Testimony before the Subcommittee on Health Committee on Energy & Commerce U.S. House of Representatives

Statement of

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Good morning Chairman Pallone, Ranking Member Shimkus, and members of the Subcommittee. I am Ali Khan, an Assistant Surgeon General and acting Deputy Director of the National Center for Emerging & Zoonotic Infectious Diseases (proposed), at the Centers for Disease Control & Prevention (CDC). Thank you for the invitation to address the Subcommittee on the available data as it relates to antimicrobial use in food animals. Today I will expand upon the recent testimony before this Subcommittee by CDC Director Dr. Thomas Frieden, and describe: 1) CDC's role in monitoring antimicrobial resistance in humans as it relates to the food supply, 2) data available from North America, 3) data available from Europe, and 4) why appropriate antimicrobial use is critical to protecting human and animal health, as outlined in the Food and Drug Administration's (FDA) recently released draft guidance.

Background

Antimicrobial agents[1] are used to treat infections by different disease-causing microorganisms, including bacteria, mycobacteria, viruses, parasites and fungi. In the vast majority of cases where antimicrobials are used, the microorganisms have found a way to evade or resist the antimicrobial agent.[2] Resistance occurs wherever antimicrobials are used [3]-- in the community, on the farm, and in healthcare settings. Antimicrobial resistance is a global problem, and our most significant global health threats include multi-drug resistant tuberculosis and drug-resistant malaria. Today, however, I will focus on a specific antimicrobial resistance, antibiotic-resistant bacteria as they relate to food animals.

[1] Antimicrobial agents or antimicrobials are general terms for the drugs, chemicals, or other substances that either kill or slow the growth of microbes. Among the antimicrobial agents in use today are antibiotic drugs (which kill bacteria), antiviral agents (which kill viruses), antifungal agents (which kill fungi), and antiparisitic drugs (which kill parasites). An antibiotic is a type of antimicrobial agent made from a mold or a bacterium that kills, or slows the growth of other microbes, specifically bacteria. Examples include penicillin, streptomycin, and other antibiotics discussed below.
[2] Levy, S, Marshall B, Antibacterial resistance worldwide: causes, challenges and responses. NATURE MEDICINE SUPPLEMENT 10:12, 2004.
[3] Tacconelli, Evelina. Antimicrobial use: risk driver of multi-drug resistant microorganisms in healthcare settings.*Current Opinion in Infectious Diseases*. 2009, 22:352-358.

Many of the bacteria in food that cause disease are found in the intestinal tract of animals or people. Healthy food-producing animals commonly carry bacteria that can cause illness in humans, including *Salmonella* and *Campylobacter*.

When an ill person is treated with an antibiotic to which the bacteria is resistant, the antibiotic will not help and may even make the illness worse. In addition, sub-therapeutic use may be more likely to contribute to the development of resistant bacteria. The illness may last longer, be more serious, or more expensive to treat.

In 1989, the Institute of Medicine (IOM) published a report which concluded that the committee could not find direct evidence that subtherapeutic use of penicillin and tetracycline in animal feed was associated with a human health consequence.[4] The committee was unable to distinguish the human health consequence of subtherapuetic use in animals from the widespread therapeutic use of penicillin and tetracycline in humans and animals (primarily due to a lack of data on quantities of antimicrobials used). In 2002, the Alliance for Prudent Use of Antimicrobials (APUA) FAAIR Report (Facts about Antimicrobials in Animals and the Impact on Resistance) concluded that antimicrobial use in animals does contribute to human antimicrobial resistance and results in an adverse human health consequence.[5] The committee concluded: "the elimination of nontherapeutic use of antimicrobials in food animals and in agriculture will lower the burden of antimicrobial resistance in the environment, with consequent benefits to human and animal health."

To protect both human and animal health, appropriate antibiotic use is encouraged for food-producing animals, which is similar to actions associated with use in humans. CDC's activities

[4] Human health risks with the subtherapeutic use of penicillin or tetracyclines in animal feed Committee on Human Health Risk Assessment of Using Subtherapeutic Antibiotics in Animal Feeds, Institute of Medicine, Division of Health Promotion and Disease Prevention. Published 1989 by National Academy Press in Washington, D.C.

[5] Clinical Infectious Diseases 2002;34:i–I DOI: 10.1086/512410.The Need to Improve Antimicrobial Use in Agriculture Ecological and Human Health Consequences available at http://www.journals.uchicago.edu/toc/cid/2002/34/S3.

related to resistance from antibiotic use in humans have focused on two goals: preventing the emergence and spread of resistant bacteria, and increasing appropriate antibiotic use to reduce the emergence of resistance. In order to minimize the selective pressure of antibiotics, it is important to make sure that when antibiotics are used, they are used appropriately, for either humans or animals. Through population-based surveillance, CDC is able to provide national estimates of disease burden and to track changes in disease burden over time for both resistant community-associated and healthcare-associated bacterial infections. CDC's educational campaign Get Smart: Know When Antibiotics Work has reduced antibiotic use for acute respiratory tract infections among both children and adults.[6] Parallel to antibiotic use in humans, movement toward appropriate antibiotic use for food-producing animals is needed, as discussed in FDA's draft guidance. .

Antimicrobial resistant pathogens can move through the food supply. The use of certain antibiotics in animal feed has been a major driver for some drug-resistant organisms, such as vancomycin-resistant enterococci.[7] There is also evidence of an association between drug use in food animals and the emergence of resistance in some more common enteric pathogens like *Salmonella*.[8] Drug-resistant infections in humans could emerge from exposure to bacteria harbored by animals that are pathogenic to humans, or the genes that cause that resistance could move from bacteria harbored by animals to those bacteria harbored by humans.

[6] CDC's Get Smart: Know When Antibiotics Work program is a comprehensive public health effort to help reduce the rise of antibiotic resistance. Partnerships with public and private health care providers, pharmacists, a variety of retail outlets, and the media result in broad distribution of the campaign's multi-cultural/multi-lingual health education materials for the public and health care providers. Through Get Smart, CDC develops clinical guidance and principles for appropriate antibiotic use to prevent and control antibiotic resistant upper respiratory infections. Data from the National Ambulatory Medical Care Survey (NAMCS) confirm the campaign's impact on reducing antibiotic use for acute respiratory tract infections among both children and adults. There has been a 20 percent decrease in prescribing for upper respiratory infections (in 1997 the prescription rate for otitis media in children < 5 years of age was 69 prescriptions per 100 children compared to 47.5 per 100 children in 2007) and a 13 percent decrease in prescribing overall for all office visits (overall antibiotic prescribing dropped from 13.8 prescriptions per 100 office visits to 12.0 prescriptions per 100 office visits comparing 1997-98 to 2005-06). The Get Smart: Know When Antibiotics Work campaign contributed to surpassing the Healthy People 2010 target goal to reduce the number of antibiotics prescribed for ear infections in children under age 5.

[7] Bonten et al., Lancet 2001. Endtz et al., J Clin Microbiol 1997. Klare et al., Microb Drug Res 1999. Schouten et al.. Lancet 1997.

[8] Dutil et al., Emerg Infect Dis 2010. Angulo et al,, J Vet Med 2004. Spika et al, NEJM 1987. Holmberg et al., NEJM 1984.

NARMS

The National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria was established in 1996 for the purpose of 1) monitoring trends in the prevalence of antibiotic resistance among bacteria isolated from humans, retail meats (began 2002), and food animals; 2) disseminating public health information on antibiotic resistance; 3) promoting interventions that reduce resistance among enteric bacteria; and 4) informing the approval process for the use of antibiotic agents in veterinary medicine. NARMS is a collaboration among CDC (human samples), the Food and Drug Administration's (FDA) Center for Veterinary Medicine (retail meats), and the United States Department of Agriculture's (USDA) Agricultural Research Services (animal samples).

CDC's Role in NARMS

For the human component of NARMS, 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 antibiotic susceptibility testing.[9] Sites participating in FoodNet, the Foodborne Diseases Active Surveillance Network, also submit a representative sample of *Campylobacter* isolates from humans to CDC for susceptibility testing.[10] In addition, NARMS participates in outbreak investigations involving these bacteria and conducts further studies on resistance mechanisms.

[9] Antimicrobial susceptibility testing currently involves the determination of the minimum inhibitory concentration (MIC) for 17 antimicrobial agents: amikacin, ampicillin, amoxicillin-clavulanic acid, apramycin, cefoxitin, ceftiofur, ceftriaxone, cephalothin, chloramphenicol, ciprofloxacin, gentamicin, imipenem, kanamycin, nalidixic acid, streptomycin, sulfamethoxazole, tetracycline, and trimethoprim-sulfamethoxazole.

[10] FoodNet sites submit all Campylobacter isolates (Georgia, Maryland, New Mexico, Oregon, Tennessee), every other isolate (California, Colorado, Connecticut, New York), or every fifth isolate (Minnesota) to NARMS based on the burden of campylobacteriosis in each site. Susceptibility testing of Campylobacter is performed to determine the MICs for nine antimicrobial agents: azithromycin, ciprofloxacin, clindamycin, erythromycin, florfenicol, gentamicin, nalidixic acid, telithromycin, and tetracycline.

NARMS data for human isolates have been collected continually since 1996, which makes trend analysis possible; the data provide information about patterns of emerging resistance, which in turn guide mitigation efforts. Because antibiotic use in food-producing animals may result in antibiotic resistance among bacteria that can be transmitted to humans through the food supply, antimicrobial resistance data from humans are important for the development of public health regulatory policy for the use of drugs in food-producing animals.

In addition to NARMS, CDC has developed a prudent use educational program called "Get Smart: Know When Antibiotics Work on the Farm" to promote appropriate antibiotic use in food producing farm animals. CDC funds and provides technical assistance for several state-based efforts to educate veterinarians and food producers including those in the dairy and beef industries. Educational modules have been developed for use in veterinary professional curricula, which are case-based and are tailored for given animal species and/or food animal production type.

North American Data

Non-typhoidal *Salmonella* causes approximately 1.4 million cases of disease in humans in the United States each year. Patients with complicated or severe infections are treated with fluoroquinolones or cephalosporins, and of these two drug classes, only cephalosporins are approved for treatment of children with these infections. Since NARMS began surveillance in 1996, cephalosporin resistance among *Salmonella* isolated from humans has increased significantly, and a similar resistance also has been found among *Salmonella* isolated from livestock and retail meats. In many cases, the same types of bacteria and genetic mechanisms of resistance are found in both human and animal sources.

For example, studies related to *Salmonella* as both a human and animal pathogen, including many studies in the United States, have demonstrated that (1) use of antibiotic agents in food

animals results in antibiotic resistant bacteria in food animals, (2) resistant bacteria are present in the food supply and are transmitted to humans, and (3) resistant bacterial infections result in adverse human health consequences (e.g., increased hospitalization[11]). The following examples demonstrate the movement of resistant pathogens through the food supply, and exacerbate our concern about the link between the use of antibiotics in animals and eventual human health effects:

- Multi-drug resistant (MDR) *Salmonella* Newport has emerged, which has caused numerous outbreaks where the source was ground beef. Ground beef samples have been found with the same molecular fingerprint as the human strain.[12]
- As described in scientific articles published this year, Cephalosporin-resistant *Salmonella* Heidelberg has emerged among humans, and molecular fingerprinting indicates that strains responsible for human infections are indistinguishable from cephalosporin-resistant *Salmonella* Heidelberg isolated from retail poultry sources.[13] These findings support work done by the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) that demonstrated a strong correlation between cephalosporin-resistant *Salmonella* Heidelberg isolated from retail chicken and the incidence of cephalosporin-resistant *Salmonella* Heidelberg infections in humans across Canada. CIPARS also published this year that in Quebec, changes in cephalosporin-resistance in chicken and human *Salmonella* Heidelberg and chicken *E. coli* strains appeared to be related to changes in ceftiofur use in poultry hatcheries.[14]

[11] Varma *et al.,* J Infect Dis 2005.
[12] Gupta et al., J Infect Dis 2003. CDC MMWR Morb Mortal Wkly Rep 2002.
[13] Folster et al., Foodborne Pathog Dis 2010 and Zhao et al., Appl Environ Microbiol 2008.
[14] Dutil et al., Emerg Infect Dis 2010

Studies of another bacterium, *Campylobacter*, also demonstrate movement of resistant pathogens through the food supply. *Campylobacter* is one of the leading causes of culture-confirmed foodborne bacterial disease in humans in the United States, and consumption of poultry has been shown to be an important risk factor for *Campylobacter* infection. Fluoroquinolones and macrolides are the drug classes of choice for treating *Campylobacter* infections. Following the approval of fluoroquinolones for use in poultry, resistance to this class of drugs among human *Campylobacter* isolates rose sharply, to more than 20%.[15] FDA has since withdrawn approval of fluoroquinolones for use in poultry, and NARMS continues to monitor *Campylobacter* from humans, retail meats and food animals for fluoroquinolone resistance.

Persistence of fluoroquinolone-resistant *Campylobacter* in domestic food animal and retail meat sources suggests that these strains may be able to compete well with susceptible strains in food animal environments, even in the absence of antimicrobial selective pressure.[16] Additional studies are underway to better understand the contribution of foreign travel to fluoroquinolone-resistant campylobacteriosis and estimate the burden of illness associated with domestically-acquired infections.

The Danish Experience

Multiple studies about the Danish experience have demonstrated the link between non-therapeutic use of antimicrobial agents in food-producing animals, particularly swine and broiler

[15] Multiple NARMS related publications available at http://www.cdc.gov/search.do?subset=enterics&q=pathogencampylobacter&filter=p

[16] Zhang Q, Lin J, Pereira S. (2003) Fluoroquinolone-resistant *Campylobacter* in animal reservoirs: dynamics of development, resistance mechanisms and ecological fitness. *Anim Health Res Rev* **4:**63–71

chickens, and antimicrobial resistance found in animals and humans.[17,18,19,20,21,22] Non-therapeutic uses include promoting growth and improving feed efficiency; drugs for these purposes are typically given in animal feed.

In 1995, the Danish government banned the non-therapeutic use of avoparcin for growth promotion in Denmark; the European Union (EU) adopted the same ban in 1997. In 1998, Denmark banned use of virginiamycin for growth promotion. Subsequently, the Danish cattle and broiler industries voluntarily stopped the non-therapeutic use of all antibiotics for growth promotion in 1998, while 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. The EU phased in bans for certain drugs in 1999, and then voted to phase out all non-therapeutic use of antibiotics for growth promotion in 2002, which began 2006.

Since the stoppage of non-therapeutic use in Denmark, therapeutic use in swine has increased. However, total antimicrobial consumption in swine has decreased from 100 to 49 milligrams of antimicrobials per kilogram of meat produced, a 50% reduction. In addition, stopping the use of various non-therapeutic antibiotic growth promoters (e.g., avilamycin, avoparcin, spiramycin,

[17] 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.
[18] 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.
[19] 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.
[20] 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.
[21] 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
[22] 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.

tylosin, virginiamycin) has resulted in a major reduction in antimicrobial resistance as measured among several different bacterial species in food animals and food. Furthermore, resistance to these drugs among *Enterococcus* isolated from broilers, swine, and the meat from these animals decreased. 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.[23] However, more recent susceptibility data from enterococci isolated from healthy persons in the community show a decline in resistance of enterococci isolated from healthy people in the community in Denmark following the ban on antimicrobial growth promoters. [24]

Production and economic impacts from the ban are described in a 2003 WHO report. Mortality among weaning age pigs 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. In addition, 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 and no net cost for poultry. This translates into an increase in pig production costs of just over 1%."[25]

In summary, non-therapeutic use has been shown to lead to an increase in resistant strains in animals in Denmark. The Danish experience demonstrates that it is possible to stop these uses, reduce overall use of antibiotics in animals, reduce resistant circulating bacteria that can

[23] 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.
[24] Annual reports of the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) available at www.danmap.org
[25] 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.

infect humans, and not have industry or consumers significantly affected by decreased production or increased costs.

Conclusion

Antibiotics are a critical asset in our nation's defense against infectious disease, and we need to take strong measures to ensure that we maintain their effectiveness. Since antimicrobial agents were first used widely in the last century, almost every type of clinically relevant bacteria has developed antibiotic resistance. This Subcommittee, and my colleagues at HHS, have rightly focused on elements of a comprehensive strategy –avoiding resistance that stems from over-use in both humans and animals, and developing new antibiotics. CDC continues to take steps to minimize inappropriate use of antibiotics in humans, and today's hearing is an important opportunity to highlight the need for parallel steps to minimize inappropriate antibiotic use in animals.

As a nation, we must do more to respond to this growing problem. CDC supports FDA's approach, as described in recent guidance, that the use of antimicrobials should be limited to protecting human and animal health. Purposes other than the protection of animal or human health should not be considered judicious use.

Thank you again for the invitation to testify before you today. I will be happy to answer any questions you may have.