



The Center for a Livable Future

June 29, 2010

The Honorable Thomas R. Frieden, MD, MPH
Director, Centers for Disease Control and Prevention
1600 Clifton Rd, MS D-14
Atlanta, GA 30333

The Honorable Anthony S. Fauci, MD
Director, National Institute of Allergy and Infectious Diseases
Building 31—Claude D. Pepper Bldg, 7A03
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Bethesda, MD 20892

Dear Drs. Frieden and Fauci,

We reviewed with great interest your testimony and Q&A session before the House Energy and Commerce Subcommittee on Health on Wednesday, April 28th, 2010. What we've found in our review of the transcript underscores the need for the public health community to ensure that findings of our research are effectively and accurately communicated with those responsible for legislative and regulatory policy. To this end, we would like to share with you several key resources that address some of the concerns and help answer questions put forth by members of the House regarding the contribution of antibiotic use in the production of food animals. The attached document directly addresses a number of the queries from members of the House using referenced material from relevant peer-reviewed literature.

In addition, we wish to extend an offer to serve as a technical resource and provide assistance to you and your staff as you grapple with the issue of antibiotic resistance. The Johns Hopkins Center for a Livable Future is an academic center at the Johns Hopkins Bloomberg School of Public Health whose mission focuses on the complex interrelationships among food production, environment, diet and human health. We have funded and participated in an array of primary research projects aimed at investigating antimicrobial resistance as it relates to food animal production. We would be happy to answer any questions, prepare materials, or brief you or your staff on the latest scientific evidence related to the contribution of food animal production to the antibiotic resistance problem.

Sincerely,

Keeve Nachman, PhD, MHS
Program Director, Farming for the Future
Johns Hopkins Center for a Livable Future

Robert Lawrence, MD
Director
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Attachment

The Danish ban on non-therapeutic use of antimicrobials. Rep. Shimkus' line of questioning of Dr. Frieden regarding the Danish experience with banning antibiotics in animal agriculture included a number of mischaracterizations regarding post-ban trends in infections in humans and antibiotic use in animals. In a recent letter to House Speaker Nancy Pelosi (Aarestrup 2009), Dr. Frank Aarestrup of the Danish Technical University noted that total antimicrobial consumption fluctuated between 1992 and 2008, but ultimately declined by 51% during this period. In the same letter, Aarestrup notes, "major reductions in resistance among animal pathogens, indicator bacteria, and zoonotic bacteria", suggesting a decreased potential for resistant bacteria to be available for contact with humans, and a reduced likelihood of development of antibiotic-resistant infections.

The FDA withdrawal of approval for use of fluoroquinolones in poultry production. The transcript of the hearing includes a line of questioning from Rep. Dingell regarding the impact of the FDA decision to withdraw its approval for use of fluoroquinolones as growth promoters in poultry. Efforts to characterize the public health benefit of this ban face similar challenges encountered by other preventive and preparedness interventions – namely, how does one characterize the magnitude of the problem that society would face in the absence of the intervention? Nelson et al. (Nelson, Chiller et al. 2007) notes that the trend of fluoroquinolone resistance among isolates of *Campylobacter* from humans fits temporally with the introduction of two fluoroquinolones (sarafloxacin and enrofloxacin) in 1995-6 for use in animal production. Prior to the introduction of the drugs, a CDC report noted that no human isolates of *Campylobacter* were found to be resistant; after approval for their use, using data from the National Antimicrobial Resistance Monitoring System (NARMS), CDC determined that resistance to ciprofloxacin in human isolates rose rapidly, to 15% in 2000, 22% in 2005 (at the time of the ban) and to 26% in 2007 (Centers for Disease Control and Prevention 2009). Existing evidence, both from the CDC and from the research community, has shown that even with the ban, fluoroquinolone resistance persists. Without the ban, however, it may be reasonable to suspect that the fraction of isolates expected to be resistant could be far higher. This has been observed in Spain, where quinolone resistance rates in human isolates of *C. jejuni* skyrocketed from 4% in 1989, prior to the licensing of quinolones for use in livestock and poultry in 1990, to 88% in 1994 (Smith, Bender et al. 2000). Rates of quinolone resistance in *Campylobacter* isolates from poultry products in the late 1990s have been shown to approach 100% (Saenz, Zarazaga et al. 2000).

Five years after the ban of fluoroquinolones from animal production, it may still be too early to demonstrate a reversal in the trend of resistance in isolates from humans and from retail meats. Further, it seems likely that even in the absence of antibiotic selection pressure, resistant strains may persist. A study published by researchers at the Ohio and Iowa State Universities demonstrated that in fluoroquinolone-resistant *Campylobacter jejuni*, the C257T point mutation in *gyrA* that confers resistance results in enhanced fitness of the resistant strain – such lack of a fitness cost enables the resistant strain to remain competitive with fluoroquinolone-susceptible *Campylobacter jejuni* in the absence of selective pressure imposed by fluoroquinolone antibiotics (Luo, Pereira et al. 2005). Given the lack of a fitness cost imposed upon resistant *Campylobacter*, it has been hypothesized that elimination of antibiotic pressure may not be sufficient to facilitate a detectable decrease in the prevalence of resistance among isolates, at least in the short term (Zhang, Sahin et al. 2006). It has also been suggested that other factors, such as inadequate frequency and rigor in decontamination of poultry production facilities (Price, Lackey et al. 2007), and the potential for wild birds to serve as a reservoir for resistant bacteria (Chuma, Hashimoto et al. 2000), may contribute to the sustained persistence of fluoroquinolone resistance within the microbial community. Given this, it may be difficult to demonstrate a near-term benefit of the ban, but the long-term gain from eliminating the selective pressure for resistant strains is likely to be enjoyed by future generations.

Characterizing risks, and determination of responsibility for the public health burden of antimicrobial resistance. Rep. Dingell also inquired into which federal agency is responsible for characterizing risks from antibiotic use in animal feed, and which entity is responsible for protecting the American public from infections that no longer respond to antibiotic therapy. It is important to recognize that while the threat posed by feed-based antibiotic use in food animals originates from the drug usage approvals conferred by the Center for Veterinary Medicine at the Food and Drug Administration (FDA), the sequelae of these drug approvals fall within the mandate of numerous federal agencies beyond the FDA, including the Environmental Protection Agency, United States Department of Agriculture, the Centers for Disease Control and Prevention, the Occupational Safety and Health Administration, and numerous other federal entities. While steps towards a concerted effort to address the problem of antibiotic resistance as a whole have been made in the form of the Interagency Task Force on Antimicrobial Resistance, very little of this effort has been devoted to characterizing and addressing risks from antibiotic use in animal production.

The research community has extensively characterized how use of antibiotics in food animal production contributes to the emergence of multidrug resistant bacteria, and public health researchers have demonstrated the capacity for transport of these microbes from the animal production sites (animal houses and processing plants) to environmental media (air, water and soil) and foods with which humans have contact. Non-traditional vectors, such as flies and animal transport trucks, have also been demonstrated to serve as vectors for spreading resistant bacteria.

The search for the smoking gun. Characterization of the burden of resistant infections in humans originating from antibiotic use in food animal production is challenging. While epidemiologic studies evaluating associations between use of antibiotics in food animal production and antibiotic-resistant infections in humans are underway, these studies are largely reliant on surrogate measures of exposure, such as proximity to food animal production sites. These studies will undoubtedly provide results that are informative for public health decision-making, though their utility would be enhanced by evaluations of genetic similarities between microbes responsible for infections in the community and those found on food animals in production facilities. Private ownership of food animal production facilities precludes academic researchers from sampling that would allow for these comparisons. Development of reference databases for pathogens present at food animal production sites would allow for microbial source tracking for pathogens isolated in humans and on food. A rigorously designed, federally-managed program to collect microbial isolates from food production animals could provide the research community with the ability to characterize the contribution of food animal production to the national burden of antibiotic resistance.

References

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