

Urgent, Comprehensive Federal Action Needed To Stem Mortality and Medicare Costs Associated With Antimicrobial Resistance

Vance G. Fowler Jr,¹ Amanda Jezek,² Emily S. Spivak,³ and Kathy Talkington⁴; On behalf of the Infectious Diseases Society of America and The Pew Charitable Trusts

¹Infectious Diseases, Duke University School of Medicine, Durham, North Carolina, USA; ²Infectious Diseases Society of America, Arlington, Virginia, USA; ³Infectious Diseases, University of Utah Health, Salt Lake City, Utah, USA; and ⁴The Pew Charitable Trusts, Washington, DC, USA

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This paper is a call to action for the policies necessary to reduce the burden of antimicrobial resistance, including federal investments in antibiotic stewardship, antibiotic innovation, surveillance, research, diagnostics, infection prevention, the infectious diseases workforce, and global coordination.

Keywords. antibiotic development; antimicrobial resistance; stewardship; workforce.

In their paper “Mortality and Healthcare Costs Associated with Multidrug-Resistant Bacterial Infections Among Elderly Hospitalized Patients in the United States,” the authors raise important points that should inform federal policy. Multidrug-resistant bacterial infections cause significant mortality and result in high healthcare costs, particularly for the Medicare population. The majority of the costs and mortality identified in the analysis were caused by 2 groups of pathogens—methicillin-resistant *Staphylococcus aureus* and extended spectrum beta lactamase producing Gram-negative bacteria. Control efforts that target these specific pathogens stand to provide great potential impact. In addition, the spread of carbapenem-resistant Enterobacterales (CRE), which cause infections that are extremely difficult to treat, is cause for great concern and should be a focus of national efforts. We outline the policy recommendations necessary to reduce the burden of antimicrobial resistance (AMR), and call upon our colleagues in healthcare, public health, and research to join us in advocating for solutions needed to secure the safe and effective arsenal of antibiotics on which modern medicine relies.

Our responses to AMR as a nation must be based on data, and the federal government must strengthen our ability to collect and

analyze these data. Although improvements have been made, unacceptable gaps in our understanding of AMR continue to limit our ability to effectively target and evaluate interventions. As an example, our current understanding of the impact of AMR on mortality and healthcare costs relies on estimates and modeling. Although such analyses provide value and make clear that the AMR burden is significant, we urgently need the collection and reporting of real-time data, rather than estimates, to better inform policies and decision-making [1]. Specifically, we call for increased funding for the Centers for Disease Control and Prevention (CDC) to strengthen public health infrastructure to facilitate the necessary surveillance, including making specific resistant pathogens reportable in all hospitals nationwide. Pathogens to consider making reportable nationwide could include methicillin-resistant *S aureus* because it is the most common multidrug-resistant bacterial infection in the United States, constituting more than one-half of all multidrug-resistant infections nationwide; extended spectrum beta-lactamase producing Enterobacterales, the second most common multidrug-resistant bacterial infection in the United States [2]; and CRE, carbapenem-resistant *Acinetobacter baumannii*, and carbapenem-resistant *Pseudomonas aeruginosa*, the top 3 critical priority pathogens identified by the World Health Organization [3].

Although surveillance and data collection must improve, the available data make clear that AMR is a public health crisis that worsens patient outcomes and increases healthcare costs. A stronger comprehensive federal policy response is necessary and must include sufficiently resourced commitments to antibiotic stewardship, research, innovation, the workforce necessary to advance this work, and global coordination. The second iteration of the National Action Plan for Combating Antibiotic

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Correspondence: Amanda Jezek, 4040 Wilson Blvd, Suite 300, Arlington, VA 22203, USA (ajezek@idsociety.org).

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Tables 1. Key Federal Policy Recommendations to Combat AMR

Issues	Recommendations
Surveillance/data collection	Increase CDC funding to facilitate the necessary surveillance, including making specific resistant pathogens reportable in all hospitals nationwide.
Stewardship	Deepen funding and coordination of efforts to strengthen stewardship, including expanding the workforce and improving measurement of antibiotic use and appropriateness.
Innovation	Enact the PASTEUR Act to pay for novel antimicrobials based on value, not volume, and reinvigorate the antibiotic pipeline.
Diagnostics	Increase funding to support research and development of diagnostics that can rapidly provide accurate, actionable results on antimicrobial susceptibility. Support outcomes studies to inform impact on antibiotic use and stewardship, educational materials, and reimbursement of tests.
Research	Expand AMR research funding, including to support a clinical trials network to conduct large-scale and pragmatic studies of antibiotics for antibiotic-resistant infections.
Infection prevention	Strengthen community-based prevention (including immunization uptake) and facility-based prevention, such as containment measures recommended by CDC.
Workforce	Provide appropriate compensation, loan repayment and training opportunities for the infectious diseases workforce, spanning clinical, research, and public health settings.
Global coordination	Expand US funding to support AMR surveillance, stewardship, and prevention in low resource countries and strengthen coordination with WHO.

Abbreviations: AMR, antimicrobial resistance; CDC, Centers for Disease Control and Prevention; PASTEUR, Pioneering Antibiotic Subscriptions to End Upsurging Resistance; WHO, World Health Organization.

Resistant Bacteria, released by the US Department of Health and Human Services in October 2020, aims to address many of these priorities and includes many of the policy goals and objectives necessary to do so, but its success will hinge on the allocation of funding by Congress and improved coordination across the US government [4]. Further, the action plan lacks sufficiently bold proposals to strengthen antibiotic research and development and to secure the infectious diseases workforce necessary to combat AMR, highlighting where new legislation is urgently needed. Our specific recommendations (Table 1) are further described below.

ANTIBIOTIC STEWARDSHIP

The overuse and misuse of antibiotics in human health, animal health, and the environment drive the development of resistance, and One Health approaches to reduce inappropriate use in all settings are essential. Where antibiotic stewardship programs have been implemented, they have affected notable documented successes in improving patient outcomes and reducing inappropriate antibiotic use and resistance rates, length of hospital stay, incidence of *Clostridium difficile* infections, and healthcare costs [5–11]. In an important step forward, the Centers for Medicare and Medicaid Services issued a new Condition of Participation in September 2019 requiring hospitals to establish antibiotic stewardship programs. However, progress is uneven because many hospitals lack the resources necessary to fully implement all evidence-based stewardship protocols. The coronavirus disease 2019 (COVID-19) pandemic has further stressed hospital budgets, sometimes causing resources to be diverted away from antibiotic stewardship (including furloughing stewardship staff and eliminating stewardship staff positions), despite the pressing need given the high rates of antibiotic use among patients with invasive COVID-19, the complexity of therapeutics for COVID-19 treatment, and the important contributions of

stewardship teams to pandemic response [12]. Although long-term care (LTC) facilities are also required by Medicare to have antibiotic stewardship programs, they also need additional resources to support successful implementation. Moreover, 85%–95% of antibiotics used in human health in the United States are prescribed in outpatient settings [13], and much work remains to implement stewardship in these settings. From 2011 to 2016, oral antibiotic prescription rates decreased 5% overall, and rates of prescriptions dispensed to children decreased 13%, whereas adult rates increased 2% [14]. The United States needs a concerted, well-funded effort to improve antibiotic use in all healthcare settings, including stronger efforts to measure antibiotic use (such as through the CDC’s National Healthcare Safety Network), to better define appropriateness and establish clear benchmarks for antibiotic use, resources for technology that supports stewardship, research to develop new stewardship tools, and significant investments in the physician and pharmacist workforce to conduct day-to-day antibiotic stewardship efforts. Establishing evidence-based staffing benchmarks for stewardship programs will likely be useful. Additionally, we need policies that incentivize improvement of antibiotic prescribing by outpatient clinicians and practices, while providing resources for stewardship activities, including research in outpatient stewardship, across the different types of ambulatory care settings.

ANTIBIOTIC INNOVATION

The availability of safe and effective antibiotics underpins modern medicine, allowing for successful cancer chemotherapy, transplantation and other surgeries, and care of medically complex patients [15]. However, even appropriate use of antibiotics can contribute to developing bacterial resistance. Although we can and must slow the development of resistance through antibiotic stewardship, we cannot stop it entirely, making a renewable

antibiotic pipeline all the more essential for patients. In its 2019 review, the World Health Organization described the outlook of the clinical antibiotic pipeline as “bleak” and asserted that more public investment is needed to support antibiotic innovation [16]. Although policies such as the Generating Antibiotic Incentives Now Act and increased funding for the Biomedical Advanced Research and Development Authority and the National Institute for Allergy and Infectious Diseases are essential and have contributed to important progress, they remain inadequate. Most large pharmaceutical companies have exited antibiotic research and development, and small companies that have brought new antibiotics to market struggle to remain in business.

We must fundamentally change the way the United States pays for critical new antibiotics. We must reward value and recognize the enormous societal benefits of antibiotics [17]. Operation Warp Speed has been remarkably successful in bringing COVID-19 vaccines to market in record time, demonstrating the results that can be possible when the federal government invests sufficiently in scientific discovery and development. The bipartisan Pioneering Antibiotic Subscriptions to End Upsurging Resistance (PASTEUR) Act would achieve this goal by establishing a new subscription model for critically needed novel antibiotics that provides antibiotic developers with a predictable return on investment through federal payments that are delinked from antibiotic sales and use. It is important to target limited federal resources to areas of greatest unmet need—those infections with few or no treatment options—and we believe PASTEUR would do so effectively by directing federal experts, in consultation with nongovernment experts, to determine the ideal characteristics of antibiotics that would qualify for the bill’s subscription contracts. PASTEUR would also create a new grant program for hospitals to support the implementation of antibiotic stewardship programs. PASTEUR was introduced in the House and Senate in the fall of 2020 and was reintroduced in June 2021.

DIAGNOSTICS

Diagnostic tests, particularly rapid diagnostics, play a crucial role in supporting optimal antibiotic selection and reducing inappropriate use of antibiotics. Numerous barriers inhibit the development of new diagnostics and the clinical uptake of existing tests. We need more outcomes studies to demonstrate the large-scale benefits of diagnostic tests in improving patient care, effects on antibiotic use and need for additional antibiotic stewardship intervention, and ability to reduce and reducing healthcare costs. Such studies will improve uptake and reimbursement for tests, which can also help spur greater innovation. Outcomes studies can also inform needed educational materials to persuade providers to use diagnostic tests to guide treatment, rather than empiric administration of antibiotics. We also need increased federal funding to support the research

and development of more and better tests, in the absence of a lucrative commercial market [18]. In particular, diagnostics that can rapidly provide accurate, actionable results on antimicrobial susceptibility for bacteria and fungi are greatly needed.

RESEARCH

In addition to the research and development of new antibiotics, the United States must also invest in research that deepens our understanding and strengthens our approaches to antibiotic resistance. This should include basic research to understand the underpinnings of AMR as well as translational and clinical research, including a reliable, sustainable infrastructure for clinical trials. Similar to what has been successfully undertaken in the United Kingdom for COVID-19 clinical trials, effort should be made to create a national network across US hospitals to conduct large-scale and pragmatic studies of antibiotics for antibiotic-resistant infections. Such a network would likely contribute to better understanding of how to optimize antibiotic use.

An important step in the right direction is the Antibacterial Resistance Leadership Group (ARLG). Funded by National Institute for Allergy and Infectious Diseases, ARLG was established in 2013 to prioritize, design, and execute a clinical research agenda to improve the prevention, diagnosis, and treatment of infections caused by antibiotic resistant bacteria. The ARLG has made tremendous gains (such as creation of the Multi Drug Resistant Organism-Clinical Trials Network) [19], improving clinical trial design (including the Desirability of Outcome Ranking endpoint [20], quality of life assessment for bacterial infections [21], and the MASTERMIND study design for diagnostic platform registrational trials) [22], informing guidelines for clinical practice (including optimization of vancomycin dosing) [23], and helping to train the next generation of researchers in the field [24]. However, research needs continue to outpace available funding.

INFECTION PREVENTION

Preventing infections is an optimal strategy for reducing antibiotic use and preventing the spread of multidrug resistant infections is particularly important. The CDC recommends aggressive containment strategies, with detection and response activities, to keep new or rare resistance threats from spreading. The CDC estimates that such containment efforts could prevent 1600 CRE cases annually [25]. More resources are needed to support CDC, state and local health departments, and health facilities working together to prevent infections. Special attention should be paid to infection prevention in LTC settings. As we have seen with outbreaks of *Candida auris*, CRE, and of course COVID-19, LTC facilities play a critical role in halting transmission, and sufficient resources and standards are crucial. It is equally important for the United States to fund

community-based prevention efforts, including increasing uptake of recommended immunizations.

ID PHYSICIAN WORKFORCE

As the COVID pandemic has shown, infectious diseases physicians are essential to modern medical care. For example, infectious diseases physicians are central to the fight against AMR—leading stewardship and infection prevention programs, driving research, and caring for patients with multidrug-resistant infections. Ensuring the continued vitality of this vital but dwindling workforce must be a key component of our national strategy to combat AMR [26]. From 2010 through 2014, applications for adult infectious diseases fellowship programs declined from 342 to 254 [27]. The numbers rebounded following adoption of an “all-in match” and increased mentoring and recruitment efforts from the Infectious Diseases Society of America but then plateaued. In 2019, there were 328 applicants; 79.3% of fellowship positions were filled. Fifty-eight programs (37.7%) failed to fill all available slots in the Infectious Diseases Fellowship Match, with 30 programs (19.0%) failing to fill any slots [28]. The numbers and matching rates for pediatric infectious diseases fellowship programs are even bleaker. Ever-growing levels of medical student debt, coupled with lower salaries compared with other medical specialties, has made the subspecialty of infectious diseases financially impossible for many new physicians. Federal policies are needed to provide appropriate compensation, loan repayment and funded training opportunities for infectious diseases physicians in clinical practice, antimicrobial stewardship, research, and public health.

GLOBAL COORDINATION

Expert bodies including the World Health Organization, CDC and many others have appropriately asserted that international collaboration will be necessary to effectively combat AMR. Although new AMR threats may emerge internationally, many will ultimately reach the United States. The COVID-19 pandemic may worsen AMR, given the high rates of antibiotic use, even among patients without secondary bacterial infections. The impact may be greater in low- and middle-income countries given the limited funds to support antimicrobial stewardship and laboratory capacity [29]. Globally, there remain significant opportunities to prevent infections through increased vaccination, better sanitation, and infection prevention and control strategies in healthcare systems. Many countries need better use of and access to antimicrobials, as well as improved laboratory capacity to detect resistance threats. The CDC currently provides support to 28 countries to address AMR, but additional funding is needed to extend this support to additional countries to address unmet needs. Improved coordination between CDC and the World Health Organization will also be crucial. The United Nations Interagency Coordination Group on Antimicrobial Resistance is encouraging, as are

ongoing conversations, including the April 2021 United Nations High Level Dialogue on AMR and repeated discussions at the World Health Assembly to review progress and persistent and emerging needs.

Although Medicare costs remain a consistent point of concern for many policymakers, action to address a key driver of those costs—antibiotic resistance—remains modest. We call upon infectious diseases physicians to urge their congressional representatives to prioritize federal responses to AMR, specifically by supporting the PASTEUR Act and increased funding for stewardship, antibiotic research and development, surveillance, and prevention. We have the knowledge necessary to inform our lawmakers to help create the political will necessary for action.

Notes

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