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SUPERBUGS: THE IMPACT OF ANTIMICROBIAL RESISTANCE ON MODERN MEDICINE

HEARING

BEFORE THE

SUBCOMMITTEE ON PRIMARY HEALTH AND RETIREMENT SECURITY

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED EIGHTEENTH CONGRESS

FIRST SESSION

ON

EXAMINING THE SUPERBUGS, FOCUSING ON THE IMPACT OF ANTIMICROBIAL RESISTANCE ON MODERN MEDICINE

JULY 11, 2023

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C O N T E N T S

STATEMENTS

TUESDAY, JULY 11, 2023

SUPERBUGS: THE IMPACT OF ANTIMICROBIAL RESISTANCE ON MODERN MEDICINE

Tuesday, July 11, 2023

U.S. SENATE,
SUBCOMMITTEE ON PRIMARY HEALTH AND RETIREMENT SECURITY,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The Subcommittee met, pursuant to notice, at 10:02 a.m., in room 430, Dirksen Senate Office Building, Hon. Ed Markey, Chairman of the Subcommittee, presiding.

Present: Senators Markey [presiding], Murphy, Hassan, Smith, Hickenlooper, Marshall, Braun, and Budd.

OPENING STATEMENT OF SENATOR MARKEY

Senator MARKEY. Good morning. The Senate, Health, Education, Labor, and Pensions Subcommittee on Primary Health and Retirement Security, will come to order. Thank you for joining us today for the Primary Health and Retirement Subcommittee hearing, Superbugs: The Impact of Antimicrobial Resistance on Modern Medicine.

Thank you especially to Ranking Member Marshall, to you and your staff's shared commitment to preparing for and preventing the antimicrobial resistance crisis in the United States. This is the type of partnership that drives results ultimately in Congress. More than 100 years ago, the discovery of antibiotics revolutionized modern medicine.

Some experts consider penicillin to be the single most important drug ever created. Antibiotics alone have extended our average lifespan by 23 years. But the rise in antimicrobial resistance threatens to undo 100 years of medical progress.

Minor infections could become incurable, leaving patients with chronic illnesses like cystic fibrosis most at risk. Routine surgeries could turn into deadly procedures. A paper cut could become lethal. But with the benefit of a century of scientific advancement on our side, this does not have to be our fate.

Our scientists and medical leaders already know what needs to be done. They know that the only medicine better than an antibiotic is prevention. They know that we must use antibiotics responsibly. They know that keeping people healthy and out of the hospital is critical to reducing anti-microbial resistance. Yet more than 100 million Americans lack access to primary care. But we here in Congress can do something about that.

We can invest in our community health centers and public health infrastructure. We can build a world class health system that reaches every person in every community, from Kansas to Massachusetts, and invest in our workforce, empowering a legion of medical professionals to prevent infections from turning into pandemics. And we can keep our people healthy by keeping our planet healthy.

Last week, we saw the four hottest days on planet Earth ever recorded. While the planet will turn our coastlines and waterways into petri dishes, diseases will spread faster and new strains will spread farther. Our climate crisis feeds the antimicrobial resistance crisis, and the only answer is to act now.

We need a whole of Government approach to prevent the next public health emergency. And as we saw with COVID–19 pandemic, when crisis strikes, it doesn't strike in a vacuum. An antimicrobial resistance crisis will disproportionately threaten the people who interact the most with the medical system.

It will threaten our health care workers, our friends and family who have disabilities, who are pregnant or who are elderly. It will worsen an opioid epidemic and strike in every community whether or not they have the resources to respond. It will bankrupt our working class and strain a system already plagued by inequality.

But with this wisdom of hindsight, we can improve our pandemic preparedness. We can build a resilient health care system designed with people at the very center—designed to take care of all Americans. We can deliver the ingenuity of American innovation, but it will only save us from crisis if the treatment is accessible for everyone. Just as a vision without funding is a hallucination, innovation without access is a fantasy.

We can and must create a different future, one that does not repeat the sins of the past. The witnesses here today, doctors on the front lines, patients living with the risk of antimicrobial resistance, companies developing new medications, and researchers connecting the health of our people and our environment will light our path forward. They are fighting for a better future and Congress must listen and respond. It is time that we guarantee are prepared an equitable whole of Government plan to prevent a crisis.

With that, I will now turn to Ranking Member, Senator Marshall, for his opening statement.

OPENING STATEMENT OF SENATOR MARSHALL

Senator MARSHALL. Well, thank you, Mr. Chairman, for agreeing to hold this hearing on anti-microbial resistance. I got to tell you, I could barely sleep last night. I was so excited to get here. This is why we came to Congress, was to fix problems like this. And I will tell you why this is near and dear to my heart.

Certainly, since a second year medical student, tried to understand bacteria and yeast infections and fungus, but the story that I remember is showing up for my OB-GYN residency program. We were delivering 15 to 20 babies a day, working 36 hour shifts. But the story that haunted everybody was a young lady that had a C-section and had died maybe 3 months before I got there.

She died from a resistant bacteria, from sepsis, a complication from a C-section. And very few days or weeks went by where we didn't talk, or they didn't talk about that case. Was there a month or two and we were having a very high infection rate, higher than I was comfortable with for post-operative patients.

I started culturing patients, and that is something you typically don't do when you have a multi-bacteria gram positive, gram negatives, and anaerobes causing these types of infections. But I cultured several people, and they had a methicillin resistant staph aureus. I had never even seen a patient with it, but I had read about it, and then I started to go, why are all these patients having a methicillin resistant staph aureus?

I looked into it further and they were using Primaxin, called Gorillacillin, as a prophylactic and were treating common urinary tract infections—they were treating everything with it. And obviously this new, I suppose it was a third or fourth generation cephalosporin, was inducing drug resistance. So here we are today. And why is this important?

3 million Americans this year will get some type of an antimicrobial resistance superbug this year. 100 Americans will die today. 100 will die tomorrow and every day this year from some type of a resistant bug. And I see the need for this rising as diabetes and obesity overwhelm our society.

Those are setups for more resistant organisms. And again, in my field of obstetrics, our C-section rates are going up for the same reasons, and we are going to have more infections and more resistant bugs, and then, of course, sexually transmitted diseases. For years, we have had penicillin resistant gonorrhea, but now it is resistant to Rocephin. Zithromax is not working as well.

It is certainly something I saw every day in my practice. It is interesting, as I did some research on this, the CDC and the World Health Organization both agree that human overuse is the main cause of this increased antimicrobial infections, and I am sure Dr. Apley will talk about this.

But one of the first things I did when I was running for office, I visited most every dairy, most every feedlot in the state, and I was so impressed that there was a veterinarian, if not on staff, literally consulting on a weekly basis, focused on nutrition and cutting back the antibiotic use. And I am so impressed with how fewer antibiotics those industries are using today compared to 2017 when we passed legislation. I bet Dr. Apley will talk a little bit about that as well.

I am proud what we have done in agriculture, but we need to look in the mirror. We, meaning physicians, nurse practitioners, and PAs need to look in the mirror. Half of the antibiotics that we prescribe are probably not indicated. Now, I wish I could tell you which half it is, but certainly my profession needs to look in the mirror.

We—need to do more cultures and pay more attention to this as well. Here is the challenge before us. I talked about those 100 people dying every day from some type of resistant organism. That is probably caused by 20 or 30 different bacteria. It is not that you

are going to develop one antibiotic that is going to take care of all of these.

You develop an antibiotic, and maybe it is specific to an infection from a kidney infection, and another antibiotic could be specific for pneumonia, and another antibiotic for a pelvic infection. So that is why it is so costly.

That is why it is so costly to develop these, realizing that we need 20 or 30 new antibiotics to take on these key infections, as opposed to say a diabetic drug that's going to be able to you get that to tens of millions of patients or even Alzheimer's drug. If it is developed, it will probably be given to a million patients. When we develop these types of antibiotics, we are hopefully only going to use them each a handful of times.

It just makes the economics of it next to impossible. We have many professional friends and colleagues have asked me to have this patient centered hearing, so I am so proud of the all-star group of witnesses we have. I know it is going to be a great hearing.

Again, I want to emphasize, thank you to your staff as well, Chairman, and the Committee staff working together to bring this to light. This is an issue that this Committee can literally make a difference today.

People ask me why I left the practice of medicine to come here, and I would tell them, look, in medicine I could impact 30, 40, 50 people a day. Here, you and I can impact the lives of thousands of people, certainly 100 people a day that I mentioned dying from an antimicrobial resistant bacteria.

Proud to be here and look forward to hearing from our witnesses. Thank you.

Senator MARKEY. I would ask Senator Marshall for you to introduce our first witness, if you would.

Senator MARSHALL. [Technical problems]—his last 6 years in Congress. Dr. Apley, of course, is a veterinarian with a Ph.D. in pharmacology at the College of Veterinary Medicine at the Kansas State University, home of the fighting Wildcats.

He teaches multiple courses related to food, animal medicine, clinical pharmacology, antimicrobial resistance. His research interests include infectious disease, antibiotic efficacy, resistance, antibiotic stewardship, which is certainly an issue here today, drug residues, that will be interesting in the applications of drugs in food animals.

Dr. Apley is nationally recognized for his work and is among the most influential veterinarians in cattle industry. He recognizes the value of his work. Dr. Apley was appointed a voting member of the Presidential Advisory Council on combating antibiotic resistant bacteria. He recently completed two terms on the council serving as vice chair.

He currently serves as a diplomat of the American College of Veterinary and Clinical Pharmacology and is a member of the American Veterinary Medical Association. Dr. Apley, thank you so much for agreeing to be here and to testify. We look forward to your information. Should I introduce the next one or—Dr. Apley, go ahead.

Senator MARKEY. Dr. Apley, whenever you feel comfortable, please begin.

STATEMENT OF MICHAEL APLEY, PROFESSOR, COLLEGE OF VETERINARY MEDICINE AT KANSAS STATE UNIVERSITY, MANHATTAN, KS

Dr. APLEY. Thank you. Chairman Markey, Ranking Member Marshall, Members of the Subcommittee, and my esteemed colleagues, good morning. My name is Mike Apley. I am a veterinarian and clinical pharmacologist at Kent 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 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 the 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 worse—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 and increase 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.

Acquired antibiotic resistance may occur due to a mutation in bacterial DNA, which is passed down through the subsequent generation, but the other more alarming route for acquiring resistance occurs through the horizontal transfer of resistance genes between different bacteria by means of transferable genetic elements, which encode for a resistance mechanism, a method of transfer, and a means to be incorporated into the DNA of the bacteria receiving the genetic elements.

These transferable genetic elements may contain the genetic codes of more than one resistance mechanism, with many of these mechanisms encoding resistance to multiple antibiotics. This is termed multiple drug resistance, or MDR. The conditions leading to acquired antibiotic resistance reaching a point where this resistance has an impact on the use of an antibiotic include frequently applied antibiotic selection pressure, a highly mutable population of bacteria with a short generation time.

This selection pressure may result in a higher proportion of the 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.

Discussion 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 and in some cases all of our antibiotic options, and we have pathogens which maintain susceptibility to our most basic first line antibiotic choices.

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, or the CDC.

More specifically, there are 2019 Antibiotic Resistant 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. When severe and potentially fatal diarrhea caused by clostridioides difficile related antibiotic use is considered, this raises the estimates to 3 million infections and 48,000 deaths.

The complex relationship of antibiotic resistance to our health care system is reflected in a 2022 special report by the CDC on the impact of COVID–19 on antibiotic resistance. The American Veterinary Medical Association has also published a document identifying antibiotic resistance challenges encountered in veterinary species. Consideration of the challenge of antibiotic resistance has led to the National Action Plan for combating antibiotic resistant bacteria, or CARB. An important component of CARB is the one health approach which recognizes the relationships between the health of humans, animals, plants, and the environment.

Consistent with this one health approach, the Food and Drug Administration Center for Veterinary Medicine is in the last year of the current 5 year action plan for supporting antimicrobial stewardship in veterinary settings, with the recent progress report. I would also 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, or PACCARB.

The PACCARB produced the first of 11 reports from 2016, with the most recent report in 2023. I suggest this resource is not only a way to hear from experts, but also is a bridge to many additional resources in the field. Thank you very much for the opportunity to be here this morning, and I look forward to our discussion.

[The prepared statement of Dr. Apley follows.]

PREPARED STATEMENT OF MICHAEL APLEY

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. Resist-

ance 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 transferable 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.[1] 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.[2] 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.

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[1] Bush K. Past and Present Perspectives on β-lactamases. Antimicrob Agents Chemother 2018;62(10):e01076–18.

[2] 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.

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).[3] 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.[4] 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.[5] The American Veterinary Medical Association (AVMA) has also published a document identifying antibiotic resistance challenges encountered in veterinary species.[6] 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).[7] 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.[8] 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

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[3] 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.

[4] 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.

[5] 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.

[6] 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.

[7] 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.

[8] 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-update5-year-veterinary-stewardship-plan-publishes-report-about-antimicrobial* Accessed 7–8–2023.

Combating Antibiotic-Resistant Bacteria (PACCARB).[9] 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.

Senator MARKEY. Thank you, doctor, so much. And now I am going to introduce Dr. Helen Boucher. Dr. Boucher is the Dean, as well as Professor of Medicine at Tufts University School of Medicine and the Chief Academic Officer of Tufts Medicine Health System in Boston, Massachusetts.

She is a practicing infectious disease physician and not a Wildcat, but a Jumbo. She also serves as Director of the Stewart Levy Center for Integrated Management of Antimicrobial Resistance.

In 2015, Dr. Boucher was appointed to the Presidential Advisory Council on combating antibiotic resistance bacteria. Dr. Boucher, you may proceed.

STATEMENT OF HELEN BOUCHER, DEAN AND PROFESSOR OF MEDICINE, TUFTS UNIVERSITY SCHOOL OF MEDICINE, BOSTON, MA

Dr. BOUCHER. Thank you, Chairman Markey, Ranking Member Marshall, and distinguished Members of the Subcommittee. Thank you for holding a hearing on antimicrobial resistance and for inviting me to testify on behalf of the Infectious Diseases Society of America, in my capacity as Dean of the Tufts University School of Medicine.

As an ID physician, I see firsthand how AMR and the dearth of new antimicrobials is harming patients. AMR is everyone's crisis and everyone's responsibility. I will briefly outline key drivers of AMR, why AMR is one of the most significant health crises of our time, and urgently needed solutions. As Dr. Apley pointed out so beautifully, AMR is pathogen's ability to evolve to resist antibiotics, making those drugs ineffective. Resistance occurs in nature.

Antimicrobial overuse in humans, animals, and the environment speeds resistance. Antimicrobials are unique in that use in one individual can impact efficacy in the rest of the population.

Despite some progress, antibiotics continue to be misused. In 2016, about half of hospitalized patients were prescribed antibiotics, and 30 to 50 percent of those prescriptions were inappropriate. Environmental factors are also accelerating AMR. Climate change, pollution, wildfires, and denser population settings can all facilitate the spread of AMR through waterborne pathogens, infected burns, and increases in respiratory infections.

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[9] 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.

In 2019, an estimated 1.27 million deaths worldwide were directly caused by AMR, and AMR played a part in nearly 5 million deaths. U.S. health care costs linked to infections from six of the biggest AMR threats total more than $4.6 billion annually, with $1.9 billion of these costs borne by Medicare.

Antimicrobials enable modern medicine. Advances like cancer chemotherapy, organ transplants, hip replacement, C-sections, and other complex care carry a risk of infection and are only possible with antibiotic support.

AMR puts all these therapies to which Americans are entitled at risk due to our lack of novel antimicrobials. I specialize in caring for patients undergoing organ transplantation. These patients must be on immunosuppressive medicines to prevent rejection. Inability to eradicate or control an infection precludes transplantation, and infection following transplant is a leading cause of death in this population. I have had the sad duty of caring for a person with an infection caused by a resistant bacteria for which we had no effective antibiotic.

He was unable to proceed to the transplant he needed and had to go home on hospice, ultimately leaving his two young sons fatherless. AMR is also impacting healthy individuals in our communities. I have cared for otherwise healthy women with resistant urinary tract infections that are no longer treatable with oral antibiotics.

This has required 2 weeks of intravenous antibiotic therapy, often started in the hospital and prolonged time away from work and school. The opioid epidemic is also fueling AMR. Individuals who inject drugs are 16 times more likely to experience an invasive MRSA infection.

AMR disproportionately affects communities of color and other marginalized populations. AMR is a national security threat. Its bioterrorist agents may be engineered to resist antimicrobials, and military service people are at heightened risk for infected wounds. IDSA appreciates the HELP Committee's leadership on AMR.

We thank Ranking Member Marshall and Senator Blumenthal for spearheading an annual letter urging Congress to provide funding to support improved AMR surveillance, prevention, and research, but we must address gaps. The most important thing the Subcommittee can do is advance a policy to establish a pull incentive, such as a subscription model, to spur the discovery and development of novel antimicrobials.

A subscription model would pay for these antimicrobials based on their value instead of volume to drive private investment in antimicrobial R&D. The President's budget request proposes such a model and over 200 organizations support this approach. R&D incentives must be paired with resources for stewardship.

Stewardship programs optimize antimicrobial use, improve patient outcomes, and lower health care costs. Unfortunately, many health care facilities lack the resources necessary for stewardship. The ID workforce that is needed to confront AMR is in crisis. Patients with serious infections do better when they are treated by an ID physician, but nearly 80 percent of U.S. counties lack an ID

physician, and only 56 percent of ID physician training programs filled their positions in 2023.

Financial barriers hinder recruitment, something I personally grapple with as a dean. ID physicians are among the lowest paid specialist. Congress must help ensure the availability of the ID workforce by improving reimbursement, addressing student debt, and providing resources for training and early career development.

Thank you so much for your attention to the critical issue of AMR.

[The prepared statement of Dr. Boucher follows.]

PREPARED STATEMENT OF HELEN BOUCHER

Chairman Markey, Ranking Member Marshall and distinguished Members of the Subcommittee, thank you for holding a hearing on the critical issue of antimicrobial resistance (AMR) and for inviting me to testify on behalf of the Infectious Diseases Society of America (IDSA) and in my capacity as dean of Tufts University School of Medicine. As an infectious diseases physician who has been in practice for 30 years, I see firsthand how AMR is erasing our hard-won medical gains, making health care procedures less safe, undermining our readiness for bioterror events and public health emergencies, and routinely harming healthy people in our communities. AMR is everyone's crisis and everyone's responsibility.

I specialize in caring for patients undergoing organ transplants. Organ transplantation is undoubtedly one of the miracles of modern medicine. In 2021, 41,354 organ transplants were performed in the United States, an increase of 5.9 percent over 2020 and the first time the annual total exceeded 40,000. The three organ types most commonly transplanted are kidneys (24,669), livers (9,236) and hearts (3,817). Liver transplant totals have set annual records for the past 9 years and heart transplants have set a new record each of the past 10 years. Patients who have received a transplant are typically highly complex and often have multiple underlying conditions or medicines that put them at greater risk for contracting an infection. For example, these patients must be on immunosuppressing medicines to help prevent their bodies from rejecting their organs. Antibiotic-resistant infections are increasingly threatening this lifesaving therapy. Inability to eradicate or control an infection precludes transplantation and infection following transplant is a leading cause of death in this special population. I have had the sad duty of caring for a person with an infection caused by a resistant bacteria for which we had no effective antibiotic therapy. He was unable to have the transplant he needed and had to go home on hospice, ultimately leaving his two young sons fatherless. My ID colleagues across the country have all experienced similar cases, and while they are not yet extremely common, they are happening with greater frequency and will become even more common if we do not act urgently to address AMR.

IDSA represents more than 12,000 infectious diseases (ID) physicians, scientists and other health care and public health professionals specializing in infectious diseases. Sadly, my colleagues throughout the country and globally are seeing more and more patients with multidrug-resistant infections.

IDSA has been sounding the alarm about AMR since 2004 with the release of our "Bad Bugs, No Drugs" report. While the Federal Government has made important strides to strengthen our response to AMR with a One Health approach that covers human health, animal health, agriculture and the environment, significant work remains to protect patient safety and national security and to safeguard modern medicine as we know it.

I will outline the key drivers of AMR, why AMR is one of the most significant health crises of our time, the current state of AMR response efforts and urgently needed solutions, including a subscription model to provide a predictable return on investment for novel antimicrobial research and development that is de-linked from the volume of antimicrobials used and aligned with strong antimicrobial stewardship.

The Drivers of AMR

AMR refers to pathogens' natural ability to evolve to resist the effects of antimicrobial drugs, ultimately making those drugs ineffective. While resistance occurs in nature, the overuse and misuse of antimicrobials in humans, animals and the environment greatly increases the speed at which resistance develops, significantly

shortening the time for which antimicrobial drugs remain effective and reducing the number of useful antimicrobials. **Antimicrobials are unlike any other therapeutic in that use in one individual can impact efficacy in the rest of the population.**

Overuse and misuse of antimicrobials in any setting—human medicine, animal health, agriculture, the environment—drives the development of resistance. A One Health approach to combating AMR is critical. We must improve surveillance, data collection and antimicrobial stewardship—the appropriate use of antimicrobials—in all settings to reduce AMR and its devastating impact on human health.

Despite some progress, antibiotics continue to be misused and overused. 2016 estimates indicate that about half of hospitalized patients were prescribed antibiotics, with 30 percent–50 percent of those prescriptions estimated to be inappropriate or unnecessary.[1] It is important to note that the increasing complexity of health care, with greater numbers of highly complex procedures and new treatments that increase risk of infection, also contributes to high levels of antimicrobial use—antimicrobial use that is appropriate and necessary.

COVID–19 led to even greater antibiotic use, particularly during the early days of the pandemic when clinicians were faced with significant uncertainty about the disease and very few, if any, treatment options. In addition, our sickest COVID–19 patients on ventilators were at significantly increased risk for secondary bacterial and fungal infections. From March-October 2020, about 80 percent of patients hospitalized with COVID–19 received antibiotics, and we now know that much of this antibiotic use was unnecessary.[2]

Antibiotic misuse and overuse are prevalent in outpatient settings as well. CDC has estimated that at least 28 percent of antibiotics prescribed in the outpatient setting are unnecessary, meaning that no antibiotic was needed at all.[3] Outpatient antibiotic prescribing decreased overall during the COVID–19 pandemic, but prescribing rates still vary widely across the U.S., with some states in the South having prescribing rates more than double the rates in states in other regions.[4] Antibiotics were frequently prescribed for COVID–19. A study published in the *Journal of the American Medical Association (JAMA)* reported that among Medicare beneficiaries who had an outpatient visit for COVID–19 in the first year of the pandemic, more than 30 percent received an antibiotic.[5]

A variety of environmental factors are also accelerating the development and spread of AMR, as outlined by a February 2023 United Nations report.[6] Climate change, pollution, more extreme weather, wildfires, flooding and denser population settings can all facilitate the spread of AMR. As the Earth warms, increased temperatures increase the rate of bacterial growth and the rate at which antimicrobial resistance genes spread between microorganisms.[7] Severe flooding, which is becoming more frequent due to climate change, can increase the risk of illness caused by waterborne pathogens. For example, studies have found higher levels of pathogenic bacteria and antibiotic resistance genes in floodwaters and soil in the Houston area following Hurricane Harvey.[8,9] Flooding can also lead to conditions of overcrowding and poor sanitation, further facilitating the spread of infections, including multidrug-resistant infections. Burns from wildfires can easily become infected, and inhalation of smoke and other pollutants can worsen respiratory conditions, increasing the risk of serious infection.

AMR: Unraveling Modern Medicine

It is essential that we address AMR because resistant infections are killing millions of people every year and putting modern medicine in serious jeopardy. In 2019, an estimated 1.27 million deaths worldwide were directly caused by AMR, and AMR played a part in nearly 5 million deaths. This makes AMR a leading cause of death

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[1] *https://academic.oup.com/cid/article/63/12/1/2282817.*
[2] https://www.cdc.gov/drugresistance/covid19.html#:-:text=Antibiotic.
[3] *https://pubmed.ncbi.nlm.nih.gov/32484505/.*
[4] *https://www.cdc.gov/antibiotic-use/stewardship-report/current.html.*
[5] *https://jamanetwork.com/journals/jama/fullarticle/2791077*
[6] *https://www.unep.org/resources/superbugs/environmental-action.*
[7] *https://www.nature.com/articles/s41558-018-0161-6.epdf?sharing-token=c0EPIqc1pgNRhnrU0M59SdRgN0jAjWel9jnR3ZoTv0Pa0XQPUYlH2uhflOAVxx1GDk6ya-mYSorzT7YJqTi4iBni-y1nPhU8zgyJxgKGXHM0GJbwQwZz0psTSUavsspIEB-u8oX1DPJWk6N-1QqbGPWqzKrFp9SRh3lb7-TSwjevMNDBFSpZaoLzuEKdDa7Ys39IYFhjqUWSgOhZASHA—3D—3D&tracking-referrer=www.cnn.com.*
[8] *https://pubs.acs.org/doi/10.1021/acs.estlett.8b00329.*
[9] *https://pubmed.ncbi.nlm.nih.gov/33077230/.*

globally.[10] The post-antibiotic era is not just a looming threat—for many patients it is already here. AMR is a crisis not only for the individual patients impacted but for our entire health care system. National health care costs linked to infections from six of the biggest AMR threats are estimated to be more than $4.6 billion annually.[11] $1.9 billion of these costs are estimated to be borne by Medicare.[12]

We must protect antimicrobials because antimicrobials enable and sustain modern medicine. Most medical advances carry a risk of infection and rely upon antimicrobials. Consider procedures like cancer chemotherapy, organ transplants, hip and knee replacements, Cesarean sections, and other surgeries and complex care. All of these procedures save and enhance human lives, and they all carry risk of infection. Clinicians are only able to provide this care because they have safe and effective antimicrobials to prevent and manage infectious complications. But as our antimicrobial arsenal diminishes, our modern medical gains are unraveling, and patients are facing devastating consequences. Consider a few examples:

- **Cancer**: Cancer and many cancer treatments can weaken the immune system. Infections are a primary or associated cause of death in 50 percent of patients with cancer, as AMR can make these infections difficult or impossible to treat.[13] Sadly, I and my colleagues have seen patients cured of cancer succumb to infections caused by resistant bacteria.
- **Maternal mortality**: Sepsis—the body's overwhelming and life-threatening response to untreated infections that can result in organ failure and death—is the second leading cause of pregnancy-related deaths. AMR exacerbates the risk of sepsis by making infections much more difficult to treat. Between 2014 and 2017, infection or sepsis caused 12.7 percent of pregnancy-related deaths in the United States. Pregnancy-related infections that can lead to sepsis can be related to miscarriages, C-sections, prolonged or obstructed labor, and mastitis (breast infection).[14]
- **Biologics**: Certain biologics that are used to treat a wide range of conditions weaken the immune system, making individuals more susceptible to infections.
- **Implantable medical devices**: Prosthetic joints, pacemakers, implantable defibrillators, ventricular assist devices for patients with serious heart disease, and other implantable devices can easily become infected. In many cases, removal of these devices may be impossible or impractical, and patients may face recurring or chronic infections that can become increasingly resistant.
- **Opioid use**: The opioid epidemic is also fueling the spread of resistant infections, including life-threatening heart valve infections, skin and soft tissue infections, bone and joint infections, and more. The Centers for Disease Control and Prevention (CDC) estimates that individuals who inject drugs are 16 times more likely to experience an invasive methicillin-resistant *S. aureus* (MRSA) infection.[15] This is particularly frightening as the opioid crisis continues to worsen. In my state of Massachusetts, data announced last month indicated that the opioid-related overdose death rate in Massachusetts increased to 33.5 per 100,000 people in 2022, 2.5 percent higher than in 2021 and 9.1 percent higher than the pre-pandemic peak in 2016.
- **Fungal infections**: In March 2023, CDC warned that cases of *Candida auris*, a difficult-to-treat resistant fungal pathogen, have been increasing steadily since they were first reported in 2016. *C. auris* is resistant to multiple antifungal drugs, spreads easily in health care facilities and has high mortality rates.[16]
- **Organ transplants**: More than 42,000 organ transplants were performed in the U.S. in 2022, a 3.7 percent increase over 2021 and a new

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[10] *https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext*.
[11] *https://www.cdc.gov/drugresistance/solutions-initiative/stories/partnership-estimates-healthcare-cost.html*.
[12] *https://academic.oup.com/cid/article/74/6/1070/6374434*.
[13] *https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21697*.
[14] *https://www.sepsis.org/sepsisand/pregnancy-childbirth/*.
[15] *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7045815/#:?:text=Data—20from—206—20sites20of,develop20invasive—20MRSA—20infections—20than*.
[16] *https://www.cdc.gov/media/releases/2023/p0320-cauris.html*.

annual record.[17] Unfortunately, AMR and the dwindling arsenal of antimicrobial drugs available to support these patients means many of them face death due to infection despite a successful transplant.

- **Cystic fibrosis**: People with cystic fibrosis (CF) face a heightened, lifelong risk of infections because of the thick sticky mucus in their lungs. Routine use of antibiotics in CF care is medically necessary; however, too many people with cystic fibrosis find themselves battling difficult-to-treat infections for which existing antibiotics are not effective.

Increasing resistance is forcing physicians to turn to older, more toxic antibiotics like colistin—a drug that causes serious kidney damage. Patients are left with the unfathomable choice of dying from their infection or taking an antibiotic that could leave them in need of dialysis for the rest of their life or a kidney transplant. The rapid spread of the transferable gene, mcr–1, which confers colistin resistance, threatens the efficacy of even colistin—a last resort drug for the treatment of many drug-resistant bacterial infections.[18] We must do better.

AMR in the Community

AMR is also impacting healthy individuals in the community. Rates of a type bacteria that cause resistant urinary tract infections or UTIs (extended-spectrum beta-lactamase [ESBL]-producing Enterobacteriaceae) increased by more than 50 percent from 2013 to 2019.[19] In fact, increasing numbers of patients with UTIs that were once easily treated with oral antibiotics now require intravenous (IV) antibiotics in the hospital—increasing our health care costs and creating serious disruptions to patients' lives. In my practice, I have cared for otherwise healthy women with urinary tract infection caused by ESBL-producing organisms. This has required 2 weeks of intravenous antibiotic therapy, often started in the hospital, and prolonged time away from work or school.

As another example, an ongoing outbreak of drug-resistant eye infections due to contaminated eye drops has killed or caused blindness and the need for removal of the eye, a devastating and disfiguring complication, in several patients. This underscores that resistant infections are a threat to us all and that we must invest in the tools necessary to ensure we can manage such outbreaks with limited negative impacts.

Sexually transmitted infections like gonorrhea and syphilis that were once easily treated with antibiotics are becoming increasingly drug resistant.

AMR and Health Inequities

Like so many health conditions, AMR disproportionately impacts historically marginalized populations, though more comprehensive data is needed to fully understand the inequitable impacts of AMR. A few examples:

- Community-associated MRSA rates are higher among Black populations when compared to White populations.[20]
- American Indian and Alaska Native persons have substantially higher population rates of all invasive Group A *streptococcus* disease.[21]
- In February 2023, CDC published a health alert on an increase in extensively drug-resistant (XDR) *Shigella* infections. Historically, *Shigella* has largely impacted children under age 5. There is now an increase in *Shigella* infections among men who have sex with men, individuals experiencing homelessness, international travelers and people with HIV.[22]

AMR: A Threat to Readiness and National Security

The AMR crisis was further exacerbated by the COVID–19 pandemic. In 2020, U.S. hospitals experienced a 15 percent increase in AMR infections and deaths, though pandemic-related data gaps suggest that the total national burden of AMR may be much higher. Experts do not expect a return to pre-pandemic levels without

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[17] *https://unos.org/news/2022-organ-transplants-again-set-annual-records/*.
[18] *https://www.nature.com/articles/s41429-023-00622-1*.
[19] *https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf*.
[20] *https://www.cdc.gov/drugresistance/pdf/health-equity-antibiotic-resistance-fs-508.pdf*.
[21] *https://www.cdc.gov/drugresistance/pdf/health-equity-antibiotic-resistance-fs-508.pdf*.
[22] *https://emergency.cdc.gov/han/2023/han00486.asp*.

concerted action.[23] Any emergency resulting in high levels of hospitalization, particularly high levels of ventilator use and overwhelmed hospital staff, creates a ripe opportunity for the spread of secondary drug-resistant infections.

Addressing AMR is also important for bioterror readiness and national security, as agents used by bioterrorists may be genetically engineered to resist current antimicrobials.[24] The World Health Organization (WHO) has estimated that if 50 kg of *Y. pestis* were to be released as an aerosol over a city with a population of 5 million, 150,000 people might fall ill with pneumonic plague, 36,000 of whom would die.[25] Drug-resistant strains of *Y. pestis* have been reported, which can increase mortality.[26] As another example, modeling suggests that deliberate release of aerosolized *F. tularensis* over London would result in an estimated 130,000 infections and 24,000 deaths.[27] Natural resistance is already observed in tularemia, and the overuse of fluoroquinolones, one of the main treatments for this infection, in the last two decades has led to treatment failure and relapses in tularemia patients.[28]

Military service people, who are often critical first responders in emergencies, can be at heightened risk for resistant infections, as combat wounds and burns can easily become infected. In the current conflict in Ukraine, patients are presenting with highly complex, multidrug-resistant musculoskeletal infections from gunshot and bomb wounds. Physicians identified multiple pathogens, including *Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, E. coli* and fungal pathogens. Infections showed high rates of resistance to some of our most powerful antibiotics: 72 percent were resistant to carbapenems and newer cephalosporins (ceftazidime-avibactam and ceftolozane-tazobactam), 39 percent were resistant to cefiderocol, 20 percent to colistin and 96 percent to ciprofloxacin.[29] International travel makes it very easy for drug resistant pathogens to spread across the globe.

Insufficient Antimicrobial Pipeline

Despite the urgent and increasing need for novel antimicrobials to treat resistant infections, the current pipeline has fewer than 50 antibacterial therapeutics in clinical development worldwide—only a handful of which are for the most threatening gram-negative pathogens—a critical area of need.[30] Given that most drugs in development do not ultimately secure FDA approval, and that there is a wide array of drug-resistant bacteria and fungi for which new therapies are needed, the current pipeline is grossly inadequate. The last FDA approval of an antibiotic was in November 2019.

Novel antimicrobials must be used appropriately by prescribers with sufficient expertise to limit the development of resistance; this means ensuring that these precious medicines are not overused. This is essential from a clinical and public health perspective but creates a serious barrier to private sector investment in antimicrobial innovation. Currently, Federal and commercial payers reimburse for antimicrobials when they are used, so judicious use to preserve effectiveness severely limits the ability of an antimicrobial developer to earn a return on their investment.

Between 2010 and 2019, 18 new antibiotics were approved by FDA, which is an improvement from the 11 new antibiotics approved from 2000–2009. However, only one of those 18 antibiotics had a new mechanism of action, and it was the first such antibiotic approved since the 1980's.[31] This underscores the need not only to strengthen antimicrobial research and development but more specifically to incentivize the development of truly novel antimicrobials.

Federal support from the Biomedical Advanced Research and Development Authority (BARDA) and the National Institute of Allergy and Infectious Diseases (NIAID) has been critically important to the development of more recently approved antibiotics, and their funding for CARB-X has strengthened the pre-clinical anti-

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[23] *https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf.*

[24] *https://books.google.com/books?hl=en&lr=&id=IiGEDwAAQBAJ&oi=fnd&pg=PR1&ots=ZXqKRYXnRH&sig=39-Vf6uaisjnzSVfBI–1p-9TT4#v=onepage&q&f=false.*

[25] *https://apps.who.int/iris/bitstream/handle/10665/39444/24039.pdf.*

[26] *https://journals.asm.org/doi/full/10.1128/AAC.00306-06.*

[27] *https://www.liebertpub.com/doi/abs/10.1089/bsp.2011.0004.*

[28] *https://ami-journals.onlinelibrary.wiley.com/doi/full/10.1111/j.1751-7915.2008.00063.x.*

[29] *https://www.cidrap.umn.edu/antimicrobial-stewardship/clinicians-describe-challenge-treating-multidrug-resistant-war-wounds.*

[30] *https://www.who.int/publications/i/item/9789240047655.*

[31] *https://www.bio.org/sites/default/files/2022-02/The-State-of-Innovation-in-Antibacterial-Therapeutics.pdf.*

microbial pipeline. However, we see plain evidence of failures in the market for antimicrobials: There has been a disturbing number of instances in which small companies successfully bringing a new antibiotic to market are then pushed to file for bankruptcy due to the broken antimicrobials market that provides little to no opportunity to earn a return on investment. This can lead to the loss of U.S. patient access to these antimicrobials. There is an urgent need for a creative solution that will revitalize and sustain novel antimicrobial innovation and availability.

Antimicrobial Stewardship

Antimicrobial stewardship programs in hospitals aim to optimize antibiotic use to ensure that patients receive the right drug for the right bug with the right dosing and duration. These programs have been found to improve patient outcomes, reduce inappropriate antibiotic use and lower health care costs.[32], [33] nationwide, 98 percent of hospitals report having implemented all seven of the core elements of antimicrobial stewardship recommended by CDC[34] and as required by the Joint Commission and the Centers for Medicare and Medicaid Services (CMS). Despite this important progress, there remain many important opportunities to improve antimicrobial therapy and reduce inappropriate antibiotic use in hospitals.

While many hospitals can meet stewardship requirements on paper, they often lack the resources and experienced staff necessary to fully implement medically recommended stewardship protocols and to extend the benefits of stewardship to all patients. Studies have found consistent gaps between necessary levels of physician and pharmacist staffing and existing staffing levels. A 2018 study found that each 0.50 increase in physician and pharmacist full-time employee (FTE) support for a stewardship program predicted a 1.48-fold increase in the odds of the program demonstrating effectiveness.[35]

The COVID–19 pandemic further stressed hospital budgets, diverting resources from stewardship programs despite the unprecedented need for stewardship to manage high levels of antibiotic use among hospitalized patients with COVID–19.[36] In many hospitals, stewardship teams led the complex administration of COVID–19 therapeutics, which was an appropriate use of limited human capital resources given their expertise. This work included evaluating treatments for COVID–19 in clinical trials, developing treatment guidelines and educating providers as data rapidly evolved, partnering with state and local health departments, assessing patient risk factors to prioritize limited quantities of therapeutics, and devising innovative strategies to reach rural and other underserved populations. These efforts were crucial to reducing COVID–19 hospitalizations and deaths but came at the expense of traditional antimicrobial stewardship.

Even in Massachusetts, where we have a robust health care system, there are many hospitals and health care facilities that lack adequate stewardship infrastructure and resources, human and financial, that are needed to deliver this important part of clinical care.

AMR Surveillance and Data Collection

We need to better understand where resistance is happening and how antimicrobials are being used to better target prevention and treatment strategies. The CDC National Healthcare Safety Network (NHSN) includes the Antibiotic Use and Resistance (AUR) module, which collects and provides actionable data to inform and evaluate efforts to optimize antibiotic use. More than 2,400 acute care hospitals across the United States had submitted at least 1 month of antibiotic use data as of August 2022. Of those hospitals, 2,283 reported in the past 12 months (July 2021—June 2022). This represents a significant increase in reporting in the last several years, but gaps in data persist and more comprehensive reporting will better inform the current state of AMR in the U.S.

CMS included a requirement for antibiotic use and resistance reporting in their fiscal year 2023 Inpatient Prospective Payment System final rule. IDSA supports this requirement, which will help ensure that antibiotic stewards, clinicians and key decision-makers have access to more comprehensive antibiotic use data, enabling us to track antibiotic use and resistance over time, evaluate stewardship interventions, identify best practices and improve antibiotic use. It is critical that health care fa-

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[32] *https://academic.oup.com/cid/article/66/7/995/4851152.*
[33] *https://pubmed.ncbi.nlm.nih.gov/27246783/.*
[34] *https://www.cdc.gov/antibiotic-use/stewardship-report/current.html.*
[35] *https://doi.org/10.1093/cid/ciy255.*
[36] *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7375214/.*

cilities not yet reporting antibiotic use and resistance data be provided resources necessary to begin reporting. It is also critical to provide CDC with resources necessary to support NHSN users, analyze and share data, and promote health professional education and appropriate antibiotic use.

Workforce Needed to Combat AMR

The ID workforce that is needed to respond to AMR is in crisis. ID physicians and other ID health care and public health professionals are needed to care for patients with resistant infections, lead antimicrobial stewardship and infection prevention and control activities, and conduct surveillance and research, including clinical trials. Data consistently show that for patients with serious infections and conditions complicated by infections (e.g., transplants, cancer, etc.), ID physician care improves outcomes, decreases mortality, shortens hospital stays and lowers health care costs.[37], [38]

Workforce shortages coupled with lower pay and a lack of financial incentives for recruitment and retention persist among ID health care professionals, including ID physicians, clinical microbiologists, nurses, pharmacists, physician assistants and infection preventionists. As pharmaceutical companies leave the antimicrobials market, we are suffering a significant "brain drain" with far too few scientists with expertise in ID. I personally grapple with this challenge in my role as dean of Tufts University School of Medicine. Our MD and PA graduates increasingly select more lucrative specialties like surgery or dermatology rather than infectious diseases, further adding to the already fragile workforce.

In 2022, nearly 80 percent of U.S. counties lacked an ID physician,[39] and only 56 percent of ID physician training programs filled their positions for the 2023 appointment year, compared to most other physician specialties for which nearly all of their programs filled their positions.[40] A quarter of health care facilities have reported a vacant infection preventionist position, and a 2019 survey showed a vacancy rate for clinical microbiologists of more than 10 percent. Communities without ID health care professionals are less equipped to respond to AMR.

IDSA has conducted extensive outreach and mentoring to medical students and residents, and we routinely find high levels of interest in the field of ID, but financial challenges consistently pose barriers to recruitment. ID physicians are among the lowest paid medical specialists, earning even less than general internal medicine physicians who lack the additional years of training that an ID physician undergoes.[41] High levels of student debt often understandably drive physicians to higher paying specialties, leaving our Nation without enough experts to combat AMR. The ID specialty is at an inflection point, and without action to recruit, train and retain the next generation of ID specialists, we can expect to see an increase in mortality due to infectious diseases for years to come.

Solutions

IDSA is grateful for the HELP Committee's long history of leadership on AMR, including passage of the Generating Antibiotic Incentives Now (GAIN) Act in 2012 and enactment of the Limited Population Antibacterial Drug (LPAD) review mechanism in 2016 as part of the 21st Century Cures Act, which helped improve the regulatory environment for the study and evaluation of new antibiotics and antifungals to address unmet needs in limited patient populations.

The National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) was launched in 2015 and provided an important framework for a coordinated, comprehensive Federal response to AMR. The second iteration of the plan was released in 2020 and largely aims to build upon the progress made since 2015. The five goals of the plan, which IDSA supports, are: (1) slow the emergence of resistance and prevent resistant infections; (2) improve One Health surveillance; (3) advance development and use of diagnostics; (4) advance research and development of antibiotics, other therapeutics and vaccines; and (5) improve international collaboration. We greatly appreciate Ranking Member Marshall and Senator Blumenthal's leadership of an annual letter urging Congress to provide sufficient funding to BARDA, CDC

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[37] *https://academic.oup.com/jid/article/216/suppl-5/S588/4160394.*
[38] *https://academic.oup.com/cid/article/58/1/22/372657.*
[39] *https://www.acpjournals.org/doi/10.7326/m20-2684.*
[40] *https://www.nrmp.org/wp-content/uploads/2023/04/2023-SMS-Results-and-Data-Book.pdf.*
[41] *https://www.medscape.com/slideshow/2022-compensation-overview-6015043?icd=login-success-email-match-norm.*

and NIAID to advance critical AMR efforts. These resources have supported improved surveillance, clinician education about AMR, research and innovation, and it is critical that funding for these efforts continues. Through our Tufts Levy Center for Integrated Management of Antimicrobial Resistance, I and my colleagues gratefully receive funding from NIAID to innovate in clinical trials through the NIH Antibacterial Resistance Leadership Group (ARLG), investigate new therapies, and advance stewardship and prevention efforts.

In addition, the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), on which I served, convenes key experts to provide a diverse array of perspectives to help inform Federal AMR response activities. The PACCARB's recommendations have allowed Federal efforts to benefit from a wide range of expertise, and the PACCARB should be reauthorized so this important work may continue.

It is also critical that we address gaps in existing efforts, specifically with regard to antimicrobial innovation, stewardship and the AMR workforce. The PACCARB released a March 2023 report, "Preparing for the Next Pandemic in the Era of Antimicrobial Resistance," and recommended urgently needed efforts to strengthen antimicrobial stewardship, infection prevention and control, the ID workforce, data sharing and medical countermeasure innovation.[42]

Subscription Model to Finance Novel Antimicrobial Research & Development

To build on current Federal AMR efforts **the single most important thing this Subcommittee can do is advance a policy to establish a pull incentive, such as a subscription model, to finance the discovery and development of novel antimicrobials**. This approach would have a transformative impact on antimicrobial innovation, revitalizing the discovery and development of truly novel antimicrobials by providing a predictable, reasonable return on investment for novel antimicrobials. The Federal Government already pays for antimicrobials through various health programs including Medicare, Medicaid, Tricare and Veterans Affairs (VA), but it pays in a way that fails to incentivize innovation and appropriate use. Conversely, a subscription model is smart spending that would pay for the value rather than volume. Under a subscription model, the Federal Government would enter into contracts with antimicrobial developers to pay predictable fees for a steady supply of a novel antimicrobial. This approach would help drive more private investment to antimicrobial research and development and help ensure that novel antimicrobials developed with critical support from BARDA, NIAID and CARB-X remain available to U.S. patients.

It is particularly important to front-line ID clinicians like me that incentives are designed to deliver truly novel antimicrobials that provide important clinical benefits for patients.

Equally important, incentives for antimicrobial development must be paired with policies to support appropriate use of antimicrobials by providing urgently needed funds to health care facilities to support their antimicrobial stewardship programs.

The President's Budget Requests for fiscal year 2023 and fiscal year 2024 have proposed a subscription model to strengthen antimicrobial innovation and stewardship and more than 200 organizations representing health care professionals, public health, patients, scientists, advocates and industry have endorsed this approach.

AMR Workforce Investments & Physician Reimbursement

In addition, Congress must take steps to ensure the availability of the expert ID workforce needed to combat AMR, including ID physicians, ID physician-scientists, clinical microbiologists, infection preventionists, pharmacists and nurses. We must make ID a financially feasible choice for health care professionals by addressing student debt, improving reimbursement, and providing sufficient resources for training and early career development. Specific recommendations include:

- Enhance Medicare reimbursement for ID physicians, through one or more of the following approaches: Increase the value of the codes most frequently billed by ID physicians (i.e., inpatient evaluation and management codes); provide a Medicare incentive payment for ID physicians (e.g., similar to the Medicare incentive payments for primary care physicians and general surgeons); and create new mechanisms to pay for critical population health activities to combat AMR that benefit the general

[42] *https://www.hhs.gov/sites/default/files/paccarb-pandemic-preparedness-report.pdf*.

patient population, but are not necessarily directly tied to the care of an individual patient (e.g., leading stewardship programs, infection prevention and control programs, and outpatient parenteral antimicrobial therapy or OPAT programs).

- Fund implementation of the Bio-Preparedness Workforce Pilot Program to incentivize individuals to pursue careers in ID in health professional shortage areas. IDSA greatly appreciates that Senators Baldwin (D-WI), Collins (R-ME), Rosen (D-NV) and Murkowski (R-AK) spearheaded the authorization of this pilot as part of the PREVENT Pandemics Act last year.
- Increase NIAID funding to support training and early career ID and AMR researchers. IDSA greatly appreciates the annual appropriations letter led by Ranking Member Marshall (R-KS) and Senator Blumenthal (D-CT) to support funding for this and other AMR efforts across HHS.

Once again, on behalf of IDSA, thank you very much for your attention to the critical issue of antimicrobial resistance and for inviting me to testify. IDSA looks forward to working with you and your colleagues to advance the solutions necessary to confront the AMR crisis, protect modern medical gains and save lives.

Senator MARKEY. Thank you, doctor, so much. And next, we are going to hear from Ms. Melanie Lawrence.

Ms. Lawrence is a Massachusetts resident and health care advocate living with cystic fibrosis. Ms. Lawrence serves on committees for the Cystic Fibrosis Foundation, Boston Children's Hospital, and Cystic Fibrosis Learning Network.

She is also a recipient of the Alex Award, the highest award that CF Foundation gives for her volunteer work to help and support people with cystic fibrosis. Whenever you feel comfortable, please begin, Ms. Lawrence.

STATEMENT OF MELANIE LAWRENCE, HEALTHCARE ADVOCATE, FAIRHAVEN, MA

Ms. LAWRENCE. Thank you so much. Good morning, and thank you, Chairman Markey, Ranking Member Marshall, and distinguished Members of the Subcommittee for inviting me here to testify.

My name is Melanie Lawrence. I am 43 years old, living with cystic fibrosis. While I am here to speak to you about my experience with infection, drug resistant bugs are not a problem exclusive to people living with CF.

This is a human issue, and last I checked, we are all humans. They are a problem that all Americans will face if we don't find a solution to jumpstart innovation in antimicrobial development. CF is a rare genetic disease affecting nearly 40,000 people in the U.S. that causes the body to produce sticky mucus in the lungs, heightening the risk of infection.

When I was diagnosed, my parents were told that my life expectancy would be 16 years old. Today, the median life expectancy for people with CF has increased to 56, but there is still no cure. CF is only a part of who I am though, it does not define me.

I am a single mother to a most amazing 12 year old son. I am a daughter, a sister, a friend, a proud aunt, and I am passionate about making sure that patients like me, and others have access to treatment they need to have fulfilling lives, as well as in a health care system that is rooted in humanity.

Every day I spend hours taking medications, doing physical therapy, exercise, meditation, breathwork, all while raising a very active 12 year old, trying to create as many meaningful memories with him as I can. Despite being proactive, infections due to drug resistant Pseudomonas, MRSA—or MRSA, impact, my health and I have relied heavily on antibiotics my whole life.

Earlier, I could trust that a two-week antibiotic course of oral antibiotics would do the trick. This meant—as the bacteria in my lungs began outsmarting the antibiotics, I also needed IV antibiotics to keep my infections under control.

This meant a two-week stay in a hospital, and I would have to have antibiotics administered through a pick line, threaded up the vein in my arm. By 18, I needed a larger dose of IV antibiotics for up to 5 weeks at a time. Losing hope, I participated in a clinical trial for IV Tobramycin, which ended up causing chronic tinnitus, a severe kidney damage, and I was ultimately removed from the study because of it.

Over the next two decades, antibiotic resistance became a bigger threat to my health, as did the subsequent side effects of more potent antibiotics. My airways became so damaged that I began having hemoptysis, which is bleeding in my lungs. I also began developing blood clots. Because of that, my only option for IV antibiotics became a temporary IV line placed through my jugular vein. It was no longer possible to eradicate the bacteria, so the goal was to keep my head above water.

Now, in my 40's, the bacteria in my lungs are resistant to nearly every antibiotic, except for Tobramycin, which I cannot take because it is so toxic to my already damaged kidneys and hearing.

My focus is to manage my symptoms and maintain the best quality of life possible. Without the security of effective antibiotics to help me heal, I find myself living with chronic fear and anxiety about when the bacteria residing in my lungs will act up or when another infection will take me away from truly living.

On a deeper level, I am often navigating a humbling loss of control, loss of autonomy, and a deep, subconscious fear of death. Of leaving my son without his primary caregiver, the person who knows him best and loves him without abandon, his mom.

My body is both my biggest ally, keeping me alive and fighting off these infections, whilst also being my biggest threat, trying to kill me from the inside. And yet, living with CF has been a gift, not a curse. It has opened my eyes to the fragility of time and the importance of connection, and that is a gift we should all be so lucky to receive while we are healthy and able to appreciate it rather than when it is too late.

My story is not an uncommon experience in the CF community, nor is it unique to people with CF. Bacteria are abundant and it is inevitable that more Americans will encounter resistant infections. It is not a question of if you can catch them, it is a question of when. Without new antibiotics, the bacteria will win this war.

I thank the Subcommittee for giving me the opportunity to share my story and ask that you work together to find innovative policy

solutions for patients like me and for all Americans like the PASTEUR Act.

Personally, I would love to see my son graduate college or even to become a grandparent, something that I have never even allowed myself to imagine because it feels so out of reach without new antibiotics. Time is ticking, and we need your help. Thank you.

[The prepared statement of Ms. Lawrence follows.]

PREPARED STATEMENT OF MELANIE LAWRENCE

Good morning. Thank you, Subcommittee Chairman Markey, Ranking Member Marshall, and distinguished Members of the Senate Primary Health & Retirement Security Subcommittee, for inviting me to testify before you today. My name is Melanie Lawrence, I am 43 years-old, and I am living with cystic fibrosis (CF). I am grateful to be part of this Subcommittee's discussion on a subject that I am unfortunately all too familiar with, antimicrobial resistance. While I am here to speak to you about my experiences with infection, drug-resistant bugs are not a problem exclusive to people living with CF—they are a problem for everyone. People with CF provide a glimpse into a future that everyone will experience if we don't address this growing threat. As I share more about my experience, I ask that you consider the public health risks that all Americans face if we do not jumpstart innovation and develop new, more effective antimicrobials as soon as possible.

I was diagnosed with CF at age 5. At the time, my parents were told that my life expectancy was 16 years old. When I turned 16, the median life expectancy had grown to 31 years old—and now, at age 43, it is 56 years old.

As you are aware, cystic fibrosis is a life-threatening genetic disease that causes persistent lung infections and makes it very difficult to breathe, often leading to respiratory failure. More than 40,000 people in the United States live with CF and there is no known cure. People with CF face a heightened, life-long risk of infections, and often rely on antibiotics as part of their daily care. Still, all too many—like me—battle antibiotic resistant infections for which there are no effective treatment options available.

However, cystic fibrosis is only a *part* of who I am and it does not define me. I am a single mother to the most amazing 12-year-old son. I am a daughter, a sister, a friend, a proud aunt, and a passionate contributor to the greater good. I believe that it is my life's purpose to connect with others and remind the healthcare industry that patients are human beings with full, complex lives outside of the exam room who deserve to be treated as such. I find my work serving on volunteer committees with the Cystic Fibrosis Foundation, the Cystic Fibrosis Learning Network, and patient advisory boards extremely rewarding. I am grateful for the opportunities to give back and improve how health care is delivered and how providers think about patients—as people first. I love being out in nature and catching the sunrise, I am a hot yoga enthusiast and enjoy challenging myself wherever possible.

Sadly, I have lost many friends to CF-related infections over the years, some dying before their 21st birthday. Many other CF friends continue to struggle with the management of their symptoms. I believe the stable health I do have is a combination of luck, new therapies, and hard work. Each and every day I spend hours taking medications, doing physical therapy, exercise, meditation, and breathwork—all while raising a very active 12-year-old and trying to create as many meaningful memories with him as I can while I am physically able to do so.

Since I was a teenager, I have participated in as many clinical trials and research studies as I can. Despite significant medical advances and new therapies that have helped stabilize my health, lung infections due to multi drug-resistant Pseudomonas aeruginosa and Methicillin-resistant Staphylococcus aureus (MRSA) bacteria are the chronic complications of CF that impact my life the most.

Chronic respiratory infections continue to be a hallmark of living with CF because of the persistent mucus in the lungs of people with the disease. More than 60 percent of people with CF culture positive for at least one chronic pathogen in their lungs starting from a very young age and that figure climbs to over 80 percent among adults living with CF. Like me, nearly 20 percent of CF adults have chronic infections caused by pseudomonas and 25 percent of people with CF will culture MRSA each year.

As a result, I have relied on antibiotics my whole life. Throughout my childhood and early teenage years, antibiotics were highly effective. Each time I caught a cold or contracted an infection, I could trust that a two-week course of antibiotics would have me feeling better and back to living life as usual. By age 13, the bacteria in my lungs were already outsmarting oral antibiotics and I needed intravenous (IV) antibiotics once a year in addition to oral antibiotics to keep my infections under control. The IV antibiotics were administered via a peripherally inserted central catheter (PICC) line—an IV that was threaded into a vein up my arm. For the next 5 years, IV antibiotics were administered in the hospital one to two times each year and required me to stay in the hospital for 2 weeks, often missing school and many holidays with my family. My hospital refers to this time as "cleanouts" when CF patients would have a two-to-five-week course of IV antibiotics and respiratory therapy to help prevent exacerbations and lengthier hospital stays as a result of infection.

By age 18, a two-week course of IV antibiotics was no longer enough to combat the bacteria growing in my lungs. I needed larger doses of IV antibiotics for up to 5 weeks at a time. This took place partially inpatient at the hospital and partially during regular hospital visits. Looking for a better solution, I participated in a clinical trial for IV Tobramycin that ended up being so damaging to my kidneys (nephrotoxic) that I was prematurely removed from the study. That trial also resulted in constant tinnitus (high-pitched ringing in my ears) that I still have, and will continue to have every minute, of every day, for the rest of my life.

In my twenties, antibiotic resistance became a bigger issue as did the subsequent side effects the more potent antibiotics caused. As the bacteria became resistant to antibiotics, I began to lose many of the "tools" in the toolkit to combat drug resistant bugs and treating my lung infections. It was also the decade where my lung infections first began leading to hemoptysis, or the coughing up of blood from my lungs. Sometimes the bleeding can be so severe and life-threatening that I need a medical procedure called an arterial embolization to block the bleeding arteries. The bleeding in my lungs can then become a breeding ground for bacteria, resulting in a vicious cycle of infections. Due to these complications, I need antibiotics more frequently and for longer periods of time than typically prescribed.

By age 30, I began having chronic upper extremity blood clots and could no longer receive IV antibiotics via a PICC line. The blood clots also made me a poor candidate for a port, a device that can be inserted as an alternative delivery method for antibiotics over a long course of treatment for people with CF. My only option for IV antibiotic treatment was to get a temporary IV threaded through my jugular vein During this time, the bacteria in my lungs became so resistant that one antibiotic alone did not stand a chance. I needed to take a combination of two to three antibiotics at a time just to keep my infections at bay. However, even multiple antibiotics couldn't eradicate the bacteria in my lungs, they just bought me time and allowed me to get my head above water.

Now in my forties, the bacteria in my lungs are resistant to nearly all antibiotics except for Tobramycin, which I cannot take because it is so toxic to my already-damaged kidneys and hearing. There is no eradicating the bacteria in my lungs and the recurrent infections have led to permanent scarring in my lungs along with pockets of collapse. My focus is now on managing my symptoms and maintaining the best quality of life possible. Every single antibiotic I try results in insufferable side effects that require me to take additional drugs to counteract them, or I am forced to discontinue the course early because they make me feel so miserable. The side effects vary and impact my body as well as my mental health. They cause rashes, kidney damage, depression and everything in between. Today's antibiotics are not nearly the friendly savior I used to depend upon, and I regularly have to ask myself which is worse: the infection or the side effects?

These challenges have led to a more stressful life experience for not only me, but for my son, my family, and my friends as well. In the past, infections were stressful, but we knew that there was an "easy fix" with a quick course of antibiotics. Now, it feels like much more of a gamble with my life. For me, something as simple as the common cold can take months to rebound from and often turns into pneumonia. I no longer have the security of relying on antibiotics to help me heal, so I live with chronic fear and anxiety about when the bacteria residing in my lungs will act up or when another infection will take me away from the moments I cherish for a few months or the even the simple daily tasks that we often take for granted. Ultimately, on a deeper level, I am always navigating a humbling loss of control, loss of autonomy, and a deep subconscious fear of death—and mostly, of leaving my son without his primary caregiver—the person who knows him the best and loves him without abandon. His mom.

I live in a constant state of introspection—both mind and body. Up to this point, much of my life has depended on me being attuned with my body and hyper-aware of what my body is trying to tell me. This year, I've learned that this has caused me more anxiety than I wanted to admit. I realized I had an inability to be still or to sit with my body in silence. My body is both my biggest ally, keeping me alive and fighting off infection, whilst also being my biggest threat, trying to kill me from the inside.

Yet, I am not a victim by any means, and I am committed to doing everything in my power to stay as healthy as I can for as long as I can. Living with CF has been a gift, not a curse. It has opened my eyes to the fragility of time and the importance of connection, and that is a gift we should all be so lucky to receive while we're healthy and able to appreciate it, rather than when we're dying and it's too late.

I am a big believer in the mind/body connection so I work hard at staving off the threat of lung exacerbations as much as I can. I combine both Western and Eastern medicine, work with a therapist to keep my anxiety low, practice mindfulness, meditate, do breathing exercises, and lead a healthy lifestyle. I wash my hands constantly, take vitamins, get rest, and constantly assess the risk vs. benefit of social interactions. My friends know to disinvite me to events if someone is sick and are mindful of my germ exposure. It has become second nature for my son to sanitize his hands every day when he gets out of school. He doesn't complain when we have to leave a party early because mom is tired, and he understands when he has to skip a birthday party or social gathering because the germ risk is too high. It pains me that he's had to grow up in a more heightened state of awareness, but I like to think he's more empathetic because of it.

For me, my family and all people living with CF, it can be a challenge to navigate social risks because a part of feeling alive is joining in social events. We want to travel, we want to go to the movies, we want to go to concerts, and we want to attend family gatherings in the winter even though the flu is circulating. We want to feel alive and actively participate in life just like you do. Life is for living after all.

This is my story, my experience of what it's been like to live with antibiotic-resistant bacteria. While my life may look quite differently from yours, it is not an uncommon experience in the CF community. And while right now it may seem like it is unique to people living with CF, these bacteria are abundant and it is inevitable that more people will encounter antimicrobial resistant bacteria. It is not a question of if you can catch them, but when.

I am grateful for organizations like the Cystic Fibrosis Foundation that recognize the significant threat antimicrobial resistance poses to the CF community, and in 2018 created the Infection Research Initiative as part of a sweeping effort to advance infection research. To date, the Foundation has committed over $140 million to the initiative because they know that for people with CF—and all of us—to lead full lives our providers need more tools in their toolbelts. They need more antibiotics. Better antibiotics. Full stop.

We have all relied on antibiotics at some point in our lives and how lucky are we that they've been available and effective for many of us? But the bacteria are outsmarting us and without new and novel alternatives, they will win this war. Private sector investments alone won't solve the problem. We need the Federal Government to lead and support innovative policy solutions with an all of the above approach to help people like me live long enough to see our children thrive. Personally, I want to see my son graduate college or even become a grandparent—something I've never even allowed myself to imagine because it feels so out of reach without new antibiotics.

I thank the Subcommittee for giving me the opportunity to share my story and I ask that you work to help find solutions for patients with a heightened risk for infection like me, and for all Americans, as you consider legislation this Congress.

Senator MARKEY. Beautiful. Thank you. Senator Marshall, would you introduce the next witness?

Senator MARSHALL. All right. Thank you, Mr. Chairman. I want to introduce Ms. Christine Miller, who is testifying on behalf of the Antimicrobials Working Group in the Biotechnology Innovation Organization. Ms. Miller is the CEO of the Melinta Therapeutics, a

biopharmaceutical company that specializes in novel, broad spectrum antibiotics to help patients in hospital and community settings.

With a background and chemical engineer, Ms. Miller has spent over 20 years championing life sciences innovations, working for small companies to some of the leading innovators in the world.

Ms. Miller will shed light on why the commercial marketplace for antibiotics in the United States is at serious risk of collapsing, something my colleagues tell me over and over again. The risk of collapsing due to ongoing reimbursement challenges and supply chain shortages.

Again, my friends back home tell me this every day I go back home, and I talk to my friends, still practicing. She is going to share why small companies are now responsible for over 95 percent of global novel antimicrobial development, and even then they face bankruptcy in the coming years.

Thank you so much for agreeing to testify and share your story, Ms. Christine Miller.

STATEMENT OF CHRISTINE ANN MILLER, PRESIDENT & CHIEF EXECUTIVE OFFICER, MELINTA THERAPEUTICS, NEW YORK, NY

Ms. MILLER. Thank you, Chairman Markey, Ranking Member Marshall, and distinguished Members of the Subcommittee. Thank you for the opportunity to speak with you today.

My name is Christine Miller. I am President and CEO of Melinta Therapeutics, and Melinta is a small biotech providing innovative therapies to people impacted by acute and life threatening illnesses.

My story begins in New York with two amazing parents who immigrated here from Jamaica. The women in my family dedicated their careers to helping patients. My mother, a registered dietitian, worked at Montefiore Hospital. And as a child, I remember visiting her at the hospital, watching her solve patients' problems.

I was inspired to pursue a career in pharmaceuticals when I realized I could use my education, like the women of my family, to help patients. This is why being here today is so important to me. I want to help identify the unmet need of patients and address the issues of availability and access to lifesaving antimicrobial medicines.

Antimicrobial drugs are the cornerstone of modern medicine. These drugs are critical to effectively deliver medical care for patients receiving chemotherapy, organ transplants, and patients undergoing routine surgical procedures like hip replacement and C-sections. However, bacteria and fungi are living organisms that adapt and evolve over time and become resistant to antimicrobials, a phenomenon known as antimicrobial resistance, or AMR.

In the United States, AMR is a third leading cause of death behind heart disease and cancer. Things have gotten worse since the pandemic. In 2020, hospital acquired drug resistant infections and deaths jumped 15 percent as COVID erased years of progress in the fight against superbugs.

While drafting my testimony, I was reminded of a story from a patient, Sue Paxton. Sue, who was a recipient of a successful liver transplant, who also found out she had a severe fungal infection when hospitalized. After multiple rounds of antifungals and further deterioration of her condition, Sue and her doctor were able to gain early access to rezafungin, a novel antifungal developed by Cidara Therapeutics that Melinta will launch later this month.

Within days, Sue was on the path to recovery. Unfortunately, what happened to Sue happens all too often in hospitals, and the only way to combat these life threatening infections is to continually innovate newer, safer antimicrobials, and ensure that patients have access to these innovations.

It is important to understand that we do not have an innovation problem. The U.S. Government recognized the need and has taken action to support research and development needed to address resistant infections. Programs like CARB-X have done an amazing job and reinvigorating the pre-clinical pipeline. Also, programs through BARDA have been vital to combat AMR.

Melinta is a partner in a public, private collaboration with BARDA to advance two FDA approved antibiotics for use in pediatric patients and for use against biothreat pathogens. We also do not have an approval problem. Congress already enacted a policy to streamline regulatory approval for antimicrobials.

Companies are getting innovative products approved but are failing after launch. What we do have is a commercial marketplace problem that is fundamentally unique to antimicrobials, driven by reimbursement and access challenges.

As a result, many biotech companies run out of money in the quest to provide patients with access to lifesaving therapies. Unless we see changes to the post-approval side of the equation, the ability to bring these products to patients remain in jeopardy.

The good news is that Congress and the Federal Government are in the position to solve this problem. Policies to increase access to new antimicrobials through reforms to antimicrobial reimbursement and novel payment mechanisms called pull incentives that decouple payment from the volume of antimicrobials used are urgently needed now.

Without changes to the system, we will continue to see access challenges and further deterioration of the innovation pipeline, and patients, our family members, our neighbors will continue to die.

My hope for today is that this Committee views all of today's testimony as a call to action to fix the commercial marketplace. AMR remains a silent killer in hospitals every day. Every year we wait to address this crisis is another year more patients are at risk for losing their lives.

Thank you for your attention to this public health crisis, and I look forward to your questions.

[The prepared statement of Ms. Miller follows.]

PREPARED STATEMENT OF CHRISTINE ANN MILLER

I—Opening Remarks

Chairman Markey, Ranking Member Marshall, and distinguished Members of the Committee, thank you for the opportunity to speak with you today. My name is Christine Miller, and I am President and Chief Executive Officer (CEO) of Melinta Therapeutics. Melinta is a small, innovative biotechnology company providing life-saving therapies to patients impacted by acute and life-threatening illnesses. In addition to my role as CEO, I serve as Chair of the Antimicrobials Working Group—or AWG—a coalition of emerging antimicrobial companies committed to improving the commercial environment for drug development. Melinta is also a member of the Biotechnology Innovation Organization (BIO), the largest trade organization representing biotechnology companies, academic institutions, state biotechnology centers and related organizations in the U.S. and 30+ countries.

My story begins in the New York, the product of two amazing parents who immigrated from Jamaica. I grew up in a family where the women were all in healthcare as either nurses or dietitians and dedicated their careers to helping patients. My mother, a Registered Dietitian, worked at Montefiore Hospital for 38 years. I remember visiting her at the hospital as a child and watched her solve patients' problems. I too have always been passionate about problem solving and applied that to degree in Chemical Engineering. I was inspired to pursue a career in pharmaceuticals when I realized I could use my education, like my mother and the women of my family to help patients. Everything that I have tried to do in my 20 plus year career is about creating access for patients so that they can get the medicines they need. That's why being here in front of you is so important to me. I want to help identify the unmet need of patients and providers and address the issue of how we can create the access needed to live-saving antimicrobials medicines.

Put simply, antimicrobial drugs are the cornerstone of modern medicine. These drugs are critical for the effective delivery of medical care more broadly for patients receiving chemotherapy, organ transplants, and even those undergoing routine surgical procedures like hip replacements and cesarean sections. However, bacteria and fungi adapt and evolve over time and become resistant to these treatments—a phenomenon known as "antimicrobial resistance," or AMR for short. Overuse and misuse of current antibiotics accelerates AMR. For example, in the outpatient settings, the CDC estimates that one-third of antibiotics are used improperly. [1] This rise in AMR is rapidly rendering our antimicrobial arsenal ineffective and represents a problem in the here and now—it will also continue to get progressively worse over time. As AMR becomes more prevalent, many medical procedures that are commonplace today will become too risky to undertake, with catastrophic consequences to medical care, including death.

As I was drafting my testimony today, I was reminded of a story from one of our patients—Sue Paxton. Sue, who is a resident of Manakin Sabot, Virginia, was the recipient of a successful liver transplant, and while hospitalized, found out she had a severe fungal infection. After multiple rounds of antifungals and further deterioration of her condition, Sue and her infectious disease physician were able to gain early access to rezafungin, a novel anti-fungal developed by Cidara Therapeutics and that Melinta will launch later this month, and within a few days, Sue was on the path to recovery. When I asked Sue, a mother and grandmother about her experience, she was extremely grateful to her medical team that they were knowledgeable about the latest in the field and could help her get access to the innovative medicine she needed. I was moved, when she said, "It was a live-saving drug for me, I wouldn't be here without it". New, innovative, and effective antimicrobials used in the hospital setting are critical to saving lives like Sue's—and her story is a testament to the importance of today's hearing.

Unfortunately, what happened to Sue happens all too often in hospitals. The only way to combat these life-threatening infections is to continually innovate newer, safer antibiotics, and to ensure their access and appropriate use. AMR is a "silent pandemic" in the American healthcare system. In my testimony today, I hope to convey how serious a threat AMR is to our Nation, and why the challenges surrounding this issue have become so difficult for our health system to overcome.

The problem right now is that our Nation's physicians lack the access needed to prescribe these innovative products, and in turn, patients are not receiving the care that they need. This broken ecosystem for antimicrobials has created an unviable marketplace that renders innova-

[1] *https://www.cdc.gov/media/releases/2016/p0503-unnecessary-prescriptions.html*.

tive drugmakers unable to develop the products needed to catch up—and keep up—with the growing threat of resistance.

From an industry perspective, antimicrobial development is uniquely different than any other area of biotechnology. Unlike a disease area like oncology, it is very rare for a patient to know *exactly* what type of infection they have and *exactly* what drug they are being given.

Remember, also, that antibiotics are intended to be used sparingly and only until the infection has resolved to prevent further exacerbation of resistance. What this means for industry is that many companies have tended to focus on other novel product areas, such as chronic diseases, where there is a more stable and long-term market for therapies. It is not surprising then that the vast majority of research being done in the antimicrobial space today is led by small companies like ours, and not large pharmaceutical firms.

Many are familiar with the concept of the "valley of death"—the period between promising lab research and clinical trial launch when biotech companies run out of funding. It takes 10–15 years to develop one successful drug, and despite significant investments in time and money, 90 percent of drug candidates fail in clinical trials fail, never reaching regulatory approval.[2,3] The antimicrobials sector faces another unique obstacle, what many of my colleagues have termed the "***second valley of death***", which occurs after FDA approval. In most areas of biotech, the period after FDA approval is a time for celebration for both providers and patients. Unfortunately, for the antimicrobials sector, it can take years for newly approved therapies to *actually* reach patients. This is due in part to the flawed reimbursement structure for antimicrobials, which disincentives hospitals from giving physicians access to the newest, safest, and most appropriate drug. This is also due to the unique way that innovative antimicrobials are held in reserve in the hospital setting to guard from exacerbating resistance.

Since antimicrobials companies are unable to recoup their investment under traditional volume-based payment structures for drugs alone, many are unable to remain commercially viable and end up failing shortly after launch. The loss of a company in the antimicrobials sector does not just represent an economic loss. In some cases, it represents the loss of intellectual property to foreign adversaries and the outflow of talent and scientific expertise. This, in turn, results in industry specific skilled workforce challenges, commonly known as "brain drain."

Most importantly, the loss of these companies poses an existential risk to patients. Without immediate solutions, the antimicrobial development industry will wither away, and we will face a daunting future without effective antibiotics, where commonplace procedures and infections can become fatal.

I am here today to characterize the unique problem facing the antimicrobial sector.

- We do **not** have an innovation problem. Recognizing the need for novel antimicrobials to address resistant infections, the U.S. Government has taken action to support the critical research and development of these important therapies. U.S. Government programs like CARB-X have successfully funded over 90 early stage clinical candidates and diagnostics.
- We do **not** have an approval problem. In 2012, Congress enacted a policy to streamline regulatory approval for antimicrobials to address serious and life-threatening infections. As I mentioned earlier, companies are getting innovative products approved, but are failing ***after*** launch. This has a ripple effect that has a chilling impact on the pipeline of drugs in development.
- What we **do have** is a commercial marketplace problem—driven by reimbursement and access challenges—that is fundamentally unique to antimicrobials. Without reforms on the post-approval side of the equation to increase access to new antibiotics—through reforms to antimicrobial reimbursement and novel payment mechanisms called "pull incentives" that decouple payment from the volume of antimicrobials used—hospitals will continue to be forced to rely on older medications. Without changes to this system, we will continue to see further deterioration of the innovation pipeline, and patients—grandmothers, children, fathers, mothers, our neighbors—will continue to die.

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[2] *https://www.nature.com/articles/d41573-021-00190-9*.
[3] *https://www.nature.com/articles/nrd.2016.136*

The good news is that Congress and the Federal Government are in a position to solve this problem. There are already policy solutions that could make a significant impact to correct the broken antimicrobial marketplace in both the short-term to sustain patient access and in the long run to "pull" other novel products across the finish line and ensure they reach patients.

My hope for today is that this committee views the collective expertise of this panel as a "call to action" to address AMR both as the threat it poses to our public health and to our Nation's preparedness in the event of future biosecurity threats such as pandemics, and as the silent killer in hospitals every day.

II. AMR Is a Societal Issue of Mass Scale

The patients our novel antimicrobials can save have no bounds—children with cancer, a marathon runner post routine surgery, a new mother delivering a child via c-section. It does not take a lifetime of antibiotic exposure to fall victim to a resistant infection that can change your life, or a loved one's life forever. In 2023 alone, a number of superbug outbreaks have gripped the attention of health experts, the media, and the public.[4]

- *Candida auris* is a fungus that can cause serious bloodstream, skin, and other infections and is often multi-drug resistant—and has caused recent outbreaks in healthcare settings. In 2021, there were nearly 1,500 clinical cases of *Candida auris* in the United States—more than a 300 percent increase since 2019.
- *Pseudomonas aeruginosa* is a strain of bacteria that can cause infections in the lung or blood or other parts of the body post-surgery and is often drug resistant. This year, contaminated eyedrops caused severe *Pseudomonas aeruginosa* infections in at least 68 patients in 16 states, including 8 who suffered permanent vision loss, 4 who needed surgical removal of their eyeball, and 3 deaths.
- *Shigella* are bacteria that cause the infection shigellosis, which often manifests itself as a stomach bug. Extensively drug-resistant strains of *shigella* are on the rise. 5 percent of Shigella cases in 2022 were extensively drug-resistant—up from 0 percent in 2015.

As mentioned previously, AMR threatens to undermine the major advances in medicine made over the last 90 years. Globally, AMR has become a leading cause of death having killed over 1.2 million people in 2019 and played a part in nearly 5 million deaths that year.[5] In the United States, AMR was associated with over 173,000 deaths in 2019—the third leading cause of death, behind only heart disease and cancer.[6] By 2050, AMR infections will result in over 10 million deaths per year globally. The economic impact on the United States will also be substantial—a $20 billion per year cost to the U.S. healthcare system and $35 billion annual loss in productivity.[7]

The burden of AMR has become even more prominent since the start of the COVID–19 pandemic and threatens future responses to biosecurity threats. In 2020, hospital-onset drug-resistant infections and deaths jumped 15 percent as COVID–19 erased years of progress in the fight against superbugs. AMR also threatens to undermine other areas of medicine. One report cites that infections are a primary or associated cause of death in 50 percent of patients with cancer."[8]

Recognition of these alarming trends and a realization that safer and more novel products are needed have led Congress to take a series of actions over the years to address AMR.

In 2012, Congress passed the Generating Antimicrobial Incentives Now (GAIN) Act to promote the development of new antimicrobial products known as Qualified Infectious Disease Products, or QIDPs, intended to address "unmet medical need" for the "most serious and life-threatening infections."[9] Passage of the GAIN Act was

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[4] Superbugs Are Here The Time to Act is Now. *BIO*. Infographic.
[5] Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Murray, Christopher J L et al. The Lancet, Volume 399, Issue 10325, 629–655.
[6] *https://vizhub.healthdata.org/microbe/*.
[7] *https://www.cdc.gov/nchs/data/nvsr/nvsr70/nvsr70-09-508.pdf*.
[8] O'Neill, J. "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations," 2016.
[9] Nanayakkara, AK, Boucher, HW, Fowler, VG, Jezek, A, Ouerson, K, Greenberg, DE. Anbioc resistance in the patient with cancer: Escalating challenges and paths forward. CA Cancer J Clin. 2021: 71: 488–504. *https://doi.org/10.3322/caac.21697*.

intended to spur antimicrobial innovation. However, it has fallen short in "pulling" novel drugs to approval, and even more importantly, ensuring patients have access to those drugs once they are approved.

The Federal Government also implemented additional incentives to support the research and development of new drugs, such as the CARB-X program under the Biomedical Advanced Research and Development Authority (BARDA). These programs have been resoundingly successful in their mission and have become vitally important to antimicrobial development.

Subsequent to these important steps, and as stated earlier—

- We do **not** have an innovation problem
- We do **not** have an approval problem

What remains is a commercial marketplace problem underpinned by systemic post-approval and reimbursement challenges which must first be acknowledged, and then corrected for.

III. State of Innovation of the Antimicrobials Pipeline

Antimicrobial drug development is at an all-time low. Unlike other areas of biotechnology, where investors typically see high returns upon a drug's FDA approval, antimicrobial products are used sparingly and can take years to see appropriate uptake in a clinical setting. Oncology companies raised close to $7 billion in 2020 (up 900 percent from 2011), whereas antibiotic companies raised just $0.16 billion (less than what they raised 10 years prior).[10] For drugs in human testing, there are about four dozen antibiotics currently undergoing trials compared to more than a thousand cancer drugs.[11]

Small biotech companies remain committed to bringing novel drugs across the finish line. More than 60 companies and non-profit research institutes are developing the 64 clinical-stage drug candidates to meet the growing need for differentiated antibacterials. In recent years, small companies accounted for 80 percent of novel antimicrobial drug discoveries, with 8 percent being discovered by non-profit institutes and universities, and only 12 percent originating from large companies.[12] In terms of characterizing the entire R&D engine, there remains a $150 billion cumulative revenue gap since 2001 for on-patent global antibiotic sales, an unheard-of trend in any other area of biotechnological development.[13]

IV. Innovation Without Implementation

The answer to fixing the commercial marketplace for these drugs is not as simple as inventing new therapies. First, the principle of antimicrobial stewardship dictates that antibiotics should be used only when appropriate and should always be the foremost consideration in care. Nevertheless, there are a combination of factors that lead to slow uptake and a lack of implementation in hospitals:

1. New AMR drugs when approved are most critical for inpatient care, especially for hospital-acquired infections.

2. Hospitals are currently incentivized to hold in reserve, or rely on cheaper, inferior generic antibiotics—a function of how reimbursement for inpatient care, which is currently capped by bundled payments set by CMS known as a diagnosis related group (DRG), is

designed. As a result, generic antibiotics are used as first line drugs, even when newer drugs may be more appropriate.

3. At the same time, companies see a weak demand for new antibiotics. Low revenues fail to offset the high costs of research and development, as well as costs to support production, commercialization, and post-approval regulatory requirements.

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[10] Jonathan J Darrow , Aaron S Kesselheim, Incentivizing Antibiotic Development: Why Isn't the Generating Antibiotic Incentives Now (GAIN) Act Working?, Open Forum Infectious Diseases, Volume 7, Issue 1, January 2020, ofaa001, *https://doi.org/10.1093/o.d/ofaa001*.

[11] The State of Innovation in Anbacterial Therapeutics. *BIO Industry Analysis*. February 2022.

[12] Kevin Outterson Testimony to House Energy & Commerce Committee. 28 April 2023.

[13] The State of Innovation in Anbacterial Therapeutics. *BIO Industry Analysis*. February 2022.

4. These market realities have led investors to flee antibiotic development. The combined market capitalization of all publicly traded antimicrobial companies is .01 percent of the top 10 global pharmaceutical companies.

As a result of these factors, numerous small biotech companies have ceased operations in recent years. One example is a company that, less than a year after approval, was forced to sell its assets to two principal buyers based in China and India.[14] In the past 2 years alone, two other companies, both of which have drugs addressing CDC-identified AMR threats—have faced extreme financial difficulties.[15]

V. Solutions Are Needed to Right a Market in Free Fall

The Federal Government currently pays for antimicrobials in a way that fails to drive innovation or appropriate use. The unique way that innovative antimicrobial products are used requires fundamentally unique solutions to address the broken marketplace for antimicrobial innovation. Policy concepts that aim to achieve this goal include:

1. Fixing Reimbursement to Reflect the Market Dynamics Unique to Antimicrobials

Addressing antimicrobial reimbursement is two-fold. Companies, like mine—a clear and timely pathway to patient access and market uptake. Also, we need to address barriers to entry that are preventing biotechs from entering this space today. New, alternative payment models can create that signal needed to drive research and development back to this pipeline and catch-up in our battle against resistant infections.

First, we need to address hospital formularies head-on.

Currently, hospitals perceive that they lose money whenever a new antimicrobial is introduced to their formularies, which in turn blocks access to the therapy. However, numerous studies have demonstrated that better patient outcomes are strongly associated with the use of newer antimicrobial agents, meaning that patients who receive newer treatments spend less time in the hospital. Several studies indicate that the time to initiation of appropriate therapy is the key to improved patient outcomes and saves lives.

In the past few years, the Centers for Medicare and Medicaid Services (CMS) has introduced new tools to support antimicrobial innovation. However, structural issues remain with these reimbursement tools that continue to disincentivize hospitals from properly utilizing novel antibiotics. Difficulties with hospital formularies under the DRG payment structure in the inpatient system also represent a persistent challenge. In general, reviewing reimbursement mechanisms for antimicrobials and further educating providers about novel products would help strengthen market uptake.

At the same time, we also need to implement novel antimicrobial payment mechanisms i.e., 'Pull Incentives'. To promote necessary innovation in the antimicrobial industry, Congress should consider novel pull incentives such as subscription models that pay for a reliable supply of novel antimicrobials with payments that are decoupled from volume of the product used. This type of novel payment mechanism would incentivize the development of novel antimicrobials based upon the value they provide for public health, rather than the volume used. Such a model would directly support the appropriate use of the antimicrobials it supports while also providing support for antimicrobial stewardship programs (which improve patient outcomes, reduce AMR, and save money) in rural, safety net and critical access hospitals.

2. Reviewing Administrative Actions on AMR

In March of this year, the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) released an updated report with clear recommendations to prepare for the next pandemic. Congress should review these recommendations for relevant areas of legislative action.

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[14] Outterson. K. "Trends in the Global Antibiotics Market. Nature Reviews Drug Discovery 22, 174 (2023).

[15] Crisis Looms in Antibiotics as Drug Makers Go Bankrupt. *New York Times*. 25 December 2019.

3. Strengthening Procurement and Late-Stage R&D for Novel Antimicrobials

As mentioned previously, during any public health emergency—a pandemic, terrorist attack, or natural disaster—secondary and opportunistic AMR infections are likely to increase morbidity and mortality in hospitalized patients. This is particularly important for pandemic preparedness, where bacterial infections secondary to viral pneumonia can be the primary driver of death, as was seen in the 1918–19 Spanish Flu Pandemic.[16]

Project BioShield, or PBS, was created in 2004 to accelerate the availability of medical countermeasures (MCMs) to protect against recognized threat agents. Administered by BARDA, PBS contracts fund both late-stage development activities and drug procurement for the Strategic National Stockpile (SNS). To date, BARDA has awarded two PBS contracts to develop/procure small molecule antimicrobials to counter bacterial biowarfare agents.[17,18] These contracts provide a near-term stabilizing effect to the recipient companies through procurement sales and support for mandatory post-approval studies. It is important to maintain and increase funding for PBS to align with current public health needs, specifically for procuring antimicrobials as outlined in BARDA's current Strategic Plan.

VI—Conclusions

Thank you for this opportunity to testify and allowing me to share the positions of small, innovative biotechnology professionals. Every year we wait to address the crisis in the antimicrobial ecosystem is another year patients like Sue Paxton and our dedicated healthcare providers must wait to have access to life saving medicines. Strengthening investments in our Nation's public health preparedness, ensuring readily available stock of innovative antimicrobials in all hospitals and transforming the way we pay for innovation of antimicrobials is paramount to the health and security of our Country's patients. AWG, BIO, and our member companies are committed to serving a resource to the HELP as it works to address AMR and strengthen American innovation.

Senator MARKEY. Thank you, Ms. Miller. Thanks to this great panel. I will turn to questions from the Subcommittee. Ms. Lawrence, as a cystic fibrosis patient, you know more than anyone. CF patients are more prone to infection and must be able to rely on antibiotics that are effective and that you also have to be able to access and afford.

This on top of what can be dozens of pills a day for a CF patient. So can you talk about the importance of developing new antibiotics, Ms. Miller just talked about that, and making sure those antibiotics are available and affordable for people like you.

Ms. LAWRENCE. Yes. Thank you for the question, Chairman Markey. I think that antibiotics are not the most expensive of all of the drugs that I take. They are probably the most affordable. I am a very avid participant in clinical research to try to bring new drugs and therapies to market.

Of all the studies I have done over the decades, I have only done one new antibiotic trial. And even though it did result in lasting permanent side effects, I would do another one in a heartbeat. It is just they are not—we don't have the opportunities to find more antibiotics. So, it doesn't—it's not so much as a cost issue, as it is an availability and development issue.

Senator MARKEY. Thank you. Dr. Boucher, you are treating patients in Boston every single day. You are seeing how bad the

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[16] An Antibiotics Biotech Begins Wind Down, Lays O. Nearly All Works. *Endpoints News*. 6 January 2023.

[17] Fauci, et al. "Predominant Role of Bacterial Pneumonia as a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness".

[18] Venatorx Pharmaceucals Awarded BARDA Project BioShield Contract. 3 October 2022.

opioid crisis has become. Tufts is right there at the center of it in downtown Boston, and it puts people at risk of antimicrobial resistance. So, can you explain to us why people with opioid use disorder are at risk and how can we mitigate that risk?

Dr. BOUCHER. Thank you for the question, Chairman Markey. Yes, sadly, we saw data released about a week ago that in Massachusetts, the opioid epidemic is at its worst, and we are seeing increased numbers of patients with MRSA infections, invasive infections.

The way these individuals get sick, it starts often with a very simple thing, interruption of the skin. So, injection interrupts the protective layer that the skin gives our body. And people are colonized, the skin is colonized with the staph bacteria that gets into their system.

What happens in these individuals is that they become sick, or many of them are also malnourished, have other underlying diseases, hepatitis C, other things, so treating them is complicated. Many of them experience homelessness, so following through on treatment is complicated.

They go into environments where they can spread the infection. That propagates the problem, so it gets into more social problems as well as medical problems. In the hospital, these patients require greater care.

They need to be isolated in private rooms and we have to protect ourselves so that we don't spread the infection to other patients. It adds greatly to costs, to morbidity, and mortality for those patients.

Senator MARKEY. Okay, great. Thank you. And there is no silver bullet. Dr. Apley, could you tell us about the orchestra of different entities that will be needed to work together in order to prevent this crisis from spreading further?

Dr. APLEY. Thank you, Chairman Markey. When I look at that, the combination, it is infection prevention, which is very, very, very important—a huge part of our efforts. Diagnostics. We have challenges with having access to rapid diagnostic tests.

As I understand from my days on PACCARB, we sometimes have challenges getting reimbursed for the tests we do have that we are able to put in.

Accurate tests, and then our antimicrobial susceptibility testing interpretation and continuing to develop breakpoints and more rapid tests for pathogen identification and determining which antibiotics might be the best. Those are really the main components.

The other thing is on both human and veterinary sides are very, very focused initiatives on antimicrobial stewardship. And this also gets into the realm of behavior as it relates to antimicrobial prescribing.

Senator MARKEY. Okay. Thank you. And Ms. Miller, for infectious diseases. Like Dr. Boucher, what is stopping them from using the most innovative antibiotics that they have decided would be best for their patients? What role does your company and companies like it have in helping to ensure that there isn't red tape in between the doctor and their patients?

Ms. MILLER. Well, thank you for the question. So, companies like ours, like Melinta, we are very much focused on creating access anytime we can for patients. When we are working with hospitals and hospital systems, it definitely is quite complicated to get a new product on formulary. There is a bit of a red tape, but our organization works tirelessly to make sure that hospitals are aware of the new—the latest therapies and provide them all the information that they need in order to get our products onto hospital formularies.

However, what we do know is that hospitals are disincentivized from putting new or innovative products on their formulary and having their use because of the cost. It is definitely more of an incentive because of the way reimbursement works in the hospital for hospitals to use older, cheaper generic drugs as front line versus using newer, innovative products.

Senator MARKEY. Great. Thank you.

Senator Marshall.

Senator MARSHALL. Thank you, Chairman. I yield to Senator Budd.

Senator BUDD. Thank you, Ranking Member. Thank the Chairman for having this hearing as well. Mrs. Miller, thank you all and thank the whole panel for being here today. Ms. Miller, your testimony mentions a period between lab research to clinical trial launch as the valley of death, taking anywhere from 10 to 15 years and billions of dollars, as I understand it, before a new antibiotic can come to market. So how can we build on successful public, private partnerships like CARB-X to bring more clinical antibiotic candidates to the market?

Ms. MILLER. As I mentioned before, CARB-X has been really great at reinvigorating the pipeline. Unfortunately, some of those products are far from actually coming to market.

But BARDA has other programs, other private public, partnerships that are helping to bring innovation to the marketplace faster than if companies were trying to do that on their own.

We just announced a recent partnership with BARDA for a public—a private, public partnership. And what that will allow us to do is bring innovation for pediatric patients to market faster.

Senator BUDD. Thank you for that. When I go on their website for CARB-X, it shows a little under—a little over $300 million, little under $400 million that has been invested. What attracted those dollars and how do we make that more, if it is a good program?

Ms. MILLER. Well, I think the first thing is focusing on where is there unmet medical need, right. So, we see the trends. We see where infections are higher, where resistance is higher.

When companies can bring forward ideas to CARB-X for funding, there is an opportunity there for collaboration. There is also the need to focus on preparedness, right.

Not just the infections that we are battling today, but what could be the infections in the future, the pathogens that we need to be most concerned about from a bio threat perspective. There are opportunities to collaborate there as well.

Senator BUDD. Thank you. Now, you also mentioned a second to valley of death when the FDA approves a new drug, but patients can't access it because hospitals keep physicians from prescribing the newest therapies.

Can you go into more detail about the perverse incentives that are out there that keep new therapies on the shelf instead of being prescribed to patients? And then what reforms to the GAIN Act should Congress pursue to bring more novel drugs forward and to ensure patients have access to those drugs?

Ms. MILLER. Well, I want to make sure that it is clear that we support antimicrobial stewardship. We believe it is important to use the right drug at the right time for the right bug. And so, stewardship is important. And as a result, antibiotics and antifungals are going to be used more sparingly than you would see at typical products, especially in a hospital setting.

However, the way reimbursement is set up in the hospital with DRG, hospitals are incentivized to use cheaper or less expensive medication than newer, more potentially costly innovation.

What we would like to see is a reform to reimbursement so that hospitals are not incentivized to put our new—newer antibiotics on the shelf, in reserve, but to use them when it is appropriate.

They need to do the right testing, of course. But when they see that a bug is susceptible to a newer antibiotic or to a newer antifungal, they shouldn't be prohibited from using that because of cost.

At the end of the day, the cost of inaction, of not using the right products sooner cost the health care system money, and of course, it cost lives.

Senator BUDD. Thank you for that. Again, thank you all. I yield.

Senator MARKEY. Thank you, Senator.

Senator Hassan.

Senator HASSAN. Well, thank you, Chairman Markey and Ranking Member Marshall for this hearing. I just also want to thank all the witnesses for your participation and testimony. And Ms. Lawrence, I am especially grateful for your testimony. It is hard to talk about personal experience in a large setting like this, but it is really, really important, so thank you. I want to start with a question to you, Ms. Miller.

You have just been having some of this discussion with Senator Budd, but antibiotic resistance is obviously a serious and emerging threat to global health, and we need to work together to encourage the development of new products that can treat infections that resist current antibiotics.

That is obviously the whole point of our discussion today. What I am understanding is that many large drug companies used to—sorry, used to develop antibiotics, but over the last decade, this field has narrowed to a handful of small biotech companies, right.

You have just been talking with Senator Budd about some of the obstacles for investment here, but for these smaller operations that are now driving the research, are there any obstacles you haven't

discussed to antibiotic innovation and bringing new antimicrobial drugs to market?

Ms. MILLER. Thank you. The crux of it is the commercial marketplace problem. If there were to be a sound commercial marketplace, then you would see larger companies and investors willing to invest in the space. Because of the broken marketplace, this is why you have only a few companies actually doing development in the space.

Fortunately, we do have collaborations with BARDA and other private, public partnerships that are helping and assisting, but it is not enough. We need to fix reimbursement. We need to have pull incentives that will help address the commercial marketplace and make it possible for companies to be sustainable in the space.

Senator HASSAN. Well, thank you for that. One of the things that I think we could do, in addition to pursuing Government investments in boosting the demand for new antibiotics, is to look at ways we could leverage the tax code to provide incentives to startups so that they would engage in this kind of innovative research.

I will continue to pursue that as well. Dr. Boucher, while drug innovation is essential, bringing new anti-microbials to market only addresses part of the problem. And Dr. Apley was just discussing some of that with Senator Markey.

Doctors also need tools like testing capabilities and advanced equipment that can mitigate the threat of drug resistant infections. So outside of new drug development, can you speak to other areas of innovation that are critical to meeting the threat of drug resistant infections, such as diagnostic tests and more advanced antimicrobial surfaces in hospitals?

Dr. BOUCHER. Sure. Thank you, Senator Hassan. Absolutely. So, this problem is a wicked problem, and it requires a multi-pronged approach.

Infection prevention is vitally important, and that is everything from washing our hands to making sure every procedure that we do on a patient is done in the best way to prevent as many infections as possible. Diagnostic testing, which Dr. Apley raised, very important.

We are in a situation where we have the science that has brought us incredible technology for diagnostic testing, but there is this disconnect in both the way they are developed and approved by the Food and Drug Administration, in the way they are reimbursed by the Government and private payers and in hospitals. That has been a barrier. Then I will come back to the workforce.

In my role as a dean, I have the privilege to help educate the workforce of tomorrow. And that is not just physicians, it is all other health professionals. We need experts to do this work.

You heard from Dr. Apley a little bit of how complicated it is to actually choose the right drug for the right patient. We need to be able to attract people to do this work so that our children and their children will be protected.

Senator HASSAN. Well, thank you for that. And that takes me to my last question, which is to Dr. Apley. You have written exten-

sively about promoting the responsible use of antibiotics in animals. How do we engage all providers in a broader conversation to promote responsible, medically appropriate use of antibiotics?

Dr. APLEY. Thank you for that question. I will address from the veterinary side what we are doing. We work through both producer organizations and veterinary associations.

We have developed guidelines for our veterinarians to put stewardship programs in action, and we spend a lot of time starting right at the start with case definitions, diagnostics, and applications, and then reasonable choices.

It is a combination effort between everyone on our side of caring for animals, and the—we have had one whole meeting at PACCARB that based on—was based on communication. And that communication aspect and aiding in that communication is the basics of all of it.

Senator HASSAN. Well, thank you. And I will yield back and may follow-up in terms with all of you about what resources and guidance is useful to practitioners, and how we can make sure they have the best information readily available. Thanks.

Senator MARKEY. Thank you.

Senator Marshall.

Senator MARSHALL. Right. Thank you, Mr. Chairman. Ms. Lawrence, you are a living, breathing miracle. And we want you to know that we want you to see your son graduate from high school. We want to see you have grandchildren someday as well. And I remember my first patient—with cystic fibrosis.

I mean, there was once upon a time no cystic fibrosis patients would think about conceiving, and it was certainly just an incredibly tough pregnancy if they did. So, in many ways, the innovation is working because of these innovative drugs as well. What is the doctor, your doctor says about your future? What does your future look like?

Ms. LAWRENCE. Thank you for the question, Ranking Member Marshall. There have been so many medical advances, especially with the highly effective modulators, but they are not a cure and they do not prevent infection. They have offered a level of stability, which has been really nice——

Senator MARSHALL. Is that gene therapies, the modulators?

Ms. LAWRENCE. Not—the highly effective modulators as in Trikafta, which I can explain more but it would take me a long time.

Senator MARSHALL. That is Okay.

Ms. LAWRENCE. It stabilizes the experience. It stabilizes—for many patients, it raises pulmonary function tests and decreases infection. I have been in clinical trials for every generation of these modulators, and it has made a big difference, but it is not stopping me from getting infections.

That is my biggest threat. And also, like the infection breeds pneumonia, breeds hemoptysis, and it is just this vicious cycle. So that is my biggest threat by far. And if I may, Ranking—Chairman

Markey, I just wanted to add to my answer to your question about new antibiotics.

There is also a timing factor. And while I have very good access to health care and affordable insurance, in order for them to cover a new antibiotic, they make it extremely hard, and there are hoops that need to be jumped through and cultures take days to come back, while my infection is rapidly like progressing to pneumonia and other——

Senator MARSHALL. Is there like a prior authorization issue that your doctors have to go through?

Ms. LAWRENCE. With some of the newer antibiotics, you have to submit a culture. You have to prove that all the antibiotics are resistant. You have to test it to see if you are—it is this whole process that requires often in-patient hospital stays. So, they definitely do not make it easy to access the newer antibiotics.

Senator MARSHALL. Thank you. Dr. Boucher, I am going to get a free medical consult from you here. Most of your patients you see are probably people that survive organ transplants. That they have—maybe they have taken cancer therapy recently and then we lose them to an infection. What would the message of hope you give to a cystic fibrosis patient like Ms. Lawrence? What do you need to be successful so she can see her grandchild?

Dr. BOUCHER. Yes, thank you for the question. It is a huge privilege to take care of patients before and after transplants, and after lifesaving chemotherapy, and with cystic fibrosis.

What we physicians and all clinicians need is we need tools in our toolbox, right. We need ways to prevent infection and we need drugs to treat those infections, which still happen. So, and it is not just one, as was pointed out earlier.

We need a pipeline that is robust and renewable because we know resistance will march on. And so really finding a solution to that. That is the idea of the subscription model as a way to focus on value, not volume, of antibiotics, to use them well through stewardship, but to have them be developed and delivered to our patients in ways that are predictable and reproducible so that those drugs that the Government invests in will be on the shelf in my pharmacy when a patient has a life threatening infection.

Not requiring a weeklong prior approval, but on the shelf, in the pharmacy, in Boston for the patient.

Senator MARSHALL. Got it. Dr. Boucher, not many people have watched somebody die. What is it like to watch your patients die because you don't have the right antibiotic? It starts off as a kidney infection, starts off with the pneumonia. What is it like to watch them die and not have the antibiotic that you need?

Dr. BOUCHER. Well, I will just start by saying I chose the profession of infectious diseases 30 years ago to cure patients, right. Antibiotics, as Senator Markey said at the open, are curative, lifesaving drugs.

I came into this field to cure people of infections and send them home to live their lives—to enjoy the transplant, that precious gift that they get. So, coming to the point where I have had the sad duty to sit with a lady who lived through rounds of chemotherapy

for her leukemia, who had an infection for which we had no therapy, and to watch her go from sitting in the chair to sicker and sicker and dead in a number of days, is beyond heartbreaking.

It is a privilege to care for patients at that time in their life, but it is absolutely heartbreaking and not the reason that I went into medicine or so many others go into medicine.

Senator MARSHALL. Thank you. Dr. Apley, speak a little bit about what agriculture protein production that we have done to decrease the use of antibiotics and to address these issues, and specifically talk a little bit about how the 2017 law has impacted your world.

Dr. APLEY. Thank you, Senator Marshall. If you go back to 2017 and look at the FDA sales data for antibiotics following that, and 2017 was the start of the transition to all medically important antibiotics used in feed to the veterinary feed directive, and any used in water to under veterinary control.

The next year we saw, for example, tetracycline use dropped by around a third as the veterinarians took control of that and had discussions with their clients based on the stewardship principles.

The last time a new antibiotic group was approved that we use in food animals was 1978, that a new group was approved. So, we are using tried and true older compound groups. We get new members of them. Also, if you look at our veterinary organizations, we ascribe to the AVMA stewardship definition and the ways we go through to look at those.

The other thing that just happened July 1 of 2023 was that all of our antimicrobials now that were previously over the counter have gone under veterinary control. So, veterinarians are involved in all decisions.

We have some very frank and candid discussions about what we should and shouldn't be doing and how we address the issues of prevention control, animal movement, etcetera, biosecurity to decrease the need.

Senator MARSHALL. That is great. And by the way, we have some agriculture initiatives with food supplements, feed supplements that would also decrease a lot of those bacteria as well. Ms. Miller, I am going to finish up with you, several questions here as well. Big picture, how many failures does your company have before they get a—get one across the finish line?

Ms. MILLER. Well, I mean, in this space, you probably have a 1 percent chance of getting a product from initial idea of conception to approval. It is a pretty high failure rate when it comes to development and a pretty costly one.

Senator MARSHALL. Yes. When—I used to help run a hospital and you try to keep your formulary tight from a cost management standpoint. And some of the antibiotics that you would make maybe only be used 5, 10, 20 times a year as well, and there is no way that my hospital could afford to keep that in stock.

We think about the DRG reimbursement. So, we would—if a patient is admitted for pneumonia, we are going to get a lump sum of money, whether we use ampicillin or a cephalosporin, or maybe

your miracle drug as well. So, a basic DRG, and I know there is exceptions to that.

Can you just kind of walk us through what your solution would look like for that type of patient that probably is going to be resistant. They have got COPD and they have been in the ICU for 3 days already.

They are not getting better. It is drug resistant antibiotic. What would the solution be look like from a reimbursement model?

Ms. MILLER. Well, I think it is important to look at the big picture. So, yes, there is a DRG, and I do believe that we need to reform reimbursement. We can look at using NTAP as an example. That is already a framework in place, and we can make reforms to it so that antimicrobials are better suited for use in the NTAP construct.

However, we have to look at what does it cost to have that patient hospitalized for extended period of time. I can tell you that every day a patient is in a hospital not getting the care that they need, further deteriorating, costs the hospital and costs health care much more than it would be——

Senator MARSHALL. Probably $5,000 or $10,000 a day, literally——

Ms. MILLER. Exactly. We have to really consider that the products that we have developed, that we have made available, or we are making available to patients, are curative, right. This is invaluable.

Senator MARSHALL. Right. I appreciate the answer and be respectful. I need to move on. I do appreciate everybody coming to—your testimoneys. I need to go to another hearing. I would like to come back, and circle back about how do hospital share that particular drug.

Not all small hospitals could keep every one of those in stock, but how do we better share those as well, and so that Tufts can get it tomorrow, but also Great Ben Regional Hospital can get it tomorrow as well. So, thank you so much, Chairman.

Ms. MILLER. Thank you.

Senator MARKEY. Thank you, Senator Marshall. And again, thank you for your partnership on this issue.

Senator Hickenlooper.

Senator HICKENLOOPER. Thank you, Mr. Chairman. Thank all of you for your time. I still—I was trying to come up the stairs. I still barely have caught my breath coming up the four floors here. Obviously, microbiologically weakened somehow. On a more serious note, I first learned—I learned firsthand the importance of what we are talking about today.

My father passed away in 1960 after a long battle with colorectal cancer. But a big part of his challenge was the fact that they pretty much only had penicillin in those days, and after a couple of years, several operations, he would get infections that they were unable to treat.

My mother would tell stories about waking up in the middle of the night several times and having to—he would have had cold

sweats and she would have to roll him over and get clean sheet under him, then roll him back on a clean sheet, get the rest of the sheet put down, and what a trial that was for him every night.

It is amazing that we have come so far and yet we still haven't progressed as far further as one would hope in this issue. So, I will start with Dr. Boucher. The development of new antimicrobial drugs hasn't kept pace with the increasing rate with—these pathogens become drug resistant.

Obviously in large part due to the fact that there is not much financial incentive, as we are hearing discussed today, to innovate in this drug space. We have co-sponsored the PASTEUR Act, which you referred to, which would allow the Federal Government to enter into subscription contracts with critical need antimicrobials.

Dr. Boucher, how would the subscription mechanism embedded in the PASTEUR Act incentivize the development of new antimicrobials?

Dr. BOUCHER. Thank you very much for your question, Senator, and for your support of the PASTEUR Act. The PASTEUR Act uniquely values antibiotics for their value, not for their use. So, it delinks any incentive to overuse antibiotics, and it focuses on the most needed antibiotics for the most resistant infections.

There are clear criteria the developer needs to meet to get this benefit of this subscription reimbursement, guaranteed reimbursement, and it is linked to stewardship, which is very, very important to ensure that we clinicians use the antibiotics in the best way possible so that they are preserved for as long as possible.

This is felt to be a much needed first step in getting us back to a healthy economic framework for antibiotics. And I just wanted to come back to the comment about CARB-X that was made earlier. CARB-X is probably the most successful public, private partnership with BARDA and many other agencies.

To date, CARB-X has over a dozen products in clinical trials—that is in patients. And if we don't see progress in something like the PASTEUR Act, all that investment will go to waste, and those medicines won't get to our patients. So really, really important, and thank you so much for your support.

Senator HICKENLOOPER. Of course. And thank you for all your work. Ms. Miller, a lot of the drug research and development is obviously, as has been discussed by all of you, hard work and doesn't often have many victories.

Many of the skilled professionals behind this research the creators of these innovations, are often lured away from the uncertain antimicrobial drug market for more commercially viable pursuits. The PASTEUR Act is designed specifically to help reduce some of that uncertainty and to improve the viability of the market.

In your opinion, how would the stability of the PASTEUR Act help support recruitment and retention, not just recruitment, but retention of the workforce we need to develop these drugs?

Ms. MILLER. Thank you, Senator, for the question. Absolutely, there has been a brain drain, we call it, in the ID space. You have talent within the industry who really have concerns about how much there has been an underinvestment in antimicrobials.

People have left and gone to other pursuits like oncology and other chronic diseases where the marketplace is more certain. What PASTEUR does and novel pull incentives, it creates the possibility of stability in the marketplace.

Knowing that there would be a sustainable marketplace would then help bring people back into the space, not just people from a development point of view, but investors as well.

Senator HICKENLOOPER. Right. And I see I am out of time already. That is impossible, but anyway, I will try to get back. If I don't, I will make sure that my additional questions get entered into—you all get a chance to see them and respond in writing. Thank you all again for your great public service.

Senator MARKEY. Thank you, Senator.

Senator Braun.

Senator BRAUN. Thank you, Mr. Chairman. It is an interesting discussion because it looks like we are up against a foe that so easily out maneuvers us. The more you use something that is effective, temporarily, the more you are giving it the chance to change and require something different.

I got interested in this, and it is I think called a spirochete instead of a bacterium, but it was something that we didn't know much about at all—tick borne diseases. And then you find out that it is an old drug called doxycycline, that is the only thing that can knock them out. And I guess what I am wondering is, are we in a never ending battle of where we can never get ahead of this?

When you are saying only 1 percent of any investment in something to waylay any new malady hits paydirt, where does this dynamic end? Because it looks like the dynamic generally favors the micro-organism.

My question would be, start with Dr. Boucher, what is the most recent example where there has been something so bad, so widespread, where a current antibiotic wasn't working? How long did it take to marshal the resources when you knew that you needed to, to actually get something to the marketplace that was going to work?

Dr. BOUCHER. Thank you for your question, Senator Braun. I think we have to look at the example of COVID, right. It is a virus, not a bacteria, but we marshaled—we marshaled, right, and got a vaccine into arms in less than a year, right, and drugs into patients very quickly, remdesivir, etcetera.

We can do this, right. The science exists. There are numbers of candidates, drugs, the vaccines, diagnostics that have advanced scientifically. There is no dearth of science. The issue is really this economic problem and solving that at the same time as we enact the multi-pronged approach of prevention, surveillance, good diagnostic tests, all the other things that are required to combat this wicked problem, but we live in a country where technology is advanced.

We transplant every day. Heart transplant is normal—at normal business in a hospital today——

Senator BRAUN. We did that in the matter of—because a lot of that research was kind of building toward it, and it finally got ap-

plied. What would you say if that urgency is there, because sooner or later it will be either another virus or a bacterium or even like a spirochete currently where we have so many more diseases that are out there, tick borne that we didn't know about.

Thank goodness, doxycycline, very inexpensive, still works. So, what would you say when it comes to an antibiotic, not an antiviral, unless they are completely analogous in terms of how you would get there. Was there anything recently when it has come to something that had to have an antibiotic and how long did it take?

Dr. BOUCHER. Yes, I guess I would say, if we look at the most recent antibiotic approvals, go back and drill back to them, that was approved for Acinetobacter infections, that is less than 10 years.

That was—that is an infection that we know is coming. It is multi-drug resistant. So, this is a game where there needs to be planning in advance for the threats we know and some we don't know. Someone mentioned candida infections earlier. Candida auris was not on the CDC threat list in 2015. It is in 2019.

Senator BRAUN. Is it one of the biggest concerns right now—?

Dr. BOUCHER. It is a big concern.

Senator BRAUN. Yes.

Dr. BOUCHER. We need infrastructure, and we need something like the PASTEUR Act. I think that is the one thing that you all can do is to advance that bipartisan——

Senator BRAUN. That we are not doing it ad hoc based upon the very urgent need. Someday that may not be quick enough.

Dr. BOUCHER. Correct.

Senator BRAUN. Ms. Miller, would you want to weigh in?

Ms. MILLER. Well, we—so definitely there is a cost to inaction, and we do need to be planful, we do need to prepare. There is great science out there. It is just waiting to have a stable home to land in.

If there is one thing that I would ask that be done today is we need to reform the commercial marketplace. We need reforms to reimbursement. We need pull incentives. We need to fix the commercial marketplace.

Senator BRAUN. Anybody else want to weigh in quickly?

Dr. BOUCHER. I will just add one thing, that the PACCARB released a report in March, linking pandemic preparedness to AMR, right. This is not if, it is when, and this report goes through all the different aspects that need to be addressed, including the PASTEUR Act.

Senator BRAUN. Thank you.

Senator MARKEY. Thank you, Senator.

Senator Smith.

Senator SMITH. Thank you, Mr. Chairman. Thanks for this hearing. I don't know if everyone in this room knows this, but today is Senator Markey's birthday, I believe. I could not miss this opportunity to embarrass you in front of the whole Committee staff.

Senator MARKEY. You have been very successful.

[Laughter.]

Senator SMITH. It is always dangerous to go against your Committee, your Subcommittee Chairman, your Committee Chair like this, but happy birthday Ed.

Senator MARKEY. Thank you.

Senator SMITH. I really appreciate all of you, and I appreciate very much this hearing. And I am getting clearly this—the broad message of this hearing, which is that we need to take a comprehensive and holistic approach.

We need to improve access to education about infection prevention measures like vaccines and handwashing. We need to make sure that we are using antimicrobials responsibly, whether it is in the hospital or in agriculture or in veterinary medicine.

We need to be investing in the development and manufacturing of new antibiotics in a market that isn't broken, in a market that is really fix, that is working well. And so, I want to dive into this from the perspective of shortages in antibiotics and what we have seen with this issue, and whether or not this question of a supply chain is part of the broken part of the market. We saw shortages of antibiotics in this last year.

We know that this is about, sometimes it is the antibiotic itself or sometimes it is the component of the drug that we don't have. And it was with this in mind that caused me to team up with Senator Cassidy on our now bill, now law, the Onshoring Essential Antibiotics Act, which basically helps to expand—the concept is to expand domestic manufacturing capabilities by allowing HHS to award grants to antibiotics manufacturers to build or upgrade facilities here in the U.S. to basically onshore our supply chain.

Let me start, Dr. Boucher, could you just talk a little bit about how you see this shortage affecting patients and your view of this?

Dr. BOUCHER. Thank you, Senator Smith, for the question. We have seen antibiotic shortages for some years, and we see them almost routinely. Our hospital pharmacists, send a thing out every week telling us about shortages, and we manage them often creatively thinking about substitutions and ways to manage.

But sometimes it is not easy and sometimes it does affect patients. I am in a very fortunate position to have expert pharmacists who work with me and supply chain experts. In rural hospitals, in critical access hospitals, it is not so easy, and the impact is greater.

Addressing this is a huge need, and thank you for your attention. I will mention that especially injectable antibiotics require very special kinds of manufacturing, often, which is difficult.

This is part of the reason we need a more robust pipeline, and we need to think about things like oral antibiotics. We haven't had a new oral antibiotic in over a decade.

Senator SMITH. Well, I think one of the things that we learned from the pandemic is the threats that we have when we do not have onshored manufacturing of so many things, including antibiotics.

Maybe, I am wondering, Ms. Lawrence, if you would like to comment from your own personal experience whether you have seen

issues with not being able to get access to an antibiotic that you really needed because it just wasn't available? Not about price, it is about availability.

Ms. LAWRENCE. Yes, thank you for the question, Senator Smith. I have been impacted by antibiotics shortages and other medical or medicinal shortages as well. And I am extremely fortunate to have an amazing care team at Boston Children's Hospital that knows how to work, pull, navigate.

I also happen to have a best friend who is a pharmacy manager and can help with the pharmacy side. But I am very lucky to have that, and if I didn't have that, if I were elderly and didn't know how to navigate the system, or if I didn't have the connections that I have, I would not know even where to begin to work around that shortage.

Senator SMITH. Yes, thank you for that. I think that is really important. And you both are making the comment about how antibiotic shortages affect different people differently based on who they are, where they live. I just have a few more minutes.

Dr. Apley, I wanted to ask you about the concept of One Health, and the idea that human health and animal health are inextricably linked and that too often our Federal agencies that oversee these—oversee this sort of work in their silos, rather than thinking about how we need to be thinking, again, holistically and comprehensively about bugs.

I am wondering if you could talk a bit about this concept, what you see around the One Health framework. Senator Young and I worked on this together, and we have been working hard with the Department of Agriculture in particular to get this One Health framework adopted. Could you just talk a bit about where you see this going?

Dr. APLEY. Again, going back to experiences on PACCARB, that was one of the fundamental underlying things, is we are all in this together. If you look at the list of the American Veterinary Medical Association's important resistant organisms in veterinary medicine, and you look at the CDC's list in human medicine, you will see pseudomonas staph aureus, nontyphoidal salmonella listed in both.

We share a lot of organisms that we have challenges with, and we also share a lot of the same needs for diagnostics, for helping get the best information to our practitioners together, understanding our human behavior and its interaction with how we dispense, and so many of the same messages, so many—so much of the same information is vital to both physicians and veterinarians that it is absolutely wrapped up together.

Senator SMITH. Thank you. I know I am out of time, Mr. Chairman. I appreciate this hearing very much.

Senator MARKEY. You can have extra time for wishing me a happy birthday. Thank you so much, Senator Smith. Let me ask you, Ms. Lawrence, your disease is one that actually has had enormous progress because of what the families have done. My friend who I went to Malden Catholic High School with, Joe O'Donnell, his boy Joey contracted cystic fibrosis and there was no cure.

Companies really weren't doing the research on it. So, he along with the families each year raised money and then said to biotech companies, if you do research in cystic fibrosis, we will give you our money to do the research. And ultimately, the families raised hundreds of millions of dollars in order to incentivize research. And that is where a company named Vertex got their funding. It was from the families, to give them that incentive.

These breakthroughs have all come because of that incredible entrepreneurial activity. My friend ultimately wound up, Joe O'Donnell, going to Harvard Business School. So, we use that model to incentivize the private sector to move. And Joey, little Joey would be your age today, but he passed away at a very, very young age.

But now life expectancy has been lengthened dramatically. So, we know that it can happen. We know that the breakthroughs are there. And we just have to find the methodologies that ensure that we are going to have research, be medicine's field of dreams from which we harvest the findings to give hope to families that they won't suffer unnecessarily from diseases in their family's lives.

How, Ms. Lawrence, can we better support patients in response to anti-microbial resistance?

Ms. LAWRENCE. Thank you for the question, Chairman Markey, and happy birthday as well. I actually met Joe last July at a conference and he is wonderful, and he has done so much for the community, as has the Cystic Fibrosis Foundation.

I work with them on several levels, and I think that they are—one thing that they really do well to drive community incentive in working together and funding different things is that they have a patient centered model of care. So, they hear the patient voice. They take into account the community needs and where the lack is, and that better directs the science.

They have like patients like myself have input at a research level, at a grant level, at a need—like at a workshop level. At every level of the process, the patient voice is front and center, and that has really driven where the money goes and progress.

Senator MARKEY. Beautiful. Thank you. Dr. Boucher, in your written testimony, you talked about how climate change facilitates the risk of anti-microbial resistance. Can you talk more about that?

Dr. BOUCHER. Thank you, Senator Markey, for the question. We know that climate change leads to more antimicrobial resistant infections through a number of ways. One is through wound infections in warmer temperatures often are infected with antimicrobial resistance organisms.

Waterborne organisms travel more, and we see more antimicrobial resistance there. And a lot of pathogens are picked up from the soil that has more resistant organisms in warm and hot climates.

We are already seeing the impacts and we are doing studies in the Tuft Center looking at wastewater to see—and we are seeing changes already with just the small incremental changes in temperature we have seen.

Certainly, very linked, and linked in a one health way, right, from humans, animals, and the environment, as we see climate change evolve.

Senator MARKEY. As temperatures warm, insects, animals now migrate to other parts of the planet that otherwise they would never have moved. And then that causes disease to migrate in ways that perhaps those populations are not as protected against.

Dr. BOUCHER. Absolutely. We see migration of vectors of illness, things like animals, and we see evolution in places where infection isn't recognized because people haven't put two and two together that the area is moving. For example, moving South like we have seen with Lyme disease, something very endemic in Massachusetts, which has now moved way South in our Country.

Lots of change, lots of room to act in the positive as well. And truly back to the wicked problem, one of the multipronged approaches needs to be really thinking about climate active impacts on AMR.

Senator MARKEY. Again, wicked is such a Massachusetts, Boston word as well, so it is bad. So, Dr. Apley, you are an advocate of the one health perspective. Could you explain the One Health approach and how our environment affects the people's health in the context of antimicrobial resistance?

Dr. APLEY. I think we have been able to identify common approaches that by supporting them we advance stewardship and our antibiotic decisions across every place we use them. One of the things that has happened in the PACCARB, again, was as we start to look at issues of fungi, we have brought in someone on that committee—that counsel, excuse me, that is an expert in agricultural applications of antimicrobials.

We realized that this One Health really does involve the environment and any place we might be using the antimicrobials. And again, it involves diagnostics, preventives, new and novel ways of preventing disease and dampening it down.

Once you break down the silo, just personally from seven and a half years on PACCARB, the things I learned from the human side that I take the veterinary medicine, and I think maybe that went the other way too, that having a group that is just really focused on breaking down those silos is incredibly important.

Senator MARKEY. Thank you. Ms. Miller, you are the chair of the Antimicrobials Working Group, the pharmaceutical and medical device industries coalition on this issue.

According to the Government Accountability Office, the existing development of new drugs that could treat bacteria currently resistant to medications is insufficient.

Ms. Miller, how are companies partnering with the Federal Government to incentivize drug development with FDA pathways and exclusivity periods, and is that partnership working?

Ms. MILLER. Thank you for the question. Happy birthday. So there are really good and productive public, private partnerships to support AMR. It isn't enough in the end, right, because we need to make sure that we are continually innovating because the bugs are continually evolving.

We need to ensure that we have an ongoing stream of innovation to have newer, safer antimicrobials over time. But existing relationships, they are working though, right, and we need to continue that.

At the crux of it, though, we do need to address the commercial marketplace because I believe that if we do that, we will create an incentive for companies and for investors to come back into the space to do more development and to ensure that the relationships that we do have, the partnerships that we do have, these products can actually land in the marketplace effectively.

Senator MARKEY. Again, let's talk about that. The families with cystic fibrosis, I think there were only 35,000 in America, they saw a market inefficiency. They saw where the private sector was not going to respond.

They injected themselves into it, raised the money, said to a number of companies, you do the research we will help to fund you, and ultimately Vertex emerged out of those companies as the one that was doing the best work. So that was a market inefficiency. Just too few people are affected.

What do we have to do, Dr. Boucher, in order to deal with this issue that such a small number of people potentially benefit from it, but by benefiting from it, they also stop the spread of it, potentially.

Dr. BOUCHER. Senator Markey, happy birthday. I don't want to forget. And thanks for the question. So, you hit on one of the key really important criteria for antibiotics, right. The use in one patient affects the whole community. So that is the way we should care, even if this particular infection only impacts a few.

I am going to come to something that we haven't talked about explicitly that I think is really important, and that is awareness. So, it is a sad reality that in 2023 we still have an awareness problem for this AMR in our Country. And holding this hearing is a good step in that, and that is what many of us at this table spend our time trying to do. But we have to do better, right.

We still lack a clear voice and a clear patient voice. The National Action Plan has called for a Federal champion for AMR. In the UK, you might have seen Dame Sally Davies. She is the champion of AMR. She is now a U.N. Ambassador. She has done more for this in the world. She is leading and I think we need that in our Country.

I hear you loud and clear. We are doing more clinical trials with patients at the table. As we develop the questions and trials through the NIH and Antibacterial Resistance Leadership Group, we are making progress on looking at quality of life. Lots more to do and lots more rallying from the base in terms of patients and families.

Senator MARKEY. Talk a little bit more about the champion. Who is that person and what are they doing?

Dr. BOUCHER. The champion that I have seen is this—Dame Sally is the spokesperson in Europe and globally now for this problem. So, across the Government, across the globe, actually speaking

for the different stakeholders and bringing very practical things to the table with one voice and really being recognized.

We at PACCARB recognized this back in 2015, 2016, and it was incorporated into the National Action Plan, it just hasn't been implemented. But I think appointing such an individual would help advance this problem and our response to it.

Senator MARKEY. You are saying that the Administration should appoint, name a champion.

Dr. BOUCHER. Yes, the ask is the President——

Senator MARKEY. A person has a spotlight to continue to keep this issue front and center.

Dr. BOUCHER. Yes, sir. That is the ask.

Senator MARKEY. Okay. We will try to help you to accomplish that goal. I think that is a great idea. And we need to have somebody who is in charge to be applying the pressure that all of the families in our Country feel on this issue.

Let's do this, let's—and thank you all, by the way, so much for this incredible hearing today. I think you are really advancing the cause, and you can see the enormous interest which the Subcommittee has in this subject.

Let's do this, let's give each one of you 1 minute to summarize what you want the Subcommittee to retain from your testimony today. Just to—and we will go in reverse order of the original testimony so that you can give us your summary to the jury, to the Subcommittee in terms of what our agenda should be. What should we remember from today's hearing? So, we will begin with you, Ms. Miller.

Ms. MILLER. Thank you. And maybe what I will also start by saying is that while AMR is an issue where sometimes we only have antibiotics or antifungals to address a few patients, what we do know is that there are a number of patients that are affected by AMR every day. They are dying from infections.

They may have cancer and maybe their loved one thinks that they are dying from cancer, but they actually die from an infection. And so, this is an everyday person's problem. It is not something that is in the future to be a problem for our families and our loved ones. It is a today problem for folks.

What I would definitely like for everyone to walk away from today's discussion is to really understand that AMR is a threat to us, to our society, to our medical and health care system. That we need to have adequate development and ongoing innovation in this space to ensure that we will be able to save patients' lives. We also need to address the commercial marketplace.

This is definitely something that really needs the Federal Government to step in and address. We need to see reforms in reimbursement. We need to see pull incentives like the PASTEUR Act be put in place so that all of the development, all the public, private partnerships that are happening today actually have a place to land and that patients can get the lifesaving medicines that they need.

Senator MARKEY. Thank you. Ms. Lawrence.

Ms. LAWRENCE. I hope that I have given a human depiction of what antibiotic resistance looks like so that it becomes more relatable to most. And I hope that I brought a sense of humanity to the issue that it is not, many of us are not as impacted by something until it happens to us, and until we are personally affected by it.

I hope that I can shed some light or that the Committee takes away, this is a global problem that will affect you at some point in time. So how proactive do you want to be? And I second the PASTEUR Act before this Congress as well.

Senator MARKEY. Thank you. And thank you for your powerful testimony here today. You were invaluable in putting the human face on this crisis.

Dr. Boucher.

Dr. BOUCHER. Thank you, Senator Markey. I echo the gratitude for being here and emphasizing that this problem is here and now, affects all of us, and we need to act immediately.

We need to ensure that we have a workforce to prepare for and address this problem, and we need to advance the PASTEUR Act, the bipartisan act supported by the IDSA and over 200 organizations that will provide a subscription model for the most needed antibiotics and is linked to good stewardship and the prudent use of those antibiotics. Thank you.

Senator MARKEY. Thank you, doctor.

Dr. Apley.

Dr. APLEY. Thank you, Chairman Markey. Two things. I want to be very clear that new antibiotics are very, very important. But as a clinical pharmacologist, I also see a need for advancing our understanding of the regimens we use for existing antimicrobials. I think that could be a very big thing we could support.

No. 2, one of the words we really haven't used here today is risk. And when a physician or a veterinarian takes a stand on antimicrobial stewardship and saying, I know you want one, but we are not going to, there is a risk that is undertaking, and supporting physicians and veterinarians in undertaking that risk with information and collaboration is incredibly important.

Senator MARKEY. Okay. Thank you, Dr. Apley, very much. And we thank everyone who has participated today, especially our witnesses who have traveled here today from Massachusetts, Kansas, and New York.

Each witness here told us loud and clear, if we do not address antimicrobial resistance, we will face a growing health care threat to our Country. And today, we are not only illustrating the problem, but illuminating the path forward. We need a health care system that puts people first, providers to have all the tools readily available to treat patients with the best medications available.

We need to find a way in which we incentivize the development of new solutions to this problem, and we need a healthy planet that doesn't facilitate the spread of these deadly diseases.

Ordinarily, at this point, I would ask unanimous consent to revise and extend my remarks or the remarks of the Committee

Members here. But in this instance, I am going to ask to revise and delete any references to my birthday from the record.

[Laughter.]

Senator MARKEY. Without objection. And I ask unanimous consent to have a statement from stakeholders outlining priorities for addressing antimicrobial resistance.

[The following information can be found on page 50 in Additional Material:]

Senator MARKEY. For any Senators who wish to ask additional questions for the record, it will be open for 10 business days until July 25th at 5.00 p.m., and all Senators are invited to ask those questions in writing, and for the witnesses then to answer them in writing as well.

With that, this very important hearing is adjourned. Thank you.

ADDITIONAL MATERIAL

HEALTHCARE LEADERSHIP COUNCIL,
July 11, 2023.

Hon. ED MARKEY *Chairman*,
Hon. ROGER MARSHALL, MD, *Ranking Member*,
Senate Committee on Health, Education, Labor, and Pensions,
Subcommittee on Primary Health and Retirement Security,
Washington, DC.

DEAR CHAIRMAN MARKEY AND RANKING MEMBER MARSHALL:

The Healthcare Leadership Council (HLC) appreciates the opportunity to provide comments in advance of your hearing, "Superbugs: The Impact of Antimicrobial Resistance on Modern Medicine."

HLC is a coalition of chief executives from all disciplines within American healthcare. It is the exclusive forum for the Nation's healthcare leaders to jointly develop policies, plans, and programs to achieve their vision of a 21st century healthcare system that makes affordable high-quality care accessible to all Americans. Members of HLC—hospitals, academic health centers, health plans, pharmaceutical companies, medical device manufacturers, laboratories, biotech firms, health product distributors, post-acute care providers, homecare providers, group purchasing organizations, and information technology companies—advocate for measures to increase the quality and efficiency of healthcare through a patient-centered approach. We are uniquely positioned to address innovation comprehensively from all perspectives in the healthcare industry.

HLC thanks you for focusing on the critical issue of antimicrobial resistance (AMR) and urges Congress to enact S. 1355/H.R. 2940, the "Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act of 2023," as an important step in this effort.

AMR poses a serious threat in the U.S. and around the world. AMR is the leading cause of death globally. It is estimated to have directly caused at least 1.27 million death and contributed to another 5 million deaths in 2019.[1] In the U.S., more than 2.8 million antimicrobial-resistant infections occur and are responsible for more than 35,000 deaths each year.[2] Because emergencies often exacerbate the AMR crisis, measures to address AMR should be incorporated into broader emergency preparedness efforts. For example, the COVID-19 pandemic caused a surge in hospitalizations and ventilator use. As a result, U.S. hospitals experienced a 15 percent

[1] Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis, The Lancet, (January 19, 2022), *https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-90/fulltext*.

[2] National Infection & Death Estimates for Antimicrobial Resistance, Centers for Disease Control and Prevention (December 13, 2021), *https://www.cdc.gov/drugresistance/national-estimates.html*.

increase in AMR infections and deaths in 2020.[3] Hurricanes and other natural disasters also increase the spread of infections. AMR should also be considered in bioterror preparedness, as agents used by bioterrorists may be genetically engineered to resist current therapeutic antimicrobials.

Despite tremendous need, there is still a lack of progress in the development of critical new antibacterial therapies to tackle the threat of AMR. Of the 12 antibiotics that have been approved since 2017, 10 belong to existing classes with established mechanisms of AMR. In 2021, the World Health Organization (WHO) reported only 27 new antibiotics in clinical development against priority pathogens, down from 31 products in 2017. Of the 27, only six products meet at least one of the WHO's criteria for innovation—which include absence of known cross-resistance, new target, new mode of action, and/or new class—and only two acts against critical gram-negative bacterial pathogens, which are multidrug-resistant and have few other treatment options.[4]

This stagnant innovation not only fails to meet the serious current threats AMR poses, but we can expect the consequences to modern healthcare to continue to grow in the future if no action is taken. It is important that new incentives, including post-market incentives, are put in place to help provide the economic certainty needed to bring these critical medicines to the market. HLC supports the innovative subscription model proposed in the PASTEUR Act. Payment modes based on volume only exacerbate the risks of AMR, as over-usage of antibiotics is a major driver of resistance. Under the PASTEUR Act, the Federal Government can enter into contracts with innovators to pay for a reliable supply of novel antimicrobials with payments that are decoupled from the volume of antimicrobials used.

This delinked approach is similar to Project Bioshield, which provides multi-year funding to support procurement of medical countermeasures (MCM) for national security. Like MCM, antimicrobials have a very limited commercial market. The PASTEUR Act will provide antimicrobial innovators with a more predictable return on investment necessary to revitalize the antimicrobial pipeline.

Thank you for your efforts to address the AMR crisis. HLC looks forward to working with you on our shared priorities. If you have any questions, please do not hesitate to contact Debbie Witchey.

Sincerely,

MARY R. GREALY,
President.

[Whereupon, at 11:39 p.m., the hearing was adjourned.]

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