Statement Submitted for the Hearing Record,

"Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture"

House Committee on Energy and Commerce, Subcommittee on Health

July 14, 2010

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Introduction

Much of the improvements during the 20th century in longevity may be attributed to the "miracle drugs," antimicrobials developed in the early 1900s. Combined with improvements in sanitation, housing, nutrition, poverty, and health care, antimicrobials saved lives and relieved fear and suffering of millions of persons. A resurgence of infectious diseases in the 1980s countered the complacency of the 1960s and 70s that we had conquered infectious diseases. (53) History offered a lesson. Coincident with the discovery of antibiotics in the 1930s, researchers sounded notes of caution. In his Nobel Prize acceptance speech in 1945, Alexander Fleming said: "The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." (26)

A year later at the University of Wisconsin, small quantities of antibiotics (AB) were found to stimulate growth of young animals (69); by the early 1950s, the use of animal feeds containing antibiotics to spur growth had become commonplace in advanced countries of the world. (83). This was followed, in the 1950s and early 1960s, by research showing that non-medical use of AB in animal feed caused antimicrobial resistance (AMR) in bacteria in animals and in their human attendants. (62, 84) By February 1, 1972, after extensive review of FDA, NIH, USDA, CDC, universities and industry, the FDA reviewed the hazards to humans of use of antibiotics in "growth promotant and subtherapeutic amounts" and proposed a "statement of policy" placing restrictions on "use of antibacterial agents in animal feeds at growth promotion and sub-therapeutic levels." (23, 54)

Despite these warnings and evidence that AMR in food animals may cause AMR bacterial infections in humans, use of antibiotics for non-therapeutic purposes, such as livestock growth promotion, has proliferated. (15, 23, 28, 31, 32, 37, 47, 53, 59, 68, 73, 74, 80, 91, 94-97) It is estimated that 70% (13 million pounds) of all AB produced each year in the United States are used for such purposes in poultry, swine and beef cattle. Many of these AB are in classes of drugs used in human medicine (penicillins, tetracyclines, and erythromycin). The majority are administered to animals throughout their lives in feed and water to counter increased risks of microbial infections in the stressful and unhygienic environments of industrial animal production operations. (67)

Approximately one million metric tons of antibiotics have been released into biosphere in past 50 yrs (63). All aspects of microbial genetic ecology have changed through mutation and in gene transfer between microbes and other living things. The global emergence over the decades of AMR "superbugs" has suggested to experts that unless definitive action is taken, we may return to the "pre-antibiotic" age of the early 1900s. Gro Brundtland, M.D., MPH, Director-General of WHO said: "Our grandparents lived during an era without effective antibiotics. We don't want the same situation for our grandchildren." (92)

Antimicrobial Resistance (AMR) and Industrial Farm Animals

When food animals receive antibiotics that expose their intestinal microbes to non-lethal concentrations of the drugs, they develop, often within hours, drug-resistant bacteria that are transmitted widely and rapidly in animal waste, ground water, soil, and air, to other farm animals or wild animals and to farm attendants, who, in turn, may transmit antibiotic-resistant organisms to their families and into the community. (2, 13, 33, 41, 78, 82, 91) Slaughter house personnel are often infected. (65, 88) Grocery store meat and produce often harbor antibiotic resistant bacteria. (29, 64, 79) With extensive global travel today and importation of animals, antimicrobial-resistant organisms spread quickly around the world. (14, 30, 77, 81, 94)

Most science and health professional organizations and health-related Federal Agencies in the U.S. believe there is incontrovertible evidence that inappropriate use of AB in agriculture is generating more virulent pathogens and making once effective antimicrobial agents for human use obsolete. (21-23, 29, 39, 42, 54, 56, 68, 73, 74, 92-94, 96)

Antimicrobial resistance from improper use of antimicrobials in humans.

It is estimated that each year 24.6 million lb of antimicrobials are used for nontherapeutic purposes in animals and 2 million lb for treating animal infections. Only 3 million lb are given to humans for treatment of infections. (67) But, inappropriate use of AB in clinical medicine is a well-documented and a major source of AMR infections in patients. (9, 34, 71)

Importantly, there are major public and private sector initiatives to decrease inappropriate AB use. (37, 40) These have been developed and supported by medical societies and organizations and the government and the pharmaceutical industry. Prescribing guidelines for antibiotics are widely available and used by licensed health professionals in clinical medicine but are much less available and used in industrial farming operations, where antibiotics for non-therapeutic use are given in feed or water by farm workers, not licensed veterinarians.

Formulary restrictions, feedback, and medical education programs have improved the prescribing behaviors of physicians. (5, 21, 46, 61)The Centers for Disease Control program: CDC "Get Smart: Know When Antibiotics Work" is widely disseminated to health professionals and the public, and research has shown significant decrease in inappropriate antibiotic prescribing for upper respiratory infections and for otitis media in children. Other programs have shown effectiveness. (6, 10, 24, 61)

Antimicrobial Resistance in the U.S. in 2010

It is the faces of those who suffer and die from AMR infections that best describe the human dimensions of our crisis in 2010—the young and old, the previously well, the pregnant woman or elderly man, the cancer patient or woman undergoing a routine knee replacement, the newborn—all succumbing to the ravages of multi-drug resistant bacterial infection that often kill or maim for life.

I spoke with the medical faculty and staff leadership of Indiana University School of Medicine and Clarian Health in Indianapolis in preparing these comments. All called antimicrobial resistance a crisis of this young 21st century. All said that it threatens lives needlessly, creates enormous budgetary problems for hospitals, and creates doubt about using high tech medical interventions that require availability of effective antimicrobials to treat often inevitable infections associated with cancer therapy or organ transplantation.

In 2002, there were an estimated 1.7 million healthcare-associated infections in U.S. hospitals with 98,987 deaths, a number that exceeded deaths attributable to several leading causes of death in the U.S. (51). In 70% of deaths, the microbe was resistant to one or more antibiotics. (38) The annual direct medical costs of healthcare-associated infections were $28.4 billion to $45 billion. (12)

Over the past thirty years, the number of human infections caused by drug-resistant bacteria has increased markedly. (31, 32) In 2005, there were an estimated 94,360 cases of invasive Methicillin-Resistant Staphylococcus aureus (MRSA) infections in the U.S. with 18,650 (19.8%) deaths, an incidence rate of 31.8/100,000 persons which is much higher than rates for most other invasive pathogens. Two-thirds of these MRSA infections occurred outside of the hospital. (52) Disturbingly, 13.7% of persons without known risk factors for MRSA had community-associated infections. From 1999 to 2005, the estimated number of MRSA related hospitalizations more than doubled and the authors from NIH said MRSA should be considered a national priority for disease control. (50)

Antimicrobial resistance is directly related to food safety. Surprisingly, the U.S. ranks 7th among 17 industrialized nations for food safety. At least 76 million new cases of food-borne disease occur annually in the U.S. with 5,000 deaths and 325,000 hospitalizations. (66) More than 80% of human infections with salmonella and campylobacter are acquired from farm food animals; in the U.S., there are 1.4 million cases of illness due to salmonella and 2.4 million cases of illness due to campylobacter infection. (66, 70) Salmonella and Campylobacter are the most common sources of food-borne illnesses in the U.S., accounting for more than one million resistant infections annually. (11, 86) One-half of human Campylobacter infections are resistant as are one in five Salmonella infections. All ground beef recalled in 2009 for Salmonella was due to a resistant strain. (87) The transfer of resistant salmonella, Campylobacter and Escherischia coli from food animals to humans is common. (21, 22, 97) Enterococcus faecium resistant to quinupristin-dalfopristin, a “last resort” antibiotic for severe drug resistant infections in humans, have been found in 17% of chickens obtained at supermarkets. (64) Recent data suggests Clostridium difficile, a serious problem in hospitals, has potential of foodborne transmission to humans. (45)

A recent estimate of the Alliance for the Prudent Use of Antibiotics and Cook County, IL Hospital in 2009 estimated the cost of these food-borne infections at $17-26 billion annually in the U.S. (3) But, the Produce Safety Project at Georgetown University published a report that estimates the direct and indirect costs of food-borne illnesses at $150 billion a year, more than four times an earlier report by the USDA. (79) The young, frail and elderly and chronically ill persons are particularly vulnerable to such infections.

Today, there is a voluminous body of basic, clinical, applied and epidemiological human, veterinary, and agricultural science that concludes there is clear evidence of adverse human health consequences from agricultural use of antibiotics (23, 29, 33, 48, 82, 95, 96)

Solutions to the problem of antimicrobial resistance

Our crisis in 2010 was anticipated in the 1940s by Fleming and others. By 1960, the transfer of drug resistance among bacteria was known, and by 1965, preeminent scientists warned that drug resistance was "largely due to the widespread use of antibiotics ... in animal husbandry" and that "The infective hazards of intensive farming, combined with the widespread use of antibiotics ...for the treatment of actual infections …and for their so-called prevention, favour … the spread of bacterial infection and that of contagious drug resistance in pathogenic Enterobacteriaceae. The time has clearly come for a re-examination of the whole question of the use of antibiotics and other drugs in the rearing of livestock." (4)

Our collective failure to adopt prudent public policy to address the growing problem of AMR over several decades is stimulating reflection and constructive dialogue regarding corrective action and opportunities for improvement. (1, 7, 8, 16, 17, 38, 39, 43, 47, 55-58, 89, 93) Areas critically in need of attention include: L**eadership:** Leaders must correct the **c**hronic **"**paralysis" in creating public policies to prevent enormous health and economic impacts of drug resistant organisms. **Organization:** Focus of accountability in government, coupled with streamlined organization, will lessen often competing interests. **Systems thinking and applications:** AMR arises within a complex system involving microbes, humans, animals, and the broader animate and inanimate environment. Systems thinking, planning, implementation and evaluation allow rational decision-making amid complexity. "Collaboration" and "coordination" are important but are often mistaken as equivalent to systems-based strategies. **Evidence-based decision making:** will minimize the risk that policy is driven primarily by uninformed bias, myth, ideology, and personal gain. **Investments in research & development, including outcomes based research**: Experts consistently complain about the lack of basic information to improve policy recommendations. Example: The estimates of the fraction of all U.S. produced antibiotics used in animals in the U.S. range from about 15% to 80%. Federally funded research must address such basic deficiencies in knowledge. **Will to regulate:** Major industries have chronically thwarted efforts to adopt evidence - based policies. The benefits these industries bring to our economy must be weighed fairly against the adverse economic and public health impacts of their practices and must be regulated accordingly. **Health System Reform:** There are few incentives for healthcare systems or clinicians to continually improve prescribing practices for antimicrobials. The problem of AMR will be improved with health reform policies that address this issue.

Next Steps

There is growing consensus that several issues must be addressed soon: 1. The failing pipeline for new antimicrobial drugs; 2. Development of new rapid diagnostic tests to make more efficient the diagnosis and treatment of infectious diseases; 3. Health systems policies that promote infection control, the prevention of AMR; and evidence-based antimicrobial prescribing and education regarding the judicious use of antimicrobial agents; 4. Expansion of vaccination services and development of new vaccines, and 5. Legislation to address AMR.

On June 28, 2010, the FDA released Draft Guidance #209: "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" for public comment. (23, 72) An important, but tentative step, the FDA's public comments and the Guidance itself suffer from lack of a clear statement of urgency, lack of specific time lines, and lack of key definitions to prevent loopholes in regulations.

Legislation proposed

Chronic failure by the FDA to implement substantive regulations regarding uses of medically important antimicrobial drugs in food-producing animals since the 1970s (20, 23, 58) has prompted various legislative proposals through the years, including the following:

The STAAR Act (H.R. 2400): "Strategies to Address Antimicrobial Resistance" would establish a focus of leadership for surveillance, coordination of data collection and research into novel interventions to limit spread of resistant microbes. (35)

The Preservation of Antibiotics for Medical Treatment Act (PAMTA, H.R. 1549, S. 619) addresses the near term and compelling need to provide regulatory oversight of drug use on industrial farms. (36, 48, 76) There is major support for dramatic reductions in routine uses of antibiotics in food animal production: F**ederal research based health agencies**: U.S. FDA; National Academy of Sciences, Institute of Medicine; **National medical organizations:** American Medical Association, American Public Health Association, American Academy of Pediatrics, American College of Preventive Medicine, Infectious Diseases Society of America; World Health Organization; **Non-governmental organizations:** Consumers Union, The Pew Charitable Trusts, Union of Concerned Scientists, Environmental Defense Fund, Physicians for Social Responsibility; and **more than 300 additional organizations:** health, consumer, agricultural, environmental, humane and others. (44)

Alternatives are available

Research has shown that the use of AB for growth promotion and feed efficiency may be eliminated. (19, 43, 75, 95, 96) Alternative food animal production techniques, including improvements in animal husbandry practices are effective. (1, 48, 60, 73, 74) The USDA has shown that successful producers who don't use growth promoting antibiotics rely on alternative strategies, such as extensive testing and sanitary protocols, to prevent disease and promote growth. (60)

WHO has found little or no adverse impact on agricultural production or efficiency and animal welfare in their analysis of the Danish experience that banned all use of antimicrobial growth promoters. (49, 75, 85, 90, 93, 95) The European Union (EU) ban on non-therapeutic uses of antibiotics is spawning other countries to adopt such practices. (18) The GAO has found such practices could put the current U.S. animal agriculture industry at market competitive risk. (27)

Conclusions:

Researchers, health professionals, public health experts, NGOs and the public have been sounding the alarm for too long regarding AMR diseases. We are now in a "perfect storm". There is a critical need for new effective antimicrobial agents to treat increasingly complex clinical problems associated with high tech medicine. But our supply of effective AB is vanishing because of proliferation of AMR microbes. It is imperative that Congressional and regulatory action be taken soon to 1. Intensify current efforts to reduce the inappropriate use of antimicrobial agents in clinical medicine and agriculture, 2. Eliminate the use of routine non-therapeutic AB in industrial agriculture and 3. Boost research & development for new antimicrobial agents.

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