. When it is necessary to treat sick cattle with antimicrobials, choose a single antimicrobial with the pharmacodynamics and pharmacokinetics appropriate for the bacteria causing the disease you are trying to treat. For example, benzathine penicillin is unlikely to be effective against any pathogen except the most sensitive bacteria or infections in the lower urinary tract unless extremely high doses are used.

5. When two or more antimicrobials are reasonable for therapy, choose the antimicrobial with the narrowest spectrum possible and use it for the least amount of time necessary for a successful treatment. Conserve the use of the most effective antimicrobials for conditions where they are definitely indicated, such as when other therapies have failed or clinical experience indicates other therapies will be ineffective. Veterinarians must resist the temptation to routinely use the "big gun" as first line therapy in every case.

6. Use antimicrobials only when a meaningful therapeutic response can be expected. Continued therapy of chronic conditions (e.g. chronic respiratory disease) which have histories of poor response are an unwise exposure of the bacterial population to antimicrobials.

7. Maintain records concerning antimicrobial use and review them for ideas to reduce use, modify regimens, or switch to narrower spectrum antimicrobials. Routine rotation of antimicrobials to reduce resistance development has not been shown to be beneficial in veterinary medicine, and may only widen the antimicrobial exposure of a bacterial population. There is some indication that withdrawal of an antimicrobial may beneficially affect pathogen susceptibility for some antimicrobial/pathogen combinations in human hospitals. This effect is dependent on the mechanism of resistance and the homogeneity of the pathogen isolates being addressed, as well as the degree of control over prescribing practices. Some public health officials feel this approach would work on a nation-wide basis for veterinary medicine. Blindly extrapolating from human hospital settings

to veterinary production medicine is irresponsible and fails to address the diversity of production settings.

These suggestions for antimicrobial use should allow for optimum animal care and public health safety, while at the same time continuing to establish veterinarians as responsible stewards of antimicrobials. This record of stewardship will be vital to the continued availability of new and existing antimicrobials for use in food animals.

References

1. Angulo, FJ. Personal communication, 1997. 2. Morse DL, Birkhead GS, Guardino J, *et al.* Outbreak and Sporadic Egg-Associated cases of Salmonella enteritidis: New York Experience. *American Journal of Public Health* 84:859-860, 1994. 3. Passaro DJ, Reporter R, Mascola L, *et al.* Epidemic Salmonella enteritidis infection in Los Angeles County, California the Predominance of Phage Type 4. *Western Journal of Medicine* 165:126-130, 1996. 4. Levy SB. Multidrug Resistance A Sign of the Times. Editorial, *N Engl J Med* 338:1333-1378, 1998. 5. Angulo FJ, Tauxe RV, Cohen ML. Significance and Sources of Antimicrobial-Resistant Nontyphoidal Salmonella Infections in Humans in the United States: The Need for Prudent Use of Antimicrobial Agents, Including Restricted Use of Fluoroquinolones, In Food Animals. *In Proceedings*, The Role of Veterinary Therapeutics in Bacterial Resistance Development: Animal and Public Health Perspectives, College Park, MD, 1998, pp. 63-78. 6. Glynn MK, Bopp C, Dewitt W, *et al.* Emergence of Multidrug-Resistant Salmonella Enterica serotype Typhimurium DT104 Infections in the United States. *N Engl J Med* 338:1333-1378, 1998. 7. Bell DM. Prudent Use of Antimicrobials in Humans. *In Proceedings*, The Role of Veterinary Therapeutics in Bacterial Resistance Development: Animal and Public Health Perspectives, College Park, MD, 1998, pp. 101-106. 8. Dowell SF, Editor. Principles of Judicious Use of Antimicrobial Agents for Pediatric Upper Respiratory Tract Infections. *Pediatrics* 101:163-184. 1998. 9. McCaig LF, Hughes JM. Trends in Antimicrobial Drug Prescribing Among Office-Based Physicians in the United States. *JAMA* 273:214-219, 1995. 10. The Role of Veterinary Therapeutics in Bacterial Resistance Development: Animal and Public Health Perspectives, College Park, MD, 1998. 11. Sanders CC. Microbiology of Fluoroquinolones, in Fluoroquinolones in the Treatment of Infectious Diseases. Sanders WE, Sanders CC, ed. Physicians & Scientists Publishing Co., Inc., Glenview, IL, pp 8-14, 1990.

CVM Update

FDA, Center for Veterinary Medicine

"Helping man and animals by ensuring the availability of safe and effective animal health products."

June 29, 1998

FDA Publishes Labeling Rules for Animal Drugs

In the June 17, 1998, Federal Register, FDA published a final rule on the labeling of drugs for use in milk-producing animals. This rule removes the existing 96-hour withdrawal time limitation, eliminates the requirement to calculate and label on the basis of the number of 12-hour milking periods that have elapsed since treatment, and permits a milk-discard or withdrawal time to be calculated by elapsed hours since treatment. FDA is taking these actions to allow greater flexibility in the labeling of these drugs which will make it easier and more economical for sponsors to comply with the regulations.

The previous 96-hour limitation was based on FDA's perception that 96 hours constituted a maximum practical withdrawal time for the dairy industry. However, FDA now recognizes that a withdrawal time longer than 96 hours may be desirable and practical in certain circumstances. Removal of the 96-hour limitation will allow the possibility of a longer withdrawal time to be considered for milk-producing animals on a case-by-case basis depending on the use and safety of the drug.

Similarly, the 12-hour milking schedule was established to calculate the number of milkings that occur during the withdrawal period. The 12-hour milking interval was considered to be generally reflective of dairy practice when this regulation was published; however, alternative milking schedules, such as three times a day milking, are in common use in the dairy industry today. The new rules revise the regulation so that the length of the milk cycle is not specified, eliminating the reference to the milking interval as long as milk is discarded the assigned number of hours after the latest drug treatment.

Additional information about this rule is available in the Federal Register (Volume 63, Number 116, pp. 32978-32980) and from Dr. Steven D. Vaughn, Center for Veterinary Medicine (HFV-100), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-594-1620.

Issued by: FDA, Center for Veterinary Medicine
Office of Management and Communications, HFV-12 7500 Standish Place, Rockville, MD 20855
Telephone: (301) 594-1755 FAX: (301) 549-1831
Internet Web Site: http://www.fda.gov/cvm