



## Perspectives on Bacterial Resistance and Veterinary-Use Antibiotics

by Robert B. Nicholas and Arnold I. Friede

Since the large scale production of penicillin for humans began in the 1940s, antibiotics have been hailed as miracle drugs. They likewise play a critical role in treating bacterial infections in food producing animals, thereby ensuring the wholesomeness, safety, and abundance of the food supply, as well as in companion animals (dogs and cats), horses and other animals.

There are many potential sources of human bacterial infections, including environmental exposure, and exposure through food and drinking water.<sup>1</sup> One acknowledged source is consumption of some meat and poultry products that are not fully cooked. This may occur because bacteria can colonize in food producing animals and may be spread during processing. If the food is not thoroughly cooked before it is consumed, there is a resulting risk of illness. While most food-borne bacterial infections are mild and self-limiting (i.e., resolve themselves without antibiotic treatment), some are not. If an antibiotic becomes less effective or altogether

ineffective because of the development of bacterial resistance, there may be no treatment available for the infection, particularly in the case of “multi-drug-resistant” organisms. Because some bacterial infections may be life threatening, particularly in elderly and pediatric populations, common sense and sound public policy reasons justify strategies to maintain the effectiveness of existing antibiotics. They likewise suggest a need for incentives for the development of new products for human and animal use that help to ameliorate concerns about antibiotic resistance.

In recognition of the problem, Congress is considering a number of bills intended to address the development, spread, and potential adverse public health impact of antibiotic resistance. Among these is proposed legislation that would:

- a) establish a new office in the Department of Health and Human Services that would focus on antibiotic resistance;<sup>2</sup>
- b) promote research on antibiotic resistance,<sup>3</sup> c) withdraw



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approved applications for certain uses of antibiotics in veterinary medicine;<sup>4</sup> and d) to provide incentives for new antibiotic research and development.<sup>5</sup> Given the short legislative session, and the focus on the Presidential election, it seems unlikely that any of these proposals will be enacted this year. Nevertheless, reauthorization of user fees to fund the Food and Drug Administration's (FDA's) review and approval of animal drug applications is widely perceived as the likely vehicle for consideration of legislation on the use of antibiotics in veterinary medicine and its benefits and risks for human and animal health.

As Congress and FDA focus on strategies to preserve the medical utility of antibiotics, it is crucial that research funds be provided to better understand the development and spread of antibiotic resistance, and that incentives be provided for development of new antibiotics. Above all, however, it is important that Congress allow the science, not the rhetoric, to drive the legislative debate.

## Veterinary Use of Antibiotics

There are analogous medical reasons for using antibiotics to treat animals as there are for using them to treat humans. Antibiotics are useful in veterinary medicine to prevent and treat a wide range of bacterial infections in cattle, swine, poultry and other food producing animals, as well as in the family pet and other animals. In addition to their treatment use, older antibiotics are sometimes also used in food producing animals to enhance feed efficiency and promote growth. Antibiotics may be administered to animals through individual injection or oral administration, or included in animal feed or drinking water particularly when individual animal injection is not practical.

Just as certain bacterial infections may be spread between humans in close

proximity, bacteria can spread between animals raised in close proximity. As a result, it may be prudent to treat an entire herd or flock to prevent the spread of an incipient outbreak. Appropriate use of antibiotics in veterinary medicine can also help alleviate animal suffering from disease, produce healthier animals entering processing facilities, reduce opportunities for cross-contamination of the food supply,<sup>6</sup> and help provide abundant and low cost meat and poultry products to domestic and world markets.

There are unquestionably serious and legitimate concerns about the complex problem of the development of antibiotic resistant bacteria and the consequent impact on human health. Particularly in the Washington "blame game" culture, however, there seems to be a reflexive tendency to find an easy scapegoat whose sacrifice would result in a quick fix to the problem. Often readily, and most often without data that withstands scrutiny, these critics point the proverbial finger at antibiotic use in veterinary medicine. Largely unfamiliar with veterinary practices, the critics mistakenly believe that antibiotics are not really necessary for the treatment of animals, are not strictly regulated by FDA, are used indiscriminately by veterinarians and food producers, and are providing no public health benefit.

The recent news stories concerning methicillin-resistant *Staphylococcus aureus* (MRSA), and the ensuing congressional hearings on the subject, is a perfect case in point.<sup>7</sup> While development and spread of MRSA is a serious public health concern that was first reported in the 1980s, the scientific consensus, as reported by the Director of the U.S. Centers for Disease Control (CDC) herself, is that the vast majority of MRSA infections, and the most serious, are acquired primarily in hospitals (HA-MRSA) due to poor management

practices.<sup>8</sup> An increasing but comparatively small secondary source of infections is called "community acquired" MRSA (CA-MRSA), which is not directly associated with the human health care system.<sup>9</sup> The overwhelming majority of CA-MRSA cases appear to be uncomplicated skin and soft tissue infections, spread by skin-to-skin contact.<sup>10</sup> Very recently, there have been a few scientific papers reporting MRSA in food animals and pets, particularly in swine in the Netherlands, Germany and Canada. There do not appear to be any scientific data implicating beef, pork or other animal food products as a source of MRSA infections in humans. Nor do the data support the conclusion that veterinary use of antibiotics is a cause or source of MRSA.<sup>11</sup> While these reports should be taken seriously and investigated fully, they are hardly sufficient cause, as some would argue, for an outright ban on the use of antibiotics that are necessary and appropriate in veterinary medicine.<sup>12</sup>

## The Resistance Story

The development of bacteria resistant to penicillin was reported within a few years after such use began. The development of resistance is a biological fact. Bacteria acquire resistance traits through random and spontaneous gene mutations, largely in the absence of antibiotic use, or in some cases, resistance genes may be transferred between bacteria (so-called "plasmid-mediated resistance"). Use of an antibiotic exerts "selective pressure," i.e. bacteria that are susceptible to the antibiotic are killed, and the bacteria resistant to the antibiotic are "selected," survive and multiply.<sup>13</sup> When the resistant bacteria that are human pathogens survive in food producing animals, they may later enter the food chain if not destroyed during processing, may cross-contaminate other food products, and may cause illness in people who consume the food.

Resistant bacteria are, however, only a very small subset of all bacterial infections in humans. Enhanced slaughter standards and education about proper cooking have helped during the past several years to reduce significantly the number of cases of food-borne illnesses in the United States.<sup>14</sup> Good animal husbandry practices, including prudent use of antibiotics, also plays a role in lessening the potential that resistant organisms will enter the food chain. Much of modern agricultural production is highly integrated, managed like other large businesses, and overseen by competent trained professionals, including veterinarians. It might seem obvious that food producing animals do not have health insurance, and there is no Medicare Part D drug coverage for them. The natural corollary is that decisions about medication use in food producing animals is principally an economic one, greatly reducing any incentive to overmedicate through unnecessary use of expensive veterinary antibiotics. Indeed, as the public debate has escalated over the past dozen or so years, the American Veterinary Medical Association and the species specific veterinary medical associations, have established comprehensive guidelines for the judicious and prudent use of antibiotics in veterinary medicine.<sup>15</sup> While these efforts can reduce potential development of resistance, they will not eliminate meat and poultry as a potential source of bacterial infections.

Appropriately managing antibiotic use in humans and in animals lessens the selective pressure leading to antibiotic resistant bacteria and decreases the possibility of the spread and prevalence of such bacteria. Therefore, the question for public health officials is not whether resistance can be prevented entirely but whether and how it can be managed successfully. The keys to preserving the value of any antibiotic—whether for human or veterinary

use—are 1) prudent use, including selection of the appropriate antibiotic for the targeted pathogen and administration at the proper dose and dosing regiment, and 2) having multiple antibiotics available so that there are effective alternative antibiotics should resistance develop to the first line therapy. Adhering to these basic fundamentals of antibiotic use, regardless of species, will lessen selective pressure and help preserve the value of antibiotics.<sup>16</sup>

### CVM's Regulation of Antibiotics

The Federal Food, Drug, and Cosmetic Act defines a drug in part as “articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man *or other animals*” and “articles (other than food) intended to affect the structure or any function of the body of man *or other animals*.”<sup>17</sup> FDA’s Center for Veterinary Medicine (CVM) regulates veterinary drugs<sup>18</sup> in a manner, procedurally and substantively, quite similar to the regulation of human use drugs by FDA’s Center for Drug Evaluation and Research. To be approved, an animal drug that is the subject of a new animal drug application (NADA) must be shown to be safe and effective for its intended use. “Safe” in this respect means that the benefits of the use of the drug in the animal exceed its risks.<sup>19</sup> One very significant difference, however, is that the edible tissue of an animal intended to be used for food must also be shown to be “safe.”<sup>20</sup> “Safe” in the context of human food safety means a demonstration of “a reasonable certainty of no harm.”<sup>21</sup> CVM has in place a rigorous process for reviewing all NADAs. Those for antibiotics to be used in food animals are comprehensively evaluated for the potential for the antibiotic use to lead to the development of resistant bacteria and the potential for adverse impacts on human health as a result.<sup>22</sup> Antibiotics

administered to animals in feed may be subject to additional requirements.<sup>23</sup>

As concerns about the development of resistant bacteria have become more frequent and vocal, CVM has responded by establishing an increasingly stringent process for review and approval of veterinary use antibiotics.<sup>24</sup> For example:

- Together with CDC and the U.S. Department of Agriculture, CVM in 1996 established the National Antimicrobial Monitoring System—Enteric Bacteria (NARMS). NARMS is used to monitor changes in antimicrobial drug susceptibilities of selected enteric bacteria in humans, animals and retail meat to a panel of antimicrobial drugs important in human and veterinary medicine.<sup>25</sup>
- In 2003, after extensive scientific consideration and public debate, CVM promulgated Guidance No. 152,<sup>26</sup> which outlines a risk assessment approach for evaluating the microbial food safety of antimicrobial new animal drugs.<sup>27</sup> The Guidance focuses “on the concern that the use of antimicrobial new animal drugs in food-producing animals will result in the emergence and selection of antimicrobial resistant food-borne bacteria which impact human health adversely.” The Guidance also addresses risk management options, such as refusal to approve the NADA, establishing safe conditions of use, such as limitations on marketing status (e.g., Rx only), prohibition on extra-label use, post approval monitoring, and review by the Veterinary Medicine Advisory Committee.<sup>28</sup>
- In 2005, after a full evidentiary hearing, CVM withdrew approval for an NADA for a veterinary antibiotic, concluding that the antibiotic was “not shown to be safe” because of concerns about the development and spread of antibiotic resistant bacteria and the resulting potential to adversely impact human health.<sup>29</sup>

## Congressional Action Pending

One of the bills currently pending before Congress—"Strategies to Address Antimicrobial Resistance Act" (STAAR)—would amend the Public Health Service Act to establish an Office of Antimicrobial Resistance under the Secretary of the Department of Health and Human Services.<sup>30</sup>

The Director of that Office would convene an Antimicrobial Resistance Task Force with government-wide representation from all federal agencies that touch on the issue. A parallel Public Health Antimicrobial Advisory Board, with public members representing an array of relevant human and veterinary health constituencies, would likewise work on the problem with the Director and the Task Force.

The proposed legislation lays out a broad mandate for comprehensive antibiotic resistance research, including ways to foster innovation and the development of new products that themselves might, so to speak, be more "resistant" to antimicrobial resistance. In addition, the Brown/Hatch bill lays out the multifactorial dimensions of the problem and establishes a mandate for consideration of each of these elements in order to develop integrated proposals for recommended next-steps.

To be sure, only a ban or other drastic restriction on the veterinary use of antibiotics will satisfy the critics. But in the STAAR Act, Senators Brown and Hatch have made responsible suggestions for a balanced discussion about how to address the complex problem of antibiotic resistance.

## Conclusion

Every thoughtful participant in the debate about antibiotic resistance agrees on the public health imperative to develop effective strategies to combat antibiotic resistance. At the same time, however, the "answer" is not yet readily apparent. Ac-

tion for its own sake, without full consideration of the human and animal health consequences, may well be a cure worse than the disease itself.  $\Delta$

- 1 Many infections are caused by viruses that are not amenable to antibiotic treatment.
- 2 See, e.g., Strategies to Address Antimicrobial Resistance Act, S. 2313, ("STAAR") introduced in the Senate on November 6, 2007, by Senators Brown (D. OH) and Hatch (R. UT), and in the House of Representatives (H.R. 3697) by Representatives Matheson (D. UT), Ferguson (R. NJ), Waxman (D. CA) and Baldwin (D-WI) on September 27, 2007.
- 3 Food and Energy Security Act of 2007, H.R. 2419 (Farm Bill), Engrossed Amendment as Agreed to by Senate, Dec. 14, 2007, §§ 7307, 7313.
- 4 Preservation of Antibiotics for Medical Treatment Act of 2007, S. 549 ("PAMTA"), introduced in the Senate by Senators Kennedy (D. MA), Snow (R. ME), Reed (D. RI) and Brown (D. OH) and in the House of Representatives (H.R. 962) by Representative Slaughter (D. NY).
- 5 See STAAR, *supra* note iii.
- 6 Russell, S. M. The effect of air sacculitis on bird weights, uniformity, fecal contamination, processing errors, and populations of *Campylobacter* spp. and *Escherichia coli*. *POULTRY SCI.* 82:1326-1331 (2003).
- 7 See Drug-Resistant Staph Germs' Toll Is Higher Than Thought, *Washington Post*, Oct. 17, 2007; Infection Killed 19,000 in 2005, Study Says, *New York Times*, October 16, 2007; Hearing on Drug Resistant Infections in the Community: Consequences for Public Health Before the House Oversight and Government Reform Committee, Nov. 7, 2007.
- 8 "Statement of Julie Louise Gerberding, M.D., M.P.H., Director, Centers for Disease Control and Prevention, Administrator, Agency for Toxic Substances and Disease Registry, U.S. Dept. of Health and Human Services, Hearing on Drug Resistant Infections in the Community: Consequences for Public Health Before the House Oversight and Government Reform Committee, Nov. 7, 2007.
- 9 *Id.*
- 10 *Id.*
- 11 Gerberding did not even mention veterinary use as a potential source of infections, nor did she implicate veterinary use when questioned during the hearing about its contribution to the problem. *Id.*
- 12 See, e.g., <http://www.keepantibioticsworking.com>.
- 13 The development of resistance is complicated, involves multiple factors and is "drug and bug" specific. The ability of an antibiotic to kill a bacteria is related to the mechanism of action of the antibiotic, the concentration of the antibiotic, and the genetic makeup of the organism, among other factors. One reason doctors advise patients to "finish their prescriptions" of antibiotics, even though they may be feeling better, is in order to lessen the chance that the "stronger" and more resistant bacteria will survive, multiply, become the dominant strain, and thereafter be more difficult to eradicate.
- 14 Department of Health and Human Services, Centers for Disease Control and Prevention, Questions and Answers Related to the 2007 FoodNet MMWR, at [http://www.cdc.gov/foodnet/QA\\_2007\\_MMWR.html](http://www.cdc.gov/foodnet/QA_2007_MMWR.html). The Foodborne Diseases Active Surveillance Network (FoodNet) is the principal food-borne disease com-
- 15 American Veterinary Medical Association, Issues, at <http://www.avma.org/issues/default.asp#antimicrobials>.
- 16 For a comprehensive discussion of CVM's regulation of veterinary drugs see R. Nicholas, K. McClure, "The Regulation of Biomedical Products for Animals," in *Biotechnology and the Law* (2007).
- 17 21 U.S.C. § 321(g) (emphasis added).
- 18 Animal vaccines and other biological products are not ordinarily subject to FDA jurisdiction but are instead subject to regulation by U.S. Department of Agriculture's Animal Plant Health Inspection Service ("APHIS") under the Virus-Serum-Toxin Act ("VSTA"), 21 U.S.C. §§ 151-159.
- 19 HHS/FDA, Final Decision of the Commissioner, Withdrawal of approval of the New Animal Drug Application for Enrofloxacin in Poultry," (Docket No. 200N-1571; July 27, 2005) pp. 93-100.
- 20 CVM's setting of drug residue tolerances largely mimics setting of food additive tolerances by FDA's Center for Food Safety and Applied Nutrition.
- 21 Final Decision of the Commissioner, *supra* note 19 at 93-100.
- 22 Center for Veterinary Medicine, Guidance for Industry, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Health Concerns," October 23, 2003 (Guidance # 152), at <http://www.fda.gov/cvm/Guidance/published.htm>.
- 23 See Veterinary Feed Directive, 21 C.F.R. Part 558; Feed Mill Licensure, 21 C.F.R. Part 515.
- 24 CVM has a web page on antibiotic resistance issues. See <http://www.fda.gov/cvm/antimicrobial.html>.
- 25 [http://www.fda.gov/cvm/narms\\_pg.html](http://www.fda.gov/cvm/narms_pg.html).
- 26 Guidance # 152, *supra* note xxii.
- 27 For example, the risk assessment for virginiamycin examines the potential food-animal use of streptogramin antimicrobials on resistance to chemically similar streptogramins used to treat human enterococcal infections. FDA, Notice, Draft Risk Assessment of Streptogramin Resistance in *Enterococcus faecium* Attributable to the Use of Streptogramins in Animals; Availability, 69 Fed. Reg. pp. 68384-68385 (November 24, 2004); CVM update, Nov. 2, 2005 at [http://www.fda.gov/cvm/CVM\\_Updates/Virginiaup.htm](http://www.fda.gov/cvm/CVM_Updates/Virginiaup.htm).
- 28 The VMAC recently recommended that CVM not approve a NADA for a veterinary antibiotic because of concerns about potential development of antibiotic resistance. Transcript, Official Meeting of the Veterinary Medicine Advisory Committee, New Drug Microbial Safety Review Under Guidance #152, September 26, 2006, at <http://www.fda.gov/cvm/VMAC/VMAC>.
- 29 FDA, Animal Drugs, Feeds, and Related Products; Enrofloxacin for Poultry; Withdrawal of Approval of New Animal Drug Application, 70 Fed. Reg. 44048-44049 (August 1, 2005). CVM also has authority to prohibit the extra label use of veterinary drugs and, in fact, has used its authority to ban such use of certain veterinary antibiotics because of concerns about development of antibiotic resistance. 21 C.F.R. § 530.41.
- 30 *Supra* note iii.