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IDSA
Infectious Diseases Society of America

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Committee on Health, Education, Labor
and Pensions
United States Senate
Washington, DC 20510

Dear Senate Health, Education, Labor and Pensions Committee Members:

On behalf of the Infectious Diseases Society of America (IDSA), thank you for holding the hearing to consider the reauthorization of the Pandemic and All-Hazards Preparedness Act (PAHPA). However, we were dismayed to review Dr. Reshma Ramachandran's testimony and to see several assertions related to the PASTEUR Act that we believe are unsupported by facts.

The bipartisan PASTEUR Act would support the development of novel antibiotics to address unmet needs and support their appropriate use to optimize patient outcomes and limit the development of resistance. The legislation is strongly supported by IDSA, along with more than 200 organizations representing health care professionals, patients and scientists.

Antibiotics are central to preparedness. Secondary resistant infections complicate outbreaks and pandemics. During hurricanes, loss of electricity and safe water and interaction with flood waters increases the risk of foodborne infections and waterborne pathogens. During wildfires, burns can quicky become infected. And resistant pathogens can be weaponized for bioterror purposes.

There is broad expert consensus about the need to develop novel antibiotics to treat resistant infections. Below we address claims about how those antibiotics should be studied and evaluated and the role of the PASTEUR Act.

Current Clinical Trial Approaches Already Yield Superior, Clinically Meaningful Antibiotics

Dr. Ramachandran states that FDA has approved antibiotics "of unclear benefit and at worst, antimicrobials that are less effective than what is currently available." In reality, daptomycin, dalbavancin, ceftazidime-avibactam, and ceftolozane-tazobactam — all antibiotics to treat multi-drug resistant infections — were approved through traditional non-inferiority trials that primarily enrolled people with non-resistant infections. Pre-approval, extensive pre-clinical data showed a high likelihood these drugs would be superior to existing drugs; clinical trials showed they were as safe and effective as existing treatments. Post-approval data clearly showed these drugs are superior in patients with life-threatening multidrug-resistant infections. The actual problem is that far too few novel antibiotics are being developed at all, due to significant financial hurdles.

Superiority Trials for Antibiotics are Typically Infeasible and Unethical

Requiring antibiotics to outperform existing ones via superiority trials reflects a fundamental misunderstanding of how drug-resistant infections work and how clinical trials are conducted. Such a requirement would actually undermine efforts to develop the antibiotics our patients need. Superiority trials for antibiotics are extremely difficult because they can put patients' lives at risk and require a large number of study participants. Requiring that a new antibiotic be proven superior in a clinical trial presupposes that patients in the control group receive a drug that may be unsafe or ineffective. Unlike many other medical conditions, untreated or inadequately treated bacterial infections can worsen within a few hours, putting patients at imminent risk of sepsis and death. Ethically, we must give these patients the best available treatments. We cannot give them a drug that we suspect won't work. In the field of HIV we have approved many antiretroviral drugs based on the fact that they are non-inferior to available therapies. This non-inferiority approach is sound and well established.

Enrollment of Only Patients with Confirmed Resistance is Infeasible and Fails to Prepare for Future Threats

Dr. Ramachandran further criticizes antibiotic clinical trials for failing to enroll a sufficient number of patients with confirmed resistant infections. First, a lack of rapid diagnostics makes it challenging to confirm resistance in a timely fashion, and patients who are critically ill must often be treated empirically, meaning they are given antibiotics while physicians await test results in an effort to avoid serious consequences like sepsis and death. This treatment may disqualify patients for a trial. Second, patients with resistant infections are often seriously ill from other health conditions as well, further complicating efforts to enroll them in trials. Third, the best time to develop a novel antibiotic is before we need it for large numbers of patients. Our pace is already far too slow to keep up with emerging resistance and slowing it further will cost more lives needlessly.

PASTEUR is Designed to Deliver the Antibiotics Patients Need

To receive a contract under PASTEUR, antimicrobials must meet certain characteristics, including:

- improving clinical outcomes for patients with multi-drug resistant infections;
- treating an infection for which there is unmet need;
- being a new class of antibiotic;
- having a novel target or novel mechanism of action; or
- having an improved route of administration, such as oral.

The more characteristics the drug meets, the higher the value its contract can be. An interagency committee, advised by non-government experts, would develop a list of infections for which new antimicrobial drugs are needed and regulations regarding the drug characteristics and how the characteristics will adjust the monetary value of a subscription contract.

Importantly, PASTEUR would also provide much needed resources to hospitals and long-term care facilities to support their antimicrobial stewardship programs, to guide appropriate antibiotic use in order to improve patient outcomes and limit the development of resistance.

Urgency of Addressing Antimicrobial Resistance

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 globally. The post-antibiotic era is not just a looming threat — for many patients it is here.

Antibiotics enable and sustain modern medicine because so many of our modern medical advances carry a risk of infection and rely upon antimicrobials. Cancer chemotherapy, organ transplants, hip and knee replacements, C sections and other surgeries and complex care save and enhance human lives, but carry risk of infection. Clinicians are only able to provide this care because they have safe and effective antibiotics to prevent and manage infectious complications. As our antibiotic arsenal diminishes, our modern medical gains are unraveling, and patients are facing devastating consequences.

Considering the scope of the problem, it is particularly troubling that Dr. Ramachandran would make these unfounded statements.

IDSA represents over 12,000 infectious diseases physicians, scientists and other health care and public health professionals dedicated to the prevention, diagnosis and treatment of infectious diseases. Our members have been on the front lines of the COVID-19 pandemic and other outbreaks including Ebola, Zika and mpox. Infectious diseases (ID) physicians are also leading the fight against the public health crisis of antimicrobial resistance (AMR)—caring for patients with resistant infections, leading antimicrobial stewardship and infection prevention programs, and conducting research, including clinical trials. IDSA is proud to support the PASTEUR Act and we encourage the HELP Committee to include it in PAHPA reauthorization.

Sincerely,

Carlos del Rio, M.D, FIDSA

President, IDSA