TESTIMONY OF LANCE B. PRICE, Ph.D.

Professor, Department of Environmental and Occupational Health,
Milken Institute of Public Health, The George Washington University
lprice@email.gwu.edu, (443) 527-8750 mobile
PCAST Meeting, April 4, 2014

Good morning, members of the President's Council of Advisors on Science and Technology. My name is Lance Price and I am a professor of environmental and occupational health at George Washington University. Thank you for the opportunity to give testimony regarding the scientific evidence linking the overuse of antibiotics in animal agriculture to antibiotic resistance.

Antibiotic resistance, as you know, is a public health crisis of growing concern, perhaps one of the greatest health crises facing humanity. I would like to thank PCAST for taking a closer look and for issuing a report soon with recommendations for action.

In my post at George Washington University, I study the connections between antibiotic use in food animals and antibiotic-resistant infections in people. I also direct a lab at the Translational Genomics Research Institute in Arizona, where we use state-of-the-art technology to fingerprint the DNA of foodborne bacteria and, with the precision of whole genome sequencing, have revealed compelling evidence linking drug-resistant human infections with livestock production.

Several of my colleagues from research institutions across the globe have joined me in writing a letter to PCAST to underscore how clear the science is. In this letter, we cite landmark studies going back as far as 1969, and continuing over the last few decades that link agricultural use of antibiotics to the development and spread of drug resistance, and ultimately to human infection and death. Dr. Stuart Levy's early work in the 1970s observed in real-time that feeding farm animals antibiotics generated antibiotic-resistant bacteria that spread to farm workers in a matter of weeks. I have additional copies of the letter with me today and respectfully request that it be added to today's meeting record.

The CDC has estimated very conservatively that more than 2 million Americans are sickened every year by antibiotic-resistant infections, and at least 23,000 die. Many of these infections are foodborne. There are 310,000 drug-resistant *Campylobacter* infections each year, and 120 deaths. There are also 100,000 drug-resistant *Salmonella* infections resulting in $365 million in medical costs each year.

For some time, the literature has linked illness and death caused by drug resistant foodborne pathogens—like *Salmonella*, *Campylobacter*, and *E. coli*—to food animal use of antibiotics. The federal government samples meat and poultry every year for the presence of drug-resistant pathogens, through the National Antimicrobial Resistance Monitoring System (NARMS). The NARMS reports tell us that half of the ground turkey products on our grocery store shelves are

contaminated with multidrug-resistant *E. coli*, including strains resistant to some of our most important antibiotics, such as cephalosporins. The 2010 NARMS report revealed a strain of *Salmonella* resistant to all antibiotics tested.

In my work, I have been fortunate to take part in new discoveries deepening our understanding of the health risk posed by frequent antibiotic use in farming. For example:

- One study matched strains of antibiotic-resistant *E. coli* from grocery store samples of meat and poultry to drug-resistant urinary tract infections in local hospital patients in Flagstaff, Arizona. This study suggests that a substantial portion of urinary tract infections may be derived from foodborne *E. coli* and broaden the potential negative health consequences of using antibiotics in food-animal production beyond the classic foodborne pathogens.

- Other research provides compelling evidence that a new lineage of livestock-associated methicillin-resistant *Staphylococcus aureus* (MRSA) actually began as methicillin-susceptible (or treatable) *Staph* in people; jumped to pigs, where it acquired the methicillin resistance gene; and then began infecting humans as MRSA. This study highlights the bidirectional exchange of *Staph* between livestock and humans and, again, underscores the potential unforeseen risks of antibiotic use in food-animal production.

The U.S. Food and Drug Administration provides a useful discussion and endorsement of key studies and reports as the basis for its recommendation that antibiotics be used judiciously in food animals.

With Guidance for Industry #213, the FDA is taking steps to eliminate the most egregious uses of antibiotics in food-animal production—use for growth promotion and feed efficiency, which are purely economic uses. This is long overdue. The agency is also rightfully seeking to make all other uses in feed and water prescription-only, so that producers can no longer purchase vital antibiotics over the counter. These steps are only voluntary and rely on drug company participation to make the desired drug label changes. Fortunately, nearly all drug companies have announced they will comply.

Even so, the public health community has doubts regarding the adequacy of FDA's actions. Will veterinarians have meaningful oversight of antibiotic use, or will they phone in prescriptions from out of state without ever seeing a farm? Will producers be able to easily acquire prescriptions so that they can continue using antibiotics as cheap production tools to "prevent disease" in crowded and unhygienic farming environments? In other words, will overall antibiotic use remain the same, and fail to decrease the risk to public health?

Guidance #213 provides some criteria to distinguish between appropriate and inappropriate antibiotic uses for disease prevention, suggesting that feeding these drugs to animals for an indefinite period without an identified disease is injudicious. Yet while the Guidance urges drug

companies to remove "growth promotion" indications from their products' labels, it does not instruct them to change "disease prevention" indications so that they are in line with its criteria.

FDA has acknowledged these are first steps, and I hope they will lead to additional policy changes. However, bacteria continue to develop resistance at an alarming pace, paying no heed to the politics and protocols of the rulemaking process. The public cannot wait much longer for a solution that is comprehensive and bold enough to effectively fight this growing epidemic.

I urge PCAST to make strong recommendations to the President that include meaningful next steps to reduce antibiotic overuse in the agricultural sector. Phasing out growth promotion is a good start, but much more is needed to save human lives.

The FDA should immediately begin working with drug companies to modify antibiotic product approvals to narrow the allowable uses for disease prevention, based on criteria outlined in FDA's own guidance. Antibiotic use for disease prevention should be targeted to specific, identified bacterial diseases, used in as few animals and for as short a duration as possible, and sufficient in dosage to kill bacteria. More importantly, a veterinarian should work with animal producers to enact other measures to protect animal health, resorting to antibiotics as a last resort solution to production problems.

If drug companies balk, the agency should respond with formal regulatory action.

On a parallel track, the agency should maintain the existing statutory standard ensuring real veterinary oversight of antibiotic use in feed—the veterinarian-client-patient relationship. The agency has proposed eliminating this standard, which jeopardizes the success of the entire voluntary policy in reducing overuse. After all, the agency cannot pretend it is adding police enforcement if it is simultaneously allowing cops to walk off the beat.

Finally, the agency should also complete its rulemaking process to collect more and better antibiotic sales and use data as quickly as possible. We must know the extent to which these drugs are being used in each major food animal species, for which purpose, by which means, and under what level of veterinary care. This information is not necessary to justify FDA action, but it can be used to track the success of its policies and strengthen them as needed.

As a public health researcher and microbiologist, I implore PCAST to consider the mounting scientific evidence and recommend policy actions that more dramatically reduce antibiotic use in industrial food-animal production. As my colleagues and I say in our letter to the Council, "More research can always improve our understanding of microbiology and epidemiology, and enhance clinical care, but we know enough to act boldly and swiftly to eliminate the nontherapeutic use of antibiotics on industrial farms."

Thank you for your time. I am happy to speak with PCAST further if I can be of assistance.

March 18, 2014

John P. Holdren, Ph.D.
Eisenhower Executive Office Building
1650 Pennsylvania Avenue, NW
Washington, DC 20504

Dear Dr. Holdren:

We are writing to respectfully ask the White House Office of Science and Technology Policy (OSTP) and the President's Council of Advisors on Science and Technology (PCAST) to heed the body of scientific evidence showing that antibiotic overuse in food animal production contributes to antibiotic-resistant infections in people. We also call on you to explore actions that the U.S. Administration can take, including in collaboration with other nations, to swiftly curtail the problem.

Beginning with the United Kingdom's 1969 Swann Report[1], hundreds of studies over the last few decades have drawn links between agricultural use of antibiotics, the development and spread of drug resistance, and resulting human infection. Several U.S. and international governmental reports summarize the literature. In fact, the U.S. Food and Drug Administration provides a useful discussion and endorsement of these studies and reports in Guidance for Industry #209[2] as the basis for its recommendation that antibiotics be used judiciously in food animals. It is difficult to single out any study from the literature as more significant than another, but in our view, several are worth highlighting.

In Sept. 1976, Dr. Stuart Levy reported a seminal study[3]—the first "smoking gun"— that showed resistance to tetracycline in chickens emerging within 36 to 48 hours of administering the drug in feed. With time, chickens began to excrete bacteria resistant to not only tetracyclines, but also unrelated antibiotics, a phenomenon which has been reported to occur in people only on long term antibiotic use. Within five to six months, the people who lived on those farms had a large increase in tetracycline-resistant bacteria. In summary, the chronic use of a single antibiotic will produce an environment of multidrug resistance.

In Feb. 2012, Dr. Lance Price published another "smoking gun" study[4] that used whole genome sequencing to trace the origins of a new strain of livestock-associated MRSA, called ST398. Dr. Price's study provided compelling evidence that ST398 originated in humans as methicillin susceptible *Staph* (MSSA), then jumped into pigs, where it became methicillin resistant and subsequently began infecting humans with direct exposure to livestock. The antibiotic-resistant strain has since spread more widely in the community, causing illnesses and even deaths in

Northern Europe. An Aug. 2013 study[5] used similar genomic sequencing techniques to reinforce these findings and document transmission of MRSA from cows to humans.

Scientific research also demonstrates that resistant bacteria spread from livestock to people via food. A December 2011 study[6] coauthored by Dr. Peter Collignon found that "resistance in *E. coli* isolates from food animals (especially poultry and pigs) was highly correlated with resistance in isolates from humans. This supports the hypothesis that a large proportion of resistant *E. coli* isolates causing blood stream infections in people may be derived from food sources."

Dr. James Johnson published a June 2007 study[7] conducted in Wisconsin and Minnesota, which found that antibiotic-resistant *E. coli* in people was likely to have come from poultry. Additional U.S. studies published in October 2001[8] and September 2008[9] concluded that the data suggest that drug-resistant *E. coli* strains in the human urinary tract may have an animal origin. In response to a suggestion by the National Academy of Sciences, a study[10] conducted in 1984 by the U.S. Public Health Service, FDA, and Seattle-King County found that tetracycline-resistant *Campylobacter* appeared "to flow from chickens to man via consumption of poultry products."

Encouragingly, a landmark January 2010 study[11] indicated that meat and poultry producers could reverse emerging resistance by curbing antibiotic overuse. After a change in policy, poultry farmers in Quebec stopped routinely injecting cephalosporins into eggs before they hatched. This change in drug use was followed by an immediate and dramatic decrease in cephalosporin-resistant *Salmonella* and *E. coli* in chicken, with a similar decrease in drug-resistant *Salmonella* infections in people.

The FDA's data from the National Antimicrobial Resistance Monitoring System[12] has also measured declines in nalidixic acid-resistant *E. coli* and *Enterococcus* since peaking in 2005, the year that the FDA withdrew approval[13] for use of fluoroquinolones in poultry production. Nalidixic acid is considered the prototypical quinolone and tests using nalidixic acid are reliable and valid for determining quinolone resistance.[14]

Permanent bans on nontherapeutic antibiotic use in the Danish and Dutch livestock industry also demonstrate that resistance can be reversed. Following the bans in both countries, antibiotic use dropped 50 percent in each, and resistant bacteria became less prevalent in animals and on meat. In Denmark, where a ban was instituted nearly 15 years ago, officials have also observed a resulting decrease in resistant infections among people. Plus, production costs and consumer prices remained stable, while output actually increased. Antibiotic use restrictions in the Netherlands began in 2012 and are still underway, though it is expected that the early decrease in drug resistant bacteria on the farm and in meat will result in human health benefits.[15]

More research can always improve our understanding of microbiology and epidemiology, and enhance clinical care, but we know enough to act boldly and swiftly to eliminate the nontherapeutic use of antibiotics on industrial farms. An October 2011 review[16] by Dr. Levy and Bonnie Marshall summarized the science thoroughly and concluded:

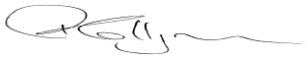
> "Data gaps continue to fuel the debate over the use of NTAs [nontherapeutic antibiotics] in food animals, particularly regarding the contribution and quantification of commensal reservoirs of resistance to resistance in human disease. Nonetheless, it has been argued reasonably that such deficits in surveillance or indisputable demonstrations of animal-human linkage should not hinder the implementation of a ban on the use of nontherapeutic antibiotics. … The current science provides overwhelming evidence that antibiotic use is a powerful selector of resistance that can appear not only at the point of origin but also nearly everywhere else. … Continued nontherapeutic use of antimicrobials in food animals will increase the pool of resistance genes, as well as their density, as bacteria migrate into the environment at large."

We do need to know more about how antibiotics are being used by meat and poultry producers in order to target solutions to antibiotic resistance. We have gross sales data from the FDA, but we do not have the level of detail needed to determine use by species, production stages, indications, or even how often they are used without any veterinary oversight. The agency has issued an advance notice of proposed rulemaking to improve its antibiotic data collection and reporting. We would encourage the administration to pursue this process aggressively.

In addition, while scientific evidence has clearly linked antibiotic overuse in livestock with drug-resistant *E. coli*, *Salmonella*, *Staphylococcus*, and *Campylobacter* infections in people, more research is needed to determine the extent to which agricultural practices are driving the evolution of other resistant bacteria. Recent research, for example, is revealing that a significant proportion of urinary tract infections may be foodborne associated. Similarly, research is needed to identify the extent to which other microbial threats, such as the evolution and transmission of antibiotic-resistant *Klebsiella pneumonia*, may be related to food production. Further, research is suggesting that the transmission of resistance genes between bacteria may compound the human health impact of any drug resistance created on the farm.

Enclosed with this letter please find copies of the studies, filings, and statements referenced in this letter as well as a more comprehensive list and description of other relevant studies. We urge you to advise the President on a swift and comprehensive course of action to address the overuse of antibiotics in animal agriculture, as it poses a serious threat to human health.

Sincerely,



Peter Collignon, M.D.
Director of the Infectious Diseases Unit and Microbiology
Canberra Hospital
Professor
Medical School of the Australian National University

James Johnson, M.D.
Professor of Medicine
Senior Associate Director, Infectious Diseases Fellowship Program and the VA Molecular Epidemiology Unit
University of Minnesota

Jan Kluytmans, M.D., PhD
Professor of Medical Microbiology and Infection Control
VU University Medical Center Amsterdam

Stuart Levy, M.D.
Professor, Molecular Biology & Microbiology and of Medicine
Director of the Center for Adaptation Genetics & Drug Resistance
Tufts University School of Medicine

Lance Price, Ph.D.
Professor, Department of Environmental and Occupational Health
George Washington University

Jørgen Schlundt, D.V.M, Ph.D
Director
National Food Institute, Technical University of Denmark

Cc: Members of PCAST
Michael Stebbins, Ph.D., Assistant Director for Biotechnology, OSTP

---

[1] M.M. Swann, K.L. Baxter, H.I. Field, et al, "Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine," HMSO, 1969.
[2] U.S. Food and Drug Administration, "Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals," Apr 2012, http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216936.pdf.
[3] S.B. Levy, G.B. Fitzgerald, and A.B. Macone, "Changes in intestinal flora of farm personnel after introduction of a tetracycline-supplemented feed on a farm," New England Journal of Medicine, Sep 1976, 295(11): 583-88 http://www.ncbi.nlm.nih.gov/pubmed/950974.
[4] L.B. Price, M. Stegger, H. Hasman, et al, "Staphylococcus aureus CC398: Host Adaptation and Emergence of Methicillin Resistance in Livestock," mBio. 3(1), 2012, http://mbio.asm.org/content/3/1/e00305-11.
[5] L.E. Spoor, P.R. McAdam, L. A. Weinert, et al, "Livestock Origin for a Human Pandemic Clone of Community-Associated Methicillin-Resistant Staphylococcus aureus," mBio, vol 4 no 4, Aug 2013, http://mbio.asm.org/content/4/4/e00356-13.
[6] A.R. Vieria, P. Collignon, F.M. Aarestrup, et al, "Association between antimicrobial resistance in Escherichia coli isolates from food animals and blood stream isolates from humans in Europe: An ecological study," Foodborne Pathogens and Disease. Dec 2011, http://www.ncbi.nlm.nih.gov/pubmed/21883007.
[7] J.R. Johnson, M.R. Sannes, Cynthia Croy, et al, "Antimicrobial Drug–Resistant Escherichia coli from Humans and Poultry Products, Minnesota and Wisconsin, 2002–2004," Emerging Infectious Diseases, June 2007, http://wwwnc.cdc.gov/eid/article/13/6/06-1576.htm.
[8] A.R. Manges, J.R. Johnson, B. Foxman, et al, "Widespread distribution of urinary tract infections caused by a multidrug-resistant Escherichia coli clonal group," New England Journal of Medicine, 2001. 345(14): 1007-1013, http://www.nejm.org/doi/pdf/10.1056/NEJMoa011265.
[9] T.J. Johnson, Y. Wannemuehler, S.J. Johnson, et al, "Comparison of Extraintestinal Pathogenic Escherichia coli Strains from Human and Avian Sources Reveals a Mixed Subset Representing Potential Zoonotic Pathogens," Applied and Environmental Microbiology, Sep 2008, vol 74 no. 22 7043-7050, http://aem.asm.org/content/74/22/7043.
[10] U.S. Bureau of Veterinary Medicine, U.S. Public Health Service, Seattle-King County Dept. of Public Health, et al, "Surveillance of the Flow of Salmonella and Campylobacter in a Community," Seattle-King County Department of Public Health, 1984, http://books.google.com/books/about/Surveillance_of_the_Flow_of_Salmonella_a.html?id=SmapNAAACAAJ.
[11] L. Dutil, R. Irwin, R. Finley, et al, "Ceftiofur Resistance in Salmonella enterica Serovar Heidelberg from Chicken Meat and Humans, Canada," Emerging Infectious Diseases, 2010 Jan, http://wwwnc.cdc.gov/eid/article/16/1/09-0729_article.htm.
[12] U.S. Food and Drug Administration, "2011 Retail Meat Report: National Antimicrobial Resistance Monitoring Report," http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM334834.pdf.
[13] U.S. Food and Drug Administration, "FDA Announces Final Decision About Veterinary Medicine," News and Events Archive, Jul 2005, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108467.htm.
[14] See: T Butt, Khan MY, et al, "Validity of nalidixic acid screening in fluoroquinolone-resistant typhoid salmonellae," J Coll Physicians Surg Pak. 2006 Jan;16(1):31-4.
[15] For Denmark, see: F.M. Aarestrup et al, "Changes in the use of antimicrobials and the effects on productivity of swine farms in Denmark," AVJR 71(7): 726-733. For the Netherlands: see, Nethmap/MARAN Report 2013, available at: http://www.wageningenur.nl/nl/Expertises-Dienstverlening/Onderzoeksinstituten/central-veterinary-institute/Publicaties-CVI/MARAN-Rapporten.htm.
[16] B.M. Marshall and S.B. Levy, "Food Animals and Antimicrobials: Impacts on Human Health," Clinical Microbiology Reviews, Oct 2011, vol. 24 no. 4 718-733, http://cmr.asm.org/content/24/4/718.abstract.