IDSA Headquarters
1300 Wilson Boulevard
Suite 300
Arlington, VA 22209
TEL: (703) 299-0200
FAX: (703) 299-0204
EMAIL ADDRESS:
info@idsociety.org
WEBSITE:
www.idsociety.org

IDSA
Infectious Diseases Society of America

November 5, 2018

The Honorable Alex M. Azar II
Secretary
United States Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Secretary Azar:

The Infectious Diseases Society of America appreciates the administration's National Biodefense Strategy. We specifically offer our strong support for the goals and objectives relating to antimicrobial resistance (AMR) domestically and internationally. We are pleased to share policy recommendations below. Further, we welcome the opportunity to collaborate closely with you and your staff on these priorities.

IDSA represents over 11,000 infectious diseases physicians, health care professionals and scientists who are on the frontlines of preparedness and response activities related to biodefense and, more specifically, antimicrobial resistance. IDSA members care for patients with serious infections, including those caused by multidrug-resistant pathogens; lead emergency preparedness programs and antimicrobial stewardship programs at their health care facilities; collaborate with other public health leaders; and lead basic, translational and clinical research necessary for the development of medical countermeasures, including new antibiotics, diagnostics and vaccines.

Background: AMR Threatens Biosecurity and Routine Patient Care

Antimicrobial resistance threatens our biosecurity and poses significant challenges for patients and public health. From a security standpoint, resistant pathogens complicate the wounds of our soldiers, increasing their risk of limb loss, additional complications, and death, and compromise our military's combat-readiness and effectiveness. Alarmingly, resistant pathogens are also a prime candidate for weaponization by our nation's enemies, both state and non-state actors. Further, wounds and burns resulting from a mass casualty event can become infected quickly, and AMR makes those infections much more challenging to treat.

From a clinical perspective, antibiotics are the foundation upon which many medical advances rest. As AMR makes infections more difficult and, sometimes, impossible to treat, a wide variety of medical services are becoming increasingly risky, including solid organ and bone marrow transplants, cancer chemotherapy,

joint replacements and other complex surgeries as well as care of preterm infants and other immunocompromised patients. Thus, biodefense-focused strategies to combat AMR can also have a broad positive impact on patient outcomes and public health.

Strengthen awareness of drug-resistant pathogens and their associated diseases and improve stewardship of medically important drugs.

IDSA Recommendations:

- **Provide increased funding for the CDC Antimicrobial Resistance Solutions Initiative to strengthen surveillance.**
- **Provide increased funding for the CDC National Healthcare Safety Network and consider additional policies to increase the number of healthcare facilities reporting data on antibiotic use and resistance and make that aggregate data available to investigators for research.**
- **Require all hospitals to implement infectious diseases physician-led antibiotic stewardship programs as a Condition of Participation in Medicare and ensure full implementation of existing stewardship requirement for long term care facilities. Explore opportunities to expand infectious diseases physician-led stewardship in outpatient settings.**
- **Utilize grant funding to support stewardship implementation in all healthcare settings.**
- **Expand opportunities to utilize telehealth to broaden access to stewardship experts.**
- **Invest in research to evaluate and understand best practices in stewardship specific to various health care settings.**
- **Support AMR public awareness efforts.**
- **Invest in strategies to address global resistance rates and to reduce the spread of resistance across countries and into the United States.**

IDSA strongly supports the goals of improving awareness about AMR and implementing antimicrobial stewardship. A robust surveillance system is essential to ensure that clinicians, public health officials and other key stakeholders recognize emerging resistance threats and understand resistance patterns. This knowledge is fundamental for developing optimal responses. The Centers for Disease Control and Prevention (CDC) Antibiotic Resistance Solutions Initiative has developed infrastructure for AMR surveillance in all 50 states and some major cities. Increased investment is needed to allow state and local health departments to keep pace with additional pathogens and resistance patterns, and evolving technologies. AMR is a threat that does not respect international borders and some very serious AMR threats that have spread to the United States have originated in other countries. Thus, global AMR surveillance is also essential. Increased funding will allow CDC experts to inform and support global AMR surveillance.

The CDC National Healthcare Safety Network (NHSN) offers a module through which healthcare facilities may report data on antibiotic use and resistance. As of January 1, 2018, over 616 facilities from 48 states are reporting antimicrobial use data and over 231 facilities from 27 states submitted at least some antimicrobial resistance data. This represents a 40 percent increase for hospitals reporting use data and a 27 percent increase for resistance data over the previous six

months. While the upward trend is encouraging, there are still significant gaps in reporting which hinder our understanding of antibiotic prescribing and resistance trends and how to best improve them. We strongly encourage you to invest additional resources in NHSN so that it can provide the necessary technical assistance to allow additional health care facilities to report antibiotic use and resistance data. In addition, we encourage consideration of additional policies to strengthen reporting, such as incentives for facilities and providers.

Antimicrobial stewardship is critical to stem the tide of resistance. In the US, CDC estimates that about 50 percent of antibiotic use in outpatient settings and about 30 percent in inpatient settings is inappropriate. Similarly, studies have shown that up to 75% of antibiotics prescribed in nursing homes may be unnecessary or inappropriate. Robust antimicrobial stewardship programs led by infectious diseases physicians have demonstrated notable effectiveness in reducing inappropriate antibiotic use. Further, these programs reduce health care costs and improve patient outcomes.

About three quarters of all acute care hospitals in the US currently have stewardship programs that are aligned with the CDC Core Elements. While this represents important progress over the last 9 years, we urge universal adoption of stewardship as critical to effectively address resistance and ensure that all patients benefit from stewardship. We strongly encourage you to require that all hospitals implement infectious diseases physician-led stewardship programs that align with the CDC Core Elements as a Condition of Participation in the Medicare program.

We greatly appreciate that a Condition of Participation requiring stewardship is already in place for long-term care facilities, given the high volume of antibiotics prescribed in these settings and the vulnerable nature of many of their patients. We would greatly appreciate an update regarding compliance with this policy, including activities underway to ensure complete implementation. One of the critical barriers in stewardship implementation in long-term care facilities is lack of on-site expertise. We encourage HHS to facilitate greater collaboration between long-term care facilities and infectious diseases physicians to increase compliance and ensure that the programs implemented are appropriately robust. Telemedicine offers an important tool to expand access to infectious disease physicians with stewardship expertise.

We encourage HHS to strengthen partnerships between public health departments and local infectious diseases physicians focused on promoting antibiotic stewardship program development in additional healthcare facilities, including not only hospitals and longer-term care facilities, but also dental clinics, dialysis centers, urgent care and other healthcare settings. We also encourage the administration to explore opportunities to expand stewardship in outpatient settings. CDC has provided guidance for stewardship specific to outpatient settings, but much work remains to promote and measure uptake.

To support stewardship implementation in all health care settings, we encourage you to provide grant funding and additional appropriate support to ensure that stewardship programs have the necessary resources to support stewardship leaders by providing the needed protected time to develop and implement effective programs. In addition, we also want to emphasize the important role of telehealth in expanding access to stewardship experts for health care facilities that may not have sufficient infectious diseases physician support on-site. Telehealth-based stewardship

programs are already demonstrating impressive results, and we encourage you to consider opportunities to expand use of this approach. As stewardship programs are more widely adopted, it will be important to invest in research to evaluate the effectiveness of specific approaches and share best practices.

While facility-level stewardship programs have a strong, proven track record and should be universally adopted, additional efforts to help patients and their families better understand antimicrobial resistance and the risks associated with inappropriate antibiotic use could be extremely beneficial as well. IDSA is a longstanding partner of World Antibiotic Awareness Week and we conduct significant media and public outreach, including sharing stories of patients who have been harmed by antimicrobial resistance. We would welcome the opportunity to partner with the administration on additional awareness efforts.

Finally, we must all remember that infectious diseases do not respect national borders. It is essential to expand stewardship efforts globally to reduce resistance around the world, particularly in countries with some of the highest rates of antibiotic misuse and resistance. HHS may wish to consider funding research to better understand optimal approaches for reducing the spread of resistance across multiple countries.

Strengthen understanding of the drivers of drug resistance and improve the development and adoption of effective mitigation measures.

IDSA Recommendation:

- **Provide increased funding for AMR research through the National Institute of Allergy and Infectious Diseases, Department of Defense, Veterans' Administration, Agency for Healthcare Research and Quality, and other agencies as appropriate**

IDSA greatly appreciates growing investment from the National Institute of Allergy and Infectious Diseases on AMR research. One important example of supported research is the Antibacterial Resistance Leadership Group (ARLG), which was launched in 2013 to prioritize, design and execute clinical research that will reduce the public health threat of antibacterial resistance. ARLG research focuses on several key areas, including early clinical evaluation of new antibacterials, strategy trials to optimize the use of currently available antibacterials, treatment-based prevention measures, diagnostics testing, and effective infection control and stewardship programs and activities.

Since June 2013, the ARLG has initiated over 40 studies that include over 18,000 patients. The ARLG also activated over 130 clinical trial sites and established collaborations in 19 countries. The ARLG developed a virtual biorepository catalogue, a web-based system that provides researchers with access to well-characterized bacteria for the development of diagnostic tests, novel antimicrobial compounds and for studies evaluating mechanisms of resistance. The ARLG has shipped over 1400 strains to 28 approved requestors.

ARLG has maintained a strong focus on multidrug-resistant pathogens classified as urgent or high priority threats. Two key projects have focused on Carbapenem-resistant

Enterobacteriaceae (CRE), also known as the "nightmare bacteria." These studies have sought to develop a national understanding of these pathogens, their epidemiology and their clinical burden. Together, to date, these studies included more than 3000 patients across 17 states and the District of Columbia.

Additional funding would allow the ARLG to expand its efforts to target additional high priority pathogens as well as add sites in more states and countries. Such funds would also mean that ambitious, but essential, interventional trials can be performed to define best treatments for highly antibiotic-resistant bacterial infections. The knowledge gained from ARLG research will be essential in guiding further government and private sector efforts to address AMR and develop new antimicrobial drugs, diagnostics and preventive measures.

Promote the use of preventive and therapeutic options other than antimicrobial drugs.

IDSA Recommendations:

- **Promote strong vaccine requirements to boost and maintain high immunization rates.**
- **Advance policies to increase access to vaccines, including comprehensive Medicare coverage of vaccines with zero out-of-pocket costs.**
- **Increase CDC funding to support vaccine infrastructure.**

Vaccines are one of the best tools we have for preventing infections, but their impact is limited by suboptimal uptake. Childhood vaccine rates remain strong throughout most of the US, but misinformation is driving vaccine hesitancy and suppressing immunization rates in various communities. CDC recently reported an increase in the number of children in the US who reach their second birthday with zero vaccinations and further estimated that 40,000 child-lives are saved each year through childhood vaccination. While many of the serious vaccine preventable illnesses making resurgences in recent years are caused by select viruses and bacteria, including measles, mumps and pertussis, these infections can result in antibiotic use due to secondary bacterial infections. Similarly, influenza immunization rates continue to lag far below national targets, prompting increased use of both antiviral medication for influenza (for which rapid development of resistance is also a concern) and antibiotics for secondary bacterial infections. Among older adults—a population at increased risk for many infectious diseases and complications—immunization rates for recommended vaccines are disturbingly low. Only 66.9% of adults aged 65 or over received the pneumococcal vaccine in 2016, and only 33.4% of those over 60 received the herpes zoster (shingles) vaccine.

These data indicate that we must do more to increase vaccine uptake, including supporting strong immunization requirements and strengthening policies to improve access to immunization. For seniors, fragmented Medicare coverage of vaccines contributes to depressed immunization rates. Vaccines covered by Medicare Part B with no out-of-pocket costs (influenza and pneumococcal) have significantly higher uptake rates than those covered by Part D with out-of-pocket expenses of up to $102. IDSA recommends that all recommended vaccines be covered by Medicare with zero out-of-pocket costs to increase uptake and prevent infections that lead to antibiotic use and the development of resistance.

While improved coverage for vaccines is an important step, we must also invest in vaccine infrastructure to adequately raise immunization rates. This includes increased investment in CDC to support state and local health department immunization programs, education and support for providers, immunization information systems or registries, vaccine storage, vaccines for the uninsured and quality measures.

Accelerate basic and applied research and development of new antimicrobials, novel preventatives and therapeutics, vaccines, and diagnostic tests.

IDSA Recommendations:

- **Implement new "pull" incentives for antibiotic R&D that are de-linked from antibiotic sales and use.**
- **Increase investment in existing "push" incentives for antibiotic R&D, including funding for NIAID and BARDA, and create new "push" incentives such as tax credits.**
- **Target incentives toward unmet medical needs and require companies receiving incentives to make commitments regarding stewardship and appropriate access.**
- **Optimize use of the new Limited Population Antibacterial Drug (LPAD) approval pathway.**

The antibiotic pipeline is insufficient to meet patient needs or to address serious biosecurity threats. We are grateful that the pipeline has improved as a result of federal interventions, including the Generating Antibiotic Incentives Now (GAIN) Act, the Limited Population Antibacterial Drug (LPAD) approval pathway, and increased investment in antibiotic research and development (R&D) by the Biomedical Advanced Research and Development Authority (BARDA) and NIAID.

Unfortunately, the pipeline remains very fragile, with very few new antibiotics in development that target critical needs; frighteningly few companies engaged in antibiotic discovery and development; and the vast majority of new antibiotic R&D being conducted by small companies struggling to attract investors. Antibiotics are very costly and risky to develop, and it is very challenging for companies to secure a return on their investment because new antibiotics must be used judiciously to preserve their utility.

While antibiotic approvals have been declining for decades, we have experienced a small uptick after 2012, due in large part to the new incentives described above. However, the companies responsible for this uptick are struggling. Over the last 18 months, stock prices for all late stage antibiotic companies have fallen significantly. With extremely little or no opportunity for these companies to be acquired by large pharmaceutical companies (as these companies see no financial gain to such an investment), small companies are faced with very high infrastructure costs to bring new products to market. Securing investment to fund commercial infrastructure is extremely difficult given minimal opportunities for return on investment. If these companies fail, not only will they be unable to continue antibiotic R&D, but such failures could send even worse

signals to investors and other companies, further weakening the antibiotic pipeline. We must act quickly to prevent this potentially catastrophic downturn.

Innovative approaches are necessary to provide companies with a reasonable opportunity for return on investment in antibiotic R&D. Traditional sales-based revenue is insufficient and inappropriate for antibiotics because it fails to incentivize R&D and is misaligned with the goals of antimicrobial stewardship. The true value of an antibiotic cannot be captured only through the prescriptions of that antibiotic. We must consider the broader value of having safe and effective antibiotics available to make possible a wide variety of life-saving medical interventions, to protect the broader public health by limiting the spread of infections, and to be readily available in the event of a serious bio-emergency. Creative incentives should reflect this value without jeopardizing stewardship or appropriate access.

For example, prizes or awards could be provided to new antibiotics upon approval to provide a timely, predictable return on investment that is de-linked from the antibiotics' sales or use. Previous estimates have indicated that awards of $500 million or more would be a powerful incentive. However, more modest awards could be meaningful, particularly for small companies in the near term. A US launch of such an award could encourage other nations and non-government partners to launch similar awards. Further, legislation to reauthorize the Pandemic and All Hazards Preparedness Act that passed the House of Representatives in July 2018 and is pending in the Senate would provide BARDA with broad new authority to undertake new strategic initiatives to support antibiotic R&D, and IDSA believes this provision would permit BARDA to offer such an award.

While we strongly support a new antibiotic prize or award through BARDA, we recognize that BARDA's funding and other important priorities may limit the number of such awards it could offer. We encourage you to explore additional financial and regulatory funding opportunities through the various departments and authorities identified under the National Biodefense Strategy. Collaborative financing proposals could pool resources across agencies to provide the types of incentives necessary to meet antibiotic R&D goals. This would be appropriate, as AMR impacts many aspects of national security, health care and public health. IDSA was also very encouraged by Food and Drug Administration (FDA) Commissioner Scott Gottlieb's repeated calls for new models of reimbursement for antibiotics, and we encourage you to work with the Centers for Medicare and Medicaid Services (CMS) to reimburse for new antibiotics in a fashion that reflects their high value to society and promotes their appropriate use.

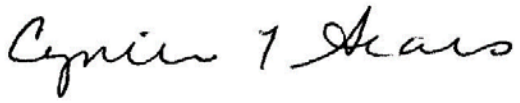
IDSA recognizes the importance of careful use of taxpayer resources and supports targeting new incentives to antibiotics that address unmet needs. The funding opportunities identified above are suggestions on ways in which the federal government can bring new and valuable resources to bear in ways that are fiscally sensitive. We also believe that companies receiving such incentives should be required to make commitments in support of stewardship and appropriate access.

While new "pull" incentives, as described above, are necessary, continued investment in "push" incentives is equally essential to develop a robust, renewable antibiotic supply. We strongly support increased funding for NIAID and BARDA and encourage the administration to advance new "push" incentives such as tax credits to help reduce high antibiotic R&D costs.

In addition to economic incentives, IDSA also urges you to continue improving the regulatory environment for antibiotic R&D. Over the last few years, improved guidance from FDA has been very important for developers. IDSA strongly believes that the new LPAD pathway has the opportunity to be a powerful tool for bringing urgently needed new drugs to market. We encourage the FDA to optimize use of this new pathway by supporting more innovative clinical trial designs and providing developers the opportunity to share clinical trial data with clinicians even if such data is insufficient to warrant an indication. Given our extremely limited antibiotic arsenal, such data may still be valuable for expert clinicians who need to treat patients infected with multidrug resistant organisms.

Once again, IDSA thanks you for your commitment to biosecurity and developing approaches to limit AMR. We would welcome the opportunity to discuss our recommendations with you at your earliest convenience and we stand ready to assist you with your important efforts.

Sincerely,



Cynthia Sears, MD, FIDSA
President, IDSA