

# ANTIBIOTICS IN FOOD ANIMALS: THE CONVERGENCE OF ANIMAL AND PUBLIC HEALTH, SCIENCE, POLICY, POLITICS AND THE LAW

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## I. INTRODUCTION

The development of antibiotic resistance in human medicine has led to a global concern about our continued ability to control bacterial infections that result in human disease and death.<sup>1</sup> While there are many causes of antibiotic resistance, the antibiotic treatment of food animals has been increasingly blamed as an unnecessary risk to human health. With the decreasing effectiveness of many antibiotics universally, greater emphasis is placed on judicious antibiotic

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1. KENNETH H. MATHEWS, JR., USDA, ANTIMICROBIAL DRUG USE AND VETERINARY COSTS IN U.S. LIVESTOCK PRODUCTION, 1 (Agric. Info. Bulletin No. 766, 2001).

use to preserve efficacious use in both veterinary and human medicine.<sup>2</sup> Calls to prohibit use in food animals in deference to human health concerns have persisted for at least a quarter century, with increasing success. However, the evidence to support such bans is circumstantial and heavily contested by evidence demonstrating that the benefits to humans and animals far outweigh the minimal risk associated with continued use. The core of the debate involves a fundamental disagreement about the breadth and balance of risks and benefits that can be considered when analyzing the effects of antibiotic treatment of food animals.

Some public health advocates insist that a partial or total ban of antibiotic use in food animals is warranted to preserve antibiotic effectiveness for human illness, disregarding any benefits from continued use, or harm caused by denying access for animal treatment. There is particular concern about the use of antibiotics for growth promotion and feed efficiency which is considered by some to provide merely an economic benefit that therefore cannot justify the potential harm to human health. Additionally, ready access to these over-the-counter feed supplements creates concerns about their potential misuse. Alternatively, many animal health proponents maintain that the use of antibiotics in food animals—including those labeled for growth promotion—enhances food safety by providing for animal health and welfare which results in safer food and greater consumer protection.<sup>3</sup> They insist that decisions to alter or prohibit antibiotic use in food animals will negatively impact animal production and can result in increased animal illness and eventually increased human illness from exposure to contaminated food.<sup>4</sup>

Regulators and policy makers disagree about the extent to which benefits may be considered when evaluating the use of antibiotics in animals raised for food. In the United States, the governing statute requires proof of safety for humans and animals prior to approval of antibiotics by the Food and Drug Administration (FDA), but does not expressly limit or allow benefit analysis.<sup>5</sup> In the past,

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2. See generally Michael P. Doyle et al., *Antimicrobial Resistance: Implications for the Food System*, 5 COMPREHENSIVE REVIEWS IN FOOD SCIENCE & FOOD SAFETY 71, 72 (2006) (an Expert Report from the Institute of Food Technology); H. Harbottle et al., *Genetics of Antimicrobial Resistance*, 17 ANIMAL BIOTECH. 111, 120 (2006) (noting that risk assessment strategies are being developed to address the serious health risk posed by the emergence of human and veterinary resistant pathogens).

3. COMM'N OF THE EUROPEAN CMTYS., WHITE PAPER ON FOOD SAFETY 24 (2000), [http://ec.europa.eu/dgs/health\\_consumer/library/pub/pub06\\_en.pdf](http://ec.europa.eu/dgs/health_consumer/library/pub/pub06_en.pdf) [hereinafter COMMISSION].

4. See Randall S. Singer et al., *Modeling the Relationship Between Food Animal Health and Human Foodborn Illness*, 79 PREVENTIVE VETERINARY MED. 186, 197-198 (2007).

5. 21 U.S.C.A. § 355(b)(1) (2009).

the FDA considered benefits to animal health, the environment and the economy as well as harm resulting from prohibitions, when reviewing approval or withdrawal of approval for antibiotic use in food animals.<sup>6</sup> However, when issuing a final report withdrawing approval of an antibiotic used to treat a disease of poultry, the FDA Commissioner stated that benefits were not allowed to be considered when the agency reviews a new animal drug application (NADA) for food animals which potentially exposes humans to safety risks through food consumption.<sup>7</sup> While prior FDA decisions allowed for consideration of risk and benefit, the agency has increasingly rejected scientific findings that seriously question the risk to humans from continued use of antibiotics in animals, finding that such use benefits both animals and humans.<sup>8</sup> Public health advocates are equally upset by the FDA's failure to prohibit additional food animal antibiotics. A review of the statutes, case law and agency actions may help clarify the legal boundaries affecting the FDA's authority and the relevance of risk benefit analysis in legal considerations of food animal antibiotic use.

An understanding of this complex issue begins with a basic review of the pharmacological interactions of antibiotics and bacteria; the etiology<sup>9</sup> and epidemiology<sup>10</sup> of antibiotic resistance in animal and human populations; the risks and benefits of antibiotic use; and national and global aspects of food production. The issue cannot be adequately understood without also understanding the basic infrastructure of animal agriculture in the United States, including relevant animal welfare, environmental, economic and political components. We must then consider how to effectively balance all the variables—scientific, political and legal—to resolve the question of whether treatment of food animals with antibiotics creates a sufficient risk of harm to humans that such use should be restricted or prohibited.

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6. Withdrawal of Approval of the New Animal Drug Application for Enrofloxacin in Poultry, No. 2000N-1571, at 95 (Dep't Health & Human Servs. July 27, 2005) (final decision), available at <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=09000064804cddd9.pdf> [hereinafter *Withdrawal*].

7. *Id.* at 107.

8. See generally *Withdrawal*, *supra* note 6, at 98-100 (considering health risks and benefits in the past).

9. STEDMAN'S ONLINE MEDICAL DICTIONARY (27th ed. 2009), <http://www.stedmans.com/section.cfm/45> (etiology is "[t]he science and study of the causes of disease and their mode of operation").

10. *Id.* (epidemiology is "[t]he study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems").

## II. BACTERIA, ANTIBIOTICS, AND THE MECHANICS OF ANTIMICROBIAL RESISTANCE

Bacteria are single-celled microorganisms that existed on the planet before human evolution began.<sup>11</sup> Two types of bacteria exist in mammals: pathogenic, or disease-causing bacteria, and non-pathogenic, or commensal bacteria.<sup>12</sup> Enteropathogens are pathogens that inhabit mammalian digestive tracts and cause diarrhea or occasionally more serious systemic, multi-organ infections. Typical enteropathogens include campylobacter, Salmonella, Shiga toxin-producing *E. coli* and listeria, all of which are considered the common etiologic agents of human foodborne illness.<sup>13</sup> The commensal bacteria that normally do not cause disease greatly outnumber these pathogens, and the importance of antibiotic resistance in this bacterial population in humans or animals has not been adequately investigated.<sup>14</sup>

[H]uman oral antibiotic use might predispose some parts of the population to increased susceptibility to enteric clinical infection with food-animal enteric pathogens; there are few data for assessing how genes that code for resistance in bacteria move among and between bacterial species, and there is no concrete information on whether or how nonpathogenic bacteria exposed to antibiotics participate in the resistance emergence phenomenon.<sup>15</sup>

The scarcity of scientific research into the population dynamics of human enteropathogens and commensal bacteria, leads to important gaps in our understanding

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11. See MARK S. SMOLINSKI ET AL., MICROBIAL THREATS TO HEALTH: EMERGENCE, DETECTION, AND RESPONSE I (2003).

12. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (2007), <http://www.credoreference.com/entry/ehsdor/and/commensal> (commensal is "an organism living on or within another, but not causing injury to the host").

13. Dennis G. Maki, *Coming to Grips with Foodborne Infection—Peanut Butter, Peppers, and Nationwide Salmonella Outbreaks*, 360 NEW ENG. J. MED. 949, 951 (2009); see also CDC, Dep't Health & Human Servs., *Foodborne Illness Frequently Asked Questions*, Jan. 10, 2005, [http://www.cdc.gov/ncidod/dbmd/diseaseinfo/files/foodborne\\_illness\\_FAQ.pdf](http://www.cdc.gov/ncidod/dbmd/diseaseinfo/files/foodborne_illness_FAQ.pdf) ("The most commonly recognized foodborn infections are those caused by the bacteria Campylobacter, Salmonella, and E. coli O157:H7 . . .").

14. See RICHARD E. ISAACSON & MARY E. TORRENCE, THE ROLE OF ANTIBIOTICS IN AGRICULTURE 8 (2002) (from a meeting sponsored by the American Academy of Microbiology, Nov. 2-4, 2001); see also Scott A. McEwen, *Antibiotic Use in Animal Agriculture: What Have We Learned and Where Are We Going?*, 17 ANIMAL BIOTECH. 239, 240 (2006).

15. JAMES R. COFFMAN ET AL., Nat'l Research Council, THE USE OF DRUGS IN FOOD ANIMALS: BENEFITS AND RISKS 9 (1999).

of the role and impact these commensals play in the transmission of antibiotic resistance.

Antibiotics can be naturally occurring or synthetic, with bacteriocidal or bacteriostatic mechanisms of action. Bacteriocidal antibiotics kill bacteria, while bacteriostatic action inhibits bacterial growth.<sup>16</sup> These actions can vary with the concentration or dosage of the drug used.<sup>17</sup> Depending on the desired outcome, the same drug may be used at dosages that either kill or inhibit bacterial growth. Bacteria can develop resistance in the face of minimal or maximum antibiotic concentrations assuming as least some organisms survive treatment, but theoretically more resistant bacteria survive when exposed to bacteriostatic dosages.

Antibiotic resistant bacteria date back thousands of years, long before the discovery of penicillin by Alexander Fleming in 1929:<sup>18</sup>

[A]ntimicrobial resistant bacteria estimated at being over 2000 years old have been recovered from glacial samples obtained from the Canadian Arctic Archipelago, while a more recent study detected TEM-type  $\beta$ -lactamases from a metagenomic library of cold-seep sediments of deep-sea Edison seamount (near Papua New Guinea) estimated to be about 10,000 years old.<sup>19</sup>

While bacterial resistance initially developed naturally, the explosion of antibiotic resistance is believed to have resulted from selective pressure following exposure to man-made drugs.<sup>20</sup> Regardless of the method of resistance, bacteria exposed to antibiotics have evolved numerous mechanisms to survive such assaults.<sup>21</sup>

Consistent with other evolutionary selection mechanisms, resistant bacteria that survived exposure passed those traits to other bacteria.<sup>22</sup> Resistance may

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16. Steeve Giguère, *Antimicrobial Drug Action and Interaction: An Introduction*, in *ANTIMICROBIAL THERAPY IN VETERINARY MED.* 3, 5-6 (Steeve Giguère, et al. eds., 4th ed. Blackwell Publishing 2006).

17. *Id.* at 6.

18. Patrick Boerlin & David G. White, *Antimicrobial Resistance and Its Epidemiology*, in *ANTIMICROBIAL THERAPY IN VETERINARY MED.* 27, 32 (Steeve Giguère, et al. eds., 4th ed. Blackwell Publishing 2007).

19. See Harbottle et al., *supra*, note 2 at 112.

20. See José L. Martínez et al., *Antibiotics and Antibiotic Resistance Genes in Natural Environments*, *SCIENCE*, July 18, 2008 at 365 (noting the finding of antibiotic-producing microorganisms in soil as the origin from which resistance has primarily evolved).

21. Boerlin & White, *supra* note 18, at 27.

22. See Nat'l Antimicrobial Resistance Monitoring Sys., Dep't of Health & Human Servs., *Frequently Asked Questions (FAQ) About Antibiotic Resistance—Why are Bacteria Becoming Resistant to Antibiotics?* (2005), [http://www.cdc.gov/narms/faq\\_pages/3.htm](http://www.cdc.gov/narms/faq_pages/3.htm).

be inherited and passed to future generations, similar to hair and eye color in humans; or resistant traits may be shared between co-resident bacteria.

Sometimes one of the bacteria survives because it has the ability to neutralize or evade the effect of the antibiotic; that one bacteria can then multiply and replace all the bacteria that were killed off. Exposure to antibiotics therefore provides selective pressure, which makes the surviving bacteria more likely to be resistant. In addition, bacteria that were at one time susceptible to an antibiotic can acquire resistance through mutation of their genetic material or by acquiring pieces of DNA that code for the resistance properties from other bacteria. The DNA that codes for resistance can be grouped in a single easily transferable package. This means that bacteria can become resistant to many antimicrobial agents because of the transfer of one piece of DNA.<sup>23</sup>

While the pathophysiological mechanisms of bacterial resistance are beyond the scope of this discussion, we must recognize that resistant bacteria have now outpaced the discovery and development of new antibiotics, creating a risk of return to the pre-antibiotic era.<sup>24</sup> Before the advent of antibiotics, bacterial infections caused significant illness and death amongst human and animal populations.<sup>25</sup> Many fear that unless new pharmaceutical mechanisms are developed, bacteria will lose all susceptibility to antibiotics, medical treatments will fail and the expanding global human population will suffer from antibiotic-resistant infections with increased resultant mortalities. This concern is not new: it began almost as soon as the pharmacologic production of these drugs began.

### III. ETIOLOGY OF ANTIMICROBIAL RESISTANCE

As explained *infra*, antibiotics are used in human and veterinary medicine, aquaculture, horticulture—they exist in the environment both naturally and as contaminants. Sorting out how these uses create a quantifiable and unacceptable risk to human health is a task scientists have painstakingly analyzed for the past forty to sixty years. While scientific knowledge has expanded, significant gaps remain in our understanding of the physiologic and epidemiologic nature of antibiotic resistance and more specifically how it is influenced by interactions amongst species, space and time. These uncertainties present a serious challenge

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23. *Id.*

24. *Statement by Bernadette Dunham, D.V.M., PH. D., Director, Ctr. for Veterinary Med., FDA, Dep't of Health & Human Services, Before the Subcomm. on Livestock, Dairy, & Poultry of the H. Comm. on Agric., 110th Cong. 3 (2008), available at <http://agriculture.house.gov/testimony/110/h80925/Dunham.pdf> [hereinafter *Statement*]*

25. *See id.*

to policy-makers attempting to base important decisions on sound science. The uses and effects of antibiotic therapy are briefly outlined, including observations of the effects of antibiotic bans in European countries.

Humans and animals have both benefited from antibiotics used to forestall or eliminate bacterial infections that might otherwise have resulted in serious illness or death.<sup>26</sup> However, these benefits were accompanied by the development of bacterial resistance.<sup>27</sup> National and international public and animal health organizations, recognizing the impending expansion of pathogen resistance, have developed and encouraged the use of judicious-use guidelines in an attempt to preserve antibiotic effectiveness. The World Health Organization (WHO) has issued continuous warnings since 1978 about the impending global resistance of pathogens, blaming the problem on “the widespread and the indiscriminate use of antimicrobial drugs in man and animals.”<sup>28</sup>

Guidelines promoting judicious use of antibiotics in human medicine recommend elimination of wasteful practices including: under-dosing; prescribing antibiotics without pathogen culture and sensitivity-testing; prescribing antibiotics to appease the patient or family members pressuring the doctor for antibiotic prescriptions; and patient non-compliance in following prescribed dosages.<sup>29</sup> In some cases, doctors prescribe antimicrobials too frequently or inappropriately. Sometimes patients do not complete the prescribed course of an antimicrobial, making it more likely that surviving microbes will develop resistance.<sup>30</sup> Antibacterial resistance can develop even when prescriptions are medically necessary. However, eliminating irresponsible use would theoretically prolong antibiotic effectiveness by decreasing exposure to pathogen that developed resistance in the face of unnecessary treatment.

Antibiotic resistance resulting from non-judicious medical practice pales in comparison to hospital-transmitted infections (nosocomial infections).<sup>31</sup> Inten-

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26. *Id.*

27. *See id.* (explaining diminished benefits from continued antibiotic use).

28. *Animal Legal Def. Fund Boston, Inc. v. Provimi Veal Corp.*, 626 F. Supp. 278, 286 n.5 (D. Mass. 1986) (citing ORVILLE SCHELL, *MODERN MEAT* 18 (1984)).

29. *See generally* CDC, *Get Smart: Antibiotic Resistance Questions & Answers*, <http://www.cdc.gov/getsmart/antibiotic-use/antibiotic-resistance-faqs.html> (last visited Nov. 25, 2009); CDC, *Fast Facts About Antibiotic Resistance*, <http://www.cdc.gov/getsmart/antibiotic-use/fast-facts.html> (last visited Nov. 25, 2009).

30. *Statement, supra* note 24, at 2-3.

31. *See* GRO BRUNDTLAND, WORLD HEALTH ORG., *WORLD HEALTH REPORT ON INFECTIOUS DISEASES 2000, OVERCOMING ANTIMICROBIAL RESISTANCE*, ch. 3 (2000), <http://www.who.int/infectious-disease-report/2000/index.html>.

sive care units, where antibiotics are used extensively, provide the ideal setting for the establishment and transmission of resistant pathogens to patients already compromised by their immuno-suppressed condition.<sup>32</sup> One of the most prevalent nosocomial infections, methicillin-resistant *staphylococcus aureus* (MRSA), has now spread beyond the hospital environment, establishing community-associated infections.<sup>33</sup>

While antibiotic use in humans is considered the greatest risk factor in the development of pathogen resistance, humans are also susceptible to resistant pathogen transmission from companion animals, the environment and antibiotic-treated or pathogen-contaminated produce, and food animals.<sup>34</sup> The risk from exposure to treated companion animals (pets) is a potentially significant yet commonly overlooked factor in the prevalence of antibiotic resistance. Human interaction with companion animals has been evolving throughout history, beginning with the domestication of the dog in the late pre-agricultural period of man's evolution over 10,000 years ago, and as currently reflected by our ever-growing infatuation with pet ownership.<sup>35</sup> Zoonotic infections, including bacteria that can be spread between humans and animals, have been the focus of public health concern for some time.<sup>36</sup> Increased animal-human contact has been identified as one of the greatest risk factors for emerging zoonotic diseases.<sup>37</sup>

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32. Robert E. Siegel, *Emerging Gram-Negative Antibiotic Resistance: Daunting Challenges, Declining Sensitivities, and Dire Consequences*, 53 RESPIRATORY CARE 471, 472 (2008).

33. Scott K. Fridkin et al., *Methicillin-Resistant Staphylococcus Aureus Disease in Three Communities*, 352 NEW ENG. J. MED. 1436, 1437 (2005), available at <http://content.nejm.org/cgi/reprint/352/14/1436/pdf> (discussing emergence of MRSA infection within the community).

34. Peter M. Rabinowitz et al., *Pet-Related Infections*, 76 AM. FAM. PHYSICIAN 1315, 1318 (2007); BRUNDTLAND, *supra* note 31, at ch. 3.

35. See Sherwood L. Washburn & C.S. Lancaster, *The Evolution of Hunting*, in MAN THE HUNTER 293, 294 (Richard B. Lee & Irven Devore eds. 1968); see also K. Kris Hirst, About.com, *Dog History: How were Dogs Domesticated?*, <http://archaeology.about.com/od/domestications/qt/dogs.htm> (last visited Nov. 25, 2009).

36. See generally WHO, *Zoonoses and Veterinary Public Health (VPH)*, <http://www.who.int/zoonoses/en/> (last visited Nov. 25, 2009) (any disease and/or infection which is naturally "transmissible from vertebrate animals to man" is classified as a 'zoonosis'); see also CDC, *The CDC Leaders: Lonnie King, DVM*, <http://www.cdc.gov/about/leadership/leaders/king.htm> (last visited Nov. 25, 2009).

37. Rabinowitz et al., *supra* note 34, at 1314.



Current reports estimate that nearly 60% of households in the United States include pets.<sup>38</sup> Of the 7.6 million households with pets, about half considered their pets to be family members.<sup>39</sup> One of the measurements of family status was the provision of veterinary care which includes antibiotic treatment of bacterial infections.<sup>40</sup> Humans and animals share susceptibility to many bacteria and are treated with similar classes of antibiotics. Therefore treating pets for bacterial infections presents a risk of transmission of any surviving, resistant pathogens between pets and their families.<sup>41</sup> The risk of exposure increases proportionally with increased human-animal interaction. Sharing homes, beds and food, and failing to wash hands after handling pets facilitates sharing of disease organisms, including *Campylobacter* and *Salmonella*, also considered foodborne pathogens.<sup>42</sup> Exposure to asymptotically-infected (carrier) dogs and cats has resulted in an estimated 200,000 cases of human gastroenteritis.<sup>43</sup> Multi-drug resistant *Salmonella* in contaminated pet food has been identified as a high risk factor, particularly for children.<sup>44</sup>

Even when diseases result primarily from human exposure, animals are often erroneously implicated as the etiologic source, as recent news coverage of MRSA infections in animals demonstrates. MRSA, as described *supra*, represents the greatest overall prevalence of antibiotic resistance in humans.<sup>45</sup> There is widespread acknowledgment that hospitals created and spread MRSA in human populations, but with the identification of MRSA in pets and food animal species, blame has shifted to animals, particularly food animals.<sup>46</sup> While cases of MRSA infection in pets are rising, the American Veterinary Medical Association

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38. Elizabeth Weise, *We Really Love—and Spend on—Our Pets*, U.S.A. TODAY, Dec. 10, 2007, available at [http://www.usatoday.com/life/lifestyle/2007-12-10-pet-survey\\_N.htm](http://www.usatoday.com/life/lifestyle/2007-12-10-pet-survey_N.htm) (citing a survey released that day by the American Veterinary Medical Association).

39. *See id.*

40. *Id.*

41. *See* Rabinowitz et al., *supra* note 34, at 1318.

42. *Id.* at 1314.

43. *Id.* at 1318.

44. *Id.*

45. Robin J. Bywater & Mark W. Casewell, *An Assessment of the Impact of Antibiotic Resistance in Different Bacterial Species and of the Contribution of Animal Sources to Resistance in Human Infections*, 46 J. ANTIMICROBIAL CHEMOTHERAPY 643, 643 (2000).

46. *See generally* E. van Duijkeren et al., *Transmission of a Panton-Valentine Leucocidin-Positive, Methicillin-Resistant Staphylococcus Aureus Strain Between Humans and a Dog*, 43 J. CLINICAL MICROBIOLOGY 6209, 6210 (2005) (finding that PVL-positive MRSA might emerge in the hospital environment and has recently been found in animals).

notes that humans are the likely cause of these animal infections.<sup>47</sup> However, once infected, the pets may transmit the bacteria to others in the home, requiring antibiotic treatment of all human and animal household residents.<sup>48</sup>

While MRSA has been identified in livestock and humans associated with livestock, the strains are usually different than those isolated from hospitals and community-based outbreaks.<sup>49</sup> The mere identification of a resistant pathogen in food animals is insufficient evidence of transmission to humans. As with pets, humans may be the source of infection.<sup>50</sup> Despite *de minimis* evidence that swine are the root of the problem, a New York Times Op-Ed columnist recently implied that a definite link exists between the 18,000 fatal MRSA human infections reported by the Centers for Disease Control and Prevention (CDC) and infected swine.<sup>51</sup> Experts from the United Kingdom and the United States refute those claims. In the U.K., experts considered animal sources unlikely causes of resistance in human MRSA infections.<sup>52</sup> A U.S. Congressional report, comparing risk of human exposure from hospital-based infections with potential exposure through food animals came to similar conclusions:

While the use of antibiotics in food animals can cause resistance emergence, not all instances of resistance are clinically significant, involve resistance in pathogens, or cause an actual illness. In contrast, because the occurrence of infection in hospitals is often considered life-threatening, the risk to human health of hospital-acquired infections might be thought of as a greater risk.<sup>53</sup>

Even exotic animals have acquired human-transmitted MRSA infections.<sup>54</sup> In 2008, an elephant calf requiring intensive neonatal care was infected

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47. Am. Veterinary Med. Ass'n, *Education is Key to Combating Rise in MRSA*, JAVMA NEWS, Jan. 15, 2009, <http://www.avma.org/onlnews/javma/jan09/090115g.asp>.

48. See, e.g., van Duijkeren et al., *supra* note 46, at 6209 (showing the treatment plan used for one family).

49. Olivier Denis et al., *Methicillin-Resistant Staphylococcus Aureus ST398 in Swine Farm Personnel, Belgium*, EMERGING INFECTIOUS DISEASES 1, 1 (2009), available at <http://www.cdc.gov/eid/content/15/7/pdfs/08-0652.pdf>.

50. van Duijkeren et al., *supra* note 46, at 6209.

51. Nicholas D. Kristof, Op-Ed., *Pathogens in Our Pork*, N.Y. TIMES, Mar. 15, 2009, at WK.

52. Bywater & Casewell, *supra* note 45, at 643.

53. MATHEWS, *supra* note 1, at 1-2 (quoting Office of Technical Assessment, U.S. Congress, *Impacts of Antibiotic-Resistant Bacteria* (OTA-H-629 1995)).

54. See D. Janssen et al., *Methicillin-Resistant Staphylococcus Aureus Skin Infections from an Elephant Calf – San Diego, California, 2008*, 301 J. Am. Med. Ass'n 1872, 1872 (2009), available at <http://jama.ama-assn.org/cgi/content/full/301/18/1872>.

with MRSA by a human handler at the San Diego Zoo.<sup>55</sup> Transmission occurred when caretakers, later identified as subclinical carriers of MRSA, failed to adhere to universal sanitary precautions.<sup>56</sup> Certain activities, including grooming, bottle feeding, medicating, and trunk blowing (to stimulate nursing) were identified as heightened risk factors.<sup>57</sup> A total of twenty human cases (suspected or confirmed) were identified, but all the other elephants tested negative for infection.<sup>58</sup> The epidemiologic investigation clearly identified humans as the source of this outbreak.<sup>59</sup>

Other sources of human exposure to resistant bacteria include the consumption of fruit treated with antibiotics to eliminate bacterial infections or produce contaminated with human or animal-based fertilizers.<sup>60</sup> Antibiotics and other pharmaceutical compounds have also been identified in U.S. watersheds and drinking water in major cities.<sup>61</sup> These potential sources of resistant pathogens have been inadequately considered when analyzing overall causation of antibiotic resistance in humans.

The full extent of the antibiotic resistance problem remains unknown and the use of antibiotics in agriculture is only one of many factors that contributes to antibiotic resistance in humans.<sup>62</sup>

#### IV. ANTIBIOTICS IN FOOD ANIMALS

The greatest criticism of antibiotic use in animals involves the treatment of food animals. Humans may be exposed to infectious bacteria from direct con-

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55. *Id.*

56. *Id.* at CDC Editorial Note.

57. *Id.* at 1872.

58. *Id.*

59. *Id.*

60. Matthew Cimitile, *Crops Absorb Livestock Antibiotics, Science Shows*, ENVTL. HEALTH NEWS, Jan. 6, 2009, <http://www.environmentalhealthnews.org/ehs/news/antibiotics-in-crops>; SHANE ROGERS & JOHN HAINES, ENVTL. PROTECTION AGENCY, DETECTING AND MITIGATING THE ENVIRONMENTAL IMPACT OF FECAL PATHOGENS ORIGINATING FROM CONFINED ANIMAL FEEDING OPERATIONS: REVIEW 46 (2005), available at <http://www.epa.gov/ORD/NRMRL/pubs/600r06021/600r06021.pdf>.

61. *U.S. Drinking Water Contains Wide Variety of Pharmaceuticals*, HEALTH DAY, Mar. 10, 2008, available at 2008 WLNR 4699333.

62. U.S. GEN. ACCOUNTING OFFICE, FOOD SAFETY: THE AGRICULTURAL USE OF ANTIBIOTICS AND ITS IMPLICATIONS FOR HUMAN HEALTH, GAO/RCED-99-74, at 5 (1999), available at <http://www.gao.gov/archive/1999/rc99074.pdf>.

tact during animal production, slaughter or processing; or indirectly, through foodborne contamination.<sup>63</sup>

Farm workers and pharmaceutical technicians who work with antibiotic compounds, feeds, feed premixes, and concentrates, and people who work with sick and therapeutically treated animals also could be at greater risk for clinical resistance . . . [but] [d]ata suggest that most human disease scenarios associated with food-animal pathogens are related to enteric diseases contracted principally through consumption of pathogen-contaminated foods.<sup>64</sup>

Antibiotics have been used in food animals for more than fifty years and the transfer of resistant pathogens from cattle, swine and poultry to farmers and animal handlers has been documented without evidence of increased disease in this at-risk population.<sup>65</sup> No evidence of human disease was detected in people living on or near a farm with known transmission of resistant pathogens spread from exposure to chickens fed medicated poultry feed.<sup>66</sup>

In the first reported case of ceftriaxone-resistant salmonella infection in the United States.; a 12-year-old boy who was recovering from an appendectomy and following a course of antibiotic treatment for a sinus infection developed cephalosporin-resistant salmonellosis while hospitalized.<sup>67</sup> Sick cattle from one herd were culture-positive for the same strain of Salmonella.<sup>68</sup> Cattle from the child's herd were positive for a similar but different strain of Salmonella.<sup>69</sup> The report concluded that the cattle produced resistant pathogens after they were treated with cephalosporin antibiotics, but no history of antibiotic use in these herds was reported by the farmers.<sup>70</sup> The conclusion that antibiotic treatment in cattle presented a human health risk in this case, is not supported by facts.<sup>71</sup> Alternate sources of infection or explanations were not described.<sup>72</sup>

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63. COFFMAN ET AL., *supra* note 15, at 73.

64. *Id.* at 8.

65. Doyle et al., *supra* note 2 at 72, 93.

66. *Id.* *Contra* U.S. GEN. ACCOUNTING OFFICE, ANTIBIOTIC RESISTANCE: FEDERAL AGENCIES NEED TO BETTER FOCUS EFFORTS TO ADDRESS RISK TO HUMANS FROM ANTIBIOTIC USE IN ANIMALS. GAO-04-490, at 18 (2004) [hereinafter ANTIBIOTIC RESISTANCE].

67. Doyle et al., *supra* note 2 at 93; Paul D. Fey et al., *Ceftriaxone-Resistant Salmonella Infection Acquired by a Child from Cattle*, 342 NEW ENG. J. MED. 1242, 1242-1243 (2000).

68. *See* Fey et al., *supra* note 67, at 1246-1247.

69. *Id.* at 1247.

70. *Id.* at 1243, 1247.

71. *But see id.* at 1247.

72. *Id.* at 1247-1248.

The possibility that both cattle and humans could have been exposed to the same source of *Salmonella* was not discussed in the case study. Clustering of human and animal salmonellosis has been observed,<sup>73</sup> but the nidus of infection, whether through domestic or wild animals, vegetation or water, must be determined on a case-by-case basis.<sup>74</sup> The allegation that antibiotic treatment resulted in resistant bovine pathogens may also be erroneous. Isolation of tetracycline and penicillin-resistant *E. coli* pathogens have been cultured from herds and flocks with no prior antibiotic treatment.<sup>75</sup> Finally, since prior antibiotic usage in humans has been identified with the increased risk of subsequent resistant pathogen infections, the child's recent antibiotic treatment may have facilitated his salmonella infection.<sup>76</sup>

While direct contact between humans and food animals may present a low risk for resistant pathogen transmission, foodborne illness caused by human exposure to pathogens in food represents a greater potential risk for the transmission of resistant organisms and is a significant public health concern. To understand how antibiotics used in food animals may contribute to foodborne disease, the indications for treatment and the structure of animal agriculture in this country must be considered. Antibiotic usage in food animals falls into one of two broad categories: therapeutic and subtherapeutic use.<sup>77</sup> Therapeutic use includes treatment of: clinically ill animals, those infected but without evidence of illness, healthy animals with known or anticipated exposure to sick animals, and animals expected to develop illness secondary to certain unavoidable physical stressors.<sup>78</sup> While there is a universal acceptance of treatment of diseased animals with antibiotics not used in human medicine, treatment to prevent the incidence or spread

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73. See J. Oloya et al., *Evaluation of Salmonella Occurrence in Domestic Animals and Humans in North Dakota (2000-2005)*, 4 *FOODBORNE PATHOGENS & DISEASE* 551, 561 (2007).

74. See MO SALMAN ET AL., CO. STATE UNIV., *GLOBAL FOOD SYSTEMS AND PUBLIC HEALTH: PRODUCTION METHODS AND ANIMAL HUSBANDRY IN THE UNITED STATES* 100 (2008), <http://www.cvms.colostate.edu/APHI/> (follow "Report (PDF)" hyperlink under "Technical Report") (illustrating broad range of sources responsible for infection).

75. See T.W. Alexander et al., *Effect of Subtherapeutic Administration of Antibiotics on the Prevalence of Antibiotic-Resistant Escherichia Coli Bacteria in Feedlot Cattle*, 74 *APPLIED & ENVTL. MICROBIOLOGY* 4405, 4406 (2008).

76. Doyle et al., *supra* note 2, at 111.

77. See COFFMAN ET AL., *supra* note 15, at 4 (defining therapeutic and subtherapeutic use).

78. See *generally id.* (describing therapeutic uses of antibiotics in food animals).

of disease is increasingly criticized.<sup>79</sup> These treatment regimes have been labeled, “subtherapeutic” or “nontherapeutic” by critics, even though they were developed by animal scientists and veterinarians and are used in modern production settings, where animals are raised in large groups, to maintain animal health.<sup>80</sup>

Given the close proximity of the animals to one another (commingling), physiological and environmental stressors, and immature immune systems, any underlying viral infections, or bacterial respiratory or enteric diseases that may occur in a few animals can spread to others, including entire herds or flocks. Within the limits of the production system, and depending on the nature of the disease, the producer and/or veterinarian may intervene in such situations by medicating the entire group via the feed or water rather than treating each affected animal.<sup>81</sup>

In addition to criticism over the practice of treating large groups of clinically normal animals to prevent illness, the method of delivery—by feed or water—is also criticized. Concerns involve the potential for imprecise dosages delivered to individual animals, which may increase the risk of pathogen resistance if inadequate antibiotic concentrations result.<sup>82</sup> However, this method of treatment is the least stressful for the animals, and the only practical way of administering antibiotics to large numbers of animals to prevent and treat illness.

Subtherapeutic treatment occurs when food animals are fed low dosages of antibiotics in medicated feeds for the labeled purpose to enhance growth while improving feed efficiency.<sup>83</sup> Subtherapeutic dosages are generally, but not always lower than concentrations used for disease treatment, and are often fed for at least two weeks. Medicated feeds may be used intermittently to coincide with stressful situations, such as weaning or transportation, or for longer durations without specific indications. The approval process and oversight of antibiotics administered through animal feed is stringently regulated by FDA, but critics object to the ease of access to medicated feeds by producers, without a veterinary prescription, which they believe may lead to unnecessary use.<sup>84</sup> As importantly, some

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79. See H. Scott Hurd et al., *Public Health Consequences of Macrolide Use in Food Animals: A Deterministic Risk Assessment*, 67 J. FOOD PROTECTION 980, 980 (2004) (noting the use of antibiotics for disease prevention has been suggested as a cause of antibiotic resistance).

80. See COFFMAN ET AL., *supra* note 15, at 4.

81. Doyle et al., *supra* note 2, at 78.

82. COFFMAN ET AL., *supra* note 15, at 4.

83. *Id.*

84. Thomas R. Shryock & Stephen W. Page, *Growth Promotion Uses of Antimicrobial Agents*, in *ANTIMICROBIAL THERAPY IN VETERINARY MEDICINE* 389, 393 (Steeve Giguère et al. eds., 4th ed. Blackwell Publishing 2006).

critics believe that the sole benefit from subtherapeutic use is economic and insist that human health should take precedence over financial gain.<sup>85</sup>

While not as important as human health, the economic benefits derived from antibiotic use in food animals are significant for producers and consumers. Antimicrobial treatment under experimental conditions increases animal growth by 1-15% which reduces feed costs and time to market, produces higher yields, and decreases animal illness and death.<sup>86</sup> Veterinary costs of dairy, beef, pork, and broiler production are estimated at \$1.6 billion per year.<sup>87</sup> Food animal antibiotic bans are predicted to increase consumer costs by more than \$700 million per year for pork alone.<sup>88</sup> Increased costs to producers, passed on to consumers, must be weighed against the medical expenses resulting from antibiotic use in food animals if proven to cause human harm. Human antimicrobial resistance costs in the 1990's were estimated at \$100-200 million.<sup>89</sup> Assuming the worst case scenario, that food animal antibiotics contribute to human disease, only 10% of those costs are estimated to be food animal related.<sup>90</sup> Actual costs must be determined from data documenting the extent of antibiotic use in both human and animal populations and the actual human health harm from antibiotic resistance that results. The controversy over the use of subtherapeutic antibiotics is confounded by conflicting data about the prevalence of and risks of antibiotic use in human and veterinary medicine and conflicting evidence over its animal health benefits.<sup>91</sup>

To adequately understand the risk factors associated with antibiotic use, accurate data capturing the type, amounts, and duration of antibiotics used in various settings must be obtained. Unfortunately exact quantities of antibiotics used in human and animal medicine are not known and estimates vary significantly with the source of the data.<sup>92</sup> The Union of Concerned Scientists (UCS), a public health advocacy group intent on banning antibiotic use in food animals,

85. See generally COFFMAN ET AL., *supra* note 15, at 1-2 (noting drug use is fundamental to economics of the industry, but has negative effects on humans).

86. COFFMAN ET AL., *supra* note 15, at 74.

87. See MATHEWS, *supra* note 1, at 5.

88. ANTIBIOTIC RESISTANCE, *supra* note 66, at 14.

89. Doyle et al., *supra* note 2, at 112.

90. MATHEWS, *supra* note 1, at 1.

91. See *id.*; *Concerning Advancements of Animal Health Within the Livestock Industry: Hearing Before the H. Subcomm. on Livestock, Dairy & Poultry*, 110th Cong. 3 (2008) (testimony of Christine Hoang, Assistant Dir. American Veterinary Medical Association), available at <http://agriculture.house.gov/testimony/110/h80925/Hoang.doc> [hereinafter *Concerning Advancements*].

92. MATHEWS, *supra* note 1, at 1; *Concerning Advancements*, *supra* note 90, at 4.

extrapolated from agricultural surveys to estimate that 70% of the antibiotics in the United States are used for non-therapeutic agricultural purposes.<sup>93</sup> The Animal Health Institute (AHI), an animal health industry trade association, rejected this estimate and, relying on member-submitted reports, found that 87% of antibiotic use in food animals is therapeutic and 13% is for subtherapeutic use.<sup>94</sup> Notably, the UCS and AHI use different definitions for non-therapeutic and subtherapeutic use, contributing to the discrepancy of their findings.<sup>95</sup> Without accurate data, projections about the impact of future bans on antibiotic usage in food animals are unpredictable. National and international pressure to create reliable and robust databases tracking antibiotic use has been mounting.<sup>96</sup> The FDA's efforts to require reporting of antibiotic use in food animals have been bolstered by a recent amendment to the Food and Drug Cosmetic Act (FDCA), mandating expanded reporting.<sup>97</sup>

The most debated questions about antibiotic resistance involve the mechanism and extent to which subtherapeutic use benefits or harms animals and humans, and the harm that might result if this use were prohibited. Some public health advocates and animal rights activists consider subtherapeutic use equivalent to non-therapeutic use, deny that any health benefits result, and insist such use unnecessarily risks human health. On the other hand, supporters of subtherapeutic treatment argue that the practice enhances both animal and human health by modifying or eliminating intestinal bacterial organisms. This primary action has significant animal health, welfare and food safety benefits including:

[E]nhance[ed]...efficiency of nutrient utilization . . . . allow[ing] increased lean muscle gain to be added per pound of feed consumed, resulting in an overall reduction in feed consumption . . . . reduced fecal output, lessening the environmental burden from excess nutrients such as nitrogen and phosphorous . . . . maintaining a stable fermentation process within the rumen, small intestine and hindgut of ruminants [that] . . . . decreases the likelihood of metabolic disorders, such as ketosis, [and] can reduce emissions of methane, an important greenhouse gas . . . . reduced

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93. MARGARET MELLON ET AL., HOGGING IT: ESTIMATES OF ANTIMICROBIAL ABUSE IN LIVESTOCK at xiii (2001), available at [http://www.ucsusa.org/food\\_and\\_agriculture/science\\_and\\_impacts/impacts\\_industrial\\_agriculture/hogging-it-estimates-of.html](http://www.ucsusa.org/food_and_agriculture/science_and_impacts/impacts_industrial_agriculture/hogging-it-estimates-of.html).

94. ANIMAL AGRIC. ALLIANCE, STATEMENT BY THE ANIMAL AGRICULTURE ALLIANCE COALITION ON ANTIMICROBIAL RESISTANCE 2 (2009), [http://www.animalagalliance.org/images/ag\\_insert/Pew/Antibiotic\\_Resistance.pdf](http://www.animalagalliance.org/images/ag_insert/Pew/Antibiotic_Resistance.pdf).

95. Doyle et al., *supra* note, 2 at 88.

96. *Id.*

97. 21 U.S.C.A. § 360 (2008) (noting that the APUA and FAAIR recommend the data be made available, and guidelines have been proposed by OIE and UPUA's Advisory Committee on Animal Antimicrobial Use Data Collection).



need for the animal's immune system to respond, thus contributing to a healthier animal and improvement in animal welfare . . . . suppression of potential pathogens that may be present in low numbers can prevent important enteric diseases, which in a group setting, benefits overall flock or herd health and welfare . . . . reduce[d] the variation in size of slaughter animals. . . . thereby simplify[ing] carcass processing and improve[ing] the quality of the meat product.<sup>98</sup>

The primary food safety benefits result from the decreased overall bacterial load in the animal, which decreases bacterial contamination of food ultimately handled and consumed by humans.<sup>99</sup> While health benefits are most significant, there are important secondary economic and environmental benefits that also occur. The feed efficiency created by medicated feeds decreases the amount of land required for crop production. Further environmental benefits result from decreased manure and methane gas production resulting from consumption of medicated feeds. These benefits, combined with improved animal health, create an economic cushion that sustains the viability of U.S. producers.

The prohibition of subtherapeutic antibiotics in Europe, beginning in 1986, provides evidence of the intended and unintended effects of these bans.<sup>100</sup> Except for a slight decrease in vancomycin-resistant enterococci, the expected decrease in the incidence of resistant human pathogens did not occur.<sup>101</sup> Instead, prevalence of many resistant human pathogens increased, in some cases up to 49% of the pre-ban incidence.<sup>102</sup> This may have resulted from the increased use of veterinary-prescribed antibiotics required to treat food animals experiencing significantly increased disease and death following the removal of subtherapeutic antibiotics.<sup>103</sup> Humans may have been exposed to more resistant pathogens from the sick animals treated with antibiotics also used in human medicine. The use of similar antibiotics in human and veterinary medicine is common and in this case, the shift from subtherapeutic to therapeutic antibiotics in animals resulted in increased use of these antibiotics in animals to treat disease. This shift was also observed in 1970, following a similar ban in the U.K. that was also intended to

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98. Shryock & Page, *supra* note 84, at 395.

99. Singer et al., *supra* note 4, at 187.

100. Mark Casewell et al., *The European Ban on Growth-Promoting Antibiotics and Emerging Consequences for Human and Animal Health*, 52 J. ANTIMICROBIAL CHEMOTHERAPY 159, 159 (2003) [hereinafter *European Ban*].

101. *Id.* at 159-60.

102. *Concerning Advancements*, *supra* note 91, at 7.

103. See Louis A. Cox, Jr. & Paolo F. Ricci, *Causal Regulations vs. Political Will: Why Human Zoonotic Infections Increase Despite Precautionary Bans on Animal Antibiotics*, 34 ENVTL. INT'L 459, 466 (2008); see also *European Ban*, *supra* note 100, at 160.

decrease the prevalence of antibiotic resistance: “[T]he Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (the Swann Report) warned that uncontrolled use of similar antibiotics in humans and food animals could promote the emergence of resistant strains of foodborne bacteria that could endanger human health.”<sup>104</sup> While the overall use of food animal antibiotics decreased following the European ban, these bans appear to have unintended harmful effects in both human and animal populations.<sup>105</sup> In other instances, a decrease was documented in the prevalence of certain resistant pathogens in animals, but an unexplained increased prevalence was concurrently observed in humans.<sup>106</sup> Antibiotic-resistant enterococci increased in prevalence by 25% in humans, while decreasing by 8-20% in poultry and swine.<sup>107</sup>

This demonstrates that the correlation between antibiotic usage in food animals and humans must be more extensively explored before a definitive cause and effect can be established. Additionally, these unexpected results should help inform policies about the future use of antibiotics in food animals. It appears that the risk to humans would increase, not decrease, if administration of antibiotics were limited to therapeutic usage. Further harm would result if antibiotics considered important for human medicine were entirely prohibited from use in food animals, since few alternate efficacious treatments are available.

The Preservation of Antibiotics for Medical Treatment Act of 2009 (PAMTA), recently introduced in Congress, would harm animal and human health by prohibiting the use of medically important human antibiotics “for non-therapeutic purposes in food-producing animals.”<sup>108</sup> “Nontherapeutic use” as defined in the bill, prohibits the use of antibiotics unless the animal exhibits signs of illness:

The term ‘nontherapeutic use,’ with respect to a critical antimicrobial animal drug, means any use of the drug as a feed or water additive for an animal in the absence of

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104. Cox, Jr. & Ricci, *supra* note 103, at 459.

105. *European Ban*, *supra* note 100, at 159.

106. Cox, Jr. & Ricci, *supra* note 103, at 466.

107. *Concerning Antimicrobial Resistance: Before the Senate Comm. On Health Education, Labor and Pensions*, 110th Cong. 2008 (statement of Lyle P. Vogel, Assistant Executive Vice President, Am. Veterinary Med. Ass’n), available at [http://www.avma.org/press/testimonies/vogel\\_testimony\\_080624.asp](http://www.avma.org/press/testimonies/vogel_testimony_080624.asp).

108. Preservation of Antibiotics for Medical Treatment Act of 2009, H.R. 1549, 111th Cong. § 3 (2009).

any clinical sign of disease in the animal for growth promotion, feed efficiency, weight gain, routine disease prevention, or other routine purpose.<sup>109</sup>

If enacted, PAMTA would likely eliminate the use of subtherapeutic and therapeutic use that normally prevents the entry or spread of disease to non-infected cohorts.<sup>110</sup> Proponents believe that such treatment would be unnecessary with simple modifications to animal husbandry practices.<sup>111</sup> A persisting misperception, cited in the bill, states that antibiotics are used in modern agricultural settings to “[compensate] for crowded, unsanitary, and stressful farming and transportation conditions.”<sup>112</sup>

Intensive livestock agriculture that uses subtherapeutic doses of antibiotics has led to the emergence of antibiotic strains of *Salmonella*, *Campylobacter*, and *Escherichia coli* bacteria. Overcrowded and mixed livestock practices . . . can facilitate interspecies host transfer of disease agents, leading to dangerous novel pathogens, such as SARS and new strains of influenza.<sup>113</sup>

Unless raised in germ-free environments, however, animals will always be susceptible to infectious diseases, with increased transmissibility in larger production units. The infrastructure of animal agriculture in the United States involves the comingling of large numbers of animals within constructed environments. In 2004, more than 8 billion chickens (broilers), 264 million turkeys, 103 million hogs and 37 million head of cattle were produced.<sup>114</sup> Since 1987, more animals are raised on a smaller number of farms, with increased productivity, resulting from fundamental improvements in technology, nutrition, and genetics.<sup>115</sup>

Whether raised inside or outdoors, the co-location of large numbers of animals results in the increased likelihood of disease transmission. Those raised indoors are spared the effects of weather extremes, environmental hazards, predation, parasitic infestation and diseases spread through vectors (insects and wild animals). However, once a pathogen is introduced in an indoor environment,

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109. *Id.* at § 4(a).

110. *See id.* at § 4(c).

111. *See generally id.* at § 2.

112. *Id.* at § 2(5).

113. RASHID HASSAN ET AL., ECOSYSTEMS AND HUMAN WELL-BEING: CURRENT STATE AND TRENDS 393 (2005).

114. Doyle et al., *supra* note, 2 at 79-80.

115. JAMES M. MACDONALD & WILLIAM D. MCBRIDE, USDA, THE TRANSFORMATION OF U.S. LIVESTOCK AGRICULTURE: SCALE, EFFICIENCY, AND RISKS, at iii, 2 (Elec. Info. Bulletin No. 43, 2009), available at <http://www.ers.usda.gov/publications/eib43>.

more animals may be infected.<sup>116</sup> Comparisons of disease prevalence in animals raised in cages, buildings and outdoors have demonstrated the advantages and disadvantages of these management practices. In Sweden, morbidity and mortality of chickens raised in indoor cages with indoor litter-based systems and free-range conditions were compared.<sup>117</sup> Free-range chickens had the highest rates of cannibalism, bacterial and parasitic infections, while the caged birds experienced the highest incidence of viral infections.<sup>118</sup> Overall, non-caged birds were found to be more prone to disease.<sup>119</sup> In another study, antibiotic-free hogs raised outdoors had 54% and 7% seroprevalence rates for *Salmonella* and *Toxoplasma*, respectively, compared with 39% and 1% rates in conventionally raised hogs.<sup>120</sup> Only outdoor-raised swine were seropositive to *Trichinella*, a swine parasite that can infect humans through consumption of undercooked meat.<sup>121</sup> However, the number of animals raised together creates the greatest risk of disease transmission, whether raised indoors or outside.

The number of animals raised for food is driven by consumer demand, here and abroad, and is expected to increase as the global population continues to expand to approximately nine billion by 2050.<sup>122</sup> “Since 1960, global meat production has tripled; milk production has doubled, and egg production has increased four-fold . . . . A 2004 report indicated that between 2000 and 2030, global meat production was expected to increase by 1.9% per annum until 2015 and then by 1.5% per annum until 2030.”<sup>123</sup> Claims that antibiotics are only used in animal agriculture because animals are raised in filthy settings that would be remedied by simply moving animals to pasture, are scientifically and medically unsupported.

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116. OFFICE OF TECH. ASSESSMENT, DRUGS IN LIVESTOCK FEED 4 (1979) available at <http://www.princeton.edu/~ota/disk3/1979/790s/790s.PDF> (describing how cleaning large production units would not be practical).

117. See Tim Lundeen, *Free-Range Chickens More Prone to Disease*, FEEDSTUFFS, JAN. 26, 2009.

118. *Id.* at tbl.

119. *Id.*

120. Wondwossen A. Gebreyes et al., *Seroprevalence of Trichinella, Toxoplasma, and Salmonella in Antimicrobial-Free and Conventional Swine Production Systems*, 5 FOODBORNE PATHOGENS & DISEASE 199, 201 (2008).

121. *Id.* at 200-201.

122. Population Div., U.N., *World Population Prospects: The 2004 Revision* (2005), available at [http://www.un.org/esa/population/publications/WPP2004/World\\_Population\\_2004\\_chart.pdf](http://www.un.org/esa/population/publications/WPP2004/World_Population_2004_chart.pdf).

123. SALMAN ET AL., *supra* note 74, at 12-13.

To those who believe that the solution is a return to a pastoral, early-20th-century model with millions of small farms producing more “natural” food, I would point out that even if the millions of farm workers who would be required were available to produce food on a quasi-boutique scale, the costs would be enormous; it would be impossible to feed 300 million Americans, let alone the rest of the world. Efficient, industrialized production of huge quantities of food is an inescapable necessity to avoid food shortages and global famine.<sup>124</sup>

Assuming the number of animals produced for food will not decrease, antibiotics should not be prohibited in food animal production without definitive evidence of harm to human health, so that animal health does not unnecessarily suffer. However, greater emphasis should be placed on prudent antibiotic use in all species, and research into antibiotic alternatives should be encouraged and funded.

Antibiotic use should be targeted to maximize the effectiveness of treatment in food animals: “[T]he magnitude of the response to antibacterial agents varies with stage of life cycles, stage of production, and the environmental conditions to which animals are exposed . . . . The response is greater during critical stages of production such as weaning, breeding, farrowing or immediately post hatching in chicks and turkeys.”<sup>125</sup> Subtherapeutic antibiotics that provide medical advantages, in addition to increased growth and feed efficiency, can be relabeled for therapeutic treatment, requiring veterinary oversight, thereby limiting over-the-counter and possibly, unnecessary use. Vaccines developed to reduce the incidence of infections requiring antibiotic treatment have been successful; an *E. coli* vaccine produced for cattle has recently been conditionally approved by USDA.<sup>126</sup> Further developments in this area should be pursued. Unfortunately, other alternatives to antibiotics in food animal production have not been as successful. Neither probiotics, that may work to increase beneficial intestinal bacteria and interfere with pathogens, nor *mannan oligosaccharides*, sugars that theoretically interfere with bacterial attachment to the intestinal lining, have enhanced growth or feed efficiency in clinical trials in pigs.<sup>127</sup>

However, proven methods in food production and distribution have significantly decreased bacterial contamination of meat and poultry, with concomitant decreases in the incidence of *Salmonella* and *Campylobacter* confirmed hu-

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124. Maki, *supra* note 13, at 951-52.

125. Shryock & Page, *supra* note 84, at 390-91 (citation omitted).

126. The Associated Press, *Nation's First E. coli Vaccine for Cattle Approved*, Mar. 12, 2009, available at <http://www.msnbc.msn.com/id/29665562/>.

127. A.F. Harper & M.J. Estienne, *Efficacy of Three Potential Alternatives to Antimicrobial Feed Additives for Weanling Pigs*, 18 PROF. ANIMAL SCIENTIST 343, 343, 349 (2002), available at <http://pas.fass.org/content/18/4/343.full.pdf+html>.

man foodborne infections.<sup>128</sup> These successes have been partially attributed to the Hazard Analysis and Critical Control Points (HACCP) system, initiated by the U.S. Department of Agriculture (USDA) in 1995 and adopted by FDA.<sup>129</sup> This comprehensive program identifies and attempts to eliminate hazards of food contamination throughout all critical points in food production.<sup>130</sup> Expanding this system to on-farm production may help minimize contamination before processing and identify methods to reduce environmental contamination from pathogens in manure. Adequate manure management should minimize the infiltration of water supplies from unintended spillage, or crop contamination with resistant pathogens in animal-produced fertilizers. Finally, practices that increase exposure to contaminated foods, such as raw milk consumption, should be discouraged; while technologies that reduce bacterial contaminants like irradiation, pasteurization, freezing and refrigeration should be encouraged.<sup>131</sup>

#### V. THE LAW AND ANTIBIOTICS IN FOOD ANIMALS

The legal debate surrounding the use of antibiotics in livestock in the U.S. spans decades. The FDA is squarely at center stage, interpreting the governing statute as informed by case law and scientific evidence from epidemiologic and surveillance data used in ever-evolving risk assessment models. The FDA has predominantly upheld existing uses of antibiotics and medicated feeds despite increasing pressure to ban such uses. “As of 2007, the US FDA has withdrawn only one antibiotic, enrofloxacin, a fluoroquinolone used to cure fatal respiratory illnesses in chickens.”<sup>132</sup> The FDA’s failure to prohibit subtherapeutic antibiotic use has been criticized by some public health advocates, while the decision to withdraw approval of one poultry antibiotic has been denounced by animal health advocates joined by the pharmaceutical and animal agricultural industries. All interested parties agree that risk analysis must form the founda-

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128. See Elizabeth Ailes et al., *Continued Decline in the Incidence of Campylobacter Infections, FoodNet 1996-2006*, 5 *FOODBORNE PATHOGENS & DISEASE* 329, 334 (2008); see also Singer et al., *supra* note 4, at 187.

129. Nat’l Advisory Comm. on Microbiology Criteria for Foods, USDA, Hazard Analysis and Critical Control Point Principles and Application Guidelines, Aug. 14, 1997, <http://www.cfsan.fda.gov/~lrd/bghaccp.html>.

130. *Id.*

131. See Justin Denny et al., *Outbreak of Escherichia Coli O157:H7 Associated with Raw Milk Consumption in the Pacific Northwest*, 5 *FOODBORNE PATHOGENS & DISEASE* 321, 327 (2008); see, e.g., Hurd et al., *supra* note 79, at 984.

132. Cox, Jr. & Ricci, *supra* note 103, at 465.

tion on which food safety policy is based,<sup>133</sup> but there is little agreement about the particular assessment tool to use, as well as great disagreement about the extent to which both benefit and risk may be considered. There are additional conflicts over the validity and strength of data relied upon in analyses, yet all agree that more robust, reliable data is required. All of these factors create a tension between scientists and legal scholars which gives rise to an infectious legal environment, making it difficult for objectivity to prevail and the law to provide the

The federal authority governing antibiotic use in food animals falls largely upon the FDA which approves applications of new animal drugs for sale. The FDA also regulates the manufacture and distribution of antibiotics used in animals, as prescribed by veterinarians or through access to licensed feed mills that add specific antibiotics to animal feed in subtherapeutic dosages for growth promotion.<sup>134</sup> Once medicated animal feeds are approved by the FDA, they are available over the counter without veterinary oversight.<sup>135</sup> Two other federal agencies, the CDC and USDA, assist FDA with the collection of pathogen resistance data from human and animal populations, food processors, and distributors.<sup>136</sup>

Congress gave the FDA authority to approve new animal drugs<sup>137</sup> and withdraw prior approvals pursuant to the FDCA.<sup>138</sup> The statute is administered by the FDA Commissioner with input from the Director, Center for Veterinary Medicine (CVM), using decisional law to supplement statutory interpretation. While the safety of drugs approved by FDA must be determined with regard to human health, that is not the only parameter the agency must consider:

The FDCA and its regulations establish complicated procedures by which new drugs proposed to be used in treating animals both subtherapeutically as feed additives and therapeutically, are approved before they can be marketed. Human safety is specifically considered, because it is in animals raised for food that these drugs and feeds will be used.<sup>139</sup>

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133. Hurd et al., *supra* note 79, at 980.

134. ANTIBIOTIC RESISTANCE, *supra* note 66, at 15; *see* 21 U.S.C.A. § 360b(m) (2008).

135. *See* Animal Legal Def. Fund Boston, Inc. v. Provimi Veal Corp., 626 F. Supp. 278, 282 (D. Mass. 1986).

136. ANTIBIOTIC RESISTANCE, *supra* note 66 at 15.

137. 21 U.S.C.A. § 321(v) (2009) (“The term ‘new animal drug’ means any drug intended for use for animals other than man, including any drug intended for use in animal feed. . .”).

138. *See* 21 U.S.C.A. § 360b(c) (2008).

139. Animal Legal Defense Fund Boston, Inc., 626 F. Supp. at 284 (citing 21 U.S.C.A. § 360b(d)(2) (2008)).

Prior to approving a new animal drug application, the FDA must determine that the drug is safe and effective for its intended use and that any residue that may exist in animal-based food is safe with regard to human health.<sup>140</sup> “[S]afe” as used in the animal drug sections of the FDCA “has reference to the health of man or animal.”<sup>141</sup> There are several ‘safety clauses’ in the statute which acknowledge the inherent risks of drug use, yet provide for their use under prescribed guidelines. The statute also references a number of considerations in addition to safety that must be considered.

Animal drugs with identified risks may be approved, at dosages that do not result in residue levels, pursuant to 21 U.S.C. §360b(a)(4)(B):

(B) If the Secretary finds that there is a reasonable probability that a use of an animal drug authorized under subparagraph (A) may present a risk to the public health, the Secretary may—

(i) establish a safe level for a residue of an animal drug when it is used for such different use authorized by subparagraph (A);

In addition to human safety, other factors the Secretary “shall” consider, when reviewing new animal drug approvals include:

(A) the probable consumption of such drug and of any substance formed in or on food because of the use of such drug, (B) the cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance, (C) safety factors which in the opinion of experts, qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal experimentation data . . .<sup>142</sup>

Finally, when considering withdrawal of prior approval, based on new evidence of risks to human and animal safety, the Secretary must consider this information along with the facts included in the initial drug application, including those mentioned above:

(e)(1) The Secretary shall . . . issue an order withdrawing approval of an application. . . if the Secretary finds...

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140. See generally 21 C.F.R. § 514.1(b)(8) (2007) (allowing drugs to be refused if reports show they are not safe).

141. 21 U.S.C.A. §321(u) (2009).

142. 21 U.S.C.A. §360b(d)(2) (2008).



. . . (B) that new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved or that subparagraph (I) of paragraph (1) of subsection (d) of this section applies to such drug.<sup>143</sup>

The statute appears to provide the flexibility needed to consider the benefits of use, negative impacts from prohibited use, and the myriad of other factors relevant to antibiotic use in food animal production, in addition to the overarching concerns about human safety. “The production and consumption of food is central to any society, and has economic, social and, in many cases, environmental consequences. Although health protection must always take priority, these issues must also be taken into account in the development of food policy.”<sup>144</sup>

Until recently, the FDA acknowledged the importance of the benefits of antibiotic use in response to comments of regulatory proposals.<sup>145</sup> In 1977, when abandoning a proposal to withdraw approval of sulfonamide drugs in animal feeds,<sup>146</sup> the agency remarked on the importance of continued access to these drugs to maintain animal health. At that time, antibiotics had been used safely and effectively in billions of animals for nearly twenty years and this use was considered pivotal in maintaining the health of these animals raised in concentrated and intensified production systems.<sup>147</sup> “The Commissioner acknowledges the benefit from such drugs, when properly used, [including] increased rate of gain, improved feed efficiency, and animal disease control. Immediate and total withdrawal of these drugs from animal feeds could seriously disrupt the quality and quantity of an important portion of our total human diet.”<sup>148</sup>

The Commissioner commented that, “[t]he concept of “safety” as used in the act does not require complete certainty of the absolute harmlessness of a drug, but rather the reasonable certainty in the minds of competent scientists that it is not harmful, *when balanced against the benefits to be obtained from the*

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143. 21 U.S.C.A. § 360b(e)(1), (e)(1)(B) (2008).

144. COMMISSION, *supra*, note 3, at 6.

145. See ISAACSON & TORRENCE, *supra* note 14, at 6.

146. See Penicillin-Containing Premixes: Opportunity for Hearing, 42 Fed. Reg. 43772, 43774 (Aug. 30, 1977) (codified at 21 C.F.R. § 558.15).

147. New Animal Drugs 38 Fed. Reg. 76,9811, 76,9811 (Apr. 20, 1973).

148. *Id.* at 76,9812.

drug.”<sup>149</sup> The FDA required enhanced testing and reporting of antibiotic use, but declined to ban the use of sulfonamides in all animal feed without sufficient evidence of harm to humans to counterbalance the benefits.<sup>150</sup>

Following a similar proposal in 1977 to withdraw approval of subtherapeutic use of penicillin and tetracycline, the FDA again determined there was insufficient evidence of harm to human health, relying on equivocal data from the National Academy of Sciences.<sup>151</sup> Since that time, FDA has continued to revisit the question of subtherapeutic use. However, both former and current FDA-CVM directors continue to recognize the value of properly managed antibiotic use in food animals, despite some risks, noting that “[w]hile potential public health concerns must be addressed, it is critical that veterinarians continue to have access to effective antimicrobial drugs for the treatment, control, and prevention of disease in animals.”<sup>152</sup>

The federal courts have confirmed this position. In 1974, the D.C. Circuit reviewed an FDA decision to withdraw approval of a food animal hormone and concluded that since drugs were inherently unsafe to some degree, decisions allowing continued sales of drugs with demonstrated risks required the agency to determine whether the benefits of use outweighed the risk of use.<sup>153</sup> In another case, the Supreme Court, reviewing the FDA’s decision on the approval of a cancer drug for terminal patients, acknowledged that, “Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk. Thus, the Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use.”<sup>154</sup> Several years later, the Court, while rejecting the FDA’s assumed authority over tobacco, nevertheless upheld FDA’s reasoning that allowed for considerations of risks of continued use and the effects of a withdrawal, “[i]n determining whether a device is safe under the Act, it must consider ‘not only the risks presented by a product but also any of the countervailing effects of use of that product, including

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149. *Id.* (emphasis added).

150. *Id.* at 76,9813.

151. Elizabeth Barclay, *Subtherapeutic Use of Antibiotics in Animal Feed: In Light of an Unresolved Clash of Expert Paradigms Should We Punt to the Consumer in Decade Four?* 4 (1998), <http://leda.law.harvard.edu/leda/data/195/ebarclay.html>.

152. *Statement, supra* note 24, at 10.

153. *Hess & Clark, Div. Rhodia, Inc. v. FDA*, 495 F.2d 975, 993-994 (D.C. Cir. 1974).

154. *United States v. Rutherford*, 442 U.S. 544, 555-556 (1979) (discussing the safety of a drug used to treat terminally ill patients).

the consequences of not permitting the product to be marketed.<sup>155</sup> Based on these court decisions, FDA's 2005 decision to withdraw approval of the new animal drug application (NADA) for use of the fluoroquinolone enrofloxacin in poultry, without any consideration of benefits, seems inconsistent.

At least since this 2005 decision, The FDA rejects the consideration of benefits when reviewing the safety of drugs with regard to the safety of food produced for human consumption.<sup>156</sup> In its Final Decision, the FDA Commissioner remarked:

I find that the FDCA as a whole, as well as its legislative history, makes clear that Congress did not intend to allow FDA to weigh costs or benefits associated with the use of a new animal drug in deciding whether its use has been shown to be safe for humans when used in food-producing animals. . .

. . . .

. . . [The] FDA is not authorized under the FDCA to weigh economic, health, or other benefits that the drug provides against a health risk to the ultimate human consumers of food from or contaminated by treated animals.<sup>157</sup>

No benefits of any kind are relevant when assessing the human safety of a new animal drug used in a food-producing animal.<sup>158</sup> The FDA follows a two-step analysis to determine first, that the drug is safe and effective in the animal, and then determines that any food produced from the animal presents a reasonable certainty of no harm to humans.<sup>159</sup>

Based on this analysis, FDA concluded that enrofloxacin, a fluoroquinolone antibiotic used to treat a respiratory condition of poultry (air sacculitis), created resistant *Campylobacter* species in poultry resulting in reasonable certainty of harm to humans.<sup>160</sup> While there is agreement that fluoroquinolone-resistant *Campylobacter* was isolated from poultry and poultry products following its approval, respondent Bayer and amicus Animal Health Institute insist that proof of harm to humans was not sufficiently proven.<sup>161</sup> In addition to rejecting

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155. FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 139 (2000).

156. Withdrawal, *supra* note 6, at 100.

157. *Id.* at 94, 120.

158. *Id.* at 93-94.

159. *Id.*

160. *Id.* at 82.

161. See Respondent Bayer Corp.'s Reply to CVM's Post-Hearing Brief, at 4, *In re* Enrofloxacin for Poultry, No. 00N-1571 (Ct. Aug. 15, 2003) [hereinafter Respondent].

the bulk of the scientific evidence relied upon by the FDA, there was disagreement about the FDA's ability to consider the benefits of antibiotic use for animals and humans.<sup>162</sup>

The Commissioner rejected consideration of all benefits in his analysis, including those permitted by the agency's Administrative Law Judge, "to the extent it deals with human health effects, *i.e.*[,] whether the human health benefits of using the drug outweigh the human health risks from use of the drug."<sup>163</sup> In addition to a lengthy review of the legislative evolution of the FDCA, the Commissioner referenced two Supreme Court decisions in support of his decision.<sup>164</sup> However, reliance on each of these cases may be flawed.

In *American Textile Manufacturers. Institute, Inc. v. Donovan*, the issue was whether a cost/benefit analysis was permitted by OSHA when establishing a cotton dust standard.<sup>165</sup> The Court held that a cost-benefit analysis was not required for consideration because it was not expressly included in statutory language, but a feasibility analysis was required.<sup>166</sup> This case is distinguishable from the FDA's enrofloxacin decision. First, while safety is a consideration for both the FDA and OSHA, respectively, the statutes in question have sufficiently different language to preclude a cross interpretation from the statute in *Donovan* to the FDCA.<sup>167</sup> The critical language in the OSHA statute required consideration of human safety, "to the extent feasible."<sup>168</sup> There is no similar language in the FDCA.<sup>169</sup> Therefore, the Court's conclusion in *Donovan* does not necessarily direct FDA action pursuant to the FDCA. Equally important, as Chief Justice Rehnquist noted in his dissent, while the Court did not require a cost-benefit analysis, they also did not conclude that such consideration was prohibited, "at least as to the 'Cotton Dust Standard,' the Act does not require the Secretary to engage in a cost-benefit analysis, which suggests of course that the Act *permits* the Secretary to undertake such an analysis if he so chooses."<sup>170</sup> Therefore, the

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162. See Withdrawal, *supra* note 6, at 93 (noting that Bayer believed a cost-benefit or risk benefit analysis should be used while the FDA did not).

163. *Id.* at 94.

164. *Id.* at 100-103 (discussing *Donovan* and *American Trucking*).

165. *Am. Textile Mfrs. Inst., Inc. v. Donovan*, 452 U.S. 490, 495 (1981).

166. *Id.* at 509.

167. See *generally id.* at 508 (stating that their starting point of analysis was the language of the statute).

168. *Id.*

169. See *generally* 21 U.S.C.A. §360b (2008) (requiring human safety to the extent feasible).

170. *Am. Textile Mfr. Inst. Inc.*, 452 U.S. at 509, 544.

FDA Commissioner's reliance on *Donovan* to prohibit his consideration of risk-benefit is not valid.

In the second case, *Whitman v. American Trucking Associations*, the Court reviewed the provisions required in the Clean Air Act (CAA) for the Environmental Protection Agency's (EPA) establishment of national ambient air quality standards (NAAQSs), for ozone and particulate matter.<sup>171</sup> The Court found that Congress had recognized, but did not permit, the consideration of economic factors when establishing NAAQSs:

In particular, the economic cost of implementing a very stringent standard might produce health losses sufficient to offset the health gains achieved in cleaning the air—for example, by closing down whole industries and thereby impoverishing the workers and consumers dependent upon those industries. That is unquestionably true, and Congress was unquestionably aware of it.<sup>172</sup>

However, as in the FDCA where Congress recognizes the multiple variables involved even in matters affecting public health and safety, Congress allowed for the consideration of other factors in other CAA statutory sections:

Congress . . . not only anticipated that compliance costs could injure the public health, but provided for that precise exigency. Section 110(f)(1) of the CAA permitted the Administrator to waive the compliance deadline for stationary sources if, *inter alia*, sufficient control measures were simply unavailable and “the continued operation of such sources is *essential . . . to the public health* or welfare.” (citation omitted). Other provisions explicitly permitted or required economic costs to be taken into account in implementing the air quality standards.<sup>173</sup>

Therefore, the Commissioner's reliance on this case may also be faulty. Instead of supporting the FDA's new position, both cases may support the FDA's previous approach to subtherapeutic antibiotics that allowed for consideration of factors in addition to human safety. However, until the FDA's interpretation is reviewed by the Courts, or readdressed by Congress, they will likely continue their current line of reasoning.

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171. *Whitman v. Am. Trucking Ass'ns*, 531 U.S. 457, 462 (2001).

172. *Id.* at 466.

173. *Id.* at 466-67.

## VI. APPLICATION OF RISK ASSESSMENT IN ANTIBIOTIC TREATMENT OF FOOD ANIMALS

Fortunately, the FDA's policies and regulations allow for and recommend the use of risk assessments in the application process for new animal drug approvals.<sup>174</sup> Risk assessment is considered integral to the regulation of antibiotic use in the United States. "In contrast, in 1998, the European Union banned five antibiotics . . . including streptogramins, macrolides, and fluoroquinolones by appeal to the Precautionary Principle . . . [N]o [risk assessment] predicting human (or animal) health consequences was considered necessary."<sup>175</sup> In the United States, all parties agree that risk assessments are essential to provide objective, science-based information to help inform the decision-making process:

[M]any government regulatory authorities, industry associations, and other organizations are proposing that risk assessment (RA) methods be applied to the issue of antibiotic resistance associated with food-producing animals. An RA combines information on the consequence of an event with the probability of occurrence of that event, within the current state of technology and common practice.<sup>176</sup>

However, there are many types of risk assessments, and both the type and process of choosing the risk assessment creates additional conflicts. The difficulties inherent with risk assessments have been recognized by other agencies also reliant upon their use. The EPA, concerned about the validity of its risk assessments to identify human risk, recently requested assistance from the National Research Council to assess and improve upon their risk analysis tools.<sup>177</sup> The Council found that reliance on risk assessments was increasingly used as a primary tool to ensure public health, and specifically "to address broader environmental questions, such as life-cycle analysis and issues of costs, benefits, and risk-risk tradeoffs."<sup>178</sup> They identified the criticality of addressing uncertainty and variability within the risk-assessment process:

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174. FDA, GUIDANCE FOR INDUSTRY: EVALUATING THE SAFETY OF ANTIMICROBIAL NEW ANIMAL DRUGS WITH REGARD TO THEIR MICROBIOLOGICAL EFFECTS ON BACTERIA OF HUMAN HEALTH CONCERN, No. 152, 3 (2003), <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf> [hereinafter FDA].

175. Cox, Jr. & Ricci, *supra* note 102, at 465 (citations omitted).

176. Hurd et al., *supra* note 78, at 980.

177. NAT'L RESEARCH COUNCIL, SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT 4 (2009), available at [http://www.nap.edu/catalog.php?record\\_id=12209](http://www.nap.edu/catalog.php?record_id=12209) [hereinafter SCIENCE AND DECISIONS].

178. *Id.* at 3.

Uncertainty can be reduced by the use of more or better data. Variability is an inherent characteristic of a population, inasmuch as people vary substantially in their exposures and their susceptibility to potentially harmful effects of the exposures. Variability cannot be reduced, but it can be better characterized with improved information.<sup>179</sup>

Variability is the heart of a valid risk assessment model for antibiotic resistance analysis.<sup>180</sup> A risk assessment is only predictive if it can analyze the multiple factors that impact the prevalence of resistant pathogens. The FDA's selection of a simplistic risk assessment to evaluate the risk of enrofloxacin use in poultry was criticized since it excluded considerations of issues other than the risk to human health, despite the relevance of other complex factors.<sup>181</sup> Notably, the FDA has abandoned this particular risk assessment tool and adopted others.

There are two basic types of risk assessments used to analyze antibiotic resistance: quantitative tools measuring the amount of resistant pathogens present or qualitative tools that identify the presence of resistant bacteria. While quantitative assessments identify the concentration of pathogens, qualitative tools do not measure pathogen concentrations. This deficiency has been heavily criticized, since establishing the dose of resistant pathogens needed to result in human harm is considered a fundamental factor in disease pathogenesis. While reviewing human risk associated with Salmonella exposure from eggs and poultry, the WHO considered quantitative tools the best predictive measure of microbial loads.<sup>182</sup> The National Research Council also recommended quantitative assessments and "encourage[d] EPA to move toward the long-term goal of quantifying population variability more explicitly in exposure assessment and dose-response relationships."<sup>183</sup> Furthermore, the failure to use quantitative assessments may yield erroneous results, leading policy makers to disallow practices that are not harmful to human health.<sup>184</sup>

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179. *Id.* at 6.

180. *Id.*

181. See CATHERINE E. WOTEKI, USDA & JANE E. HENNEY, U.S. DEP'T HEALTH & HUMAN SERVS., USDA/HHS RESPONSE TO HOUSE AND SENATE REPORTS: AGRICULTURE, RURAL DEVELOPMENT, FOOD AND DRUG ADMINISTRATION, AND RELATED AGENCIES, APPROPRIATIONS BILL 2000, ANTIBIOTIC RESISTANCE IN LIVESTOCK, at 2 (2000), available at <http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/UCM134733.pdf>.

182. WHO & FOOD & AGRIC. ORG. OF THE U.N., RISK ASSESSMENTS OF SALMONELLA IN EGGS AND BROILER CHICKENS: INTERPRETIVE SUMMARY 18 (2002), available at [http://www.who.int/foodsafety/publications/micro/en/salm\\_summary.pdf](http://www.who.int/foodsafety/publications/micro/en/salm_summary.pdf)

183. SCIENCE AND DECISIONS, *supra* note 177, at 7.

184. See Singer et al., *supra* note 4, at 199 (pointing out the harm to humans could be entirely missed if focus was on prevalence of contamination rather than microbial load).

Even though the currently recommended tool by the FDA is a qualitative analytical model,<sup>185</sup> a draft quantitative risk assessment was recently published by FDA evaluating whether virginiamycin, a streptogramin antibiotic used in food animals for over 20 years, presents a risk to human health following the 1999 approval of the human antibiotic equivalent, Synercid®.<sup>186</sup> The report concluded that there was insufficient evidence that use in animals resulted in transmission of resistant organisms to people with resulting harm.<sup>187</sup> Without the quantitative analysis applied, a different conclusion may have been reached. Fortunately, the tools used for risk assessment have begun to evolve, incorporating both quantitative and qualitative measurements that capture dose-response data required to determine the actual risk of infection, as described below.

Not only must the risk assessments be reliable, they require accurate, reliable data obtained from robust national surveillance systems to provide valid data points for sound analysis. The current surveillance systems in use to collect data from human and animal populations and in food production systems remain suboptimal and yield inconsistent results, adding to discrepancies between scientists and officials studying the issue.<sup>188</sup> Surveillance data is collected by FDA, CDC and USDA:

FDA, CDC, and USDA have six surveillance activities ongoing to identify and assess the prevalence of resistant bacteria in humans, animals, or retail meat... [National Animal Resistance Monitoring System] NARMS and Collaboration in Animal Health, Food Safety and Epidemiology (CAHFSE)—focus on antibiotic resistance from animals. The other four activities—Foodborne Diseases Active Surveillance Network (FoodNet), PulseNet, PulseVet, and National Animal Health Monitoring System (NAHMS)—focus on foodborne disease or animal health in general. . . .<sup>189</sup>

Surveillance includes bacterial isolation from human and animal samples, farm animals, carcasses, slaughter plants, meat, and other animal derived foods.<sup>190</sup> The bacterial varieties monitored have varied over time, but currently include: Sal-

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185. FDA, *supra* note 174, at 5.

186. H. GREGG CLAYCAMP & BARRY H. HOOBERMAN, FDA CTR. FOR VETERINARY MED., RISK ASSESSMENT OF STREPTOGRAMIN RESISTANCE IN ENTEROCOCCUS FAECIUM ATTRIBUTABLE TO THE USE OF STREPTOGRAMINS IN ANIMALS: VIRGINIAMYCIN RISK ASSESSMENT, at iii (2004), *available at* <http://www.fda.gov/downloads/AnimalVeterinary/NewsEvents/CVMupdates/UCM054722.pdf>.

187. *Id.*

188. ANTIBIOTIC RESISTANCE, *supra* note 66, at 7.

189. *Id.* at 27.

190. *Id.* at 28.



monella, Campylobacter, E. coli, Enterococcus and Shigella.<sup>191</sup> Laboratory testing methods and the concentrations of bacteria considered critical also vary, making comparisons of data obtained difficult, if not impossible.

These discrepancies were one source of contention between FDA and Bayer in the Enrofloxacin decision.<sup>192</sup> Bayer identified flaws in laboratory methods used in scientific studies reviewed by FDA, and demonstrated how the variant critical concentrations of pathogens identified in epidemiological findings skewed results, invalidating conclusions.<sup>193</sup> Scientists and policy makers must establish universally acceptable, science-based testing methods, critical pathogen concentration points and surveillance tools so that uniform data is available for analysis in appropriate risk assessment tools.

## VII. RISK ASSESSMENT FACTORS FOR CONSIDERATION IN FOODBORNE ILLNESS

Once the risk assessment model is chosen and the data used for analysis is reliable and robust, there must be agreement about the quantity and quality of factors to be considered. As discussed before, a simplistic model that allows only for the consideration of human health risks cannot provide an understanding of the overall impact of antibiotic use in food animals. For an adequate understanding, variables affecting human and animal risk and benefits must be considered.

Of the 76 million annual CDC-estimated cases of foodborne illness in the United States, only a fraction are laboratory-confirmed bacterial infections,<sup>194</sup> and an undetermined portion of those cases involve bacteria transmitted from food animals. To result in human harm, food animals treated with antibiotics must produce resistant bacteria that contaminate the food products marketed to consumers.<sup>195</sup> Following improper product handling and preparation exposure that allows the bacteria to survive, the person must become infected, instead of merely exposed to bacteria transiting through their intestinal tracts. Finally the resistant bacteria must either cause a more serious disease than its non-resistant counterpart, or require treatment that fails as a result of the antibiotic resistance

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191. Doyle et al., *supra* note 2 at 96.

192. See Respondent, *supra* note 161, at 3.

193. *Id.* at 46.

194. See CDC, *Preliminary FoodNet Data on the Incidence of Foodborne Illnesses—Selected Sites, United States, 1999*, 49 MORBIDITY AND MORTALITY WKLY REP. 201, 201 (2000).

195. Nat'l Coop. Grocers Ass'n, *Antibiotics in Meats, Medicine and Produce*, <http://www.ncga.coop/newsroom/antibiotics> (last visited Nov. 25, 2009).

created. Bayer described these required levels of causation of fluoroquinolone-resistant-*Campylobacter* gastroenteritis in humans:

Even if enrofloxacin use selects for fluoroquinolone ("FQ") resistant *Campylobacter* ("CP") in poultry (which it does), and even if clinically relevant microbial loads of FQ-resistant CP are transferred from chickens or turkeys (which does not seem to occur detectably often under current conditions), such resistance does not harm human health unless FQ-resistant infections in humans are worse in some way than FQ-susceptible infections.<sup>196</sup>

The FDA found sufficient proof of reasonable harm to humans from continued use of this antibiotic to treat poultry disease, despite evidence that *Campylobacter* resistance in humans decreased during the period of time this drug was used in poultry in the U.S.<sup>197</sup> Risk factors that were insufficiently considered in FDA's analysis, but may have yielded a different result include: human disease caused by international travel or prior antibiotic exposure; prevalence of resistant pathogens in humans eating poultry in commercial establishments compared with home consumption; increase in enteropathogens in poultry and poultry products following removal of access to enrofloxacin; and greater overall risk to human health resulting from enrofloxacin bans.

It seems reasonable to include all of these relevant factors in a risk assessment attempting to analyze the interrelated parameters of this complex issue. If the use or lack of use of antibiotics in food animals can result in human harm, both alternatives should be considered. Fortunately, the statutory language provides for the inclusion of impacts to animal health in any analysis.

"The health status of food animals destined to enter the human food supply chain is an important, although often overlooked, factor in predicting the risk of human foodborne infections."<sup>198</sup> Without antibiotics, a greater number of food animals processed will have higher levels of intestinal pathogens that will contaminate carcasses and processed food.<sup>199</sup> Failure to treat certain bacterial diseases can result in diminished intestinal integrity leading to increased contamination at slaughter.<sup>200</sup> Whether the risk of increased microbial carcass contamination is greater than the risk of exposure to a smaller number of potentially resistant pathogens is a question that must be captured in the analysis and considered by policy-makers. The benefit to animals and humans of antibiotic use

196. Respondent, *supra* note 161, at 1.

197. *Id.* at 2; Withdrawal, *supra* note 6, at 45.

198. Singer et al., *supra* note 4, at 187.

199. *Id.* at 188.

200. *Id.* at 187.

compared with the risk of transmission of resistant pathogens can be incorporated in the robust risk assessment models recently developed:

[They] evaluate the relationship between on-farm animal health status, animal health interventions and human foodborne disease risks. [By] assessing pre-harvest animal health intervention strategies, such as the use of antibiotics in animals, and the potential human health risks and benefits from these interventions.<sup>201</sup>

When applied to scenarios in which important human antibiotics are used to treat animals, these tools have demonstrated minimal risk of antibiotic treatment failure in humans (less than one in 10 million *Campylobacter* and one in three billion *E. faecium* human infections).<sup>202</sup> A study, analyzing the removal of a medicated feed for poultry, predicted “[an] increased rate of clinically and subclinically ill animals [that] could harm human health by increasing the level of *Campylobacter*-contaminated chicken.”<sup>203</sup> Another study, examining the benefits and risks of continued access to virginiamycin, a food animal antibiotic following the release of a similar human drug, predicted that 6,660 additional cases of human campylobacteriosis would result if this drug were no longer available for the treatment of food animals.<sup>204</sup>

The effects of bans on animal health must be considered in terms of the welfare of the animals in addition to the increased costs resulting from animal illness and death. Animal welfare suffers with increased disease and death. While economic benefits of antibiotic use cannot outweigh harm to human health, detriments to animal health cannot be discounted merely as an economic loss. For those who may not consider animal health an important independent consideration, there is ample evidence that continued use of antibiotics in food animals should be continued, if only to protect human health. “Healthy animals make healthy food; for veterinarians to be effective in protecting our food supply, the appropriate tools for preventing, mitigating and treating disease, which includes antimicrobials, are paramount for veterinarians to be able to utilize.”<sup>205</sup>

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201. *Id.* at 188-89.

202. *Concerning Advancements*, *supra* note 90, at 16-17. *See generally* Hurd et al., *supra* note 79, at 980 (contending that the occasional occurrence of antibiotic resistance cannot be generalized to an entire national food production and health care system).

203. Singer et al., *supra* note 4, at 198.

204. *Concerning Advancements*, *supra* note 91, at 17 (citing L. A. Cox, *Potential Human Health Benefits of Antibiotics Used in Food Animals: A Case Study of Virginiamycin*, 31 ENVTL. INT’L 549-63 (2005)).

205. *Id.* at 3.

## VIII. CONCLUSION

The preservation of the effectiveness of antibiotics is essential to protect the health of animals and humans. Insufficient evidence currently exists to support prohibitions on the use of antibiotics in food animals, even those currently labeled for subtherapeutic treatment. The advantages provided to both human and animal populations from continued use of antibiotics in food animals outweigh the minimal risk to humans currently documented. The unintended consequences resulting from prohibitions in Europe, negatively impacting both human and animal health, must inform future decisions. The FDA should consider benefit and risk to humans and animals when implementing the FDCA with analyses obtained from robust risk assessment tools that measure critical quantitative and qualitative data points from farm to fork. While developing more uniform and robust surveillance programs to collect data about antibiotic usage and resistant-pathogen prevalence in human and animal specimens, the judicious use of antibiotics in all species should be encouraged.

At the same time, techniques successfully used in food production to minimize bacterial contamination of food can also be implemented on the farm. Since subtherapeutic or therapeutic antibiotics can contribute to the reduction of bacteria in manure, minimize carcass contamination, and decrease the microbial load of food consumed, such use should continue. Tools to eliminate pathogens from animal-produced fertilizer, and to advance food preparation methods to eliminate surviving bacteria, can be employed. Unexplained illness from food consumed at commercial establishments should be investigated and identified hazards should be targeted for elimination. Objective, science-based analyses are required to satisfactorily understand the complex factors contributing to the risk of antimicrobial resistance.

Preconceived notions of agricultural management techniques must be replaced by an understanding of the full range of medical, nutritional and technical tools that allow for the production of healthy animals and wholesome, safe food. Our tendency to create homocentric policies and laws must be tempered by an obligation to maintain the health and welfare of animals raised for food production, which will allow us to provide food for the world's ever-expanding population. In conclusion, the cost to animal health resulting from prohibitions on the use of antibiotics in food animals is unwarranted without definitive evidence that such use creates a public health risk. Until sufficient evidence proves that antibiotic treatment of animals results in disease or harm to humans, prohibitions should not be pursued.