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TESTIMONY OF DR. STUART B. LEVY

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Distinguished Professor of Molecular Biology & Microbiology and of Medicine
Tufts University School of Medicine
Before the Subcommittee on Health of the
U.S. House Committee on Energy and Commerce
July 14, 2010

Mr. Chairman, I want to express my appreciation to the House Energy and Commerce Committee for convening today's hearing, for its ongoing work to help stem the crisis of antibiotic resistant bacteria and for inviting me to share my thoughts on these issues.

By way of background, my name is Dr. Stuart B Levy and I am Distinguished Professor of Molecular Biology and Microbiology and of Medicine, as well as the Director of the Center for Adaptation Genetics and Drug Resistance at Tufts University School of Medicine and Staff Physician at Tufts Medical Center. I also serve as President of the Alliance for the Prudent Use of Antibiotics (APUA), an international organization with members in over 100 countries and am Chief Scientific Officer of Paratek Pharmaceuticals. I am a Fellow of the American College of Physicians, Infectious Disease Society of America, the American Academy of Microbiology, and the American Association for the Advancement of Science. I am a past President of the 40,000-member American Society for Microbiology.

For more than three decades, I have been studying and following the issue of antibiotic use in animal husbandry and its effect on bacteria associated with the animals, on the farm workers and families, and the environment in general. Throughout my career, I have been happy to appear before Congressional panels like this one to share my views on the science and solutions surrounding these issues. I vividly recall testifying in December 1984 before the House Subcommittee on Investigation and Oversight of the Committee on Science and Technology on antibacterial resistance and the data showing spread of resistant bacteria among animals and among animals and people.

In that testimony and throughout my career, I have noted the paradoxical nature of human engagement with antibiotics (1). On the one hand, these miraculous drugs are pillars of modern medicine, helping us to manage and prevent dangerous bacterial infections and save lives. On the other hand, the widespread use – and misuse – of antibiotic drugs has spawned the evolution of life-threatening bacteria that render our current antibiotics useless.

In 1975-76, my research group performed the first, and I believe only, prospective study of the effect of introducing antibiotic-laced feed on a farm (2). We established a family farm about 40 miles West of Boston. We introduced chickens, hatching from eggs laid from pathogen-free hens, and separated them into two groups of 150 chickens each. One group received low dose antibiotic-laced feed (oxytetracycline (100g/909kg)), and one did not. The findings were striking. Within 24-48 hours, the chickens given the oxytetracycline-laced feed began to excrete tetracycline-resistant *E. coli*, a common bacterium in the feces of chickens, people and other mammals. The control group did not. By one week, almost all *E. coli* in the intestinal tracts of the antibiotic-treated chickens were tetracycline-resistant. As time continued on this single low-dose antibiotic, the bacteria in the feces of the chickens began to acquire more and more resistances. By 3 months, the chickens were excreting *E. coli* resistant not only to tetracycline, but also to sulfonamides, ampicillin, streptomycin and carbenacillin.

Most striking was that the farm family, as compared to the control group of neighborhood farm dwellers – none using antibiotics – also showed an increasing number of fecal *E. coli* resistant to multiple antibiotics.This study demonstrated the ecologic and environmental impact of an antibiotic, in this case low-dose antibiotics, on the animals housed in the farm and on the farm dwellers themselves. It answered one principal question at that time: that low-dose nontheraputic amounts of antibiotics can, in fact, select for, and help propagate, bacteria resistant to the drug at high levels. The study also resulted in other important findings. There were increased numbers of multidrug resistant bacteria among people on the farm, even though they were not taking antibiotics. Of note, transfer of *E. coli* from the chickens to the farm workers was also observed (3). In subsequent studies, we haved demonstrated that even in the absence of an antibiotic, resistant bacteria will move from animal to animal, in this case from bull to calf, to pigs to chickens, presumably through the air (4). Additionally, we demonstrated the presence of resistant bacteria on flies. In the study, it was clear that farm workers could pick up the biochemically-marked *E. coli* that was initially put into the bull, where it remained in their intestinal tracts at a detectible level for several weeks. Thus, there is no containment of antibiotic or antibiotic resistant bacteria in the farm environment.

As you can see, Mr. Chairman, much of my personal energy and professional endeavors have been given to better understanding the causes of antibiotic resistance and advancing solutions to this growing threat to human health. Drawing on that experience, I regret to report to this Committee that we are not gaining ground in the struggle against antibiotic resistance and all of us – you, me and your constituents – are at ever greater risk of contracting a resistant bacterial infection and even one that is untreatable.

- Antibiotics continue to be misused and overused on a massive scale in both human medicine and animal agriculture; and

- There is a dearth of activity in large pharmaceutical firms to develop new drugs that can best antibiotic resistant bacteria. Fortunately, the void has been filled by work performed in small biopharmaceutical companies like the one I co-founded, Paratek Pharmaceuticals.

Some progress has been made in developing protocols and encouraging more judicious use of antibiotics in human medicine. There is awareness of the crisis and our public health agencies have developed protocols for promoting proper use of antibiotics by doctors and patients alike.
But there has been precious little progress with regard to stemming the spigot of antibiotics flowing into animal agriculture. Indeed, the Food and Drug Administration has attempted on several occasions to initiate prudent steps for curtailing the misuse of antibiotics in industrial agriculture, only to be thwarted by powerful industry interests, which have questioned the science and mobilized

Congressional allies at every step of the way. These efforts have been undertaken despite a mountain of domestic and international scientific evidence demonstrating the linkages between the use of antibiotics in animal agriculture and the emergence of bacteria resistant to antibiotics of critical importance to human health and to the frequency of resistant strains of bacteria in human beings.

There are a number of common concepts in the antibiotic resistance field that we have learned over the years, which I think are relevant when in evaluating the nontheraputic use of antibiotics in animal husbandry (5).

One, antibiotics are "societal drugs." Their use in one individual can affect the level of resistance and the presence of resistant organisms in other individuals sharing the same environment. An excellent demonstration of the concept came from Dr. William Cunliffe's dermatologic group in London, which showed that those sharing the household with patients treated for acne picked up and began to shed *staphylococci* from their skin that were multidrug-resistant, as were the bacteria found on treated patients. This was not true among households where an antibiotic was not used (6).

Secondly, as discussed earlier, antibiotics have an environmental impact. They are ecologic agents – they can change the bacterial environment, largely from drug-susceptible organisms to resistant ones (7). Moreover, these do not have to be therapeutic amounts of antibiotics; nontheraputic low-dose antibiotics have a similar profound ecologic effect. Furthermore, an important finding was that the length of time on the antibiotic (tetracycline) selected bacteria with resistances to more than the tetracyclines. In animals, long term use of the single antibiotic led to multidrug resistant bacteria. This phenomenon has been seen among women taking tetracycline for treating urinary tract infections. In these patients, 1-to-2-week-use led to multidrug resistant *E. coli* in their intestinal tracts (8). This is critical when we begin to discuss the total time of antibacterial treatment of animals whether it is for growth promotion, for disease prophylaxis, or for therapy. The amount of time on the antibiotic can influence the numbers of resistances that appear in the bacteria associated with these animals.

Third, a point that I think is missed often, is that the total amount of antibiotic does not tell us enough about what is happening in that environment. We need to know about the distribution of the antibiotic. For example: You have 100 grams of antibiotic, and you give all of it to one animal. That animal becomes the single producer of resistant bacteria, which it can shed to the environment. On the other hand, if you give those 100 grams to 100 different animals, you now have 100 times more "factories" of resistant bacteria that are being propagated by the selection of the antibiotic. This point, I stress, is critically important in evaluating the data when amounts are only presented in total numbers, in grams, in kilograms. We need to know how many animals are being affected. There is no doubt that with billions of animals being treated with antibiotics in our country, as opposed to millions of people sporadically, that there are many more "factories" of antibiotic resistant organisms among the animals, then the people, and especially in those instances where the therapy is prolonged for weeks and at less-than-therapeutic amounts.

APUA has been following this issue for some time. We have looked at the different routes of transfer of antibiotics and antibiotic resistant bacteria, as shown in the attached figure. At each step of the way, there are data demonstrating the means of transfer of either the antibiotic or the resistant bacteria, or both. Water downstream from farms has been found contaminated with antibiotics leeching through the ground. It is critically important to look at how the drug and the amount of the drug is being given in water or by injections. If it is given in a way that is not contained, there is much more environmental contamination. So if one can focus on the amount of drug, how it's being delivered, and

how it's being distributed – that is, the vehicle and how many individuals (animals, people, plants) are being given the antibiotic, one can appreciate better how to control the unwanted consequences of antibiotic use (9).

Several years ago, APUA put together a stakeholders' group that came up with recommendations for improving antibiotic use in the raising of farm animals. It was concluded that antibiotics for nontheraputic use should be eliminated, since the benefit was unclear and did not merit the practice. On this point it is noteworthy that there are no current studies to show that a growth promotion effect still exists. Other industrialized nations, most notably in Europe, have come to similar conclusions and have taken steps to curtail the use of antibiotics for the purpose of growth promotion and feed efficiency. But the United States lags behind and has done almost nothing to curtail non-therapeutic uses. In view of this history, it was very encouraging that the FDA announced on June 28, 2010 its draft guidance to industry on the use of antimicrobial drugs in food-producing animals. The FDA is to be applauded for stating boldly and accurately that: "Overall, the weight of evidence 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."

The FDA's draft guidance establishes a number of key foundations for the future: first, that there is broad agreement that antibiotics should be deployed under the guidance of veterinarians to treat sick animals; second, that antibiotic use for growth promotion and feed efficiency is not judicious, is contrary to human health and should be stopped; and third, that antibiotics may be used on a prophylactic basis for short-durations with at-risk animal populations under the direction of a veterinarian. These are important building blocks for forging consensus between public health and agriculture interests in the future.

There is less consensus around the use of antibiotics in generalized prevention, where antibiotics are used in the absence of specific animal health risks to guard against infections that might otherwise be prevented with additional sanitation measures and less crowded conditions. There is an absence of studies to show the scientific basis for prophylaxis and the time and dose required. Such studies have improved prophylaxis use in human medicine, most notably in surgery.
The FDA's draft guidance is a welcome step and reflects the kind of foresight and wisdom I've waited years, even decades to hear from this institutional guardian of animal and public welfare. Nonetheless, the FDA's recent action represents only voluntary guidelines that would take many months, perhaps years to finalize. Even if finalized as voluntary guidance to industry, the reality is that agribusiness has fought efforts to curtail overuse of antibiotics every step of the way and there is no basis for confidence that industry will do anything but dodge and challenge the FDA's guidance. Because most antibiotics currently approved for growth promotion are also approved for routine disease prevention, I have great concerns that industry will continue feeding massive quantities of antibiotics non-therapeutically, rendering meaningless the FDA guidance on eliminating antibiotic us as growth agents.

Mr. Chairman and Committee Members, in view of the urgency of the public health threat, the history of regulatory inaction, and the unyielding nature of the relevant industry, it is now clear that even a well-intentioned FDA is unable to overcome the power and influence of agribusiness. We've given moral suasion, medical urgency, scientific study and voluntary guidance its chance and the problem has only grown worse. We can't wait any longer. Congress must act.

I applaud you for convening today's hearing and for developing a Congressional record on the evidence of this significant challenge. But the evidence is clear and compelling and it is time to move from educational hearings to legislative mark-ups.

Legislation pending in this session of Congress, the Preservation of Antibiotics for Medical Treatment Act (PAMTA, H.R. 1549, S. 619), would withdraw the use of seven classes of antibiotics vitally important to human health from food animal production unless animals or herds are sick with disease or unless drug companies can prove that their nontherapeutic use is needed for disease prevention and only at high risk times in their rearing and does not represent the threat to human health. This is a sensible and effective approach toward curtailing the use of antibiotics in industrial farming and I urge this Committee to move expeditiously to consider and approve this important legislation.

Thank you for your consideration of my testimony and I would be happy to answer any questions you may have.

References

1 - Levy, S.B. (2002) *The Antibiotic Paradox: How misuse of antibiotics destroys their curative powers.* Perseus Books, Boston

2 - Levy, S.B., G.B. FitzGerald and A.B. Macone (1976) Changes in intestinal flora of farm personnel after introduction of tetracycline-supplemented feed on a farm. New Eng. J. Med. 295:583-588.

3- Levy, S.B., G.B. FitzGerald, and A.B. Macone (1976) Spread of antibiotic resistance plasmids from chicken to chicken and from chicken to man. Nature 260:40-42.

4 - Marshall, B.M., D. Petrowski and S.B. Levy (1990) Inter and intraspecies spread of *E. coli* in a farm environment in the absence of antibiotic usage. Proc. Nat'l Acad. Sci (USA) 87:6609-6613.

5- Levy, S.B. & B. Marshall (2004) Antibacterial resistance worldwide: Causes, challenges and responses. Nature Med. 10:S122-S129

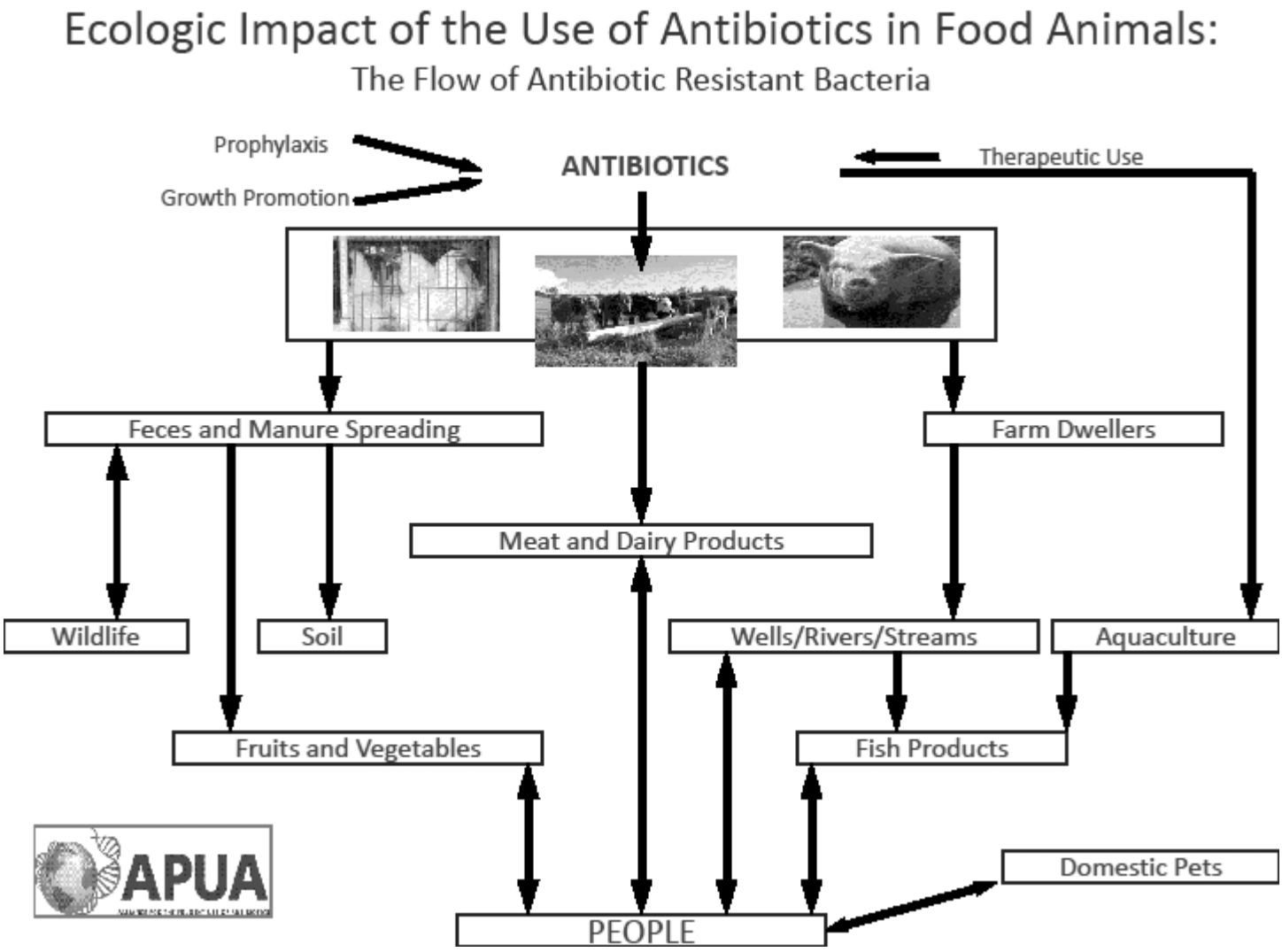
6 - Cunliffe, W.J., Miller, Y.W., et al: (1996) Sequential antibiotic therapy for acne promotes the carriage of resistant staphylococci on the skin of contacts. J. Antimicrob. Chemother. 38:829-837.

7 - Levy, S.B. (1984) Playing antibiotic pool: time to tally the score. New England J. Med. 11:663-665.

8 - Datta N, Faiers MC, Reeves DS, et al: (1971) R factors in Escherichia coli in faeces after oral chemotherapy in general practice. Lancet 1:312-315.

9 - Barza, M., Gorbach, S., (eds.) (2002) The Need to Improve Antimicrobial Use in Agriculture. Report from the Alliance for the Prudent Use of Antibiotics. Clin. Infect. Dis. 34:Sup.3.

Figure:


Ecologic Impact of the Use of Antibiotics in Food Animals:
The Flow of Antibiotic Resistant Bacteria
Prophylaxis
Growth Promotion
ANTIBIOTICS
Therapeutic Use
Feces and Manure Spreading
Farm Dwellers
Meat and Dairy Products
Wildlife
Soil
Wells/Rivers/Streams
Aquaculture
Fruits and Vegetables
Fish Products
APUA
Domestic Pets
PEOPLE