PETITION BEFORE THE UNITED STATES DEPARTMENT OF AGRICULTURE, FOOD SAFETY AND INSPECTION SERVICE

FSIS Docket Clerk
Department of Agriculture
Food Safety and Inspection Service
Room 2534 South Building
1400 Independence Ave. SW
Washington, D.C. 20250-3700

ANIMAL LEGAL DEFENSE FUND
170 E. Cotati Ave.
Cotati, CA 94931
707-779-2055

Petitioner,

FILED WITH:

TOM VILSACK
in his official capacity as Secretary,
United States Department of Agriculture
1400 Independence Avenue SW
Washington, D.C. 20250

and

ALFRED ALMANZA
in his official capacity as Administrator
Food Safety and Inspection Service
United States Department of Agriculture
1400 Independence Avenue SW
Washington, DC 20250

EXHIBITS IN SUPPORT OF CITIZEN'S PETITION SEEKING MANDATORY MEAT AND POULTRY LABELING TO PREVENT THE SALE OF MISBRANDED PRODUCTS

Respectfully Submitted,

Attorney for Animal Legal Defense Fund
Alison M. Langlais
alanglais@proskauer.com
PROSKAUER ROSE LLP
One International Place
Boston, MA 02110
(617) 526-9765

Dated: May 15, 2013

APR 2 6 2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

APR 19 2011

The Honorable Louise M. Slaughter
House of Representatives
Washington, D.C. 20515-3221

Dear Ms. Slaughter:

Thank you for your letter of December 29, 2010, regarding antimicrobial resistance. The Food and Drug Administration (FDA or the Agency) is very concerned about preserving the effectiveness of current antimicrobials which are vital to protecting human and animal health against infectious microbial pathogens.

In your letter, you raise the following recommendations regarding the Agency's surveillance of antibiotic usage including: (1) expanding public reporting on antibiotic usage in the agricultural sector by providing more detail on classes critical to human medicine, (2) increasing reporting on the route of antibiotic administration in order to shed light on the pervasiveness of sub-therapeutic usage in agriculture, and (3) enhancing reporting on antibiotics produced for human use.

In response to your request, we have included the data on antimicrobial sales and distribution that are more detailed than those reported in FDA's 2009 summary report, *Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, published in compliance with section 105 of the Animal Drug User Fee Amendments of 2008 (ADUFA 105). While we are providing most of the requested data, please be aware that any totals provided are subject to many of the important caveats outlined in the paragraphs below.

Unfortunately, the data you requested regarding certain subsets of the "Not Independently Reported" (NIR) group in the ADUFA Report includes nine classes of antimicrobials that, in accordance with confidentiality provisions in ADUFA, could not be reported separately. However, we are able to provide the distribution data on (1) fluoroquinolones and diaminopyrimidines combined, and (2) the combination of those antimicrobials used only in animal medicine (aminocoumarins, glycolipids, and quinoxalines). Those data are 11,101 kg and 802,388 kg, respectively.

The requested ADUFA 105 summary data reported by route of administration, specifically: (1) in feed, (2) in water, and (3) by injection are: 9,701,180 kg, 2,065,433 kg, and 422,818 kg, respectively. However, as noted in the bulleted list, the route of use cannot be used as a simple proxy for indication.

The ADUFA 105 summary data cannot be further subdivided into four groups by degree of importance in human medicine as you requested. The data needed to generate the disclosures above (route of administration data, and specific data for fluoroquinolones and diaminopyrimidines) were readily obtained from the ADUFA 105 sponsor submissions themselves, and a list of the antimicrobials that are used only in animal medicine is publicly available through the National Library of Medicine's DailyMed database. As such, these data are factual reports that reflect what is known about the various drug classes that were reported under ADUFA 105 without any need for further interpretation. In contrast, further subdividing these data by degree of importance in human medicine, per your second request, would involve an interpretive analysis that the Agency is not prepared to make in the context of providing antibiotic sales and distribution data. FDA intends to address this issue in an upcoming draft guidance which will be the companion to our recently published guidance on antimicrobial use in animals entitled *The Judicious Use of Medically Important Antimicrobial Drugs in Food Producing Animals* (GFI #209). This next guidance will propose more specific information on approaches for implementing the recommendations outlined in GFI #209, including clarifying the definition of the term "medically important" antimicrobial.

In preparing the first ADUFA 105 summary report for 2009, FDA adhered closely to the reporting requirements set forth in the statute. However, FDA agrees there may be alternative approaches to summarizing the ADUFA 105 sales and distribution data. Prior to making significant changes to the content and format of our annual summary reports, we intend to seek public comment on this issue when we publish proposed implementing regulations for ADUFA 105. Such rulemaking would incorporate the new ADUFA 105 reporting requirements into the existing records and reports regulations for new animal drugs, as well as the provisions for the Agency's annual summary report.

In response to your request that FDA publicly report the quantity and type of antibacterial drugs used in human medicine, we have included estimates of antibacterial drug sales based on IMS Health, IMS National Sales Perspectives™ data. It is important to note that these sales data represent the volume of product being sold to the various outlets from the manufacturer (i.e., "in the back door"), and not the volume of product being sold by the outlets to patients (i.e., "out the front door"). Similarly, the animal data represent a summary of the volume of product sold or distributed (through various outlets) by the manufacturer, and not the volume of product purchased by the end user for administration to animals. We have attached a copy of a report that summarizes these data. Importantly, as we have continued to consider these data, it has become apparent that there are a number of differences in the circumstances of use of antibacterial drugs in human and veterinary medicine that must be carefully considered, including:

- The number of humans in the population compared to the number of animals in each of the many veterinary populations (veterinary data provided to FDA are not broken down by species)
- Differences in physical characteristics of humans compared to various animal species (e.g., weight)

- Antibacterial drug use in humans can be for the treatment or prevention of an infection, whereas animal use may include treatment, control, prevention, and growth promotion. The available animal data are not reported to the FDA by indication and so do not allow us to distinguish between or among these different types of uses. For example, the majority of antimicrobial drugs used in animal feed are approved for both therapeutic and production purposes. Therefore, the route of use cannot be used as a simple proxy for indication.
- Milligram dosages for different antibacterial drugs differ (e.g., the usual adult human dosage for amoxicillin is different from the usual adult dosage for doxycycline). Total weights across different antibacterial drug classes (and even, to a lesser extent, within classes) are therefore difficult to interpret.
- Duration and dosage of antibacterial drug administration may also vary by indication and, in general, will also vary between the various animal species and humans.

With the above points in mind, it is difficult to draw definite conclusions from any direct comparisons between the quantity of antibacterial drugs used in humans and the quantity used in animals.

Thank you again for contacting us concerning this important matter. If you have further questions, please let us know.

Sincerely,

for Karen Meister
Supervisory Congressional
Affairs Specialist

Enclosure

Department of Health and Human Ser
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Resea
Office of Surveillance and Epidemiolo

Date:	November 30, 2010
To:	Edward Cox, M.D. Director Office of Antimicrobial Products
Through:	Gerald Dal Pan, M.D., MHS Director Office of Surveillance and Epidemiology
	Judy Staffa, Ph.D. Acting Director Division of Epidemiology Office of Surveillance and Epidemiology
From:	Grace Chai, Pharm.D. Acting Drug Use Data Analyst Team Le Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Sales of Antibacterial Drugs in Kilogram
Drug Name(s):	Antibacterial Drugs
Application Type/Number:	Multiple
Applicant/sponsor:	Multiple
OSE RCM #:	2010-2472

Table 1, Part 2: Sales of Antibacterial Drugs by Drug Class and Molecule in Number of Kilograms Sold, Year 2009

Antibacterial Drug Class	Years 2009	
Drug name	Sales in Kilograms	Kg Share %
- Cephalosporins	499,616	15.1%
--First generation	357,828	71.6%
Cephalexin	306,928	85.8%
Cefazolin	38,705	10.8%
Cefadroxil	12,196	3.4%
Cephalothin		0.0%
Cephapirin		0.0%
Cephradine		0.0%
--Second generation	49,103	9.8%
Cefuroxime axetil	26,224	53.4%
Cefprozil	11,578	23.6%
Cefaclor	4,542	9.3%
Cefoxitin	4,404	9.0%
Cefuroxime	1,548	3.2%
Cefotetan	807	1.6%
Cefamandole		0.0%
Cefonocid		0.0%
Cefmetazole		0.0%
Loracarbef		0.0%
--Third generation	81,018	16.2%
Cefdinir	40,874	50.4%
Ceftriaxone	28,604	35.3%
Ceftazidime	5,697	7.0%
Cefotaxime	2,683	3.3%
Cefixime	1,503	1.9%
Cefpodoxime (proxetil)	1,059	1.3%
Cefditoren (pivoxil)	535	0.7%
Ceftibuten	65	0.1%
Ceftizoxime	0	0.0%
Cefoperazone		0.0%
Moxalactam		0.0%
--Fourth generation	11,667	2.3%
Cefepime	11,667	100.0%
-Sulfa and TMP	471,442	14.2%
Sulfamethoxazole	386,002	81.9%
Trimethoprim	78,763	16.7%
Sulfadiazine	4,847	1.0%
Sulfisoxazole	1,830	0.4%
-Quinolones	304,741	9.2%
Ciprofloxacin	220,115	72.2%
Levofloxacin	68,106	22.3%
Moxifloxacin	15,418	5.1%
Ofloxacin	679	0.2%
Norfloxacin	257	0.1%
Gemifloxacin	163	0.1%
Naladixic acid		0.0%
- Macrolides	176,278	5.3%
Azithromycin	90,317	51.2%
Clarithromycin	54,542	30.9%
Erythromycin	31,419	17.8%
Dirithromycin		0.0%

Source: IMS Health, IMS Nationals Sales Perspectives™, Year 2009. Data extracted 11/10. File: 1011abx8

*Beta-lactamase inhibitors that are part of a beta-lactam/beta-lactamase inhibitor combination (e.g., clavulanic acid, tazobactam, and sulbactam) and cilistatin are not included in this table. See text fo combination molecules are quantitated.

Table 1, Part 3: Sales of Antibacterial Drugs by Drug Class and Molecule in Number of Kilograms Sold, Year 2009

Antibacterial Drug Class	Years 2009	
Drug name	Sales in Kilograms	Kg Share %
-Tetracyclines	131,137	4.0%
Doxycycline	59,535	45.4%
Tetracycline	48,206	36.8%
Minocycline	22,063	16.8%
Demeclocycline	1,180	0.9%
Tigecycline	153	0.1%
Oxytetracycline	0	0.0%
-Nitroimidazoles	109,963	3.3%
Metronidazole	109,022	99.1%
Tinidazole	941	0.9%
- Lincomsamides	69,737	2.1%
Clindamycin	69,415	99.5%
Lincomycin	323	0.5%
-Carbapenems/penems	12,942	0.4%
Meropenem	5,246	40.5%
Imipenem	3,343	25.8%
Ertapenem	3,171	24.5%
Doripenem	1,182	9.1%
-Aminoglycosides	9,381	0.3%
Neomycin	5,459	58.2%
Tobramycin	1,868	19.9%
Gentamicin	1,155	12.3%
Amikacin	532	5.7%
Kanamycin	287	3.1%
Paromomycin	51	0.5%
Streptomycin	28	0.3%
Spectinomycin		0.0%
-Oxalozolidinones	5,487	0.2%
Linezolid	5,487	100.0%
-Monobactams	2,618	0.1%
Aztreonam	2,618	100.0%
-Lipopeptides	1,115	0.0%
Daptomycin	1,115	100.0%
-Ketolides	101	0.0%
Telithromycin	101	100.0%
-Streptogrammins	39	0.0%
Dalfopristin	27	70.1%
Quinupristin	12	29.9%
-Others	63,092	1.9%
Vancomycin	36,187	57.4%
Nitrofurantoin	18,842	29.9%
Rifampin	7,343	11.6%
Fosfomycin	529	0.8%
Colistin	138	0.2%
Chloramphenicol	51	0.1%
Telavancin	3	0.0%
Colistimethate sodium		0.0%
Polymixin B	1.14E+12 (I.U.)	--

Source: IMS Health, IMS Nationals Sales Perspectives™, Year 2009. Data extracted 11/10. File: 1011abx8.xls
*Beta-lactamase inhibitors that are part of a beta-lactam/beta-lactamase inhibitor combination (e.g., clavulanic acid, tazobactam, and sulbactam) and cilistatin are not included in this table. See text for how combination molecules are quantitated.

increases the opportunity for individuals to become infected by resistant bacteria."[9] Also in 2012, the FDA, in its final rule banning certain extralabel uses of cephalosporin antimicrobial drugs in certain food producing animals, stated "In regard to antimicrobial drug use in animals, the Agency considers the most significant risk to the public health associated with antimicrobial resistance to be human exposure to food containing antimicrobial-resistant bacteria resulting from the exposure of food-producing animals to antimicrobials."[10]

Nevertheless, the livestock industry continues to argue that while antibiotic use may have something to do with antibiotic resistance in bacteria on the farm, it is not an important human health issue, and little change in current practices are needed.

What Happens on the Farm

Numerous studies have demonstrated that routine use of antibiotics on the farm promotes drug-resistant superbugs in those facilities. Some of the most dramatic evidence came as a result of FDA approval of flouroquinolones--a class of antibiotics that includes Cipro (ciprofloxacin), which has been used in poultry production since 1995. By 1999 nearly 20 percent chicken breasts sampled contained ciprofloxacin-resistant *Camplobacter*, a disease-causing bacteria.[11] After a long fight in the courts, FDA finally banned use of the drug in 2005, at which point nearly 30 percent of *C. coli* found in chicken breasts were ciprofloxacin resistant; by 2010, resistance to ciprofloxacin had declined to 13.5 percent.[12]

The reason for this is that when you feed antibiotics to animals, the bacteria in and around the animals are exposed to the drug, and many of them die. But there are always some that the drug can't kill, and those survive and proliferate. Voila, superbugs.

While not disputing these facts, the industry argues essentially that what happens on the farm stays on the farm. There may be some superbugs there, but they don't affect people. There are two main routes, however, by which superbugs can leave the farm and infect humans. One is a direct route, in meat and poultry products, and the other is an indirect route through the environment.

---

[9] Pg. 3 in Food and Drug Administration (FDA). 2012. Guidance #209: the Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals. At: http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216936.pdf

[10] Pg. 738 in FDA. 2012. New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition. Federal Register, Vol. 77(4). http://www.gpo.gov/fdsys/pkg/FR-2012-01-06/pdf/2012-35.pdf

[11] Smith KE, Besser JM, Hedberg CW, Leano FT, Bender JB, Wicklund JH, Johnson BP, Moore KA, Osterholm MT et al. 1999. Quinolone-resistant *Camplybacter jejuni* infections. *New England Journal of Medicine*, 340(20): 1525-1532. At: http://loyce2008.free.fr/Microbiologie/diarrh%E9es%20infectieuses/Campylobacter/bla.pdf

[12] Food and Water Watch. 2012. *Antibiotic Resistance 101: How Antibiotic Misuse on Factory Farms Can Make You Sick.* 21pp. At: http://documents.foodandwaterwatch.org/doc/AntibioticResistance.pdf

Superbugs Move From Farm to Kitchen

Once they appear on the farm, superbugs most definitely move from the farm to the kitchen, via uncooked meat and poultry. *Consumer Reports* tests of chicken in both 2006[13] and 2010[14] revealed widespread presence of antibiotic-resistant pathogens in retail poultry products. In both years, more than two thirds of chicken samples were contaminated with *Salmonella* and/or *Campylobacter*, and more than 60 percent of those bacteria were resistant to one or more antibiotics.

The industry argues that even this is not a concern because people know to cook poultry thoroughly. Indeed they do, but packages can drip in the refrigerator, or cutting boards can become contaminated, as well as other problems. There aren't good data on how frequently this causes illness, especially difficult-to-treat illness, because most people just ride out an infection and it fades into the background of the estimated 48 million cases of food borne illness we have annually in the US.

But occasionally a superbug outbreak is serious enough to command the attention of the Center for Disease Control. One such case occurred in 2011, in which ground turkey was linked to 136 illnesses and one death, all caused by a strain of *Salmonella* resistant to four different antibiotics, ampicillin, streptomycin, tetracycline and gentamicin.[15] Some 36 million pounds of ground turkey were recalled.

Another case was ground beef from the Hannaford grocery store chain in New England linked in 2011 to 19 infections and at least seven hospitalizations, all caused by a strain of *Salmonella* resistant to multiple antibiotics, including amoxicillin/clavulanic acid, ampicillin, ceftriaxone, cefoxitin, kanamycin, streptomycin, and sulfisoxazole.[16]

Superbugs Move From Farm to the Environment

Superbugs can also spread beyond the farm and threaten public health through environmental transmission. This can happen in various ways, particularly via workers, or farm runoff. Once farm-raised superbugs make it off the farm, they can exchange genetic material and give their resistance to other bacteria, even of other genera and species, that have never been anywhere antibiotics. This can happen in lakes, in wild animals, and even in the human digestive tract.

Workers are particularly likely to pick up resistant bacteria from animals and take them elsewhere. A study of poultry workers in the Delmarva peninsula found they were 32 times more likely to carry gentamicin-resistant *Escherichia coli*, and more than five times more likely to carry multi-drug resistant *E. coli*, compared to other community

---

[13] Consumer Reports, 2007. Dirty Birds. January 2007, pp. 20-23. Consumers Union.
[14] Consumer Reports, 2010. How safe is That Chicken. January 2010, pp. 19-23. Consumers Union.
[15] Centers for Disease Control (CDC). 2011. Investigation Update: Multistate Outbreak of Human *Salmonella* Heidelberg Infections Linked to Ground Turkey. At: http://www.cdc.gov/salmonella/heidelberg/111011/index.html
[16] CDC. 2012. Investigation Update: Multistate Outbreak of Human *Salmonella* Typhimurium infections Linked to Ground Beef. At: www.cdc.gov/salmonella/typhimurium-groundbeef/010512/index.html

members.[17] A study performed in the Midwest found methicillin-resistant *Staphylococcus aureus* (MRSA) in 70 percent of the pigs and 64 percent of the workers at one facility, while no MRSA was found in pigs or workers at a facility in another state, strongly suggesting that the MRSA strain moves between pigs and humans.[18] Indeed, a careful genetic analysis has found that a particular MRSA strain found in pigs (e.g. ST398) originated as a methicillin-susceptible *S. aureus* (MSSA) in humans, jumped into pigs, where it acquired resistance to methicillin and tetracycline, and then jumped back to humans, where it's known as livestock-associated MRSA (LA-MRSA).[19] This LA-MRSA (e.g. ST398) is quite prevalent in the Netherlands, where it is responsible for over 20% of all MRSA.[20]

However, resistant bacteria can also escape from a large livestock operation (often known as a confined animal feeding operation, or CAFO) by a number of routes, including via manure applied to fields as fertilizer,[21] from trucks transporting animals,[22] the wind leaving hog facilities[23] or even via flies attracted to the manure which can pick up and transmit resistant bacteria.[24] A recently released study of the South Platte River found that antibiotic resistance genes (coding for resistance to sulfonamides) were 10,000 times higher in river sediments downstream from larger feedlots (ones with 10,000 cattle)

---

[17] Price LB, Graham JP, Lackey LG, Roess A, Vailers R and E Silbergeld. 2007. Elevated risk of carrying gentamicin-resistant *Escherichia coli* among U.S. poultry workers. *Environmental Health Perspectives*, 115(12): 1738-1742. At: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2137113/pdf/ehp0115-001738.pdf

[18] Smith TC, Male MJ, Harper AL, Kroeger JS, Tinkler GP, Moritz ED, Capuano AW, Herwalt LA and DJ Diekema. 2009. Methicillin-resistant *Staphylococcus aureus* (MRSA) strain ST398 is present in midwestern U.S. swine and swine workers. *PLoS One*, 4(1): e4258. At: http://www.plosone.org/article/info:doi/10.1371/journal.pone.0004258

[19] Price LB, Stegger M, Hasman H, Aziz M, Larsen J, Andersen PS, Pearson T, Waters AE, Foster JT et al. 2012. *Staphylococcus aureus* CC398: Host adaptation and emergence of methicillin resistance in livestock. *mBio*, 3(1): e00305-11 At: http://mbio.asm.org/content/3/1/e00305-11.full.pdf

[20] van Loo I, Huijsdens X, Tiemersma E, de Neeling A, van de Sande-Bruinsma N, Beaujean D, Voss A and J Kluytmans. 2007. Emergence of methicillin-resistant *Staphylococcus aureus* of animal origin in humans. *Emerging Infectious Diseases*, 13(12): 1834-1839. At:

[21] Chee-Sanford JC, Mackie RI, Koike S, Krapac IG, Lin Y-F, Yannarell AC, Maxwell S and RI Aminov. 2009. Fate and transport of antibiotic residues and antibiotic resistance genes following land application of manure waste. *Journal of Environmental Quality*, 38(3): 1086-1108. At: https://www.crops.org/publications/jeq/articles/38/3/1086

[22] Rule AM, Evans SL and EK Silbergeld. 2008. Food and animal transport a potential source of community exposure to health hazards from industrial farming (CAFOs). *Journal of Infection and Public Health*, 1(1): 33-39. At: http://www.academia.edu/591772/Food_animal_transport_a_potential_source_of_community_exposures_to_health_hazards_from_industrial_farming_CAFOs_

[23] Gibbs SG, Green CF, Tarwater PM, Mota LC, Mena KD and PV Scarpino. 2006. Isolation of antibiotic-resistant bacteria from the air plume downwind of a swine confined or concentrated animal feeding operation. *Environmental Health Perspectives*, 114(7): 10323-1037. At: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1513331/pdf/ehp0114-001032.pdf

[24] Graham JP, Price LB, Evans SE, Graczyk TK and EK Silbergeld. 2009. Antibiotic-resistant Enterococci and Staphylococci isolated from flies collected near confined poultry feeding operations. *Science of the Total Environment*, 407(8): At: http://www.jhsph.edu/sebin/q/h/AntibioticResistantEntero.pdf

compared to river sediment upstream from such feedlots.[25] The same study found these same antibiotic resistance genes were only 1,000 times higher from sewage treatment plants that discharge ten million gallons of effluent per day, compared to pristine sediments.

Bacteria in many environments can readily exchange genes coding for antibiotic resistance with neighboring bacteria. Antibiotic resistance genes are often located on mobile genetic elements, especially plasmids, transposons and integrons which can easily move between bacteria of the same or different species, which facilitates the spread of resistance to multiple drugs by multiple types of bacteria.[26]

The industry says that 40 percent of all the antibiotics used on the farm are drugs (called ionophores) not used in human medicine, so it doesn't matter if bacteria become resistant to them. However, a study by scientists from the United States Department of Agriculture (USDA) and Cornell University involving monensin, one of the most commonly used ionophores in cattle production in the U.S., demonstrated that use of monensin in cattle feed and the selection of monensin-resistant ruminal bacteria lead to a 32-fold increase in resistance to bacitracin, which is used in human medicine.[27] This study demonstrates that one cannot claim that ionophores cannot select for cross resistance to any antibiotic used in human medicine. The study called for more research.[28] So, it is appropriate to consider ionophore use as part of the antibiotics used in animal agriculture.

Conclusion

Use of antibiotics on the farm most definitely poses a risk to human health. Antibiotic use can promote creation of superbugs which can contaminate meat and poultry and cause hard-to-cure disease in people.

Superbugs can also exit the farm via farm workers, wind, runoff, and wildlife. Even if they don't immediately cause illness, bacteria are uniquely equipped to exchange genetic immunity via their plasmids, with other bacteria wherever they encounter them.

It is for these reasons that the public health community and FDA have been proposing to limit use of antibiotics on livestock for more than three decades (see list below). Consumers Union believes that as a prudent measure, we should drastically reduce use of antibiotics on food animals, and eliminate use altogether for growth promotion or disease prevention in healthy animals.

---

[25] Pruden A, Arabi M and HN Storteboom. 2012. Correlation between upstream human activities and riverine antibiotic resistance genes. *Environmental Science & Technology*, dx.doi.org/10.1021/es302657r At: http://pubs.acs.org/doi/abs/10.1021/es302657r

[26] Marshall BM and SB Levy. 2011. Food animals and antimicrobials: impacts on human health. *Clinical Microbiology Reviews*, 24(4): 718-733. At: http://cmr.asm.org/content/24/4/718.full.pdf

[27] Houlihan AJ and JB Russell. 2003. The susceptibility of ionophores-resistant *Clostridium aminophilum* F to other antibiotics. *Journal of Antimicrobial Chemotherapy*, 52: 623-628. At: http://jac.oxfordjournals.org/content/52/4/623.full.pdf

[28] Pg. 627 in Ibid.

Some of the Organizations Supporting Restrictions on the Use of Antimicrobials in Animal Production

American Medical Association, 2001

Adopted Resolution 508, Antimicrobial Use and Resistance, which states, in part, "AMA is opposed to the use of antimicrobials at non-therapeutic levels in agriculture, or as pesticides or growth promoters, and urges that non-therapeutic use in animals of antimicrobials (that are used in humans) should be terminated or phased out".[29]

American Public Health Association, 1999, 2004

Policy Number 9908: Addressing the Problem of Bacterial Resistance to Antimicrobial Agents and the Need for Surveillance, which urged "FDA to work for regulations eliminating the non-medical use of antibiotics and limiting the use of antibiotics in animal feeds"[30] In 2004, passed a resolution urging "bulk purchasers of foodstuffs to adopt procurement policies that encourage and, where feasible, require procurement of meat, fish, and dairy products produced without nontherapeutic use of medically important antibiotics."[31]

Infectious Diseases Society of America, 2009

"IDSA supports efforts to phase out the use of antimicrobial drugs for growth promotion, feed efficiency, and routine disease prevention in food animals."[32]

World Health Organization, 2001

The WHO Global Strategy for Containment of Antimicrobial Resistance, recommends that governments "terminate or rapidly phase out the use of antimicrobials for growth promotion if they are also used for treatment of humans."[33]

---

[29] http://www.keepantibioticsworking.com/new/KAWfiles/64_2_36325.pdf

[30] http://www.keepantibioticsworking.com/new/Library/UploadedFiles/American_Public_Health_Association_Policy_Numb.htm

[31] http://www.keepantibioticsworking.com/new/KAWfiles/64_2_37751.pdf

[32] http://www.keepantibioticsworking.com/new/KAWfiles/64_2_107287.pdf

[33] Pg. 10 in http://www.who.int/drugresistance/WHO%20Global%20Strategy%20-%20Executive%20Summary%20-%20English%20version.pdf

USATODAY.com

DRUGS CAN'T STOPTHIS KILLER

'nightmare' decade, bacteria that resist even 'drugs of last resort' have spread to health care facilities in 42 states

USA TODAY - McLean, Va.
Author: Peter Eisler
Date: Nov 29, 2012
Start Page: A.1
Section: NEWS
Text Word Count: 2803

Document Text

The doctors tried one antibiotic after another, racing to stop the infection as it tore through the man's body, but nothing worked.

In a matter of days after the middle-age patient arrived at University of Virginia Medical Center, the stubborn bacteria in his blood had fought off even what doctors consider "drugs of last resort."

"It was very alarming; it was the first time we'd seen that kind of resistance," says Amy Mathers, one of the hospital's infectious-disease specialists. "We didn't know what to offer the patient."

The man died three months later, but the bacteria wasn't done. In the months that followed, it struck again and again in the same hospital, in various forms, as doctors raced to decipher the secret to its spread.

The superbug that hit UVA four years ago -- and remains a threat -- belongs to a once-obscure family of drug-resistant bacteria that has stalked U.S. hospitals and nursing homes for over a decade. Now, it's attacking in hundreds of those institutions, a USA TODAY examination shows. It's a fight the medical community is not well positioned to win.

The bacteria, known as Carbapenem-Resistant Enterobacteriaceae, or CRE, are named for their ability to fight off carbapenem antibiotics -- the last line of defense in the medical toolbox. And so far, they've emerged almost exclusively in health care facilities, picking off the weakest of patients.

The bacteria made headlines this summer after a CRE strain of Klebsiella pneumoniae battered the National Institutes of Health Clinical Center outside Washington, D.C. Seven died, including a 16-year-old boy. (Hospitals don't reveal victims' names due to medical privacy rules.) But that case was neither the first nor the worst of the CRE attacks.

USA TODAY's research shows there have been thousands of CRE cases throughout the country in recent years -- they show up as everything from pneumonia to intestinal and urinary tract infections. Yet even larger outbreaks like the UVA episode, in which seven patients also died, have received little or no national attention until now.

The bacteria's ability to defeat even the most potent antibiotics has conjured fears of illnesses that can't be stopped. Death rates among patients with CRE infections can be about 40%, far worse than other, better-known health care infections such as MRSA or C-Diff, which have plagued hospitals and nursing homes for decades. And there are growing concerns that CRE could make its way beyond health facilities and into the general community.

"From the perspective of drug-resistant organisms, (CRE) is the most serious threat, the most serious challenge we face to patient safety," says Arjun Srinivasan, associate director for prevention of health care-associated infections at the Centers for Disease Control and Prevention.

Since the first known case, at a North Carolina hospital, was reported in 2001, CREs have spread to at least 41 other states, according to the CDC. And many cases still go unrecognized, because it can be tough to do the proper laboratory analysis, particularly at smaller hospitals or nursing homes.

To assess the threat and what's being done to stop it, USA TODAY interviewed dozens of health care authorities and reviewed hundreds of pages of journal articles, clinical reports, and state and federal health care data. The examination shows:

CRE infections already are endemic in several major U.S. population centers, including New York, Los Angeles and

Chicago, which account for hundreds of confirmed cases. Smaller pockets of cases have been reported across much of the country, including Oregon, Wisconsin, Minnesota, Pennsylvania, Maryland, Virginia and South Carolina.

There is no reliable national data on the scope of the CRE problem. The CDC has urged states to track cases, but only a handful do so -- and they're just getting going. "We don't have enough ... data to tell what the trend looks like," says Stephen Ostroff, director of epidemiology at the Pennsylvania Department of Health. "All we know is that it is here."

There is little chance that an effective drug to kill CRE bacteria will be produced in the coming years. Manufacturers have no new antibiotics in development that show promise, according to federal officials and industry experts, and there's little financial incentive because the bacteria adapt quickly to resist new drugs.

Many hospitals -- and an even greater percentage of nursing homes -- lack the capacity, such as lab capability, to identify CRE, or the resources to effectively screen and isolate patients carrying it. And even when screening is possible, there's a lack of consensus on whom to target.

"We're working with state health departments to try to figure out how big a problem this is," says the CDC's Srinivasan, noting that his agency can pool whatever incidence data states collect. "We're still at a point where we can stop this thing. You can never eradicate CRE, but we can prevent the spread. It's a matter of summoning the will."

Other experts are less optimistic.

"My concern is that there aren't a lot of methods in our tool kit that are significantly effective in curbing the spread of these infections," says Eli Perencevich, a professor and infectious-disease doctor at the University of Iowa's Carver College of Medicine.

The spread of CRE threatens to change the face of health care, crippling hospital units that specialize in treatments such as organ transplants and chemotherapy, which rely on the ability to control infections in patients with weak immune systems.

If unchecked, "these (bacteria) are going to greatly impact the kind of surgeries (and) treatments we can have," Perencevich says. "We're entering the post-antibiotic era; that's a very big problem."

Tracking an elusive killer

The UVA epidemiologists knew their CRE outbreak would be tough to contain -- they'd read about other cases in medical literature and knew that the bacteria spread fast, with frighteningly high death rates.

But it quickly became clear that this case would be even more difficult than most.

When the doctors began analyzing the bacteria in their first patient, who'd transferred from a hospital in Pennsylvania, they found not one, but two different strains of CRE bacteria. And as more patients turned up sick, lab tests showed that some carried yet another.

"We were really frustrated; we hadn't seen anything like this in the literature," says Costi Sifri, the hospital epidemiologist. "The fact that we had different bacteria told us these cases were not related, but the shoe leather epidemiology suggested to us that all these (infections) came from the same patient. We realized we might be seeing a mobile genetic event."

In other words, it looked like a single resistance gene was jumping among different bacteria from the Enterobacteriaceae family, creating new bugs before their eyes.

The doctors went back to the lab with even more urgency. It was January 2008, five months after the first case turned up, and they'd identified five patients harboring three distinct species of CRE.

Three of those patients already were dead.

Mobile patients, mobile bugs

There are many challenges to containing the spread of CRE, but one of the most daunting -- and immediate -- is knowing where it's showing up.

There is no billing code for CRE infections under Medicare or Medicaid, and there's no federal requirement for reporting cases. So getting a national picture of prevalence or where cases are concentrated is a challenge.

Based on academic studies and data from the handful of states and counties that require at least some reporting, it's clear that CRE is spreading fast. USA TODAY surveyed those [illegible] and counties, and every one of them has found cases.

In Los Angeles County alone, a year of surveillance through mid-2011 turned up 675 cases at hospitals, nursing homes and clinics. In Maryland, a 2011 survey by the state health department identified 269 patients carrying CRE and estimated that up to 80% of the state's hospitals had seen at least one case that year.

But the data are so isolated, and the reporting so variable, that the reports are of little practical use.

"If we don't know the scope and we don't know the distribution -- how big is the problem and where is the problem -- it's hard to know the next piece, which is what (prevention strategies) are you going to implement and where?" says Claudia Steiner, a physician and research officer at the U.S. Agency for Healthcare Research and Quality.

It's especially important to know where CRE bacteria are emerging because they spread with patients who bounce between clinics, surgical centers, rehabilitation facilities, nursing homes and, of course, hospitals.

In the Chicago area, where scores of CRE infections have been found since 2008, studies show that about 3% of hospital patients in intensive care carry the bacteria, says Mary Hayden, director of clinical microbiology and an infectious-disease doctor at Rush University Medical Center. Those same studies found CREs being carried by about 30% of patients in long-term care facilities.

Not all of those patients are symptomatic: The bacteria can lurk, unseen, until a carrier's immune system is weakened or the bug finds a path into the body. As those patients move between facilities, the bacteria move, too, often clinging to caregivers' hands – and finding new victims.

"We have to think about a new approach, a regional approach, to controlling these organisms, because ... no facility is an island," Hayden says. If a nursing home patient carries CRE and gets sick at night, "the staff there just want to get him to a hospital," she adds. "They may not know much about his (history), so that information doesn't come with him."

But the bacteria do.

The problem shows the need for a universal patient record system that allows clinicians to see key aspects of a patient's medical history as that person moves among facilities, Hayden says. The technical hurdles and privacy concerns are challenging, she adds, but some Chicago-area hospitals are working with public health agencies to develop a model.

Meanwhile, the bacteria cycle from one facility to the next.

"It is continually reintroduced," says David Landman, an infectious-disease doctor at the State University of New York's Downstate Medical Center in Brooklyn. "You need extreme control efforts."

A new tracking plan

Back at UVA, the doctors' theory was proving correct: They identified a common resistance gene among the different CRE bacteria attacking the hospital, and it matched what they found in the initial patient from Pennsylvania. The gene was jumping, one by one, to other species of Enterobacteriaceae bacteria, creating new carbapenem-defying bugs.

The doctors were seeing, in real time, a phenomenon that had worried researchers for years: the ability of CRE to share resistance genes across different members of the Enterobacteriaceae family.

The big fear is that the genes may start to convey resistance to more common strains of the bacteria, turning routine illnesses, such as urinary tract infections, into untreatable nightmares. Worst-case scenario: Resistance could move to bacteria outside of health care, so people could pick it up in the community through something as simple as a handshake.

The UVA doctors were in uncharted waters. Medical literature on CREs said to look for resistance in certain types of Enterobacteriaceae bacteria, "but we were seeing it in all kinds of bacteria," says Mathers, the infectious-disease

specialist.

The doctors sent out new instructions: Patients sickened with any form of Enterobacteriaceae bacteria should be checked immediately to see whether it is carbapenem-resistant, even if it's a strain not normally associated with CRE infections.

"We told the lab to look at anything that has a possible link with this (resistance) gene," Mathers says. "Any hint of resistance, then we need to know about it."

Stopping the untreatable

There's not much hope for a new treatment of CRE infections.

A few drugs show marginal effectiveness, including an old antibiotic shelved decades ago because of high toxicity. And there's little incentive for drug companies to invest in developing alternatives. Effective medications would be taken only until a patient recovered, making them far less profitable than life-long drugs for chronic illnesses. Plus, CREs develop new resistance quickly, so any new antibiotic isn't likely to last.

"If you look at the current pipeline of antibiotics (in development) ... none of them really is going to be active against these bacteria," says Gary Roselle, director of the Infectious Diseases Service for the Department of Veterans Affairs health system.

"The reality is, (CRE infections) are remarkably difficult to treat, they often have bad outcomes ... and they're increasing nationally," adds Roselle, who oversees infection control for the VA's hundreds of hospitals, clinics and nursing homes. "I'm assuming this is going to get worse, and there likely won't be new antibiotics to treat it in the near future, so the focus has to be on prevention."

CDC guidance for controlling CRE rests on traditional infection control strategy: rigorous hand cleaning by staff and visitors; isolating infected patients and requiring gowns and gloves for anyone contacting them; cutting antibiotic use to slow the development of resistant bacteria; and limiting use of invasive medical devices, such as catheters, that give bacteria a path into the body.

But the measure that may hold the most promise is contentious: screening patients for the bacteria so carriers can be isolated. There's disagreement over whom to screen. Every patient? Only those whose history makes them a risk for infection? Only those showing symptoms?

Because many hospitals and nursing homes lack resources for screening, some patient advocates say the priority should be looking for more common bugs, such as MRSA (Methicillin-resistant Staphylococcus aureus), which is more treatable than CRE infections.

"Why cause hospitals to use resources for a pathogen with unknown (prevalence)?" says Michael Bennett, president of the Coalition for Patients' Rights. "Doesn't it make sense to attack the biggest problem?"

Screening has proved effective at facilities that cut high CRE rates.

In New York City, where CRE is endemic at many facilities, Bronx-based Montefiore Medical Center cut prevalence rates in half at its nine intensive-care units with a program that relied heavily on screening. The initiative tested all intensive-care patients using an experimental, high-speed assay for the bacteria, and carriers were isolated immediately.

The initiative, which grew to include sampling of patients across all units of Montefiore's three-hospital network, revealed that 40% of CRE cases involved patients who arrived with the bacteria when transferred from other institutions.

"So even if I had a perfect program to stop all patient-to-patient transmission in the hospital, the maximum impact I could have would be a 60% reduction in prevalence," says Brian Currie, the hospital's vice president for research and an assistant dean at the affiliated Albert Einstein College of Medicine.

Currie sees the cut in Montefiore's CRE rates as "a significant achievement," but he notes that the initiative underscored the trials ahead. He and his staff identified 11 nursing homes and several hospitals that regularly -- and unwittingly -- send CRE-infected patients to his facility. "It's amazing how little awareness many of the providers have," he says.

The challenge at nursing homes, which typically have no labs to test patients for bacteria, is even greater.

"Personnel working in long-term care facilities may be unaware of 'new' resistance (bacteria)," researchers concluded in a 2008 study of CRE infections in New York nursing homes, published in Clinical Infectious Diseases. The risk of CRE in nursing home patients "should be of great concern."

New tools in the fight

Once the UVA doctors figured out that a single gene was driving the spread of CRE through the hospital, they still needed a way to find it -- and stop it. And the clock was ticking.

By April 2008, eight months after they'd identified their first infection, 13 additional patients had been infected with related strains of the bacteria. Seven were dead.

Back in the lab, the doctors figured out that the gene was hitching a ride among bacteria on mobile pieces of DNA, called plasmids, that can move from one cell to another. They developed a genetic test that could identify those plasmids -- and the bacteria they'd affected -- in days.

"Half the story is the outbreak and half the story is how we figured it out," says Sifri, the epidemiologist. "We had to understand what was happening before we could attack the problem."

The lessons learned at UVA have helped them target CRE screening of at-risk patients. And with rapid identification and isolation of carriers, vigilant hand washing, and other infection-control measures, the outbreak was controlled, Sifri says.

But the bacteria are there to stay, lurking somewhere, always a threat.

"We have continued to have patients with CREs that are related to this (first) event," Sifri says. "We haven't been able to close the door on this. I'm not sure you ever can."

Contributing: Kaitlyn Ridel

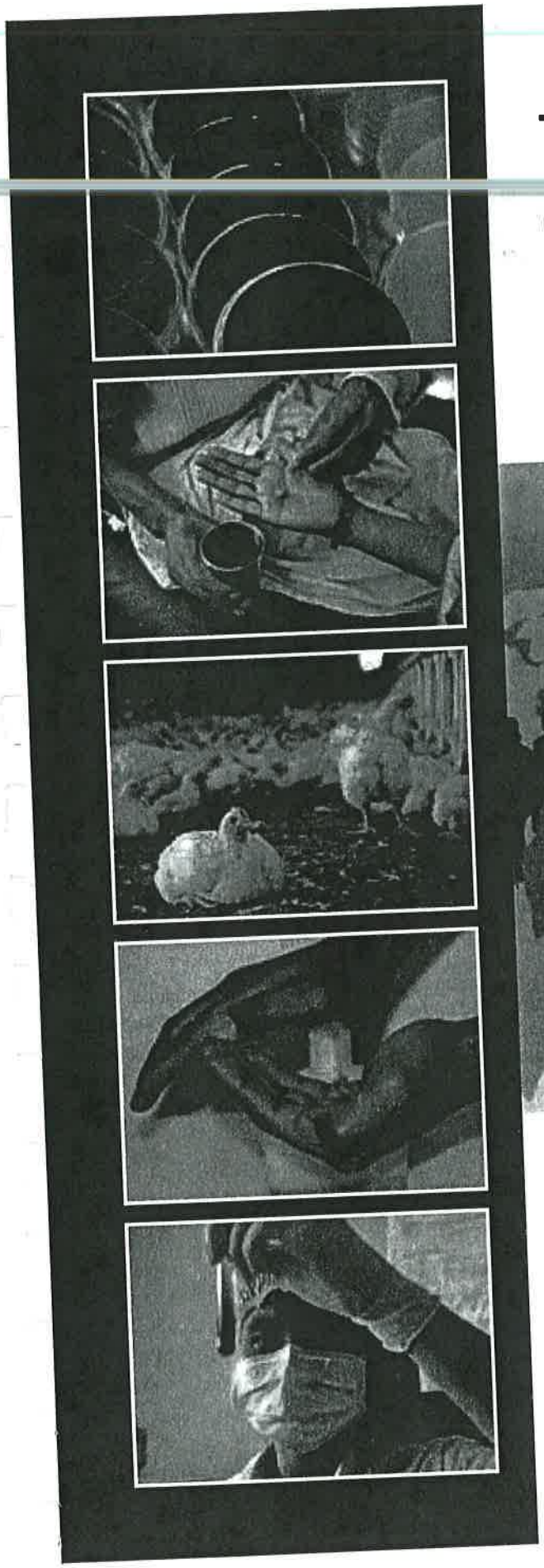
Credit: Peter Eisler, USA TODAY,

[Illustration]
GRAPHIC, Color, Frank Pompa, USA TODAY (map); GRAPHIC, Color, Frank Pompa, USA TODAY (diagrams); Caption:

Abstract (Document Summary)

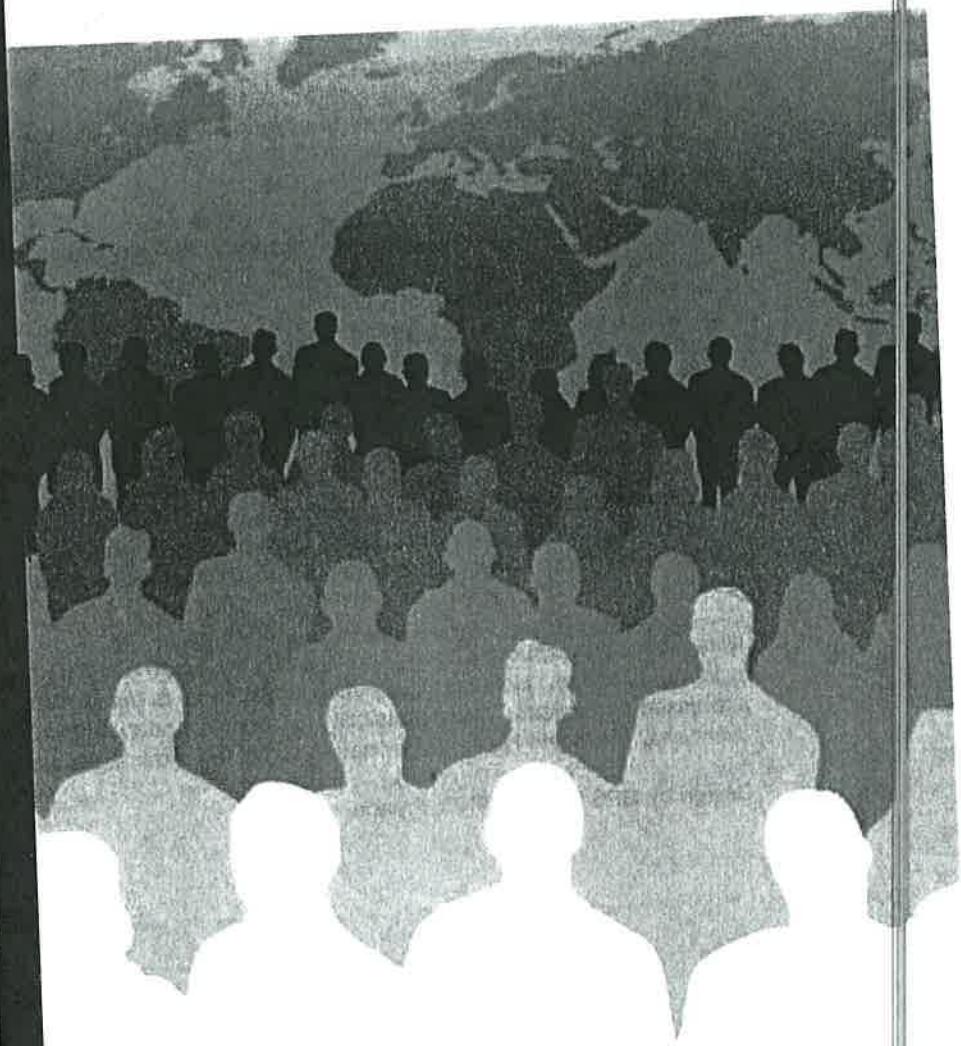
The superbug that hit UVA four years ago -- and remains a threat -- belongs to a once-obscure family of drug-resistant bacteria that has stalked U.S. hospitals and nursing homes for over a decade. "From the perspective of drug-resistant organisms, (CRE) is the most serious threat, the most serious challenge we face to patient safety," says Arjun Srinivasan, associate director for prevention of health care-associated infections at the Centers for Disease Control and Prevention. Since the first known case, at a North Carolina hospital, was reported in 2001, CREs have spread to at least 41 other states, according to the CDC.

Reproduced with permission of the copyright owner. Further reproduction or distribution is prohibited without permission.



The evolving threat of antimicrobial resistance

Options for action



World Health Organization

WHO Library Cataloguing-in-Publication Data

The evolving threat of antimicrobial resistance: options for action.

1.Anti-infective agents - adverse effects. 2.Drug resistance, microbial - drug effects. 3.Anti-bacterial agents - administration and dosage. 4.Drug utilization. 5.Health policy. I.World Health Organization.

ISBN 978 92 4 150318 1 (NLM classification: QV 250)

Design by GPS PUBLISHING, France.

H

United States District Court,
S.D. New York.
NATURAL RESOURCES DEFENSE COUNCIL, INC., et al., Plaintiffs,
v.
UNITED STATES FOOD AND DRUG ADMINISTRATION, et al., Defendants.

No. 11 Civ. 3562 (THK).
March 22, 2012.

Background: Advocacy organizations brought action seeking to compel Food and Drug Administration (FDA) to initiate proceedings to withdraw its approval of use of penicillin and tetracycline in livestock for subtherapeutic purposes. Parties cross-moved for summary judgment.

Holdings: The District Court, Theodore H. Katz, United States Magistrate Judge, held that:
(1) statute at issue prescribed a set of "discrete agency actions";
(2) statute required withdrawal of approval of any new animal drug found not to be safe, provided the sponsor had notice and an opportunity for hearing;
(3) Commissioner of the FDA delegated to Director of the Bureau of Veterinary Medicine (BVM) authority to make findings required to issue withdrawal notices;
(4) Director explicitly concluded that penicillin and tetracycline had not been shown to be safe; and
(5) FDA's rescission of withdrawal notices during the pendency of the action did not moot case.

Plaintiffs' motion granted; defendants' motion denied.

Subsequent determination, 884 F.Supp.2d 108, 2012 WL 3229296

West Headnotes

[1] Administrative Law and Procedure 15A 811

15A Administrative Law and Procedure
15AV Judicial Review of Administrative Decisions
15AV(F) Determination
15Ak811 k. In general. Most Cited Cases

When an agency is compelled by law to act within a certain time period, but the manner of its action is left to the agency's discretion, a court can compel the agency to act under the Administrative Procedure Act (APA), but has no power to specify what the action must be. 5 U.S.C.A. § 706(1).

[2] Health 198H 324

198H Health
198HI Regulation in General
198HI(E) Drugs; Medical Devices and Instruments
198Hk324 k. Animal drugs. Most Cited Cases

Statute governing the withdrawal of approval of new animal drug applications (NADAs) and abbreviated NADAs (ANADAs) and the accompanying regulations required the Food and Drug Administration (FDA) to implement several related "discrete agency actions," as required to permit a court, pursuant to the Administrative Procedure Act (APA), to compel the FDA to act under the statute; discrete actions the act and the accompany regulations required the FDA to implement included (1) providing notice of the FDA's finding and intent to withdraw approval, (2) providing an opportunity for a hearing to the relevant animal drug sponsors, (3) if an applicant timely requested a hearing and raised a genuine issue of fact, holding a hearing, and (4) if the applicant failed to show that the drug was safe, issuing an order withdrawing approval of the drug. 5 U.S.C.A. § 706(1); Federal Food, Drug, and Cosmetic Act, § 512(e)(1), 21 U.S.C.A. § 360b(e)(1); 21 C.F.R. §§ 12.87, 12.120(a, b), 12.125(a), 514.200.

[3] Statutes 361 ⚿1080

361 Statutes
361III Construction
361III(A) In General
361k1078 Language
361k1080 k. Language and intent, will, purpose, or policy. Most Cited Cases
(Formerly 361k188, 361k181(1))

Statutes 361 ⚿1109

361 Statutes
361III Construction
361III(C) Clarity and Ambiguity; Multiple Meanings
361k1107 Absence of Ambiguity; Application of Clear or Unambiguous Statute or Language
361k1109 k. Purpose and intent; unambiguously expressed intent. Most Cited Cases
(Formerly 361k190)

In interpreting a statute, a court must give effect to the unambiguously expressed intent of Congress; to ascertain Congress's intent, a court begins with the statutory text because if its language is unambiguous, no further inquiry is necessary.

[4] Statutes 361 ⚿1127

361 Statutes
361III Construction
361III(D) Particular Elements of Language
361k1127 k. Grammar, spelling, and punctuation. Most Cited Cases
(Formerly 361k200)

Statutes 361 ⚿1152

361 Statutes
361III Construction
361III(E) Statute as a Whole; Relation of Parts to Whole and to One Another
361k1152 k. Design, structure, or scheme. Most Cited Cases
(Formerly 361k200)

Statutory interpretation must take into account the structure and grammar of the provision.

[5] Administrative Law and Procedure 15A ⚿433

15A Administrative Law and Procedure
15AIV Powers and Proceedings of Administrative Agencies, Officers and Agents
15AIV(C) Rules, Regulations, and Other Policymaking
15Ak428 Administrative Construction of Statutes
15Ak433 k. Permissible or reasonable construction. Most Cited Cases
(Formerly 361k219(2))

Statutes 361 ⚿1104

361 Statutes
361III Construction
361III(C) Clarity and Ambiguity; Multiple Meanings
361k1103 Resolution of Ambiguity; Construction of Unclear or Ambiguous Statute or Language
361k1104 k. In general; factors considered. Most Cited Cases
(Formerly 361k190)

Statutes 361 ⚿1242

361 Statutes
361III Construction
361III(H) Legislative History
361k1242 k. Plain, literal, or clear meaning; ambiguity. Most Cited Cases
(Formerly 361k217.4)

If statutory language is ambiguous, a court will resort first to canons of statutory construction, and, if the statutory meaning remains ambiguous, to legislative history to determine the intent of Congress; if the intent of Congress remains unclear, a court will defer to an agency's interpretation of the statute, so long as it is reasonable.

[6] Health 198H ⚿324

198H Health
198HI Regulation in General

198HI(E) Drugs; Medical Devices and Instruments

198Hk324 k. Animal drugs. Most Cited Cases

Statute governing the withdrawal of approval of new animal drug applications (NADAs) and abbreviated NADAs (ANADAs) requires the Secretary of the Department of Health and Human Services (HHS) to issue notice and an opportunity for hearing whenever he finds that a new animal drug is not shown to be safe; if the drug sponsor does not meet his burden of demonstrating that the drug is safe at the hearing, the Secretary must issue an order withdrawing approval of the drug. Federal Food, Drug, and Cosmetic Act, § 512(e)(1), 21 U.S.C.A. § 360b(e)(1).

[7] Health 198H ⚿324

198H Health
198HI Regulation in General
198HI(E) Drugs; Medical Devices and Instruments

198Hk324 k. Animal drugs. Most Cited Cases

Food and Drug Administration (FDA) regulation, requiring the Commissioner to notify in writing the person holding a new animal drug application (NADA) or abbreviated NADAs (ANADA) and afford an opportunity for a hearing on a proposal to withdraw approval of such NADA/ANADA if he found that such drug was "not shown to be safe," unambiguously referred to same findings as statute governing the withdrawal of approval of NADAs an ANADAs, and, therefore, agency's interpretation of the regulation as creating a different set of findings based on a lower standard than the "not shown to be safe" standard for the statutory findings was not entitled to deference; although several of the FDA's notices of proposed withdrawals rested on a finding that there was a "reasonable basis from which serious questions about the ultimate safety of [the drug] may be inferred," the regulation described the requisite findings in exactly the same language as the statute. Federal Food, Drug, and Cosmetic Act, § 512(e)(1), 21 U.S.C.A. § 360b(e)(1); 21 C.F.R. § 514.115(b)(3)(ii).

[8] Health 198H ⚿324

198H Health
198HI Regulation in General
198HI(E) Drugs; Medical Devices and Instruments

198Hk324 k. Animal drugs. Most Cited Cases

By explicitly delegating to the Director of the Bureau of Veterinary Medicine (BVM) the authority to issue withdrawal notices under statute governing the withdrawal of approval of new animal drug applications (NADAs) and abbreviated NADAs (ANADAs), the Commissioner of the Food and Drug Administration (FDA) delegated to the Director the authority to make the findings that were a statutory prerequisite to any such notice; under the relevant regulation, any such notice was required to "specify the grounds upon which" the proposal to withdraw was based. Federal Food, Drug, and Cosmetic Act, § 512(e)(1), 21 U.S.C.A. § 360b(e)(1); 21 C.F.R. § 514.115(b)(3)(ii).

[9] Health 198H ⚿324

198H Health
198HI Regulation in General
198HI(E) Drugs; Medical Devices and Instruments

198Hk324 k. Animal drugs. Most Cited Cases

In notices of an opportunity for hearing (NOOHs) on proposals to withdraw approval of subtherapeutic uses of penicillin and tetracycline in animal feed, the Director of the Bureau of Veterinary Medicine (BVM) explicitly concluded that the drugs had not been shown to be safe and cited statute governing the withdrawal of approval of new animal drug applications (NADAs) and abbreviated NADAs (ANADAs), legally requiring the Food and Drug Administration (FDA) to institute withdrawal proceedings under the statute. Federal Food, Drug, and Cosmetic Act, § 512(e)(1), 21 U.S.C.A. §

360b(e)(1).

[10] Federal Courts 170B ⚿12.1

170B Federal Courts
170BI Jurisdiction and Powers in General
170BI(A) In General
170Bk12 Case or Controversy Requirement
170Bk12.1 k. In general. Most Cited Cases

A federal court has no authority to give opinions upon moot questions or abstract propositions, or to declare principles or rules of law which cannot affect the matter in issue in the case before it.

[11] Federal Courts 170B ⚿12.1

170B Federal Courts
170BI Jurisdiction and Powers in General
170BI(A) In General
170Bk12 Case or Controversy Requirement
170Bk12.1 k. In general. Most Cited Cases

The "mootness doctrine" provides that an actual controversy must be extant at all stages of review, not merely at the time the complaint is filed.

[12] Federal Courts 170B ⚿12.1

170B Federal Courts
170BI Jurisdiction and Powers in General
170BI(A) In General
170Bk12 Case or Controversy Requirement
170Bk12.1 k. In general. Most Cited Cases

The existence of a real case or controversy is an irreducible minimum to the jurisdiction of the federal courts; accordingly, if an event occurs while a case is pending that makes it impossible for the court to grant any effectual relief whatever to a prevailing party, the case must be dismissed. U.S.C.A. Const. Art. 3, § 2, cl. 1.

[13] Health 198H ⚿324

198H Health
198HI Regulation in General
198HI(E) Drugs; Medical Devices and Instruments
198Hk324 k. Animal drugs. Most Cited Cases

Food and Drug Administration's (FDA) rescission of notices of an opportunity for hearing (NOOHs) on proposals to withdraw approval of subtherapeutic uses of penicillin and tetracycline in animal feed, during the pendency of advocacy organizations' action seeking a court order compelling the FDA to complete the withdrawal proceedings for the antibiotics in the notices, as required by statute governing the withdrawal of approval of new animal drug applications (NADAs) and abbreviated NADAs (ANADAs), did not moot organizations' claims, absent any evidence that the rescission of the NOOHs rescinded the original findings that the subtherapeutic use of penicillin and tetracycline in food-producing animals had not been shown to be safe. Federal Food, Drug, and Cosmetic Act, § 512(e)(1), 21 U.S.C.A. § 360b(e)(1).

[14] Health 198H ⚿324

198H Health
198HI Regulation in General
198HI(E) Drugs; Medical Devices and Instruments
198Hk324 k. Animal drugs. Most Cited Cases

The trigger for the Food and Drug Administration (FDA) to initiate mandatory withdrawal proceedings under statute governing the withdrawal of approval of new animal drug applications (NADAs) and abbreviated NADAs (ANADAs) is not the issuance of a notice of an opportunity for hearing (NOOH) on a proposal to withdraw approval of a new animal drug but a finding that a drug has not been shown to be safe. Federal Food, Drug, and Cosmetic Act, § 512(e)(1), 21 U.S.C.A. § 360b(e)(1).

[15] Health 198H ⚿324

198HI Regulation in General

198HI(E) Drugs; Medical Devices and Instruments

198Hk324 k. Animal drugs. Most Cited Cases

Statute governing the withdrawal of approval of new animal drug applications (NADAs) and abbreviated NADAs (ANADAs) does not empower the agency to choose a different course of action in lieu of withdrawal proceedings. Federal Food, Drug, and Cosmetic Act, § 512(e)(1), 21 U.S.C.A. § 360b(e)(1).

***130** Mitchell S. Bernard, Natural Resources Defense Council, Inc., New York, NY, Avinash Kar, Jennifer Ann Sorenson, Natural Resources Defence Council, Inc., San Francisco, CA, for Plaintiffs.

Amy Ann Barcelo, Ellen Melissa London, United States Attorney Office, New York, NY, for Defendants.

MEMORANDUM OPINION AND ORDER

THEODORE H. KATZ, United States Magistrate Judge.

Plaintiffs Natural Resources Defense Council, Inc. ("NRDC"), Center for Science in the Public Interest, Food Animal Concerns Trust, Public Citizen, and Union of Concerned Scientists, Inc. (collectively "Plaintiffs") bring this action against the United States Food and Drug Administration ("FDA"), Margaret Hamburg, in her official capacity as Commissioner of the FDA, the Center for Veterinary Medicine ("CVM"), Bernadette Dunham, in her official capacity as Director of the CVM, United States Department of Health and Human Services ("HHS"), and Kathleen Sebelius, in her official capacity as Secretary of HHS, alleging that the FDA withheld agency action in violation of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 360b(e)(1), and the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(1). The parties have consented to trial before this Court, pursuant to 28 U.S.C. § 636(c). Presently before the Court [illegible] cross motions for summary judgment. For the reasons that follow, Plaintiffs' motion is granted and Defendants' motion is denied.

BACKGROUND [FN1]

FN1. Except where otherwise noted, the following facts, derived from the parties' Statements Pursuant to Local Civil Rule 56.1, are undisputed.

I. *Overview*

For over thirty years, the FDA has taken the position that the widespread use of certain antibiotics in livestock for purposes other than disease treatment poses a threat to human health. In 1977, the FDA issued notices announcing its intent to withdraw approval of the use of certain antibiotics in livestock for the purposes of growth promotion and feed efficiency, which the agency had found had not been proven to be safe. The FDA issued the notices pursuant to 21 U.S.C. § 360b(e)(1), which states that

> ***131** [t]he Secretary shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application ... with respect to any new animal drug if the Secretary finds ... (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 ....

21 U.S.C. § 360b(e)(1)(B). Although the notices were properly promulgated and over twenty drug sponsors requested hearings on the matter, the FDA never held hearings or took any further action on the proposed withdrawals.

In the intervening years, the scientific evidence of the risks to human health from the widespread use of antibiotics in livestock has grown, and there is no evidence that the FDA has changed its position that such uses are not shown to be safe. In May 2011, after the FDA failed to respond to two Citizen Petitions urging the agency to follow through with the 1977 notices, Plaintiffs filed this action seeking a court order compelling the FDA to complete the withdrawal proceedings for antibiotics included in the 1977 notices. In December 2011, the FDA withdrew the original notices on the grounds that they were outdated, and it now argues that Plaintiffs' claim is moot.

II. *Use of Antibiotics in Food–Producing Animals*

Antibiotics, also known as antimicrobials, are drugs used to treat infections caused by bacteria. Although antibiotics have saved countless lives, the improper use and overuse of antibiotics has led to a phenomenon known as antibiotic resistance. Specifically, the misuse of antibiotics creates selective evolutionary pressure that enables antibiotic resistant bacteria to increase in numbers more rapidly than antibiotic susceptible bacteria, increasing the opportunity for individuals to become infected by resistant bacteria. People who contract antibiotic-resistant bacterial infections are more likely to have longer hospital stays, may be treated with less effective and more toxic drugs, and may be more likely to die as a result of the infection. The FDA considers antibiotic resistance "a mounting public health problem of global significance." (First Amended Complaint ("First Am. Compl.") ¶ 38; Answer ¶ 38.)

In the 1950s, the FDA approved the use of antibiotics to stimulate growth and improve feed efficiency in food-producing animals, such as cattle, swine, and chickens. Antibiotics used for growth promotion are typically administered through animal feed or water on a herd—or flock-wide basis. The approved doses of antibiotics for growth promotion are typically lower than the approved doses for disease treatment. The administration of "medically important" [FN2] antibiotics to entire herds or flocks of food-producing animals, at "subtherapeutic" [FN3] levels, poses a qualitatively higher ***132** risk to public health than the administration of such drugs to individual animals or targeted groups of animals to prevent or treat specific diseases. (*See* Answer ¶ 34.) Research has shown that the use of antibiotics in livestock leads to the development of antibiotic-resistant bacteria that can be—and has been—transferred from animals to humans through direct contact, environmental exposure, and the consumption and handling of contaminated meat and poultry products. Consequently, the FDA has concluded that "the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes [in livestock] is not in the interest of protecting and promoting the public health." (Guidance No. 209, attached as Exhibit B ("Ex. B") to Declaration of Assistant United States Attorney Amy A. Barcelo ("Barcelo Decl.") at 13.)

> FN2. The term "medically important antibiotics" refers to antibiotic drugs that are important for therapeutic use in humans.
>
> FN3. The term "subtherapeutic" was commonly used in the 1960s and 1970s to refer to any use of antibiotics for purposes other than disease treatment and prevention, including growth promotion and feed efficiency in animals. Although FDA no longer uses the term, in this Opinion the Court uses the term "subtherapeutic" to refer to the use of antibiotics in food-producing animals for growth promotion and feed efficiency.

III. *Penicillin and Tetracyclines*

The present action pertains to the use of three different antibiotics in animal feed: penicillin and two forms of tetracycline — chlortetracycline and oxytetracycline (" tetracyclines "). Pursuant to the FDCA, any "new animal drug" [FN4] that is introduced into interstate commerce must be the subject of an FDA approved new animal drug application

breviated NADA ("ANADA"). *See* 21 U.S.C. § 360b(b)-(c). Drug companies that submit NADAs/ANADAs are typically referred to as "applicants" or "sponsors." The FDA lawfully issued NADAs and ANADAs for penicillin and tetracyclines in the mid–1950s. Since that time, penicillin has been used to promote growth in chickens, turkeys, and swine, and tetracyclines have been used to promote growth in chickens, turkey, swine, cattle, and sheep.

> FN4. A new animal drug is defined, in part, as "any drug intended for use for animals other than man, including any drug intended for use in animal feed but not including such animal feed ...." *See* 21 U.S.C. § 321(v).

In the mid–1960s, the FDA became concerned that the long-term use of antibiotics, including penicillin and tetracyclines, in food-producing animals might pose threats to human and animal health. As a result, in 1970, the agency convened a task force to study the risks associated with the use of antibiotics in animal feed. The task force was composed of scientists from the FDA, the National Institutes of Health, the U.S. Department of Agriculture, the Center for Disease Control, as well as representatives from universities and industry. In 1972, the task force published its findings, concluding that: (1) the use of antibiotics in animal feed, especially at doses lower than those necessary to prevent or treat disease, favors the development of antibiotic-resistant bacteria; (2) animals receiving antibiotics in their feed may serve as a reservoir of antibiotic pathogens, which can produce human infections; (3) the prevalence of bacteria carrying transferrable resistant genes for multiple antibiotics had increased in animals, and the increase was related to the use of antibiotics; (4) antibiotic-resistant bacteria had been found on meat and meat products; and (5) the prevalence of antibiotic resistant bacteria in humans had increased. *See* Antibiotic and Sulfonamide Drugs in Animal Feeds, 37 Fed.Reg. 2,444, 2,444-45 (Feb. 1, 1972). The task force made several recommendations, including that (1) antibiotics used in human medicine be prohibited from use in animal feed unless they met safety criteria established by the FDA, and (2) several specific ***133** drugs, including penicillin and tetracyclines, be reserved for therapeutic use unless they met safety criteria for non-therapeutic use. *See id.* at 2,445.

In response to the findings of the task force, the FDA, in 1973, issued a regulation providing that the agency would propose to withdraw approval of all subtherapeutic uses of antibiotics in animal feed unless drug sponsors and other interested parties submitted data within the next two years "which resolve[d] conclusively the issues concerning [the drugs'] safety to man and animals ... under specific criteria" established by the FDA. Antibiotic and Sulfonamide Drugs in the Feed of Animals, 38 Fed.Reg. 9,811, 9,813 (Apr. 20, 1973) (codified at former 21 C.F.R. § 135.109; renumbered at 21 C.F.R. § 558.15). One of the most important of the human and animal health safety criteria that the FDA established for drug safety evaluations under the regulation involved the transfer of antibiotic resistant bacteria from animals to humans. The FDA regulation required that "[a]n antibacterial drug fed at subtherapeutic levels to animals must be shown not to promote increased resistance to antibacterials used in human medicine." Penicillin–Containing Premixes Notice (" Penicillin Notice"), 42 Fed.Reg. 43,772, 43,774 (Aug. 30, 1977). The other health safety criteria involved showing that use of antibiotics would not increase salmonella in animals, would not increase the pathogenicity of bacteria, and would not increase residues in food ingested by man, which may cause "increased numbers of pathogenic bacteria or an increase in the resistence of pathogens to antibacterial agents used in human medicine." *See id.*

Over the next two years, the Bureau of Veterinary Medicine ("BVM"), FN5 a subdivision of the FDA, reviewed the data submitted by drug sponsors

to support the subtherapeutic use of antibiotics. By April 20, 1975, all data concerning the safety and efficacy criteria for antibiotic drugs had been received. *See id.* at 43,774. The BVM was assisted by a sub-committee of the FDA's National Advisory Food and Drug Committee ("NAFDC") in its review of the data. The NAFDC sub-committee issued a report and recommendations on the subtherapeutic use of penicillin in animal feed, which the NAFDC adopted in 1977. *See id.* The NAFDC "recommended that FDA immediately withdraw approval for the subtherapeutic uses of penicillin, i.e., growth promotion/feed efficiency, and disease control." *Id.* Similarly, the NAFDC sub-committee made certain recommendations regarding the use of tetracyclines in animal feed. Specifically, for tetracyclines, the sub-committee recommended that the FDA "(1) discontinue their use for growth promotion and/or feed efficiency in all animal species for which effective substitutes are available, (2) permit their use for disease control where effective alternate drugs are unavailable ..., and (3) control the distribution of the tetracyclines through ... a veterinarian's order to restrict their use." Tetracycline (Chlortetracycline and Oxytetracycline)-Containing Premises; Opportunity for Hearing ("Tetracycline Notice"), 42 Fed, Reg. 56,264, 56,266 (Oct. 21, 1977). The NAFDC rejected the first two recommendations, but adopted the third recommendation. *See id.*

> FN5. The BVM was renamed the Center for Veterinary Medicine ("CVM") in 1984.

IV. *The 1977 NOOHs*

After carefully considering the recommendations of the NAFDC and the NAFDC subcommittee, the Director of the BVM issued notices of an opportunity ***134** for hearing ("NOOHs") on proposals to withdraw approval of all subtherapeutic uses of penicillin in animal feed, *see* Penicillin Notice, 42 Fed.Reg. at 43,772, and, with limited exceptions, all subtherapeutic uses of oxytetracycline and chlortetracycline in animal feed, *see* Tetracycline Notice, 42 Fed.Reg. at 56,264. In the Penicillin Notice, the Director reported that "[n]one of the specified human and animal health safety criteria [for the subtherapeutic use of antibiotics in animal feed] have been satisfied...." Penicillin Notice, 42 Fed.Reg. at 43,775. With respect to the transfer of antibiotic-resistant bacteria, the Director surveyed the available data and found that (1) the pool of bacteria carrying transferrable resistance genes was increasing; (2) the increase was due in part to the subtherapeutic use of penicillin in animal feed; and (3) antibiotic-resistant bacteria were transferred from animals to humans as a result of direct human-animal contact, the consumption of contaminated food, and the widespread presence of resistant bacteria in the environment. *See id.* at 43,781. Studies submitted by penicillin applicants and sponsors had failed to rebut theses findings. *See id.* Based on this evidence, the Director of the BVM proposed to withdraw approval of all NADAs/ANADAs for the use of penicillin in animal feed on the grounds "that the[se] drug products are not shown to be safe...." *Id.* at 43,792. The Director further cautioned that "[t]he evidence, in fact, indicates that such penicillin use may be unsafe ...." *Id.*

Similarly, the Director of the BVM announced health and safety concerns regarding the subtherapeutic use of tetracyclines in animal feed. The Director explained that "[e]vidence demonstrates that the use of subtherapeutic levels of the tetracyclines ... in animal feed contributes to the increase in antibiotic resistant *E. Coli* and in the subsequent transfer of this resistance to *Salmonella.* Further, some strains of *E. Coli* and *Salmonella* infect both man and animals.... Thus, the potential for harm exists ...." Tetracycline Notice, 42 Fed.Reg. at 56,267. The Director also noted that, in response to the 1972 FDA regulation announcing the health safety criteria for use of antibiotics in animal feed, the studies submitted by the holders of tetracyclines NADAs/ANADAs "were inconclusive because the studies were inappropriate." *Id.* The Director concluded that he "is unaware of evidence that satisfies the requirements for demonstrating the safety of extensive use of subtherapeutic tetracycline-contain-

Exhibit A	*National Resources Defense Council (NRDC) v. U.S. Food & Drug Admin. (FDA)*, 884 F. Supp. 2d 127 (2012)
Exhibit B	Excerpt from: Mark S. Smolinski et al., *Microbial Threats to Health: Emergence, Detection, and Response*, INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMIES (2003).
Exhibit C	*2009 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals*, FDA (2010), http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ UCM231851.pdf
Exhibit D	Letter from Karen Meister, Supervisory Congressional Affairs Specialist, to Louise M. Slaughter, United States Representative (D-NY) (Apr. 19, 2011)
Exhibit E	*The Overuse of Antibiotics in Food Animals Threatens Public Health*, CONSUMER REPORTS (Nov. 9, 2012), http://consumersunion.org/wp-content/uploads/2013/02/Overuse_of_Antibiotics_On_Farms.pdf
Exhibit F	Peter Eisler, *Drugs Can't Stop This Killer*, USA TODAY, Nov. 29, 2012, at 1A
Exhibit G	*Ch. 4: Reducing the use of antibiotics in animal husbandry*, WORLD HEALTH ORGANIZATION, THE EVOLVING THREAT OF ANTIMICROBIAL RESISTANCE: OPTIONS FOR ACTION (2012), http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf
Exhibit H	Letter from Thomas R. Frieden, M.D., M.P.H., Director, CDC and Administrator, Agency for Toxic Substances and Disease Registry to the Honorable Frank Pallone, Jr., Chairman, Subcommittee on Health (July 13, 2010)
Exhibit I	Antibiotic Resistances: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals (excerpts), GAO-04-490 (April 2004), at 11, 17-23, *available at:* http://www.gao.gov/new.items/d04490.pdf
Exhibit J	*2009 Retail Meat Report, National Antimicrobial Resistance Monitoring System*, FDA (2009), http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM257587.pdf
Exhibit K	*Antibiotic Resistance and Food Animal Production: a Bibliography of Scientific Studies (1969-2012)*, THE PEW CHARITABLE TRUSTS,

	http://www.pewhealth.org/uploadedFiles/PHG/Content_Level_Pages/Issue_Briefs/HHIFBibliographyFinal%20with%20TOC%20_111312.pdf
Exhibit L	M.E. Anderson & M.D. Sobsey, *Detection and occurrence of antimicrobially resistant E. coli in groundwater on or near swine farms in eastern North Carolina*, 54:3 WATER SCIENCE AND TECHNOLOGY, 211-18 (2006).
Exhibit M	S.R. Ladely et al., *Development of Macrolide-Resistant Campylobacter in Broilers Administered Subtherapeutic or Therapeutic Concentrations of Tylosin*, 70:8 JOURNAL OF FOOD PROTECTION, 1945-1951 (2007).
Exhibit N	*How safe is that chicken?*, CONSUMER REPORTS (Jan. 2010), http://www.consumerreports.org/cro/magazine-archive/2010/january/food/chicken-safety/overview/chicken-safety-ov.htm
Exhibit O	*What's in that pork?*, CONSUMER REPORTS (Jan. 2013), http://www.consumerreports.org/cro/pork0113.htm
Exhibit P	*Superbugs Invade American Supermarkets,* ENVIRONMENTAL WORKING GROUP (April 2013), http://www.ewg.org/meateatersguide/superbugs
Exhibit Q	Per Hennksen, DVM, PhD, Ministry of Food, Agriculture & Fisheries, Danish Testimony on the July 14th Hearing about Antibiotic Resistance in the Livestock Industry Organized by the Subcommittee on Health (July 12, 2010).
Exhibit R	*Antibiotic Resistance Poses "Catastrophic Threat" to Medicine, says Britain's Top Health Official*, HUFFINGTON POST (March 10, 2013), http://www.huffingtonpost.com/2013/03/10/antibiotic-resistance-catastrophic-threat_n_2850651.html
Exhibit S	*Raising Resistance: Feeding Antibiotics to Healthy Food Animals Breeds Bacteria Dangerous to Human Health*, NATIONAL RESOURCES DEFENSE COUNSEL (October 2011), http://www.nrdc.org/health/files/raisingresistance.pdf
Exhibit T	Steve Ellis & Russ Kremer, Op-Ed., *Regulate the use of antibiotics on farm animals*, DENVER POST (May 9, 2013), http://www.denverpost.com/opinion/ci_23201599/regulate-use-antibiotics
Exhibit U	JR Johnson et al. *Antimicrobial drug-resistant Escherichia coli from humans and poultry products, Minnesota and Wisconsin, 2002-2004*, 13:6 EMERGING INFECTIOUS DISEASES, 838-46 (2007).

Exhibit V	Warren RE et al., *Imported chicken meat as a potential source of quinolone-resistant Escherichia coli producing extended-spectrum beta-lactamases in the* [illegible] JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY 504-08 (2008).
Exhibit W	L. Unicomb et al., *Low-level Fluoroquinolone Resistance among Camplyobacter jejuni Isolates in Australia*, 42 CLINICAL INFECTIOUS DISEASES, 1368-74 (2006).
Exhibit X	A.R. Manges et al., *Endemic and epidemic lineages of Escherichia coli that cause urinary tract infections,* 14:10 EMERGING INFECTIOUS DISEASES 1575-83 (2008).
Exhibit Y	S.P. Smith et al., *Temporal changes in the prevalence of community-acquired antimicrobial-resistant urinary tract infection affected by* Escherichia coli *clonal group composition*, 46 CLINICAL INFECTIOUS DISEASES, 689-95 (2008).
Exhibit Z	C. Vincent et al., *Food Reservoir for* Escherichia coli *Causing Urinary Tract Infections*, 16:1 EMERGING INFECTIOUS DISEASES, 88-95 (2010).
Exhibit AA	L. Jakobsen et al., Escherichia coli *Isolates from Broiler Chicken Meat, Broiler Chickens, Pork, and Pigs Share Phylogroups and Antimicrobial Resistance with Community-dwelling Humans and Patients with Urinary Tract Infection*, 7:5 FOODBORNE PATHOGENS AND DISEASE, 537-47 (2010)
Exhibit BB	*Meat on Drugs*, CONSUMER REPORTS (June 2012), http://www.consumerreports.org/content/dam/cro/news_articles/health/CR%20Meat%20On%20Drugs%20Report%2007-12b.pdf
Exhibit CC	*Our Meat: No Antibiotics, Ever,* http://www.wholefoodsmarket.com/blog/whole-story/our-meat-no-antibiotics-ever-0 (last visited May 12, 2013).
Exhibit DD	*About FSIS,* FOOD SAFETY INSPECTION SERVICE, *available at:* http://www.fsis.usda.gov/About_FSIS/index.asp (last visited May 12, 2013)
Exhibit EE	*Meat and Poultry Labeling Terms,* FOOD SAFETY INSPECTION SERVICE, http://www.fsis.usda.gov/FACTSheets/Meat_&_Poultry_Labeling_Terms/index.asp (last visited May 12, 2013).
Exhibit FF	*FSIS as a Public Health Regulatory Agency: FSIS Statutes and Your Role,* FOOD SAFETY INSPECTION SERVICE (Nov. 9, 2007), http://www.fsis.usda.gov/PDF/PHVt-Statutes_Role.pdf
Exhibit GG	*U.S. v. Jorgensen*, 144 F.3d 550 (8th Cir. 1998)

Exhibit HH	*Grocery Mfrs. of America, Inc. v. Department of Public Health*, 379 Mass. 70 (1979)
Exhibit II	FDA Directive 73171.006, Illegal Residues in Meat, Poultry, Seafood, and Other Animal Derived Foods, 5-6 (H.H.S. 2005), http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/ComplianceEnforcement/ucm113433.pdf
Exhibit JJ	*Sanderson Farms, Inc. v. Tyson Foods, Inc.*, 547 F. Supp. 2d 491 (D. Md. 2008)
Exhibit KK	Restatement (Second) of Torts § 538(a) (1977)
Exhibit LL	*Consumer Reports Investigation: Talking Turkey,* CONSUMER REPORTS (June 2013), http://www.consumerreports.org/cro/magazine/2013/06/consumer-reports-investigation-talking-turkey/index.htm
Exhibit MM	*Stauber v. Shalala*, 895 F. Supp. 1178 (W.D. Wis. 1995)
Exhibit NN	Enrofloxacin for Poultry, 65 Fed. Reg. 64954 (Oct. 31, 2000)
Exhibit OO	67 Fed. Reg. 79552 (Dec. 30. 2002)
Exhibit PP	*NRDC v. FDA*, 872 F. Supp. 2d 318 (2012)

ence, the Director proposed to withdraw approval of certain NADAs/ANADAs for the subtherapeutic use of tetracyclines "on the grounds that they have not been show to be safe...." *Id.*

In response to the 1977 NOOHs, approximately twenty drug firms, agricultural organizations, and individuals requested hearings. *See* Penicillin and Tetracycline in Animal Feeds Hearing, 43 Fed.Reg. 53,827, 53,826 (Nov. 17, 1978). On November 9, 1978, the Commissioner of the FDA granted the requests for hearings, stating that "there w[ould] be a formal evidentiary public hearing on [the proposed withdrawals]." *Id.* at 53,827. The Commissioner stated that a date for the hearing would be set "as soon as practicable." *Id.* at 53,827–28. According to the statutory and regulatory scheme, at the hearing, the drug sponsors would have the burden of proving that the drugs were in fact safe. (*See* FDA, Final Decision of the Commissioner, Withdrawal of Approval of the New Animal Drug Application for Enrofloxacin in Poultry ("Enrofloxacin Decision"), attached as Ex. N to Barcelo Decl. at 8–9.)

***135** V. *The FDA's Actions Following the Issuance of the 1977 NOOHs*

The Commissioner never set a date for the hearings on the BVM's proposal to withdraw approval of the use of penicillin and tetracyclines in animal feed. In the late 1970s and early 1980s, Congressional committees issued three reports that contained statements that the FDA interpreted as requests to postpone the withdrawal hearings pending further research. Specifically, in 1978, the House Committee on Appropriations "recommend[ed]" that the FDA conduct research regarding "whether or not the continued subtherapeutic use of [penicillin and tetracyclines] would result in any significant human health risk" before revoking such approval. H.R. Rep. No. 95–1290, at 99–100 (1978). In 1980, the House Committee on Appropriations requested that the FDA "hold in abeyance any implementation" of the proposed revocation pending further research. H.R. Rep. No. 96–1095, at 105–06 (1980). In 1981, the Senate Committee on Appropriations made a similar request. *See* S. Rep. No. 97–248, at 79 (1981). Importantly, none of these recommendations was adopted by the full House or Senate, and none was passed as law.

Regardless of the legal effect of these Congressional statements, the FDA never held hearings on the proposed withdrawals, and instead engaged in further research on the risks associated with the subtherapeutic use of antibiotics in food-producing animals. Soon after the initial House Appropriations Committee request, the FDA contracted with the National Academy of Sciences ("NAS") to assess the human health consequences of the subtherapeutic use of penicillin and tetracyclines in animal feed by evaluating existing data, and to recommend areas for additional research. The NAS issued its report in 1980, drawing no conclusions about the safety of the subtherapeutic use of antibiotics in animal feed and recommending additional epidemiological studies. The FDA then contracted with the Seattle–King County Department of Public Health ("Seattle–King County") and the Institute of Medicine for further research. In 1984, Seattle–King County published its study, finding support for FDA's concerns about the risks posed by antibiotics in animal feeds. For example, the study found that *Campylobacter* bacteria were likely transferred from chickens to humans through the consumption of poultry products; samples of such bacteria taken from poultry products and humans exhibited "surprisingly high" rates of tetracycline resistance; and drug-resistant *Campylobacter* could transfer resistant genes to other bacteria. (*See* Excerpt from Seattle–King County Department of Public Health 1984 Report, attached as Ex. G to Declaration of Jennifer A. Sorenson ("Sorenson Decl.") at 3, 169.) The Institute of Medicine issued its report in 1988. Like the NAS, it could not conclude that the subtherapeutic use of antibiotics in animal feed was safe. However, it found several sources of "indirect evidence implicating subtherapeutic use of antimicrobials in producing resistance in infectious bacteria that causes a potential human health hazard." (

See Excerpt from Institute of Medicine 1988 Report, attached as Ex. H to Sorenson Decl. at 194.)

After the publication of the Seattle–King County and the Institute of Medicine studies, the FDA took little action on the still-pending 1977 NOOHs. In 1983, the Commissioner denied requests from several drug sponsors to rescind the 1977 NOOHs. *See* Penicillin and Tetracycline in Animal Feeds, 48 Fed.Reg. 4,554, 4,556 (Feb. 1, 1983). The Commissioner explained that the 1977 NOOHs "represent[ed] the Director's formal position that use of the drugs is not shown to be safe" and that the Commissioner "concur[red]" with the decision***136** of the Director. *Id.* In 2003, the FDA published a proposed rule that referenced the risks to human health from the subtherapeutic use of antibiotics in animal feed. *See* New Animal Drugs; Removal of Obsolete and Redundant Regulations, 68 Fed.Reg. 47,272, 47,272 (Aug. 8, 2003). The FDA referenced the NAS and Institute of Medicine reports, as well other relevant studies. *See id.* at 47,275. The FDA "(1) [c]oncluded that the risks were neither proved nor disproved, (2) did not deny there was some degree of risk, and (3) did not conclude that the continued subtherapeutic use of penicillin and tetracyclines in animal feed is safe." *Id.* In 2004, the BVM, now known as the Center of Veterinary Medicine ("CVM"), sent letters to several manufacturers of approved animal feed products containing penicillin and tetracyclines, explaining that "[t]he administrative record does not contain sufficient information to alleviate the CVN's concerns about the use of [these] product[s] and [their] possible role in the emergence and dissemination of antimicrobial resistance." (FDA Letters to Drug Sponsors (2004), attached as Ex. N to Sorenson Decl. at 2.) The FDA invited manufacturers to meet with the agency to discuss the agency's findings. (*See id.*)

On June 28, 2010, the FDA released a non-binding Draft Guidance entitled The Judicious Use of Medically Important Antimicrobial Drugs in Food–Producing Animals ("2010 Draft Guidance"). (*See* Guidance No. 209, attached as Ex. B to Barcelo Decl. at 1.) In the Draft Guidance, the FDA reviewed recent scientific studies on the risks posed by the subtherapeutic use of antibiotics in animal feed, including a 1997 World Health Organization expert committee report that "recommended that the use of antimicrobial drugs for growth promotion in animals be terminated if these drugs are also prescribed for use as anti-infective agents in human medicine or if they are known to induce cross-resistance to antimicrobials used for human medical therapy." (*See id.* at 8.) After reviewing the scientific evidence, the FDA concluded that "the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health." (*Id.* at 13.) The FDA announced two non-mandatory principles to guide the use of antibiotics in animal feed: (1) "[t]he use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health[;]" and (2) "[t]he use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation." (*Id.* at 16–17.)

On December 16, 2011, nearly twenty-five years after their initial publication and during the pendency of this action, the FDA rescinded the 1977 NOOHs. *See* Withdrawal of Notices of Opportunity for a Hearing; Penicillin and Tetracycline Used in Animal Feed ("NOOH Withdrawals"), 76 Fed.Reg. 79,697, 79,697 (Dec. 22, 2011). The FDA explained that it was rescinding the NOOHs because the "FDA is engaging in other ongoing regulatory strategies developed since the publication of the 1977 NOOHs" and that if the FDA were to move forward with the NOOHs it would need to "update the NOOHs to reflect current data, information, and policies" and "prioritize any withdrawal proceedings." *Id.* The FDA noted that "although [it] is withdrawing the 1977 NOOHs, FDA remains concerned about the issue of antimicrobial resist-

ance." *Id.* at 79,698. The FDA explained that the withdrawal of the NOOHs "should not be interpreted as a sign that FDA no longer has safety concerns or that FDA will not consider re-*137 proposing withdrawal proceedings in the future, if necessary." *Id.* at 79,698.

VI. *The Present Action*

Plaintiffs filed the present action on May 25, 2011, alleging that the FDA's failure to withdraw approval of the subtherapeutic use of penicillin and tetracyclines pursuant to the 1977 NOOHs constituted an agency action unlawfully withheld or unreasonably delayed in violation of the APA, 5 U.S.C. § 706(1), and the FDCA, 21 U.S.C. § 360b(e)(1).[FN6] Plaintiffs seek a Court order compelling the FDA to withdraw approval for the subtherapeutic use of penicillin and tetracyclines in animal feed, unless, after a hearing, the drug uses at issue are determined to be safe. (*See* Amended Compl. ¶ 101(C).) Plaintiffs further request that the Court set a deadline by which the FDA must hold hearings and issue a final decision on the withdrawals. (*See id.*) Plaintiffs maintain that under the FDCA,[FN7] 21 U.S.C. § 360b(e)(1), once the FDA found that the subtherapeutic use of penicillin and tetracyclines in animal feed was not shown to be safe to humans, the agency was statutorily obligated to withdraw approval of those uses, unless the drug sponsors demonstrated the safety of the drugs. Defendants contend that withdrawal was not legally required, and, in any event, the issue is now moot because the 1977 NOOHs have been withdrawn. Plaintiffs reply that the recent withdrawal of the NOOHs was in response to this litigation and has no bearing on the FDA's obligation to act.

FN6. The First Amended Complaint contained an additional claim pertaining to two Citizen Petitions submitted by Plaintiffs to the FDA in 1999 and 2005. (*See* First Amended Compl. ¶¶ 99–101.) In those Citizen Petitions, Plaintiffs petitioned the FDA to immediately withdraw approval for certain uses of penicillin and [illegible] in livestock given the evidence of the risks posed to human health. (*See id.* ¶¶ 82–87.) The FDA never issued a final response to these petitions. On November 7, 2011, the FDA issued final responses to both Citizen Petitions, denying the requested action. (*See* Stipulation and Order, dated Jan. 6, 2012). Consequently, Plaintiffs withdrew their claim as to the Citizen Petitions as moot, and the Court dismissed the claim without prejudice. (*See id.*) On January 9, 2012, Plaintiffs filed a motion for leave to file a supplemental complaint, which the Court granted on January 31, 2012. (*See* Scheduling Order, dated Jan. 31, 2012.) Plaintiffs filed their Supplemental Complaint on February 1, 2012, which added a claim that the FDA's final responses to the 1999 and 2005 Citizen Petitions were "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law, in violation of the [FDCA], 21 U.S.C. § 360b, and the APA, 5 U.S.C. § 706(2)." (Supplemental Compl. ¶ 38.)

FN7. Within the internal numbering of the FDCA, the statute at issue in this case is § 512.

DISCUSSION

I. *Legal Standard*

A. *Summary Judgment*

A motion for summary judgment may not be granted unless the Court determines that there is no genuine issue of material fact to be tried, and that the facts as to which there is no such issue warrant judgment for the moving party as a matter of law. *See Celotex Corp. v. Catrett,* 477 U.S. 317, 322–23, 106 S.Ct. 2548, 2552–53, 91 L.Ed.2d 265 (1986); *Patterson v. Cnty. of Oneida,* 375 F.3d 206, 219 (2d Cir.2004); *Shannon v. N.Y. City Transit Auth.,* 332 F.3d 95, 98 (2d Cir.2003). The burden of demonstrating the absence of any genuine dispute as to a

material fact rests upon the party seeking summary judgment, *see Adickes v. S.H. Kress & Co.*, 398 U.S. 144, 157, 90 S.Ct. 1598, 1608, 26 L.Ed.2d 142 (1970), but once a properly supported motion for summary judgment has been made, the burden shifts to the nonmoving ***138** party to make a sufficient showing to establish the essential elements of that party's case on which it bears the burden of proof at trial. *See Hayut v. State Univ. of N.Y.*, 352 F.3d 733, 743 (2d Cir.2003) (citing *Celotex*, 477 U.S. at 322, 106 S.Ct. at 2552). Where, as here, a court considers cross-motions for summary judgment, the court applies the same legal principles and "must evaluate each party's motion on its own merits, taking care in each instance to draw all reasonable inferences against the party whose motion is under consideration." *Make the Road by Walking, Inc. v. Turner*, 378 F.3d 133, 142 (2d Cir.2004) (citations omitted).

Here, the parties do not dispute the essential facts. The only issue before the Court is the legal conclusion resulting from those facts.

B. *The Administrative Procedure Act*

[1] "The APA authorizes suit by '[a] person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of the relevant statute.' " *Norton v. S. Utah Wilderness Alliance ("SUWA")*, 542 U.S. 55, 61, 124 S.Ct. 2373, 2378, 159 L.Ed.2d 137 (2004) (quoting 5 U.S.C. § 702). Under the APA, an "agency action" includes the "failure to act." 5 U.S.C. § 551(13).[FN8] Section 706(1) provides relief for an agency's failure to act by empowering reviewing courts to "compel agency action unlawfully withheld or unreasonably delayed[.]" 5 U.S.C. § 706(1); *see SUWA*, 542 U.S. at 62, 124 S.Ct. at 2378. The Supreme Court has made clear that § 706(1) applies only when an "an agency failed to take a *discrete* agency action that it is *required to take.*" *SUWA*, 542 U.S. at 64, 124 S.Ct. at 2379 (emphasis in original); *see also Benzman v. Whitman*, 523 F.3d 119, 130 (2d Cir.2008). The limit to discrete actions precludes a court from authorizing "broad programmatic attack[s]" on agency policy, and the limit to legally required actions ensures that a court will not interfere with an agency's discretionary functions. *See id.* at 64–65, 124 S.Ct. at 2379–80. Accordingly, "when an agency is compelled by law to act within a certain time period, but the manner of its action is left to the agency's discretion, a court can compel the agency to act, but has no power to specify what the action must be." *Id.* at 65, 124 S.Ct. at 2380. The Court further explained that the purpose of the limitations under § 706(1) "is to protect agencies from undue judicial interference with their lawful discretion, and to avoid judicial entanglement in abstract policy disagreements which courts lack both expertise and information to resolve." *Id.* at 66, 124 S.Ct. at 2381.

FN8. Specifically, the APA provides that " 'agency action' includes the whole or a part of an agency rule, order, license, sanction, relief, or the equivalent or denial thereof, or failure to act[.]" 5 U.S.C. § 551(13).

II. *Application*

Here, the Director of the BVM, issued the penicillin and tetracyclines NOOHs pursuant to 21 U.S.C. § 360b(e)(1), which governs the withdrawal of approval of NADAs/ANADAs. Specifically, § 360b(e)(1) reads:

> The Secretary shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application ... with respect to any new animal drug if the Secretary finds ... (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 ***139** 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 ....

21 U.S.C. § 360b(e)(1)(B),[FN9] In order to obtain the relief they seek, Plaintiffs must establish that § 360b(e)(1) legally requires the FDA to take a discrete action.

FN9. Section 360b(e)(1) lists six findings by the Secretary that prompt withdrawal. *See* 21 U.S.C. § 360b(e)(1)(A)-(F). The most relevant findings for the present action are those described in subsection (B).

A. *Discrete Action*

[2] Plaintiffs maintain that § 360b(e)(1) prescribes a set of discrete actions to be taken by the FDA in the event that new evidence shows that a new animal drug has not been shown to be safe. The statute requires that prior to issuing an order withdrawing approval of a NADA/ANADA, the FDA must provide notice to the drug sponsors and an opportunity for a hearing. *See* 21 U.S.C. § 360b(e)(1). If a drug sponsor or other interested party timely requests a hearing, the FDA must hold a public evidentiary hearing prior to issuing a final withdrawal order.

The FDA has promulgated numerous regulations to guide the withdrawal process. First, the notice issued by the FDA "must contain enough information to provide the respondent a genuine opportunity to identify material issues of fact." *Hess & Clark, Div. of Rhodia, Inc. v. Food & Drug Admin.* (*"Hess & Clark"*), 495 F.2d 975, 983 (D.C.Cir.1974); *see also Rhone–Poulenc, Inc., Hess & Clark Div. v. Food & Drug Admin.* (*"Rhone–Poulenc"*), 636 F.2d 750, 752 (D.C.Cir.1980); 21 C.F.R. § 514.200(a). If a NADA/ANADA applicant requests a hearing, he must submit, in writing, an explanation of why the NADA/ANADA "should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition to the [proposed withdrawal]." 21 C.F.R, § 514.200(c). If, in his application for a hearing, an applicant fails to raise a genuine and substantial issue of fact, the Commissioner may deny the request for a hearing and summarily withdraw approval for the NADA/ANADA based on the data presented in the original notice. *See id.*; *Hess & Clark,* 495 F.2d at 984–85 (approving the FDA's use of the summary judgment procedure where the NOOH presents a "prima facie case for withdrawal"). If a hearing is granted, "the issues will be defined, an Administrative Law Judge will be named, and he shall issue a written notice of the time and place at which the hearing will commence." 21 C.F.R. § 514.200(c). The purpose of the hearing is to provide a "fair determination of relevant facts consistent with the right of all interested persons to participate ...." 21 C.F.R. § 12.87. At the hearing, the FDA has the initial burden of producing evidence that the drug has not been shown to be safe, which is generally contained in the notice. *See Rhone–Poulenc,* 636 F.2d at 752, (Enrofloxacin Decision at 8.) However, the drug sponsor has the "burden of persuasion on the ultimate question of whether [the drug] is shown to be safe." (Enrofloxacin Decision at 9); *see also Rhone–Poulenc,* 636 F.2d at 752. As soon as possible after a hearing, the presiding officer issues an initial decision that includes findings of fact, conclusions of law, a discussion of the reasons for the findings and conclusions, and appropriate citations. *See* 21 C.F.R. § 12.120(a)-(b). A participant in a hearing may appeal an initial decision to ***140** the Commissioner. *See* 21 C.F.R. § 12.125(a).

Defendants argue that given the procedural complexity of issuing a notice and holding a hearing, which may take months or years to complete, the relief sought by Plaintiffs is not discrete. The Court disagrees. Upon a finding that a new animal drug has not been shown to be safe, § 360b(e)(1) and the accompanying regulations require the FDA to implement several related discrete actions: (1) provide notice of the FDA's finding and intent to withdraw approval; (2) provide an opportunity for a hearing to the relevant animal drug sponsors; (3) if an applicant timely requests a hearing and raises a genuine issue of fact, hold a hearing; and (4) if the

applicant fails to show that the drug is safe, the Commissioner must issue an order withdrawing approval of the drug. The first three steps are statutory precursors to issuing the final withdrawal order. The APA defines "agency action" to include the issuance of an order, *see* 5 U.S.C. § 551(13), and the Supreme Court has defined an order as a discrete agency action. *See SUWA,* 542 U.S. at 62, 124 S.Ct. at 2378. Moreover, the APA anticipates that an order will be preceded by a hearing or a similar process, as it defines "adjudication" as the "agency process for formulation of an order[.]" 5 U.S.C. § 551(7); *see also* 5 U.S.C. § 551(6) (defining "order" as "the whole or part of a final disposition ... of an agency in a matter other than rulemaking but including licensing."). The fact that § 360b(e)(1) requires notice and an opportunity for a hearing prior to the issuance of a withdrawal order does not undermine the fact that the requested relief is a discrete agency action. *See id.* Plaintiffs are not launching a "broad programmatic attack" on the FDA's animal drug policies; rather, Plaintiffs have identified certain new animal drugs that the agency has publicly concluded are "not shown to be safe" and is requesting that the agency move forward with its statutory duty to hold the requested hearings and withdraw approval if the drug sponsors fail to show that the drugs are safe.[FN10] *See SUWA,* 542 U.S. at 64, 124 S.Ct. at 2379–80 (contrasting a "discrete" agency action with a "broad programmatic attack").

FN10. Plaintiffs have not asked the Court to direct the outcome of the requested hearings or to compel Defendants to issue a final withdrawal order.

B. *Legally Required Action*

The parties dispute whether, given the facts of this case, § 360b(e)(1) legally requires the Commissioner of the FDA to hold withdrawal proceedings for the relevant penicillin and tetracyclines NADAs/ANADAs. Defendants acknowledge that § 360b(e)(1) contains language mandating the Secretary to act ("[t]he Secretary *shall,* after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application ... if the Secretary finds ..."). *See Nat'l Ass'n of Home Builders v. Defenders of Wildlife,* 551 U.S. 644, 661–62, 127 S.Ct. 2518, 2531–32, 168 L.Ed.2d 467 (2007) (interpreting the statutory language "shall approve" to impose upon the agency a mandatory duty); *Lopez v. Davis,* 531 U.S. 230, 241, 121 S.Ct. 714, 722, 148 L.Ed.2d 635 (2001) (noting Congress' "use of a mandatory 'shall' ... to impose discretionless obligations"); *Lexecon Inc. v. Milberg Weiss Bershad Hynes & Lerach,* 523 U.S. 26, 35, 118 S.Ct. 956, 962, 140 L.Ed.2d 62 (1998) ("[T]he mandatory 'shall' ... normally creates an obligation impervious to judicial discretion."). However, Defendants disagree with Plaintiffs as to when and how the Secretary's duty to act is triggered. Defendants contend that the statute only requires the Secretary to ***141** withdraw approval of a NADA/ANADA if the Secretary makes a finding after a formal hearing. Since the FDA never held hearings and has now withdrawn the 1977 NOOHs, Defendants argue that no findings have been made and no further action is required. Plaintiffs contend that under § 360b(e)(1) the Secretary makes a finding prior to a hearing, and that upon making such a finding, the Secretary is legally required to withdraw approval of a drug, unless the drug sponsor requests a hearing and shows that the drug is safe. They further argue that the FDA's recent withdrawal of the 1977 NOOHs does not disturb the agency's original findings and that the FDA is legally required to hold withdrawal proceedings for the relevant penicillin and tetracyclines NOOHs. The question before the Court is whether the FDA is legally required to proceed with the hearing and withdrawal process.

1. *Statutory Interpretation*

a. *Legal Standard*

[3][4][5] In interpreting a statute, a court "must give effect to the unambiguously expressed intent of Congress." *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.,* 467 U.S. 837, 843, 104 S.Ct.

Congress's intent, [a court] begin[s] with the statutory text because if its language is unambiguous, no further inquiry is necessary." *Cohen v. JP Morgan Chase & Co.*, 498 F.3d 111, 116 (2d Cir.2007) (citations omitted); *see also Tyler v. Douglas*, 280 F.3d 116, 122 (2d Cir.2001) (" 'If the statutory terms are unambiguous, [a court's] review generally ends and the statute is construed according to the plain meaning of its words.' ") (quoting *Sullivan v. Cnty. of Suffolk*, 174 F.3d 282, 285 (2d Cir.1999)). Statutory interpretation must take into account the "structure and grammar" of the provision. *See Bloate v. United States*, 559 U.S. 196, ——, 130 S.Ct. 1345, 1354–55, 176 L.Ed.2d 54 (2010). "If the statutory language is ambiguous, however, [a court] will 'resort first to cannons of statutory construction, and, if the [statutory] meaning remains ambiguous, to legislative history' " to determine the intent of Congress. *Cohen*, 498 F.3d at 116 (quoting *Daniel v. Am. Bd. of Emergency Med.*, 428 F.3d 408, 423 (2d Cir.2005)). If the intent of Congress remains unclear, a court will defer to an agency's interpretation of the statute, so long as it is "reasonable." *See Chevron*, 467 U.S. at 843–44, 104 S.Ct. at 2782.

b. *Application: Findings Pursuant to § 360b(e)(1)*

[6] Here, the statute unambiguously commands the Secretary to withdraw approval of any new animal drug that he finds is not shown to be safe, provided that the sponsor of the animal drug has notice and an opportunity for a hearing. *See* 21 U.S.C. § 360b(e)(1). The statute does not explicitly state the order in which this process must occur. Defendants maintain that the Secretary can only issue a finding after a hearing, whereas Plaintiffs claim the Secretary makes a finding first, which then triggers the Secretary's obligation to provide notice and an opportunity for a hearing.

The Court finds that Plaintiff's interpretation provides a common sense reading of the statute based on its text and grammatical structure. The statute states that "[t]he Secretary shall, after due notice and opportunity for hearing to the applicant ... issue an order withdrawing approval of a [ ] [NADA/ANADA] ... if the Secretary finds ... [that a drug is not shown to be safe] ...." The "after due notice and opportunity for hearing" clause is setoff by commas and immediately precedes the words "issue an order withdrawing approval,"***142** indicating that the "notice" clause modifies the "issue an order" clause and not the findings clause. *See United States v. Liranzo*, 729 F.Supp. 1012, 1014 (S.D.N.Y.1990) (interpreting a modifier to apply to the verb closest to it) (citing W. Strunk, Jr. & E.B. White, *The Elements of Style* 30 (3d ed. 1979)). Accordingly, the statute only requires the Secretary to give notice and provide an opportunity for a hearing before issuing an order of withdrawal and *not* before making findings. Under this reading, if the Secretary finds that an animal drug has not been shown to be safe, he is statutorily required to withdraw approval of that drug, provided that the drug sponsor has notice and an opportunity for a hearing. *See Rhone–Poulenc*, 636 F.2d at 752 ("[T]he Commissioner must withdraw his approval [of an animal drug] whenever he finds that 'new evidence ... shows that such drug is not shown to be safe ....' ") (quoting 21 U.S.C. § 360b(e)(1)(B)). If, after a hearing, the drug sponsor has not met his burden of proving the drug to be safe, the Secretary must issue a withdrawal order.[FN11]

> FN11. Admittedly, the Secretary will make a second set of findings after a hearing, but the initial findings trigger the mandatory withdrawal process and, if not rebutted, provide a basis for mandatory withdrawal.

The text and grammar of other provisions within § 360b support this interpretation. For example, § 360b(d)(1) explicitly requires the Secretary to provide notice and an opportunity for a hearing before making findings regarding the approval or refusal of a NADA. *See* 21 U.S.C. § 360b(d)(1). Section 360b(d)(1) reads: "If the Secretary finds, after due notice to the applicant ... and giving him an opportunity for a hearing, ... he shall issue an order re-

fusing to approve the application." By placing the "notice" clause immediately after the phrase "[i]f the Secretary finds," § 360b(d)(1) clearly requires notice and an opportunity for a hearing prior to the issuance of findings by the Secretary. The fact that Congress used such language in § 360b(d)(1) and used different language in § 360b(e)(1) supports the Court's conclusion that notice and an opportunity for a hearing are not required before the Secretary makes findings under the latter provision. *See Novella v. Westchester Cnty.*, 661 F.3d 128, 142 (2d Cir.2011) (explaining that the presence of a term in one provision and not in another was deliberate and meaningful).

Moreover, § 360b(e)(1) includes a specific note about the notice and hearing requirement when the Secretary finds that a new animal drug poses an imminent risk to humans or animals, which indicates that findings are made before a hearing. Specifically, the statute states that

> [i]f the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the health of man or of the animals for which such drug is intended, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection ....

21 U.S.C. § 360b(e)(1). This provision anticipates the Secretary making findings in advance of a hearing; otherwise, the clause requiring the Secretary to provide notice and an opportunity for an expedited hearing would be redundant and nonsensical. The Court cannot adopt such an interpretation. *See Conn. ex rel. Blumenthal v. Dep't of Interior*, 228 F.3d 82, 88 (2d Cir.2000) ("... [courts] are required to 'disfavor interpretations of statutes that render language superfluous.' ") (quoting ***143** *Conn. Nat'l Bank v. Germain*, 503 U.S. 249, 253, 112 S.Ct. 1146, 1149, 117 L.Ed.2d 391 (1992)). Although the Secretary's authority to make a finding of imminent hazard "shall not be delegated," the fact that this finding is made before notice or an opportunity for a hearing are provided supports that findings pursuant to § 360b(e)(1) are made prior to a hearing. This interpretation is further buttressed by the statutory purposes underlying the FDA, the agency tasked with implementing § 360b(e)(1) and the FDCA. Specifically, the FDA "shall ... promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner; [and] with respect to such products, protect the public health by ensuring that ... human and veterinary drugs are safe and effective [.]" 21 U.S.C. § 393(b)(1)-(2). According to its statutory mandate, the FDA is responsible for continuously monitoring regulated drugs and reviewing new studies of their effectiveness and safety. Given this regulatory structure, it seems clear that Congress intended the FDA to monitor approved animal drugs and issue findings when new evidence indicates that a drug is no longer shown to be safe, triggering the withdrawal process.

Accordingly, based on the text and grammar of § 360b(e)(1), as well as the structure of § 360b as a whole and the overriding purpose of the FDA, the Court finds that the plain meaning of § 360b(e)(1) requires the Secretary to issue notice and an opportunity for a hearing whenever he finds that a new animal drug is not shown to be safe. If the drug sponsor does not meet his burden of demonstrating that the drug is safe at the hearing, the Secretary must issue an order withdrawing approval of the drug.

This interpretation is consistent with how courts have interpreted 21 U.S.C. § 355(e), the human drug parallel to § 360b(e). *See Food & Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 134, 120 S.Ct. 1291, 1301, 146 L.Ed.2d 121 (2000) ("If the FDA discovers after approval that a drug is unsafe or ineffective, it 'shall, after due notice and opportunity for hearing to the applicant, withdraw approval' of the drug,") (quoting 21 U.S.C. § 355(e)(1)-(3)); *Mylan Labs., Inc. v. Thompson*, 389 F.3d 1272, 1281 (D.C.Cir.2004)

Cross must move forward.

c. *Application: Authority of the Director of the BVM*

Defendants assert that even if a finding triggers the FDA's obligations pursuant to § 360b(e)(1), there have been no such findings in this case. Defendants maintain that the Director of the BVM, who issued the 1977 NOOHs, is not authorized to make findings pursuant to § 360b(e)(1). The statute does not explicitly authorize the Director to make findings, and Defendants therefore argue that the Court should defer to the agency's position that the Director of the BVM is not authorized to make the requisite findings. *See Chevron,* 467 U.S. at 842–43, 104 S.Ct. at 2781–82.

As discussed *supra,* if a court determines that a statute is ambiguous and that "Congress has not directly addressed the precise question at issue," the court must defer to an agency's "reasonable" interpretation of the statute it administers. *Id.* at 842–44, 104 S.Ct. at 2781–82. "[An] administrative implementation of a particular ***146** statutory provision qualifies for *Chevron* deference when it appears that Congress delegated authority to the agency generally to make rules carrying the force of law, and that the agency interpretation claiming deference was promulgated in the exercise of that authority." *United States v. Mead Corp.,* 533 U.S. 218, 226–27, 121 S.Ct. 2164, 2171, 150 L.Ed.2d 292 (2001). An agency has been delegated such authority if it has the "power to engage in adjudication or notice-and-comment rulemaking" or if there is "some other indication of a comparable congressional intent." *Id.,* at 227, 121 S.Ct. at 2171. Factors to consider when determining whether the *Chevron* framework applies to an agency interpretation include "the interstitial nature of the legal question, the related expertise of the [a]gency, the importance of the question to administration of the statute, the complexity of that administration, and the careful consideration the [a]gency has given the question over a long period of time ...." *Barnhart v. Walton,* 535 U.S. 212, 222, 122 S.Ct. 1265, 1272, 152 L.Ed.2d 330 (2002). The Second Circuit has been hesitant to apply *Chevron* deference to nonlegislative rules issued by agencies and has "made clear that 'interpretations contained in policy statements, agency manuals and enforcement guidelines, all of which lack the force of law—do not warrant *Chevron* style deference.' " *De La Mota v. U.S. Dep't of Educ.,* 412 F.3d 71, 79 (2d Cir.2005) (quoting *Christensen v. Harris Cnty.,* 529 U.S. 576, 587, 120 S.Ct. 1655, 1662, 146 L.Ed.2d 621 (2000)); *see also Estate of Landers v. Leavitt,* 545 F.3d 98, 106 (2d Cir.2008).

[8] Here, § 360b(e)(1) is ambiguous as to whether the Director of the BVM may make the requisite findings. The text of the statute refers to findings made by the "Secretary," which the FDCA defines as the Secretary of HHS. *See* 21 U.S.C. § 321(d). The Secretary, in turn, delegated to the Commissioner of the FDA all of the authority vested in him pursuant to the FDCA. (*See* § 1410.10 of Volume III of the FDA Staff Manual Guides, Delegations of Authority to the Commissioner Food and Drugs, attached as Ex. A to Barcelo Decl., ¶ 1(A)(1).) The Commissioner, in turn, delegated authority to the Director of the BVM to issue notices of opportunity for a hearing on proposals to withdraw approval of new animal drug applications, and the authority to issue orders withdrawing approval when the opportunity for a hearing has been waived. (*See* § 1410.503 of Volume II of the FDA Staff Manual Guides, Issuance of Notice, Proposals, and Orders Relating to New Animal Drugs and Medicated Feed Mill License Applications ("Staff Manual"), attached as Ex. A to Barcelo Decl., ¶ 1(A)(1)-(2).) The question before the Court is whether the authority delegated to the Director includes the authority to make findings that trigger the FDA's non-discretionary duties pursuant to § 360b(e)(1).

Defendants urge the Court to defer to their interpretation that the Director does not have authority to make such findings. Defendants argue that because the Commissioner did not delegate author-

ity to the Director to issue orders of withdrawal after a hearing, the Director cannot make the findings necessary to trigger the FDA's non-discretionary duties under § 360b(e)(1). However, this argument hinges on Defendants' incorrect interpretation of § 360b(e)(1), whereby a finding can be made only after a hearing. As the Court reads § 360b(e)(1) and the accompanying regulations to contemplate findings made prior to a hearing, Defendants' reliance on the Staff Manual is of no avail. In fact, the delegations within the Staff Manual support Plaintiffs' position that the FDA is legally required to re-institute ***147** withdrawal proceedings for penicillin and tetracyclines in animal feed.

By authorizing the Director to issue notices of an opportunity for a hearing, the Commissioner necessarily authorized the Director to make the findings on which such notices of withdrawal are based. Any notice issued must "specify the grounds upon which" the proposal to withdraw is based. 21 C.F.R. § 514.200(a). Under both the statute and the regulation, a proposal to withdraw may be based on a finding that an animal drug has not been shown to be safe. *See* 21 U.S.C. 360b(e)(1)(B); 21 C.F.R. § 514.115(b)(3)(ii). In practice, the Director generally states his conclusion that the drug has not been shown to be safe and cites § 360b(e)(*1*). *See* Dimetridazole; Opportunity for Hearing, 51 Fed.Reg. 45,244, 45,244 (Dec. 17, 1986) ("This [notice of intent to withdraw approval] is being [issued] in accordance with section 512(e)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. § 360b(e)(1)(b)). That section requires FDA to withdraw approval of an NADA if the agency finds ... that such drug is *not shown to be safe ... [T]he Center [for Veterinary Medicine] has determined that dimetridazole is not shown to be safe for use within the meaning of section of 512(e)(1)(B) [.]* ") (emphasis added); Enrofloxacin Notice, 65 Fed.Reg. at 64,954 ("CVM is proposing to withdraw the approval of the new animal drug application for use of enrofloxacin in poultry on the grounds that new evidence shows that the product *has not been shown to be safe as provided for in the Federal Food, Drug, and Cosmetic Act* ....") (emphasis added). It is clear from the FDA's own practice that the Director of the BVM is authorized to make the requisite findings that trigger withdrawal proceedings pursuant to § 360b(e)(1). Accordingly, by explicitly delegating to the Director the authority to issue withdrawal notices, the Commissioner delegated to the Director the authority to make the findings that are a statutory prerequisite to any such notice.

This conclusion is further supported by the fact that in the event that the Director issues a notice and the drug applicant does not request a hearing, the Director is authorized to summarily issue an order withdrawing approval. (*See* Staff Manual ¶ 1(A)(2).) In such cases, the findings made by the Director—and upon which the initial notice was based—provide a sufficient basis to withdraw approval of a NADA under § 360b(e)(1). *See* Shulcon Industries, Inc.; Withdrawal of Approval of a New Animal Drug Application ("Shulcon Withdrawal"), 59 Fed.Reg. 1950, 1950 (Jan. 13, 1994) ("The notice of opportunity for a hearing stated that CVM was proposing to issue an order under [§ 360b(e)] withdrawing approval of the NADA .... Shulcon Industries, Inc. failed to file [a] request for a hearing.... [U]nder authority delegated to the Commissioner of Food and Drugs ... and redelegated to the Center for Veterinary Medicine ... notice is given that approval of NADA 111–068 ... is hereby withdrawn.").

Although the FDA has been delegated the authority to pass rules and regulations carrying the force of law, the agency has not promulgated any regulation, opinion letter, or internal agency guidance specifying the limits of the Director's delegated authority to which the Court could defer. Moreover, in practice, the Director routinely exercises the authority that the FDA now claims the Director lacks. The Court cannot defer to an interpretation that the FDA appears to have adopted solely for litigation purposes. *See Bowen v. Geor-*

468, 473–74, 102 L.Ed.2d 493 (1988) ("[The Supreme Court] h[as] never applied the principle of [*Chevron* deference]***148** to agency litigating positions that are wholly unsupported by regulations, rulings, or administrative practice."). Finally, any doubt that the Director was authorized to issue the findings in the 1977 NOOHs is conclusively dispelled by the Commissioner's acknowledgment and endorsement of the Director's findings. *See* Penicillin and Tetracycline in Animal Feeds, 48 Fed.Reg. 4,554, 4,556 (Feb. 1, 1983).

2. *Findings Regarding the Subtherapeutic Use of Penicillin and Tetracyclines*

[9] Having found that the Director of the BVM is authorized to make findings under § 360b(e)(1), the question becomes whether the Director made such findings for the subtherapeutic use of penicillin and tetracyclines. In the 1977 Penicillin Notice, the Director stated that he is

> unaware of evidence that satisfies the requirements for the safety of penicillin-containing premixes as required by [§ 360b of the FDCA] and § 558.15 of the agency's regulations. Accordingly, he concludes, on the basis of new information before him with respect to these drug products, evaluated together with the evidence available to him when they were originally approved, *that the drug products are not shown to be safe* .... The evidence, in fact, indicates that such penicillin use may be unsafe ....

Penicillin Notice, 42 Fed.Reg. at 43,792 (emphasis added). Similarly, in the 1977 Tetracycline Notice, the Director stated that he is

> unaware of evidence that satisfies the requirements for demonstrating the safety of extensive use of subtherapeutic tetracycline-containing premixes established by section [360b] of the [FDCA] .... Accordingly, he concludes, on the basis of new information before him with respect to these drug products, evaluated together with the evidence available to him when they were originally approved, that the drug products are safe

the Notice].

Tetracycline Notice, 42 Fed.Reg. at 56,288. Accordingly, in both the Penicillin and the Tetracycline Notices, the Director explicitly concluded that the drugs had not been shown to be safe and cited § 360b. Such a conclusion is the statutory trigger for the FDA to institute withdrawal proceedings, which it in fact did. Based on the language of the 1977 Notices, the Director made the findings necessary to trigger mandatory withdrawal proceedings for the subtherapeutic uses of penicillin and tetracyclines in animal feed.[FN15]

> FN15. Furthermore, during oral argument, counsel for the FDA acknowledged that the Director lawfully issued the NOOHS in 1977 and that they were not *ultra vires,* indicating that the Director has the authority to make findings sufficient to institute withdrawal proceedings. (*See* Transcript of Hearing dated Feb. 23, 2012 ("Transcript"), at 12.)

Even if the Court were to adopt Defendants' interpretation that the Director is not authorized to make the requisite findings under § 360b(e)(1), the Court would still conclude that the FDA is legally required to hold withdrawal proceedings because the Commissioner has made the requisite findings by noting and ratifying the Director's findings. In 1983, the Commissioner published a statement of policy in the Federal Register denying several requests from drug sponsors to rescind the 1977 NOOHs, in which the Commissioner "concurr[ed]" with the Director's findings that the drugs had not been shown to be safe. *See* Penicillin and Tetracycline in Animal Feeds, 46 Fed.Reg. at 4,556 (explaining the Director of BVM's decision not to rescind the 1977 NOOHs because ***149** they "represent the Director's formal position that use of the drugs is not shown to be safe" and stating that "[t]he Commissioner has reviewed the Director's decision and concurs with it."). Based on this concurrence, the Commissioner has adopted and, there-

fore, issued findings, and the § 360b(e)(1) mandatory withdrawal proceedings have been triggered.

III. *Mootness*

A. *Legal Standard*

[10][11][12] "It has long been settled that a federal court has no authority 'to give opinions upon moot questions or abstract propositions, or to declare principles or rules of law which cannot affect the matter in issue in the case before it.' " *Church of Scientology of Cal. v. United States,* 506 U.S. 9, 12, 113 S.Ct. 447, 449, 121 L.Ed.2d 313 (1992) (quoting *Mills v. Green,* 159 U.S. 651, 653, 16 S.Ct. 132, 133, 40 L.Ed. 293 (1895)). "The mootness doctrine provides that 'an actual controversy must be extant at all stages of review, not merely at the time the complaint is filed.' " *Conn. Office of Protection & Advocacy for Persons with Disabilities v. Hartford Bd. of Educ.,* 464 F.3d 229, 237 (2d Cir.2006) (quoting *British Int'l Ins. Co. v. Seguros La Republica, S.A.,* 354 F.3d 120, 122 (2d Cir.2003)). "The existence of a real case or controversy is an irreducible minimum to the jurisdiction of the federal courts." *United States v. City of New York,* 972 F.2d 464, 469–70 (2d Cir.1992) (quoting *Valley Forge Christian Coll. v. Ams. United for Separation of Church and State,* 454 U.S. 464, 471, 102 S.Ct. 752, 757–58, 70 L.Ed.2d 700 (1982)). Accordingly, "if an event occurs while a case is pending ... that makes it impossible for the court to grant any effectual relief whatever to a prevailing party, the [case] must be dismissed." *Church of Scientology of Cal.,* 506 U.S. at 12, 113 S.Ct. at 449 (internal quotation marks and citation omitted).

B. *Application*

Here, Defendants maintain that Plaintiffs' claim is now moot because, during the pendency of this case, the FDA rescinded the 1977 NOOHs for the subtherapeutic use of penicillin and tetracyclines in animal feed. *See* NOOH Withdrawals, 76 Fed.Reg. 79,697, 79,697 (Dec. 22, 2011).

[13][14] Plaintiffs' claim arises under § 706(1) of the APA, which authorizes the Court to grant Plaintiffs relief if they establish that the FDA failed to take a legally required discrete action. Plaintiffs contend, and the Court agrees, that upon a finding by the FDA that a new animal drug has not been shown to be safe, the FDA is required to withdraw approval of that drug after providing notice and an opportunity for a hearing. Therefore, the trigger for FDA to initiate mandatory withdrawal proceedings is *not* the issuance of a NOOH but a finding that a drug has not been shown to be safe. The issuance of a NOOH is simply the first step in the mandatory withdrawal process. Accordingly, Plaintiffs are still entitled to relief and their claim is not moot if they can establish that the rescission of the NOOHs did not rescind the FDA's findings that the subtherapeutic use of penicillin and tetracyclines in animal feed has not been shown to be safe.

The record makes clear that the FDA did not rescind its findings when it rescinded the 1977 NOOHs. In the official notice rescinding the 1977 NOOHs, the FDA provided three justifications for the rescission:

> (1) FDA is engaging in other ongoing regulatory strategies developed since the publication of the 1977 NOOHs with respect to addressing microbial food safety issues; (2) FDA would update the ***150** NOOHs to reflect current data, information, and policies if, in the future, it decides to move forward with withdrawal of the approved uses of the new animal drugs described in the NOOHs; and (3) FDA would need to prioritize any withdrawal proceedings....

NOOH Withdrawals, 76 Fed.Reg. 79,697, 79,698 (Dec. 22, 2011). None of these reasons addresses the initial findings that prompted the NOOHs or suggests that the FDA is rescinding those findings. Rather, in the notice rescinding the 1977 NOOHs, the FDA emphasized its continuing concerns about the subtherapeutic use of penicillin and tetracyclines. "Although FDA is withdrawing the 1977 NOOHs, FDA remains concerned about the issue of antimicrobial resistance. Today's action

should not be interpreted as a sign that FDA no longer has safety concerns or that FDA will not consider re-proposing withdrawal proceedings in the future, if necessary." *Id.* at 79,698. This public announcement of the FDA's continuing safety concerns and its attempts at other strategies support the view that the FDA has not rescinded its original findings that use of the drugs has not been shown to be safe.[FN16]

FN16. Any claim that the 1977 NOOHs are out-of-date does not relieve the FDA of its obligation to proceed with the withdrawal process. First, the agency cannot, through its own prolonged inaction, create obstacles to its statutorily mandated obligation. Second, while there have been additional scientific studies since the 1977 NOOHs were issued, they all appear to support the FDA's original finding that the use of these drugs has not been shown to be safe. Finally, nothing precludes the FDA from updating the NOOHs, so long as it does so in a reasonably prompt manner.

In addition, the 2010 Draft Guidance, which represents the FDA's current strategy to address microbial food safety issues, emphasizes the FDA's continuing concerns about the safety of the subtherapeutic use of penicillin and tetracyclines in animal feed. (*See* Guidance No. 209, attached as Ex. B to Barcelo Decl. at 4.) In preparing the Guidance, the FDA reviewed key scientific studies and reports and concluded that "the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production purposes is not in the interest of protecting and promoting the public health." (*See id.* at 13.)[FN17] The FDA has not issued a single statement since the issuance of the 1977 NOOHs that undermines the original findings that the drugs have not been shown to be safe. The FDA's recent decision to rescind the 1977 NOOHs, while reiterating its continuing concerns about the safety risks posed by the subtherapeutic uses of penicillin and tetracyc-

[illegible] *151 the agency of its statutory duty to initiate and complete withdrawal proceedings. *See Am. Pub. Health Ass'n v. Veneman*, 349 F.Supp. 1311, 1315–16 (D.D.C.1972) (requiring the FDA to initiate withdrawal proceedings after finding that the agency's "many announcements ... in the Federal Register regarding FDA conclusions about the efficacy of various drugs" constituted findings under 21 U.S.C. § 355(e), the human drug corollary to § 360b(e)).

FN17. The 2010 Draft Guidance recommends that medically important antibiotics, including penicillin and tetracyclines, be used "judiciously." (*See* Guidance No. 209, attached as Ex. B to Barcelo Decl. at 16.) "In light of the risk that antimicrobial resistance poses to public health, FDA believes the use of medically important antimicrobial drugs in food producing animals for production purposes (e.g., to promote growth or improve food efficiency) represents an injudicious use of these important drugs." (*See id.* at 16.) Strict adherence to the 2010 Draft Guidance would not permit the subtherapeutic use of penicillin and tetracyclines. However, the 2010 Draft Guidance merely provides recommendations, there are no penalties for failing to adhere to the 2010 Draft Guidance. Nonetheless, the Draft Guidance makes clear that in the approval process for new NADAs/ANADAs, "products that ultimately move forward toward approval are those products that include use conditions that are consistent with the guidance and are intended to minimize the extent to which the product use would contribute to [antibiotic-] resistance development." (*Id.* at 15.) Under the FDA's current model, therefore, the NADAs/ANADAs at issue in this case would not be approved.

[15] Lastly, the fact that the FDA "is engaging in other ongoing regulatory strategies," NOOH

Withdrawals, 76 Fed.Reg. at 79,698, does not relieve it of its statutory obligation to complete withdrawal proceedings. Upon a finding that the use of a drug under certain conditions has not been shown to be safe, § 360b(e)(1) prescribes a clear course of conduct: issue notice and an opportunity for a hearing, and, if the drug sponsor does not demonstrate that the drug use is safe at the hearing, withdraw approval of such use.[FN18] The statute does not empower the agency to choose a different course of action in lieu of withdrawal proceedings, such as that embodied in the 2010 Draft Guidance. *See Pub. Citizen, Inc. v. Nat'l Highway Traffic Safety Admin.*, 374 F.3d 1251, 1261 (D.C.Cir.2004) ("[A]n agency ordered by Congress to promulgate binding regulatory requirements may not issue a non-binding policy statement that encourages but does not compel action.") (citing *Pub. Citizen v. Nuclear Regulatory Comm'n*, 901 F.2d 147, 157 (D.C.Cir.1990)); *Natural Res. Def. Council, Inc. v. Envtl. Prot. Agency*, 595 F.Supp. 1255, 1261 (S.D.N.Y.1984) ("The agency charged with implementing the statute is not free to evade the unambiguous directions of the law merely for administrative convenience.") (internal quotation marks and citations omitted).

FN18. Of course, if the drug sponsors demonstrate that the use of the drug is safe, then the Commissioner cannot withdraw approval.

Accordingly, because the rescission of the 1977 NOOHs did not rescind the original findings that the subtherapeutic use of penicillin and tetracyclines in food-producing animals has not been shown to be safe, Plaintiffs' claim is not moot.

CONCLUSION

For the foregoing reasons, Plaintiffs' Motion for Summary Judgment on their first claim for relief is granted and Defendants' Motion for Summary Judgment is denied. Defendants are hereby ordered to initiate withdrawal proceedings for the relevant NADAs/ANADAs. Specifically, the Commissioner of the FDA or the Director of the CVM must re-issue a notice of the proposed withdrawals (which may be updated) and provide an opportunity for a hearing to the relevant drug sponsors; if drug sponsors timely request hearings and raise a genuine and substantial issue of fact, the FDA must hold a public evidentiary hearing. If, at the hearing, the drug sponsors fail to show that the use of the drugs is safe, the Commissioner must issue a withdrawal order.

The Court notes the limits of this decision. Although the Court is ordering the FDA to complete mandatory withdrawal proceedings for the relevant penicillin and tetracycline NADAs/ANADAs, the Court is not ordering a particular outcome as to the final issuance of a withdrawal order. If the drug sponsors demonstrate that the subtherapeutic use of penicillin and/or tetracyclines is safe, then the Commissioner[FN19] ***152** cannot withdraw approval.

FN19. At oral argument, both parties agreed that additional briefing is necessary on the issue of a time-line for holding a hearing and issuing a final decision in the matter. (*See* Transcript at 10.)

So Ordered.

S.D.N.Y.,2012.
Natural Resources Defense Council, Inc. v. U.S. Food and Drug Admin.
884 F.Supp.2d 127

END OF DOCUMENT

MICROBIAL THREATS TO HEALTH

EMERGENCE, DETECTION, AND RESPONSE

Mark S. Smolinski, Margaret A. Hamburg,
and Joshua Lederberg, *Editors*

Committee on Emerging Microbial Threats to Health
in the 21st Century

Board on Global Health

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

termined to be the appropriate drug in this situation, and an ample supply was readily available. The same may not be true when the next influenza pandemic eventually occurs, likely resulting in tens of thousands of deaths. Although stockpiling of antiviral drugs for influenza is a component of the pandemic plan developed by the United States and WHO (WHO, 1999e), we have yet to begin stockpiling antivirals effective against influenza. The time has come to move forward with this plan and determine which drugs are needed; the quantity required; the costs of production, storage, and distribution; and the authority under which the drugs will be used.

The U.S. Secretary of Health and Human Services and the U.S. Secretary of Homeland Security should protect our national security by ensuring the stockpiling and distribution of antibiotics, antivirals (e.g., for influenza), and antitoxins for naturally occurring or intentionally introduced microbial threats. *The federal government should explore innovative mechanisms, such as cooperative agreements between government and industry or consortia of government, industry, and academia, to accelerate these efforts.*

INAPPROPRIATE USE OF ANTIMICROBIALS

For a variety of reasons previously discussed, the pharmaceutical industry is developing fewer new antimicrobials than in previous years. Whereas it appeared at one time that an endless supply of effective new drugs to treat resistant infections would exist, such is no longer the case. Therefore, immediate action must be taken to preserve the effectiveness of available drugs.

Factors leading to the increasing problem of antimicrobial resistance are well known and understood. Many genes for resistance occur on cassettes that can move between organisms, across species boundaries (Leverstein-van Hall et al., 2002), and between chromosomes and plasmids. Resistance genes in bacteria are commonly grouped together on the same mobile genetic elements, with the crucial practical consequence that the use of any single drug may select for resistance to a wide group of drugs. Thus, an antimicrobial employed in food and animal production that has never before been used to treat infection in humans can select for resistance to other drugs used to treat humans.

Resistant bacteria often persist in vivo even in the absence of continued selection by antibiotics, although in some cases resistance gradually diminishes once antibiotic pressures have been reduced. One explanation for continued resistance involves the lethal effect of the loss of certain plasmids when bacteria divide. Some resistant microbes are less fit, but resistant strains arising in a clinical context are generally virulent and can often

prescribing of these newer drugs, even in areas where there is no demonstrated resistance to first-line therapies. The use of first-line therapies must be continued in areas where resistance has not been documented, and newer therapies should be used only when first-line therapies are ineffective or in areas of resistance. To this end, it is essential to monitor resistance patterns around the world.

Decreasing Inappropriate Use of Antimicrobials in Human Medicine

Decreasing the inappropriate use of antimicrobials in human medicine is a complex task that requires a multipronged effort fueled by a sense of urgency. The inappropriate use of antibiotics for treatment of viral diseases can be averted by the increased use of available diagnostic tests and the development of better point-of-care, inexpensive, rapid, sensitive, and specific diagnostic tests, which would enable the rational use of new antivirals as they become available (see the earlier discussion of the development of diagnostics). The decreased use of antibacterials for viral respiratory infections and other syndromes should lessen selective pressures for the emergence of resistant bacteria. FDA has recently included this message on label inserts of antibiotics.

If this important objective is to be achieved, the general public and health care providers must be better educated and informed about the importance of administering antimicrobial therapy properly. The need is urgent to both educate and monitor all categories of practitioners and drug dispensers in developing countries where medicines are sold directly to the public over the counter and dispensed by private practitioners in an ad hoc manner. More attention needs to be given to improving practitioner education and compliance. Patient care would be improved by the development and dissemination of better evidence-based treatment guidelines. More research is needed on methods for treating infections to minimize the emergence of resistance without a loss of efficacy. Infection control programs must be supported in hospitals in an effort to decrease the transmission of resistance both within the hospitals and in the community. Surveillance for patterns of resistance in hospitals and in the community must be continued and expanded; this will require a coordinated effort among public health organizations, private medicine, and industry. Because resistant microbes arise throughout the world and travel broadly to all regions, the needs and problems of the economically and health care disadvantaged regions of the world must be considered.

The world is facing an imminent crisis in the control of infectious diseases as the result of a gradual but steady increase in the resistance of a number of microbial agents to available therapeutic drugs. Although defining the precise public health risk of emergent antimicrobial resistance is not

persist for extended periods of time once established. Therefore, it is imperative to actively pursue and address the problem; it will be too late to effect useful change once most microbes have become resistant to the available drugs.

Antibiotic resistance resulting from the inappropriate overuse of antibiotics is not a new problem. A number of expert committees and professional organizations have studied the problem, issued reports, and made recommendations (Alliance for the Prudent Use of Antibiotics, 2001; CDC, 2001o; FDA, 2000; GAO, 1999; Center for Science in the Public Interest, 1998; NRC, 1999). Unfortunately, little has been done to change the situation, especially in the United States. Resistance due to the inappropriate use of antibiotics compromises the efficacy of many classic and highly effective antibiotics, such as penicillin for pneumococci and vancomycin for enterococci, as well as that of some newer antibiotics, such as ciprofloxacin and other types of fluorinated quinolones for gonococci, *Salmonella*, and *Campylobacter*. The recent discovery of an enterococcal gene for vancomycin resistance in *S. aureus* was alarming even though it had been predicted on the basis of the ability of the genes to transfer across species boundaries during mixed culture (CDC, 2002d). In the case of enterococcal and staphylococcal infection, alternative therapies have been introduced, but resistance to these new drugs has already been documented (Tsiodras et al., 2001; Herrero et al., 2002). The specter of untreatable infections—a regression to the pre-antibiotic era—is looming just around the corner.

Preventing the overuse of antimicrobials is not an easy task because of the revolutionary effects the drugs have had on human and animal health. Because antimicrobials are highly effective, there is an understandable tendency to use them in any situation in which they might be helpful. These effective drugs are relatively inexpensive compared with other medical interventions. Patients demand the drugs when they have an illness they imagine to be treatable with antibiotics. Doctors prescribe antibiotics for that same reason, often in the absence of diagnostic tests to determine the etiology of infection, and also because patients want and expect to be treated with them. In many areas of the world where little money is available for health care, antimicrobials are readily available without a doctor's prescription, and as a result are often taken unnecessarily or inadequately. Many problems associated with antimicrobial resistance have arisen in poor and developing areas of the world, and have subsequently spread globally.

In addition to avoiding the inappropriate use of antibiotics to treat viral disease, prudence dictates use of the appropriate antimicrobial when an etiologic diagnosis is made. For example, the rapid rise in drug-resistant malaria has led to the development of newer, generally more expensive therapies for the disease. This in turn has resulted in an increase in the

("[S]ection 355(e) simply sets out specific, not necessarily exclusive, circumstances under which the FDA must withdraw any [human drug] approval (whether final or otherwise) after notice and hearing."); *Dobbs v. Wyeth Pharms.*, 797 F.Supp.2d 1264, 1270–71 (W.D.Okla.2011) ("The FDA is statutorily responsible for continually monitoring the safety of approved drugs and is authorized to take actions including, *inter alia,* withdrawal of approval if scientific data indicates the drug is unsafe. 21 U.S.C. § 355(e). Approval must be withdrawn if the FDA finds that ... [a] drug is unsafe for use[.]") (internal quotation marks omitted). Although § 355(e) concerns withdrawal of FDA approval of human drugs, it contains nearly identical language to that in § 360b(e), and, in both the House and Senate Reports on the 1968 Amendments to the FDCA, § 360b(e) was described as "correspond[ing]" to § 355(e). *See* H.R. Rep. No. 90–875, at 5 (1967); S. Rep. No. 90–1308, at 5 (1968), 1968 U.S.C.C.A.N. 2607, 2611.

Were the Court to conclude that § 360b(e)(1) is ambiguous as to when the Secretary makes findings, the Court would defer to the agency's reasonable interpretation of the statute. *See Chevron,* 467 U.S. at 842–43, 104 S.Ct. at 2781–82. Although in this litigation the FDA has maintained that findings pursuant to § 360b(e)(1) can only be made after a hearing, the agency's implementing regulation,***144** 21 C.F.R. § 514.115, interprets § 360b(e)(1) to require the agency to make findings prior to a hearing. The regulation reads: "The Commissioner shall notify in writing the person holding [a NADA/ANADA] and afford an opportunity for a hearing on a proposal to withdraw approval of such [NADA/ANADA] if he finds ... that such drug is not shown to be safe ...." 21 C.F.R. § 514.115(b)(3)(ii).[FN12] The plain language of the regulation requires the Commissioner to provide notice and an opportunity for a hearing to a drug sponsor *after* making a finding that a drug has not been shown to be safe. It logically follows that findings are made by the Commissioner *before* a hearing.[FN13] Accordingly, if the Court were to defer to the agency's interpretation of the statute it would reach the same conclusion: findings pursuant to § 360b(e)(1) are made before a hearing and trigger the withdrawal process.

FN12. Although § 360b(e)(1) refers to the "Secretary," defined as the Secretary of HHS in § 321(d), the Secretary has delegated to the Commissioner of the FDA all of the authority vested in him pursuant to the FDCA. (*See* § 1410.10 of Volume III of the FDA Staff Manual Guides, Delegations of Authority to the Commissioner Food and Drugs, attached as Ex. A to Barcelo Decl., ¶ 1(A)(1).)

FN13. Moreover, this interpretation is consistent with how the FDA has implemented § 360b(e)(1) and the accompanying regulations in practice. The FDA consistently represents § 360b(e)(1) as requiring notice and an opportunity for a hearing on a proposed withdrawal whenever there is a finding that a new animal drug has not been shown to be safe. Findings are consistently made pursuant to § 360b(e)(1) *prior* to a hearing and provide the grounds for issuing a notice and opportunity for a hearing. *See* Enrofloxacin for Poultry; Opportunity for Hearing ("Enrofloxacin Notice"), 65 Fed.Reg. 64,954, 64,954 (Oct. 31, 2000) ("CVM is proposing to withdraw the approval of the [NADA] for use of enrofloxacin in poultry on the grounds that new evidence shows that the product has not been shown to be safe as provided for in the [FDCA]."); Dimetridazole; Opportunity for Hearing ("Dimetridazole Notice"), 51 Fed.Reg. 45,244, 45,244 (Dec. 17, 1986) ("The [FDA], [CVM], is proposing to withdraw approval of [NADAs] for dimetridazole ... for use in turkeys. This action is based on the [CVM's] determination that the drug is not shown to be safe for use ....").

[7] Defendants, nevertheless, argue that the regulation does not mean what it says. They claim that the regulation does not refer to the same findings as those in § 360b(e)(1); rather, Defendants assert that the regulation creates a different set of findings that are based on a lower standard than the statutory findings. To support this proposition, Defendants point to several notices of proposed withdrawals that rest on a finding that there is a "reasonable basis from which serious questions about the ultimate safety of [the drug] may be inferred." *See* Enrofloxacin for Poultry; Opportunity for Hearing ("Enrofloxacin Notice"), 65 Fed.Reg. 64,954, 64,955 (Oct. 31, 2000). Defendants maintain that this "serious question" standard is less stringent than the "not shown to be safe" standard in § 360b(e)(1).

The Court is not persuaded by Defendants' argument. First, although the FDA references the "serious question" standard in several withdrawal notices, the regulatory standard for issuance of any such notice is a finding that the drug is "not shown to be safe." *See* 21 C.F.R. § 514.115(b)(3)(ii). In fact, the regulation implementing § 360b(e)(1) and authorizing the Commissioner to issue notices describes the requisite findings in exactly the same language as the statute. *Compare* 21 U.S.C. § 360b(e)(1)(B) ("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***145** 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") *with* 21 C.F.R. § 514.115(b)(3)(ii) ("[n]ew 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 safe for use under the conditions of use upon the basis of which the application was approved"). Based on this language, the regulation unambiguously references and incorporates the findings referred to in § 360b(e)(1). In addition, the Commissioner considers the two findings to be interchangeable. *See* (Enrofloxacin Decision at 45 ("[T]he relevant statutory question is whether the animal drug 'has been shown to be safe,' 21 U.S.C. § 360b(e)(1), which, as explained earlier, has been interpreted to require that CVM show that there are serious questions about the safety of [the drug].").)

Because the Court reads 21 C.F.R. § 514.115(b)(3) as unambiguously referencing the findings in 21 U.S.C. § 360b(e)(1), the Court cannot defer to Defendants' interpretation that the regulation creates a different set of findings based on a different standard. *See Christensen v. Harris Cnty.*, 529 U.S. 576, 588, 120 S.Ct. 1655, 1663, 146 L.Ed.2d 621 (2000) ("[A]n agency's interpretation of its own regulation is entitled to deference. But [such] deference is warranted only when the language of the regulation is ambiguous.") (internal citations omitted); *Gonzales v. Oregon,* 546 U.S. 243, 257, 126 S.Ct. 904, 915–16, 163 L.Ed.2d 748 (2006) (refusing to apply deference to an agency's interpretation of its own regulation where the regulation merely "parroted" the statute because "[a]n agency does not acquire special authority to interpret its own words when, instead of using its expertise and experience to formulate a regulation, it has elected merely to paraphrase the statutory language.").[FN14]

FN14. In any event, the 1977 NOOHs at issue in this case were based on findings that the drug uses in question were "not shown to be safe" and *not* on the "serious question" standard. And, the Court is not called on here to determine whether the standard for withdrawal of approval has been met. The only issue presently before the Court is whether the withdrawal pro-

2009

SUMMARY REPORT

on

Antimicrobials Sold or Distributed for Use in Food-Producing Animals

FDA

Food and Drug Administration
Department of Health and Human Services

Section 105 of the Animal Drug User Fee Amendments of 2008 (ADUFA) (110 P.L. 316; 122 Stat. 3509) amended section 512 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b) to require that sponsors of applications for new animal drugs containing an antimicrobial active ingredient submit an annual report to the Food and Drug Administration on the amount of each such ingredient in the drug that is sold or distributed for use in food-producing animals, including information on any distributor-labeled product. This legislation was enacted to assist FDA in its continuing analysis of the interactions (including drug resistance), efficacy, and safety of antibiotics approved for use in both humans and food-producing animals (H. Rpt. 110-804).

Each report submitted to the FDA must specify: (1) the amount of each antimicrobial active ingredient by container size, strength, and dosage form; (2) quantities distributed domestically and quantities exported; and (3) a listing of the target animals, indications, and production classes that are specified on the approved label of the product. Sponsors of antimicrobial drug products that are approved and labeled for more than one food-producing animal species are not required to report sales and distribution information for each individual animal species. Only total product sales information is required. The first report must be submitted not later than March 31, 2010, and each year's report will provide monthly sales and distribution data for the preceding calendar year. These reports are separate from periodic drug experience reports that are required under 21 CFR 514.80(b)(4).

Section 105 of ADUFA also directs the FDA to make annual summaries of the reported information publicly available. In accordance with statutory requirements designed to protect confidential business information, annual sales and distribution data will be summarized by drug class and only those antimicrobial classes with three or more distinct sponsors of approved and actively marketed animal drug products are independently reported. Antimicrobial classes with fewer than three distinct sponsors are reported collectively as "Not Independently Reported" (NIR) if the product was marketed domestically or "Not Independently Reported Export" (NIRE) if the product was exported. The number of distinct sponsors in a particular antimicrobial class is determined by two criteria: (1) the sponsor must be named in 21 CFR 510.600 as the holder of an approved application for an animal drug product in that particular class on the last day of the annual reporting period, and (2) the sponsor must have actively sold or distributed such animal drug product at some point during that annual reporting period.

FDA's annual summary report for 2009 is presented in Table 1. The annual totals provided in Table 1 reflect all approved uses of all dosage forms (e.g., injectable, oral, medicated feed) of the identified classes of actively marketed drugs in food-producing animals. Table 2 lists the 17 antimicrobial drug classes represented in the report. As reference, this table also lists the specific drugs in each class for which there are approved animal drug products. However, the fact that an animal drug product is approved does not necessarily mean that it was actively marketed during this particular annual reporting period. This summary report includes antimicrobial drugs that are specifically approved for antibacterial uses or are known to have antibacterial properties. Anti-fungal and anti-viral drugs are not included in this report because, with the exception of formalin and hydrogen peroxide water immersion products, there are currently no approved drug products actively marketed for these purposes in food-producing animals.

Table 1. Antimicrobial Drugs Approved for Use in Food-Producing Animals: 2009 Sales and Distribution Data Reported by Drug Class

	Antimicrobial Class	Annual Totals (kg[1])
Domestic	*Aminoglycosides*	339,678
	Cephalosporins	41,328
	Ionophores	3,740,627
	Lincosamides	115,837
	Macrolides	861,985
	Penicillins	610,514
	Sulfas	517,873
	Tetracyclines	4,611,892
	NIR[2]	2,227,366
Export	*Tetracyclines*	515,819
	NIRE[3]	1,115,728

[1] kg = kilogram of active ingredient. Antimicrobials which were reported in International Units (IU) (i.e., Penicillins and Polypeptides) were converted to kg.

[2] NIR = Not Independently Reported. Antimicrobial classes for which there were less than three distinct sponsors actively marketing products domestically were not independently reported. These classes include: Aminocoumarins, Amphenicols, Diaminopyrimidines, Fluroquinolones, Glycolipids, Pleuromutilins, Polypeptides, Quinoxalines, and Streptogramins.

[3] NIRE = Not Independently Reported Export. Antimicrobial Classes for which there were less than three distinct sponsors exporting products were not independently reported. These classes include: Aminocoumarins, Aminoglycosides, Amphenicols, Cephalosporins, Diaminopyrimidines, Fluroquinolones, Glycolipids, Ionophores, Lincosamides, Macrolides, Penicillins, Pleuromutilins, Polypeptides, Quinoxalines, Streptogramins and Sulfas.

Table 2. Antimicrobial Drugs and Drug Classes Approved for Use in Food-Producing Animals

Aminocoumarins Novobiocin **Aminoglycosides** Apramycin Dihydostreptomycin Efrotomycin Gentamicin Hygromycin B Neomycin Spectinomycin Streptomycin **Amphenicols** Florfenicol **Cephalosporins** Ceftiofur Cephapirin **Diaminopyrimidines** Ormetoprim **Fluoroquinolones** Danofloxacin Enrofloxacin **Glycolipids** Bambermycin **Ionophores** Laidlomycin Lasalocid Monensin Narasin Salinomycin Semduramicin **Lincosamides** Lincomycin Pirlimycin	**Macrolides** Carbomycin Erythromycin Oleandomycin Tilmicosin Tulathromycin Tylosin **Penicillins** Amoxicillin Ampicillin Cloxacillin Hetacillin Penicillin **Pleuromutilins** Tiamulin **Polypeptides** Bacitracin Polymixin B **Quinoxalines** Carbadox **Streptogramins** Virginiamycin **Sulfas** Sulfachlorpyridazine Sulfadimethoxine Sulfamerazine Sulfamethazine Sulfaquinoxaline Sulfathiazole **Tetracyclines** Chlortetracycline Oxytetracycline Tetracycline

a simple task, there is no doubt that the problem is of global concern and is creating dilemmas for the treatment of infections in both hospitals and community health care settings.

CDC, FDA, professional health organizations, academia, health care delivery systems, and industry should expand efforts to decrease the inappropriate use of antimicrobials in human medicine through (1) expanded outreach and better education of health care providers, drug dispensers, and the general public on the inherent dangers associated with the inappropriate use of antimicrobials, and (2) the increased use of diagnostic tests, as well as the development and use of rapid diagnostic tests, to determine the etiology of infection and thereby ensure the more appropriate use of antimicrobials.

Decreasing Inappropriate Overuse of Antimicrobials in Animal Husbandry and Agriculture

Clearly, a decrease in the inappropriate use of antimicrobials in human medicine alone is not enough. Substantial efforts must be made to decrease inappropriate overuse of antimicrobials in animals and agriculture as well.

Although estimates vary widely, the total amount of antimicrobials used in Europe and the United States in animal husbandry and agriculture far outweighs the total used in humans (McEwen and Fedorka-Cray, 2002). The majority of this use is for growth promotion or preventive therapy in healthy animals. Mounting evidence suggests a relationship between antimicrobial use in animal husbandry and an increase in bacterial resistance in humans (Alliance for the Prudent Use of Antibiotics, 2002), a view supported by an IOM committee that reviewed the use of drugs in food animals (IOM, 1999b). The use of antimicrobials in food animals leads to antibiotic resistance, which can then be transmitted to humans through the food supply (Swartz, 2002; Fey et al., 2000; Smith et al., 2002; White et al., 2001).

A study published in 2001 found that 20 percent of ground meat samples obtained from supermarkets in the Washington, D.C., metropolitan area were contaminated with *Salmonella*. Of these bacteria, 84 percent were resistant to at least one antibiotic and 53 percent to at least three antibiotics (White et al., 2001). This study supports previous findings that foods of animal origin are potential sources of ceftriaxone-resistant *Salmonella* infections in humans. Similarly, researchers found that between 17 and 87 percent of chickens obtained in supermarkets in four states contained strains of *Enterococcus faecium* that were resistant to quinupristin–

dalfopristin, an approved antimicrobial for use in humans (McDonald et al., 2001). The researchers believed that the use of virginiamycin, an antibiotic of the streptogramin group, in farm animals had created a reservoir of streptogramin–resistant *E. faecium* in the food supply, which could contribute to foodborne dissemination of resistance as the clinical use of quinupristin–dalfopristin increases.

Substantial evidence supports that certain types of resistant organisms, such as vancomycin-resistant enterococci, emerged initially in animals because of the use of similar drugs for growth promotion or prophylaxis (O'Brien, 2002). Consideration of this association led to a ban on the use of avoparacin, a vancomycin analogue, in Europe (Wegener et al., 1999). The decreased use of antimicrobials for growth promotion or prophylaxis in many European countries has been associated with a subsequent stabilization in resistance or a gradually decreasing resistance in animal flora (Aarestrup et al., 2001). WHO has called for all antimicrobials used for disease control in food animals to be prescribed by veterinary health care providers, and for termination or rapid phase-out of antimicrobials used for growth promotion if they are used for human treatment (WHO, 2000f). Various other groups have suggested that because of the increasing risk of antimicrobial resistance, the subtherapeutic use of antibiotics for growth promotion should be banned (some would include use for prophylaxis in the ban as well) if they are also used in humans (Union of Concerned Scientists, 2002; Alliance for the Prudent Use of Antimicrobials, 2002).

The main argument against a ban is the potential economic hardships to livestock and poultry producers, which would result in higher costs for consumers. According to the IOM Committee on the Use of Drugs in Food Animals, such a ban would increase the price of meat by an estimated 0.013 to 0.06 cents per pound; this translates to $4.84 to $9.72 per person each year, depending on the meat and the cut (IOM, 1999b). Yet, evidence suggests that animals can be raised efficiently without the use of growth-promoting antimicrobials (Emborg et al., 2001; Wierup, 2001).

Critics of the ban also argue that it would result in poorer production efficiency and an increased incidence of infectious disease in animals. However, it has been noted that subtherapeutic antibiotics are most effective in animals under the stress of inadequate nutrition and suboptimal sanitary conditions (Braude et al., 1953); therefore, improved hygiene and changes in animal husbandry practices to control disease could potentially eliminate the need for growth promoters (Emborg et al., 2001). In Denmark, the elimination of antimicrobial growth promoters from broiler chicken feed did not result in a change in death rates or a decrease in kilograms of broilers produced per square meter. Danish scientists also reported that the decreased use of virginiamycin and avilamycin in animals was followed by decreases in resistance to these drugs (Aarestrup et al., 2001).

FDA should ban the use of antimicrobials for growth promotion in animals if those classes of antimicrobials are also used in humans.

The committee endorses the Public Health Action Plan to Combat Antimicrobial Resistance developed by the Interagency Task Force on Antimicrobial Resistance and the recommendations of the WHO Global Strategy for the Containment of Antimicrobial Resistance (see Boxes 4-9 and 4-10). Although the broad scope of these recommendations defies easy implementation, we must seize the opportunity immediately to do as much as we can while organizing the resources and plans needed to carry out other initiatives. To do nothing is, in effect, to allow the continued evolution of antimicrobial-resistant microbes, which poses serious near- and long-term threats to global health. The total burden of human illness due to resistant bacteria that have been transferred from animals to humans is unknown, but the guiding principle should be that we must do what the available evidence suggests will help stem the tide of increasing resistance before it is too late. By endorsing these recommendations, we will join belatedly much of the rest of the developed world, which already has made similar recommendations and, in many cases, implemented them. These changes should be accompanied by substantial outcomes research on the effects on animal health, resistance prevalence in animals and humans, and the economics of food production.

VECTOR-BORNE AND ZOONOTIC DISEASE CONTROL

The majority of emerging infectious diseases are zoonoses (i.e., diseases transmitted from animals to humans under natural conditions). Vector-borne and rodent-borne diseases are especially notable in this regard, remaining major causes of morbidity and mortality in humans in the tropical world and representing a large proportion of newly emerged diseases (see the discussion in Chapter 3). Exacerbating the situation is the potential for many of these agents to be weaponized and used by bioterrorists. Because of their resurging public health importance and their exceptional ability to cause epidemics, vector-borne and zoonotic diseases will undoubtedly continue to pose significant risks to human health in the future.

Unfortunately, the national and international capacity to address these diseases is limited. The many reasons for this include (1) the lack of efficacious vaccines for many of these pathogens; (2) decreased support for and deterioration of the public health surveillance and control infrastructure for vector-borne and zoonotic diseases; (3) erosion in the numbers of scientists trained in relevant fields, including medical entomology, vector ecology, zoonoses, and tropical medicine; (4) the development of resistance to drugs

BOX 4-9
WHO Global Strategy for Antimicrobial Resistance

In response to the growing problem of antibiotic resistance, WHO has worked with many partners, including the American Society for Microbiology and the Alliance for the Prudent Use of Antibiotic (APUA), to develop the WHO Global Strategy for Containment for Antimicrobial Resistance. The seven key recommendations emanating from the 25 expert reports used to formulate the strategy are summarized below.

Increase Awareness of the Antibiotic Resistance Problem

International organizations:
- Obtain worldwide commitments to establish prudent antibiotic use policies

National and municipal organizations:
- Publicize the outcomes of programs from other countries
- Educate the general public
- Promote communication
- Evaluate the curricula of universities

Health care institutions:
- Use effective teaching methods for education prescribers

Health care workers:
- Educate the general public

Improve Surveillance of Antibiotic Resistance

National and municipal organizations:
- Coordinate local surveillance networks
- Recruit leaders for surveillance networks
- Support a reference laboratory
- Share results of surveillance with international organizations
- Monitor resistance in food animals
- Monitor sentinel human populations

Health care institutions:
- Develop local surveillance network
- Maintain a laboratory with adequate quality assurance and trained technicians

Health care workers:
- Initiate a local surveillance network

Pharmaceutical companies:
- Undertake postmarking surveillance to detect the emergence of resistance to new antibiotics
- Support surveillance networks

Improve Antibiotic Use in People

National and municipal organizations:
- Enforce the prudent use of antibiotics
- Create national and regional guidelines
- Update guidelines based on surveillance data
- Eliminate financial incentives that promote the misuse of antibiotics
- Monitor advertising
- Consider the impact of new drugs on resistance during the drug approval process
- Limit general access to new drugs
- Establish postmarking surveillance accords

Health care institutions:
- Establish an Infection Control Committee
- Establish a Drugs and Therapeutics Committee
- Establish guidelines for appropriate antibiotic use
- Appoint an antimicrobial resistance monitor
- Reduce the spread of infection
- Create pharmacy reports

Establish and disseminate list of essential drugs
Educate employees
Maintain a laboratory
Health care workers:
Prescribe antibiotics prudently
Improve hygiene

Improve Antibiotic Use in Animals
National and municipal organizations:
Increase awareness of the antibiotic resistance problem
Regulate antibiotic prescriptions for animals
Restrict growth promoter use in animals
Regulate antibiotic use in animals
Set a risk standard for resistance
Consider human and nonhuman uses simultaneously
Monitor advertising
Veterinarians:
Promote a prudent use of antibiotics in animals
Develop local guidelines for antibiotic use
Food animal producers:
Improve farm hygiene
Reduce the use of antibiotics as growth promoters
Improve animal husbandry
Researchers:
Perform risk–benefit analysis of growth promoter use
Assess environmental impact
Examine food processing and distribution methods

Encourage New Product Development
National and municipal organizations:
Provide incentives to industry
Protect intellectual property rights
Facilitate networking
Pharmaceutical companies:
Increase research and development in several areas

Increase Resources to Curb Antibiotic Resistance in the Developing World
International organizations:
Share results of surveillance internationally
Secure technical and financial support for developing countries
Invest in a worldwide vaccine strategy to reduce antibiotics
Ensure the availability of vaccines and quality drugs
Facilitate communication among the countries of the world
Safeguard privacy and human rights
Promote appropriate international laws
National and municipal organizations:
Decrease the risk of infectious disease
Ensure antibiotic availability
Share resources with other countries

Increase Funding for Surveillance, Research, and Education
National and municipal organizations:
Increase funding for a surveillance network
Increase funding for research
Increase funding for education

SOURCE: World Health Organization, 2001i.

Acknowledgements

This publication has been produced by the WHO Patient Safety Programme as part of its solid commitment to promoting safer care worldwide. It is the result of an international consultation process started in 2008, which gathered input from over 50 international experts in the field of antimicrobial resistance.

Coordinated by WHO, under the auspices of Sir Liam Donaldson, WHO Envoy for Patient Safety, with the leadership and expert advice of David Heymann, Chairman of the Health Protection Agency, UK, and Didier Pittet, Director of the Infection Control Programme, University of Geneva Hospitals, Switzerland, world experts worked for over two years on five main technical areas, which are central to the AMR problem, in order to provide the best evidence and the appraisal of experiences that form the core of this book.

The WHO Patient Safety Programme is indebted to the international experts who contributed to this process. A full list of contributors is provided at the end of the book. The working group leads and main authors were Frank M. Aaerestrup, Technical University of Denmark; Awa Aidara-Kane, World Health Organization; Otto Cars and Andreas Heddini, both at Action on Antibiotic Resistance (ReAct), Sweden; Shaoyu Chang and Anthony So, at Duke University, USA; Barry Cookson, at the Health Protection Agency, UK; Petra Gastmeier at Charité University Hospital, Germany; Lindsay Grayson at the University of Melbourne, Australia; Hajo Grundmann, at the National Institute for Public Health and the Environment, The Netherlands; Stuart Levy, from Tufts University School of Medicine, USA; Thomas F O'Brien and John M Stelling, at Brigham and Women's Hospital, USA; and Wing-Hong Seto, from Queen Mary Hospital, Hong Kong SAR, China. The working groups comprised specialists in AMR who together brought their knowledge and understanding of the risks and challenges in the fight against AMR and of the most effective interventions to tackle the problem.

Thanks are due to the following WHO Patient Safety Programme staff: Elizabeth Mathai for her lead in harmonizing and editing the contributions of the different experts and Gerald Dziekan who as well as editing, steered and coordinated the development process from consultation to finalization. The programme's Coordinator, Itziar Larizgoitia Jauregui, its Director, Najeeb Al-Shorbaji, and Assistant Director-General, Marie-Paule Kieny, provided overall supervision of the project.

Thanks are also due to the WHO technical teams and international experts who developed the 2001 WHO Global Strategy for Containment of Antimicrobial Resistance, and the 2011 World Health Day policy briefs, led by Mario Raviglione, Director of Stop TB, and Hiroki Nakatani, Assistant Director-General, and the Stop TB Team, as well as to those who reviewed the various drafts.

The financial contribution of the Swedish International Development Cooperation Agency (SIDA) through Action on Antibiotic Resistance (ReAct), Uppsala, Sweden towards design of this publication is gratefully acknowledged.

Foreword

Antimicrobial resistance (AMR) is not a recent phenomenon, but it is a critical health issue today. Over several decades, to varying degrees, bacteria causing common infections have developed resistance to each new antibiotic, and AMR has evolved to become a worldwide health threat. With a dearth of new antibiotics coming to market, the need for action to avert a developing global crisis in health care is increasingly urgent.

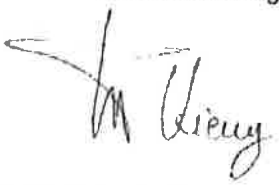
In addition to a substantial financial burden that national health-care budgets can ill afford, AMR has economic consequences far beyond the health sector, such as damaging repercussions on international travel and trade resulting from the cross-border spread of resistant infections. The cost of *not* acting against AMR needs to be considered when deciding resource allocation and assessing interventions.

We know how and why AMR develops, what factors favour its emergence and spread, and what measures can be taken to limit it. Why then are we now facing an impending crisis in the treatment of many infections? This book describes the context of the problem, some of the progress made in recent years to tackle it, and what more should be done. Without question, more information and new tools are needed, but available strategies and interventions can go a long way towards minimizing the scale and impact of AMR, and maximizing the effective lifespan of existing antibiotics. Much more could be achieved by better and more widespread application of these measures, and there are many promising opportunities for innovation in this area.

Infections which are increasingly resistant to antibiotics together account for a heavy disease burden, often affecting developing countries disproportionately. The use of vast quantities of antibiotics in food-producing animals adds another dimension to a complex situation. Several sectors and services are involved and each, from public health to animal husbandry, has an important role to play in counteracting AMR. Responsibility needs to be shared, and coordination of the separate necessary inputs requires determined leadership, additional resources, and solid commitment at many levels.

The World Health Organization (WHO) has long recognized AMR as a growing global health threat, and the World Health Assembly, through several resolutions over two decades, has called upon Member States and the international community to take measures to curtail the emergence and spread of AMR. The WHO Global Strategy for Containment of Antimicrobial Resistance, published in 2001, set out a comprehensive set of recommendations for AMR control which remain valid today. This book examines the experiences with implementing some of those recommendations ten years on, the lessons learnt along the way and the remaining gaps. On World Heath Day 2011, WHO again highlighted AMR and urged countries to commit to a comprehensive financed national plan to combat AMR, engaging all principal stakeholders including civil society.

I am pleased to present this book during the campaign year chosen by WHO for special emphasis on the importance of AMR. It testifies to the Organization's commitment to promoting and facilitating global action to contain AMR and ensuring that effective antibiotics will be available worldwide in the future.



Dr Marie-Paule Kieny
Assistant Director-General
Innovation, Information, Evidence and Research
World Health Organization

Chapter 4.

Reducing the use of antibiotics in animal husbandry

Antibiotics are used widely and in vast quantities to ensure the health and promote the growth of livestock, poultry and fish reared for food production. The fact that greater quantities are used in healthy animals than in unhealthy humans is a cause for serious concern, particularly as some of the same antibiotics are involved and food animals have been shown to carry resistant human pathogens. Some countries have banned the use of antibiotics as growth promoters but the practice remains widespread. Legislation and regulation with enforcement are needed to control the use of antibiotics for these purposes in many countries.

Summary

Antibiotics are used in greater quantities in healthy food-producing animals than in the treatment of disease in human patients. In animal husbandry, antibiotics are used extensively for disease prevention and as growth promoters, involving mass administration to many animals at the same time. This practice constitutes the main difference between the use of antibiotics in animals and in humans. Some of the same antibiotics or classes are in use in food animals and in human medicine, carrying the risk of emergence and spread of resistant bacteria, including those capable of causing infections in both animals and people. The importance of food animals as reservoirs of resistant human pathogens is well documented. The spread of resistance genes from animal bacteria to human bacteria is another potential danger. The problems associated with the use of antibiotics in animal husbandry, including in livestock, poultry, and fish farming, are growing worldwide without clear evidence of the need for or benefit from it, leading to increasing recognition that urgent action is needed.[109]

There appear to be major differences in the amounts of antimicrobials used per kilogram of meat produced in high-income countries, which together account for 70% of global meat production. Working groups hosted by WHO, the Food and Agriculture Organization (FAO), and the World Animal Health Organisation (OIE) have proposed options for actions to be taken by national and international authorities. Large-scale interventions are already being instituted in a number of countries, mainly aimed at reducing the use of specific classes of antimicrobial agents, especially those used in human clinical practice. The steps to be taken include the introduction and enforcement of regulations, methods to promote the prudent use of antibiotics, and measures to improve animal health so that less antibiotic treatment is needed. Several such interventions have led to a demonstrable reduction in AMR, though this is not always the case.

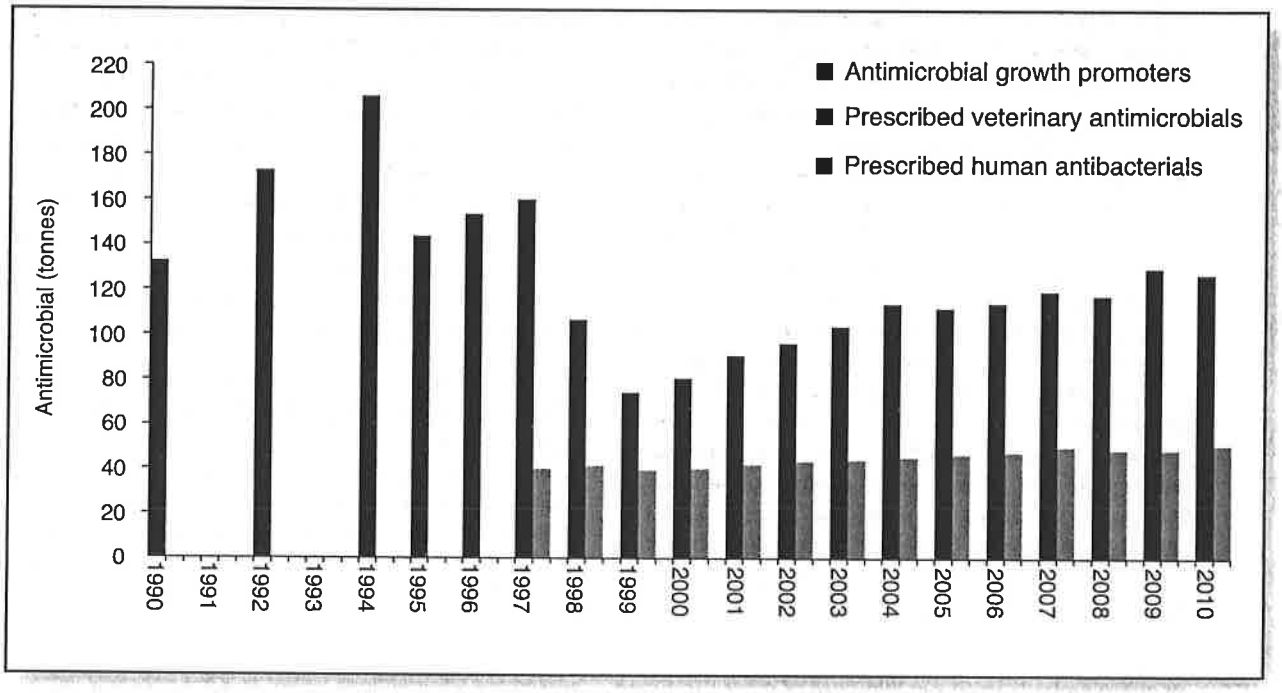
Important gaps and challenges remain. More information is needed on the prevalence of AMR in bacteria of animal origin and its impact on human health, on the quantity of antibiotics used for different indications and on the classes of antibiotics used. Risk assessments and risk management are impeded by a lack of data and/or inability to access available data. Legislations and regulatory frameworks for the approval of veterinary medicines and for controlling their use need strengthening in many countries. Capacity to implement interventions varies and the potential impact of specific interventions in different settings is largely unknown. This chapter considers the present situation and the range of options for action, citing examples of experiences with different interventions.

1. Reducing antimicrobial use in animal husbandry to reduce AMR

As in medical care for people, the introduction of antimicrobials was a significant milestone in veterinary practice. As in humans, these medicines are used for the treatment of infectious diseases in individual domestic pets and in farm and food-producing animals to ensure animal welfare and global food production. The development and spread of AMR is therefore also of concern in veterinary medicine. Furthermore, resistant bacteria carried by food-producing animals can spread to people, mainly via the consumption of inadequately cooked food, handling of raw food or by cross-contamination with other foods, but also through the environment (e.g. contaminated water) and through direct animal contact.

Use is the main driver for resistance in all of these situations. For companion animals such as cats, dogs and horses, the use is similar to that in general human medical practice, with individual animal treatment being the norm. The main difference between antibiotic use in humans and animals is seen in the context of food production, where there is mass administration of antimicrobials to many animals at the same time for the purposes of disease prevention and growth promotion. Such practices provide favourable conditions for the emergence, spread and persistence of AMR bacteria capable of causing infections not only in animals, but also in people. The antimicrobial agents used for food-producing animals are frequently the same, or belong to the same classes, as those used in human medicine. The total amount used in animals accounts for well over 50% of total antibiotic use, according to the available evidence (Figure 4.1).[21]

Figure 4.1 Annual antibiotic use for human and veterinary practice in Denmark



Source: Reproduced from [21] with permission.

importance of food animals as reservoirs of AMR bacteria which are pathogenic for humans is well documented for zoonotic bacteria such as non-typhoidal *Salmonella enterica* serovars[110] and *Campylobacter* spp.[111] It has been frequently demonstrated that the use of antimicrobial agents in food animals favours the development of resistance among bacteria which can then be transmitted to people, and may cause infections and illness. Bacteria and resistance to critically important antimicrobial agents associated with food animals include: *Escherichia coli* and *Salmonella* spp resistant to 3rd and 4th generation cephalosporins and to fluoroquinolones; *Campylobacter* spp resistant to macrolides and fluoroquinolones; *Staphylococcus aureus* resistant to beta-lactam-type drugs (i.e. MRSA); enterococci resistant to vancomycin (VRE) and *C. difficile*.

There are significant direct and indirect effects of antimicrobial use in animals on AMR in human pathogens, as several lines of evidence have indicated. Data are as yet insufficient to allow this relationship to be fully evaluated, but it is clear that action is needed to reduce the use of antibiotics in food animals, and to obtain further information on the impact on AMR. This chapter describes experiences with the implementation of some of the most important interventions worldwide, recognizing the differences in situations between countries and regions.

2. WHO guidance on reducing antimicrobial use in animal husbandry

The 2001 WHO Global Strategy for Containment of AMR includes specific recommendations on the use of antimicrobials in animal husbandry which are based on *WHO global principles for the containment of antimicrobial resistance in animals intended for food, 2000* (Box 4.1).[109] The recommendations include phasing out the use in food animals of antimicrobials which are used in human medicine, improving their use through regulation, education and guidelines, and monitoring use and resistance in this sector (Appendix1).[1]

Box 4.1 WHO principles for the containment of AMR in animals intended for food

- Introduce pre-licensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs.
- Monitor resistance to identify emerging health problems and take timely corrective action to protect human health.
- Develop guidelines for veterinarians to reduce the overuse and misuse of antimicrobials in food animals.
- Require obligatory prescriptions for all antimicrobials used for disease control in food animals.
- In the absence of a public health safety evaluation, terminate or rapidly phase out the use of antimicrobials for growth promotion if they are also used for the treatment of humans.
- Create national systems to monitor antimicrobial use in food animals.

The importance of the problem and the urgent need to take action were again stressed during the 2011 World Health Day. The core actions called for in the WHD policy briefs include the creation and enforcement of an enabling regulatory framework, strengthening surveillance and monitoring, promoting education and training on antimicrobial use in food-producing animals, and reducing the need for antimicrobials through better animal husbandry. The needs for national leadership and intersectoral collaboration are also emphasized (Appendix 2).[2]

3. The present position regarding these recommendations

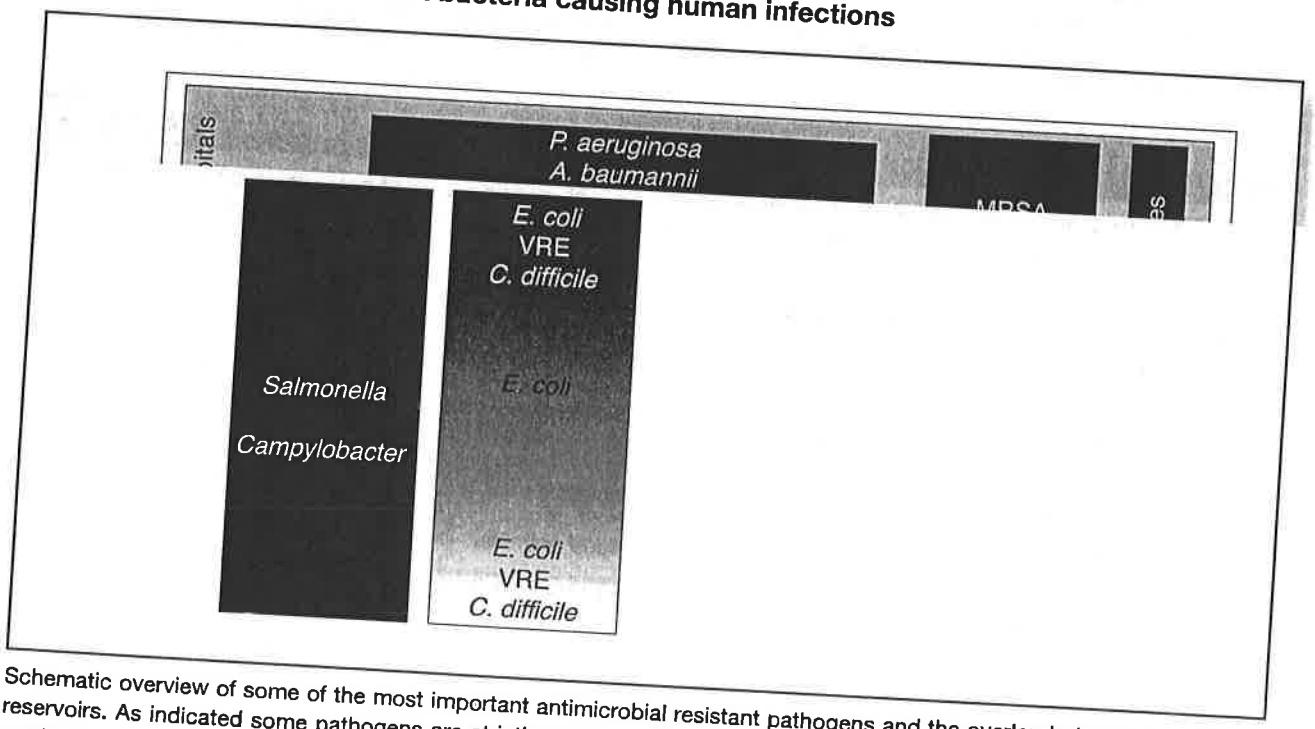
The following sections examine key factors in the role of antimicrobial use in food animals which contribute to the growing threat of AMR, and national and international actions taken to tackle the problem, illustrated by experiences from different parts of the world.

3.1 Increasing recognition of the problem of AMR through food of animal origin

Extensive and effective monitoring of AMR in animals is carried out in only a very limited number of countries, and frequently these monitoring systems are not comparable due to differences in methodology. However, AMR among bacteria of animal origin is certainly prevalent throughout the world, at varying rates in individual countries and regions. With increasing global trade in food products of animal origin, the numbers of reports documenting resistant bacteria spreading from one country to another through food, and thereby causing infections, are also increasing. The international spread of resistant pathogens calls for urgent global initiatives to minimize the risk of AMR bacteria developing and spreading from food animals to people, and further within communities and hospitals. Working groups hosted by WHO, FAO and OIE have reviewed these issues extensively and proposed options for action to be taken by national and international authorities.[109,112-114]

Figure 4.2 is a schematic overview depicting the overlap between different reservoirs for some AMR pathogens. While some are strictly confined to the human reservoir, others have a mainly or partially animal reservoir.[66]

Figure 4.2 Reservoirs of AMR bacteria causing human infections



Schematic overview of some of the most important antimicrobial resistant pathogens and the overlap between the different reservoirs. As indicated some pathogens are strictly confined within the human reservoir, whereas others have a mainly or partly animal reservoir.

Source: Reproduced from[66] with permission

The use of fluoroquinolones (e.g. enrofloxacin) in food animals resulted in the development of ciprofloxacin-resistant *Salmonella*, *Campylobacter* and *E. coli*, which have caused human infections and spread worldwide through travel and food trade. An increasing number of studies indicate that a major proportion of resistant *E. coli* that cause extra-bowel infections in humans may have originated in food animals, especially poultry.[115,116]

Since 2003, a new variant of MRSA has emerged and spread among food animals, primarily in pigs, in many countries. The importance of this new farm-associated MRSA for human health has not yet been fully assessed, but it is already a problem for the control of MRSA in some countries and the prevalence appears to be increasing.[117]

C. difficile colonizes many food animals and also causes disease in food animals such as piglets, with an associated high mortality rate[118] and has been found in 4.6%–45% of retail meat samples.[119] Since 2005, in the Netherlands and other countries, there has been an increase in community-acquired human infections caused by *C. difficile* strain types similar to those found in food animals.[120] Community human carriage of *C. difficile* is likely to increase the risk of *C. difficile* disease, especially among patients who enter health-care facilities and are treated with antibiotics. It may also increase the likelihood of *C. difficile* spores contaminating the hospital environment and spreading from person to person. However, the overall contribution of animal *C. difficile* to human disease is not well documented.

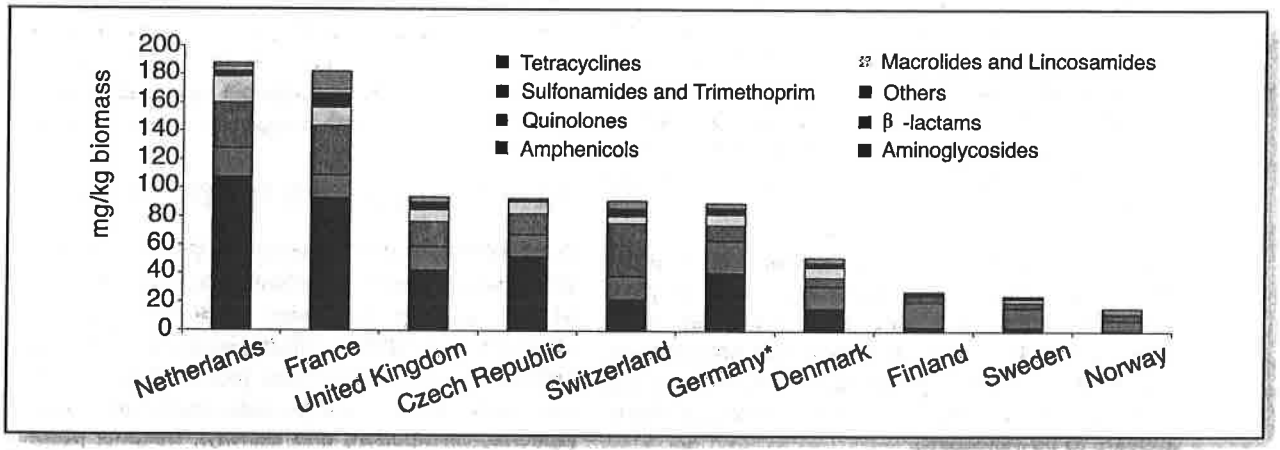
As well as selecting for resistant bacteria, the use of antimicrobial agents in food animals also selects for transferable resistance genes. This phenomenon raises the possibility that resistance genes could be transferred from animals to humans via non-pathogenic bacteria in food products, and that they could then be transferred to bacterial pathogens in the human gastro-intestinal tract. Consistent with this hypothesis is the presence of similar vancomycin and cephalosporin resistance genes in both human and animal bacteria.[121]

3.2 Antimicrobial use in food production

In modern food production systems, there is widespread and intensive use of antimicrobial agents. The impact of this practice may vary considerably between countries and regions, influenced by the interaction between human populations (social structure), land use, contaminated water sources, animal demography (species, distribution, and density), national policies (production, trade, food security, animal health, etc), and national and international trade. The production systems also vary between countries according to technological, social, and economic circumstances. More than 50% of the world's pork production and over 70% of poultry meat currently originate from industrialized countries.

In general, the quantities and classes of antimicrobials used in food animals today are insufficiently documented or controlled worldwide. Monitoring of antimicrobial consumption is carried out in only a limited number of countries and, with very few exceptions, this is restricted to total amounts used, and not categorized by animal species and antimicrobial classes. Initial crude estimates from different countries which do measure antimicrobial use show major differences in the amounts used per kilogram of meat produced (Figure 4.3). This implies that there is considerable scope for reduction in countries where the higher amounts of antimicrobials are in use.[122]

Figure 4.3 Estimated antimicrobial use to produce one kilogram of meat in different countries



Amounts in mg of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data
Source: Reproduced from [122] with permission from Oxford University Press.

Data on antimicrobial use are necessary for risk analysis, interpreting resistance surveillance data, and to assess the impact of interventions to promote prudent use. Sales data are the usual source of information on antimicrobial use. Data which can have an impact on policies and practice are very often lacking from developing countries, but Kenya is a notable exception where both the total amounts and the classes of antibiotics are monitored: from 1995–1999, Kenya used on average 14 594 kg of antibiotics distributed as 7975 kg of tetracyclines, 3104 kg of sulfonamides, 955 kg of aminoglycosides, 905 kg of betalactams, 94 kg of quinolones, 35 kg of macrolides and 24 kg of others, including tiamulin.[123]

Depending on the species of animals, periods of higher risk for infection can be identified. For example, when animals from different origins are assembled and first placed together, physiological stress is at its highest level and there is increased potential for inter-animal transmission of infections. Antimicrobial prophylaxis of all animals is often carried out to prevent clinical disease in such situations. In some countries, mass treatment is timed to an epidemic (either started or expected), a practice termed "metaphylaxis". The regulatory status of such use often resides on the fringe of labelled use for the 'control' of disease. To facilitate administration to a large number of animals, oral routes (water and/or feed) are used in addition to parenteral injections. Prophylaxis and metaphylaxis practices need to be carefully assessed to find an appropriate balance between the need to prevent diseases during high-risk periods and the potential to contribute to AMR.

3.3 Actions being taken worldwide

Awareness of the risks for human health which can result from the use of antibiotics in animal husbandry appears to be on the increase, as evidenced by the many media reports and scientific publications on this topic in recent years, and the large-scale interventions which are being instituted in different parts of the world.

There are several international networks which coordinate AMR surveillance in human and animal populations (see Chapter 2). The WHO-Global Foodborne Infections Network (GFN) and the international molecular subtyping network for foodborne disease surveillance (PulseNet International[a]) are examples. The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) has developed guidance documents for global standardization of methods for monitoring AMR and antimicrobial use in food animals[b].

[a] http://www.pulsenetinternational.org/Pages/default.aspx
[b] http://www.who.int/foodborne_disease/resistance/agisar/en/index.html

Most interventions are aimed at reducing the use of specific classes of antimicrobial agents in food animals, especially those classes which are used in human clinical practice. The measures which have been implemented include the introduction and enforcement of regulations governing the use of antimicrobials, methods to promote the prudent use of antibiotics by end-users, and measures to improve animal health so that less antibiotic treatment is needed.

Regulations to restrict the use of antibiotics in animals

National and international efforts to control AMR require a firm legal and regulatory foundation on which measures can be introduced and enforced. Regulations can contribute at many levels, from licensing to end use of antimicrobials. While regulatory frameworks exist in most countries, there are differences in the extent to which regulations are implemented. In most countries, veterinary pharmaceutical products undergo a licensing process that assesses the risk/benefit balance of the proposed products, similar to the process followed for human use products. For antimicrobials, an evaluation of the potential impact on human health is also included in many countries. Initially this evaluation focused on avoiding antimicrobial residues in food products, but more recently it has been extended to include effects on AMR in bacterial populations in slaughter-ready animals. The approval process may also include consideration as to whether specific antimicrobials are of critical importance for human health,[124] often with measurable impact on AMR (Box 4.2). WHO has categorized antimicrobials which are critically important for human use.[125] However, current national legislations do not always restrict the use of such critical antibiotics in animals.

In many countries, it can be difficult to withdraw approval for an already licensed pharmaceutical product. However, it is often possible within the existing legislation to implement restrictions on the approved usages of licensed antimicrobials (Box 4.2). For example, it is possible to limit off-label / extra-label use or to restrict use to individual animals.

Box 4.2 **Approval and regulations on use of antimicrobials of critical importance**

The U.S. Food and Drug Administration successfully withdrew the approval of fluoroquinolones for use in poultry on 12 September, 2005.[126] To achieve the withdrawal, the agency had to demonstrate that the use of enrofloxacin in poultry causes the development of fluoroquinolone-resistant Campylobacter in poultry, that these fluoroquinolone-resistant organisms are transferred to humans, that they may cause the development of fluoroquinolone-resistant Campylobacter in humans, and that fluoroquinolone-resistant Campylobacter infections in humans are a health hazard. The process began in 2000, involved the collection and evaluation of thousands of studies, expert testimony, an oral hearing, and a complex risk assessment.

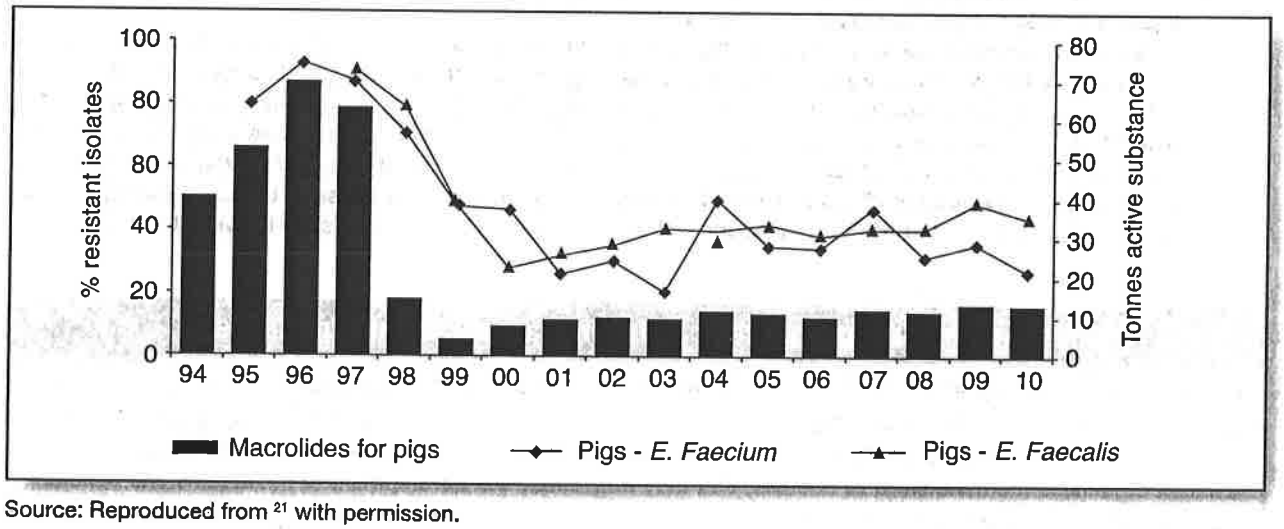
In Australia, fluoroquinolones (e.g. ciprofloxacin), which are antimicrobials of 'critical importance' in human use, have never been approved for use in food production animals. Fluoroquinolone-resistant bacteria are either at very low levels or else non-existent in food animals and resistance is very low in Australian human bacterial isolates in comparison with other countries. Data from the Australian Group on Antimicrobial Resistance 2006 surveillance report show fluoroquinolone resistance in 2006 to be less than 5% in clinical isolates of Gram-negative bacilli.[127]

The approval of fluoroquinolones for use in food animals in 1993 in Denmark saw the rapid emergence of resistance to this class, with 23% of C. coli isolates from pigs found to be resistant during 1995 to 1996. Consequently, in 2002 restrictions were imposed on the veterinary use and prescription of fluoroquinolones for food-producing animals: fluoroquinolones could only be used in food-producing animals for the treatment of infections proven by laboratory tests to be resistant to all other antimicrobials, and administered only by injection by a veterinarian, with the use reported to the regional veterinary officer. This reduced fluoroquinolone use in animals in Denmark from 183 kg in 2001 to 49 kg in 2006 and it has remained low since then. Resistance was detected in just 12% of C. coli isolates from pigs tested in 2009.[21]

Restrictions on the mode of administration could be another useful means of limiting use in animals, particularly for antimicrobials that are critically important for human use, for example, by limiting them to injection-only. However, this type of restriction is applicable in individual animal treatment, but may not always be feasible for large numbers, for example in poultry flocks.

Increasing numbers of countries are banning the use of antibiotics as growth promoters, a very positive development which has been highlighted in recent media reports. Experiences following cessation of use of antimicrobial agents are encouraging. By January 2000, the use of all antimicrobials as growth promoters had been prohibited in Denmark. This has resulted in an overall reduction in resistance among bacteria in animals. The temporal association between the reduction of macrolide use and the prevalence of AMR among enterococci isolated from pigs in Denmark is shown in Figure 4.4. Resistance will probably never return to pre-antibiotic use levels, and so consumption of antimicrobials needs to be kept at low levels as excessive use could again rapidly drive AMR upwards.

Figure 4.4 Macrolide use and resistance among *enterococci* in pigs, Denmark

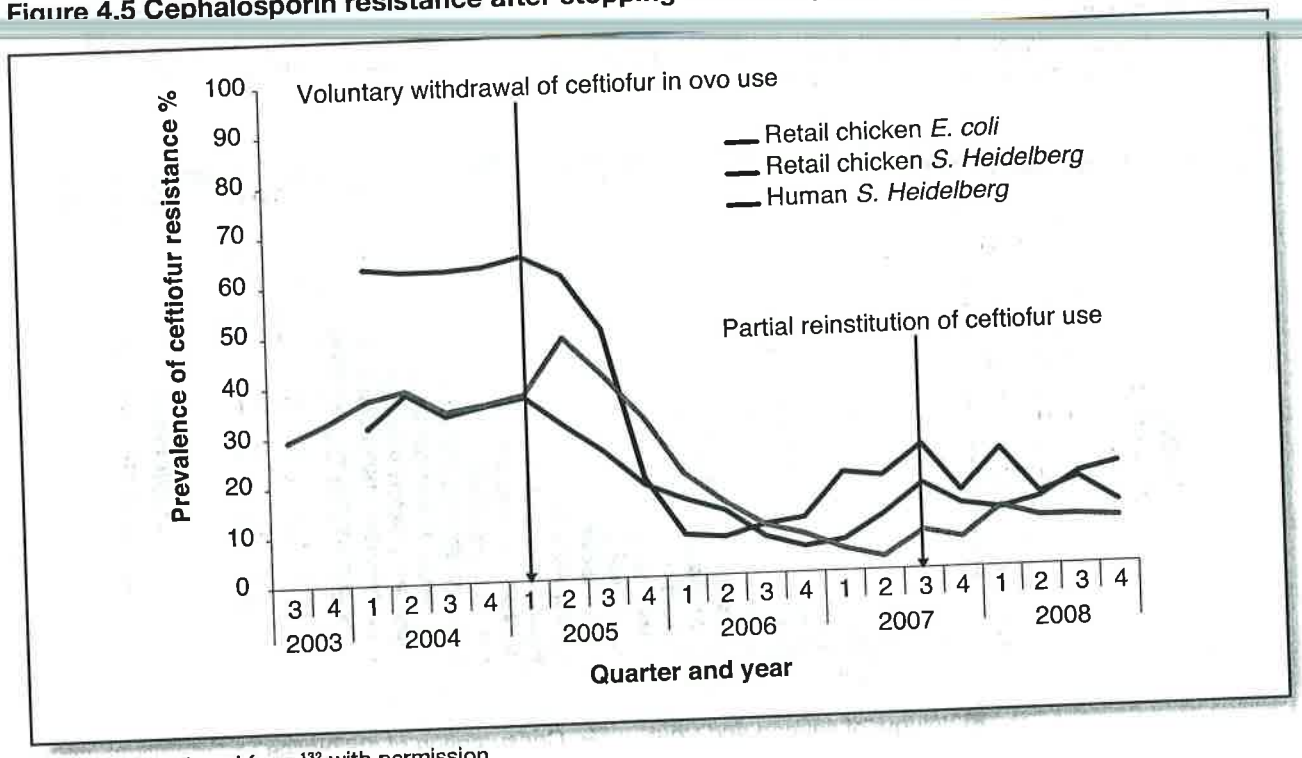


Source: Reproduced from [21] with permission.

In 1995 a ban of the growth promoter avoparcin (a glycopeptide) which selects for vancomycin-resistant enterococci (VRE) in Denmark led to a reduction in the prevalence of VRE among animals and in the general human population. However, VRE has persisted for up to 12 years in poultry farms after the ban and is likely to persist for many more years. The complex relationship between reducing use and the levels of resistance is being explored.[128-130]

Experience has shown that any negative effects due to the prohibition of growth promoters are minimal in the long term, once industry adapts to the changes.[131] Apart from prohibitions on the use of antibiotics in food animals, there have also been a number of voluntary withdrawals. In Canada and the USA, ceftiofur, a 3rd generation cephalosporin, may legally be used in an extra-label manner for routine administration into eggs or one day-old chicks in hatcheries, to prevent infections. Surveillance in the province of Quebec, Canada, demonstrated a marked increase in the prevalence of resistance to 3rd generation cephalosporins and penicillins among *S. enterica* serotype Heidelberg isolates from humans and chickens in early 2005. A survey of antimicrobial use in hatcheries in Quebec confirmed that in 2004 all chicken hatcheries switched to exclusive use of ceftiofur. In early 2005, Quebec hatcheries stopped this use voluntarily, after which there was a dramatic decline in the prevalence of ceftiofur resistance (Figure 4.5). Anecdotal reports indicate that the industry has subsequently re-introduced alternating use of ceftiofur with other antimicrobials, and that this has been followed by a resurgence of resistance.[132]

Figure 4.5 Cephalosporin resistance after stopping its use in poultry in Quebec, Canada



Source: Reproduced from [132] with permission.

Unfortunately, there are few incentives to encourage voluntary withdrawal of growth promoters and no barriers or sanctions for re-introducing them.

Easy access to antimicrobials through sources such as online pharmacies, animal feed outlets and pet shops contributes to their overall excessive use and makes it increasingly difficult to enforce regulations on the use of these products.

Financial incentives

Ideally, sales of an antimicrobial should never involve financial benefit for the prescriber. Limitations on the sales profits obtained by veterinarians in Denmark from 1994 to 1995 led to major reductions in the therapeutic use of antimicrobials, especially tetracyclines, without any obvious overall harm to animal health.

Prudent use guidelines and education

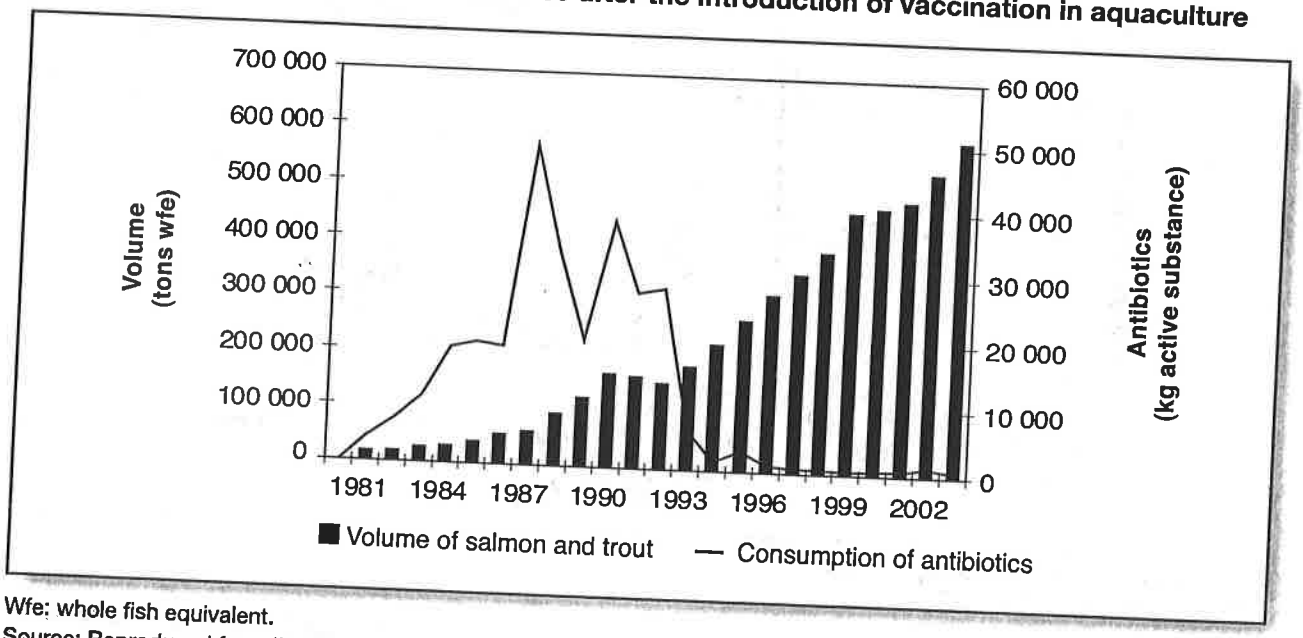
To reduce inappropriate use and promote prudent use, developing treatment guidelines and popularising them among veterinarians and farmers is likely to be helpful. Prudent use guidelines have been issued in the Netherlands (1986), Denmark (1998), USA (1999/2000), Germany (2000), and in many other countries more recently. However, the influence of these guidelines has not been monitored adequately, for example the Netherlands is still among the highest users of antimicrobials in food animals in Europe.

Improving animal health to reduce the need for antibiotics

The most effective means to reduce the use of antimicrobials and thus prevent AMR is to reduce the need for antimicrobial treatment. This could be achieved by improving animal health through measures such as immunization against prevalent infections. In Norway, the introduction of effective vaccines in farmed salmon and trout in 1987 and improved health management reduced the annual use of antimicrobials in farmed fish by 98% between 1987 and 2004 (Figure 4.6).[133] Many countries and

the EU already have regulations in place to enforce and promote vaccination as a method of reducing infections in food animals. However, even if health improves, it is not certain that established practices and consumption will change, since most antimicrobial agents for growth promotion and prophylaxis are used without any evidence of the need for, or benefit from, their use.

Figure 4.6 Reduction in antimicrobial use after the introduction of vaccination in aquaculture



Wfe: whole fish equivalent.
Source: Reproduced from [133] with permission.

Improving hygiene in food production

The FAO/WHO Codex Alimentarius[c] provides recommendations for many aspects of food production including hygiene, from primary production through to final consumption, highlighting the key controls at each stage. It recommends a *Hazard Analysis and Critical Control Point (HACCP)* approach. Good agriculture practices particularly at the farm level have also been defined. The Codex Task Force on Antimicrobial Resistance recently developed a risk analysis and management tool to assess the risks to human health associated with foodborne antimicrobial resistance.

In 2006, the EU put in place a programme with specific targets for reduction in salmonella contamination. Based on data from 27 EU Member States in 2009, 18 have reached the EU reduction targets in breeding flocks of fowl and the decreasing trend in human salmonellosis cases is continuing.[134] Microbiological criteria for a maximum acceptance level for certain types of AMR *Salmonella enterica* in food animals have been implemented in Denmark. The impact of these interventions has not yet been fully evaluated but Denmark has a low rate of domestically-acquired salmonella infections.

Applying advances in data management technology

Herd Health and Production Management (HHPM) programmes have been used to improve productivity

[c] http://www.codexalimentarius.org/

incrementally, mainly in intensive production systems. HHPM monitors the interaction between farm management, herd health and production, and integrates these components in order to obtain optimal results. These programmes use computer-based Management Information Systems (MIS) and the databases thus developed could direct attention to AMR and allow recognition of the contributions of local management, and of environmental and biological factors, to the development of AMR (Box 4.3).

Box 4.3 Computer-based monitoring of antimicrobial use and resistance to improve production

The MIS database used in Costa Rica records both prophylactic use (uterine infusion after artificial insemination, dry-off treatment etc), and therapeutic use (disease treatment, mastitis treatment, uterine infusions, etc) of antimicrobial agents in cattle. It includes a module for drugs, which allows the personnel responsible for use to register the drug used. This module enables data gathering for surveillance of antimicrobial use, AMR, and monitors the actions of veterinarians and/or producers. Similar HHPM programmes could be used more widely to monitor AMR at farm level, and correlate the data with environmental and managerial aspects to identify risk factors for AMR.

4. Gaps and challenges

Data on AMR associated with animal husbandry: The extent of AMR in foodborne bacteria, and the global burden of human infections due to such bacteria, are unknown. Continuous and updated information on foodborne pathogens, their spread and the status of AMR is necessary to guide risk profiling, risk assessment and risk management and to measure the impact of interventions. However, very few countries appear to have these monitoring systems in place, and where data are collected, they are often not comparable because of methodological differences (Chapter 2). Regional and national laboratory networks using standard methods would alleviate this situation.[135] There is scope for widening participation in existing networks and for strengthening the capacity of the participating laboratories. Databases could also be usefully improved to include phenotypic and genotypic features of the bacteria being monitored.

Data on quantities used: Data on total volumes of antimicrobials used and the indications for which they are used are also limited. The use of antimicrobials in animal husbandry is generally not based on sound scientific principles. Although use for growth promotion is being reduced in many countries, the practice is still widespread in many parts of the world. Correct use for prophylaxis and metaphylaxis is the subject of ongoing debate, and more could be done to limit antimicrobial use in these areas. The agents used and the modality of use differs widely between countries and within countries. OIE has published a list of critical antimicrobial agents needed for animal health[136] with an overview of the agents used and considered important in different countries.

Regulatory provisions: In many countries, the legal and regulatory framework to control the use of antimicrobials in animals could be strengthened. Regulations governing the approval of veterinary medicines and restrictions on their use are often lacking, or not adequately enforced. Restricting the use in food production animals of antibiotics that are "critically important" for human health is recommended by many experts and authorities. Currently, WHO gives priority to restricting the use of 3rd generation cephalosporins and fluoroquinolones.[125] Regulations could also include provisions for prohibiting for animal use any new drug class developed for human medicine, and of those that are used only in human medicine (e.g. linezolid, daptomycin, carbapenems, glycopeptides). Regulations also have a potentially valuable role in supporting compliance with the international standards for food safety practices in the production of food of animal origin, developed by the FAO/WHO Codex Alimentarius and OIE.

Data for registration of antimicrobials: It is standard practice for regulatory agencies to require data on the efficacy of a new medicine prior to registration, but these data are rarely available in the public domain.

This particularly applies to older products that have not been subjected to recently-introduced rigorous approval processes. Pharmacovigilance systems in place in many countries include the obligation to declare lack of efficacy, which could be a problem with drugs that have been in use for a longer period of time.

Routine, usually qualitative, assessments of risks for developing AMR are now incorporated into the pre-market authorization process for veterinary antimicrobials in some countries. However, these assessments are made difficult by the complexities of the producer-to-consumer continuum and lack of data in several important areas. Positive, albeit modest, developments include quantitative risk assessment for specific antimicrobial/organism combinations (e.g. fluoroquinolone resistance in *C. jejuni*). Improvements in methodologies for risk assessment, risk management and risk communication could be beneficial and additional guidance in this area from Codex Alimentarius would be helpful. The application of such guidance at national/regional and international levels could be improved.

Evaluation of impact: The potential impact of different interventions in different settings is still largely unknown. Measuring impact on food safety, enteric and other zoonotic diseases in people, animal health, animal productivity, national economy and other indicators at the regional/national level requires standardized indicators and sustainable capacity for monitoring AMR and antimicrobial use. At a local level, the impact could probably be determined by targeted research studies, and meta-analyses of such available global data could prove useful.

Capacity to respond to AMR: National capacity to respond to problems due to AMR is not uniform at either country or local level. Capacity at farm level is lacking in many countries, for reasons such as a lack of effective organizational structure, trained personnel, and sufficient knowledge about the risks involved. To improve this situation, instruments to guide the characterization and evaluation of institutional and operational capabilities, measure advancement, and propose strategic actions for technical cooperation have been developed by the Pan American Health Organization (PAHO)[d].

Application of modern technologies: Available technologies could be better harnessed to analyse local situations and risk factors, and for effective communication including the improvement of existing communication networks to disseminate already available information. The possibility of developing new vaccines, particularly against the infections for which most antibiotics are being used, such as gastro-intestinal infections in pigs and calves, mastitis in cattle and *E. coli* infections in poultry, could be explored. Another possible option is the development and evaluation of probiotics, which are probably valuable alternatives to antibiotics in the control of gastro-intestinal infections in food animals.

Selection of appropriate interventions: Different commodity groups in different settings may require different interventions. For example an intervention to reduce resistance in 180-day swine system may not be directly applicable to a 42-day broiler chicken system, and interventions suited to extensive agriculture are unlikely to be of equivalent efficacy in intensive settings. Thus, the choice of interventions could be based on a process of identification, analysis and prioritization of needs and options which could include the introduction and/or enforcement of regulations on the use of antimicrobials in animals; measures to improve animal health; promotion of prudent antimicrobial use; strengthening hygiene in the food chain; and specific targeted measures in areas with a higher risk of AMR development or serious consequences.

Capacity building activities including staff training are still needed in many places. Public education on issues related to the use of antibiotics in food-producing animals may be needed to raise awareness of the potential harm and unclear benefit from their use in agriculture and aquaculture.

[d] http://www.paho.org/English/AD/DPC/VP/fos-program-page.htm

List of authors, contributors and reviewers

List of Authors, contributors and reviewers

(listed in alphabetic order in each section)

Authors

Chapter 1. The evolving threat of antimicrobial resistance
Authors: M. Lindsay Grayson, University of Melbourne, Australia; David Heymann, Health Protection Agency, UK; Didier Pittet, Hôpitaux Universitaires de Genève, Switzerland.

Chapter 2. Surveillance to track antimicrobial use and resistance
Authors: Hajo Grundmann, National Institute for Public Health and the Environment, The Netherlands; Thomas F. O'Brien, Brigham and Women's Hospital, USA; John M. Stelling, Brigham and Women's Hospital, USA.

Contributors: Luis Bavestrello Fernández, Centro Médico Clinica Reñaca, Chile; John Chalker, Management Sciences for Health, USA; Marcelo Galas, Instituto Nacional de Enfermedades Infecciosas, Argentina; Herman Goossens, University of Antwerp, Belgium; Elizabeth Mathai, World Health Organization, Switzerland; Sachiko Satake, Gunma University, Japan.

Chapter 3. Measures to ensure better use of antibiotics
Authors: Otto Cars, Action on Antibiotic Resistance (ReAct), Sweden; Andreas Heddini, Action on Antibiotic Resistance (ReAct), Sweden; Stuart Levy; Tufts University School of Medicine, USA.

Contributors: Inge Gyssens, Radboud University Nijmegen Medical Centre, The Netherlands; Stephan Harbarth, Hôpitaux Universitaires de Genève, Switzerland; Kathleen Holloway, WHO Regional Office for South-East Asia, India; Keith P. Klugman, Emory University, USA; David Ofori-Adjei, Centre for Tropical Clinical Pharmacology and Therapeutics, Ghana; Iruka Okeke, Haverford College, USA; Eva M.A. Ombaka, Business Network International (BNI) Tanzania Pwani, United Republic of Tanzania; Chitr Sitthi-Amorn, Chulalongkorn University, Thailand.

Chapter 4. Reducing Antimicrobial use in Animal Husbandry
Authors: Frank M. Aarestrup, Technical University of Denmark, Denmark; Awa Aidara-Kane, World Health Organization, Switzerland.

Contributors: Peter Collignon, Canberra Hospital, Australia; Ran Lu, Chinese Center for Disease Control and Prevention, People's Republic of China; Scott McEwen, University of Guelph, Canada; Eric Mitema, University of Nairobi, Kenya; Gérard Moulin, Agence Nationale du Médicament Vétérinaire (ANMV), France; Enrique Perez-Gutierrez, World Health Organization, Republic of Panama; H. Morgan Scott; Kansas State University College of Veterinary Medicine, USA.

Chapter 5. Prevention and control of infection in the health care facilities
Authors: Barry Cookson, Health Protection Agency, UK; Petra Gastmeier, Charité University Hospital, Germany; Wing-Hong Seto, Queen Mary Hospital, Hong Kong SAR, People's Republic of China.

Contributors: Benedetta Allegranzi, World Health Organization, Switzerland; Hu Bijie, Zhongshan Hospital of Fudan University, People's Republic of China; Ian Gould, Aberdeen Royal Infirmary, UK; Victor Lim, International Medical University, Malaysia; Ralf-Peter Vonberg, Institute for Medical Microbiology and Hospital Epidemiology, Germany.

Chapter 6. Fostering Innovation to Combat Antimicrobial Resistance
Authors: Shaoyu Chang, Duke University, USA; Anthony So; Duke University, USA.

Contributors: Robert A. Bonomo, Case Western Reserve University, USA; Kelly Chibale, University of Cape Town, South Africa; Ramanan Laxminarayan, Center for Disease Dynamics, Economics and Policy, USA; Evan Lee, Foundation for Innovative New Diagnostics (FIND), Switzerland; Rohit Malpani, Oxfam America, USA; Piero Olliaro, UNICEF/UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases, Switzerland; Rosanna Peeling, The London School of Hygiene and Tropical Medicine, UK; Nina Schwalbe, Global Alliance for Vaccines and Immunization, Switzerland; Els Torreele, Open Society Foundations, USA; Bernhard H. Weigl; PATH, USA.

Chapter 7. The way forward: political commitment to enable options for action
Authors: Gerald Dziekan, Itziar Larizgoitia Jauregui, and Elizabeth Mathai, World Health Organization, Switzerland .

Reviewers

International
Alix Beith, Center for Disease Dynamics, Economics & Policy, USA; John Conly, University of Calgary/Alberta Health Services, Canada; Gabriel Levy Hara, Maimónides University, Argentina; David Heymann, Health Protection Agency, UK; Po-Ren Hsueh, National Taiwan University, Taiwan, People's Republic of China; Mohan P. Joshi, Strengthening Pharmaceutical Systems, USA; Niyada Kiatying-Angsulee, Chulalongkorn University, Thailand; Anke Meiburg, Ecumenical Pharmaceutical Network (EPN), Kenya; Lindsay Nicolle, University of Manitoba, Canada; Arturo Quizhpe Peralta, University of Cuenca, Ecuador; Didier Pittet, Hôpitaux Universitaires de Genève, Switzerland; Victor Rosenthal, International Nosocomial Infection Control Consortium (INICC), Argentina; Gunnar Skov Simonsen, University Hospital of North Norway, Norway; Arjun Srinivasan, Centers for Disease Control and Prevention (CDC), USA; Evelina Tacconnelli, Università Cattolica del Sacro Cuore, Italy; Linda Tollefson Food and Drug Administration, USA; as well as all authors.

World Health Organization Headquarters, Switzerland
Susanne Carai, Yves Chartier, Daniel Chemtob, Sergey Romualdovich Eremin, Dennis Falzon, Martin Friede, Tauhidul Islam, Ernesto Jaramillo, Douglas Macpherson, Paul Nunn, Charles Penn, Carmem Lucia Pessoa Da Silva, Mario Raviglione, Douglas Wares, Diana Weil, Matteo Zignol.

World Health Organization Regional Offices
WHO Western Pacific Region: Henk Jan Bekedam, Eva-Maria Christophel, Catharina van Weezenbeek.
WHO Region of the Americas: Jose Luis Castro, Jorge Matheu, Pilar Ramon Pardo.

Consultation process participants

Frank M. Aaerestrup, Denmark; Awa Aidara-Kane, WHO; Benedetta Allegranzi, WHO; Luis Bavestrello Fernandez, Chile; Sepideh Bagheri Nejad, WHO; Silvia Bertagnolio, WHO; Hu Bijie, People's Republic of China; Robert A. Bonomo, USA; Andrea Bosman, WHO; Samir Brahmachari, India; Jean Carlet, France; Yehuda Carmeli, Israel; Otto Cars, Sweden; John Chalker, USA; Shaoyu Chang, USA; May Chu, WHO; Sébastien Cognat, WHO; Peter Collignon, Australia; Barry Cookson, UK; Sara E. Cosgrove, USA; Sarah Deeny, UK; Sir Liam Donaldson, UK; Gerald Dziekan, WHO; Sittana S. Elshafie, Qatar; Dennis Falzon, WHO; Christophe Fraser, UK; Martin Friede, WHO; Marcelo Galas, Argentina; Petra Gastmeier, Germany; Hellen Gelband, USA; Herman Goossens, Belgium; Ian Gould, UK; Felix Greaves, WHO; Hajo Grundmann, The Netherlands; Inge Gyssens, The Netherlands; Valentina Hafner, WHO; Julie Hall, WHO; Stephan Harbarth, Switzerland; Andreas Heddini, Sweden; Ole Heuer, Sweden; David Heymann, UK; William Hanage, UK; Kathleen Holloway, WHO; Ernesto Jaramillo, WHO; Edward Kelley, WHO, Iain Kennedy, WHO; Keith Klugman, USA; Paul Lalvani, USA; Angela Lashoher, WHO; Itziar Larizgoitia Jauregui, WHO; Ramanan Laxminarayan, USA; Evan Lee, Switzerland; Stuart Levy, USA; Victor Lim, Malaysia; Knut Lonnroth, WHO; Ran Lu, People's Republic of China; Elizabeth Mathai, WHO; Colin Mathers, WHO; Scott McEwen, Canada; Eric Mitema, Kenya; Gérard Moulin, France; Doris Murgditchian, WHO; Nabila N'Metwalli, WHO; Lai King Ng, WHO; David Ofori-Adjei, Ghana; Iruka Okeke, USA; Eva M.A. Ombaka, United Republic of Tanzania; Fernando Otaiza, WHO; Enrique Perez-Gutierrez, Republic of Panama; Carmem Pessoa da Silva, WHO; Pauline Philip, WHO; Didier Pittet, Switzerland; Rose Pray, WHO; John Rainford, WHO; Pilar Ramon Pardo, PAHO/WHO; Cathy Roth, WHO; Matthew Samore, USA; Sachiko Satake, Japan; Fabio Scano, WHO; Nina Schwalbe, Switzerland; H. Morgan Scott, USA; Wing-Hong Seto, Hong Kong SAR, People's Republic of China; Marcus Shepheard, UK; Chitr Sitthi-Amorn, Thailand; Ian Smith, WHO; Anthony So, USA; Sri Suryawati, Indonesia; John Stelling, USA; Vivian Tang, WHO; Wayne Van Gemert, WHO, Ralf-Peter Vonberg, Germany; Mohammad Youssef, WHO; Matteo Zignol, WHO.

Book editing and project management

Editing: Lindsay Martinez, Switzerland.
Project management: Gerald Dziekan, Itziar Larizgoitia Jauregui, Elizabeth Mathai, with the support of Katthyana Aparicio, Armorel Duncan, Margaret Kahuthia and Laura Pearson, WHO, Switzerland.

World Health Organization
20 Avenue Appia
CH - 1211 Geneva 27
Switzerland
Tel: +41 (0) 22 791 50 60

Email
patientsafety@who.int
Please visit us at:
www.who.int/patientsafety/en/

ISBN 978 92 4 150318 1

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

Centers for Disease Control
and Prevention (CDC)
Atlanta GA 30333

July 13, 2010

The Honorable Frank Pallone, Jr.
Chairman
Subcommittee on Health
House Committee on Energy and Commerce
Washington, D.C. 20515

Dear Chairman Pallone:

Please find attached written responses to questions for the record from the Subcommittee's April 28 hearing on antimicrobial resistance. These responses provide additional detail on the strong scientific evidence of a link between antibiotic use in food animals and antibiotic resistance in humans.

There are multiple North American studies describing how:

- Use of antibiotics in animals results in resistant bacteria in food animals
- Resistant bacteria are present in the food supply and transmitted to humans
- Resistant bacteria result in adverse human health consequences (such as increased hospitalizations)

In addition, a strong body of evidence from Europe demonstrates that antibiotic use in animals is linked with antibiotic resistance in humans. Multiple studies looked at the effects of the Danish ban on non-therapeutic use of antibiotics in food animals. We have thoroughly reviewed these studies and have found them to be well-designed and rigorous, and to establish a clear link between antibiotic use in animals and antibiotic resistance in humans.

I appreciate this opportunity to restate my conclusions from the April hearing, and provide you additional detail. This opportunity is particularly important because some discussion at the hearing has been mischaracterized. To be clear, the Centers for Disease Control and Prevention (CDC) finds that there is a compelling body of evidence to demonstrate this link, as summarized above, in my April testimony, and in the attached responses to questions for the record. I am pleased that the Subcommittee is holding another hearing in its series on this important issue, and that Dr. Ali Khan will be able to represent CDC to further elaborate on this evidence regarding the relationship between antibiotic use in food animals and antibiotic resistance in humans.

CDC remains committed to working with Congress and our colleagues at the Department of Health and Human Services and the U.S. Department of Agriculture to identify the best ways to address the health risks posed by antibiotic resistance.

Sincerely,

Thomas R. Frieden, M.D., M.P.H.
Director, CDC, and
Administrator, Agency for Toxic Substances
and Disease Registry

Cc: Rep. John Shimkus, Ranking Member
Anthony Fauci, NIH
Margaret Hamburg, FDA
Josh Sharfstein, FDA
Ali Khan, CDC

QUESTIONS SUBMITTED FOR THE RECORD
HEARING ENTITLED,
"ANTIBIOTIC RESISTANCE AND THE THREAT TO PUBLIC HEALTH"
SUBCOMMITTEE ON HEALTH
COMMITTEE ON ENERGY AND COMMERCE
UNITED STATES HOUSE OF REPRESENTATIVES
APRIL 28, 2010

Thomas Frieden, M.D., M.P.H.
Director
Centers for Disease Control and Prevention
U.S. Department of Health and Human Services

Representative Henry A. Waxman

Q1. You mentioned data from Europe demonstrating the link between animal antibiotic use and antibiotic-resistant microbes in people, in particular the example of avoparcin and vancomycin-resistant enterococcus. You also mentioned the data from Denmark, where antibiotics were banned for growth promotion uses for animals. Please evaluate the lessons from these European data and provide your views on any relevant lessons for the United States.

A. The Danish studies have focused on non-therapeutic use of antimicrobial agents in food-producing animals, particularly swine and broiler chickens. Non-therapeutic uses include promoting growth and improving feed efficiency; drugs for these purposes are typically given in feed.

- In 1995, the Danish government banned the non-therapeutic use of avoparcin for growth promotion in Denmark. In 1997, the commission of the European Union (EU) countries adopted the same ban for all of its member states.
- In 1998, Denmark banned use of virginiamycin for growth promotion. Also in 1998, the agriculture ministers in the EU voted to ban use of virginiamycin, bacitracin, tylosin, and spiramycin for growth promotion; this ban became effective for EU member states in 1999.
- The Danish cattle and broiler industries voluntarily stopped the non-therapeutic use of all antibiotics for growth promotion in February 1998.
- The Danish swine industry through voluntary and regulatory action stopped all non-therapeutic use of antibiotics for growth promotion in swine above 35 kg by February 1998 and for all age groups by December 1999.
- In 2002, the EU voted to phase out all non-therapeutic use of antibiotics for growth promotion (AGPs, i.e., all non-prescription use) beginning in 2006.

Effect of these actions[1,2,3,4,5,6]

[1] World Health Organization. 2003. Impacts of antimicrobial growth promoter termination in Denmark: The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark.Available at: http://www.who.int/salmsurv/en/Expertsreportgrowthpromoterdenmark.pdf.

[2] DANMAP. 2008. *Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark*. Available at: http://www.danmap.org/pdfFiles/Danmap_2008.pdf.

- While there has been an increase in therapeutic use of antimicrobials in animals, total antimicrobial consumption in animals in Denmark has decreased by over 50%. From 1998 to 2008, total antimicrobial consumption reduced from 100 to 49 milligrams of antimicrobials per kilogram of meat produced.
- Stopping the use of various non-therapeutic antibiotic growth promoters (e.g., avilamycin, avoparcin, spiramycin, tylosin, virginiamycin) has resulted in a major reduction in antimicrobial resistance as measured among several different bacterial species in food animals and food. This has been thoroughly documented in scientific publications from Denmark.
- Denmark measured total consumption of antimicrobial agents by food animals and resistance to those drugs among *Enterococcus* isolated from food animals and the foods derived from them.
- Resistance to these drugs among *Enterococcus* isolated from broilers, swine, and the meat from these animals decreased after AGPs were discontinued. However, in 2003, the World Health Organization (WHO) could not determine the ban's direct and total effect on antimicrobial resistance in humans because of limited data. Newer monitoring data available since then show that human resistance trends appear to be mirroring the decline in on-farm use of antibiotics; however, newer monitoring data on human resistance must be considered carefully. The trend must first be determined to be sustainable. Second, although the trend may mirror decreases in resistance in animals, more needs to be known about the potential causes for decrease in humans. If present, the trend toward decreased resistance is likely due to many factors including those aimed specifically at human antimicrobial usage and transmission of resistant bacteria.
- Weaner (swine) mortality increased several years before as well as a few years after non-therapeutic use stopped, but has drastically decreased in recent years, indicating that the termination had no effect on swine mortality.
- Production and economic impacts are described in a 2003 WHO report. The WHO reports that: "Overall, total volume of pork production in Denmark continued to increase in the period following the termination of antimicrobial growth promoters... The net costs associated with productivity losses incurred by removing antimicrobial growth promoters from pig and poultry production were estimated at 7.75 DKK (1.04 €) per pig produced

---

[3] Aarestrup, F.M., A.M. Seyfarth, H.D. Emborg, K. Pedersen, R.S. Hendriksen, and F. Bager. July 2001. "Effect of Abolishment of the Use of Antimicrobial Agents for Growth Promotion on Occurrence of Antimicrobial Resistance in Fecal Enterococci from Food Animals in Denmark," *Antimicrobial Agents and Chemotherapy* 45(7): 2054-2059. Available at: http://aac.asm.org/cgi/reprint/45/7/2054.

[4] Boerlin, P., A. Wissing, F. M. Aarestrup, J. Frey, and J. Nicolet. 2001. "Antimicrobial Growth Promoter Ban and Resistance to Macrolides and Vancomycin in Enterococci from Pigs," *Journal of Clinical Microbiology* 39(11): 4193–4195. Available at: http://jcm.asm.org/cgi/reprint/39/11/4193.

[5] Evans, M.C. and H.C. Wegener. 2003. "Antimicrobial Growth Promoters and Salmonella spp., Campylobacter spp. In Poultry and Swine, Denmark," Emerging Infectious Diseases 9(4): 489-492. Available at: http://www.cdc.gov/ncidod/eid/vol9no4/pdfs/02-0325.pdf

[6] Gravea, K., V.F. Jensen, K. Odensvik, M. Wierup, and M. Bangen. 2006. "Usage of veterinary therapeutic antimicrobials in Denmark, Norway and Sweden following termination of antimicrobial growth promoter use," Preventive Veterinary Medicine 75(1-2): 123-132.

and no net cost for poultry. This translates into an increase in pig production costs of just over 1%."[7]

In general, subtherapeutic use has been shown to lead to an increase in resistant strains in animals. The European experience demonstrates that it is possible to stop these uses, reduce overall use of antibiotics in animals, reduce resistant circulating bacteria that can infect humans, and not have industry or consumers affected by decreased production or increased costs. Additional information, such as reliable data on quantities of antibiotics used in animals for various purposes and comprehensive on-farm studies of the relationship between use and resistance, would be needed to study the same effects in the United States.

Q2. The rates of foodborne illnesses—particularly those generated by antibiotic resistant organisms—have risen in this country. Ms. Capps asked about the National Antimicrobial Resistance Monitoring System data and suggested that much of the nation's meat and poultry products are tainted with some kind of antibiotic resistant bacteria. There are a number of studies, both in Europe and in the United States, suggesting a link between the use of certain antibiotics in animals and bacteria resistant to those antibiotics in food products and humans. For example, a study in Minnesota and Wisconsin found evidence indicating that antibiotic-resistant E. coli in people were likely to have came from poultry, while antibiotic-sensitive E. coli in people likely did not come from poultry (J.R. Johnson et al., *Antimicrobial Drug-Resistant Escherichia coli from Humans and Poultry Products, Minnesota and Wisconsin, 2002-2004*, Emerging Infectious Diseases (June 2007) (online at http://www.cdc.gov/EID/content/13/6/838.htm). Can you expand on this information, and comment on whether CDC believes such antibiotic resistant bacteria from animals and their meat have been transmitted to people?

A.

- CDC is familiar with the J.R.Johnson article referenced and concurs with the conclusions described in the study. Johnson et al analyzed the distribution and virulence genotypes of drug-susceptible and drug-resistant E. coli isolates from human volunteers and poultry products. They found that drug resistant E coli isolates from humans were more similar to drug resistant isolates from poultry then they were from drug susceptible isolates from humans. This work as well as other work from Johnson's group has contributed to the evidence that drug resistant E coli found in humans is most similar to that found in poultry.
- The National Antimicrobial Resistance Monitoring System (NARMS)[8] has demonstrated a steady and statistically significant increase in the prevalence of resistance to the two

[7] World Health Organization. 2003. Impacts of antimicrobial growth promoter termination in Denmark: The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark.Available at: http://www.who.int/salmsurv/en/Expertsreportgrowthpromoterdenmark.pdf.

[8] NARMS is a collaboration among CDC (human samples), FDA's Center for Veterinary Medicine (retail meats and animal feeds), and USDA's Food Safety and Inspection Service and Agricultural Research Services (animal samples). Participating health departments forward every twentieth non-Typhi Salmonella isolate, every Salmonella Typhi, every twentieth Shigella isolate, and every twentieth E. coli O157 isolate received at their public health laboratories to CDC for susceptibility testing. NARMS investigates outbreaks involving these bacteria and conducts research on resistance mechanisms.

most clinically important antimicrobial agents, ciprofloxacin and ceftriaxone, in *Salmonella* strains isolated from ill humans in the United States.

- A multidrug resistant (MDR) *Salmonella* Typhimurium emerged in the 1990s in cattle and in people, and has persisted since then (associated with ground beef).
- MDR *Salmonella* Newport emerged in 1998 in cattle and humans and has persisted since then (associated with ground beef).
- Resistance to ciprofloxacin in *Campylobacter* in poultry and people emerged in the late 1990s and steadily increased (associated with chicken and turkey).
- In 2005, FDA withdrew approval for fluoroquinolone use in poultry due to evidence it might be associated with resistant human infections.
- Although it has not been demonstrated conclusively in a single study that use of antimicrobial agents in food animals results in adverse human health consequences, numerous studies have demonstrated the movement of resistant pathogens through the food supply. Studies related to *Salmonella*, including many studies in the United States, have demonstrated that (1) use of antimicrobial agents in food animals results in antimicrobial resistance in food animals, (2) resistance strains are present in the food supply and commonly transmitted to humans, and (3) increases in resistant strains results in adverse human health consequences (e.g., increased hospitalization).[9],[10]

Q3. Mr. Dingell asked that you provide the level of your request for financial support for antimicrobial programs in the President's budget, the amount CDC has been given for these programs during each of the last 3 years, and the amount anticipated for the next 3 years. Please provide such information, including your professional judgment budget for the appropriate level of funding for antibiotic resistance programs at CDC.

A.

- In FY 2008, FY 2009, and FY 2010, antimicrobial resistance was funded ($16.9 million per year), either through specific Congressional appropriations or agency allocations.
- The FY 2011 President's Budget includes $8.7 million available to fund AR activities. The FY 2011 Budget also includes an increase of $19.6 million for the Emerging Infections program, which supports antimicrobial resistance activities, such as surveillance, technical assistance, and epidemiological and laboratory support.

CDC is committed to maintaining a strong AR program and is exploring the high value investments moving forward. CDC will work to prioritize funding through the Emerging infections program and antimicrobial resistance program to combat AR.

In CDC's professional judgment, to fully combat the growing problem of antimicrobial resistance, and to fully implement the CDC-coordinated sections of the Federal Inter-Agency Task Force on Antimicrobial Resistance *Action Plan* (surveillance, prevention and control), CDC requires an annual budget of $50 million phased in over a three year period (i.e. $30 million in FY 2012, $40 million in FY 2013, and $50 million in FY 2014). An incremental increase in the annual budget will allow for a stepwise expansion of surveillance, prevention and control

[9] Dutil et al., Emerg Infect Dis 2010

[10] Folster et al., Foodborne Pathog Dis 2010 and Zhao et al., Appl Environ Microbiol 2008.

activities described in the *Action Plan*. This does not include funding of antimicrobial resistance activities for specific diseases (such as tuberculosis and gonorrhea) funded through other CDC budget lines. This represents the professional judgment estimates of CDC staff on the size and scope of the AR activities, and is provided without regard to the competing priorities that the agency, the President, must consider to develop the Budget.

CDC would use this increase in funding to continue its antimicrobial resistance activities and add new applied research grants and demonstration projects; 75% of the division projects would be funded extramurally (both domestic and international) and 100% of the applied research grants and demonstration projects would be funded extramurally to domestic grantees. This increase in funding would also allow states via the Emerging Infections Program (EIP) and the Epidemiology and Laboratory Capacity (ELC) program to expand surveillance activities (e.g., to include antimicrobial resistance in healthcare-associated infections) and to increase state laboratory capacity to detect new and emerging resistance. CDC would also hire personnel to coordinate new surveillance activities and coordinate projects at state levels. This professional judgment budget also includes funding for capital expenses to reinforce select CDC reference laboratories and to develop and implement rapid diagnostic methods to determine the susceptibility of select microorganisms to new anti-infective agents. Funding would support an expansion of current databases of both antimicrobial use and antimicrobial resistance patterns, and expand web based reporting capabilities. Finally, the increase in funding would provide continued support for the Antimicrobial Resistance Task Force and allow CDC to plan and hold an antimicrobial resistance conference that will bring together scientists and consultants to update the Action Plan and discuss the latest scientific trends and developments in the field of antimicrobial resistance.

Professional Judgment Annual Budget for Antimicrobial Resistance Activities

Category	**Explanation**	**Cost (in millions)**		
		FY12	**FY13**	**FY14**
Continuing & new division projects	75% extramural, both domestic and international, Interagency Agreements	$7	$10	$12
Continuing & new research grants	100% extramural applied research grants and demonstration projects; educational activities	$5.5	$8.5	$15.5
Ongoing and new State-based AR activities	EIP and ELC funding to increase State-level capacity for surveillance, prevention activities, and reference laboratory services	$9	$10	$12
CDC Support for on-going and new AR	CDC funding for FTEs, laboratory supplies,	$8	$11	$10

activities	laboratory equipment, and software			
Task Force Support	Antimicrobial Resistance meeting, conference planning, Antimicrobial Resistance Task Force, consultants' meetings	$0.5	$0.5	$0.5
Total		$30	$40	$50

Q4. Your testimony before the Committee cited the theoretical risk of the use of antibiotics in animal feed. You also stated that you supported further action to ensure judicious use of antibiotics. Do you consider the use of antibiotics in animal feed for growth promotion or feed efficiency a judicious use of antibiotics, given these risks to public health?
A. CDC believes that the use of antimicrobials should be limited to protecting human and animal health. Purposes other than for the advancement of animal or human health should not be considered judicious use.

Q5. You spoke in your testimony about the need to judiciously prescribe antibiotics for humans. All antibiotics for humans in this country are prescribed under the oversight of a physician. In your view, should antibiotics used for animals be under the oversight of a veterinarian?
A. Yes, the use of medications for the prevention, treatment, and control of disease in animals should be under the supervision of a veterinarian. CDC supports the WHO's principles on containment of antimicrobial resistance in animals intended for food. Veterinarian oversight is a key principle in the "WHO Global Principles for Containment of Antimicrobial Resistance in Animals intended for Food" which is available at http://whqlibdoc.who.int/hq/2000/WHO_CDS_CSR_APH_2000.4.pdf

Q6. I understand that the CDC's National Nosocomial Infections Surveillance (NNIS) does not track infections in long term care facilities or ambulatory surgical centers. Can you explain why that is? In your view, would it be useful for the system to encompass long term care facilities and ambulatory surgical centers?
A. CDC agrees that it would be useful to expand healthcare-associated infection (HAI) surveillance and prevention activities to non-hospital settings. The National Healthcare Safety Network (NHSN – formerly NNIS) is successfully used by healthcare facilities in all 50 states (with 21 states using NHSN to fulfill their public reporting mandates) to collect and use HAI data for prevention activities, determine which practices help prevent HAIs, and to share data with other facilities within a healthcare system and/or public health agencies for collaborative prevention activities. Participation in NHSN has grown significantly in the past few years. As of March 20, 2009, over half of the approximately 5,000 U.S. hospitals are enrolled in and utilizing NHSN. Some states are already using NHSN for HAI surveillance and prevention activities in non-hospital settings. In October 2008, Colorado used American Recovery and Reinvestment Act funds awarded by CDC to extend its NHSN reporting of HAIs from ambulatory surgical centers. Additionally, there are 122 long-term acute care facilities, 51 outpatient surgical centers, and 109 hemodialysis facilities enrolled in NHSN.

Nationally, there are about 26,000 non-hospital facilities, including ambulatory surgical centers, dialysis centers, and long term care facilities where complex procedures are increasingly performed. CDC does currently have surveillance in these settings, though only a small portion of these non-hospital facilities are enrolled in NHSN because we are still refining the best way to capture surveillance data and modifying surveillance definitions for use in these settings. Currently, CDC's long-term care work group is using and modifying existing long-term care infection surveillance definitions in order to decrease surveillance burden on facilities. The FY 2011 Budget included an increase of $12.3 million for NHSN to support the expansion to 2,500 additional hospitals, and facilitate the implementation of prevention activities to achieve HHS HAI goals and targets.

Representative Jim Matheson

Q1. It is my understanding that in December 2007, the federal Interagency Task Force on Antimicrobial Resistance held a consultation in Atlanta bringing in 60 external consultants to help the task force revise the 2001 Action Plan on Antimicrobial Resistance. A draft revision was promised in 2008. We are now in 2010 and are waiting to see a product. a. Can you provide the committee with an update on the status of this action plan? Will this revised action plan contain benchmarks, as would be required by legislation that I introduced –the STAAR Act– to measure progress including for CDC, FDA and NIH? b. If no, then why not?

A. The *Action Plan* is currently under development and is expected to be released this year. This *Action Plan* includes benchmarks and timelines and will be made available for public comments upon release when it is published in the *Federal Register*. The *Action Plan* identifies four focused areas and each one has an agency coordinator and timeline:

- Surveillance: CDC is coordinating most action items
- Prevention and Control: CDC is coordinating most action items
- Research: NIH is coordinating most action items
- Product Development: FDA is coordinating most action items

CDC plans to regularly update the *Action Plan* with specific project and implementation steps at least every 2 years so that it becomes an even more informative and useful document.

Q2. In November of last year, President Obama, along with our European partners, announced the creation of a Transatlantic Task Force on Antibiotic Resistance to strengthen the antibiotic pipeline, develop interventions to address resistant infections in hospitals and communities, and opportunities to eliminate inappropriate uses in human and veterinary medicine. I am aware that it takes time to set up such an entity, but we are approaching 6 months from the announcement and I am not aware of word from the Administration on how this group is going to operate, what its charge will be, and whether it will include nongovernment experts. Including external experts to advise the government is a critical component of the Strategies to Address Antimicrobial Resistance (STAAR) Act, which I sponsored. a. What is the status of this international group and what is the charge of the transatlantic task force? b. Please provide the Committee with the list of participants, both domestic and international.

A. The Transatlantic Task Force on Antibiotic Resistance (Task Force) EU-US planning group has had a series of videoconferences and a kickoff meeting of the Task Force is scheduled for

June 2010. The Task Force will develop an action plan focused on the areas defined by the 2009 EU-US Summit declaration:

- Developing appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities
- Preventing both healthcare- and community-associated drug-resistant infections
- Developing strategies to improve the pipeline of new antimicrobial drugs

The Task Force is composed of experts and officials from the European Union and the United States. The United States is represented by the following individuals and agencies of the Department of Health and Human Services:

US Department of Health and Human Services (HHS), Office of the Secretary
Nils Daulaire, Director, Office of Global Health Affairs
Mary Lisa Madell, Director, Europe and Eurasia, Office of Global Health Affairs

Centers for Disease Control and Prevention (CDC)
Denise Cardo, Director, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases (proposed)
J. Todd Weber, CDC Liaison to the European Centre for Disease Prevention and Control, National Center for Immunization and Respiratory Diseases
Jean Patel, Deputy Director, Office of Antimicrobial Resistance

National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health
Dennis Dixon, Chief, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Disease
Jane Knisely, Scientific Program Analyst, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Disease

Food and Drug Administration
Edward Cox, Director, Office of Antimicrobial Products, CDER Drug Shortage Coordinator
Linda Tollefson, Director, FDA Europe Office

The European Union will be represented as follows:

European Commission (EC)
Andrzej Rye, Public Health Director, Directorate General Health and Consumers
Martinue Nagtzaam, Policy Officer, Directorate General Health and Consumers
Anna Lonnroth Sjoden, Deputy Head of Unit, Directorate General Research, Health-Infectious Diseases

European Centre for Disease Prevention and Control (ECDC)
Dominique Monnet, Senior Expert and Programme Coordinator, Scientific Advice Unit

European Medicines Agency (EMEA)
David Mackay, Head of Unit, Veterinary Medicines and Product Data Management

European Food Safety Authority (EFSA)
Marta Hugas, Scientific Coordinator, Head of Unit, Biological Hazard

Council of the European Union will be represented by the TRIO Presidency: Spain, Belgium, and Hungary
Jose Campos, Head of Unit, Antibiotic Laboratory, Instituto de Salud Carlos III
Nathalie Denecker, Clinical Assessor, Federal Agency for Medicines and Health Products
Karolina Borocz, Head of Department, National Centre for Epidemiology

Q3. In the STAAR Act, I have suggested a holistic approach to the problem of antibiotic resistance and establish a network of experts across the country to conduct regional monitoring of resistant organisms as they occur—which would be like a real time snapshot to pick up on problems early. Would you agree that there is importance in augmenting CDC's current surveillance system with some sort of expert surveillance network system?
A: CDC thinks it is important that legislative provisions enhance and complement CDC's existing surveillance systems, research and prevention efforts in order to avoid duplication of efforts. Surveillance is part of CDC's core mission and CDC agrees surveillance of resistant organisms is important. CDC's current surveillance system for antimicrobial resistance, the Emerging Infections Program (EIP), is a network of 10 state health departments working with collaborators in laboratories, healthcare facilities, and academic institutions to conduct population-based surveillance. Through this surveillance system, CDC provides national estimates of disease burden and tracks changes in disease burden over time for both resistant community-associated and healthcare-associated bacterial infections.

CDC also has other surveillance networks for bacterial resistance because surveillance strategies, goals and objectives vary for different problems: the National Healthcare Safety Network (NHSN) and the National Antimicrobial Resistance Monitoring System (NARMS). These surveillance systems complement EIP and are used to assess and monitor the scope, magnitude and trends of the antibiotic resistance problems and also to drive and direct prevention efforts, determine treatment recommendations, guide new drug development, and evaluate the effectiveness of prevention programs.

The National Healthcare Surveillance Network (NHSN) is a web-based surveillance tool for hospitals and state health departments to monitor healthcare-associated infection (HAI) rates, such as those caused by MRSA, *Clostridium difficile*, and multi-drug resistant gram-negative bacteria. Approximately half of U.S. hospitals (over 2,500) are currently enrolled in NHSN. The National Antimicrobial Resistance Monitoring System (NARMS) is a lab-based surveillance system between CDC, the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and all 50 states. NARMS is used to detect resistance in enteric bacteria that are commonly transmitted from animals to humans through food, such as *Salmonella*, *Campylobacter*, and *E. coli* and monitors trends in the prevalence of resistance among bacteria isolated from humans, retail meats, and livestock.

CDC is taking steps to connect these systems including developing and launching networks of acute care facilities reporting HAI data through NHSN within the EIP, building an infrastructure to link pathogen-based evaluation, developing innovative surveillance methodologies, and translating surveillance data between population-based and hospital-based systems.

Q4. In your written testimony (p. 7) you reference that the VA reduced their rate of MRSA infections by 60% in part by implementing universal screening of all ICU and high-risk patients for MRSA (VA MRSA Initiative 2007). As part of the recommended test methods to identify patients colonized with resistant bacteria to prevent transmission, would CDC consider studying the effectiveness of rapid pre-surgical screening?

A. The subject of pre-surgical screening has been studied in the past and a recently published, well-conducted trial suggested that this may be an effective approach in select settings and for select surgical procedures (Bode LGM, Kluytmans JAJW, Wertheim HFL, et al. Preventing surgical site infections in nasal carriers of Staphylococcus aureus. *New England Journal of Medicine* 2010;362:9-17). CDC agrees that prevention research is needed to define the optimal strategy for using rapid pre-surgical screening, and we have much to offer in making sure such research is aligned with public health goals. CDC is currently providing technical assistance for a national survey of infectious disease physicians to assess the prevalence of pre-surgical *S. aureus* screening in the US.

CDC guidelines recommend that hospitals tailor their MRSA prevention strategies to their individual institution. CDC recommends that hospitals consider active surveillance as part of a comprehensive strategy to reduce MRSA infections if initial measures are not effective in reducing MRSA infections. CDC guidelines point out that the current science shows that active surveillance for MRSA might have an impact in reducing MRSA infections but only as part of a comprehensive strategy. What matters are the steps a hospital takes after it has identified colonized or infected patients and what subsequent prevention measure it uses. CDC guidelines recommend that hospitals achieve a reduction in MRSA using a comprehensive approach to prevention. For hospitals not showing a reduction using CDC's initial or first tier recommendations, CDC directs them to add additional measures, including screening of high risk patients for MRSA colonization, until success is demonstrated.

Q5. As you may know, The Infectious Diseases Society of America (IDSA) has urged the Administration and Congress to adopt the goal of developing 10 new antibiotics by 2020. Obviously, this is a large undertaking considering how few novel antibiotics there are currently in the pipeline. Has the Administration reviewed IDSA's 10 x '20 Initiative? What policies do you think this Committee should take into consideration to spur antibiotic development – especially for gram negative bacteria which has little, if anything in the pipeline?

[Please note that the response to this question was prepared by the National Institutes of Health, in response to the same question. We defer to NIH's expertise on this particular issue.]

The National Institute of Allergy and Infectious Diseases (NIAID), the lead component of the National Institutes of Health (NIH) for research on infectious diseases, is aware of the IDSA's initiative and supports its intent of bringing attention to the need for new antibiotic drug development. While there may be a number of policies that may provide incentives for the pharmaceutical and biotechnology industries to further engage in antibiotic drug development, the key to spurring antibiotic drug development is continued support of the drug development pipeline from the earliest stages through advanced development. NIAID recognizes the need to develop new antibiotic drugs and has a longstanding commitment to facilitate such development.

NIAID plays a critical role in the federal government's comprehensive efforts to combat the problem of antimicrobial resistance, with a particular emphasis on the issue of drug development. NIAID conducts and supports basic research to identify new antimicrobial targets and translational research to apply this information to the development of therapeutics; to advance the development of new and improved diagnostic tools for infections; and to create safe and effective vaccines to control infectious diseases and thereby limit the need for antimicrobial drugs. NIAID supports research and development of diverse products through a variety of mechanisms, including grants and contracts to academic laboratories, non-profit organizations, and small and large companies. Research and development of novel agents with activity against Gram-negative pathogens is being supported via all of these mechanisms.

Since 2002, NIAID has supported translational research efforts through its Challenge Grant/Partnerships Program, which was created to stimulate collaborative efforts and multidisciplinary approaches to rapidly advance promising candidate products for infectious diseases through the product development pathway. This program has uniquely fostered many new research collaborations between experts from different disciplines of academia and industry and has significantly accelerated the development of numerous new or improved countermeasures against many pathogens and toxins. Each year, the initiative targets different pathogens based on scientific needs and priorities, and selected Gram-negative pathogens have frequently been the focus of this program. Drug-resistant Gram-negative pathogens of concern were specifically targeted in the 2009 initiative.

To complement these collaborative research efforts, NIAID provides a broad array of pre-clinical and clinical research resources and services to researchers in academia and industry designed to facilitate the movement of a product from bench to bedside. By providing these critical services to the research community, NIAID can help to bridge gaps in the product development pipeline and lower the financial risks incurred by industry to develop novel antimicrobials. Importantly, development activities for several therapeutics with activity against Gram-negative bacteria are being carried out through these mechanisms.

Through an initiative initially introduced in 2007, NIAID has made a sustained effort to support clinical trials aimed at prolonging the effectiveness of currently available antibacterial drugs. The contracts awarded under this initiative support studies designed to help answer key questions about proper antimicrobial dose, treatment duration and whether antimicrobial treatment is necessary in all cases. The contracts provide for the design and conduct of Phase III and/or Phase IV clinical trials to test different therapeutic approaches and regimens that will reduce overexposure to antimicrobial drugs, thereby decreasing the likelihood of antimicrobial drug resistance and preserving the effectiveness of existing antimicrobials. For example, one of these clinical trials is focused on evaluating the optimal duration of therapy for urinary tract infections in children. Since urinary tract infections are caused primarily by Gram-negative organisms, the potential to decrease antibiotic use in this area would help to alleviate the selective pressure that drives the development of resistance in Gram-negative bacteria. This initiative will continue with new trials this year aimed at *pneumonia,* Gram-negative *bacteremia, acute otitis media and pulmonary tuberculosis.*

In late July, NIAID will co-sponsor, along with IDSA and FDA, a public workshop on antibiotic resistance. Topics for discussion will include an overview of the scale of the current bacterial resistance problem; the current understanding of the science and mechanisms of bacterial

resistance; the use of rapid diagnostics in diagnosis and management of bacterial infections; and the science of antibacterial drug development.

Representative Marsha Blackburn

Q1. On November 3rd of last year, President Obama, along with our European partners, announced the creation of a Transatlantic Task Force on Antibiotic Resistance [to strengthen the antibiotic pipeline, develop interventions to address resistant infections in hospitals and communities, and find opportunities to eliminate inappropriate uses in human and veterinary medicine]. Obviously, it takes time to set up such an entity, but now 6 months later, there has been no word from the Administration on how this group is going to operate, what its charge will be, and whether it will include non-government experts. Can you give us the status of this international group? Also, can you please provide the Committee with the list of participants, both domestic and international?

A. The Transatlantic Task Force on Antibiotic Resistance (Task Force) EU-US planning group has had a series of videoconferences and a kickoff meeting of the Task Force is scheduled for June 2010. The Task Force will develop an action plan focused on the areas defined by the 2009 EU-US Summit declaration:

- Developing appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities
- Preventing both healthcare- and community-associated drug-resistant infections
- Developing strategies to improve the pipeline of new antimicrobial drugs

The Task Force is composed of experts and officials from the European Union and the United States. The United States is represented by the following individuals and agencies of the Department of Health and Human Services:

US Department of Health and Human Services (HHS), Office of the Secretary
Nils Daulaire, Director, Office of Global Health Affairs
Mary Lisa Madell, Director, Europe and Eurasia, Office of Global Health Affairs

Centers for Disease Control and Prevention (CDC)
Denise Cardo, Director, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases (proposed)
J. Todd Weber, CDC Liaison to the European Centre for Disease Prevention and Control, National Center for Immunization and Respiratory Diseases
Jean Patel, Deputy Director, Office of Antimicrobial Resistance

National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health
Dennis Dixon, Chief, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Disease
Jane Knisely, Scientific Program Analyst, Bacteriology and Mycology Branch, Division of Microbiology and Infectious Disease

Food and Drug Administration
Edward Cox, Director, Office of Antimicrobial Products, CDER Drug Shortage Coordinator
Linda Tollefson, Director, FDA Europe Office

The European Union will be represented as follows:
European Commission (EC)
Andrzej Rye, Public Health Director, Directorate General Health and Consumers
Martinue Nagtzaam, Policy Officer, Directorate General Health and Consumers
Anna Lonnroth Sjoden, Deputy Head of Unit, Directorate General Research, Health-Infectious Diseases

European Centre for Disease Prevention and Control (ECDC)
Dominique Monnet, Senior Expert and Programme Coordinator, Scientific Advice Unit

European Medicines Agency (EMEA)
David Mackay, Head of Unit, Veterinary Medicines and Product Data Management

European Food Safety Authority (EFSA)
Marta Hugas, Scientific Coordinator, Head of Unit, Biological Hazard

Council of the European Union will be represented by the TRIO Presidency: Spain, Belgium, and Hungary
Jose Campos, Head of Unit, Antibiotic Laboratory, Instituto de Salud Carlos III
Nathalie Denecker, Clinical Assessor, Federal Agency for Medicines and Health Products
Karolina Borocz, Head of Department, National Centre for Epidemiology

Q2. In its Fiscal Year 2011 Congressional Justification, CDC calls antimicrobial resistance "one of the world's most pressing public health problems." However, within the Preparedness, Detection, and Control of Infectious Diseases program's proposed budget, CDC's already severely strapped Antimicrobial Resistance budget would be cut dramatically by $8.6 million—just over 50 percent! The FY2011 budget would allow only 20 state/local health departments and health care systems to be funded for surveillance, prevention, and control of antimicrobial resistance, down from 48 this past year. Can you tell us which states will no longer receive funding under the Antimicrobial Resistance program at CDC?
A. The FY2011 budget request would allow 20 state/local health departments and health care systems to be funded for surveillance, prevention, and control of antimicrobial resistance. It is not possible at this time to determine which states would receive funding. Its possible that more state and local health departments could be funded through the $ 19 .6 million increase in the emerging infections program.

Q3. Additionally, in the budget justification, CDC states that the number of states to receive funds under the Get Smart in the Community program will go from 12 to zero. Can you give us the rationale for your decision to cut back so drastically on this important program given the dire health implications of antimicrobial resistance?
A.. The program has contributed to a 25 percent reduction in antimicrobial use per outpatient visit for presumed viral infections. In addition, more than 959 campaign partners and 166 funded state-based programs collaborate with the Get Smart campaign.Given competing priorities, CDC is looking for ways to efficiently use funding and make difficult decisions based

on available funds. Activities will continue on a prioritized basis, as funding exists through the Emerging Infections program.

Q4. For the past 18 months or more, there has been no full-time director for the Antimicrobial Resistance program, since the departure of the most recent permanent director. What is the status of appointing a new director to oversee the Antimicrobial Resistance programs at CDC?

A. CDC's Director of the Office of Antimicrobial Resistance (OAR) retired in April 2010. An acting director has been appointed and will remain in place until CDC hires a new permanent director. CDC is conducting a national search for an individual who is a recognized leader in the field of infectious diseases and antimicrobial resistance.

United States General Accounting Office

GAO

Report to Congressional Requesters

April 2004

ANTIBIOTIC RESISTANCE

Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals

G A O

Accountability * Integrity * Reliability

GAO-04-490

April 2004

GAO
Accountability · Integrity · Reliability

Highlights

Highlights of GAO-04-490, a report to congressional requesters

ANTIBIOTIC RESISTANCE

Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals

Why GAO Did This Study

Antibiotic resistance is a growing public health concern; antibiotics used in animals raised for human consumption contributes to this problem. Three federal agencies address this issue—the Department of Health and Human Services' (HHS) Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC), and the Department of Agriculture (USDA). GAO examined (1) scientific evidence on the transference of antibiotic resistance from animals to humans and extent of potential harm to human health, (2) agencies' efforts to assess and address these risks, (3) the types of data needed to support research on these risks and extent to which the agencies collect these data, (4) use of antibiotics in animals in the United States compared with its key agricultural trading partners and competitors, and (5) information on how use has affected trade.

What GAO Recommends

GAO recommends that (1) FDA expedite its risk assessments of drugs used in animals that are critical for human health and (2) USDA and HHS develop and implement a plan to collect data on antibiotic use in animals. USDA and HHS generally agreed with GAO's findings. With respect to the recommendations, HHS agreed that it is important to review animal drugs that are critical to human health and both agencies discussed ways to better collect antibiotic use data.

www.gao.gov/cgi-bin/getrpt?GAO-04-490.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Anu Mittal at (202) 512-3841 or Marcia Crosse at (202) 512-7119.

What GAO Found

Scientific evidence has shown that certain bacteria that are resistant to antibiotics are transferred from animals to humans through the consumption or handling of meat that contains antibiotic-resistant bacteria. However, researchers disagree about the extent of harm to human health from this transference. Many studies have found that the use of antibiotics in animals poses significant risks for human health, but a small number of studies contend that the health risks of the transference are minimal.

Federal agencies have expanded their efforts to assess the extent of antibiotic resistance, but the effectiveness of their efforts to reduce human health risk is not yet known. FDA, CDC, and USDA have increased their surveillance activities related to antibiotic resistance. In addition, FDA has taken administrative action to prohibit the use of a fluroquinolone in poultry. FDA has identified animal drugs that are critically important for human health and begun reviewing currently approved drugs using a risk assessment framework that it recently issued for determining the human health risks of animal antibiotics. However, because FDA's initial reviews of approved animal drugs using this framework have focused on other drugs and have taken at least 2 years, FDA's reviews of critically important drugs may not be completed for some time.

Although federal agencies have made some progress in monitoring antibiotic resistance, they lack important data on antibiotic use in animals to support research on human health risks. These data, such as the type and quantity of antibiotics and purpose for their use by species, are needed to determine the linkages between antibiotic use in animals and emerging resistant bacteria. In addition, these data can help assess human health risks from this use and develop and evaluate strategies for mitigating resistance.

The United States and several of its key agricultural trading partners and competitors differ in their use of antibiotics in animals in two important areas: the specific antibiotics allowed for growth promotion and availability of antibiotics to producers (by prescription or over the counter). For example, the United States and Canada allow some antibiotics important in human medicine to be used for growth promotion, but the European Union (EU) and New Zealand do not. Regarding over the counter sales of antibiotics, the United States is generally less restrictive than the EU.

Antibiotic use in animals has not yet been a significant factor affecting U.S. international trade in meat and poultry, although the presence of antibiotic residues in meat has had some impact, according to government and industry officials. Instead, countries raise other food safety issues, such as hormone use and animal diseases. However, according to these officials, antibiotic use in animals may emerge as a factor in the future. They particularly noted that the EU could object to U.S. use of antibiotics for growth promotion as its member countries are phasing out that use.

Contents

Letter

Appendixes

Tables

Figures

4 LIMITATIONS

databases used. We estimated that the majority of sales in kilograms of antibacterial drugs were distributed primarily to the outpatient retail setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for human use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

5 CONCLUSIONS

Sales data in kilograms sold for selected antibacterial drugs were obtained as a surrogate of human antibacterial drug use in the U.S. market. Approximately 3.3 million kilograms of antibacterial drugs were sold in year 2009. The sales data were provided as a surrogate for human use to compare to antibacterial drug use in animals provided by sponsors.

APPENDIX 1: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

The Overuse of Antibiotics in Food Animals Threatens Public Health

Antibiotics have been used since the 1940s and have led to a dramatic reduction in illness and death from infectious diseases. But according to the federal Interagency Task Force on Antimicrobial Resistance, "[t]he extensive use of antimicrobial drugs has resulted in drug resistance that threatens to reverse the medical advances of the last seventy years."[1] Since antibiotics have been used so widely and for so long, antibiotic resistance has become a major public health threat.

In response, there has been a concerted effort by the Centers for Disease Control and Prevention (CDC) and others to encourage doctors and patients to use antibiotics more wisely. Unfortunately, little progress has been made to reduce the use of antibiotics on farms, where most of these drugs are administered.

Approximately 80 percent of the antibiotics sold in the United States are used in meat and poultry production.[2] The vast majority is used on healthy animals to promote growth, or prevent disease in crowded or unsanitary conditions. The meat and poultry production industry argues, however, that that there is no harm in this. They say for example that "animal use contributes little, if anything, to the burden of human antibiotic resistance..."[3].

A key question is, can antibiotic use in animals promote the development of hard-to-treat antibiotic-resistant superbugs that make people sick? And if it can, are the illnesses rare occurrences, and the risks theoretical, or could current usage in animals pose a serious threat to human health.

But Consumers Union has concluded that the threat to public health from the overuse of antibiotics in food animals is real and growing. Humans are at risk both due to potential presence of superbugs in meat and poultry, and to the general migration of superbugs into the environment, where they can transmit their genetic immunity to antibiotics to other bacteria, including bacteria that make people sick.

Numerous health organizations, including the American Medical Association, American Public Health Association, Infectious Disease Society of America, and the World Health Organization, agree and have called for significant reductions in the use of antibiotics for animal food production.

---

[1] Pg 5 in Interagency Task Force on Antimicrobial Resistance, 2012. A Public Health Action Plan to Combat Antimicrobial Resistance. Washington, D.C. at: http://www.cdc.gov/drugresistance/pdf/actionplan-2012.pdf

[2] Confirmed: 80 Percent of all antibacterial drugs used on animals, endangering human health. At: http://www.louise.house.gov/index.php?option=com_content&task=view&id=2697&Itemid=100065

[3] Pg 5 in American Farm Bureau Federation et al June 12, 2012 letter to Congressperson Slaughter

History of Expert Opinion

Scientific expert bodies for more than two decades have concluded that there is a connection between antibiotic use in animals and the loss of effectiveness of these drugs in human medicine. In 1988, the Institute of Medicine (part of the National Academy of Sciences) concluded that "the committee believes that important, although as yet sparse, data show the flow of distinct salmonella clones from farm animals medicated with antibiotics in subtherapeutic concentrations, through food products, to humans, who thus acquire clinical salmonellosis."[4]

Ten years later, the National Research Council (part of the National Academy of Sciences) concluded that "a link can be demonstrated between the use of antibiotics in food animals, the development of resistant microorganisms in those animals, and the zoonotic spread of pathogens to humans."[5]

In 2003, an Expert Workshop co-sponsored by the World Health Organization, Food and Agricultural Organization (FDA), and World Animal Health Organization (OIE) concluded "that there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials. These consequences include infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death) and increased severity of infections"[6].

In 2010, the U.S. Food and Drug Administration, U.S. Department of Agriculture, and the CDC all testified before Congress that there is a connection between the routine use of antibiotics for meat production and the declining effectiveness of antibiotics for people.[7] Dr. Thomas R. Frieden, Director of the CDC, noted that "there is strong scientific evidence of a link between antibiotic use in food animals and antibiotic resistance in humans."[8]

Most recently in 2012, the FDA stated "Misuse and overuse of antimicrobial drugs creates selective evolutionary pressure that enables antimicrobial resistant bacteria to increase in numbers more rapidly than antimicrobial susceptible bacteria and thus

---

[4] Pg. 2 in Institute of Medicine (IOM). 1988. *Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed.* National Academies Press. Washington, D.C.

[5] Pg. 6 in IOM. 1998. *The Use of Drugs in Food Animals: Benefits and Risks.* National Academies Press. Washington, D.C.

[6] Pg. 1 in WHO/FAO/OIE. 2003. *Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific assessment, Geneva, December 1-5, 2003.* At: http://www.who.int/foodsafety/publications/micro/en/amr.pdf

[7] Hearing: Antiobiotic Resistance and the Use of Antibiotics in Animal Agriculture, Subcommittee on Health, Energy and Commerce Committee, U.S. House of Representatives, July 12, 2010

[8] Letter from Thomas R. Frieden, Director, Centers for Disease Control and Prevention, to Keeve Nachman, Program Director, Farming For the Future, at http://www.livablefutureblog.com/wp-content/uploads/2010/11/ar-m455n_20101129_182057.pdf

1 INTRODUCTION

The Center for Veterinary Medicine is evaluating data on the use of antibacterial drugs in food-producing animals. The Office of the Commissioner has requested antibacterial drug use data in humans as a comparator. In support of FDA's efforts, the Division of Epidemiology (DEPI) has been requested to provide sales data of antibacterial drugs in kilograms to various retail and non-retail channels of distribution as a surrogate for nationwide antibacterial drug use in humans.

2 METHODS AND MATERIALS

2.1 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (*see **Appendix 1 for full data description***). IMS Health, IMS National Sales Perspectives™ was used to provide sales data of selected antibacterial drugs in kilograms distributed in the U.S. market to various retail and non-retail channels of distribution. These sales data represent the volume of product being sold to the various outlets from the manufacturer (e.g., "in the back door"), and not the volume of product being sold by the outlets to patients (e.g., "out the front door").

The number of kilograms sold were reported for the active molecule, regardless of formulation (I.V., oral, topical, etc). In addition, the data were reported for the total number of kilograms sold of the active molecule, single-ingredient and combination products combined. For example, the number of kilograms sold of amoxicillin included kilograms sold of single-ingredient amoxicillin and amoxicillin from combination products, such as amoxicillin-clavulanate. Additional combination products reported by the single active ingredient were: ticarcillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, imipenem-cilastatin, quinupristin-dalfopristin, and trimethoprim-sulfamethoxazole.

All data in this analysis have been cleared for public use by IMS Health, IMS National Sales Perspectives™.

3 RESULTS

3.1 SALES DATA BY SETTING OF CARE

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for antibacterial drugs. Examination of wholesale data by number of kilograms sold in year 2009 indicated that the majority of antibacterial drugs were sold to retail pharmacy settings, accounting for approximately 75% of antibacterial drugs sold, followed by non-retail settings at 24% (mainly to hospitals) and mail order settings at 1% *(data not shown)*[1]

[1] IMS Health, IMS Nationals Sales Perspectives™, Year 2009. Data extracted 11/10. File: 1011abx7.xls

3.2 *Sales Data by Drug Class and Molecule*

Table 1 shows the total number of kilograms sold of selected antibacterial drugs by drug class and molecule. There were approximately 3.3 million kilograms of antibacterial drugs sold in the U.S. market during year 2009. The penicillin drug class accounted for the largest proportion of kilograms sold accounting for approximately 44% of the market (1.5 million kilograms sold). Amoxicillin accounted for the highest number of kilograms sold with approximately 1.1 million kilograms sold in year 2009. The total number of kilograms sold for amoxicillin included amoxicillin from single-ingredient amoxicillin and combination products of amoxicillin-clavulanate.

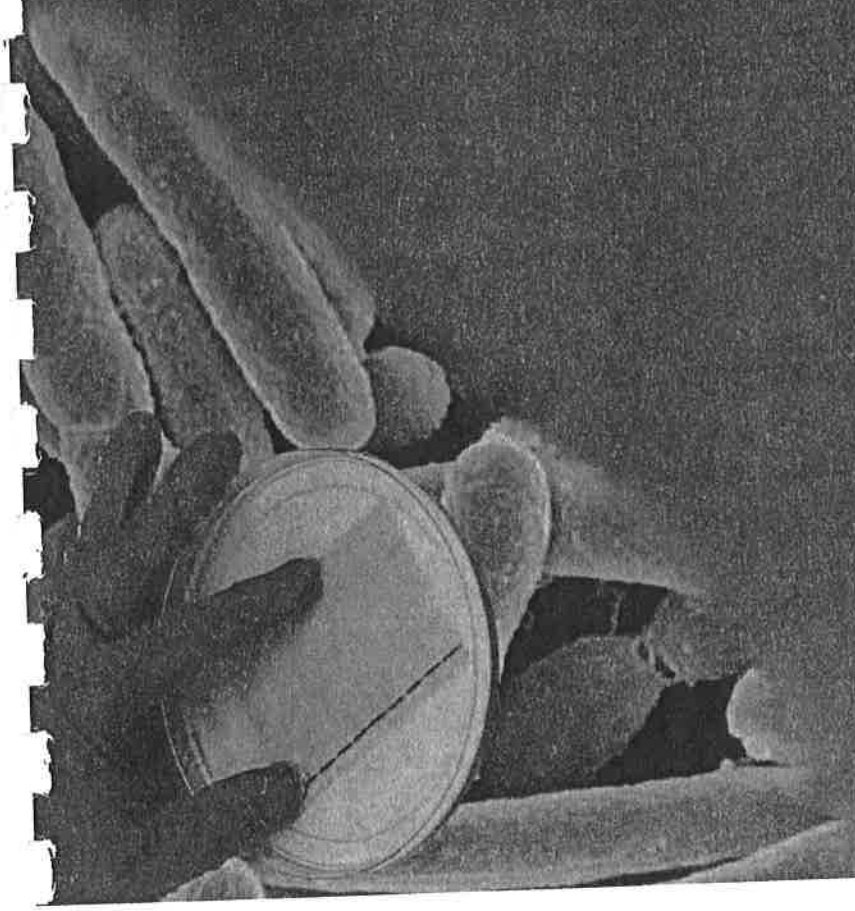
Table 1, Part 1: Sales of Antibacterial Drugs by Drug Class and Molecule in Number of Kilograms Sold in Year 2009

Antibacterial Drug Class	Years 2009	
Drug name	Sales in Kilograms	Kg Share %
Grand Total	**3,316,906**	**100.0%**
-Penicillins	**1,459,219**	**44.0%**
Amoxicillin	1,123,551	77.0%
Piperacillin	142,849	9.8%
Penicillin V	130,953	9.0%
Ampicillin	41,962	2.9%
Dicloxacillin	7,936	0.5%
Nafcillin	6,262	0.4%
Oxacillin	2,875	0.2%
Ticarcillin	2,833	0.2%
Penicillin G	2.56E+13 (I.U.)	--
Mezlocillin		0.0%
Azlocillin		0.0%
Carbenicillin		0.0%
Cloxacillin		0.0%

Source: IMS Health, IMS Nationals Sales Perspectives™, Year 2009. Data extracted 11/10. File: 1011abx8.xls
*Beta-lactamase inhibitors that are part of a beta-lactam/beta-lactamase inhibitor combination (e.g., clavulanic acid, tazobactam, and sulbactam) and cilistatin are not included in this table. See text for how combination molecules are quantitated.

2009 Retail Meat Report

National Antimicrobial Resistance Monitoring System



NARMS

TABLE OF CONTENTS

ABBREVIATIONS USED IN THE REPORT, 2009

General Abbreviations

AR	Antimicrobial Resistance
BAP	Blood Agar Plate
CCA	Campy-Cefex Agar Plate
CDC	Centers for Disease Control and Prevention
CLSI	Clinical and Laboratory Standards Institute
CVM	Center for Veterinary Medicine
EAP	Enterococcosel Agar Plate
EIP	Emerging Infections Program
EMB	Eosin Methylene Blue
FDA	Food and Drug Administration
FoodNet	Foodborne Diseases Active Surveillance Network
MIC	Minimum Inhibitory Concentration
NARMS	National Antimicrobial Resistance Monitoring System
PCR	Polymerase Chain Reaction
PFGE	Pulsed Field Gel Electrophoresis
PulseNet	National Molecular Subtyping Network for Foodborne Disease Surveillance
QC	Quality Control
RVR10	Rappaport-Vassiliadis Medium
USDA	United States Department of Agriculture
XLD	Xylose Lysine Deoxycholate

Antimicrobial Abbreviations

AMC	Amoxicillin/Clavulanic Acid
AMI	Amikacin
AMP	Ampicillin
AXO	Ceftriaxone
AZI	Azithromycin
CHL	Chloramphenicol
CIP	Ciprofloxacin
CLI	Clindamycin
COT	Trimethoprim/Sulfamethoxazole
DAP	Daptomycin
DOX	Doxycycline
ERY	Erythromycin
FFN	Florfenicol
FIS	Sulfisoxazole
FOX	Cefoxitin
GEN	Gentamicin
KAN	Kanamycin
LIN	Lincomycin
LZD	Linezolid
NAL	Nalidixic Acid
NIT	Nitrofurantoin
PEN	Penicillin
QDA	Quinupristin/Dalfopristin
STR	Streptomycin
TEL	Telithromycin
TET	Tetracycline
TGC	Tigecycline
TYL	Tylosin
TIO	Ceftiofur
VAN	Vancomycin

Meat Types Abbreviations

CB	Chicken Breast
GB	Ground Beef
GT	Ground Turkey
PC	Pork Chop

State Abbreviations

CA	California
CO	Colorado
CT	Connecticut
GA	Georgia
MD	Maryland
MN	Minnesota
NM	New Mexico
NY	New York
OR	Oregon
PA	Pennsylvania
TN	Tennessee

NARMS Retail Meat Working Group

U.S. Food and Drug Administration

Jason Abbott
Sherry Ayers
Sonya Bodeis-Jones
Kristin Cooley
Sharon Friedman
Stuart Gaines
David Heller
Claudia Lam
Patrick McDermott
Shawn McDermott
Sadaf Qaiyumi
Emily Tong
Niketta Womack
Shenia Young
Shaohua Zhao

Centers for Disease Control and Prevention

Fred Angulo
Ezra Barzilay
Olympia Anderson
Sharon Greene
Felicita Medalla

Many thanks to Denise Benton and Laura Alvey for providing outstanding web support to the NARMS program.

Participating State and Local Health Departments

California
Richard Alexander
Melody Hung-Fan
Maribel Rickard

Colorado
Joe Gossack
Dee Jae Dutton
Dave Heltzel
Hugh Maguire

Connecticut
Aristea Kinney
Mona Mandour
Ruthanne Marcus
Michael A. Pascucilla
Laurn Mank
Diane Barden

Georgia
James Benson
Cherie Drenzek
Tameka Hayes
Lynett Poventud
Elizabeth Franko
Mary Hodel
Mahin Park
Melissa Tobin-D'angelo

Maryland
David Blythe
Beverly Jolbitado
Jennifer Kiluk
Kirsten Larson
Amanda Palmer
Patricia Ryan
Chengru Zhu

Minnesota
John Besser
Craig Braymen
Karen Everstine
Gary Horvath
Billie Juni
Fe Leano
Stephanie Meyer
Kirk Smith
Leeann Johnson

New Mexico
Adreiena Armijo
Lisa Butler
Carlos Gonzales
Cindy Nicholson
Nicole Espinoza
Erica Swanson
Paul Torres
Frederick Gentry
Jennifer Hollander

New York
Dale Morse
Marsha Peck
Timothy Root
Shelley Zansky
Ariel Endlich-Frazier
Suzanne Solghan

Oregon
Elizabeth Baldwin
Emilio DeBess
Helen Packett
Robert Vega
Veronica Williams
Marianna Cavanaugh
Dawn Daly
Barbara Olson
Vicki A. Hafits

Pennsylvania
Michael Nageotte
Stanley Reynolds
Deepanker Tewari
Anthony Russell
Ann Rosenberg
Carol Sandt
Lisa Dettinger
Susan Johnston
Nkuchia M. M'ikanatha

Tennessee
Parvin Arjmandi
Samir Hanna
Henrietta Hardin
Tim Jones
Ryan Mason
Sheri Roberts
John Dunn
Stephanie Estes
Kenneth Mitchell
Robyn Atkinson
Bobby Price
Henry Davis
Julie Montgomery

NARMS Retail Meat Annual Report 2009

Introduction

The primary purpose of the NARMS retail meat surveillance program is to monitor the prevalence of antimicrobial resistance among foodborne bacteria, specifically, *Salmonella, Campylobacter, Enterococcus* and *Escherichia coli*. The results generated by the NARMS retail meat program serve as a reference point for identifying and analyzing trends in antimicrobial resistance among these organisms.

NARMS retail meat surveillance is an ongoing collaboration between the U.S. Food and Drug Administration/Center for Veterinary Medicine (FDA/CVM), the Centers for Disease Control and Prevention (CDC), the 2009 FoodNet laboratories and an additional State Department of Public Health Laboratory: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, Tennessee, and Pennsylvania. From January to December, each site purchased approximately 40 food samples per month, which are comprised of 10 samples each from chicken breast, ground turkey, ground beef, and pork chops. All sites culture the meat and poultry samples for *Salmonella* and only poultry samples are cultured for *Campylobacter*. In 2009, 3 of the 10 participating FoodNet laboratories (Georgia, Oregon, and Tennessee) also cultured meat and poultry samples for *E. coli* and *Enterococcus*. Bacterial isolates were sent to FDA/CVM for confirmation of species and serotypes, antimicrobial susceptibility testing, and genetic analysis.

As a public health monitoring system, the primary objectives of NARMS are to:

- Monitor trends in antimicrobial resistance among foodborne bacteria from humans, retail meats, and animals
- Disseminate timely information on antimicrobial resistance to promote interventions that reduce resistance among foodborne bacteria
- Conduct research to better understand the emergence, persistence, and spread of antimicrobial resistance
- Assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals

What is New in the NARMS Retail Meat Report for 2009

A total of 5,280 meat samples were collected in 2009, compared with 5,236 in 2008. The Pennsylvania Department of Public Health Laboratory joined the NARMS retail meat surveillance program in 2008 but was only testing meat samples for *Salmonella*. As of 2009, Pennsylvania has increased their testing to include *Campylobacter* isolation from poultry samples.

In 2008, both CMV2AGPF and CMV3AGPF Sensititre™ plates were used for *Enterococcus* testing and the smaller range from either plate was used in the report. In 2009, all *Enterococcus* testing were performed using the CMV3AGPF Sensititre™ plate. Resistance data for flavomycin was excluded from this report as the new CMV3AGPF plate does not include this antimicrobial. Flavomycin resistance data can be found in prior NARMS Retail Meat Reports. The CMV3AGPF range of dilutions tested expanded for daptomycin, erythromycin, penicillin, quinupristin-dalfopristin and tetracycline, while ranges decreased for lincomycin and vancomycin.

Prior to 2009 NARMS reports used ceftiofur (an extended-spectrum cephalosporin used in food animals) to represent resistance to third-generation cephalosporins in the multidrug resistance patterns. In 2009 ceftriaxone replaced ceftiofur in the multidrug resistance patterns presented in this report, resulting from revised ceftriaxone breakpoints where ceftriaxone resistance (MIC ≥ 4 µg/ml) is nearly identical to ceftiofur resistance.

A new table (Table 6.) was added to the *Salmonella* multidrug resistance section of this report. This table highlights the number of resistant isolates by *Salmonella* serotype for each retail meat. This table is very useful for comparing the distribution of *Salmonella* serotype specific resistance among the different classes of antimicrobials. *Salmonella* antigenic formulas I 4,12:i:- and I 4,5,12:i:- were included with serotype I 4,[5],12:i:- to correspond with the NARMS Executive Report.

Highlights of the NARMS Retail 2009 Report

Salmonella[1]
Salmonella serotypes Typhimurium, Saintpaul, and Heidelberg account for 53% of retail meat isolates (Table 4). *S.* Typhimurium and *S.* Saintpaul increased markedly from an average of 11.4% and 8.9% from 2002–2008 to 25.6% and 16.4% in 2009, respectively. In 2009 *S.* Saintpaul became the most common serotype in ground turkey. Also never seen before was a higher prevalence of *S.* Heidelberg among chicken breast over ground turkey. *S.* Heidelberg prevalence among all retail meat continued to decrease from 22.8–11.5% from 2002–2009.

First-line antimicrobial agents recommended for treating salmonellosis are ciprofloxacin, ceftriaxone and trimethoprim-sulfamethoxazole.[2]

- Quinolones - Resistance to nalidixic acid corresponds to decreased fluoroquinolone susceptibility; however, fluoroquinolone resistance has never been detected in *Salmonella* recovered from any retail meat since the program began in 2002. Only 0.8% of *Salmonella* (4/489) were nalidixic acid resistant (Table 5). Nalidixic acid resistance was detected for the first time in ground beef and 2 of 3 ground beef isolates resistant to nalidixic acid were also ceftriaxone resistant.
- Cephalosporins – Third-generation cephalosporin resistance rose in all retail meats compared to 2008, with > 10% increases detected in chicken breast.
- There were highly significant increases in ampicillin resistance among chicken breast (16.7–45.8%) and ground turkey isolates (16.2–57.9%) from 2002 to 2009.
- Trimethoprim-Sulfamethoxazole - Resistance to this antimicrobial is extremely rare and 6 (of 489) isolates were resistant in 2009 compared to only 1 in 2008.
- Multidrug Resistance – 48.4% of chicken breast isolates were resistant to ≥ 3 antimicrobial classes in 2009 compared to 26.3% in ground turkey, which is an increase in chicken breast from previous years (ranging 20–38.2%). More than 30% of chicken breast isolates showed resistance to ≥ 5 classes in 2009 (Table 8), to which *S.* Typhimurium accounts for more than half of them (Table 6).
- *Salmonella* isolates susceptible to all antimicrobials (Table 8) decreased in chicken breast (45.7–29.2%), ground beef (79.2–57.1%), and pork chops (65.2–50%) from 2008 to 2009. Meanwhile, *Salmonella* pansusceptibility slightly increased among ground turkey (20.8–22.1%) isolates.

Campylobacter[3]
More than 90% of *Campylobacter* are recovered from chicken breast each year and of those isolates, the proportion of *C. jejuni* to *C. coli* is about 2:1 (Table 10).

Macrolides and fluoroquinolones are used in the treatment of *Campylobacter* infections. It is well known that *C. coli* tend to be more resistant than *C. jejuni* regardless of source, and this is reflected in the 2009 NARMS retail data with the exception of quinolones and tetracycline.

- Macrolide resistance in chicken breast isolates was seen in 4.5% of *C. coli* and 1% of *C. jejuni* in 2009, with no significant changes over time (Table 13).

---

[1] Nearly all salmonellae were recovered from poultry. Due to the low recovery from ground beef and pork chops (< 2%), statistical analysis of trends in resistance from these sources should be considered with caution.
[2] IDSA, Practice Guidelines for the Management of Infectious Diarrhea. *Clinical Infectious Diseases* 2001; 32:331–50.
[3] Ground beef and pork chop samples are no longer cultured for *Campylobacter*, due to their low recovery (<0.5%) from 2002–2007.

- Ciprofloxacin resistance in *C. coli* from chicken breast rose from 10% in 2002 to its highest peak of 29.1% in 2005. Since the fluoroquinolone ban in September 2005, ciprofloxacin resistance in *C. coli* has decreased to 18.4% in 2009 (Table 13), while *C. jejuni* significantly increased from 15.2–21.1% from 2002 to 2009 (p=0.0296).
- Tetracycline resistance decreased in both *C. jejuni* (49.8–46.2%) and *C. coli* (46.4–38%) compared to 2008.
- Gentamicin resistance in *C. coli* has increased with 5.6% in 2009, up from 1.7% in 2008 (p<0.0001).
- Multidrug resistance is rare in *Campylobacter*. There were only 9 (of 606) *Campylobacter* isolates resistant to ≥ 3 antimicrobial classes in 2009 (Table 14).

<u>*Enterococcus*</u>

E. faecalis (67.6% [884/1307]) was more prevalent than *E. faecium* (27% [353/1307]) in 2009 (Table 16). Chicken breast was the only meat type where *E. faecium* was more prevalent than *E. faecalis*.

Enterococcus is used as a sentinel for antibiotic selection pressures by compounds with gram-positive activity. This spectrum of activity is exhibited by many antimicrobials used in food animal production; and the same classes of antibiotics are also used to treat human infections.

- No isolates were resistant to vancomycin or linezolid. These classes of compounds are critically important in human medicine but are not used in food animal production (Table 17).
- Since 2002, streptogramin resistance has decreased in ground beef (46.2–13%) and pork chop (27.2–11.4%) but has remained above 50% in poultry isolates.
- *E. faecalis* from poultry showed markedly higher aminoglycoside and macrolide resistance than *E. faecium*, with exception of streptomycin. *E. faecium* had much higher resistance to nitrofurantoin, penicillin and ciprofloxacin from all sources compared to *E. faecalis* (Table 18a-b).
- Multidrug resistance from 2002–2009 was highest in *E. faecium* isolates from poultry which more than doubled the amount of multidrug resistant *E. faecalis* (Table 19a-b).

<u>*Escherichia coli*</u>

E. coli are common in all retail meat products tested in NARMS. Nearly 71% of the 1,440 retail meats tested in 2009 were culture positive for *E. coli*, with pork chops having the lowest prevalence (40.8%) and chicken breasts the highest (87.5%).

- Ceftriaxone resistance among *E. coli* isolates from chicken breast is consistently higher than any other retail meat tested. Chicken breast (7.8–12.4%), Ground turkey (1.3–6.9%), and pork chop (0.5–6.8%) had statistically significant trends in ceftriaxone resistance from 2002–2009 at the $p < 0.05$ level (Table 22).
- Ciprofloxacin resistance remained low (< 1.0%) among *E. coli* isolates (Table 22).
- From 2002–2005, nalidixic acid resistance in *E. coli* from chicken breast increased from 2.8–6.6% and increased in ground turkey from 4.3–10.4%. Since the fluoroquinolone ban in September 2005, resistance has decreased to 2.9% in chicken breast and 2.6% in ground turkey (Table 22). Nalidixic acid resistance in ground beef and pork chops remains < 2%.
- Gentamicin resistance is much higher in retail poultry isolates (> 20%) than ground beef and pork chop isolates (< 5%), with a statistically significant increase among chicken breast at the $p < 0.05$ level (Table 22).
- A highly statistically significant trend (p<0.0001) in ampicillin resistance was seen among ground turkey with 56.2% resistance in 2009, up from 31.3% in 2002.

Table 3. Percent Positive Samples by Bacterium and Meat Type, 2002-2009

2002	Chicken Breast			Ground Turkey			Ground Beef			Pork Chop		
Bacterium (A)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Campylobacter (2513)	616	288	(46.8)	642	4	(1.0)	642	-	-	613	5	(0.8)
Salmonella (2513)	616	60	(9.7)	642	74	(11.5)	642	9	(1.4)	613	10	(1.6)
Enterococcus (1574)	390	381	(97.7)	395	387	(98.0)	399	383	(96.0)	390	369	(94.6)
Escherichia coli (1574)	390	282	(72.3)	395	304	(77.0)	399	295	(73.9)	390	184	(47.2)

2003	Chicken Breast			Ground Turkey			Ground Beef			Pork Chop		
Bacterium (A)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Campylobacter (3533)	897	469	(52.3)	857	5	(0.6)	880	1	(0.1)	899	4	(0.4)
Salmonella (3533)	897	83	(9.3)	857	114	(13.3)	880	10	(1.1)	899	5	(0.6)
Enterococcus (1873)	477	466	(97.7)	447	418	(93.5)	470	432	(91.9)	479	426	(88.9)
Escherichia coli (1873)	477	396	(83.0)	447	333	(74.5)	470	311	(66.2)	479	218	(45.5)

2004	Chicken Breast			Ground Turkey			Ground Beef			Pork Chop		
Bacterium (A)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Campylobacter (4699)	1172	706	(60.2)	1165	12	(1.0)	1186	-	-	1176	3	(0.3)
Salmonella (4699)	1172	157	(13.4)	1165	142	(12.2)	1186	14	(1.2)	1176	11	(0.9)
Enterococcus (1900)	476	466	(97.9)	466	437	(93.8)	480	448	(93.3)	478	404	(84.5)
Escherichia coli (1900)	476	400	(84.0)	466	376	(80.7)	480	338	(70.4)	478	232	(48.5)

2005	Chicken Breast			Ground Turkey			Ground Beef			Pork Chop		
Bacterium (A)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Campylobacter (4777)	1190	554	(46.6)	1195	20	(1.7)	1196	-	-	1196	2	(0.2)
Salmonella (4781)	1194	153	(12.8)	1195	183	(15.3)	1196	8	(0.7)	1196	9	(0.8)
Enterococcus (1880)	470	457	(97.2)	470	452	(96.2)	470	447	(95.1)	470	409	(87.0)
Escherichia coli (1871)	468	393	(84.0)	470	396	(84.3)	468	316	(67.5)	465	205	(44.1)

2006	Chicken Breast			Ground Turkey			Ground Beef			Pork Chop		
Bacterium (A)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Campylobacter (4766)	1193	572	(47.9)	1185	24	(2.0)	1196	-	-	1192	3	(0.3)
Salmonella (4769)	1196	152	(12.7)	1185	159	(13.4)	1196	19	(1.6)	1192	8	(0.7)
Enterococcus (1893)	478	469	(98.1)	465	435	(93.5)	478	438	(91.6)	472	389	(82.4)
Escherichia coli (1884)	475	418	(88.0)	466	388	(83.3)	471	295	(62.6)	472	182	(38.6)

2007	Chicken Breast			Ground Turkey			Ground Beef			Pork Chop		
Bacterium (A)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Campylobacter (4278)	1070	475	(44.4)	1065	34	(3.2)	1071	5	(0.5)	1072	4	(0.4)
Salmonella (4282)	1072	99	(9.2)	1066	190	(17.8)	1071	13	(1.2)	1073	18	(1.7)
Enterococcus (1407)	351	342	(97.4)	348	341	(98.0)	352	336	(95.5)	356	313	(87.9)
Escherichia coli (1379)	342	299	(87.4)	338	315	(93.2)	343	256	(74.6)	356	152	(42.7)

2008	Chicken Breast			Ground Turkey			Ground Beef			Pork Chop		
Bacterium (A)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Campylobacter (2379)	1190	510	(42.9)	1189	31	(2.6)						
Salmonella (5236)	1310	199	(15.2)	1309	245	(18.7)						
Enterococcus (1440)	360	346	(96.1)	360	345	(95.8)	1310	24	(1.8)	1307	23	(1.8)
Escherichia coli (1440)	360	306	(85.0)	360	300	(83.3)	360	336	(93.3)	360	310	(86.1)
							360	250	(69.4)	360	146	(40.6)

2009	Chicken Breast			Ground Turkey			Ground Beef			Pork Chop		
Bacterium (A)	N	n	(%)	N	n	(%)	N	n	(%)	N	n	(%)
Campylobacter (2640)	1320	582	(44.1)	1320	24	(1.8)						
Salmonella (5280)	1320	277	(21.0)	1320	190	(14.4)						
Enterococcus (1440)	360	349	(96.9)	360	328	(91.1)	1320	14	(1.1)	1320	8	(0.6)
Escherichia coli (1440)	360	315	(87.5)	360	306	(85.0)	360	327	(90.8)	360	303	(84.2)
							360	247	(68.6)	360	147	(40.8)

A = Total number of meat sampled
N = Number of samples tested
n = Number of isolates
Where % = Number of isolates (n) / number of samples per meat type (N)
Dashes indicate no positive isolates.
Gray area indicates not tested.

Table 5. Trends in Antimicrobial Resistance among *Salmonella* by Meat Type, 2002-2009[1]

Meat Type	Year (N)	Aminoglycosides				Penicillins	β-Lactamase Inhibitor Combinations	Cephems			Folate Pathway Inhibitors		Phenicols	Quin	Tetra-cyclines
		AMI (MIC ≥ 64)	GEN (MIC ≥ 16)	KAN (MIC ≥ 64)	STR (MIC ≥ 64)	AMP (MIC ≥ 32)	AMC (MIC ≥ 32)	TIO (MIC ≥ 32)	AXO (MIC ≥ 4)	FOX (MIC ≥ 32)	FIS[2] (MIC ≥ 512)	COT (MIC ≥ 4)	CHL (MIC ≥ 512)	CIP (MIC ≥ 4	NAL (MIC ≥ 32)	TET (MIC ≥ 16)
Chicken Breast	2002 (60)	–	10.0%	6.7%	28.3%	16.7%	10.0%	10.0%	10.0%	10.0%	16.7%	–	–	–	–	33.3%
	2003 (83)	–	6.0%	4.8%	26.5%	33.7%	25.3%	25.3%	26.5%	25.3%	14.5%	–	2.4%	–	1.2%	27.7%
	2004 (157)	–	3.8%	11.5%	28.0%	30.6%	24.8%	24.8%	24.8%	24.8%	28.7%	–	1.9%	–	–	46.5%
	2005 (153)	–	3.3%	4.6%	30.1%	26.8%	21.6%	20.9%	21.6%	20.9%	17.0%	–	0.7%	–	0.7%	43.8%
	2006 (152)	–	9.2%	9.9%	36.2%	22.4%	19.1%	19.1%	19.1%	18.4%	23.0%	1.3%	2.6%	–	0.7%	46.7%
	2007 (99)	–	6.1%	5.1%	30.3%	18.2%	16.2%	16.2%	16.2%	15.2%	25.3%	–	1.0%	–	–	41.4%
	2008 (199)	–	7.0%	10.6%	23.6%	29.2%	22.6%	22.6%	22.6%	21.6%	39.2%	–	0.5%	–	–	46.7%
	2009 (277)	–	3.6%	15.2%	23.1%	45.8%	37.2%	36.8%	37.5%	32.5%	48.0%	0.4%	–	–	0.4%	59.9%
	Z Statistic	**N/A[4]**	**0.7344**	**-2.8960**	**1.6064**	**-3.9729**	**-3.8154**	**-3.7823**	**-5.2988**	**-2.7345**	**-7.7961**	**-0.5376**	**1.8103**	**N/A**	**0.5126**	**-4.9733**
	P Value[3]	**N/A**	**0.4627**	**0.0038**	**0.1082**	**<0.0001**	**0.0001**	**0.0002**	**<0.0001**	**0.0062**	**<0.0001**	**0.5909**	**0.0702**	**N/A**	**0.6082**	**<0.0001**
Ground Turkey	2002 (74)	–	14.9%	18.9%	37.8%	16.2%	12.2%	8.1%	8.1%	8.1%	20.3%	1.4%	1.4%	–	8.1%	55.4%
	2003 (114)	–	22.8%	27.2%	45.6%	28.9%	11.4%	2.6%	2.6%	2.6%	33.3%	–	0.9%	–	4.4%	39.5%
	2004 (142)	–	20.4%	18.3%	34.5%	20.4%	7.7%	4.9%	5.6%	4.9%	28.2%	–	2.8%	–	–	56.3%
	2005 (183)	–	26.8%	20.2%	44.3%	26.8%	8.7%	7.1%	7.1%	7.1%	34.4%	0.5%	0.5%	–	1.1%	39.9%
	2006 (159)	–	28.9%	15.1%	40.9%	25.8%	5.0%	5.0%	5.0%	5.0%	32.1%	–	0.6%	–	–	56.0%
	2007 (190)	–	24.7%	23.7%	45.8%	42.6%	5.3%	5.3%	5.8%	5.3%	34.7%	0.5%	1.6%	–	2.6%	67.4%
	2008 (245)	–	27.8%	18.0%	58.8%	50.6%	5.3%	4.5%	4.5%	4.5%	27.4%	0.4%	1.6%	–	0.4%	66.1%
	2009 (190)	–	18.4%	6.8%	27.9%	57.9%	5.8%	5.8%	5.8%	5.8%	20.0%	1.6%	1.6%	–	–	65.3%
	Z Statistic	**N/A**	**-0.7436**	**3.1403**	**-0.6484**	**-9.5415**	**2.7790**	**0.1584**	**0.2268**	**0.1584**	**1.3050**	**-1.1119**	**-0.2226**	**N/A**	**3.9396**	**-5.5360**
	P Value	**N/A**	**0.4571**	**0.0017**	**0.5167**	**<0.0001**	**0.0055**	**0.8741**	**0.8206**	**0.8741**	**0.1919**	**0.2662**	**0.8238**	**N/A**	**<0.0001**	**<0.0001**
Ground Beef	2002 (9)	–	–	–	22.2%	22.2%	22.2%	22.2%	22.2%	22.2%	22.2%	–	22.2%	–	–	22.2%
	2003 (10)	–	–	–	40.0%	40.0%	40.0%	40.0%	40.0%	40.0%	40.0%	–	40.0%	–	–	40.0%
	2004 (14)	–	–	–	14.3%	21.4%	14.3%	14.3%	14.3%	14.3%	14.3%	7.1%	14.3%	–	–	14.3%
	2005 (8)	–	25.0%	25.0%	25.0%	25.0%	–	–	–	–	25.0%	–	12.5%	–	–	12.5%
	2006 (19)	–	–	5.3%	10.5%	10.5%	–	–	–	–	10.5%	–	5.3%	–	–	21.1%
	2007 (13)	–	7.7%	–	–	–	–	–	–	–	7.7%	–	–	–	–	–
	2008 (24)	–	8.3%	8.3%	20.8%	12.5%	8.3%	8.3%	8.3%	8.3%	20.8%	–	12.5%	–	–	20.8%
	2009 (14)	–	14.3%	14.3%	28.6%	28.6%	14.3%	14.3%	14.3%	14.3%	35.7%	–	21.4%	–	14.3%	42.9%
	Z Statistic	**N/A**	**-1.5925**	**-1.4143**	**0.4633**	**1.1473**	**1.9680**	**1.9680**	**1.9680**	**1.9680**	**0.0221**	**0.9210**	**1.2510**	**N/A**	**-1.9480**	**-0.2929**
	P Value	**N/A**	**0.1113**	**0.1573**	**0.6431**	**0.2513**	**0.0491**	**0.0491**	**0.0491**	**0.0491**	**0.9823**	**0.3571**	**0.2109**	**N/A**	**0.0514**	**0.7696**
Pork Chop	2002 (10)	–	30.0%	10.0%	70.0%	40.0%	20.0%	20.0%	20.0%	20.0%	70.0%	20.0%	40.0%	–	–	70.0%
	2003 (5)	–	–	–	40.0%	40.0%	20.0%	20.0%	20.0%	20.0%	40.0%	–	40.0%	–	–	80.0%
	2004 (11)	–	–	9.1%	27.3%	9.1%	–	–	–	–	18.2%	–	18.2%	–	–	54.5%
	2005 (9)	–	–	–	33.3%	22.2%	–	–	–	–	33.3%	11.1%	22.2%	–	–	55.6%
	2006 (8)	–	50.0%	25.0%	25.0%	25.0%	–	–	–	–	75.0%	50.0%	–	–	–	25.0%
	2007 (18)	–	5.6%	5.6%	16.7%	5.6%	–	–	–	–	16.7%	5.6%	–	–	–	50.0%
	2008 (23)	–	13.0%	–	13.0%	13.0%	–	–	–	–	30.4%	–	–	–	–	34.8%
	2009 (8)	–	–	12.5%	37.5%	37.5%	25.0%	25.0%	25.0%	25.0%	37.5%	25.0%	12.5%	–	–	37.5%
	Z Statistic	**N/A**	**0.7698**	**0.4114**	**2.7069**	**1.2488**	**1.0744**	**1.0744**	**1.0744**	**1.0744**	**1.5624**	**0.3396**	**3.7087**	**N/A**	**N/A**	**2.2864**
	P Value	**N/A**	**0.4414**	**0.6808**	**0.0068**	**0.2117**	**0.2827**	**0.2827**	**0.2827**	**0.2827**	**0.1182**	**0.7341**	**0.0002**	**N/A**	**N/A**	**0.0222**

[1] Dashes indicate 0.0% resistance to antimicrobial. Where % resistance = (# isolates resistant to antimicrobial per meat type) / (total # isolates per meat type).

[2] Sulfisoxazole replaced Sulfamethoxazole on NARMS panel in 2004.

[3] P value for percent resistant trend was calculated using the Cochran-Armitage Trend Test method.

[4] N/A = No Z statistic or P value could be calculated.

Table 8. Multidrug Resistance among *Salmonella* Isolates by Antimicrobial Class, 2002-2009[1]

Year		2002	2003	2004	2005	2006	2007	2008	2009
Number of Isolates Tested by Source	Chicken Breast	60	83	157	153	152	99	199	277
	Ground Turkey	74	114	142	183	159	190	245	190
	Ground Beef	9	10	14	8	19	13	24	14
	Pork Chop	10	5	11	9	8	18	23	8
Resistance Pattern[2]	Isolate Source								
1. No Resistance Detected	Chicken Breast	51.7% 31	45.8% 38	40.1% 63	46.4% 71	38.8% 59	47.5% 47	45.7% 91	29.4% 81
	Ground Turkey	37.8% 28	34.2% 39	28.9% 41	30.1% 55	17.6% 28	15.3% 29	20.8% 51	22.1% 42
	Ground Beef	77.8% 7	60.0% 6	78.6% 11	75.0% 6	73.7% 14	92.3% 12	79.2% 19	57.1% 8
	Pork Chop	20.0% 2	20.0% 1	45.5% 5	44.4% 4	25.0% 2	44.4% 8	65.2% 15	50.0% 4
2. Resistant to ≥ 3 Antimicrobial Classes	Chicken Breast	20.0% 12	30.1% 25	34.4% 54	25.5% 39	24.3% 37	25.3% 25	38.2% 76	48.4% 134
	Ground Turkey	20.3% 15	29.0% 33	26.1% 37	29.0% 53	24.5% 39	42.6% 81	51.0% 125	26.3% 50
	Ground Beef	22.2% 2	40.0% 4	14.3% 2	25.0% 2	10.5% 2	–[2]	20.8% 5	35.7% 5
	Pork Chop	60.0% 6	40.0% 2	18.2% 2	22.2% 2	25.0% 2	5.6% 1	17.4% 4	50.0% 4
3. Resistant to ≥ 4 Antimicrobial Classes	Chicken Breast	5.0% 3	16.9% 14	24.2% 38	18.3% 28	15.1% 23	13.1% 13	23.1% 46	34.7% 96
	Ground Turkey	13.5% 10	24.6% 28	12.7% 18	7.7% 14	8.2% 13	14.7% 28	15.1% 37	12.1% 23
	Ground Beef	22.2% 2	40.0% 4	14.3% 2	12.5% 1	5.3% 1	–	12.5% 3	35.7% 5
	Pork Chop	40.0% 4	40.0% 2	18.2% 2	22.2% 2	25.0% 2	5.6% 1	13.0% 3	25.0% 2
4. Resistant to ≥ 5 Antimicrobial Classes	Chicken Breast	3.3% 2	13.3% 11	22.3% 35	17.7% 27	14.5% 22	12.1% 12	19.1% 38	31.4% 87
	Ground Turkey	12.2% 9	14.0% 16	4.9% 7	2.7% 5	3.1% 5	3.2% 6	2.9% 7	3.7% 7
	Ground Beef	22.2% 2	40.0% 4	14.3% 2	12.5% 1	5.3% 1	–	12.5% 3	14.3% 2
	Pork Chop	40.0% 4	40.0% 2	9.1% 1	22.2% 2	–	–	–	25.0% 2
5. Resistant to ≥ 6 Antimicrobial Classes	Chicken Breast	–	4.8% 4	5.7% 9	3.9% 6	5.9% 9	4.0% 4	4.0% 8	11.2% 31
	Ground Turkey	10.8% 8	3.5% 4	2.8% 4	2.2% 4	1.9% 3	2.1% 4	2.0% 5	2.6% 5
	Ground Beef	22.2% 2	40.0% 4	14.3% 2	–	–	–	8.3% 2	14.3% 2
	Pork Chop	20.0% 2	40.0% 2	–	–	–	–	–	12.5% 1

[1] Dashes indicate 0.0% resistance.

[2] Cephem class includes Cephalothin for 2002 and 2003.

Table 13. Trends in Antimicrobial Resistance among *Campylobacter* Species from Chicken Breast, 2002-2009[1]

Species	Year (N)		Aminoglycosides	Ketolides	Lincosamides	Macrolides		Phenicols	Quinolones		Tetracyclines[2]
			GEN (MIC ≥ 8)	TEL (MIC ≥ 16)	CLI (MIC ≥ 8)	AZI (MIC ≥ 8)	ERY (MIC ≥ 32)	FFN[3] (MIC > 4)	CIP (MIC ≥ 4)	NAL (MIC ≥ 64)	TET (MIC ≥ 16)
C. jejuni	2002 (198)	n (%R[4])	–	Not Tested	Not Tested	Not Tested	–	Not Tested	30 (15.2)	Not Tested	76 (38.4)
	2003 (325)		1 (0.3)	Not Tested	Not Tested	Not Tested	–	Not Tested	47 (14.5)	Not Tested	132 (40.6)
	2004 (510)		–	2 (0.4)	2 (0.4)	4 (0.8)	4 (0.8)	–	77 (15.1)	77 (15.1)	256 (50.2)
	2005 (403)		–	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)	–	61 (15.1)	60 (14.9)	187 (46.4)
	2006 (426)		–	3 (0.7)	3 (0.7)	4 (0.9)	4 (0.9)	–	71 (16.7)	71 (16.7)	201 (47.2)
	2007 (332)		–	2 (0.6)	2 (0.6)	2 (0.6)	2 (0.6)	–	57 (17.2)	57 (17.2)	161 (48.5)
	2008 (329)		–	1 (0.3)	3 (0.9)	4 (1.2)	4 (1.2)	–	48 (14.6)	48 (14.6)	164 (49.8)
	2009 (403)		–	1 (0.2)	2 (0.5)	4 (1.0)	4 (1.0)	–	85 (21.1)	85 (21.1)	186 (46.2)
	Z Statistic		**1.2403**	**0.4375***	**-0.5290***	**-0.7058***	**-1.9629**	**N/A[6]**	**-2.1757**	**-2.0382***	**-1.8933**
	P Value[5]		**0.2149**	**0.6617**	**0.5968**	**0.4803**	**0.0497**	**N/A**	**0.0296**	**0.0415**	**0.0583**
C. coli	2002 (90)	n (%R)	–	Not Tested	Not Tested	Not Tested	7 (7.8)	Not Tested	9 (10.0)	Not Tested	40 (44.4)
	2003 (142)		–	Not Tested	Not Tested	Not Tested	10 (7.0)	Not Tested	19 (13.4)	Not Tested	72 (50.7)
	2004 (196)		–	16 (18.2)	14 (7.1)	18 (9.2)	18 (9.2)	–	32 (16.3)	32 (16.3)	91 (46.4)
	2005 (151)		–	12 (7.9)	13 (8.6)	15 (9.9)	15 (9.9)	–	44 (29.1)	44 (29.1)	64 (42.4)
	2006 (145)		–	7 (4.8)	7 (4.8)	8 (5.5)	8 (5.5)	–	32 (22.1)	30 (20.7)	68 (46.9)
	2007 (143)		1 (0.7)	10 (7.0)	7 (4.9)	9 (6.3)	9 (6.3)	–	37 (25.9)	37 (25.9)	57 (39.9)
	2008 (181)		3 (1.7)	14 (7.7)	9 (5.0)	18 (9.9)	18 (9.9)	–	37 (20.4)	37 (20.4)	84 (46.4)
	2009 (179)		10 (5.6)	8 (4.5)	6 (3.4)	8 (4.5)	8 (4.5)	–	33 (18.4)	33 (18.4)	68 (38.0)
	Z Statistic		**-4.8698**	**1.1070***	**2.0125***	**1.3466***	**0.8853**	**N/A**	**-2.1215**	**0.2090**	**1.6998**
	P Value		**<0.0001**	**0.2683**	**0.0442**	**0.1781**	**0.3760**	**N/A**	**0.0339**	**0.8344**	**0.0892**

[1] Dashes indicate 0.0% resistance.

[2] Results for 2002 and 2003 are for Doxycycline.

[3] Percent non susceptible is reported rather than percent resistant as no CLSI breakpoint has been established. NARMS breakpoint established to determine resistance.

[4] % R = the number of resistant isolates (n) / the number of positive isolates (N).

[5] P value for percent resistant for trend was calculated using Cochran-Armitage trend test method.

[6] N/A = Z Statistic and P value could not be calculated due to insufficient data or no resistance observed.

* Z statistic and P value calculated based on 6 years data.

Table 22. Trends in Antimicrobial Resistance among *Escherichia coli* by Meat Type, 2002-2009[1]

Meat Type	Year (N)	Aminoglycosides				Penicillins	β-Lactamase Inhibitor Combinations	Cephems			Folate Pathway Inhibitors		Phenicols	Quinolones		Tetra-cyclines
		AMI (MIC ≥ 64)	GEN (MIC ≥ 16)	KAN (MIC ≥ 64)	STR (MIC ≥ 64)	AMP (MIC ≥ 32)	AMC (MIC ≥ 32)	TIO (MIC ≥ 32)	AXO (MIC ≥ 4)	FOX (MIC ≥ 32)	FIS[2] (MIC ≥ 512)	COT (MIC ≥ 4)	CHL (MIC ≥ 512)	CIP (MIC ≥ 4)	NAL (MIC ≥ 32)	TET (MIC ≥ 16)
Chicken Breast	2002 (282)	–	23.1%	6.0%	49.3%	21.6%	12.1%	7.1%	7.8%	11.0%	32.3%	3.6%	0.7%	–	2.8%	46.1%
	2003 (396)	–	29.3%	6.8%	56.1%	25.3%	13.6%	7.6%	9.1%	9.3%	38.4%	7.1%	–	–	4.0%	42.9%
	2004 (400)	–	30.0%	6.8%	56.8%	17.0%	10.0%	5.8%	6.5%	8.3%	41.3%	4.3%	1.8%	–	7.0%	48.0%
	2005 (393)	–	37.7%	7.1%	50.6%	24.7%	12.2%	8.7%	10.2%	11.2%	48.1%	7.4%	0.5%	–	6.6%	46.6%
	2006 (418)	–	37.3%	11.5%	48.1%	20.1%	11.5%	8.6%	9.1%	11.2%	46.9%	8.9%	2.6%	–	5.0%	50.5%
	2007 (299)	–	34.4%	9.0%	46.8%	18.1%	7.4%	6.0%	6.4%	7.4%	42.1%	5.0%	2.0%	–	3.0%	40.5%
	2008 (306)	–	34.0%	6.9%	43.8%	23.5%	11.8%	10.8%	11.1%	11.8%	39.2%	3.6%	1.0%	–	2.9%	43.8%
	2009 (315)	–	34.3%	5.4%	38.1%	22.2%	13.3%	11.7%	12.4%	13.3%	40.6%	2.2%	0.6%	0.3%	2.9%	41.6%
	Z Statistic	**N/A[3]**	**-1.8718**	**-0.4489**	**5.0655**	**0.2597**	**0.4139**	**-2.5399**	**-1.9681**	**-1.3229**	**-1.7099**	**1.4534**	**-1.0737**	**-1.6400**	**1.4100**	**1.1513**
	P Value[4]	**N/A**	**0.0612**	**0.6535**	**<0.0001**	**0.7951**	**0.6789**	**0.0111**	**0.0491**	**0.1859**	**0.0873**	**0.1461**	**0.2830**	**0.1010**	**0.1585**	**0.2496**
Ground Turkey	2002 (304)	–	27.0%	13.2%	57.6%	31.3%	5.6%	1.0%	1.3%	3.3%	48.0%	4.0%	0.3%	–	4.3%	77.0%
	2003 (333)	–	29.7%	16.8%	54.7%	35.7%	3.0%	0.3%	0.3%	1.2%	51.7%	6.9%	3.6%	0.3%	11.7%	77.8%
	2004 (376)	–	29.3%	16.0%	49.2%	33.2%	5.3%	1.1%	1.3%	4.5%	48.4%	3.7%	0.8%	0.8%	10.6%	74.2%
	2005 (396)	–	27.5%	11.4%	43.4%	38.1%	3.8%	1.8%	2.3%	3.3%	48.0%	5.1%	4.0%	–	10.4%	78.0%
	2006 (388)	–	29.6%	14.7%	43.8%	42.0%	6.7%	3.1%	3.1%	6.2%	48.5%	8.0%	2.3%	0.5%	5.2%	76.5%
	2007 (315)	–	27.0%	15.6%	44.8%	48.3%	6.3%	6.0%	6.0%	6.3%	48.9%	7.9%	2.9%	0.3%	2.2%	80.0%
	2008 (300)	–	37.0%	19.0%	57.3%	58.0%	8.3%	3.7%	3.7%	6.3%	51.0%	5.3%	3.7%	–	3.7%	85.7%
	2009 (306)	–	37.9%	20.6%	57.5%	56.2%	9.8%	6.2%	6.9%	7.8%	53.9%	5.9%	3.3%	0.7%	2.6%	82.0%
	Z Statistic	**N/A**	**-3.1541**	**-2.3795**	**0.0369**	**-9.2751**	**-3.6245**	**-5.8556**	**-5.7139**	**-4.2615**	**-1.0620**	**-1.3181**	**-2.1290**	**-0.4651**	**4.7865**	**-3.0311**
	P Value	**N/A**	**0.0016**	**0.0173**	**0.9705**	**<0.0001**	**0.0003**	**<0.0001**	**<0.0001**	**<0.0001**	**0.2882**	**0.1874**	**0.0333**	**0.6419**	**<0.0001**	**0.0024**
Ground Beef	2002 (295)	–	0.3%	2.4%	9.5%	6.1%	2.0%	–	–	1.4%	9.8%	0.7%	1.0%	–	–	30.9%
	2003 (311)	–	1.0%	2.9%	9.0%	5.1%	2.3%	0.3%	0.3%	0.3%	10.3%	0.3%	2.3%	–	1.0%	25.1%
	2004 (338)	–	0.6%	2.4%	11.8%	5.3%	3.9%	0.9%	1.5%	1.2%	13.0%	0.6%	3.6%	–	1.5%	22.8%
	2005 (316)	–	–	0.6%	5.4%	3.5%	1.3%	0.6%	1.9%	1.0%	7.0%	0.6%	1.6%	–	1.3%	16.5%
	2006 (295)	–	4.1%	4.7%	14.2%	9.2%	2.4%	1.0%	1.7%	2.0%	12.5%	1.4%	1.4%	–	0.7%	25.4%
	2007 (256)	–	–	1.6%	6.3%	6.6%	0.8%	0.8%	0.8%	0.8%	9.4%	1.2%	3.9%	–	0.4%	21.9%
	2008 (250)	–	2.0%	4.0%	10.4%	6.4%	2.4%	1.6%	1.6%	2.4%	11.6%	2.0%	0.8%	–	0.4%	24.0%
	2009 (247)	–	0.8%	2.0%	8.1%	4.9%	1.6%	0.8%	0.8%	1.6%	7.7%	2.0%	2.4%	–	0.4%	18.6%
	Z Statistic	**N/A**	**-1.4761**	**-0.4190**	**0.4405**	**-0.4781**	**0.9595**	**-1.8333**	**-1.2963**	**-1.3887**	**0.5706**	**-2.5432**	**-0.2672**	**N/A**	**0.5612**	**2.5861**
	P Value	**N/A**	**0.1615**	**0.6752**	**0.6596**	**0.6326**	**0.3373**	**0.0668**	**0.1949**	**0.1649**	**0.5683**	**0.0110**	**0.7893**	**N/A**	**0.5747**	**0.0097**
Pork Chop	2002 (184)	–	1.1%	5.4%	22.3%	13.6%	5.4%	0.5%	0.5%	3.3%	12.5%	1.1%	1.6%	–	0.5%	52.7%
	2003 (218)	–	1.4%	8.7%	19.7%	13.3%	5.1%	0.9%	0.9%	2.3%	15.1%	2.8%	4.1%	–	0.5%	46.3%
	2004 (232)	–	1.3%	8.2%	21.1%	15.1%	5.6%	0.4%	0.4%	2.2%	19.4%	3.9%	4.3%	–	–	56.0%
	2005 (205)	–	–	7.3%	13.2%	16.1%	2.9%	–	0.5%	1.5%	14.2%	1.5%	3.4%	–	1.5%	45.9%
	2006 (182)	–	1.1%	6.0%	13.7%	15.9%	2.2%	–	0.6%	1.6%	20.3%	2.2%	6.6%	–	0.5%	52.7%
	2007 (152)	–	1.3%	4.6%	13.8%	15.8%	0.7%	0.7%	0.7%	0.7%	11.8%	1.3%	3.9%	–	–	50.0%
	2008 (146)	–	1.4%	6.2%	19.9%	15.1%	3.4%	3.4%	3.4%	3.4%	16.4%	6.2%	3.4%	–	–	54.8%
	2009 (147)	–	4.1%	6.1%	19.7%	11.6%	6.8%	6.8%	6.8%	6.8%	14.3%	2.7%	4.8%	–	–	46.9%
	Z Statistic	**N/A**	**-1.7338**	**0.8817**	**1.2484**	**-0.0126**	**0.9516**	**-4.5868**	**-4.4349**	**-1.4454**	**-0.1036**	**-1.1923**	**-1.0975**	**N/A**	**0.9618**	**0.1653**
	P Value	**N/A**	**0.0829**	**0.3779**	**0.2119**	**0.9900**	**0.3413**	**<0.0001**	**<0.0001**	**0.1483**	**0.9175**	**0.2332**	**0.2724**	**N/A**	**0.3362**	**0.8687**

[1] Dashes indicate 0.0% resistance to antimicrobial. Where % resistance = (# isolates resistant to antimicrobial per meat type) / (total # isolates per meat type).

[2] Sulfisoxazole replaced Sulfamethoxazole on the NARMS panel in 2004.

[3] N/A = No Z statistic or P value could be calculated.

[4] P value for percent resistant trend was calculated using the Cochran-Armitage Trend Test method.

Table 24. Multidrug Resistance among *Escherichia coli* Isolates by Antimicrobial Class, 2002-2009[1]

Year									
Number of Isolates Tested by Source	Chicken Breast	282	396	400	393	418	299	306	315
	Ground Turkey	304	333	376	396	388	315	300	306
	Ground Beef	295	311	338	316	295	256	250	247
	Pork Chop	184	218	232	205	182	152	146	147
Resistance Pattern[2]	Isolate Source								
1. No Resistance Detected	Chicken Breast	27.0% 76	20.5% 81	20.8% 83	20.6% 81	23.7% 99	29.1% 87	33.3% 102	34.3% 108
	Ground Turkey	16.8% 51	14.7% 49	19.1% 72	16.2% 64	16.0% 62	13.0% 41	8.3% 25	11.8% 36
	Ground Beef	63.1% 186	66.9% 208	73.1% 247	80.4% 254	71.5% 211	77.0% 197	73.2% 183	78.1% 193
	Pork Chop	41.3% 76	44.5% 97	37.9% 88	48.8% 100	42.9% 78	48.0% 73	43.8% 64	51.0% 75
2. Resistance to ≥ 3 Antimicrobial Classes	Chicken Breast	36.2% 102	42.2% 167	35.3% 141	45.0% 177	43.3% 181	33.8% 101	36.6% 112	37.5% 118
	Ground Turkey	55.6% 169	55.6% 185	51.9% 195	52.8% 209	55.2% 214	57.5% 181	63.7% 191	66.3% 203
	Ground Beef	10.2% 30	7.4% 23	10.4% 35	5.4% 17	11.5% 34	9.0% 23	11.2% 28	6.9% 17
	Pork Chop	17.4% 32	17.9% 39	21.1% 49	16.1% 33	15.9% 29	15.1% 23	17.8% 26	15.0% 22
3. Resistance to ≥ 4 Antimicrobial Classes	Chicken Breast	13.8% 39	13.6% 54	12.5% 50	12.2% 48	14.6% 61	10.4% 31	13.7% 42	13.7% 43
	Ground Turkey	23.0% 70	30.0% 100	24.5% 92	24.2% 96	25.8% 100	27.0% 85	32.3% 97	38.9% 119
	Ground Beef	1.7% 5	4.2% 13	4.7% 16	1.9% 6	5.8% 17	4.7% 12	4.4% 11	3.6% 9
	Pork Chop	5.4% 10	6.9% 15	7.8% 18	4.9% 10	7.7% 14	3.3% 5	7.5% 11	10.9% 16
4. Resistance to ≥ 5 Antimicrobial Classes	Chicken Breast	6.0% 17	7.3% 29	6.0% 24	5.9% 23	7.4% 31	5.7% 17	8.2% 25	6.3% 20
	Ground Turkey	9.2% 28	14.7% 49	6.9% 26	6.3% 25	5.7% 22	4.1% 13	6.3% 19	7.8% 24
	Ground Beef	0.3% 1	2.6% 8	2.7% 9	1.0% 3	2.4% 7	0.4% 1	2.0% 5	1.2% 3
	Pork Chop	3.3% 6	2.8% 6	2.2% 5	1.5% 3	3.3% 6	1.3% 2	4.1% 6	5.4% 8
5. Resistance to ≥ 6 Antimicrobial Classes	Chicken Breast	3.9% 11	3.5% 14	3.3% 13	3.6% 14	5.3% 22	3.3% 10	6.2% 19	4.4% 14
	Ground Turkey	2.6% 8	4.2% 14	3.2% 12	1.8% 7	3.1% 12	2.9% 9	4.0% 12	3.6% 11
	Ground Beef	0.3% 1	1.3% 4	2.1% 7	0.6% 2	1.7% 5	–[2]	1.6% 4	0.4% 1
	Pork Chop	1.6% 3	1.8% 4	0.4% 1	0.5% 1	1.1% 2	0.7% 1	2.1% 3	4.1% 6

[1] Dashes indicate 0.0% resistance.

[2] Cephem class includes Cephalothin for 2002 and 2003.

THE PEW CHARITABLE TRUSTS

Antibiotic Resistance and Food Animal Production:

a Bibliography of Scientific Studies (1969-2012)

This bibliography lists the latest published scientific and economic literature concerning the contribution of routine antibiotic use in food animals to the growing public health crisis of human antibiotic resistance. Research on how antibiotic use in food animal production contributes to the growing health crisis of antibiotic resistance dates back more than 30 years. As Dr. Frederick J. Angulo, then acting associate director of science in the Centers for Disease Control and Prevention's National Center for Environmental Health and the Agency for Toxic Substances and Disease, said in a August 1, 2009, news article in the *Journal of the American Veterinary Medical Association*:

> "There is scientific consensus that antibiotic use in food animals contributes to resistance in humans. And there's increasing evidence that such resistance results in adverse human health consequences at the population level. Antibiotics are a finite and precious resource, and we need to promote prudent and judicious antibiotic use."

Table of Contents:

ANTIBIOTIC RESISTANCE IN ANIMAL AGRICULTURE

The impacts of antibiotic resistance in animal agriculture on livestock, the environment and the spreading of infectious diseases.

Joint Committee on the use of antibiotics in animal husbandry and veterinary medicine ("Swann Report"). M.M. Swann, K.L. Blaxter, H.I. Field, J.W. Howie, I.A.M. Lucas, E.L.M. Millar, J.C. Murdoch, J.H. Parsons and E.G. White. Cmnd. 4190. London: Her Majesty's Stationery Office, 1969.

Summary: Reports on the status of antibiotic use in man and animals. Outlines the uses and amounts consumed for both. Reviews the reasons for which antibiotics are administered to food animals, including disease prevention, use in growth promotion, stress reduction and therapy. States that there are possible dangers to the human population stemming from the administration of antibiotics to animals, such as the rise of antibiotic-resistant strains of bacteria in animals that could cause disease in humans. The resulting infection could then be difficult to treat due to the null effect of antibiotics. Other dangers include the transmission of resistance determinants from animal strains to human strains of bacteria. It is known that such transfers take place and the fear is that resistance may be transferred to normal bacteria that inhabit the human bowel and/or to pathogens that may then cause disease. Discusses the prevalence of multiple antibiotic-resistant strains of bacteria and how they may arise. States that even though there are multiple antibiotics available for treatment of certain diseases, those reserved as a drug of choice may have a number of advantages over alternative treatment. Strains with multidrug resistance pose a greater threat in that the only effective drugs left for treatment in humans may be unsuitable because of toxicity or allergy. These infections are likely to arise where humans and animals share a pathogen such as *Salmonella* and the administration of antimicrobials to animals no doubt encourages the prevalence of resistance in these strains. Concludes that the use of antimicrobials in food animal production, especially when used in growth promotion, is of great concern and that limiting factors should be put in place to secure the use of antibiotics of greatest importance in human administration for therapeutic uses only and in some cases excluded from animal use altogether.

Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm. S.B. Levy, G.B. Fitzgerald and A.B. Macone. *New England Journal of Medicine,* 1976. 295(11): 583-588.

Summary: Reports a study to determine if giving animals antibiotics in feed caused changes in intestinal bacterial flora and if workers and neighbors of the farm were affected. Chickens were screened for bacteria before and after a diet that included tetracycline-supplemented feed. Resistance to tetracycline changed dramatically within 36 to 48 hours of changing the diet of the animals. Within two weeks, 90 percent of the chickens were found to excrete essentially all tetracycline-resistant organisms. Within five to six months, there was a large increase in tetracycline-resistant bacteria in farm dwellers while the neighbors showed no change in bacterial count.

An epidemic of resistant *Salmonella* in a nursery: Animal-to-human spread. R.W. Lyons, C.L Samples, H.N. DeSilva, K.A. Ross, E.M. Julian and P.J. Checko. *Journal of the American Medical Association*, 1980. 243(6): 546-547.

Summary: Studies the case of a pregnant woman, infected with *Salmonella heidelberg*, who worked on her father's farm until four days before delivery. Her baby subsequently developed mild diarrhea, as did two others sharing the hospital nursery. *Salmonella heidelberg* was isolated

antimicrobial residues for the environment as a detectable level of antimicrobial compounds was found in waste-storage lagoons and surface and groundwater proximal to these operations.

Antimicrobial use and resistance in animals. S.A. McEwen and P.J. Fedorka-Cray. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S93-106.

Summary: Describes antibiotic use in each animal class. Discusses a 1999 report on the economic effects of banning subtherapeutic antibiotic use in the U.S. Concludes that meat producers following good management practices would not be adversely affected by such a ban. Reviews antimicrobial-resistance-monitoring programs in bacteria of animal origin and the techniques involved. States alternatives to using antibiotics in food animals, such as providing good sanitation, air temperature and clean water, as well as vaccine use and development and use of probiotics that consist of live, beneficial bacteria.

Emergence, spread and environmental effect of antimicrobial resistance: How use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else. T.F. O'Brien. *Clinical Infectious Diseases*, 2002. 34(Suppl 3): S78-84.

Summary: Discusses how a bacterial community responds to antimicrobial use by obtaining resistance genes as well as how these genes are spread around the globe and between different bacterial populations. States that in Europe a ban of avoparcin, an antibiotic similar to vancomycin, was implemented in 1997 because of rising concerns that strains of vancomycin-resistant *Enterococci* were being used for growth promotion.

Generally overlooked fundamentals of bacterial genetics and ecology. A.O. Summers. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S85-92.

Summary: Reviews how treatment with any given antibiotic may result in resistance to several antibiotics because of the ability of bacteria to obtain genetic elements that code for multidrug resistance. States that the exchange of bacteria between a host and its environment is a continual process and that selective pressure applied to any part of the ecosystem will result in a highly resistant bacterial population. Also states that once resistance is acquired it will be hard to reverse because of molecular mechanisms inherent in bacteria that ensure future generations hold on to resistance characteristics.

Human diseases caused by foodborne pathogens of animal origin. M.N. Swartz. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S111-122.

Summary: Evaluates the likelihood that emergence of several resistant strains of bacteria occurred first in animals rather than humans. Reviews studies that correlate antimicrobial use on farms to the occurrence of colonization and infection of farm workers and residents of the surrounding communities. Discusses the trend in antibiotic resistance in commensal microorganisms and their opportunistic infection of hospitalized patients.

Antimicrobial resistance of *Escherichia coli* 0157 isolated from humans, cattle, swine, and food. C.M. Schroeder, C. Zhao, C. DebRoy, J. Torcolini, S. Zhao, D.G. White, D.D. Wagner, P.F. McDermott, R.D. Walker, and J. Meng. *Applied and Environmental Microbiology*. 2002. 68(2): 576-581.

Summary: Examines the prevalence and antimicrobial resistance of Shiga toxin-producing *E. coli* (STEC) 0157 in a collection of samples collected for diagnostic purposes from humans, swine, cattle, and food between 1985 and 2000. Of 361 isolates available to analyze, 210 (58

amount of antibiotics used in food animals in order to protect public health and safeguard the efficacy of antibiotics in veterinary medicine.

Selective pressure by antibiotic use in livestock. W. Witte. *International Journal of Antimicrobial Agents,* 2000. 16: S19-S24

Summary: Describes the selective pressures seen in the use of antibiotics as growth promoters. States that discovery of glycopeptide resistance outside of hospitals in *Enterococcus faecium* is linked to avoparcin use in animals. The review concludes that the spread of resistance is worrisome as mobile genetic elements are seen transferring between bacterial species that could lead to non-resistant pathogens picking up resistance from non-pathogenic strains. It concludes in support of the ban on growth promoters introduced in Europe as this might interfere with treatment in humans.

Quinolone and macrolide resistance in *Campylobacter jejuni* and *C. coli*: Resistance mechanisms and trends in human isolates. J. Engberg, F.M. Aarestrup, D.E. Taylor, P.Gerner-Smidt and I. Nachamkin. *Emerging Infectious Diseases,* 2001. 7(1):24-34.

Summary: Reviews the increasing resistance of *Campylobacter* strains to macrolide and quinolone antibiotics in human clinical isolates with respect to the use of these agents in food animals. Data suggest that while erythromycin and other macrolides should continue to be the antibiotics of choice in most regions, fluoroquinolones may be of limited use in many areas as the overuse of enrofloxacin and other drugs in food animals has caused a sharp upswing in the resistance of *Campylobacter* to these antibiotics.

The need to improve antimicrobial use in agriculture: Ecological and human health consequences. Alliance for the Prudent Use of Antibiotics. *Clinical Infectious Diseases*, 2002 supplement. 34 (S3): S71-144.

Summary: Reviews more than 500 studies relating to agricultural uses of antibiotics and concludes that "elimination of nontherapeutic use of antimicrobials in food animals and agriculture will lower the burden of antimicrobial resistance."

Potential mechanisms of increased disease in humans from antimicrobial resistance in food animals. M. Barza. *Clinical Infectious Diseases*, 2002. 34 (Suppl 3): S123-125.

Summary: Summarizes five potential mechanisms by which antimicrobial resistance may adversely affect human health. Two of the five relate to antimicrobial use in animals: (1) that resistant pathogens acquired by animals as the result of treatment with antibiotics transmit these pathogens through the food chain; and (2) that commensal flora of animals may acquire resistance traits from the previous pool of resistant pathogens, which then may be passed to human commensals and/or pathogens through the food chain.

Antimicrobial residues in animal waste and water resources proximal to large-scale swine and poultry feeding operations. E.R. Campagnolo, K.R. Johnson, A. Karpati, C.S. Rubin, D.W. Kolpin, M.T. Meyer, J.E. Estaban, R.W. Currier, K. Smith, K.M. Thu and M. McGeehin. *The Science of the Total Environment,* 2002. 299: 89-95.

Summary: Reports on data from numerous antimicrobial residues collected from animal wastes, surface water and groundwater proximal to large-scale swine and poultry operations. Data indicate that animal waste applied as fertilizer to the land may serve as a contaminating source of

Ceftriaxone-resistant *Salmonella* infection acquired by a child from cattle. P. Fey, T.J. Safranek, M.E. Rupp, E.F. Dunne, E. Ribot, P.C. Iwen, P.A. Bradford, F.J. Angulo and S.H. Hinrichs. *New England Journal of Medicine,* 2000. 342: 1242-1249.

Summary: Reports the case of a 12-year-old boy who lived on a farm in Nebraska and was infected with a ceftriaxone-resistant strain of *Salmonella enterica* serotype typhimurium that was traced to his father's herd of cattle using molecular techniques. States that this finding adds to the growing body of evidence suggesting that the use of antibiotics in livestock is the prominent source of resistance to these agents in *Salmonella* infection.

Appropriate regulation of antibiotics in livestock feed. R.L. Goforth and C.R. Goforth. *Boston College Environmental Affairs Law Review*, 2000. 28(1): 39-77.

Summary: Reviews nontherapeutic uses of antimicrobials in food animals and their impact on human health. States that this practice is creating possibly irreversible effects on the viability of antibiotics used to treat human disease. Concludes that despite short-term economic benefits associated with the widespread use of antibiotics in agriculture, the risk to human health justifies a change in policy.

Antibiotic resistance in *Campylobacter* strains isolated from animals, foods and humans in Spain in 1997–1998. Y. Saenz, M. Zarazaga, M. Lantero, M.J. Gastaneres, F. Baquero and C. Torres. *Antimicrobial Agents and Chemotherapy,* 2000. 44(2): 267-271.

Summary: Studies *Campylobacter* isolated from foods, animals and humans. Finds that a high percentage of *Campylobacter jejuni* contaminates food (54.4 percent), broilers (81 percent) and pigs (88.9 percent). Isolates collected from broilers and pigs showed a 99 percent resistance rate to ciprofloxacin, with only a slightly lower number of human isolates (72 percent) also resistant. High resistance percentages to ampicillin, erythromycin, gentamicin and amikacin also were detected for *C. coli* isolated from these sources. Concludes that "more restrictive policies on the use of antibiotics in animals may result in an improvement of the current situation in the medium term."

The effect of banning avoparcin on VRE carriage in The Netherlands. A.E. van den Bogaard, N. Bruinsma and E.E. Stobberingh. *Journal of Antimicrobial Chemotherapy,* 2000. 46: 146-148.

Summary: Discusses the removal of avoparcin, an antimicrobial similar to vancomycin, from commercial food animal production in several settings. Sweden, which banned the use of antibiotics as growth promoters in 1986, has not reported any vancomycin-resistant *Enterococci* (VRE). This example strongly suggests that the removal of selective pressure will remove VRE from the human population over time. Denmark also banned the use of avoparcin in 1995 and saw the prevalence of poultry-isolated cases of VRE drop from greater than 80 percent in 1995 to less than 5 percent in 1998.

Epidemiology of resistance to antibiotics: Links between animals and humans. A. Van der Bogaard and E.E. Stobberingh. *International Journal of Antimicrobial Agents*, 2000. 14: 327-335.

Summary: Discusses the ban on avoparcin in food animals in the European Union and resulting significant decreases in resistance to vancomycin (a related drug) in intestinal *Enterococci* bacteria in animals and humans. States that resistant bacteria from animals can infect or reach the human population by direct contact and via food products of animal origin. Shows evidence for transfer of resistant genes between bacteria in humans and animals and recommends reducing the

from each and in all cases was resistant to chloramphenicol, sulfamethoxazole and tetracycline. The strain was presumed to originate from a herd of infected dairy cows at the woman's father's farm as those bacteria showed the same resistance pattern as did those collected from the father.

Emergence of multidrug-resistant *Salmonella enterica* serotype Typhimurium DT104 infections in the United States. M.K. Glynn, C. Bopp, W. Dewitt, P. Dabney, M. Mokhtar and F.J. Angulo. *New England Journal of Medicine,* 1998. 338(19): 1333-1338.

Summary: Reviews *Salmonella* data collected by local and state health departments and public health laboratories between 1979 and 1996. Finds that a rapid increase of multidrug-resistant *Salmonella enterica* serotype typhimurium (DT104), a strain widely distributed in food animals and known to cause disease in humans, occurred in this period. The percentage rose from 0.6 percent in 1979–1980 to 34 percent in 1996. Concludes that more prudent use of antibiotics on farms is necessary to reduce the dissemination of multidrug-resistant *Salmonella* and emergence of further resistant strains.

Epidemiologic aspects, control, and importance of multiple-drug resistant *Salmonella* typhimurium DT104 in the United States. J.E. Akkina, A.T. Hogue, F.J. Angulo, R. Johnson, K.E. Petersen, P.K. Saini, P.J. Fedorka-Cray and W.D. Schlosser. *Journal of the American Veterinary Medical Association,* 1999. 214(6): 790-798.

Summary: Studies an animal strain of *Salmonella* and its prevalence of infection in humans. States that multidrug-resistant *Salmonella* DT104 is the second-most-prevalent *Salmonella* organism isolated from humans in England and Wales in the time frame of this study. Gives numerous examples of outbreaks in the U.S., most of which are traced to milk. Cattle, along with pigs, sheep, chickens, turkeys and several other animals, are known carriers of this strain.

Transfer of antibiotic resistant bacteria from animals to man. H.C. Wegener, F.M. Aarestrup, P. Gerner-Smidt and F. Bager. *Acta Veterinaria Scandinavica Supplementum*, 1999. 92: 51-57.

Summary: Describes zoonotic bacterial infections and their treatment. States that most *Salmonella, campylobacter, yersinia* and entero-haemorrhagic *E. coli* (EHEC) infections do not require antibiotic therapy, but in some cases these tools provide life-saving cures. Increasing levels of resistance in these bacteria, especially fluoroquinolone resistance, give rise for concern when it comes to human infections. Calls for infection control at the herd level and the need for prudent use of antibiotics in food animals.

The use of drugs in food animals: Benefits and risks. Committee on Drug Use in Food Animals, Panel on Animal Health, Food Safety, and Public Health, National Research Council. 1999.

Summary: This review focuses on the following topics associated with antibiotic use in animal agriculture: background and perspectives; production practices and drug use; benefits and risks to human health; drug development, government approval and the regulatory process; drug residues and microbial contamination in food costs of eliminating sub-therapeutic use; and approaches to minimize antibiotic use in food animal production. Primary findings include 60 to 80 percent of livestock and poultry receive antibiotics. This use of antibiotics increases the potential for resistant zoonotic bacteria to impact humans and for resistant genes to be shared by species of bacteria. The review finds an increase cost of $4.84 to $9.72 per consumer per year should sub-therapeutic use be banned.