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Subcommittee on Primary Health and Retirement Security

Hearing

"Superbugs: The impact of Antimicrobial Resistance on Modern Medicine"

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Testimony of Dr. Michael D. Apley

Kansas State University College of Veterinary Medicine

Chairman Markey, Ranking Member Marshall, members of the subcommittee, colleagues, good morning. I am Mike Apley, a veterinarian and clinical pharmacologist at the Kansas State University College of Veterinary Medicine. I also serve as an alternate member on the American Veterinary Medical Association Committee on Antimicrobials. Clinical use of antibiotics and research into their optimal use has been my professional focus since 1987.

Today we are addressing the issue of antibiotic resistance, more specifically the issue of acquired antibiotic resistance where antibiotics that were previously effective against a bacterial pathogen have lost the ability to have an impact on the outcome of disease caused by that pathogen in humans or animals. We can think of resistance as the worst case scenario of there being no possible treatment for a bacterial disease. Or, resistance can mean that our initial antibiotic choice doesn't work, and it is later in the disease process when an effective antibiotic is used. This delayed effective intervention can result in a more prolonged disease course, an increased chance of debilitation, or an eventual failure of antibiotic therapy. Resistance to our initial antibiotic choice can also mean that the remaining options have undesirable side effects which complicate recovery.

How we identify resistance in the laboratory

We identify and quantify resistance through antimicrobial susceptibility testing. Currently, the most common method is to grow the offending bacteria in the lab and expose it to multiple concentrations for each of multiple antibiotics. Whether or not growth of the bacteria occurs at different concentrations allows the classification of the bacteria as "susceptible" or "resistant" to each antibiotic based on established interpretive criteria. The methods and application of antimicrobial susceptibility testing continue to evolve. We are in a period of transition to more rapid tests, such as detecting genes identifying both the bacterial pathogen and the resistance genes present. The importance of continuing to advance rapid tests which identify the disease, and the most appropriate therapeutic approach cannot be overstated.

How resistance happens

Acquired antibiotic resistance may occur due to a mutation in bacterial DNA which is passed down through subsequent generations. The other more alarming route for acquiring resistance occurs through the horizontal transfer of resistance genes between different bacteria by means of transferrable genetic elements which encode for a resistance mechanism, a method of transfer, and the means to be incorporated into the DNA of the bacteria receiving the genetic elements. These transferrable genetic elements may contain the genetic codes for more than one resistance mechanism, with many of these mechanisms encoding resistance to multiple antibiotics. This is termed multiple drug resistance (MDR).

The number and types of antibiotic resistance genes which have been identified are extensive. Resistance mechanisms include altering antibiotic binding sites, efflux pumps which pump the antibiotic back out of the bacterial cell, altered physiological processes, and enzymes which inactivate the antibiotic. As examples related to specific antibiotic groups, approximately 2,800 unique proteins functioning as β-lactamases have been identified.[i] Depending on their specific structure and activity, these enzymes are capable of inactivating antibiotics such as the penicillins, cephalosporins, monobactams, and carbapenems. There are 46 different genes identified which encode for tetracycline resistance, and resistance to phenicols is due to genes which are categorized into 37 different groups.[ii] An important concept is that antibiotic use does not create these resistance mechanisms but can select for them when they exist in a population of bacteria exposed to an antibiotic. It is also important to recognize that even appropriate antibiotic use targeting a specific pathogen may select for a resistant subpopulation of that pathogen, and also for resistant subpopulations in the surrounding "bystander" bacterial populations.

The conditions leading to acquired antibiotic resistance reaching a point where this resistance has an impact on the use of an antibiotic include (1) frequently applied antibiotic selection pressure on (2) a highly mutable population of bacteria with (3) a short generation time. This selection pressure may result in a higher proportion of a pathogen population being resistant as well as the expansion of an already resistant bacterial population by reducing the numbers of other bacteria competing for the same resources. The latter situation highlights the importance of the health impact of our normal bacterial flora.

To be clear, this is a generalized account of the nature of acquired antibiotic resistance. Discussions should be held in relation to specific combinations of antibiotic exposure, the bacteria of interest, and the environment in which the antibiotic – bacterial interaction occurs. We have pathogens which have acquired resistance to most (in some cases all) of our antibiotic options, and we have pathogens which maintain susceptibility to many of our most basic, first-line antibiotic choices.

Antibiotic resistance vs. virulence

Antibiotic resistance is not necessarily combined with virulence, which is the ability to cause disease. However, when we have the combination of antibiotic resistance and virulence in a readily communicable pathogen, we have the potential for a substantial challenge across the one health spectrum.

What are the challenges?

The severity of the antibiotic resistance challenge to our health is illustrated in the characterization of the major resistance threats to human health by the Centers for Disease Control and Prevention (CDC).[iii] More specifically, their 2019 antibiotic resistance threats report identifies 18 bacteria and fungi estimated to be involved in more than 2.8 million antibiotic resistant infections each year, resulting in 35,000 deaths.[iv] When severe and potentially fatal diarrhea caused by *Clostridiodes difficile* related to antibiotic use is considered, this raises the estimates to 3 million infections and 48,000 deaths. The complex relationship of antibiotic resistance to our healthcare system is reflected in a 2022 special report by the CDC on the impact of COVID-19 on antibiotic resistance.[v] The American Veterinary Medical Association (AVMA) has also published a document identifying antibiotic resistance challenges encountered in veterinary species.[vi] Antibiotic resistant pathogens in common between the CDC report and at least one veterinary species in the AVMA report are multidrug-resistant *Pseudomonas aeruginosa*, drug-resistant non-typhoidal *Salmonella*, and methicillin-resistant *Staphylococcus aureus*.

What are plans for responding to the threat of antibiotic resistance?

Consideration of the challenge of antibiotic resistance has led to the National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020-2025 (CARB).[vii] An important component of CARB is a one health approach "which recognizes the relationships between the health of humans, animals, plants, and the environment". CARB has 5 major goals.

- Slow the emergence of resistant bacteria and prevent the spread of resistant infections
- Strengthen national One Health surveillance efforts to combat resistance
- Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria
- Accelerate basic and applied research and development for new antibiotics, antifungals, other therapeutics, and vaccines
- Improve international collaboration and capacities for antimicrobial-resistance prevention, surveillance, control, and drug research and development

Consistent with this one health approach, the Food and Drug Administration Center for Veterinary Medicine (FDA CVM) is in the last year of the current 5-year action plan for supporting antimicrobial stewardship in veterinary settings, with a recent progress update.[viii] The FDA CVM plan has 3 major goals.

- Align antimicrobial drug product use with the principles of antimicrobial stewardship
- Foster antimicrobial stewardship in veterinary settings
- Enhance monitoring of antimicrobial resistance and antimicrobial drug use in animals

I would like to highlight a resource on antibiotic resistance within the U.S. Department of Health and Human Services, The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB).[ix] The PACCARB produced the first of 11 reports in 2016 with the most recent report in 2023. The agendas and presentations by experts for 23 public meetings are available on the website. As a past member of the PACCARB, I suggest this resource as not only a way to hear from experts in the field of antibiotic resistance, but also as a bridge to many additional resources in this field. My exposure to the other members of PACCARB, and to the experts who gave their time to educate us, showed me that we have some truly talented and dedicated people working on antibiotic resistance.

Thank you for the invitation to be present today. I look forward to questions and discussion.

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[i] Bush K. Past and Present Perspectives on β-lactamases. Antimicrob Agents Chemother 2018;62(10):e01076-18.
[ii] Roberts MC and Schwarz S. Tetracycline and Phenicol Resistance Genes and Mechanisms: Importance for Agriculture, the Environment, and Humans. J Environ Qual 45:576-592, 2016.
[iii] Centers for Disease Control and Prevention. Antimicrobial Resistance - National Infection & Death Estimates for Antimicrobial Resistance. https://www.cdc.gov/drugresistance/national-estimates.html Accessed 7-8-2023.
[iv] Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2019. https://www.cdc.gov/drugresistance/biggest-threats.html Accessed 7-8-2023.
[v] Centers for Disease Control and Prevention. 2022 Special Report: COVID-19 United States Impact on Antibiotic Resistance. https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf Accessed 7-8-2023.

[vi] American Veterinary Medical Association. Antimicrobial-Resistant Pathogens Affecting Animal Health. https://www.avma.org/resources-tools/one-health/antimicrobial-use-and-antimicrobial-resistance/antimicrobial-resistant-pathogens-affecting-animal-health Accessed 7-8-2023.

[vii] U.S. Department of Health and Human Services. Office of the Assistant Secretary for Planning and Evaluation. National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020-2025. https://aspe.hhs.gov/reports/national-action-plan-combating-antibiotic-resistant-bacteria-2020-2025 Accessed 7-8-2023.

[viii] U.S. Food and Drug Administration Center for Veterinary Medicine. FDA Delivers Progress Update on 5-year Veterinary Stewardship Plan… https://www.fda.gov/animal-veterinary/cvm-updates/fda-delivers-progress-update-5-year-veterinary-stewardship-plan-publishes-report-about-antimicrobial Accessed 7-8-2023.

[ix] U.S. Department of Health and Human Services. Office of the Assistant Secretary for Health. Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB). https://www.hhs.gov/ash/advisory-committees/paccarb/membership/index.html Accessed 7-8-2023.